Cone increment thresholds were measured psychophysically in 42 patients (ages 10 to 59) with retinitis pigmentosa and visual acuities of 20/20 to 20/70. A 6-min arc diameter stimulus was flashed to the foveola at a background retinal illuminance for which Weber's law was in effect; under these test conditions, cone increment thresholds depended on the number of remaining functioning cones (cone spatial density) but not on their outer segment length (cone optical density). Log threshold and log visual acuity were correlated inversely ($P < 0.001$). The slope of the regression line relating these two measures was compatible with the idea that reduced cone spatial density is a major determinant of reduced visual acuity in retinitis pigmentosa. In a subset of these patients with visual acuities of 20/25 or better, results of cone increment threshold testing suggested that cone spatial density was reduced significantly less in the foveola than in the parafovea.

Postmortem ultrastructural studies of donor eyes of patients with retinitis pigmentosa and impaired Snellen visual acuities have revealed reductions in the number of cones per unit area (cone spatial density) and in the outer segment length of remaining cones (cone optical density) in the posterior pole. The impaired visual acuities could be due to reduced cone spatial densities in that visual acuity within the fovea is approximately inversely proportional to the distance between neighboring cones, to reduced cone optical densities since visual acuity worsens with reduced illumination, or to both factors. The present study was done to assess patients with retinitis pigmentosa and different visual acuities with a psychophysical cone increment threshold test designed to monitor reductions in cone spatial density irrespective of reductions in cone optical density. Increment thresholds were measured in the foveola to determine whether and how cone spatial density correlated with visual acuity, and in the parafovea to determine whether cone spatial densities were comparably reduced below normal in different regions of the posterior pole.

**Materials and Methods.** Forty-two patients (ages 10 to 59) with retinitis pigmentosa and corrected Snellen visual acuities between 20/20 and 20/70 were evaluated at the foveola; patients included 14 with dominantly-inherited disease, 15 with recessively inherited disease, 10 with sex-linked disease, and 3 with no family history of disease. All had full-field rod and/or cone electroretinograms that were reduced in amplitude and delayed in b-wave implicit time. Thirty-two patients had clear media on slit-lamp examination; eight had minimal central posterior subcapsular lens opacities; and two were aphakic. Forty-one normal observers (ages 7 to 59) with visual acuities of 20/20 or better were also tested at the foveola to provide a mean and confidence, tolerance limits.

Cone increment thresholds were measured psychophysically with a hand-held, dual-beam, Maxwellian-view stimulator-ophthalmoscope; its design has been described elsewhere. Pupils were dilated maximally with 1% cyclopentolate hydrochloride and 10% phenylephrine hydrochloride. A 6-min arc diameter white stimulus of 20 msec duration and flashing at 5 Hz was visualized on the fundus, focused, and maintained on the foveola throughout the testing by the examiner. This stimulus was centered on a steady, co-axial 10° white background of 5.0 log photopic trolands that was above rod saturation. The increment threshold in log trolands (up to a maximum of 7.0 log trolands) was determined by a method of limits in steps of 0.1 neutral density. Pilot studies on two normal subjects showed that these patients with retinitis pigmentosa had summation coefficients that were normal or occasionally slightly greater than normal. In the present study a 6-min arc stimulus was chosen as this stimulus approximates Rico’s area of perfect spatial summation.

Cone increment thresholds were independent of reductions in cone optical density under these test conditions. Pilot studies on two normal subjects showed that stepwise attenuation of the background retinal illuminance from 5.0 to 3.0 log photopic trolands to simulate a 2.0 log-unit reduction in cone optical density was accompanied by a 2.0 log-unit reduction in stimulus retinal illuminance at threshold; that is, the threshold ratio of stimulus retinal
Previous studies have shown that cone increment thresholds of patients with retinitis pigmentosa and reduced visual acuity obey Weber’s law for backgrounds of 4.0 log photopic trolands and greater. Therefore, under these test conditions, reductions of up to 99% in the amount of visual pigment within a cone outer segment in retinitis pigmentosa would be expected to reduce sensitivity to the stimulus and background proportionally and leave the increment threshold unchanged. Cone increment thresholds were also independent of central cataracts because the stimulus and background beams could be directed around the cataract on to the fundus without changing the ratio of stimulus to background retinal illuminance.

On the other hand, cone increment thresholds would be expected to vary with reductions in cone spatial density. For the 6-min arc diameter stimulus, approximating Ricco’s area of perfect spatial summation in the fovea, and for the 10° diameter background, exceeding Westheimer’s areas of spatial interaction in the fovea, the increment threshold should be inversely proportional to the number of stimulated cones, or proportional to the intercone distance squared. Since visual acuity is approximately inversely proportional to the intercone distance in the fovea, the relationship between log threshold and log acuity should be linear with a slope of -2.0. For example, a fourfold (0.6 log-unit) increase in threshold should be associated with a twofold (0.3 log-unit) decrease in visual acuity.

A subset of 12 patients with visual acuities of 20/25 or better and with visual fields to the V-4e white test light in the Goldmann perimeter extending to or beyond the 10° isopter and a subset of 33 normal subjects were tested also in the parafovea (10° nasal to the foveola along the horizontal meridian). Cone increment thresholds in the foveola and parafovea were compared to determine whether cone spatial densities in these two areas were comparably reduced below normal in these patients.

**Results.** Log cone increment threshold in the foveola and log visual acuity for the 42 patients with retinitis pigmentosa were correlated inversely ($r = -0.73$, $P < 0.001$). All 11 patients tested with visual acuities of 20/50 or less had thresholds above the upper 95% confidence, 90% tolerance limits for normal subjects (Fig. 1). The best-fitting regression line intersected the mean normal threshold and had a slope of -2.4. This slope was significantly different ($P < 0.001$) from a slope of zero that would be expected if visual acuity depended solely on cone optical density, but was not significantly different from a slope of -2.0 that would be expected if visual acuity depended solely on cone density.
spatial density (right ordinate). Within the limits of this sample size, the slopes for the three genetic types were not significantly different from one another.

For the subset of 12 patients with visual acuities of 20/25 or better, cone increment thresholds were elevated about two times above normal in the foveola ($P < 0.005$) and about ten times above normal in the parafovea ($P < 0.001$) (Fig. 2). This regional difference in threshold elevation was significant ($P < 0.001$).

**Discussion.** The present findings support the conclusion that reduced visual acuity in retinitis pigmentosa is primarily due to a reduced number of functioning cones in the foveola. The slope ($-2.4$) of the regression line describing the relationship between log cone increment threshold and log visual acuity approximated the slope ($-2.0$) predicted if visual acuity depended solely on the spatial density of remaining cones (see Methods). On the other hand, the obtained slope was significantly different from the slope ($0.0$) predicted if visual acuity depended solely on the outer segment length (optical density) of remaining cones. If lowered cone optical density had substantially contributed to visual acuity impairment, the obtained slope should have been between $0.0$ and $-2.0$; this also was not observed.

Although log threshold and log visual acuity were significantly correlated, the regression line accounted for only 53% ($r^2$) of the log threshold variance. The remaining variance (which reflects the variance of log threshold after controlling for log visual acuity) was still about three times as large as the variance of log threshold in normals. This could reflect at least two factors. First, some of these patients with visual acuities of 20/40 or better had normal thresholds that fell near the horizontal dashed line (Fig. 1). These patients may have profoundly shortened cone outer segments which have contributed to their visual acuity reduction. Second, other patients with visual acuities of 20/40 or better had thresholds that lay far above the oblique dashed line. These patients may have lost cone photoreceptors in the central fovea in an uneven distribution, such that small clusters of closely packed cones remain and subserve good visual acuity.

Cone increment threshold testing was applied also to a consideration of the relative involvement of cones in different retinal locations. The finding that cone increment thresholds for patients with visual acuity of 20/25 or better were elevated an average of two times above normal in the foveola and ten times above normal in the parafovea suggests that cone spatial density was reduced 50% below normal in the foveola and 90% below normal in the parafovea. Therefore, reduction in the number of cones per unit area in retinitis pigmentosa does not appear to proceed evenly across the posterior pole. The mechanism that leads to an uneven decline in cone spatial density remains to be defined.

**Key words:** cone, fovea, macula, retinitis pigmentosa, outer segment, visual acuity, ophthalmoscope, retina, retinal degeneration.

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