Visual function and dysfunction in early and late age-related maculopathy

R.E. Hogg, U. Chakravarthy*

Ophthalmology and Vision Science, Queen’s University and Royal Victoria Hospitals, Belfast BT12 6BA, UK

Abstract

Late age-related maculopathy (ARM) is responsible for the majority of blind registrations in the Western world among persons over 50 years of age. It has devastating effects on quality of life and independence and is becoming a major public health concern. Current treatment options are limited and most aim to slow progression rather than restore vision; therefore, early detection to identify those patients most suitable for these interventions is essential.

In this work, we review the literature encompassing the investigation of visual function in ARM in order to highlight those visual function parameters which are affected very early in the disease process. We pay particular attention to measures of acuity, contrast sensitivity (CS), cone function, electrophysiology, visual adaptation, central visual field sensitivity and metamorphopsia. We also consider the impact of bilateral late ARM on visual function as well as the relationship between measures of vision function and self-reported visual functioning.

Much interest has centred on the identification of functional changes which may predict progression to neovascular disease; therefore, we outline the longitudinal studies, which to date have reported dark-adaptation time, short-wavelength cone sensitivity, colour-match area effect, dark-adapted foveal sensitivity, foveal flicker sensitivity, slow recovery from glare and slower foveal electroretinogram implicit time as functional risk factors for the development of neovascular disease.

Despite progress in this area, we emphasise the need for longitudinal studies designed in light of developments in disease classification and retinal imaging, which would ensure the correct classification of cases and controls, and provide increased understanding of the natural course and progression of the disease and further elucidate the structure–function relationships in this devastating disorder. © 2005 Elsevier Ltd. All rights reserved.

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*Corresponding author. Tel.: +44 2890 240503x2516; fax: +44 2890 330744.
E-mail address: u.chakravarthy@qub.ac.uk (U. Chakravarthy).

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1. Age-related maculopathy (ARM)

ARM is a degenerative disorder of the central retina, most commonly encountered in older people. In this condition, morphological changes in the macular retina are observed in people over the age of 50 years, and a proportion of those affected develops a profound irreversible loss of central vision in one or both eyes. When central visual dysfunction is present, it is often due to either an extensive atrophy of the tissues of the macular region or because of scarring following the development of a neovascular lesion.

1.1. Nomenclature

The terminology used to describe the different manifestations with or without vision loss of this ageing disorder has undergone several modifications over time. Early in the 20th century, exudative lesions in the posterior pole were referred to as Kuhnt Junius disease or disciform degeneration (Duke-Elder, 1940; Ryan et al., 1980) owing to the circular disposition of the macular scar. In the nineteen sixties, the term senile macular degeneration was coined (Gass, 1973; Bird, 1974), but more recently this was considered to have pejorative tones and has been substituted by the term age-related macular degeneration (AMD). More often than not the term AMD is used when an exudative lesion is found in the posterior pole of the eye, though it may also be employed to include a characteristic confluent area of atrophy, which is also referred to as geographic atrophy (GA). More recently the terms neovascular (nvAMD) and geographic atrophy (gaAMD) AMD have been utilised.

Prior to the development of noticeable vision loss, a variety of other clinical manifestations are seen in the macular retina. Typically, a reduction in the foveal reflex and abnormalities of pigmentation are observed. Characteristic yellow-whitish spots known as drusen are seen concentrated in, and around, the posterior pole of the eye. Diffused as well as focal areas of depigmentation form due to atrophy of the RPE (hypopigmentation) as well as areas of increased pigmentation (hyperpigmentation). Usually, these manifestations are not accompanied by overt visual dysfunction. Epidemiological and histopathological studies provided some evidence to link these features that appear in the ageing macula with the subsequent development of...
GA and/or a disciform scar. The absence of a universally accepted definition of what truly constituted AMD led to the use of a wide variety of terms in the many publications on this topic and discordant epidemiological findings (Bressler et al., 1990; Goldberg et al., 1988; Klein et al., 1992). Therefore, the International Classification and Grading System was developed to standardise the terminology used and to provide researchers with a common nomenclature for undertaking, recording, analysing and reporting their findings, enabling robust comparisons to be made between studies (Bird et al., 1995) (Table 1). This system proposed the use of the term ARM to describe the entire spectrum of changes, ranging from the early manifestations to advanced features accompanying vision loss. A further sub-division was proposed to distinguish the early manifestations from late disease with vision loss; and the terms ARM or early ARM used to describe the former, and late ARM or AMD the latter, respectively.

All the features of nvAMD suggest the presence of abnormal blood vessels derived from the choroidal circulation that have breached the normal anatomical barriers and make their presence in the sub-pigment epithelial or sub-retinal spaces. This process is termed choroidal neovascularisation (CNV). Other studies including the Eureye (Augood et al., 2004) and Age-Related Eye Disease study (AREDS, 2001) have introduced the concept of staged disease severity with ARM 1, 2 and 3, representing combinations of drusen and pigmentary irregularities, and 4 when CNV or GA is seen (Fig. 1).

### 1.2. Clinical classification

Traditionally, clinicians and patients tend to refer to the characteristic macular changes as dry or wet AMD. The term dry is used to denote the absence of CNV, and thus could refer to the presence of early ARM features or GA.

![Stage 0](image1.png) ![Stage 1](image2.png) ![Stage 2](image3.png) ![Stage 3](image4.png) ![Stage 4](image5.png)

**Fig. 1.** Four stage ARM disease severity with ARM 1, 2 and 3 representing combinations of drusen and pigmentary irregularities and 4 when CNV or GA are present.

### 1.3. Histopathology

Histopathological techniques have revealed that eyes from donors with AMD show accumulation of membranous debris on both the outer and inner aspects of the
basement membrane of the retinal pigmented epithelium known as basal linear deposit and basal laminar deposit, respectively (Curcio, 2001). On the basis of immunohistochemical analyses, drusen have been shown to contain a variety of complex lipid, protein and carbohydrate moieties. These are most probably derived from the shed outer segments of photoreceptor cells following phagocytosis by the RPE. Curcio et al. (1996) demonstrated cone photoreceptor degeneration is present in most eyes with early ARM. The investigators obtained post-mortem material from donor eyes, and on application of a systematic method of grading they noted shortening of outer segments and broadening of the inner segments in eyes with ARM when compared with those without ARM features. It has, therefore, been suggested that the morphological and functional changes in Bruch’s membrane and the RPE result in disordered phagocytosis and recycling of the photoreceptor outer segments.

The onset of aberrant choroidal angiogenesis with vessels transgressing Bruch’s membrane results in the formation of the neovascular complex, which comes to lie in the sub-pigment epithelial and sub-retinal spaces (Green and Enger, 1993). The vessels are incompetent and leak serous fluid and blood. Ultimately, the vessels involute leaving behind a non-perfusing scar, which enmeshes the delicate retina causing distortion and disorganisation of the cellular architecture. These changes are incompatible with normal visual function and often irreversible, and dense central vision loss supervenes. The exact mechanism for angiogenesis is unknown, although a variety of growth factors have been postulated (Das and McGuire, 2003).

1.4. Prevalence

The prevalence of ARM increases markedly with increasing age, although ARM is uncommon before the age of 50 years; by the age of 90, one in four persons will have lost vision owing to AMD. Therefore, it is feared it will become one of the biggest health problems in the next few decades. In the US, persons aged over 65 form the fastest growing segment of the population and the proportion is expected to increase by 53% between 2000 and 2020 (Bartlett et al., 2004b). Likewise, this sector of the population of the UK is set to increase by over 29% in the next 20 years (Owen et al., 2003). Nonetheless, in the UK, 3.7% of the population aged 75 years or older and 14.4% of the population 90 years or older are visually impaired due to AMD (Evans et al., 2004a, b). Although ARM has been principally considered to be a disease confined to the developed world, increasing evidence shows that it is also a common cause of visual impairment in developing countries (Nirmalan et al., 2004).

1.5. Symptoms

In cases of bilateral early ARM, visual acuity may be within normal limits in both eyes and many patients are asymptomatic. A few may complain of symptoms, such as difficulty in reading under dim light, metamorphopsia and problems on dark adaptation after exposure to sunlight, indicating retinal functional deficits not reflected in traditional measures of visual acuity. The development of GA can cause a corresponding central scotoma if it occurs within the central 1–2°. The onset of CNV is often accompanied by a sudden dramatic reduction in central visual function. The patient will complain of distortion, inability to distinguish fine detail and central blurring. In some people, the onset of nvAMD in the first eye can be asymptomatic, particularly if the loss has occurred in the non-dominant eye. Frequently, a patient may only seek help when the second eye becomes involved.

2. Measures of visual resolution in ARM

2.1. Distance visual acuity (DVA)

It has been reported that each of the early ARM lesions (soft indistinct drusen, RPE degeneration, increased retinal pigment, early ARM) is associated with a decrease in acuity of approximately two letters or fewer, compared to eyes without those lesions (Klein et al., 1995); although a statistically significant result, this level of visual deficit is neither clinically meaningful nor reliably detectable, given that the test–retest variability of Log MAR charts between one and two lines (Rosser et al., 2003; Arditì and Cagenello, 1993; Lovie-Kitchin and Brown, 2000). Therefore, it is generally accepted that the measurement of visual resolution by using the commonly available distance acuity charts is inadequate for the assessment of functional deficits in early ARM and also for monitoring progression of the disorder (Sarks et al., 1988), and longitudinal studies have confirmed that visual acuity is a poor predictor for conversion to nvAMD (Mayer et al., 1994). Nonetheless, in terms of the ease of use and widespread availability, acuity testing using the Log MAR or EDTRS chart is commonly undertaken as a large measurement range is possible and crowding effects are better controlled. Log MAR charts by virtue of their design have better reproducibility and sensitivity to acuity changes when compared to the standard Snellen chart (Ferris et al., 1982; Lovie-Kitchin, 1988).

In advanced disease, distance acuity testing by itself yields limited information. Notably, eyes with advanced AMD with similar lesion characteristics exhibit a wide range of acuity (Table 2) (MPS Group, 1994).

Measures of acuity are also often a poor indicator of ability for visual tasks, such as face recognition and mobility (Rubin et al., 2000). Despite these caveats, distance acuity measured under standardised conditions using the EDTRS LogMAR charts remains the most commonly used outcome measure in studies and clinical trials in AMD.
Table 2
Distribution of initial lesion size and initial visual acuity at study entry in MPS study

<table>
<thead>
<tr>
<th>Visual acuity Log MAR</th>
<th>Lesion size at study entry, MPS disc areas (no. of eyes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small (≤ 1)</td>
</tr>
<tr>
<td></td>
<td>Medium (&gt; 1 to ≤ 2)</td>
</tr>
<tr>
<td></td>
<td>Large (&gt; 2)</td>
</tr>
<tr>
<td>Poor (≤ 1.0)</td>
<td>21</td>
</tr>
<tr>
<td>Medium (0.7–1.0)</td>
<td>34</td>
</tr>
<tr>
<td>Good (≥ 0.70)</td>
<td>48</td>
</tr>
</tbody>
</table>

Note the wide range of acuity despite similar lesion characteristics. Adapted from Table 1, MPS Group (1994).

2.2. Near visual acuity (NVA)

NVA is routinely measured in the form of word acuity as opposed to single-letter acuity and, therefore, disparities may be expected when comparing this measure to distance acuity as a result of the increased complexity of the task. Despite this, it is generally assumed that a linear relationship is present between distance visual acuity (DVA) and near visual acuity (NVA) (Bailey and Lovie, 1980). For example, an individual with 0.0 Log MAR (6/6 Snellen) would be expected to read 0.25 M (N2). However, in a small study of 15 AMD sufferers, Kitchin and Bailey (1981) found that word acuity was invariably worse than what might be expected from the measured DVA, regardless of its level with the magnitude of the difference averaging 0.3 Log units (Kitchin and Bailey, 1981; Lovie-Kitchin and Bowman, 1985). In a recent study to examine the relationships between measures of vision, which are normally used in clinical practice, in a population of 469 subjects with a diagnosis of AMD in one or both eyes, Muldrew et al. (2003) found that the least concordance between the DVA and NVA occurred in the mid-range, suggesting that NVA decreases at a faster rate than that of either DVA or contrast sensitivity (CS).

2.3. NVA and reading speed

Word reading has been suggested as a better discriminator of early deficits in visual function in ARM than that of distance acuity. Word reading is a complex task requiring visual resolution of the text, stable retinal images, saccadic accuracy, word encoding, lexical accessing, and short- and long-term memory (McMahon et al., 1991). Reading rate is dependent not only on the functional capability of the visual system but also on stimulus conditions such as the numbers of characters in the field, magnification, blur, contrast and the colours of the text and background and non-visual features, such as cognitive abilities, motivation, memory storage and procedural-factors-associated reading (Legge et al., 1992).

Although all of these features are inter-related, it is worth remembering that not all of these processes primarily limit reading performance of patients with advanced AMD (Baldasare et al., 1986). Since most patients are typically adept readers before disease onset, the decrease in reading ability can be attributed to factors disrupting visual-processing ability. Reading speed has been used in many studies and has been shown to be useful in the evaluation of disability. In contrast to NVA, reading speed provides an indication of reading performance and is a function of both scanning rate and proportion of words correctly read. Whether the central visual field is intact is the single most important factor in reading (Legge et al., 1985). It is acknowledged that considerable variability may be experienced in reading speed rates despite similar near acuities; therefore, Legge et al. (1992) attempted to predict reading speed from a set of routine clinical measures, such as age, Snellen distance acuity, central visual field status (scotoma present or absent), ocular media status (clear or cloudy) and disease diagnosis. These were found to account for only 30% of the variance in reading rate, and the authors speculate that the addition of letter CS to the portfolio of tests would at best account for up to 55% of the variance. A subsequent review of the literature by Whittaker and Lovie-Kitchin (1993) looking at the problem from the standpoint of a low-vision practitioner highlighted four clinical measurements, which they showed provided improved prediction of reading rates, they were as follows: an accurate measure of field of view, central scotoma size, contrast reserve and acuity. They derived visual requirements for different types of reading rate from published research. As expected, the reading rate of patients with longstanding AMD was shown to decrease rapidly with increasing scotoma size. They concluded that contrast and print size needed to be several times threshold and the diameter of the central scotoma needed to be less than 22° to make fluent-reading possible. However, correlations were weak and it is evident that non-visual factors play an important role in a subject’s reading performance. Thus, it appears that performances on other clinical tests of vision are poor predictors of reading speed, and emphasizes the importance of routine measurement of reading performance within a clinical setting.

2.4. NVA and eye movements

Reading performance is also strongly influenced by eye-movement control (Cummings et al., 1985; McMahon et al., 1991). Saccadic eye movements are required to shift the fovea along the retinal image of the text line, with the fovea held in position using the fixational oculomotor system (slow control and microsaccades). The sequence of saccades and fixation is repeated over and over to bring the text further along the line to the fovea, allowing the experienced reader to read at the rate of hundred words per minute (Timberlake et al., 1986). Eye movements have been noted to be abnormal in patients with AMD (Cummings et al., 1985; McMahon et al., 1991). Patients with AMD and other maculopathies exhibit an increased
number of fixations during a reading task (Rayner and Bertera, 1979), abnormal eye movements (Whittaker et al., 1988; Cummings et al., 1985), poor saccadic accuracy and an increase in saccadic frequency to reach the intended target (McMahon et al., 1991). However, a study by Bullimore and Bailey (1995) found similar fixation rates in ARM subjects to normals despite averaging fewer letters per forward saccade and more backward regressions. They, therefore, concluded that poor oculomotor control plays a lesser role in comparison to reduced perceptual span. As the tests were carried out over a range of luminances, this study also highlighted the important relationship between reading performance and illumination in AMD patients, as reductions in luminance produced changes in scotoma size and shape with resultant decreased acuity and reading speed. This emphasises the clinical importance of determining optimal levels of illumination for reading for AMD patients and advising them accordingly (Eldred, 1992; Bowers et al., 2001).

The advent of scanning laser ophthalmoscopy (SLO) microperimetry in the late eighties allowed many fundamental questions about reading with a macular scotoma to be investigated and provided some crucial insights into the relationships between reading rate, fixation stability and eye movements. Initial reports showed that patients with dense macular scotomas involving the fovea used a single unique retinal area immediately adjacent to the scotoma to fixate (Timberlake et al., 1986). This locus of fixation was also used to inspect targets and read simple text. The authors termed this as the preferred retinal locus (PRL). Further, studies indicated that the PRL did not have a predilection for any specific retinal quadrant, but did find that the least-diseased area of the retina closest to the foveola was used. This corresponded to an area of RPE hyperplasia in well over half of the cases examined (Tezel et al., 1996). In general, the PRL is located in an area immediately adjacent to the scotoma (Timberlake et al., 1987; White and Bedell, 1990; Sunness et al., 1996), in the lower part (Weiter et al., 1984) and to the left of the visual field (Guez et al., 1993; Fletcher and Schuchard, 1997). This is surprising as subjects with normal eye sight obtain textual information in the English language much more efficiently from the right visual field than from the left, implying that placement of a scotoma to the left of the lesion would be more advantageous. The majority of patients with a central scotoma due to AMD are thought to develop a PRL. A large study of 825 patients with AMD tested using SLO macular perimetry revealed that 84% had an established PRL. Interestingly, a sixth of these patients had a PRL that was surrounded by a dense scotoma (Fletcher and Schuchard, 1997). More recently, it has been recognised that patients often adopt multiple PRLs in which each can be used predictably depending on the task parameters (Duret et al., 1999; Lei and Schuchard, 1997; Deruaz et al., 2002). This explains the finding of saccades and eye movements that at first appear inappropriate and uneconomical for the formation of a well-structured reading strategy. It also helps understand eye movements that involve purposeful changes of PRL (Safran et al., 1999). The PRL can shift in response to change in stimulus size (Guez et al., 1993) or illumination (Lei and Schuchard, 1997). In some cases, patients appear to use a combination of PRLs. Thus, a patient may use a PRL, which has a high spatial resolution, but textual information may fall partially within a scotoma. To overcome this, the patient may switch to another PRL where entire words are visible but with lower spatial resolution. Switching allows the patient to localise the word in its entirety (Duret et al., 1999). Adaptation of the oculomotor system is also necessary in order to accurately search for, position and stabilise text at a non-foveal location (Heinen and Skavenski, 1992). That a significant proportion of patients choose a PRL so that it lies to the left of the scotoma in the visual field necessitating forward saccades into the scotoma has created much discussion. Recent evidence has suggested there may be a correlation between the retinal area with higher attentional capability (which is patient specific) and a patient’s choice of location of PRL when AMD develops. This is based on the finding that eight out of nine patients with AMD show a PRL position corresponding to a location with good attentional performance. The authors caution that prospective studies will be required to substantiate these findings (Mackeben, 1999; Alpeter et al., 2000).

To investigate the extent to which fixation stability influences reading speed, Crossland et al. (2004) undertook a longitudinal study to assess the development of viewing strategies in macular disease. They followed a cohort of subjects for up to 1 year when the second eye developed macular disease. A linear relationship between fixation stability and reading speed was noted with 54% of the variance in change of reading speed, accounted for, by changes in fixation stability. As with other studies, there was no relationship between scotoma size and fixation stability (Timberlake et al., 1986, 1987; White and Bedell, 1990) and nor did measured visual acuity and CS correlate with fixation stability. On investigating, the correlation between reading speed and size and nature of the scotoma (absolute or relative) by using SLO microperimetry in patients with AMD, Ergun et al. (2003) found that only the size of the absolute scotoma demonstrated significant relationships with measures of reading.

2.5. Fixation pattern and rehabilitation

A recent study investigating the success of training patients in eccentric viewing confirmed the finding that a PRL to the left of the retinal lesion is unfavourable for reading. The investigators used the SLO to establish a new trained retinal locus either above or below the retinal lesion that is more favourable as there are no blind spots at this horizontal level. The range achieved by most of the AMD patients was between 50 and 106 words despite the group being over 77 years of age and with an average
best-corrected distance visual acuity of 20/500 (Nilsson et al., 2003). These findings are very encouraging as after an average of 5–6 h of formal training, patients were able to read at a speed close to that achieved by similar age-group with normal visual acuity, who averaged a reading speed of 83 words/min (Lott et al., 2002).

2.6. Reading test design for AMD patients

Tests of reading function should contain unrelated words as patients may mask their visual disability by guessing words correctly on the basis of the context derived from the sentence (Fine et al., 1999; Bailey and Lovie, 1980). Syntactic and semantic clues are absent in text composed of unrelated words forcing the patient to rely exclusively on the visual information gathered from the printed page (Baldasere et al., 1986). It has been shown that sentence context increases reading speed, regardless of where the text is positioned on the retina (Fine et al., 1999). The number of words per line must also be considered as the crowding phenomenon may be more severe in AMD patients (Rubinstein and Underwood, 1985; Kitchin and Bailey, 1981) causing reading difficulty to increase as word length increases. Large words require the use of increasingly more eccentric retinal locations. Performance measured in terms of accuracy or latency decreases as a stimulus is moved further from the foveal centre (Eriksen and Schultz, 1977; Leflon and Haber, 1974; Rayner and Bertera, 1979; Baldasere et al., 1986). Varying the word length of the textual information is an important parameter to allow approximation to normal reading as the task requires the planning and execution of saccadic eye movements of various extents (Rayner, 1978).

While evaluating the Pepper visual skills for reading test, which was designed to assess the visual components of the reading process in low-vision individuals, Baldasere et al. (1986) identified three categories of AMD patient. They were those who are (a) inaccurate and slow, (b) accurate but slow and (c) accurate and quick. These findings had important implications for the most effective reading strategy for each patient. Those who are inaccurate may need eccentric viewing- or fixation training, whereas the accurate but slow reader may need extensive word recognition training. Elliott et al. (2001) have shown that subjects with cataracts have an optimal reading speed similar to that of a control group, whereas in those subjects with AMD it was substantially worse. Therefore, reading speed has also been proposed as a useful test to differentiate loss of acuity due to lenticular changes from that caused by undetected macular disease.

3. CS and ARM

CS is a measure of the threshold contrast for seeing a target whereas acuity is a measure of the spatial-resolving ability of the visual system under conditions of very high contrast (Owsley, 2003). CS relies on lateral inhibitory mechanisms mediated by horizontal and amacrine cells, thus may enable subtle deficits to be detected when there is widespread yet early pathological change.

3.1. CS in ARM

As early as 1977, Sjostrand and Frisen (1977) used a television-based display and sinusoidal gratings of variable contrast and spatial frequency to test patients with macular disease against age-matched controls. In early ARM, there were decreases in CS at high and intermediate frequencies whereas in eyes with AMD, impairment across the whole spatial frequency range was observed. Another small study (Wolkstein et al., 1980) reported losses at both low and high spatial frequencies and a high-frequency cut-off frequency measured using a grating above that, which would be expected from the patient’s letter acuity scores.

As only four patients with ARM were evaluated in this study along with the absence of information on disease severity, rendering comparisons between this study and that of Sjostrand is difficult.

The concept of “hidden vision” in which patients with macular degeneration may have greatly reduced visual acuity or nearly normal CS at low spatial frequencies and reasonably good CS at intermediate spatial frequencies was first proposed by Hyvarinen et al. (1983). In this study, CS function was measured in a group of 17 patients with macular or optic nerve disease; only two patients had AMD. The investigators found that when a small 5˚ grating field was used, threshold CS was low at all spatial frequencies, however, when a 20˚ grating field was used, threshold CS was nearly normal at spatial frequencies below 0.7 cyc/deg, but above this there was a marked loss of sensitivity. In contrast, Loshin and White (1984) tested 40 patients with AMD, and found a decrease in sensitivity at all spatial frequencies. These findings highlight the difficulties encountered when comparing studies that have employed varying stimulus parameters.

Brown and Lovie-Kitchin (1987a) assessed the contrast sensitivity functions in the central retina and at 2˚, 5˚ and 10˚ eccentricity in the paracentral retina of 8 patients with varying degrees of early ARM and 8 age-matched controls. ARM patients and controls had normal visual acuity. Contrast sensitivity was depressed in ARM patients compared to that of normals, when tested at the fovea and at all levels of eccentricity. Although the overall difference between ARM and normals failed to reach significance, all individual points plotted for the former were below those of the latter. A greater loss was found for high spatial frequencies than for low spatial frequencies at all eccentricities.

Further, evidence for the existence of a loss of vision in ARM, which remains undetected by conventional acuity measures, was reported by Kleiner et al. (1988). Regan letter charts, which are similar to LogMAR charts, except that the test letters are available in varying degrees of contrast, were used in a group of 52 patients with macular
drusen and VA of at least 20/20. An age-matched control group of 27 normals were also assessed. The drusen groups read fewer letter than the control group and the difference increased as the contrast of the charts decreased. The difference also was found to correlate with disease severity when CS was measured using a Ginsburg CS chart. A reduction in CS at high spatial frequencies along with a loss of peak CS with increasing drusen severity was noted when eyes were placed into four categories. Category 1 consisted of eyes with a few fine discrete drusen, while category 4 demonstrated numerous large confluent drusen, with eyes at grades 2 and 3 exhibiting changes of intermediate severity. Stangos et al. (1995) also sought to evaluate CS in eyes with drusen and good visual acuity, and found that CS loss was found in all eyes with drusen and normal visual acuity and although this loss occurred at all spatial frequencies, it was more significant in the middle range and high spatial frequencies. They did not, however, find a greater CS loss with increasing drusen severity as found by Kleiner et al. (1988).

The use of low-contrast Regan letter charts was also investigated in a small case-control study of six ARM cases and 12 normal controls (Abadi and Pantazidou, 1996). Since differences in acuity between ARM and age-matched controls were found at all letter contrast levels, the investigators concluded that the use of low-contrast letter charts was not warranted. However, a larger study that investigated relationships between visual acuity and peak CS in 100 patients with early and late ARM with visual acuities ranging from 0.7 to 0.1 Log MAR (Alexander et al., 1988) found a significant correlation between these two measures (r = 0.62) and also noted the wide range of CS at every level of visual acuity. The authors recommend that CS testing can provide important additional information over, and above, that obtained by measuring acuity alone.

Although the majority of studies specifically designed to assess contrast function in early ARM were of small size and did not stringently evaluate disease severity, the evidence is in favour of a loss of CS at mid-to-high spatial frequencies and also suggests that lower spatial frequencies may be spared in the early stages of the disease, especially at low luminance.

3.2. Luminance and CS in ARM

The observation that patients with ARM often have difficulties in adapting to changing luminance levels led Brown and Garner (1983) to examine the effect of luminance on the CS function in six patients with ARM (pigmentary irregularities, drusen, serous and sub-retinal detachment) and in five age-matched normal persons. ARM patients showed a greater loss of CS at the higher luminance levels, indicating that contrast detection mechanisms at low luminances were intact. In the ARM patients, the peak of the curve was shifted to lower spatial frequencies at all the luminance levels tested. The authors also noted that despite ARM patients having similar acuity, there was considerable variation in contrast functional though this may have been due to poor control of fixation. A subsequent study by Brown et al. (1984) examined the effect of luminance on low-contrast visual acuity in ARM and compared this with six normal participants of approximately the same age. ARM patients had difficulty in performing the tasks at the lower luminances and showed little or no increase in visual acuity with increasing contrast levels. All patients had relatively good acuity, and yet small decreases in luminance (about 1.7 Log units) had profound effects on acuity. Thus, one may conclude that adaptation mechanisms that allow the normal visual system to operate efficiently over a wide range of luminances are affected in ARM, even when clinically measured acuity is only moderately depressed.

3.3. CS and monitoring disease progression

Since CS is a measure of more extensive retinal involvement with deficits noted in eyes with early ARM features despite the presence of a normal visual acuity, this measure was mooted as a potential prognostic indicator for progression to more advanced disease. Stangos et al. (1995) in their cross-sectional analysis of eyes with drusen and good acuity concluded that CS was not a prognostic indicator since all the eyes in this study with drusen had CS loss, yet longitudinal studies have shown that only a small proportion of eyes with drusen develop nvAMD. Similarly, Midena et al. (1997) measured CS with sinusoidal gratings at several different spatial frequencies in 34 eyes of patients with drusen and normal visual acuity, 13 fellow eyes of patients with AMD and 36 age-matched control eyes. They found progressive impairment of spatio-temporal CS at all spatial frequencies. Both static and dynamic CS measured at 20 cyc/deg correlated with disease severity when this was measured by the presence of focal hyperpigmentation or GA. Since drusen number did not influence spatio-temporal CS, the investigators concluded that a reduction in CS and the degree of CS loss were not prognostic indicators for the development of nvAMD. One of the limitations of CS is that a reduction is not specific to retinal disease and may be seen in the presence of medial opacities. However, CS may be useful in the monitoring of disease progression particularly as a marker of outcome in clinical trials. Various clinical trials of interventions for nvAMD have measured multiple parameters such as visual acuity and CS and these have provided opportunities for examining relationships between these measures of vision in a longitudinal manner (Bellmann et al., 2003). Only moderate agreement was found between change in visual acuity and change in CS. Therefore, the authors recommend that both be considered as important independent parameters for visual impairment. Also, as CS loss at middle and low spatial frequencies have important consequences for tasks, such as recognition of faces, seeing kerbs and low-contrast structures (Owsley et al., 1981;
Marron and Bailey, 1982), it may be useful as a surrogate marker for a patient’s ability to undertake daily living tasks.

4. Cone function and ARM

It has long been accepted that retinal diseases, including degenerative macular conditions, lead to tritan-like defects particularly in the early stages when visual acuity is within the normal range (Francois and Verriest, 1961; Hart, 1987; Campbell and Rittler, 1972; Bowman, 1980a, b; Barca and Vaccari, 1978; Applegate et al., 1987; Trusiewicz et al., 1984). Köllner’s rule states that generally blue–yellow defects occur in retinal disease whereas red/green are associated with optic nerve disease. These observations imply that in early AMD, chromatic mechanisms necessary for colour vision are selectively damaged (Hart, 1987) whereas spatial discrimination and luminance detection are spared.

4.1. Short-wavelength sensitive (SWS) cones and ARM

The blue on yellow deficits seen in retinal disorders has evoked interest in the potential role of short-wavelength sensitive (SWS) cones as a site of early involvement in AMD. These cells, together with the small bistratified ganglion cell layer (Dacey, 1993), are known to be associated with an “opponent” psychophysical channel, which sub-serve the discrimination of blue from yellow hues (Calkins, 2001). The unique properties of SWS cones in terms of morphology, distribution, origin and behaviour have been extensively reported and summarised (Calkins, 2001). The apparent vulnerability of the SWS cone function early in pathological processes has stimulated debate on whether this system is selectively damaged, or is intrinsically prone to injury (Hood and Greenstein, 1988), since increased susceptibility of this system to light damage has been shown (Marc and Sperling, 1977; de Monasterio et al., 1981; Sperling et al., 1980). Their increased vulnerability to biochemical perturbations is one of the theories promoting a selective loss of SWS cones, as changes that occur at the level of the RPE as a result of a thickened Bruch’s membrane (Spraul et al., 1999) increased diffusion distance for photopigment turnover may create the conditions for the development of a prominent tritan deficiency. However, SWS cones are fewer numerically and more sparsely distributed as compared to the other cone classes and their output appears to be pooled (Calkins et al., 1996). Therefore, non-selective destruction of the ganglion cell fibres would result in a more apparent blue/ yellow deficit when compared to red/green (Hart, 1987). Thus, an alternative hypothesis for the occurrence of tritan deficits in early disease processes is that blue cones are no more vulnerable than other retinal cell types, but because of the nature of their connections, the psychophysical losses might appear greater than that for other modalities.

Psychophysical testing of the SWS system is facilitated by its spectral properties, in that the peak in sensitivity of 440–450 nm is distinct from the other two cone types by approximately 100 nm. This allows the selective isolation of the channel that serves the s-cones when appropriately designed stimuli and background are utilised (Calkins, 2001). The acquired trianopic defect can also be detected by traditional colour-vision tests, such as the Farnsworth–Munsell 100 hue test and the Farnsworth D-15 test.

4.2. Surface colour methods

The Farnsworth–Munsell 100 hue test has been used by several groups to characterise the relationship between early ARM and colour vision. These studies showed an increase in the error scores with typically tritan defects in patients with macular changes (Trusiewicz et al., 1984; Bowman, 1980a, b; Applegate et al., 1987) and the extent of the defect is affected by illuminance (Bowman, 1978; Bowman, 1980a, b; Bowman and Cameron, 1984). An improvement in colour discrimination is found as illuminance increases but reaches a threshold beyond which further increases in illuminance do not improve colour discrimination. Conversely, discrimination decreases as illumination decreases and this takes place to a greater extent in subjects with ARM as compared with an age-matched elderly control group.

Despite only following three patients with varying degrees of ARM, a longitudinal study for over 2 years using Farnsworth–Munsell D-15 and Panel D-15 tests suggested that tritan defects increased over time and appeared to accelerate at or near the time when one of the patients developed a small exudative pigment epithelial detachment (Applegate et al., 1987). At this stage, an increase in the number of red–green type errors also became evident. The D-15 and the desaturated D-15 have also been used to demonstrate significant and predominantly tritan dyschromatopsias in early ARM in comparison to normal controls (Collins, 1986). It is noteworthy that increased sensitivity of the desaturated version is offset by a lack of specificity (Cheng and Vingrys, 1993).

Midena et al. (1997), in a study of early ARM in 83 patients, found no colour discrimination abnormalities, although other tests of vision indicated measurable visual impairment. However, the authors acknowledge that their findings are inconsistent with the majority of the literature and they suggest that commercially available colour-vision tests may not be sensitive enough to detect the subtle changes.

4.3. Colour-matching procedures

The trichromatic nature of colour vision allows almost any colour to be matched by a mixture of three colours. This principal can be used to provide a method to assess the integrity of the cone’s outer segments where the subject matches a standard light of intermediate wavelength with
a mixture of longer and shorter wavelength lights (Elsner et al., 2002). This allows the quantification of the amount of photopigment in long- and middle-wavelength cones. Elsner et al. (1987) used a free viewing anomaloscope in deutan mode to obtain Raleigh matches (primaries of peak wavelengths 536, 588 and 649 nm with half bandwidths of 10 nm) in subjects whose fellow eye has nvAMD (Group 1) and compared the results with a age-matched control group (Group 2), which contained patients with no fundus changes or druses and/or hypopigmentation. Group 1 subjects were more likely to have a colour-match area of magnitude zero or less in their good eye than Group 2 subjects in either eye. The size of the colour-match area relates to the effective photopigment density of the foveal cones, implying a substantially reduced density in those whose fellow eye has suffered from nvAMD compared to those eyes whose fellow eye has not suffered from nvAMD. Eyes with colour-match area effects of less than 0.3 were also found to have lower sensitivities at absolute threshold which suggests defects can be found in both chromatic and achromatic systems early in ARM when measured carefully. This was consistent with the data found by Smith et al. (1988), who used an early classification system proposed by Sarks (1976) to show that abnormalities of colour matching increased with increasing retinal abnormality. In the longitudinal study, Elsner et al. (1992) followed 47 patients with nvAMD in the fellow eye for at least 18 months, using a similar battery of visual function tests and fundus photographs to assess progression. During the follow-up period, 11 subjects had neovascular outcomes and four eyes had acuity loss outcomes but without nvAMD. Morphologically, the summed area of confluent drusen and atrophy within the central 3000 μm could be used to effectively distinguish eyes with neovascular outcomes from eyes with minimal-acuity loss outcomes. Functional data suggested that the combinations of dark-adaptation time constant and colour-match area effect (implying low foveal quantum absorption capabilities) were good at predicting outcome. The morphological risk factors identified were systematically related to the functional risk factors. However, despite the association between low s-cone sensitivity and a neovascular outcome, as a prognostic test, its age dependence and association with pre-retinal absorption makes its use in establishing risk cross-sectionally problematic.

The awareness of functional damage to cone photoreceptors in early AMD prompted Elsner et al. (2002) to investigate whether the damage caused by early ARM (reduced photopigment density) could be explained principally by RPE/Bruch’s membrane changes slowing regeneration of photopigment, altering bleaching and kinetic measurements, or whether it was just a more extreme form of ageing causing decreased quantal catch and decreased optical density of photopigment. This was achieved by performing colour matching over a series of light levels in patients with early ARM and a normative group. Although visual acuity was not correlated with maximum optical density, early ARM subjects had significantly lower optical density than that of normals. Analysis of the data indicated that the kinetic hypothesis (reduced trafficking through the RPE) could not explain the changes in photopigment density and they concluded that reduced photosensitivity of the cones had the larger effect prior to severe vision loss. This study also did not support the hypothesis that abnormal cone orientation was the cause of the decreased photosensitivity. The authors felt their results were suggestive of an altered microenvironment reducing the quantal catch of the cone.

4.4. Short-wavelength automated perimetry (SWAP)

Despite SWAP being principally used to detect visual loss due to glaucoma, it has been applied to retinal diseases, such as retinitis pigmentosa and macular oedema (Greenstein et al., 1989, 1992). A standard HFA perimeter modified for SWAP using a commercially available program was chosen by Remky et al. (2001) to explore SWS in ARM. They measured SWS cross-sectionally in 126 patients with non-neovascular ARM (drusen, hyperpigmentation and/or small atrophic lesions <200 μm) with visual acuity >20/50, 75 of these had a sight-threatening complication in the fellow eye. Besides finding a significant decrease in mean SWS with age, they found that eyes with soft drusen had significantly reduced mean sensitivity compared to those without despite no difference in age or Log MAR visual acuity. They adhered to strict entry criteria to ensure that media changes did not influence the age-related findings. Comparison of the 75 patients with neovascular or atrophic AMD with the rest showed that while the incidence of soft drusen was not significantly different between these two groups, hyperpigmentation was more common in the unilateral AMD group. Despite those with focal pigmentation having no significant decrease in sensitivity as compared to those without, they did have a significant decrease in the central part of the field when compared with the more eccentric. The authors suggest the use of this method to assess ARM progression or treatment outcomes in future clinical trials; however, the distinction between SWS loss due to media changes and that due to retinal factors in a general, elderly clinic population would be difficult.

4.5. Cone sensitivity

Several studies have specifically measured s-cone sensitivity or compared each of the three retinal cone mechanisms in early ARM. Applegate et al. (1987) used chromatic backgrounds to optimise the individual sensitivities of the short-, medium- and long-wavelength sensitive cone mechanisms in three patients with ARM. They found that sensitivities were within normal limits when test conditions used the red and green cone mechanisms whereas significant losses in the sensitivities of blue cone mechanisms were found in both non-neovascular and neovascular
eyes. This finding was confirmed by Eisner et al. (1987), who measured s-cone sensitivity in eyes whose fellow eye has nvAMD and age-matched controls and found a statistically significant difference. Two-increment thresholds were measured in ARM patients and pre-ARM patients with relatively small acuity losses as well as in a group of elderly control patients, using conditions designed to isolate each of the three cone mechanisms (Haegerstrom-Portnoy and Brown, 1989). The short(s) wavelength sensitivities were corrected for losses due to media absorption. Once again s-cone sensitivity was depressed in the ARM group as compared to the pre-ARM and elderly group, interestingly they found loss was significantly greater among females. Their findings were also correlated with the error score on the D-15 test that is consistent with receptorial loss. Despite finding only a weak association between high-risk drusen characteristics (presence of soft drusen, confluence of drusen and focal hyperpigmentation) and a lower s-cone pathway, Sunness et al. (1989) suggested that alterations in s-cone sensitivity might be indicative of more severe pathology not clinically apparent since drusen alone do not appear to alter sensitivity.

4.6. Colour CS

Colour CS tests, in which isoluminant stimuli are used, allow the separation of a luminance defect from a chromatic defect. The hues are modulated along colour confusion lines for trichromatic vision, therefore, changes in colour contrast are the only cues to image recognition (Holz et al., 1995). Early studies using them as a perimetric technique reported that all visual field defects, which were demonstrable by conventional forms of perimetry were also detectable by the colour contrast technique (Hart, 1987). A computer graphics system developed by Arden and co-workers was used by Holz et al. (1995) to evaluate colour-vision deficits in patients with macular drusen. In total, 84 eyes from 84 patients with macular drusen and clear media were tested, and compared to an age-matched normal control group. Interestingly, at baseline, foveal measurements showed a markedly elevated tritan threshold for the drusen patients and proton and deutan thresholds which were slightly above the normal limit, however, parafoveally the tritan threshold was normal whereas the red and green were abnormal. Throughout the 2-year follow-up, tritan thresholds changes were significantly different from baseline in the fovea whereas colour sensitivity for red and green showed no change at either a foveal or parafoveal location. Within the follow-up period, eight patients developed a complicating macular lesion (foveal GA in one patient and CNV in the others) and these patients had a significantly higher tritan threshold at baseline than those who did not develop late-stage disease. More recently, Arden and Wolf (2004) used two sizes of optotypes (6.5° and 1.5°) to assess colour CS by using a computer graphics technique along both proton and tritan confusion axes. He assessed better eyes of 24 patients with unilateral AMD or bilateral early ARM and found that the thresholds for both sizes of optotypes were raised, but tritan losses were greater in the smaller optotype and disproportionate to those seen with the larger optotype. Even patients with minimal fundal changes had results outside the normal range and these thresholds varied with the severity of the ARM.

5. ARM, AMD and electrophysiology

Measuring gross electrical potentials provide an objective means of evaluating the functional capacity of a large number of neurons. The methodology can be manipulated in order to focus on the anatomical structures most vulnerable to degenerative changes, such as the interaction between the RPE, choroid and photoreceptor layer. Much investigation has centred on the influence of various stages of ARM on the electroculogram (EOG), the electroretinogram (ERG) and visually evoked potentials (VEPs). Although notable pathological changes have been reported in EOG and ERG in patients with AMD (Henkes, 1954; Arden et al., 1984), other investigators have found no significant EOG abnormalities in AMD eyes or in the fellow eyes of AMD patients (Shirao et al., 1997; Marcus et al., 1983; Holoopigian et al., 1997; Sunness et al., 1985; Sunness and Massof, 1986). Such inconsistent reports in the literature have resulted in a debate on the value of electrophysiological tests as diagnostic and prognostic markers for AMD. Therefore, a more recent study by Walter et al. (1999) sought to determine systematically whether there were EOG and ERG changes in patients with AMD and while doing so, they sought to answer two important questions as: (1) are there any differences between age-matched normal controls and AMD using standardised test protocols? and (2) is the morphological appearance of AMD related to abnormalities in EOG and ERG? Sixty-six patients with AMD underwent EOG, ERG, triple scotopic ERG and fluorescein angiography, 83 normal persons served as age-matched controls for EOG and 47 for ERG. Both the Ganzfeld EOG and ERG responses were found to be abnormal in AMD, suggesting a global impairment of retinal function beyond that suggested by fundoscopic appearance. Significant EOG changes suggested that RPE function is also altered while a significant increase in the light rise (ratio of light peak portion to dark trough portion of the EOG trace) in patients with soft drusen led the authors to suggest that this may prove useful as a marker of risk in the development of advanced disease. They also showed that both the cone-driven and rod-dominated ERG were significantly different in AMD patients when compared to normal controls, with both reduced amplitude and prolonged implicit times suggesting that not only are there fewer cells present but also that those remaining have a slower synaptic transmission than that in elderly normals. Nonetheless, the absence of clearly defined normal limits for some of these parameters, the global nature of the full-field ERG, and
the fact that the ERG is usually normal unless a disease affects 20% or more of the retina limits the sensitivity of the test, particularly when used in focal lesions such as those typically seen in AMD.

5.1. Focal ERG (fERG)

The ERG recorded from the fovea was designed to test for focal disease within the fovea by using a small flickering spot to elicit a local response (Sandberg et al., 1993). An early study using this methodology with a procedure which involved testing temporal frequencies ranging from 10 to 60 Hz showed that besides a general amplitude loss associated with macular degeneration, there appeared to be a relative sparing of the mid-temporal frequencies (Seiple et al., 1986). The value of fERG was further acknowledged when Fish and Birch (1989) demonstrated it to have a sensitivity of 87% for distinguishing between eyes with macular disease and those eyes with other causes of acuity loss, such as amblyopia, cataract and optic neuropathy (Fish and Birch, 1989). This was investigated further by Sandberg et al. (1993), who measured foveal ERG in the asymptomatic fellow eye of patients with unilateral nvAMD and compared this to age-matched normal eyes. Although the amplitude of the response was similar between groups, the AMD patients had delayed implicit times, suggesting that these eyes had normal numbers of foveal cones but they functioned abnormally. It is suggested by some that vascular changes are responsible for the global retinal dysfunction associated with AMD (Friedman, 1997). Remulla et al. (1995) used focal cone ERGs to explore this hypothesis by attempting to establish a link between prolonged choroidal perfusion in AMD and retinal malfunction. In 67 patients with AMD, 42% had a choroidal perfusion defect and these patients had significantly delayed implicit times after controlling for age, acuity and extent of drusen. Abnormal oscillatory potentials (OPs) found on the ascending side of the b-wave in AMD patients also implicate a vascular mechanism in the pathogenesis of AMD. OPs are thought to reflect electrical activity in the amacrine cells and these cells lie in the inner retina, which is nourished by the retinal circulation. The focal nature of the test prompted much attention to be focused on clarifying the relationship between retinal morphology and function. Falsini et al. (1999) used fERG and graded fundus photographs and fluorescein angiograms in 25 patients with bilateral early ARM, compared to 10 age- and gender-matched controls. They found the fERG paralleled the extent and severity of the fundus lesions, which were assigned severity stages based on the WARMGS grading system. It was notable, however, that patients with early ARM had a reduced amplitude in the fERG compared with that seen in control eyes, suggesting that this procedure enabled functional losses to be detected, which precede the morphological changes, which characterise AMD.

5.2. Multi-focal ERG (mfERG)

The mfERG, which was developed and introduced by Sutter and Tran (1992), allows retinal activity in the form of fERGs to be recorded simultaneously from 100 or more retinal locations over a brief period of time. As the responses originate mainly from the outer retina with relatively little contribution from the ganglion cells, much attention has been focused on its ability to detect and monitor the various stages of ARM. Attempts have been made to evaluate both rod- and cone-mediated ERGs by using this method and although the cellular origins of these components are still not completely clear, both have revealed deficits in early ARM (Gerth et al., 2003; Li et al., 2001; Jurkli et al., 2002; Feigl et al., 2004). Controversy exists, however, as to the spatial resolution of the data and its ability to accurately reflect morphological abnormality. Palmowski et al. (1999) performed mfERG on three patients with AMD and compared the findings with fundus photography and fluorescein angiography, and found that mfERG allowed accurate topographic mapping of focal areas of retinal dysfunction in all patients tested, including the abnormal changes detected by fluorescein angiography. Other investigators have reported poor morphologic-functional relationships between mfERG and retinal appearance (Gerth et al., 2003) and only weak-to-moderate statistical correlations between the greatest linear dimension of the CNV lesion and mfERG response density (Jurkli et al., 2002). Despite the apparent lack of correlation, functional changes in cone-driven pathways evaluated by the mfERG, indexed by the first-order kernel implicit times have been shown to occur consistently in patients with early ARM and in asymptomatic fellow eyes, compared to normal control eyes (Gerth et al., 2003; Li et al., 2001). Jurkli et al. (2002) followed four patients with AMD on a 3-monthly basis over a period of 15 months, using mfERG and concluded that it also has potential as a valuable tool in the longitudinal monitoring of patients with CNV in that response densities correlated well with visual acuity and were reduced within the central 5°, which was the area affected by the CNV. A recent cross-sectional study of 17 subjects with early ARM and 20 age-matched normals, which involved a series of psychophysical tests and fundus photographs as well as mfERG revealed that the mfERG protocol employed was unable to discriminate between the ARM and normal groups despite significant differences between groups being apparent for CS, high- and low-contrast visual acuity and colour vision (Feigl et al., 2004). It is evident that this is burgeoning field of technology and much of the apparently disparate findings may be clarified as protocols are developed, guidelines established, and analyses are refined to include adequate age-related corrections, and in the case of rod-mediated mfERGs, adequate lens density correction factors (Marmor et al., 2003; Feigl et al., 2004; Jackson et al., 2004).
5.3. Visually evoked potentials

VEPs are traditionally used to assess the integrity of the optic nerve. The cortical magnification of foveal vision, however, supports the view that the VEP is largely a foveal phenomenon, particularly if it is recorded using a stimulus of small check size and small field size. Therefore, eyes with advanced AMD and low visual acuity may show no recordable transient or steady-state VEP (Sokol, 1971; Negishi et al., 2001) and several groups have shown amplitude attenuation and latency delay of this measure in eyes with AMD and moderate or good visual acuity (Sokol, 1971; Celesia and Kaufman, 1985; Negishi et al., 2001; Lennerstrand, 1982; Junghardt et al., 1995) as well as in their fellow eye (Marcus et al., 1983).

6. Visual adaptation and ARM

Light adaptation refers to the remarkable ability of the human eye to rapidly adjust to a large range of light intensities from intense sunlight to low levels of illumination (Leibrock et al., 1998). Visual transduction involves the capture of light by the photoreceptors, activation of the photopigments, followed by their regeneration. These processes require correctly aligned, structured and functioning photoreceptors, intact post-receptorial pathways, as well as metabolic support from the surrounding tissues, such as the RPE, choriocapillaris and Bruch’s membrane. The integrity of these structures and processes can be assessed using tests, such as glare recovery, cone and rod adaptation and flicker sensitivity. Studies have shown that many of these processes are compromised in the early stages of ARM.

6.1. Photostress test

Glare recovery, macular recovery or the photostress test refers to the technique of assessing the integrity of the dynamic response of the retina by exposing it to a controlled glare source and measuring the time course to the return of sensitivity (Collins and Brown, 1989a) (either contrast discrimination (Collins and Brown, 1989a, b) or visual acuity (Schmitt et al., 2001; Bartlett et al., 2004a; Midena et al., 1997; Sandberg and Gaudio, 1995; Sandberg et al., 1998)). It has traditionally been used as a tool to differentiate macular disease from optic neuropathy and early studies investigating a variety of retinal diseases reported prolonged recovery times in ARM patients (Glaser et al., 1977). One study investigating visual function and prognosis in patients with bilateral drusen found a poor correlation between photostress results, and visual acuity or drusen severity (Smithy and Fine, 1984). Others, however, have reported significant correlations with clinical measures of vision, such as visual acuity, colour vision, contrast threshold and subjects’ subjective complaints (Collins and Brown, 1989a, b). Studies have also shown substantial delays in glare-recovery time in early ARM patients despite good visual acuity (Collins and Brown, 1989a) and the measured times appear to parallel the worsening of disease severity in the early stages (Collins and Brown, 1989a; Sandberg and Gaudio, 1995; Midena et al., 1997). The value of glare recovery as a prognostic indicator of severe AMD was investigated by Sandberg et al. (1998), using a method that flashed letters on a computer screen in random order before and after a 10 s bleach. One hundred and twenty-seven patients with unilateral nvAMD were followed for 4½ years, and macular morphometry was also graded based on the number and type of drusen, presence of focal hyperpigmentation and the presence and extent of atrophy. They showed that a slower recovery from glare and the severity of ARM features were independent risk factors for the development of a CNV in fellow eyes. These results suggest the test that reflects cone sensitivity and RPE integrity and has the potential to be used as a prognostic marker.

Variability in the intensity and duration of the light stimulus makes it difficult to compare the results from the various studies. The Eger Macular Stressthemeter (EMS) was developed in an attempt to provide a standardised method applicable in clinical settings as well as a non-invasive screening test for AMD. A pilot study using this instrument did not find a significant difference in the glare-recovery times between patients with AMD, cataract, diabetic retinopathy and glaucoma (Schmitt et al., 2001). However, when the instrument was used to obtain normative data and to investigate the effect of ARM/AMD on the photostress recovery time, the EMS displayed a sensitivity of 29% for ARM and 50% for AMD (Bartlett et al., 2004a, b).

6.2. Dark adaptation and scotopic sensitivity

Dark adaptation refers to the recovery of visual sensitivity in darkness, following exposure of the eye to intense illumination, which bleaches the photopigment rhodopsin. The classical bi-phasic curve is obtained after almost total bleach and contains an initial phase, which reflects cone function and the slower component, which occurs when rod threshold drops below cone threshold (Leibrock et al., 1998) (Fig. 2).

Although age-related increases in the time constant of rod-mediated dark adaptation and scotopic sensitivity have been reported (Jackson et al., 1999), numerous psycho-physical studies have shown that these occur to a significantly greater extent in those with early ARM (Owsley et al., 2000, 2001; Steinmetz et al., 1993; Haimovici et al., 2002; Brown and Lovie-Kitchin, 1983; Eisner et al., 1987; Sturr et al., 1997) (Fig. 3).

These findings are in accord with histopathological observations that rods are lost earlier than cones in both ageing and early AMD (Curcio et al., 1993, 2000). It is interesting to note that studies have shown deficits in dark adaptation are not always correlated with scotopic sensitivity, suggesting that the mechanisms underlying
these parameters are not the same (Jackson and Owsley, 2000); therefore, a patient with early AMD may have normal scotopic sensitivity but abnormal dark adaptation, the reverse scenario, however, is uncommon.

A common complaint made by the most ARM patients is that they experience difficulty when transiting from a bright to a dark environment. In exploring this observation, several groups have shown good correlations between subjective complaints and tests of scotopic threshold and dark-adaptation kinetics (Brown and Lovie-Kitchin, 1983; Steinmetz et al., 1993). Measurement of the dark-adaptation time constant was incorporated into a battery of tests by Eisner et al. (1992) in their longitudinal study of eyes whose fellow eyes had nAMD (Group 1) and an age-matched control group (normals + bilateral early ARM). The initial cross-sectional analysis found that eyes with the most drusen and/or atrophic change were the ones with the slowest rates of sensitivity recovery during dark adaptation (Eisner et al., 1987, 1991). The subsequent longitudinal analysis of 47 patients after 18 months follow-up found that the dark-adaptation time constant together with colour-match area effect was positively correlated and also provided the best predictor for the development of a neovascular lesion (Eisner et al., 1992).

The nature of these tests is such that they should be particularly sensitive at evaluating those eyes with substantial RPE disturbance, i.e., multiple drusen, pigment irregularities, RPE detachments and choroidal perfusion defects. It is recognised that CNV can occur in the absence of these defects and, therefore, Haimovici et al. (2002) postulated that dark adaptation would be significantly worse in the fellow eyes of patients with pigment epithelial detachments and tears of the retinal pigment epithelium, compared to the fellow eyes of patients with just CNV or just drusen. Although the differences that were noted between the groups were in the direction expected, they did not reach statistical significance due to the small sample size. Therefore, this area merits further investigation and the authors’ recommend using a more rigorous classification of CNV sub-type and increasing the sample sizes.

6.3. Cone adaptation

Cone dysfunction in the early stages of AMD was initially identified by Brown and Lovie-Kitchin (1983) while undertaking experiments that were designed primarily to test rod threshold. Cone thresholds were shown to be elevated in early AMD despite the eyes having good visual acuity. In further work, Brown et al. (1986) measured cone adaptation at 5°, 10°, 20° and 40° eccentricity, using incremental thresholds in six patients with early AMD (drusen and pigmentary irregularities) and an unspecified number of age-matched controls. Elevated cone thresholds were found in ARM patients in the central and peripheral retina when compared to the age-matched controls. Surprisingly, time constants for photopigment recovery appeared unaffected. This study provided evidence that the functional consequences of early ARM are not limited to the macula. In an effort to compare static and kinetic aspects of cone function, Phipps et al. (2003) tested various aspects of cone function, using spatial and temporal CS, colour thresholds and light- and dark-adaptation dynamics. In all cases, contrast thresholds were measured in order to minimise the effect of pre-retinal absorption in the

Fig. 2. Dark-adaptation curve. Adapted from web-vision (http://webvision.med.utah.edu/light_dark.html#dark) with permission. The shaded area represents 80% of the group of subjects. Hecht and Mandelbaum’s data from Perenne M.H. (1962). Dark adaptation and night vision. In: Davidson (Ed.), The Eye, vol. 12. London Academic Press (Chapter 5).

Fig. 3. Frequency histogram of mean field (central 19° radius visual field) dark-adapted sensitivity in patients with early ARM. Box plots above the histogram compare the distribution of ARM patients to a group of age-matched subjects with good retinal health. Box represents 25th and 75th percentile and whiskers, 10th and 90th percentile. Solid line within the box is the median and the filled symbols, the mean. Vertical line in the histogram represents the lower normal limit (mean = –2.5 SD). Investigative ophthalmology and vision science by Owsley et al., Copyright 2000 by Investigative Ophthalmology and Visual Science. Reproduced with permission of Investigative Ophthalmology and Visual Science in the format journal via Copyright Clearance Centre.
ageing eye. In the high-risk patients (good acuity but either multiple soft drusen bilaterally with or without pigmentary changes, or unilateral soft and a CNV in the other eye), 44% had abnormal cone steady-state thresholds. The constant of cone adaptational recovery was the single most affected parameter in most patients with ARM (69%) and this was found to be a more sensitive discriminator than steady-state thresholds. The time constant did not correlate significantly with steady-state functions (photopic, spatiotemporal and colour) and, therefore, appears to identify a unique aspect of visual function in ARM that is not covered by the other tests. These functional deficits are thought to involve a slowing of cone photopigment regeneration in both ageing and disease. Possible causes for these functional deficits that occur in ARM eyes include morphological alterations in Bruch’s membrane and RPE, which would slow the recycling of visual photopigments (Leibrock et al., 1998; Pianta and Kalloniatis, 2000), misalignment of the cone’s outer segments resulting in a lower optical density of photopigment and reduced quantum catch by the photopigment (Eisner et al., 1992; Elsner et al., 2002).

6.4. Flicker sensitivity

Flicker sensitivity is a useful marker of retinal integrity. The detection of flicker of a spectral light on a bright white background is mediated by both the opponent or chromatic system for low alteration rates and by the luminance or non-opponent system for high alteration rates (Applegate et al., 1987; Mayer et al., 1994). It may also be able to detect metabolic compromise of the outer retina better than a static stimulus because of the increased metabolic demand needed to detect flicker (Anderson and Vingrys, 2001; Phipps et al., 2004). Investigators commonly use two different types of flickering stimuli, which are drawn schematically in Fig. 4 (Anderson and Vingrys, 2000):

1. Mean-modulated flicker: Modulating a stimulus about a mean background level in order that there is no change in the time-averaged luminance (Mayer et al., 1994).
2. Pedestal flicker: This involves modulating a stimulus concurrent with a light increment. This results in both a flickering component and an increase in time-averaged luminance above background level. Detection thresholds are increased by the low-frequency luminous pedestal created for the stimulus duration, by invoking local adaptation and contrast-dependent masking effects or rod–cone and cone–cone interactions from surrounding regions. A loss suggests adaptational abnormalities, which have been reported previously in ARM patients (Phipps et al., 2003; Owsley et al., 2001).

The loss of sensitivity for medium temporal frequencies, in patients with early ARM, but good visual acuity, was first proposed by Brown and Lovie-Kitchin (1987b). Using the classification of ARM based on visual acuity as well as morphology, they found that the ARM (VA > 6/6) patients possessed a significant depression of the temporal contrast-function across a wide range of frequencies whereas the pre-ARM (VA < 6/6) showed similar results to the normal control group except for mid-temporal frequencies. A subsequent study suggested that the processes responsible for temporal summation spared in ARM in contrast to those mediating temporal discrimination (Brown and Lovie-Kitchin, 1989). A study principally investigating two-increment colour thresholds in ARM revealed that the ability to detect 25 Hz flicker was significantly depressed in a group of ARM patients group when compared to the elderly control subjects despite these patients having normal L-cone increment thresholds (Haegerstrom-Portnoy and Brown, 1989). Whether a loss of flicker sensitivity reflects retinal or post-receptorial damage has stimulated much debate. It is thought that the luminosity channel involved in flicker detection receives a summed input from both medium (M) and long (L) wavelength receptors with the long-wavelength receptors predominating by a ratio of around 2:1. Therefore, Haegerstrom-Portnoy and Brown (1989) postulated that the change of 0.3 Log unit in M-cone sensitivity noted in the study yet no significant change in L-cone sensitivity, would have only produced minor changes in the flicker sensitivity if the loss had occurred at the receptor level. They, therefore, proposed the alternative hypothesis that a post-receptorial channel for detecting flicker may be affected by the disease, as this was also suggested by Applegate et al. (1987), who noted that flicker sensitivity was depressed by 0.5 Log units in the non-neovascular eye of an ARM patient with L–M-cone sensitivities remaining normal.

6.5. Cone flicker sensitivity

Recently, Falsini et al. (2000) used focal electrogram modulation sensitivity to evaluate retinal cone flicker sensitivity. Focally recorded electroretinography is thought
to reflect the activity of cone photoreceptors and bipolar cells and, therefore, provides a functional index of the outer retina. The investigators reasoned that the assessment of outer retinal sensitivity using this method might help to evaluate early cone dysfunction in ARM. They undertook a cross-sectional study in which fERGs as a function of sinusoidal flicker modulation was recorded in patients with early ARM and in age-matched control subjects. Response gain losses and modulation depth-dependent phase delays, with normal thresholds, were associated with early lesions. It is thought that these may result from early degenerative changes of cone photoreceptors whose numbers at this stage may be normal or near normal. Retinal gain may be affected by both shortening of cone outer segments, thereby reducing quantum catch and the effective retinal intensity of the stimulus, as well as by the alteration of photoreceptor membrane properties (time constants) by delaying reestablishment of equilibrium. Increased thresholds, in addition to gain and phase abnormalities, were found in more advanced lesions, which suggest more widespread disease. The investigators also found that the temporal characteristics of foveal cone photoreceptors are altered in AMD.

The possibility that the changes in temporal characteristics of the retina may be associated with early metabolic changes in the choriocapillaris and Bruch’s membrane was proposed by Anderson and Vingrys (2001) and Phipps et al. (2004). This impairment, which is thought to occur early in AMD, should therefore be more readily detected by a flickering stimulus than by a static one. They chose to use a pedestal flicker as it has been shown to be robust to the effects of both blur and pre-retinal absorption, which is particularly important when testing an elderly population. It also exposes rod–cone interactions and, therefore, may allow detection of early rod dysfunction as well as providing a good indication of local adaptation and temporal sensitivity changes (Anderson and Vingrys, 2001; Phipps et al., 2004). Individuals with early AMD were compared with control subjects of a similar age, using both static and flicker perimetry. The use of flickering targets resulted in larger and deeper visual field deficits than static targets, and the investigators postulate that the selective loss to flickering targets may be seen earlier in the disease process and perhaps act as a better prognostic indicator. It has been suggested that the increase in local metabolic demand and thus retinal blood flow required by a flickering stimulus may be hindered by the pathological changes that occur in the RPE, choriocapillaris and Bruch’s membrane in the early stages of AMD (Van Toi and Riva, 1994; Kiryu et al., 1995).

6.6. Flicker sensitivity and progression to AMD

A series of studies by Mayer et al. (1992a–c, 1994, 1995) provided valuable insights both into the visual mechanisms underlying flicker sensitivity and its value as a method for detecting and monitoring progression in ARM. They measured sensitivity as a function of flicker rate in eyes at risk for AMD (“good” eye of patients with unilateral AMD) and age-matched healthy older eyes. ARM eyes were less sensitive overall to flicker than healthy older eyes, especially at mid-temporal frequencies. Eyes with ARM features were significantly less sensitive to frequencies between 10 and 28 Hz when compared with the healthy older group (Mayer et al., 1992a). In a second paper, they used a stepwise discriminant analysis to classify ARM-risk eyes from healthy older eyes with 78% accuracy based on foveal flicker sensitivity at the two most affected mid-temporal frequencies, 10 and 14 Hz (in order of estimated weight) (Mayer et al., 1992b). Preliminary data suggested that sensitivity at these temporal frequencies may also predict which eyes would develop nvAMD (Mayer et al., 1992c). They tested their hypothesis using follow-up data collected over a 4-year period at which point seven of the initial group of 13 patients had converted to nvAMD. By comparing the baseline characteristics of foveal flicker sensitivity along with the fundus appearance of eyes with ARM but without CNV, with the healthy, age-matched eyes, the investigators showed that a linear combination of flicker determined at 5 and 10 Hz could discriminate between eyes that went on to develop nvAMD from those that did not, with an accuracy of 100%. Despite a similar fundus appearance, eyes without nvAMD and non-converted eyes had very different outcomes weakening the prognostic value of fundus grading. Thus, the researchers concluded that neovascular changes might occur in the absence of RPE abnormalities. Mayer et al. (1992c) proposed a variety of causes for the loss of temporal CS. They felt that it was unlikely to be due to a decrease in photoreceptors as when the groups were restricted to subjects with acuities better than 20/25, the differences in sensitivity still remained. Furthermore, spatial blurring of up to four dioptres of the flicker test had no effect on flicker sensitivity. They then considered the temporal CS curve as a de Lange function (an envelope that describes the combined response profile of the mechanisms whose individual response spectra are overlapping). Within the context of this multi-channel temporal processing model, the mid-temporal frequency losses reported in this study could be attributed to reduction in sensitivity in a “high-temporal frequency” mechanism (Mayer et al., 1995). Given that the magnocellular pathway is believed to be principally responsible for high-temporal and low spatial frequency vision, the authors suggested that it may be particularly susceptible to changes in the early stages of ARM. However, most eyes with late AMD continue to maintain low spatial frequency CS and this is not in accord with an early dysfunction of the magnocellular pathway.

7. Central visual field sensitivity and ARM

Central field defects have been reported in the eyes of patients exhibiting features of early ARM, with the defect
most commonly located in the parafovea (Swann and Lovie-Kitchin, 1991; Cheng and Vingrys, 1993; Midena et al., 1994, 1997; Hart and Burde, 1983). In contrast to these findings, Atchison et al. (1990) using the Humphrey field analyser found no significant differences between eyes with early ARM (ophthalmoscopically visible hard drusen and/or fine pigmentary stippling or depigmentation with a Snellen visual acuity of 6/6 or better) and the eyes of 15 age-matched normal controls. Similarly, Midena et al. (1994) examined the relationship between severity of ARM changes and central visual field sensitivity. Although mean sensitivity did not correlate with the number of drusen, presence of focal hyperpigmentation or RPE atrophy, it was significantly decreased in eyes with confluent drusen. On the other hand, Tolentino et al. (1994) concluded that drusen had little effect on the central visual field whereas the deficits in sensitivity were correlated with RPE attenuation or atrophy.

The lack of consistency in the evidence may be a reflection of the limited ability of both kinetic and static perimetry to accurately measure macular function as they assume stable foveal fixation, which is rarely present in AMD (Sunness, 1999). Many of these limitations are overcome by the use of microperimetry through SLO. Compared to traditional perimetry, the SLO offers many advantages such as real time ophthalmoscopic imaging, which allows fixation control with correction for eye movements, an accurate determination of preferential fixation location and point-to-point correlation of fundus pathology and related functional deficits (Sunness et al., 1995).

By using a fundus camera stimulator, it was demonstrated that the retinal sensitivity over drusen and non-drusen areas was not significantly different, a finding that was in accord with those obtained on static perimetry (Sunness et al., 1988). Nonetheless, a more recent study has questioned these findings and shown a decrease in sensitivity in retina overlying drusen (Takamine et al., 1998). In this study, more than half of the retinal areas with underlying drusen, which were sampled, showed decreases in sensitivity. The decrease was only noted over large drusen (amorphous substance with a clear border) as opposed to soft drusen (amorphous substance with an indistinct border); however, no relationship was found between drusen size and the amount by which retinal sensitivity was decreased, implying that small differences in the degree of separation between the RPE and choriocapillaris do not influence retinal function. The incongruity between these results and those of Sunness et al. (1988) was attributed by the authors to the better instrumentation, which allowed them to delineate the margins of the retinal areas overlying the drusen and to undertake selective stimulation of these areas without a contribution from the surrounding normal retina.

The impact to visual function of the various morphological features of late AMD has also been investigated. Tezel et al. (1996) explored the relationship between SLO microperimetry and anatomic abnormalities in patients with sub-foveal neovascularisation. They superimposed SLO microperimetry on colour fundus photographs and fluorescein angiograms of 21 eyes with sub-foveal neovascular membranes secondary to AMD (14 eyes) and POHS (7 eyes). They found that the relative risk of an absolute scotoma is highest over areas of chorioretinal scars (RR = 107.61), RPE atrophy (RR = 9.97), sub-retinal haemorrhage (RR = 2.88) and the neovascular membrane (RR = 1.86). Schneider et al. (1996) combined SLO microperimetry with simultaneous Indocyanine Green angiography and noted that the depth of the CNV correlated with both duration of symptoms (Fig. 5) and the size and type of CNV with well-defined CNV producing significantly deeper scotomata than eyes with occult CNV. Clinically, these findings emphasise the necessity of prompt referral and treatment with the aim of keeping the associated scotoma as small as possible.

The application of SLO in monitoring visual function in longitudinal studies has provided crucial insights into the natural history of vision loss. Sunness et al. (1997) undertook a longitudinal study of the visual function abnormalities and prognosis in eyes with GA. They found that areas of GA are associated with absolute scotomas and that GA tends to spare the foveal centre until late in the disease, providing further evidence of the limitation of visual acuity at reflecting visual function.

The sequence of events in AMD, which leads to loss of visual function was investigated by Fuji et al. (2003), using the SLO in 175 eyes with CNV. In addition, 15 patients who elected not to have any treatment for CNV were also kept under observation with SLO testing every 3 months for up to 18 months after the onset of visual symptoms. Visual impairment in eyes with sub-foveal CNV secondary to AMD was seen to be associated with decreased fixation stability, loss of central fixation and impaired retinal sensitivity. Thus, the authors postulate that the sequence of events consists of an initial mild decrease in central

![Fig. 5. Relationship between the depth of the scotoma measured using SLO microperimetry and the duration of symptoms. Taken from Schneider et al. (1996), used with permission.](image-url)
retinal sensitivity and visual acuity, which is followed by a progressive increase in fixation instability and ultimately, the development of an absolute central scotoma with eccentric fixation. Once again the necessity of prompt treatment is reinforced because in the sub-group of patients with symptoms for 3 months or less, 89% had predominantly central fixation and 58% had stable fixation suggesting the presence of viable photoreceptors. In this sample, considerable functional variability was observed among lesions occupying a similar area and thus implying that inferences on retinal viability should not be made based solely on lesion size.

SLO microperimetry has also proved useful in the monitoring of response to new treatment modalities. Schmidt-Erfurth et al. (2004) used SLO perimetry to document the size of absolute and relative scotomas during a single centre double-masked study of verteporfin therapy in 46 consecutive patients with sub-foveal CNV. Thirty-three patients received verteporfin and 13 received placebo and all underwent SLO at 3-monthly intervals over the 2-year follow-up period. Statistical analysis showed that the mean absolute and relative scotoma sizes were significantly smaller in the verteporfin group than that in the placebo group, at all points beyond 6 months after baseline. These findings have important implications for reading ability and visual rehabilitation.

8. Indices of metamorphopsia and ARM

Distortion or metamorphopsia is one of the earliest symptoms reported by patients at the onset of neovascular macular disease. Therefore, there has been considerable interest in the development of methods to identify and quantify distortion.

8.1. Amsler charts

In 1947, a simple grid of squares known as the Amsler charts were printed and proposed as a screening test for macular disease (Marmor, 2000). They have traditionally been used as a screening test for diagnosis of nvAMD; however, most studies have found poor specificity and sensitivity, and its usefulness for this purpose has been questioned (Zaidi et al., 2004; Schuchard, 1993). Amsler charts have the obvious disadvantage of providing a supra-threshold stimulus that is insensitive for the detection of relative scotomas and depressed retinal sensitivity (Wall and May, 1987). An improvement to the Amsler was proposed by Wall and May (1987), who used cross-polarised filters to vary the luminance to a threshold level where even a small drop in retinal sensitivity could be measured. This modification yielded a six-fold increase in scotoma detection over standard testing. As it involves a change in luminance levels, Wall's method was found to yield inconsistent results (Cheng and Vingrys, 1993) if a period of dark adaptation is not built into the test protocol.

Recently, a computerised automated version of the Amsler has been developed which incorporates resolution and retinal CS to produce a 3-D map of the central visual field to reveal the shape, location, extent, slope and depth of the retinal deficit at a resolution of 1° (Fink and Sadun, 2004). This test may have potential as a screening tool in macular disease.

8.2. Preferential hyperacuity perimeter (PHP)

The PHP is another screening device that has recently become commercially available (Lowenstein et al., 2003). It exploits the high sensitivity of hyperacuity to detect very early retinal elevations. Hyperacuity may be defined as the ability to discern misalignment of objects at the fovea and is about 10 times higher than resolution acuity. Hyperacuity also has the advantages of being much more robust to optical blur and age-related decline than other measures of acuity (Lakshminarayanan and Enoch, 1995). The test involves a dotted line flashed on a computer screen, and any perceived distortion or scotoma is recorded and analysed. A macular map is obtained with quantitative values of the area and intensity of the metamorphopsia. Initial validation studies showed that the PHP was better than the Amsler grid at detecting AMD-related lesions and that it may be able to differentiate between intermediate ARM (the presence of large drusen) and incipient CNV, and thus may be beneficial for monitoring progression from early ARM to late AMD.

8.3. Shape-discrimination charts

The recently developed shape-discrimination charts may also prove useful in detecting and monitoring macular disease (Wang et al., 2002). These require patients to identify a deformed circle from a group of perfect circles; this also represents a form of hyperacuity (Fig. 6).

Viewing of the test target results in integration across a wide retinal area and consequently may be more sensitive than visual acuity to irregular sampling or under sampling by the photoreceptors, especially when patients have parafoveal or paracentral visual defects common in early ARM. It also has the advantage that patients are unable to achieve artificially good results by using visual search as they would need to locate a large enough healthy area to process the whole stimulus. In a computerised version of the test, 97% of early ARM patients showed a significant elevation in threshold in comparison with normal older volunteers.

9. Self-reported visual functioning and ARM

Within a clinical setting, it is often evident that performance on conventional tests of vision such as Snellen acuity is at variance with the patient’s perception of their visual disability. To better understand these relationships, a number of quality of life (QOL) instruments have been
devised, which provide a semi-quantitative measure of self-reported health and visual functioning.

9.1. Evaluation of QOL

QOL encompasses four dimensions as: a physical dimension (disease symptoms and their treatment), a functional dimension (self-care, mobility, activity level and activities of daily living), a social dimension (social contact and interpersonal relationships) and a psychological dimension (cognitive function, emotional status, wellbeing, satisfaction and happiness) (Aaronson, 1988; de Boer et al., 2004). Questionnaires or instruments can be disease specific or generic. A keen interest in this area has led to the proliferation of instruments making it difficult to both to compare outcomes and for researchers in the choice of an appropriate outcome measure. Several helpful reviews of vision-related questionnaires have been published (Massof and Rubin, 2001; Margolis et al., 2002; de Boer et al., 2004). de Boer et al. provided a systematic review of 31 vision-related QOL questionnaires, which they rated on their psychometric quality using a pre-defined rating list. They also emphasised the advantage of applying Rasch theory to aid analysis and interpretation of data. The majority of questionnaires on vision have been developed for use in patients with cataract, although other disease-specific questionnaires exist for AMD, retinitis pigmentosa, glaucoma, ocular melanoma, cytomegalovirus and Graves ophthalmopathy. Although some instruments were initially developed to assess the impact of visual impairment due to cataract, and the alleviation of symptoms by surgery (VF-14 and activities of daily vision scale (ADVS)) their validity as a tool in the measurements of functional impairment in retinal diseases has been demonstrated (Linder et al., 1999; Mangione et al., 1999).

9.2. Relationship between self-reported difficulties and clinical tests of vision

Various studies have attempted to identify those aspects of visual functioning which correlate with different objective clinical tests. Thus, e.g., the relationships between measured visual acuity, CS and visual field have been correlated with the scores obtained on self-reported questionnaires (Carta et al., 1998; Rubin et al., 2001). Rubin et al. found that measured stereoacuity and glare exhibited weak correlations with self-reported difficulty with everyday tasks. Interestingly, each of these measures was significantly associated with the questionnaire scores independently suggesting that reduction in visual functioning along several dimensions contributes to the difficulty experienced in the undertaking of daily living tasks. Other studies have attempted to identify which daily living tasks are represented by which clinical measure of vision. Hazel et al. (2000) found that low-contrast visual acuity and CS account for most of the variance (83%) reading performance whereas binocular text-reading speed provided the best indicator of overall visual function. They highlighted the fact that discrepancies often exist between self-reported visual performance and measured reading speed, which they suggested, was because spot-reading tasks are considerably more important to patients with low vision, so visual resolution is more important than fluency. McClure et al. (2000) used a QOL instrument constructed and validated specifically for patients with AMD (the daily living tasks dependent on vision DLTs) with the ability to discriminate between AMD sufferers, cataract sufferers and those with no history of visual problems. Reading index (a novel derivative of reading speed) and DVA showed the strongest correlations with tasks such as reading correspondence and newspapers, ability to sign documents, detect facial features across a room and

Fig. 6. Examples of test targets used in the shape-discrimination charts: (a) a radial frequency pattern without radial modulation and (b) a radial frequency pattern with 4% of radial modulation with a radial frequency of 8 cyc/2π. Investigative Ophthalmology and Visual Science by Zi-Zhong Wang et al., Copyright 2002 by Investigative Ophthalmology and Visual Science. Reproduced with permission of Investigative Ophthalmology and Visual Science in the format Journal via Copyright Clearance Centre.
identify cash, emphasising the important role the resolution plays in the performance of many daily tasks.

It would be expected that habitual acuity would correlate more closely than best-corrected acuity with self-reported visual function. However, a recent report has questioned this assumption and shown that best-corrected acuity was a better predictor of self-rated health than habitual acuity (Wang et al., 2000). Sciley et al. (2002) observed that even in the early stages of ARM when eyes have good acuity patients are more likely to experience difficulty in night-driving, near-vision activities and glare disability as compared to normal controls. In particular, the most frequently reported difficulty in the early stages of the disease is difficulty with night driving, a low-luminance task. Difficulty with night driving was also related to scotopic sensitivity, which supports the hypothesis that rod photoreceptor dysfunction occurs early in the disease process. The profound impact of bilateral severe AMD on vision-related QOL has recently been demonstrated in a group of patients by using the National Eye Institute Visual Function Questionnaire (Cahill et al., 2005); QOL is significantly worse in these patients than that in patients of varying AMD severity and in persons without ocular disease. The study also highlighted the more important NEI-VFQ-25 sub-scales, such as general vision, difficulty with distance tasks and difficulty with near-task sub-scales as these proved sensitive to different levels of VA. A higher level of anxiety concerning vision was also noted when compared with a low-vision group who would have had longer to adapt and come to terms with their vision loss. This is in accordance with several studies, which have highlighted the significant emotional distress and prevalence of syndromal depression associated with the disease (Williams et al., 1998; Brody et al., 2001; Rovner et al., 2002), and the fact that both clinicians and community members often underrate the impact of this disease on health-related QOL (Stein et al., 2003).

The ability of various instruments to detect clinical changes has also been investigated. The summary score from the ADVS instrument and the domain scores relating to daytime driving, near vision and glare disability were found to correlate significantly with ARM severity by Mangione et al. (1999). However, after adjustment of the models for visual acuity, morphological severity was not an independent correlate of reported difficulty with common visual tasks. This was also found to be the case in a study using VF-14 scale; however, when the population was restricted to those with 20/20 vision in the better eye, AMD severity was found to be an independently significant predictor of the VF-14 score after adjusting for visual acuity in the worse eye (Mackenzie et al., 2002).

10. Bilateral late AMD impact on visual function

In normal subjects, the old adage that “two are better than one” appears true. There is a 40–50% improvement in grating CS with a 7–8% increase in the high-frequency cut-off when stimuli are viewed binocularly (Campbell and Green, 1965; Legge, 1984; Zlatkova et al., 2001), with the greatest summation occurring under conditions of reduced illuminance (Home, 1978). Faubert and Overbury (2000) first reported the phenomenon of contrast inhibition when AMD patients view stimuli binocularly. The investigators tested a group of 59 subjects, 49 of whom had AMD and 10 normal participants of similar age range. Almost half of the subjects with AMD had worse spatial CS when recordings were made from both eyes simultaneously when compared with the peak contrast achieved when stimuli were viewed with one eye only. This binocular inhibition was not related to the CS of the better eye or to acuity. The inhibition effect occurred mainly in the medium and lower spatial frequencies that are generally related to tasks, such as orientation and mobility. Valberg and Fosse (2002) confirmed these findings. They used a group of 13 AMD patients with unequal acuities, and again showed that many subjects had a better monocular than binocular contrast function, indicating inhibition of CS in the better eye. This may be due to the stimulation of non-responding retinal areas for binocular viewing. On the other hand, this inhibitory effect is not a feature of resolution. In a study of 2520 subjects over the age of 65 (Rubin et al., 2000), a small binocular summation of approximately 0.03 Log MAR units of DVA was found in those subjects with less than a one-letter acuity difference between eyes, which the authors conceded was of doubtful clinical significance. Interestingly, binocular distance acuity was shown to be able to be predicted with reasonable accuracy (less than a one-letter difference) from the monocular acuity in the better eye.

Doris et al. (2001) examined the relationships between clinical measures of vision and macular pathology, and found that these were more strongly correlated when the study eye was the worse eye. They observed that when not completely depended upon, visual function in that eye (the worse eye) is more closely correlated with the pathology observed in the macula. Whereas when the study eye was the better eye, the relation was less clear, possibly owing to interplay of psychophysical factors, such as retinal reserve. Perceptual filling-in is another visual phenomenon that has been found to occur principally in patients with bilateral scotomas. Cohen et al. (2003) used scotometry to delineate the anatomic edges of the lesion in patients with unilateral and bilateral central scotomas, as well as the perceived scotoma. They found that the perceptual filling-in phenomenon was more likely to occur in the eye with the smaller lesion.

Longitudinal studies have made some interesting observation on the impact to visual function of a patient developing bilateral disease. An improvement in visual acuity in the eye with the primary AMD lesion has been noted to occur in the event of vision loss in the better-seeing eye; this is thought to be due to an improvement in fixation in the worse-seeing eye (Sunness et al., 2000). A similar trend has been noted in patients with a history of
Table 3
Longitudinal studies investigating visual function parameters which may predict neovascular AMD development

<table>
<thead>
<tr>
<th>Study</th>
<th>Average follow-up</th>
<th>No. subjects enrolled</th>
<th>No. subjects progressed to neovascular AMD</th>
<th>Visual function parameters measured</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smiddy and Fine (1984)</td>
<td>4.3 years</td>
<td>71 (bilateral drusen)</td>
<td>8 eyes in 7 patients</td>
<td>Visual acuity photostress test</td>
<td>No correlation with photostress test</td>
</tr>
<tr>
<td>Eisner et al. (1992)</td>
<td>18 months</td>
<td>47 (unilateral nvAMD)</td>
<td>11 eyes (16.5%/year)</td>
<td>s-Cone sensitivity</td>
<td>Strong correlation for dark adaptation time and colour-match area effect</td>
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<td></td>
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<td></td>
<td>Absolute sensitivity</td>
<td>s-Cones good at distinguishing outcome groups</td>
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<td></td>
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<td></td>
<td></td>
<td>Dark adaptation</td>
<td>Summed drusen and atrophic area also good</td>
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<td></td>
<td>Flicker sensitivity</td>
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<td></td>
<td>Rayleigh colour matching</td>
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<td>D-15</td>
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<tr>
<td>Sunness et al. (1989)</td>
<td>45 months</td>
<td>18 (unilateral nvAMD), 7 (bilateral ARM)</td>
<td>1 eye nvAMD</td>
<td>Foveal dark-adapted sensitivity</td>
<td>Foveal dark-adapted sensitivity predicted development of advanced AMD with 100% sensitivity and 92% specificity</td>
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<td></td>
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<td>3 PED</td>
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<td></td>
<td></td>
<td>1 GA</td>
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<tr>
<td>Sandberg (1998)</td>
<td>4.5 years</td>
<td>127 (unilateral nvAMD)</td>
<td>27 developed nvAMD (8.8%/year)</td>
<td>DVA</td>
<td>Independent risk factors for CNV development were slow glare recovery and extent of fundoscopic changes</td>
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<td></td>
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<td>Macular visual field</td>
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<td>Glare-recovery time</td>
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<td>Foveal ERG amplitude</td>
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<td></td>
<td></td>
<td></td>
<td>and implicit time</td>
<td></td>
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<tr>
<td>Mayer et al. (1994)</td>
<td>1.5–4 years</td>
<td>16 (unilateral nvAMD)</td>
<td>7 with unilateral nvAMD converted to bilateral nvAMD</td>
<td>Foveal flicker sensitivity</td>
<td>Flicker sensitivity at 5 and 10 Hz predicted converting eyes from non-converting and healthy older eyes with 100% accuracy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 normals</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Fundus appearance could not discriminate ARM from pre-nvAMD eyes</td>
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</table>
amblyopia, with apparent recovery of visual function in the amblyopic eye over a period of time after the previously normal eye develops visual loss due to advanced AMD (El Mallah et al., 2000).

These studies suggest that the functional status of the fellow eye is an important factor that should be taken into consideration. This has important implications for controlled clinical trials that employ change in visual acuity in the study eye as a primary outcome measure.

11. Predictive markers of nvAMD

Table 3 summarises the longitudinal studies investigating functional risk factors for the development of nvAMD.

Despite substantial variety in follow-up time, patient characteristics and AMD classification, the functional deficits consistently noted to predict conversion to nvAMD appear to be a combination of s-cone sensitivity, flicker sensitivity and dark-adapted sensitivity and glare recovery. Larger-scale studies are required to substantiate these findings, with particular attention to AMD classification and the sub-type of the CNV, which may subsequently develop. Such markers of risk could have considerable value when designing controlled clinical trials of prevention or when longitudinal follow-up is occurring as part of therapeutic trials in subjects with unilateral AMD.

12. Summary and future directions

This review has highlighted the various functional consequences of the alteration in retinal architecture that occurs in early and late ARM (Table 4).

The early detection of nvAMD is becoming increasingly important as new treatments continue to emerge, which are able to minimise disease progression with the potential to arrest visual decline (Comer et al., 2004). To date, there has been a heavy reliance on DVA and it has been used as the outcome measure in both therapeutic, as well as prevention trials. As DVA is insensitive to subtle changes in vision and is a poor marker for progression, rapid, reliable and simple psychophysical methods of monitoring progression from early ARM to AMD are needed. Ideally, the tests would be robust to physiological age-related decline of visual function as well as functional impairment due to medial opacities and other co-existing pathology. Reliable screening tests are also required, and should be inexpensive and easy to perform to facilitate self-monitoring at home.

While a plethora of studies have investigated visual function and dysfunction in early ARM, many of the study samples were not well defined. Recent improvements in retinal imaging, such as ultra-high-resolution optical coherence tomography (Drexler et al., 2003), multi-modal macular mapping (Bernardes et al., 2002) and polarisation-sensitive retinal imaging (Burns et al., 2003) will permit

<table>
<thead>
<tr>
<th>Structural changes that occur in AMD</th>
<th>Functional consequences</th>
</tr>
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<tr>
<td>Increased rod cell loss</td>
<td>Reduced scotopic sensitivity</td>
</tr>
<tr>
<td>Convolution, deflection and shortening of the rod's outer segments</td>
<td>Prolonged dark adaptation</td>
</tr>
<tr>
<td>Abnormalities of the synaptic terminals of the rod's outer segments</td>
<td>Decrease the amplitude of the rod a-wave in the ERG</td>
</tr>
<tr>
<td>Short-wavelength sensitive cone loss</td>
<td>Tritan defects on surface colour tests</td>
</tr>
<tr>
<td>Loss of photopigment reducing the quantum-catching ability of the photoreceptors</td>
<td>Reduced s-cone sensitivity</td>
</tr>
<tr>
<td></td>
<td>Abnormal colour-match area</td>
</tr>
<tr>
<td>Slowed recycling of photopigments</td>
<td>Decrease the intensity of a stimulus on the retina</td>
</tr>
<tr>
<td>Geographic atrophy (photoreceptors can be viable over areas of RPE atrophy)</td>
<td>Reduced photopic sensitivity, visual acuity and contrast sensitivity</td>
</tr>
<tr>
<td>Compromised retinal metabolism</td>
<td>Altered retinal gain</td>
</tr>
<tr>
<td>Collection of blood and fluid under the retina causing surface irregularities</td>
<td>Increase in the time constant of adaptation</td>
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<tr>
<td>Extensive photoreceptor loss</td>
<td>Gradual vision loss</td>
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<tr>
<td></td>
<td>Poor dark adaptation</td>
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<td></td>
<td>Decreased scotopic sensitivity</td>
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<td>Decreased contrast sensitivity</td>
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<td>Scotomas near fixation</td>
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<td>Reduced reading speed</td>
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<td>Reduced kinetic functions such as dark adaptation, glare recovery and flicker sensitivity losses</td>
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<td>Metamorphopsia</td>
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better classification of potential cases and controls in future studies and thus more accurate correlations of structure–function relationships while reducing the possibility of uncontrolled confounding. ARM encompasses a broad morphological spectrum of disease. The substantial variety in presentation, natural history of progression and associated risk factors suggests that several phenotypes of ARM may exist and different patterns of disease progression and functional impairment may reflect distinct underlying aetiologies. In order to investigate this further, longitudinal studies are required and should involve a detailed analysis of macular retinal function (spatial and temporal measures), careful morphological phenotyping (lesion components, classification, extent and location of abnormalities) along with systematic recording of exposure to putative risk factors and genetic profiling in order to achieve a better understanding of the pathogenesis of ARM.

13. Method of literature search

References for this review were identified through a comprehensive literature search of the following electronic databases: MEDLINE, 1966–2005, Science Direct (all years). The literature search was not confined to the English language as non-English language publications were translated. Additional articles, textbooks and abstracts thought relevant were selected from review of the bibliographies of the articles generated from the above search. To ensure the up-to-date nature of our review article, e-mail alerts were set up through Science Direct. The following key words and combinations of these words were used in compiling the search: age-related macular degeneration/maculopathy, visual acuity, contrast sensitivity, colour vision, short-wavelength cone, electrophysiology, flicker sensitivity, rod/cone adaptation, vision-related quality of life, scotopic/photopic sensitivity, macula imaging.

Acknowledgement

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References


Evans, J.R., Fletcher, A.E., Wormald, R.P., 2004a. Age-related macular degeneration causing visual impairment in people 75 years or older in Britain: an add-on study to the medical research council trial of assessment and management of older people in the community. Ophthalmology 111, 513–517.


