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Major review

Acquired color vision deficiency

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ARTICLE INFO

Article history:

Received 1 November 2014
 Received in revised form 6 November 2015
 Accepted 11 November 2015
 Available online 30 November 2015

Keywords:

dyschromatopsia
 color vision deficiency
 acquired color vision deficiency
 color vision testing
 color perimetry

ABSTRACT

Acquired color vision deficiency occurs as the result of ocular, neurologic, or systemic disease. A wide array of conditions may affect color vision, ranging from diseases of the ocular media through to pathology of the visual cortex. Traditionally, acquired color vision deficiency is considered a separate entity from congenital color vision deficiency, although emerging clinical and molecular genetic data would suggest a degree of overlap. We review the pathophysiology of acquired color vision deficiency, the data on its prevalence, theories for the preponderance of acquired S-mechanism (or tritan) deficiency, and discuss tests of color vision. We also briefly review the types of color vision deficiencies encountered in ocular disease, with an emphasis placed on larger or more detailed clinical investigations.

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1. Introduction

Color vision deficiency secondary to ocular or visual pathway disease—known as acquired color vision deficiency—was perhaps the first recorded form of dyschromatopsia.⁸⁶ The English oculist, Dawbeney Turberville, described a case of probable cerebral achromatopsia in a letter to the Royal Society published in 1684.²⁰⁷ A similar—and most probably the same—case was elucidated by the natural philosopher, Robert Boyle, in his treatise *Uncommon observations about vitiated sight*²² in 1688. Although these reports postdate by several centuries Albertus Magnus' description of a patient with probable cone dystrophy, the latter's report makes reference only to hemeralopia.²⁰² The traditional classification of color vision deficiency suggests that congenital and acquired

deficiencies form 2 distinct entities.⁶⁶ Congenital color vision deficiency is said to be present from birth, stable, bilaterally symmetrical, and is thought to affect the entire field of vision. Acquired color vision deficiency, by contrast, may demonstrate progression or regression, may affect one eye or both eyes asymmetrically, and may affect only a portion of the visual field. In contrast to congenital color vision deficiency, acquired color vision deficiency is believed to be highly symptomatic.⁶⁶ Although acquired color vision deficiency may have a higher overall prevalence than congenital color vision deficiency,⁴³ there are limited data. With improved understanding of both the etiology of congenital color vision deficiency and of other congenital cone photoreceptor disorders, a degree of overlap is evident.¹⁸⁴ Acquired color vision deficiency may be classified by the site of pathology or by its

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<http://dx.doi.org/10.1016/j.survophthal.2015.11.004>

clinical characteristics. Although congenital color vision deficiency has a predilection for affecting an individual cone class—and thereby a single subsystem of color vision—such characteristics are far less frequently encountered in acquired color vision deficiency.¹⁸⁴

2. The substrate of color vision

2.1. Receptor

Normal human color vision is trichromatic¹²⁷; that is, any color can be matched by a mixture of 3 judiciously selected primary colors (provided that their wavelength may be varied or that color subtraction is permitted). The physiologic substrate of trichromatic color vision is the cone photoreceptor, of which there are 3 classes: the short- (S-), medium- (M-), and long- (L-) wavelength sensitive cones. The different classes of cone have overlapping, but distinct, spectral sensitivities (see Fig. 1). The peak sensitivities lie at about 419 nm, 531 nm, and at 558 nm for the S-, M-, and L-cones (see Fig. 1).²¹ Under certain testing conditions²⁵—and in certain pathologic states¹⁶¹—rods may influence, or participate in, the perception or discrimination of color. The response of any individual photoreceptor is unidimensional and cannot alone convey unambiguous information about the spectral nature of incident light (the so-called *principal of univariance*). Color vision is derived from a comparison of the rates of quantum catches signaled from the different classes of cone. The S-cones are absent from the foveola, comprise approximately 7%–10% of the cone photoreceptor population based on histologic observation,² and form $5.7 \pm 0.7\%$ (mean \pm standard deviation) of the photoreceptor mosaic imaged *in vivo* about 1° from fixation.⁷² The M- and L-cones share many similarities in terms of their known histology, physiology, and molecular genetics. These cone types comprise the remainder of the cone population, though considerable variability in the L-cone:M-cone ratio occurs among those with normal vision. Adaptive optics imaging suggests a range

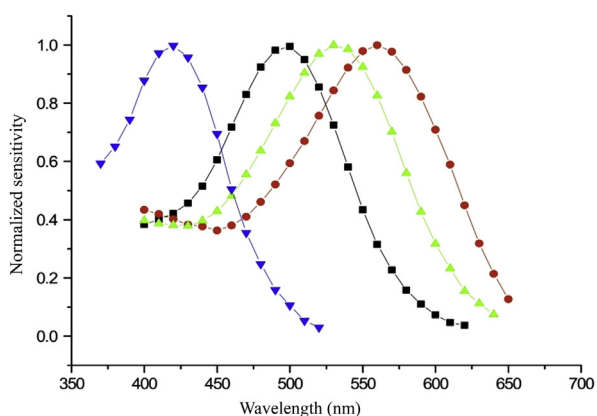


Fig. 1 – The spectral sensitivities of the 3 classes of cone photoreceptor (S-cones, blue inverted triangles; M-cones, green triangles; L-cones, red circles) and of the rods (black squares) plotted against wavelength in nm. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

in males from 1.1:1 to 16:1 (with more extreme ratios favoring M-cones occurring in female carriers of protanopia).⁷² The spectral sensitivity of the photopigments is determined by the protein portion or “opsin.” Opsins are heptahelical proteins that are bound to 11-cis-retinal and are members of the G-protein coupled superfamily of receptor molecules. The M- and L-cone photopigments are coded in an array on the X-chromosome and share a 96% similarity with each other in terms of primary structure, whereas the S-cone photopigment is coded on chromosome 7 and shares 43% identity with the M- and L-cone photopigments.¹⁴¹

2.2. Postreceptor

There is evidence to suggest that the processing of spectral information from the visual scene is conducted via 2 subsystems of color vision that are phylogenetically distinct.¹²⁸ The first, and more ancient, system compares quantum catches in the S-cones to the M- and L-cones. The second, more recent, subsystem is thought to have partially commandeered a system initially specialized for spatial resolution. This is an important point in the context of acquired color vision deficiency as it has ramifications on the anticipated concomitant clinical features.

The S-cones synapse with S-cone bipolar cells and then with at least 4 different types of ganglion cell.¹⁹³ The most extensively studied of these is the small bistratified ganglion cell which receives “on” excitatory input from S-cone “on” bipolar cells with the “off” input derived from the M- and L-cones via diffuse “off” bipolar cells.¹⁰⁷ The details of the remaining ganglion cell types subserving the S-cones are yet to be fully elucidated, though at least one of these cell types receives an inhibitory S-cone input¹⁰⁷ (The existence of such inputs has been a matter of some controversy).⁵⁵ Ganglion cell axons subserving the S-cone system synapse in the intercalated layers of the lateral geniculate nucleus⁷¹ and input into the lower echelons of layer 3 and 4A of the visual cortex.¹⁹³

Spectral information from the M- and L-cones is carried by the midget ganglion cells. The center of the receptive field of the midget cells—at least in the central retina—is drawn from a single cone (via a single midget bipolar cell) and the surround from multiple cones, though there exists some controversy regarding the nature of such inputs (i.e., whether the surround is drawn from cones of a different class or indiscriminately from both).¹⁹³ The midget cells synapse in the parvocellular layers of the lateral geniculate nucleus (3, 4, 5, and 6) which in turn project to layer 4C β of the visual cortex.¹⁹³

Like the responses from individual photoreceptor cells, the response from individual ganglion cells is unidimensional and does not alone convey an unambiguous signal regarding the spectral nature of a stimulus: this is in effect an extension of the principle of univariance. As a consequence, the spatial resolution of color vision is necessarily inferior to that for luminance discrimination.⁵⁵ For small targets, color vision is tritanopic.¹³¹ Although there are fewer reliable data regarding the point discrimination acuity of the M/L-subsystem, other measures suggest that its resolution is superior to the S-cone system,^{30,57} although the magnitude of this superiority is again a matter of conjecture.¹²⁰

3. Abnormal color vision

Disorders of color vision are traditionally classified into congenital and acquired forms. Acquired color vision deficiency has received far less attention than congenital color vision deficiency, which is known to affect as many as 8% of males and 0.5% of females^{182,184} (with considerable variation among populations).¹⁶

Congenital color vision deficiency arises from disorders in the genes coding for the cone photopigments,^{142,221,222} in genes controlling the expression of the cone photopigments,^{140,208,217} in genes coding proteins involved in the phototransduction cascade (cone guanylate cyclase, GNAT2^{3,95} and cone phosphodiesterase [PDE] subunits, PDE6C³¹/PDE6H⁹⁶) or from genes coding for the α - or β -subunits of the cone cyclic guanosine monophosphate-gated cation channels.^{94,97} Congenital color vision deficiency is subclassified by the severity of the defect and the class(es) of cone affected. Anomalous trichromats display trichromatic color vision; however, they will accept color matches that a normal will not. Often, though not always, the converse is also true. Dichromats are able to match any other color using 2 carefully selected primary colors. Finally, monochromats can match any color by adjusting the brightness of a single primary. Under some circumstances, monochromats may display residual color discrimination either through cone-cone interactions in residual or surviving cones or via cone-rod interactions.¹⁶⁰ The various forms of congenital color vision deficiency are summarized in Table 1, and the reader is directed to recent reviews for further information on these conditions and their current and possible future management.^{144,184}

Although acquired color vision deficiency occurs secondary to ocular or visual pathway disease, it is important to note that the causative disease may be hereditary. Just as molecular genetics has divided what clinicians unite, the converse also holds. The causative genes in several forms of congenital color vision deficiency have been implicated in several retinal dystrophy phenotypes. Because of the early processing of color vision in different subsystems, combined with the limited repertoire of responses to pathology, ocular disease tends to cause stereotypical alterations to color vision that lend

themselves to classification.⁸⁵ There are, however, notable exceptions (e.g., color vision deficiency associated with pathology of the visual centers).⁹⁰ Acquired color vision deficiency may be classified by its mechanism or primary site of pathology or by the type of color vision deficiency encountered.

In a recent review of the epidemiology of color vision deficiency, it was suggested that acquired forms affect between 5% and 15% of the population, but this claim appears to be based primarily on level IV evidence (i.e., expert opinion) rather than on large surveys.⁴³ The limited evidence from 2 subsequently published epidemiologic studies in part confirms this claim. One study from Iran using the Farnsworth-Munsell (F-M) D-15 in a population of 5,102 adults aged 40–64 years old suggests a prevalence of 10.1% in those surveyed, though the precise criteria for diagnosis were unclear.⁸¹ Of those diagnosed with acquired color vision deficiency, 66.1% had an acquired tritan deficiency (hereafter referred to as S-mechanism deficiency) while the remainder had acquired red-green deficiency (hereafter referred to as M-L mechanism deficiency). Another smaller North American study¹⁷⁸ using the D-15 and desaturated D-15 in an older population of 865 patients aged from 58 to 102 years (mean, 75.2 years) found an overall prevalence of 20.8% (using a previously described method of scoring²¹⁵ as the criterion for failure). Of those who failed the F-M D-15, 75.6% had an acquired S-mechanism deficiency, with the remainder having either acquired M-L mechanism deficiency or nonspecific loss. The prevalence of acquired color vision deficiency within populations would be anticipated to be influenced by the population tree (older subjects are more likely to have acquired color vision deficiency) and by the means of detection (e.g., studies using the standard F-M D-15 alone would be predicted to underestimate the prevalence of color vision deficiency).

3.1. Classification of acquired color vision deficiency

3.1.1. von Kries

In 1897, von Kries described 3 abnormalities of color matching, all of which may occur in acquired color vision deficiency.¹⁵⁹

1. Increased matching range (i.e., reduced color discrimination)

Table 1 – Summary of congenital color vision deficiency

Deficiency	Cone(s) affected	Inheritance	Prevalence
Anomalous trichromacy			
Protanomaly	L-cones	XLR	1.1% ¹⁸²
Deuteranomaly	M-cones	XLR	4.6% ¹⁸²
Incomplete tritanopia (syn. tritanomaly)	S-cones	AD	See tritanopia
Dichromacy			
Protanopia	L-cones	XLR	1.0% ¹⁸²
Deuteranopia	M-cones	XLR	1.3% ¹⁸²
Tritanopia	S-cones	AD	1 in 500 ²²³
Monochromacy			
M-cone monochromacy	L- and S-cones	Combined XLR and AD	≤1 in 1,000,000 ¹⁸²
L-cone monochromacy	M- and S-cones	Combined XLR and AD	≤1 in 1,000,000 ¹⁸²
S-cone monochromacy	M- and L-cones	XLR	1 in 100,000 ¹⁸²
Rod monochromacy and incomplete achromatopsia	S-, M-, and L-cones	AR	1 in 33,000 to 50,000 ⁸⁶

2. A shifted match caused by an absorption system (i.e., pre-receptor spectral modification)
3. A shifted match caused by an alteration system (i.e., altered sensitivity of the photopigments, either in peak sensitivity or spectral profile).

von Kries' elegant observations can still be used today to form the framework for the taxonomy of acquired color vision deficiency or to explore the mechanism of a particular acquired color deficiency.¹⁵⁹

3.1.2. Köllner

More commonly, however, acquired color vision deficiencies are classified according to the subsystem of color perception chiefly affected. In his exhaustive study of color vision deficiency in ocular and visual pathway pathology, Köllner indirectly spawned the rule which today bears his name.⁹⁹ This "rule" states that retinal disease most commonly results in blue-yellow (i.e., S-mechanism) color vision deficiency while optic nerve disease most commonly results in red-green (i.e., M-L mechanism) deficiency. The clinical utility of this "rule" is questionable, as there are multiple exceptions; dominant optic atrophy, for example, may produce S-mechanism deficiency¹⁰¹ (though this is often not the case)¹⁸⁸ and numerous retinal diseases may cause M-L mechanism deficiency.¹⁸⁷

3.1.3. Verriest

The most widely used classification of acquired color vision deficiency is that of Verriest²¹²: his classification scheme was based on a retrospective analysis of a series of 544 eyes of 476 patients examined with a battery of color vision tests. The latter consisted of both tests of discrimination (Hardy Rand Rittler Plates, F-M D-15 and F-M 100-Hue) as well as tests of matching (Rayleigh equation). He classified acquired color vision deficiency as follows:

1. Type I acquired color vision deficiency is an M-L mechanism (termed by Verriest "red-green") deficiency with a shift in peak spectral sensitivity to shorter wavelengths.

2. Type II acquired color vision deficiency is an M-L mechanism deficiency in which there is relative preservation of the spectral sensitivity function.
3. Type III acquired color vision deficiency is an acquired S-mechanism (termed by Verriest "blue-yellow") deficiency that may be accompanied by a shift in peak spectral sensitivity to shorter wavelengths.
4. Ill-defined or not classifiable.

Verriest's classification system is elaborated in Table 2. Of note, Verriest observed that when acuity is affected by a disease process, M-L mechanism discrimination appears to be concomitantly disturbed. Furthermore, he found that most of the conditions he studied were associated with type III S-mechanism deficiencies. Both these points will be taken up in subsequent sections. Verriest's classification also referred to pseudoprotanomaly and scotopization, each of which may occur in retinal diseases. Pseudoprotanomaly is a form of alteration system characterized by a Rayleigh match in which the subject requires more red in the red-green mixture to match the yellow primary than a normal subject.¹⁹² It is distinguished from the congenital color vision deficiency protanomaly by (generally) a smaller magnitude of mid-matching point shift and by an absence of a significantly aberrant brightness matching function. This defect results from decreased effective optical density of the cone photopigments via reduced "self-screening" (self-screening has the effect of broadening the absorption profile of photopigments).²⁰⁴ The reduction in effective optical density may result either from decreased photopigment concentration and/or from photoreceptor disarray and/or from shortened photoreceptor outer segments. Scotopization refers to intrusion of the rod system under the photopic conditions in which color vision tests are conducted.¹⁵⁵ The exemplar of this phenomenon is rod monochromacy or achromatopsia, and similar phenotypes can be observed at certain stages of other retinal dystrophies. Mesopization is a loosely defined term initially used to describe performance at the F-M 100-Hue in patients with acquired S-mechanism deficiency after it was

Table 2 – A summary of the Verriest classification of acquired color vision deficiency: His original nomenclature is retained

Type	Severity	F-M 100-Hue axis	Rayleigh match	Exemplars
No defined axis	Trichromatic	Mild red-green and tritan	Increased Rayleigh matching range	Macular cysts and toxic amblyopia
Type I Red-green	Monochromatic	No color discrimination	Variable	End-stage of type I-III
	Trichromatic	Mostly between protan and deutan	Protanomalous	Choroidal atrophic processes
Type II Red-green	Dichromatic	As above, then between deutan and tritan	First protanopic then scotopization	Stargardt's
	Trichromatic	Mostly between protan and deutan	Mostly deuteranomalous	Usher's; optic nerve disease, optic neuritis, toxic amblyopia, optic atrophy, chiasmal disorders, peripheral chorioretinal degenerations, angioid streaks, myopic choroidal degeneration, RRD, CSR, and chorioretinitis
Type III tritan	Dichromatic		Deuteranopic	
	Trichromatic	Tritan	Mostly protanomalous	Vascular retinopathies and papilledema, glaucoma, dominant optic atrophy
	Dichromatic	Tritan (eventually tetartan ^a)		

CSR, central serous retinopathy; RRD, rhegmatogenous retinal detachment.

a An antiquated term for a hypothetical defect of the "yellow mechanism" which could theoretically also occur as a congenital color deficiency through a combination of tritanopia and deuteranomaly.

noted that performance of those with normal color vision made similar arrangements under mesopic conditions.⁴⁰

3.1.4. Marré

Marré posited that the type of acquired color vision deficiency encountered was a function of fixation (the “fixation-eccentrization” theory). This classification system was based on empirical observations of threshold sensitivity (using a Wald’s²¹⁶ modification of a 2-color technique first introduced by Stiles^{194,195}) in those with acquired color vision deficiency and in normal subjects at various retinal eccentricities.¹¹⁸ Marré observed that eccentric fixation could occur in patients with decreased acuity and further observed that in normal subjects, perifixation threshold sensitivity measures mediated by the M- and L-cones decline while those mediated by the S-cones improve. If central fixation is disrupted by a pathologic process, the “red and green” (i.e., L- and M-cone) color vision mechanisms (CVMs) will automatically be affected whereas the “blue” (i.e., S-cone) CVM may show a paradoxical improvement or, if affected by the pathology, may show falsely “normal” sensitivity. Conversely, if fixation is not disrupted, an S-mechanism deficiency is more likely to occur.

This theory is conceptually attractive because it appears to explain the apparent selectivity of color vision deficiency based solely on the portion of the visual field affected. Certainly, observations regarding fixation may account for some alterations, but are not—as Marré and Pinckers later noted¹⁵⁷—wholly satisfactory. First, the claimed decrement in threshold sensitivity from fixation to 6° for the L- and M-cone mechanisms of 5.2 dB and corresponding increase of 4.0 dB for the S-cone mechanism may be an overestimate.¹⁵⁷ The seminal report on the peripheral sensitivity of the CVMs by Wooten and Wald found that the total increase in sensitivity for the S-cone mechanism relative to the loss in sensitivity for the M- and L-cone systems was about 5 dB at an eccentricity of 7°. ²²⁸ Furthermore, they found that the differential effect is abolished once absorption by macular pigment is taken into account, suggesting a likely interindividual variability in the effect (mirroring the known individual differences in macular pigment optical density).⁶⁵ A second, and related point, is that such observations regarding fixation and the CVMs are unlikely to account for changes in color discrimination at certain color vision tests, which may be relatively robust to changes in fixation.¹⁸⁵ Third, the effect is likely to be highly dependent on the stimulus size used, with smaller stimuli favoring this difference. Finally, the instrumentation available to Marré at the time would not have allowed for accurate assessment of habitual fixation patterns in her subjects. Nevertheless, such objections downplay the important empirical observations Marré made regarding the pattern of fixation and preponderant acquired color vision deficiency.

3.1.5. Pinckers

Pinckers took up and elaborated on the findings of Verriest in an attempt to use the level and topographic location of pathology (the “depth-localization” theory) to account for the observed color deficiency in a variety of disease states. He suggested that disease of the choroid and retinal pigment

epithelium resulted in nonselective loss of rods and cones and that inner retinal or optic nerve disease never demonstrated the stigmata of cone damage and loss (pseudoprotanomaly and scotopization). Peripheral photoreceptor disease, he suggested, tended to cause a type III acquired color vision deficiency (see Fig. 2), whereas photoreceptor disorders involving the central retina tended to cause a type I acquired color vision deficiency leading ultimately to scotopization. It will be noted that there is some overlap in the localization part of Pinckers’ “depth-localization” classification scheme and Marré’s “fixation-eccentrization” theory: indeed, Marré and Pinckers later reconciled their classification systems.¹⁵⁷ The implicit assumption of Pinckers’ treatise is that falling acuity is associated with eccentric fixation and this, for the reasons elaborated in the previous section, leads to an M-L mechanism deficiency.¹⁵⁸ Although this may account for some of the changes observed in CVMs in some patients, another explanation that does not rely on eccentricization can also explain the relationship between disturbance of acuity and acquired M-L mechanism deficiency. This is dealt within the following section.

3.1.6. A current interpretation

An interpretation informed by our current knowledge of the apparatus of color vision would suggest a physiologic explanation for Verriest’s original observations such as the association between loss of visual acuity and loss of M-L mechanism color discrimination. Losses in visual acuity imply impairment of the midget cell pathway and its associated apparatus. This system is specialized for what has been described by some as the “main business” of vision—spatial discrimination.¹²⁹ Superimposed on this system is a mechanism specialized for red-green color discrimination. Diseases affecting this pathway will therefore be generally expected to affect both spatial vision and red-green color discrimination. Conversely, diseases selectively affecting the S-cones and their pathways would not be anticipated to have any effect on acuity or luminance contrast detection. Again, the relationship between decreased acuity and M-L mechanism deficiency is not invariable, nor should a precise relationship be anticipated as no clinical test determines the spatial acuity of color vision. First, violations can occur *via* concomitant disease; for example, many retinal dystrophies are accompanied by media opacity. Second, pseudoprotanomaly may occur in the presence of normal visual acuity.^{192,206} Third, specific congenital disease mechanisms that are generally classified as “cone dysfunction syndromes” illustrate that under certain conditions this relationship may break down. For example, patients with M-cone opsin mutations have been described in which there are optically empty cones with deuteranopic color vision, but normal acuity.²⁸ Such phenotypes can be explained by the observation that “normal” visual acuity can be supported by a “normal” complement of L-cones (with concurrent loss of all M-cones, i.e., with roughly 70% of the total normal cone complement). Conversely, patients with a rare cone dysfunction phenotype known as oligocone trichromacy²⁷ may demonstrate reduced acuity (usually about 20/40–20/80) with “normal” color vision.¹²² Imaging studies suggest that this rare phenotype may result in some patients from a

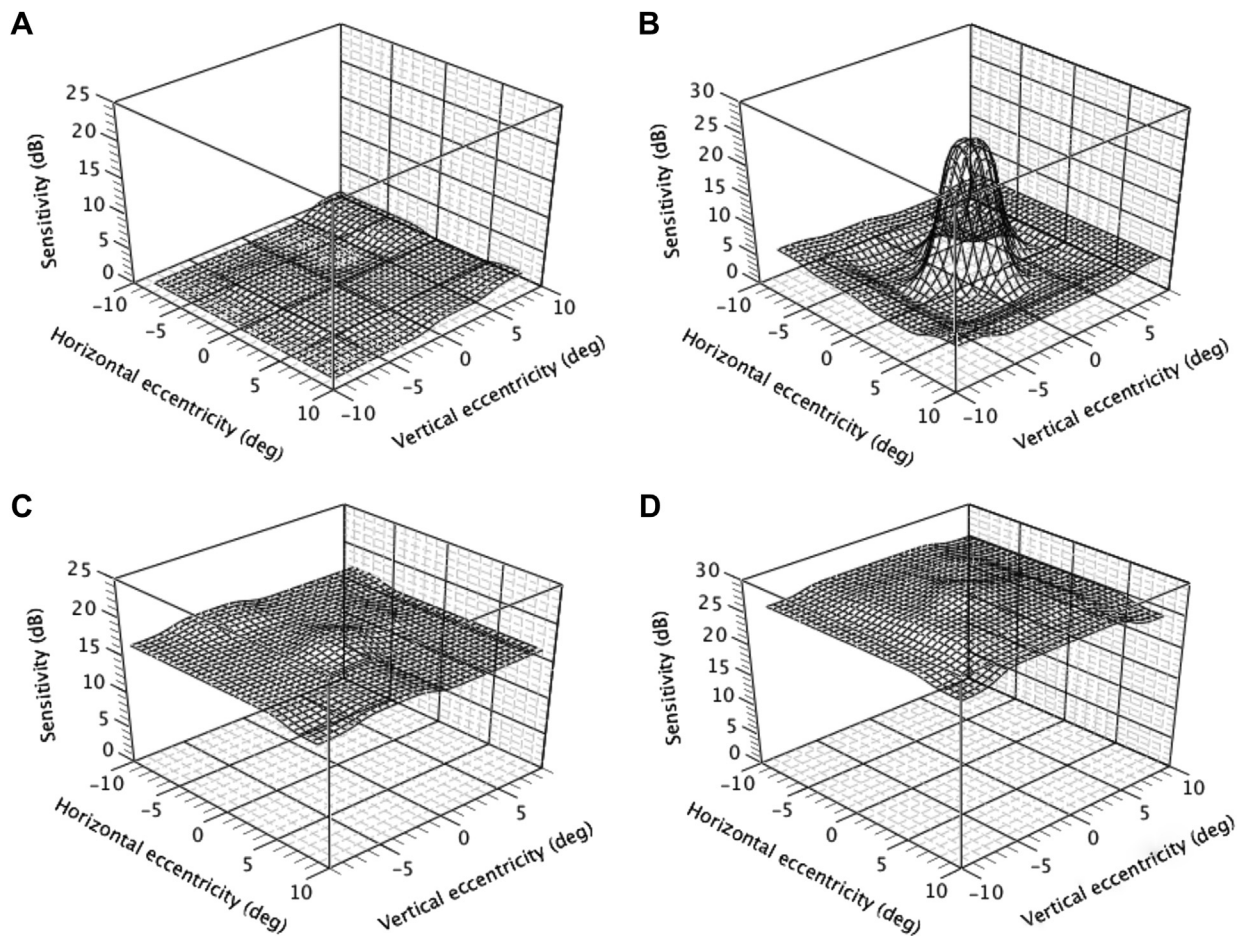


Fig. 2 – Humphrey 10-2 visual field plots for a patient with autosomal recessive progressive cone dystrophy demonstrating behavior predicted by the Marré and Pinckers model. The x and y axis depict eccentricity in degrees and the z axis sensitivity in dB. **A:** The top left plot shows sensitivities for Goldmann size V blue (460 nm) stimulus on a 100 cd.m^{-2} yellow background, whereas **B:** the top right shows sensitivities for Goldmann size III red (dominant wavelength 650 nm) targets presented on a 10 cd.m^{-2} white background. Equivalent plots for normal observers are plotted on the bottom row (**C:** left blue-on-yellow; **D:** right red-on-white). Despite evidence of a significant reduction in L- and M-cone mediated sensitivity in the periphery (as evidenced by reduced sensitivity for red-on-white perimetry) the patient with cone dystrophy demonstrated an isolated S-mechanism/tritan deficiency at clinical color vision tests (consistent with widespread loss of the S-cone mechanism).

decrease in the normal complement of cones and in others from presumed dysfunction in a normal complement of cones.¹²⁵ In both mechanisms, the disease causes dysfunction such that acuity is disrupted, but not color discrimination on standard clinical color vision tests. By way of example, a 20/80 letter subtends $20'$, of which $4'$ is deemed the critical detail size, whereas clinical color vision tests use targets of about 1.75° or more, over which enough functional cones may be recruited to demonstrate reasonable color discrimination. Not all these subjects, however, have “normal color vision.” Even those who are able to pass standard clinical tests of color vision appear to have decreased color discrimination at other color tests,¹²⁵ such as that described by Regan and colleagues.¹⁶⁶ Finally, some patients with this condition—such as the patient with normal cone density described by Michaelides and colleagues—also manifest nystagmus, which may contribute to the asymmetry in visual acuity and color vision findings.¹²⁵

3.2. Why is S-mechanism–acquired color vision deficiency more common than acquired M-L mechanism deficiency?

In contrast to congenital color vision deficiencies,²²³ acquired color vision deficiency commonly affects S-cone mediated discrimination, and recent epidemiologic surveys suggest that acquired color vision deficiency affecting the S-mechanism outnumbered those affecting the M-L mechanism by at least 2 to 1.^{81,178} Several hypotheses have been proposed to account for the apparent “vulnerability” of the S-mechanism. Different single, or combinations of multiple, mechanisms may contribute to type III defects in certain disease states.

3.2.1. The pseudoproblem hypothesis

This hypothesis is based on the observation that certain tests of color vision are inherently more likely to reveal S-mechanism deficiency. Exemplars cited in an article of a discussion of

the International Research Group on Color Vision Deficiencies allude to both the F-M D-15 and F-M 100-Hue as culprits.¹³⁰ In fact, the F-M D-15 is less likely to demonstrate S-mechanism deficiency than M-L mechanism deficiency because of the large chromaticity difference between the pilot cap and cap 15, thus offering the subject fewer opportunities to make tritan crossings (see the following). A similar phenomenon has been observed to occur with the City University Test (CUT; which is a derivative of the F-M D-15). It is true, however, that normal trichromats make more errors in the region of caps 40–50 when performing the F-M 100-Hue test.¹⁶¹

3.2.2. *The scarcity hypothesis*

This hypothesis supposes that, if a fixed proportion of all cone types are lost, the effect will be greatest for the S-cones because of their paucity.¹³⁰ Similar arguments are proposed for the S-cone pathways. Although such a hypothesis might not initially seem consistent with classical signal detection theory, where likelihood of detection is considered proportional to the square root of receptor number, it might be supposed that a critical number of receptors are required to generate a reliable signal and that this number is fractionally higher (but not necessarily absolutely) for the S-cone system.¹⁹⁹ The physiologic breakdown of color discrimination for small or fine targets gives us some clue; small field tritanopia exists for targets at, or smaller than, about 15'.²²⁶ No such effect has been demonstrated to date for the M-L mechanism, although the experimental paradigms previously used to investigate wavelength discrimination for small targets (1.5') did not even elucidate small field tritanopia because fixation was not controlled.¹¹ If we assume that color discrimination for small targets scales in proportion to cone subtype resolution for gratings^{30,57,120} then the chromatic point resolution of the M- or L-mechanisms is at least 1.67 times finer than for the S-cone mechanism. Assuming that the area of point resolution (for circular or square targets) represents an area containing the minimum number of detectors required to make color discriminations, then the most conservative estimate suggests the M-L mechanism could theoretically make do with 2.8 (i.e., 1.67²) fold fewer cones. This rough calculation should be taken with a grain of salt as it makes several assumptions in addition to those already mentioned. It assumes that the remaining cones and their postreceptor connections are normally functional, that topographic variations in their subtype ratios are insignificant, that summation coefficients over the areas are constant, and it ignores prereceptor filtering. Nevertheless, and as noted previously, M-L mechanism color discrimination is retained at stimulus sizes where small field tritanopia occurs, thus providing some semi-quantitative support for this observation. A variation of the scarcity hypothesis points to the central absence of S-cones within the foveolar region: should a pathologic process affect the juxtafoveolar area, a selective S-mechanism deficiency could ensue with comparatively less S-cone loss. Such a mechanism has been observed in some diabetics.⁴¹ This theory could also be invoked to explain why some patients with the same condition may display differences in M-L mechanism discrimination as a consequence of the disease: patients with extreme L-cone:M-cone ratios would be anticipated to be especially susceptible to acquired M-L mechanism

deficiency. Thus in the context of retinal disease, generalized cone loss in a patient with the “normal” L-cone:M-cone ratio might result in S-mechanism deficiency. While in patients with highly biased ratios, there might be concomitant acquired M-L mechanism deficiency.

3.2.3. *The vulnerability hypothesis*

In addition to being scarce, there are physiologic and histologic differences between the S-cones and their pathways and the other cone classes and their pathways. The vulnerability hypothesis supposes that these peculiarities render the S-cones more vulnerable to pathologic processes.⁷⁴ There is indirect evidence from psychophysical data to support such a hypothesis in the case of diabetes and retinitis pigmentosa.^{59,74,198} Furthermore, there is histopathologic evidence to suggest that the S-cones are selectively affected in certain diseases, such as diabetic retinopathy and retinal detachment.^{34,147} Similarly, it has been suggested that the koniocellular system may be more vulnerable to glaucomatous optic neuropathy when compared to the midget ganglion cell pathway, though this is a matter of conjecture.¹⁷⁴

3.2.4. *The reduced redundancy hypothesis*

This hypothesis is based on the observation that the S-cone system is devoted almost exclusively to the sense of color, with little contribution to spatial and temporal resolution and contrast detection. Certain tests of the M- and L-cone subsystems (e.g., testing the “red” and “green” CVMs using the Wald-Marré technique) might therefore be anticipated to be less likely to be affected by pathologic processes because of detection—and therefore built-in redundancy—by a number of mechanisms.¹³⁰ Careful experimentation, such as the use of silent substitution techniques, should overcome this problem.

3.2.5. *The M- or L-subsystem input hypothesis*

The S-mechanism relies on a comparison of quantum catches from the M- and L-cones to the S-cones,^{34,147} making it inherently reliant on M- and L-cones. This renders the S-cone mechanism vulnerable to loss of M- and L-cones as well as to loss of S-cones. Although this hypothesis expresses what is in essence a truism, in practice severe loss is probably required for this pathophysiologic mechanism to have a perceptible effect on S-mechanism discrimination at clinical color vision tests.^{124,185} Indeed, patients with selective and profound losses of the M- or L-cones have been described in which there is no concomitant loss of S-mechanism discrimination; for example, patients with S-cone monochromacy are typically able to make discriminations along a tritan line.¹⁸⁵ Furthermore, this mechanism should not adversely affect S-cone mediated detection tasks, such as short wavelength automated perimetry (SWAP).¹⁸⁵

3.2.6. *Aberrant adaptation hypothesis*

The aberrant adaptation hypothesis supposes that certain tests place the S-cone system at an operational disadvantage. Examples include using yellow high-luminance backgrounds to test the Stiles π_1 mechanism. Although the law of adaptive independence suggests that such fields should not significantly affect S-cone mediated sensitivity, they in fact do, as is

evinced by the phenomena of combinative euchromatopsia¹⁶² and transient tritanopia.¹³⁴ Both are thought to occur at a postreceptoral site that sets the gain of the S-cone pathway.¹³¹ S-cone sensitivity is proposed to be optimal for neutral backgrounds that leave this mechanism in the middle of its operating range. Adaptation to yellow backgrounds suppresses this mechanism initially, after which further adaptation is supposed to bring it again to the center of its operating range.¹³¹ This hypothesis assumes either a faulty restorative mechanism or a decreased operating range. Although similar effects can be demonstrated for the M- and L-cones, they are comparatively modest.¹³³ Therefore, asymmetry in departure from adaptive independence may account for some of inconsistencies between different tests. For example, some subjects with acquired color vision deficiency may demonstrate very profound reductions in S-cone sensitivity (reportedly up to 2 log units) when assessed using intense yellow backgrounds, and yet, they may demonstrate normal tritan discrimination at clinical color vision tests.¹³⁰

3.2.7. Mesopization (“filter effect”) hypothesis

The mesopization (“filter effect”) hypothesis was first applied to the color vision deficiency in glaucoma after it was observed that glaucomatous individuals made similar F-M 100-Hue errors to those made by normal subjects under mesopic conditions.⁴⁰ Subsequent investigation, however, has suggested that this particular observation reflects an inherent bias in the F-M 100-Hue (see point 1).⁴⁰ Taking up a related argument, Kalloniatis and Harwerth observed that many experimental paradigms use background intensities which adapt the M- or L-cone mechanisms such that Weber’s law holds while simultaneously placing the S-cone mechanism in a state of adaptation in which it will not display such behavior.⁸⁸ This places the S-cone mechanism at an adaptational disadvantage such that a “filter mechanism” (such as decreasing the size of the eye’s effective entrance pupil) would cause a disproportionate loss of sensitivity in S-cone mediated detection tasks. This led them to propose a “filter effect” hypothesis for S-mechanism deficiency secondary to retinal disease. Although this mechanism could account for discrepancies between increment threshold paradigms and clinical color vision tests, it cannot explain the preponderance of S-mechanism deficiencies at clinical tests of color vision, such as the F-M 100-Hue.⁶⁰ Furthermore, Kalloniatis and Harwerth themselves found that such a mechanism did not wholly account for S-cone-mediated sensitivity losses in the animal model of blue-light phototoxicity used to test their theory.⁸⁸ Nevertheless, theirs is an astute observation and may account for some discrepancies between increment threshold testing and clinical color vision testing.

3.2.8. Absorption mechanism hypothesis

The absorption mechanism hypothesis states that many ocular diseases are associated with changes in prereceptoral filtering. For example, many retinal dystrophies may be associated with cataract. A prereceptoral mechanism appears to contribute in part to the S-mechanism deficiency encountered in diabetic eye disease, which is known to be associated with lens yellowing.¹¹⁰ Although certain cataracts may cause an induced S-mechanism deficiency through an absorption mechanism, this

does not hold for all forms of cataract. For example, patients with retinitis pigmentosa and other retinal dystrophies commonly develop posterior subcapsular cataract, which would not alone be expected to cause color vision deficiency.

4. Tests of acquired color vision deficiency

Tests of color vision may be broadly categorized into tests of discrimination, of matching, or of detection.

4.1. Tests of discrimination

4.1.1. “Pseudoisochromatic” plate tests

Pseudoisochromatic plate tests rely on known characteristics of color vision deficiencies to detect and diagnose patients with dyschromatopsia. The first successful plate test was produced by Stilling, who bypassed the confounding problems of edge and luminance artifacts that had previously provided impediments to the production of effective plate tests. He did this by using 2 key innovations.¹⁶⁶ The first was to make both the figure and the background discontinuous by breaking each up into a number of discrete elements, negating the possibility of edge artifacts. The second was to make each element differ randomly or pseudorandomly in lightness (from its neighbors), so that the need to produce isoluminant pigments was overcome. It is still important that the luminance of the elements composing the figure, on average, is close to that of the background; a 5% (or greater) difference in lightness may lead to the figure being detected by luminance cues alone.¹⁶¹ A typical Stilling-type array consists of circles, sometimes of varying size, that form both the target and the background. The subject “assembles” the target by perceptually grouping certain elements of the array by color. All Stilling-type tests rely on this principle. The color of the array may be selected such that a target may only be seen by normal subjects (vanishing plates), or only seen by subjects with color vision deficiency (hidden plates), or seen differently by subjects with color vision deficiency (transformation and diagnostic plates). The main advantage of Stilling-type tests is that they are quick and easy to administer. For example, certain editions of the Ishihara plate test are capable of rapidly and efficiently screening for M-L mechanism deficiency.³⁸ The disadvantage of Stilling-type tests is that they do not readily lend themselves to differentiating types of M-L mechanism deficiency, and they cannot reliably distinguish between anomalous trichromacy and dichromacy.

There are variations in the design of plate tests, and these include the type of color vision deficiency the test has been designed for, the form of the figure, and the perceptual effect for the color deficient.

The Ishihara plates were first developed in 1917 for screening M-L mechanism deficiencies and are probably the most popular color vision test ever made. The Ishihara plates efficiently identify those with congenital M-L mechanism color vision deficiency.^{15,18} Their usefulness in the context of acquired color vision deficiency is severely limited. First, they are poor at quantifying the severity of color vision deficiency. Second, they make particular assumptions regarding the color confusions or perceptual grouping of those with color vision

deficiency. This raises 2 difficulties. The most commonly encountered acquired defect of color perception is S-cone mechanism deficiency, which the Ishihara test cannot detect. Second, the test may be defeated by a patient with an acquired color vision deficiency who also has a highly aberrant spectral sensitivity function. Nevertheless, it is common to see these plates being used in an attempt to quantify acquired color deficiency in many clinics; however, the test may justifiably be used in conjunction with Sahlgren's saturated test (SST) in the assessment of acquired color defects.⁵⁰

The standard pseudoisochromatic plate test seeks to address some of the shortcomings of the Ishihara plate test and is comprised of 2 series of tests: the first is designed to detect and diagnose congenital color vision deficiency and the second detects acquired color vision deficiency. The tests, as a combined series feature protan, deutan, tritan, and "scotopic" plates (the latter are used to detect "scotopization"). The first series is reported to be reliable in differentiating color deficient from color normal subjects.⁷³ The second series has been shown to be slightly more sensitive than the first for detecting congenital M-L mechanism deficiency.⁷⁶ False positive tritan diagnoses are frequent with the second edition.¹⁰⁴

The American Optical Hardy Rand Rittler (AO H-R-R) test has been published in 4 editions. The original test included plates for protan, deutan, tritan, and tetartan deficiencies and also featured plates with different chromatic separations between the figure and background in an attempt to quantify the magnitude of the color deficiency. Its advantage over the Ishihara test in the context of acquired color vision deficiency is the inclusion of plates designed to test for S-cone mechanism defects. A recent comparison of the fourth edition of this test and the Ishihara test suggests that the AO H-R-R is superior in the detection and diagnosis of acquired color vision deficiency in optic neuropathies.⁷⁸ Similarly, the test was found to outperform both the Ishihara test and the desaturated D-15 test in the assessment of patients with cone dystrophy.²⁰³

The Berson plate test was designed specifically for differentiating S-cone monochromatism from rod monochromatism¹³ and has limited clinical utility given that other more readily available tests make similar distinctions.¹⁸⁵ The test comprises 2 demonstration plates together with 4 test plates. Each test plate consists of 3 blue-green arrows and 1 blue-purple arrow (the subject's task is to identify the latter). Rather than using luminance or lightness noise, this test matches the arrows for scotopic lightness. This means that any subject with a nonscotopic spectral sensitivity function should pass the test based on luminance cues alone. Although the test can successfully identify S-cone monochromats from rod monochromats,⁶² Pinckers has shown that it cannot differentiate between S-cone monochromats and some progressive cone dystrophy patients.¹⁵⁶

4.1.2. Ordering tests

The F-M 100-Hue test was designed by Farnsworth and originally consisted of 100 disks of Munsell paper.⁴⁶ The subject's task was to order the disks in a gradual progression in color. After preliminary experiments, 15 disks were removed from the test to provide it with improved uniformity in terms of perceptual spacing between adjacent caps. The disks used in the test are mounted in black-bottle tops, each having a

central circular aperture measuring 13 mm in diameter, through which the Munsell paper may be viewed. The viewing distance is not specified, but is usually 40 to 50 cm (and therefore the corresponding angular subtense of the aperture is 1.79° to 1.44°). The Munsell papers used in this test have a value of 5, and a chroma of 4. The caps are organized into 4 boxes; the first consisting of 22 caps, and the remainder of 21 caps. To perform the test, the subject is instructed to arrange the colors in each box so that they form a gradual progression. The subjects' ordering is then scored and charted on a polar plot (see Pokorny and colleagues¹⁶¹ and Dain³⁸ for a review of scoring methods); other scoring methods such as Kitahara's Fourier analysis⁹³ and Vingrys and coworkers' "moment of inertia" analysis²¹⁵ have been used to score the F-M 100-Hue. These offer the advantage of quantifying overall discrimination, type of loss, and selectivity.

The F-M 100-Hue is often considered the test of choice in the detection and diagnosis of acquired color vision deficiencies. The principal reason for such a view is that the test assumes nothing about the color vision of the subject performing the test, who may demonstrate nonclassical "confusion axes."⁴⁹ A further advantage sometimes cited is that it may elucidate unipolar losses in discrimination, though such losses may owe more to artifacts of the test than the pathophysiology of acquired color deficiency.⁴⁹

The D-15 test was designed to dichotomize the color normal from the color deficient subject⁹³ (hence the designation "D").⁴⁶ This test, like the F-M 100-Hue, originally consisted of more caps, but their number was reduced to provide more consistent spacing in chromaticity. The test consists of a total of 16 caps that are similar in design to those of the F-M 100-Hue. The subject's task is to arrange the colored caps so that they appear to form a gradual progression in color, beginning with the pilot cap (which is in a fixed position). Unlike the 100-Hue test, patients may place colors from opposite sides of the hue circle next to one another in this test. The F-M D-15 is assessed visually by plotting the subject's arrangement graphically: subjects with congenital color defects tend to place the caps in a characteristic order (see Fig. 3), and the test may be scored dichotomously (pass vs fail) using various criteria,¹⁷ or quantitatively.²¹⁵ In addition to the classical confusion axes, there is a distinct scotopic arrangement displayed by those with rod monochromatism or scotopization, where the apparent axis of confusion lies between the tritan and deutan axes. S-cone monochromats, by contrast, demonstrate apparent M-L mechanism confusion axes (see Fig. 3). The test tends to favor M-L mechanism confusions as a result of the color spacings used in the test (There is a large gap in chromaticity between the pilot cap and 15, thus limiting the opportunities for tritan crossings). The F-M D-15 remains a popular test as it is easy to administer, can detect a wide variety of color defects, and because it is suitable for assessing acquired color vision deficiencies. Like the F-M 100-Hue, the D-15 is not a particularly good screening test. Depending on the criteria used for failure,^{39,46} the test will provide a false negative diagnosis for around one-third of all patients with congenital color vision deficiency.³⁹ This feature of the D-15 is sometimes seen as an advantage as it has been argued that the test is useful for purpose of vocational testing because it will pass those with color vision deficiency who are considered "color safe."³⁸ The

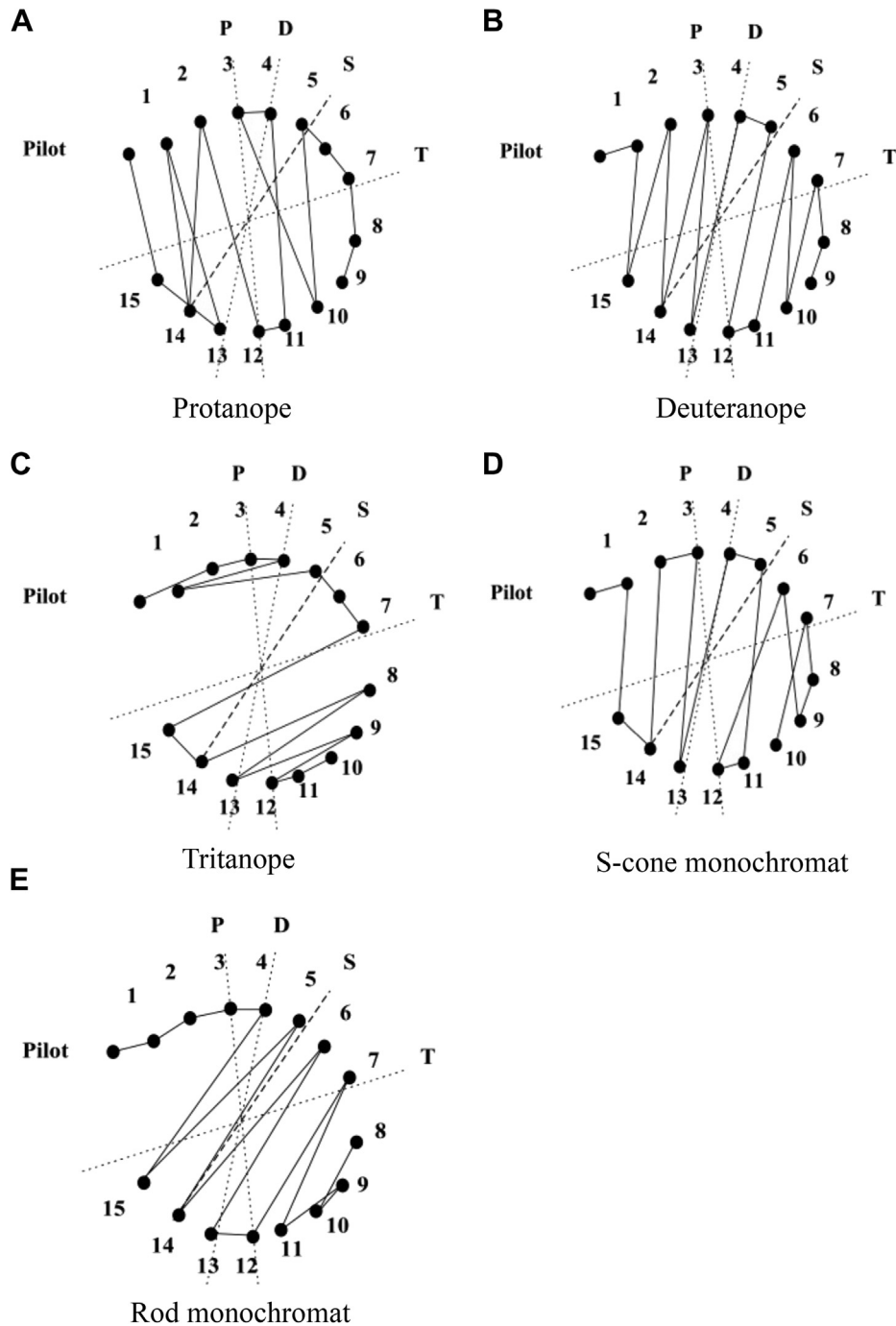


Fig. 3 – D-15 arrangement plots of patients with A: protanopia (top left), B: deuteranopia (top right), C: tritanopia (middle left), D: S-cone monochromacy (middle right), and E: rod monochromacy (bottom).

test will fail all those with dichromatic vision.⁷⁰ An enlarged version of the test (the “PV-16”; Lea-Test Ltd., Helsinki, Finland) in which the colored disk diameter is about 2.5 times the standard size is available for testing patients with low vision. Desaturated versions^{1,63,105} have been also developed in an effort to improve test sensitivity.^{1,63,105} The F-M D-15 also forms the basis of the City University Test (CUT), whose main recommendation is that it is perhaps more convenient to perform.¹⁹ The CUT’s principal disadvantage is that it assumes the color confusions likely to be encountered, thereby losing

some of the advantages of the D-15 in assessing those with acquired deficiency.

The Mollon-Reffin test is a saturation discrimination type test.¹³² The caps used in this test are of a similar design to those used in the D-15 and F-M 100-Hue tests. The test features a series of caps that lie along protan, deutan, and tritan lines. In addition, there is one demonstration cap, which does not lie along a dichromatic confusion axis. The rest of the caps are all neutral but have a varying lightness (there are a total of 9 gray caps). The examiner places one colored cap among a

group of neutral caps and asks the subject to identify the cap that is colored. The colored caps vary in their saturation, so discrimination along the 3 cardinal axes can be assessed. Although the test is quick and easy to administer, like many pigment-based tests, it cannot always successfully differentiate protan from deutan defects. Similarly, it cannot precisely differentiate dichromats from anomalous trichromats.¹³² An enlarged version of the test has been developed for use in patients with low vision.¹⁸⁵

Sahlgren's Saturation Test (SST) was developed specifically for use in patients with acquired dyschromatopsias and consists of 12 caps similar in design to those used in the F-M D-15 and F-M 100-Hue tests: 2 caps are neutral, 5 are greenish blue, and 5 are bluish purple.⁵⁰ The subject's task is to sort the colored caps from the neutral. A score is derived by summing the saturation of the caps that are grouped with the neutral caps. When used in conjunction with the Ishihara test, the SST may help to distinguish congenital from acquired color deficiency.⁵⁰

4.2. Tests of matching

4.2.1. Rayleigh match

The Rayleigh equation was first described by Lord Rayleigh in 1881 and is based on metameric matching principles.¹⁶⁵ The equation is usually obtained by mixing monochromatic 670 nm (red) and 546 nm (green) light to obtain a match with light of 589 nm (yellow). Because these primaries lie at wavelengths to which the S-cones are extremely insensitive, the match depends (for the normal trichromat) on the absorption characteristics of the M- and L-cones.²⁰⁵ The object of the Rayleigh match is to determine the range of red or green primary mixtures that can be matched in color to the yellow primary. Those with X-linked dichromacy are able to match both the red and green primaries to the yellow merely by altering the latter's luminance. A protanope's matching function relies solely on the rate of quantal absorption by the M-cones, and a deuteranope's matching function relies on the rate absorbed by the L-cones. If we plot a protanope's and deuteranope's yellow luminance settings versus the red/green ratio, this will graphically represent the quantal absorption of the M- and L-cones, respectively (see Fig. 4). A normal trichromat will be able to obtain a color match only when the quantum catches in each of the cones is equal for the test (i.e., yellow) and the mixture (i.e., red/green mixture) lights: this is about where the protanope's and deuteranope's yellow brightness matching lines intersect (with variations in midmatching point depending on the λ_{\max} and optical density of the M- and L-cone photopigments).²⁰⁵ Those with rod-dominated spectral sensitivity functions will make brightness matches resembling those of a rod monochromat (see Fig. 4).

Although traditionally considered a test for congenital color vision deficiency, the Rayleigh equation is also an important tool in the assessment of acquired color vision deficiency.¹⁷¹ It remains the test of choice for detecting and diagnosing M-L mechanism deficiencies; it will separate protans from deutans, and anomalous trichromats from dichromats. In addition, it is possible to diagnose other phenotypes with the Rayleigh equation, including pseudoprotanomaly, and extreme anomalous trichromacy.¹⁷¹ It is also possible to determine suspect rod-like luminosity functions, and if variable field sizes are

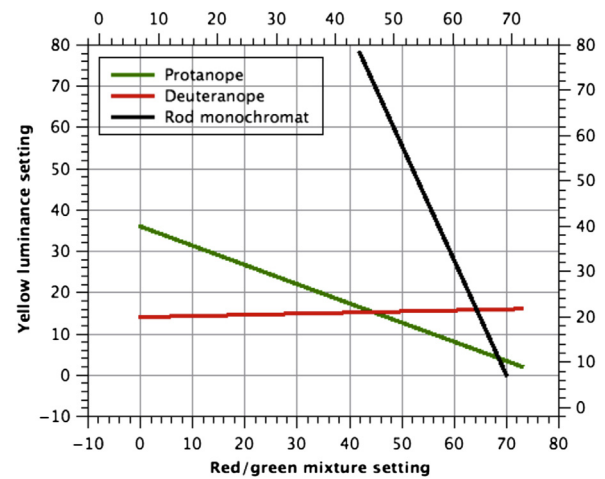


Fig. 4 – Yellow luminance setting versus red-green ratio for protanopic (green line), deuteranopic (red line), and rod monochromat (black line) subjects on the Nagel I anomaloscope. A normal subject's mid-matching point is predicted by the intersection of the protanopic and deuteranopic matching functions. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

used, to distinguish between (some) recessive achromatopsia phenotypes (incomplete achromats with residual M- or L-cone function have predicted midmatching points at the intersection of a rod monochromat's brightness matching function and those of protanopes and deuteranopes, respectively).¹⁸⁵ A similar phenomenon may be observed in patients with scotopization from acquired color vision deficiency (e.g., in Stargardt's disease).¹⁶¹

4.2.2. Tritan matches

Obtaining a satisfactory tritan matching function has proven difficult for 2 principal reasons. First, such matches are by necessity trichromatic (in contrast to the Rayleigh match). Second, there is wide interindividual variation in the pre-receptoral filtering of short wavelength light (these variations arise from 2 sources: the lens pigments and the macular pigments). The most widely used tritan matching function used today is the Moreland equation, which requires the subject to match a mixture of indigo and green (originally 430 nm and 500 nm, respectively, but subsequently revised twice to 436 and 490 nm and then to 440 and 488 nm) to a cyan primary (a fixed ratio of 480 nm and 580 nm).^{136,137,191} The primaries were selected and adjusted to minimize the combined effects of individual variations in macular pigment and lens pigment optical density on the midmatching point of normal subjects.¹³⁶ Such adjustment, however, simultaneously shifts the match from a tritan axis; therefore, it cannot distinguish complete tritanopia from incomplete forms in which there is residual tritan color discrimination. Nevertheless, the Moreland equation has been used in combination with the Rayleigh equation to assess acquired color deficiency.¹⁷¹ This so-called 2 equation method classifies deficiencies according to their effects on 2 key parameters: matching range and midmatching point.¹⁷¹

4.3. Computerized color tests

A variety of computer-controlled tests of color vision have been described. Earlier tests used colored targets, for example, gratings or spots.^{4,32,179} Modulations in the color contrast of these targets were used to probe the subjects' color discrimination. The disadvantages of such test designs are similar to those enumerated for early plate tests. Misalignment of guns on cathode ray tube display monitors may lead to an edge artifact and, because of individual differences in luminosity function, these would have to be determined before or during testing, thus increasing testing time.¹⁶⁶ One notable exception is the method of Chioran and colleagues,^{32,179} which simultaneously gathers data pertaining to luminance discrimination. Regan and colleagues describe an approach which combines the innovations of Stilling with a technique to probe color discrimination along predefined axes.¹⁶⁶ The test, known (and commercialized) now as the "Cambridge Colour Test" uses a C-shaped colored target presented in a neutral Stilling-type array. The C itself subtends 4.3° and its gap 1° with the subject viewing the test at 2.4 m.¹⁶⁶ The color of the test target may be varied in chromaticity along the protan, deutan, and tritan axes in the shortest version of the test, or along 20 axes evenly spaced in the CIE 1976 L*u*v* color space. The test uses an interleaved staircase procedure to determine the threshold for color discrimination along each of the axes probed. In the case of the longer version of the test, threshold data may be fitted with discrimination ellipses. Similar tests have subsequently been developed,²¹⁹ one of which uses temporal modulations in luminance noise.²⁰ A further development of the test, known initially as the P4 test but commercialized as the "low vision module" of the Cambridge Colour Test, uses "dithering" to improve color resolution and alters the stimulus display to comprise 4 circular targets subtending 4° and separated from neighboring circles by 2.5° so that the test could be performed by those with low vision.^{185,188} Each of the circles varies randomly in brightness such that the subject cannot use luminance cues to guess correctly the location of the colored target. The test has been used successfully in subjects with visual acuities down to 1.3 logMAR (20/400).¹⁸⁸ Theoretical ellipse axes may be calculated for subjects in whom color vision is dependent on rod-cone interactions,¹⁸⁵ and the test has accordingly been used in a number of studies investigating cone function in patients with retinal dystrophies,¹²¹ including those treated with gene therapy.²³⁰ A version of the CCT for testing children has been described.⁵⁴

4.4. Perimetric tests or tests of detection

Color perimetry enjoyed a period of renewed interest from the late 1980s, but owes much in its modern incarnation to the work of Stiles.^{194,195} His technique of selective adaptation was first applied to isolate cone from rod responses but was later used to isolate responses from individual cone types. This technique was modified by Wald,²¹⁶ who used broader band adapting lights and later applied to the clinical assessment of patients by Marré.¹¹⁸ More recently, such tests were popularized for the assessment of so-called preperimetric glaucoma through the work of Sample and coworkers, who

combined this technique with automated perimetry.¹⁷³ The 2-color technique relies on the principal of adaptive independence, which supposes that selectively adapting 1-cone mechanism will have no effect on the sensitivity of the remaining cone mechanisms. Thus, yellow backgrounds have been used to differentially adapt the M- and L-cone mechanisms to study S-cone sensitivity. Similarly, blue backgrounds have been used to study L-cone sensitivity and magenta backgrounds to study M-cone sensitivity.¹⁸⁶ Although it is possible to provide significant isolation of both the S-cones and L-cones with such techniques, isolating M-cone responses is more difficult.¹⁸⁶ While flickering stimuli have been proposed as a means of improving cone isolation, this does not solve the problem of modest M-cone isolation.¹¹¹ It has been suggested that paradigms using silent substitution techniques or random luminance noise may improve isolation, especially of the M-cone system.¹⁸⁶ Color perimetry underwent something of a renaissance in the late 1980s and 1990s, with SWAP touted as a means of assessing patients with, or at risk of, glaucoma.^{52,108,115,163,172} Numerous studies suggest that losses in SWAP sensitivity precede those of standard white-on-white perimetry. There are, however, distinct disadvantages to SWAP. It is time consuming to perform, difficult and highly variable for inexperienced observers and vulnerable to perturbations in the density of the lens pigments. Furthermore, other tests such as the so-called frequency doubling paradigm have proven as effective, quicker, and easier for subjects to perform.¹⁰⁸

Tests of spectral sensitivity on white backgrounds have been used to explore so-called color opponent processes. At the background luminances typically used by modern perimeters (10 cd m⁻²), the normal spectral sensitivity function departs from the of the $V_{(\lambda)}$ function and is dominated by 3 peaks believed to reflect the peaks of opponent processes (one of the peaks of the S/M + L opponent system is believed to be obscured by the M/L peaks). Although this form of perimetry was favored by Verriest and colleagues,⁶⁹ subsequent simian trials of this technique suggest that the sensitivity may nevertheless be governed by the $V_{(\lambda)}$ function at certain stimulus locations depending on the target size and wavelength.⁶⁷ Furthermore, these data suggest poor isolation of opponent systems even when these governed target detection using this paradigm.⁶⁷

5. Color vision in ophthalmic and neurologic disease

5.1. Disorders of the ocular media

Possibly the commonest mechanism of acquired color vision deficiency is a so-called absorption mechanism secondary to the age-associated increase in optical density of the lens pigments.¹⁴⁹ The latter are characteristically yellow in color and absorb of short-wavelength radiation, including ultraviolet and short wavelength visible light. Because of the gradual nature of such changes, they are seldom noticed. Furthermore, there is evidence to suggest that increased media absorption may be offset by increased S-cone sensitivity.⁸³ Implanted intraocular lenses with yellow tints modulate the

spectral quality of light (when compared to aphakia).¹⁸³ Most yellow intraocular lenses would not be anticipated to induce color vision deficiency,²⁰⁹ and the empirical evidence supports this assertion.¹⁸³ Although other conditions (e.g., jaundice) may also modify the spectral nature of light incident on the retina, their visual effects are seldom noticed by patients, presumably because they are dwarfed by other symptoms.

Aberrantly elevated levels of macular pigment may also induce or modify color vision deficiency. For example, “excessive” prereceptor pigment density has been observed to modify the phenotype of tritanopia such that the defect simulates tetartanopia⁸⁷ (an antiquated term for a hypothetical defect of the “yellow mechanism” which could theoretically also occur as a congenital color deficiency through a combination of tritanopia and deuteranomaly).¹⁸⁵

5.2. Retinal disorders

5.2.1. Photoreceptor disorders

5.2.1.1. Cone dystrophies.

5.2.1.1.1. *Photopigment defects.* Pedigrees in which either progressive or stationary cone dystrophy is associated, at least in the early stage of the disease process, with either a protan¹⁶⁷ or deutan²⁷ deficiency have been described. Affected patients in some pedigrees are thought to have causative defects in either the photopigment genes or their regulatory elements.

Reichel and colleagues describe a pedigree in which deletion of a major portion of the L-cone photopigment gene resulted in a protanopic color vision deficiency in younger patients with subsequent profound cone degeneration leading ultimately to scotopization.¹⁶⁷ Other defects have also been described in which patients display both a color vision deficiency resembling congenital M-L mechanism deficiency in combination with frank cone dysfunction. A relatively common opsin gene mutation that can cause congenital M-L mechanism deficiency results in a cys203arg mutation with subsequent disruption of a disulphide bond. This mutation is known to cause dysfunction of the opsin molecule through impairment of folding, half-life, and light activation.⁸⁹ Such mutations have been reported in association with S-cone monochromatism (when both the M- and L-photopigments carry the mutation¹⁶⁹ or in patients with single X-chromosome coded opsin arrays carrying the mutation)¹⁴⁰ and also with a phenotype known as Bornholm eye disease.¹²³ Adaptive optics imaging of patients with congenital M-L mechanism deficiency with this mutation occurring in either the second or third gene in the X-chromosome coded opsin array has demonstrated disrupted cone mosaics.²⁷ These patients may have subtle macular disturbance, though with good visual acuity.²⁷ Molecular analysis suggests that rare exon 3 genotypes (LVAVA, LIAVA) that have been proposed to render the opsin product nonfunctional may also cause Bornholm eye disease when occurring in the first gene in the array.¹¹⁹ The LIAVA mutation has also been demonstrated to cause deuteranopia when occurring in the second position of the opsin array (i.e., within the M-cone photopigment gene, with a normal L-cone photopigment gene in position one): *in vivo* imaging has shown that this causes a functional loss of cones which appear intact but optically empty.²⁸ Thus, it appears

that the consequences of deleterious mutations in the opsin genes (e.g., cys203arg, LIAVA, LVAVA) are partially dependent on the position of the gene in the array.¹⁸⁴ When occurring in the first gene—which enjoys preferential expression—frank cone dystrophy is noted. When occurring in the second or third gene, congenital color vision deficiency is observed, with subtle abnormalities suggestive of mild dystrophy being detected clinically or experimentally.

As alluded to previously, S-cone monochromatism may arise from a number of mechanisms, including mutations to the locus control region lying upstream of the X-chromosome opsin array,²¹⁷ mutations to one opsin gene in patients with single gene arrays,²¹⁷ or to both the M- and L-photopigment gene in patients with 2 gene arrays.¹⁶⁹ Patients with this condition may show slow progression.¹²⁴ It is also suggested that tritanopia represents a mildly progressive form of cone dystrophy. Baraas and colleagues describe 3 members of a pedigree with tritanopia in which the eldest individual has a demonstrable loss of tritan discrimination with concomitant implied disruption of the cone photoreceptor mosaic on adaptive optics imaging.⁷ The 2 younger individuals demonstrated well-preserved color discrimination. One of the younger patients underwent adaptive optics imaging, which suggested a comparatively normal photoreceptor array and a full S-cone complement. Whether the dystrophy observed in the eldest patient occurred early in life or later is unclear, though Baraas and colleagues favored the latter hypothesis.⁷ An alternative explanation is that these patients simply display variable expressivity. Although patients with frankly progressive cone dystrophy with typical symptoms of decreased acuity, hemeralopia, photophobia, and abnormal photopic electroretinograms (ERGs) have been described in whom an S-mechanism defect is present, no evidence for a defect in the S-cone photopigment gene has yet been revealed in such patients.²²⁴

5.2.1.1.2. *Phototransduction defects.* Defects of the cone phototransduction mechanism are associated with profound cone dysfunction. The α -transducin defects have been reported in association with a phenotype resembling incomplete autosomal recessive achromatopsia in which evidence of progression was observed in older individuals.¹²¹ Mutations in the cone-specific PDE α - and β -subunits have also been demonstrated to result in achromatopsia.^{56,96} Retinal guanylate cyclase defects have been reported in association with cone dystrophy⁶¹ and also in association with central areolar choroidal dystrophy⁷⁷ and Leber congenital amaurosis.¹⁵⁴ In the autosomal dominant guanylate cyclase cone-rod dystrophy pedigree described by Gregory-Evans and colleagues, only the youngest member demonstrated residual color vision.⁶¹ There was a profound loss of tritan discrimination with Rayleigh matches shifted to longer wavelengths, possibly consistent with a mechanism relying on rod input to color matching.¹⁸⁵

5.2.1.1.3. *Channelopathies.* Defects in genes coding for both the α - and the β -subunits of the cone cyclic guanosine monophosphate gated cation channels have been implicated in the pathogenesis of complete and incomplete forms of rod-monochromatism.^{94,97,98,168} Evidence from animal

models and natural history studies suggest that these conditions represent a form of sequential retinal degeneration in which there is early loss of cone photoreceptor function which may later be accompanied by a slow decline in rod function^{82,91}; similarly, retinal ultrastructure has been proposed to show sequential degenerative changes.⁵⁸ Patients with rod-monochromatism commonly demonstrate residual, though rudimentary, color discrimination at certain color vision tests.¹⁸⁵

5.2.1.2. Rod dystrophies or retinitis pigmentosa. Retinitis pigmentosa generally causes a type III acquired color vision deficiency while vision is well-preserved.¹¹⁷ This feature may help distinguish this condition from other retinal dystrophies causing a type I defect (e.g., Stargardt disease, cone-rod dystrophy). In a minority of patients, there is a concurrent M-L mechanism defect that appears to be more common with worsening visual acuity.¹⁵⁸ Verriest, using the battery of tests described previously, found that in 70 eyes of 65 patients, 14 (20%) had normal color vision, 3 (4%) had congenital color vision deficiency, 6 (9%) had diffuse loss, 2 (3%) had type I M-L mechanism deficiency, and 45 (64%) had S-mechanism deficiency.²¹² Pinckers and colleagues examined 98 eyes of 49 patients with the F-M 100-Hue and anomaloscopy (Rayleigh matches).¹⁵⁸ They found that 30 (30.6%) had normal color discrimination, 4 (4.1%) had nonspecific decreased sensitivity, 30 (30.6%) had an acquired S-mechanism deficiency, 31 (31.6%) had combined acquired M-L mechanism and S-mechanism deficiency, and 3 (3.1%) had an isolated M-L mechanism deficiency. They suggest that patients with decreased acuity ($\leq 20/40$) were more likely to have an F-M 100-Hue plot consistent with an acquired M-L mechanism defect.

5.2.2. Other retinal and chorioretinal dystrophies

5.2.2.1. Congenital stationary night blindness. The color vision deficiency associated with congenital stationary night blindness may be mild and only evident at certain tests.²⁰¹ Bijveld and colleagues found that 35.8% (4 of 14 patients with congenital stationary night blindness type 1 and 25 of 53 patients with congenital stationary night blindness type 2) of their cohort examined with the Ishihara, D-15, and AO H-R-R had an acquired dyschromatopsia. Although the precise nature of the deficiency is not described, they state that patients with severe deficiency (17% of patients with congenital stationary night blindness type 2) tended to have M-L mechanism defects.¹⁴

5.2.2.2. Fundus albipunctatus. Although color vision may be “normal” in fundus albipunctatus, S-mechanism deficiency has been reported in some pedigrees in which 11-cis retinol dehydrogenase 5 mutations have been demonstrated. For example, Hotta and colleagues describe male and female siblings in their sixth decade who had S-mechanism deficiency.⁷⁵

5.2.2.3. Oguchi disease. Color vision is reported to be commonly “normal” in this condition,²²⁹ though phenotypes have been reported in which there is an S-mechanism deficiency.¹⁶¹

5.2.2.4. Gyrate atrophy. Although color vision may be unremarkable in the early stages of this chorioretinal disease, it is

affected with disease progression. Takki reports that of the 15 patients tested at the F-M D-15, the youngest 6 (40%) passed the test, 5 (33%) had an acquired type III S-mechanism defect, and 4 (27%) had ill-defined defects.²⁰⁰

5.2.2.5. Benign concentric annular dystrophy. This condition, first described by Deutmann in 1974, appears to be associated with a type III S-mechanism deficiency.⁴⁴ For example, van Lith-Verhoeven and colleagues found that 7 of 9 patients they tested (method not given) had S-mechanism deficiency.²¹⁰

5.2.2.6. Choroideremia. Although color vision may be normal early in the disease process, it appears to be affected in the majority of individuals with progression of the condition.⁶⁸ Of 31 cases tested (with the AO H-R-R; Ishihara, D-15, anomaloscope), Kurstjens found 2 (6%) patients with mixed S- and M-L mechanism disturbance, 3 (10%) with isolated type III S-mechanism deficiency, and 10 with M-L mechanism defects (32%), though up to half of these latter may have had congenital M-L mechanism defects.¹⁰³ More recently, Jolly and colleagues reported their findings in 30 patients (28 with proven mutations of the CHM gene) tested with the F-M 100-Hue.⁸⁴ They found that color discrimination was abnormal, even in those with acuities of 20/20 or better. Furthermore, there was evidence of decline in color discrimination with declining acuity.

5.2.2.7. Best or vitelliform dystrophy. In their review, Krill and Deutman remark that color vision is generally reduced once vision falls to less than 20/40.¹⁰⁰ They also suggest that while the F-M 100-Hue shows a predominantly tritan axis, there is a protan shift when performing Rayleigh matches: this would be anticipated if we extrapolate the findings in other conditions causing retinal elevation or traction.¹⁹² Castelo-Branco and colleagues investigated 34 patients with Best disease and found that color discrimination at the Cambridge Color Test was correlated with the clinical stage of the disease.^{24,29} They found that S-mechanism deficiency predominated in the early disease stages but that an M-L mechanism deficiency predominates in its later stages.

5.2.2.8. Butterfly pattern dystrophy. Fossarello and colleagues describe 6 patients from 2 families in whom peripherin or retinal degeneration slow mutations were identified.⁴⁸ They suggested that performance at the F-M 100-Hue was normal until ophthalmoscopically visible changes were evident, when anarchic arrangement patterns were observed. In a single small pedigree (of 11 subjects, with 3 having butterfly pattern dystrophy) followed up over a period of 3 years by Mantyjarvi and Tuppurainen, color vision (assessed using the standard pseudoisochromatic plate plates, Rayleigh equation, and F-M 100-Hue) was normal in the youngest patient (age 34 years).¹¹⁶ The eldest patients (58 and 61 years old at presentation) demonstrated progressively decreased generalized loss of color discrimination over the 3 year follow up, with error scores falling just less than,²¹³ or just greater than, previously published age normals.⁹²

5.2.2.9. Doyme honeycomb degeneration or Malattia Leventinese. Although color vision is commonly normal in the early stages

of this condition, there is phenotypical variation. For example, Haimovici and colleagues used a computer-controlled test of color discrimination to study 6 patients with EGF-containing fibulin-like extracellular membrane protein 1 mutations who had symptomatic reductions in scotopic vision that occurred without clinically identifiable atrophy or choroidal neovascularization.⁶⁴ They found global elevations in color discrimination along protan, deutan, and tritan axes in all affected patients, with profound defects occurring in some individuals.⁶⁴

5.2.2.10. *North Carolina macular dystrophy*. Color vision may be normal in the early stages of this disease. For example, Rosenberg and colleagues studied 10 patients with North Carolina macular dystrophy: data on color vision were reported for 4 patients, each of whom passed the tests used (Ishihara test and Lanthony tritan album).¹⁷⁰ In contrast, Godley and colleagues found that the 2 patients (from a pedigree containing 15 affected individuals) tested had profoundly reduced sensitivities along the protan, deutan, and tritan axes at a computer-controlled test of color discrimination.⁵³

5.2.2.11. *Sorsby fundus dystrophy*. Capon and coworkers found evidence to suggest a prodromal loss of tritan discrimination at the F-M D-15 in 3 patients examined with this condition which preceded vision loss.²⁶ Atchison describes a large pedigree with this dystrophy in which the clinical picture was clouded by the presence of congenital deuteranomaly in some family members; although those with the condition were noted to have acquired defects, little detail is given regarding their nature.⁶

5.2.2.12. *Stargardt disease*. Stargardt disease is perhaps the archetypical cause of a type I acquired M-L mechanism deficiency which leads to scotopization.¹⁶¹ The condition is most frequently inherited as an autosomal recessive trait and the commonest causative gene, *ABCA4*, codes for an adenosine triphosphate-binding cassette transporter molecule shown to be expressed in rod¹⁹⁷ and cone¹²⁶ photoreceptor outer segments. It has previously been demonstrated that Rayleigh matches widen and sensitivity to the red primary progressively decreases with disease progression.¹⁶¹ Eventually, the brightness-matching function parallels that of a rod monochromat as rod activity dominates residual visual function.¹⁶¹ In a study of 27 patients from 21 families with Stargardt, Maia-Lopes and colleagues found that only 2 (7%) had normal color vision (as assessed using both the Rayleigh and the Moreland matches), 13 (48%) had mixed S- and M-L mechanism deficiency, 4 (15%) had M-L mechanism deficiency, 4 (15%) had S-mechanism deficiency, and 4 (15%) were unable to perform the test because of low vision.¹¹⁴ Of the 12 carriers of *ABCA4* mutations (confirmed by genotyping) and whose color vision was assessed, 6 (50%) were normal, 3 (25%) had M-L mechanism deficiencies, 2 (17%) had S-mechanism deficiency, and 1 (8%) had mixed S- and M-L mechanism deficiency.

5.2.2.13. *Enhanced S-cone syndrome*. Jacobson and colleagues found that their 11 patients with enhanced S-cone syndrome were able to pass either the F-M D-15 or the AO H-R-R plates.⁸⁰ Subtle abnormalities, however, may be detected at other tests.

For example, Nakamura and colleagues undertook extensive psychophysical testing of a single subject homozygous for a nonsense mutation the *NR2E3* (nuclear receptor subfamily 2, group E, member 3) gene and demonstrated a unilateral Verriest type II M-L mechanism disturbance not detected at the F-M D-15.¹³⁸

5.2.2.14. *Leber congenital amaurosis*. The early stages of the condition are characterized by an acquired S-mechanism deficiency that progresses to involve the M-L mechanism over time, leading to anarchic losses that accompany the profound loss of vision seen in this condition.¹⁵³

5.2.2.15. *Age-related macular degeneration*. Color vision deficiency is seldom used as a means of detecting, diagnosing, or monitoring the progression of age-related macular degeneration. Consequently, although our ability to readily monitor retinal structure in this disease has improved with the advent of modern imaging techniques, few attempts have been made to relate this to function in terms of color vision. Much of the early literature has been well-summarized previously.¹⁶¹ Recently, a small study conducted by O'Neill-Biba and colleagues investigated tritan and M-L mechanism discrimination using a computer-controlled test of color vision in 18 subjects with age-related macular degeneration.¹⁵⁰ They found evidence for a greater loss of tritan discrimination: isolated losses of tritan discrimination occurred in 5 of 36 eyes (14%, all having category 2⁴⁵ age-related macular degeneration), with one eye (3%) demonstrating normal discrimination (with category 1 changes, i.e., normal for age), and the remaining 30 (83%) demonstrated elevated M-L mechanism and tritan thresholds. Arden and Wolf investigated color discrimination in 24 patients with age-related maculopathy using 2 different sized optotypes (1.5° and 6.5°) presented within masking random dynamic luminance noise on a cathode ray tube monitor.⁵ Interestingly, they suggest that tritan discrimination thresholds for the 1.5° optotype completely separates eyes with age related maculopathy from those of normal patients (M-L mechanism thresholds were within normal limits) while some overlap occurs with the 6.5° optotype.

5.2.2.16. *Phototoxicity*. Rai and colleagues¹⁶⁴ study of patients with solar photoreinitis found no evidence for color vision deficiency at the F-M D-15 in 44 eyes examined some 1–3 years after the initial insult. A subset of their patients (10 affected eyes in total) underwent a computer-controlled test of color discrimination: 7 (70%) were found to have a selective impairment of the S-mechanism.

5.2.3. *Fundus detachments*

5.2.3.1. *Retinal detachment*. Chisholm and colleagues investigated the recovery of color discrimination after successful retinal detachment repair by “plombage” with, or without, an encircling element.³³ They found evidence for an S-mechanism deficiency at the F-M 100-Hue in patients with macula-on detachment, whereas patients with macula-off detachments had a generalized loss of discrimination. Improvements were noted over time, though at different rates depending on pre-operative macula status: those with macula-on detachment

achieved F-M 100-Hue scores equivalent to those of fellow eyes at about 3 or so months, while color vision deficiency persisted at 2 years in the macula-off group.³³ Although color vision deficiency is anticipated in macula-off detachment, the reason for dyschromatopsia in macula-on detachment is unclear. The most likely explanation is that it is due to the presence of subclinical submacular fluid postoperatively, which is a relatively common finding (occurring in more than a third of patients at 6 weeks after scleral buckling for macula-on detachment).¹² Little is known regarding color vision after detachment repair by scleral buckling versus pars plana vitrectomy. Tritan and so-called “tetartan” F-M 100-Hue axes have been reported following successful repair of macula-off retinal detachment by either scleral buckling or pars plana vitrectomy.¹⁸⁰ Although Serra and colleagues found a trend toward higher F-M 100-Hue error scores following pars plana vitrectomy (5 eyes) compared to scleral buckling (12 eyes) in phakic patients, this difference did not attain statistical significance in their small sample.¹⁸⁰ Of their 17 subjects, 12 (70%) had acquired S-mechanism deficiency, 2 (12%) had total error scores within normal limits, and 3 (19%) had anarchic losses at the F-M 100-Hue.¹⁸⁰ The finding of S-mechanism deficiencies in subjects with successfully repaired macula-off retinal detachment is supported by histologic studies that confirm selective loss of S-cones.¹⁴⁸

5.2.3.2. Central serous retinopathy. In their elegant study of 3 patients with this condition, Smith and colleagues demonstrated that central serous retinopathy may cause pseudoprotonomaly through reduced effective optical density of the photopigments: they suggested that the mechanism is aberrant photoreceptor tilt (as evidenced by an abnormal Stiles-Crawford I effect).¹⁹² Concomitant S-mechanism defects are also noted in patients with this condition.¹⁹² Maaranen and colleagues used a combination of the F-M 100-Hue and anomaloscopy (Rayleigh and Moreland equations) to demonstrate color vision abnormalities in 26 of 39 (67%) patients after the resolution of central serous retinopathy (all had achieved a final visual acuity of $\geq 20/20$).¹¹³ Of these, 20 (51%) had an acquired S-mechanism defect, 5 (13%) combined M-L mechanism and S-mechanism deficiency, and 1 (3%) an acquired M-L mechanism deficiency. Interestingly, 19 (49%) of contralateral “normal” eyes had color vision deficiency, supporting the suggestion of a high rate of resolved subclinical disease in fellow eyes.

5.2.4. Diabetic retinopathy

Diabetic retinopathy is commonly associated with acquired color vision deficiency. About half of the patients in the Early Treatment of Diabetic Retinopathy Study were found to have abnormalities on the F-M 100-Hue.⁴⁷ Barton and colleagues performed cluster analysis of F-M 100-Hue plots in 2701 patients from the Early Treatment of Diabetic Retinopathy Study cohort and found that 51% of eyes had normal color vision; 26% of eyes had an isolated acquired S-mechanism deficiency, whereas the rest had combined S- and M-L mechanism deficiency, including those patients with presumed congenital color vision deficiency.¹⁰ The mechanism of tritan acquired deficiency appears to be multifactorial, due in part (in phakic patients) to lenticular changes resulting in increased

prereceptor filtering of short-wavelength light.⁴² Decreased S-cone-mediated sensitivity has been observed, however, even after such absorption is accounted for.⁴¹ Similarly, histologic studies also support the hypothesis that S-cones are selectively affected in diabetic retinopathy.³⁴

5.3. Optic nerve disorders

5.3.1. Glaucoma

Glaucoma is a term applied to a collection of optic neuropathies that may have acute or chronic forms and which share the common feature of loss of retinal ganglion cells and excavation—or cupping—of the optic nerve head.²²⁰ Several early studies suggested that glaucoma causes an acquired M-L mechanism deficiency¹⁶¹; however, such studies concentrated on patients with advanced disease,¹⁶¹ and it is now generally accepted that glaucoma first causes an acquired S-mechanism deficiency on conventional color vision tests such as the F-M 100-Hue and desaturated D-15.¹⁷⁵ Much of the attention over the past 3 decades has been directed at detecting loss of function before this is evident with conventional visual field tests (so-called “preperimetric glaucoma”). As detailed previously, color perimetry—in the form of SWAP—underwent a brief renaissance as a test of preperimetric glaucoma, but other testing paradigms have superior screening utilities.¹³⁵

5.3.2. Hereditary optic neuropathies

5.3.2.1. Dominant optic atrophy (also known as dominantly inherited optic atrophy). This condition, most commonly associated with OPA1 gene mutations, is marked by significant phenotypical heterogeneity such that some patients within the same pedigree demonstrate mild disease while others demonstrate more severe vision loss.¹⁰⁹ Although the condition has been considered to be a notable exception to Köllner’s rule, color vision findings are heterogeneous.¹⁶¹ Several pedigrees have been described in which there is a color vision deficiency that mimics congenital tritanopia, to the point that it had been suggested that the 2 conditions may represent the same entity,^{101,102} but this hypothesis has been convincingly rejected.¹⁹⁰ Numerous cases of M-L mechanism deficiency have been reported,¹⁶¹ and although patients may demonstrate a greater loss of tritan discrimination than M-L mechanism discrimination,¹⁸⁸ patients with isolated S- or M-L mechanism defects probably represent the minority.

5.3.2.2. Leber hereditary optic neuropathy. This mitochondrially inherited disease generally causes profound loss of vision.¹⁸⁹ Although color vision may be difficult or impossible to assess with standard clinical color vision tests following the onset of the condition, type II M-L mechanism deficiencies at the F-M 100-Hue may be a prodromal sign¹⁴⁶ (Though the study cited may have been confounded by simultaneous congenital color vision deficiency).¹⁴⁶ A recent study of a large Brazilian pedigree which combined genetic analysis with computerized color discrimination testing suggests impairments in asymptomatic carriers (46 tested) of the condition. Losses of M-L mechanism discrimination were confirmed to exceed those of S-mechanism discrimination, and evidence

was found for sex-related differences in color discrimination (with males being more severely affected).²¹¹

5.3.3. Optic neuritis

By far, the largest study of color vision in optic neuritis was undertaken as part of the Optic Neuritis Treatment Trial: a total of 438 participants were tested in the acute phases of inflammation and at 6 months.¹⁷⁷ During the acute phases of optic neuritis, 93.2% of patients demonstrated abnormal F-M 100-Hue scores while at 6 months this had fallen to 39.4%. Of those patients demonstrating isolated defects, there was a slight preponderance of acquired S-mechanism deficiency at presentation (40.8% S-mechanism, 29.6% M-L mechanism, 29.6% nonselective) and of acquired M-L mechanism deficiency at 6 months (36.1% S-mechanism, 40.5% M-L mechanism, 23.4% nonselective).¹⁷⁷ A definite relationship was observed between visual acuity and likelihood of demonstrating an abnormal F-M 100-Hue score.

5.3.4. Optic nerve compression

Paulus and Plendl found no evidence for preferential impairment of either S-mechanism or M-L mechanism discrimination at the F-M 100-Hue test in 13 patients with compressive optic neuropathies from a variety of mechanisms.¹⁵² Sharanjeet-Kaur and colleagues investigated "chromatic" (including the F-M 100-Hue and spectral sensitivity estimates) and achromatic vision in 15 patients with thyroid-related orbitopathy complicated by optic nerve compression.¹⁸¹ Their results did not suggest preferential impairment of one subsystem of color over the other. In a detailed analysis, Cruysberg and Pinckers compared color vision at a battery of tests (including plate tests, the F-M 100-Hue, and anomaloscopy) in 29 patients undergoing neurosurgical treatment for a variety of underlying conditions causing optic nerve compression.³⁶ Twenty-four of 29 patients (83%) demonstrated abnormal color vision in one or both eyes. Ten eyes (of 10 patients) had acquired type II M-L mechanism deficiency while the remainder had unclassifiable defects.

5.4. Cerebral achromatopsia

Excellent reviews of cerebral achromatopsia have been published over the past 5 years, and this subject will be dealt with briefly.^{8,9} Empirical evidence of a cortical center for the sense of color was first recognized by Verrey in 1888, but his work was sidelined until the latter half of the 20th century when studies of the simian cortex, multiple clinical and neuropathologic correlations, and advanced imaging all lent support to this notion.⁸ Disorders of "human V4" in the ventral occipitotemporal cortex are associated with achromatopsia or dyschromatopsia. If unilateral, they may result in contralateral hemiachromatopsia or dyschromatopsia (including a failure of color constancy).⁸ As a rule, such lesions affect other aspects of visual function.⁵¹

5.5. Drug-induced dyschromatopsia

Numerous drugs have been observed to cause dyschromatopsia via a variety of proposed mechanisms: many of these may be of interest for historical reasons. Advances in drug development, disease patterns, and prescribing patterns

have meant that some previously important causes of medication-induced dyschromatopsia are seldom seen, while newer ones are emerging. This list is not exhaustive but concentrates on medications that are of current clinical relevance.

5.5.1. Phosphodiesterase-5 inhibitors

PDE5 inhibitors were initially marketed for erectile dysfunction, but have also been used in the management of pulmonary hypertension. There have been several reports that have linked its use temporally to the development of nonarteritic ischemic optic neuropathy, though the association may not be causal.¹⁴³ PDE5 inhibitors are known to have some cross-reactivity with other PDEs, including those found in the photoreceptors (PDE6). There may be demonstrable alterations to temporal resolution, and patients taking this medication may occasionally notice disturbances of color vision which are typically described as a bluish tinge (cyanopsia).¹⁹⁶ Minor, but statistically significant, disturbances in color discrimination at the desaturated D-15 were noted by Luu and colleagues in 10 of 14 subjects (71%) 1 hour after the ingestion of 200 mg of sildenafil, and the time course for the effect appears to be similar to that for ERG changes.¹¹² Cordell and colleagues found no evidence of disturbed color discrimination at the F-M 100-Hue in 57 patients treated with 5 mg of tadalafil or in 49 patients treated with 50 mg of sildenafil over a period of 6 months.³⁵

5.5.2. Chloroquine or hydroxychloroquine

Neubauer and colleagues compared clinical assessment, electrooculography, and color vision assessment (using a computerized test of color discrimination) in 93 patients on chloroquine or hydroxychloroquine therapy for rheumatological disease over an average of 2.6 years.¹⁴⁵ Their analysis suggests a preferential impairment of tritan discrimination that occurred in 22 of 37 patients (59%) with mild retinopathy and 100% of patients with advanced retinopathy with a classic bull's eye appearance. The calculated sensitivity and specificity of S-mechanism deficiency for predicting retinopathy are 63% and 67%, respectively. Color vision assessment is currently not recommended as a means of screening for hydroxychloroquine retinopathy, because other tests such as perimetry, multifocal ERGs, and spectral domain optical coherence tomography provide superior screening efficacy.²³

5.5.3. Ethambutol

Of all infectious agents, deaths from tuberculosis are currently only exceeded by HIV/AIDS, and ethambutol remains a mainstay of multidrug therapy for tuberculosis.²²⁵ In a detailed study of 6 patients with vision loss from ethambutol, Nasemann and colleagues found evidence of global loss of color discrimination at the F-M 100-Hue, with a preponderance of M-L mechanism errors.¹³⁹ In a short-term longitudinal study of patients undergoing quadruple anti-tuberculosis therapy with rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 months followed by 4 months of dual therapy (rifampicin and isoniazid), Cruz and colleagues found that 30 of 64 patients (47%) failed the desaturated F-M D-15 at 1 month (all had passed at baseline).³⁷ Of these, 20 (31%) patients had nonspecific deficiency, and 10 (16%) patients had S-

mechanism deficiency. All patients reverted to normal at 1 month after cessation of ethambutol.

5.5.4. Digoxin

This Na⁺-K⁺ pump blocker is primarily used in the treatment of atrial fibrillation and is notorious for its narrow therapeutic window.²¹⁸ The medication may cause nonspecific blurring of vision but may also cause chromatopsia (typically yellow in hue, “xanthopsia”) and disturbance of color discrimination. In a survey of 30 patients on digoxin (27 within the therapeutic window and 3 with slightly elevated levels, but without signs of toxicity), 8 (26.7%) patients demonstrated tritan F-M D-15 arrangements and a further 9 (30%) demonstrated nonspecific loss of discrimination.¹⁰⁶

5.6. Environmental dyschromatopsia

5.6.1. Toxins

Although an association between exposure to organic solvents and S-mechanism color vision deficiency has been reported in numerous studies, meta-analysis of 15 studies suggests only a trend toward an association between the level of occupational exposure and color discrimination (i.e., it does not attain statistical significance).¹⁵¹ Several reasons have been proposed to account for this lack of dose-effect correlation, including variation in the methods of assessing exposure to organic solvents, the inclusion of studies with subjects having only subthreshold exposures (14 of 15 studies) and the use of insensitive measures of color discrimination.¹⁵¹ Other industrial chemicals may also cause color vision deficiency (most commonly an acquired S-mechanism deficiency), and their effects have been reviewed by Iregren and colleagues.⁷⁹

5.6.2. Hypoxia

Sustained exposure to hypoxic environments (e.g., high altitudes) induces a reversible acquired color vision deficiency which predominantly affects S-mechanism discrimination.²²⁷ For acute exposures, S-mechanism and M-L mechanism discrimination losses may be similar.²¹⁴ Corresponding reductions in S-cone derived a-wave amplitudes on electroretinography have also been observed.¹⁷⁶ Hypoxic states (i.e., through systemic disease in the context of normoxic or hyperoxic environments) may similarly cause color vision deficiency.²³¹

6. Conclusion

Acquired color vision deficiency is a common condition and, though its precise prevalence is unknown, the available evidence suggests it is more common than congenital color vision deficiency in populations aged 40 years and more.¹⁷⁸ Although a wide array of diseases may affect color vision, acquired color vision deficiency results in stereotypical changes which may be classified.²¹² Because of the physiology of color processing,¹⁹³ diseases affecting M-L mechanism discrimination also tend to cause loss of spatial discrimination. S-mechanism color deficiency, in contrast, may occur independent of losses in visual acuity. There is a predilection for acquired color vision deficiency to cause S-mechanism

deficiency, and several mechanisms may be responsible for this phenomenon.²¹² These include an inherent vulnerability of the S-mechanism, a paucity of physiologic reserves, and the deployment of testing conditions which tilt the field against the S-mechanism. Although certain ocular conditions may cause a preponderance of M-L mechanism or S-mechanism defects, the effects are not invariable, and mixed defects are common. With the advent of new treatments—especially gene therapy for inherited retinal disorders—there has been renewed interest in the assessment of acquired color vision deficiency. Improvements in imaging techniques, in our understanding of the physiology of color processing, and in the pathophysiology of disease will provide further insights into acquired color vision deficiency.

7. Method of literature search

PubMed was used to search for articles: no limits were placed on date, or language, of publication. Search terms included “colo(u)r vision” and “colo(u)r vision deficiency.” The former was combined with the search terms corresponding to the headings and subheadings in the section on color vision deficiency in particular disease states (e.g., “colo(u)r vision cone dystrophy,” “colo(u)r vision retinitis pigmentosa”). The search was expanded using the “related articles” function in PubMed. The indices of the proceedings of the International Research Group on Colour Vision Deficiencies (from 1984 to 1997 inclusive) were also scrutinized via Springerlink (<http://link.springer.com>). Secondary sources were identified from the articles identified in the primary search. In addition, a personal archive of references was used.

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