THE PARALYSIS OF INVOLUNTARY MUSCLE. Part III. On the action of pilocarpine, physostigmine, and atropine upon the paralysed iris.

By H. K. ANDERSON, M.D.

(Three Figures in the Text.)

(*From the Physiological Laboratory, Cambridge.*)

CONTENTS.

INTRODUCTION. Notwithstanding numerous investigations into the action of physostigmine recent authors disagree in describing the manner in which it affects the iris. Schmiedeberg[1] thinks (1) that physostigmine can act directly upon the sphincter muscle because it constricts the pupil after moderate doses of atropine, and (2) that it acts upon the dilatator because muscarine causes greater constriction of the pupil than physostigmine. On the other hand, Schultz[2] failed to observe any constriction of the pupil four days after the removal of the ciliary ganglion even with free application of a 5% solution of physostigmine to the eye, and he, therefore, concludes that this drug acts only on the endings of the short ciliary nerves. With regard to Langendorff's[3] view that the paradoxical dilatation observed after the application of eserine is caused by a stronger contraction of the

[1] Schmiedeberg. *Grundr. der Arzneimit.* 1895, p. 108; cf. also Harnack and Witkowski, *Arch. f. exp. Path. u. Pharm.* v. p. 492, 1876, and Harnack, *Ibid.* XII. p. 337, 1880.

[2] P. Schultz. *Arch. (f. Anat.) u. Physiol.* 1898, p. 70.

[3] Langendorff. *Klin. Mon. f. Augen.* 1900, p. 823.

denervated than of the normal dilatator, I have shown elsewhere[1] that eserine does not cause paradoxical pupil-dilatation unless its application is attended by excitement of the animal. This paradoxical effect cannot, therefore, be referred to a direct action of the drug on the denervated dilatator.

The argument used by Schmiedeberg in localising the action of physostigmine has been applied to pilocarpine also by Harnack and Meyer[2]. Pilocarpine, unlike physostigmine, does not constrict the pupil after moderate doses of atropine and is, therefore, supposed to act upon the nerve-endings only. This conclusion postulates the generally accepted view that atropine acts in the first place upon the nerve endings. As regards the further question, whether atropine in larger doses paralyses the sphincter muscle opinion is divided. Harnack[3] describes such paralysis, but Schultz[4] following Bernstein and Dogiel[5] finds that the sphincter is excitable even after large doses.

But deductions from the antagonistic behaviour of drugs are to be made with caution and especially when the action of neither antagonist alone has been determined. I have, therefore, studied the action of each drug separately upon the decentralised and denervated muscle of the iris.

The drugs used were pure eserine (or occasionally physostigmine hydrochloride)[6], pilocarpine nitrate, and atropine sulphate, all of which were obtained from Messrs Merck. They were dropped into the eyes from a fine pipette, each drop being about ·04 c.c., and in comparing the action of a drug on the two sides special care was taken to add an equal amount to each eye and to see that the whole dose was absorbed. The possibilities of error in this method were controlled by repetition of the observations, and sometimes, in the event of an unequal response of the pupils, by obtaining the same result even after purposely adding more of the drug to the eye which gave less response (cf. Exp. 18). With

[1] Anderson. This *Journal*, xxxi. p. 299. 1903. Levinsohn, *Archiv (f. Anat.) u. Physiol.* 1904, p. 479, has recently criticised these observations on the supposition that I used a 5 % solution of eserine, but as stated in my paper I used a ·5 % solution. I have since repeated the observations with different strengths of eserine and with the same result.

[2] Harnack u. Meyer. *Archiv f. exp. Path. u. Pharm.* xii. p. 380. 1880.

[3] Harnack. *Archiv f. exp. Path. u. Pharm.* xii. p. 339. 1880.

[4] P. Schultz. *Loc. cit.* p. 54.

[5] Bernstein und Dogiel. *Verhandl. nat. hist. med. Verein zu Heidelberg*, 1866, quoted from Schultz, *loc. cit.*

[6] I shall speak throughout this paper of physostigmine, but in the detailed experiments I have noted which preparation was used.

these precautions the method seems to involve fewer possibilities of error than the method of injection, because after general intoxication changes may occur in the pupils which are due not really to the direct action of the drugs but to their effect on the secretions, respiration, or blood-supply.

All my experiments were performed on cats under anæsthesia with strict antiseptic precautions. The operation for the removal of the ciliary ganglion or section of its branches was that already described[1]. It can be performed without injury to the long ciliary sympathetic fibres, but some of these must be divided if the accessory ganglia are also removed. Intracranial section of the oculomotor nerve was performed after trephining the parietal bone and raising the temporal lobes of the brain from the middle fossa. For this method I am indebted to the kindness of Sir Victor Horsley.

I shall continue to use the expression 'nerve-ending' in its customary sense, and not as used by Brodie and Dixon recently[2]. I shall also speak of the sphincter as 'decentralised' after section of an oculomotor nerve and as 'denervated' after removal of the ciliary and accessory ciliary ganglia. This begs the question, it is true, whether the sphincter receives efferent fibres from other sources than the oculomotor nerve or its ganglia, but may perhaps be excused for the sake of brevity.

The eyes were examined in the dimmest light sufficient for the observation of the pupils except where a contrary statement is made. In this way the reflex tone of the normal sphincter was almost eliminated.

A preliminary account of some of the observations described later was given at a meeting of the Physiological Society in May, 1905[3].

Pilocarpine.

Action of pilocarpine on the decentralised sphincter. After section of an oculomotor nerve within the skull pilocarpine not only constricted the paralysed pupil actually more than the control, but also constricted it for a longer time (cf. Exp. 1). A similar result was also obtained on six occasions between the 151st and 286th days in Exp. 6.

[1] Anderson. This *Journal*, xxxiii. p. 158. 1905.
[2] Brodie and Dixon. This *Journal*, xxx. p. 494. 1904.
[3] Anderson. *Proc. Phys. Soc.* 1905, p. xlix (this *Journal*, xxxii.).

Exp. 1. Cat. Left oculomotor nerve cut close to the brain and reflected.

19th day. Left pupil almost maximal: no light reflex.
12.45. 2 drops 1 % pilocarpine applied to each eye.
2.45. Left pupil 2 mm. wide, right in dim light 4 mm.
3.45. Left pupil 4 mm., right widely dilated.

Similar results on the 26th, 27th, and 32nd days.

Action of pilocarpine on the denervated sphincter. After removal of the ciliary and accessory ciliary ganglia pilocarpine again caused greater and longer constriction of the paralysed pupil (cf. Exp. 2). A similar result was obtained in another cat also on the 115th and 119th days of the experiment.

Exp. 2. Cat. Ciliary and accessory ciliary ganglia removed together with the greater portion of the ciliary nerves. Both sup. cervical ganglia also excised.

9th day. Left pupil almost maximal: visible rim of iris 1 mm. wide.
11.10. 1 drop 1 % pilocarpine applied to each eye.
1.30. Left pupil 3 mm., right in dim light 8 mm.

14th day. Left pupil almost maximal.
2.25. 1 drop 1 % pilocarpine applied to each eye. Eyes examined in dim light.
2.50. Left pupil 4 mm., right 10 mm.
3.5. Left 1·5 mm., right 4 mm.
3.30. Left 1·5 mm., right 3 mm.
4.50. Left 4 mm., right 10 mm.
5.50. Left 5 mm., right widely dilated.

Similar results on the 28th, 58th, and 72nd days.

The unavoidable lesion of the long ciliary nerves in these last two experiments had to be neutralised by the excision of the superior cervical ganglia. But in Exp. 3 the ciliary ganglion alone was removed, and yet the same result was obtained. There was no reason, therefore, to suspect the sympathetic lesion even as a partial cause of the increased excitability of the denervated sphincter. It will also be seen that atropine prevented constriction by pilocarpine when applied first, and annulled it when applied afterwards. But this result will be discussed later.

Exp. 3. Cat. Left ciliary ganglion excised.

7th day. Left pupil almost maximal, visible rim of iris 1 mm. wide: no light reflex.
10.45. 1 drop 1 % physostigmine applied to each eye.
12.30. Right pupil a slit, left very slightly constricted.
12.31. 1 drop 1 % pilocarpine applied to left eye.
1.30. Left pupil 3 mm. wide.

8th day. Left pupil almost maximal.
11.0. 1 drop 0·5 % atropine applied to left eye.
12.45. 2 drops 1 % pilocarpine applied.
2.45. No constriction since.

14th day. Left pupil almost maximal: no light reflex.
2.23. 1 drop 1 % pilocarpine applied to each eye.
2.43. Left pupil 2 mm. wide, right 7 mm. in dim light.
3.3. Left a slit, right 2 mm. wide.
3.48. Left a slit, right 4 mm. wide.
5.50. Left 3 mm. wide, right much dilated.

28th day. Left pupil almost maximal as on 7th day: no light reflex.
10.25. 1 drop 1 % pilocarpine applied to each eye.
10.35. Left pupil 2 mm. wide, right 7 mm. even in dull daylight.
10.45. 1 drop 0·5 % atropine applied to each eye.
10.50. Left pupil a slit, right 6 mm. wide.
12.0. Both pupils almost maximal, left a little the larger.
3.0. Pupils equal, visible rim of iris 1 mm. wide each side.

Pilocarpine also continued to evoke an exaggerated and prolonged constriction of the paralysed pupil when the short ciliary nerves had almost regenerated after section (cf. Exp. 18).

Relative effect of pilocarpine upon the decentralised and denervated sphincter. Observations were made after the application of pilocarpine on four cats in which the sphincter had been decentralised on one side and denervated on the other. In 14 of these observations greater effect was observed on the decentralised side, but in the remaining four (three of which were made during the first five days of the experiments), the difference between the two sides was slight and inconstant, first one pupil then the other being the larger (cf. Exp. 5).

Exp. 5. Cat. Left oculomotor nerve cut, right ciliary ganglion excised.

2nd day. Pupils equal, visible rim of iris about 2 mm. wide each side.
10.45. 1 drop 1 % pilocarpine applied to each eye.
11.45. Left pupil 4·5 mm. wide, right 3·5 mm.
12.15. Left 3·5 mm., right 4 mm.
1.10. Left 5·5 mm., right 4·5 mm.
2.10. Left 8·5 mm., right 7 mm.

4th day. Similar results.

5th day. Pupils equal and dilated as before.
11.10. 2 drops 1 % pilocarpine applied to each eye.
12.10. Left pupil 1 mm. wide, right 1·5 mm.
2.0. Left 1 mm., right 2 mm.
3.0. Left 5 mm., right 6 mm.
5.0. Left 8 mm., right 10·5 mm.

Very similar results were then obtained on the 8th, 9th, and 11th days. The left pupil being 1 mm. to 2 mm. wider at corresponding times.

The balance of evidence was, therefore, in favour of a relatively greater excitability on the decentralised side as in the observations made after dyspnœa and death in similar experiments[1].

[1] Anderson. This *Journal*, xxxiii. p. 171. 1905.

PHYSOSTIGMINE.

Action of physostigmine upon the decentralised sphincter. In Exp. 6 the decentralised pupil was much smaller than the control an hour and more after the application of physostigmine to each eye on the 68th day, but it did not become as small as the control had been earlier. Similar observations were made later in this experiment, and also in two other cats, in one on the 20th and 25th days of the experiment, in another on the 7th day.

After section of an oculomotor nerve, therefore, both pilocarpine and physostigmine caused a more prolonged constriction of the paralysed pupil than of the control, but pilocarpine alone caused an actually greater constriction.

It is interesting to notice in connection with these results that Tolouse and Vurpas[1] have detected in persons suffering from general paralysis an altered reaction of the pupils even before paralysis of the striated muscles. Using physostigmine and atropine in solutions of 1 in 10,000 they find that the reaction of the pupils (1) has a longer latent period than normal, (2) is slower to attain its maximum, and (3) lasts three times as long. They attribute these changes in the reaction to weakness of cortical inhibition.

EXP. 6. Left oculomotor nerve cut close to the brain and reflected.

68th day. Left pupil almost maximal since the operation: no light reflex.

11.45. 2 drops 1 % eserine applied to each eye.
12.25. Left pupil 2 mm., right a slit, even in very dim light.
1.30. Left 2 mm. and has not been narrower, right 4 mm.
3.30. Left 4 mm., right 6 mm.

Similar results on the 108th and 146th days.

151st day. Left pupil still almost maximal.

11.45. 1 drop 1 % pilocarpine applied to each eye.
12.45. Left pupil 3 mm., right 6 mm.

Similar results on the 153rd, 214th, 227th, 271st, and 286th days.

264th day. Left pupil no longer as widely dilated, but no light reflex.

11.45. 1 drop 1 % physostigmine applied to each eye.
12.30. Left pupil 4·5 mm., right a slit, even in very dim light.
2.15. Left 5 mm., right 2·5 mm.
4.0. Left 8 mm., right much smaller.

Similar result on 284th day after the application of 2 drops of 1 % eserine to each eye.

[1] Tolouse and Vurpas. *Rev. Neur.* XI. p. 826. 1903.

310th day. Narrowing of pupil slightly greater than on 264th day, but no light reflex.
1.15. 2 drops 1 % pilocarpine applied to left eye.
2.30. Left pupil 4 mm. wide, but no light reflex.
2.45. 1 drop 1 % eserine.
3.45. Left pupil only slightly smaller, but distinct light reflex now.

325th day. Light reflex readily obtained after eserine alone, but none after pilocarpine alone on 328th, 397th, and 400th days.

392nd day. Left pupil slightly smaller, visible rim of iris now 3 mm. wide, but no light reflex.
12.16. 1 drop 1 % eserine applied to each eye.
12.46. Left pupil 8 mm., right a slit.
2.16. Left 5 mm. and responds well to light, right still a slit, even in dim light.
3.6. Left 6 mm., quick response to light, right scarcely dilates at all in dim light.

393rd day. Left pupil constricts readily from 10 to 8 mm. on bringing cat into bright light; right pupil does not dilate to more than 2 mm. even after closing eyelids. This continuance of the light reflex on the following day, after the application of eserine, was observed again with equal distinctness on the 398th and 407th days.

But after the application of physostigmine at later dates the control pupil in Exp. 6 (and in one other long experiment) did not subsequently become larger than the paralysed pupil as it had at earlier dates. It should be noticed, however, that at these later dates the control pupil was almost a slit in dull daylight, did not dilate to more than 2 mm. wide even after closing the eyelids, and even after an hour or more in darkness dilated only to 8 or 9 mm. The prolonged constriction of the paralysed pupil by physostigmine may have persisted, therefore, even on the 392nd day though no longer obvious on account of the exaggeration constriction of the control. For the latter constriction I am at present unable to account.

Effect of physostigmine on the light reflex. In Exp. 6 the paralysed pupil began to narrow slightly in the 6th month and soon afterwards responded quite well to light under the influence of physostigmine, but under normal conditions it gave no trace of a response to light even 15 months after section of the oculomotor nerve, though by this time it had narrowed to a width of 9 mm.[1] The light reflex also persisted for about 24 hours after the application of the physostigmine and during this time an increased but diminishing constriction of the pupil continued. But pilocarpine, though it constricted the pupil even more vigorously than physostigmine, did not restore the high reflex. Similar observations were also made during the 3rd to 6th months in another cat in which the paralysed pupil began to narrow even as early as the 3rd month.

[1] In the 17th month after the operation the pupil of this cat began to respond slightly to light under normal conditions.

In this latter cat, the local application of physostigmine to the ciliary nerves and ganglion did not make stimulation of the regenerating oculomotor fibres effectual or increase the excitability of the ganglion or its branches, and in Exp. 7 this application even depressed the excitability of the nerves and ganglia. The physostigmine did not, therefore, facilitate the light reflex by an action on the nerves or ganglia of the constrictor tract.

Exp. 7. Cat. 11.40. Ether, then ether and chloroform.

11.50. Left ciliary ganglion and branches exposed, oculomotor nerve not cut, ganglion stimulated, $c=27$ no effect, $c=26$ slight constriction; ciliary nerves stimulated, $c=28$ no effect, $c=27$ slight constriction. It was necessary in these observations carefully to exclude mechanical stimulation. When the electrodes were placed on the ganglion constriction was observed.

12.15. Left pupil 8·5 mm. wide. Warm 1 % eserine painted on the ciliary ganglion and nerves, excess removed with sponge.

12.25. Left pupil has gradually dilated to a width of 11 mm.

12.30. Ganglion stimulated, $c=18$ no effect, $c=16$ slight constriction; nerves stimulated, $c=20$ no effect, $c=19$ slight constriction.

12.50. Ganglion, $c=26$ slight constriction, $c=27$ none; nerves, $c=27$ slight constriction, $c=28$ none. Pupil now 8 mm. wide.

1.0. Paint nerves and ganglion again with eserine. Same dilatation of pupil and lowering of excitability with subsequent recovery of excitability and constriction of pupil.

2.2. Observation repeated again with same result.

3.25. Right ciliary ganglion and nerves exposed. Left pupil, slight constriction on stimulating ciliary nerves when $c=23$, none when $c=24$. Right pupil, the same.

3.40. Cannula in left femoral vein, pupil now 4·5 mm. on left side, and 11 mm. wide on right. Inject 1 c.c. 1 % eserine. The pupil dilated almost immediately. The breathing also became very fast and artificial respiration had to be applied.

3.45. Cat breathing again, but rapidly. Left pupil now 10 mm. Slight constriction on stimulating left ciliary nerves when $c=27$, not when $c=28$.

3.57. Slight constriction first seen when $c=28$.

4.17. Constriction when $c=29$, not when $c=30$.

4.30. The same.

The ciliary neurones could not be directly injured by section of the oculomotor nerve in the skull. There is also no evidence of change in the structure or excitability of the peripheral ganglia after decentralisation[1]. Certainly the ciliary ganglion 6 months after decentralisation

[1] Anderson. This *Journal*, XXVIII. p. 509. 1902. Levinsohn, *Arch.* (*f. Anat.*) *u. Physiol.* 1903, p. 456, finds, after section of a cervical sympathetic nerve, that stimulation of the lower end of the superior cervical ganglion is ineffectual, and concludes from this observation that the lower end of the ganglion had suffered change, but Langley and I (this *Journal*, XIII. p. 464, 1892) had already shown in the rabbit by the use of nicotine that the pupillo-dilatator cells were in the upper and not in the lower part of the ganglion.

responded as readily to electrical stimulation as the control, and showed no abnormality in the size, number, or structure of its cells. The failure of the light reflex under normal conditions in Exp. 6, and in the other experiment like it, must, therefore, have been due primarily to the feebleness of the impulses transmitted by the imperfectly regenerated oculomotor fibres.

In another experiment also (Exp. 9) in which, after removal of a ciliary ganglion, the oculomotor nerve had rejoined the accessory ganglia the direct light reflex returned several weeks before the consensual. This suggested that in the consensual reflex the impulses excited by light were weakened by their passage through one or more additional neurones in the indirect path.

Action of physostigmine upon the denervated sphincter. A few days after the removal of the ciliary ganglion physostigmine did not constrict the pupil in one cat, but constricted it slightly in another (Exp. 11). This latter result was also obtained in another cat, in which the short ciliary nerves had been recently cut (Exp. 18). But these observations did not necessarily invalidate P. Schultz's conclusion about the action of physostigmine. On the contrary, his view presupposes the possibility of slight constriction in such cases, because the accessory ciliary ganglia remain in connection with the sphincter. And indeed in nine other cats physostigmine did not constrict the pupil after excision of these accessory ganglia also. My experiments show, therefore, that physostigmine does not excite the sphincter when all the ciliary nerves have degenerated and so far they confirm the conclusion of Schultz.

Schultz removed the superior cervical ganglion in his experiments because he thought contraction of the sound dilatator might conceal a slight effect of physostigmine upon the paralysed sphincter. In my experiments also the dilatator was necessarily paralysed to some extent when the accessory ganglia were removed, and in two of them the superior cervical ganglion was excised also. But the excision of this ganglion predisposes the dilatator to paradoxical contraction and may thus introduce the very factor Schultz wished to exclude. I have, therefore, taken special care to avoid excitement of the cats when observing the pupils in such experiments.

But a few months after the removal of a ciliary ganglion the light reflex in two kittens had almost completely returned (cf. Exp. 9), and even in two adult cats physostigmine constricted the pupil to 2 or 3 mm. 2 months after such denervation (cf. Exp. 9).

Exp. 9. Kitten, 2 months old. Left ciliary ganglion excised.
17th day. Left pupil for first time seen to be slightly constricted.
22nd ,, Pupil slightly smaller, but no reaction to light.

42nd day. Good response to light, pupil of medium size in sunlight.

91st ,, Pupil constricts to 3 mm. in sunlight. Consensual light reflex detected for first time, but slight.

328th ,, Pupil constricts to 2 mm. now, not quite regular. The malar side is very slightly more dilated. Quick consensual light reflex.

336th ,, Stimulation of oculomotor nerve within the skull. Constriction of pupil before but not after injection of nicotine, but constriction obtained after nicotine on stimulating an accessory ganglion.

Exp. 10. Cat. Right ciliary ganglion excised.

2nd day. 11.15. 1 drop 1 % eserine applied to right eye.
11.45. Right pupil 3 mm. wide.

3rd ,, ? no constriction after eserine.

4th ,, Good constriction after pilocarpine.

35th ,, Pupil now constricts to 6 mm. after eserine.

54th ,, Pupil 3 mm. wide after eserine, but dilated slightly more on malar side.

170th ,, Right pupil has gradually narrowed since the operation but is still very widely dilated. No light reflex.
1.5. 2 drops 1 % eserine applied to right eye.
2.15. Right pupil 2·5 mm., almost regular.

It was evident that the oculomotor nerves had rejoined the accessory ganglia in the two kittens. But even this regeneration did not satisfactorily account for so complete a return of the light reflex, and it certainly was not the sole cause of the reaction of the paralysed pupil to physostigmine, because this reaction continued even after subsequent intracranial section of the oculomotor nerve in Exp. 11.

Exp. 11. Cat. Left ciliary ganglion excised.

7th day. Left pupil almost maximal: no light reflex.
10.45. 2 drops 1 % physostigmine each eye.
12.30. Left pupil very slightly smaller, right a slit.

49th day. Left pupil almost maximal still: no light reflex.
11.0. 2 drops 1 % physostigmine left eye.
12.0. Left pupil 7 mm. wide.

50th day. Left oculomotor nerve cut within the skull.

51st day. Left pupil almost maximal.
4.20. 2 drops 1 % physostigmine left eye.
5.20. Only very slight constriction of pupil.

52nd day. Left pupil almost maximal.
11.20. 3 drops 1 % physostigmine left eye.
12.20. Not a trace of constriction.

59th day. Left pupil maximal.
11.35. 2 drops 1 % physostigmine left eye.
12.15. Left pupil 6·5 mm. wide.

71st day. The fibres of the oculomotor nerve were all degenerated, and many degenerating fibres were traced in the scar-tissue between it and the ciliary branches. In the latter also there were many medullated fibres degenerating even close to the eyeball, but there were also many sound, the majority of which came from the long ciliary branches.

But there was another factor to be considered in these experiments besides regeneration. Denervation increases the excitability of the sphincter. This is shown by the paradoxical contraction of the denervated muscle after dyspnœa[1] and by its exaggerated response to pilocarpine (Exps. 2 and 3). This increase of excitability might, therefore, eventually enable light and physostigmine to constrict the pupil although the remaining ciliary cells were but few, and the completeness of the constriction might be merely a result of a greatly increased response from the paralysed muscle.

I, therefore, removed the accessory ganglia and part of the ciliary nerves from eight cats. But, nevertheless, there was a gradual return of the reaction to physostigmine in every case. And yet the iris, though reacting readily to physostigmine, gave no light reflex then or even much later, nor could any contraction of the sphincter be elicited on stimulation of the 'ciliary' branches on the optic nerve or in the sclerotic. Dissection after death also failed to discover any nerve cells on the remaining portions of the ciliary branches, in the scar-tissue, on the ophthalmic branch of the trigeminal, or on the oculomotor nerve (cf. Exps. 12, 13, 14) except in one experiment and then only 29 cells were found. Moreover, in two of these experiments the reaction of the denervated sphincter to physostigmine was eventually so great and so prolonged, that the paralysed pupil in dim light was smaller than the control an hour or more after an equal dose of physostigmine had been applied to each eye (cf. Exp. 17, 343rd day). And this result was not due to the lesion of the dilatator nerves involved in the removal of the accessory ganglia, because in both these experiments the superior cervical ganglia were also removed to neutralise this lesion.

Exp. 12. Left ciliary ganglion excised together with the ciliary nerves almost to the bulb of the eyeball.

10th day. Left pupil almost maximal since the operation. 4 drops 1 % physostigmine applied to left eye: no constriction.

12th day. 1 drop 1 % pilocarpine applied to left eye, left pupil constricted from almost maximal size to 2 mm. width.

14th day. 4 drops 1 % physostigmine applied to left eye: no constriction.

15th day. 1 drop 1 % pilocarpine applied to left eye, left pupil constricted to 3 mm. width in ½ an hour.

[1] Anderson. This *Journal*, xxxiii. p. 166. 1905.

32nd day. 2 drops 1 % eserine applied to left eye: no constriction.

47th day. Left pupil almost maximal still: no light reflex left eye.
10.15. 2 drops 1 % physostigmine applied to left eye.
11.25. Left pupil now only 8 mm. in width. The iris is puckered over sphincter at two points.

66th day. Left pupil still widely dilated: no light reflex.
11.40. 2 drops 1 % physostigmine applied to left eye.
12.30. Left pupil constricted to about 8 mm. in width.

68th day. Ether. Optic nerve exposed and stimulated with surrounding tissue and nerves, only dilatation seen. Oculomotor nerve in orbit stimulated, no effect on pupil. Sclerotic stimulated, only local dilatation seen, no local constriction. Cervical sympathetic stimulated, good dilatation, no constriction of sphincter.

The remaining portions of the ciliary nerves, the oculomotor nerve, and the ophthalmic branch of the trigeminal, were all carefully teased, and also the scar-tissue around the optic nerve. No nerve cells were found, however, but there were many medullated fibres in the scar-tissue and in the remnants of the ciliary branches.

In Exp. 12 the superior cervical ganglion remained and its branches had regenerated functionally across the gap in the ciliary nerves so that stimulation of the fibres replacing the old ciliary nerves caused a dilatation of the pupil which might have masked slight constriction. But in six other cats in which this ganglion had been removed there was neither dilatation nor constriction on stimulation of these fibres under normal conditions, even when the electrodes were applied over the sclerotic and a strong current employed (cf. Exps. 13, 14).

It was by no means obvious, therefore, why the sphincter responded again to physostigmine after removal of the ganglia and at first it seemed probable that it had regained excitability after a period of shock. But further observations soon suggested objections to this view: (1) the responses returned at different times after the denervation and returned later when the ciliary nerves had been more thoroughly removed, (2) it did not return equally or at the same time to the whole sphincter, and (3) it disappeared a second time when the branches round the optic nerve were cut close to the eyeball.

(1) The response generally returned from the 5th to 7th week, but this time varied from 3 weeks in an early experiment, in which the ciliary nerves were not removed beyond the accessory ganglia to 8 weeks in the last in which the greater part of these nerves were excised, and in one cat (Exp. 16) in which the oculomotor nerve had been cut within the skull before the removal of the ciliary nerves and ganglia, the response did not begin to return till 5 months after the denervation.

(2) In Exp. 12 the unequal contraction of the sphincter on the 47th day has already been noticed, but more special attention was paid to this matter in Exp. 17, and I have drawn in Fig. 1 *a*, *b*, *c*, diagrams representing the form and size of the pupil in Exp. 17 after the application of physostigmine on the 38th, 60th, and 107th days. On the 27th day no constriction was seen[1].

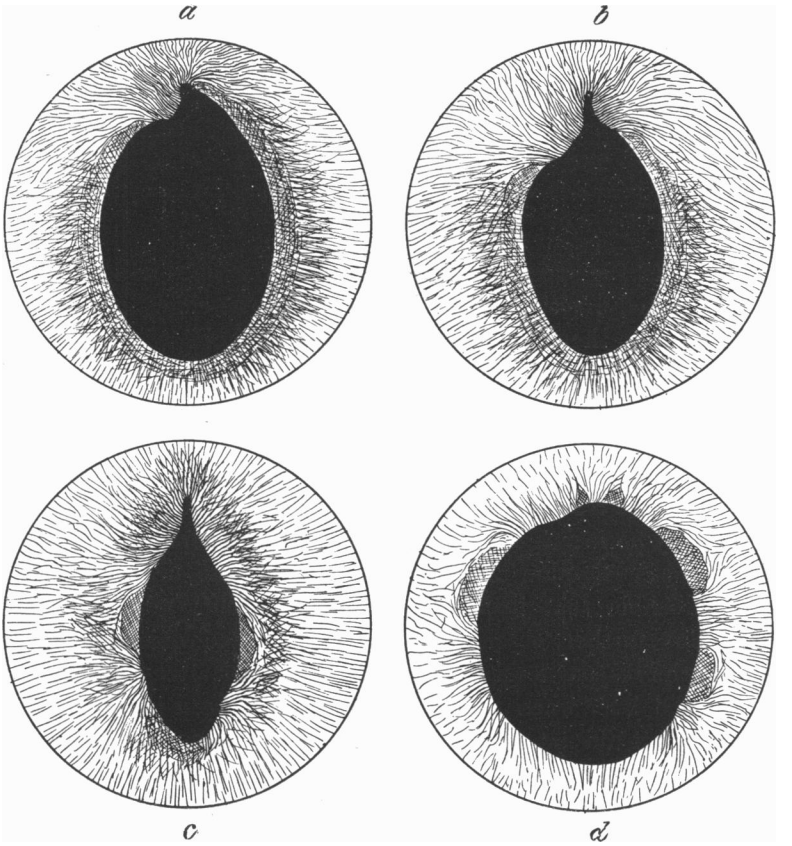

Fig. 1.

It will be noticed that the return of excitability was at first quite local and that it gradually spread as the days elapsed. But long after physostigmine had begun to constrict the pupil generally, and even more than a year after removal of the ganglia, constriction began first in the portions of the sphincter which had given the earliest signs of

[1] Details of this experiment will be found on p. 431.

returning excitability and continued to be strongest at these points. This unequal distribution of contraction was clearly shown by the greater puckering of the iris over certain portions of the sphincter. Finally, even without the application of physostigmine slight puckering was observed at certain points which corresponded with those at which constriction had been most marked after physostigmine previously. Between these puckered portions the iris seemed to be stretched and looked darker in colour. This I have indicated by cross-hatching these portions in my diagram, Fig. 1 *d*.

(3) The observations described in (1) and (2) suggested regeneration as the cause of the renewed excitability. I, therefore, waited after denervation of the sphincter, in four other cats, till the response to physostigmine had returned, and then cut the 'ciliary' nerves again, this time close to the eyeball. In two cats, in which I cut all the branches, the reaction to physostigmine was again abolished (cf. Exp. 13), but in two, in which the branches were only partially cut, it disappeared only from the twice paralysed portion of the iris (cf. Exps. 14 and 15). In the three cats which were kept longer under observation, the response, it is true, began to reappear, but only after a month when regeneration might have begun again.

EXP. 13. Ciliary, accessory ciliary and superior cervical ganglia excised on the left side.

28th day. Left pupil almost maximal, no reaction to light or eserine.

40th day. Pupil unchanged, but slight reaction to eserine.

193rd day. Left pupil slightly narrower than on 40th day, but no light reflex.
12.0. 1 drop 1 % eserine applied to left eye.
1.0. Left pupil 2·5 mm., but right smaller even in dim light.
3.0. Left pupil now distinctly smaller than right in dim light.

194th day. Cat anæsthetised with ether. 'Ciliary' branches stimulated on the optic nerve and at several places in the sclerotic. No change in the pupil.

195th day. Left pupil about ¾ full size[1].
11.0. 2 drops 1 % eserine applied to left eye.
1.0. Left pupil 4 mm. wide.
2.15. Left pupil 2·5 mm.
3.50. Left pupil 3 mm.

196th day. Left pupil widely dilated again, rim of iris 2 mm. wide.
11.0. 2 drops 1 % eserine applied to left eye.
1.0. No constriction since.

[1] The cause of such temporary constriction has been discussed elsewhere. Cf. Anderson, this *Journal*, XXXIII. p. 166. 1905.

211th day. Left pupil as on 196th day.
2.40. 2 drops 1 % eserine applied to left eye.
4.40. No change in pupil since.

224th day. Left pupil as on 196th day.
10.15. 2 drops 1 % eserine applied to left eye.
11.15. Slight but distinct constriction of left pupil.

No nerve cells found on ciliary branches after death.

Exp. 14. Cat. Ciliary, accessory ciliary and superior cervical ganglia removed on left side.

35th day. Slight reaction to physostigmine seen for first time since operation.

90th day. Left pupil almost maximal: no response to light.
2.45. 2 drops 1 % eserine applied to each eye.
4.0. Left pupil almost a slit, and smaller than right in dim light.

92nd day. Two malar ciliary branches cut near the eyeball.

94th day. Left pupil almost maximal, no irregularity of pupil.
12.0. 3 drops 1 % eserine applied to left eye.
1.15. Nasal side of pupil much straighter than the nasal.

95th day. Left pupil almost maximal.
12.0. 4 drops 1 % eserine applied to left eye.
12.45. Left pupil as in Fig. 2 *a*, but the malar rim of iris is slightly wider than before.

96th day. Left pupil almost maximal.
12.15. 3 drops 1 % eserine applied to each eye.
1.15. Right pupil a slit, left much smaller than before, but dilated more on malar side.
1.30. Chloroform, then chloroform and ether.
1.40. Pupil as in Fig. 2 *b*.
1.47. 2 drops 1 % eserine applied to left eye.
2.25. Left pupil as in Fig. 2 *c*, 1 drop 1 % eserine to left eye.
2.45. Left pupil now as in Fig. 2 *d*.

No contraction of the left sphincter was observed on stimulation of the ciliary nerves or sclerotic. No nerve cells were found on the remaining portions of the ciliary branches. The ciliary ganglion had been completely removed. There were many medullated fibres, degenerating in the two branches which had been cut, but sound in the other branches.

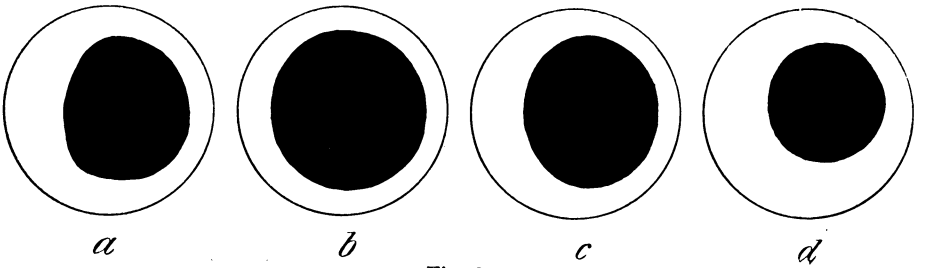

Fig. 2.

Exp. 15. Cat. Right ciliary ganglion excised.

170th day. Right pupil 11 mm. wide: no response to light.
1.5. 2 drops 1 % eserine applied to right eye.
3.40. Right pupil 2 mm., but is very slightly more dilated on malar side.

176th day. Malar ciliary branches cut close to eyeball.

179th day. Right pupil widely dilated and regular.

11.45. 3 drops 1 % eserine applied to right eye.

12.30. Right pupil as in Fig. 3 *a*, same appearance also at 1.30.

This observation repeated on the 182nd, 186th, 187th, 189th days, and even on the 189th day the pupil did not become less than 10 mm. wide after eserine.

183rd day. Right pupil almost maximal.

10.45. 2 drops 1 % pilocarpine.

11.30. Malar side of pupil almost straight, but nasal bulged, Fig. 3 *b*.

This observation was repeated on the 188th, 227th, and 245th days.

206th day. Right pupil almost maximal.

11.30. 3 drops 1 % eserine applied to right eye.

12.30. Nasal side of pupil much straighter than malar on 179th day, but the whole pupil contracts more, becoming 4 mm. wide.

This observation repeated on the 225th and 240th days.

270th day. Right pupil about 9 mm. wide, constricts almost equal now after physostigmine.

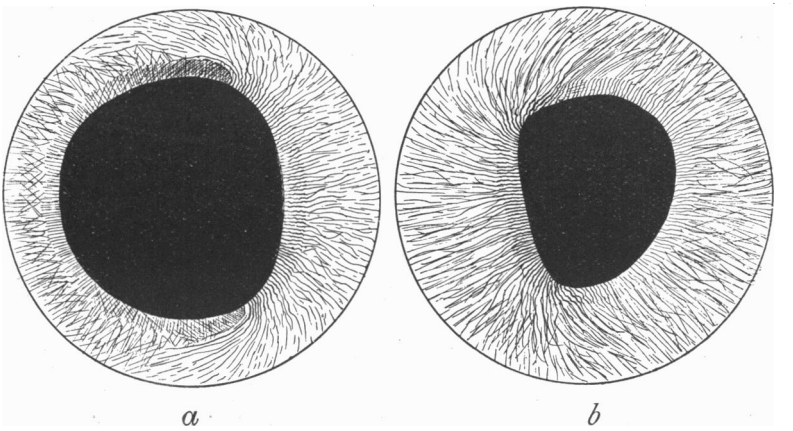

Fig. 3.

It may fairly be objected that, when all the nerves were cut, the second operation had interfered with the supply of blood to the eye and thus caused the loss of excitability. But this view was unlikely on account of the free anastomoses of vessels in the eyeball, and indeed could not be upheld in the experiments in which the nerves were not all cut, because in these cats no vessels of any considerable size were cut within the periosteal sheath of the orbit and even in Exp. 13 the response to physostigmine lasted about 24 hours after section of all the nerves as after a primary section. There was also no reason to suspect any undetected injury of the eyeball as the cause of the inexcitability, on the contrary,

in Exp. 15 pilocarpine excited an exaggerated contraction in the twice paralysed portion of the sphincter. It was thus evident, that the loss of response to physostigmine was not caused by shock or enfeeblement of this portion.

I, therefore, concluded for the reasons given in (1), (2), and (3) that the return of the reaction to physostigmine after removal of the ciliary ganglia was due not to the development of automatic tone in the denervated sphincter muscle, but to a regeneration of nerve fibres along the track of the old ciliary nerves. But it remained to investigate the source of these fibres and the nature of the regeneration.

The reaction of the denervated sphincter to physostigmine was not prevented by the simultaneous removal of the superior cervical ganglion in Exp. 13, nor abolished by its subsequent removal in another experiment. Reversely also, stimulation of the cervical sympathetic caused no contraction of the sphincter in Exp. 12 after removal of the ciliary ganglion only. It was evident, therefore, that the return of this reaction did not depend on the outgrowth of fibres from the sympathetic.

Other possible sources of the regenerated fibres were:—

(1) post-ganglionic fibres from a few ciliary cells not removed:

(2) fibres from the oculomotor nerve either præ-ganglionic or destined for striped muscles:

(3) fibres from the fourth, fifth, or sixth nerves injured by the operation.

With regard to (2) and (3), Langley found[1] that post-ganglionic fibres were not replaced functionally by præ-ganglionic. The same result was obtained by Langley and myself in further similar experiments, and we found also that they are not functionally replaced by fibres innervating striped muscles[2]. But it was nevertheless possible that these fibres might join the sphincter, and that physostigmine might stimulate such abnormal myo-neural junctions. An attempt was, therefore, made to exclude first the fibres in (2). For this reason, the oculomotor nerve was cut close to the brain in Exp. 16 and reflected. Then 37 days later the ciliary ganglia were removed with almost the whole of the ciliary nerves. Yet the sphincter began to respond to physostigmine again after 5 months.

[1] Langley. This *Journal*, xxv. p. 417. 1900.

[2] Langley and Anderson. This *Journal*, xxx. p. 385. 1904.

Exp. 16. Cat. Left oculomotor nerve cut.

37th day. Left pupil almost maximal: no response to light. Ciliary ganglia removed with nearly the whole of the ciliary nerves and portions of the branches to the inferior oblique and inferior rectus muscles.

44th day. 1 drop 1 % pilocarpine constricted left pupil almost to a slit.

45th day. 2 drops 1 % eserine no effect.

194th day. For first time very slight narrowing of pupil observed, and for the first time very slight constriction after eserine. But even on the 159th day 3 drops of 1 % eserine had not caused a trace of constriction, and the pupil was almost if not quite maximal. The constriction now caused was not regular, however, the pupil being almost lozenge-shaped. A small filamentous outgrowth was also noticed on the edge of iris.

210th day. Left pupil now constricts to a width of 6 mm. after eserine, but though irregular still, is less so.

269th day. Left pupil very nearly maximal still. 2 drops 1 % atropine left eye.

270th day. 2 drops 1 % eserine left eye, no effect.

271st day. 2 drops 1 % eserine, very slight constriction.

But three other experiments had showed (cf. Exp. 6) that the oculomotor nerve can regenerate even after intracranial section. It was possible, therefore, that it had regenerated in Exp. 16 also, and that by joining directly with the sphincter it had restored to it the power of reacting to physostigmine. The unusual long absence of the response was in favour of this. Moreover, in Exp. 11, in which the oculomotor nerve was cut 3 months after the removal of the ciliary ganglion, there were many medullated fibres degenerating in the ciliary branches close to the eyeball as well as sound fibres. The outgrowth of oculomotor fibres along the track of the old 'ciliary' nerves was, therefore, proved.

On the other hand, it should be remembered that the response of the sphincter to physostigmine was diminished in Exp. 6 and other similar experiments, although the ciliary ganglia and their terminal connections were intact. In Exp. 16, therefore, even if the response depended primarily on the presence of sporadic ciliary cells, it was but to be expected that its return would be further delayed by their decentralisation. Decentralisation of cells might also have accounted for the diminution of the response of the denervated sphincter to physostigmine after section of the oculomotor nerve in Exp. 17.

Exp. 17. Cat. Left ciliary and accessory ciliary ganglia removed with part of the ciliary nerves. Both superior cervical ganglia excised.

27th day. Left pupil almost maximal, no constriction even an hour after 2 drops of 1 % eserine has been applied to eye.

38th day. Visible rim of iris on left side 1 mm. wide.

10.40. 4 drops 1 % eserine applied to left eye, 1 drop to right.

11.40. Right pupil a slit, left as in Fig. 1 *a*. Left pupil began to dilate at 12.20.

45th day. Local patch of constriction after eserine wider.

60th day. 3 drops 1 % eserine applied to left eye, an hour later pupil as in Fig. 1 *b*.

107th day. Visible rim of iris on left side now 2 mm. wide. Left pupil an hour after 2 drops of 1 % eserine as in Fig. 1 *c*.

119th day. Left pupil a slit an hour after 1 drop 1 % pilocarpine had been applied to eye, but right not less than 8 mm. in dim light.

249th day. Visible rim of iris now 2·5 mm., left pupil 10 mm. wide. Left pupil constricted to a width of 2 mm. an hour after 2 drops of 1 % eserine had been applied to the eye.

337th day. Left pupil 10 mm. wide, but no response to light.

11.45. 1 drop 0·5 % atropine applied to each eye.
12.45. Left pupil now 12 mm., right very slightly smaller.
12.46. 2 drops 1 % physostigmine left eye.
2.45. No constriction since.
2.46. 2 drops 1 % pilocarpine left eye.
4.45. No constriction since.

Atropine had also caused dilatation of the left pupil on the 236th day.

343rd day. Left pupil 10 mm. wide.

2.40. 1 drop 1 % physostigmine applied to each eye.
3.25. In dim light both pupils 1·5 mm. wide, but in bright light right is smaller.
4.50. The left pupil has not dilated since 3.25, but the right has: even in dull daylight the left now is smaller than the right.
5.50. Left pupil unchanged, right much dilated in dim light.

379th day. Similar observations. It was also noticed that even next day the left pupil had dilated only to a width of 6 mm., though before and afterwards it was 9 mm. wide. For this reason the left pupil was smaller than the right even 24 hours after the eserine had been applied.

401st day. Left pupil 9 mm. wide, Fig. 1 *d*. No constriction even after 15 mins. exposure of the eye to the light of an electric lamp. No dilatation even after an hour in darkness.

12.20. Ether.
1.0. Oculomotor nerve exposed within skull, but not cut. Left pupil maximal.
1.40. Operation finished after cutting nerve.
5.30. Left pupil maximal, but right a slit in sunlight.
6.0. 2 drops 1 % eserine applied to left eye.
7.0. No constriction.
9.45. Left pupil now 9 mm. wide.

402nd day. Left pupil 11 mm. wide, local puckering over sphincter, as in Fig. 1 *d*, but less noticeable.

12.40. 2 drops 1 % eserine applied to left eye.
2.40. Left pupil 9 mm., local puckering stronger.

421st day. Left pupil 11 mm. wide, local puckering still as on 402nd day.

11.0. 3 drops 1 % eserine applied to left eye.
11.50. Left pupil 8 mm., local puckering stronger.

536th day. Left pupil 11 mm. wide, local puckering as before: no light reflex.

12.25. 2 drops 1 % eserine applied to left eye.

1.30. Left pupil 5 mm. wide, two marked local patches of constriction.

2.7. Tracheotomy.

2.15. Both sympathetics stimulated several times, but no effect on pupil.

4.0. 3rd, 4th, 5th, and 6th cranial nerves stimulated intracranially several times, no effect on pupil but constriction of striped muscles.

4.25. Stimulation of sclerotic with strong current caused slight but distinct local contraction of sphincter in two portions in which local puckering had been observed previously. No nerve cells found on the remainder of the ciliary branches, in the scar-tissue, on the ophthalmic branch of the trigeminal, or on the oculomotor nerve and its branches even after minute teasing of the various branches or tissue.

It was not necessary, therefore, to assume a direct union of the oculomotor fibres with the sphincter in explaining the results of Exps. 16 and 17. And indeed Exp. 17 showed that such union, even if it took part in restoring the reaction to physostigmine, was certainly not the sole cause of this restoration, but that fibres from sources (1) or (3) must also be concerned. The anatomical facts were not against the presence of fibres from (3) in the ciliary nerves, because the sound fibres in Exp. 11 might have been fibres from the fifth or other nerves on their way to join the sphincter. In Exp. 17 also, there were sound medullated fibres in these branches close to the eyeball, but in this case sound medullated fibres had reappeared in the cut oculomotor nerve. The absence of functional regeneration in the ciliary nerves also seemed to exclude the possibility of a union of the sphincter with ciliary ganglion cells. The balance of evidence seemed, therefore, at first distinctly to favour the view that after removal of the ciliary ganglia physostigmine constricted the pupil by acting on nerve-endings formed by a direct union of fibres from (2) and (3) with the sphincter.

But in my last two experiments (of which Exp. 17 was one), I was led by the results observed during regeneration of the oculomotor nerve in Exp. 6 to try the effect of stimulating the ciliary nerves after the administration of physostigmine, and in both cases I observed slight, but distinct, local contraction of the sphincter, though in the second I observed no such contraction immediately before injecting 1 c.c. of 1 % eserine into the femoral vein on the 142nd day. In this last experiment again I could find no ganglion cells on the nerves in the orbit.

These two last experiments showed, therefore, either that ganglion cells were present, or that fibres from (2) and (3) united directly with the sphincter and became functional under the influence of physostigmine.

Since careful search did not reveal a single ganglion cell[1], I find it difficult to accept the former view. On the other hand, there is no supplemental evidence to support the latter view, and for the present I must be content to leave the matter there.

Action of physostigmine upon the sphincter after regeneration of the cut short ciliary nerves. In Exp. 18 the short ciliary nerves were cut close to the ganglion and a small portion of them was removed to delay regeneration. But after regeneration was almost complete, physostigmine excited an exaggerated and prolonged constriction on the side of the lesion. It will be noticed also, in this experiment, that the paralysed pupil did not become nearly maximal, and that atropine did not dilate it further or more widely than it dilated the control.

EXP. 18. Short ciliary branches cut close to the ganglion on the left side: small portion of nerves removed.

16th day. Left pupil since operation not wider than 10 mm.: no light reflex.

11.48. 4 drops 1 % eserine applied to left eye.
1.18. Left pupil slightly smaller, 9 mm. wide.

27th day. Left pupil 10·5 mm. wide.

10.50. 3 drops ·5 % atropine.
1.50. Both pupils 10·5 mm. wide.
2.0. 2 drops 1 % atropine to each eye.
5.0. Both pupils 10·5 mm. wide still.

195th day. Pupils almost equal in dim light, but right pupil slightly the smaller in bright light.

3.45. 1 drop 1 % pilocarpine applied to each eye.
4.25. Left pupil 5 mm., right 8 mm.
5.15. Left pupil 4 mm., right 7 mm.

198th day. 2 drops 1 % eserine, right eye; 1 drop, left eye. The left pupil was much smaller than the right an hour and more afterwards in dim light.

A similar result was also obtained on the 210th, and 212th days. The left pupil was also the smaller in dim light after an equal application of eserine to each eye on the 52nd and 113th days.

[1] No medullated fibres degenerate beyond the accessory ganglia when the oculomotor nerve is cut, and no constriction occurs when this nerve is stimulated after painting the ciliary ganglia with nicotine. (Langley and Anderson, this *Journal*, XIII. p. 464. 1892.) I also dissected the ciliary nerves from the sclerotic in three eyes, and after teasing them minutely found not a single nerve cell. There was no evidence, therefore, of cells within the eyeball.

ATROPINE.

Action of atropine upon the dilatator. In Exp. 18, the pupil after section of the short ciliary nerves was not more than 10·5 mm. wide. Yet atropine did not dilate it further and both pupils were the same size after atropine had been applied to the eyes[1]. Again, in two cats, from which a ciliary ganglion had been removed[2], dyspnœa led to constriction of the paralysed pupil, but atropine did not dilate it even then. There was no evidence, therefore, that atropine could excite the dilatator to contraction.

Action of atropine upon the sphincter. The observations just mentioned showed also that atropine did not annul the contraction of the denervated sphincter[3]. Ulrich[4] has also shown that the pupil contracted well after death in an eye which had been kept under the influence of atropine for 14 days previously, and Placzek[5] has found that atropine does not alter the post-mortem constriction of the pupil. In one of my experiments also, the pupil was constricted after death as rapidly and strongly in the eye removed after an intravenous injection of 50 mgms. of atropine as in the control removed before. There was no evidence, therefore, that atropine diminished the power of the contractile substance in the denervated sphincter or altered its excitability so far as the products of dyspnœa were concerned.

But atropine, though it did not affect the contractility of the denervated sphincter, prevented its reaction to pilocarpine or anulled this reaction (cf. Exp. 3). Marshall[6] has recently discussed in this *Journal* the reasons against regarding the antagonism between the two drugs, merely as a chemical neutralisation. Indeed atropine prevents the reaction to pilocarpine so long that this fact alone seems to prove a combination of the atropine with the tissue or with some substance in it. For example, atropine may combine with some substance in the denervated sphincter as CO combines with hæmoglobin, or so may prevent or annul the combination of this substance with pilocarpine

[1] A similar result was obtained by Schiff after section of the oculomotor nerve on one side. *Beitr. zur Physiol.* III. p. 97. 1868.

[2] Anderson. This *Journal*, XXXIII. pp. 161 and 172. 1905.

[3] Magnus (*Pflüger's Archiv*, CVIII. p. 14. 1905) has also shown that the muscle of the gut may come to rest after atropine either with a high or with a low tone.

[4] Ulrich. *Archiv f. Ophthal.* XXVIII. p. 255. 1882.

[5] Placzek. *Virchow's Archiv*, CLXXIII. p. 197. 1903.

[6] Marshall. This *Journal*, XXXI. p. 141. 1904.

as CO prevents the combination of hæmoglobin with oxygen. It is possible that atropine does not act on the same substance as pilocarpine does, but that it introduces a block between it and the contractile portion of the sphincter by acting on yet another substance. But there is nothing, so far as I know, against the view that both drugs act on the same substance and this view is simpler—I, therefore, adopt it.

But even this simpler view demands the presence of three biochemically distinct substances in the normal sphincter (1) the contractile substance excited by the products of dyspnœa and not paralysed by atropine, (2) the substance excited by pilocarpine and paralysed by atropine, (3) the substance excited by physostigmine, but unlike (2), lost after degenerative section of the short ciliary nerves.

The nature of the nerve ending.

Brodie and Dixon[1] have recently defined the nerve ending as "the connecting link between the nerve fibre and muscle fibre." "This," they say, "is not necessarily a constituent part of the muscle fibre nor yet of the nerve fibre.... It can exist only when nerve fibres join on to the muscle but it does not necessarily follow that it should degenerate when the nerve fibre which terminates in it degenerates." They, therefore, say that adrenalin acts on the nerve ending even in denervated muscle.

Elliott[2] also says, "that part of the myo-neural junction which is irritable by adrenalin is on the muscular side in so far as its trophic centre lies in the muscular nucleoplasm. But though its parent is the muscle, it would not have been called into existence had it not been for the developing union with a sympathetic nerve cell."

Both these views agree, therefore, in placing the substance reacting to adrenalin under the influence of the muscle. Yet they attribute its primary origin to the influence of a nerve cell, which according to Elliott must belong to the sympathetic system.

If nerve and muscle finally merge in a common substance, this may be a myoneuroplasm having two trophic centres and changeable to a myoplasm after loss of the neuronic trophic centre—on this view physostigmine may be supposed to excite the myoneuroplasm but not the myoplasm, or to combine with some substance formed by the former but not by the latter. Equally plausible explanations of the

[1] Brodie and Dixon. This *Journal*, xxx. p. 494. 1904.

[2] Elliott. This *Journal*, xxxii. p. 436. 1905.

actions of this drug may, however, be given even on the strict neurone theory assuming the myoplasm and neuroplasm to be merely contiguous in the myoneural junction and physostigmine to act on the neuroplasm only or on some substance in it.

But whatever view is held as to the nature of the connection between nerve and muscle it seems inadvisable to use the expression nerve-ending to denote the whole myo-neural junction, because 'an action on the nerve ending' has long been defined physiologically as an action which persists after simple, but not after degenerative, section of the motor nerves. It is true, that my observations show that pilocarpine acts on a portion of the sphincter muscle which is not the contractile substance itself. If, therefore, the portion of the muscles excited by these drugs is to be included in the myo-neural junction, it is necessary to say that part of the myo-neural junction persists. But if this view is to be adopted, it will be well to adopt some new term to denote the myo-neural junction so defined. Possibly the word myoneure might be used.

On the trophic action of the ciliary ganglion upon the sphincter.

In two cats I noticed an outgrowth from the edge of the iris at one point about 6 months after denervation of the sphincter and removal of the superior cervical ganglion. This outgrowth was filamentous and about 1 mm. long, and may have indicated a loss of the trophic influence of the nervous system. But experimentally, I found that the sphincter a year after denervation responded to drugs and dyspnœa even more vigorously than the control (cf. Exp. 17), and there was no evidence of the onset of permanent contracture in the sphincter even 9 months after its denervation in Exp. 16.

On the other hand, in several experiments (cf. Exps. 6, 13, 17) tone returned to the sphincter after regeneration of the post- or præ-ganglionic tract although no impulses passed by the regenerated nerves either in response to light or to direct stimulation of the fibres. The regenerated nerves, therefore, exercised a trophic influence upon the sphincter before they allowed the passage of motor impulses under normal conditions.

For this reason, it seems premature to assume because certain muscles do not contract on stimulation of the nerves likely to innervate them, that these muscles are not connected with the nervous system. They

may be connected trophically with the nervous system but the nerves may not develope beyond the stage of development attained by the regenerating fibres in my experiments, and may therefore not respond to direct stimulation.

Summary.

After section of an oculomotor nerve within the skull, pilocarpine constricts the paralysed pupil more than the control but physostigmine constricts it less. Both drugs, however, constrict it for a longer time.

After degenerative section of the short ciliary nerves physostigmine does not stimulate the denervated sphincter, but pilocarpine excites it to an increased and abnormally prolonged contraction. Physostigmine acts, therefore, only on the nerve ending, but pilocarpine can act on the sphincter muscle itself.

After imperfect regeneration of an oculomotor nerve physostigmine restores the light reflex when it is not to be detected under normal conditions, but pilocarpine does not. Physostigmine does not increase the excitability or conductivity of the ciliary nerves or ganglia, or of the oculomotor fibres even when they are regenerating. The action of physostigmine shows, therefore, that the impulses imperfectly transmitted by the regenerating oculomotor fibres are blocked chiefly in the ciliary nerve endings.

Several weeks or months after removal of the ciliary ganglion and of the ciliary nerves with the accessory ciliary ganglia, the denervated sphincter begins to respond again to physostigmine. There is no return of the light reflex in such experiments and the 'ciliary' nerves do not respond to stimulation under normal conditions. Yet the renewed response is due to regeneration. This is shown (1) by the gradual and at first local return of the response, (2) by its longer absence after more complete removal of the ciliary nerves, and (3) by its second disappearance after a second section of the ciliary nerves. The exact nature of the regeneration is uncertain.

The expenses connected with these experiments have been chiefly defrayed by a grant received from the Government Grant Committee of the Royal Society.