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[54] **CORNEAL BATH**

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Related U.S. Application Data

[62] Division of Ser. No. 249,814, May 3, 1972, abandoned.

[52] **U.S. Cl.** **128/249**

[51] **Int. Cl.** **A61m 7/00**

[58] **Field of Search** 128/248, 249

[56] **References Cited**

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[57] **ABSTRACT**

A human eye whose intraocular pressure should, for medical reasons, be reduced, is treated with 6-hydroxydopamine to achieve sympathectomy of terminal axons of the eye, the sympathectomized eye is then treated with an adrenergic amine on a daily basis. The drop in intraocular pressure thus achieved is substantially greater than that procured by the treatment of the adrenergic amine alone.

2 Claims, 4 Drawing Figures

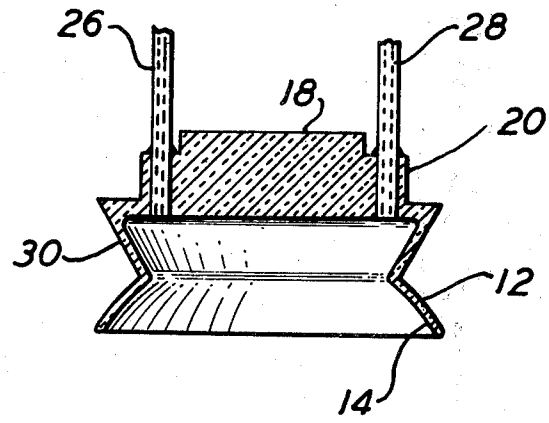


FIG. 2

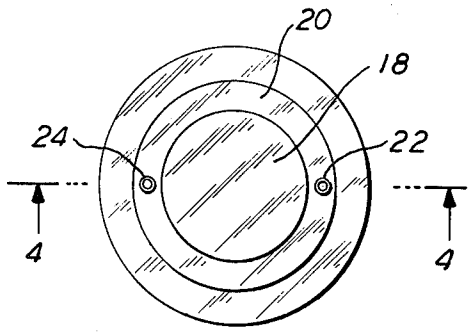


FIG. 1

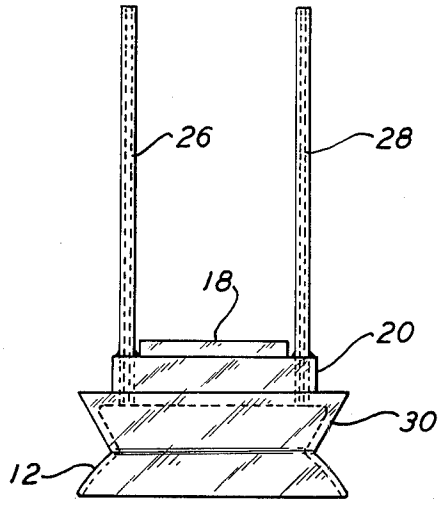


FIG. 3

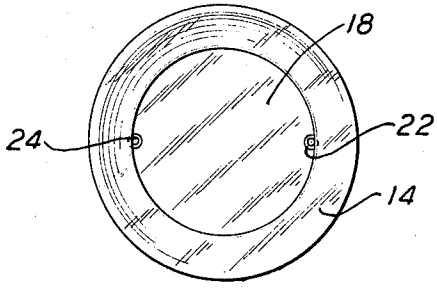
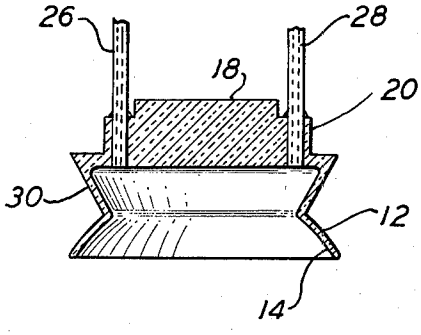


FIG. 4



CORNEAL BATH

This is a division of application Ser. No. 249,814, filed May 3, 1972 and now abandoned.

The invention described herein was made in part in the course of work under a grant or award from the Department of Health, Education and Welfare.

FIELD OF THE INVENTION

Lowering of intraocular pressure in human eyes.

DESCRIPTION OF THE PRIOR ART

It is well known that the condition of the human eye known as glaucoma results from the presence of excess pressure within the eye. Such excess pressures cause disruption of the sight processes and in serious cases lead to total loss of the faculty of sight. In many cases the pressure may be modified by the use of an adrenergic amine. Such amines fall into two categories, those having the so-called alpha effect facilitate the outflow of fluids from the eye and those having the so-called beta effect restrict the inflow of fluids into the eye. The compound epinephrine is especially favored for the treatment of glaucoma since it has the useful property of being an alpha and beta adrenergic amine. By the continuous, that is to say, daily administration of, for example, epinephrine, by means of eyedrops, many cases of glaucoma may be managed and the sight of the patient maintained. There are, however, unfortunately certain types of glaucoma such as open angle glaucoma which will not respond adequately to this form of treatment.

It is known (Horner, uber eine Form von Ptosis, Klin, Mbl. Augenheilk, **7, 193–198 (1869)**) that lower intraocular pressures result from surgical sympathetic denervation. As a result of these observations attempts were made to utilize these findings in the control of glaucoma near the turn of the century, however, these attempts were abandoned not only because of the technical difficulties involved in the surgical procedure but also due to the lack of reliable results in controlling glaucoma.

Experiments in test animals have demonstrated that the application of 6-hydroxydopamine (hereinafter 6-HDA) causes a selective yet reversible degeneration of sympathetic terminal axons but does not affect sympathetic stem axons or other nerves. Thus, 6-HDA achieves chemically, and reversibly, the effect which was drastically and surgically achieved by Horner (supra). It should be noted however, that heretofore 6-HDA has not been utilizied in human eyes.

It has also been noted in certain test animals that following sympathetic denervation certain tissues have become extraordinarily sensitive to dilute solutions of epinephrine (Burn, J.H., Rand, M.J.; The cause of the supersensitivity of smooth muscle to noradrenaline after sympathetic degeneration, J. Physiol. **147, 135–143, 1959**) (Trendelenburg, U., I. Mechanisms of supersensitivity and subsensitivity to sympathomimetic amines, Pharmacol Rev. **18, 629–640, 1966**). Again, these experiments do not concern the alpha and beta adrenergic effects in the human eye.

Heretofore certain experiments have been carried out applying 6-HDA to the corneas of rabbits and monkeys (Holland, MG. and Mims, J.L., III; Anterior Segment Chemical Sympathectomy by 6-Hydroxydopamine. I. Effect on Intraocular Pressure and Facility of Outflow, Invent Ophthal. **10:120** (February) **1971**)). In these studies epinephrine was not utilized but rather norepinephrine which has substantially solely alpha adrenergic properties and isoproterenol which has substantially solely beta adrenergic action so that the mechanisms of the effect might be more readily observed.

In the animal experiments it was found that 6-HDA caused a significant increase in fluid outflow, however, this effect did not persist into the second week after treatment. In these experiments the occurrence sympathectomy of the axons was demonstrated by methods recognized in the art and reported in detail in said paper. The term supersensitization as used hereinbelow refers to the enhancement of any known physiological effect, thus as stated hereinabove, norepinephrine is shown to have an alpha adrenergic effect, that is to say, it facilitates fluid outflow in the eye.

In rabbits and monkeys whose eyes have been chemically sympathectomized with 6-HDA an immediate drop in the intraocular pressure was noted. However, this effect did not persist. Furthermore, neither the administration of norepinephrine or isoproterenol gave rise to further pressure drops in the treated eyes. Thus, it was concluded that chemical sympathectomy in these test animals using 6-HDA did not lead to super sensitization to norepinephrine or isoproterenol.

Thus, there is nothing in the art to suggest that 6-HDA would cause chemical sympathectomy in the human eye, and furthermore there is nothing in the art to suggest that if such chemical sympathectomy did occur the sympathectomized eyes would be supersensitized to the effect of alpha or beta adrenergic amines.

SUMMARY OF THE INVENTION

The sympathetic terminal axons of human eyes, in particular, those suffering from excess intraocular pressure, are chemically sympathectomized by the application thereto of a dilute solution of 6-HDA. The 6-HDA may be administered by topical drops, by placing upon the cornea a hydrophilic contact lens previously soaked in a 6-HDA solution, by administering a solution upon the cornea by means of a specially designed corneal bath, or by subconjunctival injection of a solution of 6-HDA. The latter two modes being preferred and the last mode being especially preferred.

Following the treatment with 6-HDA, there is administered to the eye an alpha and beta adrenergically active amine such as epinephrine, or a combination of an alpha adrenergic amine and a beta adrenergic amine such as isoproterenol with norepinephrine. The use of epinephrine itself however being preferred. The administration of the adrenergic amine or amines continues to at least one month, preferably from one to three months, at the end of which time a further administration of 6-HDA by any of the foregoing methods is desirable.

Since the build-up of intraocular pressure is a continuous dysfunction of the eye, and visual faculties may only be maintained if the pressure is kept below an acceptable level in order to prevent deterioration of the optical nerve, it must be understood that the method of treatment set forth herein should be regarded as the treatment of a chronic condition, that is to say, it should be carried on continuously and that the one to three month period should be regarded as a treatment cycle.

DESCRIPTION OF THE DRAWINGS

FIG. 1 is a side-elevational view of a corneal bath of the present invention.

FIG. 2 is a top plan view of the bath of FIG. 1.

FIG. 3 is a bottom plan view of the bath of FIG. 1.

FIG. 4 is a side elevational sectional view of the bath of FIG. 1 viewed at 4—4.

The corneal bath utilized in the process of the present invention comprises substantially 4 segments; an eye contact segment 12 having a lower surface 14 shaped substantially to fit over the cornea of an eye, a lens portion 18, a lens holder portion 20 into which lens 18 is set, said lens holder 20 having at least two orifices, 22 and 24 drilled therethrough, suitably but not critically in a plane substantially perpendicular to the plane of the lens. Inflow tube 26 is attached to, and into orifice 22 and outflow tube 28 is attached to orifice 24. The lens holder 18 is attached to eye contact portion 12 by means of connecting separator 30 whereby there is provided, when the device is placed upon the surface of the eye, an enclosed void between the surface of the eye and the lens set in the holder. In the operation of the device, a very slight vacuum is applied to one of the tubes 26 or 28, for example 28, and the liquid to be applied to the surface of the eye is drawn into the aforesaid void between the surface of the eye and the lens and its holder through the other tube. The device is emptied by opening one of the tubes to the atmosphere and applying a mild vacuum to the other tube.

The dimensions of the device are not critical provided that surface 14 is of such dimensions and shape as to be substantially in contact with the surface of the eye at all point, in any case, in such a manner that the fluids normally upon the surface of the eye would provide an effective seal between the surface of the eye and its periphery.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the preferred modifications of this invention sympathetic terminal axons of a human eye may be chemically sympathectomized by the application to said eye of an ophthalmologically acceptable aqueous solution of 6-hydroxydopamine. This application may be achieved by one of four embodiments. In all of these embodiments there is utilized an aqueous solution of 6-HDA. It is known that 6-HDA is extremely sensitive to oxidation, particularly in aqueous solution. The 6-HDA is usually commercially available as a crystalline powder. This powder is dissolved in deoxygenated distilled water containing a small amount of ophthalmologically acceptable antioxidant. Sodium metabisulfite has been found suitable as such antioxidant and is utilized in a strength of between 0.02 and 0.06, suitably about 0.045 molar. The pH of the solution is then adjusted to from about pH 6.2 to about pH 6.8, suitably to about pH 6.5 by addition of aqueous sodium hydroxide, and the solution filtered through a millipore filter, a filter having a pore size of about 0.45 μ being preferred. All solutions should be immediately utilized care being taken to exclude air bubbles therefrom. Solutions should be totally colorless and solutions showing any signs of pink coloration must be discarded. The fluid should be discarded after use and the crystalline powder should be stored under liquid nitrogen.

The solutions of 6-HDA may be used in the range of 1% through 10% (w/w). It has however been found that solutions at the upper end of this range tend to cause transient corneal punctate stromal opacities which usually cleared in between one to four weeks. On the other hand, solutions having a strength of less than 2% tended to give rise to incomplete sympathectomy. It has been found that a range of from about 2 to about 3% gives the most desirable results and a solution of 2.7% has been found to be especially suitable. It has further been found desirable though not critical, to prepare the eye to be treated with an ophthalmologically effective anesthetic such as proparacaine hydrochloride. In addition to the anesthetic effects it has been found that this substance enhances the penetration of 6-HDA.

In one embodiment of the present invention, subsequent to anesthetization of the cornea two to three drops of a 1 to 10% solution of the 6-HDA as set forth above were applied to the cornea and the patient's eyelids closed. It was found desirable to repeat this application from about two to about four times at intervals of from about 15 to about 45 minutes. Although this mode of administration has been found to be fairly effective, the degree of sympathectomy revealed by pupillary response to the hydroxyamphetamine test was not as great as that in other embodiments.

In a further embodiment of the invention a solution containing from 1 to 10% of 6-HDA was utilized as a bath in which a soft (i.e. hydrophilic) contact lens had been soaked for from about 15 min. to 2 hours. The soft contact lens is then placed upon the eye to be treated for a period of from about 1 to about 3 hours and then removed. While this method is more convenient than the aforementioned eyedrop method, the degree of sympathectomy obtained is substantially of the same order or magnitude. In yet another, and preferred, embodiment of this invention there is utilized a corneal bath, suitably of the type described hereinabove and illustrated in FIGS. 1 through 3. In this embodiment, the corneal bath is placed over the eye to be treated so that surface 14 is substantially in contact with the outer surface of the eye. A very mild vacuum is applied to the void in the device through, say, outlet tube 28 whereby 6-HDA solution is drawn in through the inlet tube 26. The degree of vacuum is not critical, and should be merely sufficient to draw the aqueous solution through the narrow inlet tube. That degree of vacuum created by placing a hypodermic syringe into tube 28 and withdrawing the plunger of said syringe would be substantially satisfactory.

While there may be utilized a solution of between 1 and 10% it is especially preferred to utilize a solution of from about 2 to about 2.7% w/w. The contact time may vary from about 15 minutes to about 1 hour, however 30 minutes appears to be the optimum period. Evaluation of this embodiment by standard means, demonstrates that complete sympathectomy has been achieved.

Yet another embodiment, which is the most preferred embodiment, comprises the subconjunctival injection of the 6-HDA solution. The advantage of this method is that it is rapid, and requires the use of extremely small quantities of 6-HDA solution. In this embodiment of the present invention a solution of 6-HDA, suitably a 1 to 4% solution is prepared, suitably in an air-free syringe capped with a millipore filter, and a

small needle, suitably 25 to 30 gage. There are administered from between 0.1 to about .3 ml. of the solution, suitably about 0.2 to 0.25 ml. of the solution by a series of injections around limbus of the eye. An evaluation of this mode shows that complete sympathectomy has occurred.

Subsequent to chemical sympathectomy carried out by any of the foregoing methods, the eye whose internal pressure is to be reduced, is treated with adrenergic amines, suitably an alpha adrenergic amine, and a beta adrenergic amine preferably in combination either in the form of an adrenergic amine having alpha activity together with an adrenergic amine having beta activity or, most preferably, an adrenergic amine combining both activities such as epinephrine. There may be utilized ophthalmologically acceptable, aqueous solutions of epinephrine of between 1 and 3%, suitably 1 or 2%; isoproterenol of between 1 and 5%, suitably between 2 and 2.5%, and phenylephrine of between 5 to 10%, suitably about 10%. Especially preferred among these adrenergic amines is epinephrine. Heretofore it has been known that epinephrine, especially when administered over long periods does cause a lowering of the intraocular pressure and upon prolonged usage does facilitate the outflow of fluid from the eye. However, in very severe cases of glaucoma neither the pressure drop nor the increase in outflow achieved by long term epinephrine therapy is sufficient to prevent irreversible damage to the eye.

In this portion of the invention, a solution of the adrenergic amine suitably epinephrine is administered from one to four times a day for a period of 2 to 3 months. It has been observed that while a statistically significant lowering of the intraocular pressure does occur, no increase in the facility of the outflow is noted immediately after the first administration of the adrenergic amine. This pressure drop is not maintained in a statistically significant manner and continued application for at least one month is required in order to produce a pressure drop and enhancement of facility of outflow which is statistically significant over control. It must be realized however that recourse must be had to statistical analysis since direct control experiments are not possible. Thus, while one eye of a patient suffering from glaucoma may be chemically sympathectomized and the other eye utilized as a control, the possibility exists that the untreated eye may nevertheless become partially sympathectomized due to systemic absorption of the 6-HDA. Indeed, some evidence does exist that this does occur. On the other hand, the response of totally untreated glaucomotose eyes would clearly be slightly different because of the different chemical condition and metabolic state of the totally untreated control.

PHARMACOLOGICAL ANALYSIS AND RESULTS

All patients tested were, at the time, under maximum medical therapy, that is to say, continuous treatment with epinephrine or the like. Tests were carried out using a double control method. In seven patients, one eye was chemically sympathectomized with 6-HDA and the other eye was not treated with 6-HDA. In other patients no 6-HDA at all was administered. All results discussed below are statistical averages. Twenty-four patients constitute the sample upon which the statistical results are based. However, a total of 90 patients has been treated with substantially similar results.

Immediately following treatment with 6-HDA a statistically significant lowering of intraocular pressure as well as a statistically significant increase in facility of outflow was noted up to 2 or 3 days after sympathectomy. Repeated treatment with 6-HDA several times over a period of 3 to 4 weeks, did not control intraocular pressure.

When sympathectomized eyes were treated with epinephrine solutions, as low as 10^{-4}% and tested one-and a half hours after treatment, a statistically significant drop in intraocular pressure was noted, but no statistically significant increase in outflow facility was noted. Solutions up to a strength of 2% epinephrine were utilized in these tests. It is therefore concluded that this short-term effect of epinephrine upon 6-HDA sympathectomized eyes is due to the beta adrenergic effect, that is to say, control of fluid inflow rather than increase of facility of outflow.

Where 2% epinephrine was administered twice daily for a period of an average of 81 days after sympathectomy the lowering of the intraocular pressure from an average of 39 millimeters Hg to an average of 19 millimeters Hg was noted, which result is highly significant statistically. The untreated eye of these patients when treated with epinephrine in a similar manner, also demonstrated a statistically significant decrease in intraocular pressure, which however was substantially less than that in the sympathectomized eye and the difference in drops in pressure between the two eyes of the patient is also statistically significant. Hence, it must be concluded that the drop in pressure of the untreated eyes after prolonged epinephrine treatment must be due to partial sympathectomy caused by systemic absorption of the 6-HDA. In the same group of patients in measurements carried out after 100 days of epinephrine treatment following 6-HDA sympathectomy, facility of outflow in the sympathectomized eyes was increased by 88% with high statistical significance, there was no statistically significant change in the facility of outflow in the eyes of these patients similarly treated with epinephrine but which had not been treated with 6-HDA. Hence, it may be concluded that the 6-HDA sympathetcomy coupled with long term epinephrine therapy significantly enhances the alpha adrenergic effect.

In most patients tested after approximately 100 days it was found desirable to repeat the sympathectomy in order to maintain the enhanced pressure lowering effect of epinephrine or similar alpha or beta adrenergic effects achieved at that time.

The foregoing results are especially surprising since it has been noted that an alpha adrenergic drug, such as phenylephrine or norepinephrine, when applied per se to a sympathectomized eye does not produce immediate increased facility of outflow. Similarly, epinephrine itself does not cause an immediate increase in facility of outflow after chemical sympathectomy, although a pressure drop is noted due, presumably, to the beta adrenergic effects of epinephrine. Hence, for increased outflow to occur it would appear that subsequent to chemical sympathectomy, treatment with an adrenergically active compound exhibiting alpha activity is required, for a substantial period of time in order to achieve a greater alpha adrenergic effect on outflow facility than is observed in unsympathectomized glaucomatous eyes.

EXAMPLE I

Topical Application

Four drops of Proparacaine hydrochloride were instilled in each eye of the patient before administration of 6-HDA. Four drops of 6-HDA (10% aq.) were placed on the cornea in the left eye. This treatment was repeated three times at 30 minute intervals.

The hydroxy-amphetamine pupillary dilatation test revealed there was incomplete chemical sympathectomy. However, there was less than normal dilatation indicating that there was some effect.

EXAMPLE II

Soft Contact Lens Application

A soft contact lens was soaked in a solution of 6-HDA (10%) for three-fourths hours. The saturated soft contact lens was placed on the patient's left cornea for 1 hour.

There was dilatation of both pupils as tested with hydroxy-amphetamine. The untreated eye showed greater dilatation than the 6-HDA treated eye indicating some but incomplete sympathectomy in the treated eye.

EXAMPLE III

Corneal Bath Application

A corneal bath of the design described hereinabove was applied to the right eye of the patient, filled with 6-HDA (4% aq.) and left in contact with the eye for one hour.

Following treatment, there was subconjunctival edema and some corneal edema. The hydroxy-amphetamine test showed no pupillary dilatation in the 6-HDA treated eye.

Prior to sympathectomy this patient had an intraocular pressure of 38 mm. Hg and an outflow of 0.09 μl/mmHg/min under treatment with 0.1 ml. twice per day of 2% epinephrine.

After sympathectomy, the above sympathectomized eye was treated for 60 days with 0.1 ml. of epinephrine (2%) applied 3 times per day. At the end of this time intraocular pressure was 19 mm Hg and outflow was 0.24 μl./mm Hg/min.

EXAMPLE IV

Corneal Bath Application

2.7% 6-HDA was applied to the patient's left eye for 30 minutes, according to the method of Example III.

There was a slight superficial punctate keratitis and some conjunctival congestion. The hydroxy-amphetamine test showed an absence of dilatation of the pupil indicating a complete chemical sympathectomy.

Prior to sympathectomy this patient had an intraocular pressure of 42 mm. Hg and an outflow of 0.125 μl/mm Hg/min under treatment with 0.1 ml twice per day of 2% epinephrine.

After sympathectomy, the above sympathectomized eye was treated for 75 days with 0.1 ml. of epinephrine (2%) applied twice per day. At the end of this time intraocular pressure was 20 mm. Hg and outflow was 0.36 μl/mm Hg/min.

EXAMPLE V

Subconjunctival Injection

0.2 ml. of 6-HDA solution (2% aq.) was injected around the limbus in both eyes.

After the injections, there was redness of the conjuncitva but the patient evidenced no discomfort. Thirty minutes later, the redness began to subside and moderate redness remained which persisted for 2 to 3 days. The intraocular pressure before treatment were 50 mm. Hg in both eyes. One day after treatment the pressures were measured at 20 mm. Hg (right eye) and 18 mm. Hg (left eye), respctively. The patient was placed on 2% epinephrine (0.1 ml.) thrice a day with pilocarpine (6%, 0.1 ml.) four times per day. One month after treatment, the pressures were 19 and 20 mm. Hg respectively. Two months later, they were 20 mm. Hg in both eyes, and five months later, they were 26 mm. Hg. in both eyes. The patient was retreated at this time. Pressures again fell to 20 mm. Hg. on topical epinephrine 2% (0.1 ml.) thrice a day plus pilocarpine 6% (0.1 ml.) four times a day.

Prior to sympathectomy this patient had an intraocular pressure of 50 mm. Hg. under treatment with 0.1 ml two times per day of 2% epinephrine, together with 0.1 ml 2 times a day of 0.25% phospholine.

EXAMPLE VI

Drug Preparation

The 6-HDA was supplied (by the Regis Chemical Company, Chicago) as a crystalline powder which had to be protected from exposure to oxygen because of its strong oxidation potential. The 6-HDA was dissolved in deoxygenated distilled water with 0.045 molar sodium metabisulfite added as an antioxidant. The pH was adjusted to 6.5 by sodium hydroxide, and the solution was filtered through a 0.45 μ millipore filter. All drug solutions were made immediately prior to administration. Care was taken to exclude air bubbles from the solution. Oxidation could be detected by pink discoloration of the fluid and only solutions which were clear, colorless, and therefore free of oxidation were used. After use, the fluid was discarded and the crystalline powder was stored under liquid nitrogen for subsequent use.

I claim:

1. A corneal bath comprising:

a lens

a substantially cylindrical annular lens holder, wherein the outer circumference of the lens is sealed into the inner circumference of said annular lens holder, a cup shaped corneal eye contact portion, and

means for defining a corneal bath portion comprising a connecting and separating portion between said eye contact portion and said lens holder portion and at least two access means in said lens holder communicating with said bath portion for introducing liquid and gaseous fluids into and removing said fluids from both portions of said corneal bath.

2. A corneal bath according to claim 1 wherein the eye contact portion is in the shape of a hollow frustrum of a cone the upper portion of said frustrum being joined to said connecting means, and wherein said access means comprise aperatures consisting of substantially diametrically spaced upstanding tubes mounted in the lens holder.

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