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# THE RELATIONSHIP BETWEEN CENTRAL NUCLEAR SCATTER AND PERINUCLEAR RETRODOTS IN THE HUMAN CRYSTALLINE LENS

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## SUMMARY

**Retrodots are common perinuclear features of age-related cataract. Clinical observation suggested that retrodots were associated with increased nuclear scatter. To test this hypothesis, retrospective data were analysed from 78 non-diabetic subjects (118 eyes), of at least 50 years of age, who had neither subcapsular nor axial spoke opacities. Retrodots were graded using the Oxford Clinical Cataract Classification and Grading system and central nuclear scatter was assessed by image analysis of Scheimpflug photographic negatives. Regression analysis in groups was performed according to the "intra-class correlation model" either considering retrodots as a graded feature (grades 0-5) or as a dichotomous variable (present or absent). After adjusting for age (treated as a co-variate), a highly significant association ( $P < 10^{-6}$ ) was found between retrodots and increased nuclear scatter in each analysis. It is suggested that the co-existence of these two cataract types may reflect a common cataractogenic mechanism, possibly oxidative stress.**

Lens retrodots are small disc-shaped features seen in the perinuclear cortex.<sup>1</sup> When seen in retro-illumination they are rounded features (Fig. 1) and show reversal of background illumination.<sup>2</sup> On specular microscopy, they appear dome shaped. They are approximately 300 $\mu$  in diameter.<sup>1</sup>

Nuclear changes are a common feature of age-related cataract. In the NHANES study, they occurred in 10% of the subjects aged between 45 to 74 years.<sup>3</sup> On biomicroscopy, the features of nuclear cataract include white nuclear scatter and nuclear brunescence.<sup>4,5</sup> The terms nuclear opalescence and nuclear colour have also been used.<sup>6</sup> More complex descriptions of nuclear changes are at present being developed.<sup>7</sup>

Brown Scheimpflug slit-lamp photography<sup>8</sup> combined

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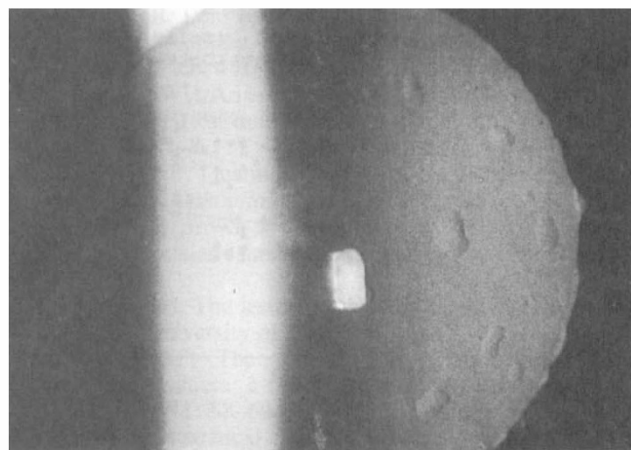
with the measurement of the density of the photographic negatives, gives an objective measure of nuclear scatter.<sup>9</sup> Central nuclear scatter has been shown to have a high correlation with age in a normal control population ( $R^2 = 0.82$ ,  $P = 10^{-6}$ ).<sup>10</sup> Nuclear brunescence is associated with a spectrally selective absorption of light. The densitometric method of measuring nuclear scatter does not allow for this factor so that the intensity of light scatter by the nucleus will be underestimated in the presence of brunescence.

Clinical observation suggested to us that the presence of retrodots was associated with an increase in nuclear changes. In this retrospective study we investigate this possible relationship.

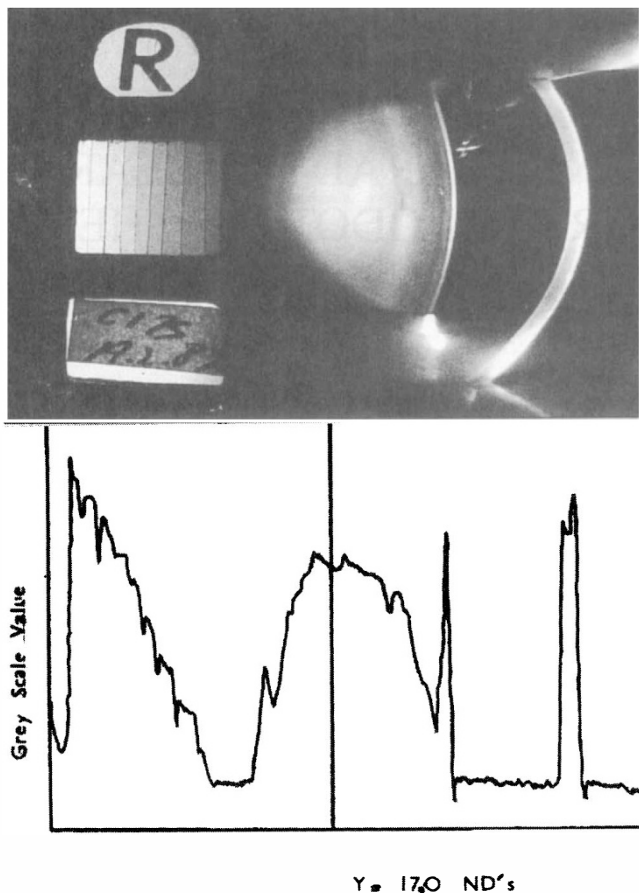
## MATERIALS AND METHODS

### *Selection of patients:*

This was a retrospective survey of the records of patients who had been examined by one observer (GASS) in the Clinical Cataract Research Unit over a two-year period. Patients aged 50 years or more, with age related cataracts

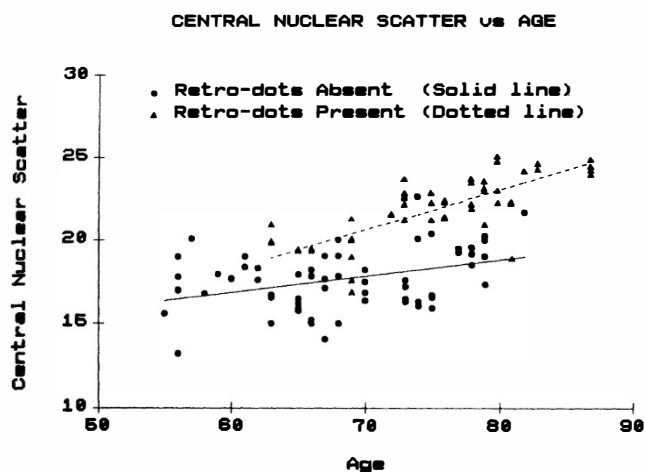


**Fig. 1.** *Lens retrodots seen in retroillumination.*



**Fig. 2** (a) Scheimpflug slit-image photograph of a lens with retrodots and nuclear scatter. Arrow points to a retrodot in peri-nuclear cortex. On the left is the neutral density scale. (b) An axial density scan of the lens in Fig. 2a. On the ordinate is the neutral density value in arbitrary units. The cursor line is just to the left of the nuclear dip. The density at the cursor is 17.0 neutral densities (in arbitrary units).

were identified. All posterior subcapsular cataracts (PSC) were excluded because the PSC can scatter light forward and thus artefactually affect the measurement of nuclear



**Fig. 3.** Graph of central nuclear scatter (arbitrary units) and age of patient. The circles represent lenses with no retrodots and the triangles, lenses with retrodots. Regression lines for the two groups are shown.

scatter. Eyes with spoke opacities were excluded if the spoke opacities involved the central 5 mm of the lens. Spoke opacities scatter light forward and cast shadows posteriorly and can thus affect the measurement of nuclear scatter.

Out of a total of 203 records examined, 78 patients with at least one suitable eye were identified. Twelve eyes were aphakic and 26 eyes were rejected because of PSC or spoke opacity. A total of 118 eyes thus fitted the inclusion criteria of the study.

**METHOD**

Lenses were examined after full pupillary dilatation to at least 7 mm diameter using G. Phenylephrine 10% and G. Tropicamide 1% repeated at least twice. The lenses were graded using the Oxford Clinical Cataract Grading System.<sup>4</sup> In this system, retrodots are graded on a 0 to 5 scale according to numbers present. Lenses were then photographed using the Brown Scheimpflug slit image camera<sup>8</sup> and the Oxford retro-illumination camera.<sup>11</sup>

The Scheimpflug slit-image photographic negatives were analysed on the Oxford Modular Cataract Image Analysis System (MCIAS).<sup>9</sup> An axial density scan was performed of the Scheimpflug negative and the density of the central nuclear dip was measured relative to neutral density standards incorporated into the Brown Scheimpflug camera. Figure 2a shows a Scheimpflug picture of a nuclear cataract and Figure 2b shows the axial density scan with the central nuclear dip.

The repeatability of the measurement of the density at the central nuclear dip has been investigated. There is a 0.95 probability that any individual measurement error will lie within the range  $\pm 0.43$  neutral density units which corresponds to  $\pm 4\%$  of the dynamic range of the measurement.<sup>9</sup>

The general statistical method employed was that described by Rosner, for use with continuous dependent variables in ophthalmology where two eyes are involved in the analysis.<sup>12,13</sup> Rosner's "intraclass correlation model" is an efficient statistical technique in studies with a two eye design such as this, and avoids over-estimation of significance levels associated with the high inter-eye correlation found in ophthalmological data.<sup>12,13,14</sup> The poten-

**Table I.** Analysis of variance using interclass correlation model

Source	Retro-Dots SSq	Clinical Grading Scale DF	MS	F	P
Age	427.2	1	427.2	111	< 10-6
Retro-dots (GR)	250.6	4	62.65	16	< 10-6
Patients	257.8	67	3.8478	1	
Eyes	28.1	45	0.6244		
Total	963.7	117			

(R<sup>2</sup> for the model = 0.70, R = 0.83).

SSq = sum of squares

DF = degrees of freedom

MS = mean square

F = variance ratio

P = probability

On average lenses with retro-dots scatter by 2.8 units more than those without

**Table II.** Analysis of variance using interclass correlation model

Source	Retro-Dots, Dichotomous Scale			F	P
	SSq	DF	MS		
Age	427.2	1	427.2	102	< 10-6
Retro-dots	188.1	1	188.1	45	< 10-6
Age retro-dots	40.1	1	40.1	9.6	0.0028
Patients	278.8	67	4.16	1	
Eyes	29.5	47	0.62		
Total	963.7	117			

( $R^2$  for the model = 0.68,  $R = 0.82$ ).

SSq = sum of squares

DF = degrees of freedom

MS = mean square

F = variance ratio

P = probability

On average lenses with retro-dots scatter by 2.8 units more than those without

tially confounding effect of age was accounted for prior to fitting other terms of interest in the multivariate model. The program used for statistical analysis was the Generalized Linear Interactive Modelling System (GLIM) of the Numerical Algorithm Group.

## RESULTS

Figure 3 shows a plot of the central nuclear scatter against the age of the patient. Both eyes are plotted. Circles represent lenses without retrodots and triangles lenses with retrodots. From the regression lines, it is evident that central nuclear scatter in lenses with retrodots is greater than in those without.

In the first statistical analysis, the effect of the grade of retrodots (grade 0 to 5) was examined. In this multiple regression analysis, the grade of retrodots was significantly associated with central nuclear scatter after accounting for age (See Table I "Retrodots-clinical grading scale"). This effect was such that increased retrodots were associated with increased central nuclear scatter.

In the second analysis, the grading scale was collapsed and retrodots were regarded as either present or absent (See Table II. "Retrodots—dichotomous scale"). The presence of retrodots was clearly associated with increased central nuclear scatter. The significant interaction term (Age. Retrodots) indicated that the slopes for the age vs scatter regression lines were different for the two groups as illustrated in Figure 3.

Holding the age slopes parallel for the two groups showed that on average the central nuclear scatter was 2.8 neutral density units greater for lenses with retrodots compared to those without ( $P < 10^{-6}$ ).

## DISCUSSION

There is a statistically significant relationship between the presence and grade of retrodots and central nuclear scatter as measured by image analysis of Scheimpflug photographic negatives. The aetiology of these features is uncertain. Retrodots are thought to contain calcium oxalate<sup>15</sup> and it has been postulated that oxalate is the result of oxidation of ascorbate.<sup>1</sup> Benedek has suggested that lens protein aggregates of molecular weight greater than

$50 \times 10^6$  will cause light scatter.<sup>16</sup> The high molecular weight aggregates occur mainly in the lens nucleus and have been correlated *in vitro* by Spector with increases in light scatter.<sup>17</sup> Harding has postulated that nuclear cataract results in part from post-translational modification of long lived lens crystallins. This alters surface charge and allows unfolding of the crystallin tertiary structure. The unfolded crystallins display reactive thiol groups and form disulphide bonds. This results in disulphide-bonded macromolecular aggregates capable of light scatter. The causes of crosslinking are probably multifactorial and include oxidative stress in the lens.<sup>18</sup> However, whether or not oxidative stress is important the two types of cataract appear to share a common aetiology.

## CONCLUSIONS

In this study a significant association is demonstrated between two morphologically distinct lens features i.e. perinuclear retrodots and central nuclear scatter. It is suggested that retrodots and nuclear scatter may act as markers for oxidative stress in the lens. The evolution of retrodots and nuclear scatter in ongoing trials of anti-oxidant drugs in the medical treatment of cataract will thus be of great interest.

Key words: Lens retrodots, nuclear cataract, scheimpflug photography, image analysis.

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