(54) Title:  METHOD FOR CHANGING THE REFRACTIVE POWER OF AN EYE

(57) Abstract

A method provides for changing the refractive power of an eye, and includes the step of selecting a dioptic correction for an eye without compromise for regression of refractive power due to biological response to a change in corneal profile, changing the corneal profile of the eye in order to change the refractive power of the eye to the selected dioptic, (e.g. by laser of surgical procedures) and limiting regression in corneal profile due to the biological response at about to the selected diopter by applying to the corneal composition comprising an agent for controlling the biological response. The agent comprised in the composition may be a steroid, a non-steroidal anti-inflammatory agent or a basement membrane component. The change in the refractive power is intended to achieve emmetropia. The method of the present invention allows the correction of refractive/focusing disorders of the eye such as myopia, hyperopia, (a)stigmatism and so on.
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METHOD FOR CHANGING THE REFRACTIVE POWER OF AN EYE

BACKGROUND OF THE INVENTION

The present invention generally relates to a method for changing the refractive power of an eye and is more particularly directed to changing the profile of the cornea of an eye to correct refractive disorders.

The refractive power of an eye, that is, its diopter, is expressed by the inverse number 1/f of the focal length, f, of the object. In this context, myopia and hyperopia result from conditions in which light entering an eye is not exactly focused on the retina. Another condition resulting from improper focusing of light is that of a stigmatism. A stigmatism is the result of unequal curvature of the refractive surface of the eye as result of which a ray of light is not sharply focused on the retina but is spread over more or less a diffuse area.

In general, the structure of an eye includes an eyeball filled with a vitreous body with the top most surface of the eye being a transparent cornea followed by an iris, a pupil and a crystalline lens respectively.

Refractive index of the cornea is about 1.38 compared to 1.0 of air and incident light entering the cornea is refracted before being focused on the retina. Since the refraction by the cornea is not alone sufficient for an image of an external object to be focused properly in the retina, the crystalline lens is varied in thickness and the focal length thereof is adjusted accordingly.
A number of procedures have been utilized to alter the shape, or the profile, of the cornea in order to change its refractive index to correct for the hereinabove noted conditions resulting in improper focusing of an object on the retina of an eye.

For example, radial keratotomy utilizes incisions in a radial pattern around an outer periphery of the cornea enabling the periphery to expand slightly and flattened the center of the cornea. Surgical procedures such as lamellar refractive keratoplasty involves the thickening of the cornea by suturing of a material thereto.

Another procedures includes the use of lasers for photorefractive keratectomy which shapes anterior layers of the cornea by photoablation. The vaporization of portions of the center of the cornea effectively change the cornea shape as portions of the cornea relax into the oblated areas.

Still another procedure such as thermal keratoplasty effects a change in corneal profile by shrinking collagen fibrils in the cornea. Unfortunately, trauma associated with the alteration of corneal tissue results in apoptosis, programmed cell death, an active process of a gene-directed physiological event that plays a crucial role in the regulation of tissue homeostasis such as development, maintenance of tissue morphology and cellular reorganization after tissue wounding.

This differs from necrosis where cell contents are spilled in surrounding tissue space provoking an inflammatory response.
The stroma of an eye includes lamellae which run in flat layers from limbus to limbus and consist of uniform, parallel collagen fibrils, which are regularly spaced within the lamellae and separated by the glycoproteins.

The uniformity of the collagen fibrils results in the transparency of the cornea and when is this uniformity of size or spacing of the fibrils is disrupted, necessary transmission of light directed into the eye is altered. Naturally, any surgical procedure which results in a disruption or alteration of light entering the eye causes a refractive disorder.

Thus, alterations such as shrinking preexisting collagen at the cornea treatment site results in a change in refractive index. The biological response hereinabove noted which includes the process of keratocyte reproduction, migration and repopulation results in an addition of new collagen and other compounds to the preexisting stromal configuration over a period of time.

Consequently as a result of this biological response, the stroma develops a different shape that alters the corneal curvature subsequent to surgery. Thus, a regression of the refractive properties of the eye occurs due to this biological response to surgical procedures on the corneal surface. Accordingly, immediate changes to a corneal profile or a curvature are not stable but change as a result of the biological response over a period of time consequent to the corneal trauma.

In accommodation, or in compromise, for the known regression of refractive power due to biological responses to a change in corneal profile, heretofore
procedures for altering corneal profile have as an immediate goal a change in refractive power, or diopter, which is not emmetropic. That is surgical procedures have as a target a diopter value which is expected to change due to biological response to the procedure with such biological change hopefully resulting in a stable zero dioptic (emmetropia).

It should be appreciated that greater cornea trauma results in a correspondingly greater biological response and accordingly accommodation, or compromise for expected biological response becomes particularly significant when diopter changes of +6 or greater are necessary to achieve emmetropia. In other words, with diopter changes of about +6 or greater, the stroma develops a significantly different properties that alter the corneal curvature over a period of time due to biological response. As noted, this biological response includes the process of keratocyte reproduction, migration and new population which results in the addition of new collagen to the preexisting scroll configuration over a period of time subsequent to corneal trauma.

As hereinabove noted, corneal profile contouring procedures heretofore have required an "over correction" in order to accommodate for the biological response. The present invention is directed to a method for changing the refractor power of an eye by changing the shape of the cornea without concomitant biological response which causes regression of the achieved refractive power due to a change in the corneal profile. This results in more accurate dioptic correction by eliminating the effects of biological response which may not be as predictable as the calculation of necessary diopter change to achieve emmetropia.
SUMMARY OF THE INVENTION

A method in accordance with the present invention for changing the refractive power of an eye generally includes the steps of selecting a diopter correction for an eye without compromise for regression of refractive power due biological response to a change in corneal profile. In consequence thereof the present invention includes a step of changing the corneal profile of the eye in order to change the refractive power of the eye to the select diopter.

Importantly, the present invention includes the step of limiting regression in corneal profile in order to maintain refractive power at about the selected diopter by applying to the cornea a composition comprising an agent for controlling the biological response.

More particularly, the method in accordance with the present invention may incorporate into the step of changing a corneal profile a radial keratotomy procedure. Alternatively in accordance with the present invention the change of corneal profile may include a photorefractive keratectomy. Still, alternatively in accordance with the present invention the change in corneal profile may include a thermal keratoplasty procedure. Greater benefit of the method in accordance with the present invention may be achieved by changing the corneal profile to effect a refractive power change of at least 6 diopters. Preferably the method according to the present invention includes a change in a refractive power which causes emmetropia.

Also incorporated into the method in accordance with the present invention is the application of the
composition comprising an agent for controlling the biological response to the cornea in anticipation of changing the corneal profile yet after the step of selecting a diopter correction for an eye without compromise regression of refractive power due to biological response to a change in the corneal profile.

The present invention further encompasses a method for changing a refractive power of an eye which includes changing the corneal profile of the eye in order to change the refractive power of the eye to a selected dioptic and thereafter controlling biological response to the change in corneal profile in order to maintain a refractive power at about the selective diopter by applying to the cornea a composition comprising an agent for limiting the biological response. This control may be effected by either the amount of agent present in the composition or the quantity and time schedule for application of the composition.

Still more particularly, the present invention includes a method of changing the refractive power of an eye by surgically changing the corneal profile of the eye in order to change the refractive power thereof with a selected diopter and retarding regression of the selected diopter by applying to the cornea a composition comprising an agent for controlling a biological response to the surgical change to the corneal profile.

In accordance with the hereinabove defined method in accordance with the present invention the agent utilized may comprise a steroid, more specifically the steroid may be present in a concentration of about 0.1 to about 4.0 wt. % and may be selected from the group consisting of deramethasone, prednisolone, prednisone,
fluorometholone, rimexolone, medrysone, betamethasone, triamcinolone and hydrocortisone.

Alternatively, in accordance with the present invention, the agent may comprise a non-steroidal antiinflammatory, for example, a non-steroidal antiinflammatory may be selected from the group consisting of flurbiprofen, suprofen, mefenamic acid, flufenamic acid, clonixin flufenal, ibufenac 4-(t-buty1)benzeneacetic acid, ibuprofen, alkyllofenac, fenoprofen, naproxen, indomethacin, tolmetin, ketoprofen, namoxyrate, ketrolac, and loxprofen.

BRIEF DESCRIPTION OF THE DRAWINGS

The advantages and features of the present invention will be better understood by the following description when considered in conjunction with the accompanying drawing in which Figure 1 is a pod illustrating the advantages of a dioptic correction to the present invention for changing corneal profile.

DETAILED DESCRIPTION

The present invention relates to a method for changing refractive power of an eye by changing the curvature of the cornea of an eye to correct for refractive disorders.

More particularly the present invention is directed to a method for changing corneal curvature which may include radial keratotomy, laser photo refractive keratectomy, thermal keratoplasty as conventionally known and used in combination with a
selection of a diopter correction for an eye which does not include compromise for regression of the refractive power due to biological response. In combination therewith, such regression is limited or eliminated in order to maintain the refractor power at about the selected diopter by applying to the cornea a composition comprising an agent for controlling the biological response.

Thus the method in accordance with the present invention encompasses a procedure which limits the destruction, or shrinkage, or change of preexisting collagen and preexisting keratocyte population. The procedure in accordance with the present invention is neither taught or suggested by the prior art. In view of the included step of controlling biological response which includes the process of keratocyte reproduction, migration and repopulation which results in the addition of new collagen and other compounds to the preoperational stroma configuration which occurs subsequent to the change in the corneal profile.

Heretofore, the application of steroid and non-steroidal compounds to the eye in combination with laser eradication thereof have been limited to the treatment of corneal haze. See for example U.S. Pat. Nos. 4,939,135, 5,124,392, 5,271,939, 5,360,611, and 5,401,510 which are directed to compositions which contain agents that modulate wound healing. These compositions or compounds facilitate the prevention or reduction in corneal haze which refers to the clouding of the cornea resulting from exposure of the cornea to laser radiation during eye surgery. However, there is no teaching in these references of the utilization of active agents in controlling biological response which enables a change in surgical procedure for obtaining emmetropia in an eye without compromise for regression
of refractive power due to biological response to a change in corneal profile.

First it should be appreciated that while the present invention anticipates and incorporates a change in corneal profile effected by radial keratotomy, photo refractive keratectomy or thermokeratoplasty, any other procedure causing trauma to the cornea for changing the contour or profile thereof, is to be considered within the scope of the present invention and in fact all of such procedures are well known in the art.

Further, it is to be appreciated that prior to, and anticipatory of, procedures for changing the profile of a cornea well known methods may be utilized for selecting a dioptic correction for an eye which include compensation, or compromise, for expected biological response. Any suitable method for measuring the existing refractive power of an eye and for selecting an amount of change necessary to achieve emmetropia should be considered as suitable for use in combination with the other steps in accordance with the present invention as herein described.

As illustrated in Figure 1, an eye having a preexisting diopter -6 indicated as curve A would require a diopter change to, for example, +1 in order to accommodate for the regression over a period of time indicated by the curved segment 10 to achieve an emmetropia, or diopter of 0.

Greater over compensation or diopter change is necessary for an eye requiring a diopter change of more than 6, as is well known in the art.
For example, heretofore correction to an eye having a preexisting diopter of about 10 as shown by curve B in Figure 1 may require a diopter change to about .3 to accommodate regression as shown by the curve segment 12. In fact, as is typical in such diopter corrections, the regression of a diopter typically passes through 0 to ultimately settle at a lower lever, for example, about -2 as shown by segment 14 of curve B in Figure 1. Naturally such ultimate, or stable correction is undesirable, but with the current procedures inevitable because of the difficulty in accessing a biological response to the curvature change in the cornea required to effect the selected change in diopter.

In accordance with the present invention with the use of agents for controlling the biological response as hereinafter described, the selected change in diopter can be approximately equal to the change necessary to achieve emmetropia without compromise for biological response to the cornea profile.

As illustrated in Figure 1 by the dashed curve C, little over compensation as indicated by the curved segment 16 is required to offset the effects of biological response. For example, the biological response which may be expected to the profile change of the cornea corresponding to curve B of Figure 1 may amount to 4 or 5 diopters as indicated by the difference between the maximum diopter change indicated by the point 20 in Figure 2 and the stable diopter correction as indicated by the line segment 14 caused by biological change to the corneal trauma.

Thus, in accordance with the present invention the selected diopter correction for an eye without compromise for regression of refractive power amounts
to the difference between the preexisting diopter of the eye and 0 diopter (emmetropia). That is no compromise is necessary for regression of the diopter due to biological response because such response is controlled by active agents hereinafter described.

Suitable active agents include healing modulators such as steroids, growth factors, basement membrane components and regulators of collagen structure.


The steroids which can be used according to the present invention include all steroids which are capable of preventing or controlling biological response resulting from trauma to a cornea. This includes corticosteroids, preferably glucocorticoids, and all derivatives and isomers thereof. For example, steroids which can be employed in the present invention to prevent and control biological response include dexamethasone; fluorometholone; medrysone; betamethasone; triamcinolone; prednisone; prednisolone
such as prednisolone acetate; hydrocortisone and pharmaceutically acceptable salts thereof; prednicarbate; deflazacort halomethasone tixocortol; prednylidene (21 diethylaminoacetate; prednival; paramethasone; methylprednisolone; meprednisone; mazipredone; isoflupredone; halopredone acetate; halcinonide; formocortal; flurandrenolide; fluprednisolone; fluprednidine acetate; fluperolone acetate; fluocortolone fluocortic butyl; fluocinonide; fluocinolone acetomide; flunisolide; flumethasone; fludrocortisone; fluclorininde; enoxolone; difluprednate; diflucortoone; diflorasone diacetate; desoximetasone (desoxymethasone); desonide; descinolone; cortivazol; corticosterone; cortisone; cloprednol; clocortolone; clobetasone; clobetasol; chloroprednisone; cafestol; budesonide; beclomethasone; amcinonide; allopregnane acetonide; alclometasone; 21-acetoxypregnezolone; tralonide; diflorasone acetate; deacetyl cortivazol; budesonide and deacetylcortivazol oxetanone.

The above-cited steroids are known compounds. Further information regarding the compounds can be found in the Merck Index Tenth Edition, 1983, and the publications cited therein, the entire contents of which are incorporated herein by this specific reference thereto. Additional examples of steroids which can be used according to the present invention include; dexamthasone ether derivatives; alkyloid steroids of the pregnane series (Rimexolone) disclosed generally in U.S. Pat. No. 3,947,478 issued Mar. 30, 1976 and specifically for ophthalmic use in U.S. Pat. No. 4,686,214 issued Aug. 11, 1987, the entire contents of both of which are incorporated herein by this specific reference thereto.
Such steroids and combinations comprising one or more steroids will typically be combined in the compositions of the present invention at concentrations of between about 0.1 and 4.0 percent by weight (wt. %).

The following steroids are preferred; dexamethasone; prednisolone and fluoromethalone. The preferred steroids can be used at concentrations between about 0.125 and 1.0 wt. %.

Growth factors are also agents useful in accordance with the present invention which cause cells to migrate, differentiate, transform or mature and divide. They are polypeptides which can usually be isolated from many different normal and malignant mammalian cell types. Some growth factors can be produced by genetically engineered microorganisms, such as bacteria (E. coli) and yeasts; see, for example, Chapter 10 and 11 of the Molecular and Cellular Biology of Wound Repair (1986), the entire contents of the book of which are incorporated in the present specification by this specific reference thereto. Growth factors are known for their involvement in a variety of phenomena as set forth above. For example, epidermal growth factor (ECF) is known to stimulate the proliferation of epidermal and other epithelial tissues; see Barrandon et al., Cell. Vol. 50, 1131-1137 (Sept. 25, 1987) incorporated herein by this specific reference thereto. Both ECF and transforming growth factor (TSF), which has the same sequence homology as EGF and binds to the same cell surface receptor as EGF, have been suggested for use in wound healing, Id.; European Patent No. 190 018 (disclosing the use of TGF for the treatment of epithelial and stromal wounds); PCT WO 86/02271 (disclosing the use of human epidermal growth factor (hEGF) for treating epithelia and stromal wounds); and European Patent No. 140 998 (disclosing ophthalmic preparations containing hEGF for the treatment of
keratitis, corneal erosion, corneal infiltration and corneal ulcers).

Growth factors which can be used according to the present invention include EGF, fibroblast growth factor (FGF), insulin-like growth factor (IGF), platelet derived growth factor (PDGF), alpha and beta transforming growth factors (TGFA and TGFβ) and nerve growth factor (NGF). In addition, cell enhancing solutions which contain growth factors can be used, such as SGF-7, available from Scott Laboratories, Inc., and ITS, available from Collaborative Research Incorporated. Growth factors will typically be contained in the compositions of the present invention at concentrations between about 0.01 nanograms per milliliter (ng/ml) and 100 micrograms per milliliter (µg/ml). For example, EGF can be used at concentrations between about 500 ng/ml and 100 µg/ml, preferably between about 10 µg/ml and 50 µg/ml; and FGF can be used from between about 1.0 ng/ml and 50 µg/ml, preferably at about 10 µg/ml. In addition TGFβ can be used at concentrations of at least about 100 ng/ml; see Lawrence et al., Annal. Surg. 203, pp. 142-147 (1986).

Basement membrane components can be used to prevent or control collagen changes in the biological response. It has been theorized that basement membrane components promote wound healing by contributing to the reformation of destroyed basement membranes or functioning as a basement membrane, thereby providing a surface across which epithelial cells can migrate and allowing re-epithelialization of the cornea to progress; see Fajikawa, et al., Fibronectin in Healing Rabbit Corneal Wounds, Laboratory Investigation, Vol. 45, No. 2, pp. 120-8(1981) incorporated herein by reference. Basement membranes are thin amorphous, sheet-like structures which separate certain
parenchymal cell types, endothelium and epithelium, from connective tissue stroma. For a discussion of basement membranes and their role in wound repair; see The Molecular and Cellular Biology of Wound Repair, Chapter 22, specifically p. 550 (1986).

In the present invention, basement membrane components are employed to control corneal epithelial cells in division, migration and sticking. They influence endothelial cells by providing an attachment and organizational foundation for the endothelial cells. They also help with the organization of collagen in the stroma. Basement membrane components which can be used to control biological response include: heparin; heparin sulfate; fibronectin; laminin; connective tissue activating peptides such as vinculin; gelatin; glycosaminoglycans; and various types of collagen, especially type IV collagen. The present compositions will typically contain one or more basement membrane components at concentrations between about 0.01 ng/ml and 1 milligram per milliliter (mg/ml), preferably about 1 µg/ml.

Regulators of collagen structure can also be used as wound healing modulators to control biological response and regulate collagen structure. As used herein "regulators of collagen structure" are wound healing modulators which degrade or inhibit the breakdown of collagen in the stroma or the collagen released by dead or injured cells; see The Molecular and Cellular Biology of Wound Repair; at pp. 224-226. These regulators can act in two ways, to degrade damaged connective tissue, such as collagen at inflammatory sites, or to act in the reverse manner inhibiting the degradation of connective tissue. Regulators of collagen structure which can be used to degrade collagen include, for example: collagenases,
elastases, proteases and proline hydroxylase. Regulators of collagen structure which will inhibit the degradation of collagen include all known inhibitors of the aforementioned enzymes including phenylmethylsulfonyl fluoride (PMSF) and pyrroline-dicarboxylic acid esters used as proline hydroxylase inhibitors, fibrosuppressants and immunosuppressants as disclosed in U.S. Pat. No. 4,717,727, the contents of which are hereby incorporated by this specific reference in this specification. Regulators of collagen structure can be used at concentrations of between about 10 μg/ml to about 10 mg/ml.

To control biological response, various wound healing modulators can be used. Prior to, or during, photoablation or other surgical change in profile of the anterior surface of the cornea the compositions herein described may be applied. Such compositions include growth factors such as EGF, IGF, PDGF, FGF, TGFβ, TGFα and NGF and basement membrane components. These wound healing modulators can be used at concentrations previously discussed.

In addition, aldose reductase inhibitors (ARIs) can be used as wound healing modulators according to the present invention. For example, ARIs, such as those disclosed in U.S. Pat. Nos. 4,717,725, 4,600,717, 4,436,745, and 4,438,272, the entire contents of which are incorporated herein by this specific reference, can be used to central biological response. These compounds inhibit the enzyme aldose reductase. The enzyme's inhibition appears to be related to the mechanism of wound healing in the diabetic individual; see Ohasi et al., Aldose Reductase Inhibitor (CT-112) Eyedrops for Diabetic Corneal Epitheliopathy, American Journal of Ophthalmology, Vol. 105, No. 3 (March,
1988). ARIs can be used at concentrations between about 0.1 wt. % and 2.0 wt. %.

Growth factors such as EGF, FGF, IGF, PDGF, TGFα, TGFβ and NGF, and aldose reductase inhibitors are also useful in the present invention.

Additionally, nonsteroidal antiinflammatory agents (NSAIs) can be used to control biological response resulting from UV photoablation. Nonsteroidal antiinflammatory agents which can be used according to the present invention will typically comprise: loxoprofen, as disclosed in British Patent No. GB 2,144,993A, published Mar. 12, 1985, incorporated herein by reference. Compounds disclosed in U.S. Patent No. 4,559,343, issued Dec. 17, 1985 and incorporated herein by this specific reference can also be used.

Those compounds include: flubiprofen; suprofen; aryl or heteroarylcarboxylic acids such as mfenamic acid, flufenamic acid, clonixin, flufenial; aryl or heteroaryloalkynoic acids such as 4-(t-buty1) benzeneacetic acid, ibufenac, ibuprofen, alkyllofenac, fenoprofen, naproxen, indomethacin, tolmetin, ketoprofen and namoxynrate. Additionally, ketorolac, or pyrrolo pyrroles, disclosed in U.S. Pat. No. 4,454,151 issued June 12, 1984 and incorporated herein by reference, can be used. Such NSAIs can be used at concentrations of between about 0.1 and 2.0 wt. %. Preferred NSAIs include: suprofen, loxoprofen, flurbiprofen, iodomethacin and ketorolac. These compounds are typically present in the compositions at the following concentrations; suprofen at about 1.0 wt. %, loxoprofen at about 1.0 wt. %, flurbiprofen at about 0.25 wt. %, indomethacin from about 0.1 to 1.0 wt. % and ketorolac at about 0.5 to 1.0 wt. %.
Anti-oxidants can also be used to control biological response resulting from photoablation of the cornea. When tissue, such as the cornea, is subjected to trauma, for example UV radiation, reactive species in excess of those normal present as a result of enzymatic and nonenzymatic reactions are produced. These reactive species, including free radicals, can cause tissue damage; see The Molecular and Cellular Biology of Wound Repair, specifically Chaps 1, 6 and 7; and Fisher, Intracellular Production of Oxygen Radicals and Tissue Injury, Proceedings of a Book Lodge Symposium (April 1987), which is incorporated herein by this specific reference. Anti-oxidants prevent scar formation and control biological response by scavenging free radicals. Suitable anti-oxidants include, for example: ascorbic acid; glutathione; see Meister, Selective Modification of Glutathione Metabolism, Science, Vol. 220 (April 1988); alpha tocopherol; and selenous acid or sodium selenate. Such anti-oxidants can be used at concentrations between about 0.001 ng/ml and 1 mg/ml, preferably about 100 ng/ml.

Immunomodulators can also be used to control biological response. Immunomodulators which may be used include: cyclosporin A and cyclosporin G, leflunomide, N-(4-trifluoromethylphenyl)-N-(2-cyano-1-hydroxy-1-propen-1-yl) carboxamide and interferon (α, β and γ). Immunomodulators can be used at concentrations between about 2 and 10 wt. %.

Antiallergics are wound healing modulators which can also be used to control biological responses resulting from trauma to the cornea. This class of compounds includes for example: cyproheptadine, dipheniramine, azelastine, cimetidine, neodocromil, cromolyn, lodoxamide, pheniramine and 6-methyl-N-(1H-tetrazol-5-yl)-2-pyridinecarboxamide. Such
antiallergic compounds can be used at concentrations of about 0.1 to 4.0 wt. %.

Wound healing modulators which can be used to control biological response, insulin like growth factor (IGF) and insulin; and tumor necrosis factor (TNF). Such growth factors can be used in accordance with the foregoing discussion of this class of wound healing modulators. In addition, the immunomodulators, antiallergics and basement membrane components, as previously set forth, can be used in this situation.

Photoablation leaves the cornea denuded of its protective epithelial layer leaving it prone to infection. Antimicrobials can be used according to the present invention pre-operatively and post-operative thereby safeguarding against corneal infection which inhibits healing, possibly leading to corneal edema and the formation of corneal haze. Antimicrobials which can be used according to the present invention include: chloramphenicol, erythromycin, gentamycin, polymyxin, sulfacetamide, tetracycline, tobramycin, sulfisoxazole, diolamine, ciprofloxacin, natamycin, neomycin, ofloxacin, norfloxacin, trifluorothymidine, acyclovir, gancyclovir, vancomycin and other antibacterial, antiviral and antifungal agents. The compositions comprise one or more antimicrobials or combinations of antimicrobials and other wound healing modulators. Such antimicrobials are used at concentrations between about 0.05 and 3.0 wt. % preferably less than about 1.0 wt. %.

The compositions of the present invention can be applied alone or in combination with other agents to control biological response. In addition, individual agents or combinations thereof can be applied uniquely or sequentially. While the effective dose and
treatment regime are left to the discretion of the clinician, the following procedures are recommended.

The compositions which can be used to control biological response are formulated in compositions for topical application to the eye. As will be appreciated by those skilled in the art, the compositions can be formulated in various pharmaceutically acceptable forms for topical ophthalmic delivery including: solutions, suspensions, emulsions, gels and solid inserts, depending on the nature and characteristics of the agents. Preferred formulations are aqueous solutions. In addition, agents of the present invention can be applied via the use of a collagen shield, contact lens or other solid matrix placed on the ocular surface. Such shields, lenses or matrices can provide for slow release of the modulators as well as serving as a protective environmental barrier.

In addition to the principal active ingredients, the compositions of the present invention may further comprise various formulatory ingredients, such as antimicrobial preservatives and tonicity agents. For example, antimicrobial preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methylparaben, propylparaben, phenylethyl alcohol, EDTA, sorbic acid, POLYQUAD and other agents equally well known to those skilled in the art. Such preservatives, if employed, will typically be used in an amount from about 0.0001 wt. % to 1.0 wt. %. Suitable agents which may be used to adjust tonicity or osmolality of the compositions include: sodium chloride, potassium chloride, mannitol, dextrose, glycerine and propylene glycol. If used, such agents will be employed in an amount of about 0.1 wt.% to 0.0 wt.% However, preferable compositions of the present invention will not include preservatives of tonicity
agents which are known to adversely affect or irritate the eye, particularly the cornea.

As will be understood by those skilled in the art, the administration, sequence of administration when more than one composition is used, and the concentrations of the wound healing modulators used depends on numerous factors. These factors can include; the specific agents being used, the nature of the surgical procedure, and various clinical factors, including the extent and type of dioptic change, the medical history of the patient, symptoms apparent prior to, during, or after surgery, such as inflammation or edema, etc. Selection of specific agents or combinations thereof, their concentrations and sequence of delivery to the eye will be made by the skilled clinician guided by the foregoing description.

Regardless of reason, there are compounds, or compositions, collectively referred to herein as "adjuncts" which can be used alone, or in addition to the agents discussed above, that contribute to the overall health and comfort of the eye, thus contributing to its treatment.

For example, during the following photoablation of the cornea, elevation of intraocular pressure may occur. Control of intraocular pressure contributes the health of the cornea thereby allowing the cornea to heal. Adjuncts for controlling intraocular pressure which can be used in combination with agents of the present invention, include antihypertensive agents. Antihypertensive agents which can be used include, for example, timolol, betaxolol, levobunolol, glycerin, isosorbide, manitol, urea, paraminoclonidines, epinephrine and carbonic anhydrase inhibitors. The compounds can be topically applied to the eye following
photoablation at concentrations between about 0.1 and 2.0 wt. % preferably about 0.5 wt. %. In addition, miotics can be used to control intraocular pressure. For example, miotics such as carbachol, pilocarpine, physostigmine, echothiophate and isofluorophate can be used.

Humectants may be used prior to, during and after photoablation of the cornea. These adjuncts promote healing of the cornea by providing lubrication and preserving the natural tear physiology. Humectants can include preparations which typically comprise hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinyl alcohol, cellulose esters, povidone or other suitable polymeric systems.

Epithelial cell health promoters as used herein, are compounds known to contribute to the health of the epithelial cells of the cornea. The presence of these compounds prior to, during, and/or after photoablation of the cornea can encourage the rapid resumption of epithelial integrity and prevention of stromal edema. Epithelial cell health promoters which can be used as adjuncts to the agents of the present invention include: ascorbic acid; retinoids, such as retinoic acid, retinol, retinal and retinoyl B-glucuronide; aloe vera; collagenase inhibitors; prostaglandins, such as prostaglandin E2 and elastase inhibitors.

The present invention also encompasses methods of treatment of an eye exposed to laser radiation during ophthalmic procedures, particularly UV radiation. Methods of treatment, during ophthalmic surgery, with compositions containing agents disclosed above, include application of the compositions before laser exposure, during the procedures, for example when the ye is
moistened and a wet keratoscope reading is taken during corneal sculpting using a UV laser and/or immediately after irradiation. In addition, and as previously discussed, the compositions of the present invention can be applied uniquely or when the use of more than one agent is indicated, the medicaments can be administered sequentially.

The following formulation is an example of a wound healing modulator composition that can be used for the prevention and treatment of corneal haze resulting from laser irradiation. It is not limiting but considered representative of useful compositions of the present invention.

**EXAMPLE:**

The following composition can be formulated by mixing the specific components at the indicated concentrations. The compositions should be either prepared under sterile conditions or sterilized after their preparation and prior to use.

**EXAMPLE 1 (SUSPENSION)**

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>0.1 wt.%</td>
</tr>
<tr>
<td>Neomycin Sulfate</td>
<td>Equivalent to</td>
</tr>
<tr>
<td>Neomycin</td>
<td>3.5 mg/ml</td>
</tr>
<tr>
<td>Polymixin Sulfate</td>
<td>10,000 units/ml</td>
</tr>
<tr>
<td>Benzalkonium Chloride</td>
<td>0.0004 wt. %</td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulate</td>
<td>0.5 wt. %</td>
</tr>
<tr>
<td>Purified Water</td>
<td>g.s.</td>
</tr>
</tbody>
</table>
WHAT IS CLAIMED IS:

Claim 1. A method for changing the refractive power of an eye, said method comprising the steps of:
selecting a dioptic correction for an eye without compromise for regression of refractive power due to biological response to a change in corneal profile;
changing the corneal profile of the eye in order to change the refractive power of the eye to the selected dioptic; and
limiting regression in corneal profile in order to maintain the refractive power to about the selective diopter by applying to the cornea a composition comprising an agent for controlling the biological response.

Claim 2. The method according to Claim 1, wherein the step of changing a corneal profile includes radial keratotomy.

Claim 3. The method according to Claim 1 wherein the step of changing a corneal profile includes photorefractive keratectomy.

Claim 4. The method according to Claim 1 wherein the step of changing a corneal profile includes thermal keratoplasty.

Claim 5. The method according to Claim 1 wherein the step of changing a corneal profile includes a change in the refractive power of at least six diopters.

Claim 6. The method according to Claim 5 wherein the change in the refractive power causes emmetropia.
Claim 7. The method according to Claim 1 wherein the composition is applied to the cornea before changing the corneal profile.

Claim 8. The method according to Claim 1 wherein said agent comprises a steroid.

Claim 9. The method according to Claim 8 wherein the steroid is present at a concentration of about 0.1 to about 4.0 wt. %.

Claim 10. The method according to Claim 9 wherein the steroid is selected from the group consisting of decamethasone, prednisolone, prednisone, fluorometholone, rimexolone, medrysone, betamethasone, triamcinolone and hydrocortisone.

Claim 11. The method according to Claim 1 wherein said agent comprises a basement membrane component.

Claim 12. The method according to Claim 1 wherein said agent comprises a non-steroidal antiinflammatory.

Claim 13. The method according to Claim 12 wherein the non-steroidal antiinflammatory is selected from the group consisting of flurbiprofen, suprofen, mafenamic acid, flufenamic acid, clonixin, flufenisal, ibufenac, 4-(t-butyl) benzeneacetic acid, ibuprofen, alkyllofenac, fenoprofen, naproxen, indomethacin, tolmetin, ketoprofen, namoxyrate, ketorolac, and loxoprofen.

Claim 14. The method for changing the refractive power of an eye, said method comprising the steps of:
changing a corneal profile of the eye in order to change the refractive power of the eye to a selective dioptic; and controlling biological response to the change in corneal profile in order to maintain the refractive power at about the selected diopter by applying to the cornea a composition comprising an agent for limiting the biological response.

Claim 15. The method according to Claim 14 wherein the step of changing a corneal profile includes radial keratotomy.

Claim 16. The method according to Claim 14 wherein the step of changing a corneal profile includes photorefractive keratotectomy.

Claim 17. The method according to Claim 14 wherein the step of changing a corneal profile includes thermal keratoplasty.

Claim 18. The method according to Claim 14 wherein the step of changing a corneal profile includes a change in the refractive power of about six diopters.

Claim 19. The method according to Claim 18 wherein the change in the refractive power causes emmetropia.

Claim 20. The method according to Claim 14 wherein the composition is applied to the cornea before changing the corneal profile.

Claim 21. The method according to Claim 14 wherein said agent comprises a steroid.
Claim 22. The method according to Claim 21 wherein the steroid is present at a concentration of about 0.1 to about 4.0 wt. %.

Claim 23. The method according to Claim 22 wherein the steroid is selected from the group consisting of deramethasone, prednisolone, prednisone, fluorometholone, rimexolone, medrysone, betamethasone, triamicinolone and hydrocortisone.

Claim 24. The method according to Claim 14 wherein said agent comprises a basement membrane component.

Claim 25. The method according to Claim 14 wherein said agent comprises a non-steroidal antiinflammatory.

Claim 26. The method according to Claim 25 wherein the non-steroidal antiinflammatory is selected from the group consisting of flurbiprofen, suprofen, mefenamic acid, flufenamic acid, clonixin, flufenisal, ibufenac, 4-(t-butyl) benzeneacetic acid, ibuprofen, alkylofenac, fenoprofen, naproxen, indomethacin, tolmetin, ketoprofen, namoxirate, ketorolac, and loxoprofen.

Claim 27. A method for changing the refractive power of an eye, said method comprising the steps of:
- surgically changing a corneal profile of the eye in order to change the refractive power thereof to a selective diopter; and
- retarding regression of the selective diopter by applying to the cornea a composition comprising an agent for controlling a biological response to the surgical change to the corneal profile.
Claim 28. The method according to Claim 27 wherein the step of changing a corneal profile includes radial keratotomy.

Claim 29. The method according to Claim 27 wherein the step of changing a corneal profile includes photorefractive keratectomy.

Claim 30. The method according to Claim 30 wherein the step of changing a corneal profile includes thermal keratoplasty.

Claim 31. The method according to Claim 27 wherein the step of changing a corneal profile includes a change in the refractive power of at least six diopters.

Claim 32. The method according to Claim 31 wherein the change is the refractive power causes emmetropia.

Claim 33. The method according to Claim 27 wherein the composition is applied to the cornea before changing the corneal profile.

Claim 34. The method according to Claim 27 wherein said agent comprises a steroid.

Claim 35. The method according to Claim 34 wherein the steroid is present at a concentration of about 0.1 to about 4.0 wt. %.

Claim 36. The method according to Claim 35 wherein the steroid is selected from the group consisting of deramethasone, prednisolone, prednisone, fluorometholone, rimexolone, medrysone, betamethasone, triamcinolone and hydrocortisone.
Claim 37. The method according to Claim 27 wherein said agent comprises a basement membrane component.

Claim 38. The method according to Claim 27 wherein said agent comprises a non-steroidal antiinflammatory.

Claim 39. The method according to Claim 38 wherein the non-steroidal antiinflammatory is selected from the group consisting of flurbiprofen, suprofen, mefenamic acid, flufenamic acid, clonixin, flufenisal, ibufenac, 4-(t-butyl) benzeacetic acid, ibuprofen, alkylofenac, fenoprofen, naproxen, indomethacin, tolmetin, ketoprofen, namoxyrate, ketorolac, and loxoprofen.