On the mydriasis produced by the local application of cocaine to the eye / by Walter H. Jessop.

C

L. Rettleship Esq^re F.R.C.S.

with the Author's kind regards.

Action of Cocain

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"On the Mydriasis produced by the local Application of Cocaine to the Eye." By WALTER H. JESSOP. Communicated by Dr. LAUDER BRUNTON, F.R.S. Received June 4, 1885.

In a paper on "Cocaine," published in the "Practitioner" of January 1, 1885, and more fully in a paper on "The Cocainised Eye," before the Ophthalmological Society on January 8th, 1885, I mentioned most of the clinical facts concerning the drug and its action that had then come under my own investigation and treatment.

The object of this paper is to try and elucidate one of these facts, namely:—The cause of the mydriasis accompanying the application of cocaine to the eye. This research has been made chiefly on human and rabbits' eyes by conjunctival instillation, and on rabbits' eyes by experiments detailed below. The salt of cocaine used has been the hydrochlorate obtained from Merck, of Darmstadt; the strength of the solutions 2, 4, and 20 per cent., and these solutions have been used fresh to avoid any changes by the growth of fungi, &c. By means of a syringe the quantity of the solution used each time has been as nearly as possible 1 minim. The pupil has been measured by a Nettleship's pupillometer, or by means of a graduated thread, which could be easily placed across the cornea. During each experiment the subject was exposed as far as possible to the same light, so that the differences in size of the pupils should be as exact as possible.

The experiments on animals have been made strictly under the influence of chloroform, and in animals allowed to live after such experiments strict antiseptic precautions have been taken, so that apparently they scarcely suffered except from the after effects of the chloroform, the wounds being slight and quickly healed.

If only one measurement of the pupils of rabbits is given it is the transverse one.

Experiment I.

Starting first with the action of cocaine on the eye by conjunctival instillation, I found as the result of over one hundred observations on the human eye the following facts:—

The mydriasis is quickly attained and very large, and differs also from atropine in the pupil acting always to light and accommodation.

When the mydriasis is extreme, viz., 10 mm., the movement to light is very slight, and the initial contraction can only be seen by magnifying the pupil by the observer's putting on a pair of +5D spectacles. The slight contraction is immediately followed by a recoil which almost induces the belief that a dilatation has taken place.

The continuance of the mydriasis is comparatively short, the pupil attaining its normal size in from twelve to twenty-four hours. By drying the conjunctiva and cornea and placing the cocaine carefully on a limited part, the dilatation of the pupil will at first only take place at that spot, thus rendering the pupil irregularly dilated, and showing the limited action of the drug.

The following cases show the main points in the mydriasis of cocaine, and that the stronger the solution the quicker the initial and *ad maximum* dilatation.

I. H. C., 15. Pupils $6\frac{1}{2}$ mm.; cocaine 4 per cent. on right eye at 2.5 P.M.; at 2.25 P.M. pupil 10 mm., not further increased. The pupil had resumed its normal size twelve hours afterwards.

II. W. H., 30. Pupils 5 mm., cocaine 20 per cent. in left eye; in seventeen minutes pupil 8 mm., and other instillations did not increase its size.

Pupil regained its normal size ten hours afterwards.

III. E. W., 31. Pupils 5 mm., at 11.20 cocaine 2 per cent., at 11.30 cocaine 2 per cent., and at 11.50 pupils 8·5 mm.

Fourteen hours afterwards pupil normal size.

In rabbits the mydriasis induced by cocaine is, as a rule, very large, and in two cases I could not make out any action to light, but in both the pupil was 11·5 mm.; and the reason probably was the great stretching of the sphincter muscle of the pupil incapacitating its action; mydriasis was induced by conjunctival instillation, and also by injection into the anterior chamber.

Experiment II.—Cocaine and Atropine.

In cases of full cocaine mydriasis the application of atropine had no effect on the size of the pupil, but stopped its action to light and accommodation.

F. M., 25. Pupils 5·5 mm.; two instillations of cocaine 2 per cent. in right eye; pupil 9·5, acting to light and accommodation; atrop. sulph. $\frac{1}{5000}$ grain, no increase in size of pupil, although atropine put in three times, but the pupil did not act to light and accommodation.

Experiment III.—Atropine and Cocaine.

On adding cocaine to an eye fully under the influence of atropine,

an increase in the mydriasis occurs very quickly. The increase does not act to light or accommodation.

A. G., 16. Under atropine (4 grains to the ounce three times a day for ten days), both pupils 9 mm. and equal, not acting to light or movements of accommodation. In left eye cocaine 4 per cent., and in fifteen minutes pupil 10 mm.

In one case, however, in which atropine had been used for two months continually, the pupil was very much dilated, 10·5 mm., and here cocaine had no effect, the pupil being at its *ad maximum* dilatation.

F. G., 17. Has been using atropine for two months; pupils equal, regular, 10·5 mm., there being a very thin ring of iris visible; five applications of cocaine 4 per cent. in right eye, and no effect on the size of pupil.

The results of these two experiments led me to make a mixture of the two drugs, and by it an *ad maximum* dilatation of the pupil can be soon produced, which will not soon disappear like cocaine mydriasis.

The good effects of this in iritis were pointed out by me last January, and since have been fully sustained by increased experience.

E. G., 6. Pupils 5 mm., equal, act well to light and accommodation; at 2.24 P.M. a gelatine disk (of cocaine $\frac{1}{100}$ grain and atropine $\frac{1}{5000}$ grain) put on left cornea; at 2.29 P.M. no effect on pupil, slight drooping of lower lid.

2.34 P.M., pupil 9 mm. when shaded, 6 mm. in light, or on accommodating.

2.40 P.M., pupil 10 mm., acting slightly to light and accommodation.

2.42 P.M., pupil 11 mm., does not act to light and accommodation.

In this case, then, in eighteen minutes we had an *ad maximum* dilatation of the pupil. To test the difference in time between this and the action of the same quantity of atropine alone, the next experiment was done. This shows that in eighteen minutes no effect was noted on the pupil, and that in thirty-six minutes the pupil was only 9 mm., and the greatest dilatation attained was 9·5 mm.

E. G., 6. 2.46 P.M., right eye, pupil 5 mm., atropine disk $\frac{1}{5000}$ grain.

2.58 P.M., no effect.

3.4 P.M., no effect.

3.17 P.M., pupil 8 mm., does not act to light or accommodation.

3.22 P.M., pupil 9 mm.

3.45 P.M., pupil 9·5 mm., and did not increase.

Experiment IV.—Cocaine and Eserine.

The action of eserine on cocaine mydriasis was to induce myosis very easily. The myosis resembled that due to eserine alone.

On investigating more carefully I found that on taking 2 per cent.

solutions of each drug, and mixing them in the proportion of 25—28 of cocaine and 1 of eserine, the normal size of the pupil was unchanged.

J. G., 22. Pupils regular, equal, 6 mm.; 4 instillations of solution of cocaine and eserine (27 : 1) in right eye. Pupil afterwards regular, 6 mm.

Experiment V.—Cocaine and Pilocarpine.

The action of pilocarpine was to induce myosis easily.

On trying mixtures of the drugs I found that 4 of cocaine and 1 of pilocarpine, each 2 per cent. solution, had no effect on the normal pupil.

A. W., 23. Pupils regular, equal, 5 mm., left eye pilocarpine, 2 per cent. on conjunctiva, bringing pupil to 2·5 mm.; 4 instillations of cocaine, 2 per cent., brought back pupil to 5 mm.

J. B., 30. Pupils regular, equal, 5 mm.; 3 instillations of cocaine and pilocarpine (4 : 1) had no effect on pupils.

The importance of these combinations I have utilised, especially that of pilocarpine and cocaine, for keeping the pupil a normal size during the operation of iridectomy, when anæsthesia has to be induced by cocaine. The objection to the dilated pupil is that it keeps dilated both during and after the operation, and so may become prolapsed afterwards, especially in glaucoma cases; also if a tolerably large conjunctival flap has been made the iris may disappear under it, and so become difficult to catch hold of, if iridectomy is to be performed. This combination does not prevent the local anæsthesia of cocaine. The antagonism between eserine and pilocarpine on the one hand, and cocaine on the other, gives us a means of estimating the relative power of pilocarpine and eserine on the pupil.

Experiment VI.

Cocaine increases the mydriasis produced by section of the 3rd nerve.

Experiment VII.

The effect of section of the 3rd nerve on a pupil dilated by cocaine stops its action to light and accommodation, but does not increase the size of the pupil.

Experiment VIII.

On stimulation of the 3rd nerve the mydriasis induced by cocaine easily and quickly gives place to myosis.

A. B., 29, suffering evidently from syphilitic mischief, probably gummatous, implicating the right 3rd nerve, and producing complete ptosis, external strabismus, inability to move the eye up, down, or in, diplopia, loss of accommodation and mydriasis.

Right pupil, 6 mm., does not act to light or accommodation.

Cocaine, 2 per cent., twice applied, and pupil 9·5 mm.

Black and White Rabbit.—Pupils 5·5 mm. × 6·5 mm., and act well. Skull cap removed, and 3rd nerves exposed. Right 3rd nerve cut; pupil = 6·5 mm. × 7·5 mm.; nerve then irritated by faradaic current, and pupil 3 mm. × 2 mm. Cocaine 2 per cent. twice put on right conjunctiva, and pupil dilated soon to 8·5 mm. × 7 mm., and then to 10 mm.

A weak stimulation of the 3rd nerve overcame the mydriasis, producing the same myosis as before whilst the stimulant lasted, and giving rise again to mydriasis.

Experiment IX.

On tapping the anterior chamber of an eye under the influence of cocaine, the dilated pupil contracts very little or not at all. This is, of course, contrary to what occurs in a normal eye, or in one under atropine, where marked contraction of the pupil occurs in all cases.

Experiment X.

On tapping the anterior chamber of a rabbit, and placing one electrode on the surface of the iris towards the centre, a weak faradaic current gave rise to contraction of the pupil in all cases of cocaine mydriasis, except two, in which very large mydriasis had been produced.

These latter, however, could be explained by the great stretching of the sphincter muscle, and hence stimulation directly of the fibres had no effect.

Experiment XI.

On the detruncated head of a frog the application of cocaine to the conjunctiva I have generally seen followed by mydriasis, a fact also seen independently by Dr. Waller, to whom I must express my thanks for numerous suggestions, and much help in my experiments. In my first case and two others I failed to get any effect on the pupil.

Experiment XII.

On the exsected eye of rabbits I have tried several times, with failure, to increase the size of the pupil by cocaine. In two cases, on injecting cocaine into the anterior chamber immediately after exsection, the contraction of the pupil due to tapping soon passed off, and the pupil became slightly larger than before tapping.

Experiment XIII.

On the eyes of rabbits which have been bled to death, cocaine gives rise to an increase in the mydriasis produced by the effect of the hæmorrhage

Brown and White Rabbit.—Pupils 7·5 mm. × 6 mm.; right cervical sympathetic exposed and cut, very slight change in pupil; animal bled to death from ascending aorta in two minutes; pupils after death, right 7·5 mm., left 9·5 mm.; right sympathetic irritated by current, and pupil 10·5 mm.; 10.53, cocaine 4 per cent. twice to both eyes; 11.7, right eye pupil 9 mm., left eye pupil 10·5 mm.

In several experiments on the influence of cocaine on the mydriatic nerve which is to be found in the sympathetic accompanying the carotid in the neck, the following were the chief results:—

Experiment XIV.

On exposing the cervical sympathetic as it runs in proximity to the common carotid, cutting it and adding cocaine, dilatation of the pupil occurred in all cases, but less than the ordinary cocaine mydriasis, and in the first case scarcely at all.

I. Black Rabbit.—Pupils regular, equal, 6·5 mm. under chloroform; left sympathetic exposed, ligatured, cut, followed by slight contraction of pupil, and injection of vessels of ear, &c. The upper end of the nerve stimulated by weak faradaic current, and pupil 10 mm.

Right eye pupil 6·5 mm., left eye pupil 5·5 mm.; 10 A.M., cocaine 2 per cent. in both eyes; 10.8 A.M., right eye pupil 8·5 mm., left eye pupil 6 mm.

Cocaine 2 per cent. twice more in each eye; 11 A.M., right eye pupil 9·5 mm., left eye pupil 6·5 mm.

II. White Rabbit.—Pupils regular, equal, 6·5 mm. under chloroform; right sympathetic exposed, ligatured, cut; pupil afterwards 5·5 mm. On stimulation by weak faradaic current, pupil 10 mm.; 12.54 P.M., right eye pupil = 5·5 mm., left eye pupil 6·5 mm. Cocaine 2 per cent. twice on conjunctiva on each eye; 1.18, right eye 8 mm., left eye 9 mm.; 1.30, right eye 8 mm., left eye 10 mm.

Experiment XV.

On adding cocaine and producing mydriasis, subsequent section of the cervical sympathetic had no effect on the mydriasis, even when an *ad maximum* dilatation was produced.

Brown and White Rabbit.—Pupils 5 mm. × 6 mm. under chloroform; 10.35 A.M., left eye, cocaine 2 per cent.; 10.55 A.M., after three instillations of cocaine, left pupil 8 mm. × 7 mm.; 11.20, after five instillations of cocaine, left pupil 10 mm.

Left cervical sympathetic exposed, cut, and no effect followed on pupil, though all other symptoms of cutting the nerve.

Experiment XVI.

Cocaine mydriasis being produced, stimulation of the upper end of

the exposed sympathetic generally gave rise to an increase in the dilatation of the pupil.

On, however, carefully considering this, I found that it simply depended on the size of the mydriasis, as in cases where the *ad maximum* cocaine mydriasis was produced, stimulation of the sympathetic no longer increased it, though the strength of the current was increased. In some cases I found that the increase in the size of the pupil on stimulating the sympathetic was due to the fact that the animal was in a bright light, and therefore the pupil contracting to that light. On shading the eyes, and the pupil assuming its full dilatation, no extra effect was produced by stimulating the sympathetic.

I. Brown and White Rabbit.—Pupils 5 mm. × 6 mm. under chloroform, after five instillations of cocaine 2 per cent., left pupil 10 mm. On exposing the left cervical sympathetic, and stimulating it by faradaic current, no increase in mydriasis.

II. Brown Rabbit.—Pupils 7·5 mm. × 6 mm.; left eye, four instillations of cocaine 4 per cent., pupil 10 mm. On stimulating cut end by faradaic current, pupil 10·5 mm., being a very slight increase.

This, however, was done in a bright light, and on shading the eye, pupil 10·5 mm., and no increase no stimulating the cervical sympathetic.

Experiment XVII.

In three rabbits the cervical sympathetic was exposed, a piece taken out of it, and the wound stitched up, all the animals recovering without a bad symptom. The pupils on the operated side were contracted, but acted well to bright light.

In all, after a time, the result was the same, namely, no effect on adding cocaine, though applications often repeated, and of different strengths.

Large Brown Rabbit.—Pupils, under chloroform 9 mm. × 7 mm., act well.

Right eye, after 6 instillations of cocaine, 2 per cent., pupil 12 mm., and apparently they did not act to light.

On left side the cervical sympathetic exposed and 15 mm. of the nerve taken out, the upper end stimulated by faradaic current, and pupil became 12 mm.

The section was followed by contraction of the pupil to 7·5 mm. × 6·5 mm., and the other signs of cutting the cervical sympathetic. The wound was carefully stitched up and the animal soon recovered.

100 *Hours Later.*—Left eye, pupil oval, 6·5 mm. × 4·5 mm., but contracts well to light.

10.30, cocaine 2 per cent. on left eye.

This was repeated five times without effect, the pupil remaining the same.

Right eye, 5 instillations of cocaine, and pupil 12 mm.

Ten Days After.—Same experiment and same result.

Two Months After.—Left eye, pupil 6·5 mm. × 4·5 mm.; cocaine 4 per cent. three times, and no effect.

Right eye, same experiment, and pupil became 11 mm. The injection of the vessels of the ears, &c., still continues.

Brown Rabbit.—Pupils 7·5 mm. × 6 mm. under chloroform. Left cervical sympathetic exposed, and 10 mm. cut out, followed by dilatation of vessels of ear and slight contraction of pupil. Wound then stitched up four days after.

Left eye. Pupil: In bright light, 5.5 × 4 mm. In shade, 7 × 5·5 mm.

Right eye. Pupil: In bright light, 5·5 × 4 mm.; medium light, 7·5 × 6·5 mm.; shade, 8·5 × 7·5 mm.

2.30 P.M. Cocaine, 4 per cent., in both eyes.

2.35 P.M. Pupils the same. Cocaine, 4 per cent., repeated in each eye.

2.40 P.M. Left pupil in bright light, 5·5 × 4 mm.; in shade, 7 × 6 mm. Right pupil in bright light, 7 × 6 mm.; in shade, 10 × 10 mm.

Three other applications made, and same result.

Just as I had finished this paper I was enabled, through the kindness of Mr. Nettleship, to see a case of lesion of the cervical sympathetic on the right side, and am greatly indebted to him for allowing me to use the following notes. It will be seen that numerous applications of cocaine had not the slightest effect on the pupil.

B. P., 34. Married; for four years in bad health; seven months slight difficulty in swallowing, and slight dyspnœa; three months noticed difference in feelings of warmth on the two sides of the face —especially if excited; five months noticed pupils unequal in size, some fulness in middle of neck, but nothing definite to be felt. Little more pulsation in right carotid than in left.

V. Right : $\frac{6}{6}$: Jaeger i at 22 cm.
Left : $\frac{6}{6}$: Jaeger i at 22 cm.

Right eye. Palpebral fissure smaller than the left. Media clear and normal.

Pupil.—Regular, no iritic adhesions, acts to light and accommodation, smaller than left; when right pupil is 2 mm., left is 3·5 mm. Looking at distant objects right pupil becomes $2\frac{1}{3}$ mm., when accommodating for 15 cm. it is 2 mm., and when shaded and accommodation relaxed, 3 mm.

Left eye. Pupil normal, acts to light and accommodation; when well shaded and accommodation relaxed it is 6 mm. On taking these notes, the one-sided flushing of the face was noticed. Six instillations of cocaine, 2 per cent., in the right eye, gave rise to no alteration in the size of the pupil.

To make certain of this result, Mr. Nettleship and myself made ten days afterwards the following observations on the patient:—

In a good light. 11.15. A.M. right pupil 2 mm., left 2·5 mm.; 1 disk of cocaine $\frac{1}{200}$ grain placed in each eye.

11.18, three more disks of same strength put in each eye.

11.25, right pupil 2 mm., left 4·5 mm.

11.35, right pupil 2 mm., left 6·5 mm.

11.55, right pupil 2 mm., left 7 mm.

12.10, pupils the same; on shading them the right pupil 3 mm., left 9 mm.

On now putting homatropine into the right eye the pupil dilated regularly as in a normal eye as below:—

12.15 P.M., homatropine (4 grains to the ounce) put in right eye; pupil was 2 mm.

12.30, right pupil now 6·5 mm., and does not act to light or accommodation.

All the preceding experiments pointed to the action of cocaine being an irritant of the sympathetic or mydriatic nerve of the eye, and this fact is proved beyond a doubt by the last experiment (XVIII). Both in rabbits in which a piece of the cervical sympathetic had been excised for some days, and also in a case presenting all the symptoms of section of the cervical sympathetic, cocaine had not the slightest effect on the pupil.

That such action is local and not central is proved by the extremely local and limited action of cocaine on all the parts of the body, including the pupil (Experiment I), and by dilatation of the pupil following its application to an exsected eye (Experiment XII). That cocaine mydriasis is not in any way dependent on the 3rd nerve is shown by Experiments VI, VII, and VIII, and also by the pupil acting to light and accommodation (Experiment I). That cocaine mydriasis is not due to paralysis of the sphincter muscle is shown by the ease with which eserine, which acts directly on the muscular fibre, reduces it, producing the usual myosis (Experiment IV), and also by the fact that stimulation of the muscular fibre directly gives rise to contraction of the pupil (Experiment X).

The cases in which this contraction on direct stimulation did not take place were due probably to the overstretching of the sphincter muscle. Thus by excluding the other means of producing mydriasis we have next to consider whether we can produce the same kind of mydriasis as that of cocaine by excitation of the sympathetic.

We find that the faradaic stimulation of the cervical sympathetic which will give rise to a dilatation of the pupil, at the same time acting to the reflex of light, is very weak, as any slight increase of the current stops this reflex action of the pupil. But that the local excitation of the sympathetic by cocaine and its induced mydriasis is

also weak is shown by the ease with which myotics (Experiment IV and V) and stimulation of the 3rd nerve (Experiment VIII) overcome the mydriasis.

Therefore our facts bring us to the conclusion that cocaine mydriasis is induced by a local irritation of the endings of the cervical sympathetic or mydriatic nerve in the eye. But this nerve consists of two distinct sets of fibres—one set acting on the blood-vessels as a vaso-constrictor, and the other only producing dilatation of the pupil. That such is the case can be proved by bleeding an animal to death when, even after several excitations of the cervical sympathetic, fresh stimulation of this nerve again increases the dilatation of the pupil induced by the bloodless state of the eye. François Franck, in his able monograph "On the Dilatator Nerves of the Pupil,"* brings forward several other conclusive arguments to prove the dual action of the cervical sympathetic fibres. That cocaine acts on the small blood-vessels by constricting them can be proved easily by its action on the vessels of the conjunctiva.

We may therefore assume that it also acts thus on the vessels of the iris—a fact which accounts for the diminution of tension in an eye under cocaine. But that this is not the only cause of cocaine mydriasis is evident from the following facts, viz., that the full mydriasis of cocaine is much larger than that induced by the bloodless state of the eye, and that cocaine increases the mydriasis induced by bleeding the animal to death (Experiments XI and XIII). It is the action on the purely mydriatic fibres that gives rise for a time to dilatation of the pupil by cocaine after section of the cervical sympathetic (Experiment XV). That this action of cocaine on the purely mydriatic fibres passes off after a time is shown on rabbits by Experiment XVII, and this is due to cutting off its communication with the mydriatic centre of Budge and Waller in the spinal cord.

The reason of this happening so soon is the weak stimulus due to cocaine, and therefore a very slight change in the nerve endings being able to prevent its action. That cocaine also acts on this mydriatic nerve is suggested by the enlargement of the palpebral aperture following its application. Hence from these experiments it appears that cocaine produces mydriasis by acting locally on the endings of the cervical sympathetic nerve in the eye, and also that it affects both sets of fibres, namely, the purely mydriatic and the vaso-constrictor.

* "Travaux du Laboratoire de Marey," Années 1877-79.

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