Topical epinephrine effects on true outflow resistance and pseudofacility in vervet monkeys studied by a new anterior chamber perfusion technique

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Outflow facility was measured in 20 anesthetized vervet monkeys by two techniques; both involved the recording of the rate of inflow of fluid from a reservoir connected to the anterior chamber. In the first technique the pressure in the anterior chamber was periodically raised and lowered, while the extraocular venous pressure was not changed. In the second technique the intraocular pressure was kept constant and the extraocular venous pressure periodically raised and lowered by changing the positive pressure against which the animal was breathing. The trunk of the monkey was in a pressure suit, and the venous pressure was recorded from the sagittal sinus. The change in inflow rate from the reservoir divided by the pressure change that caused it gives a facility. With technique 1 the facility is the sum of true outflow facility and pseudofacility, and with technique 2 it approaches true facility. One eye of the monkeys had been treated with 2 drops of 2 per cent L-epinephrine bitartrate one hour before the experiment. Both eyes were studied simultaneously and the two techniques applied in the order No. 1, No. 2, No. 1. Pseudofacility was estimated as the difference between the results of techniques 1 and 2; epinephrine effects were estimated by comparing the two eyes. In 11 untreated eyes pseudofacility was $0.087 \pm 0.034$ (S.E.M.) and true facility $0.311 \pm 0.054$ (S.E.M.) microliter · minute⁻¹ per millimeter Hg. The effect of epinephrine on true outflow resistance in 20 monkeys was best described as a reduction in resistance by $0.49 \pm 0.20$ (S.E.M.) millimeter Hg per microliter · minute⁻¹ independent of the resistance in the control eye which was $3.35 \pm 0.37$ (S.E.M.). The effect of epinephrine on pseudofacility in 8 eyes was $0.074 \pm 0.020$ (S.E.M.) microliter · minute⁻¹ per millimeter Hg and seemed to be rather independent of starting pseudofacility. Thus, the early effect of epinephrine on outflow facility is a double one. The effect on pseudofacility will be more important when true facility is low, than on true outflow resistance, when true facility is high.

Epinephrine is widely used in chronic simple glaucoma, but the mechanism by which the hypotensive effect is exerted is not fully explained (recent discussions¹⁻³). There is general agreement about a decrease in secretion rate,³ and an increase in facility after long-term treatment has been

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Epinephrine effects on outflow resistance

An effect of epinephrine on outflow facility in normal human eyes was first claimed by Prijot. He compared a tonogram taken before the topical application of a solution containing 2 per cent of L-epinephrine base with one taken 24 hours later. Both eyes were treated simultaneously and there was thus no control eye. Prijot found an average of 30 per cent drop in resistance besides the expected drop in aqueous formation. Also using tonography, Krill, Newell, and Novak found no significant effect in 3 of 5 normal human eyes but about a 50 per cent increase in facility in 2 eyes. The authors report, speaking of normal and glaucomatous eyes together, that the increase in facility was seen already one hour after drug. This seems to be the only report of a very early effect on facility in the normal human eye.

A large number of anterior chamber perfusion experiments (still unpublished) in several species of monkey with the two-level constant pressure technique have shown an increase in outflow facility one to several hours after topical application of 2 per cent epinephrine. In the vervet, the size of the effect is about 0.15 C-units (microliter · minute⁻¹ per millimeter Hg).

Stimulation of the cervical sympathetic nerve decreases outflow facility in vervet monkeys and relaxes the ciliary muscle of several monkey species. The adrenergic receptors of the ciliary muscle of several monkey species are purely β, tending to relax the muscle. Since increased outflow facility as a rule results from contraction of the ciliary muscle and epinephrine has a β-action, augmentation of outflow facility by epinephrine is puzzling. One would have expected the opposite effect. It seemed possible that epinephrine might increase pseudofacility, the suppressibility (by pressure) of the formation of aqueous, without increasing true outflow facility. The present experiments were designed to test this point by comparing the epinephrine effect (in the same eye and on the same occasion) measured by the two techniques: (1) the conventional two-level constant pressure infusion which suffers from the effects of pseudofacility and (2) a related new technique, which should give facility values free from pseudofacility.

Methods and materials

About 50 ostensibly healthy adult vervet monkeys, Cercopithecus aethiops, of both sexes (average body weight for males 4.2 kilograms, and for females 2.7 kilograms) were used. The conventional two-level constant pressure perfusion technique as used presently has recently been described, and only the new method is therefore described.

Principle of the new method. Flow F through the outflow channels is taken to be proportional to the true facility Ctrue and to the pressure head, the difference between intraocular pressure p_i and the pressure in the recipient veins p_0:

\[ F = C_{true} \cdot (p_i - p_0) \]  (1)

As a first approximation, linear relations are assumed. Therefore a change \( \Delta(p_i - p_0) \) in the pressure head is assumed to cause a proportional change in flow \( \Delta F \) through the outflow resistance

\[ \Delta F = C_{true} \cdot \Delta(p_i - p_0) \]  (2)

In the conventional techniques the changes in the pressure head are caused by changes in \( p_i \) which in turn are caused by raising or lowering a reservoir of fluid connected to the anterior chamber. This causes not only a change \( \Delta F \) but also a change in the pressure-dependent formation rate of aqueous humor. The inflow rate Q from the reservoir therefore changes by more than \( \Delta F \) and the change \( \Delta Q \) divided by the pressure change \( \Delta p_i \) is \( C_{tot} \) which exceeds \( C_{true} \) by the amount \( C_{ps} \) of pseudofacility:

\[ \Delta Q \over \Delta p_i = C_{tot} = C_{true} + C_{ps} \]  (3)

In the new method the change in the pressure head is caused by a change in venous pressure \( \Delta p_v \) while the level of the reservoir is kept constant and above any \( p_0 \) that will occur. If the pressure in the anterior chamber were kept perfectly constant, venous pressure in the eye would not change when \( p_v \) is changed because of the collapse phenomenon at the point of exit of the intraocular veins. The pressure relations within the eye would therefore stay the same, there would be no change in blood flow, and there would be no passive change in aqueous formation rate. The change in inflow rate from the reservoir \( \Delta Q \) divided by the
change in pressure head $\Delta p$, would then be true facility, $C_{\text{true}}$.

In actual practice, the needle and tubing connecting the eye and the reservoir have some flow resistance. Pressure in the eye $p_e$ therefore rises a little when $p_e$ is increased and the rate of inflow from the reservoir is decreased. One therefore has to divide $AQ$ not by $\Delta p_e$, but by $\Delta p_e - \Delta p_i$. Since the resistance of the perfusion system is low, $\Delta p_i$ is quite small. In the present experiments, it was on an average less than 0.2 mm Hg. Nonetheless this rise causes true facility to be contaminated by a small amount of pseudofacility.

**Arrangement of the experiment.** The main experimental difficulty in this method to obtain $C_{\text{true}}$ is to measure $\Delta p_e$, the pressure change in the relevant veins, which are those where pressure is essentially independent of the amount of aqueous flowing into them. Veins closer to Schlemm's canal contribute to the measured outflow resistance.

Direct cannulation of small episcleral veins, as performed by Brubaker and Kupfer in the monkey, did not seem practical in the present connection, and a technically simpler procedure was sought.

The ocular veins in the monkey drain into the facial veins and into the cavernous sinuses. In a first series of experiments, the angular vein on one side was cannulated for the pressure recording, and the venous pressure was changed by an inflatable cuff around the neck. The results were quite variable. Sometimes even considerable rises in venous pressure recorded in the angular vein failed to affect the flow from the reservoirs into the anterior chambers. Probably intraspinal veins inaccessible to the cuff and communicating with more caudal parts of the body prevented any appreciable rise in cavernous sinus pressure when the cuff was inflated. Blood from the eye therefore could escape without pressure rise through the posterior route. Hence the actual pressure change $\Delta p_e$ in the relevant vessels was unknown in these experiments. Another unsuccessful attempt was with a tilting board by means of which the hindquarters of the monkey could be raised and lowered. The resultant venous pressure changes in the head were too small. At last spontaneous breathing against a continuous positive pressure was attempted. A cuffed tracheal tube was inserted and connected to a source of air at adjustable positive pressure (see the following discussion). However, the anesthetized monkey could not expire against sufficient positive pressure to appreciably affect the pressure in the intracranial veins. Only when a large plastic bag connected with the air pressure line as shown in Fig. 1 was wrapped around the trunk to form a pressure vest around the thorax and abdomen did it become possible to cause the desired venous pressure shifts of about 5 mm Hg by changing the pressure of the inspired air. This agrees with findings in man.

A low impedance source of adjustable positive air pressure was arranged as follows: High pressure air was passed through a needle valve into a long coil of 10 mm. internal diameter tubing. This was fitted at its end with a piece of 8 mm. internal diameter glass tube, the air overflow tube (Fig. 1). The tracheal tube and the plastic bag enclosing the trunk were connected to the heavy tubing close to each other and near its end. The pressure in the bag and in the tracheal tube therefore followed each other closely. A rapid flow of air was maintained. Thus, the positive pressure was governed by the depth of the tip of the overflow tube beneath the surface of the water in the cylinder and hardly at all by the breathing of the animal. Nonetheless, respiratory fluctuations of the venous pressure were evident and made it difficult.
to define venous pressure to better than 0.5 mm. Hg. The lowest venous pressure during the cycle was the one measured and utilized.

Venous pressure was recorded from the sagittal sinus. The animal was lying prone, with the head fixed in a holder, and the axes of the eyes horizontal. After a skin incision a small hole was drilled in the sagittal suture at the vertex down to the dura. A narrow polyethylene tubing was then introduced into the sinus through a small puncture and pushed backward several centimeters toward the confluens sinuum. The tubing was connected to a sensitive pressure-transducer recording on a strip chart recorder. An air bubble was introduced into the transducer to dampen pulsations. In order to keep the tip of the tubing open an infusion of 7.5 µL per minute heparinized saline was kept running through it at all times. A fluid surface at the level of the eye served as the zero point for venous pressure and for intraocular pressure. The zero point and calibration levels were taken with the constant rate infusion of saline running.

In a few experiments conventional blood pressure recording from the femoral artery was performed.

Protocol of the experiment. After anesthesia with intravenous pentobarbital (about 26 mg. per kilogram) 2 per cent /-epinephrine bitartrate in the form of one drop of freshly prepared clinical Lyophrin was applied to one cornea and distributed over the conjunctival sac. Five minutes later another dose was given. The other eye was not treated. The actual measurements were started 60 to 62 minutes (in one case 68 minutes) later. Meanwhile the animal had been prepared for recording by inserting the polyethylene tubing into the sagittal sinus and a cuffed tube (4 to 6 mm. internal diameter) into the trachea after spraying the larynx with 10 per cent lidocaine and smearing the tube with 1 per cent pramoxine jelly.1

The air overflow tube, Fig. 1, had been lowered 5 cm. into the water with the compressed air disconnected to give a still water surface. At the start of the experiment proper the compressed air was switched on and the tracheal tube and the plastic bag enclosing the trunk connected to the positive air pressure. One minute or so later two needles were fired into each anterior chamber and the recording of pressure without infusion started. When pressure had settled down, usually in about 5 minutes, the reservoirs were connected to the system and the perfusion experiment proper was started.

Fig. 2 indicates the sequence of the typical experiment. It consists of three parts. In part I facility determinations were made by shifting the reservoir pressure back and forth between 2.5 mm. and 11.9 mm. Hg above the initial spontaneous intraocular pressure in the conventional manner. Each pressure was kept 3 to 4 minutes, and five such periods were recorded. The tip of the overflow tube was constantly at its original setting, 5 cm. below the surface of the water. In part II the reservoirs were kept constantly at their lower level with the intraocular pressures around 12 to 17 mm. Hg. The overflow tube in the water cylinder (Fig. 1) was now periodically lowered and again raised by 10 cm., thereby causing corresponding changes in pressure in the air pressure line and in the bag. Each pressure was held 3 minutes or more until the sagittal sinus pressure had been stable for 2 minutes. Five such periods at alternating pressure was recorded. Part III consisted of a repetition of part I.

A few experiments where sagittal sinus pressure occasionally exceeded the intraocular one (set by the reservoir) were discarded.

Calculations
For reasons previously explained,17 it is essential to use procedures involving successive averages if one is to avoid a sawtooth effect in case the eye is changing. Fig. 3 illustrates how the calculated quantities are derived from the directly observed ones.

Facility and resistance. Speaking of one eye only, in each separate part of the experiment I

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*Lyophrin, prepared by Alcon Labs., Inc., Fort Worth, Texas.
‡Obtained as Tronothane, registered U. S. trademark of Abbott Laboratories, North Chicago, Ill.
to III there were five inflow rates \( Q \), caused by five pressure differences \( p_{\text{in}} \) between eye and sagittal sinus, four changes in inflow rate \( \Delta Q \), and four changes in \( p_{\text{es}}, \Delta p_{\text{es}} \). The individual \( \Delta Q \) divided by the corresponding \( \Delta p_{\text{es}} \) yielded four individual facilities \( C \). This is true in all three parts of the experiment, even if intraocular pressure was changed in parts I and III and venous pressure in part II. The successive means \( C_{n-1} \) are calculated with \( C_{n} = 0.5 \left( C_{n-1} + C_{n} \right) \) and so on. Thus \( C_{n} \) derives from inflow rates \( Q_{1}-Q_{3} \) with \( Q_{2} \) appearing twice, once in \( C_{1} \) and once in \( C_{2} \). In a few instances movements of the animal or similar causes made one \( Q \)-value unusable. In this case only 2 \( C_{n} \) were obtained. Only once was a single \( C_{n} \) used.

In the tables and further calculations the averages of the 3 \( C_{n} \) (if present) or \( 1/C_{n} = R_{n} \) for each part I to III of the experiment are used.

**Intraocular pressure in parts I and III.** Intraocular pressures as they would have been without inflow from the reservoirs were calculated as follows.

If anterior chamber pressure is kept at \( p_{a} \) by inflow \( Q \) from the reservoirs, the pressure at no inflow from the reservoirs was calculated as follows.

\[
p_{a} = p_{0} - \frac{Q}{C_{m}}
\]

(4)

\( C_{m} \) is used instead of \( C \) derived from only two periods in order to avoid the sawtooth effect. Since any \( C_{m} \) is derived from three periods with twice as much weight attached to the middle one than to the two others, a corresponding weighted average was calculated for \( p_{0} \). The three periods yielding a \( C_{m} \) were used to obtain three values for \( p_{0} \) according to equation 4. These 3 \( p_{0} \) were then averaged with twice as much weight given to the middle one than to the two others, as indicated at the bottom of Fig. 3. The figure illustrates the procedure for \( C_{m} \) and \( p_{0mn} \). It is analogous for the subsequent \( C_{m} \) and \( p_{omn} \). Evidently, period 3 affects all three \( C_{m} \) and \( p_{omn} \), periods 2 and 4 affect two each and periods 1 and 5 one only. In the tables the three \( p_{omn} \) are averaged for each part of the experiment.

**Intraocular pressure in part II.** Here venous pressure was manipulated and the reservoirs kept still. Equation 4 then does not give a correct \( p_{0} \), because the experiments yield \( C \)-values which do not contain pseudofacility and are, therefore, too small. If \( Q \) is small, however, equation 4 shows that the error caused by an underestimated \( C \) is small. In order to obtain \( p_{0} \) values at high sagittal sinus pressure, such periods were selected from the data where \( Q \) was zero or less than \( \pm 1 \mu \text{L} \) per minute. The application of equation 4 to such periods causes an error of less than 1 mm. Hg, and where \( Q \) is zero, there is no error at all. Thus, the \( p_{0} \)-values at high sagittal sinus pressure are not \( p_{omn} \)-values but individual ones and derived from only one period each, with few exceptions, where two periods happened to fulfill the criteria.

**Pressure in the recipient vessels.** These vessels by definition are those in which the pressure is no longer influenced by aqueous flow. Their pressure \( p_{r} \) thus depends solely on hemodynamic relations in the special vascular tree to which they belong. Assume that the total resistance between artery and large veins in this tree is \( R_{vasc} \) and that...
the resistance from the artery to the recipient vessels is \( \alpha \cdot R_{\text{vasc}} \). The resistance from there on to the large veins is then \((1-\alpha)\cdot R_{\text{vasc}}\). If \( p_{\text{art}} \) is arterial and \( p_{\text{vein}} \) is venous pressure in the tree under discussion, it is easily shown that

\[ p_c = p_{\text{vein}} + (1-\alpha) \cdot (p_{\text{art}} - p_{\text{vein}}). \tag{5} \]

Changes in the large vessel pressures without changes in the resistance distribution affect \( p_c \):

\[ \Delta p_c = \Delta p_{\text{vein}} + (1-\alpha) \cdot (\Delta p_{\text{art}} - \Delta p_{\text{vein}}). \tag{6} \]

Thus, if \( p_{\text{art}} \) and \( p_{\text{vein}} \) were to rise by equal amounts, \( p_c \) would follow both. If only \( p_{\text{vein}} \) rises, \( p_c \) rises less, namely, by \( \alpha \cdot \Delta p_{\text{vein}} \). In fact, the rise in \( p_{\text{art}} \) and \( p_{\text{vein}} \) is probably quite similar (see the following discussion).

**Statistics.** Means are generally shown with their standard errors. P-values from Student's t test are one-tailed when given.

**Results**

**Results pertaining to the method.**

**Arterial blood pressure.** Mean arterial pressure but nothing else was recorded in four separate experiments during pressure breathing under exactly the same conditions as in the main series. In each experiment there were 4 periods of 5 minutes each breathing against 5 cm. H\(_2\)O (5 cm. periods) and 3 periods breathing against 15 cm. H\(_2\)O (15 cm. periods). Mean arterial pressure during the four 5 cm. periods was averaged in each animal. It was 57, 72, 97, and 110 mm. Hg in the 4 animals. During the three 15 cm. periods the average mean arterial pressure was higher by 11, 5, 10, and 0 mm. Hg, respectively, in the 4 animals. The average mean arterial blood pressure in all 4 animals during the 5 cm. periods of these experiments, 84 mm. Hg, is well in the normal range usually found in these monkeys and with the present anesthesia. The average rise, 65 mm. Hg, is what would be expected from the increase in intrapulmonary pressure, which is 7.35 mm. Hg. The increase in intrathoracic pressure helps the left ventricle to eject and should be reflected in a corresponding rise in arterial blood pressure. Similar observations have been made in the human breathing against continuous positive pressure in a pressure suit. Thus, there are reasons to believe that arterial and venous pressure increase by roughly the same amount.

**Sagittal sinus pressure.** The figures refer to the stable sagittal sinus pressure during the last 2 minutes of any pressure period. With very few exceptions corresponding \( p_{\text{neg}} \) were equal to within 0.5 mm. Hg in the successive periods of any single part of the experiment.

Of 31 experiments started with the intention of carrying through the protocol described above, 20 were technically successful in all three parts. These are the ones summarized in Table I and used subsequently. Sagittal sinus pressure \( p_{\text{neg}} \) was positive in all animals breathing against 5 cm. H\(_2\)O, and very close, on an average, to the pressure in the airways, 3.68 mm. Hg. It was surprisingly low in certain cases, however. This could be a source of error. Since there is a positive pressure of perhaps a few millimeters of Hg in the orbit and the orbital fat is semifluid, conditions might be such that a collapse can occur at the point of exit of the veins from the orbit when extraorbital venous pressure is lower than the orbital one. The pressure in the orbital veins and in recipient vessels would then follow \( p_{\text{neg}} \) only when \( p_{\text{neg}} \) exceeds orbital pressure. If \( p_{\text{neg}} \) were to start below orbital pressure, only the last part of its increase would be reflected in the recipient vessels. It seems that a basal positive breathing pressure of somewhat more than 5 cm. H\(_2\)O ought to have been selected. The actual importance of this source of error is small, as will be discussed later.

**The pressure \( p_c \) in the recipient vessels.** Knowledge of \( p_c \) is necessary for an estimation of the factor \( \alpha \), the degree to which one would expect changes in orbital venous pressure to penetrate to the recipient vessels. (See Calculations, equations 5 and 6.) The pressure \( p_c \) cannot be measured directly but an approximate level can be made from the relation between intraocular pressure and sagittal sinus pressure during the 15 cm. H\(_2\)O periods of part II where orbital pressure cannot complicate the picture.
Table I. Sagittal sinus pressure ($p_{sag}$) in 20 monkeys breathing against 5 or 15 cm. H$_2$O positive pressure with trunk enclosed in a pressure suit kept at the same positive pressure as the airways

<table>
<thead>
<tr>
<th>Part of experiment</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 5 cm. H$_2$O</td>
<td>3.86 ± 0.50</td>
<td>3.50 ± 0.50</td>
<td>8.51 ± 0.54</td>
</tr>
<tr>
<td>Range 0.50 - 8.40</td>
<td>0.50 - 8.25</td>
<td>5.00 - 13.67</td>
<td>0.70 - 8.90</td>
</tr>
<tr>
<td>Mean difference</td>
<td>5.01 ± 0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range of differences</td>
<td>3.25 - 6.50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Means ± standard error of the mean and ranges, all in millimeters of Hg above a fluid surface at eye level.

In 16 experiments an excellent to fair estimate of intraocular pressure could be obtained as described in Calculations, Intracocular pressure in part II. The results are given in the upper part of Table II.

The table shows that on an average there is a difference of 4 to 5 mm. Hg between intraocular pressure and pressure in the sagittal sinus. $p_0 - p_{sag}$ is 4.56 ± 0.56 in the epinephrine eyes and 4.90 ± 0.42 in the control eyes. If one allows as little as 2 mm. Hg for the pressure drop from the anterior chamber to the recipient vessels, these latter evidently are situated only, say, 3 mm. Hg above the large orbital veins and the sagittal sinus. If the pressure there is taken as 8 mm. Hg (see Table II) and the mean arterial blood pressure as 68 mm. Hg, which is certainly too low, $a$ in equations 5 and 6 becomes 0.95. If mean arterial pressure is taken as 88 instead, and the recipient vessels are taken as 2 mm. Hg above the large orbital veins, $a$ becomes 0.975.

It is probable that breathing against 15 cm. H$_2$O causes some hemodynamic adjustments but it is not probable that these greatly affect the value of $a$. Moreover, since the arterial pressure rises approximately as much as the venous one, the nonunity of $a$ must have negligible effects. The remaining data in Table II will be discussed later.

Ocular pressures. In that majority of cases where sagittal sinus pressure responded to elevation of intrathoracic pressure with a rise and then kept constant at the new level one could see that inflow rate from the reservoirs became steady in less than 1 minute. Thus, the pressure difference between anterior chamber and recipient vessels must have become established very quickly. Measurements in this paper always refer to this steady state situation.

As the range figures of Table II show, there are cases where $p_0 - p_{sag}$ was negative. The reason for this is that $p_0$ is extrapolated to no inflow from the reservoir. If an eye has a low secretion and is kept at a higher pressure than it would have spontaneously, the uveoscleral flow which becomes pressure dependent only at extremely low intraocular pressures can cause sufficient net absorption of fluid in the eye to cause a seemingly negative outflow pressure head. If there had been no reservoir connected to the eye the pressure would have dropped so far that uveoscleral flow had become reduced. This then is a nonlinearity in the system but it appears only at extremely low pressures.

Epinephrine, intraocular pressure, and true outflow facility. Epinephrine effects in the following are always expressed as the difference between the treated and the untreated eye.

Tables II and III show that no consistent effect of epinephrine on intraocular pressure was discernible. Possibly the epinephrine
Table II. Intraocular pressure $p_0$ and sagittal sinus pressure $p_{sin}$ in millimeters of Hg during breathing against 15 cm. H$_2$O and 5 cm. H$_2$O

<table>
<thead>
<tr>
<th></th>
<th>Epinephrine eye</th>
<th></th>
<th>Control eye</th>
<th></th>
<th>Epinephrine-control</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$p_0$</td>
<td>$p_{sin}$</td>
<td>$p_0 - p_{sin}$</td>
<td>$p_0$</td>
<td>$p_{sin}$</td>
<td>$p_0 - p_{sin}$</td>
</tr>
<tr>
<td><strong>Breathing 15 cm. H$_2$O</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>12.88 ± 0.78</td>
<td>8.31 ± 0.67</td>
<td>4.56 ± 0.56</td>
<td>13.31 ± 0.68</td>
<td>8.41 ± 0.68</td>
<td>4.90 ± 0.42</td>
</tr>
<tr>
<td>Median</td>
<td>12.30</td>
<td>7.25</td>
<td>3.85</td>
<td>12.80</td>
<td>7.25</td>
<td>5.05</td>
</tr>
<tr>
<td>Range</td>
<td>8.9 to 20.1</td>
<td>5.0 to 13.5</td>
<td>-1.0 to 8.3</td>
<td>10.4 to 19.6</td>
<td>5.0 to 13.5</td>
<td>-0.3 to 8.0</td>
</tr>
<tr>
<td><strong>Breathing 5 cm. H$_2$O</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(I + III)/2</td>
<td>Mean</td>
<td>8.81 ± 0.51</td>
<td>3.57 ± 0.58</td>
<td>5.24 ± 0.54</td>
<td>8.55 ± 0.57</td>
<td>3.57 ± 0.58</td>
</tr>
<tr>
<td>Difference between breathing 15 and 5 cm. H$_2$O</td>
<td>Mean</td>
<td>4.06 ± 0.54</td>
<td>4.74 ± 0.23</td>
<td>-0.68 ± 0.61</td>
<td>4.76 ± 0.47</td>
<td>4.83 ± 0.23</td>
</tr>
</tbody>
</table>

In the 15 cm. H$_2$O section of the table, the pressures as a rule relate to only a single period. In the 5 cm. H$_2$O section they are $p_{sin}$ averaged over the ten periods of parts I and III of the experiment. Sixteen pairs of eyes. Means ± standard error of mean.
Table III. Calculated intraocular pressure: \( p_{\text{om}} \), pressure head; \( p_{\text{om}} - p_{\text{os}} \) and directly measured intraocular pressure before start of perfusion; \( p_{\text{on start}} \), all with animal breathing against 5 cm. H\(_2\)O

<table>
<thead>
<tr>
<th></th>
<th>Epinephrine</th>
<th>Control</th>
<th>Epinephrine-control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>III</td>
<td>I</td>
</tr>
<tr>
<td>( p_{\text{om}} )</td>
<td>9.73 ± 0.64</td>
<td>7.32 ± 0.59</td>
<td>9.09 ± 0.63</td>
</tr>
<tr>
<td>( p_{\text{om}} - p_{\text{os}} )</td>
<td>5.90 ± 0.60</td>
<td>3.67 ± 0.55</td>
<td>5.29 ± 0.59</td>
</tr>
<tr>
<td>( p_{\text{on start}} )</td>
<td>11.61 ± 0.44</td>
<td>10.45 ± 0.54</td>
<td>1.16 ± 0.30</td>
</tr>
</tbody>
</table>

*All values in millimeters of Hg, ± standard error of the mean, 20 monkeys.*

The effect on pressure was only under development at this stage. The values of \( p_{\text{om}} \), shown in Table III are extrapolated ones (equation 4) and subject to more sources of error than directly measured ones. Such directly measured values are available for breathing against 15 cm. H\(_2\)O in Table II. There are also some breathing against 5 cm. H\(_2\)O but only from the very beginning of the experiments, before the reservoirs were connected to the eyes and before steady state had been reached with certainty after it had been disturbed by the start of pressure breathing. Pressure in the control eyes was 10.45 ± 0.54 mm. Hg and it was 1.16 ± 0.3 mm. Hg higher on the epinephrine side.

There is a drop in pressure \( p_{\text{p}} \) and also in pressure head \( p_{\text{h}} - p_{\text{os}} \) from part I to part III. There is a rise in facility between I and III (Table IV) and the drop probably is due partly to this, partly to reduced formation of aqueous, or opening up of Bill's posterior routes. The experiments did not allow a decision between these possibilities.

Table IV shows the facility and resistance values for the same experiments. The conventional facility obtained by changing anterior chamber pressure in parts I and III is called \( C_{\text{tot}} \) in the table heading. The values obtained by changing venous pressure in part II are provisionally called \( C_{\text{vein}} \). It will later be argued that they represent \( C_{\text{vein}} \). Epinephrine caused an increase in both \( C_{\text{tot}} \) and \( C_{\text{vein}} \). We are concerned with the latter.

Is increase in facility an appropriate measure of the epinephrine effect on \( C_{\text{vein}} \)? Physiologically, the effect of epinephrine may not be to add an extra pathway, which is what “added facility” implies. In Figs. 4A \( C_{\text{vein}} \) and in 4B its inverse value, the resistance \( R_{\text{vein}} \) has been plotted showing the values of the control eye on the abscissa and the values of the epinephrine eye on the ordinate. The diagonal line connects equal values of the two, it is the line of no effect. Fig. 4A shows that the facility effect of epinephrine is poor at low starting facilities, that is, low facilities in the control eye. The amount of facility added to \( C_{\text{vein}} \) of an eye by epinephrine thus is not independent of its starting facility. Fig. 4B on the other hand suggests that the amount of resistance removed from \( R_{\text{vein}} \) by epinephrine tends to be independent of the starting resistance of the eye. It is certainly variable but the band of variation appears to be of rather even width. The distribution is quite different from that given by a small amount of pilocarpine. In the latter case the effect in R-units increases with starting resistance.

Inspection of the data shows that, in certain animals, facility, especially on the epinephrine side, increased very markedly between parts I and III. This increase was so strong and irregular (Table IV range figures in the III - I column) that the correlation between the epinephrine effect on \( C_{\text{tot}} \) in parts I and III is not significant, while there is a significant correlation \((r = 0.59)\) between the effects on \( C_{\text{tot}} \) in part I and on \( C_{\text{vein}} \). (By coincidence \( r \) is 0.59 also between the effects on \( 1/C_{\text{tot}} \) and on \( 1/C_{\text{vein}} \).) Something has evidently happened between I and III, and it affects II to a variable extent. The fact that the
Table IV. Facility and resistance measured by two techniques and the effect of epinephrine

<table>
<thead>
<tr>
<th>Part of the experiment</th>
<th>I</th>
<th>1/C_{I}</th>
<th>II</th>
<th>1/C_{II}</th>
<th>III</th>
<th>1/C_{III}</th>
<th>III - I</th>
<th>1/C_{III - I}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{cot}}$</td>
<td>$1/C_{\text{cot}}$</td>
<td>$C_{\text{cont}}$</td>
<td>$1/C_{\text{cont}}$</td>
<td>$C_{\text{cot}}$</td>
<td>$1/C_{\text{cot}}$</td>
<td>$C_{\text{cot}}$</td>
<td>$1/C_{\text{cot}}$</td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.552 ± 0.055</td>
<td>2.23 ± 0.25</td>
<td>0.468 ± 0.081</td>
<td>2.89 ± 0.35</td>
<td>0.672 ± 0.088</td>
<td>2.03 ± 0.25</td>
<td>0.120 ± 0.052</td>
<td>-0.20 ± 0.12</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.107 to +0.876</td>
</tr>
<tr>
<td>Median</td>
<td>0.504</td>
<td>2.004</td>
<td>0.416</td>
<td>2.414</td>
<td>0.569</td>
<td>1.772</td>
<td></td>
<td>0.044</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.433 ± 0.043</td>
<td>2.73 ± 0.25</td>
<td>0.371 ± 0.041</td>
<td>3.38 ± 0.37</td>
<td>0.494 ± 0.049</td>
<td>2.54 ± 0.37</td>
<td>0.061 ± 0.018</td>
<td>-0.18 ± 0.12</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.042 to +0.199</td>
</tr>
<tr>
<td>Median</td>
<td>0.388</td>
<td>2.585</td>
<td>0.299</td>
<td>3.355</td>
<td>0.466</td>
<td>2.145</td>
<td></td>
<td>0.039</td>
</tr>
<tr>
<td>Epinephrine-control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.119 ± 0.031</td>
<td>-0.498 ± 0.094</td>
<td>0.096 ± 0.040</td>
<td>-0.49 ± 0.20</td>
<td>0.178 ± 0.056</td>
<td>-0.51 ± 0.18</td>
<td>0.059 ± 0.051</td>
<td>-0.01 ± 0.20</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.204 to +0.763</td>
</tr>
<tr>
<td>Median</td>
<td>0.103</td>
<td>-0.46</td>
<td>0.025</td>
<td>-0.69</td>
<td>0.088</td>
<td>-0.54</td>
<td></td>
<td>-0.012</td>
</tr>
</tbody>
</table>

Values in parts I and III were obtained by changing intraocular pressure, those in part II by changing venous pressure; twenty pairs of eyes, mean ± standard error of the mean, facilities in microliter · minute⁻¹ per millimeter Hg.
average decrease in resistance caused by epinephrine is almost identical in the three parts of the experiments can be due only to chance. The decrease between I and III will be further discussed in connection with epinephrine effects on pseudofacility.

Before the epinephrine effect on $R_{\text{vein}}$ is accepted as indicating an effect on $R_{\text{true}}$, some possible sources of error have to be discussed.

While $p_{\text{aug}}$ is common to both eyes, the possibility exists that orbital pressure is different on the two sides. The smooth muscle of the orbit is adrenergic and its contraction would if anything be expected to increase orbital pressure. The same is true for the contracture of the other extraocular muscles which epinephrine is able to cause. If there is a collapse phenomenon at the exit of the orbital veins it should be more pronounced on the epinephrine side. The collapse phenomenon would have the effect that $\Delta p_e$, the pressure change in the recipient vessels would be smaller than $\Delta p_{\text{aug}}$.

The result can be seen from the following:

$$C_{\text{vein}} = \frac{Q}{\Delta p_{\text{aug}}}$$
$$C_{\text{true}} = \frac{Q}{\Delta p_e}$$

By division one obtains

$$\frac{C_{\text{vein}}}{C_{\text{true}}} = \frac{\Delta p_e}{\Delta p_{\text{aug}}} \quad (7)$$

Hence, if there is a collapse phenomenon at the exit of the orbital veins with $\Delta p_e < \Delta p_{\text{aug}}$ one will find a $C_{\text{vein}}$ that is lower than $C_{\text{true}}$.

Since this effect should be more pronounced on the epinephrine side, the orbital pressure effect of epinephrine cannot be responsible for the increased facility, the decreased $R_{\text{vein}}$ on the epinephrine side.

A local vascular action of epinephrine could, perhaps, cause an only apparent decrease in $R_{\text{vein}}$ and $R_{\text{true}}$ by increasing $\Delta p_e/\Delta p_{\text{aug}}$ over that of the control side. One would then expect that also the change in intraocular pressure caused by pressure-breathing, and $\Delta p_{\text{aug}}$ would be markedly increased by epinephrine. The data of Table II show that this is not so; the difference tends to be in the opposite direction, $-0.70 \pm 0.52 \text{ mm Hg}$.

The expression for $C_{\text{true}}, \Delta Q/\Delta p_e$, presupposes that aqueous humor formation stays constant while $p_e$ is changed by
changing breathing pressure. The change in breathing pressure has an effect on systemic arterial pressure, however, and the remote possibility exists that this affects aqueous formation differently in the two eyes. In order to simulate an enhancing epinephrine effect on \( C_{\text{true}} \), an increase in \( p_{\text{seg}} \) would have to be accompanied by an increase in aqueous formation rate, which is larger on the epinephrine side. One would then expect this side to show more of a rise in \( (p_0 - p_{\text{seg}}) \) than the other when pressure in the airways is elevated. Table II shows that this is not so, the difference tends to be in the opposite direction, \(-0.60 \pm 0.54 \) mm. Hg.

It is concluded then, that the effect on \( C_{\text{rel}} \) shown in Table IV is an effect on \( C_{\text{true}} \) and that epinephrine really reduces the resistance of outflow through the chamber angle. The reduction is of the order of \( 0.5 \) mm. Hg per microliter \( \cdot \) minute\(^{-1} \) and seems to be rather independent of the starting resistance in otherwise untreated eyes.

The question whether \( C_{\text{rel}} \) itself is a valid measure of \( C_{\text{true}} \) will be discussed in connection with pseudofacility.

**Epinephrine and pseudofacility.** When these experiments were planned, it was hoped that besides the primary objective of \( C_{\text{rel}} \) or \( C_{\text{true}} \), they would all be capable of yielding values for \( C_{\text{ps}} = C_{\text{tot}} - C_{\text{true}} \). However, the marked change which sometimes occurred in \( C_{\text{tot}} \) between parts I and III of the experiment and the uncertainty about how much of this change had already occurred in part II when \( C_{\text{rel}} \) or \( C_{\text{true}} \) was estimated made some of the data unsuitable for derivation of pseudofacility.

In the calculation of \( C_{\text{ps}} \), the value of \( C_{\text{true}} \) has to be subtracted from a value of \( C_{\text{tot}} \), which is strictly corresponding. With the temporal arrangement as used here, only an average between values of part I and part III would be appropriate for \( C_{\text{tot}} \). But if large changes occur between I and III, even an average becomes doubtful. The following selection procedure was therefore adopted.

The difference between \( C_{\text{tot}} \) in III and I was calculated for all control eyes, and they were arranged in ascending order of this difference. The series went from negative differences to positive ones. Starting with the eye with the smallest absolute difference, a group was built up by adding the nearest eyes from both sides of the zero-change point in as symmetrical a manner as the values allowed, so as to keep the average deviation of the group from zero as small as possible. The group could not be increased beyond 11 eyes, then the average started to deviate significantly from zero. The corresponding procedure was then applied to the treated eyes, and the 11 with the smallest change in \( C_{\text{tot}} \) from I to III were selected. There were 8 monkeys in which both eyes belonged to a selected group. The success of this procedure in the selected groups and in their only partially selected countereyes is illustrated in Table V. Evidently the selected groups are the ones best suited for the estimation of \( C_{\text{ps}} \). For estimation of epinephrine-induced changes in \( C_{\text{ps}} \), the doubly selected group is the best.

Table VI shows pseudofacility and re-

### Table V. Success of the selection procedure

<table>
<thead>
<tr>
<th></th>
<th>( n )</th>
<th>Range</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected controls</td>
<td>11</td>
<td>(-0.042 ) to ( 0.039 )</td>
<td>(+0.0024)</td>
</tr>
<tr>
<td>Corresponding treated</td>
<td>11</td>
<td>(-0.079 ) to ( 0.281 )</td>
<td>(+0.043)</td>
</tr>
<tr>
<td>Selected treated</td>
<td>11</td>
<td>(-0.079 ) to ( 0.078 )</td>
<td>(+0.006)</td>
</tr>
<tr>
<td>Corresponding controls</td>
<td>11</td>
<td>(-0.042 ) to ( 0.190 )</td>
<td>(+0.051)</td>
</tr>
<tr>
<td>Both selected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>8</td>
<td>(-0.079 ) to ( 0.068 )</td>
<td>(-0.0095)</td>
</tr>
<tr>
<td>Controls</td>
<td>8</td>
<td>(-0.042 ) to ( 0.039 )</td>
<td>(+0.0016)</td>
</tr>
</tbody>
</table>

\( C_{\text{tot}} \) of part III minus \( C_{\text{tot}} \) of part I. All values in microliter \( \cdot \) minute\(^{-1} \) per millimeter Hg.
lated results from these selected groups. A statistically significant amount of pseudo-facility existed in the treated eyes, 0.170 ± 0.036 U. (microliters • minute⁻¹ per millimeter Hg) and probably also in the untreated eyes, 0.087 ± 0.034. Consequently, there was a clear-cut increase in pseudo-facility in the treated eye; in the doubly selected group it was 0.074 ± 0.020 U. The results in the groups of countereyes are similar to those of the selected ones. Fig. 5 shows a plot of the doubly selected group. The number of cases is small but it seems as if epinephrine adds some $C_{ps}$ independently of what was there before.

Table VI also lists $C_{rel}$ and $R_{rel}$. Comparison with the group of 20 shows that the selection for stability of $C_{tot}$ from I to III has yielded a group with distinctly lower $C_{rel}$ than that of the discarded group. Simple arithmetic shows that for the control group this difference is 0.133 and for the treated group no less than 0.347 U.

Thus it seems that eyes with low starting facility $C_{vein}$ are more stable under prolonged perfusion. This could be due to the smaller amount of fluid passing the meshwork during the experiment.

A second difference between the group of 20 and the selected groups is in the effect of epinephrine on $R_{vein}$. In the singly selected groups it is only half as large. In

**Table VI. Effect of epinephrine on pseudofacility and true outflow resistance in selected groups**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>$C_{ps}$</th>
<th>$P$-value t-test</th>
<th>$C_{rel}$</th>
<th>$R_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected control eyes</td>
<td>11</td>
<td>0.087 ± 0.034</td>
<td>0.0125 - 0.025</td>
<td>0.311 ± 0.054</td>
<td>3.95 ± 0.51</td>
</tr>
<tr>
<td>Epinephrine treated belonging to selected controls</td>
<td>11</td>
<td>0.165 ± 0.054</td>
<td>0.005 - 0.01</td>
<td>0.325 ± 0.050</td>
<td>3.70 ± 0.46</td>
</tr>
<tr>
<td>Epinephrine effect, only controls selected</td>
<td>11</td>
<td>0.078 ± 0.029</td>
<td>0.01 - 0.0125</td>
<td>0.011 ± 0.027</td>
<td>-0.24 ± 0.30</td>
</tr>
<tr>
<td>Selected epinephrine treated eyes</td>
<td>11</td>
<td>0.170 ± 0.036</td>
<td>&lt; 0.0005</td>
<td>0.312 ± 0.057</td>
<td>3.88 ± 0.44</td>
</tr>
<tr>
<td>Controls belonging to selected epinephrine</td>
<td>11</td>
<td>0.097 ± 0.033</td>
<td>0.005 - 0.01</td>
<td>0.288 ± 0.039</td>
<td>4.12 ± 0.53</td>
</tr>
<tr>
<td>Epinephrine effect, only treated selected</td>
<td>11</td>
<td>0.074 ± 0.016</td>
<td>&lt; 0.0005</td>
<td>0.024 ± 0.036</td>
<td>-0.24 ± 0.31</td>
</tr>
<tr>
<td>Epinephrine effect, both controls and treated selected</td>
<td>8</td>
<td>0.074 ± 0.020</td>
<td>0.0025 - 0.005</td>
<td>-0.016 ± 0.021</td>
<td>-0.012 ± 0.35</td>
</tr>
<tr>
<td>All control eyes</td>
<td>20</td>
<td>0.092 ± 0.032</td>
<td>0.0025 - 0.005</td>
<td>0.371 ± 0.041</td>
<td>3.38 ± 0.37</td>
</tr>
<tr>
<td>All treated eyes</td>
<td>20</td>
<td>0.144 ± 0.045</td>
<td>0.0065 - 0.0025</td>
<td>0.468 ± 0.061</td>
<td>2.89 ± 0.35</td>
</tr>
<tr>
<td>Epinephrine effect all eyes</td>
<td>20</td>
<td>0.052 ± 0.023</td>
<td>0.0125 - 0.025</td>
<td>0.096 ± 0.040</td>
<td>-0.49 ± 0.20</td>
</tr>
</tbody>
</table>

For comparison, data for the unselected group are shown at the bottom of the table. Mean ± standard error of mean, $C$-values in microliter • minute⁻¹ per millimeter Hg, R-values in millimeter Hg per microliter • minute⁻¹.
the doubly selected group it is virtually absent. Thus the animals which were not selected for stability of \( C_{\text{tot}} \) between I and III are the ones mainly responsible for the average epinephrine effect on \( R_{\text{venin}} \) and \( C_{\text{venin}} \).

That selection of treated eyes for stability of \( C_{\text{tot}} \) from I to III can select poorly reacting ones would be understandable if there were a slowly developing epinephrine effect partly responsible for the difference between III and I. One has discriminated against eyes which show such an effect by the selection. This is true also for the doubly selected group. But Table VI shows that also in selecting control eyes for stability of \( C_{\text{tot}} \) from I to III one has selected animals, the real outflow resistance of which is decreased less by epinephrine in the time span of the experiment than in animals with less stable control eyes.

The 11 pairs of eyes, which were selected because of stability of the control \( C_{\text{tot}} \) are marked with a downstroke in Figs. 4A and 4B. The distribution pattern does not explain their low average reaction to epinephrine, except that they tend to have a high resistance.

In the doubly selected group virtually all of the facility effect of epinephrine on \( C_{\text{tot}} \) is evidently an effect on \( C_{\text{ps}} \). If the estimate of the effect on \( C_{\text{ins}} \), 0.074 U., were true also for the unselected material of Table IV, the epinephrine effect on pseudo-facility would contribute more than 60 per cent of the average epinephrine effect on \( C_{\text{tot}} \) in part I and 40 per cent of the average effect in part III.

As explained before, orbital pressure and venous collapse could lead to an under-estimation of \( C_{\text{venin}} \) and hence to an over-estimation of \( C_{\text{ps}} \). The conditions for venous collapse must be most favorable at low \( p_{\text{mas}} \). If the source of error is important, one should find an association between low \( p_{\text{mas}} \) during the 5 cm. H\(_2\)O periods of part II and high \( C_{\text{ps}} \). Fig. 6 was constructed to test this point. Only values from the selected groups were plotted. There is no indication that orbital pressure and venous collapse contribute appreciably to the values of \( C_{\text{ps}} \) found. A plot (not shown) of all the data shows the same.

Throughout this paper, \( \Delta p_{\text{mas}} \) has been used instead of \( \Delta p_{\text{p}} \) which could not be measured. Quite apart from the collapse problem just discussed, other sources of error connected with the hemodynamic upset caused by pressure breathing could play a part. One would expect them to be related to the degree of “choking.” Fig. 7
shows the same pseudofacility as Fig. 6 but plotted against $\Delta p_{sag}$, the rise in $p_{sag}$ caused by breathing against 15 cm. H$_2$O. There is no relation between this measure of choking and $C_{vein}$ nor is there any if the data are plotted against the higher $p_{avg}$ itself (not shown).

Fig. 8, A and B at last show the epinephrine effect on $C_{vein}$ in the doubly selected group plotted against the lower $p_{avg}$ and against the degree of choking, $\Delta p_{sag}$. The number of cases is small but if there is a relation, it is very weak.

It seems, therefore, that $C_{vein}$ as determined here is relatively free from major systematic errors caused by the determination of $C_{vein}$ by pressure breathing.

Discussion

The use of pressure breathing to cause a rise in recipient vessel pressure in order to derive a value of $C_{true}$ probably causes more of a circulatory upset than would have occurred with a suitably designed cuff around the neck. In the monkeys used, however, the relevant pressure rise caused by a cuff could not be judged reliably from the pressure rise in a facial vein. Only if direct measurement of episcleral venous pressure can be performed, as by Brubaker and Kupfer, the cuff is the better procedure. In the human, where continuous recording of episcleral pressure is difficult to arrange, it is probably better to use pressure breathing if changes in episcleral venous pressure are to be estimated from measurements in other veins.

The credibility of the facility value obtained by pressure breathing, $C_{vein}$, can best be judged by comparing the amounts of pseudofacility resulting from the measurements with values obtained by other methods.

Average pseudofacility in the untreated vervet eye was $0.087 \pm 0.034$ U. (microliter \cdot minute$^{-1}$ per millimeter H$_2$O). In the rhesus monkey, *Macaca mulatta*, also under deep barbiturate anesthesia and with a different but related procedure, Brubaker and Kupfer found 0.19 U. Their procedure has been criticized by Goldmann and their data reanalyzed by Bill.23 Bill concludes that their data allow a lower limit of 0.10 U. and an upper of 0.19 to be set for $C_{vein}$ disregarding statistical variation. A completely different procedure involving measurement of actual outflow into the bloodstream was used by Bill and Bárány.24 We found a value of 0.13 U. in the cynomolgus monkey, *Macaca irus*. With a somewhat related technique also involving measurement of actual outflow into the bloodstream, Bill has found 0.06 U. in lightly anesthetized *Macaca irus* and, with still another technique, 0.06 to 0.07 U. in *Macaca irus* and also in vervets, the species used here.25

All these figures are so similar that one can only conclude that the value of $C_{vein}$ obtained in the present experiments cannot be very far from the correct one for $C_{true}$. There is also very little room for an effect on $C_{tot}$ of scleral creep.

The effect of epinephrine on the true outflow facility in the otherwise untreated eye appeared as a decrease of the order of 0.5 R-units (millimeter H$_2$O per microliter \cdot
minute\textsuperscript{1}). The mechanism for this effect is not evident. Törnqvist has privately suggested that perhaps contraction of the dilator muscle could affect the trabecular meshwork by way of the attachment of the iris to the ciliary body. The matter needs further investigation.

The epinephrine effect on pseudofacility is the first pharmacological effect on this parameter to be described. It is possible that it is due to vascular actions. However, the posterior uveoscleral outflow routes can also be involved. In a few experiments run in the same species of monkey and with identical epinephrine treatment, Bill\textsuperscript{26} has found slightly increased outflow through these unconventional routes. As has been pointed out\textsuperscript{13} these routes would mainly have pseudofacility.

There is little reason to doubt that mechanisms which exist in the vervet eye have a counterpart in the human eye, even if quantitative differences may exist. It is therefore probable that epinephrine affects both true outflow resistance and pseudofacility in the human eye. A relatively small and constant decrease in true resistance, as found in the monkey, would be of small importance in an eye with a high starting resistance while even a modest constant addition of pseudofacility would be easily noticed in an eye with low starting facility. It is possible therefore that in glaucoma the effect on pseudofacility is the more important one of the early effects of epinephrine. It would be extremely interesting to know if the increase in tonographic facility observed after long-term treatment with epinephrine in glaucoma\textsuperscript{1,5} is also due to pseudofacility.

The author wants to thank Mrs. Malin Svensson for running the experiments.

REFERENCES


