THE ACTION OF ESERINE UPON THE EYE FOLLOWING THE USE OF ATROPINE*

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IN view of the conflicting reports in ophthalmological literature about the action of eserine on an eye previously under the influence of atropine, it seemed desirable to re-examine the problem.

Pharmacological writers are in no doubt of the mode of action of these drugs and no long discussion is proposed here. The acetylcholine produced at the parasympathetic nerve-endings is normally removed almost as rapidly as it is formed by the action of the enzyme cholinesterase which is universally present in the tissues. Eserine has no direct action on nerve-endings but acts solely as an anti-cholinesterase, thus allowing the concentration of acetylcholine to rise and so augmenting the response of the tissue to the activity of its nerve. This hypothesis depends mainly upon the fact that smooth muscle such as that in the iris, which is innervated by a cholinergic nerve, is unresponsive to eserine if the nerve is cut and time allowed for it to degenerate. Under these circumstances no acetylcholine is produced by the degenerate nerve-endings and therefore the anti-cholinesterase activity of eserine can evoke no response. Here is the distinction between eserine and pilocarpine, since the latter acts directly on the muscle of the iris.

Atropine paralyses the muscle of the iris to oculo-motor impulses, or rather it reduces the sensitivity of the muscular fibres to the presence of acetylcholine, so that dilation of the pupil results from the tonic pull of the dilator fibres. The question is whether or not the "paralysis" produced by atropine is absolute. Ophthalmological writers during the past few years almost all say that the paralysis is absolute, and many of them state specifically that "the mydriasis of atropine is irreversible" (Duke-Elder, 1932, 1934; Parsons and Duke-Elder, 1948; Traquair, 1948; Walsh, 1947; Douthwaite, 1949; Doggart, 1949).

Before reviewing some early ophthalmological writings it is as well to see what the pharmacologists have to say about this.

Goodman and Gilman (1941) say that "... physostigmine and pilocarpine are capable of contracting the atropinized pupil . . ." and there are a number of references to experimental work bearing this out. Anderson (1905), who carried out some of the work on the denervated iris which has been mentioned above and mentions the work of Schultz (1898) in the same connection, says

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that physostigmine abolishes the mydriasis of atropine and mentions incidentally that pilocarpine will not do so. The question is also discussed by Henderson and Roepke (1937) who come to the same conclusion.

Sollman (1948) in his text-book of pharmacology agrees with this view and says . . . "The atropine effects (on the pupil) may be removed by drugs which stimulate the oculomotor receptors (pilocarpine, physostigmine, choline esters, muscarine) and *vice versa*." He also records a suggestion by Gifford in 1916 that eserine should be used after atropine until the pupil and accommodation have returned to normal.

Guyton (1940) in a review of the action of these and similar drugs, in speaking of their antagonisms, says that the effect of two drugs of opposed actions may be expected to be governed on a quantitative basis and not on any special antagonistic properties that the drugs might be thought to have on one another. Earlier in the same paper, however, he says . . . "Atropine prevents the action of choline compounds on structures innervated by cholinergic nerves."

To my mind, however, the most interesting papers are now of some antiquity and they derive increased interest from the fact that one is by Argyll Robertson.

Thomas R. Fraser (1863) first described the action of eserine on the eye and it was he, incidentally, who suggested the name we all use, after esere, as the ritual poison was named in Calabar (Rodin, 1947). Fraser's paper is very interesting and the following quotation is particularly pertinent " . . . (physostigmine can be used) . . . in mydriasis, whether dependent on the overaction of belladonna, or as a symptom of amaurosis, especially the hydrocephalic variety . . . as well as in many other cases which will suggest themselves to the ophthalmologist, this agent deserves a trial."

In the same year Argyll Robertson (1863) followed with a description of a series of experiments upon his own eyes. He showed first (experiment 2) that atropine dilated the pupil after eserine and that this dilatation could be reversed by eserine, and then (experiment 3) that eserine would contract in less than an hour the pupil which had previously been placed thoroughly under the influence of atropine. He concludes " . . . it is applicable in all instances when atropine is used to render the examination of the eye more perfect or simple."

If we can say that there is no special pharmacological basis for the antagonism between atropine and eserine, and can agree with Guyton (1940) that the problem is a quantitative one, it is reasonable to think that eserine would contract the pupil of the atropinized eye. Even in what we call "full atropinization" it

is likely that the concentration of atropine within the eye is not high and we know that smooth muscle is extremely sensitive to acetyl-choline in the presence of eserine. For example, leech muscle contracts in the presence of eserine when exposed to as low a concentration of acetyl-choline as two microgrammes per litre, or 1 : 500 million. If, therefore, the concentration of acetyl-choline in the eye is raised, as it is by the action of eserine, then the probability is that the iris sphincter will contract despite the previous application of atropine.

I have carried out a short series of experiments to re-investigate the problem.

Results

I. Rabbits

The first tests were made on rabbits. Guttae atropinae 1 per cent. were applied twice daily for ten days to both eyes of two rabbits. On the tenth day intensive application of eserine (one drop of 1 per cent. every minute) was started to the right eye of each animal. From full mydriasis at the beginning, the size of the pupils was reduced to one millimetre or less in fourteen minutes. The eserine was then stopped as one of the animals showed signs of eserine poisoning. Despite intravenous atropine given at once the animal died in a few minutes with muscular twitchings and increasing respiratory difficulty due to bronchial hypersecretion. It is unlikely that the animal absorbed the whole of the drug which was placed on the conjunctiva, as there was considerable lacrimation. If it did absorb it all, the lethal dose of eserine will have been about 9 mg.

In the other animal the eserine-treated pupil remained less than three mm. dilated for twelve hours, then it dilated slowly until it was the same size as its fellow in forty-eight hours. Both pupils were normal in six days.

II. Humans

(a).—A child of seven years old who had been under treatment with Ung. Atropinae 1 per cent. twice daily for five days and in whom there was full mydriasis had one drop at a time of 1 per cent. eserine put into the eye at intervals, as shown in the table below, and the size of the pupil was recorded. Retinoscopy was also carried out at intervals and the retinoscopy findings are shown. The return of ciliary muscle activity is very striking.

TABLE

Time (min.) ...	2	4	6	8	13	18	23	28
Pupil (mm.) ...	10	—	—	—	10	5	4	2
Retinoscopy ...	+5.5	—	—	—	+5.5	+3.75	+0.50	+0.50

After eight applications of eserine the drug was stopped. There was full miosis at forty minutes, slight dilatation was occurring at two hours, and the pupil was half-dilated, but active, five hours later.

(b).—The next patient was a youth of fifteen who had been using *Guttae atropinae* 1 per cent. twice daily for six days up to the time of the trial of eserine. There was full mydriasis at the start. He was given 1 per cent. eserine every minute for five minutes, and then every five minutes for a further half hour. At the end of that time the pupil was half-contracted and there was ciliary spasm to the extent of -3.0 D.S., his refraction having been emmetropic.

Two days later, having had no treatment in the interval, he was comfortable and the near-point of the affected eye was 10 cm. as measured on the Livingston gauge, which would not have been the case had the effect of the atropine been allowed to wear off in its own time.

(c).—A man of thirty-one who had been treated with atropine 1 per cent. three times daily for seven days because of a contusion injury to the globe, was given four drops of 1 per cent. eserine at half-hourly intervals. His pupil size was 8 mm. at the start; after two hours it was 4.5 mm. and he could read comfortably. The improvement was maintained and no further eserine was required. This quite small dose of eserine was enough to restore the activity of the ciliary muscle and iris.

(d).—There is one result to record of the use of this method in an abnormal eye. A woman of fifty-two was admitted to hospital with a diagnosis of thrombotic glaucoma, after having used *Ung. Atropinae* 1 per cent. twice daily for seven days. The eye was hard and the pupil half-dilated. She was given eserine 2 per cent. to the eye three times on the day of admission and the pupil contracted. The tension also fell but this improvement was not maintained and she was later operated upon in an effort to save the eye.

(e).—A woman aged forty-three sustained accidental atropinization of an eye while at work. There was three-quarters mydriasis and the near-point was at 41 cm. One drop of eserine 0.5 per cent. produced miosis in thirty minutes and the eye was normal next day, the near-point now being 17 cm.

(f).—A technician accidentally introduced atropine into one eye. There was full mydriasis, which was counteracted by one drop of eserine 1 per cent. The eye was normal next day.

These results seem to indicate that the antagonistic effects of atropine and eserine on the eye are determined on a simple quantitative basis. This would explain the delay in the recovery of activity of the atropinized pupil which is rendered relatively insensitive to the normal concentrations of acetyl-choline present in the

eye. This insensitivity can be overcome by the administration of eserine which raises the acetyl-choline concentration.

A good deal of temporary visual disability results from the necessary use of atropine in ophthalmology and a kindness would be done to patients if they were given small doses of eserine, say 0.5 per cent. t.d.s. for forty-eight hours after atropine had been used for some relatively trivial ocular disease, or, in children, for refraction. Cycloplegia is a burden and we have here a method of enabling patients to resume close work considerably earlier than would otherwise be possible.

None of the observations here presented is original. It is interesting to speculate how the original description by Argyll Robertson was allowed to slip into the background and to give place to the constantly recurring statement—"eserine will *not* contract the atropinized pupil".

Summary

The effect of eserine on a small number of eyes after the action of atropine is reported. In all cases contraction of the pupil and activity of the ciliary muscle were restored.

A possible therapeutic use for this action is suggested.

It is shown that these effects have been previously described, but have been neglected.

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