ADIE'S SYNDROME: SOME NEW OBSERVATIONS*

BY *H. Stanley Thompson,* MD

INTRODUCTION

THIS PAPER IS NOT A DETAILED DIDACTIC REVIEW OF ADIE'S SYNDROME. THE history of the discovery and naming of the condition will not be dwelt upon since this material was carefully reviewed by Lowenstein and Loewenfeld in 1965.[1]

Only those aspects of the syndrome will be discussed to which some new information can be added. This new information is based on a series of patients with Adie's syndrome examined during the last ten years. The collection of cases began in 1966 and does not include cases previously reported by the author. The patients were encouraged to return for annual review and as many of the examinations listed in Table I were done as time and patience permitted.

CLASSIFICATION OF ADIE'S TONIC PUPILS

Damage to the postganglionic para-sympathetic innervation of the intraocular muscles produces some very characteristic signs: (1) A poor pupillary reaction to light, which, at the slit lamp, can be seen to be a regional palsy of the iris sphincter. (2) Accomodative paresis. (3) Cholinergic supersensitivity of the denervated muscles. (4) Often a pupillary response to near vision that is unusually strong and tonic, due to aberrant reinnervation of the sphincter.[2]

All patients who show these signs are said to have "Adie's tonic pupils." However, this leads to confusion because the term "Adie's Syndrome" is also used to refer to the combination of tonic pupils of obscure origin and impaired tendon reflexes in the limbs; and further, Adie's pupils are sometimes seen as part of a widespread peripheral neuropathy. In order to facilitate the discussion in this paper, the 150 cases in my files carrying the diagnosis of "Adie's tonic pupil" were divided into three categories: A. "Local Tonic Pupils" B. "Neuropathic Tonic Pupils" and C. "Adie's Syndrome." (Tables II and III)

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TABLE I: EXAMINATIONS DONE ON PATIENTS WITH ADIE'S SYNDROME

	No. of Patients
1. History: date of onset, symptoms	110
2. Ophthalmic examination	122
(with assessment of accommodation	72
3. Slit lamp examination of iris sphincter	122
(with motion pictures)	109
4. Polaroid photos of pupils in darkness, in light and at near	98
5. Electronic pupillography	107
6. Blood drawn for:	
VDRL	70
FTA	63
Viral Antibody studies	75
7. Cholinergic supersensitivity testing	
Mecholyl test	98
Pilocarpine test	59
8. Deep Tendon reflexes examined	91
9. Corneal sensitivity plotted	17

"LOCAL TONIC PUPILS"

Seven patients had definite local disease (ocular or orbital). This group has been left out of subsequent discussion because the denervation of the sphincter was only an incidental feature of their disease. In two children the condition dated from a red eye during chicken pox; one patient had had herpes zoster ophthalmicus, and three patients had orbital injury and one patient had a severe, undiagnosed bilateral choroiditis with bilateral tonic pupils. It cannot be denied that a few of these patients might have had Adie's syndrome in addition to their local orbital problem, but the circumstances speak against it.

"NEUROPATHIC TONIC PUPILS"

There were twenty-one patients in this category, all with bilateral involvement. They all had tonic pupils in the course of generalized neuropathic conditions. Seven of them were found to have a reactive VDRL and FTA

TABLE II: TYPES OF POSTGANGLIONIC PARASYMPATHETIC DENERVATION OF THE INTRAOCULAR MUSCLES

Orbital
Those due to an ocular or paraocular disease process, e.g. Varicella or other infection, orbital or choroidal tumors, retrobulbar injection of alcohol, surgical or other trauma, etc. ("local tonic pupils")

Neuropathic
Those occurring in patients with a widespread peripheral or autonomic neuropathy which happens to involve the short ciliary nerves ("neuropathic tonic pupils")

Idiopathic
Those of unknown origin and not associated with neurologic deficits other than impaired muscle stretch reflexes ("Adie's Syndrome")

TABLE III: "ADIE'S TONIC PUPILS"

Type	
A. "Local Tonic Pupils"	
unilateral	6
bilateral	1
B. "Neuropathic Tonic Pupils"	
unilateral	0
bilateral	21
C. "Adie's Syndrome"	
unilateral	98
bilateral	24
TOTAL	150

and it was considered possible that their sphincter denervation might have been caused by syphilitic damage to the ciliary ganglion. The average age of these seven patients at the time of examination was 63 years.

The other fourteen patients in this category had peripheral neuropathies. Twelve had diabetic, alcoholic, or hypertrophic neuropathies (average age 62). One had a pan-dysautonomia (age 34) and one had Fisher's syndrome (age 6). This group of patients was also left out of further discussion.

"ADIE'S SYNDROME"

One hundred and twenty-two patients had tonic pupils of obscure origin, some with and some without disturbance of deep tendon reflexes. The discussions in this paper deal with this group. Ninety-eight of them had the ocular condition in one eye only and twenty-four of them had bilateral involvement. The VDRL and FTA tests were done in sixty-three of these patients, and a VDRL alone in seven patients; all the tests were nonreactive.

FINDINGS IN ADIE'S SYNDROME

PREVALENCE

There are no firm data on this subject, but Adie's syndrome is not as rare a condition as many ophthalmologists believe it to be. During the last ten years I have been seeing these patients at a fairly steady rate of approximately one new patient a month. Because my interest in this condition is known in this area, I am probably drawing patients from a total population of three million persons. Two ophthalmologists in joint practice twenty miles away have sent me twelve new Adie's patients in six years. This suggests that each practicing ophthalmologist is likely to see at least one new case of Adie's syndrome a year. There are about seventy busy

ophthalmologists in this drawing area. When one considers the unknown number of patients with Adie's syndrome who do not seek medical attention, and the unknown number who are reassured by their family doctor or by one of the 300 optometrists in the area, with or without a diagnosis, it seems quite probable that there are 140 new cases of Adie's syndrome each year in this population of three million. This estimate, which is admittedly little more than a guess, would put the incidence of Adie's pupils at 4.7 cases per 100,000 population per year. Since the mean age at the onset of the condition in these patients was 32.2 years, they are likely to live another 42.6 years with their Adie's pupils. The prevalence of the condition would, therefore, be approximately two cases per 1,000 population.

AGE OF ONSET

Adie's syndrome is supposed to be a disease of young adults. An effort was made to obtain an accuate date of onset in each of the 122 patients. This was sometimes quite precise:

> "It was the day before Thanksgiving and my right eye went funny; I didn't pay much attention to it, but it was still there the next day and I noticed that I couldn't focus up close with that eye and my husband pointed out that the pupil was dilated . . . . I called the eye doctor the very next day . . . ."

and sometimes reasonably accurate:

> "It was last fall sometime; I started having trouble with my eyes; November, I think, — so I made an appointment to have my eyes checked . . ."

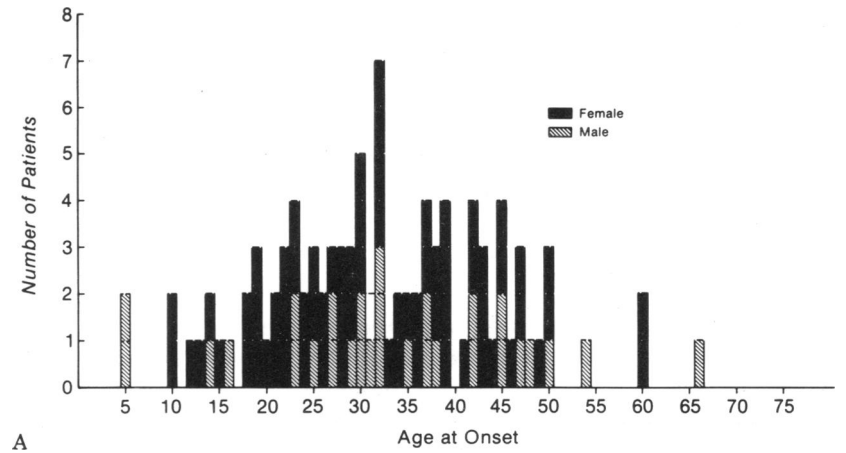
and sometimes less accurate:

"I was at a Christmas party and someone said, 'Hey, you've got one pupil bigger than the other,' so I went and looked in the mirror. I think it was the right one that was bigger. It didn't bother me any so I didn't do anything about it. But people kept saying, 'what's wrong with your eye' . . ."

and sometimes there was nothing in the history to suggest a date of onset:

> "I never knew there was anything wrong with my eyes 'til the doctor told me this morning."

Of the 122 patients, an estimated date of onset was obtainable in 98. In these patients the mean age at onset was 32.2 years. The distribution of the age of onset is shown in Figure 1A.



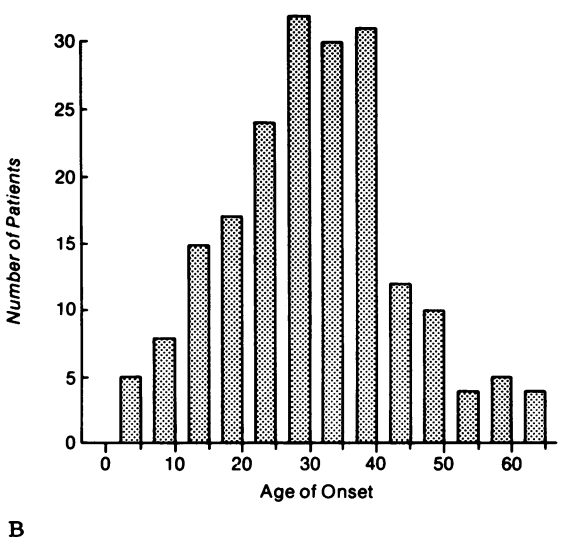


FIGURE 1

A: Age at onset of the condition in 98 patients in this series for whom the information was available. Notice that the distribution is similar among men and among women, and is quite similar to the distribution of age of onset in published cases of Adie's Syndrome. B: Age of onset in 197 patients whose case histories were described in the literature. This information is not as precise as the data in Figure 1A. When the information about date of onset was not available, the age at the time of examination was used.[3]

Notice that the age of onset was not significantly different for the men and the women in the series. It is of interest that the distribution matches closely the distribution in a large series of patients described in the literature (Figure 1B). The mean age at onset was remarkably stable in various subgroups of this population of patients with Adie's syndrome. The analysis in Table IV suggests that the age of onset is not related to the sex of the patient; nor is it related to which eye is involved, or whether one or both eyes are affected.

SEX RATIO

Prior to 1924 there had been 40 case reports of tonic pupils in the literature, and 20 of the patients were women. But in the next few years Moore, Holmes, and Adie added 46 cases to the literature and 42 of these were women.[4-8] Of 220 case reports assembled from the literature,[3] 69% were women and 31% were men (a ratio of 2.2/1). In the present series of 122 cases, 72% are women and 28% are men (a ratio of 2.6/1). Why so many more women then men should be affected is still a mystery.

Among the 98 unilateral cases of Adie's syndrome in this series the sex ratio was 2.1/1 (66 women:32 men) whereas in the 24 bilateral cases the ratio was 11/1 (22 women:2 men), many more cases would, however, be required to prove that this disparity is more than coincidence.

LATERALITY

Among the 98 unilateral cases there were approximately as many left eyes as right eyes involved (55 left, 43 right). This is not significantly different from the distribution of right and left eye involvement in the 220 cases reported in the literature[3] (see Figure 2).

TABLE IV: MEAN AGE OF ONSET IN 98 PATIENTS WITH IDIOPATHIC ADIE'S SYNDROME (FOR WHOM THE DATE OF ONSET INFORMATION WAS AVAILABLE) ANALYZED WITH RESPECT TO SEX, LATERALITY AND BILATERALITY. CONCLUSION: THE SEX OF THE PATIENT DOES NOT INFLUENCE THE AGE OF ONSET NOR IS IT RELATED TO WHICH EYE IS INVOLVED OR WHETHER BOTH EYES ARE AFFECTED

	Mean Age at Onset
All Adie's (n = 98)	32.2
All male Adie's (n = 29)	33.3
All female Adie's (n = 69)	31.7
All unilateral Adie's (n = 82)	32.2
All unilateral male Adie's (n = 27)	34.0
All unilateral female Adie's (n = 55)	31.5
All bilateral Adie's (n = 16)	32.4
All bilateral male Adie's (n = 2)	33.0
All bilateral female Adie's (n = 14)	32.3

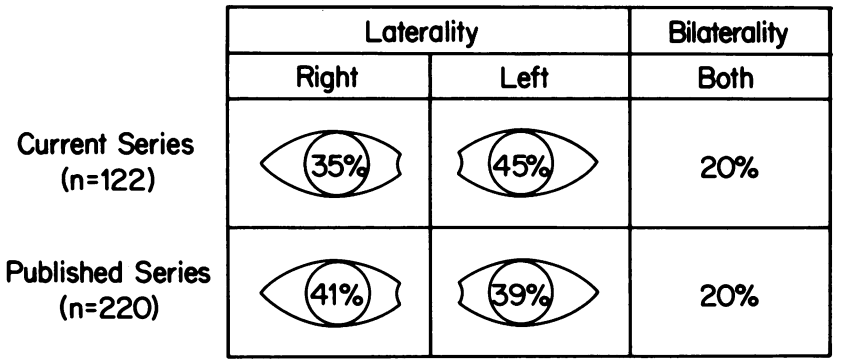


FIGURE 2
Right eyes and left eyes were involved with approximately equal frequency both in this series and in the case published in the literature.[3] In both series 20% of the patients had both eyes involved.

BILATERALITY

In 20% of the 220 cases from the literature, both eyes were involved, and the same proportion of the present series was bilateral (see Figure 2). It is interesting to note that twelve of these bilateral cases had once been unilateral. If a group of patients is followed for a number of years (as in the current series) and all cases which changed from unilateral to bilateral during the period of observation are counted as bilateral, (as in this series) then the percentage of bilateral cases will be artificially elevated. This will be discussed later under the heading "Natural History of Adie's Pupil." Furthermore, the practitioner tends to see the acute cases in his office (Fig. 3). The patients with longstanding Adie's pupils (which are more likely to have become bilateral) are less likely to take their problem to the doctor. In this series 84% of the unilateral cases were able to come up with a reasonably secure date of onset of their condition, but in the bilateral cases only 67% had any idea when their pupils became abnormal.

All this suggests that in an office practice, the percentage of bilateral Adie's may be much lower, perhaps as low as 10%. It is possible that the percentage of bilateral cases reported in the literature (Figure 2) may be artificially elevated by the inclusion of those bilateral cases which have been excluded in this paper as "neuropathic tonic pupils" (see "Classification of Tonic Pupils").

IRIS COLOR

In casual conversation with other ophthalmologists I have heard it suggested that Adie's pupils are seen less frequently in brown eyes than in blue

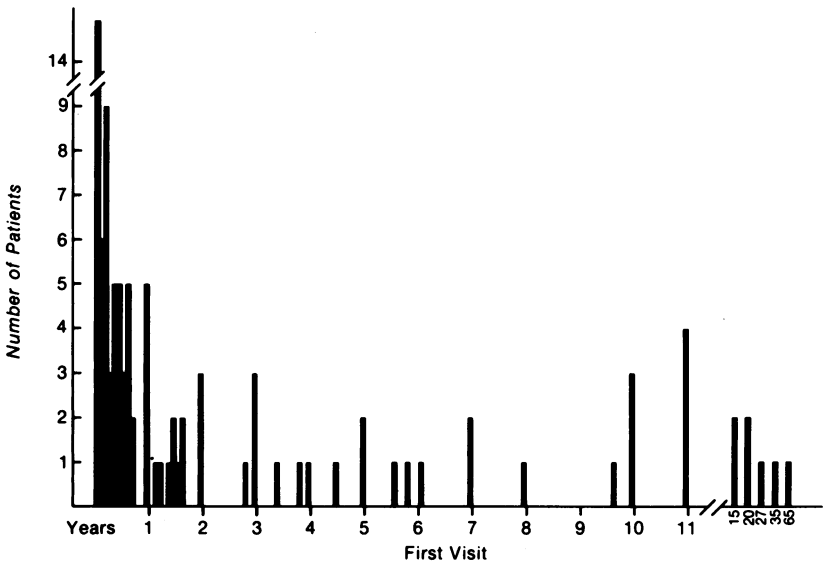


FIGURE 3
The age of the condition at the time of the first visit. This suggests that most of the patients with Adie's Syndrome in this series went to their doctor with their new symptoms soon after the onset of the condition.

eyes, and my response has always been "Naturally, the pupils are harder to see in brown eyes." It was my impression that the distribution of iris color in patients with Adie's pupil is no different from the distribution of iris color in the population from which they are selected. An effort was made to check this impression against some facts.

Color photographs of the eyes of 93 patients with Adie's pupil were available to me; and the eyes of the 93 control subjects were photographed in the same way. This control group was chosen from the employees and staff of the clinic. All the irides in all pictures were then color coded and the two groups compared[9] (see Figure 4). No difference was apparent in the distribution of iris color in the two groups.

DEEP TENDON REFLEXES

The tonic pupil was first remarked upon by Strasburger and by Saenger in 1902,[10,11] and within a few years an association with loss of the tendon reflexes had been noticed.[12,13]

During the first years of this century a pupillary "light-near dissociation" (as seen in Argyll Robertson's pupil) when combined with a tendinous areflexia, was considered to be virtually diagnostic of syphilis. Patients

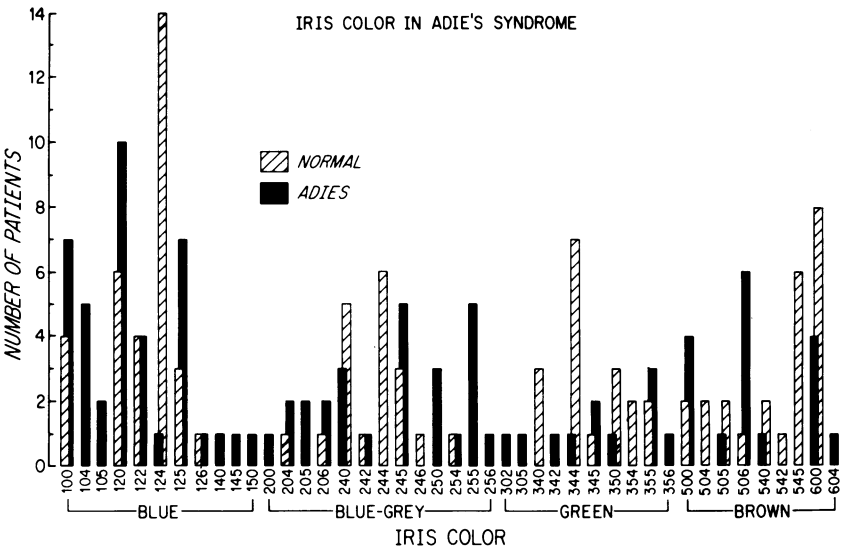


FIGURE 4

Distribution of iris color in 93 patients with Adie's pupil compared with a control population (see text). Iris color was coded numerically with the Tocher-Brownlee iris color scale as used by Riddell:

> "The general colour of the iris is recorded as blue, grey, green, yellow, tan, and chocolate, each of which is given a numerical value from 1 to 6, respectively. Secondary diffuse pigmentation is given its appropriate numeral, while small pigment spots are also recorded, zero values being used to indicate the absence of the secondary features. The iris of uniform blue, for example, is coded as 100; a grey iris with a diffuse tan colour and little masses of chocolate-coloured pigment as 256; and so on."[41]

The word "brown" was substituted for the words "tan" (500) and "chocolate" (600).

with tonic pupils had to be considered syphilitic until careful clinical judgement and the Wassermann test ruled otherwise.

Emphasizing the "non-luetic" nature of these "Argyll Robertson pupils," Foster Moore collected a series of patients with normal reflexes.[5] But others made a special point of the association between tonic pupils and hyporeflexia[6,7,14,15,16,17] and somehow Adie's name became firmly attached to this combination of signs.[1]

Of Holmes'[6] 19 patients, 17 had absent knee and ankle jerks, but no firm data were given about the biceps and triceps jerks ("In several the arm-jerks were also absent or feeble.") In many other reports one gets the impression that the arm reflexes were often not tested. In Adie's own cases, three were completely areflexic and the other ten had variable loss of reflexes in the lower extremities and it is implied but never stated that

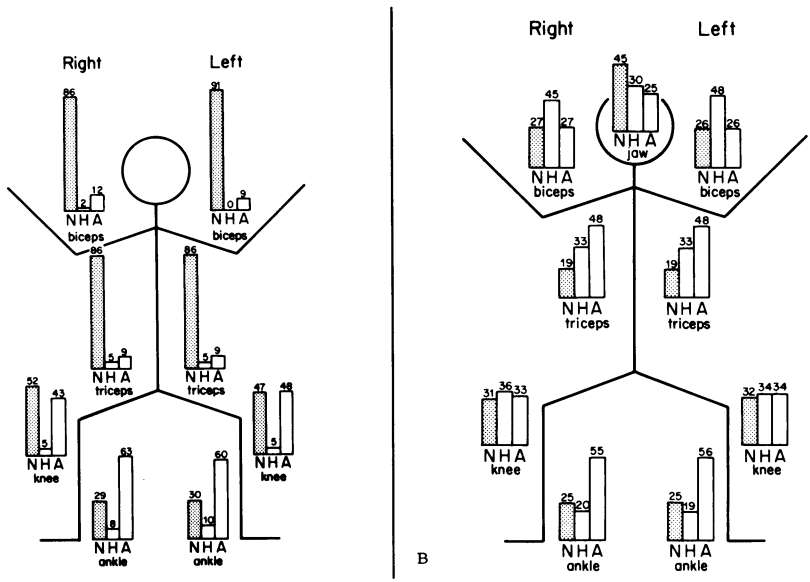


FIGURE 5

A: Distribution of impaired reflexes in 129 patients whose case reports in the literature include neurological examination[3] N = Normal, H = Hyporeflexic, A = Areflexic. The numbers in each histogram represent percentages of the 129 patients. B: Distribution of impaired reflexes in 73 patients with Adie's Syndrome seen in a five-year period by one examiner. For example, in 56% of the patients the left ankle jerk was absent (A = Areflexia), in 19% it was present but impaired (H = Hyporeflexia), and in 25% it was judged to be normal (N). Notice that in the majority of cases the tendon reflexes are abnormal throughout, but that the extent of the impairment is greater (i.e. more areflexia and less hyporeflexia) in ankles and triceps than in the knees and biceps.

the arm reflexes were examined and found to be normal. The extent of the impairment of the muscle stretch reflexes in 129 of the cases of Adie's syndrome reported in the literature is summarized in Figure 5A.

Of the 122 patients in the present series, 73 were examined at least once by the same experienced neurologist. All the patients were sent from the eye clinic to the neurology clinic, identified as having Adie's pupils, but usually with the pupillary signs obscured by drops, so that the examiner did not know which side was involved. Figure 5B summarizes the distribution of the tendon reflex impairment in this series of patients with Adie's syndrome. It is evident that the damaged reflexes are much more generally distributed than was previously suspected. One might also use Figure 5B to say that in a given case of Adie's syndrome the chances of having a normal knee jerk are approximately one in three and that the odds are about 50-50 that the ankle jerks will be absent, etc. At least

TABLE V: AMOUNT OF IMPAIRMENT OF THE MUSCLE STRETCH REFLEXES ANALYSED WITH RESPECT TO 1) SEX 2) UNILATERALITY, BILATERALITY OF THE TONIC PUPIL 3) AGE OF ONSET CONCLUSION: TENDON REFLEX IMPAIRMENT IS NOT SIGNIFICANTLY INFLUENCED BY ANY OF THESE VARIABLES

Category of Patients	Female/Male Ratio	% Unilateral Pupils	% Bilateral Pupils	Mean Age at Onset
Adie's patients w/ normal reflexes (n = 8)	3/1	88	12	35.6
Adie's patients w/ hyporeflexia (n = 53)	3/1	81	19	32.0
Adie's patients w/ complete areflexia (n = 12)	1/1	75	25	28.1
All Adie's patients w/reflexes checked (n = 73)	2.5/1	81	19	31.7
All Adie's patients (n = 122)	2.6/1	80	20	32.2

one diminished reflex was present in 53 of 73 patients of and 12 of the 73 were entirely areflexic. That is, 65 of the 73 patients (or 89%) had reflexes which were diminished or absent.

The remaining eight patients (11%) also should be considered to have "Adie's syndrome" even though their tendon reflexes were entirely normal: they were not distinguishable statistically from the patients with imparied reflexes when several variable were considered (see Tables V and VI).

When one looks closedly at the different features of Adie's syndrome, it is the variability of the denervation which is the most striking feature: some patients have very little impairment of accommodation and some

TABLE VI: THE AMOUNT OF SPHINCTER IMPAIRMENT ANALYSED WITH RESPECT TO DEEP TENDON REFLEX INVOLVEMENT, SEX, LATERALITY AND BILATERALITY. CONCLUSIONS: THERE IS NO DIFFERENCE IN SPHINCTER INVOLVEMENT BETWEEN MALES AND FEMALES. ALTHOUGH LEFT EYES SEEM TO BE SLIGHTLY MORE IMPAIRED THAN RIGHT EYES AND PATIENTS WITH COMPLETE TENDON AREFLEXIA SEEM TO HAVE MORE LOSS OF THE LIGHT REACTION THAN PATIENTS WITH NORMAL REFLEXES OR HYPOREFLEXIA, NONE OF THESE DIFFERENCES IS STATISTICALLY SIGNIFICANT

Category of Patients (Number of Patients)	No. of Eyes	Mean % of Sphincter Still Reacting to Light
Normal reflexes (n = 8)	9	28
Hyporeflexia (n = 50)	54	26
Areflexia (n = 11)	13	20
All males (n = 26)	27	25
All females (n = 68)	76	25
Unilateral cases (n = 80)	78	25
Bilateral cases (n = 16)	25	26
All right eyes (n = 44)	44	28
All left eyes (n = 59)	59	23

have a lot, some patients have only one or two clock hours of iris sphincter denervation, but most of them have a lot. The same seems to be true of the tendon reflex impairment; a few have hardly any, but most have a lot.

SECTOR PALSIES OF THE IRIS SPHINCTER

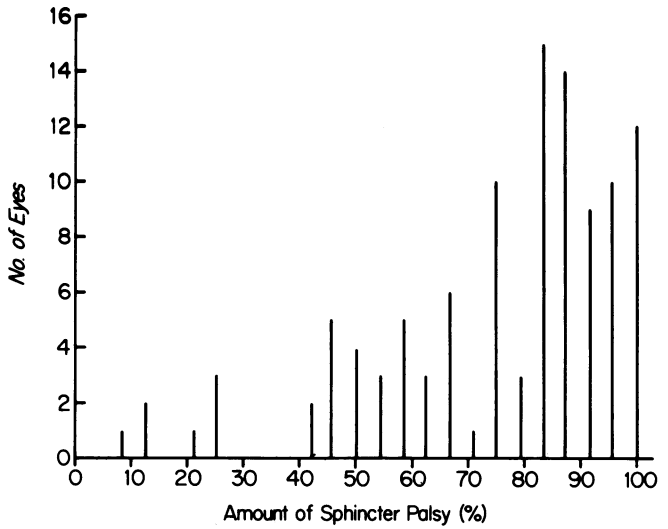
One can still find in textbooks, a brief line saying that "vermiform movements" of the pupillary margin can be seen with a slit lamp in eyes with Adie's tonic pupils. Ten years ago I started to look for this phenomenon in Adie's pupils and found it to be a disappointing sign, neither consistent nor convincing. However, I was greatly struck by the segmental palsy of parts of the iris sphincter which seemed to be present in almost every case.

"Vermiform contractions" was a phrase first used by Sattler[18] in 1911 and there was a considerable flurry of excitement in the German literature about what was though to be a newly described abnormal movement of the iris. In these old reports it is often clear that there were segmental palsies of the iris sphincter, but these, astonishingly, were disregarded while attention was focussed on the "concertina-like" contractions of the remaining sphincter segments. After Adie popularized the syndrome which bears his name, it was soon noticed that these patients often showed "vermiform movements" and irregularities of the pupillary margin[19,20,21] and a readily recognizable drawing of an Adie's iris was reproduced in Thiel's Atlas.[22]

It is my belief that "vermiform movements" of the sphincter are nothing more than physiologic pupillary unrest ("hippus") of those sectors of the sphincter which are still wired up to the light reflex; and that the real abnormality to be seen in the iris sphincter in Adie's syndrome is the segmental paralysis due to loss of some of the postganglionic nerve fibers either in the ciliary ganglion or in the short ciliary nerves.

In the 122 patients in this series a sector palsy of the sphincter was present in every Adie's pupil, which had any remaining light reaction. The sphincter segments not reactive to light were recorded in 109 eyes. Twelve of these pupils (11%) showed no light reaction whatever and therefore, no regional paralysis was seen (see Figure 6A). The percentage of eyes showing a sphincter palsy in different iris segments is shown for each clock hour position in Figure 6B.

Thirty-seven affected eyes were examined on more than one occasion. The iris sphincters were studied carefully at a slit lamp and the location and extent of the segmental palsies were recorded. These follow-up examinations were made after periods of time varying from one month to three years.



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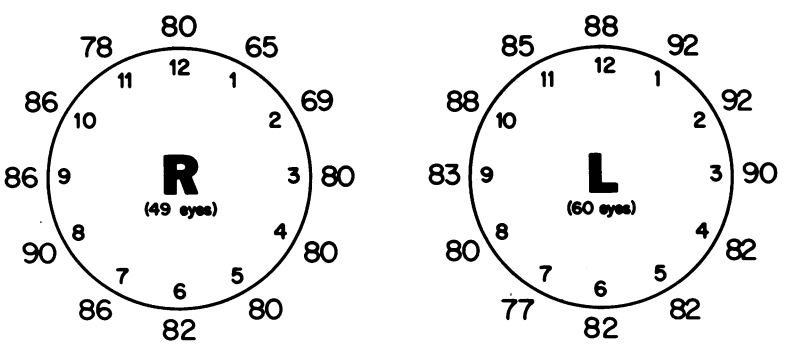


B

FIGURE 6

A: The amount of segmental palsy of the sphincter in 109 eyes with Adie's pupil. Notice that twelve eyes showed no reaction to light whatever (100% sphincter palsy). These were the only Adie's pupils in which a regional sphincter palsy could not be demonstrated. In most Adie's pupils, more than half of the sphincter was paralyzed. B: The distribution of the segmental palsy of the sphincter in the same 109 eyes as in Figure 6A. For example, the sphincter function was impaired at the 1 o'clock position in 92% of the left eyes and in 65% of the right eyes. There is no clear tendency to involve one quadrant over another.

Of the 37 eyes, 8 were noted to improve slightly, 19 lost further sphincter function, and the other 10 remained the same. The extent of these changes is shown in Figure 7A.

There seemed to be a small but definite tendency for the affected sphincter to lose more function with the passage of time (Figure 7B). This progression of the deficit did not seem to affect left eyes much more than right eyes or men more than women (see Table VI); nor did it seem to affect one quadrant of the sphincter more than another (Figure 8). It is interesting to note that the near reaction of the pupil was also often segmental and frequently involved segments of the sphincter which did not respond to light.

SYMPTOMS DUE TO CILIARY BODY DYSFUNCTION

Most patients with Adie's syndrome have an accommodative paresis in the affected eye at the onset of the condition and this is the chief source of their symptoms.

The case histories of 110 patients with Adie's syndrome in this series were reviewed and it was found that blurred near vision was the most common complaint. A relative accomodative paresis in the affected eye of half a diopter or more at the time of the first examination was present in 66% of the patients. Of those seen within two years of the onset of the condition, 86% had an accommodative weakness, but of those seen two years or more after the onset, only 47% had accommodative paresis of half a diopter or more.

Not only were there more patients with poor accommodation in the affected eye amongst the group with a recent onset but the degree of accommodative paresis was greater in the early group (see Figure 9). This suggests that there is a strong tendency for accommodation to recover in Adie's syndrome and that most of this recovery takes place within the first two years.

Some patients complained of blurred vision both at distance and at near, in the affected eye, coming on at the time the dilated pupil was noticed. Patients with a latent hyperopia and an accommodative paresis might be expected to have this complaint, but it is possible that a regional palsy of the ciliary muscle might allow the lens to shift to an eccentric position — inducing some irregular astigmatism. This idea is supported by the observation (in four out of seven patients so far) of a significant induced astigmatism (from 0.5 to 1.25 diopters) — in the affected eye only — with a maximum effort at accommodation. Pilocarpine, which would be expected to constrict the denervated part of the ciliary muscle more than the areas of normal ciliary muscle, did not produce as much cylinder as an accom-

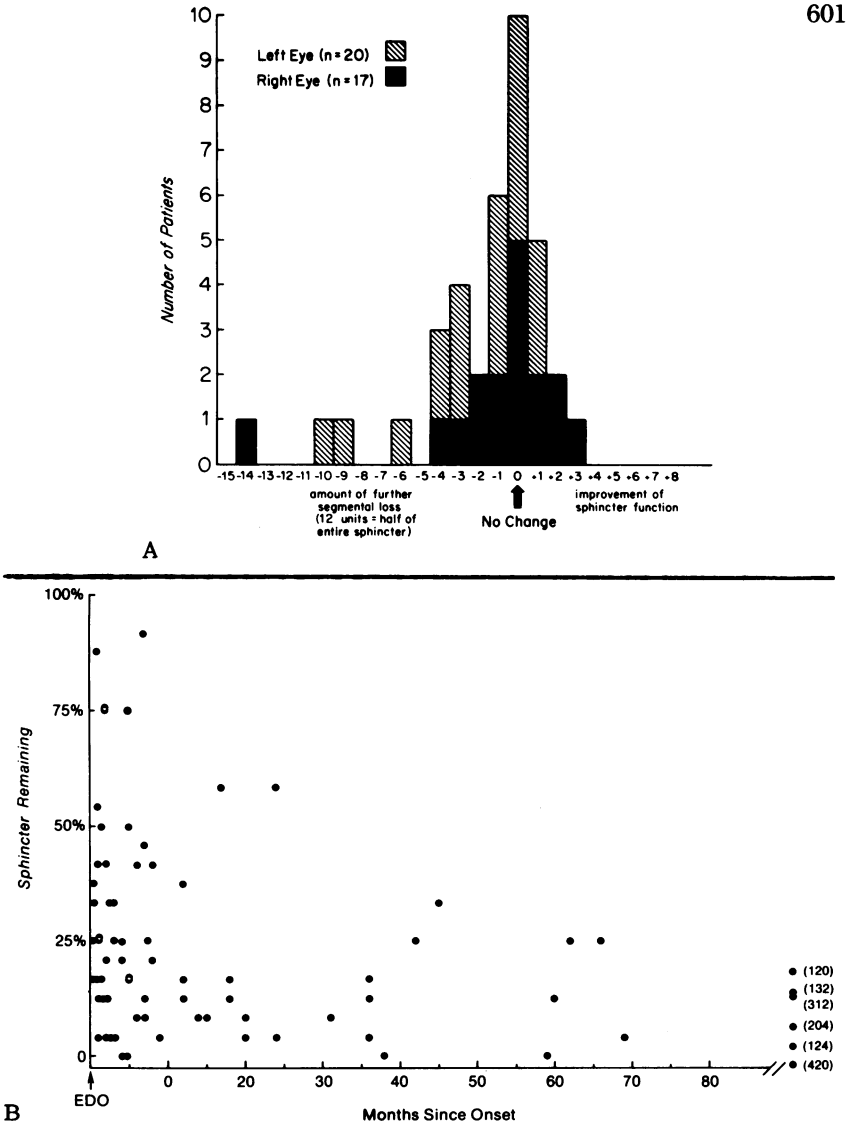


FIGURE 7

A: Distribution of changes in sphincter palsy on follow-up examination. In 37 Adie's eyes the detailed examination of the sphincter was recorded on more than one visit. Eight apparently improved, and ten remained the same but 19 suffered further segmental loss of sphincter function. Conclusion: At least a third of the Adie's pupils, when watched carefully, showed loss of the light reaction in additional segments, while in the rest there was little or no change. B: The percentage of the iris sphincter still reacting to light versus the duration of the Adie's Syndrome. None of the eyes which had the condition for more than two years had more than half of the sphincter still working. This distribution suggests that there may be a tendency for the sphincter palsy to gradually get worse.

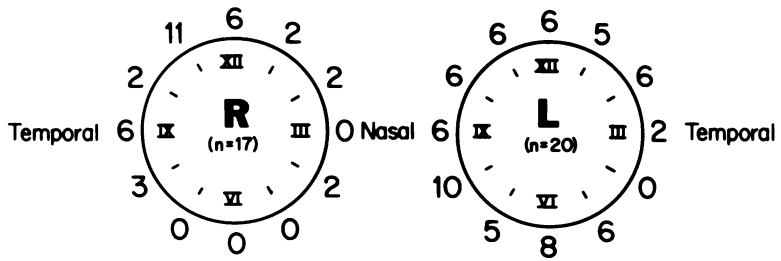


FIGURE 8

The distribution of the additional loss of sphincter function for each clock hour of the affected sphincter. The amount of change in sphincter function for each clock hour was summed algebraically for all 37 eyes, and in each of the 24 locations there was on the average either a loss of function or no change. In no location was there, on the average, an improvement of function. These changes are shown here around both sphincters as percentages of the total loss. For example: of all the further loss of sphincter function noted on follow up examinations, 5% of it occurred at the 1 o'clock position in the left eye, 3% at the 8 o'clock position in the right eye, and so on. There does not seem to be a particular predilection for further loss in any one part of the sphincter.

modative effort did. Pilocarpine (0.25%) did, however, produce a dramatic pseudomyopia in the affected eye in Adie's syndrome, presumably due to a denervation supersensitivity of the ciliary muscle. Some tonicity of accommodation was present in almost half of the patients. After a strong accommodative effort it took several seconds to relax accommodation enough to bring a distant object back into focus. The tonicity made it difficult for the patient to maintain a steady level of ciliary muscle tone in the affected eye. This can be very troublesome when the patient's dominant eye is the affected eye.

The *discomfort with near work* that these patients experience is sometimes more than just impaired accommodation or induced astigmatism: they may actually have ciliary spasm. Pain, miosis, and pseudomyopia can last for several hours after an energetic near vision effort and are promptly relieved by topical anticholinergic drugs. Some patients have learned not to accommodate too vigorously, so that they can avoid the brow ache and periocular discomfort.

Some of the patients' initial symptoms are attributable to the dilated pupil. Photophobia is seldom a serious problem, but some patients volunteer that the affected eye takes longer to adapt to darkness. This is presumably due to the fact that the retina of the affected eye, not shielded by a functioning iris, is relatively bleached out.

One patient appeared to be noticing the Pulfrich stero-phenomenon induced by his anisocoria. He played short stop for a local softball team and

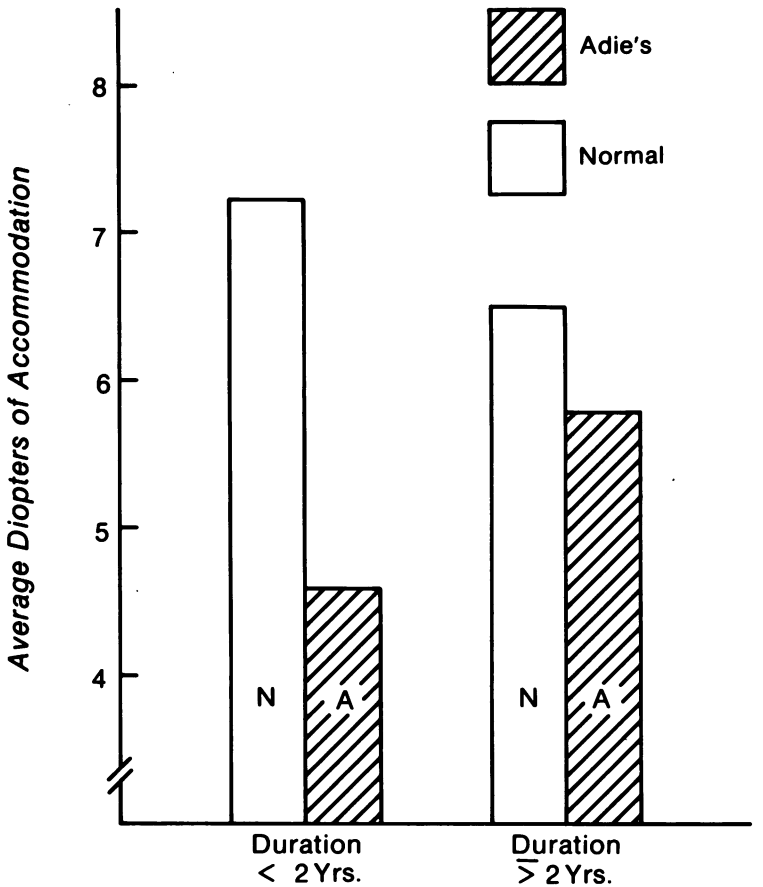


FIGURE 9
Amount of accommodation remaining in the Adie's eye (A) and in the normal eye (N). 110 patients were divided into two groups, those who had had the Adie's pupil for less than two years, and those who had had it for two years or more.

complained that he had particular trouble with balls that passed obliquely across his field of vision; he tended to misjudge their course.

For some patients the chief concern is for the cosmetic blemish of unequal pupils in blue irides. It is useless to give these patients pilocarpine — in any strength. Generally they will not tolerate it because of the intermittent accommodative spasm it produces — aggravated by the supersensitivity of the ciliary body. Even when the problem of the anisocoria seems to dominate the patient's mind, they are usually reassured by the knowledge that the dilated pupil will not last forever, that

it will come back down in a few months or at the most in a few years, and comforted when they reflect that their friends don't notice it anymore and strangers don't seem to care.

There is little doubt that accommodative paresis, tonicity of accommodation, and supersensitivity of the ciliary muscle to pilocarpine are characteristic features of Adie's syndrome. There will be many patients in whom cililary muscle dysfunction will help to make the diagnosis. But we often fail to take an adequate history, and sometimes we listen to these strange monocular complaints and never think to look carefully at the pupil because we do not associate the complaints with this well-known pupillary syndrome.

CHOLINERGIC SUPERSENSITIVITY

In 1905 Markus[13] suggested that a very weak solution of eserine could be used as a diagnostic test to localize the lesion causing a denervation of the iris sphincter; a good constriction put the lesion in the ciliary ganglion or in the short ciliary nerves. This recommendation was based on the work of Anderson who had shown differences in the behavior of the sphincter depending on the location of the lesion.[24, 25] In 1911 Stattler[18] used weak solutions of pilocarpine to localize the lesion. But it was not until Cannon and Rosenblueth had sorted out all these observations into a "Law of Denervation Supersensitivity"[26, 27] that these things were understood. Scheie and Adler[28] in 1940 clearly showed that Adie's tonic pupils were supersensitive to cholinergic substances. They chose a concentration of methacholine hydrochloride (Mecholyl 2.5%) which would not contract a normal pupil, and they showed that most Adie's pupils constricted to this cholinergic stimulus, some of them quite dramatically.

It was soon recognized that there were some tonic pupils which failed to constrict to 2.5% methacholine. At first, this was blamed on an instability of the methacholine solution and it was recommended that a fresh solution be prepared for each use. It was finally concluded[1,29] that an aqueous solution of methacholine hydrochloride is reasonably stable, but that there are large inter-individual variations in the ability of the drug to penetrate a normal cornea. In addition there appear to be large variations from one tonic pupil to another in the sensitivity of the denervated iris sphincter.

Methacholine has not been available as a commercial eye drop for a number of years and has become increasingly difficult to find. This has prompted a search for substitutes and the most readily available is pilocarpine, which is known to be stable and is cheap and always at hand. Cholinergic supersensitivity can be demonstrated with 0.25% pilocarpine,

but some patients' normal pupils constrict quite significantly to this dosage. One-eighth percent (0.125%),[30] one-tenth percent (0.1%),[31] and one-sixteenth percent (0.0625%)[32] solutions have also been recommended.

One-eighth percent pilocarpine constricts most normal pupils slightly, with a degree of miosis differing among individuals from just noticable to several millimeters, whereas Mecholyl 2.5% has no consistent miotic effect (see Figure 10). There are some advantages to using a concentration of cholinergic substance sufficient to bring the normal pupil down a small amount. If neither pupil constricts to Methacholine 2.5%, as often happens, it could be because less of the drug penetrates the patient's cornea, in this case the absence of a cholinergic supersensitivity has not been demonstrated. But when the normal pupil shows a drug effect and constricts slightly and the Adie's pupil does not constrict more than the

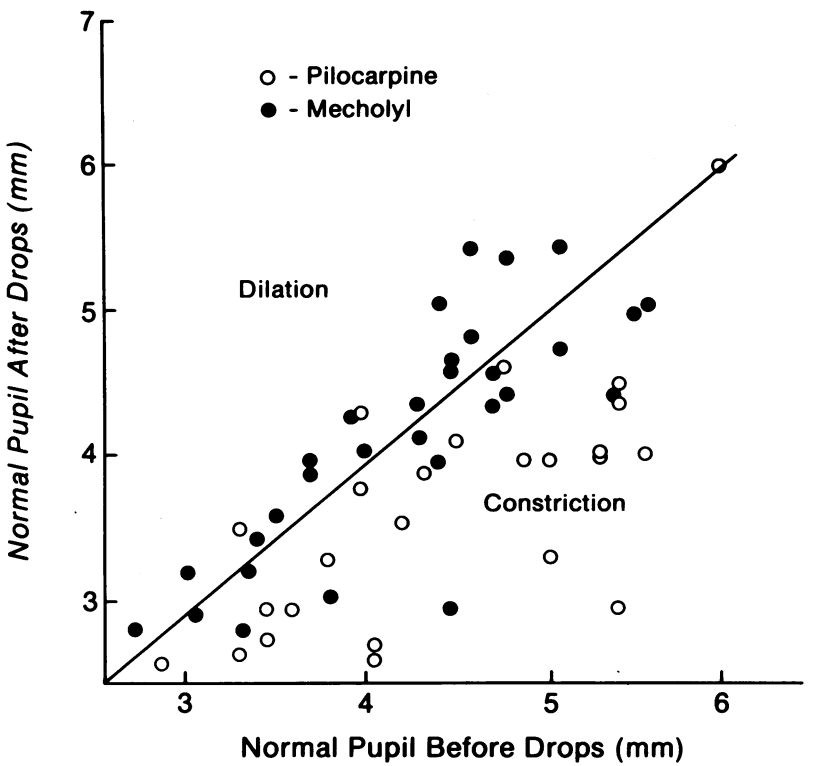


FIGURE 10

Diameter of the unaffected pupils of patients with unilateral Adie's Syndrome before and after weak cholinergic drops. Pupils are relatively small because tests were done in room light. Notice that, in general, Mecholyl 2.5% did not constrict these unaffected pupils, but that most of them constricted slightly to pilocarpine 1/8%.

normal pupil, then it can be said confidently that the affected sphincter is not supersensitive.

Cholinergic supersensitivity needs to be clearly defined: In Adie's syndrome the iris sphincter is said to be supersensitive when it contracts to a cholinergic stimulus more than the fellow normal pupil does to the same stimulus. This definition is only applicable to unilateral cases: comparing each Adie's pupil to the normal control pupil compensates in part for random fluctuations in pupillary size and emphasizes the drug-induced changes.

As shown in Figure 11 this definition can be expressed as the difference in drug-induced contraction of the two pupils: (A - a) - (N - n), where:

A = the diameter of the Adie's pupil (mm) before drugs
a = the diameter of the Adie's pupil (mm) after drug treatment
N = the diameter of the normal pupil (mm) before drugs
n = the diameter of the normal pupil (mm) after drug treatment

Supersensitivity also can be expressed as the drug-induced change in anisocoria: (A - N) - (a - n). Although these two expressions are algebraically identical, I find it easier to work with the former ("difference in drug-induced contraction") perhaps because it seems closer to the verbal definition of supersensitivity, that is the Adie's pupil constricts more than the normal pupil.

Figure 11 shows further that varying the ambient light has very little influence on the supersensitivity as calculated in this way, even though the light affects one pupil more than the other. The important thing is that the lighting was the same in the "before" and "after" pictures.

During the last few years 41 documented Mecholyl tests (2.5%) and 20 pilocarpine tests (0.125%) have been done on patients with Adie's syndrome in this series. In all instances, 1:1 Polaroid photos were taken (of both eyes together) before the drops, and again thirty minutes after the drops. The diameters of the pupils were then measured directly from the photographs. The pictures were taken in constant room illumination with the patient fixing a spot about five feet away. The results of these tests are shown in Figure 12A,B.

It is clear from these graphs that the results have been variable. In general, the larger pupils showed a more dramatic supersensitivity than the smaller pupils, but the supersensitivity did not seem to be well correlated to the amount of sphincter denervation (Figure 13A), the duration of the Adie's syndrome (Figure 13B) or the amount of light-near dissociation (Figure 13C).

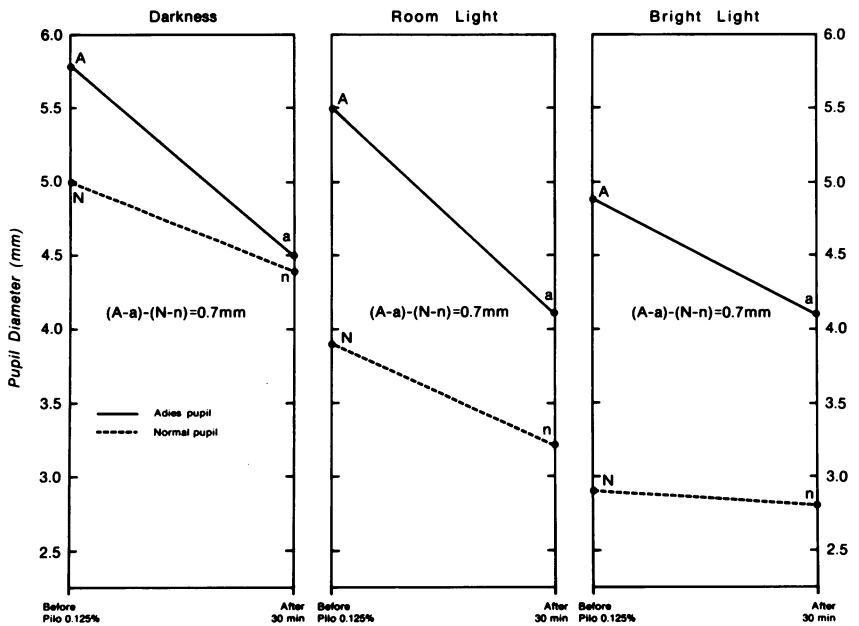


FIGURE 11

This is the record of a pilocarpine test (1/8%) in a man with an Adie's pupil of recent onset. Photos were taken before and 30 minutes after the drops at three different levels of illumination (darkness, "room light," and "bright light"). Notice that, in all three levels of illumination, the Adie's pupil's contraction (A - a) was 0.7 mm more than that of the normal pupil (N - n). The smaller the pupil is before the drug, the less actual constriction takes place. This is because a small pupil encounters increasing mechanical resistance to further miosis so that a constriction from 4 mm to 3 mm is much more of a miotic accomplishment that a constriction from 6 mm to 5 mm. This is a potential source of error in the assessment of cholinergic supersensitivity, but only when there is a considerable constriction of a small pupil.

If 0.2 mm of excess constriction of the Adie's pupil is required before it can be counted as supersensitive, then it can be said that the Mecholyl test was positive in only 64% of the patients with Adie's syndrome — the pilocarpine 1/8th test was positive in 80%. This is not an outstanding record for an allegedly pathognomonic sign!

In some patients the normal pupil seemed to be more sensitive than the Adie's pupil (points below the zero line in Figures 12 and 13). Some of these negative points are, however, probably due to artifact, such as varying accommodative effort. In Table VII are listed some of the possible reasons for the variability in apparent cholinergic supsensitivity. Nothing can be done about most of these factors, but an effort can and should be made to control the last three on the list. With this in mind, specific

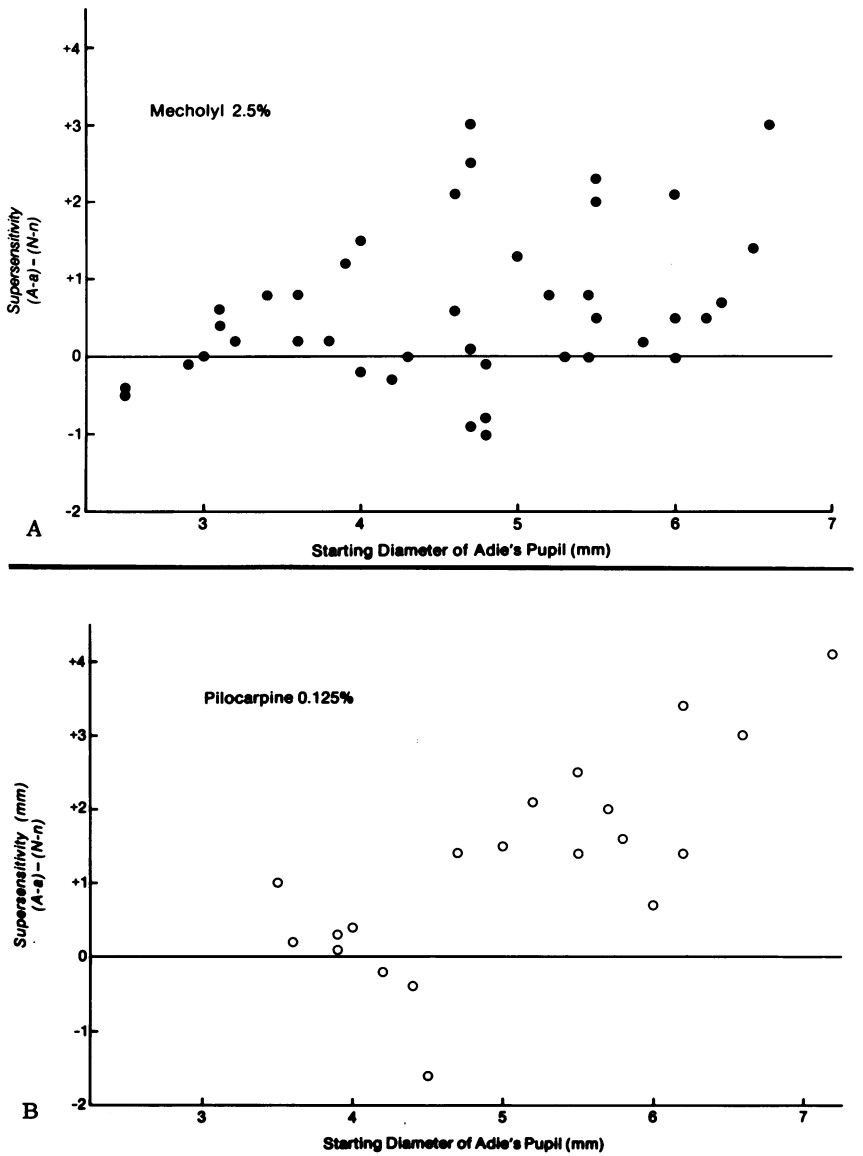
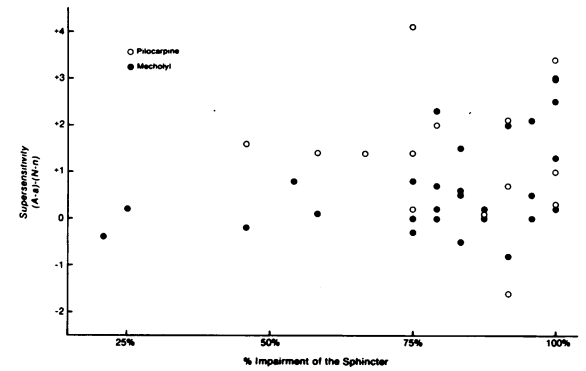
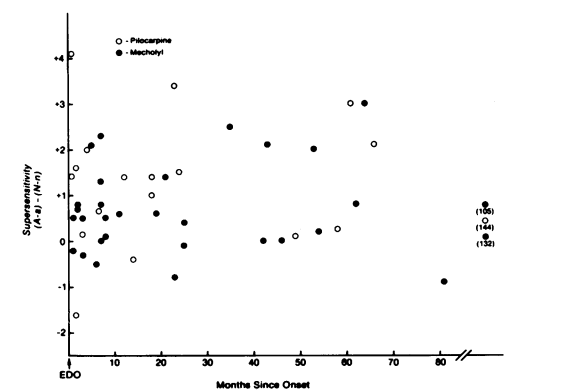


FIGURE 12

Distribution of Mecholyl (A) and pilocarpine (B) supersensitivity according to the size of the Adie's pupil in room light. Forty-one Mecholyl tests (2.5%) in 36 patients and twenty pilocarpine tests, each documented with Polaroid photographs. Supersensitivity is plotted as millimeters of excess constriction of the Adie's pupil compared with the normal pupil. There are fewer equivocal tests with pilocarpine than with Mecholyl.



A



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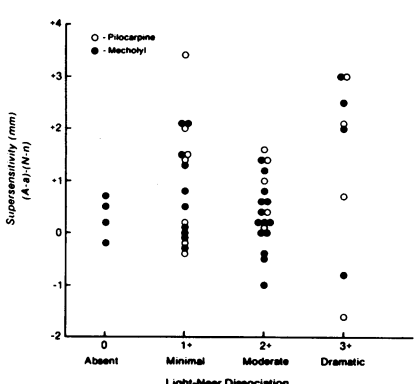


C

FIGURE 13

A: Distribution of supersensitivity to Mecholyl and to pilocarpine according to the amount of sphincter dysfunction in that eye as judged at the slit lamp at that visit. No clear-cut correlation is apparent. B: Distribution of supersensitivity to Mecholyl and to pilocarpine according to the duration of the condition at the time of the test. (EDO = estimated date of onset) It cannot be said from this information that the longer an Adie's pupil has been around the more supersensitive it gets. However, an occasional acute Adie's pupil has shown very little supersensitivity during the first few weeks and has been definitely supersensitive at the next visit, some months later. C: Distribution of the supersensitivity of the Adie's sphincter to Mecholyl and to pilocarpine according to the amount of light-near dissociation seen at that visit. It cannot be said from this information that an Adie's pupil with a big near reaction will show more cholinergic supersensitivity (or vice versa).

instructions on how to test for cholinergic supersensitivity have been listed in Table VIII.

Ambient light, patient alertness, and accommodative effort can each influence the amount of anisocoria. It is quite possible that they may change between the "before" and the "after" picture.

Ambient light:
Each "after" photo should be taken under identical lighting conditions to its matching "before" photo. It is helpful to take sets of photos at different pre-set stops of light intensity; experimental errors can be easily spotted when the data are displayed as in Figure 11: the more the pupil is constricted by light, the "flatter" the drug-induced change in pupil size should be.

Alertness:
A change in alertness, either toward arousal or somnolence usually affects the Adie's pupil less than the normal pupil. After sitting in a quiet room for half an hour between pictures the patient may become sleepy, and this will tend to diminish the apparent supersensitivity by constricting the normal pupil more than the Adie's pupil. And since the patient is generally more excited during the first set of pictures than the second, a cup of coffee during the interval may tend to alleviate this discrepancy.

Near Reaction:
An accommodative effort during the "after" picture which was not present in the "before" picture will produce the appearance of supersensitivity: the near effort may leave an Adie's pupil relatively miotic for several minutes. It is, therefore, critical that accommodation be carefully controlled.

There are two ways of judging cholinergic supersensitivity in Adie's syndrome: (1) Choose a solution weak enough so that it will not constrict a normal sphincter (Mecholyl 2.5%). Put the drop in the Adie's eye and if the pupil constricts, it is supersensitive. (2) Put the drop in both eyes. If the Adie's pupil constricts more than the normal pupil then the Adie's sphincter is supersensitive.

Even when used in this latter way, Mecholyl fails to reveal supersensitivity in approximately one out of every three patients with Adie's pupils (Figure 12A). If one takes into account the 20%-25% of patients whose pupils dilate during the testing period (Figure 10), possibly obscuring a small cholingergic constriction, and the presumed great variability in the supersensitivity which we are trying to test, then Mecholyl

2.5% when used in the affected eye only must produce a clinically visible constriction in less than one-half of all Adie's pupils. It is little wonder that Mecholyl got the reputation of being unstable and dying in the bottle. When the drops are put in both eyes in unilateral cases and the normal pupil serves as a built-in control, then it is no longer necessary to use a solution so weak that it will not affect the normal pupil. Eight patients with unilateral Adie's syndrome who had just had a Mecholyl test with equivocal results were immediately tested with 1/8th% pilocarpine. Six of them demonstrated a clear supersensitivity to this stronger dose of a cholinergic substance.

In summary, cholinergic supersensitivity of the denervated sphincter is common in Adie's syndrome. It is to be expected on the basis of what is known about denervation supersensitivity in other systems. It is characteristic, but it is not pathognomonic; nor is it a *sine qua non* of the diagnosis. It is often helpful in the diagnosis as a piece of additional supporting information, but the diagnosis can be made in the face of a negative test. The test is of little value when the drop is placed only in the affected eye. In unilateral cases the procedure outlined in Table VIII should be followed in an effort to control some of the variables.

CORNEAL SENSATION IN ADIE'S SYNDROME

Afferent trigeminal fibers that carry sensory impulses from the cornea traverse the ciliary ganglion and reach the ophthalmic branch of the fifth nerve via the "sensory root" of the ciliary ganlion.[33] Since the short ciliary nerves and the ciliary ganglion are damaged in Adie's syndrome, some impairment of corneal sensation might, therefore, be expected in this condition. Wellings' in a 1968 case report[34] described what sounded very much like such an association.

In seventeen patients with Adie's syndrome from the present series corneal sensitivity was mapped by a colleague with a special interest in the topography of corneal sensation. None of the patients had used any eye drops during the preceeding week, none wore contact lenses, and none had had prior ocular surgery. There was no evidence of corneal disease except in one patient and he was excluded from the study (he had flecked corneal dystrophy of Francois and Neetens). One patient was excluded because she had diabetes mellitus, and four additional patients were excluded because their Adie's syndrome was bilateral. The results in the remaining eleven patients are displayed in Figure 14. The examiner studied each clock-hour of the cornea at a point about 3 mm from the limbus, using the Cochet-Bonnet esthesiometer. In ten of these eleven patients, the eye with the Adie's pupil could be identified by a

TABLE VII: FACTORS TENDING TO PRODUCE VARIABILITY IN TESTS FOR CHOLINERGIC SUPERSENSITIVITY IN ADIE'S SYNDROME

1. Interpersonal variation in drug sensitivity
2. Interpersonal variation in corneal penetration of the drug
3. Interpatient variation in the amount of acquired denervation and of subsequent aberrant reinnervation of the sphincter
4. Systemic medication e.g. anticholinergics which might reduce the Mecholyl response
5. The age of the patient, affecting the size and hence the mechanical range of pupillary constriction of drugs
6. The duration of the tonic pupil syndrome
7. An additional "simple" anisocoria that may change during the testing period
8. Ambient light in testing situation
9. Altertness of the patient
10. Accomodative effort producing a tonic near reaction

patchy corneal hypesthesia not present in the other cornea. In one patient, both corneas showed normal sensation.

A wisp of cotton stroked across the cornea must sum up information from several different corneal nerve twigs because when this technique is used, most patients with Adie's syndrome seem to have normal corneal sensation. However, focal stimulation reveals the patchy focal deficit. This observation is subtle and this present report is preliminary, but is interesting because the ciliary ganglion and the short ciliary nerves are the only places where focal corneal sensory loss can be combined with ipsilateral partial internal ophthalmolegia.

A numb cornea is not a healthy cornea. Drugs will penetrate such a cornea more readily than usual. It could, therefore, be argued that the supersensitivity of the iris sphincter in Adie's might be due to enhanced penetration of Mecholyl through the cornea. However, if this were the case the Adie's pupil should be supersensitive to adrenergic drugs also, and it should dilate more extensively than the normal pupil to phenylephrine. But this is not the case. Patients with unilateral Adie's pupils, pretreated in both eyes with an anticholinergic drug (Tropicamide 1%) to balance the sphincter tone in the two eyes did not show supranormal dilations of the Adie's pupil when an adrenergic drug was placed in both eyes (Figure 15).

THE NATURAL HISTORY OF ADIE'S SYNDROME

The Tendency to Progressive Miosis:

Parkes Weber[35] in 1933 pointed out that tonic pupils tend to become smaller with time. One of Markus' original patients when first seen had a tonic pupil measuring 8 mm in diameter. When he was seen by Weber 27½ years later the pupil was still tonic, but now it measured 4 mm. A

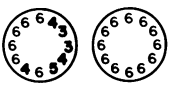
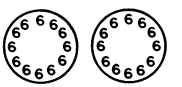
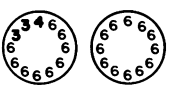
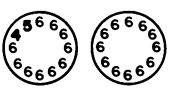
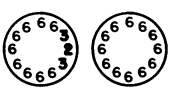
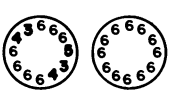
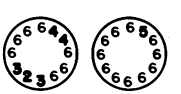
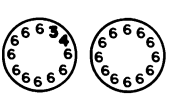
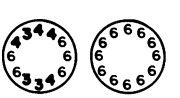
CASE #	INITIAL	AGE	SEX	EYE INVOLVED	CORNEAL SENSATION		SPHINCTER PALSY	
					ADIES	NORMAL	ADIES	NORMAL
1.	S.A.	32	F	O.D.				
2.	G.D.	58	M	O.S.				
3.	P.M.	30	F	O.D.				
4.	R.D.	37	M	O.D.				
5.	R.B.	33	F	O.D.				
6.	M.T.	40	F	O.D.				
7.	B.H.	48	F	O.S.				
8.	L.P.	20	F	O.D.				
9.	V.Q.	42	M	O.S.				
10.	L.B.	24	F	O.D.				
11.	O.T.	53	F	O.S.				

FIGURE 14

Eleven patients with unilateral Adie's. The corneal sensitivity is mapped in both eyes and displayed alongside a map of the segmental sphincter palsy in each eye. There does not appear to be any correlation. In every patient but one, a patchy hypersthesia of the cornea was found in the eye with the Adie's pupil (6 = sensitive, lower numbers = less sensitive) (2 = normal sphincter action, 1 = diminished, 0 = absent)

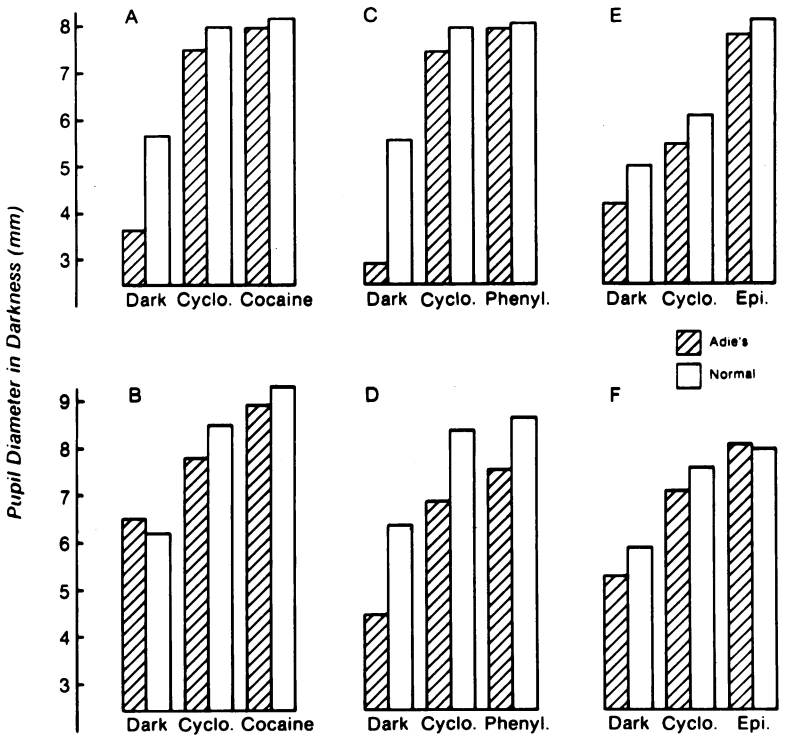
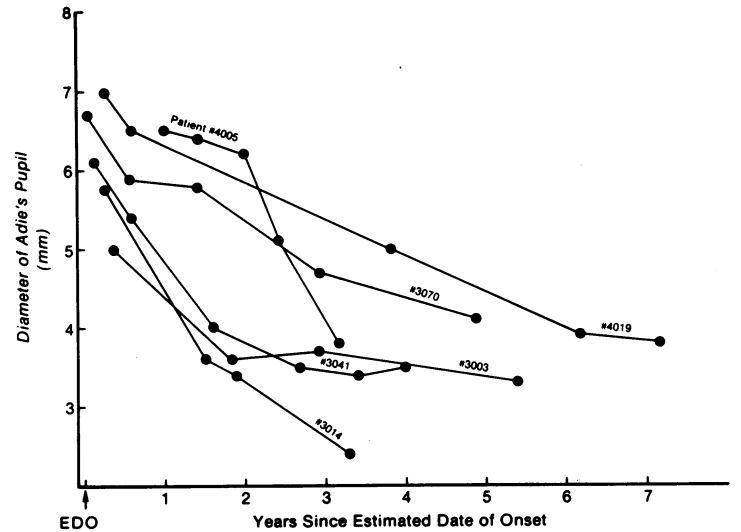


FIGURE 15

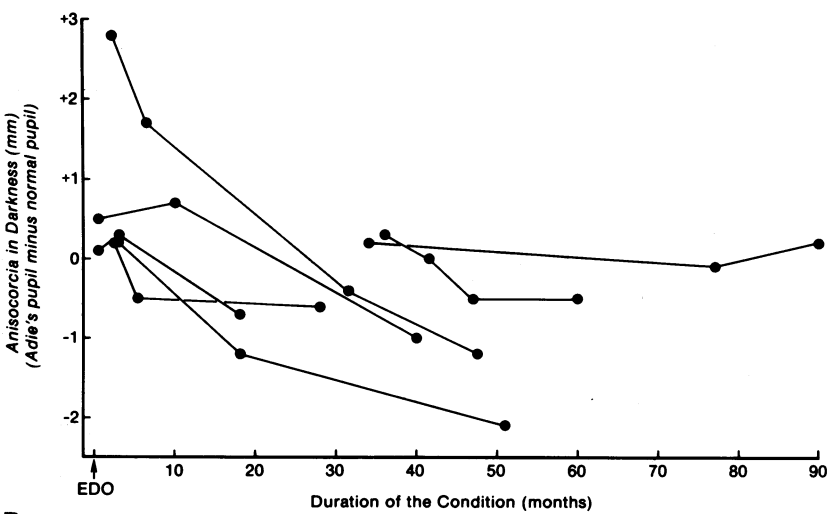
Drug-induced mydriasis in Adie's Syndrome. Each histogram is for a different patient with a unilateral Adie's tonic pupil. Before adrenergic mydriasis was compared in the Adie's and normal pupils, the spontaneous sphincter tone was abolished in both eyes with tropicamide. The first pair of columns in each histogram ("dark") represents the diameters of the Adie's pupil and of the normal pupil in darkness before any drugs were used. The second column ("cycle") shows the diameters 30 minutes after five drops of tropicamide 1% in each eye. Notice that the Adie's pupil dilated well with the anticholinergic drug, but that the Adie's pupil never became quite as large with tropicamide as the normal pupil. The third pair of columns shows the diameter of both pupils 45 minutes after an adrenergic mydriatic had been added to each eye (i.e. 75 minutes after the instillation of tropicamide). Two patients (A and B) received cocaine 5%, two drops; two patients (C and D) phenylephrine 2%, two drops; two patients (E and F) epinephrine 2%, six drops. Although the Adie's pupils dilate well, they are not supersensitive to mydriatics.

similar case, followed for 25 years, was reported by Laties and Scheie,[36] and other cases have been reported.[2]

In the present series there also has been a general tendency for the pupils to become smaller with the passage of time. Some patients have been followed for several years and have shown a striking progressive



A



B

FIGURE 16

A: Six patients followed for a number of years who showed a dramatic progressive miosis. The pupillary diameters were measured in darkness with the electronic pupillograph of Lowenstein and Loewenfeld. B: Of all the patients in this series whose Adie's pupil was larger than the unaffected pupil when first seen, seven had Polaroid photos taken in darkness on three or more occasions. The ordinate ("Anisocoria in Darkness") shows how much bigger or smaller the Adie's pupil was with respect to the unaffected pupil, and the abscissa shows the estimated duration of the condition in months.

TABLE VIII: HOW TO TEST FOR CHOLINERGIC SUPERSENSITIVITY IN UNILATERAL ADIE'S SYNDROME

1. Be sure that the patient doesn't have a residual miosis from a previous tonic near reaction. Fog the patient with a plus lenses (or take off myopic correction) for five minutes before taking pictures. Avoid accomodation throughout the test.
2. Take the "before" pictures, making sure the patient maintains distance fixation.
   a) 1st photo: after 10 seconds of darkness
   b) 2nd photo: in standard room light
   c) 3rd photo: in bright light (e.g. with a hand-light shining into the eye)
   Wait at least one minute between pictures to allow the eyes to recover from the flash.
3. Give drops. Use pilocarpine (0.1% or 0.125%) or Mecholyl (2.5%). Put one drop in each eye then wait 30 seconds and put another drop in each eye.
4. To avoid sleepiness, send the patient for a cup of coffee, to return in 30 minutes. No reading or near work is allowed in this interval. Warn the patient that the Adie's eye may get a little blurred and that near efforts should be avoided. "Just keep looking in the distance. Don't focus on anything close up."
5. Take the "after" pictures under identical conditions, as described above (point 2).
6. Measure the pupil diameters from the photos and calculate the supersensitivity, by subtracting the "after" diameter from the "before" diameter for each eye and then comparing the relative contraction of each normal and the Adie's pupil.
7. If there has been no response in either eye, you have not yet disproven a possible supersensitivity. Therefore repeat the test using a stronger drug, e.g. pilocarpine 0.2%. With stronger drugs, take photos at 15 minutes and at 30 minutes.

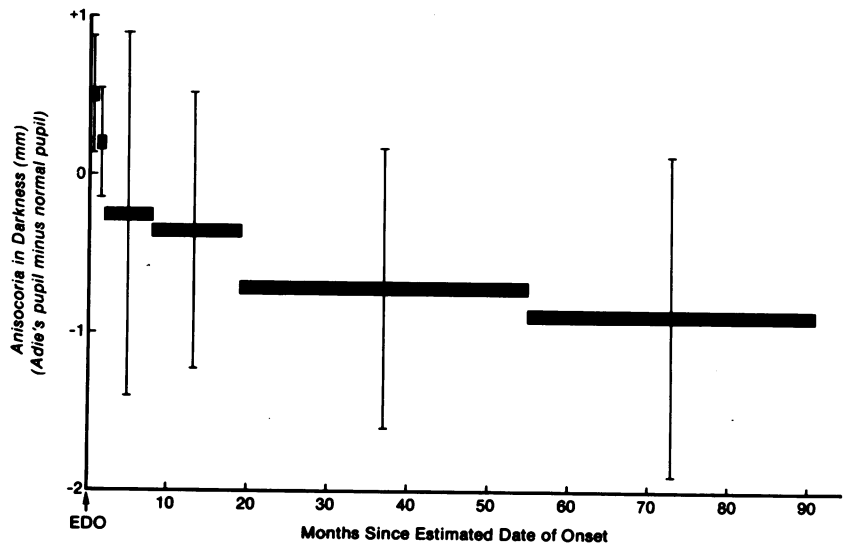
miosis (see Figure 16A). This gradual contraction was more marked than the normal miosis of aging, and it was not a matter of the patient's familiarity with the technique and consequent boredom and miosis. This was shown by plotting how much bigger and smaller than the normal pupil, the Adie's pupil was at the different examinations.

In Figures 16B and 17A these changes in aniscocoria are plotted against the duration of the condition in all patient in whom photographs were taken in darkness over an extended period of time.

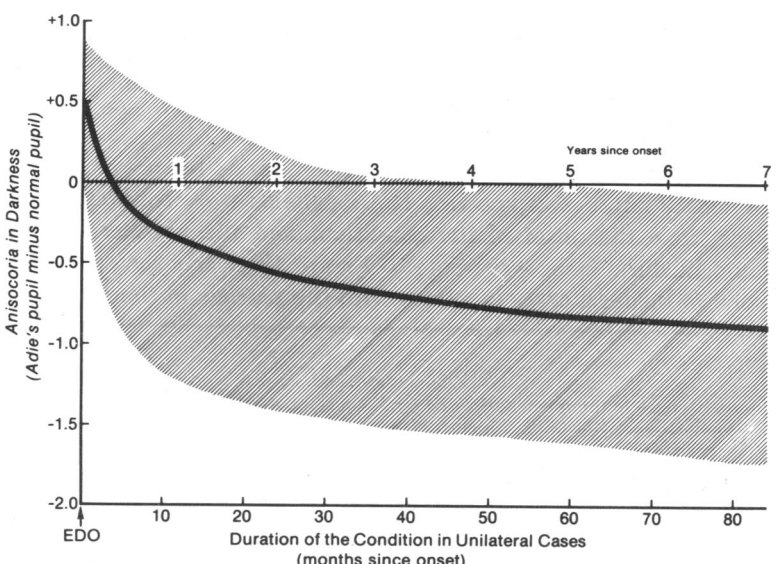
The data suggest that Adie's pupils are initially slightly larger than normal, and quickly become smaller, settling into a fairly steady, very slowly progressive miosis after about two years. This information is repeated in Figure 17B in a simplified graph which points out that (1) in darkness most Adie's pupils are smaller than normal and that (2) if a patient is found with an Adie's pupil larger than the normal pupil in darkness, then the condition is most likely of quite recent onset.

The Tendency to Bilaterality:

Gordon Holmes[6] described 19 patients with tonic pupils. Three of his four bilateral cases had once been unilateral, and the other eye had become involved while the patient was under observation. What is the incidence of second eye involvement in patients with Adie's syndrome? The patient often asks the same question: "What are the chances of my getting the same thing in my other eye?" This problem can be approached by looking at groups of patients who have had the condition for similar lengths of


Anisocoria in Darkness (mm)
(Adie's pupil minus normal pupil)
+1
0
-1
-2
EDO
10
20
30
40
50
60
70
80
90
Months Since Estimated Date of Onset

A


Anisocoria in Darkness
(Adie's pupil minus normal pupil)
+1.0
+0.5
0
-0.5
-1.0
-1.5
-2.0
Years since onset
1
2
3
4
5
6
7
EDO
10
20
30
40
50
60
70
80
Duration of the Condition in Unilateral Cases
(months since onset)

B

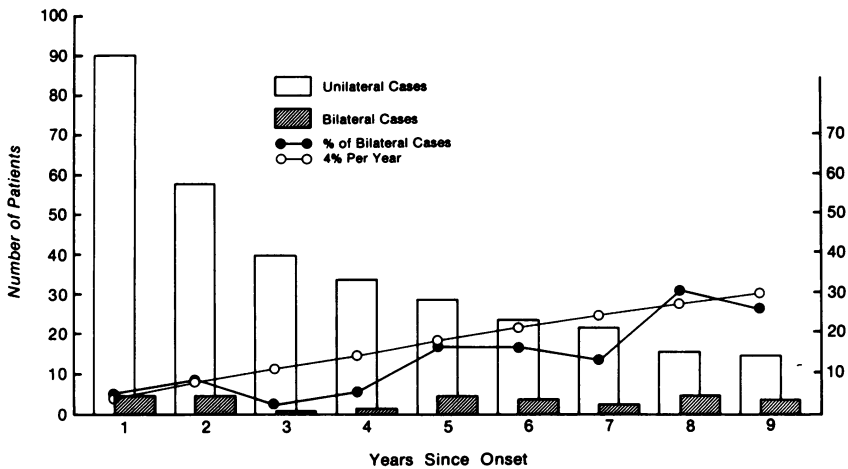


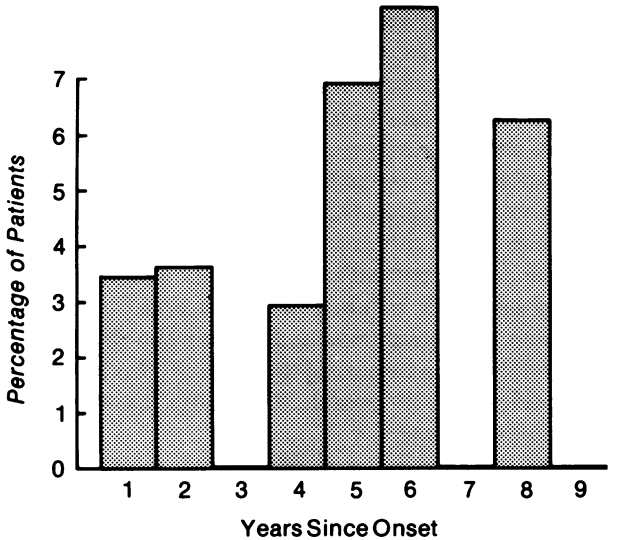
FIGURE 18

The proportion of unilateral versus bilateral cases in 99 patients (for whom an estimated date of onset was available). Unilateral cases were assumed to be unilateral from their date of onset and were counted for each year of the duration of the condition (from their date of onset until their most recent visit). Bilateral cases were counted for each year between their first and last visits. Using these criteria (which tilt the score slightly towards the unilateral cases), the proportion of unilateral to bilateral cases was noted for each year. For example: of the 95 patients seen within the first year of their disease, 90 were unilateral and 5 bilateral. Although all patients were asked to return at regular intervals, some did not. This was partially counteracted by an occasional case diagnosed several years after a clear date of onset. As the years passed, the total number of patients who still returned for follow-up gradually diminished while the number of bilateral cases among them remained fairly constant. The percentage of bilateral cases, therefore, increased gradually. The open circles show an annual rise of 4% based on the data in Figure 19A.

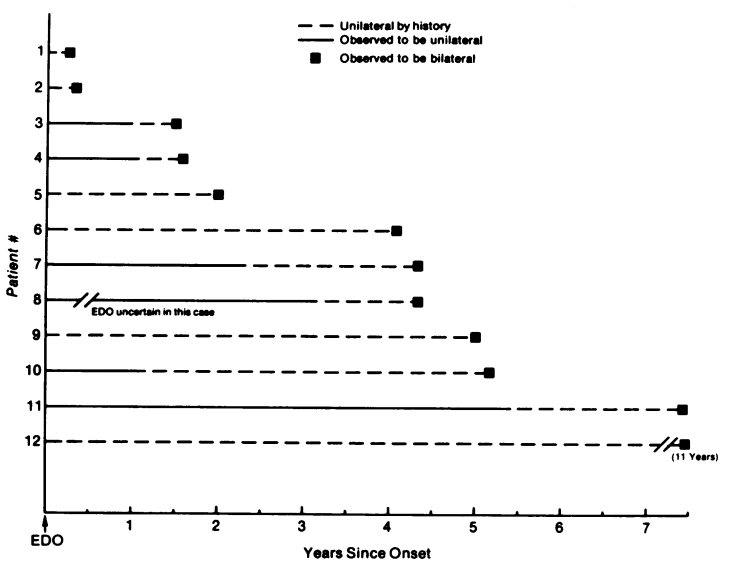
time. There were 99 patients in the present series for whom an "estimated date of onset" was known. These patients were counted during each year since the onset of the condition, and the numbers of unilateral and bilateral cases were noted. Figure 18 clearly shows that the proportion of bilateral cases increases with the passage of time.

FIGURE 17 *(overleaf)*

A: Changes with time in the mean anisocoria (and one standard deviation in each direction). Polaroid photos were taken in darkness of 67 patients with unilateral Adie's pupils on 116 separate visits. In all patients seen within one month of the date of onset, the Adie's pupil was larger than the normal pupil, but on later visits the Adie's pupil became the smaller one. B: Progressive Miosis in Adie's Syndrome. Although all Adie's pupils started out slightly larger than the other normal pupil, they very quickly became the smaller pupil in darkness. The progression of this miosis is a bit too variable to be able to pinpoint the date of onset with no other information than the amount of aniscocoria in darkness. However, if a photograph, taken in darkness, shows the affected pupil larger than the normal pupil, then the denervation of the sphincter probably occurred within the last few months.


Percentage of Patients
0
1
2
3
4
5
6
7
1 2 3 4 5 6 7 8 9
Years Since Onset

A


Unilateral by history
Observed to be unilateral
Observed to be bilateral
Patient #
1
2
3
4
5
6
7
8
9
10
11
12
EDO uncertain in this case
(11 Years)
EDO
1 2 3 4 5 6 7
Years Since Onset

B

Of the unilateral cases being followed, a certain number became bilateral each year (Figure 19A). The incidence of second eye involvement in these patients was fairly constant during the observation period. The average incidence was in the neighborhood of 4% each year. During the period of observation seven patients were seen to switch from unilateral to bilateral and five bilateral cases were seen with a clear history of prior unilaterality. These twelve case histories are diagrammed in Figure 19B. If the incidence should remain at 4% in subsequent decades, then in twenty years more than half of this group of patients will have become bilateral. So the answer to the patient's question about the chances of the other eye becoming involved, is "about 4% each year."

There have been some persistent questions about the fate of Adie's pupils: "Why is Adie's syndrome a disease of the young?"; "What happens to Adie's pupils in the elderly?"; "Where do they go?"; "Do the patients die early?"; "Do the pupils recover?"

These observations on the tendencies to progressive miosis and to bilaterality suggest that many Adie's pupils eventually either disguise themselves as Argyll Robertson pupils or simply lose themselves amongst the "senile miosis" of the elderly. Furthermore, the patient learns that the condition is benign and seeks no further medical attention.

Gordon Holmes[6] remarked that, in some of his patients, the features of this condition seemed to progress slowly, so that over the years the abnormalities became more pronounced. Axenfeld[37] and Karpow[38] had previously made similar observations.

The present study has shown:

a) a tendency for the accommodative paresis to recover during the first two years.
b) a tendency to lose the light reaction in further segments of the sphincter.
c) a tendency for the second eye to eventually become involved.
d) a slight tendency to further loss of deep tendon reflexes.

FIGURE 19 (*overleaf*)

A: Incidence of second eye involvement in cases of unilateral Adie's pupil. The ordinate shows the percentage of patients who developed a tonic pupil in the second eye. These percentages were plotted for each year of the condition as the abscissa. Although increasingly variable due to decreasing numbers of patients, the percentages are fairly constant over the nine-year observation period, and average about 4% per year. B: Second eye involvement in 12 unilateral cases. Seven of these patients were observed to have only one eye involved and later developed an Adie's pupil in the second eye (cases 3, 4, 6, 7, 8, 10 and 11). Five cases were bilateral when first seen, but had a clear history of prior unilaterality. These twelve patients represent half of all the bilateral cases in this series. The other twelve had no history of ever having been unilateral. (EDO = estimated date of onset.)

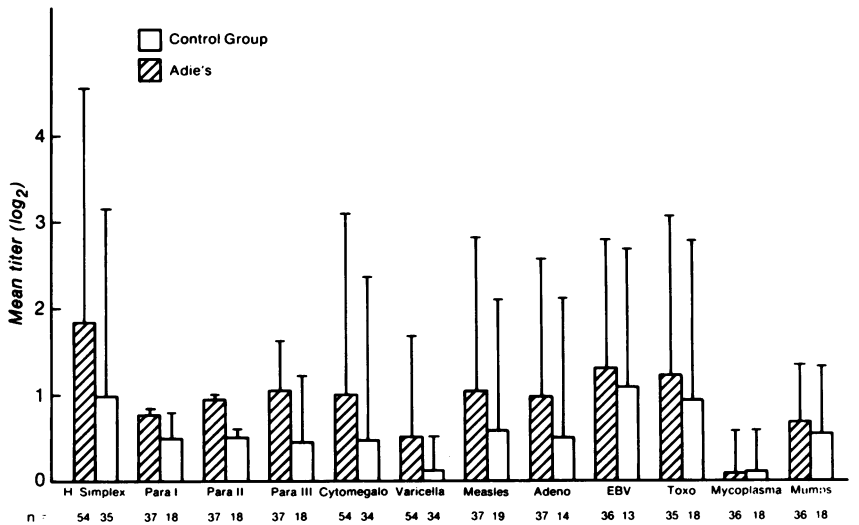


FIGURE 20

Serum antibody titers for various organisms in patients with Adie's syndrome. The mean titers for Adie's patients are shown by shaded columns, those for control subjects by white columns. The thin vertical bar represents one standard deviation. The control subjects were volunteer employees of the Eye Clinic. The numbers of patients tested are shown on the abscissa. There were no significantly elevated mean titers when compared with the control group.

Holmes was right in saying that this is a slowly progressive condition. There is a small but definite tendency for the abnormalities to worsen over the years.

Harriman and Garland[39] pointed out that in their patient, who had had an Adie's pupil for sixteen years, occasional ciliary ganglion cells could be seen still undergoing neuronophagia. This suggested that the degenerative process in the ciliary ganglion might be a progressive one.

A SEARCH FOR VIRAL ANTIBODIES IN ADIE'S SYNDROME

The cause of Adie's syndrome is still unknown, but it has frequently been suggested that the picture could be produced by a viral ciliary ganglionitis and perhaps a subclinical viral myelopathy affecting the muscle stretch reflexes. This prompted a search for viral antibodies in the serum of patients with Adie's syndrome. Frozen serum was collected for several years until serum from a large group of patients was available. Figure 20 summarizes the results of the various tests. Although the mean values were higher in the Adie's groups in all but the mycoplasma test, the wide

scatter rendered the results statistically not significant. No statistically significant elevation of antibody titers was found in the Adie's serum in any of the tests.

Harriman and Garland's[40] histopathological study indicated that the damage in the ciliary ganglion seemed to be due to a quiet neuronal degeneration rather than to a post-inflammatory scarring. The lack of any clear immunologic footprints of prior viral infections in patients with Adie's syndrome, lends some indirect support to their hypothesis. However, the tendency for the signs of Adie's syndrome to gradually get worse could be the result of either process. It is the sudden onset of the condition that suggests an infection.

SUMMARY

Adie's syndrome is a disease of unknown etiology. We know where the damage is, and which nerves are involved. We even know something of how the nerves react after the damage is done, but we don't know what causes the primary injury. The first step in working a jigsaw puzzle is to get all of the pieces right side up and take a good look at them. Some of the jigsaw pieces handled in this paper are listed below. Some of them are new observations; many of them are old concepts, partly modified and partly made secure by new facts.

1. Not all "tonic pupils" are due to "Adie's syndrome"; some are due to local injury and some to a generalized peripheral neuropathy (Table II).
2. All patients with bilateral tonic pupils should have serologic tests for syphilis. In this series one in six had positive serology.
3. The incidence of Adie's syndrome in Iowa in the early 1970's was approximately 4.7 per 100,000 population per year.
4. The prevalence of Adie's syndrome, therefore, was approximately 2 per 1000.
5. The mean age of onset of Adie's syndrome was about 32.2 years (Figure 1A).
6. The sex ratio was 2.6 females to each male.
7. Right eyes and left eyes were involved at approximately the same rate (Figure 2).
8. The incidence of second eye involvement in unilateral cases was about 4% per year during the first decade of the disease (Figure 18).
9. If this rate of second eye involvement (4% per year) persists during subsequent decades, then most Adie's pupils will eventually become bilateral.

10. The incidence of Adie's syndrome in a largely caucasian patient group is independent of iris color (Figure 4).
11. Only 10% of patients with Adie's syndrome had completely normal muscle stretch reflexes.
12. The muscle stretch reflexes in the arms were just as frequently impaired as those in the legs, but the degree of impairment tended to be more severe in the ankles and triceps.
13. When there was any light reaction remaining in an Adie's pupil, a segmental paralysis of the sphincter muscle could be seen.
14. The near reaction of the pupil was often segmental and frequently involved segments which did not respond to light.
15. The segmental paralysis to light was randomly distributed around the sphincter (Figure 6B).
16. There was some tendency for the sphincter palsy to gradually become worse. This progression was also random (Figure 8).
17. Almost all patients with Adie's syndrome had an accommodative paresis at the time of onset.
18. Reading glasses given to a patient with a fresh Adie's pupil were soon discarded as accommodation recovered (Figure 9).
19. Accommodative effort induced an astigmatism in about half of the eyes with Adie's — presumably the result of a segmental palsy of the ciliary muscle.
20. Tonicity of accommodation was present in about ½ of the eyes with Adie's, making it difficult for the patient to maintain a steady level of ciliary muscle tone.
21. An occasional patient complained of brow ache from ciliary spasm with near work.
22. In most patients with Adie's syndrome the ciliary muscle was supersensitive to pilocarpine 0.25%; a pseudomyopia of several diopters was induced by the drug.
23. Patients concerned about their appearance with one dilated pupil can be reassured that the pupil will become small again in a few months — or at the most in a year or two (Figure 19A).
24. Most Adie's pupils showed a cholinergic supersensitivity of the denervated sphincter (Figure 12).
25. When testing for cholinergic supersensitivity great care has to be taken to make the "before" and "after" conditions identical, especially with regard to ambient light, alertness, and accommodation (Table VIII).
26. Mecholyl 2.5% in the affected eye only is not much of a diagnostic test: less than half of Adie's pupils will show a convincing constriction.

27. "Cholinergic supersensitivity" should be defined as the amount which the Adie's pupil constricts more than the normal pupil when both eyes have been given the same dose of drug (Figure 11).
28. Mecholyl 2.5% in both eyes (Adie's and normal) revealed "supersensitivity" in only about 2/3 of the Adie's pupils; Mecholyl 2.5% is just not strong enough (Figure 12).
29. Pilocarpine 0.125% is a stronger miotic than Mecholyl 2.5%. It showed "supersensitivity" in about 4/5 of Adie's pupils (Figure 12).
30. Pilocarpine 1/8th% is not only an adequate substitute for Mecholyl 2.5% — it is better, because it is more sensitive, easier to read and produces fewer false negative tests.
31. Pilocarpine is better than Mecholyl in these tests only because it is a more potent miotic. A stronger solution of Mecholyl producing a comparable miosis (such as 25%) may actually out perform pilocarpine as a test for supersensitivity, but such strong solutions are irritating to the eye and pilocarpine is readily available.
32. Most eyes with Adie's pupils have a cornea that is slightly anesthetic (Figure 14).
33. Many viral antibody levels are not any higher in the serum of patients with Adie's pupils than they are in normal controls (Figure 20).
34. There is a small but definite tendency for Adie's syndrome to become worse over the years: (a) the second eye tends to become involved; (b) the light reaction tends to lose further segments of the sphincter and (c) the deep tendon reflexes may become slightly worse.

BIBLIOGRAPHY

1. Lowenstein O, Loewenfeld IE: Pupillotonic pseudotabes (syndrome of Markus-Weill and Reys-Holmes-Adie): A critical review of the literature. *Surv Ophthalmol* 10:129-185, 1965.
2. Loewenfeld IE, Thompson HS: The tonic pupil: A re-evaluation. *Am J Ophthalmol* 63: 46-87, 1967.
3. Spiewak B. I am indebted to B Spiewak of Grosse Point North High School. Grosse Pointe Woods, Michigan for assistance in assembling this information.
4. Moore RF: Physiology and pathology of the pupil reactions. *Trans Ophthalmol Soc UK* 44:38-43, 1924.
5. Moore RF: The non-luetic Argyll Robertson pupil. *Trans Ophthalmol Soc UK* 51:203-209, 1931.
6. Holmes G: Partial iridoplegia associated with symptoms of other diseases of the nervous system. *Trans Ophthalmol Soc UK* 51:209-228, 1931.

7. Adie WJ: Complete and incomplete forms of the benign disorder characterized by tonic pupils and absent tendon reflexes. *Br J Ophthalmol* 16:449-461, 1932.
8. Adie WJ: Tonic pupils and absent tendon reflexes: A benign disorder sui generis: Its complete and incomplete forms. *Brain* 55:98-113, 1932.
9. Libertin N. I am indebted to N Libertin of Campbell Memorial High School, Campbell, Ohio for assistance in assembling this information.
10. Strasburger J: Pupillenträgheit bei Akkommodation und Convergenz. *Neurol Zentralbl* 21:738-740, 1902.
11. Saenger A; Ueber die Beziehung myotonische Pupillenbewegung. *Neurol Zentralbl* 21:837-839, 1902.
12. Nonne M: Ueber die sogenannte "myotonische" Convergenzträgheit Lichtstarrer Pupillen. *Neurol Zentralbl* 21:1000-1004, 1902.
13. Markus C: A peculiar pupil phenomenon in cases of partial iridoplegia. *Trans Ophthalmol Soc UK* 26:50-58, 1906.
14. Gehrcke: Ueber tonische Konvergenzbewegungen der Pupille und tonische Akkommodation. *Neurol Zentralbl* 40:93-99, 1921.
15. Weber FP: Argyll Robertson Pupils with Mydriasis. *Proc R Soc Med (Children's section)* 16:68, 1923.
16. Weill G, Reys L: Sur la pupillotonie: Contribution a l'étude de sa pathogenese: A propos d'un cas de réaction tonique d'une pupille á la convergence et parésie de l'accomodation avec aréflexie á la lumière chez un sujet atteint de crises tétaniformes et d'aréflexie des membres inférieurs. *Rev Otoneuroophthalmol* 4:433-441, 1926.
17. Morgan OG, Symonds CP: A series of cases with rapid onset of unequal pupils and failure of accommodation. *Guys Hosp Rep* 47:13-15, 1927.
18. Sattler CH: Wurmförmige Zuckungen des Sphincter iridis. *Klin Monatsbl Augenheilkd* 49:739-745, 1911.
19. Dressler M, Wagner H: Zur Kenntnis des Adie'schen Syndroms. *Schweiz Med Wochenschr* 18:491-495, 1937.
20. Wagner H: Beobachtungen an Iris und Pupillarsaum beim Adie'schen Syndrom. *Klin Monatsbl Augenheilkd* 100:134, 1938.
21. McGregor IS: Segmental movement of the pupil. *Br Med J* 1:629-630, 1945.
22. Thiel R: *Atlas of Diseases of the Eye.* New York, Elsevier Publishing Co, 1963, vol 1, p 232.
23. Bach L: *Pupillenlehre.* Berlin, Springer, 1908, p 112.
24. Anderson HK: The paralysis of involuntary muscle: Part II: On paralysis of the sphincter of the pupil with special reference to paradoxical constriction and functions of the ciliary ganglion. *J Physiol* 33:156-174, 1905.
25. Anderson HK: The paralysis of involuntary muscle: Part II: On the action of pilocarpine, physostigmine and atropine upon the paralysed iris. *J Physiol* 33:414, 1905.
26. Cannon WB: A law of denervation. *Am J Med Sci* 198:737-750, 1939.
27. Cannon WB, Rosenblueth A: *The Supersensitivity of Denervated Structures: A Law of Denervation.* New York, MacMillan, 1949.
28. Scheie HG: Site of disturbance in Adie's Syndrome. *Arch Ophthalmol* 24:225-237, 1940.
29. Loewenfeld IE, Oono S: The iris as a pharmacologic indicator: The supposed instability of mecholyl. *Eye Ear Nose Throat Mon* 45:69-77, 1966.
30. Pilley SFJ, Thompson HS: Cholinergic supersensitivity in Adie's Syndrome: Pilocarpine vs. mecholyl. *Am J Ophthalmol* 80:955, 1975. Abstract of a paper presented at the 9th Pupil Colloquium, Iowa City, May 1975.
31. Younge BR, Buski ZJ: Tonic pupil: A simple screening test. *Canad J Ophthalmol* 11:295, 1976.
32. Cohn DN, Zakov ZN: The diagnosis of Adie's pupil using 0.0625% pilocarpine solution. *Am J Ophthalmol* 79:883-885, 1975.
33. Duke-Elder S: *System of Ophthalmology.* St Louis, CV Mosby, 1961, vol II, p 860.
34. Wellings PC: A new ocular syndrome. *Br J Ophthalmol* 52:555, 1968.

35. Weber FP: Dr. Markus' original case of Markus' syndrome ("Myotonic pupil" with absence of patellar and Achilles reflexes) shown 27 ½ years ago. *Proc R Soc Med* 26:530-531, 1933.
36. Laties AM, Scheie HG: Adie's Syndrome: Duration of methacholine sensitivity. *Arch Ophthalmology* 74:458-459, 1965.
37. Axenfeld T: Tonische Akkommodation. *Klin Monatsble Augenheilkd* 62:59-68, 1919.
38. Karpow: Myotonische Akkommodation und Puillenreaction. *Klin Monatsbl Augenheilkd* 71:218, 1923.
39. Harriman DGF, Garland H: The Pathology of Adie's Syndrome. *Brain* 91:401-418, 1968.
40. Harriman DGF: Pathologic Aspects of Adie's Syndrome. Adv Ophthalmol 23:55-73, 1970.
41. Duke-Elder S: *System of Ophthalmology*. St. Louis, CV Mosby, 1961, vol II, p 170.