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THE INFLUENCE OF SUPERIOR CERVICAL GANGLIONECTOMY ON INTRAOCULAR DYNAMICS

BY M. E. LANGHAM* AND C. B. TAYLOR

From the Medical Research Council Ophthalmological Research Unit, Institute of Ophthalmology, Judd Street, London, W.C. 1

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It is now well established that 24 hr after unilateral excision of the superior cervical ganglion in rabbits, the intraocular pressure on the operated side is reduced and that the pressure returns to normal by the third or fourth day (Hertel, 1900; Linner & Prijot, 1955; Lieb, Guerry & Ellis, 1958; Langham & Taylor, 1960). Since this is a change in the steady-state pressure it must be explained in terms of the three factors which govern intraocular pressure at equilibrium, namely rate of formation of aqueous humour, resistance to outflow and venous pressure. Linner & Prijot, and Lieb *et al.* have concluded from their tonographic studies that the observed fall in intraocular pressure is due to a marked decrease in the rate of formation of aqueous humour. In this paper more direct methods of measuring formation and resistance have been applied to this problem and our results indicate that 24 hr after ganglionectomy aqueous humour formation is normal and that the primary cause of the fall in intraocular pressure is decreased resistance to outflow. A preliminary report of this work has been published (Langham & Taylor, 1959).

METHODS

Adult rabbits of the New Zealand White strain, weighing between 2·0 and 3·0 kg, were used throughout this study.

Excision of the superior cervical ganglion was carried out under pentobarbitone sodium anaesthesia (60 mg/kg), care being taken to expose the whole ganglion before excision to ensure complete ganglionectomy.

Intraocular pressure was measured manometrically with Sanborn 267 B pressure transducers in conjunction with a Sanborn 150 M rectilinear pen recorder. The technique for studying the effect of infusion of fluid into the anterior chamber on steady-state pressure has been reported by Langham (1959).

Fluorescein was estimated in the aqueous humour of the anterior chamber by the continuous fluorophotometric method described by Langham & Wybar (1954). This permits the accurate and continuous determination of the fluorescein concentration in both eyes throughout the course of the experiment without disturbing the physiology of the eye. The

* Present address: The Wilmer Institute, The Johns Hopkins Hospital and University, Baltimore 5, Maryland, U.S.A.

total concentration of fluorescein in the plasma was determined photometrically by means of the absorption at 435 mμ exhibited by fluorescein after treatment with concentrated hydrochloric acid. The concentration of free fluorescein was read from a conversion curve constructed from the results of a dialysis study of the binding of fluorescein by plasma.

The ascorbate concentration in the aqueous humour was estimated by the method of Mindlin & Butler (1938), the samples being deproteinized by centrifugation after the addition of an equal volume of 8 % trichloroacetic acid. When it was necessary to saturate the animals with ascorbate, the schedule of intravenous and subcutaneous injections recommended by Becker (1956) was adopted. This gave a steady plasma level of 13–16 mg/100 ml. for several hours.

Measurement of aqueous flow. Flow of aqueous humour was estimated with fluorescein as test substance by a method similar in principle to that used by Goldmann (1950). An ideal test substance would be one which could be introduced into the aqueous humour under physiological conditions, the molecule of which would be large enough to preclude appreciable diffusion into the blood and adjacent tissues and yet not large enough to impede its free passage from the anterior chamber by bulk flow through the drainage channels. The transfer constant for the exit of such a substance from the anterior chamber (k_{out}) would be equal to the transfer constant for the loss of fluid from the anterior chamber by bulk flow (k_{flow}). Fluorescein being a substance of intermediate molecular weight approximates to these conditions and it will be shown that limits may be set to its deviation from this ideal behaviour.

A single intravenous injection of fluorescein (0·5 ml. 10 % solution of the sodium salt) was administered to the rabbit under light pentobarbitone sodium anaesthesia. Frequent samples of blood were taken from a cannula in the femoral artery and the concentration of free fluorescein was determined. Frequent readings were also made of the concentration of fluorescein in the anterior chambers of both eyes during the course of the experiments which were continued for 2·5 to 3·5 hr. Since fluorescein enters the eye relatively slowly and since it is rapidly cleared from the plasma, the concentration in the aqueous humour passes through a maximum, usually between 30 and 60 min after the injection.

It is assumed that fluorescein enters the aqueous humour according to equation 1.

$$\frac{\mathrm{d}C_a}{\mathrm{d}t} = k_{\text{in}} . C_p - k_{\text{out}} . C_a, \tag{1}$$

where C_a and C_p are the concentrations of free fluorescein in the anterior chamber and the plasma, respectively, and where k_{in} and k_{out} are the transfer constants for the passage of fluorescein into and out of the anterior chamber. Equation 2 is derived from equation 1:

$$C_a = r . k_{\text{out}} . \mathrm{e}^{-k_{\text{out}} . t} \int C_p . \mathrm{e}^{k_{\text{out}} . t} . \mathrm{d}t, \tag{2}$$

where the equilibrium constant

$$r = \frac{k_{\text{in}}}{k_{\text{out}}} = \left(\frac{C_a}{C_p}\right). \tag{3}$$

For each eye the curve of the aqueous humour concentration against time found experimentally is fitted with respect to the unknown constants k_{out} and r, by means of equation 2 and the plasma fluorescein concentration curve. This is practicable, since the shape of the theoretical curves obtained in this way is sensitive to changes in k_{out} and since r merely alters the vertical axis. Figure 1 shows a typical fit and demonstrates the point just mentioned. This procedure yields k_{out} for each eye.

k_{out} has two components, since fluorescein may leave the anterior chamber either by bulk flow or by diffusion. Therefore

$$k_{\text{out}} = k_{\text{flow}} + k_{\text{diff}}, \tag{4}$$

where k_{diff} is the transfer constant for diffusion between the anterior chamber and the plasma. For a given value of k_{out}, k_{flow} will be greatest when k_{diff} is zero; i.e.

$$k_{\text{flow}} \leqslant k_{\text{out}}. \tag{5}$$

The greatest value which k_{diff} may attain is k_{in}, since under these conditions entry of fluorescein into the anterior chamber would be entirely by diffusion.

Therefore
$$k_{flow} \geqslant k_{out} - k_{in}, \tag{6}$$
and since
$$k_{in} = r.k_{out}, \tag{7}$$
$$k_{flow} \geqslant k_{out}(1-r). \tag{8}$$

The results have consequently been expressed in maximum and minimum values according to equations 5 and 8.

This mathematical derivation of aqueous flow is based upon the currently accepted theory of aqueous humour dynamics and it is implicit in this treatment that transport of fluorescein and water out of the aqueous humour is passive. No such assumption is made for transport into the aqueous humour, so that the equations are equally valid whether this transport is passive or otherwise.

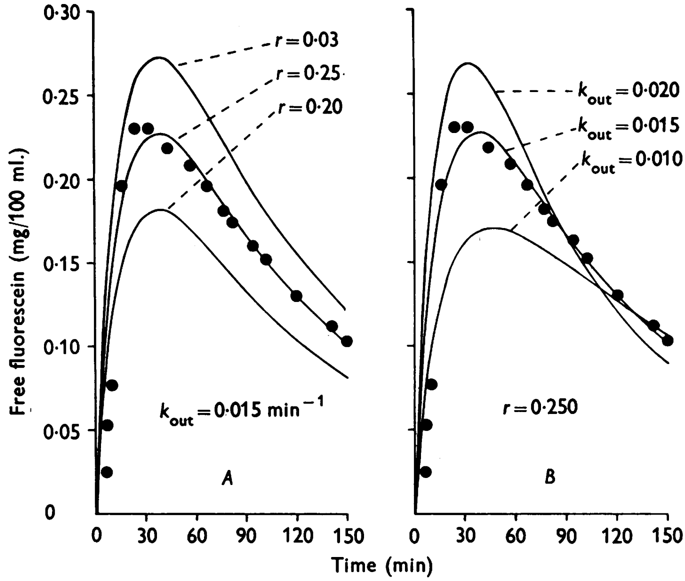

Fig. 1. A typical example of the way in which the observed values for the concentration of fluorescein in the anterior chamber are fitted with respect to k_{out} and r by means of the plasma concentration curve and equation 2. The experimental points are those for the ganglionectomized eye in Experiment 1, Table 1. *A* shows the effect of varying the equilibrium constant r when k_{out} is constant; *B* shows the effect of varying k_{out} when r is constant.

RESULTS

Effects of acetazoleamide. The aim of these experiments was to determine the effect of acetazoleamide on the intraocular pressure and the outflow pressure (intraocular pressure–episcleral venous pressure) in the two eyes of individual animals 24 hr after unilateral ganglionectomy. The episcleral venous pressure has a mean value of 9 mm Hg in rabbits (Kornbluth & Linner, 1955) and is unaffected by either superior cervical ganglionectomy (Linner & Prijot, 1955) or acetazoleamide (Linner, 1956).

Table 1 summarizes the effects of an intravenous dose of acetazoleamide on the intraocular pressure of control and experimental eyes 24 hr after unilateral ganglionectomy. It is seen that the initial pressures (13·5–19·5 mm Hg) in the experimental eyes are significantly below normal (20–22 mm Hg) and that acetazoleamide reduces the pressure still further. The mean fall in the outflow pressure in the control and experimental eyes was $33{\cdot}5 \pm 2{\cdot}4\,\%$ (5) and $44{\cdot}0 \pm 3{\cdot}0\,\%$ (5), respectively. Figure 2 shows the result of a typical experiment and also demonstrates the increased intraocular pulse beat seen in the eye on the ganglionectomized side.

TABLE 1. The effect of acetazoleamide (25 mg/kg) injected intravenously on the intraocular pressure of control and experimental eyes 24 hr after unilateral extirpation of the superior cervical ganglion. The drug was given at time 0

Control eye pressure (mm Hg)		Experimental eye pressure (mm Hg)		
0 min	15 min	0 min	15 min	Mean B.P. (mm Hg)
21	17	13·5	11·0	114
23	16	17	13	110
21·5	17·5	15	12·5	130
23·0	20·0	19·5	16	90
20·0	16·0	15	12·5	120

Rate of flow of aqueous humour. In six experiments the rate of flow of aqueous humour in the two eyes was measured simultaneously 24 hr after unilateral ganglionectomy. The results are shown in Table 2. Both maximum and minimum values for k_{flow} are given. It is clear that there is no significant difference between the values for the control and sympathotomized eyes, whether the maximum or minimum values are considered. The estimate of k_{flow} in the control eyes, 0·0133–0·0116 min^{-1}, is in good agreement with that currently accepted for the rabbit (Kinsey & Barany, 1949).

The equilibrium ratio r is higher on the operated than on the normal side by a factor of 1·7. This is the consequence of the increased permeability of the blood–aqueous barrier, a well known result of sympathotomy.

Perfusion studies. In order to obtain more direct evidence on the effect of ganglionectomy on the system draining aqueous humour from the eye, a series of infusion experiments was carried out. In these, physiological saline was infused into the anterior chamber at a known rate, and the new equilibrium pressure attained under this infusion was determined manometrically. Several measurements of this kind were made on each eye at different infusion rates and the equilibrium pressures were plotted against the corresponding rates of infusion.

Six infusion studies were carried out in this way and the results of four

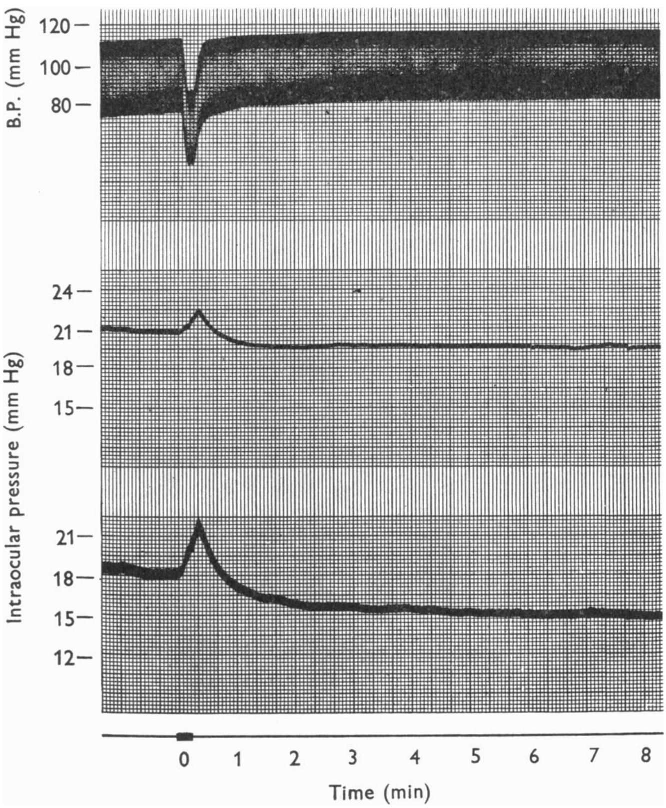

Fig. 2. The influence of an intravenous injection of acetazoleamide (25 mg/kg) at $t = 0$ min on the intraocular pressure of a rabbit 24 hr after unilateral excision of the superior cervical ganglion. Observations on the control and experimental eyes are shown in the middle and bottom records, respectively.

TABLE 2. The outflow constant (k_{out}) and the equilibrium constant (r) for fluorescein in the denervated and control eyes 24 hr after unilateral ganglionectomy in rabbits. k_{out} and $k_{out}(1-r)$ give respectively the maximum and minimum estimates of k_{flow}. See equations 5 and 8

	Ganglionectomized eye		Control eye		k_{out} ratio Ganglionectomized/Control
Expt. No.	k_{out}	r	k_{out}	r	
1	0·0150	0·250	0·0175	0·173	0·86
2	0·0140	0·079	0·0115	0·065	1·22
3	0·0175	0·253	0·0180	0·220	0·97
4	0·0170	0·350	0·0150	0·093	1·13
5	0·0075	0·150	0·0075	0·123	1·00
6	0·0175	0·130	0·0100	0·040	1·75
Mean	0·0148	0·202	0·01325	0·119	1·155
S.E. of mean	0·00156	0·0408	0·00173	0·0276	0·129
	$k_{out}(1-r)$		$k_{out}(1-r)$		
Mean	0·0117	—	0·0116	—	—
S.E. of mean	0·0012	—	0·0013	—	—

of these experiments are shown in Fig. 3. In these experiments initial infusion studies were made on the control and experimental eyes alternately. The curves relating pressure and infusions in the control eyes were similar to those previously obtained with the eyes of normal unoperated rabbits (Langham, 1955, 1959). In contrast, the curves for the denervated eyes showed distinct differences from the control curves. The initial pressures were lower and in five out of the six experiments the slopes of curves

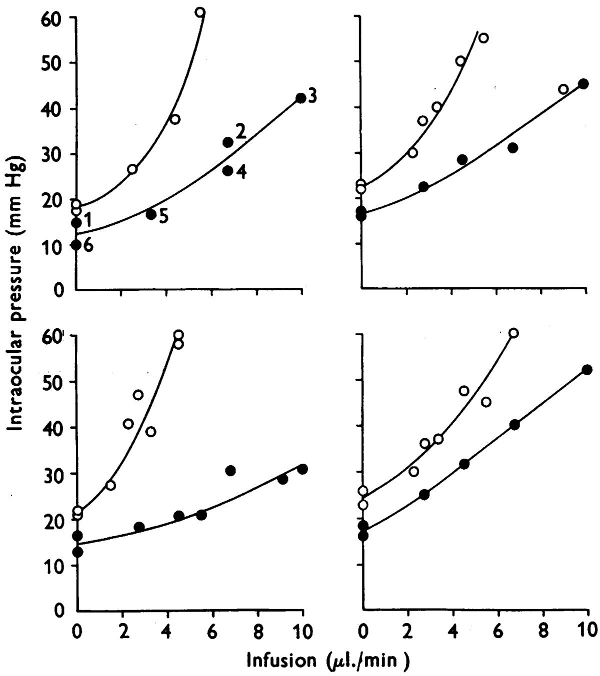

Fig. 3. The effect of superior cervical ganglionectomy on the response of intraocular pressure to the infusion of physiological saline (pH 7·4) into the anterior chamber. Each of the four graphs gives the results for a pair of eyes 24 hr after unilateral ganglionectomy. ●, denervated eye; ○, control eye.

relating pressure and infusion were significantly less than in the control eyes. The result on the sixth animal was in agreement with the rest of the series but the difference between the slopes of the two eyes was less marked (lower right-hand figure in Fig. 3).

Ascorbic acid analyses and blood flow. The concentration of ascorbic acid in the aqueous humour is dependent on the amount brought to the site of secretion in the ciliary processes (Linner, 1952; Langham, 1955). Consequently, provided the transfer mechanism is not saturated with ascorbic acid the concentration in the aqueous humour can be used to derive a measure of the blood flow through the ciliary processes. Table 4 shows the results of analysis 24 hr after ganglionectomy. It is seen that in the rabbits not given supplementary ascorbate the concentration in the aqueous humour on the operated side was higher than on the control side by a factor of 1·12. This ratio is of the same order as that found by Becker & Linner (1952) 24 hr after preganglionic section of the sympathetic chain.

TABLE 3. The effect of superior cervical ganglionectomy on the ascorbate content of aqueous humour at plasma ascorbate levels above and below saturation level in rabbits. These are compared with the effect of preganglionic section of the cervical sympathetic under similar conditions, as reported by Becker & Linner (1952). The aqueous samples were taken 24 hr after the unilateral operation. The figures in brackets indicate the number of experiments in each series and standard errors of the means are shown

		Denervated eye	Control eye	Ratio $\frac{\text{Denervated}}{\text{Control}}$
Ganglionectomy	Unsaturated	(8) 24·3 ± 1·73	21·9 ± 1·16	1·12 ± 0·04
	Saturated	(6) 58·0 ± 3·4	63·6 ± 2·76	0·91 ± 0·03
Preganglionic section	Unsaturated	(42) 26·0 ± 0·81	23·5 ± 0·91	1·11 ± 0·01
	Saturated	(18) 50·1 ± 1·14	49·8 ± 1·32	1·01 ± 0·01

TABLE 4. Sensitization to adrenaline. Rabbits were subjected to either superior cervical ganglionectomy or preganglionic section of the sympathetic chain on the left side. 24 hr later the pupil diameter was measured in both eyes, before and after intravenous injection of 10 μg adrenaline

	Pupil diameter (mm) before adrenaline		Pupil diameter (mm) after adrenaline	
	Left eye	Right eye	Left eye	Right eye
Ganglionectomy	7·5	8·5	10·5	7·0
	6·5	6·5	9·0	7·0
	8·0	9·0	10·0	8·0
	9·0	7·5	10 5	7·5
	7·5	7·5	10·0	10·0
	7·0	7·0	12·0	8·0
Preganglionic section	7·0	8·0	7·0	9·0
	7·0	8·0	7·0	8·5
	6·0	8·0	7·0	9·0
	6·0	6·0	7·0	8·0
	6·0	6·0	6·0	7·0

In the second series, the plasma concentration was raised to 13–16 mg/100 ml. for 4 hr before removal of the aqueous humour. In these rabbits the concentration of ascorbate in the aqueous from the denervated eye was less than that from the control eye: the ratio of the two concentrations was 0·91.

Sensitization to adrenaline. Paradoxical pupillary dilatation is a well known consequence of ganglionectomy in rabbits (Cannon & Rosenblueth, 1949). Table 3 shows the effect of an intravenous injection of adrenaline on pupil diameter 24 hr after preganglionic sympathotomy and also after ganglionectomy. It is evident that there was no significant difference between the diameter of the pupils before the administration of the adrenaline in the denervated and control eyes in the two series. However, in the ganglionectomized animals the pupil on the operated side was strikingly more sensitive to adrenaline than the control pupil, but sensitization was absent in the animals with preganglionic section of the sympathetic chain. In similar experiments it was found that the sensitization on the ganglionectomized animals was not evident at 6 hr.

DISCUSSION

The purpose of the studies described in this paper was to elucidate the mechanism which brings about the striking fall in intraocular pressure 24 hr after excision of the superior cervical ganglion in rabbits. Both Linner & Prijot (1955), and Lieb *et al.* (1958) found that at this time the intraocular pressure had fallen to within 1–2 mm Hg of the episcleral venous pressure, which they reported to be 9–10 mm Hg in both denervated and control eyes. This value is within the normal range of values for unoperated rabbits. These findings preclude the hypothesis that the fall in intraocular pressure is caused by a change in episcleral venous pressure, and the problem is resolved into whether the effect is due to a decrease in the rate of aqueous formation or to a decrease in the resistance between the anterior chamber and the episcleral veins or to a combination of both. The above authors determined the facility of outflow in rabbits 24 hr after unilateral ganglionectomy by tonography (Lieb *et al.* 1958) and by perfusion of the enucleated eyes (Linner & Prijot, 1955). In both cases the results on the control and experimental eyes were the same, and they concluded that aqueous humour formation had been greatly reduced; and Lieb *et al.* (1958) calculated the reduction to be more than 80 %.

We have found (Langham & Taylor, 1959), using both tonometry and the more direct method of manometry, that 24 hr after ganglionectomy the intraocular pressure fell to 15 mm Hg from its normal value of 20–22 mm Hg. If it is accepted that the episcleral venous pressure is unchanged, these results indicate that the outflow pressure has fallen by about 50 %. Therefore, unless there is an increase in outflow resistance the maximum possible fall in the rate of formation of the aqueous humour under these conditions is also 50 %.

The fluorophotometric studies indicate that the rates of flow of the aqueous humour in the eyes of individual rabbits after unilateral ganglionectomy were similar and within normal limits. A decrease of 50 % in aqueous humour flow would have been readily discernible by this technique and it must therefore be concluded that the decrease in intraocular pressure after ganglionectomy involved changes in the drainage system of the eye.

The results of the fluorophotometric studies are supported by the observations that acetazoleamide, which is known to depress aqueous humour formation, caused a fall in the intraocular pressure of eyes already hypotensive as a result of ganglionectomy. Under these conditions acetazoleamide caused a similar proportionate decrease in the outflow pressure of the normal and hypotensive eyes. It is difficult to believe that this result would have been achieved if secretion of the aqueous humour had been depressed 50–80 % as a result of ganglionectomy, whereas the result is consistent with the conclusion that aqueous flow was similar in the two eyes.

Direct evidence that the outflow system is modified by ganglionectomy was seen in the results of the perfusion studies. It is clear that the slopes of the curves relating steady-state pressure with rate of infusion are mainly dependent upon the resistance to outflow, and that a gross change in the latter will manifest itself as a change in the slope. Some caution is, however, necessary in extrapolating these results back to the point of zero infusion, for the slope cannot under all circumstances be accepted to indicate outflow resistance alone, since at low infusion rates in the normal eye the slope of the curve approaches zero, whereas in fact resistance to outflow at this point is known to be considerable. It is, however, difficult to interpret the markedly shallower slopes from the ganglionectomized eyes except as indicating a striking reduction in the resistance to outflow of aqueous humour.

In considering the fall in intraocular pressure it should be remembered that this effect is found only after ganglionectomy and not after preganglionic section of the sympathetic chain. It has been suggested to us that the difference between the effects of the two procedures might be due to the formation of an irritative lesion after ganglionectomy but not after preganglionic sympathotomy, and consequently that the fall in intraocular pressure is due to an excess of sympathetic excitation rather than to a deficiency. This appears improbable, since after ganglionectomy the pulse pressure in the denervated eye is greater than that in the control eye (see Fig. 2), despite the mean pressure in the denervated eye being low, an occurrence which of itself would tend to reduce pulse pressure. Secondly, the ascorbate concentration in the denervated eye is higher than that in the control eye (the ratio of the concentrations being 1·12:1). It has been argued (Linner, 1952; Langham, 1955) that since at normal plasma ascorbate concentrations the mechanism for secreting ascorbate into the aqueous is unsaturated, then a change in the blood flow through the secretory area (ciliary body) will bring about a change in the same direction in the aqueous ascorbate concentration. The rise in the aqueous ascorbate concentration 24 hr after ganglionectomy suggests that blood flow through this eye has been increased as a result of the operation. Furthermore, the increase would appear to be of the same order as that found by Becker & Linner (1952) after preganglionic section of the sympathetic chain.

At a plasma concentration above approximately 3 mg ascorbic acid/100 ml., the secretion of ascorbic acid into the aqueous humour reaches a maximum. Under these conditions 24 hr after ganglionectomy the concentration of ascorbate in the aqueous humour of the denervated eye was less than in the control eye, the ratio of the mean concentrations being 0·91:1. This is consistent with an increase in the rate of flow of aqueous humour in the experimental eye. However, the level of ascorbate in both eyes was very much greater than the plasma level and it is possible that the fall in concentration in the ganglionectomized eye was due to the increased permeability of the blood–aqueous barrier which accompanies pre- and post-ganglionic cervical sympathotomy.

Differences between the immediate effects on intraocular pressure of pre- and post-ganglionic sympathotomy have previously been reported. Von Hippel & Gruenhagen (1870) claimed that preganglionic section of the cervical sympathetic had no effect on intraocular pressure but that removal of the ganglion caused a rise in intraocular pressure. These authors stated that the difference was due to the preganglionic sympathetic fibre to the eye entering the sympathetic chain at the level of the superior cervical ganglion. This anatomical explanation is unacceptable, since no activity could be detected in the post-ganglionic fibres after section of the preganglionic trunk (E. S. Perkins & C. B. Taylor, unpublished), and also since the vascular changes appear to be the same for both operations. The difference between the effects of the two procedures is then the more perplexing, since apparently in both cases there is an equal and complete loss of sympathetic excitation.

There remains, however, the possibility that the differences between the action of pre- and post-ganglionic sympathotomy on the eye is linked with the phenomenon of sensitization, since this also occurs only after ganglionectomy. In this respect it should be noted that the onset of sensitization to adrenaline has approximately the same time course as the depression of intraocular pressure, both being scarcely detectable at 6 hr but very striking 24 hr after the operation. On the other hand, the parallelism ends after 24 hr, since pressure returns to normal within a few days while sensitization persists.

In conclusion, the evidence reported here points to a decrease in the resistance to outflow between the anterior chamber and the episcleral veins as the explanation for the fall in intraocular pressure observed 24 hr after ganglionectomy. The reason why this occurs after extirpation of the ganglion but not after preganglionic sympathotomy remains to be clarified.

SUMMARY

1. The cause of the fall in intraocular pressure found 24 hours after superior cervical ganglionectomy in rabbits has been investigated.

2. The rate of flow of the aqueous humour has been estimated by a fluorophotometric method and was found to be approximately the same in the eyes of individual rabbits 24 hours after unilateral ganglionectomy.

3. Evidence that ganglionectomy changed the resistance to outflow between the anterior chamber and the episcleral veins was obtained from perfusion studies on living eyes.

4. Analysis of the concentration of ascorbic acid in the aqueous humour indicated that ganglionectomy increased the blood flow through the eye.

5. Sensitization of the pupil to adrenaline, although absent 6 hours after ganglionectomy, was clearly demonstrated at 24 hours. This time course followed closely that of the pressure changes following ganglionectomy.

6. It is concluded that the fall in intraocular pressure 24 hours after ganglionectomy is due principally to a decreased resistance in the outflow system of the eye.

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