a result of the degeneration of retinal tissue and its derivatives.

The optic nerve, which is an outgrowth of ganglion cells, was affected as expected. However, the sclera, choroid, and ocular muscles arise from the mesenchyme that surrounds the original eye vesicle. As expected, they were relatively normal until the retinal degeneration reached its final stage. Most changes observed in these structures appear to be secondary to changes in the retina and the lens.

The pathologic pictures of the retinal degeneration in mice, rats, cats, and dogs appear to be quite different from those of the Syrian hamster. One of the bases of these differences appears to lie in the difference of the time of onset of the degenerative process, which sets in relatively early in mice, beginning before the rods complete their differentiation. In rats the degeneration sets in after the rods and cones have attained their normal length. The situation in cats, dogs, and man resembles that in rats. Degeneration in the Syrian hamster, however, sets in even earlier than in mice, beginning before the appearance of any sign of the photoreceptor cells. This early onset of the degenerative process appears to be, at least partially, responsible for the more extensive destruction of the eye.

The apparent pleiotropism of the Wh gene presents an intriguing problem. However, it is difficult to determine at this time whether the Wh gene in the Syrian hamster is truly pleiotropic or whether it is a set of very closely linked genes. Only a large-scale breeding experiment can clarify this problem.

The basis for the deafness observed in the Syrian hamster is not known. However, it is interesting to note that no deafness has been mentioned in mice or rats in connection with hereditary retinal degeneration, while deafness often accompanies retinitis pigmentosa in man.

The author expresses his gratitude to Mrs. J. Yoon and J. Peterson for their preparation of histological slides, and to Mr. J. Coughlin for photography. He also expresses his thanks to Mr. J. Campbell for his assistance during the course of this investigation.

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Key words: retina, retinal degeneration, anophthalmia, Syrian hamster.

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Ocular effects of diacetyl morphine and lysergic acid diethylamide in rabbit.
KEITH GREEN.

Intravenous lysergic acid diethylamide (LSD) given to rabbits in doses from 1 to 100 μg per kilogram of body weight produced a dose-related increase in intraocular pressure and outflow facility. Minor changes in systemic blood pressure were observed, but respiration rate was accelerated, and mydriasis became pronounced at higher doses. Diacetyl morphine (heroin) was given intravenously in doses from 0.1 to 2 mg per kilogram of body weight. A dose-related decrease in intraocular pressure and an increase in outflow facility was found. A dose-related miotic was observed and at higher doses respiration became markedly depressed. Neithet drug alters the permeability of the isolated ciliary epithelium. Both drugs appear to increase capillary blood pressure and, hence, aqueous humor inflow to cause the intraocular pressure to be maintained at approximately normal levels in face of increases in outflow facility of 50 per cent.
Despite their wide use as drugs of abuse, little is known of the effects of either diamyl morphine (heroin) or lysergic acid diethylamide (LSD) on aqueous dynamics. Although many of the pharmacologic effects of these two drugs, including the pupillary responses and actions on specific visual sensory systems, are well documented, there is only one report on the effect of LSD on intraocular pressure. LSD, 1 µg per kilogram of body weight given orally to male volunteer subjects caused a small (1.4 to 1.8 mm. Hg), but significant, rise in intraocular pressure between three and nine hours after administration of the drug. No investigation appears to have been made using heroin, but two studies have been made on the effect of morphine (the deacetylated form of heroin) on intraocular pressure. Intramuscularly administered morphine sulfate, 8 or 15 mg., decreased intraocular pressure by an average of 2.0 mm. Hg in normal patients and by an average of 3.5 mm. Hg in glaucomatous eyes of various etiology. Thirty minutes after an intravenous injection of morphine hydrobromide in rabbit (7.5 mg. per kilogram of body weight) a fall in intraocular pressure of 0.9 mm. Hg and an increase in total outflow facility from 0.17 to 0.43 µl per millimeter of Hg per minute was found. The present studies were made to investigate the action of heroin and LSD on intraocular pressure, total outflow facility, and blood pressure in anesthetized and conscious rabbits.

Materials and methods. Both anesthetized and conscious adult albino rabbits (3 to 4 kilograms) were used. The anesthetic was intravenous urethane solution (25 per cent in 0.9 per cent NaCl solution). The femoral artery was cannulated using PE 100 tubing for blood pressure measurement. Following light retraction of the lids, a new 23-gauge needle, which was connected to a transducer and a capillary and reservoir through PE 100 tubing for blood pressure measurement, was inserted into the anterior chamber. Intraocular pressure was recorded on a Sanborn recorder and total outflow facility was determined by the constant pressure perfusion method of Bárany measuring the flow from the capillary with a pressure increment of 5 mm. Hg. Only eyes with stable intraocular pressures and pre- and postfacility intraocular pressures within 2 mm. Hg were accepted. In conscious animals only the intraocular pressure was measured using a pneumatic tonometer, after one drop of proparacaine hydrochloride (Squibb, New York) was applied to the eye.

LSD tartrate was dissolved in a solution of 1 mg. per kilogram of ascorbic acid (as an antioxidant) and was stored in a refrigerator protected from light. Heroin was dissolved in 0.9 per cent sodium chloride solution to a concentration of 1 mg. per milliliter. Both solutions were diluted, if necessary, immediately prior to injection.

Both secretion and filtration were measured across the isolated ciliary epithelium, which was prepared and mounted as described previously. The order of testing of drug was as follows: control permeability, low, then high drug concentration, and a final control permeability determination. The drug doses employed are calculated from the plasma concentration after intravenous injection. At each drug level at least 20 minutes was allowed for any drug effects to be revealed.

Results. LSD. At concentrations of 1 and 2 µg per kilogram of body weight, a small intraocular pressure rise was observed in anesthetized animal (Table I), with pre-drug values increased by 1.1 ± 0.3 and 2.3 ± 0.4 mm. Hg (p < 0.01 for both), respectively, at 90 minutes after intravenous injection. Total outflow facility was increased by 0.12 ± 0.03 and 0.15 ± 0.03 µl per millimeter of Hg per minute, respectively (p < 0.001 for both). Both blood pressure (85/70 to 95/75) and respiration rate (60 to 85 respirations per minute) were mildly increased during the initial 20 to 30 minutes after injection but, thereafter, fell to normal levels.

In conscious animals a wider spectrum of dose levels was employed, from 1 through 100 µg per kilogram of body weight with three animals at each dose level (Table I). At both 1 and 2 µg per kilogram, there is again a small pressure rise (1.3 ± 0.5 mm. Hg), becoming significant (p < 0.005) at about two hours and lasting for up to six hours with a peak at three to four hours. With 5 µg per kilogram, the maximal pressure increase, 2.5 ± 0.6 mm. Hg (p < 0.001), occurred at about two hours. At doses of 50 and 100 µg per kilogram, the peak pressure effect was seen at about two hours with increases of 3.5 ± 0.9 and 3.6 ± 1.0 mm. Hg (p < 0.001), respectively; the effect lasted for about four hours.

With low doses (1, 2, and 5 µg per kilogram), a mild increase in respiration rate was seen together with a moderate mydriasis of 2 mm.; both effects lasted for about 90 minutes. High-dose levels of LSD, however, produced marked tachyphnea with respiration becoming very shallow and rapid (250 respirations per minute) for about one hour, falling to normal values at about four to five hours. A complete mydriasis occurred within 90 seconds after injection which lasted for about two hours and lessoned with time. The animals showed an increased sensitivity to noise levels, reacting vigorously to an auditory stimulus.

Control groups of animals, both anesthetized and conscious, show little or no change in intraocular pressure (maximum change +0.2 ± 0.2 mm. Hg) and a 4 per cent increase in outflow facility when receiving an intravenous injection of the LSD-vehicle solution.

Heroin. In anesthetized animals dose levels of 0.1 and 0.2 µg per kilogram of body weight were...
± 0.3 and 0.4 mm. Hg (p < 0.001 for the maximum fall in pressure (2.8 ± 0.4 mm. Hg)).

The fall in pressure was 2.3 per cent increase in intraocular pressure after two hours was seen in man,1 but the finding on outflow facility after receiving injections of saline vehicle. Neither drug caused a change in either secretion rate or fluid permeability across the isolated ciliary epithelium (Table III).

Discussion. LSD increases intraocular pressure slightly and this occurs concurrently with a 50 per cent increase in total outflow facility. The small intraocular pressure change is similar to that seen in man,3 but the finding on outflow facility represents a new aspect of LSD effects.

With heroin, there is a small intraocular pressure drop of 2 to 3 mm. Hg, also accompanied investigated (Table II). Both concentrations caused a marked depression of respiration, often leading to death under anesthesia due to respiratory failure. Those animals which survived the initial five minutes after injection usually endured the two-hour experimental period. Intraocular pressure fell in all animals with a minimum reached at 2 hours, the end of the experimental period. The fall in pressure was 2.3 ± 0.3 and 2.6 ± 0.4 mm. Hg (p < 0.001 for both) for 0.1 and 0.2 mg. per kilogram, respectively. Blood pressure usually rose mildly immediately after injection and, thereafter, became slightly depressed (90/75 to 80/65 at 90 minutes). Total outflow facility increased by 0.17 ± 0.6 to 0.57 ± 0.08 mm. Hg per minute; these latter respiratory movements were deep and the tidal volume would be increased. The animals also demonstrated a decreased response to physical auditory stimulation. Control groups of animals showed little or no change in intraocular pressure (maximum change +0.3 ± 0.2 mm. Hg) and 5 per cent increase in outflow facility after receiving injections of saline vehicle.

Neither drug caused a change in either secretion rate or fluid permeability across the isolated ciliary epithelium (Table III).

Discussion. LSD increases intraocular pressure slightly and this occurs concurrently with a 50 per cent increase in total outflow facility. The small intraocular pressure change is similar to that seen in man,3 but the finding on outflow facility represents a new aspect of LSD effects.

With heroin, there is a small intraocular pressure drop of 2 to 3 mm. Hg, also accompanied

Table I. Effect of LSD on intraocular pressure in anesthetized and conscious rabbits

<table>
<thead>
<tr>
<th>Dose</th>
<th>Initial P₁</th>
<th>90-min. P₁</th>
<th>Initial C₁₀₀₀</th>
<th>90-min. C₁₀₀₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 µg/Kg</td>
<td>22.0 ± 0.2</td>
<td>21.3 ± 0.2</td>
<td>21.1 ± 0.4</td>
<td>21.1 ± 0.4</td>
</tr>
<tr>
<td>0.1 mg/Kg</td>
<td>20.6 ± 0.3</td>
<td>21.0 ± 0.3</td>
<td>23.1 ± 0.3</td>
<td>23.1 ± 0.3</td>
</tr>
<tr>
<td>0.2 mg/Kg</td>
<td>21.5 ± 0.3</td>
<td>22.2 ± 0.3</td>
<td>22.8 ± 0.4</td>
<td>22.8 ± 0.4</td>
</tr>
<tr>
<td>0.3 mg/Kg</td>
<td>22.0 ± 0.3</td>
<td>22.5 ± 0.3</td>
<td>23.0 ± 0.3</td>
<td>23.0 ± 0.3</td>
</tr>
<tr>
<td>0.4 mg/Kg</td>
<td>23.0 ± 0.3</td>
<td>23.5 ± 0.3</td>
<td>24.0 ± 0.3</td>
<td>24.0 ± 0.3</td>
</tr>
</tbody>
</table>

Dose is per kilogram of body weight; P₁, intraocular pressure mm. Hg; C₁₀₀₀, total outflow facility, µl/mm. Hg/min.; n, number of eyes. Values are mean ± S.E.M.

Table II. Effect of diacetyl morphine on intraocular pressure in anesthetized and conscious rabbits

<table>
<thead>
<tr>
<th>Dose</th>
<th>Initial P₁</th>
<th>60-min. P₁</th>
<th>120-min. P₁</th>
<th>Initial C₁₀₀₀</th>
<th>60-min. C₁₀₀₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 µg/Kg</td>
<td>19.3 ± 0.3</td>
<td>17.0 ± 0.4</td>
<td>18.7 ± 0.5</td>
<td>0.35 ± 0.02</td>
<td>0.52 ± 0.04</td>
</tr>
<tr>
<td>0.1 mg/Kg</td>
<td>23.8 ± 0.3</td>
<td>23.6 ± 0.2</td>
<td>23.0 ± 0.3</td>
<td>22.5 ± 0.3</td>
<td>22.5 ± 0.3</td>
</tr>
<tr>
<td>0.2 mg/Kg</td>
<td>21.5 ± 0.3</td>
<td>21.2 ± 0.3</td>
<td>20.6 ± 0.2</td>
<td>19.8 ± 0.3</td>
<td>19.8 ± 0.3</td>
</tr>
<tr>
<td>0.3 mg/Kg</td>
<td>22.0 ± 0.3</td>
<td>19.5 ± 0.3</td>
<td>19.2 ± 0.3</td>
<td>19.7 ± 0.3</td>
<td>19.7 ± 0.3</td>
</tr>
</tbody>
</table>

Dose is per kilogram of body weight; P₁, intraocular pressure mm. Hg; C₁₀₀₀, total outflow facility, µl/mm. Hg/min.; n, number of eyes. Values are mean ± S.E.M.
Table III. Effect of LSD and diacetyl morphine on secretion and filtration across the isolated ciliary body

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>L,A</th>
<th>Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSD</td>
<td>Control</td>
<td>0.16 ± 0.01</td>
<td>0.06 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>(n = 4)</td>
<td>0.001 µg/ml</td>
<td>0.001 ± 0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01 µg/ml</td>
<td>0.01 ± 0.03</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>0.14 ± 0.01</td>
<td>0.06 ± 0.01</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>0.12 ± 0.03</td>
<td>0.07 ± 0.01</td>
</tr>
<tr>
<td>Heroin</td>
<td>0.005 mg/ml</td>
<td>0.13 ± 0.03</td>
<td>0.06 ± 0.02</td>
</tr>
<tr>
<td>(n = 4)</td>
<td>0.05 mg/ml</td>
<td>0.13 ± 0.03</td>
<td>0.07 ± 0.02</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>0.13 ± 0.03</td>
<td>0.06 ± 0.02</td>
</tr>
</tbody>
</table>

Secretion is the flow-rate across the tissue with zero hydrostatic pressure gradient and filtration is the flow-rate across the tissue with a driving force of 10 mm Hg hydrostatic pressure. The values are given in microliters per minute per milliliter of Hg (L,A) and microliters per minute (secretion) and are mean ± S.E.M. The dose levels were increased sequentially on each tissue with a control period with Ringer alone preceding and following the drug administration. n, number of tissues.

by a large increase in total outflow facility. These findings parallel those of Uusitalo following morphine injection in rabbits; the dose used was 7.5 mg per kilogram, and 2 mg heroin per kilogram used here is equivalent. The pressure fall is similar to that found previously in man. Since total outflow facility (Cui) is increased by 50 per cent with both drugs (Tables I and II), an explanation must be sought for the maintenance of almost normal intraocular pressure in the face of such a major change. The equation governing aqueous humor inflow is:

\[ L,A \times (x_c \times (P_r - P_i) - P_i) + S \]

where \( L,A \) is the ciliary epithelial permeability, \( A \) is the surface area, \( x_c \) is the "pressure index," \( P_r \) is capillary pressure, \( P_i \) is plasma colloid osmotic pressure, \( P_i \) is intraocular pressure, and \( S \) is secretion. \( P_i \) has been determined at 21 mm Hg and under the experimental conditions here is constant.

If all ocular parameters remained constant with only a change in \( C_{ui} \), then the intraocular pressure would fall to a new steady-state due to the increased capability of fluid to leave the eye. The new steady-state value would reflect both adjusted aqueous humor inflow (because of lowered intraocular pressure) and the increased outflow facility. The intraocular pressure, with both drugs is, however, maintained at levels close to normal (Tables I and II), thus there must be a compensatory change in aqueous humor inflow to sustain the intraocular pressure. The experiments made on the isolated ciliary epithelium show that there is no increase in secretion rate or fluid permeability to account for the increased aqueous humor formation despite the use of relatively high concentrations of the drug. Since the permeability of the membrane is unaltered then the driving force for aqueous production, the only other variable, must be increased. An elevation of \( P_r \), or capillary pressure, would bring about further changes in both \( A \), the perfused area of the ciliary body and \( x_c \), the "pressure index," which is a measure of the pressure distribution in the vascular system of the eye. If \( P_i \) were increased by both drugs then changes in both \( A \) and \( x_c \) could follow and increases in these parameters would generate both a greater hydrostatic pressure gradient and a greater surface area for pressure-dependent aqueous humor inflow. Changes in the permeability of iris vessels cannot be ruled out at this time, and such a change would certainly contribute to increased aqueous humor inflow. Changes in peripheral circulation are known to occur with both drugs although the mode of action, be it central or local, remains unresolved.

I thank Dr. Jonathan E. Pederson for performing the fluid permeability (L,A) measurements on the isolated ciliary epithelium in response to the drugs. I thank Miss Susan J. Downs and Mrs. Brenda Schumann for their valuable technical assistance during this work, and Mrs. Debbie Graves for her secretarial help.

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Key words: heroin, lysergic acid diethylamide, rabbit, intraocular pressure, outflow facility, blood pressure, respiration rate, pupil size.

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A method is described which enables the fundus camera to be focused objectively. This method eliminates the focus errors arising from the subjective focusing method currently used and permits the consistent attainment of high resolution fundus photographs. The objective focusing method has been evaluated on test targets and anesthetized animals and is applicable for use on unanesthetized human subjects.

In current practice, sharp fundus photographs having the highest obtainable resolution using the fundus camera are seldom obtained. To obtain such photographs the fundus camera must be properly aligned and focused. Although with practice the ophthalmic photographer can become skilled at aligning the fundus camera properly, proper focusing of the camera remains a continuing problem for many people and results in a frustrating percentage of out-of-focus pictures. One reason for this is the difficulty for many people of avoiding accommodation error which results when the retinal image is focused somewhere other than the plane of the crosshairs seen in the viewing eyepiece. A second reason for this is that the eye is a relatively poor judge of image sharpness for low magnification and low-contrast images such as the human retinal image. This report describes an objective method for focusing a fundus camera which eliminates focus error and enables high resolution fundus photographs to be consistently taken.

In general terms, the resolution of a fundus camera can be considered to be the minimum separation of two self-luminous objects (such as two adjacent fluorescein-filled capillaries) which are perceived as being separate objects (or vessels). If the resolution is poor the images of the two objects merge into one, sharp contrast boundaries of the object become fuzzy boundaries on the photographic image, and the photographic image becomes generally unsharp and "out-of-focus." Using the optical properties of the Zeiss Fundus camera and the normal emmetropic human eye, Vaughan and Laing1 have calculated the theoretical resolution of this system to be 7.5 μm on the retina for green light. This number has been verified by experiments performed in our and in other laboratories which have measured resolutions of 7 to 8 μm when photographing high contrast targets located at the "retina" of a model eye. When viewing high contrast targets under high illumination conditions one can visually resolve objects whose separation is somewhat less than the theoretical resolution limit. This too has been verified by experiments in our and other laboratories which have shown that with a Zeiss Fundus camera one can visibly resolve lines on a test chart located at the "retina" of a model eye whose spacing is as little as 4 to 6 μm. The fundus camera is thus capable of resolving the smallest retinal capillaries if it can be accurately focused.

Using the theory of Fourier optics,4 it can be shown that the effect of defocusing an image is to reduce the contrast of all the spatial fre-