THE SITE OF THE DISTURBANCE IN TONIC PUPILS*

FRANCIS HEED ADLER, M.D.
Philadelphia, Pa.

AND

(By invitation)
HAROLD G. SCHEIE, M.D.
Philadelphia, Pa.

The term "tonic pupils" has been applied to those pupils which show the following characteristics: The contraction of the pupil to light, directly and consensually, is considerably slower than normal, and when the stimulus is removed, the subsequent dilatation of the pupil to its normal size is even slower. Similarly, the contraction of the pupil at the near point is slower than normal, and its recovery is also delayed. The reaction to light is usually the slowest, and in fact it may be so long delayed in onset that it may be missed entirely, and the light reaction of the eye may erroneously be considered absent.

Although tonic pupils have been recognized for many years, it was not until 1931 that much consideration was given to this phenomenon. At this time Adie reported a number of cases, some with absent tendon reflexes, and drew attention to the importance of differentiating tonic pupils from true Argyll Robertson pupils. Since Argyll Robertson pupils are almost pathognomonic of neurosyphilis, and tonic pupils have no known pathologic significance, their differ-

* From the Department of Ophthalmology, Medical School, University of Pennsylvania. Supported by a grant from the John and Mary R. Markle Foundation, New York City.

Part of a thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania, in partial fulfilment of the requirements for the degree of Doctor of Medical Science (D.Sc.(Med.)) for graduate work in ophthalmology.

entiation is of extreme importance. Since Adie's paper was published tonic pupils are frequently referred to as "Adie's Syndrome."

The site of the lesion producing tonic pupils and their pathogenesis are as yet unknown, and it would be useless to enumerate the many hypotheses mentioned in the literature. The hypothalamic region, the sympathetic system, and the parasympathetic portion of the third nerve nucleus have been the most widely accepted locations postulated. The iris muscle itself and the ciliary ganglion have also been mentioned. No clinical or experimental proof for the choice of any of these localities has as yet been offered.

In the course of a study of a typical unilateral tonic pupil with the aid of various drugs, it was observed that the affected pupil contracted to a solution of 2½ per cent. mecholyl, whereas the normal pupil remained unaffected. This fact seemed of significance, and all cases of tonic pupils which were subsequently seen were similarly tested. The procedure consisted of instilling one drop of mecholyl in each eye, and repeating this in five minutes. A series of 11 cases was collected (Table I), and in these patients every tonic pupil showed a marked contraction to 2½ per cent. mecholyl, whereas the unaffected pupils showed no effect (figs. 1 and 2).

Forty-eight normal subjects were then tested, to determine what percentage solution of mecholyl was needed to contract the normal pupil. Mecholyl was instilled in only one eye, the other eye serving as a control. It was found that less than 15 per cent. mecholyl had no effect on the size of the normal pupil other than an occasional slight anisocoria which could well be accounted for by the irritation and hyperemia produced by this drug. Even in 15 per cent. and 20 per cent. solutions no true miosis was produced in any normal pupil, although the anisocoria was more marked.

Since the tonic pupil responds to a 2½ per cent. solution with a marked miosis, it is evident that the neuromuscular mechanism in tonic pupils has become sensitized to the drug.

Mecholyl is a cholin compound, and it has long been recognized that such sensitization to acetylcholin does occur in the parasympathetic nervous system if the terminal ganglion

TABLE I.—RÉSUMÉ OF FINDINGS IN CASES OF TONIC PUPILS

Case No.	*Age, Years*	*Duration*	*Side Affected*	*Size Relationship of Affected Pupil*	*Ciliary Muscle Involvement*	*Arreflexia*	*Serology*	*Etiologic Factors*	*Contraction to Mecholyl*
Case 1 Mrs. M. C....	28	Lifetime	Right	Smaller	+	+	Negative	None	+
Case 2 Miss E. O.....	18	At least nine years	Left	Smaller	−	−	Negative	None	+
Case 3 Mrs. H. M....	39	At least twenty-nine years	Both	Both small	+	−	Negative	None	+
Case 4 Mrs. P. W. J..	60	Many years	Left	Larger	−	−	Negative	None	+
Case 5 Miss B. S.....	26	Unknown	Both	..	−	−	Negative	None	+
Case 6 Mrs. H. R. H..	36	One month	Left	Smaller	+	+	Negative	Anemia	+
Case 7 Mrs. L. D....	32	Lifetime	Both	..	−	+	Negative	..	+
Case 8 Mrs. P. D...	35	One year	Left	Equal	+	−	Negative	Low B.M.R.	+
Case 9 Mrs. M. K....	36	Unknown	Both	..	+	−	Negative	Avitaminosis	+
Case 10 Miss M. B....	23	Unknown	Right	Larger	−	−	Negative	None	+
Case 11 Mr. C. L.....	37	Lifetime	Both	Both miotic	−	−	Negative	Congenital	+

or any part of the postganglionic fiber is damaged. This immediately suggested that the site of the lesion in tonic pupils might be in the postganglionic fibers of the third nerve. The reactions of tonic pupils to adrenalin and to cocain were nor-

mal, which eliminates the sympathetic supply of the iris from further consideration.

We then proceeded to test this hypothesis. The earlier experiments of Shen and Cannon were first repeated, and then extended, using mecholyl instead of acetylcholin, which these workers had used. The following operations were performed in a series of cats:

1. Removal of the ciliary ganglion on one side.
2. Cutting all the post-ganglionic fibers on one side.
3. Cutting some of the post-ganglionic fibers on one side.
4. Crushing all the post-ganglionic fibers on one side.
5. Cutting all the preganglionic fibers on one side.

In all these cats, after recovery from the operation, both pupils were tested for sensitization to mecholyl in 5 per cent. solution, at varying periods of time. The results were as follows:

1. The pupil on the unoperated side never exhibited sensitization.

2. Removal of the ciliary ganglion (fig. 3), cutting all or only some of the postganglionic fibers, resulted in almost immediate sensitization of the pupil on the operated side. In those cats in which only some of the fibers were cut the pupil remained larger than on the opposite side, and the reaction of these pupils to light persisted. There was prompt response of the pupil to light.

3. Crushing the postganglionic fibers gave an immediate result, similar to that on removing the ciliary ganglion or cutting all the postganglionic fibers, but at one stage (fig. 4), as the fibers regenerated and the light reflex began to return, it was observed that the response of the pupil to light was definitely sluggish, although at no time was the pupil completely tonic.

4. Cutting the preganglionic fibers produced no sensitization.

As a result of these experiments we can assert that sensitization to mecholyl develops if the ciliary ganglion or its

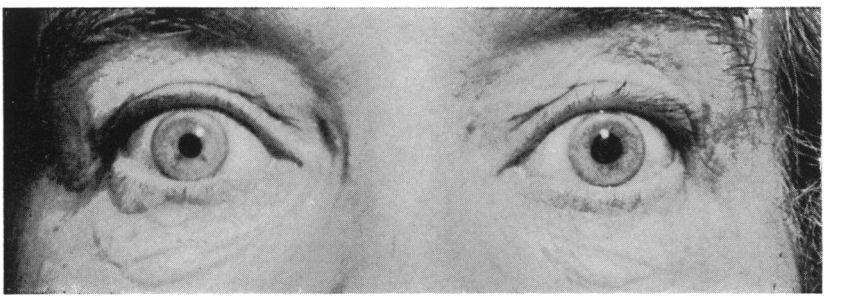

Fig. 1a.—Case 4. Pupils with eyes at rest before instilling mecholyl.

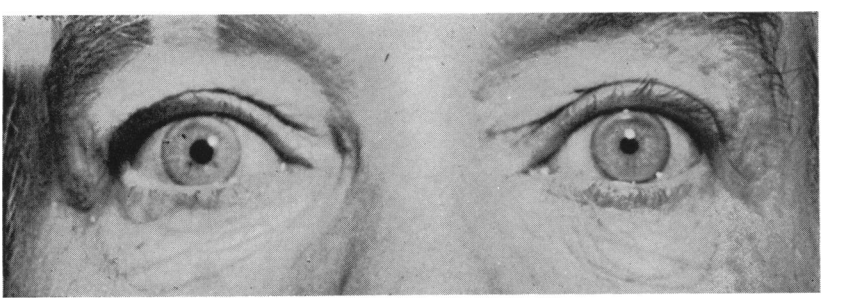

Fig. 1b.—Case 4. Pupils with eyes at rest thirty minutes after instilling mecholyl, 2½ per cent., showing contraction of the tonic left pupil.

Fig. 2a.—Case 10. Pupils with eyes at rest before instilling mecholyl.

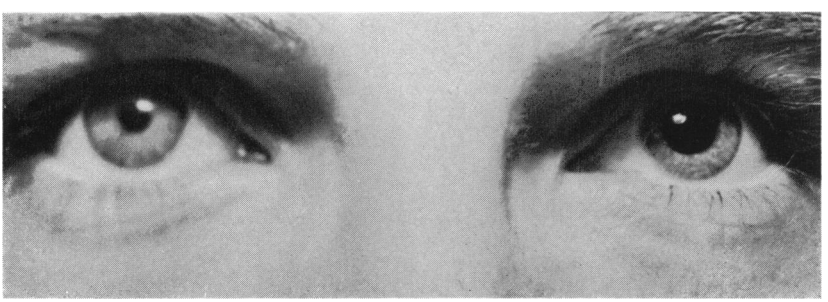

Fig. 2b.—Case 10. Pupils with eyes at rest thirty minutes after instilling mecholyl, 2½ per cent., showing contraction of tonic right pupil.

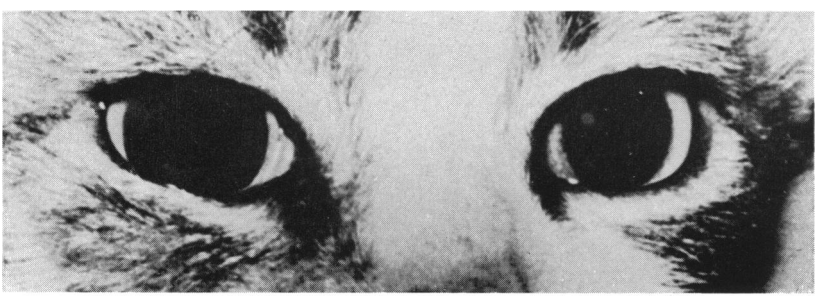

Fig. 3a.—Flash exposure of a cat with the right ciliary ganglion removed, showing size of pupils in a dark room.

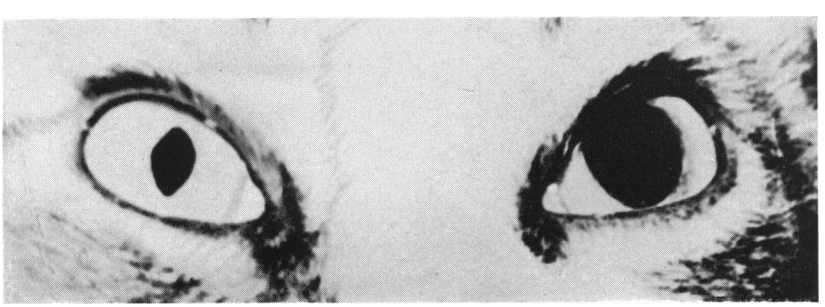

Fig. 3b.—Flash exposure showing contraction of right pupil forty-five minutes after instillation of mecholyl, 5 per cent., in both eyes.

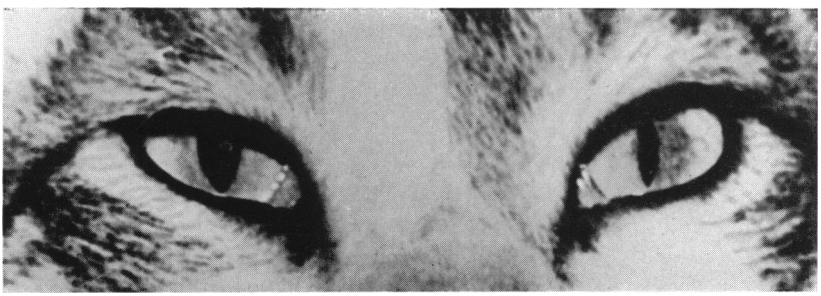

Fig. 4a.—Daylight exposure before instillation of mecholyl, showing anisocoria nine weeks after crushing the postganglionic nerve fibers of the right eye.

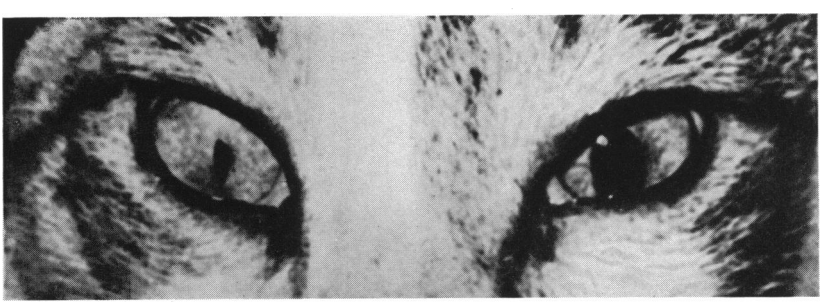

Fig. 4b.—Daylight exposure one-half hour after bilateral instillation of 5 per cent. mecholyl, showing constriction of the right pupil.

postganglionic fibers are damaged before they enter the eyeball. This statement was confirmed clinically in a patient with neurofibromata of the orbit which involved the ciliary ganglion. The pupil was semidilated, reacted poorly to light, and was sensitized to mecholyl (fig. 5). During the operation on the orbit the ciliary ganglion was removed with tumor tissue, after which the pupil was dilated and did not react to light. Sensitization to mecholyl, however, was now more marked.

The following observations confirm the finding that similar sensitization develops if the postganglionic fibers in the eyeball itself are damaged: The patient had an almost complete retinal detachment, and an extensive electrocoagulation operation was performed. After the operation the pupil was dilated, did not react to light, but was sensitized to 2½ per cent. mecholyl. Several weeks later the light reaction returned, but it was definitely tonic in character, and has remained so during the entire period of observation, which has lasted over a year. The sensitization to mecholyl has also persisted unchanged. In a second case of retinal detachment following an extensive electrocoagulation operation the pupil was slightly dilated and sensitized to mecholyl. It seems probable that, as a result of the electrocoagulation, the long ciliary nerves were partially damaged as they coursed through the eyeball on their way to the sphincter muscle.

Further confirmation of this was obtained as the result of experiments on cats. In two of the animals one eye was cauterized around the globe by two rows of punctures made with the Lacarrere instrument. In one cat a dilated fixed pupil resulted, which was sensitized to mecholyl. Several weeks later the pupil had partially recovered its reaction to light, although the response was sluggish in character. Additional evidence, which space does not permit us to describe, indicates that sensitization to mecholyl can occur by damage to the nerve endings in the muscle itself.

We believe that the evidence presented points strongly to the site of the lesion in tonic pupils as being in the postganglionic parasympathetic fibers of the third nerve, either at the ciliary ganglion or in the fibers themselves, anywhere from the ganglion up to their termination in the sphincter muscle. The lesion would presumably be only a partial denervation, for the pupils do react to all stimuli.

In our experience we found that the use of mecholyl is of distinct value in differentiating tonic pupils from Argyll Robertson pupils, in addition to the other criteria usually employed, and also from iridoplegia as seen in internal ophthalmoplegia due to lesions central to the ciliary ganglion.

The differential diagnosis of tonic pupils from Argyll Robertson pupils is made on several points (see Table II).

TABLE II.—DIFFERENTIAL DIAGNOSIS OF TONIC PUPILS FROM ARGYLL ROBERTSON PUPILS

Tonic Pupils	*Argyll Robertson Pupils*
1. Unilateral, 80 per cent.	1. Bilateral, 95 per cent.
2. Convergence reaction:	2. Convergence reaction:
a. Slow gradual contraction	*a.* Prompt contraction
b. Slow gradual dilatation	*b.* Prompt dilatation
3. Accommodation: Ciliary muscle may contract and relax slowly	3. Accommodation: Ciliary muscle not affected
4. Light reaction:	4. Light reaction:
a. Slow contraction	Absent
b. Slow dilatation	
5. Dilates normally with atropin	5. Dilates poorly with atropin
6. Normal or semi-dilated	6. Miotic
7. Wassermann reaction: Negative	7. Wassermann reaction: Positive or negative
8. Marked contraction to mecholyl, 2½ per cent.	8. No contraction to mecholyl, 2½ per cent.

Tonic pupils are unilateral in 80 per cent. of the cases; Argyll Robertson pupils bilateral in 95 per cent. The convergence reaction in Argyll Robertson pupils, in contrast to that of tonic pupils, is normal. In Argyll Robertson pupils the ciliary muscle is never involved, whereas in tonic pupils it may show the same type of reaction as the pupil. The light reaction in tonic pupils can nearly always be elicited by placing the patient in a dark room for a few minutes, whereas

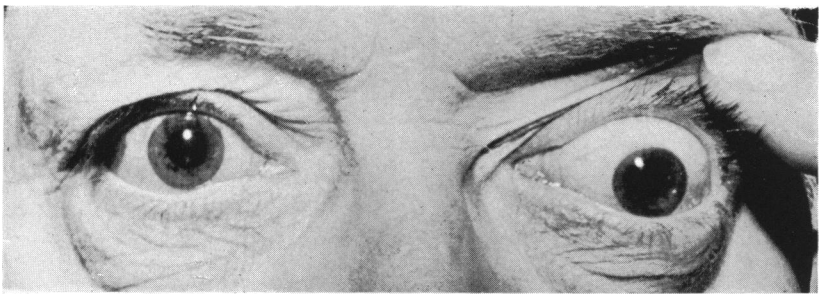

Fig. 5a.—Pupils with eyes at rest before operation.

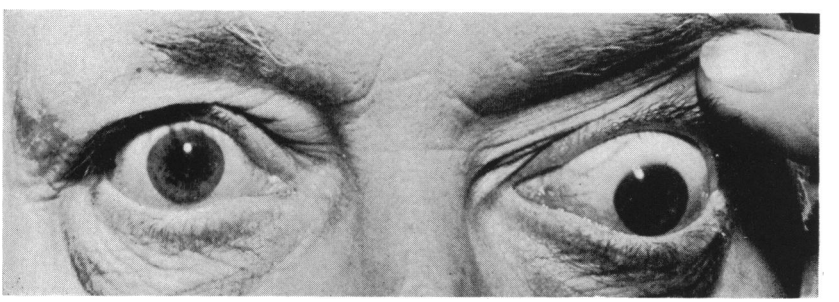

Fig. 5b.—Pupils with eyes at rest thirty minutes after instilling mecholyl, 2½ per cent., in both eyes preoperatively, showing contraction of left pupil.

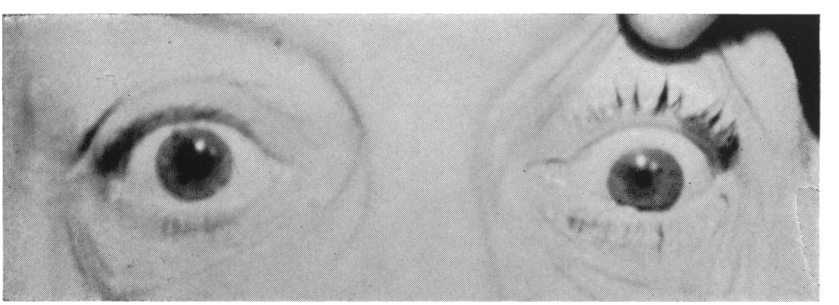

Fig. 5c.—Pupils thirty minutes after bilateral instillation of mecholyl, 2½ per cent., postoperatively, showing more marked contraction of left pupil.

in Argyll Robertson pupils the light reaction is absent. Tonic pupils are normal or semidilated in size and dilate well with atropin. Argyll Robertson pupils are miotic and dilate poorly with atropin. A positive Wassermann reaction is presumptive evidence of Argyll Robertson pupils, though tonic pupils can also occur in patients with syphilis. Finally we suggest the use of mecholyl as a diagnostic test. In our series all the tonic pupils contracted markedly to 2½ per cent. mecholyl, whereas Argyll Robertson pupils were unaffected.

SUMMARY

1. Tonic pupils in 11 patients studied showed sensitization to mecholyl.

2. Sensitivity to mecholyl was produced in experimental animals and observed clinically in patients with lesions of the parasympathetic nerves to the eye at or peripheral to the ciliary ganglion.

3. A tonic pupil developed postoperatively from electrocoagulation of a detached retina in which presumably the ciliary nerves in the globe were injured.

4. The disturbance in tonic pupils, or Adie's syndrome, is postulated as being a partial denervation of the parasympathetic supply to the pupil at or peripheral to the ciliary ganglion.

5. Mecholyl has proved of value as a diagnostic test in differentiating tonic pupils from Argyll Robertson pupils.

DISCUSSION

DR. EDWARD JACKSON, Denver, Colo.: While perhaps the two cases that I wish to mention do not strictly come under the heading of tonic pupils, they suggest an approach to the subject of tonic pupils which we ought to bear in mind. One patient was a mining engineer, a little over thirty years of age, who came to me giving the history that when he went down a shaft 500 or 600 feet deep, with three or four other men in the cage with him, on reaching the bottom of the shaft the other men could immediately see in the reduced light, but he could see nothing at first. It was ten or fifteen

minutes, and sometimes almost half an hour, before he recovered his sight, and then he could see as well as the others. I examined his eyes and found absolutely no light reaction in either pupil. The pupils were small, between 2 and 3 mm. habitually, and could not be dilated by any mydriatic.

The other case was that of a woman who came into the clinic, when a number of mydriatics, instilled by different persons at different times, for two weeks or more, never succeeded in obtaining any dilatation of the pupils beyond 2 mm. in diameter, although in every other respect the eye seemed to be normal. We were compelled to measure the refraction as well as could be done with a 2 mm. pupil, and prescribed glasses that were satisfactory. The best explanation of these two cases seems to be that the original structure of the iris rendered it incapable of light reaction. I have seen only these two cases of this kind, and probably such cases are extremely rare. They should, nevertheless, be borne in mind. Both of these were bilateral conditions. They are due, perhaps, to the essential development of the eye, without going further into the theory of it.

DR. FRANCIS HEED ADLER, Philadelphia, Pa.: The experimental and clinical data presented indicate that the site of the lesion in tonic pupils is in the third nerve, somewhere between the ciliary ganglion and the nerve endings in the sphincter muscle, and that this lesion partially destroys these fibers. The result is a pupil that is permanently sensitized to cholins, either those produced normally in the tissues of the body, or those introduced experimentally, as Dr. Scheie has shown, by using mecholyl.

In cats the experimental lesions produced sensitized pupils which were definitely sluggish in their reactions when the damage to the nerves was partial, but we were not able to produce typical tonic pupils.

In man, however, we unwittingly have produced typical tonic pupils.

We have seen sensitization to mecholyl in cases of old iritis where presumably the nerve endings in the muscle might have been partially damaged.

A number of cases of chronic glaucoma showed sensitivity, even though the tension had been normalized by a trephine operation. In these cases we believe that the previously increased tension caused partial damage to the nerve fibers.

In every case of glaucoma in which the tension was elevated sensitivity was found. This makes mecholyl a valuable drug to use in

acute glaucoma. In these cases, however, as soon as the pressure has been lowered, the sensitivity is lost. In several cats the intraocular pressure was artificially increased in one eye and sensitivity was produced on this side.

The diagnostic value of mecholyl in differentiating tonic pupils from Argyll-Robertson pupils should be stressed.

DR. DAVID COGAN, Cambridge, Mass. (by invitation): It might be worth while to report six patients with Adie's syndrome whose sensitivity to eserin I have tested. I used minimal concentrations of eserin, 1:128 per cent. All the patients had uniocular involvement, so the reaction of the eye with the tonic pupil could be compared with the other, presumably normal, eye. It was my impression that the two eyes reacted equally, that is, the induced miosis came on at about the same time, was equally marked, and lasted for approximately the same time in the two eyes. I should be interested in learning from Dr. Scheie whether or not he has had any experience with eserin. It seems to me that the significance of the eserin reaction is this: in the presence of a post-ganglionic lesion the reaction to eserin, unlike that to mecholyl, should be less on the abnormal side than on the normal side.

Another question I should like to ask is this: If the lesion is simply an interruption of the peripheral nerve pathway to the pupil, should we not expect tonic pupils with peripheral nerve palsies that cause internal ophthalmoplegia?

DR. HAROLD G. SCHEIE (by invitation), closing: I want to thank Dr. Jackson and Dr. Cogan for their discussions. In regard to Dr. Cogan's questions, I can say that we did use eserin in very dilute solution—as dilute as 1:256 per cent.—and in our cases constriction with 1:256 per cent. occurred in the tonic pupil, whereas it did not occur in the normal pupil. We cannot explain the differences in our findings, but we ran controls with eserin on normal subjects—I think 30 in number—and it was not until approximately 1:64 to 1:32 per cent. was reached that the normal pupil was affected, and even in using ¼ per cent. eserin the tonic pupil came down much quicker than the normal pupil. The amount of miosis was about the same.

As to the question regarding internal ophthalmoplegia, I believe that until we know whether the lesion is peripheral or central no conclusion can be reached. If there is damage to the peripheral nerves in glaucoma, why should we not find tonic pupils? We have not seen any.

I should like to close by re-emphasizing what Dr. Adler has said. We have some experimental evidence which points to a lesion peripheral to the ciliary ganglion, but we have not ruled out something inherent in the muscle itself. It might be approached as has Thomson's disease. Harvey has written a paper in which he shows by the use of quinine that the disturbance in myotonic goats is one of the synapse. We are working on other experiments in an attempt to localize the site of the disturbance in tonic pupils.

THE PROTEIN CONTENT OF THE REFORMED AQUEOUS HUMOR IN MAN*

PETER C. KRONFELD, M.D.
Chicago, Ill.

AND

(By invitation)

C. K. LIN, M.D.
Peking, China

AND

(By invitation)

T. H. LUO, M.D.
Peking, China

The primary aim of this and of previously reported work on the regeneration of the aqueous humor in man has been the analysis of the reactive processes which are set up in the eye by the withdrawal of the aqueous humor from the anterior chamber (hereafter referred to as ACP). As criteria of the intensity of these processes, the degree and duration of the elevation of the intra-ocular pressure after ACP (the "hypertensive phase"),[1,2,3,4] and the rate of reformation of the aqueous,[5,6] have been considered. The protein content of the reformed fluid (hereafter designated as p_2) has suggested itself as a further criterion. During the process of its formation, as well as during its stay in the chambers of

* From the Department of Ophthalmology, The Peiping Union Medical College, Peking, China.