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[54] **TREATMENT OF AGE RELATED MACULAR DEGENERATION WITH BETA-CAROTENE**

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[52] **U.S. Cl.** **514/725**; 514/912

[58] **Field of Search** 514/725, 912

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[57] **ABSTRACT**

According to the present invention, there are provided methods for treating age related macular degeneration in a mammal; for preventing impairment of the vision or for improving impaired vision of a mammal whose eye has drusen; for preventing formation or growth of drusen in the eye of a mammal; and for reducing the number or the size of drusen or for fading drusen without resultant areas of retinal atrophy, without resultant impairment of vision, or without a combination of the foregoing in the eye of a mammal. Beta-carotene in appropriate amounts is administered to the mammal.

19 Claims, 1 Drawing Sheet

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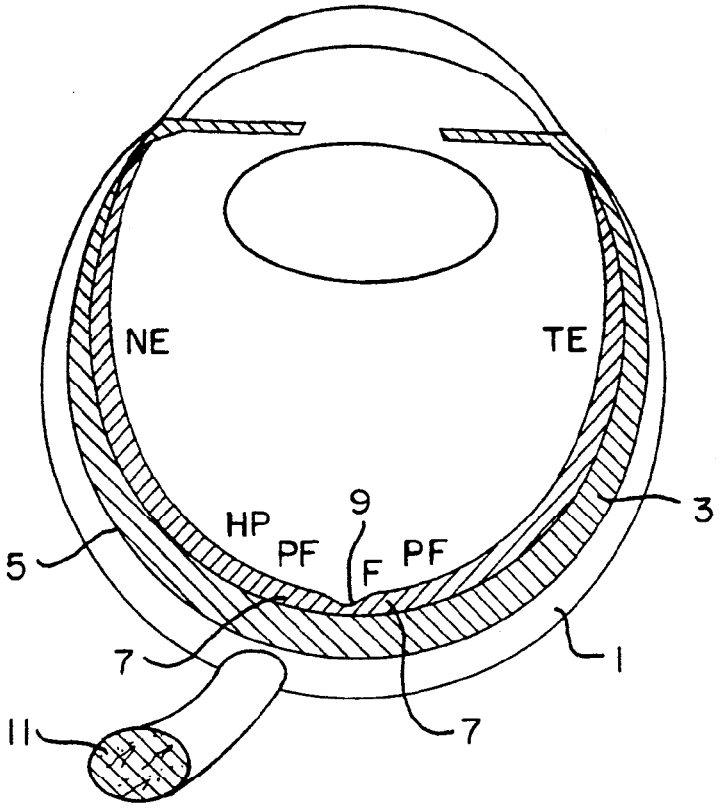
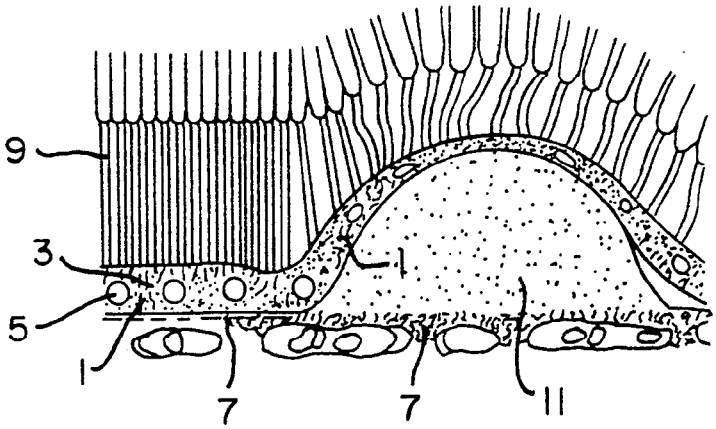


FIG. 1

FIG. 2



TREATMENT OF AGE RELATED MACULAR DEGENERATION WITH BETA-CAROTENE

FIELD OF THE INVENTION

The invention relates to a method for the treatment of age related macular degeneration (ARMD) in the eyes of mammals. Beta-carotene is administered, preferably systemically, in a therapeutically effective amount.

The administration of beta-carotene has also been found to prevent the growth or the formation of drusen, to reduce the number or the size of drusen, or to cause drusen to fade without resultant retinal atrophy or impairment of vision.

BACKGROUND OF THE INVENTION

Age related macular degeneration is a common degenerative disease of the retina and is the leading cause of blindness in the elderly. The disease is associated with chronological age, as ten percent of the individuals between the ages of sixty-five and seventy-five in the United States have lost some vision because of the disease. Thirty percent of people over the age of seventy-five have lost some vision due to the disease. Young, "Pathophysiology of Age-related Macular Degeneration", *Survey of Ophthalmology*, Vol. 31, No. 5, March–April 1987.

The basic anatomy of the eye is illustrated in FIG. **1**.

The sclera (**1**) forms the external tissue of the eyeball. The choroid (**3**) is the vascular layer beneath the sclera. The retina (**5**) lines the choroid (**3**) and is the nervous membrane upon the surface of which the images of external objects are received and then are transmitted through the optic nerve (**11**). Precisely in the center of the posterior part of the retina, corresponding to the axis of the eye, and at a point in which the sense of vision is perfect in a normal eye, is a yellowish area called the macula (**7**) which has a central depression, called the fovea (**9**). FIG. **2** illustrates that beneath the sensory retina is a single layer of pigmented epithelial cells called the retinal pigment epithelium (RPE) (**1**). Between the RPE and the choriocapillaries is a membrane known as Bruch's membrane (**7**).

ARMD is believed to be caused by the deterioration and death of the retinal pigment epithelium. The cause of the degeneration is unknown, but it has been speculated that ARMD may be an advanced stage of the normal aging process. Young, *Survey of Ophthalmology*, Vol. 31, No. 5, March–April 1987. The variability in the age of onset of the disease is likely due to the variability in biological aging.

The earliest and most obvious clinical sign of ARMD is the presence of drusen. Sarks et al. "Age-related Macular Degeneration: Atrophic Form", *Retina*, Vol. 2., The C. V. Mosby Company, 1989. Drusen are extracellular masses of heterogeneous composition containing materials excreted from aging RPE cells and remnants of dead cells. Young, *Survey of Ophthalmology*, Vol. 31, No. 5, March–April 1987. They are situated between the basal membrane of the RPE and Bruch's membrane. Young, *Survey of Ophthalmology*, Vol. 31, No. 5, March–April 1987. Clinically, drusen are seen as localized yellowish deposits or excrescences lying deep to the retina. Bressler et al. "Age-related Macular Degeneration", *Survey of Ophthalmology*, Vol. 32, No. 6, May–June 1988.

Small discrete drusen, i.e. hard drusen, are seen in eighty-three percent of normal adult eyes. Hard drusen represent a localized disorder of only a few RPE cells. The RPE cells overlying the drusen are often thinned or pigmented. Bressler et al., *Survey of Ophthalmology*, Vol. 32, No. 6, May–June 1988.

Larger areas of RPE dysfunction having ill defined, nondiscrete boundaries are termed soft drusen. Soft drusen are associated with more serious forms of ARMD in which there is significant loss of central vision. Soft drusen often merge into one another and become confluent.

The interface between the choroid and the retina, the development of drusen, and the changes induced by drusen are illustrated in FIG. **2**. On the far left, the retinal pigment epithelium (RPE) cells (**1**) contain only a few residual bodies (**3**), and these are largely confined to the base of the cells. Melanin granules (**5**) are present near the apical surface. Bruch's membrane (**7**) is thin and uncontaminated. The visual cells (**9**) (of which only the inner and outer segments are shown) are regularly aligned and densely packed. This is the typical appearance in young eyes. In the adjacent region, early senescent changes are shown: the number of residual bodies (**3**) has increased throughout the RPE (**1**) cytoplasm, and Bruch's membrane (**7**) has thickened. To the right, a druse (**11**) has been formed. On the surface of the druse, the attenuated RPE cells are engorged with residual bodies, melanin has diminished in amount, some of the visual cells have disappeared, and the remainder are physically distorted. Surviving rods and cones become shorter and broader as adjacent cells disappear.

Patients can still have excellent visual acuity in the early stages of ARMD. Bressler et al., *Survey of Ophthalmology*, Vol. 32, No. 6, May–June 1988.

Loss of central vision can be attributed to several different occurrences, all of which relate to the drusen. Vision loss can occur when RPE and photoreceptor cells over the drusen degenerate and debris accumulates. Although the drusen fade and ultimately disappear, areas of atrophy remain. This fading is believed to be due to the activity of macrophages and adjacent RPE cells. This form of ARMD is termed geographic atrophy. Sarks et al., "Evolution of Geographic Atrophy of the Retinal Pigment Epithelium", *Eye*, Vol. 2, 552–577, 1988; see also Schatz et al., "Atrophic Macular Degeneration", *Ophthalmology*, 96, October 1989.

Soft drusen can also cause vision loss by initiating breaks in Bruch's membrane which allow the egress of fibrovascular tissue from the choriocapillaries. The fibrous tissue can lead to serous or hemorrhagic detachments of the sensory retina with accompanying severe loss of central vision.

Finally, drusen may become so abundant as to involve the fovea, interrupting the function of the sensory retina and resulting in vision loss.

Research on the effects of phototoxicity in human and primate retinas has demonstrated some relationship between acute photic damage to the retina and the changes symptomatic of ARMD. Young, "Solar Radiation and Age-related Macular Degeneration", *Survey of Ophthalmology*, Vol. 32, No. 4, January–February 1988. However, if ARMD were caused by chronic phototoxicity, one would expect an association between life-long light exposure and the prevalence of ARMD. Recent epidemiological studies indicate that there is no correlation between ARMD and the cumulative exposure of UV light. West et al., "Exposure to Sunlight and Other

Risk Factors for Age-related Macular Degeneration", *Arch. Ophthalmol.*, Vol. 107, June 1989.

Furthermore, various studies have been proposed or performed to determine the ediology of ARMD. Handleman et al., "Carotenoids in the Human Macula and Whole Retina", *Investigative Ophthalmology and Visual Science*, Vol. 29, No. 6, 850–855, June 1988, found that the major carotenoids in the retina were lutea and zeaxanthin. No beta-carotene was found in the retina. Handleman et al. proposed to prevent ARMD through the use of retinal carotenoids to confer antioxidant protection. Handleman et al. classified carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a mediator of light damage in the retina. Carotenoid deficient monkeys were reported to show pigment changes in the fundus.

Ham et al., "Basic Mechanisms Underlying the Production of Photochemical Lesions in the Mammalian Retina", *Current Eye Research*, Vol.3, No. 1, 165–174, 1984, disclose that both vitamin E and beta-carotene are naturally occurring singlet oxygen quenchers and that the toxic combination of light and oxygen leads to the generation of free radicals, a possible cause of phototoxicity.

Vitamin E was suggested to be a likely vitamin A autoxidation inhibitor by Katz et al., "Relationship between Dietary Retinol and Lipofuscin in the Retinal Pigment Epithelium", *Mechanisms of Aging and Development*, Vol. 35, 291–305, 1986. See also Katz et al. "Development of Lipofuscin-like Fluorescence in the Retinal Pigment Epithelium in Response to Protease Inhibitor Treatment", *Mechanisms of Aging and Development*, Vol. 49, 23–40, 1989; Stephens et al., "Vitamin E Distribution in Occular Tissues Following Long-term Dietary Depletion and Supplementation as Determined by Microdissection and Gas Chromatography-Mass Spectrometry", *Experimental Eye Research*, Vol. 47, 237–245, 1988.

Retinoids have been demonstrated to modulate the growth and differentiation of several types of cells by Campochiaro et al., "Retinoic Acid Promotes Density-Dependent Growth Arrest in Human Retinal Pigment Epithelial Cells", *Investigative Ophthalmology and Visual Science*, Vol. 32, No. 1, January 1991.

Gottsch et al., "Hematogenous Photosensitization", *Investigative Ophthalmology and Visual Science*. Vol. 31, No. 9, September 1990, hypothesize that tissue damage due to photosensitization which in turn is due to free radical generation, may be prevented either by inducing protective enzymes using scavengers of free radicals and singlet oxygen such as vitamin E or by filtering the appropriate excitatory wavelengths. See also Boulton et al., "The Formulation of Autofluorescent Granules in Cultured Human RPE", *Investigative Ophthalmology and Visual Science*. Vol. 30, No. 1, January 1989. While Gottsch et al. suggest that beta-carotene and vitamin E are singlet oxygen quenchers, they strongly suggest that treatment of established disease is not aided by these agents and that prophylaxis by vitamin E is not always effective.

Katz et al. "Flourescent Pigment Accumulation in Retinal Pigment Epithelium of Antioxidant-Deficient Rats", *Investigative Ophthalmology Visual.*, 1049–1058, 1978, disclose that lipofuscin pigment in rats may be attributable to a diet that produces physiological antioxidant deficiency. Young, *Survey of Ophthalmology*, Vol. 32, No. 4, January–February 1988, discloses that beta-carotene can diminish photodynamic change in the retina. However, treatment of established ARMD is not disclosed, and no relationship between the presence or the growth of drusen and photodynamic damage is suggested.

Because the normal retina has a high concentration of zinc, supplemental zinc was investigated in the treatment of ARMD by Newsome et al. "Oral Zinc in Macular Degeneration", *Arch. Ophthalmology*, Vol. 106, February 1988. No correlation of ARMD with initial serum levels of zinc was observed, and progression of the disease was seen in both the treatment and the non-treatment groups. Furthermore, zinc ingestion can be accompanied by serious side effects.

It has now been discovered that the administration of appropriate amounts of beta-carotene can successfully treat ARMD. Beta-carotene had also proven useful in the inhibition and resolution of drusen, particularly without typical vision impairment or detrimental anatomical and physiological changes in the eye.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagram of the anatomy of the eye.

FIG. 2 is a diagram of the development of drusen.

SUMMARY OF THE INVENTION

According to the present invention, there is provided a method for treating age related macular degeneration in a mammal comprising administering to the mammal, a therapeutically effective amount of beta-carotene.

The invention also contemplates a method for preventing impairment of the vision or for improving impaired vision of a mammal whose eye has drusen comprising administering to the mammal a therapeutically effective amount of beta-carotene.

In a further embodiment, a method for preventing formation or growth of drusen in the eye of a mammal is provided. This method comprises administering to the mammal a drusen inhibiting effective amount of beta-carotene.

Furthermore, a method for reducing the number or the size of drusen or for fading drusen without resultant areas of retinal atrophy, without resultant impairment of vision, or without a combination of the foregoing in the eye of a mammal is provided. Beta-carotene in a drusen reducing amount is administered to the mammal.

DETAILED DESCRIPTION OF THE INVENTION

Carotinoids are terpenes that are widely distributed in the plant and animal kingdoms. Beta-carotene is a common carotinoid having the chemical structure:

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