REFRACTIVE INDEX CHANGES IN THE OCULAR LENS RESULT FROM INCREASED LIGHT SCATTER

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ABSTRACT

As the crystalline lens ages and as cataracts develop, highly concentrated proteins in lens fiber cells undergo rearrangements leading to substantial increases in scattered light. By exploiting a relationship between scattered light and refractive index, it is shown that a rearrangement of proteins necessarily leads to increased index as well. This change in refractive index is a second-order effect and must be quite small in most cases. However, it offers a possible explanation for the increase in index and refractive power associated with the development of nuclear cataract. © *1996 Society of Photo-Optical Instrumentation Engineers.*

Keywords light scatter and fluorescence; crystalline lens; refractive index; nuclear cataract.

INTRODUCTION

The crystalline lens grows throughout life and in addition undergoes a variety of biochemical changes as one ages. These changes include the possibility of cataract formation leading to greatly increased light scatter and eventually to a lens opacity.

There are at least two well-documented sets of conditions associated with refractive index changes in the lens. As the lens ages it becomes thicker and its surfaces typically develop greater curvatures. Concomitant refractive power increases, however, do not take place when averaged over a population. This apparent contradiction has been called the ''lens paradox'' and has been ascribed to a small refractive index change in one or another segment of the lens.[1–3] The biochemical basis of this index change, however, remains under debate.

A second set of circumstances leading apparently to an index change in the crystalline lens has sometimes been called ''index myopia.''[4] An increase in refractive power of the lens by 1 to 3 diopters has been shown to be a precursor to nuclear sclerosis and nuclear cataract.[5] An increase in index of the nucleus of the Gullstrand exact eye of about .005 to .01 is sufficient to accomplish this change in power. If the index is graded with the largest index at the nucleus center, then a much smaller change of index achieves the same power change.

An often studied type of change occurring in the aging and cataractous lens is the formation of protein aggregates in the cytoplasm and on the membranes of the structural cells (lens fibers). The refractive index of a medium is determined by the polarizability of its constituents, i.e., the response of each constituent to an external electric field. If a molecule is polarized, then it establishes a secondary electric field in its neighborhood affecting nearby molecules. Therefore one expects the polarizability of a protein aggregate to be slightly different than the sum of the polarizabilities of its constituent molecules. Likewise one expects the refractive index of the lens to be somewhat changed if a substantial fraction of proteins become aggregated.

The formation of protein aggregates must change the amount and angular distribution of light scattered by the lens. Therefore one might suspect that scattered light contains information about protein aggregation and the resulting change in refractive index. That this is in fact the case has been shown by van de Hulst.[6] For small index fluctuations, surely the case for the crystalline lens, the light scattered in the forward direction, i.e., in the direction of the transmitted beam, combines with the transmitted wave slightly changing its phase (and magnitude). This phase change is interpreted by van de Hulst as due to a change in index of the scattering medium.

For a medium of tenuous scatterers (small index fluctuations), the scattered electric field at any point in space can be expressed as an iterative series.[7,8] The first term in this series has been called the Rayleigh-Gans approximation[6] (or Born approximation). The second term, considerably more complex than the first, has been written in a form suitable for numerical evaluation.[7–9] To evaluate the effects of protein aggregation on refractive index, it

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is necessary to evaluate this second term in the forward direction only. This has been done for two scatterer geometries. In one, the light scattering entities are assumed randomly positioned and oriented. In the other, they are assumed to be parallel cylinders. It is plausible that these two cases are representative of actual light scattering processes in the lens.[10]

CALCULATIONS

A linearly polarized plane wave, $\mathbf{E}_0 \exp(ikz)$, is propagated in the direction of the positive z axis through a medium consisting of a cloud of particles of refractive index n in a medium of refractive index n_0. The ''wave number'' $k=2\pi/\lambda$, and λ is the wavelength inside the medium of index n_0. The incident electric field vector, $\mathbf{E}_0$, is directed along the x axis so that $\mathbf{E}_0=E_0\mathbf{x}$, where $\mathbf{x}$ is a unit vector along the positive x axis. The total electric field surrounding this medium satisfies a fairly complex integrodifferential equation.[7] When the particle indices differ little from the surrounding medium, the integrodifferential equation can be solved by an iterative series with an approximate expansion coefficient,

$$\alpha=\frac{n-n_0}{2\pi n_0}.$$

The scattered field, $\mathbf{E}_{sc}(\mathbf{r})$, at position $\mathbf{r}$ is the electric field remaining after subtraction of the incident field from the total field. It can be written formally as the iterative series

$$E_{sc}(\mathbf{r})=\alpha\mathbf{E}_1(\mathbf{r})+\alpha^2\mathbf{E}_2(\mathbf{r})+\ldots\,. \quad (1)$$

Evaluation of the scattered field at distances from the scattering medium large compared to dimensions of the medium (i.e., the far field) leads to a number of simplifications. The first term in the resulting series for the scattered field, the Rayleigh-Gans approximation, has often been used to describe light scatter by tenuous particles. It accounts for single-scattering events. The second term accounts for all double-scattering events and therefore takes into account interactions between polarizabilities at different positions in the medium.

It is the purpose of this study to evaluate the contribution of scattered light to the refractive index of a medium. Values of $\mathbf{E}_{sc}(\mathbf{r})$ in the direction of propagation of the incident light, i.e., at positions along the positive z axis, make up the ''forward scattered light.'' This portion of the scattered field adds to the incident wave slightly changing both its phase and its magnitude.[6] This can be represented symbolically as

$$\exp(ikz)\rightarrow\exp\left[ik\left(z+L\frac{\Delta m}{n_0}\right)\right],$$

where L is the thickness of the scattering medium. The quantity Δm in general has both a real and imaginary part. The real part leads to a phase change of the transmitted light, so it must be interpreted as an index change of the medium due to light scatter. The imaginary part of Δm, however, leads to an exponential decay of the transmitted wave. This decay is a consequence of the removal of scattered light from the transmitted light.

Only two cases will be considered in the following. In one, the scattering entities are randomly positioned and randomly oriented so that statistically they can be treated as spherically symmetrical. In the other, the scattering entities are assumed to be infinite parallel cylinders with axes parallel to either the x or y axis. In each of these cases, by symmetry, the forward scattered field must be parallel to the incident field. If the origin of coordinates is placed inside the scattering volume, then the far field can be written

$$\mathbf{E}_{sc}(\mathbf{z})=\mathbf{E}_0\frac{\exp\{ikz\}}{kz}S(0).$$

The forward scattering amplitude, $S(0)$, is a scalar quantity that, from Eq. (1), can be written $S(0)=\alpha S_1(0)+\alpha^2 S_2(0)+\ldots$. It is related to the refractive index change Δm by[6]

$$\frac{\Delta m}{n_0}=\frac{2\pi}{k^3V_0}\,\mathrm{Re}\{S(0)\}, \quad (2)$$

where V_0 is the volume of the scattering medium. The refractive index change, Δm, is explicitly identified with the real part of $S(0)$ in Eq. (2). The imaginary part of $S(0)$ gives a term resulting in an exponential decay of the transmitted wave due to removal of scattered light. It will be considered later. The scattering amplitude, $S_1(0)$, in the Rayleigh-Gans approximation is particularly simple because the field inside the particle is assumed to be equal to the incident field. Then,

$$\alpha S_1(0)=\frac{n-n_0}{2\pi n_0}k^3V_s, \quad (3)$$

where V_s is the total volume of scattering particles. From Eq. (2), the refractive index m of the medium is

$$m\equiv n_0+\Delta m=n_0+(n-n_0)\frac{V_s}{V_0}. \quad (4)$$

The right-hand side of Eq. (4) equals the mean index of medium and scattering particles. Therefore in this Rayleigh-Gans approximation the medium index is equal to the mean index.

Note that Eq. (4) gives no information about particle size. Such information requires going beyond the Rayleigh-Gans approximation.

To find the dependence of medium index on particle size, the second term, $\alpha^2 S_2(0)$, must be evaluated.[7–9]

$$S_2(0)=\frac{k^6}{6\pi^2}\int_{-\infty}^{\infty} d^3u G(\mathbf{u})\frac{2+u^2-3u_x^2}{u^2-1}, \qquad (5)$$

where the three-fold integral extends over all values of the components of the vector $\mathbf{u}$. Also,

$$G(\mathbf{u})=\left|\int_{\text{particles}} d^3r' \exp\{-ik\mathbf{r}'(\mathbf{u}+\mathbf{z})\}\right|^2. \qquad (6)$$

Here the three-fold integral is over the volume of all scattering particles. Also $\mathbf{z}$ is a unit vector in the direction of the positive z axis. The integral in Eq. (5) is singular. It must be evaluated by making the replacement

$$\frac{1}{u^2-1}=\frac{1}{u+1}\left(\frac{P}{u-1}+\pi i\right),$$

where the symbol P denotes the Cauchy principal value of the integral. Note also that $S_2(0)$ is thus divided into real and imaginary parts. Equations (5) and (6) allow, in principle, the evaluation of $S_2(0)$ and the corresponding change in the medium refractive index. These equations can be made more tractable by treating the medium as a random distribution of refractive index fluctuations. Let the random variable $n(\mathbf{r})$ be the index at position $\mathbf{r}$ in the scattering medium. It is convenient to define the random variable,

$$\eta(\mathbf{r})=\frac{n(\mathbf{r})}{\bar{n}}-1.$$

The bar over any quantity denotes an average of that quantity over the scattering medium. Note that $\bar{\eta}=0$. With appropriate assumptions, the correlation function,[11] defined by

$$\overline{\eta^2}\gamma(\boldsymbol{\rho})=\overline{\eta(\mathbf{r}_1)\eta(\mathbf{r}_2)}$$

with $\rho=\mathbf{r}_1-\mathbf{r}_2$, exists for all values of the vector $\boldsymbol{\rho}$. Note that $\gamma(0)=1$ and that $\overline{\eta^2}$ is the variance of index fluctuations. Also, if the index fluctuations are random, then $\gamma(\boldsymbol{\rho})$ must decline to a value of 0 for distances ρ, which are very much less than the dimensions of the scattering medium.

The coefficient of expansion in Eq. (1) is now a variable, $\eta(\mathbf{r})/2\pi$. It is correctly incorporated into Eqs. (5) and (6) by placing it under the integral sign of the expression Eq. (6), for $G(\mathbf{u})$ and extending the integral over the entire scattering medium.[9] The mean of G now becomes

$$\bar{G}(\mathbf{u})=\frac{\overline{\eta^2}V_0}{4\pi^2}\int_{-\infty}^{\infty} d^3\boldsymbol{\rho}\gamma(\boldsymbol{\rho})\ \exp\{ik\boldsymbol{\rho}(\mathbf{u}+\mathbf{z})\}. \qquad (7)$$

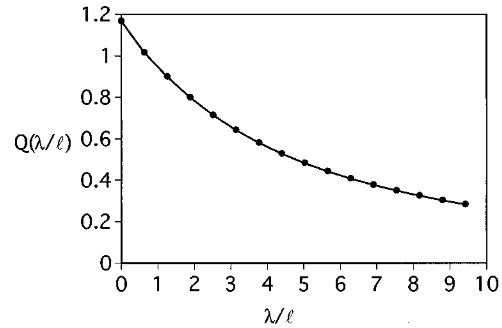

Fig. 1 Calculated values of the function Q versus λ/ℓ (wavelength/correlation length) for the case of randomly positioned and randomly oriented index fluctuations. The variance of index fluctuations times Q gives the medium index change due to aggregation.

The right side of Eq. (7) is readily evaluated in closed form if the correlation function is taken to be a decaying exponential,

$$\gamma(\boldsymbol{\rho})=\exp\left(-\frac{|\boldsymbol{\rho}|}{\ell}\right), \qquad (8)$$

where ℓ is the correlation distance, an estimate of the spatial extent of the index fluctuations. In the case of randomly positioned and oriented fluctuations, Eq. (8) holds for all directions of the vector $\boldsymbol{\rho}$. If the medium consists of parallel fibers, then Eq. (8) holds only for directions of the vector ρ perpendicular to the cylinder axes. In this latter case, $\gamma(\boldsymbol{\rho})$ is constant for directions parallel to fiber axes. Equation (7) can thus be evaluated in closed form. Substitution of the result into Eq. (5) allows it to be evaluated numerically.

Note that in the present case the relation between $S(0)$ and the change Δm in medium index given by Eq. (2) must be altered by the replacement $n_0\rightarrow\bar{n}$. Also, because $\bar{\eta}=0$, the term $S_1(0)$ (Rayleigh-Gans) makes no contribution. Finally, note that Eq. (5) has both real and imaginary parts and that it is the real part of $S(0)$ that is identified with a refractive index change. It can be seen by inspection, using Eqs. (5) and (7), that the right side of Eq. (2) is a function of the dimensionless variable λ/ℓ. Calling this quantity $\overline{\eta^2}Q(\lambda/\ell)$, the medium index m becomes

$$\frac{m}{\bar{n}}=1+\overline{\eta^2}Q(\lambda/\ell). \qquad (9)$$

The function Q is plotted in Figures 1 and 2 for the three cases of interest. In one, the index fluctuations are assumed randomly oriented and positioned. In the other two, the fluctuations take the form of randomly positioned, parallel cylinders. These latter two cases are distinguished by the direction of the incident electric field. A medium of parallel cylinders is a uniaxial birefringent medium with its optic axis parallel to the cylinder axes. Therefore the case defined by an incident electric field directed paral-

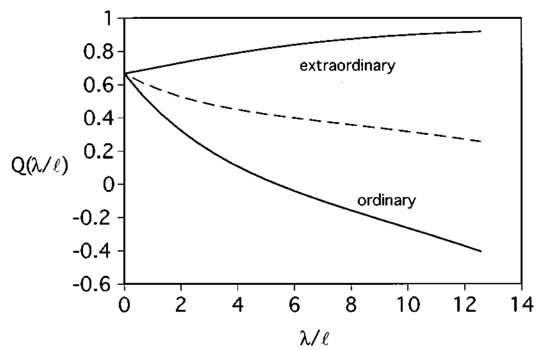

Fig. 2 Calculated values of the function Q versus λ/ℓ for the two cases of index fluctuations with the symmetry of parallel cylinders. In one case, the incident electric field is parallel to the cylinder axes (called "extraordinary") and in the other, the incident electric field is perpendicular to the cylinder axes (called "ordinary").

lel to the cylinder axes will be called "extraordinary," and the case with the incident electric field perpendicular to the cylinder axes will be called "ordinary." The difference $m_e - m_0$ between the extraordinary index [calculated from Eqs. (5), (7), and (8) for the incident electric field parallel to cylinder axes] and the ordinary index (incident electric vector perpendicular to cylinder axes) is a measure of the birefringence of a medium of cylinders. This difference is shown in Figure 3.

The imaginary part of $S(0)$ yields a term resulting in an exponential decay of the transmitted wave. Define

$$\epsilon = \overline{\eta^2} P(\lambda/\ell) = \frac{2\pi}{k^3 V_0} \mathrm{Im}\{S(0)\}. \tag{10}$$

Then the transmitted amplitude is to be multiplied by $\exp[-k\epsilon L]$ and the transmitted intensity by $\exp[-2k\epsilon L]$, where L is the path length through the scattering medium. The function P is plotted in Figure 4 for the case of randomly oriented and positioned fluctuations.

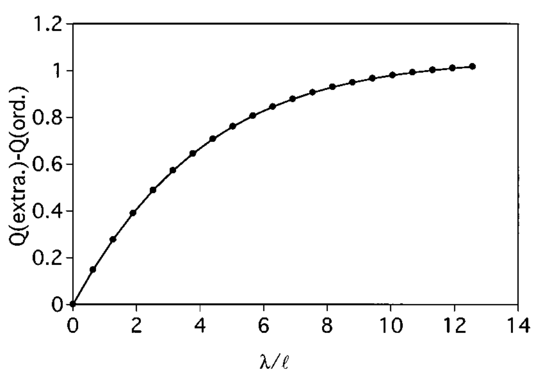

Fig. 3 The difference between the functions Q evaluated for the extraordinary case (incident field parallel to cylinder axes) and the ordinary case (incident field perpendicular to cylinder axes). This difference multiplied by the variance of index fluctuations gives the form birefringence of the medium $m_e - m_o$.

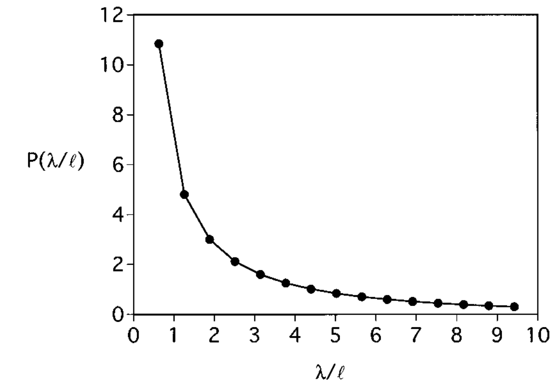

Fig. 4 Calculated values of the function P versus λ/ℓ (wavelength/correlation length) for the case of randomly oriented and positioned index fluctuations. The product of P with the variance of index fluctuations and the wave number (k) gives the space rate of decay of the transmitted wave.

DISCUSSION

As the lens ages and possibly becomes cataractous, its optical properties change. One unambiguous change is increased light scatter. There are also circumstances where it appears that refractive index changes are the source of measured changes in refractive power. An attempt has been made to exploit the relations between scattered light, protein aggregation, and refractive index to better understand these changes.

Van de Hulst[6] has shown that small changes of the refractive index of a medium are simply related to forward scattered light [see Eq. (2)]. By applying this result to the second term in an iterative series for scattered light, it follows quite generally that the increment Δm of medium index due to aggregation is equal to the variance of index fluctuations times a function of the ratio of wavelength to correlation length. From Eq. (9),

$$\Delta m = \frac{\overline{n^2} - \bar{n}^2}{\bar{n}} Q(\lambda/\ell). \tag{11}$$

The function $Q(\lambda/\ell)$ is shown in Figures 1 and 2 for the three cases described in the previous section and for a particular correlation function [see Eq. (8)]. For the case of randomly positioned and oriented index fluctuations Q=1.17 in the limit of large correlation length, $\ell \gg \lambda$, and Q=0 in the limit of small ℓ (Rayleigh limit). This provides justification for interpreting Δm as the medium index change due to aggregation.

In the case that index fluctuations take the form of parallel cylinders Q=0.67 in the large ℓ (i.e., large cylinder diameter) limit for both polarizations of incident light (see Figure 2). The difference in Δm for these two cases must be interpreted as the form birefringence of the medium of parallel cylinders.[9] Note that the difference in values of the function $Q(\lambda/\ell)$ goes from 0 (large ℓ) to 1 (small ℓ) in Figure 3.

In the Rayleigh limit (small ℓ), the form birefringence therefore becomes

$$m_e - m_0 = \overline{\eta^2} = \frac{f_1 f_2 (n_1 - n_2)^2}{f_1 n_1 + f_2 n_2}, \quad (12)$$

where f_1 is the fractional volume of the cylinders, f_2 is the ground substance, and n_1, n_2 are the indices. The birefringence of a medium of parallel cylinders in the Rayleigh limit ($\lambda \gg$ cylinder diameter) was derived in 1912 by Wiener.[12] The result given in Eq. (12) is in agreement with the result of Wiener when $|n_1 - n_2| \ll 1$. The result shown in Figure 3 when multiplied by $\bar{\eta}^2$ is therefore a generalization of the result of Wiener to cylinders of any diameter.[9] In particular, the birefringence goes to 0 for large cylinders. The very small measured birefringence of the lens has been attributed to a counterbalancing of form and intrinsic contributions.[13,14] The large (compared to wavelength) dimensions of lens fiber cells, the presumed contributors to form birefringence, offer an alternative explanation.

Is the index change Δm of Eq. (11) sufficiently large enough to produce measurable results? An increase in refractive power of the lens of 1 to 2 diopters precedes the development of nuclear cataract[5] probably due to an increased refractive index in the lens nucleus. While questions remain concerning the source of this increase in index, it is possible that the index change Δm discussed before makes a contribution. It has been observed that backscattered light from the nuclei of noncataractous lenses decreases as one moves away from the lens axis.[15] This suggests a very simple model of a nuclear cataract. Assume a spherically symmetrical distribution of protein aggregates such that backscattered light decreases from a maximum at the center to a minimum at a distance of 1 mm from the center. Also assume that the decrease is proportional to the square of the distance from the center. Then the change Δm of medium index must decrease from a maximum at the center to a value of 0 at the surface in the same way. In order that this sphere of 2 mm diam with a graded index have a refractive power of 1 diopter, the maximum value of Δm must be about 1/5000. Assume a wavelength of 550 nm and a correlation length (i.e., protein aggregate diameter) of about 50 nm. Then from Figures 1 and 4 one can estimate the decay constant ϵ [see Eq. (10)] at each position in the sphere from the index change Δm at that position. In this instance they are about equal. Calculating the transmitted light along each ray through the sphere and adding up the contributions of all rays gives a total transmittance of about 1/3 across the sphere. In summary, if this simple model of a nuclear cataract allows about 1/3 of incident light to be transmitted without being scattered, then it adds a power of 1 diopter to the lens. While this argument is certainly not conclusive, it is perhaps suggestive.

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