METHACHOLINE PUPILLARY RESPONSES IN THIRD NERVE PALSY AND ADIE'S SYNDROME

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SUMMARY

In order to examine the clinical usefulness of methacholine in assessing the site of ocular parasympathetic lesions, pupillary responses in man were measured in postganglionic (Adie's syndrome) and preganglionic third nerve lesions involving the pupil and in controls. From previous work with methacholine it might have been expected that greater constriction would occur in the postganglionic lesions but similar responses were found in both. Corneal hypoxia due to ptosis appeared unlikely to affect corneal permeability significantly and it is probable that these results reflect an increased responsiveness of the iris at, or distal to, the site of muscarinic acetylcholine receptors.

Pupils contralateral to third nerve palsy, when tested on a separate occasion, also constricted by an amount approximately proportional to that of the clinically abnormal pupil. The possibilities that this may result in some way from reduction in total retinal illumination, or from retrograde changes in preganglionic pupilloconstrictor neurons affecting contralateral pupilloconstrictor neurons via central pathways, are discussed.

It is concluded that supersensitivity to methacholine, tested carefully in the manner described, is a useful guide to the presence of parasympathetic denervation or decentralization, but that it is not reliable in distinguishing between the two sites.

INTRODUCTION

Supersensitivity to dilute methacholine is a well known although not invariable feature of the tonic pupil of Adie which is thought to result from lesions of the postganglionic parasympathetic fibres to the iris (Adler and Scheie, 1940; Loewenstein and Thompson, 1967; Harriman and Garland, 1968; Bourgon et al., 1978). The pupillary response to dilute methacholine in lesions of preganglionic parasympathetic fibres is less well described. Adler and Scheie (1940) found no significant response in cats with preganglionic as opposed to postganglionic lesions, and described the use of methacholine in man as 'of distinct value in differentiating tonic pupils from Argyll-Robertson pupils and also from iridoplegia as seen in internal
ophthalmoplegia due to lesions central to the ciliary ganglion'. However, in their comprehensive re-evaluation of the tonic pupil in 1967, Loewenfeld and Thompson commented that they were not aware of a systematic study in patients with known intracranial lesions of the third nerve. In an apparently unique case of internal ophthalmoplegia with minimal ptosis but no other extraocular involvement, due to a posterior communicating artery aneurysm, Payne and Adamkiewicz (1969) found no response to 2.5 per cent methacholine. In their case, however, the pupil was tested only shortly after becoming fully dilated and fixed, while mydriatics had been instilled four days before methacholine was given. Although Thompson (1975) reported a mild constriction at most in preganglionic third nerve lesions affecting the pupil, in comparison with a mild or marked constriction in Adie's pupil, we have found no published series of cases. We therefore report the responses seen in third nerve palsy of recent onset compared with Adie's pupil and normal and neurological controls.

METHODS

Patients

1. Third nerve palsy. Fourteen consecutive cases with solely unilateral, partial or complete pupillary involvement were tested. In each case arteriography showed an aneurysm of the posterior communicating or terminal carotid artery on the side of the lesion. In 11 cases there was associated subarachnoid haemorrhage, confirmed by lumbar puncture. Serological tests for syphilis were negative. Diabetes mellitus and other neuropathic conditions were excluded. No abnormality of corneal sensation was apparent from the response to instillation of methacholine eye drops or on routine testing with a wisp of cotton wool after completion of the test or at the time of admission several days before. In all cases the third nerve palsy was of acute onset. In 10 it had been present for between six and fourteen days and in the remainder for one to six months prior to testing.

Five normal controls who had worn hard contact lenses daily for at least five years were tested in an attempt to control for the effect of ptosis on corneal oxygenation and permeability. In each case, the test was performed after at least 8 h continuous wear, the contact lens being removed immediately before the test and being returned at its completion, 30 min later.

In addition, 17 cases of subarachnoid haemorrhage, without clinical third nerve involvement, were tested within six weeks of onset.

2. Adie's pupil. Fourteen consecutive cases were tested. Diagnosis was based on clinically obvious tonic constriction and dilatation on accommodation for near and distant objects, with an absent or markedly reduced response to light. All cases were associated with loss of some tendon reflexes; 5 patients had bilateral pupillary involvement. Cases of tonic pupil due to other causes were not included. In one case, pupillary abnormality had been observed for only one month; in the remainder duration varied from three months to several years.

3. Neurological controls. Fifty-eight cases in which there was no reason to suspect direct or indirect involvement of the pupil or its innervation. Patients with any ocular abnormality, fifth nerve signs, diabetes mellitus, other neuropathic lesions (with the exception of 4 patients with a contralateral Bell's palsy and 2 patients with contralateral Horner's syndrome) or visual failure were excluded.
4. Normal controls. Thirty-six members of the hospital administrative, nursing and medical staff and relatives of patients kindly volunteered. None was known to suffer from diabetes mellitus. As with other controls there was no evidence of pupil tonicity. In all cases informed verbal consent was given.

Procedures

On each occasion both pupillary diameters were recorded before and 30 min after instillation of 2.5 per cent methacholine to one eye only, the other acting as control. Thus the amount of any constriction or dilatation of the control pupil was subtracted from or added to any change in the size of the tested pupil, unless the latter was fixed to light. In this case no allowance was made for any dilatation of the contralateral normal control pupil. We are aware of other procedures for testing pupillary responses but this method was chosen as the best way of comparing results in conditions with either unilateral or bilateral involvement.

Initially pupils were measured to the nearest 0.5 mm by eye, using a transparent ruler held against the bridge of the patient's nose. In later cases, pupils were photographed using a 1:1 CU5 Polaroid Land camera (f 5.6; exposure 1/125 s; Polaroid 107C or 667 black and white film). Maximum pupillary diameters were measured from the film to the nearest 0.1 mm using a magnifying lens (x 7). In all cases the patient was resting, lying flat and fixating on a distant object in constant, moderate artificial illumination. In the case of tonic pupils, measurements were taken only after fixation for at least 1 min. Where ptosis obscured the pupil, the patient was asked to fixate with the normal eye while the affected eye remained closed. After measurement of the normal pupil, the ptosed lid was gently lifted for measurement, the patient continuing to fixate with the normal eye. If this proved difficult because of diplopia, each eye was measured while the other was closed.

The accuracy of direct measurement was checked in a number of patients during a wider study of pupil responses to instilled drugs in autonomic nervous system disorders. In this, pupils were measured directly and also photographed in a photographic studio in constant, moderate, indirect light, before and half an hour after instillation of different drugs to one eye. Projection of photograph negatives gave a x 10 magnification. In 27 of 30 photographs the difference in diameter in each pair of pupils, corrected to the nearest 0.5 mm, was the same as by direct measurement. The error in the remaining 3 was 0.5 mm in each case. Reasonable accuracy of direct pupillary measurement by eye was confirmed by the finding of similar responses in controls measured directly and in subsequent controls measured from Polaroid film. The latter responses were therefore adjusted to the nearest 0.5 mm and the data pooled.

Drugs

Different techniques of instillation have been described but the following was adopted to increase the certainty of instillation and in an attempt to reduce dilution by tear fluid. The patient lay flat, following the initial pupillary measurement, with eyelids held gently open by the examiner. Two drops of 2.5 per cent methacholine—prepared within two weeks of each test and stored at 4° C—were instilled from a standard commercial dropper (mean drop size = 0.07 ml) into one conjunctival sac, the eyelids then being gradually released to prevent splashing, while the head was held firmly to avoid overflow. Normal blinking in controls was mimicked in patients with complete ptosis by gentle passive movements of the upper eyelid. After 30 s the patient sat up or raised his head so that excess fluid drained away, without rubbing his eyes. After 30 min the patient resumed the original position and after again fixating on the same distant object, both pupil diameters were measured as before. In the majority of cases in which the responses of both pupils were examined, the contralateral pupil was tested 24 h before or after the abnormal one. Each solution of methacholine was used to examine controls as well as patients with third nerve palsy and/or Adie's syndrome.
RESULTS

The responses to methacholine are summarized in Table 1.

<table>
<thead>
<tr>
<th>Constriction after methacholine</th>
<th>Normal controls</th>
<th>Contact lens</th>
<th>Neurological controls</th>
<th>Third nerve palsy</th>
<th>Contralateral control</th>
<th>SAH alone</th>
<th>Adie's pupil</th>
<th>Contralateral control</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.0 mm</td>
<td>3</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>&lt;1.0 mm</td>
<td>33</td>
<td>5</td>
<td>48</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>13</td>
</tr>
</tbody>
</table>

All pupils associated with third nerve palsy and all but one of the 14 pupils with Adie's syndrome showed a response of 1.0 mm or more (100%: 95%). This was in marked contrast to pupils of subjects in all other groups studied (normal, hard contact lens, and neurological controls, and subarachnoid haemorrhage) where few responses were as great as 1.0 mm (8%: 0%: 17% and 24%, respectively) (figs. 1 and 2).

Although the pupils associated with third nerve palsy and with Adie’s syndrome showed similar high responses, the contralateral pupils in these conditions behaved differently. Seven out of 12 clinically normal pupils contralateral to third nerve palsy constricted by 1.0 mm or more, compared with only 1 out of 8 clinically normal pupils contralateral to an Adie’s pupil (fig. 2).

While many patients with third nerve palsy also had a subarachnoid haemorrhage, responses in subarachnoid haemorrhage alone were significantly different both from pupils in third nerve palsy with or without subarachnoid haemorrhage and also their clinically normal contralateral controls when accompanied by subarachnoid haemorrhage (figs. 1 and 2; Table 3). Furthermore in patients with third nerve palsy there was a significant positive correlation between responses in individual pupils associated with third nerve palsy and their contralateral controls (fig. 3).
Fig. 3. Correlation between response to 2.5 per cent methacholine in third nerve palsy and contralateral control pupil recorded on separate occasions (correlation coefficient = 0.613, \( P < 0.05 \)). X, with subarachnoid haemorrhage; O, without subarachnoid haemorrhage.

Fig. 4. Comparison of interocular difference in response to 2.5 per cent methacholine between unilateral third nerve palsy and unilateral Adie's pupil. A, third nerve palsy less contralateral response. B, Adie's pupil less contralateral response.
Table 2. Comparison of Mean Ages and Pupil Sizes in Patients and Controls

<table>
<thead>
<tr>
<th>Controls</th>
<th>n</th>
<th>Mean Age Range</th>
<th>Mean Diameter (mm)</th>
<th>Pupil Constriction (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>36</td>
<td>45(20-68)</td>
<td>5.09</td>
<td>0.25</td>
</tr>
<tr>
<td>Neurological</td>
<td>58</td>
<td>49(19-68)</td>
<td>4.79</td>
<td>0.38</td>
</tr>
<tr>
<td>Contact lens</td>
<td>5</td>
<td>25(21-30)</td>
<td>7.10</td>
<td>0.20</td>
</tr>
<tr>
<td>Subarachnoid haemorrhage</td>
<td>17</td>
<td>43(19-57)</td>
<td>5.24</td>
<td>0.50</td>
</tr>
<tr>
<td>Third nerve</td>
<td>14</td>
<td>54(18-71)</td>
<td>5.21</td>
<td>1.70</td>
</tr>
<tr>
<td>Contralateral pupil</td>
<td>12</td>
<td>56(18-71)</td>
<td>4.33</td>
<td>0.96</td>
</tr>
<tr>
<td>Adie's pupil</td>
<td>14</td>
<td>37(20-64)</td>
<td>5.14</td>
<td>1.71</td>
</tr>
<tr>
<td>Contralateral pupil</td>
<td>8</td>
<td>35(20-64)</td>
<td>5.13</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Note. In all controls and bilateral Adie's, only one pupil response is included to avoid statistical bias. Where both pupils were tested, the right or left response was selected using random number tables. No relation was apparent between response to methacholine and medication.

As a corollary, the arithmetic difference between responses in third nerve palsy and their contralateral controls (recorded on separate occasions) is compared with the arithmetic difference between unilateral Adie's pupils and their contralateral controls in fig. 4.

The two groups are not statistically different when compared in terms of responses of < 1.0 mm and ≥ 1.0 mm, but none of the third nerve palsy patients showed differences as great as 2.0 mm, in comparison with 4 out of 8 of the Adie cases.

The age distribution and sizes of resting pupillary diameter and pupillary constriction, and a statistical comparison of results in each group of subjects, are shown in Tables 2 and 3, respectively.

Table 3. Comparison of Responses ≥1.0 mm/Responses <1.0 mm Between Different Groups, Using χ² Test, with Yates' Correction [+], or Fisher's Exact Test (Two Tailed) (O)

<table>
<thead>
<tr>
<th></th>
<th>P</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Neurological controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonic pupils</td>
<td>&lt;0.0001</td>
<td>+</td>
</tr>
<tr>
<td>(contralateral controls)</td>
<td>1.2</td>
<td>O</td>
</tr>
<tr>
<td>Neurological controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third nerve palsy</td>
<td>&lt;0.0001</td>
<td>+</td>
</tr>
<tr>
<td>(contralateral controls)</td>
<td>&lt;0.01</td>
<td>+</td>
</tr>
<tr>
<td>Subarachnoid haemorrhage(SAH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupil contralateral to third nerve palsy + SAH</td>
<td>0.04</td>
<td>O</td>
</tr>
<tr>
<td>Third nerve palsy</td>
<td>Contact lens</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pupil contralateral to Adie's pupil</td>
<td>0.008</td>
<td>O</td>
</tr>
<tr>
<td>(Third nerve palsy minus contralateral control)</td>
<td>(Adie's pupil minus contralateral control)</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Among those patients with third nerve palsy seen by the Neuro-ophthalmology Department at the National Hospital, Queen Square, during the course of clinical investigation, no corneal abnormality was noted. In one case, slit lamp examination and Rose Bengal test were performed, and were normal. Schirmer's test was performed (J.R.P.) in one case of third nerve palsy showing a large methacholine response and was normal. Two cases of third nerve palsy with large responses to methacholine were subsequently tested with 0.1 per cent adrenaline and showed no response.

**DISCUSSION**

This study shows a similar increase in sensitivity to methacholine in Adie's pupil and in proximal third nerve lesions involving the pupil. The results also suggest that the observation of pupillary sensitivity to dilute methacholine is of considerable value in identifying postganglionic parasympathetic pupillary abnormality, in comparison with the finding of Bourgon et al. (1978) that only 64 per cent of Adie's pupils showed supersensitivity to methacholine. Nevertheless the occasional large response in clinically normal controls confirms Brunschwelier's (1954) observation that a large response alone cannot be taken as evidence of tonicity. It has previously been suggested by Adler and Scheie (1940) that a large response implies a postganglionic site of lesion, but in the light of these results this view has to be modified.

The main theoretical basis for clinical pupillary testing has derived from experimental work in cats by Adler and Scheie (1940) who found an increased response to methacholine with postganglionic but not with preganglionic parasympathetic lesions. They do not describe the precise site of the latter, but we presume it was intraorbital. However, Anderson (1905a, b) demonstrated, in cats, an increased response to topical pilocarpine both after ciliary ganglionectomy and after intracranial third nerve section and also 'paradoxical pupillary constriction' after section of postganglionic or preganglionic fibres in the orbit (denervation and decentralization, respectively). In both series, the majority of cats undergoing denervation on one side and decentralization on the other showed a greater response on the side of decentralization. Keil and Root (1941), using intravenous acetylcholine found a similar time course of development over about five days (five to eight days, using threshold doses of pilocarpine in cats with postganglionic iris denervation (Neidle, 1950)), and similar magnitude of iris supersensitivity in cats after either ciliary ganglionectomy or intracranial third nerve section. Cannon and Rosenblueth (1949) noted that the iris parasympathetic supply appeared to be an exception to their general conclusion that supersensitivity following denervation exceeds that after decentralization. Support for this exception and evidence that a central lesion or change may cause supersensitivity is suggested by the finding of Bito and Dawson (1970) and Bito et al. (1971) that cholinergic supersensitivity in cat iris occurring as a functional response to light deprivation for one week almost
equals that produced by denervation. The time course of development of the supersensitivity in the rat iris after light deprivation shown by Claesson and Bárány (1978) is comparable to that found by Keil and Root (1941) following denervation or preganglionic third nerve section in the cat. It should be emphasized that the majority of the present cases, unlike that of Payne and Adamkiewicz (1969), were tested at a time when maximum responsiveness might be expected by analogy with these results.

There are clearly a number of factors which have to be taken into account in the interpretation of the present results. First, despite a standardized technique for instillation of eye drops, variation in the amount of drug available to penetrate the cornea seems inevitable, as a result of individual differences in reflex tear secretion, volume of conjunctival sac and so on. Secondly, the possibility of altered corneal permeability to methacholine as a result of corneal injury has been stressed by Thompson (1977) as particularly likely to occur after fifth nerve lesions. No clinical evidence of fifth nerve abnormality was found in the present cases. Moreover, Purcell et al. (1977), using a Cochet-Bonnet aesthesiometer, found some impairment of corneal sensation in Adie’s syndrome, but no increased responsiveness to adrenergic drugs to suggest altered permeability. No increased responsiveness was seen in the two present cases of third nerve palsy tested with dilute adrenaline. No clinical abnormality was seen in any of the patients examined ophthalmologically and none was noted clinically. Altered corneal permeability might also be anticipated in third nerve palsy as a result of corneal hypoxia secondary to ptosis. Considerable changes in corneal metabolism have been shown to occur as a result of prolonged tight eyelid closure, and to a lesser extent after wear of hard contact lenses, including a dramatic fall in corneal acetylcholine concentration, a marked increase in touch threshold, and an increased corneal thickness (Mindel et al., 1979; Millodot and O’Leary, 1979). In the present study, volunteers wearing hard contact lenses daily for at least five years were tested after at least eight hours of wear. The absence of any increased response to methacholine in these cases strongly suggests that the large response in third nerve palsy is unrelated to the accompanying ptosis, which was rarely so complete as to be comparable with the tightly taped eyelids of Millodot and O’Leary’s volunteers. Furthermore it is hard to see how the ptosis could account for the increased response of the contralateral pupil in over half the cases examined. No attempt was made to study the effect of systemic cholinergic drugs in the present cases, but the similar response to intravenous acetylcholine following pre- and postganglionic parasympathetic lesions in the cat, described by Keil and Root (1941), also makes it appear unlikely that altered corneal permeability is a significant factor in the present results.

There are several theories related to the mechanism of supersensitivity, either preganglionic or postganglionic and this issue is currently unresolved. Fleming (1975) distinguished change due to alteration in uptake and/or metabolism of the drug and supersensitivity due to enhanced responsiveness of the target organ. The latter corresponded to the nonspecific supersensitivity following decentralization
described by Trendelenburg (1963), a postganglionic lesion resulting in supersensitivity by both mechanisms.

In the case of the tonic pupil it seems reasonable to suppose loss of acetylcholinesterase from the iris following postganglionic cholinergic denervation (Laties, 1972). However, Russell (1958) pointed out that in cases of Adie's pupil of acute onset with initial iridoplegia, the characteristic tonic reaction developed weeks or months after the development of demonstrable supersensitivity, suggesting that the tonic reaction is dependent on partial reinnervation. Although this would tend to restore the acetylcholinesterase content (Laties, 1972), complete recovery would seem unlikely in view of the behaviour of the tonic pupil. It is, therefore, surprising that iris supersensitivity to methacholine in Adie's pupil does not exceed that seen in preganglionic third nerve lesions which presumably does not greatly reduce acetylcholinesterase, if at all. This suggests that acetylcholinesterase deficiency is not a significant factor in iris denervation supersensitivity.

Decentralization supersensitivity, at least as described for other structures, is nonspecific, resulting in increased responses to both cholinergic and adrenergic drugs, as well as other transmitters and ions (Trendelenburg, 1963). In this context it is interesting to note that no increased response to adrenergic drugs was seen in two cases of third nerve palsy with large responses to methacholine.

It was suggested by Bito and Dawson (1970), after Dale (1934), that the supersensitivity of the target organ is inversely related to the local long term concentration of neurotransmitter, probably as a result of variation in receptor densities. Although cholinergic activity regulates muscarinic receptor density in central nervous system cultures (Siman and Klein, 1979), Kloog et al. (1979) found no increase in receptor density, measured by radiolabelled ligand binding studies in cat iris rendered supersensitive to pilocarpine by postganglionic denervation. The resulting reduction in acetylcholinesterase activity was felt insufficient to account for the change in sensitivity and would of course not affect the response to pilocarpine, which is nonhydrolysable. The supersensitivity was therefore attributed to postreceptor events, which appear likely to involve a number of factors (Trendelenburg, 1980).

The increased response of the pupil contralateral to third nerve palsy is also difficult to explain. The relative lack of response in subarachnoid haemorrhage suggests that this cannot account for the responses in patients with third nerve palsy and subarachnoid haemorrhage. Furthermore the possibility of altered third nerve function as a result of basal adhesions or communicating hydrocephalus cannot be excluded in those patients with subarachnoid haemorrhage alone. The inverse relation between chronic background illumination and iris cholinergic supersensitivity in the cat (Bito et al., 1971) raised the possibility that unilateral ptosis in third nerve palsy might sufficiently reduce retinal illumination to result in a subsequent increase in iris sensitivity. In man the light reflex innervation of the Edinger-Westphal nuclei is bilaterally symmetrical, or virtually so (Loewenstein, 1954; Smith et al., 1979), compared with the cat (Loewenstein, 1954), and a bilateral
increase in iris sensitivity would therefore be anticipated. In order to test this possibility in the present study, 4 volunteers underwent occlusion of one eye for 65, 72, 74 and 144 h, respectively, but an insignificant constriction of between 0.1 and 0.3 mm was observed after instillation of two drops of 2.5 per cent methacholine on to the contralateral eye at the end of the occlusion. Similarly, a constriction of only 0.5 mm occurred following dilute methacholine in the normal eye of a patient who had undergone enucleation of the contralateral eye two years previously, so this was not the explanation. It also seems unlikely that interruption of afferent muscle spindle fibres in the third nerve would influence the light reflex pathway.

Walter (1958) and Burn and Rand (1959) found, independently, that unilateral sympathetic iris denervation in the cat was accompanied by changes in the contralateral iris. Walter found that this resembled the denervated iris more than the control irides. Burn and Rand found the noradrenaline content of the contralateral control iris fell by over half. More recently, Case and Matthews (1979) have shown bilateral synaptic changes in the rat superior cervical ganglion following unilateral postganglionic axotomy. Nerve growth factor, carried by retrograde axoplasmic flow, is known to produce transsynaptic effects in sympathetic ganglia and the possibility of more central retrograde trophic influences has been raised by Purves and Lichtman (1978). Although, of course, there may be other explanations for these changes in the contralateral iris and sympathetic ganglion, it appears reasonable to speculate that such central, retrograde trophic influences may occur and might also account in some way for the contralateral response seen in the present patients with third nerve palsy. Other evidence for second and third order retrograde transneuronal change, summarized by Brodal (1981), provides further support for such an explanation. That no increased response to methacholine was seen in pupils contralateral to unilateral Adie’s pupils might be interpreted to mean that any retrograde effect could only cross a limited number of synapses. This difference in responsiveness makes it unlikely that the increased response to methacholine opposite to a third nerve palsy is simply another manifestation of the phenomena of ‘sympathetic ophthalmitis’ and ‘sympathetic orchiopathia’ (Wallace et al., 1981). Indeed, it is of interest that Wyburn-Mason (1981) has concluded that these phenomena are not immunological in origin but the result of retrograde neurotrophic influences.

Is there any anatomical basis by which retrograde change might directly affect contralateral preganglionic pupilloconstrictor fibres? Although Sillito and Zbrozyna (1970) found that unilateral electrical stimulation of the midbrain in the region of origin of the preganglionic pupilloconstrictor fibres, just ventral to the Edinger-Westphal nucleus in the cat, provoked bilaterally equal and maximal pupillary constriction, their findings from antidromic third nerve stimulation suggested strictly unilateral innervation, in keeping with Warwick’s (1954) finding of chromatolysis in the ipsilateral Edinger-Westphal nucleus following unilateral ciliary ganglionectomy in monkeys. Nevertheless the bilaterally equal response to
unilateral stimulation found in Sillito and Zbrozyna suggests the possibility of close interconnection between the pools of pupilloconstrictor neurons on the two sides, which might act as a route for retrograde transsynaptic change if such occurs at sites other than sympathetic ganglia.

The method used in this study of testing one pupil at a time, using the other as control, differs from that of Thompson (1975), in which supersensitivity was recorded as the difference in response between each pupil tested simultaneously. This would partly explain the greater mean constriction found in the present cases of Adie's syndrome compared with those reported by Bourgon et al. (1978), using Thompson's technique. Inspection of the results shown in fig. 4 suggests that the method of Thompson would still have shown pupillary constriction of the order of 1.0 to 1.5 mm in many cases of third nerve palsy, with a mean constriction of 0.83 mm. The present unilateral tonic pupils, after subtraction of the response of the normal contralateral control pupil, show a mean constriction of 1.69 mm. Only those showing a response, after subtraction of the contralateral response, of 2.0 mm or more exceed the largest corresponding value in the present, relatively small series of pupils with third nerve palsy. It is therefore our conclusion that iris sensitivity to methacholine is not a reliable indicator in distinguishing pre- and postganglionic pupilloconstrictor nerve lesions, and that distinction remains dependent on clinical and/or pathological evidence.

It was noted by Brunnschweiler (1954) that the frequency of response of tonic pupils to cholinergic drugs varied in different reported series. Although our findings are comparable with those of Brunnschweiler (1954) and Sigsbee et al. (1974) for normal controls, they differ from Bourgon et al. (1978) who found supersensitivity in only 64 per cent of tonic pupils, with a mean constriction of 0.7 mm. The greater response in the present series might be explained by the patients’ supine posture during instillation, perhaps reducing the rate of flow of methacholine away from the eye via the nasolachrymal duct. The importance of duration of exposure to instilled drugs was shown by Smith (1974) who found a large response to prolonged instillation of very dilute solutions. A less likely explanation is that patients with tonic pupils were selected at an earlier stage of their condition, when the pupil tends to be larger, allowing a greater constriction to occur (Thompson, 1977). Although further studies are needed to explain such variation between different series, we feel it is unlikely to be a significant factor in accounting for the similar responses in pre- and postganglionic third nerve lesions observed in the present investigation.

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