The pupil in myotonic dystrophy

H. Stanley Thompson, Maurice W. Van Allen, and Gunter K. von Noorden

The pupils of 15 patients with myotonic dystrophy were examined with the electronic pupillograph of Loewenstein and Loewenfeld. They were found to have round, equal, miotic pupils which reacted sluggishly to light and to near vision. The studies showed no defect of the sympathetic pathways. Pupillary fatigue was comparable to the normal. Various locations for a defect causing this combination of pupillary abnormalities are discussed. The midbrain is suggested as the most likely location.

Myotonic dystrophy is a heredofamilial degenerative disease, the chief signs of which are myotonia, muscular wasting, frontal baldness, testicular and ovarian atrophy, cataract, endocrine changes, cardiac anomalies, and mental deterioration. These signs and symptoms usually first appear in the third and fourth decades of life. The atrophy of the facial muscles, the ptosis, and the baldness combine to produce a long, lean, lackluster face which makes the patients resemble one another.

There are a few reports of pupillary abnormalities in patients with myotonic dystrophy, but the clinician's usual impression is that these patients have normal pupillary reactions. The question arises as to whether the reported abnormalities are simply incidental findings and unrelated to the myotonic dystrophy, or whether they are extreme expressions of pupillary abnormalities commonly present in the disease but not usually detected. We had hoped to take a step toward answering this question by studying a few patients with the Lowenstein electronic pupillograph. We did not imagine that we would find pupillary reactions as hauntingly similar to each other as were the patients' faces. Our 15 patients (10 men, 5 women) were from thirteen different families. Their ages ranged from 14 to 60 years, with an average age of 45.5 years. They all had a well-established clinical diagnosis of myotonic dystrophy, and had been followed by the Neurology Department here for periods ranging from a few weeks to several years.

Literature

Tonic pupils and pupillary fatigue associated with myotonic dystrophy. In 1902 Saenger described tonic pupils and called them "myotonic pupils." Strasburger objected to this term, and Saenger immediately made it clear that he had used the word "myotonic" to emphasize that the pupillary behavior was analogous to the behavior of striated muscle in Thomsen's disease, but that it was not necessarily part of the same process.

In 1906 Hoche described a patient who undoubtedly had myotonic dystrophy. The
patient was unable to accommodate or to relax his accommodation with the usual promptness. However, after repeated efforts at near vision he loosened up considerably and was able to switch from far to near vision without delay. After rest, accommodation became stiff again. His pupillary reaction to near vision was just as tardy and as changeable as his accommodation (see Verbiest below). No mention is made of the pupillary reaction to light.

In 1922 Kehrer\(^1\) described a patient with myotonic dystrophy whose slow pupillary reaction to light improved after repeated stimuli.

In 1937 Verbiest\(^3\) reported a case of a patient with myotonic dystrophy who, after converging his eyes strongly on some near object, was unable to straighten them again for several seconds. And, as long as his eyes were converged, the pupils remained constricted.

In 1947 Maas and Paterson\(^2\) reported that 5 of their patients with myotonic dystrophy had been examined with particular attention to the pupils, and that all of them had pupillary light reactions that fatigued easily. Just what was meant by this was not made clear.

In 1947 Maas and Paterson\(^2\) described a patient with myotonic dystrophy whose pupils constricted poorly and tonically to light, but after repeated stimuli the pupillary reactions to light became more swift and more complete. The pupillary constriction to near vision behaved in the same way. It is interesting to note that this patient's pupils were not only unequal but did not constrict equally in the horizontal and vertical meridians.

**Sluggish pupils associated with myotonic dystrophy.** In most of the reported cases of myotonic dystrophy the pupils are described as reacting normally. However, there are a few cases in which a sluggish reaction to light is noted.

In 1939 Guttman and Stokes\(^1\) described a patient with myotonic dystrophy as having delayed pupillary reactions to light.

In 1947 Maas and Paterson\(^2\) stated that "apart from cataract, abnormality of pupillary reactions seems to be the most common ocular symptom in dystrophia myotonica." They noted that "several" of their patients had delayed pupillary reactions to light. In particular, one patient was described whose "pupils were almost totally inactive to both light and accommodation, although the W. R. was negative."

In 1961 Vos,\(^3\) reviewing his many years of experience with this disease, stated that pupillary abnormalities are rare.

Caughey\(^4\) in his recent monograph (1963) states that he had never encountered pupillary changes.

**Pupillographic studies.** In 1947 Maas and Paterson\(^2\) expressed the hope that the pupils of patients with myotonic dystrophy and those of their relatives would soon be examined by some pupillographic method. In 1948 Morone\(^2\) published such a study, using a 16 mm. cinematographic technique. He examined 10 patients, 6 with myotonic dystrophy, 2 with myotonia only, and 2 unaffected relatives. He concluded that pupillary abnormalities were distinctly more common in myotonic dystrophy than had been heretofore appreciated, and that the pupillary reactions showed something
very similar to "incomplete absolute rigidity." He then suggested that the lesion might be in the "vegetative centers of the diencephalon."

In 1959 Battistini and Paganoni examined a brother and sister with myotonic dystrophy using the same 16 mm. cinematographic technique. They found pupillary abnormalities similar to those found by Morone, namely, "diminution of the amplitude and velocity" of the reactions. They also mentioned an "early tendency of the pupils to fatigue" on repeated stimulation with light, and the variability of the wave forms of the constrictions to repeated light stimuli. They then suggested that such pupillary abnormalities could best be accounted for by a defect of "the sympathetic and parasympathetic centers of the hypothalamus."

**Method**

The technique used was similar to that which has been described previously in detail by Lowenstein and Loewenfeld. The pupillograph is an infrared flying spot scanner. Both pupils are optically scanned while the patient sits comfortably in darkness, and the widest diameter of each pupil is continuously recorded on an ink-writer. Not only does the pupillograph record pupillary diameters but it measures the speed of contraction of the pupil and this can also be recorded continuously as millimeters per second against the same time base.

The reactions of the pupils to the following stimuli were observed: (1) a series of supramaximal light stimuli in each eye, each stimulus lasting 1 sec. and separated by 3 sec. of darkness; (2) a series of 0.1 sec. flashes occurring at 1 per second, 2 per second, and 3 per second; (3) a

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*"Incomplete absolute rigidity" is a term that was used to convey a partial defect of both the reaction to light and the reaction to near vision, as opposed to "incomplete reflex rigidity" which referred to a partial defect of the constriction to light only.*
Fig. 2. The chart on the left shows the initial pupillary reaction to light of a group of 9 normal subjects with normal pupils. Their ages range from 12 to 63, with an average of 32 years. On the right the initial light reactions of all 15 of the patients with myotonic dystrophy are shown together. Their ages range from 14 to 60, with an average age of 45 years. Note that there is a uniform lack of vigor of the constrictions to light even in patients in whom miosis is not present.

Fig. 3. The derivative curves. The rate of change of the pupillary diameter is measured along the ordinate in millimeters per second. Note that a peak speed of contraction is reached very soon after the iris starts to move. The darkly shaded area shows the range of the derivative curve in normal subjects, and the lightly shaded area shows the range in the subjects with myotonic dystrophy. Note that the peak speed is very much lower than normal in the patients with myotonic dystrophy, and that the peak speed occurs slightly later and is maintained a little longer than normal.

Results

Miosis. The pupils of 11 of our 15 patients did not dilate to more than 5.5 mm. in darkness. These pupils are abnormally small for this age group. Each patient had round and regular pupils and only 2 of the 15 showed anisocoria of more than 0.3 mm.

When a drop of the parasympatholytic drug tropicamide (Mydriacyl) (0.5 per cent) was put in these eyes the average increase in the darkness diameter was more than 1 mm. (Fig. 1). The normal young pupil in darkness is between 7 and 8 mm. wide (varying with age) and seldom dilates more than another 0.5 with an atropine-like drug. Fig. 1 shows the darkness diameter of one pupil of each patient before and after the application of 0.5 per cent tropicamide and demonstrates that when the parasympathetic impulses were blocked there was a greater than normal dilatation of the pupil, from which the inference is drawn that the pupils were small because of an increased level of cholinergic stimulus. These pupils cannot be expected to dilate with a parasympatholytic drug up to normal darkness diameters because they have presumably been suffering from this spastic miosis for several years, and pupils that have been constricted for a long time tend to become...
Fig. 4. A series of bright but brief flashes of light illustrates most of the differences between normal pupils and those of the patient with myotonic dystrophy: the tendency to a smaller diameter in darkness, the slowness of the response to light, and the diminished amplitude of pupillary movement.

It was found that the patients with myotonic dystrophy showed a slightly prolonged latent period of the pupillary reaction to a bright light, averaging about 325 msec. The normal latent period to light of the same intensity is approximately 250 msec. The reactions also showed a consistently diminished peak speed of contraction. Fig. 3 shows the derivative curves in which the rate of pupillary contraction is measured. The patients with myotonic dystrophy are compared with a group of normal subjects. The peak speed of contraction tended to occur later and to be maintained longer in the pupils of the myotonic subjects (Fig. 3) and the extent of the pupillary contraction was clearly diminished in the patients with myotonic dystrophy. Fig. 4 illustrates the diminished amplitude of pupillary movement in a typical patient with myotonic dystrophy as compared with a normal subject.

For the sake of brevity and clarity, all these features of the light reaction will be considered as expressions of the sluggishness of these pupils.* Figs. 5 to 7 illustrate this defect in the light reaction in 3 different age groups.

**Reaction to near vision.** The constriction of these patients' pupils when they looked at a near object appeared to suffer from a similar defect, i.e., the contraction was more sluggish and less extensive than the normal. This, however, is a difficult thing to quantify with our present techniques because the pupillary constriction seems to vary with the effort expended by the patient.

**Reaction to sound stimulus.** Fig. 8 illustrates the pupillary dilatation to a psycho-sensory stimulus in a normal subject and in patients with myotonic dystrophy. The responses can be seen to be of the same order of magnitude. In view of the fact that there is an increased level of constrictor tone for the dilator to overcome we feel that no defect of the sympathetic centers, sympathetic pathways, or dilator muscle can be shown to be present.

**Fatigue of the light reaction.** To test pupillary fatigue 3 patients with varying amounts of pupillary involvement were subjected to a long series of light stimuli (1 sec. on, 3 sec. off, for 50 to 60 stimuli). The results of these tests are compared with those of 3 normal subjects in Figs. 9 and 10. Fig. 11 illustrates the measurements

*For example, sluggishness is characterized by: (1) a prolonged latent period, (2) a diminished peak speed of contraction, (3) a peak speed which occurs later than normal, (4) a peak speed which is maintained longer than normal, and (5) a diminished extent of contraction.
Table I. Findings in 15 patients with myotonic dystrophy

The clinical severity of the disease was judged on a four-point scale: Mild (M1), Moderate (M), Moderately severe (MS), Severe (S). A patient unable to walk was considered to have severe involvement. Notice that all of our patients were ambulatory yet had very definite signs and symptoms of the disease.

The time of onset of the symptoms is difficult to determine in this disease, so these ages should be taken as approximations.

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which were made. These charts re-emphasize the decreased amplitude of contraction, the torpor and the miosis of the pupils in myotonic dystrophy. They also show that the pattern of deterioration in the light reactions with repeated stimulation is not significantly different from that of the normal subjects (Table I).

Discussion

Consideration of these pupillary findings in myotonic dystrophy raises several questions.

Are these pupils small because the cells of the iris sphincter have become supersensitive to circulating acetylcholine, perhaps as a result of the diminished stimulus from the light reflex?

If this were the case, one would expect the pupils to constrict to 2.5 per cent Mecholyl, and they do not (Fig. 12).

Could the sluggishness of the pupils be due to a defect of transmission in the afferent arm of the light reflex?

Fig. 13 shows the light reactions of a normal pupil to a stimulus light of 1 per cent standard intensity. These reactions are comparable to those of a patient with an afferent pupillary lesion such as retrobulbar neuritis. Notice that the latent period becomes even more greatly prolonged, the duration of contraction becomes shortened, and characteristic w-shapes begin to appear. These changes were not seen in the patients with myotonic dystrophy.

Only in Case 12 was a slight unilateral afferent pupillary defect found and this could be accounted for by the very much denser cataract in that eye. We encountered no patients with more visual loss than could be accounted for, roughly, by the extent of the cataractous changes in the lenses.

Could the miosis of myotonic dystrophy be due to increased cholinergic activity at the iris?

It has been suggested that the myotonia of skeletal muscle, which is so prominent in this disease, is due to an excess of acetylcholine or a deficiency of cholinesterase at
the myoneural junction and that the situation is thus the opposite of that which obtains in myasthenia gravis.\textsuperscript{36, 37} Grashchenkov\textsuperscript{4} reported that he found free acetylcholine in the blood of patients with myotonic dystrophy, but that the amount of cholinesterase in the blood was normal. However, no quantitative differences in the acetylcholine-cholinesterase activity have ever been detected at the myoneural junction in any of the myotonias.\textsuperscript{5, 28} Further, the fact that the myotonic reaction is not abolished or diminished when the end plate is blocked by curare\textsuperscript{15–16} would seem to imply that the myotonia is not due to abnormal neuromuscular transmission.

It is, nevertheless, possible that the iris sphincter is kept in spasm by a chemical defect at the myoneural junction. However, miosis caused by small doses of pilocarpine is not associated with sluggish light reactions,\textsuperscript{24} and small doses of physostigmine enhance the peak speed of the light reflex,\textsuperscript{24} so, if the miosis is due to increased circulating acetylcholine or to a defect in the acetylcholinesterase mechanism, then an entirely unrelated sluggishness of the pupillary reactions must be assumed to be obscuring the signs of the pharmacologic disturbance. This sluggishness could be mechanical and due to structural, degenerative changes in the iris itself. However, spastic miosis and sluggish light reactions usually occur together. They are seen together in central nervous system syphilis, in alcoholism, and in arteriosclerosis cerebri as well as in myotonic dystrophy, so it is not difficult to think of the two signs as having an etiologic factor in common.

Could a lesion of the intercalated, central neurones of the light reflex path cause sluggish pupillary reactions?

Yes, presumably this is occurring with the Argyll Robertson pupil. However, it should be noted that these patients with myotonic dystrophy showed no dissociation between the constriction to near vision and the constriction to light; both were diminished in a similar fashion.

It is also worth noting that these patients showed no alternating contraction anisocoria, which speaks for intact pupillary pathways in the pretectal region.\textsuperscript{*}

If there is then no lesion of the afferent side of the reflex arc, perhaps there is a defect of the efferent pathways, or a disturbance of the forces which work on the pupil through the efferent path, i.e., supranuclear inhibition of the Edinger-Westphal nuclei.

In patients who are excited, there is an enhanced supranuclear inhibition of the

*In alternating contraction anisocoria the direct constriction to a light stimulus is more extensive than the consensual. Löwenstein has, by a process of elimination, reasoned that this finding is probably due to a defect in the region of the pretectal nucleus.\textsuperscript{20}
Figs. 9 and 10. These figures compare 3 normal subjects with 3 patients with myotonic dystrophy. An attempt was made in each case to fatigue the pupillary light reaction by presenting repeated stimuli. If the patient could tolerate it, he was subjected to a series of bright flashes in one eye for 5 minutes. For each contraction the following measurements were made and the results plotted: extent of contraction, peak speed of contraction, duration of contraction, and the pupillary diameter at the beginning of each contraction (see Fig. 11).

Fig. 9 shows that with respect to the extent of contraction and the speed of contraction the patients with myotonic dystrophy can easily be separated from the normal subjects, but that, as far as pupillary fatigue (or the lack of it) is concerned, the patients with myotonic dystrophy are indistinguishable from normal persons.

Fig. 10 shows that only the miosis found in some of the patients with myotonic dystrophy separates them from the normals when the diameter at the beginning of each contraction is measured and that the contraction time and the pattern of pupillary fatigue are the same in both myotonic and normal subjects,
Edinger-Westphal nuclei, and the pupillary reaction to light can, in extreme cases, become sluggish. Our patients with myotonic dystrophy cannot be said to show this pupillary pattern, first, because their pupils are miotic and the pupils of an excited patient are dilated, and, second, because their pupillary reactions are still sluggish after many stimuli, whereas light reactions which are blocked by excitement always improve after a few repeated stimulations.

If the supranuclear path is interrupted by a lesion in the diencephalon, or if the patient is asleep or anesthetized, then supranuclear inhibition is diminished and the pupils become miotic and a square-shaped reaction develops because the speed of contraction is increased. A psychosensory stimulus will tend to restore the shape of the reaction toward normal. The patients with myotonic dystrophy do not have pupils like this; their pupils are small and sluggish, not small and snappy. Since the sluggishness is not directly related to the patient's level of alertness, it is not surprising to find that a psychosensory stimulus does not improve the sluggish light reactions.

It has long been suggested that an Argyll Robertson pupil might be explained by a lesion in the midbrain near the Edinger-Westphal nuclei which cuts off the impulses of the light reflex without affecting the presumably more ventral path of the near reflex. It was further suggested by Lowenstein that the miosis of the Argyll Robertson pupil might be explained by assuming that the deprived Edinger-Westphal nuclei, according to Cannon's law, become hypersensitive to acetylcholine, and that a steady stream of parasympathetic impulses then flows to the iris sphincter because of the acetylcholine released near the sensitive Edinger-Westphal nuclei from central synapses.

Our patients with myotonic dystrophy have a cholinergic miosis and a defect of the light reflex. There is a parallel sluggishness of the reflex for near vision. Their pupillary findings could be explained by a diffuse midbrain defect similar to that postulated for the Argyll Robertson pupil.

Could a defect of the peripheral third nerve cause the sluggishness?

This is unlikely, for two reasons; first, frank paresis of extraocular muscles is not seen in myotonic dystrophy and, second, the pupils are equal and behave symmetrically in all the patients tested.
Could the neurones of the ciliary ganglia be defective?

This is unlikely because of the symmetry of the pupillary defects and the failure of the pupils to react to 2.5 per cent Methochyl.

Could an iris fibrosis or a dystrophic process of the iris muscles be the cause of these pupillary findings?

It is possible that some as yet unknown disturbance of the smooth muscle of the iris could be causing these pupillary findings, but the following facts speak against this location:

1. The pupils of all our patients were round and regular.
2. There was very little anisocoria in the group.
3. There is a defect of pupillary constriction but pupillary dilatation is normal. If the sphincter itself is involved, why not also the dilator?
4. The pupillary reactions of the normal subject show some deterioration with repeated stimuli. This fatigue has been shown to be of central origin. The pattern of pupillary fatigue in our patients was identical with that of the normal subjects. If there is some disturbance of the iris muscles themselves in myotonic dystrophy, then one might perhaps expect to see some increased fatigability or increased facility of movement with repeated stimuli comparable to the well-known behavior of the striated muscle in this disease.
5. Although hypotony of the bowels is sometimes seen with myotonic dystrophy and cardiac conduction defects are common, the sphincters of the urinary tract are not generally involved, and it can be safely said that no consistent disturbance of smooth muscle is recognized as part of the syndrome.

The iris could be bound down by hyaline degeneration near the pupillary margin such as is found in normal old age, and the miosis could be either the cause or the effect of such a degenerative process.

In Case 14 (a 14-year-old girl), pupillary sluggishness is present without miosis. This suggests a more likely sequence of events, namely, that the sluggishness is soon followed by the miosis, both being of central
origin, and that the slow-moving iris develops local degenerative changes which are the direct result of its diminished activity.

Myotonic dystrophy is by no means only a disease of muscle; the central nervous system and the endocrine system are involved. Although the myotonia of this disease has been fairly well established as a muscular phenomenon, and although the brain is usually exonerated in autopsy reports, there are some definite indications of cerebral involvement. For example, there is the progressive mental enfeeblement, premature senility, and social deterioration which these patients very consistently demonstrate. There are at least two reports in the literature which describe atrophy of the nucleus oculomotorius medius, which would be difficult to explain as transsynaptic retrograde degeneration. Curschmann describes degeneration in the basal ganglia and in the hypothalamus in this disease. In 1959 Refsum and associates performed pneumoencephalographic studies on 16 patients with myotonic dystrophy and found enlargement of the third ventricle and noted that there was a parallelism between the degree of cerebral atrophy and the extent of the clinical deterioration.

Conclusions

It was found that the pupils of patients with myotonic dystrophy react sluggishly and inextensively to light and to near vision, that they tend to be miotic, that they react normally to a psychosensory stimulus, and that they do not fatigue any more readily than do normal pupils. Many possible causes for such pupillary behavior have been discussed and from them two possible explanations have emerged. A single midbrain defect might both impair the pupillary light reaction and result in miosis (cf. Argyll Robertson pupil), or there could be two peripheral lesions, a pharmacologic miosis and a structural sluggishness. The present authors favor the former explanation.

We would like to acknowledge our indebtedness and gratitude to Professor Otto Lowenstein and Dr. Irene Loewenfeld for the many hours of help and advice which they have so freely given.

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Discussion

Dr. M. Alpern, Ann Arbor, Mich. I find this paper interesting, refreshing, and stimulating. The authors have succeeded in raising doubts in my mind as to whether or not we can assume that myotonic dystrophy is merely a disease of the muscles, but they have not succeeded in proving to my satisfaction that it is not.

There is an abundance of worthwhile data reported in this paper, and we should feel indebted to the authors for specifying in such accurate quantitative detail the characteristics of the pupil light reflex in patients with the disease. If one cannot agree with every detail of their interpretation of these data, this in no way detracts from the importance of their achievement. The problem is important enough that we must encourage the authors to pursue this matter with renewed vigor so that, ultimately, the proof of the location or locations of the defect(s) responsible for the characteristics of the light reflex, which they have documented so beautifully will not depend upon the kind of speculation from indirect evidence which the authors confront us with in the discussion section of the article.

I have only one question and three rather trivial comments on the specific details in this paper. The question concerns how the authors interpret the deterioration of the accommodation response in these patients. One wishes the authors would have pursued the characteristics of the near response more exhaustively. Drs. Mason, Jardinico, and I (Am. J. Ophth. 52: 762-767, 1961) have shown how easy it is to quantify the relations between pupil size accommodation response, and stimulus and vergence in the normal eye. The answers to a number of empirical questions concerning A C/A ratios, pupil size accommodation response relations, and pupil size accommodation vergence relation in this disease would be very helpful in eliminating the kind of speculation on
indirect evidence with which we must be satisfied at present.

My comments refer first of all to the inference drawn from the experiments with sound stimulation. The fact that responses to sound stimulation are the "same order of magnitude" in normals as in the patients in no way justified the inference that no defect occurs in the sympathetic pathways to pupil dilation. On the contrary, it is obvious that all of the responses described in the present instance "are the same order of magnitude" in normals as in the patients, but this does not mean that there are no defects in the light reflex in the patients. Obviously, more work needs to be done with sound stimulation, but a careful examination of the results of Fig. 8 convinces me that further work will reveal a systematically smaller response to sound in the patients compared to normals.

My next comment, and I suppose it is only the same comment on another set of data, refers to the experiments with Mecholyl. One finds the results of only 3 subjects, and the authors interpret these results as negative in all 3 cases; but, even if this is the case, they have not ruled out the possibility that this may not be anything more than a failure of this drug to penetrate as adequately in these patients as in the patients with Addison's syndrome.

Finally, one wonders about making inferences from the experiments illustrated in Fig. 13. What is the evidence which shows that the response of the normal eye to the standard stimulus attenuated by a 2.0 density filter is identical with the response of a patient "with an afferent pupillary lesion" to the standard stimulus unattenuated? This is an important point—in fact important enough to be documented in its own right, but neither the authors nor their reference 38, to which they refer us, provides the kind of documentation that is required. I would urge the authors (a) to provide us with such documentation, and (b) to postpone making any premature inferences from the results illustrated in Fig. 13 until such time as this point has been established without a shadow of a doubt.

Dr. H. Stanley Thompson (closing). Using the pupillograph, we have made the same observation that Lowenstein and Loewenfeld have repeatedly made, namely, that attenuating the intensity of the stimulus produces some characteristic changes in the light reflex shape and that comparable wave forms can be seen when a patient with an afferent pupillary defect is subjected to the same light stimuli. The only point which we wish to make with Fig. 13 is that the patients with myotonic dystrophy did not show these reflex shapes.

In regard to the Mecholyl tests, Dr. Alpern has brought up a point which is crucial to pupillary pharmacodynamics. If measurements are to be made of the response of the pupil to a certain substance, then something must be known, quantitatively, about the penetrance of that substance into the eyes. But some patients have more blepharospasm than others, some produce more tears than others, and some have a damaged and perhaps more permeable corneal epithelium, so it is not possible to compare quantitatively one patient's response with that of the next patient. For this reason, we have tried to call a Mecholyl test positive only when there is a prompt and extensive constriction, and, by these standards, our 3 cases all showed unequivocally negative responses.