# The Paradoxical Action of Adrenaline on the Pupil of the Eye in Animals after repeated Treatment with that Drug.

By

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Recently during an investigation of the stimulation of sympathetic nerves, we accidently noticed that some very dilute solution of adrenaline under certain conditions gives rise to a constriction instead of a dilatation of the eye-pupil and carried out several series of experiments chiefly on cats to ascertain the conditions causing this phenomenon. The results of this investigation are briefly described in this paper.

I. The injection of a solution of adrenaline, diluted to a certain degree, into a carotid in cats, which have previously been treated with daily subcutaneous administrations of adrenaline for some weeks, is followed by a dilatation of the pupil on the side, where the injection was made.

We performed 9 experiments as regards this fact using Takamine's adrenaline chloride and always obtained coincident results without any exception. The cats were treated once daily with subcutaneous injections of 1 ‰ solution of adrenaline in a dose of 0·1—0·2 c.c. per kilogramme body weight, and after 3 weeks were subjected to the experiment. The animals were anaesthetised first with ether for the purpose of tracheotomy, anaesthesia being afterwards maintained by alcohol-chloroform-ether mixture. Having cut the cervical sympathetics on both sides, we now very slowly at the uniform rate of 1 c.c. in 60 seconds injected 1 c.c. of very dilute

solution of adrenaline at a temperature of body warmth into the carotid with a very thin syringe needle. The solution must be prepared freshly every time just before being used with saline. Now when 1 c.c. of adrenaline solution in a dilution of 1 : 2,000,000—1 : 500,000 is given, the injection is promptly followed by the constriction of the pupil on the side corresponding to the injected carotid, which usually continues for about one or two minutes. In a concentration greater than 1 : 300,000 it gives rise to the ordinary dilatation of the pupil, and in 1 : 300,000—1 : 500,000 it results occasionally in primary transient constriction followed by dilatation.

*Examples of experiments :* (1) Cat, 1460 grms.

From Jan. 7 to Jan. 31, 1917 daily hypodermic injection of 0·25—0·3 c.c. adrenaline (1 : 1,000).

Feb. 2, 1917. Ether. Tracheotomy. A.C.E. Carotid on each side of the trachea isolated from the vagus. A cannula inserted in the right jugular vein. Both cervical sympathetics cut.

2.05. P.M. 1 c c. adrenaline 1 : 5,000,000 in 60 secs. into the left carotid injected. The pupil does not move.

2.07. 1 c c. adrenaline 1 : 5,000,000 into the right carotid injected. No pupillar movement.

2.15. 1 c.c. adrenaline 1 : 1,000,000 into l. carotid. Towards the end of injection marked constriction of the left pupil lasting for 35 secs. began.

2.41. 1 : 2,000,000 into r. carotid. Intense constriction of the right pupil for 75 secs.

2.47. 1 : 500,000 into r. carotid. Very distinct miosis of the right pupil for 85 secs.

2.55. 1 : 100,000 into r. carotid. Vigorous dilatation of the right pupil for 95 secs.

3.30. 1 : 300,000 into r. carotid. Slight constriction of the right pupil for 55 secs., followed by dilatation.

3.45. 1 : 150,000 into l. carotid. Marked dilatation for 40 secs.

3.57. 1 c.c. adrenaline 1 : 1,000,000 injected into the jugular vein. No effect on the pupil.

3.59. 1 c.c. adrenaline 1 : 100,000 intravenously. No effect.

4.03. 1 c.c. adrenaline 1 : 10,000 intravenously. Slight dilatation of pupils.

Thus, a dilution of adrenaline between 1 : 500,000 and 1 : 2,000,000 provokes constriction of the pupil, while a concentration of 1 : 300,000 gives rise to a slight temporary diminution of the pupil followed by marked enlargement.

(2) Cat, 2210 grms.

From April 25, 1917 until May 14, 1917 successive subcutaneous injection of 0·2 c.c. adrenaline (1 : 1,000) once every day.

May 14, 1917. Body weight reduced to 1600 grms. Ether. Tracheotomy. A.C.E. Both carotids prepared for injection.

3.07. 1 c.c. adrenaline 1 : 3,000,000 into r. carotid. No movement of the pupil.

3.17. 1 : 2,000,000 into r. carotid. Marked constriction of pupil continuing for 25 secs.

3.26. 1 : 1,000,000 into l. carotid. Marked constriction for 65 secs.

3.37. 1 : 500,000 into l. carotid. Slight constriction for 5 secs., afterward distinct dilatation lasting for 40 secs.

3.50. 1 : 300,000 into r. carotid. Marked dilatation for 75 secs.

4.05. 1 : 2,000,000 into l. carotid. Constriction for 24 secs.

4.15. 1 c.c. adrenaline 1 : 500,000 into jugular vein. No effect on pupils.

4.17. 1 c.c. 1 : 100,000 into jugular vein. Slight dilatation for 25 secs.

4.25. 1 c.c. 1 : 250,000 intravenously. No effect.

If the treatment of animals with daily successive hypodermic administration of 0·1—0·5 c.c. adrenaline per kilogramme is continued for 3 to 5 months previously, then no change of the pupillar size occurs on the arterial injection of adrenaline in a concentration weaker than 1 : 300,000 ; in most cases the pupil constricts first on the injection of 1 : 300,000 and is enlarged by a concentration stronger than 1 : 200,000. Thus :

*Experiment.* Cat, 1770 grms.

From Oct. 16, 1917 to Jan. 18, 1918 0·2 c.c. adrenaline, and from Jan. 19, 1918 to March 23, 1918 0·4 c.c. every day subcutaneously injected.

March 23, 1918. 2100 grms. Ether. Tracheotomy. A.C.E. Insertion of cannula into the right jugular vein. Preparation of both carotids.

11.15. 1 c.c. adrenaline 1 : 500,000 into r. carotid. No effect on pupil.

11.33. 1 : 100,000 into r. carotid. Dilatation of pupil for 18 secs.

11.48. 1 : 300,000 into r. carotid. Marked constriction of the right pupil for 75 secs.

As is seen in some of the above described experiments, the intravenous administration of adrenaline in animals, previously treated with repeated adrenaline injection, exhibits no paradoxical action whatever be the dilution. But this action sometimes occurs when a diluted adrenaline solution is injected into the subconjunctival tissues of the eye-ball. For example, a cat, which has previously been treated for 10 days with hypodermic injections of 0·3 c.c. adrenaline per kilo, showed slight constriction of the pupil, when 0·1 c.c. adrenaline (1 : 1,000) was slowly injected into the subconjunctival tissues, while the intravenous administration of 1 c.c. adrenaline 1 : 10,000 resulted immediately in the dilatation of the pupil, a weaker concentration having no effect upon it.

It is to be noticed that if we stimulate the cervical sympathetic of such previously treated animals with a faradic current instead of the intraarterial administration of adrenaline, there is no constriction of the pupil at any distance of the primary and secondary coils.

Further in the case of adrenaline treated animals, whose superior cervical sympathetic ganglion is removed on one side, there is no paradoxical action of the adrenaline on the pupil on the intraarterial administration of adrenaline at any dilution, if sufficient time after the operation has elapsed, while on the other side, where previously the cervical sympathetic only has been cut, a marked constriction of pupil follows the injection of the adrenaline into the carotid of this side. Probably, the constriction of the pupil on the ganglionless side after the injection of dilute adrenaline is counteracted by Meltzer's paradoxical dilatation of pupil.

*Examples of experiments:* (1) Cat, 3560 grms.

May 2, 1917. Under ether narcosis the right superior cervical sympathetic ganglion was removed and the left sympathetic nerve cut. From April 11, 1917 until July 15, 1917 0·4 c.c. adrenaline once every day hypodermically injected and further again from March 16, 1918 until March 29, 1918 0·8—1·0 c.c. adrenaline similarly administered.

March 30, 1918. 4250 grms. Ether. Tracheotomy. A.C.E. Preparation of carotid on both sides. Cannula in right jugular vein. The left pupil a little larger than the right.

11.23. 1 c.c. adrenaline 1 : 500,000 in left carotid. No effect on pupil.

11.32. 1 : 300,000, left. Very distinct constriction of the left pupil for 2 mins. 26 secs.

11.37. 1 : 300,000, right. Marked dilatation of the right pupil for 3 mins. 35 secs.

11.44. 1 : 2,000,000, right Very marked dilatation of the right pupil for 1 min. 15 secs.

11.52. 1 : 5,000,000, right. No effect.

12.00. 1 : 3,000,000, right. No effect.

12.15. 1 : 2,500,000, right. No effect.

12.21. 1 : 2,000,000, right. Dilatation for 1 min. 30 secs.

12.25. 1 c.c. 1% atropine sulphate intravenously administered. Immediately the right pupil almost maximally, the left less widely dilated.

12.34. ½ c.c. adrenaline 1 : 300,000 into the right carotid. Dilatation of the right pupil for 15 secs.

12.41. 1 c.c. adrenaline 1 : 500,000, right. No effect.

12.46. 1 c.c. 1 : 400,000, right. No effect.

12.52. 1 c.c. 1 : 300,000, right. Dilatation.

(2) Cat, 2160 grms.

April 14, 1918. Removal of the right superior cervical sympathetic ganglion and resection of the left cervical sympathetic nerve. From July 1 until July 31, 1918 1·0 c.c. adrenaline once every day hypodermically injected.

July 30, 1918. 2100 grms. Left pupil moderately wide, right very large. Tracheotomy. A.C.E. Preparation of both carotids. Cannula in left jugular vein.

10.59. 1 c.c. adrenaline 1 : 500,000 into the left carotid. Constriction of the left pupil for 25 secs.

11.00. 1 : 300,000, left. Dilatation of the left pupil for 45 secs.

11.02. 1 : 1,000,000, right. Dilatation of the right pupil for 3 mins. 40 secs.
11.10. 1 : 2,000,000, right. No effect.

It is noteworthy that as some experiments show, the pupil, which is moderately widely dilated through the injection of a small dose of atropine, cannot be constricted by any dilution of adrenaline.

II. Similar experiments as described under I were performed on 11 animals, which have not previously been treated with repeated adrenaline injection and in most cases no paradoxical action of adrenaline on the pupil was observed. The intracarotid injection of adrenaline stronger than 1 : 500,000—1 : 1,000,000 resulted in the dilatation of the pupil. Only in two animals did we observe constriction of the pupil at 1 : 1,000,000—1 : 300,000 and dilatation at stronger concentration than 1 : 300,000.

In animals previously treated with repeated adrenaline injections (and also in normal cats, which exhibit the paradoxical action of the drug) the concentration of adrenaline necessary to dilate the pupil is greater than that for normal animals. In them 1 c.c. of adrenaline 1 : 300,000—1 : 200,000 is to be injected into the carotid in order to dilate the pupil, while in normal animals the concentration 1 : 1,000,000—1 : 500,000 is sufficient.

III. It is generally accepted that in cats the instillation of adrenaline never causes dilatation of the pupil. We instilled twice 5 drops of adrenaline into the conjunctival sack of 43 cats at an interval of 5 minutes and noticed no change in the size of the pupil in all but two, where slight constriction of the pupil was provoked. But in animals treated as above described with daily successive hypodermic adrenaline injections, after one, or sometimes as many as three weeks, from the beginning of the adrenaline injection such instillation of adrenaline is generally after half an hour to one hour followed by constriction of the pupil, which is most marked in 1½–2 hours and continues for 7 or more hours. If considerable constriction occurs, it is still after 24 hours demonstrable. We made this series of experiments on 35 cats and got positive results in all cases except one.

IV. If we treat the animals with daily successive instillations of adrenaline instead of hypodermic injections for one or two, or sometimes for seven weeks, dropping into the conjunctival sack every day 5 drops of adrenaline twice over at an interval of 5 minutes,

the instillation of adrenaline causes in 2 hours a slight constriction of the pupil which continues for 5—8 hours. In the eye on the side, which has not previously been treated, no miosis occurs. In all experiments of this sort, which numbered 13, the instillation into the previously treated eye was always followed by more or less demonstrable, though not distinct, constriction of the pupil. Some of them showed a trace of permanent miosis about one week after the beginning of daily instillation.

V. In those animals, whose eye on one side has been treated during some weeks with daily successive instillations of adrenaline as above described, the instillation of 2% solution of cocaine (twice 5 drops in 5 minutes) into the conjunctival sack of both eyes provokes on the side previously treated with adrenaline instillation a considerable, more striking dilatation of the pupil within half an hour than on the non-treated side. We can get also in the eye previously treated with adrenaline instillation a dilated effect with pituitrin. The mydriasis begins after the instillation of pituitrin in 2 hours, reaches the maximum in about 2 hours and continues for some hours. Special attention is to be paid to the fact that the instillation of physostigmine (0·5%) into both eyes in the exactly same drops causes a much less strong constriction of the pupil on the side previously treated with repeated instillation of adrenaline than on the non-treated side.

*Examples of experiments:* (1) Cat, 2050 grms. Daily instillation of 0·1% adrenaline, twice 5 drops in 5 minutes, into the right conjunctival sack from March 7, 1917 on.

May 30, 1917. Both pupils equally large. At 8 h. 20 mins. instillation of 0·5% physostigmine salicylate (Merck), exactly 4 drops on both sides.

After 10 mins. on both sides miosis, right pupil slightly larger.

After 25 mins. both-sided miosis, but the right pupil very markedly larger than the left.

After 6 hours the difference of pupils still distinct.

After 10 hours the difference of pupils still demonstrable.

(2) Cat, 1700 grms. Daily instillation of adrenaline on the right side from May 18, 1917 on.

June 25, 1917. The size of both pupils equal. At 11 h. 50 mins. A.M. exactly 4 drops of 0·5% solution of physostigmine in both eyes.

After 10 mins. miosis, right pupil a little larger?

After 70 mins. the right pupil distinctly larger.

After 7 hours the difference still demonstrable.

All the experiments above described were performed with the

0·1% solution of adrenaline chloride Parke-Davis. We have proved that the solution of suprarenin syntheticum Hoechst freshly made with diluted hydrochloric acid has the same results.

It has been recently pointed out by some investigators that adrenaline in minute doses may have a paradoxical effect upon the blood vessels. Already in 1900 Moore and Purington[1] observed that extracts of adrenal tissue cause a fall of blood pressure, which is however attributed by Pari[2] to the chemical change in the extracts, and by Vincent[3] to the common action of tissue extracts, while later Hoskins and McClure[4] demonstrated the same paradoxical phenomenon with adrenaline. Elliott[5] believes that the lowering of blood pressure caused by exceedingly dilute solution of adrenaline is due to the stimulation of supposed sympathetic vasodilatators present in some of the blood vessels. A similar opinion is insisted on by Hartman[6]. Further evidence of depressor effect of adrenaline on arterial pressure is mentioned by Cannon and Lyman[7], who suggest the occurrence of the two opposite actions of adrenaline, vasodilatation and vasoconstriction, dependent on the state of the muscle of the blood vessels, relaxation when tonically shortened, contraction when relaxed. Ogawa[8] observed in some instances an increase of outflow from perfused legs of frogs, when a minute amount of adrenaline was added to the circulating fluid and, like Hartman, supposed the presence of vasodilatator sympathetic endings in peripheral blood vessels. Not only on blood vessels but also on intestines the paradoxical effect of the drug is noted. Thus, Hoskins[9] reports that adrenaline auguments the movement of the intestines by stimulating the metabolic process of the intestinal muscle itself when used in such a small amount as not to effect the

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1) Moore and Purington: Arch. f. gesammte Physiol. 1910, Vol. 81, p. 483.
2) Pari: Arch. ital. de Biol. 1906, Vol. 46, p. 218.
3) Vincent: Internal secretion and the ductless glands, London 1912, p. 174.
4) Hoskins and McClure: Arch. Internal Medicine. 1912, Vol. 10, p. 353.
5) Elliott: Journ. Physiol. 1905, Vol. 32, p. 412.
6) Hartman: American Journ. Physiol. 1915, Vol. 38, p. 438.
7) Cannon and Lyman: American Journ. Physiol. 1913, Vol. 31, p. 371.
8) Ogawa: Arch. f. exp. Path. u. Pharm. 1912, Vol. 67, p. 89.
9) Hoskins: American Journ. Physiol. 1912, Vol. 29, p. 363.

myoneural junction. As to reversed action of adrenaline on the pupil, Elliott[1] alone observed in the dog and goat, but not in the cat, constriction of the iris on the intravenous injection of adrenaline and attributed it to the central stimulation of the cranial third nerve, probably due to the increased intracranial pressure. Whilst there is such a divergence of opinions concerning the mechanism of the paradoxical action of adrenaline Biedl[2], Vincent[3] etc. assert that they have not seen the reversed effect of adrenaline in a minimal quantity on arterial tension at all. It is here noteworthy that Falta and Kahn[4] remarked in parathyrectomized dogs a lessening of blood pressure after intravenous administration of a small amount of adrenaline and suggest the hyperexcitability of myoneural junction reacting against sympathicotropic stimulus in such animals. There is also the well known finding of Dale[5], that by previously administering ergot adrenaline causes vasodilatation due to the paralysis of motor sympathetics.*

Now the difficulty exists in the explanation of the mechanism of the paradoxical effect of adrenaline upon the size of pupils observed by us, especially in animals previously treated with repeated injections or instillations of this drug. It is quite obvious that the action is of peripheral origin, the miosis occuring only on the administered side, and in the lack of the evidence that adrenaline in small quantities may stimulate the parasympathetic nerve endings, we cannot attribute our paradoxical action to the nervous stimulation of the sphincter iridis. Furthermore, the presence of inhibition from cervical sympathetic ganglion to the dilatator of the pupil or of the sympathetic innervation of the sphincter, which might be stimulated by adrenaline, is very doubtful and, if such be allowed, there is no reason why these fibres alone are so specially sensitive to

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1) Elliott: l.c. p. 417.
2) Biedl: Innere Sekretion. Berlin & Wien 1913. 2nd ed.
3) Vincent: l.c.
4) Falta and Kahn: Zeitschr. f. klin. Med. 1911, Vol. 74. p. 108.
5) Dale: Journ. Physiol. 1906, Vol. 34, p. 163.

* After our paper was written, Cow's work "Adrenaline and Pituitrin, a study in Interaction and Interrelation" was published (Journal of Physiology, 1919, Vol. 52, p. 301). He found that the uterus both of the guinea pig and the cat, which has previously been treated with pituitrin, responds to adrenaline in the reversed way.

a minute quantity of adrenaline. It is highly probable that the reversed action of adrenaline on the pupil is due to the altered chemism in the dilatator caused by adrenaline as Cannon and Lyman[1] suggested regarding the plain muscles of the blood vessels, especially in muscles previously treated with repeated administrations of it. In muscles sympathetically innervated, some chemical change takes place on administration of minute doses of adrenaline, which results in relaxation of the fibres and yields to the constricting tonus of the spincter, while a little greater amount sufficient to stimulate the myoneural junction of the sympathetics gives rise to the dilatation of the pupil. The previous treatment of cats with repeated injections of adrenaline raises the threshold for the stimulation of the myoneural junction by adrenaline and gives an arena, so to speak, to the direct chemical response of muscles to the small quantity of adrenaline, thus inducing constant occurrence of the paradox in such animals.

## Summary.

(1) In cats, which were previously treated with daily successive hypodermic injections of adrenaline for some weeks, the administration of a minute quantity of adrenaline into the carotid gives rise to constriction of the pupil, while by intravenous injections no such paradoxical effect is obtained. This reversed action cannot be imitated by electric stimulation of the cervical sympathetic nerve. It fails also after removal of the superior cervical sympathetic ganglion.

(2) In the pupil of such treated animals constriction is usually observed after the instillation of adrenaline.

(3) The paradoxical action of adrenaline on the pupil occurs only rarely in animals previously not treated with repeated administrations of adrenaline.

(4) In animals previously treated daily for some weeks with successive instillations of adrenaline instead of hypodermic administrations the instillation of adrenaline is always followed by weak miosis lasting for 5–8 hours. The instillation of cocaine or pituitrin provokes distinct mydriasis in the previously treated eye and of

1) Cannon and Lyman: l.c.

physostigmine less marked miosis in the eye on this side than in that on the non-treated side.

(5) The paradoxical action is based probably on the altered chemism of the dilatator muscles of the pupil.