CASE 4. D. History of gonorrhoea five years ago; no rheumatism; two attacks of iritis; cured.

CASE 5. E. History of gonorrhoea six or seven years ago; cured.

CASE 6. F. History ten years; did not improve much with vaccine treatment alone, but got quite well with massage and vaccines combined.

CASE 7. Mentioned above.

CASE 8. O. R. History of gonorrhoea 17 years ago; first attack of iritis; massage and vaccines; cured.

CASE 9. M. J. History two years; third attack of iritis in five months; cured.

CASE 10. I. M. S. History of many attacks of gonorrhoea with acute epididymitis and prostatitis; one eye practically blind as the result of many attacks of iritis, cured.

Gonococci were found in the material obtained after massage in all the above cases.

THE ACTION OF HYPOPHYSIN (PITUITRIN) UPON THE PUPIL OF THE RABBIT*

BY

W. B. INGLIS POLLOCK

GLASGOW.

Introduction

THE problem of the determination of the precise seat of action of drugs has proved one of the most difficult in the whole range of pharmacology. Especially is this the case as regards their action on visceral muscular structures. While, in the skeletal muscles, a definite fibre extends from a cell in the central nervous system to one or more muscle fibres where it ends in definite end-plates, in visceral muscles the fibre is interrupted at least once in its course, and this interruption may occur almost anywhere between the spinal cord and the muscles supplied. It is generally assumed that there is but one synapse, one cell station in each fibre, but the evidence for this is far from conclusive.

Probably the most satisfactory evidence is that afforded by the action of nicotin on the heart of the frog. The vagus endings are paralysed, but the augmentor nerves still act. Hence the conclusion is arrived at that the former have their cell station in the heart, and the latter in the stellate ganglion. But while such an experiment indicates that the greater proportion of synapses of the former are

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in the heart, and the greater proportion of the latter are extra-cardiac, it does not prove that there are no synapses outside the heart in the former, or in the heart in the latter.

The fact that in certain animals, *e.g.*, some ducks, Noël Paton¹ found that stimulation of the vagus leads to augmented action, seems to indicate that augmentor fibres stream out by the vagus as well as by the sympathetic; and Miss Abel's studies² of the emigration of the neurons of the automatic system certainly give no support to the existence of one definite synapse in the course of each fibre and suggest a much less sharply demarcated distribution, with the possibility of several interruptions.

Again, if there is but one interruption in each autonomic fibre, the excision of the seat of the interruption should cause a complete disappearance of the nerve fibres in the part supplied. On this subject few observations have been made. Fletcher³ found, after excision of the first pelvic ganglion and section of the pudic nerve of the same side that the muscular plexus in the retractor penis of the hedgehog did not stain with methylene blue. He, therefore, assumed that "the peripheral nerve endings in the muscle did disappear when a section of both the inhibitor and motor sets of fibres was affected," and that "it points to the non-existence of any local trophic centres within the peripheral end-apparatus itself." Fletcher himself admits that his results were not conclusive.

Anderson⁴ in his large series of beautiful and painstaking experiments on the iris apparently did not make observations on the disappearance or persistence of a peripheral plexus after removal of the superior cervical and ciliary ganglia which he concludes leads to complete denervation.

The existence of a rich peripheral plexus of nerve fibres and nerve cells in the iris has been demonstrated by Münch⁵ and Schock.⁶ Does this consist of neurons beyond the ciliary ganglia which have been displaced from the two cardinal ganglia?

Jegerow⁷ has shown that certainly all the synapses on the third nerve are not in the ciliary ganglion, but that more peripheral ganglia exist. May the plexus in the iris be simply the most peripheral of the outlying stations, or is it a plexus beyond the post-ganglionic fibres?

Whichever it may be, there seems good reason to believe that it can survive the complete removal of the cardinal cell stations.

The author⁸, in a previous paper, has shown that the motor plexus with nerve cells lies between the individual cells of the sphincter and dilator pupillae of the rabbit, and that it contains fibres of extreme tenuity. "The plexus persists after separation of the iris from the central nervous system by removal of the ciliary ganglion, and of the superior cervical sympathetic ganglion. It

may, therefore, be regarded as of the same nature as the plexuses of Auerbach and Meissner in the intestine."

Objections have been raised to these results on the ground that the author had not removed the accessory ganglia described by Jegerow. In the operation for removal of the ciliary ganglion described by him in that paper⁹ the ciliary ganglion and the short ciliary nerves were all removed and a clean sweep made around the optic nerve at its entrance to the eyeball. He found that this and also complete removal of the superior cervical ganglion up to its uppermost portion was necessary in order to exclude all extrinsic nerve fibres from the iris. By this means, extrinsic sensory fibres were also removed.

Another objection has been raised to the author's work by suggesting that the cells figured were plasma cells, and the fibres elastic fibres. These cells and fibres were found in silver stained specimens as well as in those stained by the intra-vitam method of methylene blue staining, described by Hosch,¹⁰ which was based on the method of Dogiel¹¹. These nerve cells have been described by earlier workers with gold chloride, and also by Münch,⁵ and Schock,⁶ who employed the phosphomolybdic acid fixation method. The author did not find it difficult to distinguish the nerve cells from the stroma and plasma cells, as he had worked for a number of years on the pathology of the eye. The nerve fibres were of extraordinary fineness in the Cajal silver stained specimens, and required an oil immersion lens for their discovery.

Certain fibres could be followed for long distances in the sphincter plexus, and they could easily be distinguished from elastic fibres. With the methylene blue stain, fine fibres were also obtained. The plexuses in the sphincter muscle and in the dilator muscle appeared to be quite distinct from a plexus with few nerve cells and long delicate nerve fibres stretched widely through the iris. These plexuses were found both in the normal iris and in the iris after complete removal of the ciliary ganglion and its accessory ganglia, and the superior cervical sympathetic ganglion.

This being so, it seems so far impossible to speak of a "denervated" iris, or to conclude from the persistence of the action of drugs after removal of the cardinal ganglia that their action is upon the muscle. To argue an action on some neuro-muscular junction seems unwarrantable. The evidence we possess of the behaviour of denervated skeletal muscle indicates that, in time, this neuro-myal junction degenerates. We have no right to assume that it will persist in visceral muscle.

But the main point is that so far we cannot talk of a denervated iris, and therefore, that we cannot conclude that a drug producing its effect after so-called denervation is acting upon non-nervous structures.

Post-ganglionic fibres degenerate in two days (Tuckett¹²), and yet adrenalin stimulates the dilator pupillae for many months after so-called "denervation." This means that it acts upon the endings of peripherally placed ganglia, that some hypothetical neuro-muscular ending persists, or that it acts directly upon the contractile part of the muscle fibre. But which it is we at present do not know, nor have we any means of determining.

What applies to adrenalin applies also to other drugs, *e.g.*, physostigmin and pilocarpin. The former of these ceases to act when the nerve degenerates after section while the latter continues to act, and the conclusion is that the latter acts on the neuro-myal substances, or on the muscle. The former conclusion is unwarranted, and the latter is unjustifiable until it has been definitely shown that all the nerve plexus of the iris has disappeared.

The general validity of Elliott's law¹³ that adrenalin acts upon the nerve endings of the true sympathetic (thoracico-lumbar visceral) nerves, and that it acts with greater persistence after degeneration of the motor post-ganglionic fibres, and with more prolonged inhibition after degeneration of the inhibitor post-ganglionic fibres, may now be held as accepted.

Brodie and Dixon¹⁴ held that adrenalin acts on a neuro-muscular junction. Elliott¹⁵ proposed the "myo-neural junction which is irritable by adrenalin" and "is on the muscular side in so far as its trophic centre lies in the muscular nucleoplasm." Anderson¹⁶ proposed the word "myoneure" for the myo-neural junction.

The fact that there is no evidence that the neuro-myal substance of visceral muscle should survive nerve degeneration any more than the same substance in skeletal muscle, the fact that it has never been shown that the peripheral plexus disappears after so-called "denervation" and the evidence afforded by myself of its persistence all indicate that adrenalin probably acts upon some persistent nerve structure, and that other drugs may act upon this, or upon the muscle directly; but in which way they act the simple observation of their influence on the so-called "denervated" iris does not tell us.

The possibility of coming to some more definite conclusion by the study of the relative action of different substances seemed worth investigating. Light might be thrown upon this point; first, by the study of the relative activity of different drugs on the normal and on the "denervated" iris; secondly, by the study of the influence of thyroid extracts which are known (Asher and v. Rødt¹⁷ and Oswald¹⁸) to activate the endings of both true and para-sympathetic upon the influence of adrenalin and pituitrin on the pupil.

At the same time, it seemed desirable to attempt to get more definite information upon the somewhat contradictory statements as

regards the action of pituitrin (hypophysin) on the pupil, and to study further the action of β -iminazoly-ethylamine and of guanidin. The peculiar nicotin-like action of guanidin discovered (Noël Paton and Findlay¹⁹, Meighan²⁰) in this laboratory, made it interesting to investigate its action on the pupil.

The work thus divides itself into :

1. A study of the action of hypophysin* on the normal and deganglionated ("denervated") iris, and a comparison of its effects with those of adrenalin. This is dealt with in the present paper.
 2. A study of the relation of the action of adrenalin and pituitrin, and of physostigmin and pilocarpin on the normal and deganglionated iris.
 3. An investigation of the influence of thyroid extracts upon the action of adrenalin and pituitrin on the iris.
 4. A study of the influence of β -iminazoly-ethylamine and guanidin upon the pupil.
 5. A general consideration of the evidence afforded by these experiments, and the light thrown by them on the validity of the conclusions generally held as to the seat of action of these drugs.
- These last four subjects will be considered in subsequent papers.

Present Investigation

(i) *Methods.* For the purposes of this investigation Messrs. Parke, Davis & Co's preparation of pituitrin has been used, and has been held as equivalent to the extract of the hypophysis.

Pituitrin is preserved by the addition of a small quantity of chloretone. Pankow²¹ found that this drug had no action on blood pressure, or involuntary muscle. Wiggers²² got similar results.

The capsules supplied by the firm for subcutaneous injection were opened and the contents applied to the conjunctiva by instillation. The solutions were dropped into the eye from a fine pipette, or from a 1 c.c. hypodermic syringe.

In these experiments two drops were administered to each eye on each occasion, except in certain experiments when the fact is mentioned. The first and third drops were given on one side, with the second and fourth to the other eye, the right being always the operation side, while the left was kept as a control, no operations being performed on that side. The drops were twice repeated to each eye at intervals of fifteen or twenty minutes. Six drops were, therefore, applied as a rule to each eye in the course of an hour.

In other experiments pituitrin was given by intravenous injection. The illumination was maintained at that known as slightly darkened. This gave enough light for accurate measurement of the pupils, and, at the same time, allowed the sphincter to relax under

*By hypophysin is meant the extract of the posterior lobe of the pituitary, the hypophysis cerebri.

these conditions. Care was taken to maintain equal illumination on each side of the head during the examination, for which purpose the rabbit was placed in the special holder devised by Chasseaud²³, with its back to the window where it sits placidly for a considerable interval. It is necessary to give the animal a rest of a minute or two each time it is placed in the stand before taking the measurements, as the handling usually dilates the pupils.

The pupils were measured by direct examination by means of Fay's patent outside calipers (Messrs. Starrett & Co.). The measurements were taken to quarter millimetres on a millimetre scale. Each pupil was measured both in the vertical and horizontal diameters, before and after the application of the solutions, although in one or two of the earliest experiments they were measured more frequently.

It is important to stand exactly opposite the rabbit's eye, and to keep the points of the calipers in the direct line of vision and within 5 mm. of the cornea. It is usually best to employ only one eye in watching the points of the calipers and the margins of the pupil.

(ii) In the first experiments the right superior cervical sympathetic ganglion was removed in each case, except in the instances in which the sympathetic nerve of the same side was cut in the neck below the ganglion and the ends separated. In removing the ganglion it is necessary to excise the entire ganglion, as pointed out by Langley and Anderson²⁴ who found that the cells for the dilator muscle of the iris are situated in the upper half of the ganglion.

(iii) In another series of experiments the right ciliary ganglion and accessory ganglia were removed by the operation described in the introduction. After excision of the ciliary ganglion the short ciliary nerves were removed and the optic nerve sheath thoroughly cleared of nerve structures by gently scraping it above, below and externally. Complete removal is necessary of the ciliary ganglion and accessory ganglia so beautifully described and figured by Jegerow.²⁵ In my previous paper the test for this consisted in the presence of medullated fibres in the iris. If any such were still present complete excision had not been performed. In the present investigation there has been no time for pathological examination of the iris after the animal's death.

Some of the sensory fibres passing through the short ciliary nerves are also removed by this operation and the cornea seems to become easily liable to injury. It is, therefore, better to suture the lids together for a week, when the stitches may be safely removed.

In two instances the right pre-ganglionic fibres of the sphincter pupillae were cut immediately above the ciliary ganglion without disturbing, in so far as was possible, the vascular supply of the ganglion.

(iv) In the last experiments the right superior cervical ganglion and the ciliary ganglion and accessory ganglia were excised so as to give a completely deganglionated iris on the right side.

Anderson²⁶ employed the term "decentralised" for the cases in which the pre-ganglionic fibres were cut, and the term "denervated" for the cases in which the ganglion was excised, or the post-ganglionic fibres cut.

As already indicated, I do not agree with this latter term. I have, therefore, employed the terms "deganglionated," used by Dale and Laidlaw²⁷ for the cases in which the ganglion was excised, and Anderson's "decentralised" for the cases in which the pre-ganglionic fibres were cut.

Fourteen days were allowed for degeneration of nerves before investigating the action of the different drugs. No observations were made after the 150th day, so that the possibility of regeneration may be excluded (Tuckett²⁸, Langley²⁹.)

All operations were performed on the right side in every case, so that the left was retained as the normal or control side throughout the series.

I.—The Normal Iris

Historical Summary.—While the general action of extracts of the pars intermedia of the pituitary body, or of the hypophysis cerebri has been fairly definitely ascertained as the result of a great amount of work by many observers, their effect upon the pupil of the eye has given apparently contradictory results in the hands of competent workers.

After Ehrmann³⁰ had suggested in 1905 the mydriasis produced in the enucleated eye of the frog as a method of detecting the presence of adrenalin, a number of other substances and extracts from different organs in the body, including the hypophysis, were discovered to have the same effect, and the method was abandoned.

Cramer³¹ in 1908 was the first to describe this action with extracts of the posterior lobe of the pituitary body of the ox. Strong extracts produced a dilatation within an hour or two, which was as great as that obtained from adrenalin, and, although slower in development, it lasted longer. Dilute extracts took twelve or more hours to produce a moderate dilatation. During the same time, the pupil of the control eyeball, immersed in Ringer's solution, became completely contracted. Extracts from the anterior lobe produced a complete contraction of the pupil in sixteen hours.

These results were confirmed by Borchardt³² in 1908, by Pal,³³ and by Bayer³⁴ in 1909.

In the same year Dale,³⁵ in the course of an important paper upon the action of extracts of the pituitary body, stated that there was no action upon the mammalian pupil.

In 1910, Frankl-Hochwart and Fröhlich,³⁶ reported that the intravenous injection of 0.4 c.c. pituitrin produced a contraction of the pupil in rabbits.

Kepinow³⁷ in 1912 confirmed this result for cats and rabbits when a sufficient concentration of the extract of the hypophysis was employed for the intravenous injection. He further stated that he found that the extract of the entire gland which he was using produced a miosis in the enucleated eyeball of the frog.

But Cramer³¹ had already shown that a miosis occurred in the frog's pupil when it was placed in Ringer's solution, plus an extract of the anterior lobe, or even in Ringer's solution alone. The miosis observed by Kepinow³⁷ must, therefore, be attributed to the solution of the extract of the posterior lobe being weakened by the action of the extract of the anterior lobe, and of the sodium chloride solution in which the eyeballs were first immersed. The mydriatic action of the posterior lobe was overcome by these other factors.

These results, however, were subsidiary to the main purpose of his investigations, which was to decide whether adrenalin and the extract of the hypophysis were synergists, but this subject will be taken up in a later paper. Gottlieb³⁸ also stated in the same year that he found a miosis occurring in the frog's pupillary reaction.

Meltzer³⁹ in 1912 found that pituitrin produced in the enucleated frog's eye a dilatation of the pupil, in most instances, which was never as striking as that obtained with adrenalin. In a smaller number, no dilatation took place, but in no case was there a contraction of the pupil. In six rabbits he removed one superior cervical ganglion, and injected 1, 2, or 3 c.c. pituitrin intravenously, and did not find a dilatation "neither soon nor late on the operated side." Both pupils, and especially that on the operated side, showed a constriction of short duration immediately after the injection.

Fröhlich and Pick⁴⁰, in 1913, while investigating the action of ergotoxin upon the rise in blood pressure produced by the extracts of hypophysis, and adrenalin, which had been discovered by Dale⁴¹, found an interesting result in the pupil of the cat. They confirmed that ergotoxin inhibited the action of adrenalin and that the extract of the hypophysis (Burroughs, Wellcome & Co.) was not inhibited. If the extract was employed in a strength just enough to cause a mere rise of pressure after ergotoxin, and was followed by a small dose of adrenalin, striking rise of blood pressure was obtained, but the pupils remained contracted, which they attributed to ergotoxin.

Githens⁴² has recently, 1917, stated that ergotoxin produces a dilatation of the pupil in rabbits.

Githens and Meltzer,⁴³ in 1916, reinvestigated the pituitrin question. They found, in the normal animal, that the intravenous injection of pituitrin produced a considerable constriction of the

pupil, while adrenalin produced a moderate dilatation of short duration. When both drugs were injected simultaneously, the dilatation was much less than with adrenalin alone. They held that pituitrin produces constriction of the pupil, and "*counteracts* to a degree the dilating effect of adrenalin."

Although adrenalin produces a dilatation of the pupil after intravenous injection in nearly all animals, Langley,⁴⁴ Brodie and Dixon⁴⁵ and Elliott⁴⁶ have shown that a constriction of the pupil occurs in the dog.

Elliott⁴⁶ investigated the point and found that adrenalin produced a dilatation of the pupil when injected into the anterior chamber, or into the common carotid, but not on instillation into the conjunctival sac. He found, on the other hand, that when small doses of adrenalin were injected intravenously, the pupil contracted, while the globe of the eye sank backward and was twisted inward. He concluded that the local mydriatic action of adrenalin had been overpowered by the constriction due to central stimulation of the third cranial nerve by high intracranial pressure, because the constriction of the pupil, and the movement of the globe, did not occur if the mid-brain had been destroyed. When he increased the amount of adrenalin to 2.3 mgm., for which purpose the blood had to be defibrinated, he was able to obtain a moderate dilatation of the dog's pupil. With a medium dose of 1 mgm. the local mydriatic action of adrenalin is thus seen to be overcome by the contraction of the sphincter pupillae in response to the increased blood pressure stimulating the cranial third nerve.

In involuntary muscle in the intestine, and in the muscle of the uterus, there is no immunity produced by a first dose, although Bayer and Peter⁴⁷ noticed a diminution of effect with frequently repeated applications to the isolated intestine; but Pankow²¹ found, on the contrary, that a small dose of pituitrin might sensitize the uterus so that a second injection of the usual amount then gave a much greater effect than was normally produced.

Present Position.

The work of previous investigators is seen, therefore, to fall into two divisions. On the one hand, extracts of the posterior lobe of the pituitary body or pituitrin produces a dilatation of the pupil in the enucleated eyeball of the frog; while, on the other hand, an intravenous injection causes a constriction of the pupil in warm-blooded animals.

There is no record of previous work on the local application of pituitrin to the eyeball in warm-blooded animals by instillation.

The present experiments have been mainly devoted to this method of investigation.

Experiments

The following experiments were performed by the methods described in the introduction.

Experiment 1, Rabbit 3.—Right superior cervical sympathetic ganglion excised.

121st Day.

3.15 p.m. Right pupil 7.25×6.25 mm. Left pupil 8×7 mm. 2 drops of pituitrin applied to each eye.

3.30 p.m. Right pupil 7.25×6.25 mm. Left pupil 8.5×7.5 mm. 2 drops of pituitrin applied to each eye.

3.45 p.m. Right pupil 7.75×6.75 mm. Left pupil 8.75×8 mm. 2 drops of pituitrin into each eye.

4.15 p.m. Right pupil 8×7 mm. Left pupil 9×8 mm. The right pupil dilated 0.75×0.75 mm. The left pupil dilated 1×1 mm. during 1 hour.

Experiment 2, Rabbit 4. Right superior cervical sympathetic ganglion excised.

96th Day.

11.15 a.m. Right pupil 6×5.5 mm. Left pupil 7×6 mm. 2 drops of pituitrin in each eye.

11.30 a.m. 2 drops of pituitrin in each eye.

11.45 a.m. 2 drops of pituitrin in each eye.

12.15 p.m. Right pupil 7×6.25 mm. Left pupil 7.5×7 mm. The right pupil had dilated by 1×0.75 mm., and the left had dilated 0.5×1 mm. in the course of 1 hour.

Discussion of Results

The action of pituitrin upon the normal iris was observed in thirty-two experiments upon twelve rabbits. In thirty cases a dilatation of the pupil followed the instillation of pituitrin into the conjunctival sac.—Table I, right half.

In one experiment, the pupil contracted during the first fifteen minutes, and then dilated to its original dimensions. In only one instance did the pupil contract and remain smaller at the end of the experiment than it was at the outset.

The numbers are not very large, but the total number of actual dilatations gives a percentage of 93.75. The average dilatation observed in these thirty cases was 0.72 mm. in the vertical diameter by 0.62 mm. in the horizontal diameter.

The greatest dilatation was 1.5 mm., and the least dilatation observed was 0.25 mm. in each diameter. The pupil, therefore, did not reach a maximal dilatation in any instance.

The rabbit's pupil is slightly oval, and, in a number of cases, the dilatation was equal in both dimensions, but the pupil frequently became either a little more oval or sometimes more circular.

TABLE I.

	Deganglionated Dilator.				Control Side		Normal Iris.	
	Dilatation.		Constriction.		Dilatation.		Constriction.	
	Vert.	Horiz.	Vert.	Horiz.	Vert.	Horiz.	Vert.	Horiz.
Rabbit 1	1	0.5						
	0.5	0.5					0	0
2	1	0.5						
	1	1			1.5	1.5		
	1	1			1.25	1		
			0	0	1.25	1		
3	1.5	1.5			0.5	0.5		
			-0.75	-1			-0.25	-0.5
	0.75	0.75			1	1		
	1	0.75			0.25	0		
	1	1			1	0.75		
4	1	0.75			0.5	1		
	1	0.75			0.75	0.25		
	1	0.75			0.75	0.25		
5	0.75	1			0.25	0.5		
	0.5	0.5			0.25	0.25		
	0.75	0.75			0.25	0.25		
7	0.5	0.75			1.5	0.75		
	0.25	0.25			0.5	0.25		
	1	1			0.5	0.5		
Average ...	0.86	0.77						
Decentralised Dilator.								
Rabbit 6	0.75	0.5			0.5	0.5		
	1	0.75			1	0.5		
	1	1			0.75	0.75		
8	0.5	0.75			1.5	0.75		
	0.5	0.5			0	0.25		
	1	0.5			0.75	0.75		
Average ...	0.79	0.66						
Deganglionated Sphincter.								
Rabbit 9	1	1			0.5	0.5		
	0.5	0.75			0.5	0.5		
11	0.75	0.5			0.5	0.5		
	1	0.75			0.75	0.75		
Average ...	0.81	0.75						
Decentralised Sphincter.								
Rabbit 10	0.5	0.5			0.5	0.5		
	0.75	0.5			0.75	0.75		
12	0.75	0.5			0.75	0.75		
	0.75	0.75			1	1		
Average ...	0.62	0.56			0.72	0.62		

The observations were usually made upon several rabbits at the same time, and the change of form in the pupil might be observed to be more marked in one or two cases; but, when the results are taken in the aggregate, it is found that this increase or diminution in the ellipse of the pupil occurred with each rabbit at one time or another. The pupils always remained more elongated in the vertical meridian than in the horizontal meridian, and on no occasion did they become perfectly circular.

The rabbit which gave in its second experiment a constriction of the pupil of 0.25 by 0.5 mm., had, on four other occasions, a dilatation of the pupil. The measurements taken during the second experiment showed that the pupil contracted slightly, then dilated to normal, and then contracted slightly again.

II.—The Deganglionated Dilator Pupillae

Historical Summary.—Meltzer³⁹ in 1912, in the experiments to which reference has already been made, found that after removal of the superior sympathetic ganglion an intravenous injection of pituitrin produced immediately, especially on the operated side, a constriction of short duration.

Githens and Meltzer⁴³ in 1916 again reported that the injection of pituitrin caused a constriction of the pupil in the rabbit with a deganglionated dilator; and that it lessened the dilatation produced by adrenalin when both were injected simultaneously.

Discussion of Results.—The action of pituitrin was observed in twenty experiments upon six rabbits after removal of the right superior cervical sympathetic ganglion, and degeneration of the post-ganglionic nerve fibres. Two examples are described in Experiments 1 and 2.

Dilatation of the pupil was present in eighteen experiments, while constriction occurred in one case, and in one instance the pupil first contracted and then dilated to the dimensions at the beginning of the experiment—Table I, left side.

The percentage of dilatations is, therefore, 90, which is slightly less than the 93.75 per cent. found on the control, or normal side; while a dilatation occurred in every instance in the decentralised dilator.

The average dilatation was 0.86 mm. in the vertical meridian, and 0.77 mm. in the horizontal meridian, which is greater than the 0.72 and 0.62 mm. observed on the normal side. The greatest dilatation was 1.5 mm. in each diameter, while the least dilatation was 0.25 mm.

The same changes in contour of the pupil were observed on the deganglionated side as on the control side. The similarity of results observed in the two pupils is remarkable, notwithstanding

that eighteen of the experiments were alone carried out on both sides simultaneously, the only difference being the greater dimensions attained in the dilatation on the side without the ganglion.

The one occasion upon which constriction occurred was in the same experiment as that in which it occurred on the normal side, and the remarks which have been made above apply equally to it except that the pupil of the deganglionated side began slightly larger than upon the other four occasions, and contracted 0.75×1 mm.

The case which contracted and then dilated occurred in a different rabbit, number 2, to the similar phenomenon found on the normal side. It will be seen from Table I that on the other occasions both pupils dilated.

III.—The Decentralised Dilator Pupillae

Six experiments were performed on two rabbits in which the right sympathetic nerve had been cut in the neck below the superior cervical ganglion. The cut ends of the nerve were separated and the superior sympathetic ganglion was left *in situ*.

In each case, there was a dilatation of the pupil, the average dilatation was 0.79 mm. in the vertical, and 0.66 mm. in the horizontal diameter, Table I. These figures show a less dilatation than in the deganglionated dilator, but they are slightly greater than the average for the normal pupil, i.e., they lie between the dilatation of the normal pupil and the dilatation in the dilator with the ganglion excised.

Pituitrin acts like adrenalin in stimulating the dilator pupillae and does so more markedly in the deganglionated and the decentralised eye. But whether it acts upon the peripheral plexus or directly upon the muscle is not indicated.

IV.—The Deganglionated Sphincter Pupillae

Historical Summary.—While there is no record of previous work on the action of hypophysin on the deganglionated sphincter pupillae, Joseph⁴⁸ investigated the action of adrenalin. He stated that the irritability of the pupil of the cat to adrenalin was three to twenty times greater after excision of the ciliary ganglion than in the normal iris. He (⁴⁹) also demonstrated that adrenalin produced a relaxation of isolated strips of the sphincter pupillae and drew the conclusion that the cervical sympathetic supplies inhibitor nerve fibres to that muscle.

Reference must be made again to the effect of intravenous injection of pituitrin in the *résumé* in the section on hypophysin and the normal iris. All previous workers found a constriction of the pupil in the normal iris.

Discussion of Results.—(a) *Local Application.*—Four experiments were performed in two rabbits in which the right ciliary ganglion and accessory ganglia had been removed, and probably some of the long ciliary nerves had been cut. Anderson⁵⁰ found that the injury to the long ciliary nerves made no difference in his results with pilocarpin. The left side was kept for the control. Two drops of pituitrin were instilled in the usual manner each quarter of an hour until six drops had been applied. A dilatation of the pupil occurred in each instance. Table I.—The average dilatation was 0.81×0.75 mm, which is greater than in the normal eye, and almost identical with the 0.86×0.77 mm. observed after removal of the superior cervical ganglion. The pupil in these rabbits was very sensitive to adrenalin, confirming Joseph⁴⁷, but did not appear to have been more sensitive to pituitrin, as compared with the normal iris, than in the pupil after removal of the superior cervical ganglion. My experiments, therefore, indicate that the local effect of pituitrin upon the pupil is increased by about the same proportion by removal of either the ciliary and accessory ganglia, or of the superior cervical ganglion.

(b) *Intravenous Injection.*—Two experiments were performed by intravenous injection of 1 cc. of pituitrin into the auricular vein of another rabbit in which the right ciliary ganglion and accessory ganglia had been removed. The experiments were undertaken on the 19th and 26th days after the operation. In the first experiment the deganglionated pupil dilated 1×1 mm. within five minutes, while the left, or control, pupil dilated immediately after the injection and then became constricted by 1×1 mm. The dilatation in the right pupil was reduced to 0.25×0.25 mm. at the end of an hour, while the normal pupil returned to its original dimensions. In the second experiment the deganglionated right pupil became dilated to 0.5×0.5 mm. at the end of five minutes, while the control pupil dilated immediately after the injection and then became constricted by 0.75×0.75 mm. At the end of an hour the right pupil was only 0.25×0.25 mm. larger than at the beginning, while the left normal pupil had also dilated sometime earlier to 0.5×0.5 mm. and had remained dilated.

These results indicate that after removal of the ciliary and accessory ganglia the intravenous injection of pituitrin produces a dilatation of the pupil on the deganglionated side, while the normal pupil gives the constriction found by previous observers which may be both preceded and succeeded by dilatation.

V.—The Decentralised Sphincter Pupillae

Discussion of Results.—(a) *Local Application.*—Four experiments were also undertaken on two rabbits, in which the right pre-ganglionic

fibres of the sphincter pupillae were cut immediately above the ciliary ganglion without disturbing, in so far as possible, the vascular supply of the ganglion.

The pituitrin was instilled in the operated eye, and in the normal eye in the customary manner. The dilatation of the pupil occurred in each case. Table I.—The average dilatation was 0.62×0.56 mm., which is smaller than the average of 0.72×0.62 mm., found in the normal pupil. It is, therefore, the smallest average obtained in the whole series of pituitrin experiments.

(b) *Intravenous Injections*.—Two experiments were performed in one of the rabbits with the intravenous injection of 1 c.c. pituitrin, when a dilatation was found on the decentralised side in both instances. In the first experiment, the dilatation reached 1×1 mm., and in the second, 0.75×0.75 mm. at the end of from five to 10 minutes, but had partly passed off in the first by the end of an hour, when it was 0.5×0.5 mm., while in the second experiment the pupil remained of the same dilatation at the end of an hour as it was five minutes after the injection. In both experiments, the normal pupil dilated immediately after the injection, and then became constricted. By five minutes in the first, it measured 1×1 mm. of constriction, and in the second, 0.5×0.5 mm. By the end of an hour, the constriction had passed off and given place to a dilatation of 0.25×0.25 mm. in the first experiment, and 1.25×1.25 mm. in the second.

These results show that the intravenous injection of pituitrin does not produce a constriction of the pupil after interruption of the pre-ganglionic fibres of the ciliary ganglion, while the constriction observed on the normal side within five minutes of the injection gives place, also after a short interval, to a dilatation. They therefore prove that a dilatation of the pupil is a local action of pituitrin which is increased by decentralising and more markedly by deganglionising, and may act either on the persisting peripheral plexus or upon the muscle directly. In this way it resembles the action of adrenalin.

The possibility of abolishing the action of pituitrin by the previous administration of ergotoxin was considered. I found that ergotoxin widely dilated the pupil in the rabbit, an observation confirmed by Githens⁴².

VI.—The Deganglionated Dilator and Sphincter Pupillae

(a) *Local Application*.—The experiments have been repeated upon four rabbits in which the right ciliary ganglion and accessory ganglia and the superior right cervical sympathetic ganglion had been excised.

The accompanying Table gives the results of eight experiments on four rabbits in the right eye, the other eye being kept as a normal control iris. The average dilatation was 0.94×0.96 , which is

larger than any of the dilatations obtained in the previous experiments.

If the excess of the average deganglionated dilator dilatations over the average normal dilatation is added to the similar average excess in the case of the deganglionated sphincter muscle, then the result comes out almost equal to the figures of this last experiment.

The numbers are small to make a definite statement, but the result is that with the doubly deganglionated iris, the pupil dilates more than after deganglionation of the sphincter or of the dilator pupillae muscle separately.

TABLE II
Deganglionated Dilator and Sphincter
Right Eye.

		Vert.	Horiz.
Rabbit 1. ...	...	1 0.75	1.25 1
2. ...	...	1 0.75	1.25 1
3. ...	...	0.75 1	0.5 1
4. ...	...	1.5 0.75	1.25 0.5
Average ...	...	0.94	0.96

(b) *Intravenous Injection.*—In each of these rabbits the intravenous injection of pituitrin 1 c.c. was given, with the result that the normal pupil contracted while the doubly deganglionated pupil dilated. This effect was all the more noticeable because the left normal pupil had been the larger before the injection while with the injection it became the smaller. The first phase is sometimes a momentary dilatation of the normal pupil associated probably with the excitement, as the animal often struggles at this point. This is succeeded by a constriction which on one occasion contracted 3.25 mm. in the vertical, and 4 mm. in the horizontal, but in this instance the normal eye was facing the window with good daylight, while the right doubly deganglionated eye showed a dilatation which after a period of ten to fifteen minutes reached 0.75×0.75 mm.

On the normal side the constriction passed off in the course of twenty minutes, and was followed by a dilatation to a size larger than at the outset of the experiment. In this case the pupil ultimately reached in the course of three-quarters of an hour 0.75×1.25 , a dilatation larger than the original dimensions.

Conclusions

Hypophysin (pituirin, Parke, Davis & Co.) when applied to the eye of the rabbit by instillation, produces a mydriasis in about 94 per cent. of the experiments, although it is necessary in some cases to repeat the application several times. The effect is increased by decentralisation and still more by deganglionation of the dilator pupillae or of the sphincter pupillae; and most markedly by deganglionation of both dilator and sphincter pupillae.

When hypophysin is administered by intravenous injection, the local mydriatic effect is lost if the blood pressure is raised, when a miosis occurs, due to central stimulation of the third cranial nerve, which relaxes with the return of the blood pressure to normal, as shown for adrenalin in the dog by Elliott,⁴⁶ and is followed generally by a slight dilatation. The constriction of the pupil may be preceded by a brief dilatation due to excitement at the moment of injection.

When the third cranial nerve is interrupted by section above the ciliary ganglion or by excision of the ciliary ganglion and accessory ganglia, the pupil dilates within a few minutes of the injection and generally returns to its normal size within an hour.

Hypophysin acts on the same structure as adrenalin, and since adrenalin acts on the neuro-myal junctions, hypophysin must also act there. Since deganglionation does not cause degeneration of the terminal plexus (8), the presumption is that both drugs act upon this.

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A METHOD OF IRIDOTOMY

BY

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THE following method of performing iridotomy has been practised by the author for the last fifteen years. Taken as a whole he has found it more successful than any other method which he has tried, as it yields a much larger opening, and is therefore less liable to be closed by subsequent inflammatory exudation. He makes no claim of originality for the operation; indeed, he has seen the operation performed by other ophthalmic surgeons, but does not know who first performed it.* The method does not seem to be generally known.

The operation is usually performed under a general anaesthetic, but this is not essential.

First step. The surgeon stands facing the patient on the same

* Since writing the above, I find in the *Report* of the Ophthalmic Department of King's College Hospital, Vol. VII., 1900, a case recorded in which the operation was done by Mr. MacHardy.—M.S.M.