

Excerpts from

PROCESSES IN BIOLOGICAL VISION:

including,

ELECTROCHEMISTRY OF THE NEURON

This material is excerpted from the full β -version of the text. The final printed version will be more concise due to further editing and economical constraints. A Table of Contents is at the end of this paper.

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18 Clinical Electrophysiology & Visual Abnormalities in Man¹

18.1 Background

There is a large literature on clinical electrophysiology. The recent text by Heckenlively & Arden covers the field from the more academic perspective². Ryan, et. al. provide a comprehensive summary of the clinical and medical perspective of the retina, including electrophysiology³. Trobe has provided an extensive survey of the neurology of vision⁴. However, it only addresses achromatopsia and several other areas superficially. The field has suffered from lack of an adequate model of the visual system. This is highlighted by the content of both of the above volumes. Their discussions of the mechanisms of vision are strongly rooted in the conventional wisdom of vision dating largely from the 1950's.

The field of clinical eye disease treatment is strongly influenced by the pedagogical environment. As late as 1993, Chawla made the following statement in the second edition of his text⁵. "At the root of ophthalmic teaching lies the assumption that every syndrome is crowned with a unique fundal appearance." Chawla focuses on the "Seven Signs," the physical abnormalities visible with an ophthalmoscope. While the field does recognize the potential for chemical imbalances, it does not give significant credence to the potential for neurological abnormalities not observable by physical deformations.

In the same time period while discussing unexplained visual field losses, Burde, Savino & Trobe⁶ presented a more modern view that is contrary to that of Chawla. "Retinal diseases that cause visual field defects may not produce ophthalmoscopically obvious abnormalities." They speak of lesions or tumors found topologically beyond the retina and eye. However, the increasing knowledge of the neural system and genetics leads to a wide variety of conditions unrelated to physically observable causes of disease.

By 1999, Chawla was participating in the recent and continuing revolution⁷. He opened his third edition by saying the following. "The main obstacle to learning anything about the eye is ophthalmology itself. Its jargon obscures even the simplest idea and the quaintly named disorders are frequently taught as a mixture of pathology and therapeutics, with presenting features hidden somewhere in the middle."

A major problem may focus on the definition of ophthalmology itself. The field appears to encompass the medical treatment of diseases of the eye associated with physically observable mechanisms. It has not in the past addressed neurological diseases other than to lump them under the title, psychogenic issues. While, Burde, Savino & Trobe included the prefix neuro- in their title, the subject is only addressed by superficially describing the neural paths associated with the pointing system of the eyes.

While this work is not clinically oriented, it does reflect pertinent facts drawn from the broader clinical literature.

¹Released March 18, 2017

²Heckenlively, J. & Arden, G. ed. (1991) Principles and practice of clinical electrophysiology of vision. St. Louis, MO: Mosby Year Book

³Ryan, S. ed. (2001) The retina *In three volumes* St. Louis, MO: Mosby

⁴Trobe, J. (2001) The Neurology of Vision. NY: Oxford University Press

⁵Chawla, H. (1993) Ophthalmology, 2nd Ed. NY: Churchill Livingstone pg 46

⁶Burde, R. Savino, P. & Trobe, J. (1992) Clinical Decisions in Neuro-Ophthalmology, 2nd Ed. St. Louis, MO: Mosby Year Book, pg 1

⁷Chawla, H. (1999) Ophthalmology, 3rd Ed. Oxford: Butterworth-Heinemann preface

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Zillmer, et al. have provided the current text neuropsychology⁸. Part One provides a historical review of early surgeries involving the neural system. Part Two provides an overview of the neural system and the principle sensory modalities (including many aspects of visual abnormalities) from the psychologists perspective. Part Three discusses disorders of the brain, again from a psychologists perspective. The work includes many interesting figures. They are not particularly relevant to the study of the neural system at the functional, or specific features and performance, levels.

Lambert & Kinsley have also provided a text on clinical neuroscience that can be quite useful when discussing visual abnormalities⁹. It appears to cover a broader range of conditions than Zillmer et al. and provide more definitions of terms.

According to Webster's Medical Dictionary,

A **disease**;

1. is an impairment of the normal state of the living animal or plant body or one of its parts that interrupts or modifies the performance of the vital functions,
2. is typically manifested by distinguishing signs and symptoms, and
3. is a response to
 - environmental factors (as malnutrition, industrial hazards, or climate),
 - specific infective agents (as worms, bacteria, or viruses), to
 - inherent defects of the organism (as genetic anomalies), or
 - combinations of these factors.

A **symptom** of a disease is subjective evidence of disease or physical disturbance observed by the patient <headache is a symptom of many diseases> <visual disturbances may be a symptom of retinal arteriosclerosis>; broadly : something that indicates the presence of a physical disorder.

A **symptom complex** is a group of symptoms occurring together and characterizing a particular disease <the symptom complex of epilepsy>

A **syndrome** is a group of signs and symptoms that occur together and characterize a particular abnormality. Unfortunately, the term syndrome is frequently used rather casually to include any group of symptoms that a practitioner decides to group, regardless of whether they exhibit any common source. One syndrome of interest in this Chapter has recently gained prominence, halucigenic persistent perception disorder (HPPD).

A **chromosome** is any of the usually linear bodies of the cell nucleus of eukaryotic organisms, the usually circular bodies of prokaryotic organisms (as bacteria), or especially in some schools of molecular biology the genomes of DNA viruses (as bacteriophages) that take up basophilic stains and contain most or all of the genes of the organism.

A **gene** is a specific sequence of nucleotides in DNA or RNA that is located usually on a chromosome and that is the functional unit of inheritance controlling the transmission and expression of one or more traits by specifying the structure of a particular polypeptide and especially a protein or controlling the function of other genetic material (see expanded definition below).

—**Phobia** is a noun combining form representing an abnormal fear, or an intolerance to or aversion for some situation <photophobia>.

The definition of a trait in Webster's Medical Dictionary is not adequate and will be expanded here.

A **trait** is an inherited characteristic. Such traits can be organized into levels of significantly different importance. A high level trait represents the presence of an entire appendage. (Lee, 2004). Alternately, a trait can represent the dimple on the cheek of an individual. It can also represent any of a wide variety of conditions leading to what are described as genetic diseases. The failure of an organism to produce an important enzyme leads to a disease.

The definition of a **gene** also requires further definition. During the late 20th Century, it became quite common to

⁸Zillmer, E. Spiers, M. & Culbertson, W. (2008) Principles of Neuropsychology, 2nd Ed. NY: Barnes & Noble

⁹Lambert, K. & Kinsley, C. (2011) Clinical Neuroscience, 2nd Ed. NY: Oxford Univ. Press

speak of a direct connection between a gene and a protein that it caused to be produced. However, it is now clear that the situation is much more complex. Genes can generally be divided into at least xxx (transcription) genes and xxx (expression controlling) genes. A xxx (transcription) gene typically defines an enzyme (a member of a special subclass of proteins) that may subsequently produce multiple proteins or modify other molecules that may or may not be proteins. An xxx (expression controlling) gene may control the expression of one or more xxx (transcription) genes.

When converting a molecule into an alternate form required by the organism, multiple enzymes may be required to operate in a precise sequence. If one or more of the required enzymes are not available at the required location and time, the required molecule cannot be created and a genetically based disease results.

It becomes quite evident that there is no one-to-one relationship between most individual genes and most specific traits. It is even more evident that there is seldom or never a one-to-one relationship between a gene and a specific medically observed symptom or symptom complex (syndrome).

Burde, Savino & Trobe have reintroduced the use of failure trees into ophthalmological medicine. However, their extension of these trees into the neuro-ophthalmological environment is quite limited. They open their volume with a chapter titled, "Unexplained Visual Loss." It opens with an assertion. "One of the most challenging problems a physician faces is the diagnosis of visual loss when no structural abnormalities in the eye are apparent." Their opening failure tree related to unexplained visual loss does not address any neurological conditions other than the generic, optic neuropathy, and a designation "psychogenic." They do offer a clear distinction between illusions, misperceptions of external objects, and hallucinations, sensory experiences that are not based on incoming sensory information. Their text is remarkably lacking in discussion of the neuron and neural interconnections. Only the first order neural circuits of the ocular-motor system are even addressed, and that treatment is superficial.

Lacking an adequate model, the field has relied upon the exploratory investigations of many independent investigators. This is illustrated by the large number of arbitrarily named waveforms and/or features contributed by these different groups. The Heckenlively & Arden text introduces "waves" related to the ERG with prefixes extending almost continuously from letters A to P. In fact, most of these "waves" are only features of a given Class of waveform, as defined in this work. It also presents experimental data recording so-called oscillatory potentials. It appears that these potentials are actually electrical crosstalk involving action potentials from various ganglion cells. Their variation in amplitude could be explained by the variable impedance of the Activa collector circuits involved. That text provides considerable information on conventional experiment implementation but very little on experiment design. Most of the data is presented without significant attention paid to the definition of all of the fundamental parameters actually involved. Usually, only the obvious external features of the patient and test instrumentation are discussed. The book contains excellent material on the gross architecture (morphology) of the retina. The discussion of the vascular-retinal barriers, from a biochemical perspective, is the best available. There is also a broad discussion of the measurement of visual evoked cortical potentials, including those related to cortical blindness (See blind sight below).

The evaluation of visual, particularly chromatic, abnormalities have been attempted since the late-1800's with varying degrees of success. The field has now matured into three specialized areas; (1) the industrial screening of abnormalities, primarily for visual adequacy for specific jobs but frequently to locate abnormalities in the population, (2) more detailed academic experiments in the laboratory to quantify the abnormality and (3) medical diagnosis in the treatment of disease. Rubin and Walls provide an early scenario of the activity in the first two areas¹⁰. Their discussion of the Farnsworth D-15 test and the Farnsworth-Munsell 100 Hue test are useful in this discussion. However, many of the points made in their discussion lacks confirmation based on more recent work. They also used many terms without providing a definition or reference to a definition. The D-15 is discussed in terms of a test for color confusion. The H-100 is discussed in terms of a wavelength discrimination test. Both employ a small group of low-saturation colored caps. The medical aspects of color vision will be discussed in the later Sections of this Chapter. That discussion will focus on a cross reference between probable cause and effect.

The clinical literature of visual defects has not matured into a hierachal structure. It remains a flat file of many symptoms that have been documented when patients have presented with a wide variety of complaints. There is seldom a description of a causal mechanism or a primary disease. Collins has provided a broad handbook of clinical

¹⁰Rubin, M. & Walls, G. (1969) Fundamentals of visual science. Springfield, Ill: Charles C. Thomas pp. 321-328

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ophthalmology¹¹. However, the categories used seem to organize the symptoms more by how they appear to the clinician than to their ultimate cause. This situation is illustrated by the International Classification of Diseases, 9th Revision (ICD-9 codes) related to vision and used within the clinical field¹². ICD-10 was issued in 2003 and reorganizes the ICD codes into 21 Chapters and using new code formats. It also includes cross-reference mechanisms designed to help show causal relationships. Chapter VI now applies to diseases of the nervous system (codes G00-G99) and Chapter VII now applies to diseases of the eye and adnexa (codes H00-H59). It will likely take many years before these new codes achieve wide use in research. The codes are available at <http://www.who.int/classifications/apps/icd/icd10online/>.

Rubin and Walls stress: “The only way to prove definitely the presence of a dichromacy is the demonstration of a neutral point.” They also stress that the test apparatus must use a source with a color temperature of about 7500 Kelvin for accurate results. As seen in **Chapter 2**, such a source is very nearly an equal quantum flux density source. They also provide their interpretation of a protan, deutan and tritan on a C.I.E. Chromaticity Diagram. In their drawings, the point “C” is shown at different places. Apparently this C is meant to mean the neutral point as perceived by the person with that defect, not the neutral point as perceived by a normal subject. Their conclusion is that protans, deutans and tritans exhibit dichotomous axes terminating at 493, 497, and 568 nm. respectively. This author differs significantly with their view that only selected animals perceive color and that those that do can be grouped by a mixed list of characteristics. However, the values correspond well with the proposed termination points of the Hering axes at 494 and 572 nm under equal flux conditions.

The increased availability of rapid communications between researchers and clinicians in recent years has greatly expanded the discussion of visual abnormalities. Recent work reported in the literature, particularly that based on MRI and CT measurements, requires a new definition and understanding of the concept of blindness. The long established state of being blind has given way to a wide range of forms of blindness, many involving what is described as “blind sight.” Blind sight can be defined as including cortical, midbrain and projection abnormalities not associated with morphologically identifiable failures.

The state of definition with regard to blind sight is seen to be comical in the case of a doctor who insists the patient is cortically blind (based on Anton’s Syndrome) but the patient insists he is not¹³.

Apparently the physician overlooked the significance of the Pulvinar Pathway (an extra-geniculocalcarine pathway). A second case¹⁴ is more specific in that a one degree 20 minute area of the retina, (? the foveola) gave a response 2 to 4 months after “cortical blindness.”

Blind sight focuses on the inability of the subject to identify many parameters of a scene even though all of his physiological elements of vision are working perfectly. These shortcomings are most frequently identified following a cerebral accident. Many of these conditions may be present in a significant portion of the population but the individual subject may not be aware of his impairment except through association with others.

Color vision abnormalities occur so widely that they have long been identified as abnormalities whether they are due to physiological, perceptual or cognitive difficulties. Many of these classes of inadequate color vision will be discussed below. Other selected forms of blind sight will also be discussed.

The fact that signals from the foveola are treated differently from those of the fovea and the peripheral retina must be recognized when discussing visual abnormalities. The foveola is typically a 0.35 mm. diameter area of the retina centered on the point of fixation. This area projects into a cone in object space of 0.9 degrees using LeGrand’s paraxial focal length. A diameter of 1.2 degrees is more appropriate based on a complete optical model of the eye.

The following table represents a working description of a series of diseases encountered in the preparation of this

¹¹Collins, J. (1982) Handbook of Clinical Ophthalmology. NY: Masson Publishing

¹²Alexander, L. (1994) Primary Care of the Posterior Segment. Norwalk, CT: Appleton & Lange Appendix

¹³Heckenlively, J. & Arden, G. ed. (1991) Principles and practice of clinical electrophysiology of vision. St. Louis, MO: Mosby Year Book, pg. 562

¹⁴Perenin, M. Ruelm I. & Hecaen, H. (1980) Residual visual capacities in a case of cortical blindness. *Cortex* vol. 16, pp. 605-612

work. It is clearly not exhaustive but may help support an orderly description of eye diseases. The Internet provides rapidly expanding flat file describing various diseases but frequently only in medical or behavioral terms. [xxx Search eye disease table]. Only a few of these diseases will be discussed in detail in this work. Some information on other eye diseases may be found in **Section 18.8.9**.

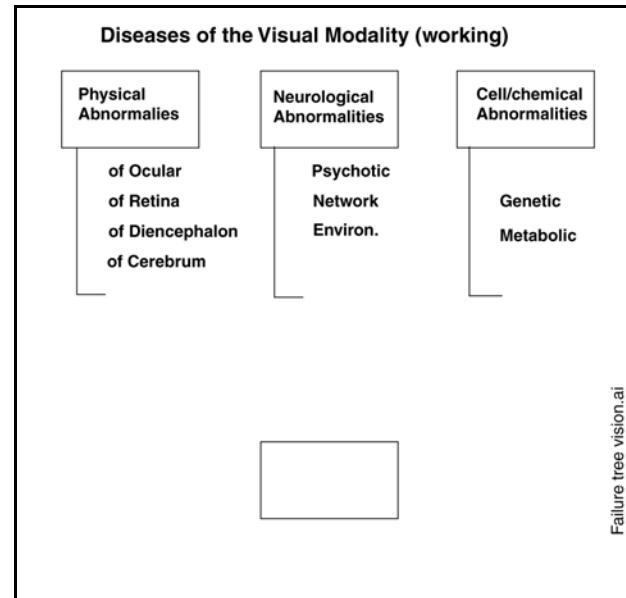


Figure 18.1.1-1 A working table of diseases of the visual modality ADD.

A simple graph from Blackwell¹⁵ indicates the difficulty of categorizing visual diseases, **Figure 18.1.1-2**

18.1.1-2 He provides an overview of various conditions presumably of the types found in his practice.

Cause	AMD	Cataract	Glaucoma	Diabetic Retinopathy	Other
White	54.4 %	8.7	6.4	5.4	25.0
Hispanic	14.3	14.3	28.6	14.3	28.6
Black	4.4	36.8	26.0	7.3	25.6

Figure 18.1.1-2 Gross disease statistics by race. From Blackwell, 2008.

There are a multitude of sources on the Internet providing guidance related to eye diseases for a popular audience. In general, their descriptions are less than adequate for a scientific discussion of vision modality diseases. Many sites provide superficial simulations on what patients perceive through their visual modality. The Discovery Eye

¹⁵Blackwell, C. (2008) <http://www.blackwelleyesight.com/eye-information/rates-of-eye-disease-in-the-us/>

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Foundation site falls into this category¹⁶. While the information is useful at a casual level, it frequently lacks or misrepresents details. A source of less utility is RetNet, dedicated totally to the description of eye diseases based on proteins generated by chromosome encoding¹⁷.

The National Eye Institute of the National Institute of Health has long sought to provide an organized mapping of eye diseases. It lists about 25 diseases and disorders on its home page. The listing is by gross name and is not categorized further. The comments under each heading are brief and aimed at a popular audience.

[xxx edit]

This chapter will examine a wide range of abnormalities in the visual system. **Section 18.2** will concentrate on failures and abnormalities not involving the afferent neurons per se. **Section 18.3** will concentrate on failures of the photodetection elements of stage 1. Abnormalities in this stage affect only individual spectral channels. **Sections 8.4 and 18.5** will address the perceptual channels of both luminance and chrominance, and how to separate abnormalities in stage 3 from those in stage 2 and stage 1. **Section 18.6** looks at failures on a more local and general basis. It is also at a more conceptual level since the operation of the cortex is peripheral to the goals of this work. **Section 18.7** is very brief. It looks at only a few of the afterimage effects of vision. **Section 18.8** places a number of medical conditions in context with the bulk of this work.

18.1.1 Functional block diagram of vision

There are a wide variety of abnormalities associated with human vision. Many of them have been given a symptom-related name. Only a few have a cause-related name. Some only enjoy the label of a syndrome. The most widely discussed are the abnormalities of color vision. This chapter will attempt to place all of these failures, named abnormalities and syndromes in a framework based on the model developed here. In this model, there are nine functionally separate but highly integrated areas devoted to making vision possible:

- | | |
|--|---------|
| 1. The optical image forming apparatus, including the shutter--eyelid | Stage B |
| 2. The mechanisms for pointing to and scanning the important elements of a scene | Stage 5 |
| 3. The metabolic support to the eye | Stage 0 |
| 4. The quantum mechanical photodetection, or transduction, function related to the chromophores in the Outer Segment | Stage 1 |
| 5. The quantum mechanical translation function, creating the initial neural signal | Stage 1 |
| 6. The analog signal processing function in the retina | Stage 2 |
| 7. The encoding function within the retina that generates action potentials | Stage 3 |
| 8. The decoding function within the brain that decodes the action potentials | Stage 3 |
| 9. The signal projection function between the encoder and the decoder | Stage 3 |
| 10. The functions related to cognition and located within the brain | Stage 4 |

Without considering all of these areas in the proper context, it is impossible to understand how the visual process in animal works. In the context of this work, it is possible to define a matrix of abnormalities with considerable precision. **Figure 18.1.1-3** illustrates the functional block diagram of vision. This diagram is more detailed than most others in the literature. The top portion is similar to that presented by Rubin & Walls¹⁸ in their figure 20. It

¹⁶Discovery Eye Foundation (2015) <http://discovereye.org/>

¹⁷RetNet (2015) <https://sph.uth.edu/retnet/disease.htm>

¹⁸Rubin, M. & Walls, G. (1969) Op. Cit. pp. 104

differs substantially from their expanded and speculative model in figure 57. It is not consistent with those diagrams incorporating an incompletely defined “rod” mechanism, those proposing cross coupling between various channels and those proposing external feedback mechanisms within or between channels. Omitting total blindness from the top, the diagram begins with a single thread series of functions that effect the operation of all later functions. Many of these rely upon control signals from the brain for proper operation. These are the only situations involving external neural feedback within the afferent and efferent elements of the visual system.

Below this initial zone of serial functions, the diagram shows a series of parallel functions that operate essentially independently, although the adaptation amplifiers of level 7 share and depend on the limited capability of the choroidal portion of the vascular system. These functions are all important in creating the initial electronic signals used in vision. These parallel channels are labeled, according to the spectral absorption region of their associated chromophore, as the UV-, S-, M- and L-channels.

The intrinsic tetrachromatic capability of vision is obvious. Also illustrated is the polarization sensing capability associated with the UV-channel.

Below level 7 is a reorganization of the signal channels from those oriented toward photodetection, and initial electronic signal generation, to those related to perception. The initial elements of the perception channels include those related to signal processing prior to projection of the signal from the retina to the rest of the brain. This is accomplished in the matrix shown. The matrix itself is usually associated with the interface between the pedicles of the photoreceptor cells and the various lateral cells and dendrites of the bipolar cells found in the Outer Plexiform Layer, levels 8 & 9.

The signal channels in this region are labeled the N-channel, O-channel, P-channel, Q-channel and R-channel. The R-channel is a summation channel and it carries only luminance information. The N- and O-channels are only functional in tetrachromats and short wavelength trichromats. The R-channel is devoted to the luminance characteristics of the scene. The P-channel carries the short wavelength difference information as shown and the Q-channel carries the long wavelength difference information. Note the luminance channel includes a threshold function that is not normally found in the differencing channels (level 11). This feature is created by a very subtle difference in the biasing situation associated with the input structure of the ganglion cells.

Below this region of parallel processing activity is a second area of matrixing designed to support two separate portions of the brain. It is important to differentiate between those signals going to the cortex via the LGN and those reaching the cortex via the Pretectum. There are substantial differences between these signals. The signals proceeding via the LGN are primarily associated with the wide visual field aspects of vision. These are initially responsible for threat detection and establishing the line of sight to best evaluate that threat. They also play a major role in parallax reduction to support stereopsis. The signals passing through the Pretectum are concerned primarily with threat evaluation followed by detailed analysis of objects in the scene. These signals originate in the foveola, the core of the fovea. The signals proceeding to the Pretectum are shown by the looping lines in the lower part of the figure. All of the other signals follow the straight lines to the cortex.

There is ambiguity in the literature concerning the signal manipulation of signals from the foveola. The most common view is that the foveola is achromatic at both the perceptual and photodetection level based on morphological grounds that it only contains “rods.” Such a situation is demonstrably wrong and cannot be supported.

There is strong evidence for special treatment for the signal manipulation and signal projection neurons associated with the foveola. It appears that each of the spectral channels of the foveola is treated like a separate R-signal and

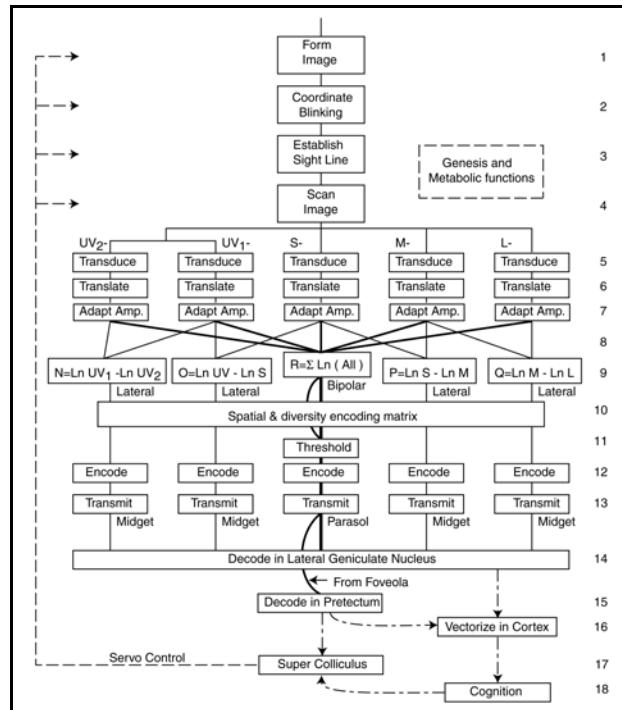


Figure 18.1.1-3 Functional block diagram of Vision

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sent directly to the Pretectum without summation. The summation of these signals into a conventional R-signal may occur in the Pretectum for transfer to the LGN or area 17 of the cortex. Signals from the spectral channels may also participate in the normal R-signal formation in which case the composite signal would follow the normal path to the LGN and cortex. Whichever case is correct, the human is clearly able to perceive detailed chromatic information concerning the scene imaged on the foveola.

In either case, it is important to note the special handling provided for the signals related to the foveola and their delivery to the cortex via the pulvinar pathway and area 5 instead of via the optic radiation and area 17.

The above matrixing functions have a geometric aspect with respect to the field of view. The signals related to the foveola, and normally consisting of a small circular region centered on the point of fixation of the retina, are transmitted to area 5 of the cortex as mentioned above. The remainder of the visual field is divided along a vertical line through the fixation point. All signals related to the left half of the field of view of both eyes are delivered to the right side of the LGN and then to the right side of area 17 of the cortex. Signals from the right half of the field follow the complementary route.

It is readily seen that there are a large number of failure modes associated with the architecture of the visual system. Relating these modes to the clinically determined forms of visual abnormalities is a goal of this Chapter.

18.1.2 Terminology and Glossary

It should be noted that the terms associated with color vision defects are based primarily on early (generally 19th Century) clinical diagnoses. Much of the terminology originated, or was formalized by von Kries in the late 19th Century. As found in the literature, the terminology frequently suffers from a lack of precision. Many of the terms are assembled from simple Greek roots. The prefixes proto-, deuto-, tri- & tetra- translate as 1st, 2nd, 3rd & 4th. The prefixes a- and an- are equally simple and translate as either without or not. A form frequently found in vision is to use a prefix to designate the order of the deficiency and a suffix to designate the degree of the disorder. In this case the suffixes are -anopia for a complete loss (protoanopia) and -anomalia for a partial loss (protanomaly). Some authors have used only the prefixes and associated them with the suffix (-an) as nouns, protans, deutans and tritans to indicate unspecified defects¹⁹. Unfortunately, other authors use these terms as short hand when they are speaking repeatedly of the -anopia or -anomalia forms.

There is considerable confusion in the terminology at the current time. There is a problem in the clinical literature that relates to adding suffixes to the above terms. The terms achromatopia, achromatopsia, achromatopsias, and other terms associated with a complex syndrome of many individual symptoms require more careful definition than usually found in the literature. This work will segregate these terms. Those with a suffix containing -ps- will be reserved for syndromes. Achromatopia will be reserved for an individual system abnormality (i.e., symptom), lack of perception to chromatic stimulation. While this differs from the practice in Trobe, it is followed in much of the non-clinical literature. See the glossary below and definitions in **Sections 18.1.5.8.6 & 18.1.5.8.7**. Krill reviews the clinical situation in the preceding reference and assigns an inheritance property to most forms of color-vision defects along with an incidence rate. The incidence rates of some of these conditions are so low that they are difficult to calculate with any precision. **Section 18.8.3.xxx** will provide a useful analysis of Damasino et al. using the more restrictive form achromatopia, because that is the only symptom of the achromatopsia syndrome their patients exhibited.

The neurology literature (Trobe, p. 369) makes a distinction between organic and nonorganic visual disturbances that seems awkward. An organic disease is limited to those involving anatomic or biochemical abnormalities. Non-organic diseases include clinical features based on psychiatric or behavioral disorders. This division overlooks a variety of electrophysiological conditions that are not visible to the anatomist or chemist, are recognized psychologically, and are (unfortunately) frequently described as psychiatric in the neurology literature. Blindsight, achromatopsia and various migraine images are good examples. All of these conditions are organic in a broader sense. Many arise because of an imbalance in the provisioning of glutamate and/or removal of excess GABA from the immediate vicinity of a group of neurons. They may not be physically recognizable or isolatable by current

¹⁹Krill, A. (1968) in Beard, C. et. al. Congenital anomalies of the eye. St. Louis, MO: C. V. Mosby.
Chapter 16 beginning on pg. 422

chemical means.

Nolte has provided a review of many failures in the visual system primarily from a clinical perspective²⁰.

Leigh & Zee have provided an excellent glossary of terms applying to the general area of abnormal oculomotor conditions in vision²¹.

18.1.2.1 Functional forms of blindness (in general)

The definition of blindness has taken on new shades of meaning in recent years. This section will attempt to provide a comprehensive organization of the currently defined conditions. Based on the block diagram of vision, blindness falls into one of three broad categories, physiological, perceptual and cognitive blindness. Physiological blindness is the classical case involving obvious failure to image the scene onto a functional retina. Perceptual blindness is defined as blindness due to failures in the perceptual system extending from the Outer Segments of the photoreceptor cells to the signal decoding circuits of the cortex. Cognitive, or cortical, blindness is due to failures within the cognitive system. Our understanding of cognitive blindness is changing rapidly. Approximately 32 different forms of cognitive blindness are currently listed.

The sophistication of clinical diagnosis is becoming so sophisticated that once a patient is examined, several anomalies in his visual performance are frequently uncovered. The tendency is to lump the observations into a single syndrome. A situation where color abnormalities are uncovered simultaneously with acuity abnormalities and possibly photophobia is quite common.

18.1.2.1.1 amblyopia, color blindness and hemeralopia/photophobia

Amblyopia is a loss in visual acuity without obvious organic cause, i. e., without poor performance of the physiological optical system. It appears it can be due to problems in either the perceptual system, the servosystem or the cognitive system. Problems of cognition or training are specific candidates. The association with color abnormalities observed in the clinical situation is an awkward one because amblyopia is usually evaluated with respect to the foveola, involving less than a one degree diameter portion of the retina surrounding the point of fixation, while color blindness is usually evaluated using a larger diameter region, frequently selected to omit the foveola. Hemeralopia/photophobia is also a frequently recognized symptom associated with either amblyopia or color abnormalities. It usually involves a qualitative determination.

Much greater care must be taken in the research community to determine any relationship between amblyopia, color abnormalities and hemeralopia if individual traceable causes are to be isolated. This can lead to a better understanding of their direct interrelationship if any.

An interesting chronology of amblyopia in one subject is found on the web site, <http://www.tfn.net/~kate901/amblyopia.htm>. It appears to demonstrate that training at the cortical level can overcome this condition if caught at an early age. Recent clinical investigations into amblyopia appear to focus on the dichotomy of a problem in the retina or a problem in the primate visual cortex²². Little discussion of the midbrain and the POS was found.

Srebro has attempted to quantify the source of amblyopia in terms of a deviation of the line of fixation from the center of the fovea²³. He used differential VEP techniques on the assumption that they would demonstrate a inter cerebral hemisphere difference if the line of fixation was not centered on the center of the fovea in the horizontal plane. He indicated his method did not support a finding in the vertical plane. He found that the line of fixation exhibited an error of forty minutes of arc in five of seventeen amblyopic eyes. Concurrently, he found the

²⁰Nolte, J. (1999) The Human Brain. St. Louis, MO: Mosby pp 421-430

²¹Leigh, R. & Zee, D. (1999) The Neurology of Eye Movements, 3rd Ed. NY: Oxford University Press, Chapter 9

²²Hess, R. et. al. (1985) The pattern evoked electroretinogram: its variability in normals and its relationship to amblyopia Invest Ophthal Vis Sci vol. 26, no. 11, pp 1610-1623

²³Srebro, R. (1983) Measurements of eccentricity of fixation in normals and in amblyopes by evoked potentials. *Vision Res.* vol. 23, no. 12, pp 1527-1532

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nonamblyopic eyes in the same individuals also exhibited an average error of this magnitude. His “most plausible conclusion” was “that in some amblyopes the vertical meridian defined by the topology of the VEP does not correspond to the center of the fovea.” He suggested two candidate mechanisms leading to this error. First, he suggested an error in the decussation in the optic chiasm. Second, he suggested an asymmetric representation of the two visual fields in the occipital lobe. A third candidate offered here concerns a DC offset error in the POS leading to a quiescent pointing error of approximately one-half the diameter of the foveola (not fovea). Such an error would significantly interfere with the nominal operation of the two-dimensional correlator in the pretectum used to extract interps from the imaged scene. Typically syllables would be fixated on so as to position them only partly within the spatial range of the correlator. As a result, either the signal to noise ratio of the output would be reduced or the correlator would not provide a usable interp to the cerebellum and the system would revert to the much slower learning mode (see **Section 17.8**) and analyze words on a letter-by-letter basis. Such operation is fatiguing.

The Visually evoked potential (VEP) technique²⁴, and any evoked potential technique is a very coarse technique by any current standard. It typically uses half inch diameter electrodes placed on the scalp using a conducting jelly to make electrical contact. These electrodes are typically placed at a spacing on the order of two inches. Each of the resulting set of measurement points assimilate signals from at least 10 million neurons associated with unspecified engines of the brain. The stimulation generally involves a two color checkerboard arranged to reverse colors periodically at a rate on the order of once per second. The colors used are not generally monochromatic (or carefully specified as to spectral content). Some recent VEP helmets have been prepared using closer spacing of the electrodes, but the measurements are still coarse and not well localized to the engines of the brain. The technique is not amenable to investigating the ventral portions of the cerebrum.

18.1.2.2 Historical terminology of color abnormalities

18.1.2.2.1 References to historical terminology

Pokorny, et. al. give a more extensive review of the historical terminology than of interest here. Much of the early theoretical work is associated with von Kries (1897). At that time the idea of equal energy per unit wavelength was at best a new concept. The idea of an equal photon flux per unit wavelength spectrum would have to wait for Einstein’s Photoelectric Effect of 1905 and the maturity of the quantum theory in the 1920’s.

Pokorny, et. al²⁵, provide one of the most comprehensive and consistent discussions of color abnormalities. They discuss the classification of abnormalities from at least four different perspectives. They provide additional data showing the sex linked characteristics of color abnormalities, most occurring predominantly in males. They also discuss the invaluable condition, for research purposes, of the patient with asymmetrical color deficiencies. Dr. W. D. Wright says in the Forward to that work, “In my estimation, Congenital and Acquired Color Vision Defects is destined to become the definitive handbook on defective color vision . . .”. However, he caveats rather strongly, and correctly, some of the terminology used in Chapters 4, 7 & 8. There are other caveats that should be mentioned. The work has not incorporated C.I.E. changes related to color vision subsequent to 1951. It also speaks of a rather obscure standard light of 2042 K color temperature. This light was defined in 1948 and is useful primarily in illumination engineering. It has little relevance to visual research. Pokorny et. al. do stress that “rather few measurements of luminance or illuminance in the color vision literature can be considered precise (accuracy within 1 percent).” They continue, “Errors of estimation (in the vision laboratory) may be as high as 50 percent.”

For a more in depth understanding of the parameters of color abnormalities, the work of Lakowski is the Bible²⁶. He provides very specific comments about the intensity and color temperature of the light sources to be used, etc. He also provides a much more comprehensive data set than any other publication. There is a very relevant discussion of the shortcomings of the C.I.E. (1931) Diagram. The breadth of the work introduces a variety of terms not commonly found in the literature that have a significant impact on understanding the mechanisms of color vision perception and the errors therein. Many of these performance terms will be married to the associated and underlying functional

²⁴Heckenlively, J. & Arden, G. (1991) Principles and Practice of Clinical Electrophysiology of Vision. St Louis, MO: Mosby Year Book pp. 400-404

²⁵Pokorny, J. Smith, V. Verriest, G. & Pinckers, A. (1979) Congenital and acquired color vision defects. NY: Grune & Stratton

²⁶Lakowski, R. (1969) Theory and practice of colour vision testing; A review. *British J. Industr. Med.* vol 26, pp. 173-180 and 265-288

terms in this Chapter.

Pokorny, et. al. also give the most succinct description of the importance of field size on color abnormality measurements on page 45. They note that measurements at two degrees will not be representative of larger or smaller fields. They expressly describe the condition with respect to the foveola using a field size criterion of 30 minutes of arc (0.5 degrees).

Schmidt has provided a review of tritanomaly that includes many detailed case histories²⁷. She also reviews in some detail the reported confusion encountered by “tritans” as documented originally by Engelking in 1926. Unfortunately, she used spectral differencing techniques to define the difference between a tritanomal and a normal trichromat. In general, her instrumentation level did not separate tritanopes from tetartanopes.

Stockman, et. al. present some data of good precision concerning deutanopes and a few protanopes as conventionally defined²⁸. Those papers continue to assume system linearity and additivity. There are many terminology differences between those papers and this work. In defense of their reliance on spectral differencing based on linearity, they dismiss Wald’s spectral data for individual chromophores. This work sides with Wald with regard to this data. It should be noted that their comment on page 2509 is specific to transverse microspectrophotometry (MSP). In that context, it is in agreement with this work. Only axial MSP provides the actual spectral performance of individual chromophores. They also touch on the subject of color abnormalities as a function of field position.

Greenstein, et. al., have described an Enhanced S cone syndrome and documented the performance of three subjects at a location six degrees superior to the point of fixation²⁹. An increased sensitivity of the S-channel relative to the M- and L-channels appears evident.

Krill has provided a review of clinical color-vision testing that is a useful reference³⁰.

Most recently, Merin has attempted to simplify some of the nomenclature of color vision disorders, particularly related to cone dystrophies³¹. He has included excellent material on basic genetics and basic molecular genetics. His list of the names synonymous with cone dystrophy (page 254) is instructive as to the state of the art in clinical practice.

18.1.2.2.2 Classification based on performance testing

Categorization by performance has been based on one of two procedures in the past, simple color matching experiments and more difficult chromatic discrimination experiments. Unfortunately, much of the work has been based on the use of imprecise terminology. Partly because of the inadequate terminology, there has been an ongoing conflict between those claiming the fundamental color space is defined trilaterally and those claiming it is defined by two orthogonal axes. The former color space is generally defined in terms of a red-green-blue triad. The latter color space is generally defined in terms of two opponent color pairs, blue-yellow and red-green.

An additional difficulty has been the assumption that the visual system was linear and based on additive color. This has led to the definition of a Chromaticity Diagram that has little foundation in reality. The widely used C.I.E. (1931) Chromaticity Diagram is highly non-conformal and based on a fundamental assumption that is not relevant to the visual process. As a result of these two major theoretical difficulties, investigators have struggled to interpret their data in a meaningful way.

An additional problem related to performance testing is the historical legacy. Many of the terms used were adopted

²⁷Schmidt, Ingeborg (1970) On congenital tritanomaly. *Vision Res.* vol. 10, pp. 717-743

²⁸Stockman, A. MacLeod, D. & Johnson, N. (1993) Spectral sensitivities of the human cones. *J. Opt. Soc. Am. A* vol. 10, no. 12, pp. 2471-2490 & 2491-2521

²⁹Greenstein, V. Zaidi, Q. Hood, D. Spehar, B. Cideciyan, A. & Jacobson, S. (1996) The enhanced S cone syndrome: an analysis of receptoral and post-receptoral changes.

³⁰Krill, A. (1968) Op. Cit. pg. 423-425

³¹Merin, S. (2005) Inherited Eye Diseases. NY: Taylor & Francis

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prior to the availability of adequate instrumentation. The resulting lack of precision has led to a great deal of inconsistency in the literature.

This work has called for a theoretical understanding of the visual system before any attempt to define its performance parameters. The resulting work has shown that the performance of the visual system is most succinctly defined using a precisely defined set of orthogonal chromatic axes. These axes are those usually used within the visual system. Based on these axes, it is possible to define a broad range of distinct performance paameters, performance failures and performance anomalies. In some cases, it has shown that there are clearly defined types of failures that have not been successfully isolated from the database because of the inadequacy of previous terminology.

Although the current literature records and discusses failures associated with the short wavelength and long wavelength spectral channels of vision, there is no equivalent for a failure associated with the middle wavelength spectral channel. To complete the failure mode matrix, the term pentanopia has been adopted. With this addition to the failure mode matrix, it becomes possible to complete a matrix of color abnormalities with a degree of logic and precision not previously available. This matrix provides additional clarity with regard to subjects like that of achromatism. The literature defines a variety of achromatic conditions semantically but not scientifically.

There appear to be two primary forms of achromats defined in the literature, the typical and atypical. The literature is inconsistent as to both the existence and characteristics of the two forms. In one scenario, the typical achromat exhibits a photopic luminosity function that resembles the normal scotopic function and is frequently described as photophobic. The atypical type exhibits a normal luminosity function that transitions between the photopic and scotopic condition. It normally is not described as exhibiting hemeralopia. In this work, there are three possible types of achromat, (1) the anomalous achromat with noticeably abnormal chromatic capabilities with respect to red-aqua and violet-yellow differences but normal luminous efficiency functions, (2) the intrinsic achromat with a complete loss of chromatic response in both the P- and Q- chrominance channels but normal luminous efficiency functions, and (3) the induced achromat. In the induced achromat, the complete loss of response in both of the chrominance channels is due to pentanopia, the complete failure of the middle wavelength or M- spectral channel. These definitions do not address the characteristic of hemeralopia but treat it as a separate condition. Note the impossibility of a subject losing the M-channel photodetectors and retaining either normal red/green discrimination capability or normal purple/yellow discrimination capability. Loss of the M-spectral channel can not result in a deuteranope!

18.1.2.2.3 Discussion of historical terminology and classification

Since color vision abnormalities have been recognized since the dawn of civilization, the terminology used in discussing them has evolved over a long time. In modern English parlance, the custom of using roots from the Greek language in technical definitions is well entrenched. This procedure adds specificity to the science but in many cases, the definitions are now being perfected to the point where the root used is no longer descriptive.

To provide a jumping-off point, three introductory thoughts are offered for consideration:

“The term ‘color blindness’ is a bad one, for it seldom means what it seems to say.³²”

In the Science of Color (a 1963 rewrite of 1953), “The three forms of abnormal (photopic) color systems are monochromatism (‘total color-blindness’) in which all hues and saturations are absent; dichromatism (‘partial color-blindness’) in which only two distinct hues are sensed, variation of intermediate wavelengths causing the same kind of variation of saturation as does purity; and anomalous trichromatism, which departs least severely from normal trichromatic vision.”

In Congenital anomalies of the eye, Krill’s introduction³³ is useful: “By convention the Greek words for first, second, and third (*protos*, *deuteros*, and *tritos*) are substituted for red, green and blue in naming partial color defects (e.g., any word for a red defect has the prefix *proto* or *prot*). The suffix used with the prefix indicates whether the individual has a partial (*anomaly*), complete (*anopia*), or unspecified (*an*) pigment defect.”

³²Rubin, M. & Walls, G. (1969) Fundamentals of visual science. Springfield, Ill: Charles C. Thomas pg. 287

³³Krill, A. (1968) Congenital color-vision defects. *in* Congenital anomalies of the eye. St. Louis: C. V. Mosby

The first thought is worthy of being taken seriously. The second thought is clearly incomplete and lacks the required precision. The third thought attempts to add precision but fails to do so. Whereas protos and tritos are consistently used to describe defects related to the red and blue portions of the spectrum, deuteros is used to define a second type of defect. However, this defect involves the perceived difference between red and green and not a defect related to the green portion of the spectrum exclusively. Krill also omits discussing what color is correlated with the prefix *tetartos*.

An additional reference point is also useful if substantiated; Gerling et. al.³⁴ says (referencing Smith & Pokorny³⁵) "Dichromats tend to turn into trichromats when very large test fields are used." No numbers were given to define the size of the fields involved. It is suggested that three different field sizes need study, the foveola at less than 0.35 mm diameter, the fovea from 0.35 to 1.85 mm diameter, and the retina beyond 1.85 mm diameter centered on the fixation point.

It is impossible to rationalize the field of chromatic aberration based on the totality of the literature. A major problem is that workers in various disciplines have taken different approaches to the definition of various conditions. The clinician has adopted one approach based primarily on the use of a nondescript and/or archaic tricolorimeter. The psycho-physicist has adopted an approach based on spectrometry. There has been very little reliance on an understanding of the functional aspects of the eye. Instead, the results have been used to hypothesize on the function of the eye. These hypotheses have invariably assumed linearity. These problems have led to a nearly infinite variety of papers presenting conflicting analyses. These analyses are generally based on data acquired from laboratory work involving inadequate experimental design.

³⁴Gerling, J. Meigen, T. & Bach, M. (1997) Shift of equiluminance in congenital color vision deficiencies: pattern-erg, VEP and psychophysical findings. *Vision Res* vol 37(6) pp 821–826

³⁵Smith, V. & Pokorny, J. (1977) Large field trichromacy in protanopes and deutanopes. *J. O. S. A.* vol 67, pp 213-220

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It is difficult to recommend a specific text or paper as a concise and definitive reference on visual abnormalities, however, the papers of Lakowski are probably at the top with regard to color abnormalities. He combines both theory and practice as it was understood in the 1960's and provides a significant amount of statistical data. Wyszecki & Stiles³⁶ accumulates a large amount of material without sufficient rationalization of the material. Smith & Pokorny³⁷ provides some good color blind data. Rubin & Walls³⁸ provide a subjective historical review of abnormal color vision. That review provides several definitions of color abnormality seldom seen in other works. It stresses the fact that most color abnormalities are rare and congenital, only a few being acquired. Their table IV provides some initial data on the incidence of color deficiencies. Krill provides the same data and introduces an estimate of the genetic origin of these conditions. Neither source provides a reference and Rubin & Walls uses a different value on page 314 for one of the classes in the table. The data is not related to a functional framework and it shows a proliferation of only two numeric values that makes the tabulation suspect.

They stress "Here, the classification is based on *stimulus terms*--that is, on how many primary color stimuli (say on a tricolorimeter) are necessary and sufficient for each type of color-defective patient to match any given color." Schmidt³⁹ provides a set of essentially raw laboratory data that is valuable. Mollon & Sharpe⁴⁰ provide a series of articles in one book that are highly inconsistent as a group but provide some potentially useful formats for data reduction and presentation.

Color abnormalities have been loosely based on the concept of additive color mixing in the visual system. The terminology of color blindness also suffers considerably from the common wisdom that there are functional analogs to the morphologically forced dichotomy between rods and cones.

Initially, tritanopes were assumed to require three "colors" to match an arbitrary color sample. Soon thereafter, protanopes and deuteranopes were found to be able to match any color using only two "primaries" for full color matching. They were defined as dichromats. Those with no sense of color, achromats, were able to match any color by using only one primary and varying only its intensity. Based on these crude observations, the definitions of a trichromat, dichromat and monochromat evolved. This bit of conventional wisdom is unfortunately not true as will be discussed in the next section. If spectral lights are used, the trichromat only requires two lights to match any third light.

Because both a trichromat and a dichromat require only two lights to match an arbitrary third light, it is necessary to develop more detailed definitions of the difference between these classifications. Alternately, these terms can revert to their original reference to the number of active spectral channels in each classification.

The difference between an achromat and a monochromat is also unclear in the literature. These terms are frequently used interchangeably. While it is clear that an achromat does not perceive any color, he usually exhibits a normal luminous efficiency function based on three functional spectral photodetection channels. On the other hand, a monochromat is usually defined as being achromatic but only employing a single photodetection channel.

The term monochromat is also given widely disparate meanings in the literature. In one case, Farley & Heckenlively describe a complex syndrome with no functional S-channel response and then define the syndrome as X-linked blue cone monochromatism⁴¹. Stockman, on the other hand, describes a subject with only one active spectral channel, the S-channel, as a blue monochromat. More recently, Ayyagari, et. al. recognized a problem with the earlier definitions. They defined blue cone monochromacy as "an X-linked ocular disorder in which affected males have normal short-wavelength-sensitive (blue) cone and rod function but lack medium-(green) and long-wavelength-sensitive (red) cone function."⁴² This work takes the following view. The majority of those with a deficiency in blue sensitivity are affected by a bias problem in the P-channel of the neural system. Tetartanopia is the term used to describe mild cases. Intrinsic tetartanopes is the term for complete cases. A very small number of those with a deficiency in blue sensitivity lack S-channel photoreceptors and are therefore classified as tritanopic.

³⁶Wyszecki & Stiles op. cit. pp. 458-472

³⁷Smith, V. & Pokorny, J. (1975) Spectral sensitivity on the foveal cone photopigments between 400 and 500 nm. *Vision Res.* vol 15, pp. 161-171

³⁸Rubin, M. & Walls, G. (1969) Fundamentals of visual science. Springfield, Ill: Charles C. Thomas

³⁹Schmidt, I. (1970) On congenital tritanomaly. *Vision Res.* vol. 10, pp. 717-743

⁴⁰Mollon, J. & Sharpe, L. (1983) Colour Vision. NY: Academic Press

⁴¹Farley, M. & Heckenlively, J. (1991) *in* Principles and practice of clinical electrophysiology of vision, Heckenlively, J. & Arden, G. ed. St. Louis, MO: Mosby Year Book, Section 104.

⁴²Ayyagari, R, et. al. (1999) Blue cone monochromacy, *in* Hollyfield, et. al. Retinal Degenerative Diseases and Experimental Therapy, NY: Plenum Publishers

Categorizations of color abnormalities have always been complex because of their association with the clinical community, among other things. The practice of that community has been to look at the subject as a “black box” and attempt to collect all of the observable symptoms that might be related into a syndrome. The list of syndromes grows quickly when discussing a complex situation since the lists of symptoms seldom correlate, the laboratory conditions are seldom the same in psychophysical testing, and the list of syndromes grows.

Pokorny et. al⁴³. discuss the myriad additional conditions under which perceived color performance varies. If these conditions are all controlled, it is observed that some humans respond abnormally to various color stimuli. These people constitute the population known as “the color blind,” in fact **the color deficient versus the statistical norm**.

Historically, there have been three principal ways of classifying the multiple conditions shared by those with a color deficiency: The three categories have related to:

- + **Origin**, either congenital (pre-partum) or acquired
- + **Performance** against “standardized” tests
- + **Presumed failures** with respect to putative mechanisms.

The **first** category allows relatively orthogonal groupings except recently some diseases are being observed pre-partum. On the plus side, some of these diseases are even being treated and cured pre-partum. The great majority of color deficiencies appear to be congenital but the presentation in Table 4.1 of Pokorny et. al. is instructive. Note the persistent use of indefinite adjectives and adverbs. This categorization is only a superficial one.

The **second** category, based on psychophysical performance, has always been a difficult one. However, it has been the normal clinical and laboratory method for many years. In the absence of a thorough understanding of the system being evaluated, it is difficult to control the required parameters in order to obtain unequivocal and repeatable results. This has led to “standardized tests” that are invariably of empirical origin. Consider the various tests for color blindness. Although empirical, and prone to multiple misinterpretations due to the poor control of variables, performance has been the primary criteria in categorizing the color deficient. Pokorny, et. al. credit von Kries for playing a major role in this categorization as well, although the two efforts appear unrelated. They credit him with the initial notation using the Greek prefixes, prota-, deutra-, tri-, tetarta- etc.

The **third** category has provided a fruitful one for academics but has not proved successful. The title includes the words presumed and putative intentionally. Again lacking a suitable model of the visual system, it has been common to propose overly simple models, usually based on linearity and additivity and define mechanisms within that context that could explain the observed syndrome. The most famous of the putative mechanisms were those of von Kries in 1897.

Academic papers still relate to these mechanisms today although they were, and remain, terribly elementary in concept⁴⁴. Von Kries proposed those defects in color performance could be explained in terms of three types of mechanisms gone wrong, absorption, alteration and reduction systems. The term absorption was taken as a literal filter in front of the photodetectors. Alteration involved a substitution of a chromophore. A reduction defect was characterized as either a loss of one photoreceptor mechanism or the fusion of two mechanisms. The von Kries mechanisms are attempts to define a complex process using global terms from outside the black box. This approach normally leads to a rigid conceptual framework that does not accept inconsistent new evidence.

In summary, discussions of abnormal vision in the past suffered from the lack of a functional model of the system. The empiricist was forced to struggle with a very complex system hidden behind a veil. The underlying mechanisms have been largely unknown up to this day. The mechanisms in the literature, other than those associated with the pre-retinal visual elements, are therefore highly speculative.

There is a crying need for another category related to failures among fundamental functions related to considerably more basic mechanisms than those of von Kries. These functional abnormalities can only be described through the use of a detailed model of the visual system. The system is much too complex for external analysis using the black box approach of first year engineering courses. Therefore, this work will introduce a fourth criteria for categorization,

⁴³Pokorny, et. al. Op. Cit. Pg. 45-56

⁴⁴Pokorny, et. al. Op. Cit. Pg. 73

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+ **Functional failures** related to specific circuit elements of the visual system.

See **Section 18.1.5** for a discussion of these types of failures and abnormalities. Subsequent sections provide detailed discussions of specific failure mechanisms.

18.1.2.2.4 Cone & cone-rod dystrophies

Burde, Savino & Trobe⁴⁵, quoting Krill et al., have defined cone-rod dystrophy as “a condition in which cone dysfunction predominates over rod dysfunction.” A more precise definition would be, a condition in which the photopic ERG is suppressed relative to the scotopic ERG. Their figure 1-15 provides no calibration of the light levels involved. The loss in amplitude of the flicker response is indicative of the saturation encountered within the sensory neurons when stimulated in the photopic intensity regime.

Merin (pages 251-254) has reviewed the confusion over the terms cone dystrophy and cone-rod dystrophy and made the following comment. “The cone dystrophies are a group of diseases frequently described in the literature under a confusing list of names. Sometimes, a cone dystrophy can even be found classified under altogether different headings, such as macular dystrophy, tapeto-retinal degeneration, inherited optic atrophy, or inborn color vision disorders.” He then gives a precise definition that may be over-precise. “A disorder is classified as a cone dystrophy, if it is inherited, if it affects predominantly the cones, if cones are diffusely affected all over the fundus, and if both color vision and other retinal functions are severely abnormal or absent. The cone dystrophies are further subclassified into separate clinical and genetic entities according to the quantity of cone function involvement (completer or incomplete) the amount of rod involvement (cone or cone-rod dystrophies), the presence or absence of progressiveness, and the genetic background.”

Based on this work, the emphasis on cones should be replaced by an emphasis on photoreceptor performance in the photopic illumination regime.

18.1.2.3 Proposed terminology traceable to functional abnormalities

The primary goal of this section is to introduce new or modified terminology that more clearly delineates the various forms of color blindness but is traceable to the historical nomenclature with minimal confusion. It appears that this goal can be met by merely lengthening the formal name associated with a historically defined condition. However, it is best done in conjunction with, and will be deferred until, the discussions under **Section 18.1.3**.

Originally, at least among the followers of the Young-Helmholtz school, it appears that the term trichromat was associated with an animal employing three spectral channels. Somewhere along the line, it became associated with the *empirical* need for three primaries for full-spectrum color matching by a trichromat⁴⁶. This bit of conventional wisdom is unfortunately not true as seen in the New Chromaticity Diagram for Research and more specifically in the New Sensation Space of trichromatic vision.

Historically, a color to be matched was only defined subjectively, usually by producing a sample. In recent times, the sample has been described in terms of the location of its spectral centroid in either a C.I.E. Chromaticity space, a Munsell Color Space, or a variant of one of these spaces. The distribution of the spectral content with relation to the centroid has usually not been considered although colors with the same centroid but different distributions have been defined conceptually as metameres.

Consider the number of degrees of freedom required by a subject to match an arbitrary color sample of arbitrary intensity, spectral centroid and spectral distribution. Each centroid and distribution can be factored into two orthogonal components. Such a sample is seen to exhibit five orthogonal characteristics (separating the shape of each spectral distribution from the wavelength of its nominal centroid).

As seen in the functional block diagram of vision and in the performance descriptors based on that diagram, a trichromat only requires two spectral colors to match any arbitrary color sample. The requirement is that each of the spectral colors have a specific spectral distribution, a specific centroid wavelength and a specific intensity. Neglecting intensity for the moment, **any perceived color can be precisely matched by a trichromat using only two spectral colors that are properly selected based on center wavelength and spectral distribution.** It is just

⁴⁵Burde, R. Savino, P. & Trobe, J. (1992) Clinical Decisions in Neuro-Ophthalmology, 2nd Ed. St. Louis, MO: Mosby Year Book, pg 26

⁴⁶Pokorny, J. et. al. (1979) Congenital and acquired color vision defects. NY: Grune & Stratton. pg. 73

easier to make a crude match with three colors. This fact totally undermines the simple conventional definitions of dichromats and monochromats based on performance.

Because of the integration performed within the photodetection channels on the product of the spectral distribution of each color in object space and the absorption spectrum of each individual chromophore, the requirement on the spectral distribution and spectral centroid given above can frequently be relaxed. The visual system cannot distinguish between colors in object space that result in the same values for the integrals associated with each spectral channel. Colors in object space that meet this criteria are known as visual metameres.

If the difference between the integrals associated with the S- and M-channels and the M- and L-channels, when properly weighted, are both zero, the subject perceives the scene in object space as colorless regardless of the visual metameres involved. This colorless scene is defined as "white."

It is important to note that visual metameres are not equivalent to metameres obtained by additive color mixing as measured with a man made spectrometer that assumes additive linear color mixing.

It is also important to note that the above discussion applies in the absence of chromatic (i. e., differential) adaptation. Adaptation attempts to automatically change the weighting in the above differences in order to maintain a constant perception of "white" under varying levels of intensity and color temperature in the object space scene.

The formation of the luminance signal in vision relies upon the same integration process as above. However, the values of the integrals from all of the functional spectral channels are summed (in logarithmic perceptual space) to obtain the luminance signal. Thus, all spectral distributions of light that give the same signal value in the luminance channel can be considered iso-lumes.

Including intensity in the discussion, ignoring adaptation and moving beyond empiricism, a trichromat requires six degrees of freedom to match any color of arbitrary spectral distribution and intensity. Two spectral lights, each with an arbitrary intensity and arbitrary spectral distributions about a given median wavelength allow him to precisely match any sample. If desired, the trichromat may use any larger number of lights (whether spectral or not) to match an arbitrary color as long as the appropriate values of the integrals are obtained.

Looking now at the color abnormals, the key characteristic of these subjects is that they exhibit a spectral sensing capability that is restricted with respect to one or more chromatic axes. As an example, a deutanope lacks the ability to evaluate the difference in the integrals presented by the M- and L-channels. Therefore, he can perceive a match between any arbitrary color and only two lights of prescribed characteristics. These characteristics are specific. They must provide the proper signal levels in the luminance channel and in the functional chrominance channel of vision. This constrained match requires four degrees of freedom.

A deutanope or tetartanope can match any color precisely with only four degrees of freedom. He requires one light within the spectral range of his functional chrominance channel of arbitrary intensity, wavelength and spectral distribution and one light within the spectral range of his non-functional chrominance channel of an arbitrary intensity and any wavelength and any spectral distribution. The latter light is only used to establish the proper signal level in his luminance channel.

An achromat only requires one degree of freedom to match any color. He can match any color presented using a single light of any wavelength and any spectral distribution by merely varying its intensity. Since neither of his chrominance channels are functional, he need only establish the appropriate signal level in his luminance channel. He may do this using a light that will excite any of his spectrally selective photosensitive channels. The required light level will vary with wavelength in accordance with his luminous efficiency function.

In the latter two cases, the question of metameres reappears in a different context. In the last case, the achromat can match a very large group of colors varying in spectral characteristics and intensity with one light of a fixed intensity level.

The use of anomaloscopes exploring only a single chromatic axis of the chromaticity diagram has frequently obscured the importance of the above discussion. In these instruments, no attempt is made to match the spectral distribution of the test source and the two primary sources are chosen to avoid excitation of the fully functional chrominance channel. These choices limit the number of degrees of freedom available to the subject. Normally, only the intensity of the test source and the ratio of intensities between the two primary sources can be adjusted. A ratio is not and, by definition, does not represent an independent degree of freedom. Single axis anomaloscopes are clinical devices and should not be considered adequate for research.

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In the case of subnormal color performance but not complete failure in one or both chrominance channels, the situation becomes more complex. The same relationships apply, however, the weighting factors in the above summations and differences are different. Furthermore, another variable becomes important. The quiescent signal level within the individual circuits of the chrominance channels becomes a parameter affecting the overall chromatic performance of the subject. The impact of these changes will be explored in **Section 18.1.5.8.3.**[xxx chk number]

As discussed above, and as will be discussed in Section **18.1.5.8.3.**, the use of the terms dichromat and monochromat based on common performance tests are ambiguous. They will not be used in that context in the remainder of this work. Henceforth, these classifications will be restricted to describing the performance of the spectrally selective photodetection channels of vision. **A dichromat is a subject with only two functioning spectral detector channels.** In the same domain, **a monochromat exhibits only one functioning spectral detector channel.** **An achromat exhibits three fully functional spectral detector channels but is unable to process the information to perceive color.**

All of the above concepts and processes can be related directly to functional segments of the overall block diagram of the visual process presented here. There need be no conjecture or conceptualization concerning the possible sources of malfunction. The detailed causes of failures observed through performance testing can be easily isolated.

18.1.2.4 Protocols used in evaluating vision abnormalities

The current standard for ERG recording was provided by Marmor et al. in 2004⁴⁷. The purpose of the standard is to achieve the greatest possible consistency between laboratories, while recognizing the need to maintain maximum repeatability within a given laboratory. It is worth noting the protocol does not define the color temperature of the light source. It makes the assumption that a flash lamp has an intrinsic color temperature near 7000 Kelvin. Any background field is described in terms of candela/meter² across the full surface of the bowl of a Ganzfeld illuminator. The standard calls for an illumination intensity range of only 3 log units in steps no greater than 0.3 log units. The required pre-adaptation is described. It also notes the difficulty of allowing a “dim red light” during operations.

18.1.2.5 Glossary

The definitions under this section are extracted from the Glossary of the main work for convenience. An extensive glossary of clinically observed cerebral visual defects is in Miller & Newman⁴⁸.

Achroma—(from the Greek, without color).

Achromat—An individual that is unable to perceive any color or to differentiate between any two color samples except based on luminosity differences. Occurs in two sub-types. (1) Pentanopia in which the M-channel is nonfunctional (extremely rare or unknown). In this case, the luminous efficiency function is abnormal and there is induced failure of both the P- and Q-channels. (2) Intrinsic achromatism (normal case) due to a failure in both the P- and Q-channels of the visual system. The luminous efficiency function is normal in this case.

Achromatopia—The basic condition of being completely unable to perceive chromatic differences. See achromat. See also the syndrome achromatopsia.

Achromatopsia—A clinical syndrome normally including achromatopia, nystagmus, amblyopia, hemeralopia (photophobia) and pupillary irregularities. See also achromat and achromatopia.

Agnosia—Loss of the ability to interpret sensory stimuli.

Amaurosis—(from the Greek, without light) Total loss of vision without pathologically recognizable change in the eyes. Often associated with a cortical lesion.

⁴⁷Marmor, M. Holder, G. Seeliger, M. & Yamamoto, S. (2004) Standard for clinical electroretinography *Documenta Ophthalmologica* vol 108, pp 107-114

⁴⁸Miller, N. & Newman, N. ed. (1998) Walsh and Hoyt's Clinical Neuro-Ophthalmology, 5th ed, vol. 1. Baltimore, MD: Williams & Wilkins

Amblyopia--Classical definitions regard amblyopia as loss of visual acuity with no organic defect. However, many groups are beginning to expand this definition as specific organic (or electronic) defects are noted in various parts of the visual system⁴⁹. See Blind Sight.

Anomalous trichromats –A broad term for individuals unable to distinguish between color samples to a normal degree but without a specification with regard to their luminous efficiency function. The two most common forms are deutanopia and tetranoia. Those with lesser grades of difficulty are known as deutranomalous and tetranoia. A third form would be pentanopia, the lack of a functional M-channel, resulting in the induced failure of both the P- and Q-channels. The subject is an induced achromat under this condition.

Anton's Syndrome–A condition of blind sight where the diagnostician insists the patient is totally cortically blind and the patient insists he is not. Generally found in the case where the diagnostician is depending on PVEP's and observations of the condition of area 17, 18, and/or 19 of the Occipital Lobe without considering the extrageniculocalcarine pathways (the Pulvinar pathways).

Atrophy– The general physiological process of reabsorption and breakdown of tissues, involving apoptosis. When it occurs as a result of disease or loss of trophic support due to other disease, it is termed pathological atrophy, although it can be a part of normal body development and homeostasis as well.

Blindness–Total inability to perceive the parameters of a scene in the nominal visual field of a subject in the presence of illumination.

Blindness, partial–Inability to perceive, either totally or partially, one or more characteristics of a scene in the nominal field of view of the subject in the presence of illumination. The functional deficiency can be further defined by introducing a prefix to indicate one of a large number of special cases. The physical deficiency can be further defined by introducing an additional prefix to indicate the nature of the failure causing the functional deficiency.

Blind sight–Typically a partial blindness due to a functional failure or deficiency of the perceptual or cognitive part of the visual system. Usually described in terms of an inability to recognize or interpret a parameter of a scene normally requiring cognition. Examples are motion blindness and inability to identify common objects (particularly faces). Approximately 32 varieties of blind sight is reported in the current literature. Most color perception anomalies are fall into this category.

Center of confusion –The apparent convergence point for a set of isochromatic lines for a color abnormal based on the assumption of additive color in the visual system. Usually plotted on a C.I.E. (1931) Diagram although it is recognized that this is erroneous. A conformal diagram is required.

Cerebral achromatopia– Achromatopia of cerebral origin.

Color confusion – A gross characteristic associated with major errors in color perception.

Color discrimination –A characteristic associated with small errors in color perception.

Color rendition – The precision with which a subject perceives a specific wavelength of light compared to a color normal subject.

Computer (aided) Tomography –A non-invasive three dimensional imaging technique involving the introduction of a nuclear isotope into the blood stream and tracing its location in the organism as a function of time with an array of sensors. The image is created by assembling a Fourier Transform of the emission maps with a computer.

Confusion loci – The systematic and directional lines of chromatic confusion for a color abnormal.

Copunctal point – Also known as the center of confusion or point of convergence. An empirical concept based on the apparent convergence of the isochromatic lines of a color abnormal, especially a protanope or tritanope, when lines are constructed and then extended beyond the data base on a C.I.E. (1931) Chromaticity Diagram. A nonexistent point from a theoretical perspective as the lines actually diverge as they approach the limit of luminous sensitivity.

⁴⁹Delint, P. Weissenbruch, C Berendschot, T. & van Norren, D. (1998) Photoreceptor function in unilateral amblyopia. Vision Res. vol 38, no. 4, pp. 613-617

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Deuteranopia--Form of anomalous trichromatism in which there is no perceived difference between reds and greens caused by a failure in the Q-channel of vision. In the intrinsic form, the luminous efficiency function is nominally normal.

- Dichromat –1. *Functional definition.* An individual that has two functional spectrally distinct photodetection channels. Protanopes and tritanopes (and a putative pentanope) are typical functional dichromats.
2. *Performance definition.* An individual that has only one functioning chrominance channel and is limited in his ability to discriminate colors to those along either the aqua-red or violet-yellow Hering axes.

Dominant wavelength –An approximate term used with the C.I.E. Chromaticity Diagram. It is the spectral wavelength arrived at by extending a straight line from a specific point of interest through the white point being used until it intersects the spectral locus. The value, related to a given sample, changes with source characteristics.

Dorsal terminal nucleus--A structure of the brain connected between the Pretectum and other elements of the Tectum. Part of the Precision Optical System. The interface between the afferent signal paths from the eye and the efferent signal paths to the motor neurons. Controls the position of the ocular globes through the posterior and anterior rectus muscles.

DTN--See dorsal terminal nucleus

Dystrophy– The degeneration of tissue, due to disease or malnutrition. Usually used with an accompanying adjective or prefix to describe the type of tissue involved. See atrophy.

Entopic imagery– Reproducible visible phenomena arising from within the eye.

Hemeralopia– Abnormal visual intolerance to photopic light intensities.

Idiopathic– Relating to or denoting any disease or condition that arises spontaneously or for which the cause is unknown.

Isochromatic lines –The confusion loci for a given individual or a class of color abnormals.

Lateral terminal nucleus--A structure of the brain. One of three small nuclei in the Precision Optical System. The interface between the afferent signal paths from the eye, decoded by the Pretectum, and the efferent signal paths to some of the motor neurons controlling the ocular globes.

Lazy eye –The vernacular for Amblyopia. Not to be confused with wandering eye.

Lesion –Any pathological or traumatic discontinuity of tissue or loss of function of a part.

LTN--See lateral terminal nucleus

Magnetic resonance imaging–A technique relying upon the molecular asymmetry of certain molecules. By exciting these molecules and measuring their response, an image of a large mass of tissue can be mapped with significant resolution in three dimensions without invasive surgery.

Match point – In the colorimetry of vision, the mean of the statistical spread in values obtained with an anomaloscope for an individual or a class of individuals.

Match range --In the colorimetry of vision, the range in the statistical spread in values obtained with an anomaloscope for an individual or a class of individuals.

Medial terminal nucleus--A structure of the brain. One of three distinct small parts of the Precision Optical System. The interface between the afferent signal paths from the eye, decoded by the Pretectum, and the efferent signal paths to the motor neurons. Controls the angular position of the ocular globes via the superior rectus and inferior rectus.

Monochromat –1. *Functional definition.* An individual that has only one spectrally effective photodetection channel. A very rare condition. Not to be confused with a protanope or tritanope who lack one functional spectral channel but have two functioning channels.

2. *Performance definition.* An individual that has no ability to discern color. He can match any color to any reference color based only on intensity. The term achromat is preferred.

MTN—See medial terminal nucleus

Neuralgia— an intense burning or stabbing pain caused by irritation of or damage to a nerve.

Neuritis— Inflammation of a peripheral nerve or nerves, usually causing pain and loss of function.

Neuropathy— Any of numerous functional disturbances and pathologic changes in the peripheral nervous system. The term is also used to designate noninflammatory lesions in the peripheral nervous system, in contrast to inflammatory lesions (neuritis).

Neutral axis —The confusion locus of the color abnormal passing closest to the white point (typically taken as the point of the standard illuminant in use). Also known as the axes of confusion

Nystagmus--This term is used variously in the literature to describe both normal and pathological conditions.

1. A pathological condition involving an uncontrolled oscillatory movement of the axes of the eyes during which the amplitude of oscillation is tens to hundreds of times greater than the amplitude of the tremor, while the frequency of the nystagmus is tens of times lower than the frequency of the tremor. (Yarbus pg 120)
2. Pursuit nystagmus, generally not exhibited until several months post-partum in humans and probably learned, is the ability to maintain the image of a smoothly moving object on the point of fixation of the retina.
3. Optokinetic nystagmus allows the eye to track successive points in a continuously moving scene. It is characterized by a slow component in the direction of scene movement during observation and a fast component in the opposite direction as the line of fixation jumps to a different location in the scene. This appears to be a learned capability in man.

Optical Coherence Tomography (OCT)— A very sophisticated marriage of interferometric and conventional imaging to provide a three dimensional map of the retina.

Photophobia – The avoidance of high light intensity situations by sufferers of hemeralopia.

Protanopia--Form of dichromatism in which the long wavelength spectral channel, the red or L-channel is non-functional. Accompanied by induced deutanopia, failure of the Q-channel, due to the lack of an input signal. Colors along the aqua-red axis are confused, and the perceived relative luminosity of red is much lower than for the normal observer.

Pseudo-isochromatic –A color performance test that is readable by a color normal but appears to be of uniform color (isochromatic) to a color abnormal.

Scotoma—An area of less than nominal visual performance within the visual field, surrounded by an area of less depressed or of normal vision. The source of the scotoma need not involve the photoreceptors or the physiological optics.

Sensation –Used in its first order psychological context without regard to cognition. A signal propagating within the neural system or a general name for the initial interpretation (an interp) or perception (a percept) achieved by the cortical processes.

Strabismus --<clinical sign> A deviation of the eye which the patient cannot overcome. The visual axes assume a position relative to each other different from that required by the physiological conditions. The various forms of strabismus are spoken of as tropias, their direction being indicated by the appropriate prefix, as cyclo-tropia, esotropia, exotropia, hypertropia and hypotropia. Also called cast, heterotropia, manifest deviation and squint. See also nystagmus.

Tetartanopia--Rare form of dichromatism (based on performance definition) in which blues and yellows are

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confused but the luminous efficiency function is nominally normal. Caused by a failure in the P-channel of vision and leaving the subject a functional dichromat.

Tritanopia-Form of dichromatism in which the short wavelength spectral channel, the blue or S-channel is not functional. Accompanied by induced tetartanopia, failure of the P-channel, due to the lack of an input signal. Blue and yellow are confused, and the perceived relative luminosity of blue is much lower than for the normal observer.

Wandering eye –See strabismus and nystagmus. Not to be confused with Lazy Eye.

18.1.3 Overview of functional failure modes related to vision

The **initial** observation is that the visual system has been designed with a considerable degree of attention to providing some amount of vision under even significant conditions of malformation or damage. The luminance channel will provide a perceptible image with only one functioning photodetection channel. Furthermore, the sight line can be considerably misaligned and a useful image will still be obtained, albeit at reduced resolution because of the physical matrixing of the neurons projecting to the Pretectum. It is also possible to obtain some chromatic information even if one of the chromatic channels is inoperative or seriously impaired. Because of the inherent overlap in the wavelength discrimination capability of each channel, there is reasonable discrimination of color in the middle of the spectrum no matter which channel is not operating properly.

The **second** observation is that the clinically used descriptions for color defects are not sufficiently compartmentalized to be used here. An anomalous trichromat, as an example, is a general term for a performance abnormality that does not relate to a specific type of functional color abnormality. An anomalous trichromat could have difficulties in the photodetection, analog signal processing, or signal decoding and perception areas. Several correlation tables are provided within this chapter, attempting to relate the performance abnormalities described in the clinical literature to the more specific functional abnormalities defined here.

Third, because of the poor choice of illuminants used to characterize color aberrant visual performance, the titles used based on Greek roots are quite awkward. These titles are essentially archaic and, at most, indicate by their numeric sequence the historical order in which the disorder was recognized in the ancient scientific community. This problem is compounded by the tendency of researchers to use “equal energy” light sources behind filters in their experiments under the mistaken impression that the visual process uses energy sensitive, as opposed to photon sensitive, detectors. An “equal flux density” source, 7,000 to 8,000 K color temperature, is far more appropriate. It gives equal weighting to the short and long wavelength photodetectors. “White illuminant C,” a 6,500 K source, can be used for general tests where an accuracy of about 20% is acceptable. Most current tests for color abnormalities suggest a higher color temperature source, typically a Macbeth easel light with a color temperature of 6740 Kelvin. The claim is that this light is closer in practice to indirect solar illumination. This work continues to recommend 7053 Kelvin based on an equal photon flux per unit wavelength criteria.

Fourth, the label of rod-monochromat suffers from two difficulties. The performance of an eye can be achromatic. However, it is not known to be monochromatic in the scientific sense of sensitive to only a very narrow spectral range. Secondly, this achromatic condition is frequently associated with a normal luminance spectral sensitivity obtained by combining the spectral sensitivity of three chromatic photodetection channels. It has never been successfully associated with a photoreceptor having an absorption characteristic other than that of one of the normal chromatic channels. Rod-monochromat is an archaic and misleading term. A recent investigation into cone-rod dystrophy using the latest high resolution imaging techniques failed to find any sign of rods in the human retina⁵⁰. See also **Section 18.8.3.3.2**.

Because of the above conflicts within the literature, the remainder of this Chapter will be organized functionally. A correlation will be provided in this chapter between many of the terms in the literature and the functional failures highlighted herein.

The combination of series and parallel functional elements in the functional block diagram lead to perceived chrominance and luminance characteristics that are highly intertwined. This makes their scientific elucidation, in the absence of a satisfactory model, difficult under the best laboratory conditions and very difficult under less precise conditions. With an adequate model, the problem of describing the fundamental failure modes is greatly simplified but the number and variety of partial failure modes increases substantially. Many failure modes are seen to impact

⁵⁰Wolffing, J. Chung, M. Carroll, J. Roorda, A. & Williams, D. (2006) High-resolution retinal imaging of cone-rod dystrophy *Ophthalmology* vol 113, pp 1014-1019

multiple parameters related to brightness, hue and saturation.

As will be seen below, a number of failure modes impact both the chromatic and the transient performance of the eye. The transient failure modes are complex and involve both short term and long term transient phenomena. The long term failure modes will be discussed in **Section 18.2.2**. The shorter term failures that are more properly defined as artifacts of the design will be discussed in **Section 18.5**.

Although the previously defined functional block diagram of **Figure 18.1.1-1** can be used to account for many of the failures found in the visual system, using the level numbers on the right for added precision, there are additional failure modes not shown in this figure. To account for these “out of plane” failure modes, a new figure is introduced as **Figure 18.1.3-1** in **Section 18.1.3** replacing the physiological portion of the original figure, stage B, with a stage 0 closely aligned to the genetic and metabolic failure modes of the system. To avoid confusion, the levels related to this change will be given letter designations. This new figure will explain how the classical names for the anomalies of color vision can be used as a short hand for the new precise and functionally defined names for these same syndromes.

The advent of MRI, PET and CAT imaging techniques have introduced a new age in determining the causes and locations of visual system failure. Prior to this time, the description of a visual failure usually relied upon morphological examination, frequently post mortem, following major damage due to disease or accident. A comparison between a normal and an impaired subject was usually limited to psychophysical evaluation. Recently, Zeki and associates have provided new and detailed information relative to the impact of a visual failure and the resulting changes in the operation of the cortex compared to a normal subject⁵¹. The most recent advance has been the marrying of full motion picture recording to technique of functional MRI. The result is the ability to record in real time, the activity level in the brain as a function of normal external stimulation (motion-FMRI). Massachusetts General Hospital is a leader in this field.

Visual system failures can be most appropriately divided into two super classes, organic failures of the neural system and psychotic failures (based on more subtle failures in forming neural interpretations, or possibly interconnections, within the CNS).

A wide variety of failure modes (that are also medically identified conditions) within the visual modality can not be observed by a medical or behavioral observer. The term hallucigenic is used in these instances; something that is perceived by the patient only and not observable by a trained observer. The patient must describe his perceptions via a well trained observer to be useful in the research environment.

Since the 1980's, a new syndrome has been gaining prominence in medicine largely associated with visual disease, Hallucigenic Persistent Perceptual Disorder (HPPD). It has gained medical acceptance with a number of caveats. The most significant is that “the symptoms cannot be due to another medical condition.” Unfortunately, this caveat has seldom been honored. As many as 14 distinct symptoms have been grouped within this syndrome; “Typical symptoms of the disorder include: halos or auras surrounding objects, trails following objects in motion, difficulty distinguishing between colors, apparent shifts in the hue of a given item, the illusion of movement in a static setting, air assuming a grainy or textured quality (visual snow or static, by popular description, not to be confused with normal “blue field entoptic phenomenon”), distortions in the dimensions of a perceived object, and a heightened awareness of floaters. The visual alterations experienced by those with HPPD are not homogeneous and there appear to be individual differences in both the number and intensity of symptoms. The last clause is clear, HPPD is not an adequately defined syndrome but a catch-all at this time for a variety of organic and psychotic symptoms.

On final editing, it is expected this chapter will be organized to address these two super classes, organic and psychotic failures separately. [xxx note]

18.1.3.1 Failures based on signal flow within the neural system

The description of visual failures based on signal flow is logically divided into two parts. **Figure 18.1.3-1** shows the visual failures that relate to the *sensory signal* paths of the neural system. It provides a straight forward description of various forms of partial blindness. The first part shows sensory signals traversing from the visual field through the visuotopic portion of the system. The second part is fundamentally different. It shows the flow of *information*

⁵¹Zeki, S. Aglioti, S. McKeefry, D. & Berlucchi, G. (1999) The neurological basis of conscious color perception in a blind patient. Proc. Nat. Acad. Sci. Vol. 96, pp.14124-14129

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signals (that are not visuotopic) through the higher levels of the central nervous system. It should be emphasized that while the signal delivered to the occipital lobe, primarily area 17, are visuotopic, they are not rectilinear with respect to either the visual field or the retina. They have undergone a conformal transformation that aids the information extraction mechanisms. Thus the mapping found in the occipital lobe is related to but not representative of the visual fields (**Section 15.2.5**). As will be discussed further below, the relationships between objects in the visual field are passed to the parietal lobe (area 7) via the TRN where they are stored in an inertial space related to the orientation of the subject but not the visual field of view.

In the first figure, horizontal bars in a particular frame indicate loss of vision in the particular field due to severing of the visual nerves at the location marked by the corresponding letter.

This figure shows the central region of the field of view, specifically the 1.2 degree diameter foveola, in slightly different form than some earlier versions. Beginning in frame D, it is shown specifically. Earlier versions omitted the region of the foveola because it was not normally identified using perimetry (example, Harrington, 1981, page 108), or even the subject's own (less than educated) descriptions. The field of the foveola is processed in parallel by two different signal paths, a low resolution path compatible with the rest of the peripheral field and a high resolution path used only to analyze fine detail within the field of view. Thus, if visual performance is the criteria instead of visual perimetry, frames D through G are appropriate. If only perimetry is the criteria, D through G can be used without recognizing the cutout for the foveola.

The description portrayed in frame G (boxed) is subject to revision. Because of the overlap in the signal processing of the foveola, and the character of the PGN/pulvinar processing, the loss of perception related to loss of signals related to one-half the foveola field prior to the PGN may be difficult to identify. Alternately, it may explain some of the more unusual perceptual failures associated with failures of the analytic mode of stage 4. If there is a major failure within the PGN/pulvinar, it is likely the loss will be represented by an oval representing the entire foveola. path. In that case, the grandma effect described below is likely.

Kandel et al⁵², began to recognize this situation beginning in 1991 and Cook introduced a modern version of this figure to the Wikipedia more recently⁵³. Their 2000 version includes a long caption to describe the complexities of the situation. Cook's figure shows two versions of D (with and without the cutout). His figure suggests the foveola is merely a part of the visual cortex instead of a separate identifiable PGN/pulvinar pathway (note his differences in field of view when path 4 and path 6 are individually cut).

Frame A	Individual retina and optic nerve failures
Frame B & C	Individual field failures
Frame D	Indiv. Field failures after the foveola path has been stripped out for PGN processing
Frame E & F	Quadrant failures w/o loss of foveola processing
Frame G	Foveola, PGN and/or pulvinar failures without loss of peripheral vision

Failures related to frames D, E & F can lead to two forms of "blindsight." The first has been defined as keyhole vision; the subject remains capable of perceiving the scene imaged on his foveola, but not the broader peripheral

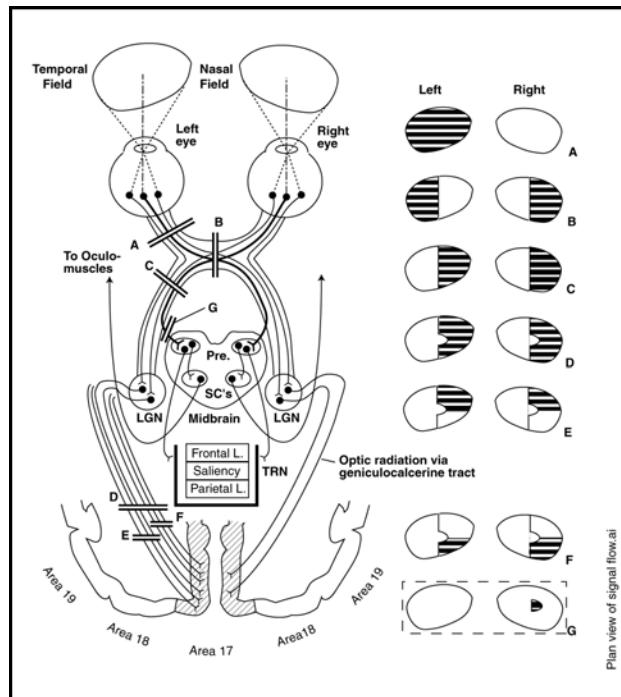


Figure 18.1.3-1 Failure modes in the sensory signal paths of human vision. Failures documented primarily through lesions of the various nerve paths.

⁵²Kandel, E. Schwartz, J. & Jessell, T. (1991) Principles of Neural Science, 3rd Ed. NY: McGraw-Hill (also 4th Edition, page 544)

⁵³Cook, {Search Google for hemianopsia and have Google translate the Netherlands version at <http://nl.wikipedia.org/wiki/Hemianopsie>}

scene imaged on the periphery of his retinas. The second is more intriguing to the laboratory or medical investigator; the ability of the subject to perceive motion in the visual field due to signal processing in the LGN associated with the auxiliary optical system supporting version, vergence and stereopsis. While the eyes may actually track a physiologically important object, the subject does not perceive the content of the visual scene.

The failure illustrated in Frame G can result in the Grandma Effect; the ability to interpret a scene based on the signals processed within the visual cortex but the lack of ability to recognize and identify fine detail associated with a specific scene because of the lost ability to process high acuity imagery by the pulvinar.

There are additional failure modes not easily illustrated in the above figure. These generally relate to the assembly of the information extracted in the occipital lobes via the LGN/occipital couple, and the information extracted via the PGN/pulvinar couple. Errors related to the PGN/pulvinar couple and occurring subsequent to processing by this couple, will be designated **GG** errors. Errors related to the LGN/occipital couple and occurring subsequent to processing by this couple, will be designated **DD** errors. The **GG** and **DD** errors may occur prior to the saliency map of stage 4 or may occur during formation of the saliency map.

Figure 18.1.3-2 describes the information signal paths within the central nervous system associated with vision by example. These paths are much more difficult to identify and to characterize for multiple reasons. Individual information paths have been identified primarily by traffic analysis, i.e., identifying performance failures after injury (or after lesions in lower species). The signals are mainly symmetrical between the two sides of this figure. However, for simplicity, the major afferent signal paths are shown on the left and the major efferent paths are shown on the right. Only the awareness, analytical, cognition and volition and initial command mode signals are shown in this figure. A broader discussion of the sensory and command modes within the CNS appears with [Figure 15.2.5-5].

Failures in paths 6, 7 & 8 can result in very unusual diseases involving losses in high level feature extraction and specific forms of agnosia.

Section 18.8.9 will link the major medically defined diseases with their functional description based on this work.

The complexity of the TRN interface with the saliency map of the parietal lobe and the frontal lobe is so great that it can only be shown in a third and separate expanded figure that remains largely conceptual and undocumented.. This figure appears in the next figure.

The actual coding of the information signals has not been determined. Neither has the manner in which it is stored been determined. It appears the various pieces of information passed to the TRN from the information extraction engines is combined and stored in an inertially-oriented saliency map using essentially bidirectional signal paths. This map can be accessed bidirectionally by the cognitive engines of the frontal lobe (the xxx path). Following cognition, the cognitive engines can return instruction to the motor system via the saliency map and TRN using the volition path. Sensing changes in the saliency map resulting from cognition the TRN routes the appropriate volition signals to the superior colliculi (and frequently the cerebellum) for generation of the

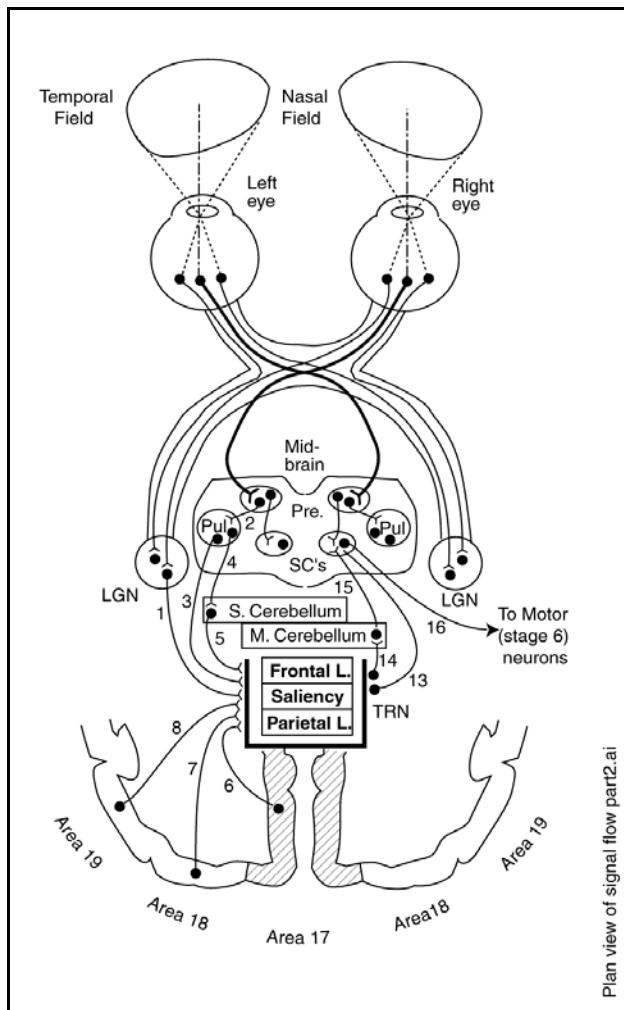


Figure 18.1.3-2 Failure modes in the information signal paths of human vision. The results of failures along the numbered paths are discussed in the text. S.—sensory; M.—motor; L.—lobe.

Plan view of signal flow part2.ai

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necessary command level signals. These command level signals are then propagated to the appropriate muscles and/or glands.

Failures along the numbered information signal pathways can have substantial, and sometimes multiple consequences relative to overall visual performance. **Table 18.1.3-1** provides a short-form description of these failures. The following paragraphs will expand on these failures.

Table 18.1.3-1
Information signal path failures and performance consequences

Path #	Path Name	Consequence of path failure
1	LGN-TRN	Loss of version/vergence signals to eyes & perception of rapid object movement
2	PGN-Pulv	Loss of interp information resulting in prosopagnosia, frequently includes alexia
3	Pulv-TRN	Loss of first level percepts related to analytical mode (foveola analysis)
4	Pulv-Cerebellum	Loss of 2 nd level percepts related to complicated objects imaged by foveola
5	Cerebellum-TRN	Loss of 2 nd level percepts as in path #4.
6	Brodmann17-TRN	Loss of shape and orientation information for objects in peripheral vision
7	Brodmann18-TRN	Loss of <i>some</i> velocity information concerning objects in peripheral vision
8	Brodmann19-TRN	Loss of high level correlation of information for objects in peripheral vision
9	TRN-Parietal Lobe	Failure to forward all information extracted from Stage 4 sensory engines
10	Parietal L.-Saliency M.	Failure to collate all information supplied by the Stage 4 sensory engines.
11	Saliency M.-Frontal L	Loss of image fidelity (e.g., Melting Clocks of Dali)..
12	Frontal. L.-Sup Coll.	Failure of Sup. Coll. to implement instructions as commands to PNS
13	TRN-Sup. Colliculus	Loss of simple instructions for primarily binary actions.(e.g., closing eye lids)
14	TRN-Cerebellum	Loss of sophisticated instructions from cognitive engines to motor system
15	Cerebellum-Sup. Colic.	Loss of detailed commands for implementation by superior colliculus
16	Sup. Colic-Stage 6	Loss of motor responses as commanded by cognitive engines

The LGN-TRN path (#1) is used primarily to deliver signals to the TRN related to vergence (the pointing of the eyes needed to achieve stereoscopic vision). It also provides information about the relative motion of the subject along the forward vector of vision.

Afferent paths #2 through #5 are associated with the analytical mode processing associated with the foveola. The information signals along these paths become more abstract with path number. Afferent paths #6 through #8 are associated with the awareness mode processing associated with the peripheral retina (including the fovea outside of the foveola). The information signals of these paths also become more abstract with path number. Efferent paths #11 through #14 are only representative of the many paths emanating from the TRN and controlling virtually all responses of the organism (including glandular responses) to sensory stimulation. These paths also carry signals endogenous to the frontal lobe.

The PGN-Pulvinar path (#2) transfers interps (the lowest form of information signal) developed in the PGN to the pulvinar for correlation against its stored memory in order to develop the initial percept of the scene imaged on the foveola. In the case of reading, an interp tends to be the coding of a single short word or a syllable.

Marzi et al. have identified an “SC/extrastriate” couple in 2009 without further identification⁵⁴. It is proposed their SC refers to the region of the LGN to SC path (the Brachium of the Superior Colliculus) and their extrastriate area refers to the pulvinar of this work. Thus, their SC/extrastriate couple is the first empirical citation in the literature relating to the PGN/pulvinar couple defined in this work. The PGN is occasionally inadequately identified as a bulge on the side of the SC.

The Pulv–TRN path (#3) transfers simple initial percepts (such as the one word of a stop sign or a simple sentence) to the TRN for insertion into the saliency map. This path involves minimal temporal delay.

The Pulv–Cerebellum path (#4) and the Cerebellum–TRN path (#5) provide a detour through the cerebellum for percepts too complex for the pulvinar to process. They require further correlation by the cerebellum to create a single percept encompassing a more complex idea or image. It is the cerebellum’s task under these conditions to provide a higher level percept (that encompasses the complete meaning of a complex sentence or even a paragraph). This pathway may involve significant delay because of the time required to capture all of the initial percepts needed to correlate into a higher level percept (the thought included in an entire paragraph of text as an example).

The Brodmann17–TRN path (#6) is that typically associated with the visual cortex. It propagates typically simple interps relating to the shape, orientation and color of objects imaged on the peripheral retina and extracted by area 17.

The Brodmann18–TRN path (#7) and the Brodmann19–TRN path (#8) propagate higher order interps or percepts (the terminology is still fluid) to the TRN describing more sophisticated features of objects such as their velocity and potentially the relative position of multiple objects.

It is important to note that paths #6, 7 & 8 each consist of multiple sub-paths representing the four quadrants of the visual field. No one sub-path represents an entire visual field. They combine with the path from the pulvinar representing the central field associated with the foveola at the TRN, the first location where the entire visual field is represented.

Both the pulvinar and the cerebellum are major elements of memory functioning independent of the cerebral cortex. Much of the stored memory is associated with the sensory level afferent signals and command level efferent signals as discussed further below.

Following information collation and cognition (#9 through #12), discussed in the next figure, the TRN issues a broad range of commands to the motor/glandular system. This range is only illustrated here in conceptual form.

The efferent TRN–Sup. Collic. path (#13) propagates simple instructions (commands) to the superior colliculus for immediate implementation.

The efferent TRN–Cerebellum path (#14) and the Cerebellum–Sup. Collic. path (#15) provide a detour through the cerebellum in order for the cerebellum to accept complex instructions from the TRN and generate a large array of individual commands required for the organism to implement the instructions in a smooth and coordinated manner.

The efferent Sup. Collic.–Stage 6 path (#16) represents the large number of individual neural paths required to implement a large scale coordinated response to either an ingenuous or sensory-instigated response.

The functional operation of the elements within the TRN shell can be discussed using **Figure 18.1.3-3** which also appears as [Figure 15.2.5-xxx in xxx]. The figure relies upon much of the discussion concerning the higher level functions of the visual cortex in **Sections 15.5 and 15.6**.

⁵⁴Marzi, C. Mancini, F. Metitieri, T. & Savazzi, S. (2009) Blindsight following visual cortex deafferentation disappears with purple and red stimuli: A case study *Neuropsychologia* vol 47, pp 1382–1385

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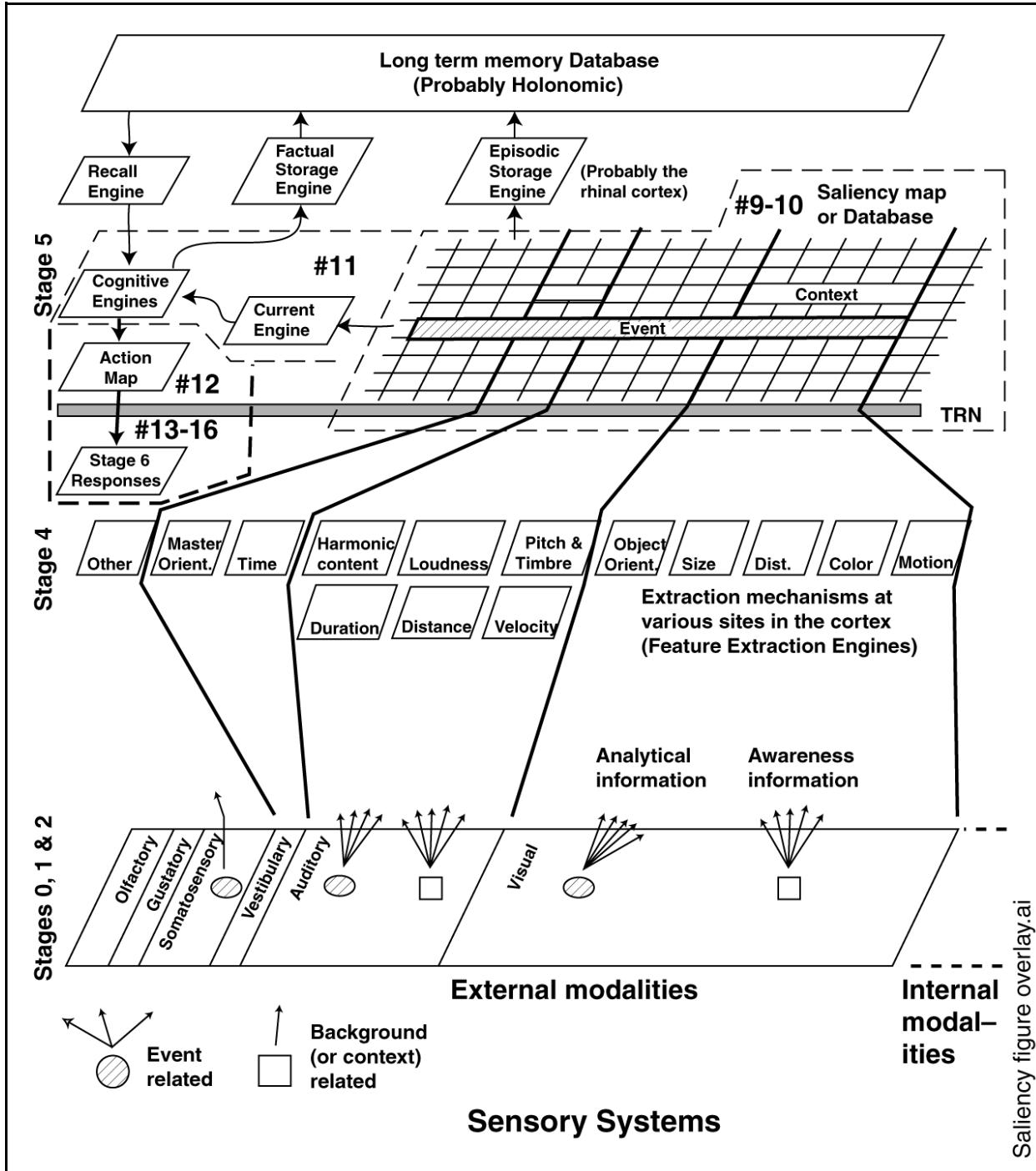


Figure 18.1.3-3 The TRN as gatekeeper to the saliency map and cognition. Areas #9 to #11 and #12–16 are highlighted for discussion in the text.

The TRN acts as the gatekeeper between the sensory modalities and the saliency map (shown as the grid in this figure), the rest of the high level memory system (of the type identified by Fuster), the cognitive engines and other interfacing engines of stage 5. It also acts as the gatekeeper between the cognitive engines and a variant of the saliency map described as the action map, and the stage 6 response system.

A major role of the TRN is to direct the myriad sensory modality signals directed to it to the appropriate stage 4 engines of the parietal lobe. The parietal lobe engines associated with sensory inputs (Brodmann area 7) then complete extraction of the information and collation of that information (sensory integration or SI) into the representation of the external environment as the saliency map. This highest level can be thought of as including the conscious and near conscious levels and of operating within the neocortex.

The saliency map is then accessed by the cognitive engines of stage 5 using path #11. After cognition, instructions are sent back through the TRN (path #12) to the superior colliculus over path #13. After expansion of these instructions into operational commands by the superior colliculus (aided by the cerebellum if appropriate (paths #14–15), these commands are dispersed to the stage 6 engines over path #16.

The neurological definition of sensory integration defined here is grossly different from the use of the term sensory integration by the occupational therapy (based on Ayres⁵⁵) and behavioral science communities. Her early work related to the loading of the cerebellum through early training, and not necessarily integration from multiple sensory modalities for purposes of cognition.

Cursory analysis of the valuable work of Ayres suggests she was primarily discussing problems in young children centered around delayed or inadequate loading of the memory of the cerebellum, and possibly the limited communication between the two halves of the cerebellum in unusual left-side/right-side cooperation tasks. It is suggested the children's performance reflected failure or inadequacy of the information signal path labeled Cerebellum–Sup. Collic. (path # 13 above) due to inadequate training or experience via the Pulv–Cerebellum path (path #4). These paths are illustrated here using the visual sensory modality. See Section xxx in xxx.

From that perspective, Ayres' use of the term sensory integration related more closely to the sensory-motor interchange at the subconscious level that occurs in the paleocortex.

18.1.3.1.1 Synesthesia and allesthesia – mis mappings within the neural system

Synesthesia is a clinical condition where a patient perceives a response normally associated with one sensory modality when actually stimulated by a signal associated with a different sensory modality. It can also be associated with a misreading of extracted information related to one operating mode within a modality with a second operating mode within the same modality. The correct perception may also be maintained. Currently, the definition of synesthesia remains primarily conceptual and without precision. Because of this, its relative occurrence within the human population is difficult to resolve. Wikipedia provided a nice overview of the problem in 2014⁵⁶.

Quoting Wikipedia, “Depending on the study, researchers have suggested 1 in 2,000 people have some form of synesthesia, while others have reported 1 in 300 or even as many as 1 in 23. One problem with statistics is that some individuals will not self-classify as they do not realize that their perceptions are different from those of everyone else.” It is common enough to spawn local groups of sufferers of this condition. It is discussed more fully from a physiological perspective in **Section 15.4.6**.

The Wall Street Journal provided a general article for the popular press⁵⁷. “Synesthesia isn't considered a condition that needs to be cured. Most people with synesthesia actually report deriving pleasure from it.” It suggests a more specific prevalence of synesthesia than Wikipedia, when all of its variations are considered, “the condition has 100 variations and affects about 4.5% of people. Julia Simner is director of the Multisense Synesthesia Lab and a psychology professor at the University of Sussex in England, and is often quoted. Currently, most of the reports are anecdotal in character with little in-depth study. “Often, individuals will have more than one kind. About 40% of people with synesthesia have at least one family member with it, though it may be a different type.”

⁵⁵Ayres, A. (1963) The development of perceptual-motor abilities: A theoretical basis for treatment of dysfunction *Am J Occup Therapy* vol 17(6), pp 127-135

⁵⁶<http://en.wikipedia.org/wiki/Synesthesia>

⁵⁷Reddy, S. (2017) Synesthesia: A Disorder That Blurs the Senses *Wall Street Journal*, 17 January, page A13

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Many forms of synesthesia have been documented;

- Grapheme-color (sometime indicated as grapheme → color synesthesia), perceiving a particular color that is associated with each letter or number is one of the most common types of synesthesia.
- Chromesthesia (association of sound with a color, can be impulse- or tone-related and related to notes, intervals or timbres.)
- Spatial sequence synesthesia (numerical sequences tend to appear at different depths in stereoscopic space)
- Auditory-tactile synesthesia (auditory → tactile couplings, a less common form)
- Lexical-gustatory synesthesia (hearing or reading a word elicits a taste perception)
- Touch: Some synesthetes find that pain elicits colors. Others have mirror touch synesthesia which is when they experience touch by looking at someone else who is being touched.

"The most frequently discussed type of synesthesia is grapheme-color (most well documented, number-color or letter-color) synesthesia." However, there are significant reports of grapheme-color involving other shapes, such as in the case of aquarium fish exhibiting different colors of body parts based on the shape of the parts (personal communications with Snodgrass). **Figure 18.1.3-4** shows a casual representation of the effect. It is not clear that the colors associated with letters and numbers remain the same when the characters are grouped together. Nor is it clear whether the colors are maintained when the object is observed in the peripheral field compared to when it is near the point of fixation. The effect appears to be more common for white letters on a dark background than for black letters on a white background but the degree of prevalence has not been established.

The grapheme-color form has generally been associated with the association areas of the CNS near the occipital-temporal lobe boundary⁵⁸.

Ramachandran & Hubbard have proposed a linkage between several disparate properties; among these properties are;

- 5) Patients with damage to the left angular gyrus have dyscalculia — they can not perform even elementary arithmetic. But they can still recognize number graphemes.
- 6) The angular gyrus is a seat of polymodal convergence of sensory information.
- 7) Angular gyrus lesions also lead to anomia and, intriguingly, loss of ability to understand metaphors.

Ramachandran & Hubbard have also sought to delineate two classes of synesthetes, higher synaesthetes and lower synaesthetes, depending on the extent to which a specific gene is expressed.

As Wikipedia notes, the available data suggests a strong correlation between artistic people and one form of synesthesia or another. Although often termed a "neurological condition," synesthesia is not listed in either the DSM-IV or the ICD since it most often does not interfere with normal daily functioning.[medical citation needed] Indeed, most synesthetes report that their experiences are neutral or even pleasant.

The utility of synesthesia to an artist can be recognized from **Figure 18.1.3-5** from Ramachandran & Hubbard. On the left, the perception of a field of numbers presented in black and white by a normal visual modality. When presented with a matrix of 5s with a triangle composed of 2s embedded in it, the pattern is not obvious to the control group. When the same black and white field is presented to a grapheme→color synesthete, the visual perception is totally changed as shown on the right.

For artists with the more general form of grapheme→ color abnormality, individual shapes may lead to perceptions



Figure 18.1.3-4 A caricature of what a synesthete might see. Note the caricature is formed from white letters on a black surround. The effect is apparently less common, but not absent) for black letters on a white (or lighter) surround. From Wikipedia, 2014.

⁵⁸Ramachandran, V. & Hubbard, E. (2001) Synesthesia: A window into perception, thought and language Journal of Consciousness Studies 8 (12). pp. 3–34
http://ww2.psy.cuhk.edu.hk/~mael/papers/RamachandranHubbard_Synesthesia.pdf

of color not recognized by those with normal vision. This may lead to more vivid color renditions in their paintings, etc.

Ramachandran & Hubbard also note, “A colour-blind synaesthete sees colours in numbers that he cannot otherwise see in real-life visual scenes. Such a situation clearly shows the synesthesia is arising in a region late in visual modality signal processing, after a number of locations potentially contributing to color blindness have already been passed in the signal chain.

See additional analysis in **Section 18.6.1** related to both synesthesia and other -esthesiae.

18.1.3.1.2 Dyslexia–mis calculations within the neural system

Dyslexia is a broad term lacking precise definition within the medical community. It occurs in several forms, those forms that are developmental in nature and those that are long term in nature. Fundamentally, dyslexia is a failure by a person to correctly perceive a graphic image presented to the person without any intent to deceive (such as may be observed in a magicians act intended to deceive the audience).

The developmental forms of dyslexia are of great concern to parents, probably out of proportion to the seriousness of the condition. The developmental forms can generally be characterized as

1. mis-perceiving printed letters standing in isolation, such as confusing a “b” and a “d” or a “g” and a “q” typically found among children when they are learning the alphabet and in very early reading. Usually overcome within 6 months.
2. mis-perceiving printed letter order in simple words, such as confusing “dog” and “god” typically found following cessation of the mis-perception of individual letters and again lasting on the order of six months.
3. reversing word order in simple sentences, typically following the cessation of letter order dyslexia and lasting for six-12 months.

These situations are very common. They are inherently dependent on the maturity of the neural system of the child and the amount of time the child spends reading . Reading involves storing a wide range of visual memories. As their experience grows in each of the above phases, the dyslexia is normally reduced to being totally absent.

Verpalen & van de Vijver provided a study on developmental dyslexia in 2015⁵⁹. Unfortunately the study included a variety of complications (student groups with disparate educational and language backgrounds) that tend to obscure the basic factors in dyslexia. They provide a simple definition, “Dyslexia is defined as a disorder in reading skills, reading, and spelling development.” The paper provides a good review of current thinking among pedagogists. It also notes the different ages at which children begin encountering reading studies in European schools. It also includes a useful figure 2 and associated discussion suggesting the complexity of the subject and its dependence on the language involved.. They concur in the earlier statement of this work, “Individual differences in reading ability in monolingual and bilingual children are also influenced by reading experience: the more children read, the more skilled they become in reading (Stanovich 1986).” They also provide a road map of neural paths involved in reading reciting read material, and dyslexia. The mapping is based strictly on traffic analysis based on fMRI experiments (which areas of the brain light up the most during BOLD studies).

The long term forms of dyslexia are of greater concern for they may impact career choices and to some degree the

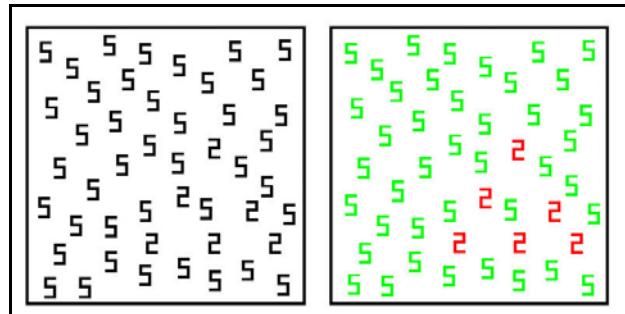


Figure 18.1.3-5 The utility of synesthesia to an artist is evident. Left; perception of a field of numbers presented in black and white by a normal visual modality. When presented with a matrix of 5s with a triangle composed of 2s embedded in it, the pattern is not obvious. Right, same field of numbers as perceived by a visual modality exhibiting synesthesia. From Ramachandran & Hubbard, 2001. The figure is not properly represented as Figure 1 in all renditions of the paper.

⁵⁹Verpalen, J. & van de Vijver, F. (2015) Differences in neurocognitive aspects of dyslexia in Dutch and immigrant 6-7- and 8-9-years old children *SpringerPlus* vol 4, pg 105 DOI 10.1186/s40064-015-0874-1

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quality of life. The subject continually encounters the mis-perceptions associated with one or more of the above developmental conditions. The condition is truly a disease from the medical perspective. The long term forms of dyslexia appear to involve failures in the computational processes occurring within various neural engines of stage 4, visual information extraction, and stage 5, cognition. They are generally psychotic conditions and not identifiable by any currently known medical tests. Many of the long term conditions can only be diagnosed precisely via specially drawn up test protocols. These protocols may be able to identify the specific neural engine where the problem arises but currently, no treatment for the condition is known (except possibly a focus on rote repetition of certain procedures related to the above protocol).

More discussion of the functional characteristics of dyslexia, including certain forms of dyslexia beyond those associated with reading, can be found in [Section 19.10](#) of [Chapter 19](#) of this work on reading and the perception of fine details in graphic material. It also addresses some problems involving motor skill problems related to these misperceptions. The case of A. H. discussed in Section 19.10 represents one of the more rare forms of dyslexia. Other case studies related to dyslexia, and a more serious form—alexia, appear in [Section 18.8.6.3 & 18.9.1](#) of this chapter. [Section 18.9.1](#) also includes a series of definitions related to dyslexia and related diseases.

18.1.3.1xxx Color vision implementation EDIT & MOVE TO 18.1.5

Figure 18.1.3-6 is a modification of the Functional Block Diagram developed in [Section 11.6.3](#) and expanded in [Section 15.6.4](#). An expanded Stage 0 replaces stage B, the section on physiological optics. The description of the boxes in the upper part of the figure can be deduced from the next table and the discussion to follow.

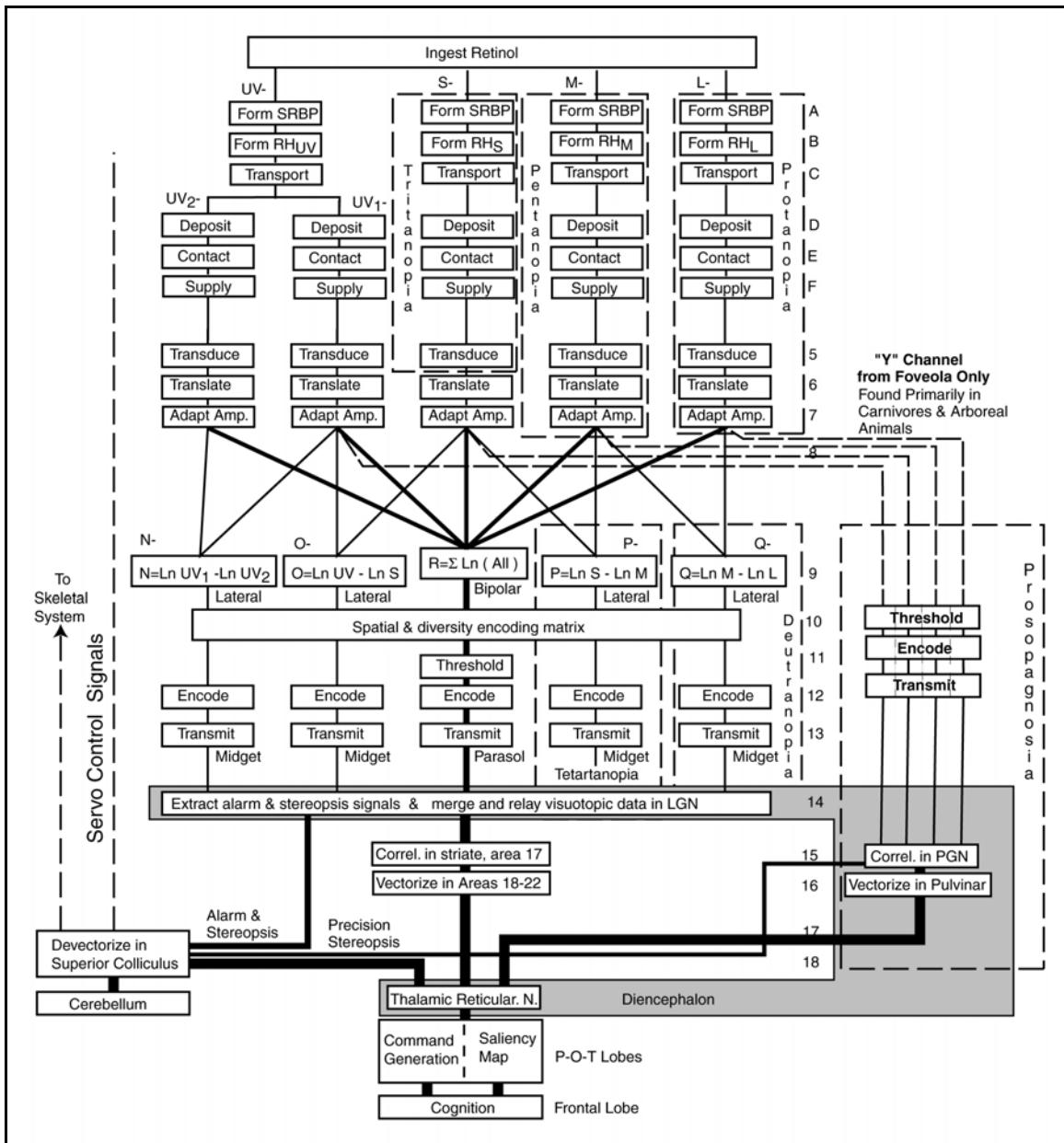


Figure 18.1.3-6 Major (non-visuotopic) failure modes of the visual system. Circuit or component failure within the dashed boxes lead to the type of failures listed. Failure in the dashed box on the right leads to Prosopagnosia, the inability to recognize detailed features, such as faces. See text for details.

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Before proceeding, it is important to have several facts related to human vision in mind:

- + the common channel, used by all visual functions, extends from the optical system to the pedicles of the (nominal) triad of chromophoric photoreceptors. There are three subchannels originating in the Outer Segments of the retina, one for each chromophore and its associated photoreceptor cell.
- + the initial signal paths described by the above three chromatic subchannels are matrixed into three distinctly different signal channels following the pedicles. These are the luminance channel and the two orthogonal chrominance channels, the short wavelength difference channel and the long wavelength difference channel.
- + the fact that all neural activity prior to the ganglion cells of the retina involves analog signal waveforms.
- + the fact that the fundamental signal related to photon detection and generated in the adaptation amplifier of the photoreceptor cells consists of a quantity of free electrons.
- + the importance of the vascular system in supplying bioenergetic material to the retina.
- + the Outer Segments and the adaptation amplifiers of the photoreceptor cells are intimately related to the vascular system through the choroid artery.
- + most of the signal processing of raw visual data is performed in the retina, which is recognized as a protruding portion of the central nervous system.
- + initial information extraction of image information occurs in the mid-brain. Information required for stereopsis is extracted in the LGN and information required for pointing detailed analysis of foveal information is extracted in the Pretectum of the POS.
- + the cortex of the brain concentrates on higher level cognition, interpretation and initial command generation for both the eyes and the musculo-skeletal system.

Failures, or serious abnormalities, involving any of these conditions will also lead to clinical conditions.

Of even greater importance is to understand how the concept of white light is treated in the visual system. It is conventional to think of the perception of “white” in the visual system to follow the concept in object space based on additive color mixing. Under this concept, “white” is a sum in object space obtained by adding multiple colors. In the visual system, the perception of “white” is quite different. Perceptual “white” is a null condition. It is perceived when there is no signal input to the cortex from either the P- or Q- chrominance channels. This difference has a profound impact on the analyses of color abnormalities.

There is a long list of specialized terms used in defining abnormalities of vision. The definition of these terms will be taken up in the appropriate Sections that follow.

[xxx coordinate material below with 17.2.2.8]

Five dashed boxes appear in the figure to indicate the areas where failures may occur related to the most prevalent forms of clinically identified abnormalities in color vision. Protanopia relates to the loss of functional long wavelength, L-channel, performance. Tritanopia relates to a similar loss in the S-channel performance.

Deuteranopia relates to abnormal performance in distinguishing reds from greens in the presence of normal M- and L-channel performance. This condition represents a failure in the Q-channel of the chrominance channels.

The precise definition of deuteranopia has had a checkered past. Helmholtz (1868) first defined it as due to the loss of the M-channel photoreception element (the Helmholtz Hypothesis). Alternately, Fick (1888) argued that it could be due to a neural processing failure that did not require the loss or failure of the M-channel elements (the Fick Hypothesis). Konig is credited by many with first defining it (mistakenly) as the loss of the M-channel or green photoreceptors in the 1900's. This definition was successfully disputed by Marriott writing in Davson in 1962⁶⁰, along with others. The fact that deuteranopia exists in the presence of a normal visibility function was demonstrated by Wright in 1946 and documented in Wyzsceki & Stiles (pg

⁶⁰Marriott, F. (1962) Colour vision: colour-matches *In* Davson, H. The Eye. NY: Academic Press pg 280

462). Judd discussed the inadequacy of the Konig approach in 1949⁶¹.

With the advent of the Zone Theory of Muller (ca. 1926) and its elaboration in this work, a deutanope can be shown to exhibit a failure in the M – and L– differencing circuit (the Q–channel). Such an individual exhibits a normal spectral sensitivity characteristic.

In recent years, Pokorny & Smith and Stockman & Sharpe have attempted to invoke the Helmholtz (and Konig) definition of a deutanope, a subject lacking the M-channel photoreceptors. This effort, although extensively documented has not produced physiologically valid results. Neither has it recognized that the loss of the M-channel results in total achromatopia (not deutanopia) because the inputs to both the P– and Q–channels are lost (**Section 18.1.5**). Under the assumption that functionally defined deutanopes lack the M-channel photoreceptors, these groups have documented the spectra of many deutanopes (frequently under some level of S–channel suppression) and defined the resulting spectra as due to L-cones. Interestingly, Stockman & Sharpe have also documented the spectra of a large group of tritanopes. **Figure 18.1.3-7** shows the purported spectra of a large group of deutanopes (labeled as L-cones) overlaid by a band representing the outer limits of the spectra of 22 color normals reported by Stockman & Sharpe in 1999⁶². Clearly, these deutanopes exhibited normal trichromatic spectra to well within the combined experimental and graphic presentation errors. Their spectral responses do not illustrate any lack of M–channel photoreceptors. The above conclusions are important because all of the data came from the same laboratory. There is little difference in the protocols used for each set of experiments. The deutanopes did exhibit neurological failures associated with the Q–channel of the visual system, as do most if not all deutanopes. The early premise attributed to Helmholtz and Konig cannot be supported based on a modern detailed model of the visual system and the assertions of Wright, Judd and Marriott. Reliance upon a zone theory, as in this work, provides a more appropriate description of the deutanopic condition and a more rational set of photoreceptor spectra.

It should be noted the Vos & Walraven curve in this figure was not the result of experimental activity⁶³. It was the result of a linear analysis using matrix algebra. While it compared spectra of protanopes and deutanopes, it did not compare these spectra to that of normals. This lack undermines their thesis. They indicated that the comparisons would be provided in a subsequent paper. The subsequent paper by Vos, Estevez & Walraven appeared 20 years later⁶⁴. **Section 17.2.2** discusses this second paper more fully.

The conclusion that the L-channel peak is in the vicinity of 570 nm and the M-channel peak is in the vicinity of 540 nm is not compatible with the wavelength difference data of Smith (2000)⁶⁵. The minimums at 580 & 640 nm and the maximum at 625 nm in his data are incompatible with a difference signal created using spectra with peaks at 540 & 570 nm. The maximum wavelength differences (poorest discrimination values) in the vicinity of 450, 532 and 625 nm, and the corresponding interdigitated minimums, correspond well with the expected performance based on the spectral peaks proposed in this work.

⁶¹Judd, D. (1949) The color perceptions of deutanopic and protanopic observers *J Opt Soc Am* vol 39(3), pp 252-256

⁶²Stockman, A. Sharpe, L. (1999) Color spectral sensitivities and color matching *In Gegenfurtner, K. & Sharpe, L. eds. (1999) Color Vision: From Genes to Perception.* Cambridge Univ. Press.

⁶³Vos, J. & Walraven, P. (1970) On the derivation of the foveal receptor primaries *Vis Res* vol 11(8), pp 799-818

⁶⁴Vos, J. Estevez, O. & Walraven, P. (1990) Improved color fundamentals offer a new view on photometric additivity *Vis Res* vol 30(8), pp 937-943

⁶⁵Smith, W. (2000) *Modern Optical Engineering*, 3rd Ed. NY: McGraw-Hill pg 133

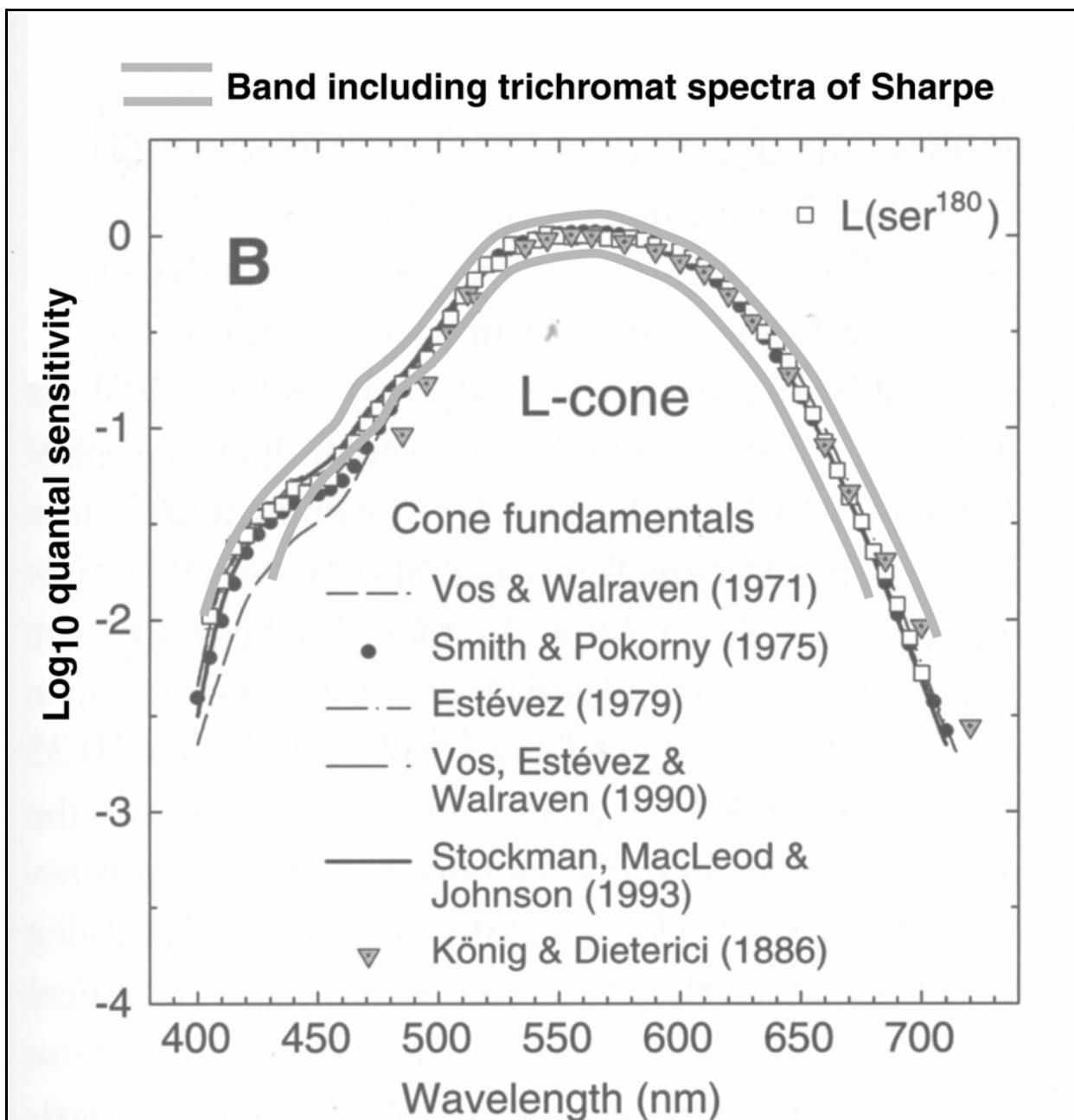


Figure 18.1.3-7 A comparison of the purported cone fundamentals of the L-cones compared with the band incorporating the overall spectra of 22 color normals reported by Sharpe. The putative L-cone fundamentals appear to be congruent with the data for the color normals within the limits of experimental error. Graphic created from figures 2.9B and 2.13C of Stockman & Sharpe, 1999.

Tetartanopia relates to a similar difficulty in differentiating blues from yellows in the presence of normal M- and S-channel performance. This condition represents a failure in the P-channel of the chrominance channels. The data suggests this last form is quite rare. The literature does not define a loss of M-channel performance in the presence of normal S- and L-channel performance. However, such a condition is shown here and labeled pentanomia. Such a

condition may exist but it may be confused with other syndromes involving apparent lack of overall sensitivity to light, i. e., a form of anomalous trichromatism wherein the perceptual response of the M-channel is less than nominal and the subject exhibits induced failure in both the P- and Q-channels. In this case, the subject is achromatic. The basic structure of these abnormalities is in line with those “receptoral and post receptoral defects” postulated by Mueller in 1924 and further defined by Judd in 1943.

Without success by the research community in isolating the specific chromophores of vision and a detailed schematic of the visual system, it is difficult to trace the location and fundamental mechanisms related to the identified failure modes found in color vision with certainty. However, **Figure 18.1.3-2** provides a prediction of the dominant failure mode associated with each level of **Figures 18.1.1-1** and **18.1.3-1**. The possible failure modes at each level are discussed in the following sections along with some of their clinical designations.

Brightness is a perception of luminance in the object field. In vision, it is the summation, in logarithmic signal space, of the signals from all of the active photodetection channels, followed by a thresholding operation prior to the encoding of the data for transmission to the brain. Total loss of one or two photodetection channels can cause an abnormality in this characteristic, a discreet change from normal, but not the total loss of the brightness perception. A total failure in the perception of brightness, while maintaining some sense of color must involve elements proximal to the pedicels of stage 1.

The proper perception of hue and saturation in the object field requires the proper operation of two chrominance channels. Total loss of one of the photodetection channels can cause an abnormality in the perception of hue and saturation, but not the total loss of the perception of color. Total loss of two spectral photodetection channels does result in a complete loss of color perception. A partial or total failure in the perception of color while maintaining normal perception of luminance must involve elements proximal to the pedicels of stage 1.

This Chapter will concentrate on defining the principal failure modes of the visual process and the most likely source of each type of failure.

The most commonly observed failure of the brightness type is a partial one associated with the loss of the long wavelength chromatic sensitivity in the luminance function under all illumination conditions. As can be seen from the functional block diagram, this failure can be traced to a failure in the photodetection function associated with the L-channel or of the interconnecting synapses between the pedicels and the bipolar cells. No other circuit failure in the system can cause this observed failure. Similar failures involving either the S- or M- channel are possible but are very rare. There are only a few documented reports of subjects having lost two spectral photodetection channels.

18.1.3.2 Initial categorization of vision abnormalities

The activities described in the previous sections and figures provide valuable information with regard to potential failure modes within the visual modality and other neural areas.

The medical observations related to a range of abnormalities are discussed in **Section 18.8**. Auras are addressed in **Section 18.8.2**. As an example, any abnormality affecting the full sweep of the perceived visual field, and not dependent on a specific eye, can be attributed to abnormalities affecting the neural system at or beyond path #9. **Section 18.8.2.2** addresses such full field geometric distortions in visual perception. As developed in **Section 18.5.1**, visual snow as an example cannot be attributed to the eyes, the optic nerve, the lateral geniculate nuclei or the occipital lobe (the primary visual cortex).

18.1.3.3 Genetic versus other causes of abnormalities

Although some of the abnormalities of vision clearly have a genetic component, and high level relationships between specific mutations have been associated with specific medical symptoms, many mutations have yet to be associated directly with a specific functional failure in the visual system. The following sections will discuss a variety of abnormalities. Most of these abnormalities are found to be present over a distinct range of performance parameters. Only a few abnormalities involve complete failure modes in one parameter or another. In those situations where a complete failure is involved, it is possible to conceive of a unique genetic source for this problem. In most of the other conditions, the symptom is more likely the result of a group of individual mutations in the genetic instructions. It is less likely that these situations will be describable by a specific series of mutations in the near future.

The field of genetics is moving forward very rapidly. As a result, much of the material published during the 20th Century is already obsolete or requires a new interpretation. A popular book by the academician Gee has provided a

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very important summary of the state of the genetic art as of 2004⁶⁶. Unfortunately, the index of the book is focused on people and places rather than the elements of the genome. As a result, the serious student will be forced to read large pieces of the text. Ruse & Travis have recently edited a large group of significant essays, with a focus on genetics⁶⁷. The overview by Charlesworth & Charlesworth is very useful when discussing the size of the genome of various species and recognizing that much of the genome does not code for proteins but remain functionally important. These or similar recent works should be reviewed before the older works listed below are reviewed. Lyle presented a large work in 1993 focused on the genetically based problems of vision⁶⁸. The work is comprehensive and reflects a long career in the field. However, it is text-based and does not provide unique classifications of the various diseases. Webster, et. al., writing in Ryan, et. al.⁶⁹ have provided a good overview of both basic genetics and the current state of genetics in clinical medicine. Weleber & Gregory-Evans have provided an interesting graphic of the complete human genome, at the gene level, and the loci of genetic failures associated with retinitis pigmentosa⁷⁰. Kandel, et. al. have provided a description of the human chromosomes including their morphology⁷¹. Deeb has also provided information on the putative relationship between certain gene mutations and abnormal color vision⁷². These papers do not recognize the existence of a UV sensitive human chromophore and have not sought a gene that relates to this chromophore or spectral channel. The Deeb paper does reflect the presence of a fourth gene that they associate with an alternate L channel chromophore in women (which has been described as leading to a possible tetrachromacy). This is not the meaning of tetrachromacy in this work.

Stockman, Sharpe, Merbs & Nathans have provided some useful background on genetics in a paper that is otherwise not supported here⁷³. They develop the fact that the known genes for the photosensitive channels of vision (not necessarily the chromophores) are found in head-to-tail pairs and that a variety of mutations within these genes are found widely (pgs 630, 632, 633, 637 & 649). The complexity of the discussion is a clear indication that the true character of the genetic code related to the visual system has not yet evolved. Page 633 suggests each X-chromosome array contains up to at least six pertinent genes.

18.1.3.4 The accumulation of genetic information

This is the age of molecular biology and information concerning the genetics of life is accumulating at an astonishing rate. The US Government has established a repository for this type of information at <http://ghr.nih.nlm.gov/ghr/>. Although it is written for a lay reader, the information contained is quite amazing. As an indication of its scope in some areas, it includes over 60 genes concerned with various retinal dystrophies⁷⁴. It is interesting that the list by Bessant et al does not contain any of the genes described below and in **Section 18.8.3** related to Achromatopsia.

It is interesting to note the above Genetic Home Reference defines three genes ostensibly responsible for color vision, it does not include any gene responsible for the putative “rod” vision. Nor does it include any gene for the ultraviolet chromophore that is present in the human visual system.

It only contains one gene for each of the three photoreceptor chromophores. It describes these genes using the designation Opsin 1 LW (OPN1LW), Opsin 1 MW (OPN1MW) and Opsin 1 SW (OPN1SW). It has dropped the prefix rhod- leaving only the root opsin which implies the chromophores of vision are proteins. Unfortunately, the chromophores of vision are not proteins. The Reference would have been better served if the root opsin had been dropped and the prefix rhod- had been associated with the actual structure of the chromophores. Chemically, the chromophores are dienes, suggesting the names should be Rhodonine 1 LW,

⁶⁶Gee, H. (2004) Jacob's Ladder: The History of the Human Genome. New York: Norton

⁶⁷Ruse, M. & Travis, J. eds. (2009) Evolution: The First Four Billion Years. Cambridge, Mass: Harvard Univ Press

⁶⁸Lyle, W. (1990) Genetic Risks: A Reference for Eye Care Practitioners. Waterloo, Ontario, Canada: Waterloo Univ Press

⁶⁹Webster, A. et. al. in Ryan, et. al. (2001) Retina, 3rd ed. Vol. One, St. Louis, MO: Mosby, Chap 17

⁷⁰Weleber, R. & Gregory-Evans, K. (2001) Retinitis Pigmentosa and allied disorders, in Ogden, T. et. al. ed. Retina, St. Louis, MO: Mosby Chapter 18

⁷¹Kandel, E. Schwartz, J. & Jessell, T. (2000) Principles of Neural Science, 4th Ed. NY: McGraw-Hill, pg 39

⁷²Deeb, S. (2005) The molecular basis of variation in human color vision *Clin Genet* vol 67, pp 369-377

⁷³Stockman, A. Sharpe, L. Merbs, S. & Nathans, J. (2000) Spectral sensitivities of human cone visual pigments determined *in vivo* and *in vitro*. *Meth Enzymol* vol 316, pp 626-650

⁷⁴Bessant, D. Ali, R. & Bhattacharya, S. (2001) Molecular genetics and prospects for therapy of the inherited retinal dystrophies *Cur Opinion Gen & Devel* vol 11(3), pp 307-316

Rhodonine 1 MW Rhodonine 1 SW respectively and Rhodonine 1 UV .

Other rapidly maturing genetic databases are found at www.sph.uth.tmc.edu/Retnet/disease.htm and at www.omim.com/ .

A second revolution is under way in genetics. Whereas the first great step in the field was to define the portions of the genetic code responsible for gene expression as proteins, and the rest was considered “Junk,” it is now becoming clear that this junk is critically important material that (among other things) controls the time of expression of the previously defined genes. XXX was awarded a Nobel Prize recently for describing the role of what might be called junk⁷⁵. As Venter has noted in many of his lectures⁷⁵, “There is a difference between junk and rubbish. Junk you needed once and may need again so you put it in the attic. Rubbish has no known use and you put it into the trash.” This differentiation remains elementary and designed for the popular reading audience. An additional feature of this revolution is the recognition that there is seldom a 1-to-1 relationship between any specific trait or disease and a single genetic mutation. Unless all of the relevant genetic code relevant to a given gene mutation is understood, that mutation cannot be logically associated with a given trait or disease.

Muraki-Oda et al. have recently expanded the data base related to genetic missense mutations related to the inadequately defined disease of rod-monochromacy⁷⁶. They define rod-monochromacy as “achromatopsia or total color blindness” when many of those diagnosed as suffering from rod-monochromacy or achromatopsia exhibit perfectly normal color vision at reduced (mesotopic) light levels. Their paper contains no conformation that any of the research material was derived from subjects who actually lacked functional spectrally-selective photoreceptors.

The recent report of clinical efforts to improve vision in the case of Leber’s congenital amaurosis is indicative of the maturity of the field. The experiments were “tiny human gene therapy trials” of very limited scope and without any control group. An adeno-associated virus was used to surgically deliver a functioning version of a previously identified bad gene (RPE65) into a peripheral area of the retina⁷⁷. The reported improvement was from 20/2000 to 20/710. 20/2000 is an order of magnitude worse than the top line of a normal eye chart (20/200).

Many genetic diseases exhibit quite complex physical symptoms. It is important to recall that the connection between a gene and its purported action or physical role in the phenotype is largely inferred. There may be many other unrecognized actions or structural modifications resulting from a single genetic mutation.

18.1.3.5 Genetics and evolution

There has recently been a flurry of activity attempting to explain the evolution of the visual system based on genetics, particularly the analysis of DNA similarities and differences. As a result of this, a series of dendograms have appeared. Goldsmith presents one of these with additional references⁷⁸. His particular dendrogram is based on the similarity between the substrate material used in the disks of the photoreceptor cell. These disks have no direct role in the visual process. They are a mechanical protein substrate not unlike fingernails in their origin. There is no correlation or relationship between the specific structure of these protein materials and the first occurrence of a particular chromophore in the visual system. Furthermore, there is even less correlation between the genes causing the formation of these specific proteins and the chromophores of vision. It is also interesting that the dendrogram of Goldsmith includes rods and channel specific cones but does not include ultraviolet chromophores of any species (although he has hinted at the broad existence of ultraviolet vision among the chordates in the same article).

As indicated in Goldsmith, there has been an interesting, and important, recent observation. The monoclonal antibodies originally used during the early 1990's to differentiate between chromophores (actually protein substrates) have been shown not to be specific to the presumed chromophore across species lines.

A second problem has arisen with the attempts to correlate genes with the “three chromophores of vision” related to the S-, M- and L-channels. Since the work is all inferential, success has been suggested by the isolation of three

⁷⁵Venter, J. (2007) A Life Decoded. xxx

⁷⁶Muraki-Oda, S. Toyoda, F. Okada, A. et al. (2007) Functional analysis of rod monochromacy-associated missense mutations in the CNGA3 subunit of the cone photoreceptor cGMP-gated channel Biochem Biophys Res Comm vol 367. pp 88-93

⁷⁷Langreth, R. (2008) Gene therapy is opening doors–finally. R & D Magazine of 28 April

⁷⁸Goldsmith, T. (1990) Optimization, constraint, and history in the evolution of eyes. *Quart. Rev. Biol.* vol 65, no. 3, pp 281-322

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sections of a gene that all relate to color vision. Unfortunately, such a correlation is extraneous. There are four explicitly different spectral channels in vision (including human vision at the retinal level—See **Section 17.2.2**). This logic has led to very extraneous hypotheses with regard to achromatopsia (See **Section 18.8.3**).

By reviewing the phylogenetic trees based on vision in Chapter 1, it is clear that trichromatic (if not tetrachromatic) vision has been in use since the epoch of the insects. This is far earlier than the Paleozoic era addressed in Goldsmith's figure 13. The ancient *Limulus* exhibits at least two chromophores of vision. Unless one argues that recent mice are better than earlier mice, rodents have exhibited tetrachromatic since well before the emergence of man. If these assertions are correct, the whole conventional wisdom of genetic history needs to be rewritten, if a basis for writing such a history can be found.

An excellent lecture series on genetics at the university level, dating from 2005, was available on the internet in mid-2008 at www.ucl.ac.uk/~ucbhjow/b241/lectures.html

The staff of Forbes magazine has recently provided a diagram that aids in interpreting the formation of the human anatomy based on the different types of stem cells. **Figure 18.1.3-8** shows the differentiation of the original stem cells into three major types before further differentiation into a variety of types associated with individual organs. One should not assume all of the tissue of a given organ originates with a specific stem cell type. They are frequently created from mixtures of cell types when fully developed. Where shown, muscle should probably be further subdivided into smooth and regular muscle.

Paths to a Person

What stem cell researchers are really studying is how your body was made and how to do it all over again. Embryonic stem cells (or the newer induced-without-embryos variety) can travel down any of the paths below to become skin, heart, brain and other body parts. So-called adult stem cells are stuck in the middle, able to become certain types of cells but not others. In nature, cells don't travel backward on these developmental paths; stem cell researchers hope to treat disease by getting them to do just that.

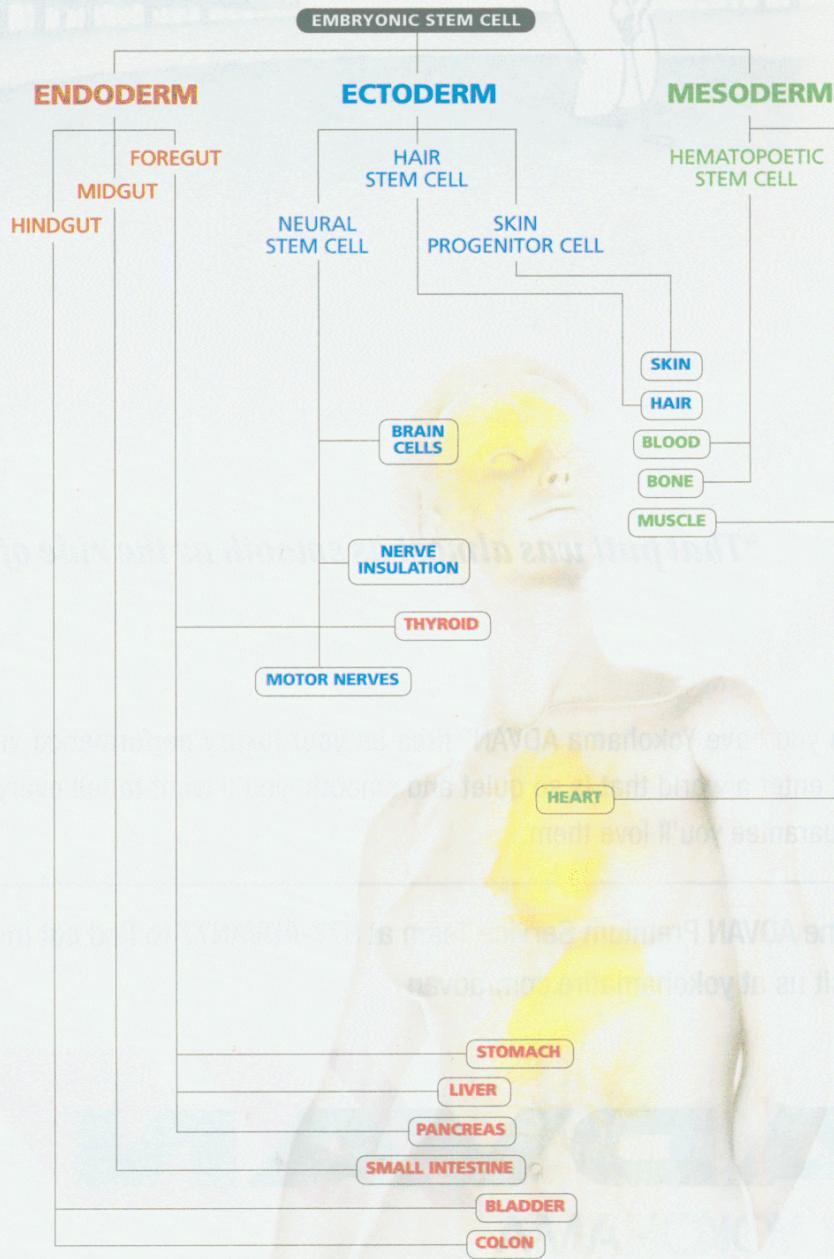


Figure 18.1.3-8 Identification of the stem cells forming the organs of the body. From Forbes, 2008.

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18.1.4 Defining spatial and spatial frequency abnormalities of vision

As noted in Miller & Newman, visual acuity measurements are the primary method of evaluating the integrity and performance of the visual system⁷⁹. These measurements assess the performance of both the optics and the neural components of the visual system are functioning properly. They are performed almost exclusively achromatically. Evaluating the chromatic acuity of the visual system introduces a large group of additional variables that are not usually addressed in visual experiments. (However, based on some of the garish colored text printed in recent magazines, the color acuity of the human eye probably should be addressed and documented more fully.) This work will not address the clinical aspects of acuity. Miller & Newman is the authority in this area. However, there is a functional aspect of acuity not covered in their presentation. The distinction between refractive myopia and neurological myopia. This distinction is particularly significant in man and may only be found in the primates. The earlier text by Records has a chapter on visual acuity⁸⁰. Kennard & Rose have provided some readable material on visual acuity⁸¹.

When investigating more serious disease of the visual system, it is necessary to go beyond evaluating acuity and explore the more subtle aspects of visual performance. Many diseases are related to small infarcts, lesions or conditions of hypoperfusion that have occurred within the visual portion of the neural system. Many patients observe visual hallucinations due to these types of failures. Glaser has provided a section on this subject⁸². Sacks has recently published a book on hallucinations⁸³.

18.1.4.1 Terminology introduced in this section

Section 2.4.8.4.1 reviews the terminology used to describe a range of performance errors in vision. Of particular importance is the broader definition provided for myopia. In abnormal vision, this term frequently consists of two components, one correctable with external appliances and a second that is uncorrectable. The first term is a refraction error, usually hypometropia. The second is a neural error, usually described as amblyopia, and usually due to poor performance of the precision optical system, POS.

Amblyopia– A developmental anomaly of spatial vision (Levi, 1988). Clinically divided into two classes of distinctly different origin.

Anisometropia– An inequality in the refractive error of the two eyes. Underlying mechanism appears to be associated with poor correlation parameters in the pretectum.

Strabismus– A pathological failure of the two eyes to converge on a given target in the visual field. Found in horizontal, vertical and torsional situations. Underlying mechanism appears to be associated with inadequate merging of the information from the foveola of the two eyes.

Isopter plot– In perimetry, the plot of the visual field for a specified stimulus.

Perimetry– The mapping of the visual field of one eye (unilateral) or both eyes (bilateral) using a variety of small light sources of varying intensity.

Presbyopia– The continual recession of the nearpoint, parallel to the continuous growth of the lens. (Donders, 1864)

Prosopagnosia– A general inability to identify specific members within large classes of similar items, faces being the most striking example.

⁷⁹Miller, N. & Newman, N. ed. (1998) Walsh and Hoyt's Clinical Neuro-Ophthalmology. 5th ed, vol. 1. Baltimore, MD: Williams & Wilkins

⁸⁰Records, R. (1979) Physiology of the Human Eye and Visual System NY: Harper & Row, chapter 15

⁸¹Kennard, C. & Rose, F. (1988) Physiological Aspects of Clinical Neuro-Ophthalmology Chicago, IL: Year Book Medical Publishers, pp 6-10

⁸²Glaser, J. (1999) Neuro-ophthalmology, 3rd ed. NY: Lippincott, Williams & Wilkins. pg. 35 & Chap. 7

⁸³Sacks, O. (2012) Hallucinations NY: Alfred A. Knopf

18.1.4.2 Perimetry as the second tool of spatial performance evaluation

The texts by Anderson form a foundation for the understanding of perimetry and the multiple conflicting notations used in describing the spatial performance of subjects eyes⁸⁴. These texts also include a wealth of perimeter plots for different field of view failures and the most frequent sources of these failures. The text and atlas by Harrington provides many isopter maps, including many special cases of interest in this work⁸⁵.

Page 45 of Anderson discusses the problem of maintaining standard conditions in perimetry.

Page 225 of Harrington shows the minute field of view, anopia with foveola sparing, resulting from chloroquine poisoning. It can be compared with page 224 showing anopia with macular sparing. Harrington explores many visual losses not described in other texts. The differences between bitemporal hemianopia and occipital hemianopia is particularly significant. Page 125 shows how bitemporal hemianopia does not exhibit macular sparing but does exhibit sparing along the vertical meridian.

The Goldmann perimeter employs stimuli varying in intensity over a range of 34 dB and diameters from 0.05 to 1.72 degrees. The intensity range of the perimeter can be extended another factor of 100:1 with an attachment. The nominal for manual clinical evaluation is a 0.11 degree diameter white spot. However, automated perimetry typically uses a 4 mm² spot with 1 mm² and 0.25 mm² available.. Page 41 of the Anderson reference provides a description of the many automated perimeters in service.

It should be noted that subjects frequently provide different performance when measured using static test sources compared to moving test sources (the Riddoch phenomenon, pg 140). This difference is associated with the additional neural circuitry optimized for motion detection.

18.1.4.3 Review of parameters affecting spatial frequency performance

The spatial frequency performance of the human eyes are determined by the spatial frequency performance of the lens group in two orthogonal directions, a combination of the transmissivity of the lens group and vitreous humor and an internal threshold level associated with the signal processing system. The performance of the lens group and the transmissivity varies as a function of field angle relative to the optical axis. In those animals with a well developed foveola, there are additional important parameters. These animals also employ a precision optical system (POS) in conjunction with the foveola to achieve a higher degree of scene analysis than is found in other animals. This POS (which includes the auxiliary optical system) includes a closed loop servomechanism that performs a two dimensional correlation of the neural signals from the foveola. This is done in order to perceive the information content of the scene. It does this in conjunction with the tremor of the eyes. In healthy human eyes, the spatial performance of the POS/foveola combination determines the limiting spatial frequency performance of the visual system. Corrections to the refractive optical system can only correct the overall system back to the level determined by the POS.

The routine clinical ophthalmological examination measures the refractive errors of the physiological optical system of the eye and attempts to correct any refractive error with external optical appliances. This is normally able to correct the subjects visual performance back to a nominal 20/20. However, in some cases, this is not possible. In many cases of achromatopsia, the performance of the POS is severely impacted with a resultant uncorrectable myopia that is difficult to manage.

18.1.5 Defining color vision abnormalities

There are two distinctly different aspects to the discussion of color vision abnormalities. It is one thing to document a condition in text. It may be quite a different matter for both the writer and the reader to visualize the condition. The internet has provided a new capability in this area. It provides the ability to represent examples of the conditions under discussion whether they are fixed in time or dynamic. These representation are available instantaneously to any interested party any where in the world. A particularly useful site is www.visionsimulations.com. It contains a variety of simulations of abnormal conditions that will be used below.

The literature of color vision abnormalities is immense and dates from ancient times. As late as 1855, it was

⁸⁴Anderson, D. (1987) Perimetry: With and Without Automation, 2nd Ed. St Louis, MO: C. V. Mosby

⁸⁵Harrington, D. (1981) The Visual Fields: A Textbook and Atlas of Clinical Perimetry. St. Louis, MO: C. V. Mosby

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discussed primarily in anecdotal form. Maxwell's letter to G. Wilson is indicative of the state of understanding of that time⁸⁶. A majority of the discussion, even through the mid 20th century, remains highly conceptual. It has usually been discovered by observing unusual behavioral activity of a subject followed by psychophysical tests. The tests have also been highly subjective in design. Through the second half of the 20th century, the literature of the field has remained dominated by the behavioral communities, psychology and psychophysics. This appears to be due to the failure of the morphologists and electrophysiologists to discover any correlation between their work and the theories proposed by the behavioral community. Pokorny, Smith, Verriest & Pinckers surveyed the field in 1979⁸⁷. This work provides a broader block diagram and schematic of the visual system. It enumerates a broad range of possible color abnormalities that provide better correlation with the behavioral data. It also leads to grossly different probable causes of color abnormalities than suggested by the above theories.

There is frequent reference in the psychophysical literature of color abnormalities to the Rayleigh Equation and several others related to it. These are not actual mathematical equations. They are conceptual equations based on the test protocols and resulting "matches" originally developed by Lord Rayleigh (1881). These matches have been overlaid onto the C.I.E. (1931) Chromaticity Diagram on the assumption that it is a conformal chart. There is considerable data showing this is not true, including the issuance by the C.I.E. of the Uniform Color Space variant, The C.I.E. (1960) Chromaticity Diagram (u,v). Lakowski makes specific note of the need to use the UCS diagram instead of the 1931 diagram for precise work. It is also important to note that it has become conventional to perform matching experiments using a narrow band light source at 589 nm. This wavelength was chosen by Lord Rayleigh because of its convenience in the laboratory, not for any scientific reason. A paper by Breton & Cowan would suggest that the value of 572 nm associated with the null point of the Q-channel would give better results in anomaloscope testing⁸⁸. Their figures show a much sharper notch in anomaloscope readings when using 570 nm compared to 589 nm or 555 nm.

The modern work in the field of color abnormalities probably begins with Judd⁸⁹. Judd found the 1931 Chromaticity Diagram inadequate and proposed his uniform color space (UCS) version in 1935 that was finally adopted in 1960. His UCS Chromaticity Diagram blended well with the Munsell system of chromatic notation but it was still not truly conformal as shown earlier. When the UCS diagram is further modified to become equivalent to the New Chromaticity Diagram for Research, still better results are obtained. The new diagram is conformal and provides a fundamental foundation upon which the Munsell system can be overlaid with precision. Judd's terminology is drawn from that in use in his time.

The fact that a 1997 book chose to reprint an article of Hsia and Graham⁹⁰ dating from 1965 indicates the limited progress made recently in this field.

There has always been interest in describing vision abnormalities in terms of simple genetic failures. Recently, the discussion in this area has become more intense⁹¹. However, the volume of smoke is not proportional to the amount of light. The relation between any gene and any individual characteristic of an animal is based on inference. The conclusions are generally inclusive and not exclusive. There has always been a desire to relate a single, poorly defined, color defect to a specific gene abnormality. In the light of the complexity of the visual system, it seems highly unlikely that any single gene defect can be shown to cause directly any clearly defined visual performance defect. The complexity of the visual system is too great. This is not to say that genetic defects do not lead to medically recognized syndromes. However, a syndrome is by definition a more complex phenomenon than a single point failure in a system.

As an example, there are two clinically distinct first order forms of red-green color-blindness. In one case, the subject exhibits a normal luminous efficiency function under photopic conditions. In the other case, the subject exhibits a scotopic luminous efficiency function under photopic conditions. Whereas the second case can be described in terms of a genetic defect preventing the expression of the long wavelength form of Rhodopsin, the

⁸⁶Wald, G. (1964) The receptors of human color vision. *Science*, vol. 145, pp 1007-1017

⁸⁷Pokorny, J. Smith, V. Verriest, G. & Pinckers, A. (1979) Congenital and acquired color vision defects. NY: Grune & Stratton.

⁸⁸Breton, M. & Cowan, W. (1981) deutanomalous color matching in the deutanopic eye. *J. Opt. Soc. Am.* vol. 71, no. 10, pp.1220-1223

⁸⁹Judd, D. (1949) The color perceptions of Deutanopic and Protanopic observers. *J. Opt. Soc. Am.* vol. 39, no. 3, pp. 252-256

⁹⁰Hsia, Y. & Graham, C. (1965) Color Blindness, *In* Readings on Color; Vol. 2: The Science of Color, Byrne, A. & Hilbert, D. ed. Cambridge, MA: The MIT Press. pp.201-229

⁹¹Lewis, R. (2000) Total color blindness: A rare gene defect. Biophotonics International. Sept-Oct. pp. 38-39

required chromophore is clearly present in the first case and the abnormal color vision is due to a failure within the signaling system proximal to the pedicels of the L-channel photoreceptor cells. Even in the second case, the chromophore may be present but the photoreceptor cell may not be functional for other reasons.

The following discussion will generally separate failures in the afferent signal paths of the neural system from perceptual failures associated primarily with the cerebral cortex. The latter are frequently labeled cerebral color blindness or cerebral achromatopia (used without the “s” here to distinguish this condition from the more complex syndrome of similar name).

18.1.5.1 Localizing abnormal color failures

Many color abnormalities can be localized based on the overall schematic of vision. **Figure 18.1.5-1** shows the schematic of interest. The notation is discussed in detail in **Section 18.1.3**. The comments on the right aid in locating the major shortcomings of the signaling channels of vision. The major failures are outlined in the right column. The redundancy in the sensing and processing of visual information is a major factor in avoiding total blindness. The layout of the blood vessels serving the cerebral cortex is also important in minimizing vision loss due to natural abnormalities; strokes, embolisms, etc. As a result, failures of the cardiovascular system frequently result in the loss of only one quadrant (or less) of the visual field.

A failure in one LGN typically only affects one field of vision (from both eyes) and does not affect the vision associated with the foveola.

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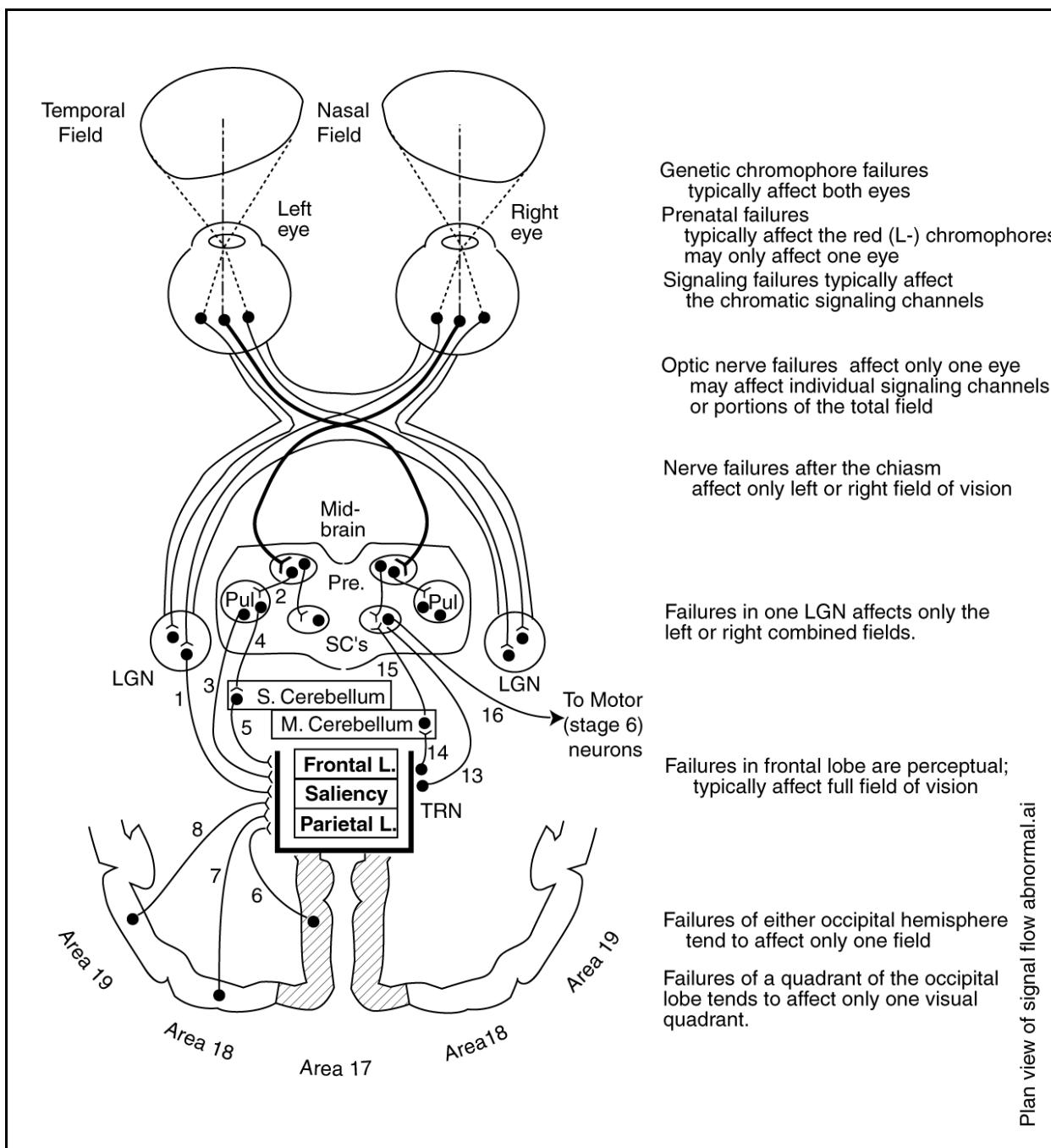


Figure 18.1.5-1 Overall schematic of vision annotated for color abnormalities SIMILAR to 18.1.3-2. ADD.

18.1.5.2 The “Equations” of abnormal color vision

Since the time of Lord Rayleigh, three conceptual equations related to abnormal color vision have evolved. These are the Rayleigh equation, the Engelking-Trendelenburg equation and the Pickford-Lakowski equation. These are all conceptual equations that have yet to be presented in empirical form. Lakowski always places these equations

names in quotation marks. The following material will present rigorous equations representing these conceptual forms. [xxx need to locate source of Moreland Equation used by Oculus and Roland in their 2-axis anomaloscopes, Section 18.1.8.2]

The equations of normal trichromatic vision were derived in **Chapter 16**. Specific equations applicable to abnormal color vision appear in **Section 16.3.4.5**. These equations can be reviewed to define the principal forms of abnormal color vision. They appear below in slightly less detailed form. There are three relevant equations that define the performance based on the functional block diagram and detailed circuits of the trichromatic visual system.

The first equation is the Equation of Brightness, or less precisely the Equation of Perceived Luminance is given by:

$$R(E) = C_S' \ln \int (E \times S) d\lambda + C_M' \ln \int (E \times M) d\lambda + C_L' \ln \int (E \times L) d\lambda \quad \text{Eq. 18.1.3-1}$$

where $R(E)$ is the unitary value of the perceived brightness at the output of the signal processing function for a given steady state stimulus, E . The normal E indicates an integrated value of intensity and the italic E indicates the intensity as a function of wavelength. *Note that the value of $R(E)$ must be accompanied by a statement as to the character of the illumination spectral density, $E(\lambda)$.* The form shown above and for the following chrominance channels will be limited to the photopic region.

C' with a subscript is indicative of the relative amount of amplification related to that channel as measured at the pedicel of the photoreceptor cell. The value of this parameter is dominated by the amplification occurring in the adaptation amplifier of that spectral channel. These primed values are usually normalized to the value for the M -channel in graphical presentations related to the composite luminosity function (also called the luminous efficiency function).

The second equation is the P-channel Chrominance Equation:

$$P(E) = \pm C_P'' (C_S' \ln \int E \times S d\lambda - C_M' \ln \int E \times M d\lambda) \quad \text{Eq. 18.1.3-2}$$

The third equation is the Q-channel Chrominance Equation:

$$Q(E) = \pm C_Q'' (C_M' \ln \int E \times M d\lambda - C_L' \ln \int E \times L d\lambda) \quad \text{Eq. 18.1.3-3}$$

The C' parameters are complex functions of time and the state of adaptation of the individual spectral channels. The C'' parameters have been added to emphasize that there are gain constants associated with these terms after subtraction is performed in the Activa circuit of the lateral cells. If not adequately characterized during experiments, they can lead to considerable error in the results. They will be examined further below. In the first order case, they will be considered constants.

The above three equations can be evaluated using a variety of spectral forms for the function E . Regardless of the form used, it is important to note that metameres play an intrinsic role in the operation of the visual system in a manner not addressed in the literature. Common metameres of additive color mixing involve only the integral of the spectral irradiance of a specimen. However, the **metameres of visual color subtraction are more complex**. They involve the integral of the spectral irradiance of the sample multiplied by the spectral absorption characteristic of the chromophore.

The most common practice in the laboratory evaluation of the visual system is to use a spectral sweep across the spectral band of interest with a narrow band spectrometer.

Note: the spectral width of the spectrometer must be less than 10 nm, and preferably less than 5 nm, for satisfactory results. It is preferred that the center values not be multiples of 10 nm because of the location of specific artifacts in the data and the resultant errors due to binning.

A spectral sweep of **eq. 18.1.3-1** produces the luminous efficiency function for the subject. A spectral sweep of **eq's. 18.1.3-2 & -3** produces two separate spectral wavelength discrimination functions. These functions are not to be confused with the minimum wavelength discrimination function. The minimum wavelength discrimination function is the derivative of the combination of these two wavelength discrimination functions combined using an OR function. The theoretical spectral wavelength discrimination functions for both the P- and Q-channels are shown in **Section 13.5.3**. The theoretical composite minimum wavelength discrimination function is also shown in that section. Although the zero crossing point of these two functions cannot be determined without detailed laboratory tests, it appears from the literature that the values for color normals are near the Hering axes locations of 494 nm and 572 nm. See **Section 18.1.5.7.3** below.

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There are a number of failure modes related to these three equations that describe the visual abnormalities encountered in humans. **These failures are functional failures and have no direct relation to the observed performance failures of the literature.**

18.1.5.2.1 Failures in the signal processing and projection channels

A failure in the signaling channel related to the P-channel causes a loss in the ability of the subject to discriminate between S and M spectral channel signals. Although generally described in terms of blue and yellow, this failure is described as **tetartanopia and is more precisely defined as a complete failure to discriminate between Unique Violet and Unique Yellow**. A similar failure in the Q-channel signaling path causes a loss in the ability to discriminate between the M and L spectral channels. This condition is known as **deuteranopia and is defined as a complete failure to discriminate between Unique Aqua and Unique Red**.

Complete Loss of the ability to discriminate between both pairs, Unique Violet & Unique Yellow, and Unique Aqua & Unique Red, results in the condition defined as achromatopia.

Achromatopia, tetartanopia and deuteranopia relate to primary functional failures in the signaling channels of stages 2 & 3 or beyond. They do not relate to the spectrally selective photodetection channels of stage 1.

18.1.5.2.2 Failures in the signal detection channels

Examination of eq. 18.1.3-1 shows several possible failure modes in stage 1 of the visual process.

Failure of the L-channel due to any reason results in the condition defined as protanopia.

A similar **failure in the S-channel due to any reason results in the condition defined as tritanopia**.

For completeness, a **failure in the M-channel due to any reason results in the condition defined as pentanopia**. Such a failure, loss of the functional performance of the M-channel photoreceptors, has not been reported in the literature.

Note that any of the above complete failures in the signal detection channels impact the equations of the signal processing stages adversely.

Thus, **protanopia will induce at least a partial failure in the Q-channel** signal processing and result in some degree of deuteranopia.

Tritanopia will induce at least a partial failure in the P-channel signal processing and result in some degree of tetartanopia.

Pantanopia will induce at least a partial failure in both the P- and Q-channels and result in some degree of achromatopia.

It is possible to find dual failures in the spectral channels leading to only a single operating spectral channel. These conditions are extremely rare but are documented. They result in functional monochromats.

The S-channel functional monochromat only senses the short wavelength spectrum and is unable to discriminate any colors.

The M-channel functional monochromat only senses the medium wavelength spectrum and is unable to discriminate any colors.

The L-channel functional monochromat only senses the long wavelength spectrum and is unable to discriminate any colors.

The S-, M- and L-channel functional monochromats and the achromat are all considered monochromats in terms of performance. However, the achromat has the same luminous efficiency spectrum as a normal subject and is clearly not monochromatic from a functional perspective.

18.1.5.2.3 Failures in the signal perception and cognition stages

Color perception occurs primarily in stage 4 of the cerebral cortex, the perception circuits of the occipital lobe in particular. The specific location of a variety of color perception failures has been described in Meadows⁹². No effort to understand color perception should be undertaken without reviewing this analysis of fourteen individual clinical reports. Visual field defects are associated with these color deficits and lead generally to the conclusion that most cerebral achromatopia is associated with lesions, infarcts or hemitomas of the lower occipital lobe. Meadows also develops the close physical association between achromatopia, dyschromatopia, alexia without agraphia, prosopagnosia (inability to recognize faces), topographic image sensing (inability to recognize scenes) and topographic memory loss.

Recently, Blue has reported a case of a man, who has been red-green color blind his entire life, achieving full color vision following a traumatic shock to his head⁹³.

18.1.5.2.4 Evaluation of functional failures using performance tests

The above equations can be used to evaluate functional failures in the visual system based on the reported performance of the subject. Rayleigh and Engelking-Trendelenburg tests usually employ narrow band lights at specific wavelengths. Some Pickford-Lakowski tests use a broadband white light. For the long wavelength case, the test light has been traditionally at a wavelength of 589 nm. Although this is the recommended wavelength in Pokorny, et. al., the paper by Breton & Cowan deserves review as a figure closer to 572 nm may be superior. The primary lights are usually near 535-540 nm and greater than 640 nm. For the short wavelength case, the test light is usually near 494 nm and the primary lights are at less than 437 nm and near 520 nm. The field illuminance must be in the photopic range, as discussed above, for both cases. Pickford & Lakowski (1960) used a short wavelength of 470 nm and a long wavelength of 555 nm for a pair of broadband lights in their paper. Both of these numbers appear too high based on the wavelength discrimination function for the short wavelength channel and the New Chromaticity Diagram for Research. 470 nm does not give optimum response compared to 420 nm and 555 nm will excite the Q-channel to a significant degree, possibly corrupting the responses.

18.1.5.2.5 Representations of these failures on chromaticity diagrams

Although Pokorny, et. al⁹⁴. have plotted the end points associated with the above wavelengths on a C.I.E. (1931) Chromaticity Diagram and connected the points by a straight line, there are no test points justifying this choice or the choice of drawing the so-called confusion lines as straight lines on the highly non-conformal C.I.E. Diagram as discussed in **Section 17.3.1** and elsewhere in this work. The New Chromaticity Diagram for Research presents a much more easily interpreted map for discussing chromatic abnormalities. This perceptual presentation is conformal and equidistant. All lines are straight lines and the diagram does not change with the state of adaptation of the subject. It can also be used to plot the reading from an anomalscope directly by adding auxiliary axes similar to those in **Section 17.3.3**. One of these graphs representing the performance of a Deuteranope is shown in **Figure 18.1.5-2**. In this graph, the locus of confusion of the Deuteranope is shown as a horizontal line beginning at a nominal 494 nm. No signal is transmitted to the cortex from the chrominance channels for a color located along this line. Additional loci can be drawn as lines parallel to the locus of confusion indicative of the level of saturation that will be perceived along the violet-yellow axis independent of the spectral wavelength in the region of 532 to 655 nm. These are called isochromatic lines. Note the locus of confusion passes through the white point defined by (494, 572) nm. These loci can be transferred to the C.I.E. (1931) Chromaticity Diagram but they will not be straight lines.

A scale is shown in the figure for a Nagel Anomaloscope, Type I or II, for reference. When used in conjunction with the New Chromaticity for Research, it is assumed that the intensity of the test light is held constant.

This figure can also be used to represent the performance of a protanope if the long wavelength performance is reduced due to the loss of L-channel sensitivity. This loss is represented by a dashed-dot vertical line at a nominal 600 nm. In a protanope, there is no sensation of color to the right of this line. Therefore, the locus of confusion of a protanope is a horizontal line through 494 nm until the area to the right of the dash-dot line is reached. Beyond that point, the locus of confusion is undefined and the isochromatic lines diverge and become parallel to the dash-dot line. When these points are transferred to the C.I.E. (1931) Chromaticity Diagram, the lines do not converge to a

⁹²Meadows, J. (1974) disturbed perception of colours associated with localized cerebral lesions *Brain* vol 97, pp 615-632

⁹³Blue, R. (2009) personal communication rblue@lccc.edu

⁹⁴Pokorny, J. et. al. (1979) Op. Cit. pp. 110-112

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point near 670 nm. Although they may begin to converge in the area of the diagram below $x=0.4$, they diverge in the area for $x > 0.4$. The isochromatic lines of a protanope do not exhibit or converge to a so-called copunctal point. A copunctal point can be defined by constructing tangents to the isochromatic lines within a specific region of the C.I.E (1931) Chromaticity Diagram. Such a point will not agree with a similar point constructed on the 1961 UCS diagram. In the New Chromaticity Diagram for Research, these isochromatic lines are parallel and do not converge in any sense.

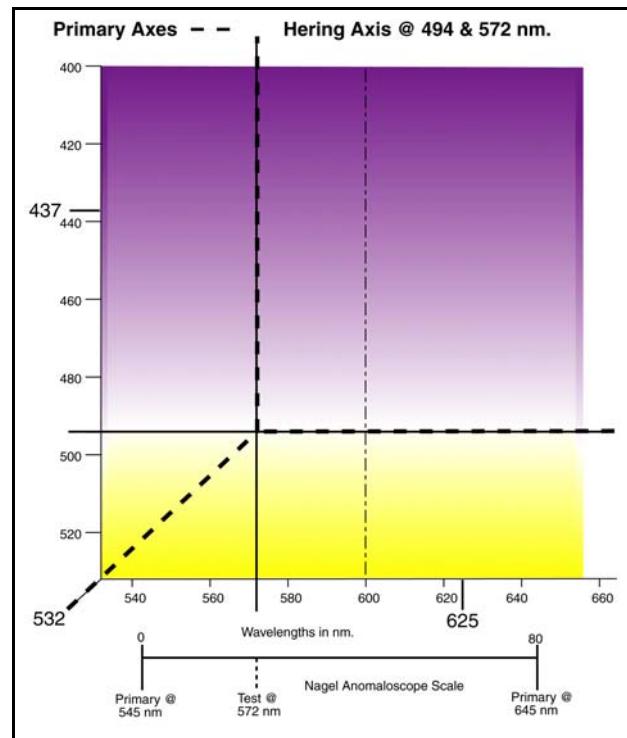


Figure 18.1.5-2 New Chromaticity Diagram as seen by an intrinsic deuteranope. The protanope exhibits a rapid loss in chromatic and achromatic sensitivity to the right of the dash-dot line. Selected radials of the Munsell Color System are also shown. The scale of a Nagel Anomaloscope is shown at the bottom of the figure.

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Figure 18.1.5-3 provides a graph of the chromatic performance of both a Tetartanope and a Tritanope. Both of these conditions are extremely rare (between 1:13,000 and 1:65,000 according to Wright). As in the above figure, the locus of confusion of the Tetartanope is shown as a vertical line beginning at a nominal 572 nm. No signal is transmitted to the cortex from the chrominance channels for a color located along this line. Additional loci can be drawn as lines parallel to the locus of confusion indicative of the level of saturation that will be perceived along the aqua-red axis independent of the spectral wavelength in the region of 400 to 532 nm. These are also called isochromatic lines. Note the locus of confusion passes through the white point defined by (494, 572) nm. These loci can also be transferred to the C.I.E. (1931) Chromaticity Diagram but they will not be straight lines.

A scale is shown in the figure for a Nagel Anomaloscope, Type II, for reference. When used in conjunction with the New Chromaticity for Research, it is assumed that the intensity of the test light is held constant.

This figure can also be used to represent the performance of a Tritanope if the short wavelength performance is reduced due to the loss of S-channel sensitivity. This loss is represented by a dashed-dot horizontal line at a nominal wavelength of 460 nm. In a Tritanope, there is no sensation of color at wavelengths shorter than this line. Therefore, the locus of confusion of a Tritanope is a vertical line through 572 nm until the area above the dash-dot line is reached. Beyond that point, the locus of confusion is undefined and the isochromatic lines diverge and become parallel to the dash-dot line. When these points are transferred to the C.I.E. (1931) Chromaticity Diagram, the lines do not converge to a point near 400 nm. Although they may begin to converge in the area of the diagram above $y=0.2$ ⁹⁵, they diverge in the area for $y<0.2$. As in the case of the Protanope, the isochromatic lines of a Tritanope do not exhibit or converge to a single so-called copunctal point although such a point is frequently defined by extending tangents to portions of the isochromatic lines. The situation is dramatized in the paper by Wright for five tritanopes⁹⁶. Quoting Wright, "It will be seen that the loci converge toward the blue corner of the chart, in agreement with the usual interpretation of tritanopia as being due to the absence of blue receptors. The loci do not, however, converge accurately towards a point, and although this might be regarded as disappointing, it is hardly surprising when account is taken of the spread in the observations and of the large extrapolation which is involved." Continuing, he says, "A more disconcerting feature of these confusions is that rather different loci would have been obtained if the equivalent wavelengths had been read off from the violet end of the coefficient curves than in the yellow part of the spectrum."

The extensions proposed in the literature frequently do not support the original conceptual proposal concerning copunctal points described by Helmholtz, and subsequently considered an outgrowth of the Young-Helmholtz Theory. In the paper by Thomson & Wright (which used the proposed Judd parameters of the 1950's), the mid-wavelength copunctal point of the "Standard Observer" is found at an extreme distance from the spectral locus and not at the expected location along the "green" portion of the locus⁹⁷.

Wright's data also confirms the luminous threshold performance of the tetartanope is not significantly poorer than one with normal vision (himself). Only the true tritanope exhibits a significant loss in S-channel sensitivity.

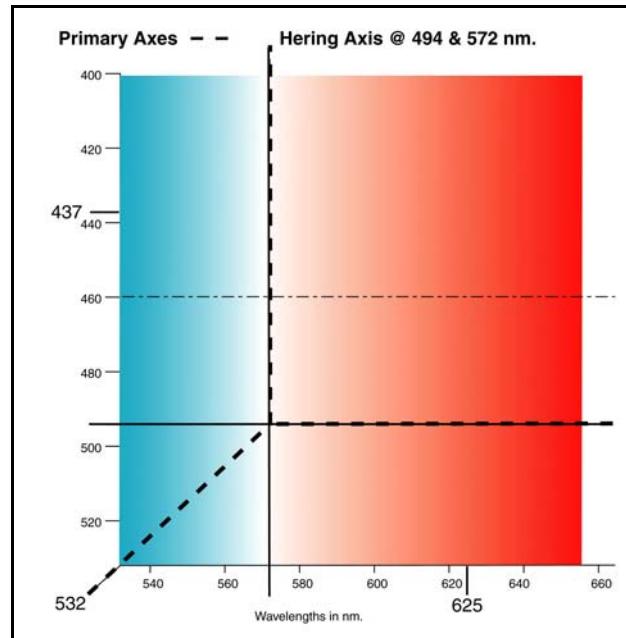


Figure 18.1.5-3 New Chromaticity Diagram as seen by an intrinsic tetartanope. The tritanope exhibits a rapid loss in chromatic and achromatic sensitivity at wavelengths shorter than the dash-dot line. Selected radials of the Munsell Color System are also shown. The scale of a Nagel Anomaloscope is shown on the left of the figure.

⁹⁵Schmidt, I. (1970) On congenital tritanomaly. *Vision Res.* vol. 10, pp. 717-743

⁹⁶Wright, W. (1952) The characteristics of tritanopia *J Opt Soc Am* vol. 42, pp 509-521

⁹⁷Thomson, L. & Wright, W. (1953) The convergence of the tritanopic confusion loci and the derivation of the fundamental response functions *J. Opt Soc Am* vol. 43, no. 10, pp 890-894

There has long been a question as to what a color abnormal actually perceives relative to the perception of a color normal. These two figures, following conformation in the laboratory with respect to the specific wavelengths shown, provide a reasonable approximation to what a color abnormal actually perceives. An interesting test is to present both the normal New Chromaticity Diagram and the one prepared to show the performance of a Deutanope to such an individual and determine any discrepancy between the proposed and the actual perception.

18.1.5.2.6 Partial failures in the detection and signaling stages

All of the above conditions, defined in terms of total channel failures, also exist in partial failure modes as well. Although this complicates laboratory investigations, it does not introduce complexity into the equations. It merely means the coefficients are abnormal. This can be due to a number of circumstances. These partial failures are normally indicated by changing the suffix to -anomalia or -anomalous.

18.1.5.2.7 Temporal performance of color abnormals

A number of researchers have reported tests for abnormal color vision under transient conditions. Frequently, the time between the end of the pre-adaptation period and the measurement is within the dark adaptation time of the eye and frequently associated with the period near the inflection in the curve that appears near 10 minutes under some conditions. The experimenter must insure the congruity between the dark adaptation characteristic for each spectral channel of vision and note the precise time of the test. The dark adaptation characteristic is frequently changing at a rate as high as a factor of three per minute in this range. A twenty-second variation can introduce a significant inconsistency in the results.

18.1.5.3 The Color Abnormality Matrix related to afferent signals

It is important to remember that the perceptual channels related to the foveola are distinctly different from those of the surrounding retina. This can cause distinctly different performance to be reported by or measured with a color blind subject as a function of field position in object space.

Some of the following discussion may only apply to a specific region of the retina. Another portion of the discussion may apply to the other region.

Hsia & Graham have provided good statistics on color abnormalities using the definitions of the conventional wisdom⁹⁸. Wright has provided excellent data on what he describes as tritanopia⁹⁹. Many of his subjects are obviously only tritanomalous under both the common definition and the definition of this work. His data also clearly shows the onset of the Bezold-Brück Effect in the R-channel with changes in the ratio of S- to M-channel signal amplitudes. The spectral peak at 437 nm is quite recognizable for his subject C.

18.1.5.4 The Color Abnormality Matrix related to the perception of color

Most abnormalities related to the loss of color vision in stage 4 have been associated with trauma to a variety of regions of the cerebral cortex. Heywood and Cowey have recently identified a number of these regions¹⁰⁰. Total loss of the perception of color (alone) is frequently an acquired defect. If not externally generated, the trauma is frequently relatable to an infarct. A very large clinical literature exists documenting the symptoms and describing the trauma associated with individual cases. There are at least three forms of cerebral color vision loss, achromatopia, color agnosia and color anomia. All of these forms involve the cerebral cortex but they suggest different locations for the source of each condition. Achromatopia is the total loss of the perception of color. A subject with color agnosia can match a given color to its twin, and associate a color with a typical object of that color but cannot name the color he is shown or point to the correct color given a name. A subject with color anomia cannot name a presented color or associate a presented color with a typical object of that color but can point to the color when the name is given and can match color samples correctly.

Burde, Savino & Trobe relate cerebral achromatopia over the entire visual field to lesions affecting the lingual and

⁹⁸Hsia, Y, Graham, C. (1965) Color blindness *in* Graham, C. ed. Vision and Visual Perception NY: John Wiley & Sons, pp 395-413 also in Byrne & Hilbert (1997) pg 221

⁹⁹Wright, W. (1952) The characteristics of tritanopia *J Opt Soc Am* vol. 42, pp 509-521

¹⁰⁰Heywood, C. & Cowey, A. (1999) Cerebral achromatopsia *in* Humphreys, G. ed. Case Studies in the Neuropsychology of Vision. Hove, England: Psychology Press, Taylor & Francis pp 17-39

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fusiform gyri of the inferior occipital lobes¹⁰¹. Pearlman, et. al. provided a 1978 review of acquired cerebral color blindness¹⁰². Their paper only addressed achromatopia. They did not consider the possibility of defects in area 7 or the frontal lobes of the cerebral cortex. These areas have been associated with the other defects mentioned above.

At this time, the primary method of classification of abnormal perception conditions remains associating the observed symptoms with the physical location of the trauma.

18.1.5.5 Proposed terminology

Color blindness is the most important class of perceptual blindness. The community has long suffered from confusion in the clinical definition of specific forms of color blindness. A classification based on function will be reviewed here. The mechanisms supporting these functions are based on the detailed topology of the visual process developed in this work.

It is important to differentiate between color blindness caused by signaling errors in stages 1, 2 & 3 of vision and the perceptual errors associated with stage 4 signal processing. The latter are frequently described as cerebral achromatopsia in the literature (although as noted above, the “s” will be omitted here in the interest of consistency).

The following definitions are based strictly on function rather than precedent and differ from the “rod-cone” based presentation of Krill. As shown in this work, all photoreceptors have the spectral characteristics usually associated with cones. There are no functional rods with a broad spectral response.

In this work, the functional definition of monochromats and dichromats will be used. A monochromat exhibits only one functioning spectral detector channel. A dichromat exhibits two functioning spectral detector channels. These definitions have nothing to do with how a subject responds to color matching experiments.

After reviewing both the historical and recent clinical literature, it is possible to assign specific functional failures to the various types of color blindness. This is done in **Figure 18.1.5-4**. In this figure, an X marks the sight of a complete failure in a signal path. Less than complete failures result in various -omalies but not -opias. Tritanopia and tetranoia usually have less impact on a subject's daily life and have not been widely reported until recent years. The failures described as tritanopia and protanopia are defined as failures in the S- and L- spectral channels respectively. A corresponding failure in the M-channel is very rare (if not unknown), induces total achromatopia, and causes significant loss in visual capability. Such an M-channel failure is frequently described as a category of blind sight. Failures in the S- and L- channels necessarily induce tetartanopia and deutanopia respectively. However, intrinsic tetartanopia and intrinsic deutanopia can be caused,

¹⁰¹Burde, R. Savino, P. & Trobe, J. (1992) Clinical Decisions in Neuro-Ophthalmology, 2nd Ed. St. Louis, MO: Mosby Year Book, pg 161

¹⁰²Pearlman, A. Birch, J. & Meadows, J. (1978) Cerebral color blindness: an acquired defect in hue discrimination Annal of Neurology vol. 5, no. 3, pp 253-261

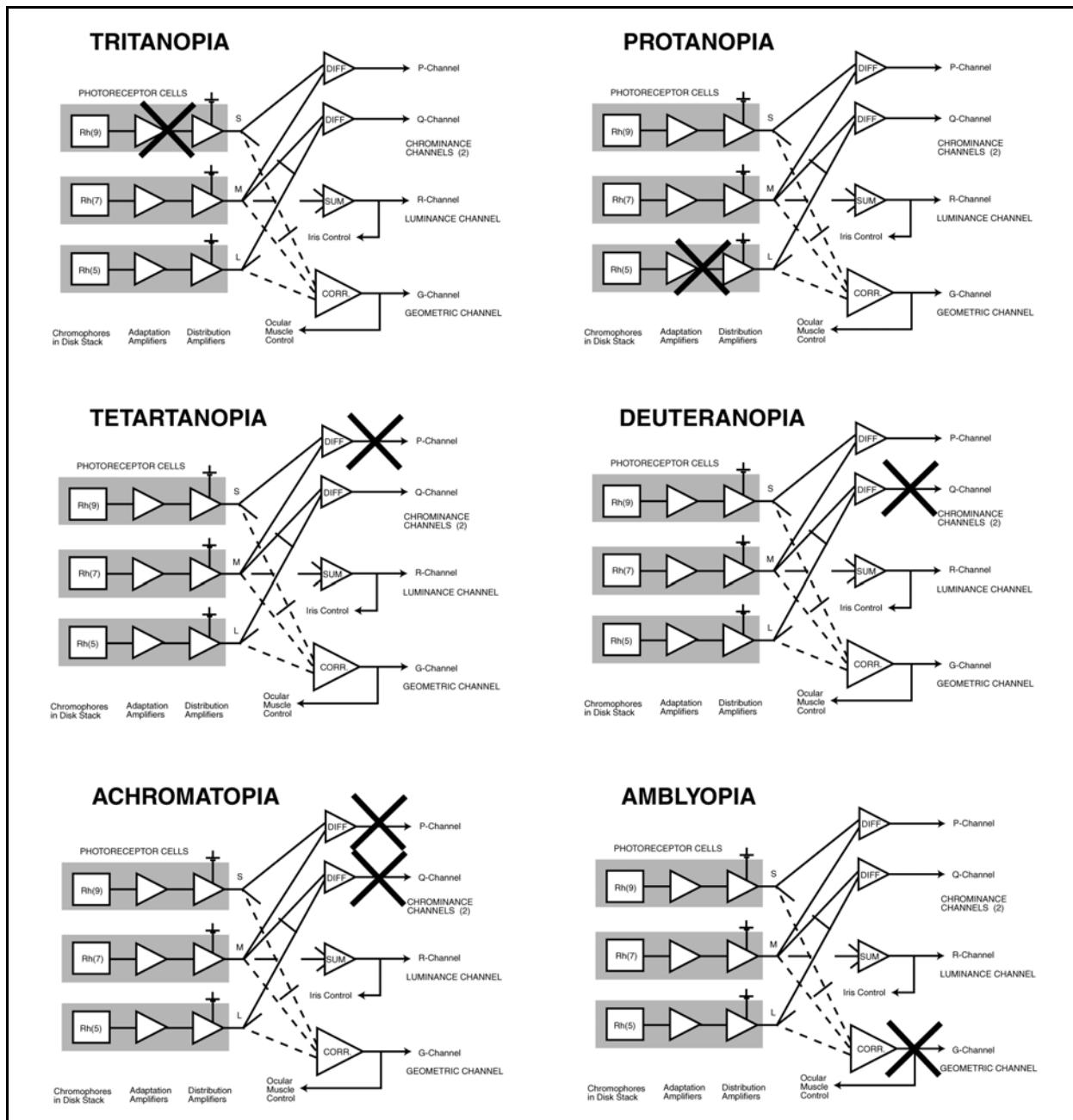


Figure 18.1.5-4 Principle failure modes in the human visual system based on frequency of occurrence. **The designations in this figure are those defined specifically in this work.** Tritanopia necessarily leads to induced tetartanopia and protanopia necessarily leads to induced deuteranopia. A complete failure in the M-channel of vision is extremely rare and typically results in a form of blindsight. A failure in the servo-loop of the POS associated with the foveola frequently results in amblyopia. See text.

independently of any spectral failure, by a failure within the P- or Q- signaling channels.

Failure in both the P- and Q- channels whether intrinsic or induced by the loss of the M-channel leads to achromatopia (without an s). This form of achromatopia can be, and usually is, encountered in subjects with normal luminous efficiency functions (demonstrating that all three of their spectral channels are operating normally).

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A primary cause of amblyopia is a failure in the servo-loop associated with the precision optical system, POS, as shown in the lower right. The major contributor to this condition appears to be the circuits between the photoreceptors of the foveola and the output of the correlator found in the pretectum area of the midbrain (labeled the G-channel in the figure but labeled the G'-channel in larger scale figures). These signals normally control the tremor or fine oculomotor motions of the eyes (only clinically observable with instruments) and the ability of the visual system to perceive and interpret fine detail in a scene.

As discussed in **Section 18.8.3**, the syndrome known as achromatopsia (with an s) is frequently the result of achromatopia, amblyopia and hemeralopia. This condition appears to be caused by a bias error in the distribution amplifiers of all of the photoreceptors. It results in a partial failure of all three spectral channels that is most obvious at high incident illumination levels. At lower illumination levels (twilight and below), the visual system appears to operate normally.

Figure 18.1.5-5 presents a tabulation traceable to the above failure mode block diagrams of this work. This figure only applies to stages 1 through 4 of the visual system. All of the defined conditions can be loosely related to reduction mechanisms as defined by von Kries (see below). Failures in stage B generally correspond to his absorption mechanism and abnormalities of stage 0 can generally be associated with his alteration mechanism (but not in the sense of merging or replacement). The characteristics of cortical color vision abnormalities in stage 5 are not sufficiently well established to allow a useful categorization.

All of the names found in the literature of abnormal color vision are found in this figure. To complete voids in the table, a few new names, such as pentanopia, have been added. A pentanope is a subject with complete loss of vision associated with the middle wavelength spectral channel. Pentanomaly would be the corresponding category for an anomalous condition. The existence of these two forms of color abnormality requires very precise instrumentation to measure. If the syndromes exist, they are easily confused with other conditions involving the state of adaptation, particularly the normal system operation under hypertopic illumination conditions.

To further clarify those with anomalous conditions versus those with complete functional failures, all of the failures are grouped under the heading of “incomplete trichromats.” This allows this category to be broken down further according to failure mode into the functional trichromats, functional dichromats and functional monochromats. The main changes are the association of explanatory clauses to the names of the functional dichromats. The result is a table of specific mode failures that is much more explicit than in previous work.

One additional form of abnormal color vision shows up occasionally in the literature. The literature is inconsistent as to its existence and characteristics. It can be defined as a subcategory of D, a protanope with induced achromatopia, or under C, an achromat with no long wavelength spectral response. It is difficult to locate a single failure mode in the functional block diagram that would result in this type of performance. If it exists, it probably represents two separate functional failures.

The table can be overlayed to group the color vision abnormalities based on performance. In this table, the performance based dichromats are shown in the upper left shaded area. Similarly, the performance based monochromats are shown in the lower right. Note the “mixed bag” nature of these performance titles compared to the functional perspective. A figure in Wyszecki & Stiles (pg 471) illustrates this point clearly. The protanope and tritanope both show significant loss in luminous efficiency due to their loss of a spectral absorption channel. The deutanope is clearly different, displaying a normal photopic luminous efficiency function.

The figure is seen to represent a stepped continuum of color abnormalities with performance degrading from top to bottom. Fortunately, the incidence of these abnormalities also drops rapidly, from both top to bottom and left to right.

The table can be directly correlated with the conventional luminous efficiency functions and the New Chromaticity Diagram for Research (particularly the variant showing the auxiliary P and Q axes) and the New Sensation Space Diagram. This demonstration is left to the reader.

FUNCTIONAL ERRORS IN LONG WAVELENGTH TRICHRMATS--HUMANS			
Mode	NORMAL TRICHRMATS		
	ANOMALOUS TRICHRMATS		
Imbalance in Chrom. channels	DEUTERANOMALIA Q-channel	TETRANOMALIA P-channel	
Inadequacy in Spectral channels	PROTANOMALIA L-channel	TRITANOMALIA S-channel	M-channel
	INCOMPLETE TRICHRMATS		
	FUNCTIONAL TRICHRMATS		
Loss of 1 or both chromatic channels	A) INTRINSIC DEUTERANOPIA (Loss of Q-chan.)	B) INTRINSIC TETARTANOPIA (Loss of P-chan.)	C) INTRINSIC ACHROMATOPIA (Loss of P & Q. chan.)
	FUNCTIONAL DICHROMATS		
Loss of 1 spectral channel	D) PROTANOPIA (Loss of L-chan.) with induced Deuteranopia	E) TRITANOPIA (Loss of S-chan.) with induced Tetartanopia	F) PENTANOPIA (Loss of M-chan.) with induced Achromatopia
	FUNCTIONAL MONOCHROMATS		
Loss of 2 spectral channels	G) S-CHANNEL MONOCHROMAT (Only "Blue" active)	H) M-CHANNEL MONOCHROMAT (Only "Green" active)	J) L-CHANNEL MONOCHROMAT (Only "red" active)
Loss of 3 spectral channels	TOTAL BLINDNESS		

Figure 18.1.5-5 Functional forms of abnormal color vision in Humans and long wavelength trichromats. The form of the table can also be used for tetrachromats and short wavelength trichromats. The upper left shaded area includes those subjects defined as dichromats based on a performance criteria. The lower right shaded area includes those defined as monochromats based on a performance criteria. The label achromatopia in the box with a border may be too strong. The best available incidence data suggest 91.2% normal, 6.3% anomalous and 2.5% incomplete, with the functional monochromats falling in the parts per million range.

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The list of possible functional abnormalities in human color vision is long. It appears simplest to present those abnormalities first in a table of proposed predominant failures related to “incomplete trichromats.” This presentation can be followed by a discussion of the functional abnormalities associated with anomalous trichromats. Both presentations will use the level codes presented in **Figure 18.1.5-1**.

18.1.5.6 Principle failure modes of color vision

A quid pro quo for avoiding blindness not included in this table is the requirement to ingest retinol or one of its precursors. As demonstrated many times since the 1930's, the ingestion of retinol is a prime requisite for normal vision. Deprivation of this material and its precursors leads to total blindness in a matter of a few months depending on the storage capacity of the animal for these materials. The material must be available in the liver as an alcohol. Whereas it is required for its hormonal properties to support growth, it is the structural properties of the molecule that are required for vision.

Using the functional block diagram and the top level schematic of vision, it is possible to establish a framework of functional causes of color vision abnormalities. The most important fact to note is that these abnormalities can occur in any of the designated stages of vision processing enumerated in this work. Historically, the abnormalities of color vision have been associated with abnormalities in the photoreceptor cells of Stage 1. However, from a functional perspective and the architecture used, this location appears to be one of the less likely sources of abnormality. From a functional perspective, the most likely sources of error would appear to occur in the area of most compact (and complex) signal encoding. This fact would suggest that the most likely errors are associated with stage 3, signal projection.

The most common error from a functional perspective appears to be the failure of the midget ganglion cells of Stage 3 to be properly biased. An associated, and complimentary error would be a failure of the output of the stellate cells of that stage to be properly biased or to be improperly sensed by later circuits. This simple error in one of the chrominance channels can lead to the red-green color error syndrome or the more seldom reported blue-yellow color error syndrome. Simultaneous failures in both of these channels can lead to complete color blindness in spite of a fully populated retinal mosaic consisting of fully operational photoreceptors of all three chromatic types **and** a fully functional cognitive capability. Failure of the midget ganglion cells is only an obvious example. Similar errors in the stellate cells of Stage 3 or the lateral cells of Stage 2 can also lead to significant or complete color perception errors without abnormal photoreceptor operation or presence.

Very carefully planned experiments are needed to confirm the precise location of failures causing color abnormalities in the visual system.

Failures further into the cortex than the stellate cells can also lead to color abnormalities. However, due to the diversity of signal paths in the cortex, this source of errors appears to be perceptually less important.

All known color abnormalities can be characterized as abnormalities of either:

Stage 0, the mechanisms involved in the creation and deposition of the chromophores

Stage 1, the chromatic detection channels, (S-, M- & L- in humans),

Stage 2, the chromatic signal processing channels (P & Q in humans)

Stage 3, the chromatic transmission channels (the encoding, projection & decoding function) or

Stage 4, chromatic perception within the cerebellum (including the Paint routine)

These conditions can be most easily related to the numeric levels assigned to the functional block diagram with the addition of stage 0, representing and including the mechanisms related to the formation of the functional disks within an Outer Segment. This stage originally appeared in the Global model of the visual process in Chapter 1.

Table 18.1.3-1 provides a matrix correlating the suggested principle failure mode related to each level of the functional block diagram of this work.

TABLE 18.1.5-1
THE COLOR VISION FAILURE MATRIX
based on the suggested principle failure mechanisms

Stage	Level	Failure to:
0	Formation & Metabolism	
	A	Form Serum Retinol Binding Proteins (SRBP)
	B	Form Rhodones within SRBP's
	C	Transport Rhodones to Outer Segment space
	D	Deposit Rhodones on Opsin as a liquid crystal (anagenesis)
	E	Insure contact between disks and the dendrites of PC's
	F	Supply correct glutamate cycle constituents to neurons (continuously)
1	Detection	
	5	Provide effective spacing between disks of Outer Segment
	6	Form Activas within the dendrites of the Photoreceptor Cells
	7	Configure electrical topology of Photoreceptor Cells
2	Signal processing	
	8	Create the appropriate 1 st lateral processing matrix
	9	Establish difference signals in two chrominance channels
	10	Diversity encode chrominance signals
3	Signal transmission	
	11	(not applicable to chrominance channels)
	12	Pulse encode chrominance signals
	13	Achieve signal projection via the optic nerve
	14	Decode, process & re-encode chrominance signals within LGN
	15	(not applicable to chrominance channels)
	16	Decode chrominance signals in cortex
4	Signal perception	
	17	(not applicable to chrominance channels)
	18	Perceive color attributes in feature extraction engines
5	Physiological optics and servomechanisms	
	1	Genesis or diseases of transmission (cataract)
	2	(not applicable to color vision)
	3	Compute complete POS command signals
	4	Connect scan generator to POS

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Reviewing the TABLE following its creation, it appears that the most frequent failures leading to chromatic abnormalities or failures reside in two areas. The **first** involves failure of the lateral cells of level 9 to form the correct difference signals (leading to tetartanomalia and deutanomaly). The **second** involves the improper biasing of the midget ganglion cells of the retina to encode, or the stellate cells of the brain to properly decode, the P- and Q-channel signals. These ganglion and stellate cells are only marginally different from the similar cells in the luminance channel. If there is a place to suggest a genetic failure associated with the evolution of man from an achromatic ancestor, this is probably it.

The simplest error in this region would result in either the P- or Q-channel midget ganglion cell encoding the bipolar signal it receives from stage 2 as a monopolar signal as if it were a monopolar signal received from the R-channel. The available data suggests the polarity of the signals delivered to the midget ganglion cells are not random or equally divided with respect to polarity. All of the available data suggests they are deterministic. Encoding the P- or Q-channel signals as if they were R-signals would result in a loss in the perception of S- or L-S-channel signals, i. e., tetranoia or deutanopia. If the bias applied between the emitter and the base of the midget ganglion cells was only marginally incorrect, tetranomalia and deutanomaly would result.

This analysis has not uncovered a single case where the perception of the M-channel was suppressed or absent. There may be such cases buried in the literature of so-called anomalous trichromats. However, the data was not glaring enough to be noticed. Such a case of complete failure would constitute pentanopia with induced tetratonoia and deutanopia. This subject would be a completely achromatic functional dichromat with reduced sensitivity in the “green” region of the spectrum.

18.1.5.7 The less significant abnormalities

Defining the myriad of minor functional abnormalities that can result in abnormal color vision performance is time consuming here. By reviewing the detailed circuit diagrams of **Section 11.7.2**, it is seen that there are a number of locations where errors in bias voltage, the size of lumped capacitances or the size of various load impedances can affect performance of the system without causing a total failure. Careful laboratory work will be needed to evaluate the rates of incidence of these possibilities.

18.1.5.7.1 Effect of aging

The visual system suffers minimal degradation due to aging. Because it is not an imaging system, it does not suffer “holes” in the field of view due to failures in individual photoreceptors. Because of the overlap of the signal processing and signal perception functions, larger areas of the field of view are not lost due to a single point failures in the system. Most of the failures affect the performance of the system at the margin. The most common partial failure is the loss of ability to focus over a significant range of distance in the field of view. This loss due to a loss in compliance in the lens is easily compensated for with the available technology. An equally common but less noticed partial failure is the loss in sensitivity in the blue/purple region of the spectrum due to increased absorption by the lens with age. Said & Weale showed that the 3Db loss in transmission occurred at ever longer wavelengths with age¹⁰³. Their values were approximately:

Age	21	25	31	37	45	63
3Db wavelength	415	425	440	455	470	505

Fortunately, this loss is compensated for to a large degree within the photopic region by the adaptation amplifiers. However, the loss will impact the chromatic performance of the eyes in the mesotopic region. It will also have a significant impact on the minimum sensitivity of the older visual system under scotopic conditions.

There may be some loss in performance of the oculomotor muscles related to tremor with age. Such loss, if present, appears to be small. It would be recognized as a slowing in the ability to perceive fine detail rapidly. This would be a difficult loss to quantify.

¹⁰³Said, F. & Weale, R. (1959) The variation with age of the spectral transmissivity of the living human crystalline lens. *Gerontology*, vol. 3, pp 213-231

Other common, though statistically infrequent, losses are the result of small strokes that impact one or more of the extraction engines of the brain. These occasionally result in the loss of ability to perceive certain images (specific faces), event sequences (motion in certain directions or within certain velocity ranges), etc. Occasionally, one of these strokes can cause a loss in the luminance channel but not the chrominance channels. As a result, the subject perceives colored images floating across part of his field of view but no detailed rendition of the object forming the image.

18.1.5.8 Comparison with the research literature

Review of the literature can resolve some questions concerning the failure modes discussed above. Piantanida & Sperling have provided excellent data supporting the above assertions. In the first of two papers, they show that the deutanope has all spectral channels operating properly in the creation of the luminance response of the subject¹⁰⁴. The deutanope clearly has a failure in a channel other than the spectral channels that causes his red-green color blindness. Similarly, Piantanida & Sperling have provided excellent data supporting the above assertions that the protanope has a major failure in the L- spectral channel¹⁰⁵. The failure in the L-channel results in a luminance channel (R-channel) signal that is clearly deficient in long wavelength sensitivity. This loss of performance in the L-channel obviously distorts the performance of the Q-chrominance channel, resulting in red-green color blindness. While the data supporting these conclusions is excellent, the investigators did not attend to the color temperature of their sources adequately. This caused a problem in calibration accuracy. It is also reported that true protanopes exhibit the same spectral sensitivity whether under photopic or scotopic conditions.

In reviewing the concept of color blindness, there is a distinct conceptual difference between the conventional performance oriented expression that the subject “confuses certain colors” and **the functional concept that the abnormal subject does not perceive a difference between certain colors**. The difference is subtle. The cortex of the subject is not confused by the chromatic information received. In most cases, the cortex receives inadequate or absent signal via either one or both of the chrominance channels. Scheibner & Kremer discussed some of these differences in the conceptual descriptions of color abnormalities recently as part of their (vector oriented but entirely linear) three dimensional opponent-color theory¹⁰⁶.

The majority of the color literature, including that of the color abnormal, is based on the equilateral trichromatic theory interpreted mathematically by Konig in 1903 and based on the linear summation of normalized absorption characteristics. Wyszecki & Stiles have presented Konig’s work along with a group of expansions including those of Vos & Walraven and Smith & Pokorny along with the “farmer’s gate” analogy often found when using floating models¹⁰⁷. **This work does not support the underlying equilateral trichromatic color theory.** Whereas that approach has traditionally calculated a peak long wavelength spectral response near 575 nm, the measured response has been known to peak near 625 nm since at least Wright in 1929-30¹⁰⁸. It has been confirmed by Wald in the 1950’s, given by Marks in the 1960’s and shown to be at the same wavelength in many chordates over the years. Up to page 604, Wyszecki & Stiles show a long wavelength peak absorption at well beyond 575 nm. In pages 605-633, they elaborate on the Konig and extended Konig models and show graphs with a long wavelength peak response at much shorter wavelengths. Wyszecki & Stiles frequently point out that there are arbitrary limitation on the values that can be used in the above mathematical analyses. No attempt is made to relate the mathematics to a formal biological or psychophysical model.

The neural system employs an orthogonal color system more aligned to the color difference concept of Hering and memorialized in the Munsell Color Space (and in the Perceptual Chromaticity Diagram of this work).

The value of 625 nm is consistent with the predicted value of this work. **Chapter 16** provides a reformulation of Konig’s basic matrix equation that leads to the above experimental efforts and the conclusions found in this work.

¹⁰⁴Piantanida, T. & Sperling, H. (1973) Isolation of a third chromatic mechanism in the deutanomalous observer *Vision Res* vol. 13, pp 2049-2058

¹⁰⁵Piantanida, T. & Sperling, H. (1973) Isolation of a third chromatic mechanism in the protanomalous observer *Vision Res* vol. 13, pp 2033-2047

¹⁰⁶Scheibner, H. & Kremer, T. (1996) Deutanomaly studied with four perceptual criteria. *Vision Res.* vol. 36, pp. 3157-3166

¹⁰⁷Wyszecki, G. & Stiles, W. (1982) Color Science, 2nd Ed. John Wiley & Sons, pp 582-633

¹⁰⁸Wright, W. (1929-30) A re-determination of the trichromatic coefficients of the spectral colours, Trans. Opt. Soc. (London) vol. 30, pp 201-218 Also in Graham, et. al. (1965) Vision and Visual Perception. John Wiley & Sons, pg 380

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One of the foundations adopted by Konig was that a deutanope was missing a functional mid-wavelength photoreceptor array (rather than being the second type of color blindness defined in antiquity). Konig was wrong in his assumption (See **Section 1.8.1.3.1**). It is well known that functional deutanopes frequently exhibit normal photopic luminosity functions. Such responses are not compatible with the absence of a mid-wavelength sensory channel. According to this work (using a bilateral difference model in the chrominance channels), a subject lacking a mid-wavelength photoreceptor array would be an achromatope since both the P- and Q-channels would be non-functional.

As shown above, this work replaces the confusion points of Konig (equated to spectral peaks of the chromophores at one point in Wyszecki & Stiles) in color normals with continuous color loci (which cannot equate to peak absorption wavelengths. As will become obvious in the next Section, the confusion points proposed by Konig, Vos & Walraven and Smith & Pokorny in terms of CIE x,y values are not supported by this work.

18.1.5.8.1 Comparison with various chromaticity Diagrams

The loci of discrimination representing a variety of color abnormalities have been published over the years. Most of them have been based on a paper issued by the National Research Council of Britain in 1935 over the signature of Pitt¹⁰⁹. They have recently been published in the second edition of Wyszecki & Stiles with modest additional notation and crediting Judd and Wyszecki (pg 466). It is not generally recognized that these curves are primarily conceptual when plotted in CIE color space.

Pitt collected his data using two narrowband (probably ~30 nm wide) spectral lines (530 nm and 650 nm) using his two-axis optical bench as an anomaloscope. **Figure 18.1.5-6** shows his data for his “average” protanope along with his nomenclature.

¹⁰⁹Pitt, F. (1935) Characteristics of dichromatic vision. Report of the Committee on the Physiology of Vision: XIV Special Report Series, London: Medical Research Council of Britain, No. 200 *Reproduced in* Dawson, W. & Enoch, J. eds. (1984) Foundations of Sensory Science. NY: Springer-Verlag pp 253-254

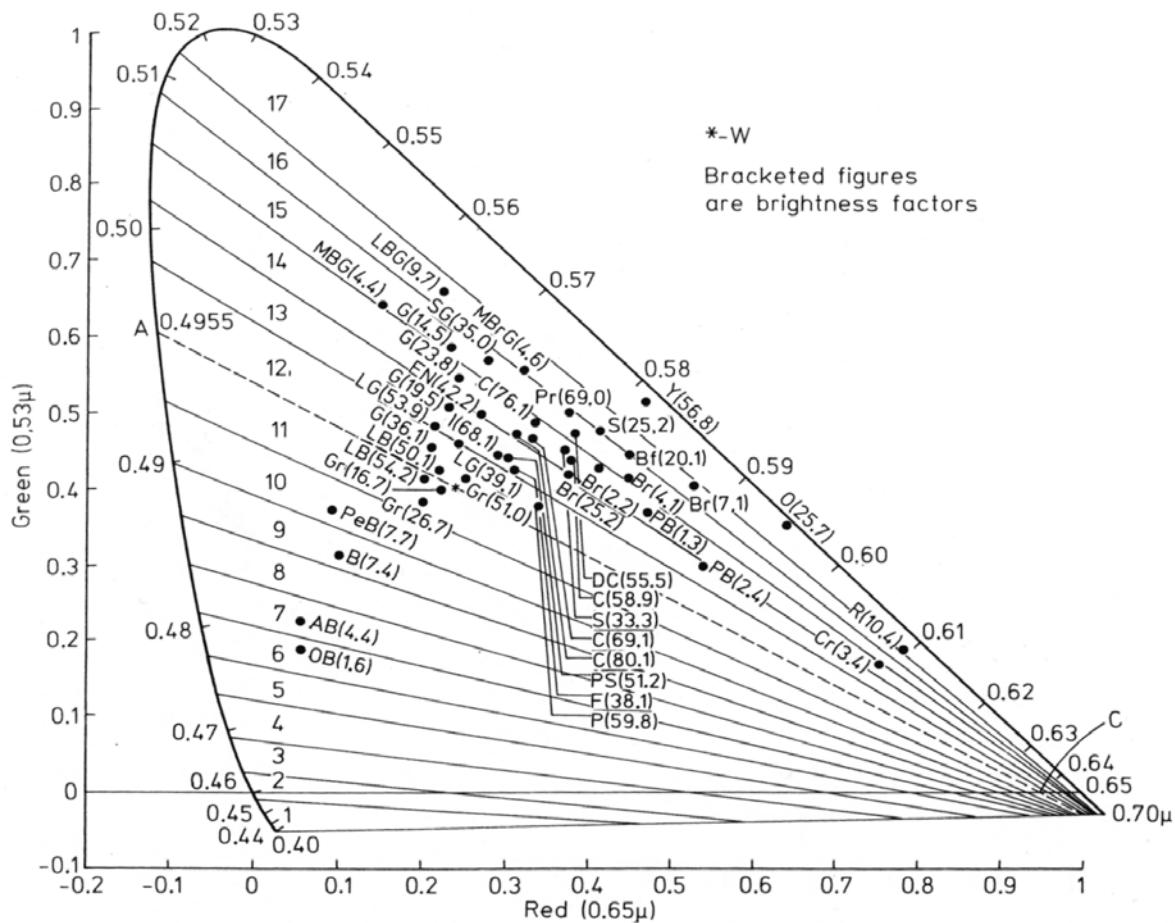


Fig. 5. The chromaticity confusion loci for an average protanope, showing the colours that the protanope would confuse when their protanopic luminances (or brightness factors) are the same. PITT (1935)

<i>OB</i> , Oxford blue	<i>PS</i> , Portland stone	<i>DC</i> , Deep green
<i>AB</i> , Azure blue	<i>F</i> , Fawn	<i>SG</i> , Sea-green
<i>B</i> , Blue	<i>I</i> , Ivory	<i>MBRG</i> , Mid-bronze green
<i>PEB</i> , Peacock blue	<i>S</i> , Stone	<i>PR</i> , Primose
<i>GR</i> , Grey	<i>BR</i> , Brown	<i>BF</i> , Buff
<i>LB</i> , Light blue	<i>C</i> , Cream	<i>LBG</i> , Light Brunswick green
<i>G</i> , Green	<i>EN</i> , Eau-de-nil (G)	<i>CR</i> , Crimson
<i>LG</i> , Light green	<i>MBG</i> , Mid-Brunswick green	<i>Y</i> , Yellow
<i>P</i> , Pink	<i>PB</i> , Purple brown	<i>O</i> , Orange
<i>AC</i> , Confusion locus through white point W (CIE source B)		
		<i>R</i> , Red

Figure 18.1.5-6 The chromaticity confusion loci for an average protanope according to Pitt. Note the limited region of data collection relative to the limits of the figure. From Pitt, 1935.

Figure 18.1.5-7 shows Pitt's data for his "average" deuteranope.

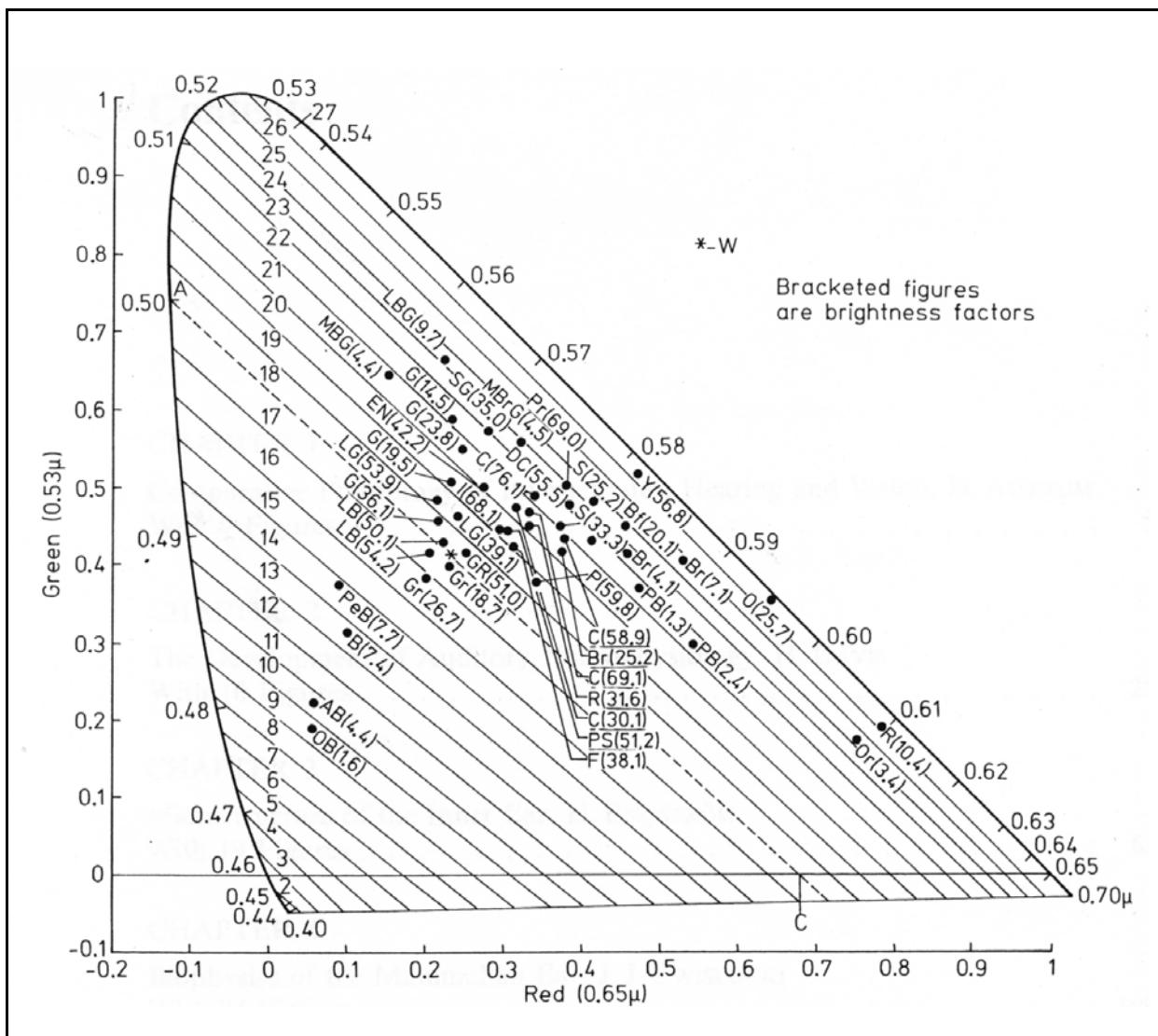


Figure 18.1.5-7 The chromaticity confusion loci for an average deuteranope according to Pitt. See nomenclature on previous figure. Note the limited region of data collection compared to the limits of the figure. From Pitt, 1935.

Note the negative red space along the abscissa in Pitt's two figures. His spectral locus is distinctly different than that plotted on the CIE color space.

These two figures have straight loci drawn through the data points (in many cases only one point) without any associated theory suggesting such straight lines in this color space. This is a particular problem with regard to the line AC in each figure. These lines are drawn through only a few data points clustered around the defined white point. There is no substantiation for the loci numbered 1 to 11 being straight lines for the protanope. Similarly, there is no substantiation for the loci numbered 1 to 17 of the deuteranope being straight lines. Interestingly, the deuteranope loci presented on a CIE color space in Wyszecki & Stiles are different. They are not parallel and converge at a high x-value of 1.080 by computation.

None of the lines in Wyszecki & Stiles are marked to indicate one is the nominal centerline of the group. It is difficult to relate the above definitions to these figures precisely because the underlying CIE Chromaticity Diagram of 1931 is not conformal. It is neither equidistant or equiangular as clearly shown by the ellipses of MacAdam. The straight lines radiating from a confusion point for each type of chromatic defect are only conceptual. The lines

should show significant curvature. If they were drawn correctly, they would suggest a different situation for the Protanope and the Tritanope using either their performance or function-based definitions. The lines would be considerably straighter if plotted on the C.I.E (1976) u, v Chromaticity Diagram. However, they would not converge as well. In fact, on the New Chromaticity Diagram for Research, the lines do not converge at all. They are parallel lines. For the Deutanope and Tetartanope, the central line of the group passes through 572 and 494 nm respectively. The subject's white point remains nominally normal. For the Protanope and the Tritanope, the central line of the set of lines may pass through a different wavelength at the axis. This is an indication of the loss of spectral absorption by one of the spectral channels. These axial intercepts and the shifts in axial intercepts are easily recognized with a conventional anomaloscope. The shape of the associated lines can be determined easily with a new anomaloscope discussed in an **Appendix**.

Recall that the New Chromaticity Diagram is based on the perceived, or psychological, performance of the visual system while the old 1931 Diagram is based on the object field, or psychophysical, performance of the system.

Figure 18.1.5-8 shows the spectral performance of those with complete failure of one of the chrominance channels of vision based on this theory using both the proposed New and the old Chromaticity Diagram formats. *The names of various types of abnormal color vision used here are specifically those defined earlier in this work.* The upper two frames show the predicted performance of a tritanope and tetartanope where the Q-channel is completely dysfunctional. The locus of confusion (**LoC**) is the vertical line at 572 nm in the proposed diagram. Other, so-called pseudo-isochromatic lines are parallel to this line in the bottom half of the frame. The horizontal line at 460 nm is shown to indicate the limit of vision for a complete tritanope compared to that at 400 nm for a normal subject.

Additional work is needed to define the location of the pseudo-isochromatic lines in the upper part of the figure. At ever shorter wavelengths, the subjects vision begins to fail and he begins to perceive only the null condition in these areas. In the case of the tritanope, he has little vision in the region between 400 and 460 nm. This fact suggests that the pseudo-isochromatic lines begin to diverge significantly in this area. In the case of both the tritanope and the tetartanope, the sensitivity of the chrominance channel decreases with the product of the absolute value of the P-signal times the light level due to the nature of the encoding algorithm of the signal projection stage. This sensitivity is controlled by the nominally fixed detection threshold associated with these channels in the cortex. This mechanism also suggests that the pseudo-isochromatic lines diverge in the upper part of the frame.

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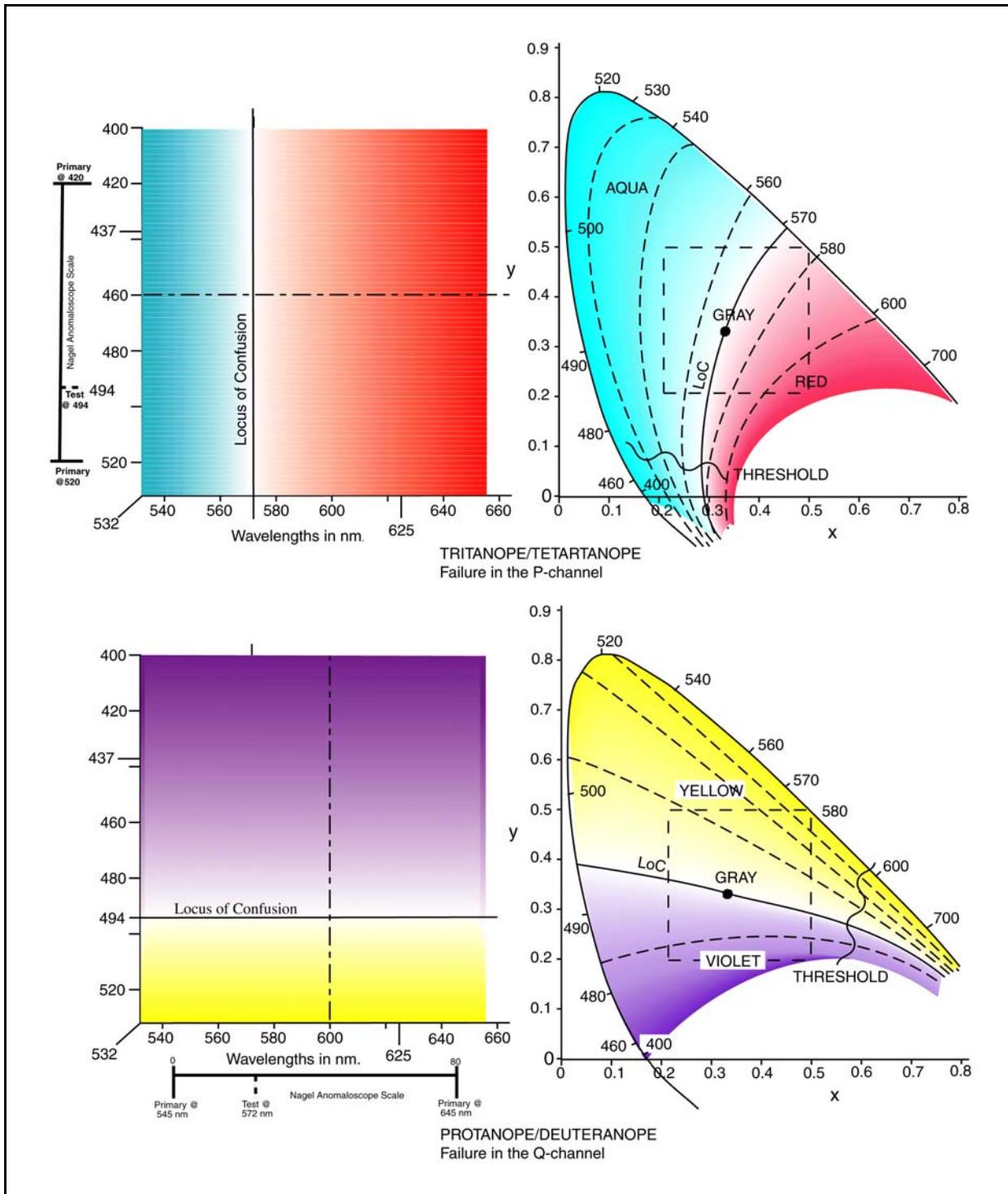


Figure 18.1.5-8 The spectral performance of color abnormals estimated using both the Perceptual (left) and Object space (right) Chromaticity Diagram formats. The upper two frames show the tritanope and tetartanope using the definition of these terms found in this work. The perceived colors are found along the 5R-5BG axis of the Munsell System. In both frames on the right, the wavy line represents the threshold of color sensitivity of the system. The lower two frames show the protanope and deuteranope. The perceived colors are found along the 10Y-10PB axis of the Munsell System. Note the isoclines do not intersect the spectral locus at both ends in the old format. The intersection of the two loci of confusion intersect at the “white point.”

It is awkward to transfer the perceived, or psychological, performance of the visual system to the old 1931 Diagram format because of the lack of conformality and linearity of that format (not to mention the theoretical difficulties related to its empirical definition). However, three points associated with the locus of confusion in the new diagram can be transferred uniquely to the old format for each of the violet-yellow and the red-green defective classes. These are the location of the line of confusion at its only intersection with the spectral locus, its passage through the white point, and the fact that the LoC is parallel to the spectral locus on the opposite side of the white point. A pair of pseudo-isochromatic (dashed) lines have been drawn in each of the frames on the left in the illustration to highlight these conditions.

For the violet-yellow defective, the signals presented to the subjects cortex represent a range of color that a normal subject would describe as azure through gray through red as indicated in the upper right frame. These colors are found along the 5R-5BG axis of the Munsell Color System. As discussed briefly above, the abnormal subject may report a complete loss of color perception in the region suggested by the wavy threshold line. This line represents the threshold level in the remaining operating chrominance channel of the tritanope or tetartanope. Note that the L-channel has no impact on the chromatic performance of the tritanope and tetartanope. Note also that for the tetartanope, the signals in the luminous or R-channel are completely normal and he exhibits a normal luminous efficiency function.

For the red-green defective, the signals presented to the subjects cortex represent a range of color that a normal subject would describe as violet through gray through yellow as indicated in the lower right frame. These colors are found along the 10Y-10PB axis of the Munsell Color System. As discussed briefly above, the abnormal subject may report a complete loss of color perception in the region suggested by the wavy threshold line. This line represents the threshold level in the remaining operating chrominance channel of the deutanopes and protanopes. Note that the S-channel has no impact on the chromatic performance of the deutanopes and protanopes. Note also that for the deutanope, the signals in the luminous or R-channel are completely normal and he exhibits a normal luminous efficiency function.

Traditionally, investigators have attempted to determine a convergence point in the lower left of the frame for the tritanopes and the tetartanopes. However, most of their data collection activity has concentrated within the area of the dashed box. Because of this concentration, recent authors have continued to follow the conceptual suggestions of Pitt dating from 1935. They have attempted to determine a point of convergence of the curving pseudo-isochromatic lines with the goal of finding a theoretical meaning to such a copunctal point. The Pitt model says the lines do not converge.

Burns, et. al. have presented empirical data that show that the lines do in fact converge according to the pattern defined by this work¹¹⁰. Their empirical measurements match the theory of this work within the range of statistical error. Pokorny, et. al. have also noted the inadequacy of the linear assumption inherent in the CIE diagram when discussing loci of confusion¹¹¹.

The lower two frames of the figure relate to the protanope and deutanope. A discussion similar to that above applies to this case involving the complete failure of the Q-channel of chromatic vision. In this case, the LoC is defined by the horizontal line intersecting the spectral locus at 494 nm. Vision beyond 600 nm is greatly reduced for the protanope. For the deutanope, the signals in the luminous or R-channel are completely normal and he exhibits a normal luminous efficiency function. The fan of lines transferred from the orthogonal New Chromaticity Diagram to the old C.I.E. format are shown forming a tight parallel group parallel to (but not intersecting) the spectral locus in the lower right of the frame. As in the above case, most investigators have only worked in the area defined by the dashed box. However, the data in a figure of Alpern, et. al. (although acquired at a different color temperature) can be favorably compared to the performance predicted by this figure¹¹². The lines predicted by this theory form a group that could easily be confused with those suggested by Pitt and often fit within the statistical variation of data points obtained by recent investigators. As in the previous discussion, these proposed pseudo-isochromatic lines do not converge to a copunctal point.

The cortex of a subject with complete failure of the Q-channel receives signals from the P-channel defining colors that the normal would describe as ranging from violet to gray to yellow and following the 10Y-10PB axis of the

¹¹⁰Burns, S, Elsner, A. Pokorny, J. & Smith, V. (1984) The Abney Effect: chromaticity coordinates of unique and other constant hues *Vision Res* vol 24(5), pp 479-489

¹¹¹Pokorny, J. vol 6 xxx

¹¹²Alpern, M. Kitahara, K. & Krantz, D. (1983) Perception of colour in unilateral tritanopia *J. Physiol.* vol 335, pp 683-697

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Munsell Color System.

Some readers have had difficulty interpreting the difference between a protanope and a deutanope, and the difference between a tritanope and a tetartanope in the above figure. **Figure 18.1.5-9** expands the left-hand frames of the above figure to illustrate the difference more clearly and to surface a subtle problem. An outline of the color space that can be provided by an Iiyama MF 8617A monitor of 1995 is also shown for discussion purposes. The conceptually more restricted color space of a tritanope (upper right pair) compared to a tetartanope is obvious. This presentation portrays an abrupt roll-off of the short wavelength sensitivity with wavelength. The lower right pair shows the similar case for a protanope compared to a deutanope. The tetartanope and the deutanope exhibit normal visibility functions across the entire visual spectrum but suffer an inability to differentiate certain colors. The tritanope and protanope exhibit restricted visibility functions as well as an inability to differentiate certain colors..

The literature does not provide a definitive answer to whether the color-blind perceived color spaces reflect a P or Q value of zero (or null) or of some other finite value. The literature does suggest the zero or null condition is most likely. Only very careful experiments asking the color-blind subject to compare the right hand pairs to the normal perceptual chromaticity diagram can answer this question.

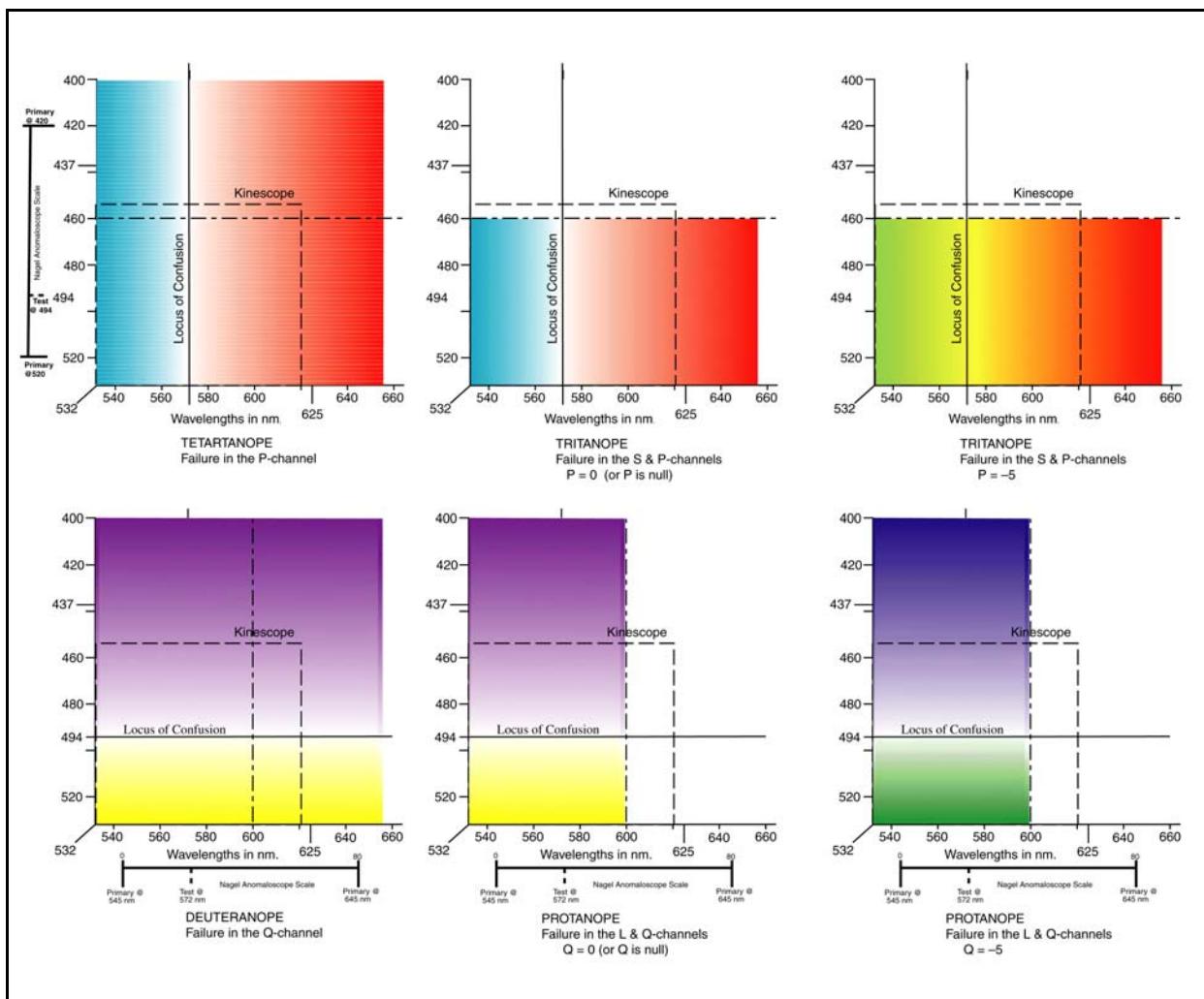


Figure 18.1.5-9 Details of common color abnormalities. The right two panels in each row show two potential perceptions that a tritanope or a protanope might experience depending on the failure mode within his system. The central panels show the potential perceived colors if the P or Q functions were at zero or were undefined (null). The right panels show the potential perceived colors if P or Q equaled -5. Only precise testing can determine what color space a defective actually perceives.

The typical color monitor color space is shown to illustrate a limitation inherent in using a monitor in color research. A conventional monitor cannot reproduce the total color space of a normal human subject. The Iiyama monitor cannot reproduce colors with a short wavelength component shorter than 450 nm or a long wavelength component longer than about 620 nm (on a weighted basis). Such a monitor can be used to explore most of the color space of a tritanope. However, it is limited in its ability to explore the color space of a protanope. The reason is the reduced sensitivity (shown as zero in this idealized caricature) of the protanope to energy with a center wavelength near 620 nm. As a minimum, an increased red-channel brightness will be required from the monitor compare to the other phosphor channels.

The above caricatures have been drawn under the assumption that a uniform photon flux intensity has been maintained over the entire color space of interest and the illumination level is within the photopic range (conditions supporting color constancy in the individual subject). Precise investigations will require careful calibration of the light source(s) to insure uniform photon flux across the spectral region of interest.

18.1.5.8.2 Comparison with available luminosity functions

Figure 3 of Smith & Pokorny (1975) provides excellent data with regard to the difference between protanopes and deutanopes based on flicker photometry. The data points at short wavelengths appear to be superior to the smoothed curve overlaying them and suggest either tritanomaly, differences in macular absorption or a different level of dark adaptation for some of the subject deutanopes. The smoothed curves are the result of a complex transformation, based on linearity, of little interest here (See **Section 18.1.5.7** above). They include it to account for problems with the C.I.E. database and adjustments suggested by Vos & Walraven. Their figure 4 demonstrates the above data differences were due to macular absorption differences.

Both figures 3 and 4 are in complete agreement with this work. They show the distinct luminous efficiency function differences between the protanope and the deutanope. The data was collected with 10-15 nm wide spectral filters (centered unfortunately at multiples of 10 nm) and clearly show the inflection points in the blue region of the luminosity function due to the logarithmic summation of the S- and M-channel signals.

As indicated in this work, and elsewhere, the long wavelength photoreceptor (L-) channel of the protanope is not functional. He exhibits a scotopic luminous efficiency function due to the remaining two functional spectral channels at all light levels. Failure of the L-channel induces deutanopia in the subject. All spectral channels of the deutanope are fully functional and he exhibits a normal luminous efficiency function as a function of illumination level. The failure of the deutanope is in the Q-channel of the chrominance signal paths. These features of the deutanope and protanope are illustrated explicitly in Records¹¹³.

The insets within figure 3 of the above work require additional discussion. The data in the insets were used to correct for macular absorption. They were not presented to suggest a difference in chromatic performance of the underlying system as a function of field angle.

The luminous efficiency of a tetartanope is normal and shows the expected transition between photopic and scotopic performance. The luminous efficiency of a tritanope is not normal. It shows a significant loss in short wavelength performance under photopic conditions. Under scotopic conditions, the luminous efficiency function of the tritanope is even more unusual. It indicates that only the M-channel photodetectors are contributing to the overall visual response. The tritanope under scotopic conditions is a true functional monochromat. He is also an achromat under scotopic conditions just like the normal subject.

18.1.5.8.3 Description of the confusion lines and “copunctal points” of abnormals

Lankowski¹¹⁴ and others have drawn lines of confusion on the C.I.E. (1931) Chromaticity Diagram to describe various lines of confusion as reported by color abnormal subjects. His results were discussed in Boynton¹¹⁵. His exploratory experiments have been concentrated in the area of the dotted box of the previous figure. Hill et. al. have performed similar experiments more recently¹¹⁶. Several comparisons can be made between their experiments and

¹¹³Records, R. (1979) Physiology of the Human Eye and Visual System NY: Harper & Row, pg 471

¹¹⁴Lakowski, R. (1969) Op. Cit. pg. 273

¹¹⁵Boynton, R. (1979) Human Color Vision, NY: Holt, Rinehart & Winston pp 371-376

¹¹⁶Hill, A. Connolly, J. & Dundas, J. (1978) An evaluation of the City Colour Vision Test *Mod Probl Ophthal* vol. 19, pp 136-141

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this theoretical work. Their conception of where the lines of confusion “should go” appear to be based on an interpretation of the Farnsworth-Munsell “100-hue” test. The resulting lines are all straight and treated as tangents to the ellipse formed by the reported perceptions from the above test. Their protan/deutan lines (within the dotted boxes in the left frames of the above figure) are in agreement with the proposed lines based on this theory. Similarly, there is good agreement within the box between their tritan/tetartan lines and the proposed lines for tritan/tetartans of this theory. However, outside the box, the two approaches predict entirely different results. The theoretical proposal does not support a convergence of these isoclines. Therefore, the concept of copunctal points representing these convergences point is not supported. Furthermore, the theoretical intercepts of the isoclines with the spectral locus of the C.I.E. Chromaticity Diagram are quite different.

The concept of copunctal points appears to originate with a misinterpretation of Grassman’s Laws. Grassman is credited with first developing the concepts of linearity as they applied to vision. However, his laws have been shown earlier in this work to apply to the small signal situation only. The visual system is basically logarithmic—not linear.

Schanda has described the mathematical foundation for the performance curves usually associated with color defectives based on Grassman’s Laws¹¹⁷. In his interpretation, based on Judd & Wyszecki (1975) and appearing in Wyszecki & Stiles (1982, pg 462), a protanope exhibits a copunctal point near the spectral locus at 680 nm. A tritanope exhibits a similar copunctal point near the spectral locus at 430 nm. A deuteranope exhibits a copunctal point far to the right of the normal CIÉ Diagram at coordinates near $x = 10$ & $y = 0.0$. The problem with this common interpretation is the fact that Grassman’s Laws do not apply to the large signal case, e. g. the space outside of the Farnsworth-Munsell ellipse. Furthermore, as shown in Hill et. al., the empirical chords do not form a tightly converging bundle in CIÉ coordinate space.

All of the above authors have restricted their tests to the area within $x = 0.2\text{--}0.5$ and $y = 0.2\text{--}0.5$ of the CIÉ Chromaticity Diagram. They have usually restricted their tests to the even narrower confines of the Farnsworth-Munsell “100 Hue” test. By extending chords, through points around the Farnsworth-Munsell ellipse matched by different defectives, they have attempted to determine a set of empirical copunctal points. As shown in the above figure, the copunctal points determined empirically or by extending Grassman’s Linear assumptions have no theoretical significance. The various lines of apparent constant chromaticity do not converge.

18.1.5.8.4 Comparison with the statistical data of Lakowski

Lakowski has provided statistical data describing the color vision system with classifications describing a variety of performance conditions¹¹⁸. By correlating this data with the functional block diagram of vision, it is possible to describe the underlying functional conditions causing a majority, if not all, of these performance conditions. The critical point was addressed briefly in **Section 11.1.2.3.1**. The individual circuits of the signal detection and signal manipulation stages of vision (1 & 2) are directly coupled making the signals carried over these circuits subject to truncation as a function of amplitude. The circuits of signal projection (stage 3) also incorporate a feature that makes them sensitive to bias problems. They employ what is conventionally described as DC recovery (or as used in color television, DC restoration). The decoding circuits are designed to generate a quiescent voltage equivalent to the quiescent voltage applied to the encoding circuit even though the intervening circuits do not transmit the quiescent value of the input waveform. If they fail to do this within a given tolerance, the perceived chromatic information will exhibit an offset in wavelength. Severe cases of quiescent voltage drift or improper quiescent voltage restoration can lead to failure in the chrominance channels independent of any specific genetic problem.

Figure 15 in Lakowski illustrates these types of functional failures to a marked degree in traceable form. The data has been acquired with a Nagel Anomaloscope and reflects the nomenclature of that device. There are three important characteristics of the data to be noted. First, the data is statistical, and represents a log-normal rather than normal distribution (Lakowski describes it as J-shaped.). Second, each data set exhibits its own matching range (MR), defined by the spectral range between $\pm 1\sigma$. Third, there is a statistical variation in the matching mid-range point (MMP) or median value of each data set. The second and third characteristics are exactly those expected to be found in a direct coupled circuit or a pulse circuit with DC recovery. They correlate well with the failure modes discussed above in **Sections 18.1.5.2**.

¹¹⁷Schanda, J. (1998) Current CIÉ work to achieve physiologically-correct color metrics Chapter 17 in Backhaus, W. Kliegl, R. & Werner, J. Color Vision: Perspectives from Different Disciplines NY: W de Gruyter

¹¹⁸Lakowski, R. (1969) Op. Cit. pg. 278

Figure 18.1.5-10 presents a composite of the data and performance labels of Lakowski and the functional labels of this work. The data sets shown in the center of the figure show clear trends from the top to the bottom of the page (Note: The order of the data sets associated with “color weak” is slightly different from those of the original paper). Each data set shown is for a single individual. Lakowski has accumulated a large data base and declares that 68.3% of the population exhibit MMP’s between the $+\!-\!1\sigma$ values. The anomaly quotients at the bottom of the page refer to the ratio of the median or MMP setting of a subject on the Nagel Anomaloscope to the same setting of a normal subject. The claim by Trendelenburg (1929) being that low values of this quotient are indicative of protanomaly and high values suggestive of deutanomaly. Caution is advised in using this ratio since the scales on all anomaloscopes do not progress in the same direction. This claim appears unfounded and archaic as will be discussed below.

The performance classifications on the right are all semantic and suggest a generally larger defect with category as the categories progress down the page. The use of the phrases “variations in normal trichromats” and “anomalous trichromats” are essentially synonymous in the absence of specific definition. Lakowski describes the first (top) normal subject and the four red-green deviants as exhibiting good color discrimination, accepting only one mixture ratio, while the four color-weak subjects accept a greater number of ratios (have wider MR’s). The latter exhibit poorer color discrimination. He defines deviants and the simple PA and simple DA subjects as having their MMP’s outside the 2σ limits while maintaining narrow MR’s. He distinguishes the anomalous types from all others by the fact that their MMP’s are always well outside the limits of the distributions for normal observers. He goes further and defines the dichromats as having MR’s that extend through all of the available mixture ratios for a given “equation” regardless of their largely undefined MMP. He does not define the difference between the incomplete and complete dichromats, apparently relying upon the graph presentation.

Lakowski does not attempt to separate the protanomalous from the deutanomalous types in this presentation. All of his categories include both types. In fact, recording only the red-green control setting on the anomaloscope does not allow the separation of these two types. This is usually done by noting the yellow intensity control setting. Intensity settings that increase with the “green” setting are indicative of protanomaly or protanopia.

Overall, the definitions provided by Lakowski do not form an orthogonal set. There are actually two underlying parameters that can be combined in four ways. Nominal values in both of these parameters suggest normal trichromatic vision. Extreme values in either of these parameters suggest deutanopia. All intermediate values are found in the figure. Mathematically, these parameters are the deviation of the mean of a subject from the normal of the population and the deviation of the standard deviation of the subject from the standard deviation of the population. In electrical engineering terminology, this corresponds to the deviation of the quiescent voltage from that of the normal (the DC signal offset) and the reduction in signal amplitude relative to the normal (the signal gain).

The functional classifications on the left relate to the above interpretation of the mathematical relationships. The normal trichromat exhibits an MMP and an MR that are the same as that of the population in-toto. Deviations from these values can occur in both directions. Note, the figure does not purport to show the MR of the total population, the statistical parameters apply to the MMP only. However, for discussion, consider the third subject from the top to be indicative of the population as a whole. In this case, the first subject shows a “normal” MMP and a better than normal MR. His color rendition is normal and his color discrimination is considerably better than normal. The second subject exhibits an error in MMP that results in a shift in his color rendition (? toward the green) but his MR, and hence color discrimination, is still better than for the total population. These interpretations can be extended down the page resulting in the detailed labels on the right. Each of these labels can be given a precise mathematical description based on the statistics. Lacking the required statistical parameters, they are grouped into minor and major categories in this figure to track the labels on the right. There are several problems related to the tracking of the labels of Lakowski:

- + there is no clear definition between the dichromats and anomalous trichromats based on performance,
- + there is no clear definition between the incomplete and complete dichromats based on performance,
- + there is no distinction between protans and deutans based on the performance presented in this figure.

The problems can be stated simply. First, the variations in MR and MMP are continuous functions that require auxiliary statistical parameters to separate them into semantically distinct bins. Second, as in the figures of **Section 18.1.5.5**, protanomalia and protanopia are distinctly different conditions than the corresponding deutanomalia and deutanopia. They describe different abnormalities related to different functional mechanisms. As shown in that section, a protan condition can induce a deutan condition, because of the location of the underlying mechanisms in the signal path, but the opposite is never true. Whereas the data may include protans, they are not separable from the deutans in this figure. Thus, the labels on the left are explicit. The table only exhibits deutan related conditions.

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However, the deutanopia can be intrinsic or induced. If the deutanopia is induced by protanopia, a definition of protanopia is needed. In this work, protanopia is defined arbitrarily as a S-channel spectral sensitivity, as measured in the luminous efficiency function, 1000:1 less than normal. Lesser losses reflect protanomaly.

As shown on the far left in the figure, there is a question mark as to where to draw the line between deutonomalia and deutronopia. The more extreme conditions can be typified by any one of three conditions. The gain in the chrominance channel can approach zero. The gain can be normal but the dynamic range of the signal can be outside of the dynamic range acceptable to subsequent circuits (stage 3), or a failure in the spectral channel can result in the initial chrominance signal falling outside of the dynamic range of the chrominance channel itself (stage 2). The last case where protanopia induces deutanopia was discussed above. In all three cases, the matching range, MR, becomes extreme. The question of how extreme is extreme calls for a standard in terms of the MR of the subject. Based on the figure, a standard of five or six sigma would appear reasonable and compatible with the known statistics. Thus, deutronopia is defined by a MR of more than five or six times the standard deviation of the population. All other conditions between a standard deviation of one and the chosen upper limit are classified as deutonomalous.

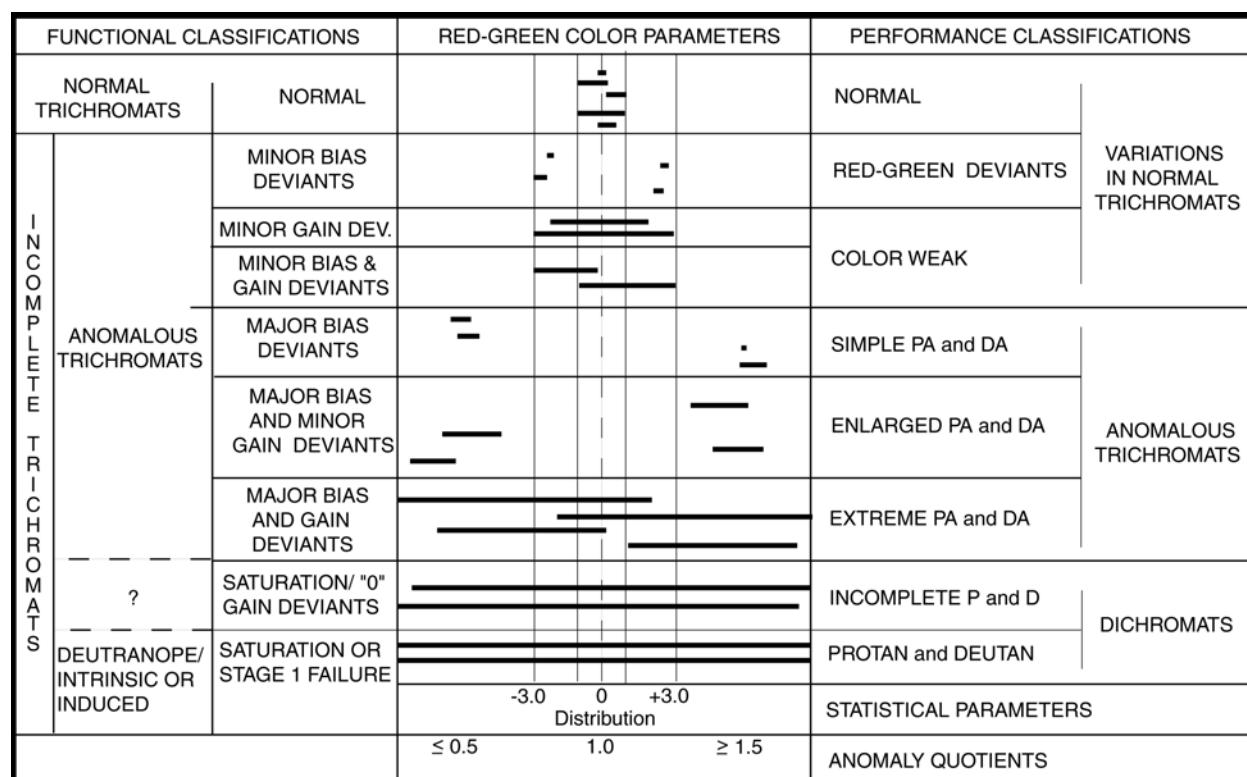


Figure 18.1.5-10 Comparison of the performance labels and functional labels of abnormal color vision and the data of Lakowski.. The statistical groups are members of a continuum within one overall statistical population. Those defined as exhibiting minor bias or gain deviations fall within plus and minus 3σ deviation of the population mean. Although the performance criteria may accept protanopes, the data only supports the designation functional deutanope, as defined in this work, in the absence of test channel intensity information from the anomaloscope.

Nagy has provided interesting data extending that of Lakowski¹¹⁹. His data shows the change in location of Rayleigh matches with background illumination for several color defectives.

¹¹⁹Nagy, A. (1980) Large-field substitution Rayleigh matches of dichromats. *J. Opt. Soc. Am.* vol. 70, no. 7, pp 778-784

18.1.5.8.5 Chromatic versus achromatic sensitivity of the deutanope

Although the terminology of Backhaus, et. al¹²⁰. is not supported here, they present data relating the chromatic versus achromatic contrast sensitivity for the human deutanope. It shows the variation in this relationship with respect to illumination level, in Trolands, with respect to flicker frequency and with respect to eccentricity.

King-Smith, Kranda & Wood have provided some very enlightening information relative to an acquired unilateral color defect in the opponent color system¹²¹. They show clearly that the subject exhibits a normal spectral response while exhibiting virtually total loss of red/green discrimination in his left eye. They propose the cause of the abnormality is “pre-cortical” and suggest its origin is at least as peripheral as the ganglion cell layer of primate retina. However, they offer no model of the retinal circuitry on which to base their proposal. They do provide data for both 200 ms flash and flicker photometry using a one degree field. There is no indication of any loss of M-channel photoreceptors.

Jack Schwartz (private communication) has suggested an alternate form of deutanomaly. It is probably a form of cerebral deutanomaly. Jack has created a “spaced” Ishihara plate of the number 2 using green filled circles on a background of red filled circles on a white surface. He claims to see both the red and green filled circles clearly and as well saturated colors. However, he does not perceive the numeral 2, claiming “It simply does not cohere into a visual gestalt.” His figure is quite large as presented on his website (~ 10 Degrees in height) and extends well outside of his foveola. It appears he is able to perceive each individual filled circle with his foveola and to scan the entire scene (See **Section 7.5.2.2.1**) but he is not able to assemble the individual foveola sized images into a correct context. This could be similar to a person scanning a room but not perceiving any vertical edges due to a lack of horizontal tremor in his precision optical system.

18.1.5.8.6 Achromatopia (without an s)—total loss of chromatic perception

The total loss of chromatic perception without other complications (symptoms) is especially interesting. The literature has had difficulty interpreting the underlying cause(s) of such a condition. Following this section, an extensively evaluated total achromat, still alive in 1996, will be discussed in **Section 18.8.3.1** A more complex situation involving an isolated population and incorporating achromatopia, as part of a larger syndrome defined as achromatopsia (with an s), will be discussed in **Section 18.8.3.2**.

This work illuminates two major causes of achromatopia and one potential cause. The latter might appear quite confusing in the laboratory. The most clear cut cause of achromatopia outside of stage 5, is the failure of both chrominance channels somewhere within stages 2 and 3. A complete functional failure of both chrominance channels is a unique situation and is defined as INTRINSIC ACHROMATOPIA. There are a variety of failures possible at the circuit level but they all have the same effect, the cortex does not receive useful information concerning the spectral characteristics of the scene.

A separate and distinct possible cause of complete loss of chromatic perception is the loss of the middle wavelength spectral channel. The loss of this channel is defined here as PENTANOPIA to conform with the historical plan of using Greek prefixes. It is believed this condition is extremely rare. It is primarily diagnosed through a detailed determination of the luminous efficiency function which will be unusual under both photopic and scotopic conditions.

Since the signal from this channel is used to compute the two chrominance signals, the loss of this signal would have two effects. It would cause a significant abnormality in the luminous efficiency function of the eye and also prevent useful chromatic information to be transmitted to the cortex via the chrominance channels (whether they were otherwise functional or not). This form of color blindness is defined as PENTANOPIA WITH INDUCED ACHROMATOPIA.

If a subject with this condition can be found, it would be interesting to observe his response to certain unusual chromatic situations. Under transient conditions, such as observing Bidwell’s disk, the subject might report an unusual sensation. He might or might not be able to associate this sensation to color, partly through lack of

¹²⁰Backhaus, W. Kliegl, R. & Werner, J. (1998) Color Vision: Perspectives from Different Disciplines. NY: W. de Gruyter pg 97

¹²¹King-Smith, P. Kranda, K. & Wood, I. (1976) an acquired color defect of the opponent-color system
Invest Ophthal Vis Sci vol 15(7), pp 584-587

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education and experience.

As will (or has) become clear, protanopia does represent a complete loss of the L- visual channel at the Transduction or photoreceptor cell stage. However, deutanopia does not refer to a similar loss. Deutanopia is actually a failure in the chrominance signaling channel and not a loss of any transduction or primary signal processing capability. The subject still exhibits a normal photopic spectral sensitivity but he fails to discriminate properly between mixtures of M- and L- inputs (the circuitry creating the null near 0.580 microns is inoperative).

A form of total performance-based monochromatism (achromatopsia without amblyopia and frequently but erroneously called Cone monochromatism) is very rare and involves a complete loss of the chromatic signal processing capability of the eye. Most visual capabilities other than color discrimination are normal (or near normal).

A unique form of achromatopsia related to the association areas of the cerebrum, and independent of the chrominance channels and the visual cortex has been reported. Damasio et al. have carefully documented a case of hemiachromatopsia (without the s in this work)¹²². [xxx add]

The capability of a small area within the association area of the CNS to determine whether the imaged scene is perceived in color sounds very similar to the “color-killer” circuit used in analog broadcast television receivers to eliminate the presentation of colored visual snow and ambiguous color fields when the broadcast signal is received at inadequate signal-to-noise ratio.

Conway & Tsao have provided information from fMRI concerning the location of the equivalent location in macaque cortex to that of Damasio et al. Citing Damasio et al., they note, “A strong piece of evidence favoring an extrastriate “color area” is the observation that stroke patients with particular circumscribed lesions acquire achromatopsia (a deficit of color vision) yet retain motion and depth perception.” Unfortunately, their protocol suffered significantly from their attempting to identify a non chromatic test signal. A problem in identifying the response of the macaque to a chromatic versus an achromatic image is also present. They go on, “To avoid ambiguity, we use the anatomical term PITd, which is consistently used to describe the region of the cortex on the posterior bank of the superior temporal sulcus (Van Essen and others 1990, 2001; Felleman and Van Essen 1991; Distler and others 1993).” And further, “We may have underestimated the overall amount of color activity in all areas because the criteria for “color bias” was stringent (see Materials and Methods); this might account for the discrepancy between our results showing little color bias in TEO, with other results showing stronger color responses in TEO (Tootell and others 2004).” For the purpose of this discussion, they conclude (page 1611) that PITd is probably the most afferent position in the visual modality chain that could be involved in the final decision to deliver chromatic information to the stage 5 engines under low signal-to-noise conditions. “...a pattern that is remarkably similar to the one found in humans (Wade and others 2002).”

18.1.5.8.7 Achromatopsia (with an s)—a complex syndrome including nearly total loss of chromatic perception

Achromatopsia is a complex syndrome, not a single symptom, resulting from an electrical bias error at the synapses between the sensory neurons, the photoreceptors, and the subsequent neurons in the retina. While it is frequently described as involving the absence or functional failure of the putative “cones” of the retina, it affects all of the photoreceptors equally when they are subjected to high stimulus levels. The precise character of this “single point failure” affecting all of the photoreceptors will be discussed in detail in **Section 18.8.3.2**. Subjects with this syndrome exhibit normal visibility functions when measured using 10 nm wide filters under high mesopic (low photopic) light conditions. They also typically report residual (though frequently useless) color sensations at this light level. Thus, all of the chromatic photoreceptors are fully operational at that light level. It is important to note these subjects have had the condition since birth and are not aware of the sensations of normal color vision. Subjects with achromatopsia are generally diagnosed with uncorrectable (neurological) myopia and usually exhibit nystagmus at least at an early age. They are also typically photophobic because of the pain generated by electrical saturation in the output circuits of the photoreceptor neurons due to excessive stimulation. This pain is similar to that encountered by a normal person exposed to high-noon sunlight at the beach in lower latitudes.

¹²²Damasio, xxx (1980) Central achromatopsia behavioral, anatomic, and physiologic aspects Neurology vol 30(10), pp 1064-xxx

Michaelides, Hunt & Moore have provided a very good review of the current state of knowledge concerning achromatopsia from a clinicians perspective¹²³. Unfortunately, it suffers from a total lack of a physiological model of the visual system and ignores the cause of all of the symptoms of the disease except for its concentration on the putative failure of the “cone” photoreceptors.

18.1.5.9 The applied research literature of color abnormalities

Many studies have been performed with the goal of either emulating color blind performance or compensating for colorblind performance in modern life. The recent activity has centered on the computer display interface. Unfortunately, much of this activity has not used a realistic model of the visual system and the resulting failure modes resulting in color blindness. The primary problem has been investigators assuming the color performance of the human is based on additive color principles within a linear system. A major problem has been the use of inappropriate terminology, such as defining deuteranopia as resulting from the failure of the spectral photoreceptors of the M-channel. Such a failure has never been documented in the literature. As discussed above, deuteranopia is the result of a computational error totally independent of the photoreceptors (Section 18.1.3.1). At least three recent papers are known to be based on and incorporate these major errors^{124,125,126}.

An additional common problem is the use of linear matrix algebra to describe isocontours in the CIE (1931) Chromaticity Diagram that are demonstrably not straight lines.

18.1.5.9.1 The ERG and EOG in applied

The electroretinograph (ERG) is a valuable electrophysiological tool in evaluating the operation of the retina as a function of light level. There are two fundamentally different methods of operating an ERG. The most widely used involves full-field (Ganzfeld) illumination, also called afocal illumination. More recent activity has centered on focal illumination (of limited areas at any given time) and multi-focal illumination (of limited areas in a sequential pattern).

The International Society for Clinical Electrophysiology of Vision (ISCEV) have promulgated a variety of standards applying to these different situations. The 2004 update is the latest standard for full-field illumination¹²⁷. There is a 2007 edition of the multi-focal situation¹²⁸. Parks et al. have provided a set of examples of a multi-focal ERG¹²⁹. A major finding of Parks et al. was that in healthy subjects, “The implicit time of the waveform components was not found to vary over the retina (peak or b-wave component, 35.52 (1.4) ms; trough or a-wave component, 17.76 (0.8) ms).” This finding shows there is no region of the retina served by slow rods versus fast cones at the level of illumination used.

18.1.5.9.2 The Ishihara plates for evaluating color blindness

Ishihara developed a set of color plates to be bound in a book and used to evaluate color abnormalities in a clinical environment¹³⁰. They are fundamentally low color contrast presentations that are very difficult to reproduce on a computer display because of the lack of display calibration and the lack of control of the lighting available. Printed copies of these plates are readily available for purchase on the Internet. A brief set of the plates are displayed at

¹²³Michaelides, M. Hunt, D. & Moore, A. (2004) The cone dysfunction syndromes *Br J Ophthalmol* vol 88, pp 291-297

¹²⁴Meyer, G. & Greenberg, D. (1988) Color-defective vision and computer graphic displays *IEEE Comp Graph Appl* vol 8, no 5, pp 28-40

¹²⁵Brettel, H. Vienot, F. & Mollon, J. (1997) Computerized simulation of color appearance for dichromates *J Opt Soc Am A* vol 14, no 10, pp 2647-2655

¹²⁶Vienot, F. Brettel, H. & Mollon, J. (1999) Digital video colourmaps for checking the legibility of displays by dichromates *Color Res Appl* vol 24, no 4, pp 243-252

¹²⁷Marmor, M. et al. (2004) Standard for clinical electroretinography (2004 update) *Doc Ophthalmol* vol 108, pp 107-114 (available free online)

¹²⁸Hood, D. et al. (2007) ISCEV Guidelines for clinical multifocal electroretinography (2007 edition) www.iscev.org (Available free)

¹²⁹Parks, S. Keating, D. Williamson, T et al. (1996) Functional imaging of the retina using the multifocal electroretinograph: a control study *Brit J Ophthalmol* vol 80, pp 831-834

¹³⁰Ishihara, S. (1917). Ishihara pseudoisochromatic plates. International edition. Technical report.

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<http://www.toledo-bend.com/colorblind/Ishihara.html>

Dr Waggoner, a practicing optometrist, has prepared a set of plates for use as a screen for young children, <http://colorvisiontesting.com/>.

A laboratory at Florida State University has provided a brief tutorial on color defects based on the conventional (and largely archaic) wisdom of the 20th Century.

<http://micro.magnet.fsu.edu/primer/java/humanvision/colorblindness/index.html>

18.1.5.10 Conclusions EMPTY

18.1.5.10.1 Generic causes of chromatic abnormalities

Based on the above discussions, several features relevant to abnormal color vision are apparent. First, the deviations in performance are closely correlated to deviations in electrolytic function. Variations in electrical quiescent values and gains within the signal paths are primary causes of chromatic irregularities. Second, the continuous distribution of the red-green defect among the population does not correlate well with a single unique genetic failure. Third, the log-normal statistical distribution is usually associated with a growth related phenomena. The fact that the frequency distribution for chromatic discrimination relative to the just noticeable difference (j.n.d) in normal eyes is log-normal in the anomalous eye suggests the defect is growth related. Based on these factors, it appears that the chromatic abnormalities of the visual system are generally associated with the values of various impedances that are growth related rather than with step changes in the electrostenolytic processes related to different chemicals acting as feedstock in the glutamate cycle. Most of these failures do not appear to relate to a specific genetic defect.

18.1.5.10.2 Super-normal chromatic performance

The first data set in the above figure suggests that there are individuals with significantly narrower than normal matching ranges. On the other hand, one of the properties of a log-normal distribution is that the incidence of individuals with better than mean performance is quite small. This suggests that the graphic may give a misleading conclusion with respect to the MR of individuals with good discrimination. It would be a rare individual that exhibited a MR a factor of two better than the norm under fully controlled conditions. Two points are important. First, a normal trichromat can define the same match repeatedly on a typical anomaloscope. This suggests the instrumentation is not sensitive enough. Second, whereas Lakowski discusses in detail the necessity of using a minimum light level that exceeds the mezotopic light level, preferably by a factor of two or three, he does not address the fact that this level may vary by spectral band due primarily to the state of adaptation of the individual. It appears critically important in the laboratory that the subject does not view any object at a color temperature other than the equal flux condition (representing the fully dark adapted condition) before the experiment is begun. It is also necessary to insure that the level of the test light is always the same when testing normal trichromats to avoid corrupting the data. Although the test light wavelength is designed to minimize its influence with regard to chromatic performance, it can significantly affect the luminous efficiency of the individual spectral channels of the subject.

18.1.5.10.3 Anomaloscope operating requirements and performance

There are various forms of anomaloscope on the market. In general, they are delivered as un-calibrated devices intended for use in a sophisticated clinic but not for research. Lakowski has pointed out that the training requirements associated with the anomaloscope are high, especially if it is to be used for research. This is primarily due to the statistical nature of the data obtained and the number of abnormalities involved. Comparison between data from machines of different manufacture may be difficult because of the lack of calibration of the red-green mixture control. Most units use narrow spectral lines for both the reference (test) source and the two primary lights and the subject views the light sources directly through an aperture. The Pickford-Nicolson design uses broadband filters and an integrating chamber. The subject views a reflective surface.

The normal procedure is to use the machine to establish the chromatic characteristics of a large population and then consider the instrument readings for a given subject against the readings of the general population. To speed the above process, it is preferred that those with abnormal chromatic performance be eliminated from the database, preferably prior to making detailed measurements with the anomaloscope. Lacking a theoretical foundation, the literature only provides subjective discussions of the meaning of deviant readings. Based on the above discussion, a more detailed set of guidelines can be developed.

Figure 18.1.5-11 presents an annotated graph based on the Nagel Model II Anomaloscope. The upper frame is used for long wavelength determinations and the lower frame for short wavelength determinations. The upper frame can be compared to that of Krill or Rubin & Walls referenced earlier. Neither of these authors provides a complete discussion of their figure. Some of their terminology is modified here because of the additional level of detail available. Each frame has a vertical axis defining the intensity of the test light. The horizontal axis presents an uncalibrated indication of the relative intensity of the two lights contained in a mixture of a shorter wavelength and longer wavelength primary. The precise wavelengths of these lights are not critical. However, best results will be obtained if the test lights have a wavelength corresponding to the null point or zero crossing in the spectral wavelength discrimination function for either the long or short wavelength portion of the overall spectral band. For discussion, it will be assumed that these wavelengths are 494 nm and 572 nm corresponding to the termini of the Hering axes of vision. Similarly, the two selected primaries should be very narrow band and preferably near 400 and 520 nm when working in the short wavelength spectrum and 545 and 655 nm when working in the long wavelength spectrum.

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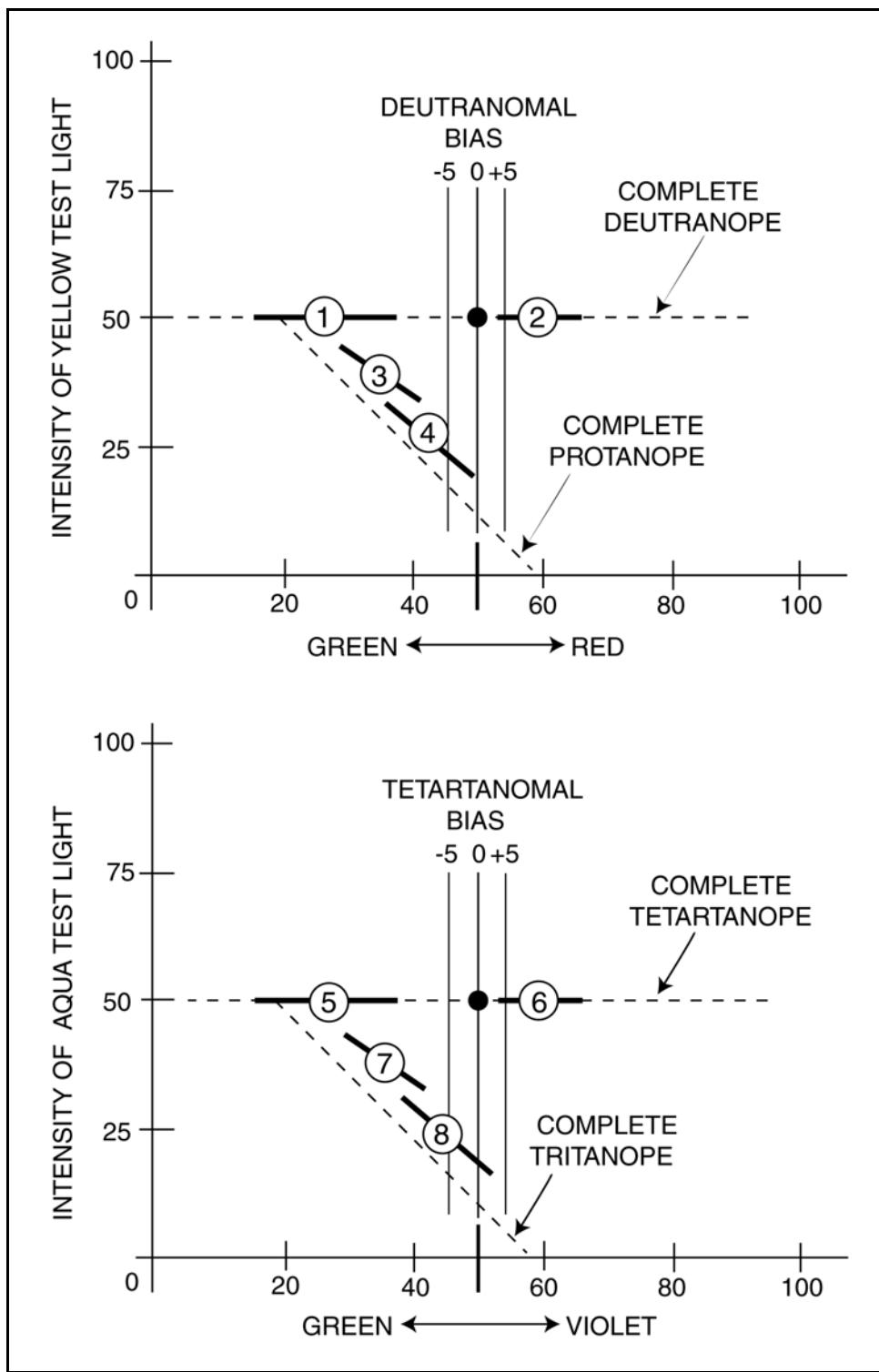


Figure 18.1.5-11 Annotated record from a Nagel type anomaloscope. See text for details.

The light levels chosen at the factory are designed to insure intensities sufficient to insure photopic operation of all of the adaptation amplifiers of the retina. Within this range, the absolute intensity levels are relatively unimportant. However, if the primary lights are not of correct magnitude relative to each other, the horizontal lines in the following discussion will not be horizontal in practice. In the upper frame, the normal population will consistently set the green-red and yellow controls to the same match mid-point, MMP, as indicated by the black dot. The matching range about this point will be small. It may not be measurable on the typical instrument. Those in the population with anomalous color vision in the long wavelength portion of the spectrum will present a range of performances on this graph. Each can be described by three values, the match range, MR, the match mid-point, MMP and the slope of the line associated with the MR range. The subject marked "1" is clearly deutanomalous. His MR is about 21 and his MMP is about 23. His MMP can also be described as a deutanomalous bias of -27 relative to the normal population. Subject "2" exhibits a lower degree of deutanomalia. His MR is less than 12 and his bias is +9. As discussed earlier, as the MR of an individual becomes larger, he approaches complete deutanopia. A complete deutanope can match a given level of yellow test light with any setting of the red-green control (his MR is 100% of the scale and his MMP is undefined). Whereas a deutanomalous may or may not accept the match of a normal subject, depending on whether his MR overlays the MMP of the color normal, a complete deutanope will accept the match of any other deutanomalous as well as a color normal. A complete deutanope is represented by the horizontal dashed line.

The performance of a protanomalous subject is slightly different because of his loss of long wavelength spectral sensitivity. This causes his match point to vary with test light intensity, requiring less test light intensity as the color control moves toward red. The performance of the complete protanope begins on the horizontal line at zero on the green-red scale. At a point determined by the test and primary light wavelengths, the protanope begins to require less and less test light intensity when it determines a match. The complete protanope can match a given test light by setting the intensity and green-red controls to any value along the bent line marked complete protanope. In general, a complete protanope will not accept a match determined by a normal subject.

The protanomalous subject has a less severe loss in the long wavelength spectrum than the complete protanope. Segments "3" and "4" represent a mildly protanomalous and a significantly protanomalous subject. Note that the MRs of these subjects do not lie along the loci of either the deutanope or protanope. In the case of subject "3," his MR is about 15 with a projection onto the horizontal axis of about 12. His projected MMP is 35 which equals a (deutanomalous) bias of -15 relative to the normal. Note that while all protanomals will exhibit a MR at an angle with respect to the deutanomalous line, the angle can vary as a function of the severity of the condition.

This figure presents a slightly more complex situation than found in the literature. While a complete deutanope may accept any match determined by a normal, since the MR of the deutanope extends over the entire horizontal axis and his luminous efficiency function is the same as the normal subject, the deutanomalous subject may not accept the match of a normal depending on the location of his MMP and his MR.

In general, the complete protanope will not accept the match of a normal subject, since his locus of confusion is not a horizontal line and his luminous efficiency function does not match that of the normal. A similar situation applies to the protanomalous subjects.

A separate line is not shown in this frame for an achromat. A complete achromat can only make matches of lights based on intensity information. In this sense, the performance of the complete achromat, of the intrinsic type, approximates the horizontal line of the complete deutanope. However, if the achromat also suffers from protanopia, his condition can be labeled protanopia induced achromatopia. His performance will closely match that of the complete protanope. For lesser degrees of loss due to protanomalia, the performance of the induced achromat will be represented by a full length sloping line at an angle between these two extremes. Similar to the condition of protanomalia, for lesser degrees of achromatomania, the subject will exhibit both an MR and an MMP located along a sloping line.

The lower frame of the figure shows a similar situation for a subject with abnormal short wavelength color vision. Note the test light has been changed to aqua and the horizontal scale in both frames has green on the left. The condition of tetartanopia is represented by the full length horizontal line. The condition of tritanopia is represented by a sloping line due to the loss of the short wavelength spectral channel. Both of these conditions are considered quite rare. Their actual rarity may be masked by the common use of artificial light deficient in the blue. Under this type of light, normals will exhibit color performance similar to that of many with short wavelength deficiencies. The achromat can be shown in this frame just as in the above frame. The performance of the intrinsic achromat would overlay the horizontal line of the tetartanope. The performance of the tritanopia induced achromat would overlay the tritanopia line and lesser degrees of achromatomania would exhibit a MR and an MMP falling on a line between the above two extremes.

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Any of the individual lines defined above to characterize various conditions can be moved vertically if the subject also shows an unusual sensitivity to light intensity.

18.1.5.10.4 Ratio of red to green sensitivity

Although it is easy to determine the role the individual spectral channels play in forming the luminous efficiency function, it is more difficult to determine the ratio between the sensitivities of the various spectral channels in the formation of the chrominance signals. The anomaloscope can provide information in this area. Although these instruments are designed to require minimal calibration and operator training, when used by a professional they can provide precise information. As an example, if individuals with progressively more severe cases of intrinsic deutanomaly report they can make matches over a wider and wider red-green range without changing the intensity of the yellow test signal, it would imply that the spectral sensitivity of the M- and L-channels were essentially constant and equal. If they require different levels of test signal intensity with different ratios of red to green illuminant, this would define the ratio between the intrinsic sensitivity of the M- and L-channels.

18.1.6 Transient abnormalities of vision

The visual system is unique in that it exhibits significant transient performance differences over time intervals from less than 3 milliseconds to over 10 minutes, a range of 180,000:1. Some of these transient effects arise between parallel processing channels and are suppressed during normal operation. Most are only noticed under artificial conditions. The principal variances between the channels of vision are related to:

- + a variance in the delay to peak response between spectral channels during photodetection, combined transduction and translation, of up to 400 milliseconds when presented with large increases in irradiation intensity from a dark adapted condition.
- + a variance of a few tens of milliseconds between individual chrominance channels, and compared to the luminance channel, based only on the spectral content of the scene.
- + a variance of both a few seconds and a few minutes between spectral channels in their adaptation to sudden decreases in irradiation level.

The variances related to adaptation can occur in unison among all spectral channels or they can occur differentially.

Many of the variances are asymmetrical with irradiation level, leading to a variety of color artifacts under specific conditions (Such as Bidwell's Disk). In other situations, such as near high contrast chromatic edges, this asymmetry is seen to be desirable if not purposeful.

18.1.6.1 The time intervals of transduction/translation

Basically a delay that is specific to each channel

18.1.6.2 The time intervals of adaptation

Technically both the amplifier and the iris, on and off are asymmetrical in both.

18.1.6.3 The time intervals of signal projection

An artifact of the encoding scheme

18.1.6.4 Critical flicker frequency in color blind subjects

Pokorny & Smith have provided the baseline for comparing protanopes and deutanopes with normals in the area of

critical flicker frequency¹³¹. The method of normalization used appears to be arbitrary. An alternate would be to overlay the short wavelength slopes.

18.1.7 Cross reference with clinical procedures

This work is not designed to provide a cross reference to the clinical literature. Only those specific conditions discussed here can be compared to their clinical correlates. It is hoped that it can provide a broader foundation to the work going on in the field.

The early 21st Century is seeing a revolution in the correlation of visual system performance with the site of chemical and electrical activity within the brain. The knowledge base is changing by the day. Kandel, et. al¹³² provide a simple tabulation of the situation with regard to agnosia, the failure of the subject to identify the characteristics of objects in the absence of obvious damage or disease in the neural pathways leading to the brain. Riddoch & Humphreys have provided a chapter on the clinical aspects of agnosia¹³³. Beard, et. al¹³⁴ also present a variety of congenital vision problems.

It is hoped the new perspectives provided, particularly with regard to the fundamental organization of the visual system and the operation of the neural system, will speed progress even more.

18.1.7.1 Radiation sources used in the clinic

There is a tendency in color abnormality studies, as well as other visual research, to use a light source that is, or is based on, a Standard developed for use in illumination. There is also a tendency, closely related to the above one, to think and act in terms of an equal energy spectral source. Both of these situations introduce an unrecognized variable into the scientific work. A more serious problem, when discussing the detection performance capability of the eye, is the use photometric units. These units are based on, and incorporate, a nominal spectral response associated with a standard eye. The response used is typically the C.I.E. (1931) Luminosity Function. The actual human eye is not well represented by this function for research purposes.

Illumination engineering generally must work with two components that are poorly matched spectrally. 1) Most light sources remain incandescent and exhibit spectrums close to that of a black body. Where fluorescent light sources are used, the phosphors are normally selected to simulate an incandescent source, either perceptually or technically. 2) The human eye has a spectral characteristic that varies significantly with excitation level. The C.I.E. Luminosity Function is a smoothed representation of the performance of the eye at a "comfortable" light level. Fortunately, the eye exhibits a spectral characteristic similar to the Luminosity Function over a wide range of excitation of about 50,000:1. Both above and below this range, the characteristic is significantly different. Because of these considerations, illumination engineering need not strive for high precision.

Research, on the other hand, has not sought great precision in the past. Much of it has been accomplished by psychophysical experimentation under less than adequately controlled conditions. Very few clinical tests of vision have specified the level of photoexcitation in the past. More recent tests have begun to specify this level in nominal photometric terms. Pokorny et. al. provide a paragraph concerning the confusion in this area¹³⁵. The fact is that color discrimination capability is inversely related to irradiance level. Based on the work of Verriest, they suggest a level of 2000 lux or about five times the level suggested by most recent clinical tests. The reason for the introduction of the unit lux appears ephemeral.

The use of inappropriate excitation sources, and relying on meters filtered and calibrated inappropriately, leads to a majority of the imprecision alluded to by Pokorny et. al. earlier. The problems of filtering and calibrating meters involve inappropriate assumptions concerning both the actual excitation source used and erroneous assumptions about the spectral performance of the eye under test.

¹³¹Pokorny, J. & Smith, V. (1972) Luminosity and CFF in deutanopes and protanopes *J Opt Soc Am* vol 62(1), pp 111-117

¹³²Kandel, E. Schwartz, J. & Jessell, T. (2000) Principles of Neural Science, 4th ed. NY: McGraw-Hill pg. 500

¹³³Riddoch, M. & Humphreys, G. (1988) Visual agnosia: anatomical and functional accounts *In* Kennard, C. & Rose, F. ed. Physiological Aspects of Clinical Neuro-Ophthalmology. Boca Raton, FL: Year Book Medical Publishers. Chapter 10

¹³⁴Beard, C. et. al. (1968) Congenital anomalies of the eye. St. Louis, MO: C. V. Mosby.

¹³⁵Pokorny, et. al. Op. Cit. pg. 103

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To avoid needing to factor out the built in functions of photometry, many researchers have employed an equal energy light source on the assumption that this source would excite all of the photoreceptors of the eye equally. This is an incorrect assumption. The photoreceptors of vision are quantum detectors, not energy detectors. A proper light source that does not color the data, pardon the pun, must be an equal photon flux source. Such a source appears even bluer, initially, than Standard Illuminant C which has a color temperature of 6774 K. An “equal flux” excitation source, optimized for experiments with long wavelength trichromats, corresponds to a black body at approximately 7053 Kelvin. Such a blackbody has an insufficient amount of energy per unit wavelength at long wavelengths. However, energy per unit wavelength is not the proper criteria. A 7053 Kelvin blackbody will equally excite all of the chromophores of human vision within +/-5.7%. An 8073 K blackbody will equally excite all of the chromophores of tetrachromatic animal vision, within +/-7.9%.

Using the flexible framework for defining illuminants adopted by the C.I.E., a true black body at 7053 Kelvin could be described as illuminant D₇₀. Use of this illuminant can considerably reduce the data reduction task associated with both luminosity and chromaticity research.

18.1.7.2 Use of broadband spectral samples

The field of Chromaticity research has grown from the simple premise that the mixture of three color samples (of appropriate individual intensities) can always match a fourth sample. This premise is based on two long standing axioms; a linearity assumption that is true in radiometry but is not generally true in vision, and the assumption that the eye employs additive color mixing. The first axiom refers to a qualitative match and can be true over the photopic region of illumination (as defined herein) due to the mechanism known as color constancy. However, it is not generally true as discussed below.

The visual system does not employ additive color mixing. It employs differencing (in a logarithmic signal space) between two pairs of spectrally selective photoreceptor channels following spectral integration. Thus, perceptual color mixing is entirely different from additive color mixing in object space. Perceptual color mixing is also fundamentally different from subtractive color mixing in object space. This is one reason why the eye has always been used as a null detector in color matching experiments.

Perceptual color mixing leads to a different conceptualization of color matching than that usually expressed in the literature. As seen from the New Chromaticity Diagram for Research, **only two lights or two reflective color samples are needed to match any color presented to a subject in object space**. One must be drawn from the short wavelength region associated with the P-chrominance channel and one must be drawn from the longer wavelength region associated with the Q-chrominance channel. Note that only two sources of specific wavelengths are required to obtain the perceptual response of “white” under dark adapted conditions. Spectral lights at nominal wavelengths of 494 and 572 nm will elicit a response of white. Under more general conditions, any two lights that result in a null signal in the P- and Q-channels after spectral integration with the chromophores will elicit a response of white.

The color differencing following spectral integration in vision provides a key to the difficulty in designing simple yet precise clinical tests for color vision abnormalities. These tests usually use reflective materials in the tests that are prepared using subtractive color mixing using the printers technique called “process color.” Process color is not compatible with the excitation of only one chrominance channel of vision. The use of process color always leads to a lower signal to noise ratio than desired in these tests.

A superior form of testing for color abnormalities would employ what the printer calls “spot color.” Spot colors are individual pigments that can be selected to have specific spectral characteristics. Using spot colors with characteristics chosen to be compatible with **Section 17.3.4.1** can lead to tests for color abnormality which are much more quantitative. Such tests are particularly capable of isolating color abnormalities of spectral absorption from those of chrominance signal processing.

18.1.7.3 The use of Purkinje Images

In an attempt to better understand the optical performance of the eye, Purkinje studied the reflections and internal images formed by the optical system of the eye. He was able to explain the individual images and catalog them in an orderly manner that is frequently helpful in the clinical situation. Bennet & Francis have provided a discussion of this area with some good photographic examples¹³⁶.

¹³⁶Bennet A. & Francis, J. (1962) in Davson, H. *ed.* The Eye, Volume 4. NY: Academic Press pp 108-120

Padgham has provided an example of the Purkinje Tree describing the blood vessels of the eye as observed by the subject, under transient conditions, using an off-axis illumination source¹³⁷.

18.1.8 Definition of new anomaloscopes and colorimeters for Research

Based on the recognition of the tetrachromatic capability of human vision (See **Section 17.3.3**), it is seen that previous anomaloscopes and colorimeters have been inadequate for research purposes. Current instruments fall into two groups, those designed for rapid clinical evaluation and more unwieldy devices designed for research. Since the spectral region between 395 and 437 nm is not used extensively in everyday vision, the common anomaloscopes may remain adequate for clinical purposes. However, research instruments must meet the requirements of the human visual system, that of a blocked tetrachromat.

18.1.8.1 Clinical Devices

The basic anomaloscope envisioned and introduced by Nagel can be considered one member of a set of such devices. The set includes:

- + single axis devices focusing on abnormal long wavelength color vision (Nagel Type I),
- + alternate axes devices capable of being configured to analyze abnormal color vision at either long or short wavelengths (Nagel Type II), or
- + dual axes devices capable of analyzing the color vision of any subject in both the long and short wavelength regions simultaneously (Proposed).

A dual axes device with scanable spectrometric sources used for the two test lights would allow the complete range of color vision to be probed. It would also allow a statistical determination of the spectral coordinates of "white" on the New Chromaticity Diagram for Research as confirmed by a large group of subjects. Such a device could also be used to determine the precise crossover wavelength of the two chrominance channels in color normals as well as color abnormals.

The scanning range of such devices must extend from at least 400 nm to 655 nm to satisfy all matches based on trichromatic vision. This range will also accommodate the actual tetrachromatic vision of humans in the 395-437 nm region. Because of this tetrachromatic corner of the visual space, the clinician should not be surprised at unexpected variations in the data for points between 395 and 437 nm. Lines that are straight over much of the chromatic space may show unexpected curvatures in this area. The matching source should not extend into the region of 655 to 700 nm because of the reversal of human chromatic perception in this region.

A simple test to determine color vision anomalies has been widely used with very mixed results. The Farnsworth 28-hue test employs 28 selected color caps arranged in a specific order around a circle. The assertion is that subjects with color deficiencies will define diagonals overlaying the predicted color deficiencies from the literature. **Figure 18.1.8-1** demonstrates the inadequacy of this test as documented by Merin, Ronen & Nawratzki¹³⁸. Their definition of congenital cone deficiency as "achromatopsia with amblyopia" is obsolete and largely misleading. The Farnsworth 28-hue test has not been generally accepted as valid and is not in common use.

¹³⁷Padgham, C. & Saunders, J. (1975) The Perception of Light and Colour London: G. Bell & Sons pg 29

¹³⁸Merin, S. Ronen, S. & Nawratzki, I. (1979) Management of patients with congenital cone deficiency (achromatopsia with amblyopia *in* Zauberman, H. ed. Proc Conf Subretinal space. Jerusalem (Documenta Ophthalmologica Proceedings Series volume 25)

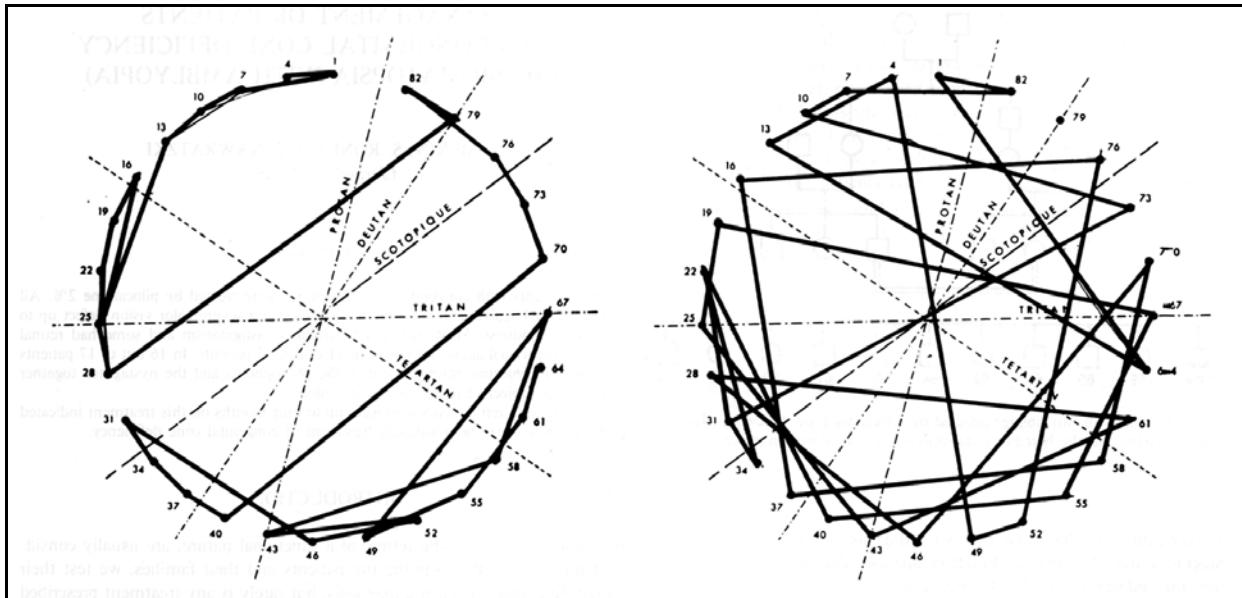


Figure 18.1.8-1 Two examples of the Farnsworth 28-hue test on two subjects with the same diagnosis, congenital cone deficiency. Zauberman describes the “scotopic” lines in a 14 year-old patient on the left and “complete confusion of line in a 13-year-old” on the right. The test has not come into wide use. From Zauberman, 1979.

18.1.8.2 Research Devices

Until the computer age, this field was barren. Available instruments included the Wright colorimeter of 1927 and its modifications, the Stiles tricolorimeter of 1955 and a host of less well known designs¹³⁹. At least three new computer-controlled dual axes anomaloscopes have recently come on the market. These include the HMC anomaloscope from Oculus and the IF-2 variant 2 from Roland Instruments and a unit from Interzeag, Schlieren, Switzerland.

The original Wright device is still in use. Originally, it used monochromatic lights centered on 460, 530 and 650 nm in matching experiments. These wavelengths closely match two of the wavelengths recommended here. However, the 460 nm source will not allow precise matching to samples with mean spectral wavelengths of 395 to 460 nm. This source should be changed to a shorter wavelength in any comprehensive experiments in the future. Similar comments concerning the wavelengths used apply to all of the other units. The restriction on the long wavelength source to a nominal 655 nm is pertinent because of the reversal in perceived color in the region beyond 660 nm.

The same caveats concerning the measured data apply as in the previous section. These are due to the tetrachromat performance of the human visual system in the 395-437 nm region.

¹³⁹Wyszecki, G. & Stiles, W. (1982) Color Science, 2nd ed. NY: John Wiley & Sons pp 472-483

The Interzeag unit uses 10 nm wide filters, a two degree bipartite field, and presents light with center wavelengths according to the following table;

Source	Wavelengths/bandwidths in nm						Field in degrees
	Rayleigh Match		Moreland Match				
	Short	Match	Long	Short	Match	Long	
Wright	530		650	460		530	
Interzeag ¹⁴⁰	545/10	589	670/10	436/10	480	490/10	2 degree bipartite

While the 589 nm wavelength is conventional, it differs from the theoretically nominal 572 nm null of the Q-channel. The match wavelength of 480 and the long wavelength of 490 are both too short to reasonably challenge the P-channel. However, they may have been chosen by Moreland to avoid exciting the Q-channel. It is proposed that better performance would be obtained using 494 nm and 520 nm in the absence of any interference from the Q-channel.

18.1.9 Adaptive optics and deconvolution as tools in evaluating the retina

A new ophthalmological tool appeared in the late 1990's for evaluating the living retina through the pupil. It employed a adaptive optic, an active deformable mirror, that could be inserted in the optical train of an imaging ophthalmoscope in order to compensate for the more significant aberrations in the human optical system. The result was unprecedented imaging resolution in pictures of the retina. The resolution provided clear images of photoreceptors of about two microns diameter. Even with this resolution, no rods have been identified in these images. Two distinct types of adaptive optics augmented ophthalmoscopes have been developed. A scanning version at the University of Houston¹⁴¹ and a pulse-flood illuminated version at the University of Rochester¹⁴². The University of Houston unit used a 37 element deformable mirror. The second generation University of Rochester (2003) unit employs a 97 element mirror. Its contrast performance has been further augmented by the use of deconvolution techniques¹⁴³.

18.2 Failures in non-afferent paths, stage B, 0 & 5

18.2.1 Abnormalities of the optical image forming apparatus, stage B

Immediately below this level is failure of the optical system to form an image on the retina. There are a number of morphological problems in this area, from cataracts to serious malformations at birth. Below the morphological level are a series of control and muscle related problems. Following those are the problems related primarily to potential cytological and molecular chemistry problems. Once the electronic signal regime is reached, the principal problems are related to metabolic and then bioenergetic support problems. These problems can be manifested as problems in signal amplification, processing, encoding, projection, decoding and cognition. It is important to recognize the very great importance of adequate bioenergetic support to the adaptation amplification process that is supported through the choroid arterial system. This is essentially the only functional aspect of vision supported by the choroid system. Problems in this area are not observable by present clinical techniques.

Failure of any of these functions to perform to nominal specification will result in a clinically identifiable condition.

These errors tend to be common to all signaling paths. Only changes in the absorption characteristics of the elements tend to affect the S-channel predominantly.

¹⁴⁰Kurtenback, A. et. al. (1999) Preretinopic changes in the colour vision of juvenile diabetics *Brit J Ophthalmol* vol. 83, pp 43-46

¹⁴¹Roorda, A. Romero-Borja, F. Donnelly, W. & Queener, H. (2002) Adaptive optics scanning laser ophthalmoscopy *Opt Express* vol 10(9), pp 405-412

¹⁴²Hofer, H. Chen, L. Yoon, G. et al. (2001) Improvement in retinal image quality with dynamic correction of eye's aberrations *Opt Express* vol 8, pp 631-643

¹⁴³Christou, J. Roorda, A. & Williams, D. (2004) Deconvolution of adaptive optics retinal images *J Opt Soc Am A* vol 21(8), pp 1393-1401

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The appearance of reasonably priced units for performing computer aided corneal topography (producing Placido images) has revolutionized diagnoses related to the cornea. Since this element provides the vast majority of the optical power associated with the imaging apparatus, variations in its precise shape contribute significantly to astigmatism.

18.2.1.1 Diffraction errors associated with the lens—the star image

When one looks at a bright point source, a significant diffraction pattern is observed that may interfere with other information in the scene. While seldom addressed in the literature, Navarro¹⁴⁴ has presented **Figure 18.2.1-1** based on two citations documenting the work of his team. The majority of the observed diffraction pattern is due to the method of construction used in the biological lens. The result of the fabrication of a biological lens is shown in the upper left frame (with detailed nomenclature available in the Navarro paper). It is typically described as having an onion like structure when cut by a plane including the optical axis. However, the anterior view along the optical axis obtained using a coherent imaging technique shows a variety of pie slices with “suture lines” connecting them. These suture lines introduce diffraction anomalies into the image of the light passing through the lens. The calculated diffraction pattern from one observed set of suture lines appears very similar to the *in-vivo* patterns obtained for four human eyes shown in his figure 8 (although the *in-vivo* patterns include contributions to the diffraction patterns from other phenomena as well. The composite observed patterns are unique to an individual eye. The variations in the patterns appear to be of the same order as that associated with the iris of individual eyes that have been used in some security identification systems.

¹⁴⁴Navarro, R. (2009) The Optical Design of the Human Eye: a Critical Review *J Optom* vol 2, pp :3-18

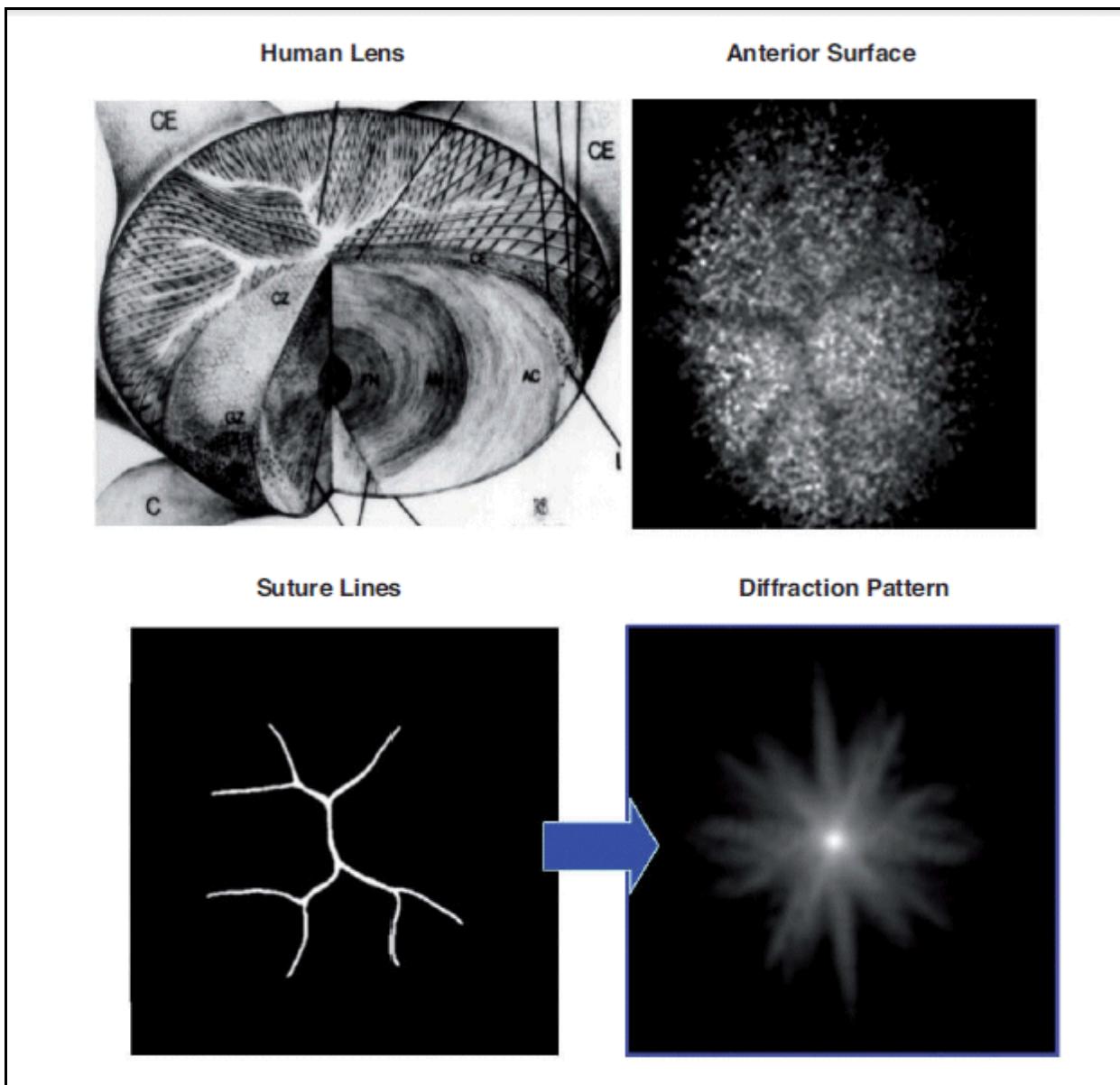


Figure 18.2.1-1 Suture lines and computed diffraction patterns of the lens. Lower left frame is drawn from a different lens pattern than at upper right. See Text for details. From Navarro, 2009.

18.2.2 Failures in the supply functions, stage 0

Failures within stage 0 of the failure mode block diagram in **Figure 18.1.3-1** result in a wide variety of serious vision disabilities. The severity of these disabilities has resulted in specific clinical names for many of the syndromes. The stage contains six principal levels. The failure modes have their origin in both genesis (genetics plus random errors in fabrication) and disease.

Level A, B & C--This work has suggested that the body creates four different serum-based retinol binding proteins (SRBP) that are specific to the implementation of vision. Each of these SRBP's accepts and reacts with retinol to form one of the four Rhodopsins (only three are fully used in the blocked tetrachromats such as humans). Each SRBP delivers a specific chromophore to the RPE for storage and/or immediate transport to the Outer Segments

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located in the IPM. The transport through the RPE and IPM is facilitated by another group of RBP's that may or may not be spectrally specific. Following transport, the Rhodones are deposited as liquid crystals on the newly formed disks within the extrusion cup of the Inner Segment of the photoreceptor cells. How the proper chromophore is selected for deposition on the proper disk is currently unknown. Failure to form the SRBP's, failure to form the chromophores, and failure to transport the chromophores to the disk stack are individual failure modes. These modes are usually, and unknowingly, lumped together by the geneticist attempting to infer the relationship between a gene and the visual process.

Levels D & E involve two parallel paths, the formation of the protein substrates of the disks and the coating of those disks with the chromophores. The formation of the disks is a prerequisite to but is not involved in the electrophysiology and performance of the photoreceptor cells. Following deposition of the chromophore, the disk stack emerges into the IPM and the dendritic structure of the photoreceptor cell is placed in the furrows of the disk stack (level E). The necessary fuels to support the electrostenolytic process must be available within the IPM and the INM to support the operation of the photodetection process. This requirement is the subject of Level F.

Level F is the most significant with regard to the routine operation of the visual system. The mechanisms associated with level F are hydraulic and electrostenolytic in nature. These mechanisms apply to all neurons but have their greatest and most crucial impact on the operation of the adaptation amplifiers of the photoreceptor cells. The first mechanism provides the physical transport of the metabolites associated with the glutamate cycle to and from specific surface areas of every neuron. The second mechanism is the electrostenolysis of these metabolites in conjunction with the neural surface to provide an electrical current source to the individual plasmas of the neuron. Failures within level F of the failure mode block diagram in **Figure 18.1.3-1** can cause problems in steps 6 & 7 of the signaling circuits. The most significant problems arise from the failures impact on step 7. The conflicting symptoms of both hemeralopia and night blindness can result from such impact.

18.2.2.1 Errors in the perceived light level reported to the brain versus light intensity

Figure 18.2.2-1 shows the circuitry of the photoreceptor cell and the errors resulting from improper operation of the electrostenolytic supply system. The bottom half of the figure shows the hydraulic model of the vascular system on the left and the electrical circuitry of the photoreceptor cell on the right. It has been discussed in detail in **Section xxx**. The important landmarks to note are Bruch's Membrane, the outer limiting membrane (OLM), the location of the electrostenolytic mechanism powering the adaptation amplifier (AS), the voltage source labeled (3) and the impedance labeled (2). The circuitry of the photoreceptor cell is complex and the two Activa operate as a differential pair. The operation of the pair introduces features that must be considered. The principle feature is that the voltage V_e tends to remain constant regardless of the current through the adaptation amplifier. To do this, the current in the distribution amplifier falls when the current in the adaptation amplifier rises.

18.2.2.1.1 Errors related to the adaptation amplifier

The combination of Bruch's membrane and the OLM isolate the inter photoreceptor matrix, IPM, from the rest of the retina and vascular system. It has been shown in Section xxx, this role is critical in preventing oxygen from destroying the chromophores of vision. It appears to also be critically important in controlling the flow of neuro-facilitators and neuro-inhibitors providing the electrical power to the collector of the adaptation amplifier (AS). The system is designed so that the collector of the adaptation amplifier Activa receives maximum voltage under low photo excitation conditions and lesser voltage as the illumination level rises. This variation controls the gain of the adaptation amplifier through the mechanism of avalanche amplification within the collector region of the Activa. If this variation is not correct, the performance of the overall circuit is jeopardized. The result is either hemeralopia or night blindness. The condition known as Oguchi's syndrome is a variant of the primary symptom of night blindness.

The control of the electrostenolytic mechanism powering the collector of the Activa is through access to the vascular circulation. This control appears to be exercised by a combination of Bruch's membrane and possibly the dense packing of RPE cells between the membrane and the IPM. These elements control the flow of glutamic acid to, and the removal of GABA from, the electrostenolytic sites. These elements and the ability of the cardiovascular system to supply the capillary beds next to Bruch's membrane constitute a hydraulic impedance that controls the voltage of the collector as a function of collector current. If this impedance is too high, avalanche multiplication gain will not be achieved and night blindness will be observed. If this impedance is too low, avalanche multiplication gain will continue to be achieved at high light levels resulting in excessively large currents passing through the adaptation amplifier circuit. The result will be saturation in the distribution amplifier (AD) and no scene related information in the output circuit.

The upper half of the figure illustrates the results of these improper impedances. The lower quadrant displays the

output current of the adaptation amplifier as a function of the light level for three conditions. The dotted herringbone on the left represents the average signal level as a function of illumination, along with the maximum and minimum excursions related to the contrast of the scene, in the absence of adaptation. The slope of the medial line is indicative of a high average signal gain achieved through avalanche multiplication of the signal. The dotted herringbone on the right represents the average signal level as a function of illumination, along with the contrast limits, in the absence of avalanche multiplication gain. The signal level at the emitter of the adaptation amplifier is quite low at all light levels. The solid lines represent the normal adaptation process. The medial line represents the average current level surrounded by the positive and negative excursions representing the maximum contrast levels in the scene. At illumination levels in the scotopic and mesotopic regions, the circuit gain is high due to avalanche multiplication. However, as the illumination level increases further, the avalanche gain decreases inversely with illumination. The result is a constant output level regardless of illumination level throughout the photopic region.

When these signal levels are processed by the distribution amplifier, significantly different results are obtained. The transfer characteristic of the distribution amplifier is shown in the upper left quadrant. For the normal eye, the mean signal level and the excursions due to scene contrast remain within the linear output range of the distribution amplifier over a very wide range, becoming low and compressed only in the scotopic region. In the absence of avalanche multiplication, the signal output is much lower at all but the highest light level and significant loss in sensitivity is observed in the scotopic and mesotopic regions. The result is described by the symptom of night blindness. At the opposite extreme is the situation where the signal level applied to the distribution amplifier is too high at high light levels due to excessive avalanche multiplication. At scotopic and mesotopic light levels, the performance of the eye is near normal. However, the signal level becomes excessively large at higher light levels. The distribution amplifier cannot faithfully reproduce the signal range and in fact goes into serious saturation. Above the mesotopic range, all output signal related to the contrast of the scene is lost. The subject is figuratively blind although they perceive an overpowering light intensity that results in photophobic activity.

18.2.2.1.1 Errors related to the distribution amplifier

The transfer characteristic of the distribution amplifier is shown in the upper left of the figure. The maximum current capability of this circuit is determined by the potential of the base of the Activa in the distribution amplifier and the impedance shown as (2). As the potential of the base rises due to the source (3), the current through the Activa also rises. As a result, the potential, V_e , at (2) becomes more negative and the potential of the collector becomes more positive. If the potential due to the source at (3) is insufficient, the collector voltage will remain near cutoff and the current capability of the distribution amplifier will be greatly restricted. This is diagramed by the alternate characteristic in the quadrant.

18.2.2.1.2 Hemeralopia (and associated behavioral response, Photophobia)

Hemeralopia (day blindness) is a medical condition wherein the subject loses all visual perception of a scene as the intensity of the light forming that scene rises. The condition is analogous to “snow blindness” in a normal subject but arises as light intensities beginning at the lower extreme of the photopic illumination range, about 300–1000 cd/m² (See **Section 2.1.1.1**). Hemeralopia is a prominent symptom of the achromatopsia syndrome with the actions of the subject, photophobia, the first characteristic noted by the parent or clinician.

Hemeralopia frequently occurs as part of the achromatopsia syndrome (**Section 18.8.3**). It is generally congenital. The subjects encounter serious signal overload within the visual system at light levels above the mesotopic level. These overloads can be traced to errors in the output signal levels at the pedicles of the photoreceptor cells. These errors can in turn be traced to errors associated with the adaptation amplifiers of the photoreceptors because of the accompanying symptoms that occur only under photopic conditions.

1. Saturation in the luminance channel circuits due to the inappropriate voltages at the pedicles of the photoreceptor cells that are presented to the bipolar cells for summation.
2. Frequently complete loss of color vision because of the inappropriate voltage levels presented to the differencing circuits, horizontal cells, of the chrominance channels.
3. Significant nystagmus at light levels above the mesotopic range due to signal levels at the pedicles causing the oculomotor positioning servomechanism to operate in an open loop condition.

Several potential sources of these problems can be defined within the photoreceptor cells. The fact that both the hemeralopia and the nystagmus largely disappear at low light levels supports the conclusion that the problem is

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related to the operation of the adaptation amplifier within each photoreceptor cell. Two aspects of adaptation amplifier operation should be considered. First, there is a shift in the DC operating point of the amplifiers output with light level. Second, there should be little change in the AC signal amplitude at the output of the amplifier at light levels above the mesotopic range. The DC level at the output pedicle normally changes by only a few millivolts. While this change can cause a DC balance shift that could account for some of the changes in color perception that Lakowski describes as PA's and DA's (see **Section 18.1.5.7.4**), it does not appear this shift can cause the gross symptoms of total blindness and nystagmus at high light levels normally encountered. Total blindness as used here relates to the total loss of spatial detail in the perceived image even though the eye is sensing the light level. This loss is due to the signal levels not being compatible with the input dynamic range of the bipolar cells of the retina. It relates most closely to the Extreme PA and Extreme DA of Lakowski in that major bias and gain anomalies are encountered.

These symptoms suggest that the AC gain of the adaptation amplifier is the primary cause of the symptom. Recall that the adaptation amplifier is designed to operate at maximum gain at levels associated with the mesotopic and scotopic ranges and to reduce its gain inversely with light levels in the photopic range. This reduction is achieved by using a high impedance power supply connected to the collector of the Activa within the adaptation circuit. These power supplies are found within the inter photoreceptor matrix, IPM, of the retina. This area is normally isolated from the vascular supply by Bruch's membrane and the barrier formed by the glial cells and photoreceptor cells forming the outer membrane of the retina. This isolation is known to be required to keep oxygen from destroying the chromophores of vision. It appears this isolation is also used to control the rate of electrostenolysis used in the power supplies described above.

It appears the primary cause of hemeralopia is the failure of Bruch's membrane, in conjunction with the outer membrane, of the retina to control the rate of the electrostenolytic reactions associated with each photoreceptor cell. (See **Figure 4.5.1-1**) This can be due to an excessive porosity to glutamic acid, leading to an excessive concentration of glutamic acid at the electrostenolytic sites, or to an abnormal porosity to GABA, leading to a lower than normal concentration of GABA. This lower concentration tends to slow the electrostenolytic reaction. Alternately, an excess of any other neuro-facilitator (as defined in **Section 8.6.4**) can cause the same effect.

The adaptation range of the subject is hard to define since unique conditions are involved.

The condition of hemeralopia is complementary to night blindness (also described as Oguchi's disease). Where the adaptation amplifiers remain perennially at low gain in night blindness, they remain at high gain in photophobia.

- - -

Detailed etiology of hemeralopia EDIT xxx

The potential specific failures that could result in hemeralopia remain multiple. They result in subtle differences when evaluated using the ERG.

A potential impedance error causing hemeralopia could result from a physical void in Bruch's membrane. Understanding this aspect of the malfunction requires considerable analysis of the medical literature. Such voids are frequently described as angiod streaks. Such voids are well documented in connection with Paget's syndrome¹⁴⁵. However, such voids are generally described as asymptomatic. They have not been documented as a symptom in hemeralopia.

The failure of the electrostenolytic mechanism to provide the correct potential at the base of the distribution amplifier appears to be the primary source of hemeralopia. This mechanism is required to provide approximately 20 mV to the base of the distribution amplifier of the photoreceptor cell. This low (~20 mV) requirement appears to be unique in the nervous system. It would suggest a principle reactant other than Glutamic acid. However, the stereochemical requirement that the source be a dicarboxylic acid limits the field of alternatives.

The fact that the distribution amplifier goes into saturation in the case of subjects with hemeralopia can be demonstrated through the flash ERG. If the equipment is sensitive enough, the ERG under low light level conditions, consisting of the Class C waveform from the adaptation amplifier and the Class D waveform from the distribution amplifier will exhibit one of two conditions. It will appear quite normal if the error is due to the adaptation amplifier. Alternately, it will appear smaller than normal if due to the bias applied to the distribution

¹⁴⁵Rosenbloom, A. & Morgan, M. (1986) Vision and Aging: General and Clinical Perspectives. NY: Fairchild Publications pp 110-111

amplifier. Such a condition has been documented in humans by Jahn & Niemeyer¹⁴⁶. These two conditions will be true for all spectral regions because all of the spectrally sensitive photoreceptors are operating normally. If the light level is raised, the ERG will begin to change dramatically. The initial, or a-wave, portion of the ERG will rise in amplitude with the light level but the b-wave, consisting primarily with the Class D waveform from the now saturated distribution amplifier, will not. In fact, the AC component of the Class D waveform will fall to zero. This condition is diagnostic for hemeralopia and is frequently used as the primary sign of both hemeralopia and achromatopsia.

It is worth noting that the photophobe perceives a maximum contrast scene near the top of the mesotopic illumination range. Their visual system performs optimally in this range. While they can read in this range, the signal-to-noise ratio in their signaling channels is quite low. Because of this situation, they usually cannot perceive color and generally require large type size printed matter. Some subjects with hemeralopia are able to perceive some color, although it is usually limited to the red spectrum due to the square law operating algorithm of the long wavelength photoreceptors. It is important to note that all of the spectral chromophores of vision are operating normally in the photophobe. It is the operation of the adaptation or distribution amplifiers associated with these spectral channels that are malfunctioning.

Additional data concerning these failures can be obtained by plotting the complete dark adaptation characteristic of the subject discussed in the next section. However a special protocol must be used to evaluate the photophobe.

18.2.2.2 Aberrations in light sensitivity versus time

Neurology texts frequently give a clinical description of congenital night blindness and/or Ouichi's disease in words¹⁴⁷. **Figure 18.2.2-1** discusses the dark adaptation characteristic associated with these conditions. The figure plots the various conditions against the theoretical dark adaptation characteristic of a healthy eye according to this theory. It can be compared to the more complete figure and discussions in **Section 17.6.1**. The dark adaptation performance of an eye is a fundamental characteristic of the adaptation amplifiers of the photoreceptor cells and their vascular supply system.

Instead of exhibiting the normal two time constants in a second order situation, only one time constant is evident. This condition suggests that the electrostenolytic process on the surface of the dendrites within the IPM is not functioning properly. It is probably indicative of the process employing the wrong chemicals in its glutamate cycle. This would result in a lower than normal voltage on the collector of the adaptation amplifier. The transient response that is observed is longer than the normally observed three minute characteristic and shorter than the normal ten minute characteristic. If the shape of the curve is correct, it suggests the vascular supply system is working in a first order mode instead of the normal second order mode.

18.2.2.2.1 Congenital night blindness

Beard¹⁴⁸ describes this condition as "a stationary retinal anomaly in which night blindness from birth is the only complaint. The ocular fundus and visual fields are normal."

The fundamental failure is a reduction in the available amount of the chromophores under low light conditions. This

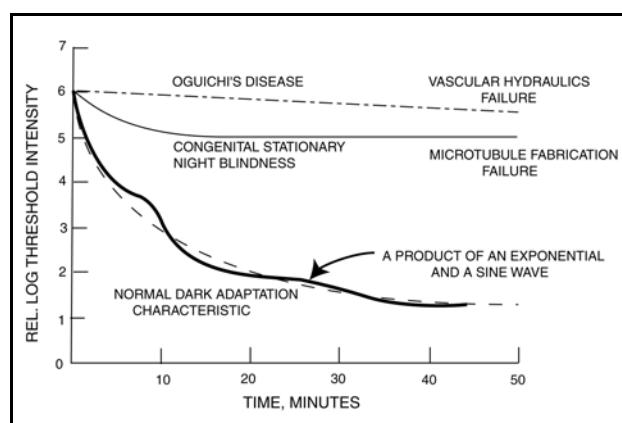


Figure 18.2.2-1 Atypical dark adaptation conditions compared to a normal eye. The presentation is similar to Adler (1992). However the form of the theoretical dark adaptation characteristic is shown.

¹⁴⁶Jahn, A. & Niemeyer, G. (2000) Reliable and variable characteristics of achromatopsia ARVO poster reported as paper 4737-B684 in *Invest Ophthalmol Visual Sci* vol. 41, no. 4, pg S891

¹⁴⁷Cogan, D. (1965) Neurology of the Visual System, 3rd Printing. Springfield, IL: Charles C. Thomas pp 88-91

¹⁴⁸Beard, C. et. al. (1968) Congenital anomalies of the eye. St. Louis, MO: C. V. Mosby, pg. 302

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may be due to a reduction in the number of disks per photoreceptor, a reduction in the degree of chromophore coverage of those disks, or in the lattice structure of the chromophores when in the liquid crystalline state. A genetic failure could result in an excessively thick dendritic (microtubule) lemma in the active region associated with the Outer Segment. Alternately, an improper bias potential generated by one of the electrostenolytic processes supporting the adaptation amplifiers can cause the problem.

The subject is considered to exhibit **congenital night blindness**. His eyes continue to operate as if the illumination level were at the high photopic level, even as the illumination level is reduced. His dark adaptation characteristic has a range of less than 10:1 and typically exhibits a true exponential response with a time constant of a few minutes.

The condition of night blindness (including Oguchi's disease as described below) is complementary to the condition of hemeralopia described in **Section 18.2.2.4**.

18.2.2.2.2 Oguchi's Disease

A condition similar to congenital night blindness has been given the name **Oguchi's Disease**. Beard¹⁴⁹ offers a discussion isolating Oguchi's Disease from congenital night blindness. They describe the condition as "A type of stationary congenital night blindness with an unusual metallic-gray or golden discoloration of the fundus which may be present in the central and/or peripheral retina."

This disease or syndrome can have the same genetic causes as above and can also be associated with an increased hydraulic impedance in the vascular system providing metabolites to the glutamate cycle of the electrostenolytic process. The dark adaptation characteristic is similar to that in congenital night blindness, however, the time constant can become progressively longer, reaching 20 minutes or more.

The affected eye does exhibit a dark adaptation characteristic. However, it is seriously abnormal. Exposure to light causes a rapid loss of dark adaptation, as in a normal eye, but the color does not occur for 10-30 minutes. Following cessation of illumination, the recovery period is extended compared to normal. Quoting Beard¹⁵⁰, "It is as if the loss of dark adaptation is a rapid neural phenomenon and the color change is a reflection of some metabolic event." Paraphrasing further, physiologically, after 30 minutes of dark adaptation, the threshold is usually still at the level of the normal plateau. Only after an extended interval is the ultimate threshold reached. Beard did not specify the level of the ultimate threshold.

This condition appears similar to that discussed above but can become more severe in terms of the time constant in the dark adaptation characteristic. The time constant is much longer than both the normal three and ten minute values. The problem is almost certainly with the hydraulic conductivity of the IPM and its vascular source of material for the glutamate cycle. As a result, there is the characteristic buildup of waste products in this space during illumination of the retina. The poor electrostenolytic condition does not support the avalanche effect found in the normal adaptation amplifier. The sensitivity of the eye is limited to that of a normal eye under high photopic conditions. The low current amplification factor associated with this condition causes the demands on the vascular system to be small. This supports the observation that it takes 10-30 minutes for the noticeable discoloration of the retina to occur.

The appearance of the retina under this condition may be instructive. Its color change is suggestive of the buildup of a waste product. In this case, the color is probably related to the buildup of glutamic acid in the IPM space. More precise data are needed with respect to this condition to understand it more clearly.

18.2.2.2.3 Late onset night blindness (nyctalopia)

I have recently encountered a 58 year old women (S. de R.) with rapid onset and progressing night blindness. Perimetry has not shown area diseases such as macular dystrophy or retinitis pigmentosa. A small amount of drusan has been observed. OCT evaluation has shown a thinning of the RPE and outer segments of the PC with the layers melding together. A greatly depressed serum retinoid level has been observed. The problem appears to be an inability to absorb the fat soluble vitamin A through the wall of her small intestine leading to the failure to provide sufficient retinenes/retinines in encapsulated form from the liver for transport to and storage of various chromophores within the RPE prior to the coating of the opsin discs with the appropriate chromophores.

¹⁴⁹Beard, C. et. al. (1968) Op. Cit. pg. 303

¹⁵⁰Beard, C. et. al. (1968) Congenital anomalies of the eye. St. Louis, MO: C. V. Mosby pg. 303

I have suggested the use of Creon, a pharmaceutical aiding in the absorption of fat and fat soluble vitamins that I have used for years for a different problem. It contains Lipase/Protease/Amylase.

18.2.2.2.4 An adaptometer for evaluating night blindness UNEDITED MATERIAL

Ophthalmologists have indicated a need for a method of evaluating patients visual modalities with respect to their dark adaptation capabilities in order to more fully understand and treat various medical conditions encountered in their practice. The applicable data base is quite limited in this area; dating primarily from Dowling and Wald in the 1960's, Beard in 1968 and Adler in 1992 as cited above.

According to Wikipedia, and many sites echoing that site, "Oguchi disease present with nonprogressive night blindness since young childhood or birth with normal day vision, but they frequently claim improvement of light sensitivities when they remain for some time in a darkened environment." Recent discussions related to Oguchi's disease remain inconsistent. On the other hand, with the advent of more driving at night, there appears to be an increase of older patients reporting lack of good night vision, indicative of a progressive form of Oguchi's disease.

Wikipedia reports minimal data related to the electroretinographic studies of Oguchi's disease that needs to be reinterpreted using the photoreceptor, cardiovascular and neural models of this work. The paragraph related to the genetic aspects of Oguchi's disease are quite sketchy and highly inferential. The connection of Oguchi's disease to retinitis pigmentosis is at best sketchy. Retinitis Pigmentosis (RP) is only generally defined in most of the literature. It is generally spoken of as of the wet type or dry type and its location with respect to markers in the retina is poorly defined (**Section 18.8.9.4**).

Wikipedia also describes night blindness without any citations to defend it. "Nyctalopia, also called night blindness, is a condition making it difficult or impossible to see in relatively low light. It is a symptom of several eye diseases. Night blindness may exist from birth, or be caused by injury or malnutrition (for example, a lack of vitamin A). It can be described as insufficient adaptation to darkness. This description is inconsistent with a major role for genetics in the development of the disease."

The ultimate achievement of normal dark sensitivity after prolonged dark adaptation is consistent with the model and data presented earlier in this work where the impedance of the electrostenolytic recharging capability of the cardiovascular system leads to the same ultimate axon electrical potential but only after an extended interval (much longer time constant than normal) due to the increase in this impedance relative to the normal value.

On examination patients have normal visual fields but the fundi have a diffuse or patchy, silver-gray or golden-yellow metallic sheen and the retinal vessels stand out in relief against the background. A prolonged dark adaptation of three hours or more, leads to disappearance of this unusual discoloration and the appearance of a normal reddish appearance. This is known as the Mizuo-Nakamura phenomena.

It is quite possible this appearance, and its variation, is due to the buildup of waste products (most likely, GABA) from the electrostenolytic mechanism and its slow removal or conversion back to glutamic acid within the neural layers of the retina by glia.

Little information exists as to the precise extent of the discolored area. However, the tone of the remarks would suggest the phenomenon relates more to the neural retina and the tissue in the optical path between the lens and the inner segments of the photoreceptors than in the tissue supporting the RPE and the outer photoreceptor segments. The tone would also suggest the phenomenon affects both the fovea and the foveola uniformly. However, the appearance of a small golden-yellow or silver-gray area bounding the foveola, within the larger fovea might not be reported adequately in the available discussions.

In the design of an instrument to determine the properties of the visual modality relative to night blindness, it is very important that a protocol leading to repeatable results with regard to a single subject as well as consistent results among members of a cohort is absolutely critical. It is also highly desirable that the protocol describe the dark adaptation properties of the foveola (1.2 degree diameter disk centered on the line of fixation) separately from the properties of the fovea (out to about 5.6 degrees diameter centered on the line of fixation). The dark adaptation performance of the area beyond 5.6 degree diameter is probably of marginal significance.

It appears a conventional perimeter found in nearly all optometric medical offices can be modified (primarily in the associated software) to provide a meaningful instrument for quantifying the dark adaptation capabilities of a given subject. The use of Gabor patterns as the movable test targets used to measure the sensitivity threshold at various positions within the total field of view might also be optimal. However, slightly smaller Gabor patterns might be preferred because the foveola is only about the size of the human thumbnail at arm's length. Most of the early dark

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adaptation experiments employed a two degree diameter test stimulus that could not support exploration of the 1.2 degree diameter foveola as a separate structure.

Initially, a carefully described light adaptation procedure should be followed by dark adaptation testing at or near the 3 minute and within the 10-20 minute intervals after the cessation of light adaptation (see **Figure 18.2.2-1**) will probably lead to a good diagnostic result. The dark adaptation testing may need to cover several locations within the retina to provide comprehensive results, not unlike current perimetry testing (including the location of scotomas within the field). The principle changes would be in the initial source of light adaptation stimulation and the duration of the testing intervals. Keeping the subject comfortable during the time between the 3 minute sampling and the 10-20 minute sampling may require specific attention.

Academics would like to collect enough information to establish the performance of the normal cadre of subjects to a standard deviation of less than 10% of the mean at each test point after light adaptation. The medical community is frequently forced to live with less precise nominal values with standard deviations closer to 30% of the mean. In this case, a 10% standard deviation goal for the normal cadre would be very useful.

[xxx below from Marc S. correspondence]
As I have probably indicated earlier, I do not feel particularly competent to discuss medical conditions, partly because of the difference in both terminology and protocol approaches employed in medicine versus physiology. However, the two of us may be able to make real progress in this area and I would be happy to work with any of your graduate students in developing a clinically useful adaptometer.

Figure 18.2.2-1 attempts to describe the various conditions superficially.

Our future discussions will hopefully lead your people to define a useful adaptometer.

I have defined processes and mechanisms that occur in the visual modality prior to (antidromic to) the actual photoreceptors as stage 0. Such processes and mechanisms can clearly involve structural abnormalities and corruptions as well as hydraulic (cardio-vascular and conditions within the retinal pigmented epithelium) abnormalities. I would hope we can agree to focus on the hydraulic aspects at this time as structural abnormalities may involve much more difficult challenges.

I believe I have put together a good and defendable description of the hydraulic systems (as an overlay on the structural elements) of the retina that can be used to describe night blindness (of the Oguchi and other types).

The attached PC RPE color interface.jpg can be used to isolate the hydraulic portions of the problem into three areas; 1) the hydraulic aspects related to providing energy to the operation of the inner segment of the neurons on the left, 2)the hydraulic aspects related to providing the retinol based chromogens to the RPE on the right, and 3)the actual generation of the chromophores in the RPE cells and within the IPM associated with the outer segments on the right.

For the record and my own bookkeeping, these aspects are discussed in greater detail in sections 4.3, 4.6, 5.1.1, 5.5.8, 7.1.2, 7.1.3, 8.6, 9.1.4 and 17.6.1.

18.2.2.3 Albinopunctatus

A disease displaying the variability in the second order dynamics of the dark adaptation characteristic (See **Section 17.6.1**) is discussed in Smith, et. al¹⁵¹. Unfortunately the data only extends to 38 minutes. This is not sufficient to include a full cycle of the sinewave component of the response. Except in the case of subjects C.C. & R.C., the responses are still falling at the end of the time period. The imagery in the reference and the discussion suggest this disease can attack different areas of the retina selectively. It appears to involve a significant change in the porosity of the vascular supply relative to the necessary metabolites.

18.2.2.4 Variants of tapeto-degeneration.

Schmidt briefly discusses tapetoretinal degeneration (retinitis pigmentosa) and tapetochoroidal degeneration (choroioderemia)¹⁵². The ERG is affected differently in these two conditions.

¹⁵¹Smith, B. Rippy, H. & Goodman, G. (1959) XXX Arch. Ophthal. vol. 61, pg. 93

¹⁵²Schmidt, I. (1970) On congenital tritanomaly. *Vision Res.* vol. 10, pp. 717-743

18.2.3 Failures in the oculomotor subsystem, stage 5

Stage 5 is illustrated in **Figure 18.1.1-1**. There are obvious failures related to genesis and disease related to the physiological optical system and the operation of the shutter, i.e., the eye lid. These are not of concern here. The area of interest is the determination of the line of visual fixation and the scanning of the scene in object space. In this area, it is important to subdivide the nature of the failures in a number of ways. First is the question of whether the failure occurred within the servo loop including both the retina and the oculomotor system or whether it occurred in one of the inputs to or outputs from the servo loop (See **Section 15.2.4**). The servomechanism controlling the oculomotor system is quite complex and operates in a variety of modes. These conditions complicate the discussion of this subsystem. There is a series of failures of the oculomotor system based on the above distinctions. These include, failure to point precisely, failure to control pointing (sometimes dramatically) and failure to produce a tremor. Some of these failures involve and are related to:

muscular implementation errors	genetics and genesis
nerve path errors and blockages	blindsight in the absence of tremor or in the presence of serious cerebral damage
analog command generation errors	nystagmus
command computation errors	nystagmus

The failure to point precisely must discuss the large and small saccades separately as they are served by different operating modes of the servomechanism. The failure to control pointing is generally described as nystagmus. It also exhibits a variety of forms that can be subdivided according to the different operating modes.

Failure to produce a tremor is probably the most severe oculomotor failure from the subjects perspective. The subject is left with a form of blind sight. No reference to this condition was found in the clinical literature. Virtually the only references, and they are generally inferred, are in the academic work of Yarbus and of Ditchburn.

18.2.3.1 Failure to effectuate a tremor

Failure of the inner servomechanism of vision associated with the Precision Optical System (POS) leads to one of the conditions categorized under blind sight. The subject's organic visual system appears intact and there are no clinically observable perceptual or cognitive problems associated with the cortex. However, the subject is unable to "see" stationary objects and reports seeing ghostly shadows or outlines of objects moving in his field of view. Close examination will show failure of the tremor generating elements of the system. The visual system is fundamentally a change detection system. Without the motion introduced between the scene and the line of sight of the subject by the POS, he is blind to fixed images. The servomechanism diagram of the POS suggests a number of possible failures resulting in this condition. One of the most common failure modes involves an actual failure in the signal projection path to the eye muscles. This failure involves the squeezing of certain oculomotor neurons passing through a small aperture in the skull.

It is important to note but difficult to experimentally determine the fact that the POS generates and the eye responds to two orthogonal tremor signals. Although the signals appear pseudo-random in relation to each other, they are actually precisely structured motions dependent on the highly structured computations performed within the POS. The bandwidth of these two signals extends to 90-150 Hertz. The creation of these commands involves a significant amount of either cognition within the old brain or memory related to the detailed structure of previously imaged objects.

18.2.3.2 Failures related to pointing of the eyes

The eye simulator at <http://cim.ucdavis.edu/eyes/> provides an excellent simulation of the potential problems of the oculomotor system. It allows simulation of both muscle-related and neuron-related problems. It also notes the tie-in of the iris muscle and the third cranial nerve. Damage to this nerve can cause loss of vertical excursion, along with dilation of the iris, in the affected eye.

The subject of nystagmus has been extensively studied clinically. It has generally not included the study of the finest pointing signals related to tremor because of instrumentation difficulties.

18.2.3.2.1 Failures in static positioning of the point of fixation

There are a number of failures in the outer servomechanism system of vision that can cause the line of fixation to not

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fall on the foveola. Such a condition generally results in loss of high resolution vision and difficulty in the perception and cognition of detail.

18.2.3.2.2 Failure to maintain the desired scene element on the foveola

There is a considerable volume of experimental data concerning subjects that cannot maintain proper pointing at fixed scenes and proper tracking of moving scenes. However, little of the work has developed, or relied upon, an adequate schematic of the visual system. Examination of the servomechanisms of the visual system suggests a number of possible failure modes leading to this condition. Some of them are related to the POS and others obviously involve higher cognitive levels within the cortex.

Slowly “wandering eyes” appear to be a clear case of an open connection failure between the vestibular system and the POS. In this case, the commands to the oculomotor system are generated without benefit of inputs from the vestibular system. These inputs establish the inertial reference between the eyes and the gravitational field of the earth. The time constant of this activity would suggest the open connection occurs at the base of an Activa. This Activa could be at an exposed junction, a synapse, or within a neuron.

Heide, Kurzidim & Kompf have provided information on pursuit failures that appear to involve errors in the sympathetic performance of the POS due to lesions in the frontal and parietal regions of the cortex¹⁵³. In the above context, these failures would be considered to involve circuits external to but providing input signals to the POS. Based on this work, the cause of failure in other studies, can be localized to the POS itself.

18.2.3.3 Abnormalities in the pointing of the eyes

18.2.3.3.1 Abnormal flutter

Ashe, et. al. have reported a rare condition involving low amplitude flutter, described as a horizontal saccadic oscillation¹⁵⁴. While they describe the condition clinically as a microsaccadic motion, it would be described as a minisaccade in the nomenclature of this work (**Figure 7.3.1-1**). As they note, tremor involves a similar oscillation at a level one order lower than their oscillation. This is the level of microsaccades in this work. Their figure 4 can be expanded to include tremor (microsaccades), their microsaccadic flutter (minisaccades) and their saccadic flutter in general accordance with the above figure.

18.2.4 Failures in eye formation and the automatic focus servomechanism, stage 5

The failures of the automatic focus mechanism can involve ontogenetic, pathological, physiological and neurological processes. While the subject was studied extensively in earlier times, it has not been a major focus of research in the academic community. The clinical record is quite voluminous but is primarily exploratory. It lacks an underlying model or structure. It also suffers from a plethora of confusing nomenclature and hypotheses¹⁵⁵. Curtin has described the problem by saying “All too often the contributions to this subject have been bewildering in their protocols, their results and their conclusions¹⁵⁶. ” And this was in a book limiting the definition of myopia to failures related to refraction. Grosvenor & Flom have edited a significant compendium on the subject (with a concentration on the physiology of myopia). Schor, writing in their book (pp 310-317), introduces the concept of a closed loop servomechanism controlling accommodation, based on his earlier work in vergence¹⁵⁷, but does not pursue it in detail¹⁵⁸. The most relevant theoretical discussions of myopia are by Wallman. The same material

¹⁵³Heide, W. Kurzidim, K. & Kompf, D. (1996) Deficits of smooth pursuit eye movements after frontal and parietal lesions. Brain, vol. 119, pp. 1951-1969

¹⁵⁴Ashe, J. Hain, T. Zee, D. & Schatz, N. (1991) Microsaccadic flutter. Brain vol. 114, pp 461-472

¹⁵⁵Grosvenor T. & Flom, M. (1991) Refractive Anomalies. Boston, MA: Butterworth-Heinemann, pg 1

¹⁵⁶Curtin, B. (1985) The Myopias Philadelphia, PA: Harper & Row pg 3

¹⁵⁷Schor, C. (1979) The relationship between fusional vergence eye movements and fixation disparity
Vision Res vol. 19, pp 1359-1367

¹⁵⁸Schor, C. (1991) Effects on the resting states of accommodation and convergence in Grosvenor T. & Flom, M. Ed. Refractive Anomalies. Boston, MA: Butterworth-Heinemann, Chapter 18

appears in two separate publications^{159,160}. While a symbolic graphic is provided, it is elementary and lacks scales or other details. This section will attempt to extend this work considerably. As mentioned, there is a major problem in nomenclature. Every book reviewed used a different definition of the relatively simple term, myopia. This problem was addressed by Weymouth & Hirsch in Chapter one of Grosvenor & Flom without achieving closure. It will be addressed again here in the terminology section below.

While the content of these books is very useful, the cover art leaves something to be desired in both cases. They both involve archaic concepts that lead to a mis-impression. This is a problem in pedagogy where first impressions are so important. The Curtin cover dates from 1899 and fails to reflect the high correlation between the sagittal and transverse diameters of the eye and the axial length of the eye (except in some pathological cases). The Grosvenor & Flom cover strongly suggests that the length of the eyeball does not change with changes in the power of the cornea and that the cornea changes from parabolic to more hyperbolic with myopia. The rules of optics require the shape to be ellipsoidal in wide angle optical systems. Since the junction with the eyeball is relatively fixed, the ellipsoid changes shape by expanding along the axis in myopia (thereby raising its optical power).

18.2.4.1 Terminology

The mechanisms and physical elements used to perceive a high acuity image in vision are extremely complex. The general field lacks a clear designation. Clinically, a nominally performing eye is described as emmetropic, one performing more poorly is described as ametropic. Below that level, it is best to provide a road map. Such a map of metropic vision is provided in **Figure 18.2.4-1**.

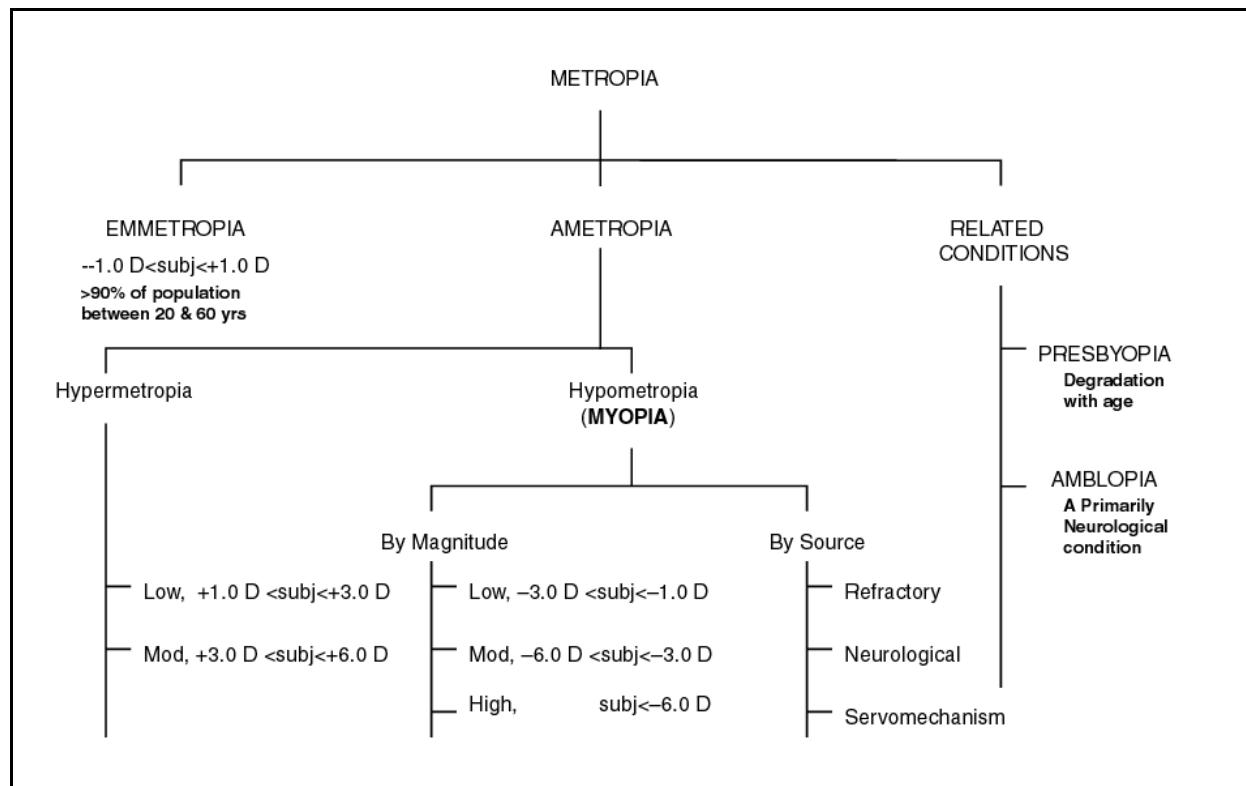


Figure 18.2.4-1 Road map through the field of metropic vision.

¹⁵⁹Wallman, J. (1990) Introduction in (Ciba Symposium 155) Myopia and the Control of Eye Growth. NY: John Wiley & Sons

¹⁶⁰Wallman, J. (1991) Retinal factors in myopia and emmetropization: clues from research on chicks in Grosvenor, T. & Flom, M. Refractive Anomalies. Boston, MA: Butterworth-Heinemann Chapter 15

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For the purpose of this map, the emmetropes represent about 91% of the adult population based on Scheerer (See below). However, metropia exhibits a strong genetic factor and certain human activities may influence performance in a significant and possibly permanently deleterious manner. Of the remaining 9% of the population, about 3% exhibit pathological disease more complicated than mere ametropia. The remaining 6% exhibit ametropia outside the optical power ranges of the table. There are many ways to categorize ametropia and particularly, hypometropia (commonly labeled myopia). The most common functional names relate to the refractory elements of the system. However, there are clearly neurological sources of the disease and the servomechanism controlling the lens can introduce significant problems.

Ametropia can be described from a variety of perspectives. Clinically, the subject is usually divided into myopia and hyperopia (colloquially near-sightedness and far-sightedness respectively). The mechanisms associated with the clinical diseases can be divided differently. Grosvenor & Flom have provided the best discussion available with respect to myopia and there text can be relied upon for excellent background material. They provide a “precise” definition of myopia from the physiological and pathological perspectives on page 12. Of course, this work will offer an alternate “precise” definition.

“Myopia is that state of refraction in which the axial length of the globe is greater than the posterior focal distance of the refracting system when only that ciliary tonus which occurs under standard conditions is active.” They go on, “In refraction, standard conditions prevail when the eye is fixating a distant object that the individual is observing through a fogging lens.” Even this detailed definition requires modification at the research (as opposed to the clinical) level. First, the syndrome is not limited to refractive errors. Second, it is not the axial length of the globe that is the definitive distance in the problem. Third, introducing a lens disturbs the experiment by definition. Thus, a broader (but compatible definition would begin with emmetropia.

Anatomical refractive error— The residual refractive error at the entry point of the photoreceptor cells within the retina due to the incompatibility between the refractive optics (including the portion of the retina in the optical path) and the position of the photoreceptor cells.

Dark accommodation— A misnomer since accommodation is based on the edges associated with contrast in the scene. A blank field of view will cause the same accommodation regardless of light level. See quiescent accommodation.

Emmetropia— that state of visual performance where the posterior focal distance of the refracting system is equal to the distance between the retina and the exit pupil of the optical system under both axial and off-axis conditions (but particularly with respect to the intersection of the line of fixation and the retina), under the conditions that the ciliary tonus which occurs under standard conditions is active, and the neurological elements of the system are operating nominally. Standard conditions are defined as the subject fixating on a distant object of less than 2:1 contrast but large enough to be easily seen.

This “standard condition” involves a tonus of the ciliary muscle quite different than that achieved by complete relaxation through the introduction of cycloplegics.

Under the above definition there are two forms of ametropia, a condition of non-emmetropia. Both myopia and hypermetropia involve deviations from the condition of emmetropia. These deviations can then be categorized and classified further.

hypermetropia— that state of visual performance that requires a positive lens in the optical path of the eye to achieve the emmetropic condition defined above.

hypometropia (myopia)— that state of visual performance that requires a negative lens in the optical path of the eye

to achieve the emmetropic condition defined above.

Weymouth & Hirsch noted the inadequacy of this definition (page 12) and offered two others:

1. "Myopia is a condition of an eye in which, when accommodation is suspended, parallel light comes to a focus in front of the retina, the latter being situated beyond the posterior principal focal distance of the refracting system."
2. "Myopia is a condition of an eye in which, when acted upon only by normal tonus of the ciliary muscle, parallel light comes to a focus in front of the retina, the latter being situated beyond the posterior principal focal distance of the refracting system."

The difference between these latter two definitions recognizes the *in-vivo* tonus of the ciliary muscle whether caused by a residual neural signal or not. It will be appropriate in this work to limit the effect of tonus of the ciliary muscle to that found in the absence of any neural signal.

Under these definitions, an absolute value of emmetropic error is given by the value of the lens required to achieve the desired performance. For reasons that will be developed below, it is optimum to approach the measurement beginning with a lens more positive than the final value. This emmetropic error is positive in the case of hyperopes and negative for myopes. The value determines the severity of the condition.

Using these definition, diseases of the visual system affecting acuity can be broken down into three primary causes. Looking first at the conditions described under the term myopia:

Refractive myopia—is that state of refraction in which the distance between the retina and the exit pupil of the optical system under both axial and off-axis conditions (but particularly with respect to the intersection of the line of fixation and the retina) is greater than the posterior focal distance of the refracting system when only that ciliary tonus which occurs under standard conditions is active, and the neurological elements of the system are operating nominally.

Neurological myopia—that state of visual performance where the muscular and neurological elements associated with the automatic focus mechanism, or the elements of the Precision Optical System responsible for the initial stages of perception are operating abnormally. The condition cannot be corrected with auxiliary lenses.

Pathological myopia—That state of visual performance where the operation of the visual system related to acquiring high acuity imagery is disturbed by other morphological conditions not directly related to refraction or neurological mechanisms.

Accommodation Servomechanism myopia—A broader label that includes causes of myopia related to both the neurological and physiological elements of the accommodation servomechanism.

Various authors have attempted to classify the severity of myopia. Some of these have been using descriptive adjectives such as school myopia. These are not useful at the research level. Using the diopter value of the lens required to reach the above emmetropic condition is more useful. Grosvenor & Flom have summarized the work of several investigators. A logical scheme would be as follows;

Level	Emmetropia -1.00 D to + 1.00 D	Hypertropia	Hypotropia (Myopia)
Low			
Moderate (medium)		More than +1.00 D +3.00 D to +6.00 D over +6.0 D	-1.00 D to -3.00 D -3.00 D to -6.00 D over -6.0 D
High			

The logic supporting these choices will be explored below.

The remaining definitions will be in alphabetical order.

Accommodation—The mechanism of adjusting the focal length of the eye to focus an element in object space onto the focal surface of the retina. More specifically, to focus the image of an element at the entrance aperture of the optical system associated with each photoreceptor cell.

Accommodation points—Specific points associated clinically with the optics and autofocus capability of the eyes.

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1. **Resting accommodation**– Essentially the standard condition defined in the definition of emmetropia. Generally assumed to be the relaxed condition of the eye when looking at a distant object.
2. **Cycloplegic accommodation**– The condition where the ciliary muscle of the lens is paralyzed (totally relaxed).
2. **Near Point accommodation**– The accommodation level associated with the closest point to the eyes that optimum focus can be achieved.
3. **Far point accommodation**– A concept of little utility in research. It is the accommodation level under the standard condition. For the typical eye, this accommodation leads to focus at infinity in object space. The hypertropic eye does not focus at any distance under this condition. The myopic eye focuses within a broad range of distances distance short of infinity.

Cycloplegic– Any pharmaceutical agent capable of paralyzing (relaxing) the ciliary muscle controlling the lens. *Care may be required to differentiate between a pharmaceutical agent that inhibits any neural signal to the muscle and one that partially relaxes the muscle without interfering with the neural system.*

Ocular refraction– Usually refers to the net error in refraction (the anatomical refraction error) when used as a noun.

Posterior focal length–The focal length of the eye measured within the eye. Should be discouraged as it may be confused with the back focal length of a lens. The back focal length is the distance between the last optical surface and the focal plane of the lens. More appropriately labeled the interior focal length or the image (space) focal length of the eye.

Quiescent accommodation– The state of accommodation, beyond that level provided by anatomical accommodation, assumed by the living accommodation system under any illumination conditions **but** in the absence of distinct edges within the field of view of the foveola. Commonly described inappropriately as dark accommodation in the vernacular.

18.2.4.2 Background

As suggested by the elaborate definitions provided above, the subject of ametropia is complex. It is also dynamic. The nominal conditions of the visual system change relatively slowly with growth and aging. They change on a shorter time scale in order to achieve accommodation (and the related subject of convergence). Unfortunately, the rapid variation in the refractive power of the lens as a function of time (similar to that of the closing of the iris) is basically unreported in the literature. This temporal performance will be addressed below from the perspective of behavioral experiments in reading.

Although old, the study of abnormalities of the accommodation system is still plagued by inconsistencies in many of the measurement techniques used¹⁶¹. Differences of 0.3 diopters between methods are common. The variation in theoretical models in the literature was addressed in **Section 7.4.8**. These differences have also led to inconsistencies in the literature. Another paradox of the literature is the fact that most papers claiming to deal with myopes actually relate to fully corrected myopes (those wearing corrective devices). The data in these papers is typically related to second order errors in optical performance rather than the first order errors corrected by the appliances.

Rosner has quoted an earlier position of Grosvenor: “In the literature concerning the refractive state of the eye, myopia has routinely received most of the attention, hyperopia being pretty well ignored.”¹⁶² He went on to say that about four times more articles have appeared concerning myopia than concerning hyperopia. He closes by saying hyperopia is perceived by much of the public and the clinical community as innocuous.

The conventional description of myopia in terms of whether a collimated image focuses in front or behind the focal plane formed by the photoreceptors of the retina is an awkward one. When describing the situation mathematically, far-sightedness is spoken of as forming a virtual image behind the retina. This is unfortunate, technically, the image

¹⁶¹Abbott, M. Schmid, K. & Strang, N. (1998) Differences in the accommodation stimulus response curves of adult myopes and emmetropes *Ophthal Physiol Opt* vol. 18, no. 1, pp 13-20

¹⁶²Rosner, J. (1991) Hyperopia in Grosvenor & Flom, Op. Cit. Chapter 7, pp 121-130

is not virtual. It is real. Similarly, this description suggests that an image formed on the retina of a hyperopic eye must be from a point located beyond infinity. Some clarity can be obtained by reversing the experiment. Consider a point source at the fixation point on the retina. Under the tonus conditions described above, this point should be projected in a collimated beam at the exit of the eye. If the projected rays are converging under this condition, the subject is exhibiting refractory myopia. If the projected rays are diverging, the subject is exhibiting refractory hyperopia.

Using this model, it is possible to bring additional clarity to the concepts of myopia, hyperopia, presbyopia, etc..

The common association of myopia with the axial length of the optical globe is also unfortunate. Refractive myopia is a disease, if it can be called that, involving differential growth rates between a considerable number of physical elements. Curtin has provided broad statistics on this situation. The growth rates of these different elements have been shown to track each other. Furthermore the distribution of the sizes of these different elements have been shown (admittedly using small samples) to follow Normal Distributions. There are two problems in this area. The distributions frequently contain pathological elements (components variously described by sub-set designations β and γ) unless carefully screened. Secondly, since these are growth related factors, their distribution will probably be shown to be described by a log-normal distribution when larger data sets are collected.

Much of the concentration in the literature has been on correlating the axial length of the ocular globe with the degree of myopia in Diopters. However, Hirsch & Weymouth have made a very significant finding, the axial length of the ocular globe also correlates highly with the lengths of the other two axes of the globe (See also Scammon & Armstrong below). Long axial length correlates most strongly with BIG EYES¹⁶³. The statistics of the dimensions of the elements impacting myopia have been accumulated by Hirsch & Weymouth in Chapter 3 of Grosvenor & Flom. They have also presented a working hypothesis related to the genesis of refractive myopia. They surface the idea that variations in corneal power, lens power, distance between these lenses, and location of the exit pupil of the lens system may counterbalance changes in axial diameter. They also point out that this point cannot be demonstrated at this time. This is partly because of the previous ability to measure these dimensions *in-vivo*. This situation is changing rapidly with the advent of acoustic imaging techniques and their wide acceptance in clinics.

Hirsch & Weymouth proceed to define four patterns of ametropia based on their statistics. They conclude that 91% of the population is closely centered on a group containing low myopes, emmetropes and low hyperopes. Within this group, the distributions associated with the above sub-groups and the elements of their eyes of interest are normally distributed. They draw a key conclusion. "Differences in refraction occurring among individuals with this group result solely from biological variability." It is the 9% represented by high hyperopes, high myopes (1-2%) and moderate myopes (6%) that are of clinical interest. A further definition of the classes and degrees related to these conditions is presented in Weymouth & Hirsch¹⁶⁴.

The ranges of ametropia by severity and age has been presented by several groups. The data is collected in Goss who prepared Chapter 5 of Grosvenor & Flom.

Erickson and Blaker have prepared vision models designed to analyze the component changes occurring during accommodation^{165, 166}. Erickson has provided a mathematical model recognizing the thick lens nature of the lens system. His calculations show the importance of the depth of the anterior chamber in the overall accommodation mechanism. He notes the range of this parameter in emmetropic eyes is 2.5-4.2 mm. This is a substantial range and results in a difference in accommodation efficiency in different eyes. Blaker provides a brief history of standard eyes. Subsequently, he offered a new model of the eye recognizing the gradient index of the lens (using the Moore model of a radial gradient lens¹⁶⁷). His model differs from that of Gullstrand. Gullstrand stated that his model was hypermetropic by at least 1.0 Diopters. The Blaker model can be used to replace that of Gullstrand in careful work. The paper also provides a measured range of at least 10 diopters for two twenty year-olds known to be about one diopter hypermetropic. Besides showing a linear variation in accommodation with the radius of the anterior surface of the lens, it also shows values for the cardinal points as a function of accommodation.

¹⁶³Hirsch, M. & Weymouth, F. (1991)Changes in Optical Elements: Hypothesis for the genesis of refractive anomalies. *in* Grosvenor & Flom, Op. Cit. Chapter 3, pg 54

¹⁶⁴Weymouth F. & Hirsch, M. (1991) Theories, definitions and classifications of refractive errors. *In* Grosvenor & Flom, Op. Cit. Chapter 1, pp 1-14

¹⁶⁵Erickson, P. (1978) Crystalline lens position and accommodative efficiency. *Am J. Optom Physiol Opt.* vol. 55, pp 571-575

¹⁶⁶Blaker, J. (1980) Toward an adaptive model of the human eye. *J. Opt. Soc. Am.* vol. 70, pp 220-223

¹⁶⁷Moore, D. ((1971) Design of singlets with continuously varying indices of refraction. *J. Opt. Soc. Am.* vol. 61, pp 886-894

18.2.4.2.1 Species specific differences

A broad range of investigators have provided snippets of data on ametropia in other species. Generally, these investigators have not provided a model of the visual system they are discussing. The data is frequently contradictory¹⁶⁸. Many of these investigators have failed to describe the retina of the species. Many animals, particularly the birds, have multiple foveas, or linearly extended foveas associated with their retina. There is no requirement that these foveas are all in focus for objects at the same distance. As an example, the pigeon is known to have part of its visual system focused on nearby objects at ground level and simultaneously on more remote objects near the horizon¹⁶⁹. As shown in **Chapter 1**, some animals have dual optical systems supporting a single retina. The subject of graded metropia as a function of angle, or regional refractive accommodation must be addressed in many species other than man.

18.2.4.2.2 Statistics of growth processes

It is not generally recognized that while Gaussian Statistics (involving normal distributions) apply to nearly all processes involving multiple underlying and independent mechanisms (due to the Central Limit Theorem), this is not the case for the growth of individual physiological elements. In biological, botanical and many physical systems, individual elements grow according to log-normal statistics. This is why there are more very short people than there are giants relative to the mean height. It is also why all of the snowflakes in a given shower seem to have a similar size. The resulting statistical parameters are based on the log-normal distribution. This distribution exhibits a conventional bell shape when the horizontal axis is logarithmic. In some of the literature of metropia, the authors have calculated second and third order statistical parameters under the assumption that the data fit a normal distribution. When these results appear inappropriate (based on the normal assumption), it is likely that the data more properly fits a log-normal distribution or is a combination of two or more independent mechanisms. Curtin discusses the situation briefly on page 22.

Hirsch & Weymouth discuss the statistics briefly beginning on page 40 and note the skewness and kurtosis found when evaluated using the assumption that the statistics are normal. A different interpretation result under a more appropriate assumption. The anatomical refractive error is due primarily to the mechanisms associated with two log-normally distributed growth processes. The first controls the refractive power of the cornea and the second controls the length of the major axis of the ocular. The “lens” is designed to compensate for any difference resulting from these processes in the majority of cases.

The literature is full of studies of large numbers of individuals. Unfortunately, a large number of variables were assumed to relate to this condition. As a result, the various longitudinal and cross section studies performed on these data sets have seldom drawn strong conclusions. It has usually been necessary to make a number of broad assumptions concerning the uncontrolled variables related to the various subclasses of the subjects. The recent paper of Nomura, et. al. demonstrates that this problem still exists¹⁷⁰. The potential number of variables is a particular problem in studies of subjects between five and twenty because of the variable rates associated with the different growth processes.

The literature also reports on a variety of animal studies. However, most of these have involved introducing pathological conditions, such as sewing the eyelids together on one eye, that have cause major deformities in the ocular independent of the operation of the visual system. While these studies may suggest possible problems in humans, the degree associated with the various results is not representative.

Figure 18.2.4-2 shows the ease with which log-normal curves can be drawn through the Hirsch-Weymouth data. The log-normal overlays are drawn with zero skewness and zero kurtosis. The degree to which the measured data is fit by a log-normal function has major implications with respect to the condition of ametropia. To the degree to which the function (or the sum of a few log-normal functions) match the data, it suggests the condition is not a disease (except in the sense of an error in development). It also suggests the differences between the data and the log-normal functions may not be divisible into separate statistical groups (such as α , β & γ , based on Gaussian statistics).

¹⁶⁸Curtin, B. (1985) Op. Cit. pg 54.

¹⁶⁹Hodos, W. et. al. (1985) in Curtin, Op. Cit. Chapter 13, pp 235-245

¹⁷⁰Nomura, H. Ando, F. et. al. (2004) The relationship between intraocular pressure and refractive error adjusting for age and central corneal thickness *Ophthal Physiol Opt* vol. 24, pp 41-45

18.2.4.2.3 Parameters of the human oculus

The human eye can be described as consisting of two merged ellipsoids. The main body of the eye is an ellipsoid and the cornea can be represented by a section of an ellipsoid grafted to that of the eye. The corneal portion cannot be a paraboloidal or a hyperboloid and meet its optical requirements associated with a wide field of view. The shape and optical geometry of the eye is shown in **Figure 18.2.4-3**. The bulk of the eye, basically that part containing the vitreous humor, is shown as circular. Regardless of the plane, this circularity is borne out by the available data. Scammon & Armstrong plotted the three diameters of the eye on a common graph in 1925¹⁷¹. The results show some divergence from circularity during the early post natal period and again in the three to six year age group. However, as maturity was reached and barring pathological situations, the eye was essentially circular (within 4-5%). Curtin showed the range of axial diameters in emmetropes was 22.4-27.3 mm (page 5). This is a range of 4.9 mm or 20%. The variation in size is considerably larger than the variation in eccentricity.

[xxx where is reference to the letters along the top of the figure?]

Light is shown entering the eye under two conditions. The collimated light parallel to the optical axis will be brought to a focus along the optical axis. The central ray passes through the object space focal point, F_0 , the two principle points, P & P' , and the image space focal point, F' . The chief ray of the off-axis collimated light bundle intersects the first principle point, P , of the optical system. This ray appears to leave the optical system at the second principle point, P' . It leaves this point at an angle given by the incident angle multiplied by the ratio of the indexes of refraction, n_o and n_h according to Snell's Law. This ray will intersect the retina as shown. It will be in focus at this point because the focal length of the optics varies with angle from the optical axis. A major part of this variation in focal length is due to the variable index of refraction of the lens. This variable index is also the primary source of the Stiles-Crawford Effects.

It is important to note that there are no nodal points in this figure. Nodal points only apply to the simplified (or reduced) models of the eye. They are limited to the paraxial condition. The off-axis chief rays do not pass through the so-called second nodal point. The back focal distance, F_B , plays no role in the performance of the system. It is shown only for reference.

The shape of the lens is shown under two conditions. In the accommodated case, the lens is shaped so as to focus an image of the near point on the retina. The minimum distance between the surface of the cornea and the near point is an indication of the accommodation range of a particular eye. In the unaccommodated case, the lens will attempt to focus an image, of an object at infinity, on the surface of the retina. Its ability to do this is a measure of its basal metropia.

There are many facets to the optical geometry of the eye. The overall goal of the system is to present an image of the scene in object space along the line of fixation of the eye, to the retina. The major quality criteria is determined by the dimension **B**. **B** describes the distance between the focal plane of the optical system and the Petzval surface formed by the entrance aperture of the photoreceptors of the retina *in banc*. If the focal plane is to the left of the retina, the eye is considered hypometric (myopic) by a positive amount that can be described in terms of diopters.

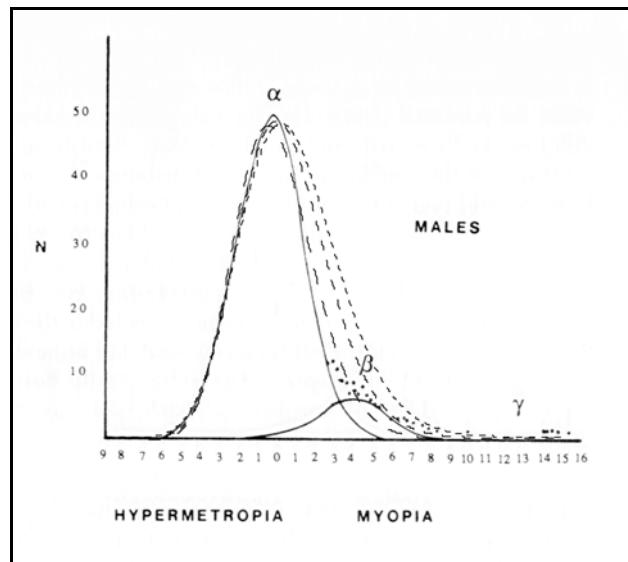


Figure 18.2.4-2 Log-normal distributions fit to the Hirsch-Weymouth figure. The dashed lines are log-normal curves exhibiting zero skewness and zero kurtosis. See text.

¹⁷¹Scammon, R. & Armstrong, E. (1925) On the growth of the human eyeball and optic nerve. *J. Comp. Neurol.* vol. 38, pg 165+. Also in Curtin, B. Op. Cit. pg 99

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To correct for this error, spectacles are usually prescribed to compensate for the error. They will have a power equal and opposite to the power associated with the error.

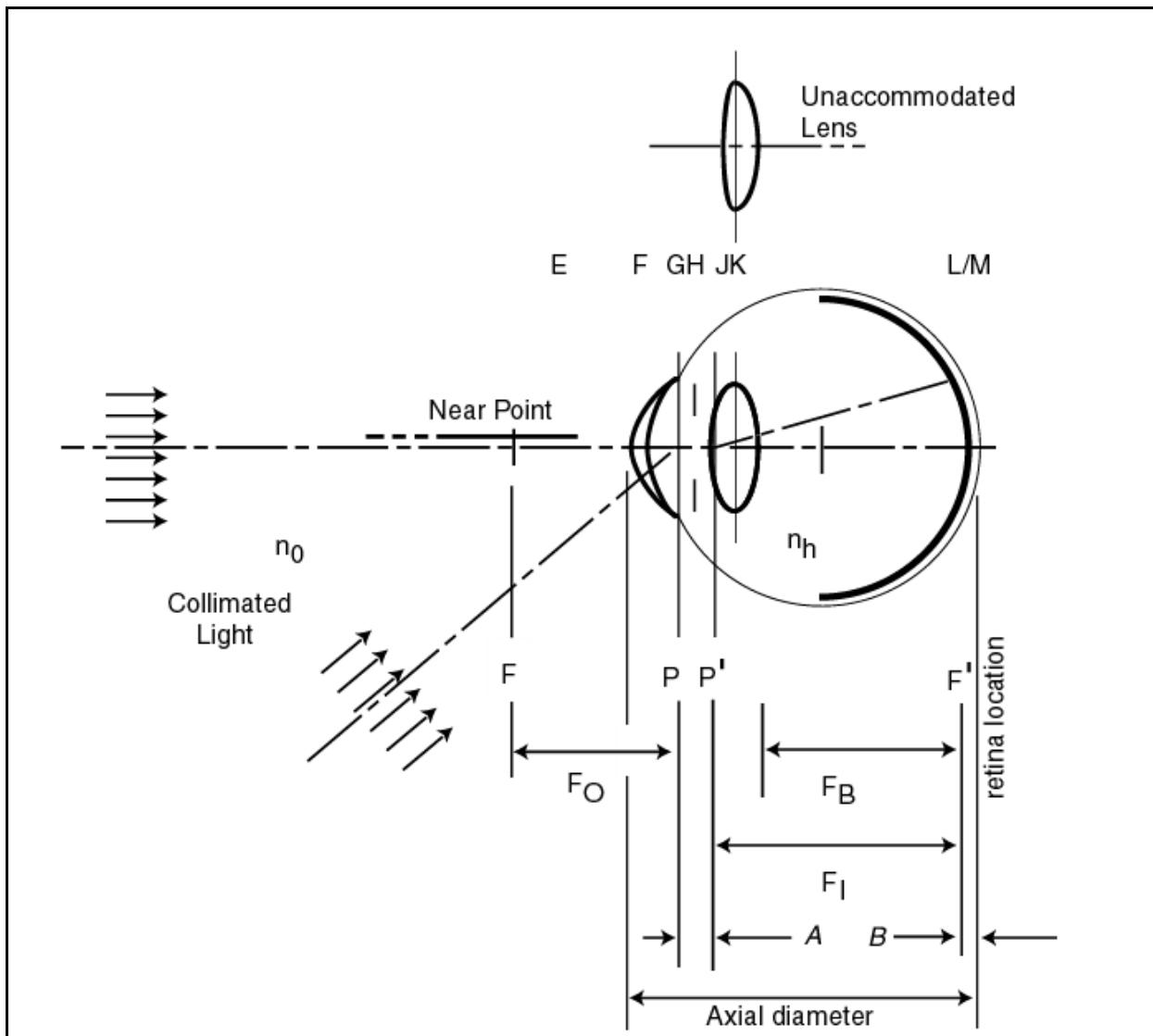


Figure 18.2.4-3 The physical and optical geometry of the human eye. It is necessary that the cornea be ellipsoidal to achieve a wide field of view optical system. See text for discussion.

The Petzval surface of the retina is not a smooth surface of fixed radius. It varies significantly in the area of the foveola.

The error in diopters can be caused by two major factors, unexpected values in the distance between the exit pupil and the retina, or by errors in the nominal exit focal length of the optics. Note that the distance between the exit pupil and the retina is not directly related to the overall axial diameter of the eye. This diameter consists of the sum of several distances:

- the distance from the surface of the cornea to the first principle point,
- The distance between the two focal points,

- The image space focal length of the optics, and
- The error between the optical focal plane and the Petzval Surface formed by the entrance apertures of the photoreceptors of the retina.

Grosvenor & Flom have suggested the contributions to the ocular refractive error relative to these elements is in the ratio of 50%:25%:25%:: total axial length : 25% cornea power : 25% lens power. It is proposed that more statistically precise ratios could be achieved if the axial length was limited to the distance between P' and F'. Both an elongation of the large ellipsoid of the eye, based on this distance, and an elongation of the corneal surface, relative to the first principle point, are major contributors to the failure of the eye to perform emmetropically. While increases in either parameter contributes to myopia, the underlying mechanisms are quite different. As noted by Grosvenor & Flom on page 46, increases in both of these parameters tend to cause their contributions to total ocular refractory error to cancel. Thus, a longer axial diameter may not result in any increase in myopia at all. Under this circumstance, the longer diameter is indicative of a BIG EYE. Sifting through the discussion of Curtin suggests that the refractory error is better correlated with the “radius of the cornea” than with the axial diameter of the eye.

This area is discussed in greater detail by Erickson in Chapter 11 of Grosvenor & Flom. As here, he suggests the greater reliance on the actual positions of the optical surfaces of the eye than on the cardinal points of conventional paraxial analysis. He even addresses the importance of the distance, A , in the overall refractory error. He also explores these dimensions as they affect astigmatism.

A major problem with the above background is its failure to be quantitative concerning the causes of ammetropia. The depth of focus of a lens (the tolerance between the effective focal length of a lens system and the distance from the 2nd principle point to the focal plane) is quite well documented, based on several criteria. The physical criteria is the least controversial. The Rayleigh equation, based on a quarter wavelength of light tolerance, is given by:

$$\delta x = \pm \frac{\lambda}{2 \cdot n \cdot \sin^2 U_m}$$

where the error is primarily dependent on the wavelength of light and the angle U_m . U_m is the angle of the marginal ray approaching the focal plane to the principal ray. A full pupil diameter of six mm for an axial principal ray and a effective focal length of 22.2888 mm gives $U_m = 7.67$ degrees. 22.2888 mm is the average value for a large population as determined by LeGrand. It does not apply to any specific individual. Using 0.5 microns for the wavelength, $n = 1.3$ for the index of the ocular medium, the focus tolerance is about ± 10 microns for a diffraction limited image. This tolerance is much finer than the accuracy with which the effective focal length of the physiological optics are measured in the clinic or laboratory. In practice, the physiological optics is not diffraction limited for a pupil diameter of more than two mm. At that size, the depth of focus is about 9.5 microns. Unless a precision of this order is achieved, and a standard was available for comparison, discussions about whether the error in focus is associated with the refractive power of the optics or the axial length of the ocular is speculative.

Another major problem with the above discussions is that the lens changes both refractive power and axial position due to the force of the ciliary muscle on the lens. The change in refractive power changes the distance, F_l , and both the change in refraction and the change in position, change the location of the 2nd principle plane, P'. This latter change is seldom addressed in the literature.

Note the important fact that errors in the axial diameter of the oculus of only 10 microns can affect the emmetropia of the eye. This is far below the precision with which this diameter can be measured.

18.2.4.2.4 Aspects of accommodation

A discussion of the dynamics of accommodation is hard to find in the literature. Schor suggests that both the accommodation and vergence systems involve closed-loop subsystem¹⁷². In a very short chapter, he only devotes one paragraph to the conceptual aspects of these loops. Based on this model, the vergence and accommodation subsystems are quite different in character. **Figure 18.2.4-4** illustrates the overall block diagram of the accommodation servomechanism. As opposed to the oculomotor system, the accommodation system is not symmetrical with pairs of muscles opposing each other. The ciliary muscle works against the mass and spring

¹⁷²Schor, C. (1991) Effects on the resting states of accommodation and vergence. In Grosvenor & Flom, Op. Cit. Chapter 18. pp 310-317

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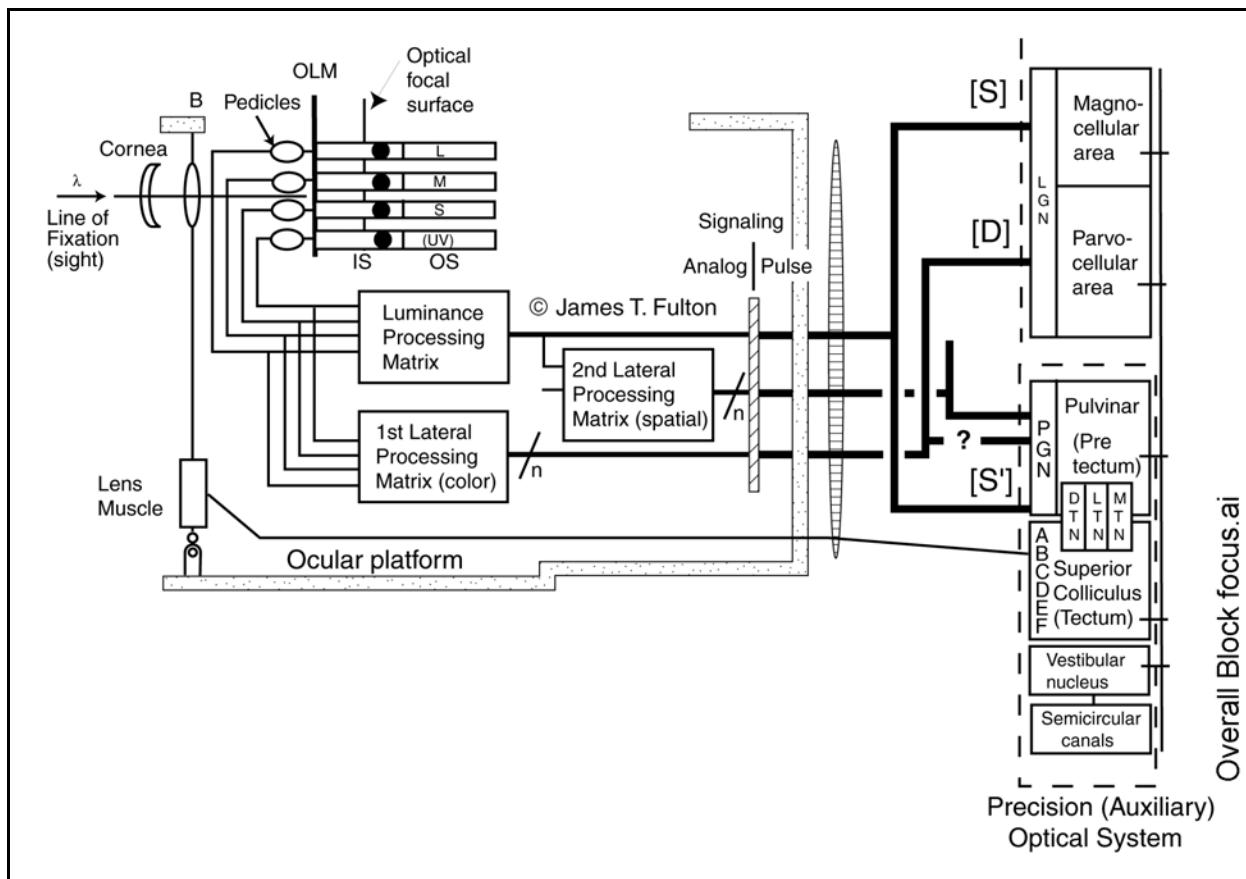


Figure 18.2.4-4 Overall block diagram of the accommodation subsystem. The signal from B of the POS to the ciliary muscle travels via nerve III and/or V.

properties of the lens and other support structure in response to commands from the accommodation nucleus of the superior colliculus. A more detailed model of the lens servosystem is presented in **Section 7.3.2**. The ciliary muscle and the sphincter pupillae muscle are innervated from the POS via the parasympathetic root, nerve III^{173, 174}.

No information was found describing how the brain extracted the accommodation error from the signals from the retina. Because of the precision required, it is safe to assume that this function is performed using the signals from the foveola and probably occurs in the pretectum. The process probably involves maximizing the slope of the signals received from the foveola over a period of a few cycles of the tremor. This would require on the order of 20 ms. It might involve a two dimensional correlation process as used in the feature extraction function leading to the initial interpretation of the scene.

No data was found on the time course of accommodation. A simple viewing experiment would suggest that accommodation is completed in considerably less than one second. A second observation was that the brain may maintain a short term map of the accommodation level required to focus on an object that has remained in the total field of vision but not within the foveola. A similar finding may apply to the level of vergence required. It appears likely that accommodation is usually accomplished within the first 50-100 ms of the interpretation process of the POS following a small saccade. [xxx confirm this value, may not be in Campbell & Green] For large saccades, the time may be extended by the need for a minor saccade to correct for initial pointing errors.

¹⁷³Newell, F. (1986) Ophthalmology, 6th ed. St. Louis, MO: C. V. Mosby, pg 37& 60

¹⁷⁴Sivak, J. (1991) Optical adaptations of the vertebrate eye In Grosvenor & Flom, Op. Cit. Chapter 12. pp 219-234

[My chart of power versus age showing challenge of adaptation. Resting states, near point and far point. /difficulty with definition of far point **XXX** instrument focus, dark focus etc.] tears

The conventional wisdom is that the lens becomes more rigid with age requiring more effort by the ciliary muscle to achieve changes in accommodation. The data of Raeder offers an alternate view¹⁷⁵. It suggests the loss in accommodation range may be due to the continual increase in the axial thickness of the lens with age. This would suggest that the tone of the ciliary muscle becomes less and less important in shaping the lens with age. The unaccommodated and accommodated lens have essentially the same shape. This thickening would also provide a different explanation for the short wavelength absorption by the lens with age. The conventional explanation is that it is due to color centers or other occlusions within the lens.

18.2.4.2.5 Behavioral methods of treating myopia

chap 20 of Grosvenor has good perspective. And alternative methods on pag 347xxx]

18.2.4.2.6 Reported flashes of clear vision

[page 346 of Grosvenor

18.2.4.2.7 Performance of the overall accommodation subsystem

[xxx Section 7.4.8.1.3 will move here]

18.2.4.3 The schematic of the accommodation mechanism

[xxx defer to section 7.4.8.1]

The material by Wallman, referenced above, presented two simple schematics that he offers might represent the accommodation mechanism. However, they require expansion in order to present a clear nomograph of the problems normally found in ametropia and to relate it to the above block diagram.

Figure 18.2.4-5 represents an expanded block diagram of the accommodation subsystem reproduced from **Section 7.4.8.**

¹⁷⁵Raeder, J. (1925) in German. Also in Curtin, B. Op. Cit. pg 20.

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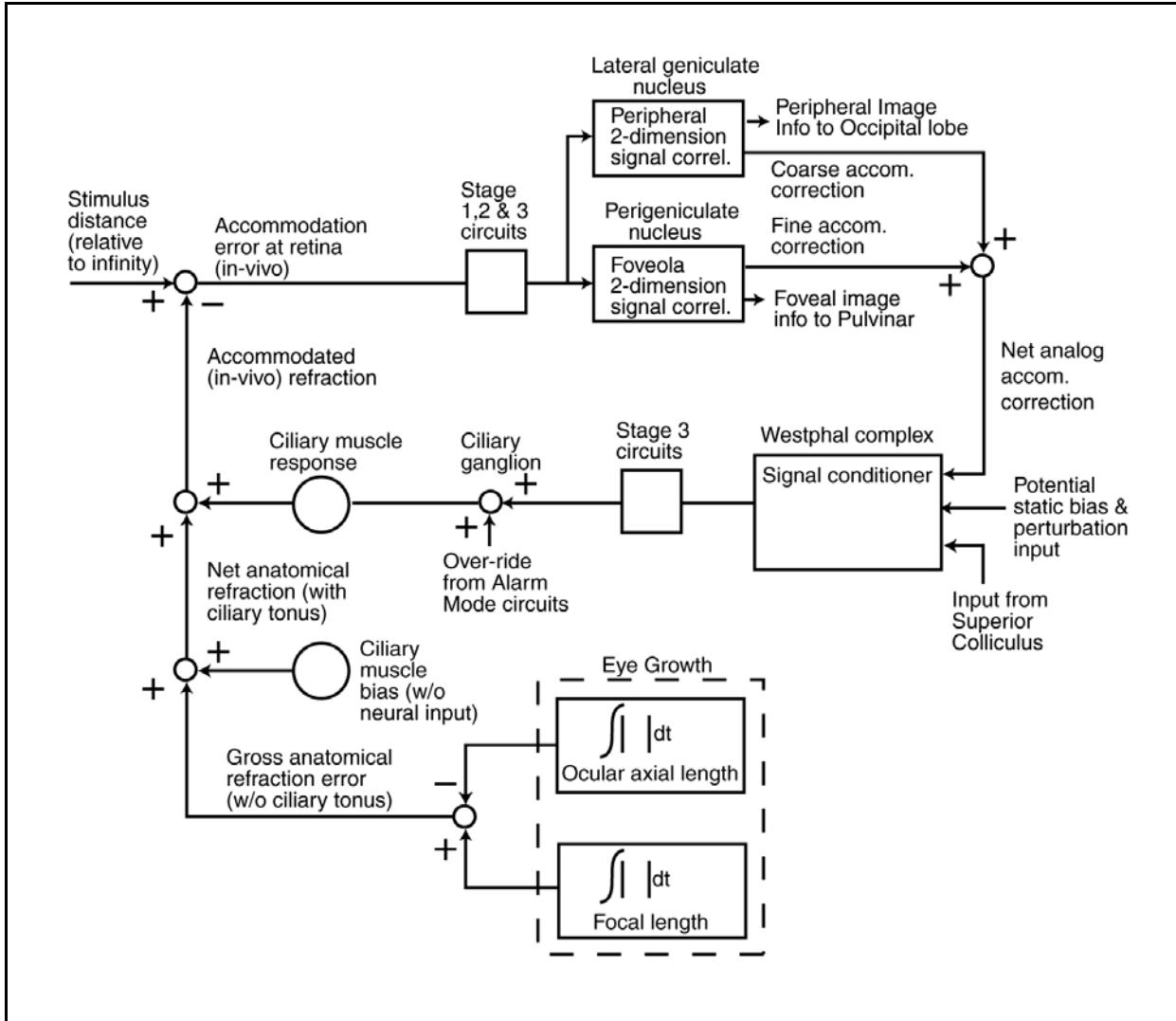


Figure 18.2.4-5 A schematic of the accommodation servomechanism.

Figure 18.2.4-6 presents a nomograph describing limits imposed by the nature of the above schematic. The nomograph starts at lower left giving the distance from the subject of a stimulus. By projecting horizontally and then vertically to the horizontal axis, from the characteristic representative of the subject, the required accommodation relative to the collimated condition is found. The two bounding curves represent the anatomical refractive error of the subject. A log-normal distribution representing the degree of ametropia found in the general population is shown at the lower right. This distribution shows a slightly sharper edge on the hypermetrope side and properly describes the slightly higher frequency of 4D hypometropes compared to 4D hypermetropes. It suggests plus and minus four diopters are reasonable values to describe the limits of ametropia found in the general population other papers have used six diopters as a criterion. Notice that a four diopter hypermetrope (myope) requires a negative degree of accommodation for stimuli at distances greater than 25 cm. By projecting the value on the horizontal axis up until it reaches the fold line and then horizontally to the vertical axis, the available correction is determined for the stimulus originally postulated. As noted above the accommodation mechanism cannot provide negative accommodation. This area of operation has been shaded.

Normally, it is found that the human visual system operates with a small amount of accommodation associated with the tonus of the ciliary muscle. This tonus may be supported by a neural signal of a nominal value as discussed in **Section xxx**. The quiescent focal condition due to this level of tonus is indicated by one diopter on the upper left scale. For the emmetrope, this level represents a normal quiescent accommodation to a stimulus distance of 100 cm, whether there is a stimulus present at that distance or not. For the four diopter myope, the quiescent accommodation distance is nominally 20 cm.

[xxx replot ages along axis and redetermine the following ages]

The limits of the nominal human eye as a function of aging is shown by the figures along the fold line. Young eyes normally provide accommodation up to at least 16 diopters [compare to later plots xxx]. As the subject ages, the maximum accommodation decreases, a condition known as presbyopia. By 48 years, the nominal emmetrope can only accommodate over a range of zero to two diopters. The subject can no longer read newspaper size text held within arms length but he can still accommodate to long distances. By the time he is 60 years of age, the lower part of the fold line will also be lost. He will need spectacles to accommodate to long distances as well. As another example, a two diopter hypermetrope will begin requiring spectacles for reading at about 30 years and also require spectacles to aid accommodation at long distances at age 48.

It is interesting to note the ability of a hypermetrope to properly image scenes presented to his eye that involve diverging light rays (a situation not found in nature). A hypermetrope with young eyes can actually bring such a scene (such as generated by a set of misadjusted binoculars) into correct focus.

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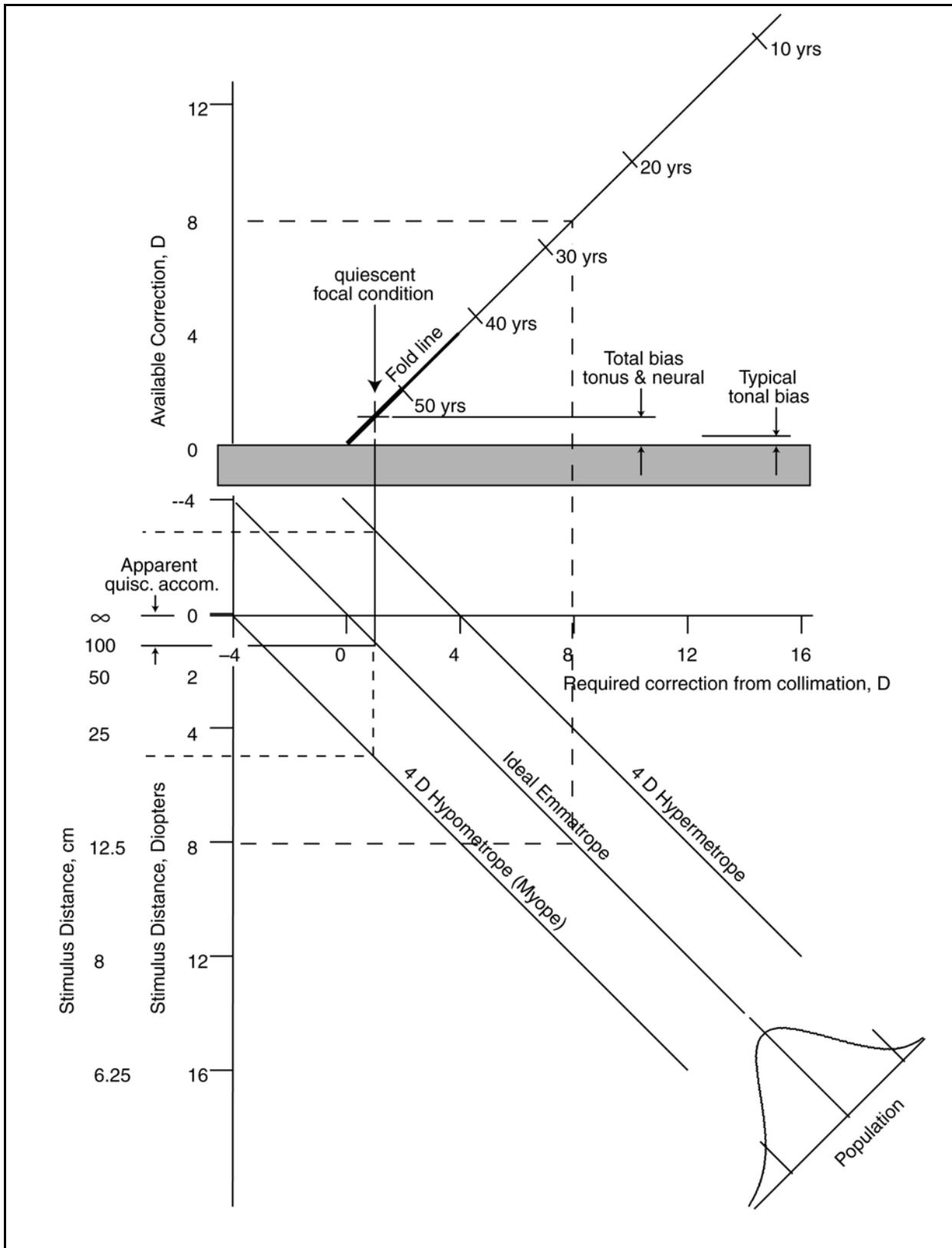


Figure 18.2.4-6 A nomograph describing the performance of the accommodation subsystem.

This nomograph can be extended to also represent the situation when the scene contrast is low. For the ideal emmetrope without any age limitation, the curve is precisely as shown by Owens (pg 324 in Grosvenor & Flom) and reproduced here as **Figure 18.2.4-7**. For other eyes, the quiescent focal condition must be determined and a similar set of lines drawn. As Owens has noted (pages 326-340), previous clinical investigations have been contradictory concerning the quiescent focal condition (also called the dark focus condition).

18.2.4.4 The course of ametropia in humans

Ametropia has been studied for a long time. With time the instrumentation has become better and the size of the statistical groups have grown. The larger groups has allowed more sophisticated statistical methods to be used. This has resulted in the isolation of various pathological groups from the general population. The result has been better numerical precision in more recent publications when discussing ametropia.

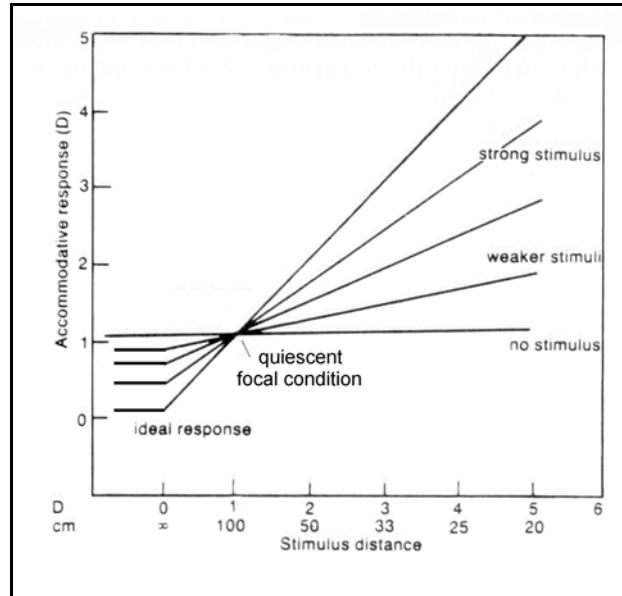


Figure 18.2.4-7 Accommodation performance of the emmetropic eye as a function of stimulus intensity. From Owens, 1991.

Figure 18.2.4-8 can be derived from the above nomograph describing the performance of the uncorrected accommodation subsystem. This figure shows the performance of the emmetrope as a function of age. The emmetropic eye exhibits several features of importance. First, note the sharp bend in the overall response at zero D effective stimulus distance (at infinity). The emmetropic eye is designed to operate over the real distance range from infinity to very close to the eyes. For children under ten years of age, the minimal distance is measured in centimeters¹⁷⁶. As age progresses, a hardening of the lens material results in presbyopia, an inability to focus at close ranges. This condition is indicated by the age markers along the emmetrope curve. Second, note the cross mark at the point of quiescent accommodation. The accommodation system is not symmetrical along the sloping part of the curve. Under quiescent conditions, the eye is normally at a refractive level only slightly higher than the anatomical (or morbid) refractive state. This departure from the anatomical state is typically less than 1 D and is due to the tonus of the ciliary muscle and any bias introduced by the neural system. The departure due to the tone of the muscle is normally about 0.25 D¹⁷⁷. The active accommodation system operates against a spring as described in **Section 7.4**. Thus it, can change the state of accommodation from the quiescent condition in only one direction (in the absence of a neural bias). This neural bias is believed to be about 0.75 D. As noted above, the precise value of this parameter is difficult to determine because of the different techniques used in the literature to measure it.

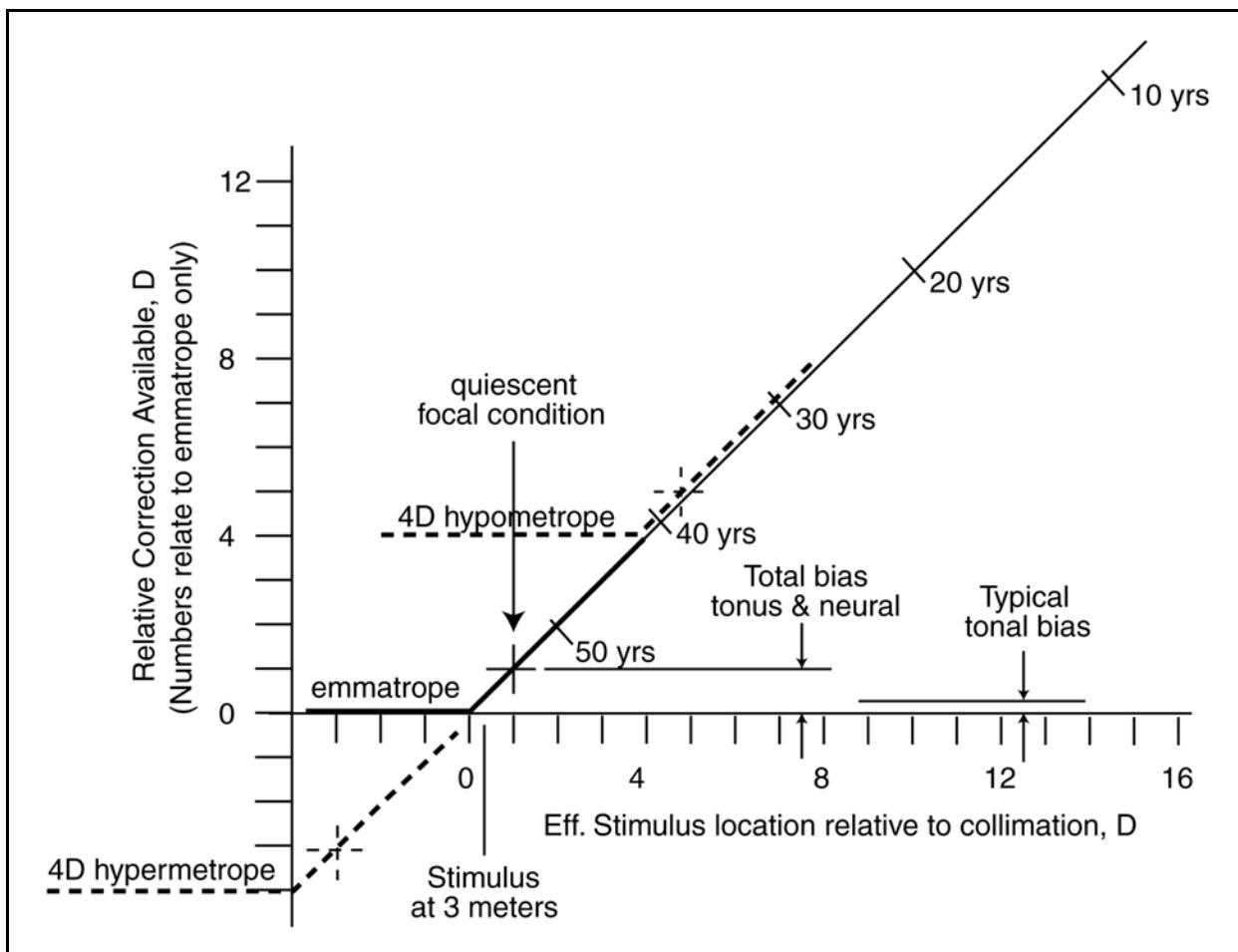


Figure 18.2.4-8 A comparison of the performance of uncorrected ammetropic eyes. The performance of the emmetropic eye is shown as a function of age. See text.

¹⁷⁶Chen, A. O'Leary, D & Howell, E. (2000) Near visual function in young children *Ophthal Physiol Opt* vol. 20, no. 3, pp 185-198

¹⁷⁷Radhakrishnan, H. Pardhan, S. Calver, R. & O'Leary, D. (2004) Unequal reduction in visual acuity with positive and negative defocusing lenses in myopes *Optom Vis Sci* vol. 81(1), pp 14-17

Ammetropia is a disease consisting of an error in the first order value of the anatomical refractive state under quiescent conditions. Hypometropis is the name of the symptom describing an anatomical refraction that is too high. Hypermetropia describes the condition where the anatomical refraction is too low. These two conditions have been described in the figure by moving the emmetropic curve to the left and right as appropriate by four diopters. These complete curves show the same age related changes as for the emmetrope but they are shown truncated for convenience.

Because of the asymmetrical character of the accommodation subsystem, the emmatrope is unable to bring converging light rays (corresponding to effective distances beyond infinity, and represented by negative absolute diopter values) into focus. Interestingly, as shown by the curve for the 4D hypermetrope, the hypermetrope can bring converging light rays into focus. On the other hand, a 4D hypometrope is unable to bring light into focus from points in the interval between 25 centimeters, infinity and beyond.

The ametropias shown in the figure are usually corrected through the use of spectacles. While means of medically preventing the occurrence of ametropia have been sought for a long time, little progress has been made. Recently, surgical intervention to reduce (after the fact) the refractive power of the cornea has become quite common.

The course of ametropia (and the broader metropia) is complex in humans. It involves distinct prenatal, post-natal, juvenile, adult and senile stages. Curtin provides a good review of these situations¹⁷⁸. The parameters of the prenatal eye show very wide standard deviations because of the variation in individual growth rates (See background in **Section 18.2.4.2.2**). These growth rates appear to accelerate during the first few years of life. The nominal sagittal diameter of the eye at birth is 18.0 mm. By age three, the average was near 22.8 mm, a growth of nearly five mm or 26%. Simultaneously, the power of the lens drops markedly. Thus a statistically poorly defined level of considerable myopia begins a rapid change toward emmetropia during the first few years of life. This change continues through the juvenile phase.

Figure 18.2.4-9 shows the convergence of the ocular refraction error during the juvenile phase¹⁷⁹. The variation about the mean reflects the variation in maturation rates between the cornea, lens and the supporting physical structure. The latter includes the positioning of the lens relative to the cornea and retina.

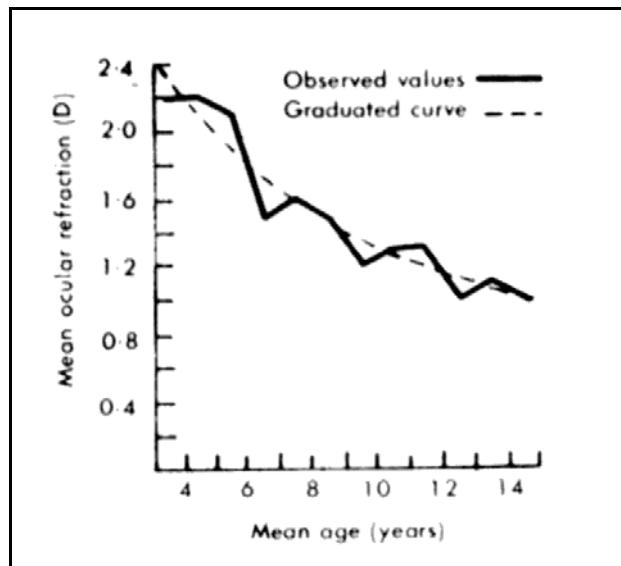


Figure 18.2.4-9 Convergence in the ocular refraction error during the juvenile stage. Sample of 628 boys between 3 and 15 years. Variation reflects the different rates of maturation of different elements of the physiological optics. From Sorsby, et. al. 1961.

¹⁷⁸Curtin, B. (1985) Op. Cit. pp 29-37

¹⁷⁹Sorsby, A. Benjamin, B. & Sheriean, M. (1961) Refraction and its components during the growth of the eye from the age of three. Medical Research Council, Special report Series #301, London: Her Majesty's Stationery Office

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Figure 18.2.4-10 describes the cumulative distribution for the cessation of this chaotic development process. [in Grosvenor & Flom, pg 91] The maturation of the physiological optics is completed between the ages of 18 and 22.

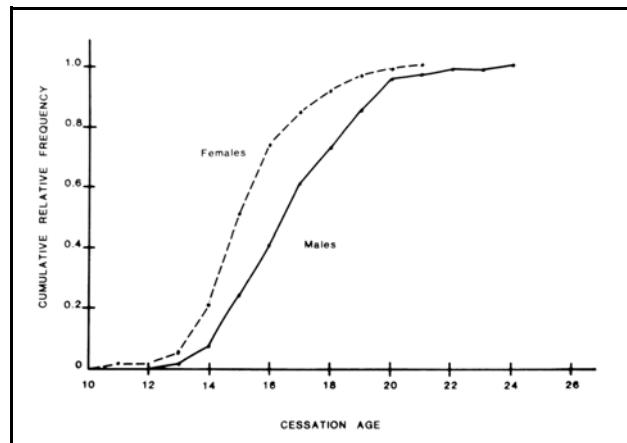


Figure 18.2.4-10 Cessation age for the development of the metropic performance of the eyes. For 66 males and 57 females. From Goss & Winkler, 1983

The data in **Figure 18.2.4-11** from Bucklers is instructive in describing the results of this maturation. Individual eyes stabilize in a metropic state that they tend to maintain for the rest of their lives. The exceptions can usually be shown to involve pathological conditions. These exceptions frequently involve the tissue behind the retina. This figure is primarily illustrative of the trends. It has omitted the many eyes clustered near the axis of emmetropia (at zero ocular refraction). The asymptotic value of the metropia of an individual will be described as the basal metropia.

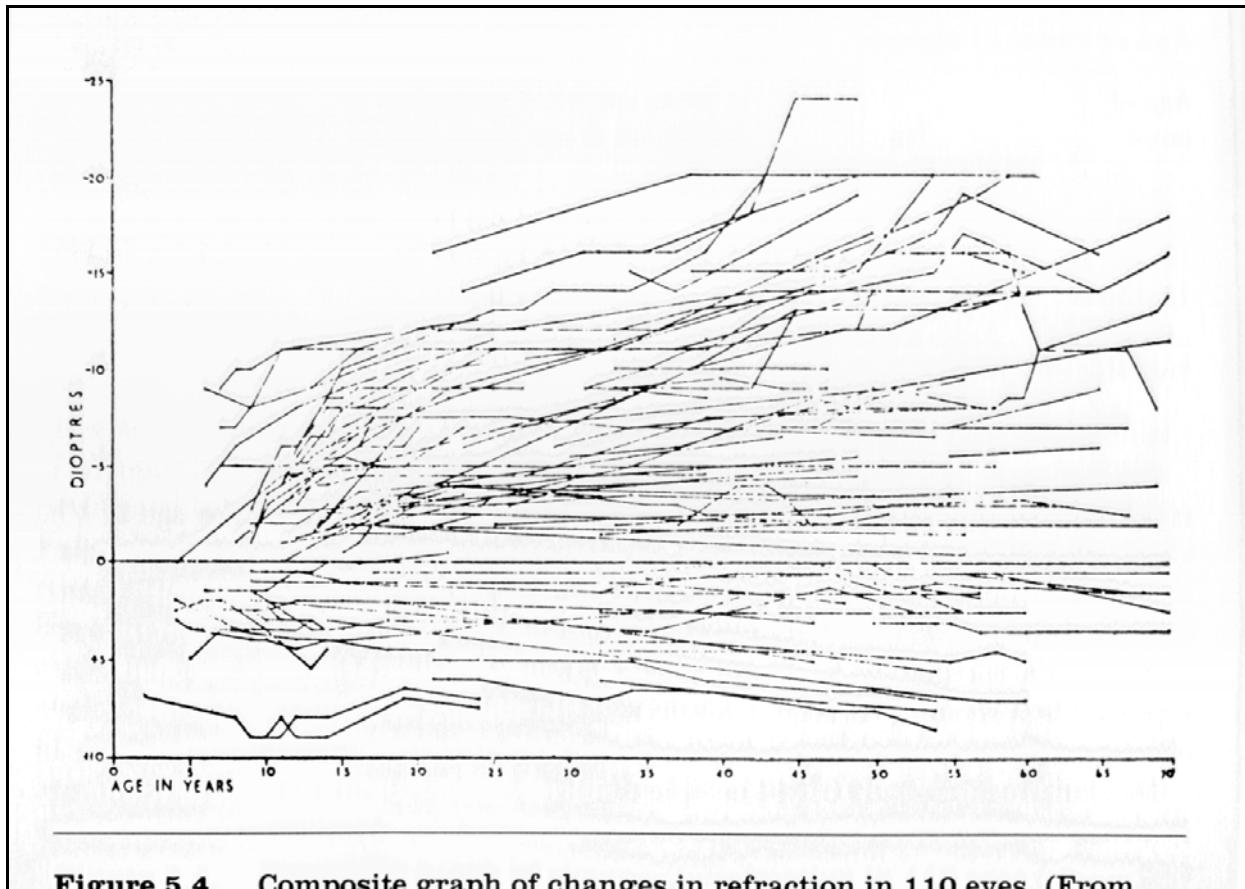


Figure 5.4. Composite graph of changes in refraction in 110 eyes. (From

Figure 18.2.4-11 FIX FIGURE Illustrative course of ametropia with age based on selected eyes. From Bucklers, 1952.

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The vast majority of eyes mature with a metropic ocular refraction error between +1.0 and -1.0 Diopters. This is best shown by the unconventional graph of Scheerer. It is reproduced as **Figure 18.2.4-12**. The hatched area represents eyes with a pathological condition known as a crescent formation. The dashed line represents the best fit normal distribution to the high side of the figure. It can be assumed that the standard deviation of this data is less than one diopter. Based on that assumption, estimates of the prevalence of ametropia of less than 9% can be offered for this very large sample obtained under a common set of conditions. The dash-dot line represents a log-normal distribution to be expected based on a growth dominated mechanism. Grosvenor & Flom have accumulated additional statistics on metropia. However, the field contains many analyses lacking precise characterization of the relevant parameters. A study prepared in 1989 highlights the difficulties¹⁸⁰. Even in that study, the definitions of ametropia were oversimplified for pedagogical reasons. The estimates in that work for myopia only spanned a range up to 30% or more based on various stratified studies. This situation makes statistically precise statements difficult. Examples are the Sheerer graph with an undefined peak value and the graphs of Hirsch reproduced in Grosvenor & Flom.

The variance in experimental procedure and criteria also impacts the available statistical data. Variations in the mean between investigators is frequently much greater than the claimed statistical error in those individual means. The same situation is found with respect to the standard deviations in the data sets. These differences are clear indications of mathematical errors or differences in protocols and/or criteria. It appears that even in groups of 500 eyes or more, the data sets contain subtle biases associated with the particular groups. These data sets also vary considerably from the Standard Eye of LeGrand (whether full or simplified).

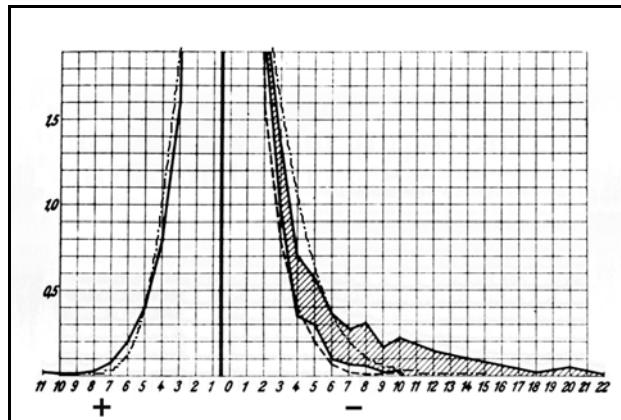


Figure 18.2.4-12 The distribution curve for the metropia of 12,000 patients over 25 years of age. Horizontal scale in Diopters, with - values to the right. The shaded area represents pathological conditions. The dashed line represents the normal distribution. The mean of this distribution is +0.6 D. The dash-dot line represents the log-normal distribution. Together they bracket most of the data. Modified from Scheerer, 1929.

¹⁸⁰---- (1989) Myopia: Prevalence and Progression. Prepared by the Committee on Vision, National Research Council. Washington, DC: National Academy Press

18.2.4.5 The mechanisms associated with presbyopia

Presbyopia is an ontogenetic condition associated with the continual recession of the near point of vision. It is paralleled by the continuous growth in axial length of the lens.

To understand the condition, it is necessary to understand the range of accommodation available at various ages. Anecdotal data suggests accommodation of up to 20 D in some ten year old individuals. The best available data on accommodation is Blaker. Unfortunately, it is based on only two 20 year-old slightly hypermetropic subjects. They both exhibited a range of over 9 diopters with one measured at 10 diopters.

It is also necessary to specify a focal length for the nominal unaccommodated eye. The value of Blaker will be used instead of Gullstrand since the Gullstrand value is known to apply to a hypermetropic eye¹⁸¹.

Based on these considerations, the unaccommodated nominal eye, compatible with the data of Scheerer, will be assumed to have a focal length of 23.71 mm (equivalent power of 60.80 diopters) and an accommodation range of at least ten diopters. **Figure 18.2.4-13** shows the performance of this eye.

18.2.4.6 The course of presbyopia in humans

It will be assumed that the performance calculated above is independent of the basal ametropia of the human eye. Based on this assumption, the performance of the typical eye can be calculated.

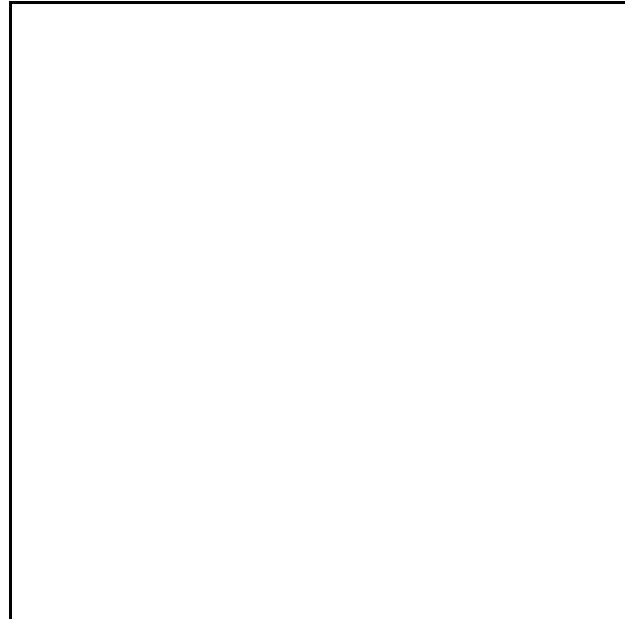


Figure 18.2.4-13 Calculated range of accommodation for the nominal eye of Blaker. A constant distance between the first principle plane and the anterior surface of the cornea is assumed. See text.

¹⁸¹Blaker, J. (1980) Op. Cit.

18.3 Failures of the afferent (signaling oriented) neurological paths

Many failures in the signaling portion of the visual system can be diagnosed most effectively using perimetry. **Figure 18.3.1-1** illustrates the power of this clinical technique.

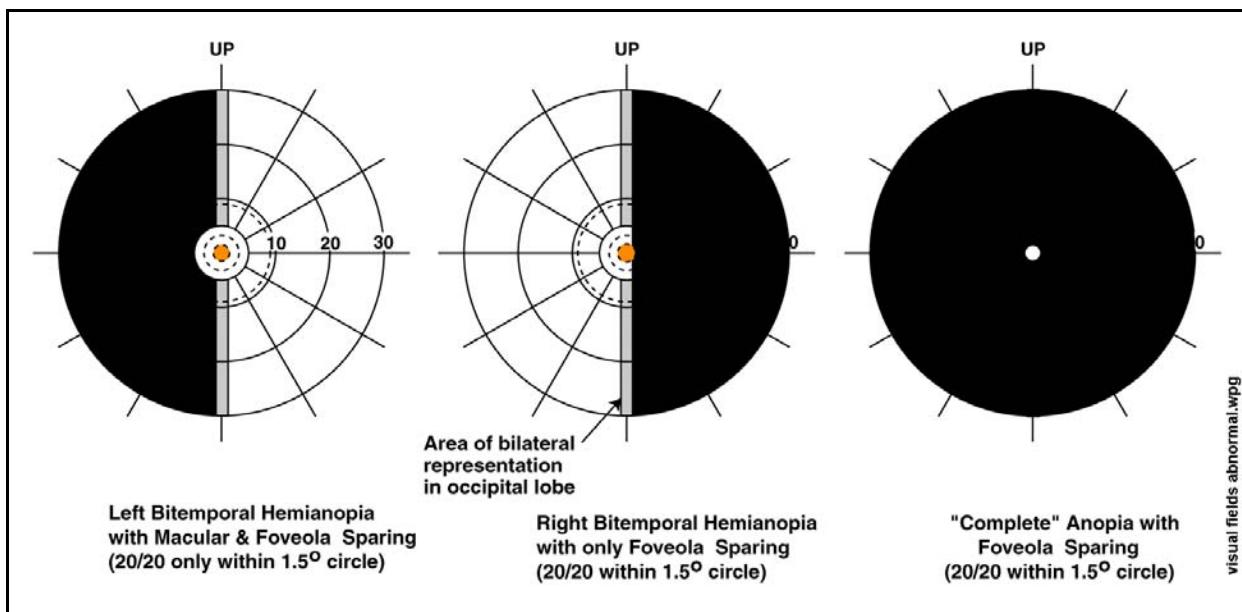


Figure 18.3.1-1 Examples of perimetry identifying complex neurological failures.

The left frame shows left bitemporal hemianopia with macular and foveola sparing. The right field and the complete macular region are normal. The area of bilateral representation along the vertical meridian is also normal except for a reduction in signal-to-noise performance resulting in some low light level performance degradation. This type of hemianopia is associated with a failure in the optic nerve as opposed to a failure in the occipital lobe. A similar failure in the portion of the occipital lobe facing the longitudinal fissure would not exhibit the area of sparing along the vertical meridian or sparing in the large macular region. The central frame shows a failure associated with the neural system after the diencephalon where the entire right field is lost except for the region of the foveola and the area near the vertical meridian. The right frame shows the loss of all vision associated with the occipital lobes and only foveola sparing via the PGN and the pulvinar-parietal lobe pathway. A very large set of isopter plots obtained using perimetry appears in Harrington (**Section 18.1.4.2**).

18.3.1 Failures of photodetection in stage 1

Assuming the proper chromophores were deposited in level D of stage 0 and the dendritic connections were made as prescribed in level E, most failures in stage 1 are common to all of the spectrally selective photoreceptor cells. The most likely failures appear to be related to the formation of the Distributed Activas of the adaptation amplifiers or bias voltage errors.

18.3.1.1 Total failures in photodetection

The great deal of overlap in the spectral response of the individual chromophores leads to complete functional redundancy in the photodetection capability of the animal eye. There are two obvious classes of malfunction in each spectral channel related to photodetection, total failure and degraded performance. Total failure in one of these channels, whether it be described as protanopia, tritanopia, or pentanopia results in dichromatic vision and is rare.

The most common failure of a photodetection channel appears to be in the L-channel (protanopia). This failure results in an overall loss of the L-channel under photopic, mezotopic and scotopic conditions. Such an eye always exhibits a scotopic luminance function in the non-adapted state.

The reported cases of complete lack of “blue” sensitivity or “green” sensitivity are rare and poorly documented. Only a carefully recorded luminosity function, spanning at least five orders of magnitude in intensity, can demonstrate either of these failure modes.

Loss of functionality related to two distinct photodetection channels results in monochromatic vision and is extremely rare. The complete loss of sensitivity in both the L- and M- channels has been documented in at least one case. Stockman reported the case of a subject with a luminous efficiency function limited to and identical with the theoretical S-channel of this work. This subject is a true functional monochromat.

Total failures in photodetection can be caused by a variety of problems. These include failures related to;

- + the formation of the Outer Segment,
- + the preparation of the chromophores in the RPE and their transport to the disks of the Outer Segment,
- + the formation of the dendritic structure of the Inner Segment in the furrows of the Outer Segment,
- + the operation of the unique distributed adaptation amplifiers within the dendritic structure (microtubules) of the photoreceptor cells.
- + the operation of the distribution amplifiers and the pedicel of the photoreceptor cell,
- + the appropriate synapsing of the photodetection channels of the photodetection stage with the subsequent cells of the signal manipulation stage.

Transduction errors related to level 5, following correct formation of the Outer Segment in stage 0, are highly unlikely due to the passive nature of the process. An error that could go unnoticed involves the improper spacing of the disks following initial extrusion and coating. If the disks become squeezed together, the effective index of refraction of the Outer Segment when viewed end-on will be so high as to reject incoming light. The retina would appear unusually glassy, as in a low grade mirror, under this condition and the subject would exhibit poor sensitivity to light.

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18.3.1.1.1 Most likely L-channel failure modes

The most common total failures appear to occur in the L-channel. There are at least three obvious failure modes related to the chemistry of this channel. One type of failure would be the failure of the required SRBP to form the L-channel chromophore prior to its distribution to the Outer Segments via the RPE(level A or B). A second could be a failure in the transport mechanism within the RPE and the IPM (level C). The third could involve the failure of the appropriate chromophoric material to be seeded during gestation of the animal (level D). This is probably one of the most common reasons for loss of the L-channel and is usually attributed to a high temperature of the fetus during specific weeks of gestation caused by illness of the mother. A high temperature will tend to cause the shorter wavelength chromophores to be seeded more easily, or more extensively with respect to the mosaic of the retina.

Much additional work is needed to differentiate between and document the actual existence of the actual failure modes. It is clear that a single genetic failure is not likely to account for all of the above failure modes.

There is a very slight difference in the translation process in the L-channel compared to the others. However, no mechanism has been found in this area that would lead to total failure of the channel.

18.3.1.1.2 Failures in the adaptation/distribution amplifiers

The amplification process is functionally identical in all of the photodetection channels although there is a slight operational variation in the L-channel, mainly related to the fact that the current flow into the adaptation amplifier has a square law characteristic with respect to illuminance. This may well cause an abnormal L-channel response, as will be discussed below, but is not likely to cause total failure.

The circuit topology of the neural portion of the photoreceptor cells is the most complex of the visual system. Containing multiple and distributed forms of Activas leave it vulnerable to failure modes not found in most, if not all, other neural cells. These failures usually do not exhibit morphological artifacts. Excessively large diameter dendrites (microtubules) in the furrows of the Outer Segment would be a clear morphological pointer to improperly formed Activas constituting the adaptation amplifiers (a mechanism in level E). If the space between the dendrolemma and the reticulolemma is too wide, an Activa will not be formed and transistor action will not be achieved.

Most other non-genetic failures are associated with improper bias conditions applied to the Activas. These can be due to the participation of the wrong metabolite in the electrostenolytic process at one of the terminal points on the lemma of a neurite or axon (level F). Alternately, the specialized area of the lemma associated with the errant bias could be improperly sized, leading to an improper impedance in series with the electrostenolytic current generator.

18.3.1.2 Partial failures

Partial failures in the photodetection process can be caused by any of the photodetection elements in the functional block diagram as well as abnormalities in the luminance channel itself, and possibly in the cerebrum.

Within the photodetection channels, the very high degree of internal electronic feedback associated with the adaptation amplifier will cause any small deviations from normal performance within the transduction and translation elements to be greatly discounted. The output will be fully compensated by the change in gain of the adaptation amplifier. Changes in performance of the adaptation amplifier on the other hand can be severe. If the vascular system is unable to supply adequate bioenergetic material to the Outer Segments of the photoreceptor cells, very significant losses in amplifier gain can result. The gain is approximately a sixth power function of the voltage applied to the Activa in each amplifier.

Whereas it is possible to have abnormalities in one or more of the adaptation amplifiers, it is more likely they will respond as a group to inadequacies in the diffusion and transport capability of the choroid/RPE/IPM system. Thus the most common problem diagnosed, related to photodetection, is probably a loss in overall sensitivity due to poor energy supply to the photoreceptor adaptation amplifiers. This is usually associated with poor vision under scotopic conditions.

The opposite condition, failure of the vascular system to restrict the voltage at the collector of the adaptation amplifiers in the presence of high irradiation levels can cause hemeralopia, extreme sensitivity to high light levels. This is a well-known problem frequently associated with albinos. Drugs causing vascular dilation can also lead to this problem. The solution to this latter problem is the prevalence of dark glasses in the community under

unexpected conditions.

A paper was recently published on a more complex genetic problem involving a disproportionate percentage, 5%, of the population on the Pacific atoll of Pingelap¹⁸². The population exhibits a set of symptoms, a syndrome, called achromatopsia. Some of these symptoms may be due to a Stage 1 failure. However, it is not likely that they are caused by a photodetection failure since the subjects exhibit a normal luminous efficiency function in the scotopic, mesopic and lower photopic illumination ranges. See Section 18.8.3.3.

There is a series of possible electrical bias errors within the photoreceptor cells that could cause unexpected luminous efficiency and chrominance discrimination abnormalities. However, no reason has been found to relate these to imbalances to a specific spectral channel.

An alternate source of partial failures would involve the synapses between the pedicles of the spectrally selective photoreceptor cells and the following cells of the signal manipulation stage (stage 2). The impedance of these synapses appears to be a significant factor in the signal matrixing of the stage 2. This alternative will be discussed further below.

18.3.2 Failures in signal matrixing in stage 2

All of the signals from the chromatic photodetection channels of stage 1 are presented to the luminance and chrominance channels in an identical manner. All stage 2 elements contact the pedicels of stage 1 through synapses. However, within the matrixing associated with the Plexiform Layer(s), there is the possibility of inappropriate connections and /or inappropriate impedances used in voltage dividers. If the synapses between the stage 1 and stage 2 cells related to luminance were misformed, the coefficients in the brightness equation of Section 17.2.2 would be in error leading to an abnormal luminous efficiency function. Alternately, if the synapses related to the chrominance channels were misformed, an abnormal response in the chrominance discrimination function or the New Chromaticity Diagram for that subject would be expected (first mechanism of level 9).

Virtually nothing is known about how and why individual cells of the luminance and 1st lateral processing matrices connect to specific photoreceptor cells. Little is actually known about the precise distribution of spectrally selective photoreceptor cell types over the mosaic of the retina. Connection problems occurring in the Outer Plexiform Layer, could lead to unusual signal levels from a particular photodetection channel being applied to the luminance and/or chrominance signal processing channels. Connection problems within the Inner Plexiform Layer could cause undesirable cross coupling between the outputs of the chrominance and luminance channels.

Errors in the operation of the luminance matrix are difficult to separate from errors in the spectral channels in the absence of careful measurements to confirm the operation of the chrominance channels. If the perceived chromatic performance of the visual system is normal but the perceived luminous efficiency function is not, it is possible to specify the errors as originating in the luminance channel beginning with the luminance matrix. Further specification as to the location of the error between the luminance matrix and the spatial encoding matrix associated with the ganglion cells requires even more study.

Since the lateral cells of the 1st lateral matrix are required to form an electrical difference between two analog signals, it is important that the size of the specialized podolemma associated with electrostenolysis, and therefore the base impedance, associated with these horizontal cells be correct. Otherwise, the coefficients applied to the two input signals will be incorrect in the output signal. This will lead to shifts in the neutral point in the P- or Q-channels and result in tetratanomalia or deutranomalia, if not complete failure, in these channels (second mechanism of level 9).

The capabilities of the 2nd lateral matrix, have not been thoroughly explored, even in humans, and it is therefore difficult to discuss abnormalities in this area. This matrix is not instrumental in color perception. Much of the matrixing has to do with spatial summation and differencing between channels. Further, much of this matrixing appears to rely upon temporal signal dispersion to avoid the requirement for a discrete short term signal storage capability. Problems in the signal matrixing do not appear to be a significant failure mode in human vision. They clearly do not relate to any total channel failure. They may have an impact on some niche related spatial integration capabilities. This field is studied and understood more fully in cats than in humans. However, both the normal and abnormal nature of these capabilities are essentially unknown and un-characterized at present.

¹⁸²Sundin, O. Yang, J-M. Li, Y. Zhu, D. Hurd, J. Mitchell, T. Silva, E & Maumenee, I. (2001) Genetic basis of total colourblindness among the Pingelapse islanders. *Nature Genetics*, vol. 25(3) pp 289-293

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Similarly, the matrixing properties associated with the dendrites of the ganglion cells are virtually unknown.

18.3.2.1 Criticality of bias levels in stage 2

As seen in the discussion of the color abnormal when tested with an anomaloscope, the fact that the neurons of stages 2 & 3 of vision are directly coupled plays an important part in the abnormalities of vision. If the quiescent voltage at a given point in the signal channel is abnormal, the perceived color capability of the subject may be skewed, and even skewed to the point of total failure of the channel to perform. Abnormal quiescent voltages in the signal channels appear to be the primary source of abnormality in the chromatic response of an individual.

The quiescent voltages associated with a given circuit are functions of the values of the various conductive impedances in the circuit as well as the voltage impressed on the circuit by the previous circuits connected to it. The voltage abnormalities are small and found in high impedance circuits. As a result, the voltages are very sensitive to small abnormalities in the above impedances. These abnormalities appear to be most likely due to questions of growth and in some cases to the viscosity of the surrounding medium to various chemical components used in the electrostenolytic process. The impact of these bias errors will be addressed more fully in **Section 18.5**.

18.3.3 Failures of signal projection in stage 3

All of the signal processing chains in the visual process are inherently the same from a functional perspective except at the input to the ganglion cells. In the luminance channel, there is a hard threshold associated with this element that is not found in the chrominance channels. This threshold prevents the oscillation of the ganglion cell output in the absence of an adequate signal at the input. No action potentials appear at the output of these ganglion cells (nominally the parasol ganglion cells) in the absence of adequate input. The ganglion cells of the chrominance channels are intended to oscillate freely at a nominal rate in the absence of an input signal. This nominal rate is determined by the values of the circuit elements associated with the ganglion cells and the quiescent bias voltage impressed on the ganglion cells from stage 2 cells. Thus these, chrominance related ganglion cells (nominally the midget ganglion cells) produce action potentials constantly that are unrelated to the luminance level applied to the eye.

If the value of the electrical elements associated with the active circuits of either the parasol or midget ganglion cells are inappropriate, these circuits will not oscillate or will oscillate with an inappropriate pulse-to-pulse interval (frequency). Either of these errors can significantly impact the operation of the stellate cells of the brain tasked with decoding these pulse trains. The stellate cells are optimized for a specific range of input pulse intervals.

The bias on the operation of these ganglion cells is a simple electrical one. In the absence of a signal from the stage 2 neurons, it is determined by the difference in voltage generated by the bioenergetic materials associated with the dendritic and poditic neuron elements. Thus, an inappropriate bioenergetic material adjacent to one of these neuron elements can cause an abnormal sensitivity in the affected signal processing channel.

Clearly, inappropriate action by the threshold circuit in the luminance channel can cause a significant change, in either direction, in the overall luminance performance of the eye. Similarly, inappropriate biasing between the emitter and base terminals of the midget ganglion cells can cause inappropriate operation of the chrominance channels.

It appears that the most common biasing failure is due to the improper sizing of the circuit elements of the ganglion cells or the application of an inappropriate quiescent signal from the stage 2 neurons. Both of these errors are ultimately traceable to growth related errors in the values of the electrical circuit elements.

An alternate, pathological, failure mode to the functional failures discussed in **Sections 18.5.1** and **18.5.2** will be discussed in **Section 18.5.3**.

18.3.3.1 Failures of brightness related functions

The primary failure modes related to brightness in stage 3 are due to severe bias irregularities resulting in the introduction of abnormal threshold levels or early saturation with regard to the normal instantaneous dynamic range of the visual system. These limitations in the instantaneous dynamic range are distinct from limitations in the overall visual dynamic range related to the photodetection and signal manipulation functions of the adaptation amplifiers.

18.3.3.2 Failures of chrominance related functions

The failure modes of the two chrominance channels are more complex than those of the single luminance channel. Although the failure modes are generally related, they usually show a first order relationship to either the matching range, MR, and the matching median point, MMP, errors observed in performance testing. Any error in the bias applied to the midget ganglion cells or in their nominal oscillating frequency, or any bias error associated with the quiescent signal recovery value of the stellate cells are reflected in an MMP error. Any error in the signal amplitude applied to the Activa of the ganglion cells or any error in the value of the circuit elements associated with the stellate cells can result in an error in the MR.

18.3.3.2.1 Steady state chrominance channel failures

The simplest error in this region would result in either the P- or Q-channel midget ganglion cell encoding the bipolar signal it receives from stage 2 as a monopolar signal. The signal recovered by the stellate cells would look exactly like a monopolar signal received from the R-channel. The available data suggests the polarity of the signals delivered to the midget ganglion cells are not random or equally divided with respect to polarity. All of the available data suggests they are deterministic. Encoding the P- or Q-channel signals as if they were R-signals would result in a loss in the perception of S- or L-channel signals, i. e., tetartanomalia or deutranomalia, and could be observed as a large MMP error. If a larger bias error were involved, it could force the midget ganglion cells to not oscillate at all. This action would result in failure of the stellate cells to recover any signal. The result would be complete tetartanopia or deutanopia.

The data published by Lakowski suggests the above errors causing observable MR and MMP abnormalities are equally likely.

18.3.3.2.2 Transient chrominance channel asymmetries

There are a number of design artifacts of the projection subsystem, stage 3, that are more useful to magicians than to clinicians. These can be documented according to their origin in the visual system. Whereas, the longer term anomalies of color were found associated with stage, 0, most of the short term anomalies associated with color are created by the signal projection neurons of stage 3. They are created due to the asymmetrical modulation scheme used in the chrominance channels, levels 12, 13, 14 & 16. They are first noticeable and recordable at levels 14 & 16.

The primary asymmetry results in the transient response associated with shorter pulse-to-pulse intervals exhibiting a shorter time constant at the output of the stellate cells than the transient response associated with longer pulse-to-pulse intervals. In general, this means that the initial sensations of blue and red are delayed relative to the green colors. These delays are easily demonstrated with various rotating wheels and shuttering mechanisms.

18.3.3.3 Pathological failures of optic nerve due to glioma

Figure 18.3.3-1 presents a caricature of the optic nerve in cross section. The vertical orientation of the contents of the nerve is presently unknown. In a recent case, a glioma formed on the nerve and caused the blockage of all chrominance signal paths from the eye to the paleo-cortex.

18.3.4 Failures of the Prepectum, LGN and Cortex, stage 4

Failures of the prepectum related to the servomechanisms of the visual system were addressed in **Section 18.2.3**. However, this element plays an additional role supporting the higher perceptual and cognitive processes along with the LGN and the cortex itself.

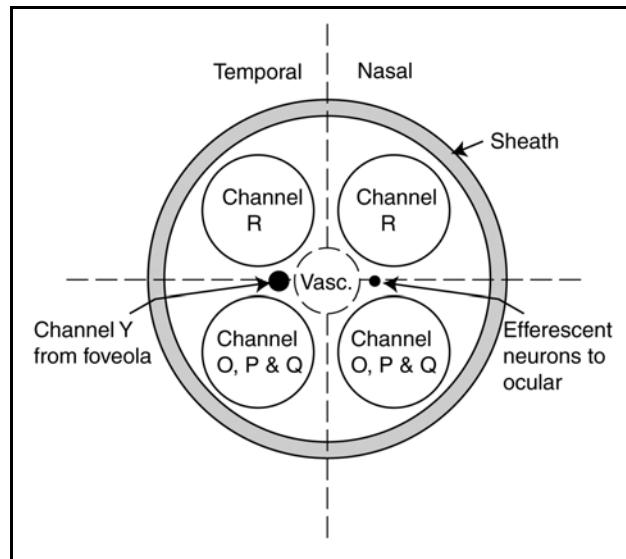


Figure 18.3.3-1 Cross section of optic nerve in caricature. The area of the channel Y bundle is estimated at two percent of the cross section devoted to neurons. The relative size of the efferent neurons is trivial. The role of the O channel is also trivial in humans. The relative size of the other bundles is unknown. The center of the nerve is shown devoted to the vascular system.

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The plan for this work was to stop short of exploring the role of the cortex in vision. However, the complete definition of the signal paths of vision led to new interpretations of some of the relevant literature. This activity led in turn to some isolation of failure modes within the cortex. The principal finding was that there were two primary entry points for visual signals into the cortex and not just the one usually recognized. *The signals from the Pretectum to Area 5, over the pulvinar pathway, are at least as important as the signals from the LGN to Area 17 over the optic radiation.* The designation of Area 17 as the primary visual cortex, V1, is probably poorly founded.

One of the most important sources, of efferent signals leaving the cortex is Area 7 (sometimes defined more specifically as Area 7a). This area contains a number of command generation engines that receive input from the higher cognitive centers of the frontal lobe as well as inputs from both Area 5 and signals originating in Area 17. The signals from Area 5 appear to be of higher entropy than those from Area 17.

The discussion of failures within the Pretectum, LGN and Cortex become awkward if the terminology is not well defined. For purposes of this Section, signals originating in the Pretectum and the LGN that proceed to the cortex will be considered efferent signals along with those originating in the frontal lobe of the cortex. In this sense, the command generation engines associated with Areas 7, 7a and similar areas, are collection and signal manipulation points for efferent commands from these other sites. In the case of vision, commands from Area 7 proceed back to Superior Colliculus, possibly via the thalamus, for further processing and execution.

The above framework allows a more definitive assignment of different failure modes to specific elements of the visual system. Failure modes can be assigned to the efferent signal paths involving the cognitive system of the frontal lobe, the Pretectum of the POS, and to the LGN and the elements of the occipital lobe. These failures are all associated with the clinical term nystagmus. A wide variety of adjectives are associated with this basic term. Some of these will be discussed explicitly in the following sections.

18.3.4.1 Failures of the Pretectum and pulvinar pathway to the precision optical loop

These failures are characterized by their relationship to the scene projected on the foveola. They include failures in the signal demodulation function of the inner servomechanism of vision as well as failures along the pulvinar pathway and failures in the feature extraction engines of stage 4, the loading of the saliency map at the output of stage 4 and possibly the saliency map itself, thought to be found in Brodmann's Area 5. **Section 15.2.5** describes these engines from the performance perspective.

18.3.4.1.1 Prosopagnosia – the Grandmother syndrome

A significant failure in stage 4 has long been labeled the grandmother syndrome in clinical medicine. It is currently described (loosely) as prosopagnosia, the inability to recognize faces. In fact, it is the inability to recognize faces in the broad sense of the image of virtually any object, including photographic images of objects.

The condition illustrates a failure in the high acuity information extraction overlay of the PGN/pulvinar couple on the lower acuity LGN/occipital lobe couple within stage 4 (See **Section 2.8.1** & xxx) The loss of part or all of the PGN/pulvinar couple signal path eliminates the ability of the subject to recognize fine details in their foveola without causing a total loss of vision in this region. As a result, a complete (holistic) perception is not presented to the stage 5 cognitive engines. **Section 19.10.4** addresses this disease in greater detail.

Documentation of this syndrome is fairly broad within the psychological testing literature. No other *explanation* of this syndrome has been found in the literature.

18.3.4.1.2 Temporary Prosopagnosia – Loss of visual acuity

The author (age 80) has also encountered a problem apparently associated with awakening in the morning. I can **not** read a newspaper for a period of about five minutes some 15 minutes after arising, even while wearing my normal reading glasses and with good lighting. I can still read major headlines but virtually nothing in the left hand column of the front page (titled "What's News") and the text on the rest of the page of the Wall Street Journal. After this interval, my acuity returns to my normal situation where it appears to remain throughout the day. This condition occurs before breakfast or ingestion of any medication. It seems to occur a few times a month.

The problem only relates to "Central visual acuity; the relatively small but vital part of the visual field used for reading. It is the visual field associated with the foveola, the 1.2 degree diameter area surrounding the point of fixation, and the associated elements of the Precision Optical System (POS) including the PGN/pulvinar couple. It appears to apply to both eyes simultaneously and equally. I attribute this loss of short term visual acuity to the

interruption of the tremor associated with the corneal muscles probably due to a failure in the Precision Optical System (POS, **Section 11.6.3 & 11.6.4** and **Sections 7.3.3.5 & 7.3.6**). The result is a loss in acuity from the maximum acuity of provided by the PGN/pulvinar couple of **Figure 7.4.5-1** to the lower value associated with the LGN/occipital couple.

There are a variety of anecdotal citations in the literature to the effect the geriatric physiological system may not all “awaken” simultaneously. The above seems to constitute one of those anecdotes. In this case, the PGN/pulvinar couple and other elements of the POS fail to operate properly for a short period. There is no difficulty in perceiving objects at the acuity of the adjacent peripheral retina during this interval.

18.3.4.2 Failures of the LGN and optic radiation through V1, V2 etc.

These failures are characterized by their relationship to the scene projected onto the retina external to the foveola. They relate particularly to the threat evaluation task and the other tasks associated with the general awareness of the visual situation of the animal. They also appear to be involved in the tracking of continually moving objects in the scene.

Meadows has provided an extensive clinical report on patients suffering color abnormalities from various conditions related to the occipital lobes¹⁸³.

18.3.4.3 Failures originating in the frontal lobe of the cortex

These failures related to vision are failures of the conscious will of the subject. His inability to command the eyes to point in a given direction in the absence of changes in the scene is a typical case. Pursuit nystagmus and optokinetic nystagmus are related to this situation and possibly that of Section 18.6.2.

18.3.4.4 Failures of efferent elements beyond Area 7

A failure in the efferent pathway beyond Area 7 can be serious. Such a failure affects the entire operation of the oculomotor sub-system. Such a failure can affect conscious eye movements as well as autonomous movements. Both position errors and velocity errors are common. Under the worst pathological conditions, the closed loop function of the POS is lost and the motions of the eyes are basically uncontrolled. The Tectum generates commands in response to noise in the system as opposed to efferent commands from Area 7 and signals derived from decoding in the Pretectum (via the DTN, LTN & MTN's) and /or LGN.

18.4 The blue-dot syndrome

A “blue dot” syndrome has been identified in the literature, primarily at the anecdotal level. The author has encountered this syndrome under two related conditions. In one case the dots have been encountered upon awakening as isolated dots spread across the entire perceived field of view as a sparse array. In a recent occurrence, the perception was quite different. The author observed an array of toroids adjacent to each other and filling the complete perceived field of view.

On two recent occasions (Sept 2016), the sparse blue dot array perceived on awakening did not include the nominal 1.2 degree diameter foveola. No explanation for this change in perception has been developed.

In both cases, the natural out door illumination was at the level of local astronomical sunrise. In the bedroom, the light level was at the low end of the photopic range. The saturated color of the bedroom walls was observed upon opening the eyes.

18.4.1 The observed toroids upon awakening but before opening the eyes

The author recently encountered a perceptual phenomenon upon awakening for the first time. It lasted only a few to 10 seconds maximum. It consisted of a large number of translucent toroids adjacent to each other and appearing to occupy the entire visual field. The toroids were all of the same size across the field. They were estimated to be equivalent to 0.25 degrees outside diameter objects if present at or near the point of regard within the foveola. The inside perceived diameter was about 0.15 degrees. A zone of each translucent torus was occupied by a brighter,

¹⁸³Meadows, J. (1974) Disturbed perception of colours associated with localized cerebral lesions *Brain* vol 97, pp 615-632

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sharply defined region of about 30 degrees arc angle. It was not possible to define this phenomenon in greater detail before it faded away.

18.4.2 The finite size blue dots seen before opening one's eyes in the morning EDIT

The author has infrequently observed a full field of distinctive blue dots scattered across the entire perceived field of view under the light conditions described above. The dots appear to be stationary during the few seconds they are typically perceived before fading away. In the absence of other imagery (see above section), it is difficult to estimate the size and relative position of the blue dots. They definitely appear to constitute a sparse array but no pattern to the array has been recognized. Based on the above section, the individual dots can be estimated to be about 0.05 degrees in diameter in the area of the point of regard (the center of the most high resolution portion of the visual field of view).

18.5 Medically identified organic (non-psychotic) failures within the CNS

18.5.1 Visual Snow EDIT

The papers by Relja et al., Chen et al., and Liu et al. cited in the Aura Section incorporate examples of patients exhibiting snowy vision for an extended period of time. They did not uncover any apparent cause of snowy vision after extensive testing on a variety of patients.

Snowy vision has been associated with migraine headaches and the use of a variety of hallucinogenic drugs. It appears to occur in at least two distinct forms. In the first, the subject observes relatively widely scattered small dark dots against a uniform background. The dots are of significant amplitude, occupy the major part of the visual field, and the density of the dots is relatively uniform. This symptom will be labeled pulse type snowy vision. In the second form, the field of view appears to be observed through a semi-transparent film on which there is noise reminiscent of the screen of a TV set tuned to an empty channel. This noise is of relatively low amplitude and consists of both white going and black going noise pulses that are very close together and of varying amplitude. The result is a perception of the scene in object space being observed through a low contrast noisy semi-transparent film. This symptom will be labeled broadband snowy vision. In broadband snowy vision, the subject frequently reports the noise is not uniform over his field of view although it is still observed over the full field of view. **Figure 18.5.1-1** presents caricatures of these two situations. The left frame is an interpretation of what some sufferers of snowy vision have described to this author. Note that no white dots appear within the black space. The right frame is an interpretation of what others have described. The art for this figure is taken from a comprehensive study comparing noise performance of human vision and television techniques in 1977¹⁸⁴. Notice the apparent variable size noise elements, and the formation of distinctive shapes within the broadband noise in the right frame.

¹⁸⁴Rose. A. (1977) Vision: Human versus Electronic in Barlow, H. & Fatt, P. Vertebrate Photoreception
NY: Academic Press pp 1-13



Figure 18.5.1-1 Examples of snowy vision based on sufferers' descriptions. Left; noise believed to originate in the pulse circuitry of stage 3 neurons. Pulses are black-going only with an amplitude of about 10% of peak scene contrast under photopic conditions. No white dots appear within the black area. Center; noise believed to originate in the analog circuitry of stage 4 neurons under photopic conditions. Noise is both black-going and white-going with a variable amplitude spectrum. From Rose, 1977. Right; noise similar to the center image but at a different scale. From The Vision Community web page. See text.

In at least two cases, broadband snowy vision has been associated with additional hallucinogenic symptoms associated with the stereopsis system of the visual system.

The gross differences in the characteristics of snowy vision suggests they are two distinct symptoms caused by two different anomalies (diseases).

The websites, www.visionsimulations.com/VisualSnow.htm ,

http://www.thevisioncommunity.com/index.php?option=com_content&task=view&id=78&Itemid=171 -- offers a comprehensive set of simulations of the analog visual snow condition (one of which is shown in the figure). The site allows the viewer to adjust the refresh rate (flicker rate) and the intensity (snow density) of the snow overlay for several scenes. The simulation do not apply to the pulse type of visual snow. They exhibit a much finer noise structure than suggested by the image from Rose. The resulting noise structure may represent sitting further away from the "noisy image television set." There is no ownership information or other attribution associated with its authenticity provided on the site.

- - - -18.8.2.3

[xxx subdivide following into two separate categories as outlined below]
 Snowy vision can be best described as asynchronous uncorrelated spatial noise in the luminance channel. Only one case has surfaced recently where the noise appears in the Q=L-M (red/green) chrominance channel. It has been described by a variety of patients as millions of dots scattered over the entire visual field and rain drops falling within the visual field. The symptom is described as a positive visual phenomenon, a phenomenon that is additive to the normal visual perception.

Patient O. S. has described a disease that has been documented by a similar sufferer, Alison Hale¹⁸⁵. It involves the perpetual presence of excess noise in the perceived imagery of the visual system largely independent of the

¹⁸⁵Liu, G. Volpe, N. & Galetta, S. (2001) Neuro-Ophthalmology. NY: Saunders

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illumination level. Hale has provided simulations and comments on her disease as she understands it¹⁸⁶. Care is required in interpreting the Hale material. She appears to suffer from a variety of individual conditions that She lumps together in ways inconsistent with the medical literature. O. S. has indicated he does not perceive the random spots as having as high a contrast as those in the simulations. This work will reinterpret some of their symptoms and differentiate this syndrome from Irlen's, or Meares-Irlen's, syndrome (**Section 18.8.5.3**).

The condition reported by O.S. is of recent origin in a young man. A. H. on the other hand has apparently had the disease, along with others, since birth.

As noted by A. H., her vision suffers from a number of problems that can be used to describe "Hales syndrome:"

1. It is largely two-dimensional (suggesting a failure shared with the stereopsis subsystem).
2. A very limited field of clear vision corresponding to the foveola (described as extending over only a few characters of text when reading).
3. Difficulty with very high contrast imagery (text appears to move, sometimes violently).
4. Difficulty with striped patterns (they may appear to move or take on a three-dimensional aspect. The latter suggests a functional stereopsis subsystem).

These conditions suggest that Hale's problem is best described as a syndrome of long standing consisting of snowy vision and a number of conditions related to Meares-Irlen syndrome. O. S. has only reported the condition related to snowy vision.

Snowy vision is a disease characterized by a large number of spots of minimal size appearing randomly across the entire visual field under all illumination conditions (including with the eyes closed). The condition has been related to scotopic vision because of the appearance of noise in the perceived image. However, the noise is not related to the noise level associated with the visual system under scotopic light conditions and this label should be discarded.

While Hale has simulated the background noise as black and white, O. S. has described it differently. He indicates the noise is colorless. On a black and white background, it appears as white and black snow not greatly different from that observed on a television set when set to an empty channel. However, on a uniform colored field, it appears as local variations in the intensity of the color, not as a change in color or an overlay of black and white spots.

S. S. has described her snowy vision differently. While describing it as twinkling white dots and uniformly present over her entire field of vision, she also has described the dots as sufficiently widely spaced to note three different conditions. The dots appear randomly dancing about her field of vision. They sometimes form corona like structures that move radially like the opening of the iris of a camera and upon awakening (for just a few seconds and before opening her eyes) they appear to form a uniform grid. The coronal motion aspects may be related to the common aura of **Section 18.8.2.2**.

Most forms of snowy vision appears to be analogous to the simpler (noise based) forms of tinnitus in hearing. Both conditions exhibit a variety of symptoms.

Schankin, Maniyar & Goadsby have recently presented a poster outlining their interests in this area¹⁸⁷. The poster described the;

Background / Purpose:

Visual snow is a disorder with continuous visual symptoms. From our experience and patient input we derived preliminary criteria:

- [A] visual snow;
- [B] at least one of the following: moving objects leave trails, persistent after-images, floaters, bright flashes, little cells that travel on a wiggly path, swirls, clouds or waves with eyes closed, hard time seeing at night, photophobia;
- [C] absence of typical migraine aura;
- [D] not attributed to another disorder. Our objective here was to test the preliminary clinical criteria for visual snow.

¹⁸⁶<http://www.hale.ndo.co.uk/scotopic/>

¹⁸⁷Schankin, C. Maniyar, F. & Goadsby P. (2012) Field-testing the criteria for "visual snow" (positive persistent visual disturbance), 54th American Headache Society Annual Scientific Meeting

Main conclusion:

- (i) Visual snow is almost always associated with at least three symptoms of criterion B.
- (ii) Visual snow represents a unique clinical syndrome. It is distinct from migraine with aura.
- (iii) There is a susceptibility for visual snow in patients with migraine and especially migraine with aura.
- (iv) Intake of illicit drugs and ophthalmological diseases might not be of pathophysiological relevance.

and Next steps:

These criteria can be used to study the mechanism and treatment of visual snow.

The poster is available on line but is difficult to interpret¹⁸⁸. The report is clearly preliminary but in general agreement with the material presented here. The text appears to focus on pulse type noise rather than the broadband form so popular in simulations on the internet. However, the drawings attributed to one patient are clearly of the broadband variety.

A more extensive report on their investigations involving 17 subjects and both MRI and PET scans appeared in 2014¹⁸⁹. Recognizing the resolution limit of these machines, they identify a hypermetabolic disorder of the right lingual gyrus and possibly an area of the anterior lobe of the left cerebellum as likely contributors to visual snow. **Figure 18.5.1-2** shows their results with an abbreviated caption, omitting their careful statistical results. The resolution is far below the level required to determine whether the disease arises among the stage 4 information extraction neurons or the stage 3 signal propagation neurons passing bidirectionally between these specified areas and the thalamic reticular nucleus (TRN) of the thalamus.

¹⁸⁸<http://cdn.f1000.com/posters/docs/250219369>

¹⁸⁹Schankin, C. Maniyar, F. Sprenger, T. Chou, D. Eller, M. & Goadsby, P. (2014) The Relation Between Migraine, Typical Migraine Aura and “Visual Snow” *Headache* pp 957-966

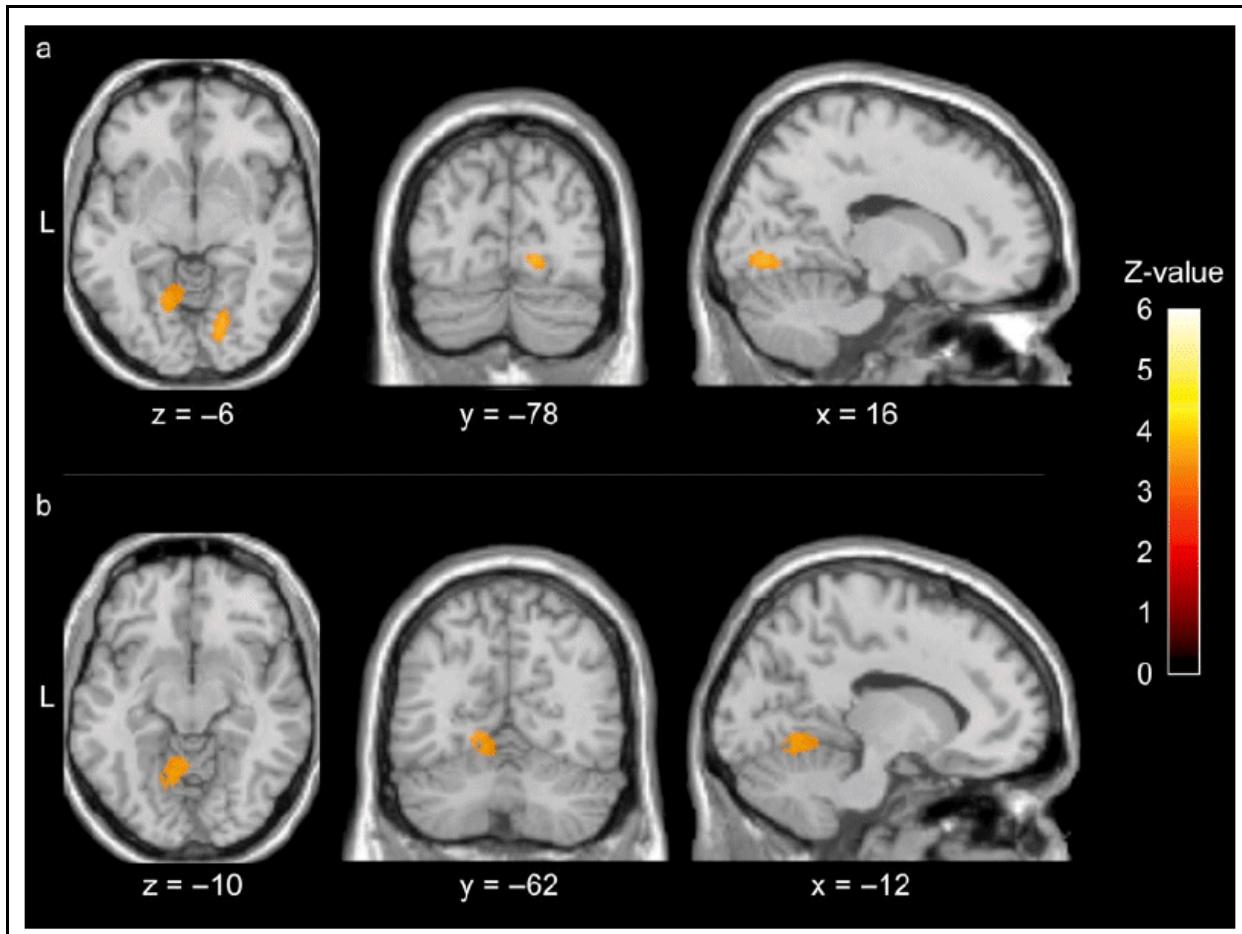


Figure 18.5.1-2 Results of scanning studies on visual snow. a: showing hypermetabolic abnormality in the right lingual gyrus. b; a metabolic abnormality at or near the boundary of the anterior lobe of the left cerebellum. The estimated voxel size for these frames was $2 \times 2 \times 2 \text{ mm}^3$. See the original paper for the statistical study supporting these findings and an explanation of the coordinates. A Z-value of 4-5 does not indicate a major anomaly in metabolism in these areas. From Schankin et al., 2014

One of their major conclusions is, “This first objective correlate of VS strongly suggests the VS syndrome is a neurological condition.” They also conclude, “VS is thus a syndrome distinct from migraine, although the hyperperfusion of this area during migrainous photophobia indicates a potential pathophysiological overlap of both conditions and possibly reflects the perpetuation of the additional visual symptoms in VS patients by comorbid migraine.”

The Schankin team won the 2014 Wolff Award presented by the American Headache Society since 1996. It is presented for the best manuscript submitted during the calendar year before their midyear convention.

The limited resolution of their state of the art MRI and PET was approximately $2 \times 2 \times 2 \text{ mm}^3$. As a result, each of the indicated areas in the imagery consist of only a few resolution elements in either the horizontal or vertical dimensions. The thickness of the neural tissue in these areas is on the order of xxx, less than xxx of a voxel linear dimension. The soma of a typical individual neuron can be considered to be 10 microns in diameter in any direction. Thus, the individual voxel would contain on the order of 8 million neurons if the neurons were present throughout a volume. In fact, the number of neurons per voxel is much lower, but still a large number, because of the thinness of the folded neural sheet.

18.5.1.1 Symptoms of pulse type snowy vision

A rare disease has been reported that causes the visual field to be obscured by high frequency noise (very fine dots appearing widely spaced and at random positions over the field of view) under all conditions of illumination (including with the eyes closed in the dark).

Visual snow of the pulse type is best interpreted as a high quality image examined by looking at it through the window frame in one of the images on the left above.

Most of the subjects have reported the noise appears to be a veil in a plane in front of, but near, the actual image. Sometimes this plane is discontinuous, giving a stereographic effect. Only a very few subjects have defined any color aspect to the snow.

The symptoms of pulse type visual snow appear to include:

- The noise is seen as very fine asynchronous dots scattered randomly across the field of view. They do not clump in order to form larger dots.
 - The dots take on the color of their background.
 - The dots are not intrinsically black and white nor do they exhibit a color shift relative to the background.
- O. S. reports the contrast associated with the noise spikes is less than that displayed in the simulations of Hale. He used the term 80% transmissibility to describe the mask associated with the noise. Alternately, the dots appear to have a peak amplitude of about 20% of the scene contrast.

The signal associated with the noise is monopolar. It can occur in either of two polarities. In the case of the "BLACK" pulse noise, the dots are always darker than the scene they obscure. In the case of the "WHITE" pulse noise, the dots are always lighter than the scene they obscure. The "WHITE" pulse noise is most prominent under low light conditions (mesotopic and scotopic conditions).

Recently two subjects reported a *different type* of pulse type noise in their visual field. CB of Baltimore, MD asked on the FACEBOOK Visual Snow page, "Does anyone have a black dot that flashes in your vision for a few seconds and disappears (not a floater)! I wouldn't even notice my VS anymore except this thing is always super alarming and reminds me of my eye troubles. Some days it doesn't happen at all, some days it happens multiple times an hour." GT responded, "Yes, is yours always in the same place or do you get different ones? I had one last for two months, a little tiny dot in my left eye above the focal point. It would be there for a second when I blinked or if I went from looking at a dark surface to a bright one. I was worried that it was permanent and I started to accept it and then it went away."

18.5.1.2 Sources of pulse type snowy vision EDIT

[xxx asynchronous spatially uncorrelated hallucinations

Figure 18.5.1-3 presents an attempt to localize the problem of pulse type snowy vision. Based on Hale, the snowy vision disease does not affect her vision related to the foveola. This would rule out a problem in the path labeled [Y] in this figure. However, the path labeled [R] is a prime suspect. Problems in this path could generate the noise perceived as snow as the signals are passed to the right from the magnocellular portion of the LGN. Errors in this path, or in the magnocellular LGN could also affect stereopsis as suggested by the dashed line leaving the magnocellular region and proceeding to the superior colliculus. The details of the version servomechanism that includes this path are discussed in **Section 7.3 & 7.4**.

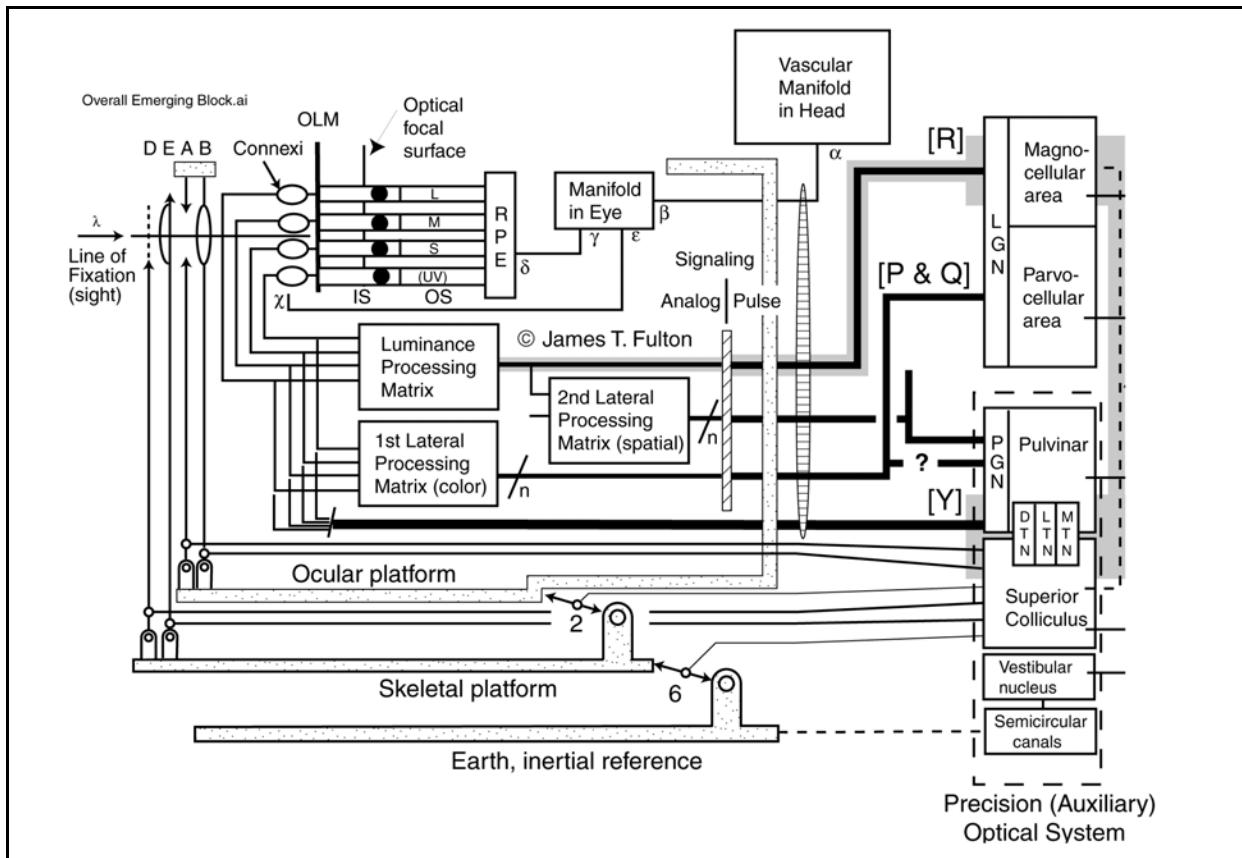


Figure 18.5.1-3 Error sources associated with the snowy vision Syndrome EDIT.

[xxx note difference in notation between [Y] and G' in the two figures]

The primary source of the origin of snowy vision can be localized further using **Figure 18.5.1-4**. The goal is to locate the earliest potential source of the noise component perceived by the subject. In the previous figure, the earliest potential source is in the 1st luminance matrix. This matrix is formed by the bipolar cell and the parasol ganglion cell of the R-channel. These two circuits very likely contain the source of the snowy noise disease. The character of this noise suggests it is caused by individual action potentials generated largely independent of any signal from the photoreceptor cells (whether due to light stimuli or with the eyes closed at night). The unitary nature of the action potentials is suggested by the spatial fineness of the perceived noise. If the phenomenon was due to a series of action potentials, the perceived spots would be at least elongated in one dimension. Individual extraneous action potentials would not be expected to cause saturated swings between a light level and a dark level. This perception of a lower contrast interfering noise is the situation reported by O. S.

There are four easily defined sources of extraneous action potentials involving the bipolar and parasol cells. An unusual value of capacitance associated with the bipolar cell is known to cause oscillation in the laboratory. Such oscillations would not be synchronous with the oculomotor system and the perceived noise from a single cell would therefore appear to move randomly over a small field within the overall field of view.

In the case of the parasol ganglion cell, there are three feasible sources. The easiest source to contemplate would be a bias error that tended to convert the normally driven parasol ganglion cell into a normally free-running (but slow) ganglion cell similar to its midget ganglion cell counterparts. Such a bias error would introduce a grouping of the perceived noise near the “leading edge” of contrast edges and a paucity of the perceived noise on the trailing edge due to the normal refractory period of such an oscillator. While this phenomenon has not been reported, neither was the subject asked about such a possibility. More experiments may be appropriate. A second possibility is that an unbypassed noise current is introduced into either the dendritic or poditic circuits. These are suggested by the elements labeled i_{en} and i_{pn} . The parasol cell is particularly sensitive to a current type of noise source in the poditic circuit. Since it is clear that the observed phenomenon can occur following normal vision of long duration, it appears likely that the disease is brought on by a chemical or hydraulic imbalance related to the electrostenolytic

supplies to the dendroplasm or the podaplasma. A genetic or developmental cause cannot be supported based on the experience of O. S. An electrical leakage path could be associated with any transition between type 1 and type 2 BLM as well as with the electrostenolytic mechanism itself. This chemical or hydraulic imbalance would be localized to the layers of the retina closest to the vitreous humor of the eye.

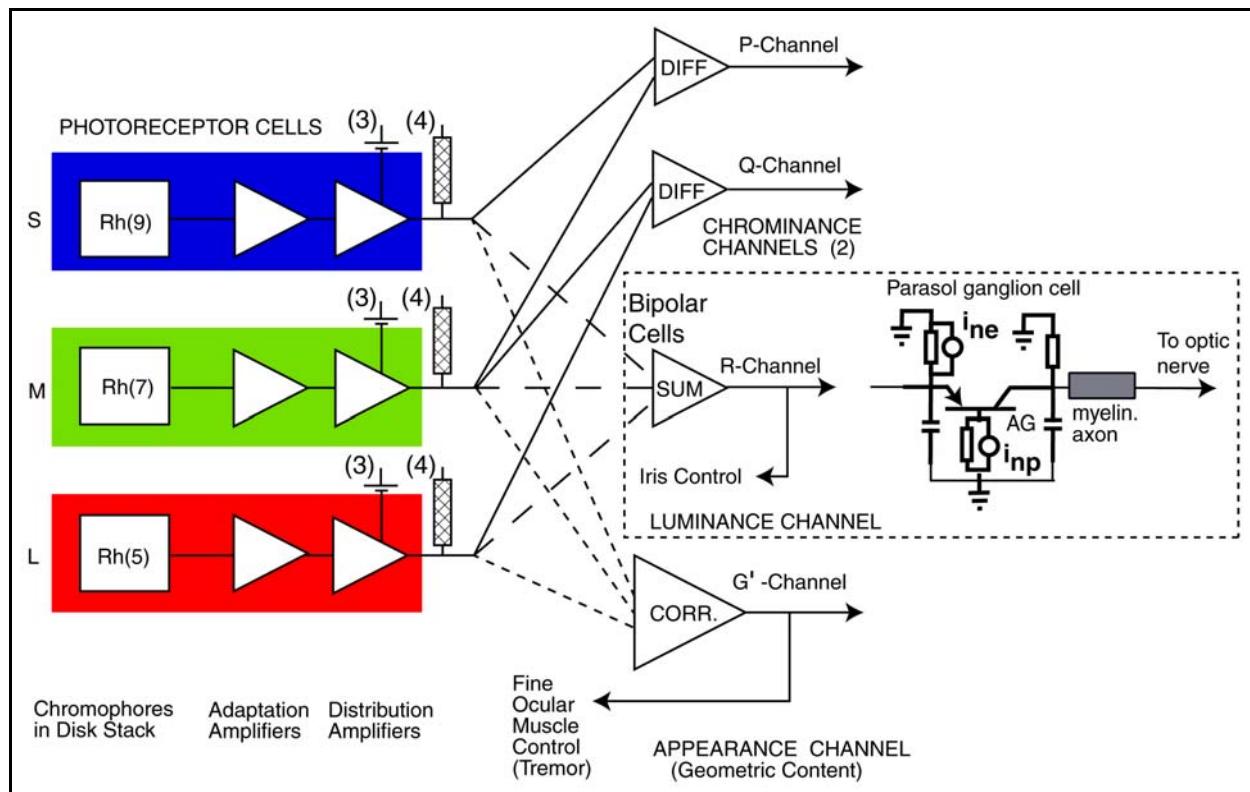


Figure 18.5.1-4 Potential error sources leading to snowy noise. Extraneous action potentials in the R-channel can occur due to parasitic oscillations in the bipolar cell or inappropriate oscillations in the parasol ganglion cells. See text.

If the source of the extraneous signal was farther to the left in this figure than discussed above, the perceived noise would be more complex. Any signal originating in the photoreceptor cells would be passed to both the P- and Q-channels as well as the R-channel. This would cause the snow to be perceived as changing the color as well as changing the luminance of the local image associated with those photoreceptor cells. This condition has not been reported. A source of extraneous action potentials within the bipolar or parasol cells would be passed to the magnocellular portion of the LGN and could interfere with the stereopsis signals extracted by that element and passed to the superior colliculus along the shaded path in [Figure 18.8.2-1]. A further discussion of problems related to stereopsis can best be associated with “Hale’s syndrome” and not with the snowy noise disease *per se*.

The visual snow syndrome is commonly found in patients suffering from HPPD (Hallucinogen Persisting Perception Disorder). Although the source of visual snow is frequently attributed to the retina, more careful research shows it to be more related to tinnitus and migraine headaches.

The intermittent appearance of a small black dot at a fixed point in the central visual field, frequently pulsating at frequencies on the order of a few cycles per minute (as reported by CB and GT) are highly suggestive of a signaling error in one of the direct neural paths from a single, or very few adjacent, photoreceptors within the foveola of one eye to the PGN of the diencephalon. The temporal cycle would suggest the photoreceptors may not be receiving adequate fuel, in the form of glutamic acid, to operate the photoreceptors in a normal manner. The condition is reminiscent of “motor-boating” in an electrical amplifier; where the amplifier begins generating intermittent pulse amplitude sounds unrelated to the input stimulus but frequently beginning after significant changes in the amplitude of the stimulus.

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18.5.1.3 “Blue dots,” an obscure potential source of snowy vision

The author occasionally encounters a visual perception that may relate to the underlying mechanism responsible for snowy vision. Upon awakening in a dimly lit room, he perceives an array of blue dots on a black or gray background with his eyes closed. The dots are always definitively blue. The perception lasts for on the order of ten seconds and cannot be recalled. The array appears to be equally spaced across the visiotopic field. The individual dots appear to be larger than a single resolution element and the space between dots appears to be between ten and 20 times the diameter of the dots. The array is perceived as stationary in position. The dots of the array do not exhibit any rectilinear, hexagonal or other obvious pattern. The pattern may relate to or underlay the phenomenon of pulse type snowy vision. The equal spacing of the dots across the visiotopic field suggests their origin is not in the retina where a retinotopic organization would be expected. There is no indication of a fovea or foveola in the perceived dot pattern.

18.5.1.4 Source of the entoptic blue field phenomenon

A phenomenon labeled the entoptic blue field phenomenon has frequently been associated with visual snow. In fact, it is a totally unrelated phenomenon associated with the blood flow within the small arterioles of the neural layers of each retina. The phenomenon is described as exhibiting very fine worm like structures following frequently curving paths for only short periods of time. The phenomenon is due to white blood cells, and possibly other transparent regions of plasma flowing through the arterioles. Since these paths are in the optical path of light from the lens, any unusual flow conditions in the arterioles appear as shadowy objects due to the shadow they produce on the photoreceptor array.

This phenomenon is best observed while looking at a very low color saturation field such as the open sky on a clear day, or any similar pale blue, azure or lime green surface. The surface need not be blue.

18.5.1.5 Symptoms of broadband snowy vision

Hale has summarized the broadband form of the disease within her larger syndrome quite carefully. The symptoms of the disease include the following:

- The perpetual presence of excess noise in the perceived imagery of the visual system largely independent of the illumination level but directly linked to the contrast of the scene.
- The noise appears to be spread evenly across the visual field with one possible (and if verified, important exception). Hale has reported in one instance that the noise is absent from the area of her field of view represented by her foveola.
- The signal associated with the dots is bipolar. Dark spots are observed in light areas and light spots are observed in dark areas of the scene.
- The dots are variable in size as illustrated on the right above.
- As will be developed below, the broadband type of noise she describes under the title "scotopic sensitivity syndrome" appears to be closely linked to the same mechanism, but possibly not the same source as the noise in scotopic vision.

A. H. has confirmed that she sees dark spots when observing a light screen and light spots when observing a dark screen. The spots are of variable size. This bipolar noise is significantly different from the monopolar noise (dark spots on a light background, but not vice versa) observed by O. S. and others. It appears to be a broadband noise of the type described by Rose in an earlier figure. The bipolar noise is suggestive of an error in the circuitry of either stage 3 or stage 4 neurons. The stage 3 error would be related to the stellate cells recovering the analog information in stage 3 delivered encoded on a stream of phasic action potentials. A stage 4 error would be associated with the circuits immediately following the stellate cells. The uniformity of the noise across the field of view suggests a source within the retinotopic portion of the visual system. It is likely that it arises in the cells of the LGN and PGN.

The eight year old daughter of S. S. has recently complained of colored sparkles not unlike the appearance of a television tuned to an unoccupied channel. The sparkles are quite small, occupy her field of view uniformly and are most apparent when her eyes are not being illuminated from an external source. The perceived colors are dominated by reds and greens. This appears to be a clear example of random noise entering the Q-channel signal processing due to a bias error affecting a yet unknown number of neurons.

The uniformity of the snow across the field of view for these two patients suggests the noise enters the system after the merging of the signatures from the two retinas within the LGNs. The perception of the snow appears to be occurring before the extraction of information from the scene as occurs in the occipital lobes. For both A. H. and the

young daughter, it is likely the noise is entering the system at the input terminals of stage 3 encoding neurons or at the output of the stage 3 decoding neurons in the pathway between the LGN and the occipital lobes. Such noise would be associated with the Awareness Mode of vision. Based on the independent layering of the LGN to accommodate the different signaling channels, a single point error associated with the permeability of one of these layers could cause noise to appear in either the luminance, R-channel, or one of the chrominance channels, O-, P- or Q-. Such an error would typically affect the entire left or right hemisphere of the visual field. However, it is difficult to see how the entire visual field could be impacted by such a single point error.

M. M-G. has reported a nominal form of broadband snowy vision with predominantly white spots associated with a white veil covering his entire field of view all of the time regardless of whether either eye is open or not. His condition appeared about 13 years ago at the age of 17. His situation continues to suggest ingestion of a hallucinogenic drug at a time when he also encountered a condition he labeled "depersonalization."

18.5.1.6 Symptoms of “color” snowy vision

A small percentage of those reporting snowy vision described theirs as colored snow. A discussion of one of these reports follows:

Your description is quite complete. Your situation is only atypical in that the dots appear in (more or less) random color. The majority of sufferers report only black and white "snow."

It would be useful if you could describe the color of the individual dots. I realize they are likely to be small and difficult to identify. A key question is can you describe any of the dots as yellow? Are any of the dots described as orange? Are any of the dots identifiable as blue? I will assume some of the dots appear red and some appear green unless you tell me otherwise. These questions are listed in order of importance and tell much about the location of the origin of the condition, in the cerebral cortex or new brain, the middle brain or the retina.

On your questions, I've tried very hard to actually distinguish colours, I would say the overall hue is blue, concentrating on the dots I don't see any standout orange, or green at all (pity, it's my favorite colour), maybe a little red, but basically blue dots with 'star' like twinkles of bright white/yellow through it.

I remember in my younger days staring at the sky looking for falling stars, I look up now and my eye's are darting all over the place due to the star like twinkles in between the other snow.

18.5.1.7 Complete patient reports on the snowy vision condition

18.5.1.7.1 The report of T. Y. of England

T. Y. of England has provided a detailed report after observing the Snowy Vision test on the Internet. Highlights of their results are the vertical orientation of the pattern and the “vortex” which suggests a delineation between the peripheral retina and the fovea (not necessarily of the foveola). The observation of the circles turning into polygons of 10-12 sides after a few seconds viewing is a new response.

Question 1: Yes, either dense and falling (rushing) down or less dense, brighter and rising like bubbles in a fizzy drink, depending on how I focus.

Question 2: No, at least not really- more grey, but the drift is up, down, up, down etc., steady and with a pronounced frequency of change.

Question 3: 10 (rushing down), 0 or maybe brighter (bubbles rising).

Question 4a: Yes, but because the "snow" blends in with light targets more than dark targets.

Question 4b: Darker.

Question 5a: lower. If I look at the circles too long (more than 3 or 4 secs.) they become concentric polygons (12 or so sided).

Question 5b: yes. Outside the circles looks grey whilst inside the circles are white. From 30 inches away from the screen the inside circle is bright white and the outside circle looks grey (a bit lighter than swatch 10 earlier), whilst outside both of them looks halfway in between.

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Question 6: <1, however I don't see black dots, except flashes.

Question 7a: Lower (slightly)

Question 7b: No (the circles turn into polygons again after 3-4 seconds)

Question 8: <1 (much, much smaller than 1 (say one pixel on my LCD from 30" away, but drifting about).

Many thanks, I hope these results help in some way! I have to say I have never considered this (the "broadband" snow) to be a disease or syndrome, always assumed everyone saw the same thing, whatever it is. I know at least two of my friends do. I wear glasses (-2.75 and -3.5 in L and R eyes respectively).

I also occasionally see flashes of phosphorescent colour (pixel sized and red, purple, orange, blue, sometimes (but very rarely) green, mostly in the dark (this I would imagine comes under "pulse" snowy vision). I imagine these static flashes can be put down to simple retinal misfiring.

In addition to broadband and pulse snow I get a "vortex" at times in the centre of my vision, like ripples moving over water except segmented, usually when staring at the sky in daytime- this I had put down as a pressure generated artefact of the eye, leaving only the broadband snowy vision without an explanation. I would say from memory the vortex is about twice size of my thumbnail at arms length.

Cheers,

Teyen Widdicombe, England.

18.5.1.7.2 The report of S. H. of Finland

S. H. was born about 1982 and responded to the Internet survey belatedly in 2015. However, his report was quite detailed and useful. His answers to the questions were nominal. However, his comments were extraordinarily detailed.

"I've always thought the dots were a violet-reddish color, but according to these tests they are very light gray (or "white"). It may be there are multiple sets of dots active, layered on top of each other. I practice meditation and the dots start to make all kinds of distractions very quickly, forming shapes and forms and spinning around like in a giant wheel centered at where the eyes are focused. Deep meditative breathing makes a light show appear after a while.

I had a pretty hard hit on the back of my head when I was about 10 years old, it was hard enough that I couldn't breathe in or out for a while (a minute? very hard to say) and thought I was going to choke right there. You list recreational drugs that I used to take as a slightly older kid. Mostly MDMA (though who knows what was mixed in those pills) and some cannabis. I only took ecstasy a few times and usually overdosed. Especially the first time was pretty bad and I probably came pretty close to dying. I took LSD once and stopped using drugs after that.

Finally you listed antibiotics as a possible culprit. When I was about 19-20 years old and used to smoke cigarettes, there was a winter where I had all sorts of illnesses and fevers. I took antibiotics four times over the winter and have since had at least problems with my digestion."

A follow-up conversation (23 July 2015) was even more illuminating. He made several references to a coin-sized area centered on his point of fixation that corresponds quite well with the 1.2 degree diameter foveola of this work. He identified at least five perceived patterns he had observed at various times. The number three was used to identify two distinctly different patterns. My interpretation of the message was,

1. TV like noise appearing uniformly across the perceived visual field is not normally observed by normal subjects at light levels above twilight conditions. The amplitude of such noise is below the threshold of perception and may even be removed by clipping of the signal level at low levels within the visual modality.
2. Your autonomously moving sun spots or bright lights making stains and swirling in toward the edges of your coin-sized area (and swirling in a different direction and rate within that area) appear to be a type of aura associated with ripples in the flow of blood plasma within an area representing the full field of view (except within the coin-sized area). These apparitions could be due to inconsistent blood plasma associated with the left and right

posterior cerebral arteries (normally separate branches serve the left and right fields of view). The pattern observed within the coin-sized area is likely to be totally separate but also due to inconsistencies in the arterial blood plasma flow.

3a. Your “weird blind spot” is in fact, the precise geometric area of your coin-sized area recovering from a period of exposure to bright light. You are observing the “dark adaptation process” that occurs after you remove the stimulation and close your eyes. The coin-sized area appears dark purple which is the complement of the dominant color of the mid-wavelength photoreceptors of the eye centered on 532 nanometers (a green). It is a manifestation of the signal processing in what I call the P-channel of the visual modality.

3b. Your description of a veil consisting of a uniform field resembling a cloth printed uniformly with size 1 printed polka-dots is frequently reported by others but without the rotational or swirling aspect that you infrequently encounter while doing your meditations “It still takes me about an hour of meditation to see it clearly and that's when they start to make shapes like tunnels or two rotating planes with something that looks like a hurricane connecting them.” Your assertion that, “When reaching a state where the hallucinogenic forms start to appear, I also sometimes get other bodily reactions like cold sweat or sudden palpitation,” is quite useful but will require more study to understand.

4. The “entopic (i.e., of unknown origin in medical nomenclature) blue field, does not appear to be directly related to visual snow. It appears to be a phenomenon relate to an internal calibration mechanism within the visual modality. I only observe it prior to arising in the morning (typically with my eyes still closed but mentally alert). Like you, I am unable to recall the phenomenon.

5. After images (and the closely related trailing images) are distinctly different phenomena than visual snow. They are typically considered under the label aura.

The symptoms of S. H. remain most easily described with respect to variations in the porosity of, and short term rates of blood plasma flow in, local areas of the neural tissue of the CNS. To involve both the foveola and the peripheral retina, and to be represented uniformly across the visual field, the disease is most likely focused in the thalamus or areas of the saliency map describing the external environment.

18.5.1.7.3 The author’s transient encounter with visual snow

On 31 January, 2015, the author (79 years old) arose from sleep around 4:00 am to use the toilet. As usual, he proceeded to the bathroom door (about 15 feet) without turning any light on. He then turned on an indirect light source in the ceiling while keeping his left eye closed to maintain its dark adaptation. After approaching the urinal, the author observed a brief period (not over 5 seconds) during which he perceived a fine noise combined with the normal imagery associated with that location. The noise was colorless and probably of the “pink noise” variety with a frequency spectrum rising with spatial frequency. No obvious low frequency components were noted. The noise covered the entire visual field uniformly as best as could be determined during the brief encounter. An attempt to repeat the experiment one hour later before sunrise was unsuccessful. This has been the only encounter with visual snow by this author. The author was experiencing his long term average level of tinnitus at the time.

The author has experienced periods of “light headed-ness” upon rising to a standing position for many years. The condition has been informally associated with low blood pressure in an unknown area of the CNS in spite of repeated examinations of the blood flow in the carotid arteries over the years by both palpitation and the use of echocardiogram techniques. The duration of this visual snow event is compatible with these periods of light headedness.

18.5.1.8 Results of a internet based survey of Visual Snow sufferers

See Visual Snow Analyses folder on computer.

On 9 October 2013, a note was posted on the VS group on Facebook by D.C. noting the complete cessation of his visual snow experience as well as his perceived tinnitus. No specifics were provided at that time and a followup effort is under way. His initial response was very enlightening;

“yes I did increase my dose of Xanax’s! I did taper off for the summer months I up my dose to .5 mg I take 2 mg a day! It seems to be only thing that works from me focusing on the tinnitus and VS I do how ever know that the Scotoma’s really come out more often when I very stressed of over work my self..All I know is it was like a peace of heaven to have it go away just for 24 hr’s. If I can help in anyway to get to the bottom of this

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feel free to ask me anymore questions as well. It does play a genetic role my mother and grandmother have it as well!

I forgot to note I do have a very small Cyst in the ninth region of the brain bowing a nerve out but most Doctors say it has nothing to do with my condition..I have always wonder if the Brain is so vast one would think even the smallest change in the brain would mess up the Brain chemically?"

While still anecdotal, it is the first report seen that correlates with a documentable change in medication. the heredity aspect is common among sufferers. Nerve IX is a mixed nerve supporting a multitude of functions including;

- taste associated with the posterior part of the tongue,
- CO₂ levels via the carotid body and
- blood pressure via the carotid sinus.

There may be a connection between the IX nerve and the chorda tympani in some individuals.

18.5.1.8.1 The casual conclusions from my visual snow surveys

Based on my surveys related to visual snow, I will present a casual (non scientific) appraisal of my database of between 100 and 200 records related to visual snow (ca. December 2015). Of these records,

1. Only a few (1-3%) relate to children probably born with the disorder. They are typically not diagnosed until the age of 4-5 when they are intellectually capable of discerning they have an abnormality and discuss it with their mother (in some sense).
2. A considerable majority of the records involve 16-30 year old people reporting they at least experimented with recreational drugs, with many experiencing a bad trip and not continuing the usage. Unfortunately they must now live with an incurable and persistent side effect.
3. About 10% of the subjects encountered some type of physical trauma to the head that appears to have instigated the first awareness of a visual snow condition within less than a few weeks after the event.
4. 5-10% of the subjects are in the 45-60 year old category that have lived with the condition for a long time (extending prior to the easy access to information via the Internet).
5. Subjects who have sought medical help have found their general practice doctor lacking experience in the subject because of its low incidence within the population. It is gaining credence as an orphan disease worth additional attention by the US National Institute of Health. The GP has generally referred the subject to an ophthalmologist. The ophthalmologist has inspected the retina without any positive finding and frequently suggested an MRI or CAT-scan in conjunction with a referral to a neurologist. The neurologist (with or without the MRI or CAT-scan) has not been able to pinpoint any problem area and the subject has generally left with the perception that the neurologist suggested they were crazy or psychotic (a minor semantic difference in the eyes of these patients)
6. The resolution (voxel size) of current MRI, fMRI and CAT-scan & PET imaging systems are far poorer than that required to identify the source neurons associated with visual snow (a voxel typically involves integrating the phenomenology associated with several million neurons using a 3.5 Tesla magnet versus a putative group of <100 neurons introducing visual snow).
7. The neurologist has frequently prescribed various drugs designed to calm their emotions and fears rather than treat the disease. These prescriptions have generally been discarded by the patient after a period of weeks (sometimes to try a new prescription from another practitioner).
8. The late Oliver Sachs encountered visual snow as a side effect of his dealing with dopamine derivatives in the treatment of the mentally ill early in his career.
9. Except for the investigations of Sachs, visual snow is repeatedly reported to be ongoing over long periods but not progressive.
10. I have encountered no subject reporting satisfactory treatment for the condition.
11. Visual snow appears to be related to the phenomenon of attention. Serious concentration generally leads to failure to notice the phenomenon during that period.

18.5.1.9 Stereoscopic hallucinations associated with broadband Snowy Vision EDIT

To interpret errors in stereopsis requires a considerable knowledge of the visual system in detail. This section will refer to a variety of sections in other chapters that form a foundation for the discussion. The overall complexity of the problem can be seen at the top level in **Figure 18.5.1-5** from **Section 15.6.5** on the schematic and **Sections 7.4.1 & 15.6.3** on the functional aspects of stereo-optic vision.

In this figure, the chiasm is shown in two places for convenience. The two nerves from the chiasm labeled binocular are meant to represent the combined output from both eyes that represent their common field of view in one field. The two nerves from the chiasm labeled monocular are meant to represent the output of the one eye that has no

counterpart from the other eye.

In this figure, each occipital lobe consists of two areas, the dorsal area above the calcarine fissure and the ventral area below the calcarine fissure. The resulting signals passing to the parietal cortex via the TRN consist of five distinct commissure representing the four quadrants of the peripheral retina and the one high acuity region of the foveola.

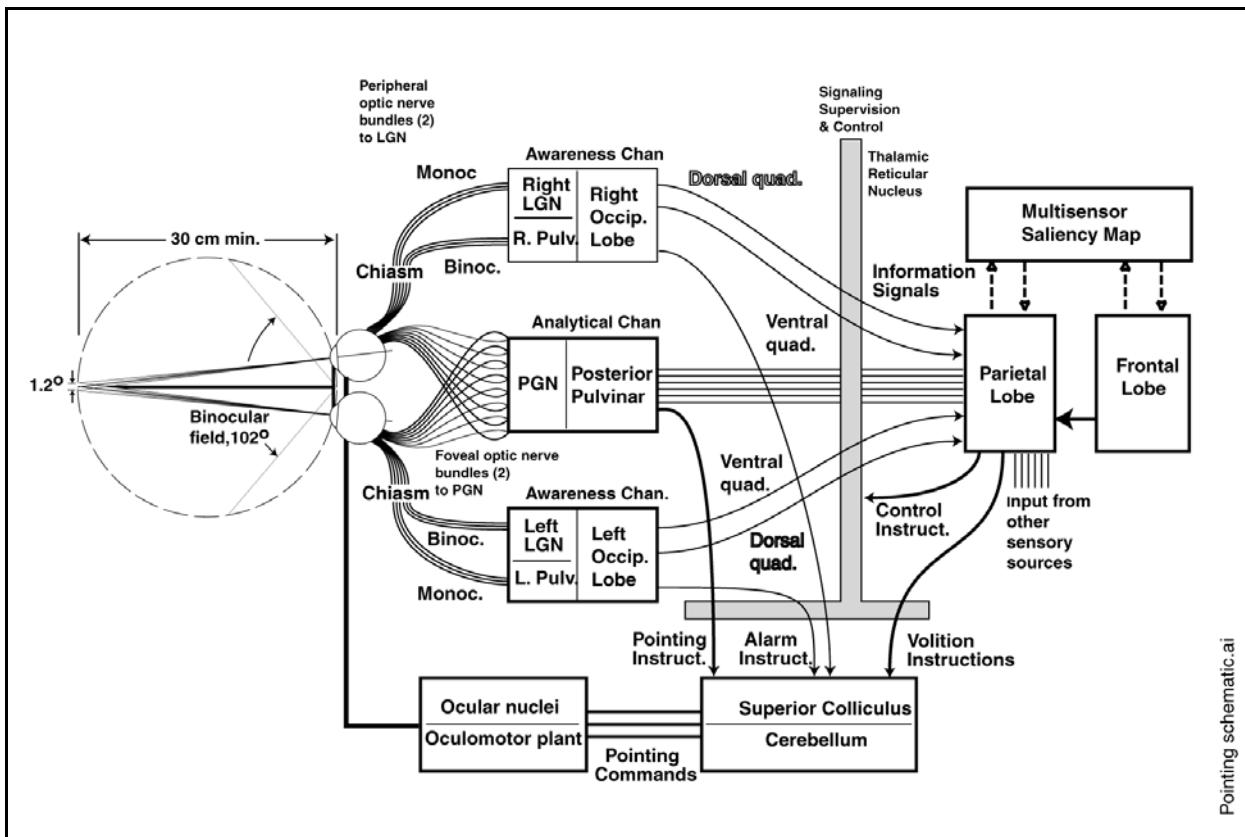


Figure 18.5.1-5 A simplified pointing and data reduction schematic. The PGN and posterior pulvinar are responsible for calculating the mean distance to the scene in object space as well as the “signed tokens” describing the relative position of each scene element. When the tokens are associated with the element, the composite signals are passed to the parietal area for insertion into the saliency map.

At a coarse level, the LGN/pulvinar couples extract the error signals used to cause the eyes to converge on a scene. The result of this effect is described as fusion. It does not relate directly to stereopsis.

At a higher level, precision convergence is a responsibility of the PGN/pulvinar complex which generates the fine pointing commands used to control the motion of the eyes, particularly in reading and the analysis of fine detail.

Figure 18.5.1-6 from [Section 7.4.4] shows the operation of the POS at a more detailed level. Precision stereopsis is the exclusive domain of the PGN/pulvinar couple operating within the POS. As described in **Section 7.4.4**, the PGN/pulvinar couple perform a two-step stereopsis routine. Using the two-dimensional associative correlator of the PGN, a precision vergence signal is generated that describes the weighted average of the distance to the elements in the scene. The circuitry of the local processing domains (within the PGN) are used to create these signals. The circuitry then calculates the distance to each significant element in the scene relative to this average and assigns it a “signed token.” These individual signed tokens are associated with the element and passed along to the saliency map of area 7. Along the way, the visuotopic signals may be compared with stored signatures within the pulvinar to prepare an initial abstract interp and/or percept concerning all or part of the scene (see **Section 19.4.3**).

Sections 15.6.4 & 15.6.5 show and discuss the signal paths emanating from the LGN and the PGN supporting the pulvinar. These signals are used by the pulvinar to generate both imaging signal information (that is passed to the

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saliency map) and the precision vergence signals used in the POS to control the oculomotor subsystem.

Calculating the signed tokens necessarily requires using the weighted average value as a reference. If this signal becomes corrupted, the perception of stereopsis can be distorted. This type of corruption appears to explain the symptoms exhibited by many subjects with various degrees of distortion in their stereoptic vision.

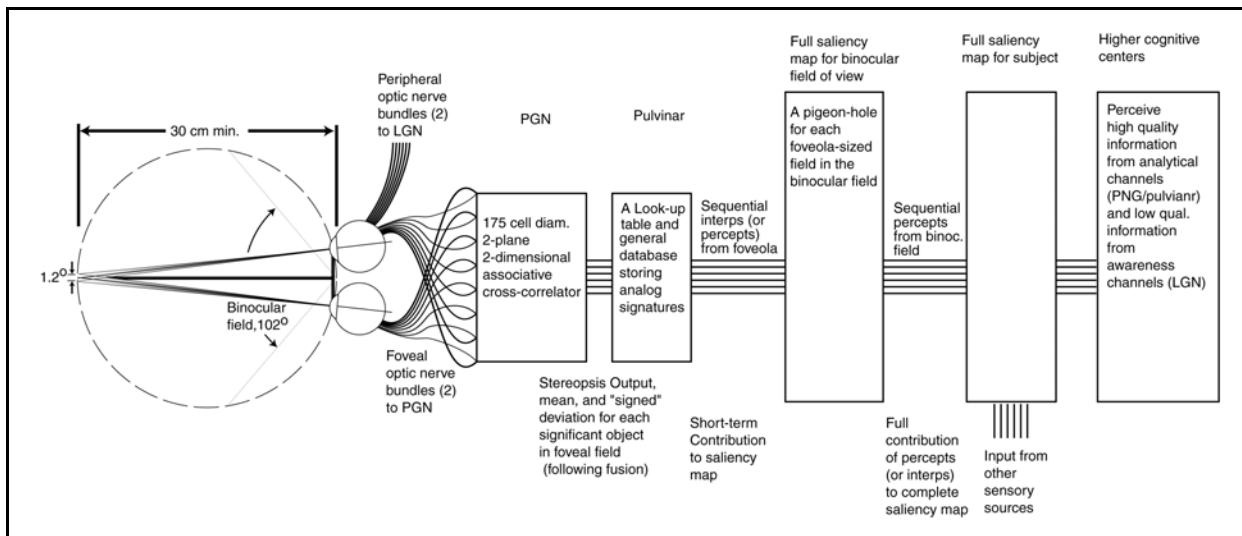


Figure 18.5.1-6 A more detailed schematic of the top level block diagram focused on stereopsis. The generation of authentic mean and signed tokens representing the radial location of elements in object space is critical to stereopsis.

Subject S. S. has reported snowy vision where the snow appears to be in a plane through which he views the external scene. This plan appears to oscillate in and out along his line of sight at up to 3-5 Hertz. Such a behavior is readily associated with an oscillation within the signal circuitry between the weighted average stereopsis signal and the stereoptic signal associated with each scene element. In this case, the extraneous noise is being treated as real information while the information from the real scene is largely ignored.

Subject A. H. has a more extreme condition. She reports no stereoscopic vision under most conditions and snowy vision. These observations would suggest that she is normally unable to compute a weighted average stereoscopic signal based on scene information. However, at times, she reports bizarre stereoscopic effects when observing multiple parallel lines. These effects may arise very quickly, even violently in her words. These effects appear to suggest that she has a significant bias error in the circuitry creating the weighted average stereopsis signal arising in her associative correlator. Under normal conditions, this error forces the signal level outside the dynamic range of the signaling channel. As a result, the error prevents the generation of any stereopsis component for individual elements in the field of view. However, when correlating long straight lines (relative to the diameter of the foveola) the correlator produces a strong signal that drives the weighted average signal back into the dynamic range of the signal channel. But the resulting signal is not a true representation of the weighted average. As a result, the perceived stereoptic properties of the lines may be greatly distorted.

18.5.1.9.1 The morphological extent of the Visual Snow syndrome EDIT

The loci of abnormalities identified in the above block diagrams can be related to the human brain as shown in **Figure 18.5.1-7**. The figure is similar to one in **Section 10.9.1**. The original figure drawn by the illustrator, Terese Winslow, has been modified to show the location of the thalamus immediately forward of and between the two LGN's (only one shown) and its covering frequently identified as the thalamic reticular nucleus (TRN). Another of its constituents, the pulvinar plays a crucial role in information extraction related to the foveola. The afferent signal processing area (Brodmann area 4) of the parietal lobe is also highlighted along with the underside and medial surfaces of the prefrontal cortex. As noted above, the occipital lobe is actually divided into two major hemispheres from a physical perspective and four independent quadrants from a vascular perspective. Thus, visual snow originating in the occipital lobe can be expected to show some geometric relationship to these two perspectives. There may also be different involvement in areas V1, V2 and V3 and also potentially V4 and V5 based on these

perspectives.

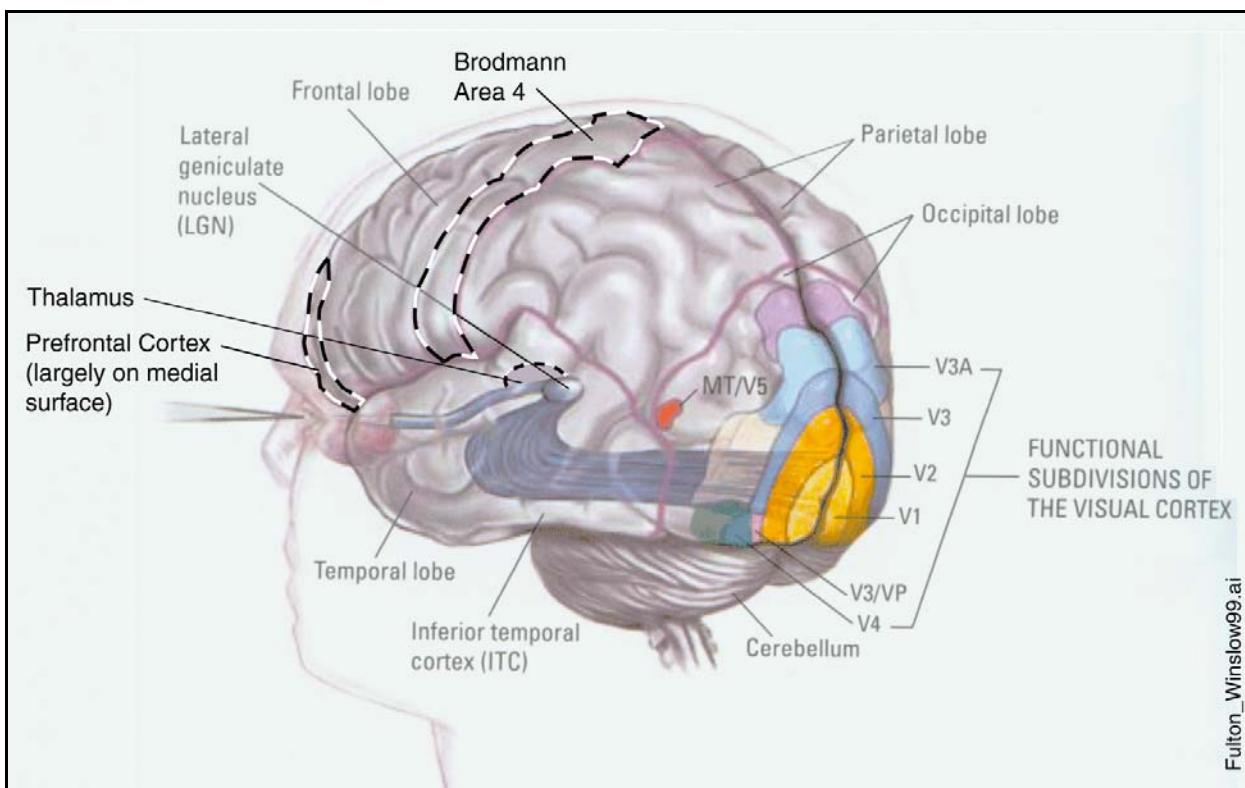


Figure 18.5.1-7 Potential locations of disease related to visual snow. The dashed lines indicate locations of major concern for most subjects reporting visual snow. Modified from Winslow, 1999.

A survey has been taken to determine what a large number of visual snow sufferers actually perceive within their overall field of view.

The majority of visual snow sufferers report that the snow is independent of which eye, which half of the visual field and whether concerned with the foveola or peripheral field. Such a condition strongly suggests the disease is centered in their thalamus, area 4 of their parietal lobe or in their prefrontal lobe *rather than being associated with the occipital lobe of the cerebral cortex.*

A few subjects have reported a lower density of snow within the field of view representing the foveola. This finding would suggest their disease is localized to the thalamus or the TRN associated with the thalamus.

The following expands the above brief comments into a more tabular listing. The data does not exist and is not within the resolution capability of current science to discover positively the source of VS. A more detailed analyses has provided evidence of where VS *does not* or *can not* originate. By combining this strong evidence, it is clear that the condition does not arise;

- in the eyes,
- in the afferent pathways through the mid brain (the lateral geniculate nuclei and the perigeniculate nuclei),
- in the occipital lobe (also called the visual cortex of Broadman area 17, or • in the pulvinar of the thalamus.

Visual snow may arise;

- in the associative areas (Brodmann area 37 & 39),
- in the isthmus or the efferent portion of the mid brain (the signal switching portion of the thalamus (generally called the thalamic reticular nucleus),
- in area 7 of the parietal lobe (the transverse coronal section) of the brain, or
- in the prefrontal cortex at the front of the brain.

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The challenge is to further circumscribe the potential source of VS. It will not be found by fMRI or CAT scans in the near future.

If in the future a chemical is found that can cure VS, then samples of that chemical can be labeled and employed in PET scanning to locate the specific neurons involved and acting as chemical receptors.

A SPECT scan in 2014 of a long time Visual Snow sufferer (B. W.) reported a potential deficiency in blood flow in the area of the temporal-parietal-occipital lobes junction. This is precisely the area generally labeled the association areas (Brodmann areas 37 & 39 for the visual modality, area 22 for the auditory modality, and potentially additional nearby areas for other sensory modalities). As noted in xxx, analyses of the source of VS based on a process of elimination also points to the same areas. Furthermore, if the neural system changes to a word serial/bit parallel form of information propagation to forward information to this region, there is reason to assign a common reference potential to a large group of neurons in this area. A failure associated with this reference potential supply circuit could provide a source of noise that could appear uniformly across the perceived output of the association areas. This is the typical condition associated with VS by behavioral analyses. [xxx cite figure number when developed]

18.5.1.9.2 Clinical treatment related to visual snow

Visual Snow is a very uncommon disease that is seldom observed by the typical physician. As a result, they have little to no exposure to the disease and the US government has shown no significant interest in its effects. It is therefore considered an orphan disease in the current American lexicon of medicine.

When encountering a patient, most doctors will call for an ophthalmological examination, and frequently an MRI or CT scan, of the eyes. Finding nothing abnormal, they frequently suggest the patient is imagining the problem and if pressed will prescribe a medication commonly used to alleviate anxiety or more serious psychoses. These treatments have been largely ineffective and the patient frequently seeks another doctor.

18.5.1.10 Functional origin of the snowy vision syndrome NEED TEXT EDITED

After reviewing about fifty cases of snowy vision reported via my website, it is possible to draw a number of conclusions about the condition.

First and foremost, the condition appears to be permanent in character. It frequently is initially perceived during childhood. There is some indication, the condition can be brought on through the use of recreational drugs. About ten of the reported cases (about 20%) appear to be initiated within weeks of a significant drug induced event. Once encountered, the condition remains present for life, although the symptoms do not progress to a more serious state.

An effort was made to determine whether the disease was distinguishable with respect to the foveola versus the parafovea of each eye, and a series of other conditions that will be discussed below

1. The perceived spots interfering with normal vision were not related to the retina of either eye. Similarly, they could not be associated with either hemisphere of the occipital lobe.
2. The perceived uniformity of the spot density indicates the disease is independent of the lens system of the eye. This system is spatially nonlinear and introduces a variation in point signal intensity with angle from the central axis of the lens.
3. The perceived uniformity of the spot density also suggests the disease is independent of the two hemispheres of the occipital lobe since these involve a significantly nonlinear projection of the visual field.
4. The perceived spot uniformity, independent of the individual eyes and hemispheres of the occipital lobe suggest the disease originates in one of two functional locations. The first is in the saliency map under the control, if not also included within the region, of Brodmann's areas 1, 2 & 3 of the parietal lobe of the brain. The second is in the stage 5 cognitive circuits of the brain that interrogate the saliency map. The affected areas of the stage 5 circuits may be located in the parietal lobe or within the prefrontal cortex behind the forehead.
5. No subject reported a dot pattern that was of significantly higher density within the field of the foveola (1.2 degrees diameter), although there are suggestions such as T. Y's that the density may be higher within

the diameter of the fovea (5-6 degrees). The observation of T. Y. that the dot pattern tended to swirl at lower radii relative to the point of fixation deserves further study. It is proposed that the observation of T. Y. that the perception of circles tended to assume a polygon form after a period of time is related to a separate phenomenon.

6. The predominant characterization of the disease is black dots appearing as an overlay on white fields or low contrast scenes. Dots of a single color, or of randomly varying color are infrequently reported. White dots appearing as an overlay on black or low contrast scenes is a rarely reported situation.

7. The predominant characterization of the disease is dots of very small diameter (not necessarily at the pixel level but described as "atomic" in size) occurring across the entire field of view. The pattern of these dots is continuously in motion relative to the external scene. The pattern does not typically move exclusively in a specific direction, or in a vertical or horizontal direction.

8. The dots are not perceived as flickering in intensity. They appear at high contrast at all times.

9. The pattern of dots is present all of the time the eyelids are open and a scene of sufficient brightness is presented to either eye. While the question was not asked in the survey, no subject reported seeing the dot pattern while awake with his eyelids closed.

For the small subset of individuals reporting finite size dots moving about in their field of vision like strings of ants, a different analysis and conclusion is appropriate.

The relative uniformity of the dot spacing within the dot pattern of an individual is suggestive of some form of image division within the neural system (not unlike some form of sub-field raster scanning— that is independent of the image information extraction process associated with the perigeniculate nucleus, PGN). In the context of a sub-field raster scan, the dots could easily be associated with a non-functional projection neuron at a specific location within the field.

The continual motion of the perceived dots across the visual field strongly indicate the disease does not involve specific photoreceptors within the retina, specific neural paths within the optic nerve or specific neural locations within either hemisphere of the occipital lobe. The constant high contrast level of the dots suggests the disease does not involve "noisy" unstable signal processing neurons. It suggests inappropriate operation among the stage 3 signal projection neurons connecting the information extraction and interpretation engines within stage 4 or stage 5 of the CNS.

Figure 18.5.1-8 illustrates the important functional elements between the scene and the perception of a veil between the scene and the sufferer's retina. It is an expansion of the earlier figure xxx, "Mechanisms of visual loss by location." [xxx previously 18.8.1-1]

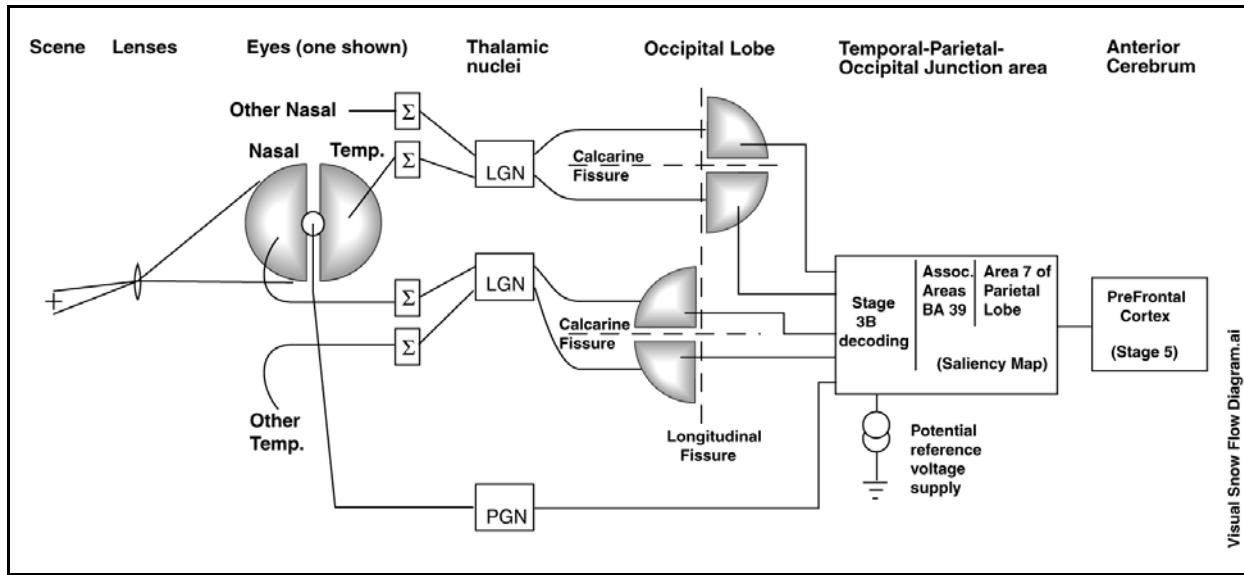


Figure 18.5.1-8 Visual Snow flow diagram for eliminating sources. Areas to the left of the association areas involve multiple parallel paths. The occipital lobe is shown divided into quadratures in analogy with how they are served by the blood supply to these regions. By eliminating potential sources based on individual interviews and the survey, the source of visual snow can be localized to the association areas, the parietal lobe and the prefrontal cortex (and stage 3 signal projection circuits between those engines. See text.

Many key points are incorporated in this illustration. Starting from the left;

1. the two optical rays from the object (a cross), through the lens to the retina are not straight lines. Combining this fact with the fact the retina are highly curved as suggested by the shading of the one retina shown, indicates the retinotopic image is a highly distorted rendition of the spatiotopic representation (the scene). The consistently reported uniformity of VS across the entire field of view indicates the origin of VS is not associated with the stage 0 optical system.
2. the fact that the eyelid of either eye can be closed without eliminating the perception of VS indicates clearly that the source of VS does not arise in either eye.
3. the fact that the signals from each eye follow three different paths to the CNS while the perception of VS remains constant across the visual field indicates the source of VS cannot be attributed to either the nasal or temporal half of either retina or to the higher resolution central region (the foveola) of either eye.
4. the fact the uniformity of the perceived pixel size remains constant across the entire visual field indicates VS does not originate in either the nasal or temporal portions of the retina. These two sections of the retina exhibit considerably lower perceived pixel density due to the summation circuits of the retina (represented by the Sigma symbols).
5. the fact that no significant variation in the presence of the perceived VS between the left and right halves of the visual field indicate the source of VS is not within either the left or right lateral geniculate nuclei (LGN).
6. the fact that each LGN supports the spatiotopic representation onto either the left or right hemisphere of the occipital lobe and no difference in perceived VS has been reported between the left and right halves of the spatiotopic field indicate the source of VS is not within the left or right hemispheres of the occipital lobe.
7. the fact that the spatiotopic representations are largely separated between the upper and lower quadrants of each hemisphere of the occipital and the fact that no reports have been documented indicating a predominance of VS arising from one quadrant indicates the source of VS does not arise from within the occipital lobe.
8. there are philosophical reasons, based primarily on the volume of information that must be handled by the stage 3

information projection circuits, that the information projected between the occipital lobe and the pulvinar is probably projected in word serial/bit parallel format in order to increase information capacity by about 10:1 compared to the word serial/bit serial format used earlier in the signal paths.

9. there is reason to believe, the stage 3b decoding circuits of the stage 3 information projection paths between both the occipital lobe and the pulvinar, and the association areas may require a common voltage reference to insure proper interpretation of the word serial/bit parallel information. Such a source is shown at lower right.

10. it is conceivable the same reference potential may be shared between the association areas and the parietal lobe information processing areas (which are intimately associated with the putative saliency map in an unknown way).

11. If all of the pixels associated with the data in the saliency map (or even the portion of the map allocated to a specific sensory modality) are driven by any noise associated with the reference voltage source, the stage 5 engines of the prefrontal cortex would perceive this noise fluctuation as uniformly spread across the perceived spatiotopic field (regardless of any intermediate spatial distortions within the signaling paths).

This list of findings provides strong support for the hypothesis that the source of VS is found in the stage 4 engines orthodromic to the occipital lobe and the pulvinar, and probably in the engines or power supply supporting the association areas and/or the afferent portions of the parietal lobe (area 7). To date, there have been virtually no investigations of the nature of the *output signals* in the afferent pathways from the association areas and/or parietal lobe. No reports could be found in the literature relating to these output signals. The potential character and circuit configuration of the reference power supply has not been explored.

18.5.1.10.1 A precision voltage reference for word serial/bit parallel signaling

[This section involves a considerably higher degree of speculation concerning physical and biological mechanisms than typically found in this work. This approach is taken in order to suggest avenues of profitable exploration leading to an eventual explanation of the cause of visual snow.]

Although not yet an established and demonstrated fact, it appears highly likely, based on efficiency and speed requirements, that the later stage 4 (and potentially stage 5) engines of the higher biological brains employ word serial/bit parallel information propagation techniques. The use of such techniques would require the use of parallel chains of single neuron channels (known as commissure within the CNS). While all histologically identified commissure may not represent such parallel chains of neuron, it is not difficult to hypothesize such arrangements. Their use would introduce a set of significant design requirements that are effectively avoided in the remainder of the neural system where word serial/bit serial techniques (chains of single neuron channels) are used exclusively.

To accommodate the potential for parallel chains of neurons carrying information, a stage 3BP (P for parallel) decoding circuit configuration will be addressed in **Section 14.3.xxx**.

The potential need for a precision voltage reference to be shared by a multitude of stage 3b decoding neurons in order to provide analog voltage output values presents a significant circuit design problem. The requirement is for a sufficiently stable reference potential to support the summation of signals derived from multiple stage 3b circuits within a continuing stage 4 engine or analysis of the individual signals in a multi-dimensional data set by a stage 5 cognitive engine.

The design of man-made voltage references within microcircuit design has become a high art in order to achieve a wide variety of sophisticated objectives. The principles involved have probably been adopted in the design of biological voltage references. However, there is not enough known about the biological requirement to sift through the possible methodologies to illuminate any potential analogies.

Within the high art of voltage reference design in man-made circuits, the subject of surface physics arises repeatedly, particularly when exploring the subject of noise within these circuits and its suppression in the ultimate voltage reference. This problem area suggests similar problems may arise in biological applications. It is conceivable that a variety of chemicals could attach themselves to specialized lemma (cell membrane) areas and thereby permanently change their electrical properties.

1. Such changes in man-made microcircuits frequently introduce “excess noise” beyond that calculated for the unadulterated lemma.

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2. Such changes in man-made microcircuits frequently lead to bias shifts in active circuits that allow noise sources normally outside of the nominal operating range of the circuit to be introduced into the signal channel and even amplified.

There is a considerable literature on the high art of voltage reference design. However, it requires a very sophisticated circuit designer to read and evaluate this material in the context of the goal of applying selected techniques to the realization of an appropriate biological voltage reference. There is a distinct separation of approaches when designing bipolar transistor reference sources and metal-oxide gate transistor reference sources. An early paper discussing the use of bipolar circuits as references for use in MOS microcircuits is by Hodges et al¹⁹⁰. An early paper discussing many of the techniques and tradeoffs involved in NMOS cirucuits is by Blauschild et al¹⁹¹.

The filling of receptor sites by an abnormal chemical is reminiscent of the action of dopamine and L-dopa in occupying the glutamic acid site and thereby interfering with the normal provision of electrical power to the neuron (**Sections 8.6.3.3 through 18.6.6 & 15.1.8**). **Section 15.1.8** describes the actions of dopamine and L-dopa with regard to the providing power to the individual neuron. The sections in Chapter 8 discuss a variety of actions related to dopamine and L-dopa. **Section 18.8.6.4** of this chapter discusses the role of dopamine and L-dopa in the treatment of ocular servomechanism disease. It also discusses some of the finer points of using these chemicals in medical treatment.

The above discussions and the available evidence from interviewing VS sufferers would suggest VS is probably caused by the occupancy of specialized receptor sites within the stage 4 engines in the association areas (nominally Brodmann's areas 22 for tinnitus and areas 37-39 for VS). The occupancy appears to be permanent as opposed to the short occupancy by L-dopa, and the longer but finite occupancy by dopamine. It also suggests the occupancy of these sites by such a permanent agent does not lead to a progression in the disease of VS over time (in the absence of continual exposure of the brain to the agent).

There are a wide variety of cannabinoids that appear to be candidates for the permanent agent described above. The family is large and found in a wide variety of plant leaves. Some of them, particularly THC (the primary active ingredient in marijuana) has a nearly planar structure and a side chain similar to that of L_dopamine after the loss of CO₂ from L-dopa. **Figure 18.5.1-9** shows that THC is much more closely related structurally to L-dopa, both being known psychoactive drugs. The replacement of the hydrogen to the right of the hydroxyl group with a second hydroxyl group would create a ligand very similar to that of L-dopa and believed to occupy the glutamic acid receptor site at the location of electrostenolities in normal neurons.

¹⁹⁰Hodges, D. Gray, P. & Brodersen, R. (1978) Potential of MOS technologies for analog integrated circuits *IEEE J Solid-State Circuits* vol SC-13, pp 285-294 Reproduced in Gray, P. Hodges, D. & Brodersen, R. eds. Analog MOS Integrated Circuits NY: IEEE Press

¹⁹¹Blauschild, R. Tucci, P. Muller, R. & Meyer, R. (1978) A new NMOS temperature-stable voltage reference *IEEE J Solid-State Circuits* vol SC-13, pp 767-774 Reproduced in Gray, P. Hodges, D. & Brodersen, R. eds. Analog MOS Integrated Circuits NY: IEEE Press

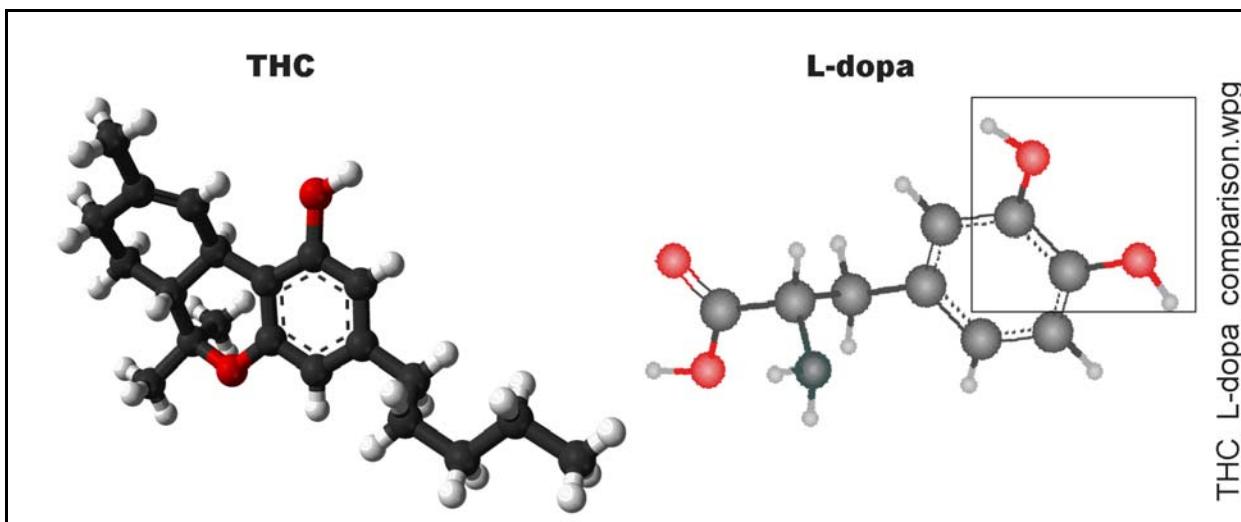


Figure 18.5.1-9 THC_tetrahydrocannabinol, the primary active agent in marijuana. The chemical would exhibit a similar ligand to L-dopa (shown boxed on the right) if the hydrogen to the right of the hydroxyl group were replaced by a second hydroxyl group. It is proposed in Chapter 8 that this ligand is used in a double anti-parallel coordinate bond (DACB) arrangement at glutamate receptors on the surface of each neuron.

Dronabinol is the synthetic form of THC (trade name, MARINOL®). For this version, the Food & Drug Administration website notes, “Capsules are dose-related and subject to considerable interpatient variability. Therefore, dosage individualization is critical in achieving the maximum benefit of MARINOL Capsules treatment.” When used to treat appetite loss, “In the clinical trials, the majority of patients were treated with 5 mg/day MARINOL Capsules, although the dosages ranged from 2.5 to 20 mg/day.” and “Patients using MARINOL Capsules should be advised of possible changes in mood and other adverse behavioral effects of the drug so as to avoid panic in the event of such manifestations. Patients should remain under the supervision of a responsible adult during initial use of MARINOL Capsules and following dosage adjustments.” Whether the oral form of THC is routinely modified within the body to incorporate a second hydroxyl group in order to pass through the blood-brain-barrier is worthy of further study. The dual hydroxyl form of L-dopa is superior at passing through the barrier compared to its sibling dopamine (**Section 18.8.6.4**).

18.5.1.10.2 Suggested means for marijuana to cause visual snow EDIT

[This section involves a considerably higher degree of speculation concerning physical and biological mechanisms than typically found in this work. This approach is taken in order to suggest avenues of profitable exploration leading to an eventual explanation of the cause of visual snow.]

For THC (dronabinol or MARINOL®) to affect the neural system and cause VS or other diseases related to the CNS, it is necessary for the material (1) to be ingested or injected into the blood stream, (2) to be modified in order to be capable of crossing the blood-brain-barrier (BBB), (3) be able to form a DACB with the target site on the specialized lemma of a cell and (4) to be stereochemically compatible with the target site. These are the same requirements that were addressed many years ago with regard to providing dopamine to the brain as a pharmaceutical. Although some dopamine is produced on each side of the BBB and dopamine does not cross the barrier readily, a mechanism was sought and found that allowed administration of the chemical L-dopa orally and its conversion into dopamine after crossing the barrier (**Section 18.8.6.4.3**).

The major challenge with THC is discovering how it crosses the BBB, at least in the case of individuals susceptible to serious complications related to THC use. Searching Scholar.Google.com leads to a great variety of articles related to the ingestion of THC and its variants, and the results thereafter. Hill et al. have studied a variety of these

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chemicals, categorizing them as phytocannabinoids, in a preclinical setting¹⁹². They identify the receptor site within the CNS by only the placemark label, CB₁, cannabinoid site #1. Drysdale & Platt have also provided a useful survey paper¹⁹³. While they enumerate both a CB₁ & CB₂, they do little to identify these receptor sites. Their abstract begins, “Cannabinoids comprise three classes of compounds, the active components of Marijuana (*Cannabis sativa*), as well as endogenous and synthetic derivatives. To date, two distinct cannabinoid receptors (CB1 and CB2) have been discovered, but evidence for further receptor types has been brought forward. The potential use of cannabinoids for medicinal purposes has long been known, but the mechanisms of action of both exogenously applied and endogenous cannabinoids are only partly established.” “A number of both *in vitro* and *in vivo* models have provided promising but diverse evidence for cannabinoid protection in glutamate-mediated excitotoxicity, hypoxia and glucose deprivation, brain trauma, epilepsy and MS. Subsequent to many preclinical investigations, clinical trials are now underway in a variety of the above applications. Overall, the understanding of the therapeutic relevance of cannabinoids will rely on further investigations.” Their mention of glutamic in the context of cannabinoid research is specific to the following discussion. However, they are also explicit, the mechanism involved in cannabis affecting the human brain remains unknown. Viveros et al. presented a recent review of the broader role of the endocannabinoid system (ECS) in the physiological system related to this discussion¹⁹⁴.

Viveros et al define the ECS as if it were a well accepted chemical system within the CNS. “The endocannabinoid system (ECS) is a lipid signaling system which includes the cannabinoid receptors, the endogenous lipid ligands (endocannabinoids), and the enzymatic machinery for their synthesis and inactivation [two citations]. It is a highly conserved system along the phylogeny and its better known and studied function is the modulation of neurotransmission.” “Endocannabinoid compounds are amides, esters and ethers of long-chain polyunsaturated fatty acids that are synthesized on demand [two citations]. This work would suggest the endocannabinoids are subsets of these very large classes of compounds exhibiting specific stereochemical properties. Viveros et al. did not identify any features of their cannabinoids that illustrated their mode of operation.

The conclusions of Viveros et al. are important but remain unspecific, “The ECS is a lipid signaling system comprising all the molecular machinery needed to properly activate the cannabinoid receptors. There is a vast array of CB1 and CB2 receptor-mediated signal transduction mechanisms that undoubtedly contributes to the diverse biological processes influenced by cannabinoids. Indeed, endogenous cannabinoid biosynthesis and cannabinoid receptor-mediated signal transduction is altered by a number of hormones and neuromodulators. At the cellular level, cannabinoids decrease stimulus-secretion coupling, and electrochemical transmission between neurons via presynaptic, trans-synaptic and postsynaptic mechanisms. At the central nervous system level, cannabinoids are involved in learning and memory, antinociception, motor function, energy balance, stress, thermoregulation, reproduction, drug reward and immunomodulation.” As an example, they continue, “The etiology of eating disorders is currently unknown and the molecular systems involved are still largely a mystery.”

Figure 18.5.1-10 shows the principle cannabinoids in the context of this work.

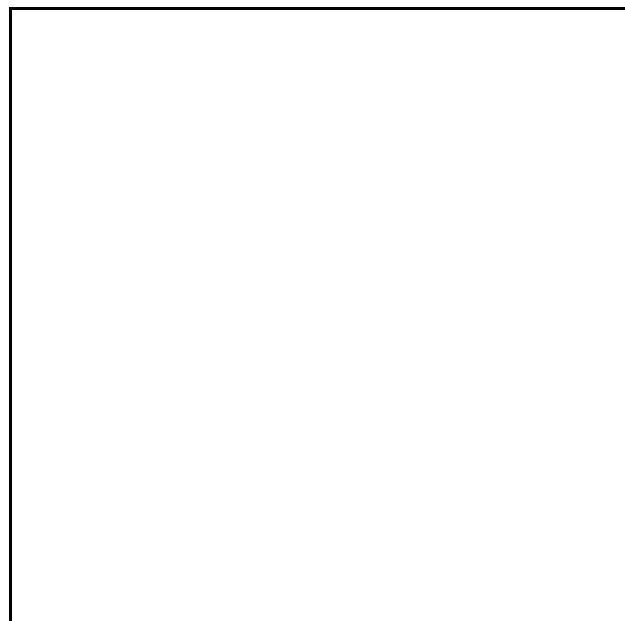


Figure 18.5.1-10 EMPTY

¹⁹²Hill, A. Williams, C. Whalley, B. & Stephens, G. (2012) Phytocannabinoids as novel therapeutic agents in CNS disorders *Pharma Therapeut* vol 133(1), pp 79–97

¹⁹³Drysdale, A. & Platt, B. (2005) Medical Marijuana in CNS Disorders *Front Med Chem - Online* vol 2(1), pp. 133-159(27)

¹⁹⁴Viveros, M-P. Bermúdez-Silva, F-JLopez-Rodriguez, A-B. & Wagner, A. (2011) The Endocannabinoid System as Pharmacological Target Derived from Its CNS Role in Energy Homeostasis and Reward. Applications in Eating Disorders and Addiction *Pharmaceuticals* vol 4, pp 1101-1136

Figure 18.5.1-11 suggests how pure THC (droneamide or Marinol®) can be combined with another ligand to produce a chemical capable of crossing the BBB. After crossing the barrier, the chemical can then be de-combined into a chemical exhibiting the necessary dual hydroxyl ring structure and a residue. The new chemical exhibiting the dual hydroxyl ring structure will only be capable of binding, via a DACB, to a target with which it is stereo chemically compatible. This may restrict the action of the THC derivative to the neuron(s) forming the putative voltage reference source.

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Figure 18.5.1-11

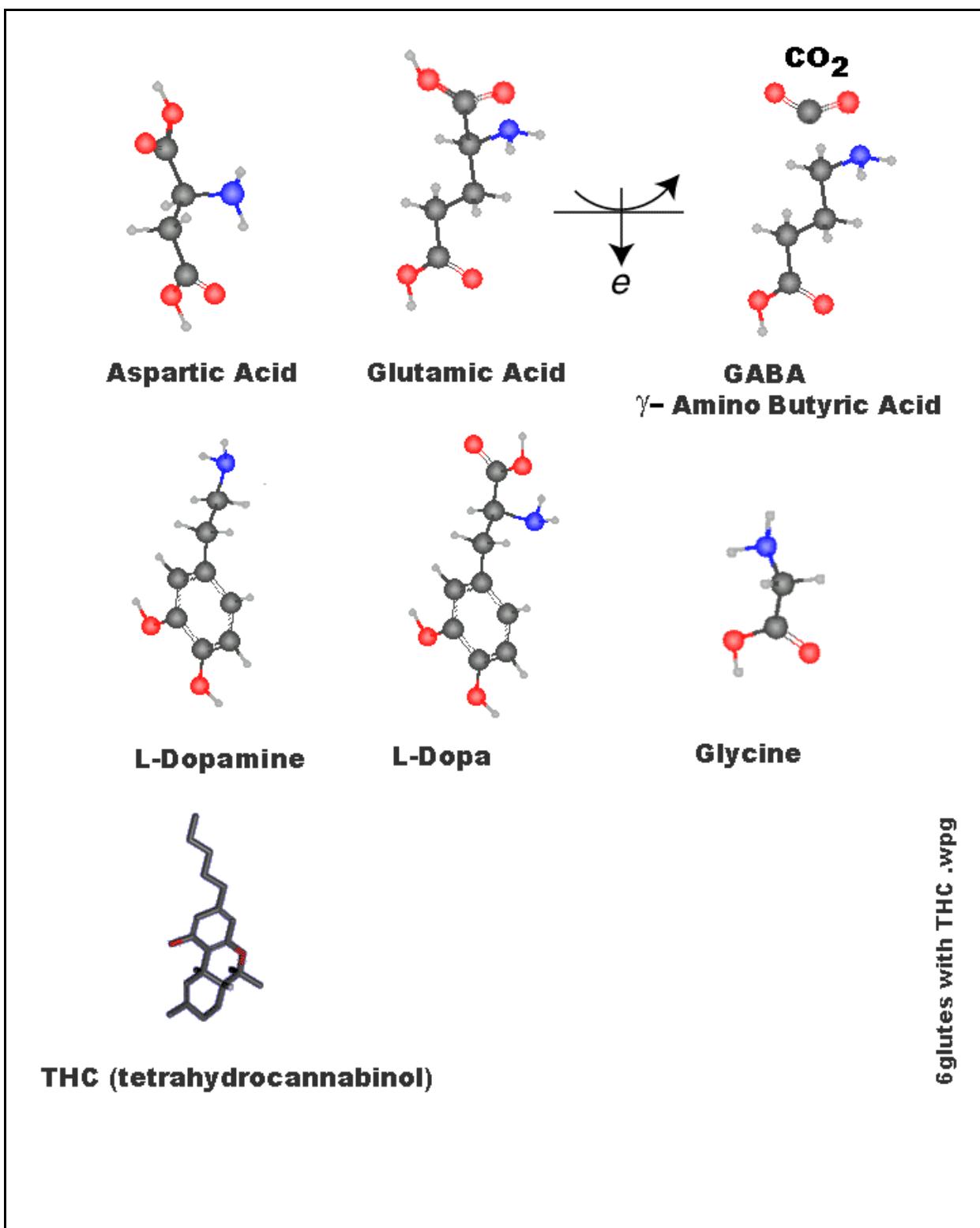


Figure 18.5.1-11 A comparison of cannabinoids and the dopamine family EDIT & ADD. DOES NOT MAKE THE POINT IF ANY. The cannabinoid, THC exhibits a side chain similar to that of L-Dopamine and could be hydrolyzed to add a hydroxyl group to the current one on the upper ring. It is likely that the THC requires a different receptor site than L-dopamine.

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The changes suggested by Nikas et al. is precisely the change suggested here for modifying xxx.

18.5.1.10.3 Paragraphs from a recent colloquia with an Australian researcher–Jan2016

During December, 2015, an extended discussion of visual snow was held with a researcher in Sidney, Australia. Following the exchange of several figures and preliminary discussions, it began to proceed beyond the above remarks.

This is where the trail relating to VS gets cloudy. There is data from Vardi et al. concerning the presence of Glutamic acid and GABA in the external environment (or matrix) adjacent to virtually every neuron in the body. The literature reports the presence of about 2-5% of glutamate and 1.5-3% of GABA in this local matrix (page 42 (Section 3.2.2.3.3) of chapter 3 of my work on “The Neuron and Neural System.”

<http://neuronresearch.net/neuron/pdf/3ThePowerSupply.pdf> These percentages are presumably for the nominal (healthy) condition. You may want to review this chapter. I would appreciate any comments you might have. The citations may provide some of the “hard evidence” you seek. However, watch out for hidden variables not controlled in the published (and ostensibly peer reviewed) literature.

Without intending to disrupt this discussion, I must take note of the potential for an entirely distinct backup to the Glutamic acid = GABA + CO₂ electrostenolytic process. That is the aspartic acid = lycine + CO₂ electrostenolytic reaction. Glutamic acid and aspartic acid are the only two acidic (negatively charged) amino acids of biochemistry capable of generating a negative potential on the interior of a neuron through an electrostenolytic process. They are the only dicarboxylic acids I am aware of in biochemistry. I repeat my assertion from the previous message, now incorporating MY alternate path using aspartic acid that I did not address earlier., “I am unaware of ANY other explanation for the negative potential of nominally –150 mV within a neuron relative to the surrounding matrix.

As you see, I am quite open minded about the role of glia as well as the homeostasis portion of individual neurons in powering the neurons. I also agree with your holistic approach. I have also incorporated the case studies reporting on what subjects with VS actually report perceiving. As a result of following this approach, I can say with confidence that VS does not occur in the eyes, the retina of the eyes, the optic nerve, the initial stages of the diencephalon (the LGN and TRN) the visual cortex (areas 17, 18 or 19 and any part of the temporal lobe) and probably not the later stages of the diencephalon (the pulvinar processing the signals from the foveola, central 1.2 degrees of the retina). The only areas of the brain that remain in contention are those areas that process the fully merged visual image of the total external field of view. These include the final stages of signal processing within the diencephalon, the parietal lobe (possibly an area of the adjacent temporal lobe) and the prefrontal cortex. It appears that the neural signals processed within these areas may involve multiple neural signal paths operating in parallel, i.e., word serial/bit parallel signaling. The data in this area is severely limited because multiple probe recording techniques (able to interrogate multiple neurons of choice within a given nerve) have only entered the biosciences field in the last decade.

It is my current position that VS is the result of abnormal flow rates to and from the electrostenolytic process(s) on the surface of a small number of neurons in one of the described target areas. These abnormal flow rates may be associated with abnormal concentration levels of glutamic acid or GABA or both.

I can now address your question 5 (that appears to have changed—with a positive intent). It is worded differently in the second rendition and is then restated relative to the “knub of my question.” I believe the conversion of glutamic acid (alternate, aspartic acid) to GABA (alternate lycine) via an electrostenolytic (decarboxylation) process is key to powering every neuron of the mammalian system. In this sense, I can use your word “epicenter” to describe their role in powering the neurons. As you note and my figures support, the process may be supported by a raft of auxiliary processes (some of which are alternatives and others are necessary prior or subsequent processes). Some of these are readily associated with glia, which may be characterized as “metabolic substrates” in this context. Glutamine is generally described as a material that is conveniently stored and easily moved within the appropriate local environment.

Your comment about the variety of potential sources of the problem perceived as VS is entirely appropriate. However, I would question your assertion that no part of the brain is separated from another by more than 5 synapses. I believe this is an off-hand calculation by a charismatic “peer” speaking without benefit of the facts. The brain is much more compartmentalized than you suggest. It appears you or the “peer” are only addressing the stage 3 action potential generating neurons of the brain that are easily isolated in the laboratory. In fact, these pulse

generating neurons represent less than five percent of all neurons of the brain. There are tens of billions of analog signaling neurons within the brain (and hundreds of billions, to thousands of billions of synapses) that have not been mapped at all. I will place a small bet with you that a neuron in the stem of the spinal chord dedicated to the somatosensory sensors related to the big toe is more than 5 synapses removed from a neuron of the parietal lobe dedicated to the saliency map representation of the upper left field of view of the foveola. Any calculation of this probability function is dependent on a large number of assumptions. Ten would be a safer number than five, and 30 would be a safe bet. Over one million of the stage 1 sensory neurons of each eye require more than 5 synapses just to communicate with visual area 19 of the cortex; the same neurons require more than 10 synapses to reach the visual section of the prefrontal cortex..

I am anxious to communicate with anyone able to perform the necessary experiments to acquire the “direct data” you and I both desire so passionately. However, I expect it will take some very careful and unique (to the biosciences) protocol planning to move out from the epicenter of the problem (the neural/glial complex associated with an unidentified but diseased area of the visual modality of the neural system) to beyond even the Krebs cycle, the backup provided by the associated astroglia and the local matrix supporting these elements. There are multiple lemma that must be penetrated by the various molecules supporting the Krebs cycle, the glutamate shunt, and any participation by the astroglia. There may also be multiple regions of the matrix with different porosity to the relevant chemicals. As noted in the earlier email, Dr. Sachs found that L-dopa had the ability to penetrate the blood-brain-barrier, affect the mood of the patient and occasionally cause a report of VS. The primary active component of marijuana, a molecule labeled THC has a similar chemical group that could act similarly to L-dopa. Both of these chemicals might be capturing the electrostenolytic site on the neural lemma. These possible sources of the VS disease must all be considered candidates in the final protocol.

I am well aware of the work of Schankin & Goadsby. Their cause is honorable and their work useful. However, a primary purpose of the quoted paper was to raise money to support further work in their laboratory (from the NIH or elsewhere). Their paper is the first from their facility (an academic “center” of only a few people) on the subject of VS. They had to ask their volunteers to pay for their own passage to San Francisco and their own per diem expenses, for purposes of examination. Using metabolic indicators at a resolution at least one if not two orders of magnitude poorer than necessary to resolve neural operations is not overly useful in the case of VS. Their fMRI machine (3-3.5 Tesla) is far below the state of the art as used by Xu and various colleagues in 2000-2003), 7 Tesla. I will not bore you with the investigations related to the fMRI of a dead salmon, I am sure you have at least heard rumbling regarding it. <http://www.uh.edu/engines/epi2883.htm> The machine shown is in the 3.0 Tesla class.”

18.5.1.10.4 Framework for solving the VS problem –Jan2016

Visual snow remains in 2016 very difficult disease to define from a functional and/or physiological perspective. There are many clues but little empirical data beyond behavioral accounts.

Potential noise character and source location:

There are three types of “random noise” that may be involved in VS;

- random noise characterized by equal energy per unit bandwidth across the spectrum of interest & known as white noise.
- popcorn noise, random noise characterized by excess noise at low temporal frequencies (aka, 1/f noise).
- pink noise, random noise characterized by excess noise at high temporal frequencies (noise density rising with frequency).

Behavioral accounts reviewed by a specialist in communications theory can help to determine whether the problem arises within stage 3 pulse circuits or stage 4-5 analog circuits.

- Sufferers have reported two significantly different types of perceived noise. The majority of sufferers have reported a very fine (in terms of pixel size) fuzzy appearance that is distributed uniformly across the complete perceived field of view (pink noise). A minority of sufferers have reported a totally different noise pattern suggestive of more equally spaced dots uncorrelated to the observed scene. These dots may have a duty cycle (dots size divided by dot spacing) of about 1/8. They have been reported to appear as machine gun bullets spraying across the field of view. Others have reported the appearance of strands of ants weaving their way across the field of view. These reports suggest the noise is due to a relaxation oscillator generating a pulse stream that is added to the information stream describing the scene at a location within stage 4 before the information extraction process has resulted in an abstract description (rather than a literal description) of the field of view. The weaving character of

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the perceived scene suggests the pulses associated with the noise are not synchronous with any other scanning or framing process.

-

- There may also be a parallel between tinnitus and visual snow. Tinnitus exhibits a pink noise characteristic in the most common form.
- If it is assumed the perceived noise arises within one or a few neurons, the noise pattern reported by subjects appears to be pink noise lacking low frequency components and appearing fuzzy, rather than white noise which shows a more blotchy appearance.
- There is no sign of any structure within the noise waveform suggestive of any scanning or framing character.

The fuzzy character of the perceived noise suggests visual snow arises within the stage 3 pulse circuits generating action potentials rather than the stage 4-5 analog circuits.

Analysis based on gross perceived imagery

There appears to be a close analogy between the symptoms of tinnitus and of visual snow. Both appear to occur in two distinct forms. Both exhibit a “pink noise” characteristic with high frequency noise predominating. This noise is perceived as a veil in between the eyes and the full field of the external scene or a non-localized noise source independent of the left and right auditory channels. These forms suggest introduction of the extraneous signal into the literal signaling channels prior to stage 4 information extraction. Both exhibit an alternate form involving a more symbol-based perception, (birds singing or thunder claps—ants crawling or machine gun fire across the field of view) suggesting the error is introduced after information extraction within stage 4. In all four cases, the diseases are essentially ignored during periods of intense concentration. Predominantly, the extraneous information is perceived as black noise on a white background with a dynamic range that is nearly constant at about five per cent of the dynamic range of the signaling channel. This dynamic range is perceived following linear to logarithmic conversion of the initial signals within the stage 1 sensory neurons, again suggesting its introduction later in the signal chain. Occasionally, again a few to very few percent of the subjects report color related to the ants/machine gun type visual signals.

Figure 18.5.1-12 provides a working description of visual snow compared to tinnitus (and potentially signals related to amputated limbs).

The discussion of phantom limbs will be limited. The column has been added on the right because of the apparent similarity of the neural signals involved. The veiling noise (numbness, burning) is more easily localized physiologically to the stage 3 neurons at the point of amputation. A random electrical signal introduced at this point can generate either a veiling noise sensation (likely to be “pink noise” in character and perceived as a littoral event) or a more symbolic sensation (associated with a perceived movement). Extraneous relaxation oscillation by the stage 3 neurons at the point of amputation can introduce signals that are processed as littoral events within the early stage 4 information extraction engines, are memorized in the appropriate neural circuits (Stage 4b and 6b as described in **Sections 4.6.3 & 19.10.4**) and subsequently reported symbolically by the late stage 4 engines as real events. As a result, these extraneous signals are interpreted by the stage 5 cognitive engines as real (although actually phantom) events

As a general rule, neither the visual snow or the tinnitus can be localized to a specific signaling channel of the neural system. As a result, most visual snow and tinnitus is recognized as a veiling noise. In a few tinnitus cases, the extraneous signal can be localized to the left or right auditory channels. In the case of structured noise, most signals are unlocalizable but a few related to tinnitus can be localized to the left or right auditory channel. The literature suggests the perceived extraneous auditory signals cannot be localized to a specific location, binaurally, in the external environment.

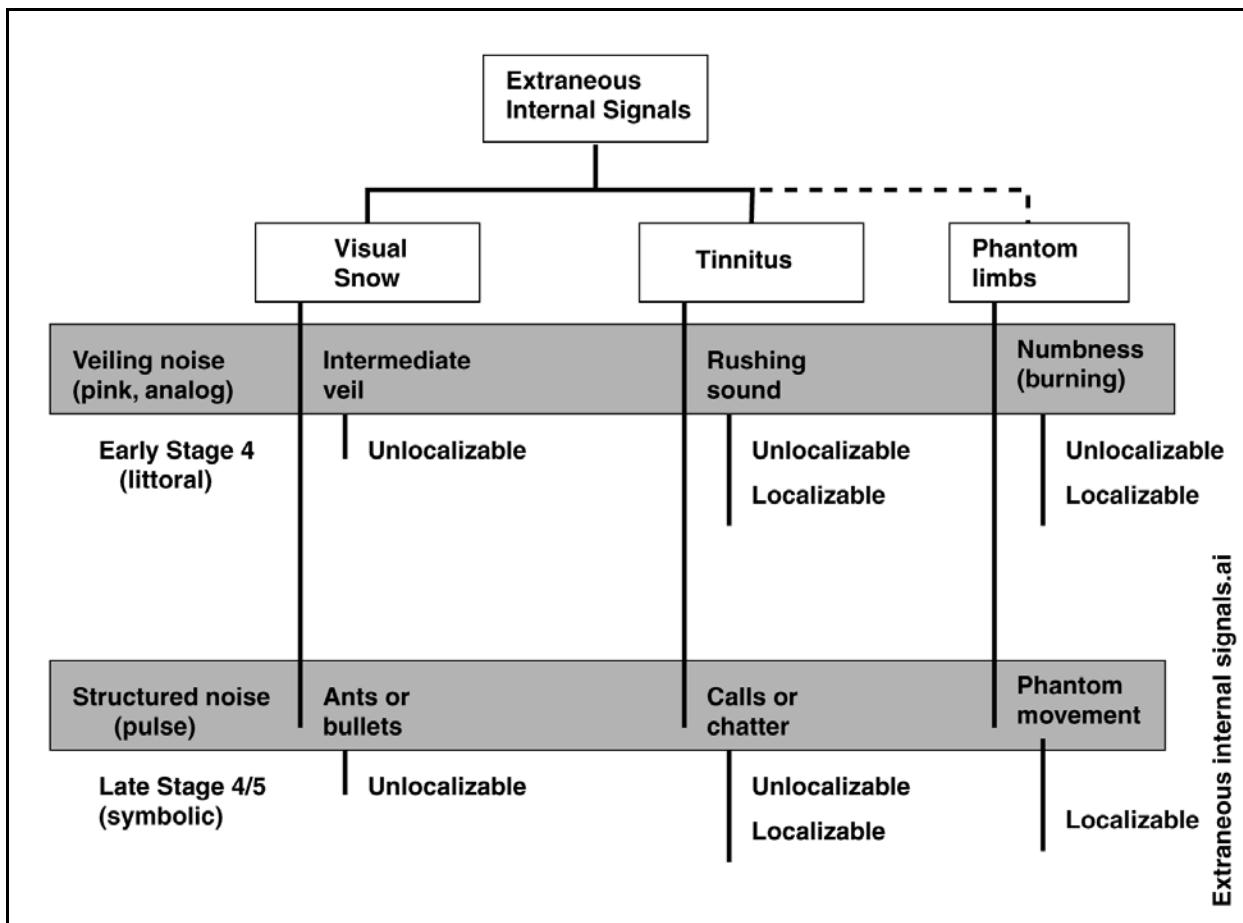


Figure 18.5.1-12 Comparison of extraneous internal neural signals, visual snow, tinnitus & phantom limbs ADD. This a working document and subject to change/expansion. Phantom limbs have been added due to the apparent similarity of characteristics. Only categories discussed in the text have been included at this time. The shading is added to indicate the similarity of features as they relate to the left hand column of parameters.

Localization to a specific finger or toe relating to an amputated limb suggests that different specific stage 3 neurons are introducing the extraneous signal(s). These extraneous signals could represent stage 2 summing or difference signals. Such specific location suggests only single malfunctioning neurons are needed to introduce extraneous internal signals into individual sensory channels.

Analysis based on the circuit configurations internal to individual neuron

Individual neurons found after stage 1 are generally six terminal devices (based on the Electrolytic Theory of the Neuron incorporated in this work). Generically, they exhibit three external electrical contact points on the surface of the signaling portion of the neuron to which electrical potentials can be applied. Generically, they also exhibit three electrical contacts to which electrical signals can be either applied or extracted. The two generic input structures, the dendrites and podites are frequently extensively arborized in support of tens to thousands of synapses. Introducing inappropriate bias potentials at any of these contact points can theoretically disturb the operations of individual neurons. It will be assumed that excessively high bias potentials are not available to cause destruction of the active element, the Activa, inside the individual neuron. Therefore, the problem is most likely due to incorrect biasing. Incorrect biasing can easily lead to a reduction of the noise thresholds at the inputs to the Activa used in stage 2, 4, 5 and 7 engines. Alternatively, incorrect biasing can easily lead to a change in the threshold of the Activa to monopulse generation in the case of stage 3a Activa. Similarly, it can lead to inappropriate demodulation at the stage 3b neurons, of the the signals generated by stage 3a neurons. These potential erroneous operating

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conditions closely match those discussed in the above *Analysis based on gross perceived imagery*.

There are a great many ways to bias the performance of an Activa through variations in the electrical components chosen for use within a neuron. These methods will not be explored here. The basic questions are 1) whether the Activa is biased to avoid excess noise entering the signal path or 2) whether the Activa is biased to generate undesirable pulses that enter the signaling channel(s).

Since the neurons of the system are direct-coupled (there are no capacitors required between neurons to isolate them electrically), it is not necessary for all of the potential six terminals of an individual neuron to appear explicitly. A neurite of a neuron may be biased via the quiescent axonal potential of one or more previous neurons.

Analysis based on thermal noise within electronic circuits

A potential problem when discussing the biasing of an electrolytic neuron is the electrical noise potential generated by the resistive component of any impedance relating to the circuit. Neurons are very high impedance devices with their impedance varying with their physical size; the larger the neuron, the lower its intrinsic impedance and therefore its potential noise voltage. **Figure 18.5.1-13** shows the nominal situation for a given resistance level. One square micron of neural lemma is reported to have a nominal impedance of 500 to 5000 megohms (**Chapter 8, page 3**). A small stage 3 pulse generating neuron might exhibit a noise bandwidth in its axonal circuit of 500 to 3000 Hertz. The resulting theoretical thermal noise associated with the circuit would approximate 100 microvolts (0.1 millivolts). Resistors frequently exhibit excess noise over the theoretical value of up to a factor of 10. The excess noise is seldom less than a factor of two even in the most sophisticated of man-made resistors.

0.1 millivolts of thermal noise accompanying a 100 millivolt pulse signal could be significant. If the real thermal noise was 1.0 millivolts, it could affect the information being propagated. Typically, it could affect the time of regeneration at a Node of Ranvier. This variation could be decoded at the stage 3b decoding neuron as a variation in the amplitude of the recovered signal.

Chapter 8 (page 130) describes a neuron exhibiting a 3 megohm impedance at 30 picoamperes of axonal current.

These values would suggest a given neural circuit may have a poor noise margin suggesting the need for the orthodromic neuron to be biased to hold the operation of that neuron just below the cutoff value under quiescent conditions.

More data is needed to more precisely predict the performance of such a circuit.

Analysis based on the chemical support to specific individual neurons.

[xxx including potential noise due to Brownian motion.
]

Analysis based on common medical interference with normal physiology

An experienced and well respected medical researcher has suggested VS may be due to ;

“(i), small tumors that influence the surrounding neurons and glia or general parenchyma; or

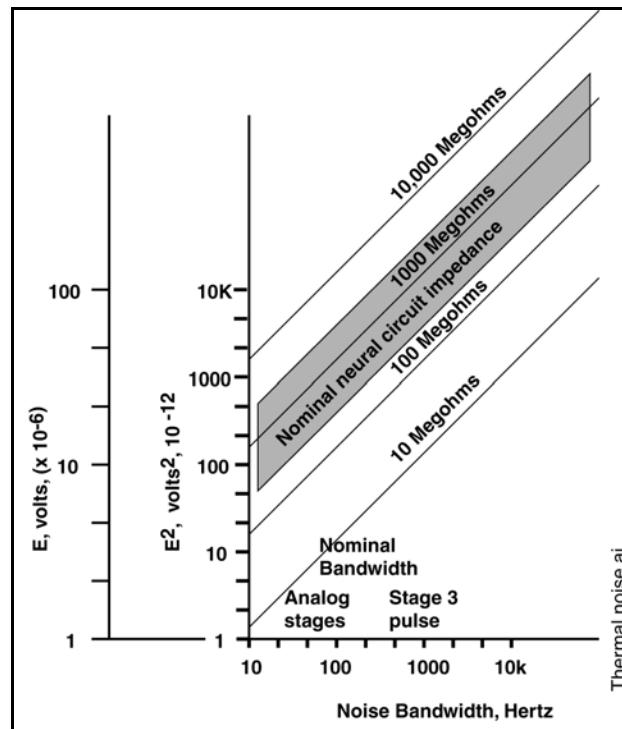


Figure 18.5.1-13 Theoretical thermal noise of a resistor. The nominal impedance level of a neural circuit is shown by the shaded box. The nominal bandwidths are shown above the horizontal scale. For a minimal size stage 3 pulse generating neuron, the noise bandwidth is on the order of 3000 Hertz and an impedance of 5000 megohms resulting in an RMS noise voltage of about 100 to 300 microvolts. See text.

(ii), viral infection of a small group of cells that are irretrievably altered metabolically to yield a hypermetabolic state;
 (iii), altered output from resident immune cells, the microglia; the list is long and the probability of any of these being causal, given current data, is difficult to determine.” The frequent occurrence of VS within a few days to weeks of the use of recreational drugs or significant trauma to the head also suggests the above are not major candidates as the cause of VS.

18.6 Medically identified psychotic perceptual (non-organic) failures within the CNS

The CNS provides a great deal of stage 4 signal processing that is presented to the stage 5 cognition function via the saliency map (and possibly other parallel circuits). Much of the stage 4 processing is performed in parallel. Hence many perceptual failures may occur without causing major shortcomings in overall visual performance. Particularly important failures are those occurring within the PGN/pulvinar couple and/or the long term memory system. They result in the subject having great difficulty in recognizing faces and other highly detailed visual scenes without any significant changes in the subjects overall field of view or light sensitivity. This type of failure has been described in the particular case as the “can’t recognize granny” syndrome or in the more general case, prosopagnosia. It can be defined as a form of agraphia. Failures in this pathway also frequently result in the reading ability of the subject being greatly reduced (frequently evaluated in terms of reading speed, see **Section 18.9**). This failure can be defined as a form of alexia. Since this pathway operates in parallel with the pathways leading to the visual cortex via the LGN’s, there is no apparent loss in visual performance associated with the foveal field from a visual perimetry perspective.

Failures of the type described above will be addressed in this section.

Many of the medical conditions of interest here have been described using a prefix followed by the suffix, esthesia. Esthesia in the context of this work will refer to the perception of a stimulus. The prefixes of the literature may be redefined more precisely here. As an example, allesthesia will be refined to refer to an atypical perception where, the perception is significantly altered. Synesthesia will be expanded to refer to an enhancement of a perception, or an expansion of a perception into more than one sensory modality. The first e in esthesia is frequently replaced by ae in the British literature.

Clinical reports of esthesia provide excellent sources of insight into the fundamental coding mechanisms employed at the detail level in the neural system. They frequently suggest a freezing of a given bit in a word in either the on or off state, thereby changing the presentation of a given scene by the stage 4 information extraction engines prior to the perception of the scene by the stage 5 cognition engines. The freezing may actually occur within these engines or in the stage 3 propagation neurons interconnecting them.

18.6.1 Major diseases involving allesthesia –significantly altered perceptions

Jacobs has presented considerable information relating a visual allesthesia to the epileptic illness of a young women¹⁹⁵. The major allesthesia involved the reproduction of a scene from her right field of vision in her left field of vision for an extended period, resulting effectively in a form of diplopia. The hallucinogenic image was frequently maintained for periods of up to 15 minutes even after the original source of the image was removed from the legitimate field of view. At the end of the interval, the image disappeared abruptly as if switched off as opposed to fading away exponentially. The report included EEG, CT and surgical investigation (craniotomy) to explore the nature of the mass found by the CT scan.

The Jacobs paper suggests a significantly more complex functional situation than just passing a portion of the visual field represented in one hemisphere of the occipital lobe by way of the corpus callosum to the other hemisphere. Unfortunately, the figure presented by Jacob shows a symmetrical true source image and a similarly symmetrical hallucinogenic image. The terms transposed and palinopsia were used but the term mirror image was not used. In fact, the term exact replica was used when referring to these hallucinations. Such replication would suggest a high level coding error associated more with the “where” aspect of stage 4 information extraction than the “what” aspect. The subject exhibited a significant degree of macular sparing.

¹⁹⁵Jacobs, L. (1980) Visual allesthesia *Neurology* vol 30, pp 1059-1063

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18.6.2 Major diseases involving synesthesia –significantly enhanced perceptions ADD

[xxx wide range of enhanced visual imagery, both mono modality and bi-modality.]

The symposia held by the American Synesthesia Association, Inc. (ASA) provides a wide range of generally first hand reports involving synesthesia¹⁹⁶. Many of the reports are by experienced teachers who are themselves synesthetes. Their perspective is generally a psychophysical one. The abstracts and archives of the papers presented at the annual convention of this organization are instructive.

A simple situation throwing light on how the “What” aspect of reading is coded within the foveola has been provided by Duffy, a founding principal of the ASA, Inc¹⁹⁷.

As a child, Pat Duffy told her father, "I realized that to make an R all I had to do was first write a P and draw a line down from its loop. And I was so surprised that I could turn a yellow letter into an orange letter just by adding a line." Another grapheme synesthete says, "When I read, about five words around the exact one I'm reading are in color. It's also the only way I can spell. In elementary school I remember knowing how to spell the word 'priority' [with an "i" rather than an "e"] because ... an 'e' was out of place in that word because 'e's were yellow and didn't fit."

Another study presented some useful information¹⁹⁸.

“The Color of O’s: Naturally-biased Associations of Shape to Colour

When adults are asked to associate colors to letters, their choices are surprisingly consistent with those of other subjects and with the percepts of individuals with coloured grapheme synesthesia (Simner et al., 2005). These consistencies could be naturally-biased (i.e., not related to specific experiences), or based in literacy (e.g., "A" is for "apple", apples are red). To explore the origin of colour/letter mappings, we developed a child-friendly game and tested three age groups. English speaking pre-literate toddlers, literate children aged 7-9, and adults were presented with letters for which the adult population exhibits consistent color mappings, namely A, G, O, and X (red, green, white, and black, respectively). On each trial, participants were presented with a letter, and chose which of two opponent colors (e.g. red/green) best corresponded. The letters O and X were consistently mapped to white and black in all three populations, while the letters A and G were consistently mapped to red and green only in the two literate populations. In subsequent experiments we explored the role of the sound of the letter versus its shape. We found that the consistent mappings for X and O in pre-literate children are determined by the shape of the letter and not its sound. These results suggest that although some shape-colour associations are literacy-based, others appear to result from naturally-biased associations between shape and colour that may reflect intrinsic cortical connectivity (Ramachandran & Hubbard, 2001). In ongoing research we are investigating other color-letter pairings and non-opponent color choices.

These snippets suggest the coding of “What” in reading (specifically a letter, but possibly a word) is probably closely aligned to the coding of the color (or rainbow in the case of a word) that is perceived by synesthetes viewing that letter. Whether the code for one of these perceptions is a subset of the code for the other, or whether the codes share a minimum difference between the pair that might cause confusion within the neural system based on signal-to-noise ratios is yet to be determined.

There are many reports of synesthetes perceiving objects of distinctive shapes as different in color from that perceived by those with normal vision. This may play a significant role in artists focused on the graphic arts where their perceptions may be more vivid than those of the norm.

18.6.2.1 Potential causes of synesthesia ADD

¹⁹⁶<http://www.synesthesia.info/aboutus.html> 6th conference; <http://www.synesthesia.info/florida.html> The 2015 conference will be held in Miami on 2-4 October.

¹⁹⁷Duffy, P. (xxx) United Nations Language and Communications Programme, New York City

¹⁹⁸Spector, F. & Maurer, D. (2007) Department of Psychology, Neuroscience and Behaviour, McMaster University 6th Annual National Conference of the American Synesthesia Association, Inc.

Figure 18.6.2-1 describes a potential explanation for synesthesia and potentially allesthesia as well but involving a more complex corruption of the data topography. The figure is discussed in greater detail in Section 11.7.8 of “The Neuron and Neural System.” [xxx add explanation]

Frame A describes a putative word in word serial/bit parallel format. Assume for the moment that a single word consists of 32 bits (the same as a typical word in a personal computer (PC) at the end of the 20th Century) with the complete word divided into three fields. As an example, the first field might describe the global feature within a sensory field (if related to vision, it might describe an object in the upper left portion of the overall merged visual field). It might use a previously assigned name, learned previously, or an arbitrarily assigned object name. The second field might describe the second feature of the object, its color, and the third field might describe the texture of the surface of the object. At this point, nothing is known about the actual neural code employed other than the fact a labeled line architecture is probably used as it is throughout all of the neural system where the coding is currently understood.

The first field is shown in histogram format to show how it would be generated by a group of independent stage 3B decoders as discrete analog values. In field 2 and field 3, only the nominal output intensity of each bit is shown. The ordinate scale is shown as relative because the absolute value of each bit is incidental in this discussion.

Frame B supports a discussion of potential failures in the interpretation of a set of stage 3 neural signals in word serial/bit parallel format as defined above. First, if only a single bit shows a high relative intensity, the resulting word probably does not appear in the lexicon of the stage 5 cognitive engines. If this bit has a constant value in a series of words, it probably indicates a circuit failure associated with that bit. One result is that any word containing this bit will be corrupted. Second, as shown, the “stuck” bit is at a value that is not at the most probable intensity expected by the cognitive circuits of the stage 5 engine processing this word. As a result, the overall word represented will be ambiguous when compared with the stored words of the stage 5 engine used in the pattern matching procedure. The output of the stage 5 engine may be reported as either of two potential words or conceivably as two distinct potential words output over separate output neurons. The latter possibility could account for the common form of synesthesia where a single black and white alphanumeric character or arbitrary shape is reported as to its true black and white character but also reported as exhibiting a hallucinogenic color or texture. If such an error occurs in an entirely different field, it could report a totally erroneous location for the object or even multiple locations for the same object as in allesthesia (as described in this work).

[xxx provide a frame C to interpret or remove it.]

18.7 After images and trails; and illusions as operational curiosities

The subject of after images and trails associated with moving images plays a significant role in the medical literature. Many of these errors in the dynamics of imaging phenomena can be interpreted within the context of the Electrolytic Theory of the Neuron and the recognition that the photoreceptors of the mammalian eye perform as change detectors and not as integrating imagers over nominal intervals of 0.05 seconds (1/20th second) as usually assumed.

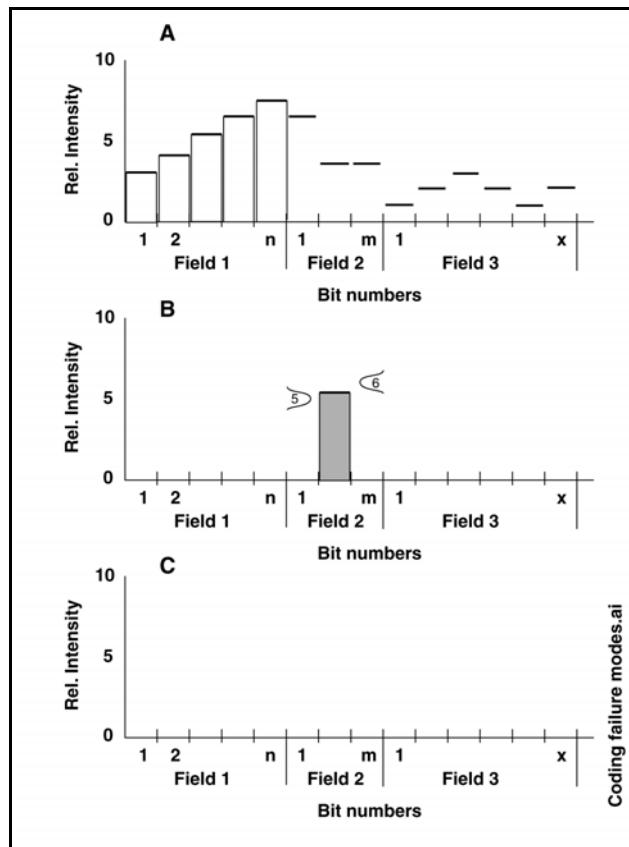


Figure 18.6.2-1 Potential coding failure modes in synesthesia. The potential errors are the same as those potentially encountered in digital computers lacking error detection and/or correction techniques. The potential for error is exacerbated by the analog mode of operation.

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The typical after image is a negative image of the original, suggestive of the change in adaptation level occurring following the presentation of the original positive image. Trails associated with high contrast portions of a moving image also are predominantly negative portrayals of the original feature.

The appearance of partial or relatively complete perceptions of Purkinje's tree is also intimately associated with the dynamics of the eyes. Purkinje's tree is a representation of the map of the vascular network found near the surface of the retina and between the lens presenting the image to the retina and the photoreceptors of the retina. The fluids within the vesicles are largely transparent and consist primarily of the plasma of the blood. Normally the photoreceptors behind a vesicle, acting as change detectors, discount the change in illuminance and or contrast reduction introduced by the vesicle. Thus, the output of the overall retina presents signals to the neural system that are devoid of any signals related to the vascular network. The perception of Purkinje's tree can be enhanced by disease or by careful manipulation of the light falling on the retina.

There is a large field of literature on the subject of illusions and after-images. These fields generally involve computational and second order transient effects of little practical value but considerable entertainment value (and in wartime, value in the field of camouflage). Uttal has presented interesting material in this field¹⁹⁹. The translation by Boeder of Tschermak-Seysenegg contains the results of the methodical study of after images by Goethe²⁰⁰.

Voke, writing a lesson for continuing education credit provides a popular discussion of a variety of these effects²⁰¹. Here material is not rigorous and several of the examination questions and answers appear to be inappropriate. Trick & Konenberg have also written comprehensively in this area²⁰².

18.7.1 After images upon cessation of the original stimulus

After images in the normal eye(s) are usually demonstrated using a test field such as **Figure 18.7.1-1** from Stone²⁰³. Each disk of the right set appears in its complementary color compared to the left set (as expected by the P- and Q-channel processing performed within the retinas). Note, the "green disk" is olive in color. This is the actual peak sensitivity of the mid-wavelength photoreceptor. The four colors shown actually form the axes of Hering's color perception space (See **Section 17.3.3.6**).

The adaptation of the photoreceptors is nearly instantaneous to high intensity illumination but their recovery times after removal of the high intensity are quite extended (and depend on the intensity of the initial illumination. See **Section 17.6** and **Figures 17.6.1-4 and -7**). In general, the most important recovery time constant of the photoreceptors (there are actually three that operate in series) is on the order of 60 seconds and accounts for the disappearance of the complementary colors in the above demonstration after some fraction of this time constant because of the illumination level used..

¹⁹⁹Uttal, W. (1981) A taxonomy of visual processes. Hillsdale, NJ: Lawrence Erlbaum Associates

²⁰⁰Tschermak-Seysenegg, A. (1952) Introduction to Physiological Optics. Springfield, IL: Charles C. Thomas, pgs 70 and 105

²⁰¹Voke, J. (2010) Common entoptic phenomena and their clinical significance.

http://www.optometry.co.uk/uploads/articles/CET%20290110%201%20POINT_1.pdf

²⁰²Trick, G. & Kronenberg, A. (2006) Entoptic imagery and afterimages In Duane's Ophthalmology, 2006 Edition. NY Lippincott Williams & Wilkins Chapter 20

²⁰³Stone J. (2012) Vision and Brain: How we perceive the world. Cambridge, MA: MIT Press plate 12

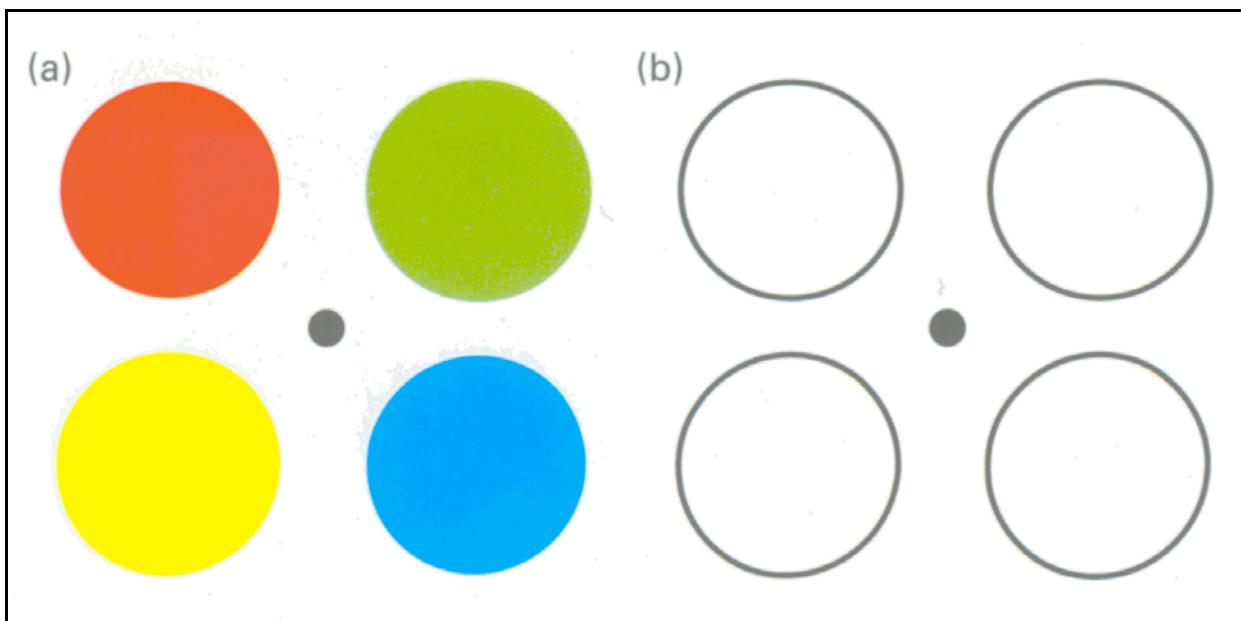


Figure 18.7.1-1 Color aftereffect. (a) Four disks colored red, green, yellow and blue. (b) Same four disks without color. Fix your gaze on the central black dot in (a) for about 30 seconds, then transfer your gaze to the black dot in (b) and notice the perceived color of the disks. Why are the four colors the complement of the equivalent color on the left. Note the upper left disk appears greenish while the upper right appears reddish. Similarly, the lower left disk appears bluish and the lower right appears yellowish. From Frisby and Stone, 2010.

18.7.2 After images combined with the presence of a moving original stimulus–trails EMPTY

18.7.3 Induction of the perception of Purkinje's tree ADD

Purkinje's tree is frequently observed when an optometrist shines a small but bright light into a subjects eyes from an off-axis position and moves it about. This process is particularly effective if the subjects eyes have been adapted to a low light level for at least a typical five minutes. The effect is to cause the shadow of the vascular mesh to move about relative to the underlying photoreceptors. The photoreceptors dutifully report the change in light level with this movement.

18.7.4 Induction of Purkinje's “blue” arcs

Mauser has described a procedure to observe what are known as Purkinje's arcs in a classroom setting²⁰⁴. His description is comprehensive and very suggestive of the source of these arcs.

“If you look at the right edge of a small red light in an otherwise dark field with a partly dark-adapted right eye, you will momentarily see faint blue arcs curving away from the light toward the right (see Figure 10). These blue arcs follow the paths of the nerves arcing away from the edge of the fovea (where the spot of light is focused) to the optic disk and were first described by Purkinje (1825). You can easily see the blue arcs at night in your home in a room with some red LED indicator lights on equipment. Turn off the room lights and close your eyes for about 30 seconds. You should see faint arcs when you open your right eye and look at the right edge of a red light. If you look at the left edge you will see a blue spear or spike extending to the right. Blinking every second or so will help prolong seeing the blue

²⁰⁴http://www.nabt.org/websites/institution/File/pdfs/american_biology_teacher/2011/ABT_Jan_Online.pdf

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arcs, as will shifting your view from side to side. If you look straight at the light, the arcs or spike will disappear, although you may see a blue haze. If you use your left eye, everything is reversed. Alternatively, a cardboard tube lined with black paper and with either a red LED or a small opening covered with a red filter at the far end can be used in a well-lit room. Moreland (1968) describes a template that produces multiple arcs suitable for classroom demonstrations, and Walker (1984) reproduces this template. See the article by Wolfe (1991) for an explanation and graphics suitable for students.”

The discontinuous lines in the image accompanying Mauser’s description are suggestive of Purkinje images due to multiple reflections in the optics rather than the pattern of myelinated axons moving toward the blind spot. An additional citation relative to this subject is Moreland²⁰⁵ and the old paper of Dolecek & Launay²⁰⁶. Trick & Konenberg (2006) have asserted,

“During monocular viewing of a dim light of any color in a darkened room with the temporal parafoveal retina stimulated (i.e., 1 degree to 2 degrees from the fixation point), two faint glowing blue-gray arcs will be seen bowing above and below fixation (Fig. 3). These arcs begin at the source (although they are noticeably wider than the source) and extend to the blind spot. If the nasal parafovea is stimulated instead, then a triangular patch of blue haze (a blue spike) with its base at the light source and its apex at the blind spot will be observed. This entoptic phenomenon, which is referred to as the blue arcs of the retina, appears briefly (0.5 to 1 second) but fades on extended observation. The position and orientation of the blue arcs are generally held to correspond to the route of the parafoveal arcuate nerve fiber bundles extending to the optic disk. Thus, this visualization is thought to be the result of secondary electrical stimulation of the retina whereby action potentials in the arcuate bundles excite adjacent neurons. Moreland suggested that both rod and cone pathways are involved in generating this entoptic image.”

and provided **Figure 18.7.4-1**. The figure has been modified to bring it closer to a scale drawing (Section 2.2.2). Both Dolecek & De Launay and Moreland varied the value of X. Dolecek & De Launay also recognized the fact the blind spot was not on the horizontal meridian passing through the point of fixation.

The above information is basically without calibration and the information is open to numerous interpretations. Recently Sobolev & Mollon have undertaken more substantive experiments following the

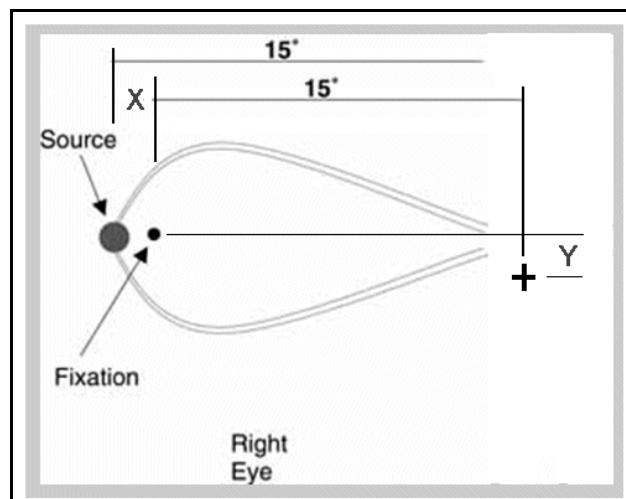


Figure 18.7.4-1 A caricature of the appearance of the blue arcs of the retina when the temporal retina is stimulated. The center of the blind spot is two degrees away from the horizontal line passing through the point of fixation. The point of fixation is 15 degrees from the center of the blind spot. The dimension X is a variable in these experiments. The point 15 degrees from the “source” was not defined in Trick & Kronenberg. Modified from Trick & Kronenberg, 2006

²⁰⁵Moreland J D (1969). Retinal topography and the blue-arcs phenomenon. *Vision Res* vol 9(8), pp 965-976

²⁰⁶Dolecek, R. & De Launay, J. (1945) Entoptic Mapping of the Purkinje Blue Arcs *JOSA* vol 35(10), pp 676-680

above conventional understandings²⁰⁷. Their abstract (which did not lead to a formal publication) notes,

"The blue arcs, discovered by Purkinje in 1825, exhibit a topography that mirrors the well-established distribution of arcuate nerve fibres passing from nasal and temporal macular ganglion cell bodies to the optic nerve. One traditional hypothesis is that electrical activity in the arcuate bundle excites nearby cell bodies giving rise to two bright blue arcs. The aim of the current work is to study the time constants of the generation and the decay of the phenomenon. Possibly for the first time, a performance measure was used to examine the blue arcs: in a spatial 2AFC task, subjects were required to detect a small blue probe presented in the path of the arc. Eye position was concurrently monitored by a Cambridge Research Systems eye tracker. We have successfully measured a delayed 'on-effect', which reaches its maximum at 400 ms after the onset of the inducing stimuli, as well as an 'off-effect' that becomes apparent for stimuli over 900 ms. We have also recorded the rate of decay of the arcs at various durations of the inducer. The results suggest that between the onset of the inducer and the generation of the blue arcs there is an integration stage with a long time constant."

Voke has also described the preferred methods of illuminating the spot on the retina in her figure 2. Citing Moreland, She notes that "Prolonged dark adaptation ruins the effect."

²⁰⁷Sobolev, A. & Mollon, J. (2006) The blue arcs of Purkinje *Perception* vol 35, ECV Abstract Supplement

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There are many photographic images of the Purkinje Tree of the human eye. **Figure 18.7.4-2** provides an image of the arcuate capillary structure of such a tree at approximately the same scale as in the previous caricature (and similarly truncated) but obtained by ophthalmological examination. Note the thinner capillaries on the left with their significant curvature. The capillaries are less curved on the right as they become larger and approach the blind spot. The image was deposited in the Wikipedia library in 2009 by Macario. Although difficult to see in this image, there is considerable scattered light associated with the illuminated spot on the retina. The scattered light masks the fact that a group of the smaller capillaries converge toward the center of the fovea in order to support the neurons surrounding that feature.

By combining the individual statements in these reports, Reviewing the arcuate vascularization as well as the arcuate nerve structure of the retina and reviewing the cross section of the human retina in the peripheral regions, a totally different interpretation of these papers can be formalized.

It is critically important to recognize the optical geometry of the eye. Illumination of a spot in the temporal field of view actually illuminates a region on the nasal portion of the retina. The blind spot is mapped in the temporal field but is physically located in the nasal portion of the retina.

The Dolecek & De Launay paper is extensive and shows the mean and statistical deviation from the mean associated with one arc in their figure 1. Their figure 2 is a collection of their means. The frames in this figure are beginning to show a grouping of the means but more individual test records would be needed to see if they form more defined bundles. Dolecek et al. have noted a long list of specific facts that includes, “4. Double and single arcs occur when the stimulus lies on the nasal side of the projected field (temporal side of the fovea on the retina). This statement is in total agreement with the image of the capillaries presented above. They conclude with “12. The general theory of the mechanisms involved in the production of the Purkinje blue arcs is still in a formative stage.” They did not address the possibility that their arcs were related to the capillary structure of the retina.

Moreland also offers an extensive paper. It includes a point relative to the above paragraph, “It is of interest to note that all of the smoothed arc loci reported by Dolecek and De Launay (1945) are shown originating from their respective stimuli. The raw data were given for only one of their arcs, however, and its plot (see Fig. 4) ceases at about 2” from the stimulus. Although errors in the smoothed mean locus are small (s.e.m.=0.10” to 0.15” taking 10 points at a time), that is too great a distance for extrapolation to detect the presence or absence of the predicted 0.6” of bypassing applicable in this instance.”

Moreland also noted, “One purpose of these was to follow up the suggestion put forward by Troland (1920) that axon induction was improbable. If such an induction did occur then ganglion axons, serving regions to the side of the light stimulus remote from the blind spot but following a path very close to those serving that stimulus, could be excited.” He further noted, “Another aim of this preliminary experiment was to detect whether the arc locus, when extrapolated, passed through the stimulus or not; since either of these results would distinguish between the photoreceptor layer or some more proximal location as the site of arc-generation.” In discussing the potential source of the elements of the retina shadowing the photoreceptors, the last paragraph of the discussion in Moreland asserted, “It would seem, since the ganglion cell layer itself is 60 μ deep, that the effects of the primary axonal discharge are felt only within the proximal regions of that layer. This would eliminate the diffuse bipolars and amacrices from the previously mentioned choice and leave the small diffuse ganglions as the most probable site of arc generation.”

The volume of the retina labeled the ganglion cell layer, is shared by both the small diffuse ganglions and the capillaries supporting those ganglia (the first figure in **Section 3.2** from Boycott & Dowling, 1969). The capillary shown in Boycott & Dowling is centered in the ganglion cell layer, has a diameter of about 50 microns and could contain on the order of 30 ganglion soma within its cross section; such capillaries are not transparent but are normally invisible because the photoreceptors are change detectors and adapt to the constant presence of the capillaries.



Figure 18.7.4-2 A photograph of Purkinje's tree obtained by ophthalmological examination of the vascularization of the human retina. From Macario, 2009.

The small diffuse ganglia are normally considered transparent. They are the only known stage 3 ganglion neurons that are not myelinated for the length of their first few axon segments in order to maintain their transparency and minimize light scatter. Histology indicates the ganglion neurons form two fans, of essentially equal density across each fan in the plain of the retina, as they emanate from the blind spot. However, Moreland makes the assumption that these neurons bunch and form nerves of significant cross section. He calculates a parameter $g \approx GG'$ representing the width of the nerve needed to satisfy his model. A capillary diameter of 50 microns is a good approximation to the diameter of the calculated parameter g . Such a capillary would provide a significant cross section for shadowing the photoreceptors at the Petzval surface (the interface between the inner and outer segments) if a suitable moving light source was used (relative to the retina). The normal tremor of the eye can provide such movement if the light from the source enters the eye as a skew optical ray.

The discussion in these papers as to whether the arcs converge on the illuminated spot or on the fovea appears unnecessary if the capillaries are accepted as the source of photoreceptor shadowing. Some of the smaller capillaries clearly converge on the fovea but terminate outside of the 1.2 degree diameter foveola.

The statement by Trick & Kronenberg, "If the nasal parafovea is stimulated instead, then a triangular patch of haze with its base at the light source and its apex at the blind spot will be observed." is referring to the nasal retina and not the field of view in object space. There is no need for the vascularization of the nasal retina to group the capillaries in order to go around the foveola. These capillaries spread uniformly in a fan and could easily be observed as a triangular "haze" at low light level.

The nominal conclusion and null hypothesis for future investigation is,

- The majority of the work relating to this phenomenon is very old and suffered from poor instrumentation.
- The Purkinje Arcs are perceived by the subject rather than observed by the ophthalmologist.
- The Purkinje Arcs or "blue arcs" are a special case of the Purkinje tree phenomenon readily observed by the ophthalmologist..
- The arcs are produced by the shadowing of the retina by the larger capillaries of the vascular system rather than any neural structures.
- The photoreceptors affected by the shadowing are functioning at the scotopic illumination level resulting in colorless perception within the neural system (except in the spatial region of the spot illumination).
- The arcs are not characteristically blue. They are generally perceived as colorless or gray. If the light level is raised marginally, they may be perceived as blue-green due to the excitation of the most sensitive mid wavelength photoreceptors.
- The photoreceptors are performing normally as change detectors and the shadowing must be moving to support continuous perception of the phenomenon.
- The initial delay in perception described as the 'delayed "on effect"' and the related 'off-effect' are compatible with the delays predicted by the Excitation/de-excitation (E/D or P/D) equation.
- The 'delayed "on effect"' is highly dependent on the intensity and wavelength of the illumination available to the retina at a distance from the illuminated spot.
- The wavelength of the illumination is not important. However, future experiments should employ narrow wavelength sources (such as narrow wavelength LEDs –not employing a phosphor–in a slit lamp configuration) at known intensity levels to insure the most repeatable results.
- The intensity of illumination at the peripheral retina distant from the illuminated spot is probably dominated by scatter within the optics of the eye and is typically age dependent.

Future experimentation should not suggest to the subject what color the arcs are but ask them in a neutral voice what they observe as a function of the intensity of illumination of the stimulus.

18.7.5 Illusions and "magic"

The stock and trade of magician is to generate illusions (mis-perceptions within stage 4 leading to incorrect cognition within stage 5). By combining such illusions with other activity occurring below the threshold sensitivity of the visual system, the magician has a considerable degree of freedom to perform. The basis of many illusions can be ascertained from [Figure 17.4.1-8] showing the generation of a perception at lower left and its comparison with various cues stored in memory on the lower right. If the magician can cause the subject to rely upon a stored cue as representative of the actual perceived situation, rather than the representation suggested by the physiological system, he has accomplished his goal. Until that mistaken perception is cancelled out, the magician is free to do almost

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anything within the visual field.

A second aspect of illusions and magic rely upon introducing ambiguity, creating a visual stimulus that can be perceived in two different ways. Such ambiguity is heavily dependent on the experience (prior learning and memorization) of the individual. Once, the ambiguous visual situation has been encountered, the subject has the option in the future of interpreting the scene in either of two or more ways at his discretion.

Adamovic has provided an entertaining website on visual illusions²⁰⁸.

18.8 Additional abnormalities from the medical perspective

This section focuses on what are typically described as organic diseases, as opposed to the non-organic or psychotic diseases. The latter are addressed more specifically in **Section 19.12**. The interface between organic and non-organic diseases is not a clear one when one considers chemical imbalances within the brain. **Section 18.8.2** addresses some of these conditions. The effect of recreational drugs, and the effects of narcotics, are becoming more clearly documented with time.

Discussing the abnormalities of vision from a medical perspective is difficult because of the limited perspective of that field provided by current texts^{209,210,211}. Most of these texts are rewrites started many years ago. They invariably lack a descriptive model and are based primarily on morphology and behavioral observation. Swash & Oxbury have provided one of the better set of definitions related to various sensory neurological disorders²¹². The new text by Liu et al. should be reviewed²¹³. While written by three medical men, it reflects much recent work and uses different terms for some visual conditions. Even those texts aligned to neurology lack any section on the operation of the neuron from a signaling perspective. To discuss the abnormalities of vision from a medical perspective, a broader view is necessary. **Figure 18.8.1-1** provides an expansion of a current, but obviously archaic, baseline to provide the necessary scope. This figure begins from a less extensive version in Glaser. By extending the figure, new explanations of Anton's Syndrome, blindsight and similar disorders achieve a new level of understanding. They can be directly related to the block and circuit diagrams of this work.

Before proceeding, it is necessary to formalize the nomenclature. Various authors use cortex in a variety of ways, sometimes in the same volume. The cortex is defined here as the complete brain beginning at the top of the spinal column. It includes all of the elements of the Old Brain, including the cerebellum and the New Brain, the cerebral cortex. The cerebral cortex is sometimes referred to as the *neo-cortex*. Unfortunately, the nouns cerebrum, plural cerebra, have not come into common usage, leading some to call the cerebral cortex just the cortex.

The figure introduces an additional set of signaling paths that have only been hinted at and discussed indirectly in the literature. This is the extremely important PGN/pulvinar pathway. In addition, the figure also highlights the Precision Optical System (POS). This system was previously known as the auxiliary optical system because lesions in this area were known to affect vision but its true purpose and function were unknown.

²⁰⁸ Adamovic, J.(2004-) Optical Illusions <http://brainden.com/optical-illusions.htm>

²⁰⁹ Newell, F. (1986) Ophthalmology, 6th ed. St. Louis, MO: C. V. Mosby

²¹⁰ Newsome, D. ed. (1988) Retinal dystrophies and degenerations. NY: Raven Press

²¹¹ Glaser, J. ed. (1999) Neuro-ophthalmology, 3rd ed. NY: Lippincott Williams & Wilkins.

²¹² Swash, M. & Oxbury, J. (1991) Clinical Neurology vol. 1. NY: Churchill Livingstone

²¹³ Liu, G. Volpe, N. & Galetta, S. (2001) Neuro-Ophthalmology. NY: Saunders

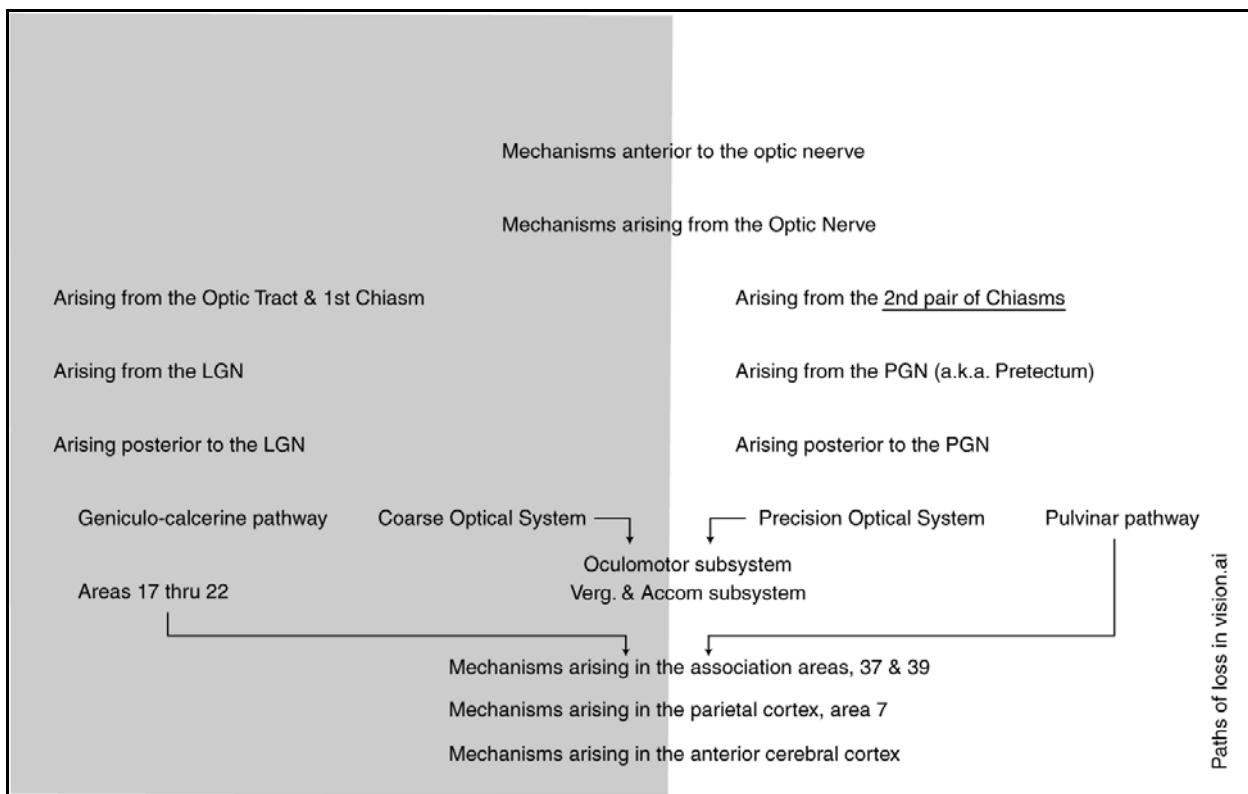


Figure 18.8.1-1 Mechanisms of visual loss by location. Shaded areas the conventional classifications of current textbooks. Unshaded areas, new categories based on this work. The pathways below the Perigeniculate Nucleus (PGN) a.k.a., pretectum divide into two, the pulvinar pathway to the cerebral cortex and the feedback pathways to the eye closing the servomechanism loops associated with pointing vergence, accommodation, and exposure control. See text.

This is the very system that makes vision as found in humans, as opposed to many lower animals, possible. It is the seat of our ability to analyze, interpret and perceive fine detail in an image. Without it reading is impossible. The figure could be extended ad infinitum under the headings, areas 17 to 22 and by subdividing the pulvinar further. These areas of the cerebral cortex contain hundreds to thousands of individual feature extraction and command generation engines associated with vision.

A complication related to clinical medicine is the common, and appropriate, practice of lumping groups of individual diseases into syndromes (groups of diseases). While the description of a syndrome is very valuable in locating the source of the problem, it frequently requires analysis of several syndromes containing common disease elements to localize the individual diseases involved. This will be illustrated in the section on achromatopsia (**Section 18.8.3**). This syndrome consists of an easily identified set of individual diseases (including the more precise achromatopia, without an “s”).

The occurrence of flashbacks following use of drugs is a recognized condition known as Hallucinogen Persisting Perception Disorders (HPPD). Such a general label can be applied to a broad range of conditions. This results in a difficult position. The medical discourse becomes complicated by many peripheral comments that may or may not belong to the defined syndrome from a physiological perspective.

The nature of the problem of relating distinct failures in the visual system to the appropriate clinically observed condition is illustrated by Table 11-1 in Glaser. That table lists forty-seven types of nystagmus with virtually no assignment of cause by physical location. There is one general group labeled vestibular since the types under this class have something to do with orientation of the subject. This work will attempt to address this list from a causal perspective in a following section.

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It appears important to document a recent message I received concerning when certain visual symptoms occur.:

One of [my friends] told me that he enjoys sleeping because he doesn't see visual distortions in his sleep. I do. All of them. My nightmares are full of flickering, flashing, after images, trails, colors changing, snow, etc. Not just nightmares of the symptoms, but the symptoms are integrated into my regular dreams and nightmares...as if that is how my brain really sees, even subconsciously. (4 December 2012)

This report seems to confirm the neurological nature of many of these problems, as opposed to problems within the retinas of the eyes, and possibly even the rest of the input structures of the visual modality. If these symptoms are seen when one is asleep, it strongly suggests they are introduced at points orthodromic to the saliency map of stage 4; i.e., the distortions are introduced after recall of the pertinent imagery from long term memory.

18.8.1 Background

While Glaser has noted the references by others that "Normal human vision is not a single unitary faculty, but rather a synthesis of multiple semi-autonomous functional subsystems, segregated into sets of separate pathways or 'channels' between the eye and the brain." He continues, "Visual stimuli are processed via multiple neural channels, or 'parallel pathways' . . ." He has not gone far enough, the pathways are not parallel within the cerebrum and are far from parallel in the thalamus. The system takes on a distinctly star-type configuration within the cerebrum, commissure forming between all combinations of semiautonomous (generally single purpose) signal processing engines. See **Chapters 11 & 15** for a broader discussion of these matters.

When discussing diseases of the visual, and probably any sensory, modality it is important to categorize a specific failure as due to one of the following causes;

- A disruption of the signaling circuits due to internal failure.
- A disruption of the signaling circuits due to external pressure, frequently due to the growth of a tumor in adjacent non-neural tissue.
- A misinterpretation or mis-perception of the information provided due to a psychotic condition.
- An abnormality in the chemical environment supporting the neural system.

Failure to explore each of these possible sources of a disease can lead to an inadequate understanding of the disease.

The merging of the data collected by different, and frequently overlapping sensory and/or signaling channels analyzing the various sectors of the field of vision is complicated. This merging frequently encounters difficulty and results in "migraine headaches" and hallucinations. The difficulties may involve other chemical or hydraulic imbalances. Glaser has provided a figure stressing the need to examine local areas along the vertical meridian when trying to diagnose visual disease. His nomenclature distinguishes between peripheral problems and foveola problems.

Many visual failures can be associated with vascular failures within the CNS. Such failures can be caused by various hydraulic changes involving local bleeding causing excessive swelling and resultant pressure on local areas of the visual cortex to major hemorrhage leading to major damage to the neurons of the visual system to blockage of key arterial paths leading to the death of large numbers of neurons in a region. The losses of visual field in the patient can frequently define where these failures have occurred. A map similar to **Figure 2.8.1-3** can be constructed in these situations.

18.8.1.1 Pathways

Glaser also notes the three pathways within the optic nerve, "(1) the papillomacular bundle, . . which serves the central field of vision; (2) the relatively thick superior and inferior arcuate bundles, which roughly parallel the respective vascular arcades; and (3) the nasal radial bundles, which expand outward from the nasal aspect of the disc." Oyster has characterized the region of the papillomacular bundle on the surface of the retina but not to scale²¹⁴. The papillomacular bundle associated with the foveola amounts to about 2.5% of the neurons in the optic nerve.

This work uses the term optic nerve up to the chiasm. However, it describes each of the two optic tracts beyond the chiasm as exhibiting a second chiasm that separates the papillomacular bundle (associated with the foveola) from the remaining nerves proceeding to the LGN. The foveola related portion of the papillomacular bundle terminates in the perigeniculate nucleus (PGN), previously labeled the pretectum in this work. In the literature, the PGN has

²¹⁴Oyster, C. (19xxx) The Human Eye. Sunderland, MA: Sinaur Associates. pg 195

occasionally been labeled the Brachia of the Superior Colliculus or the afferent portion of the superior colliculus (SC).

Within the bundles proceeding to the LGN, an additional divide occurs at the two LGNs. One portion connecting to the parvocellular layers and the other to the magnocellular layers.

The above pathways have been individually enumerated in the Top Level Schematic Diagram of the visual system presented in **Figures 1.5.2-2**, and beginning with **Figure 15.2.3-1** in Chapter 15. Using the individual schematics associated with different functional paths through the visual system, much more precise descriptions can be given for many visual diseases. These diagrams frequently show that a given syndrome can be caused by failures at multiple individual locations. Only multiple, carefully developed, psychophysical experiments can localize the problem to a specific circuit location.

Glaser has provided a breakdown of the major visual system losses associated with each of the headings on the left side of the figure (page 3). However, that list does not include such typical visual problems as strabismus, nystagmus, myopia, reading difficulties, etc. These, and other functional losses can only be explained in terms of the areas delineated on the right side of the figure.

When it is recognized that the right hand column contains the elements processing signals from the foveola, it becomes clear how important these areas are. These areas control the operation of the eyes and the extraction of the initial interps (along with the cerebellum) leading to the percepts that are required for cognition within the cerebrum.

18.8.1.2 Blindness

The above pathways also explains the concepts of blindness, blind sight, mind-blindness and the somewhat comical condition known as Anton's syndrome. In Anton's syndrome, the clinician tells a subject that they are clinically blind with respect to their cerebrum but the subject insisting that they can see just fine. This is a condition similar to the poorly named macular sparing. The subject is using the portion of his visual system related to the foveola, and possibly part of the surrounding fovea, to carry out the routine tasks of life, even if their peripheral vision is less than desired. While the subject does require some of the functions of the LGN, for purposes of vergence control, he does not require the services of areas 17 through 22 of the cerebrum. The information is transmitted to area 7 of the cerebral cortex over the pulvinar pathway from the pretectum. Anton's Sundrome is frequently labeled keyhole vision in the clinical context. The inverse of Anton's syndrome, a loss of the high acuity channels related to the foveola and the pretectum leave the subject unable to see details associated with contrast edges while still able to see shadings and colors (both stationary and moving). This condition is frequently described as the grandma syndrome. In this syndrome, the engines of the cerebrum are working normally, but the pulvinar is not extracting the high resolution information from the signal stream.

"Keyhole vision," the "grandma syndrome" and "blind sight with the ability to detect motion" are readily interpreted using the figure in **Section 18.1.3.1**. Medical observation of these syndromes and their interpretation based on this section strongly supports the parallel path signal processing employed in at least primate vision. High resolution Information is extracted via the PGN and pulvinar (the PGN/pulvinar couple), with lower resolution information extracted in the LGN and occipital lobe of the cerebrum (the LGN/occipital couple)..

The name blindsight was coined by Weiskrantz following the surgical removal of the right occipital lobe of a patient. Kennard has reviewed the subject of blindsight in some detail and provided a bibliography²¹⁵. Zeki, et. al have also provided a recent discussion of blindsight. Berlucchi has described the evolving thinking concerning blindsight but without recognizing the multiple parallel signaling paths in vision²¹⁶. See **Section 18.8.9.1**.

Because of the multitude of failures, such as those above, in the visual system, the definition of blindness is not an easy one. While a person may be totally blind for a variety of reasons. The number of ways a person can be partially blind staggers the imagination. For blindness can be associated with the failure of almost any feature extraction engine of the visual system. Thus the state of blindness requires an associated adjective in the statistical majority of cases.

²¹⁵Kennard, C. & Rose, F. (1988) Physiological Aspects of Clinical Neuro-Ophthalmology Chicago, IL: Year Book Medical Publishers pp 126-131

²¹⁶Berlucchi, G. (2004) Some effects of cortical and callosal damage on conscious and unconscious processing of visual information and other sensory inputs *Prog Brain Res* vol 144, pp 79-93

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A frequent distinction between cerebral blindness and blindness due to ocular diseases is frequently made. However, this overlooks the large class of blindness's associated exclusively with the midbrain.

18.8.1.3 Underlying pharmacological imbalances

Many of the conditions discussed below, and those related to color vision abnormalities, (particularly when they are of recent origin or short term) can be associated with chemical imbalances in the system of the subject. Diabetes mellitus (aka, diabetes) is a chronic medical condition typically classified into two forms, type 1 commonly associated by a problem of the child's pancreas that is unable to produce insulin and type 2 commonly associated with a problem of properly processing sugar (glucose) and starch within the body. Diabetes mellitus, and some shorter term blood sugar conditions, are known to introduce changes in color perception, accommodation errors, and some strabismic and nystagmic errors. These can generally be accounted for by a change in the availability of electrostenolytic supplies to the regions of the individual neurons providing power to these neurons. These supplies are interfered with by the above and other pharmacological imbalances. They usually result in an offset voltage error in the signals transmitted by these neurons. This type of error will be discussed frequently below. A variety of complications due to these causes are discussed in Glaser (pp 547-549).

Vilupuru & Glasser have studied the effects of pharmacological agents on accommodation in rhesus monkeys in considerable detail²¹⁷. They specifically studied the rate of diopteric change under various conditions using electrophysiological techniques. An extensive source list was provided.

The ability of pharmacological agents to impact the electrical operation of neurons suggests that some of the related genetically based conditions may be the result of mis-transcribing or mis-implementing the individual's genetic code. An error in the size of a feature on the wall of a neural axon can cause such a voltage offset by changing the electrical impedance of the associated circuit. No physically recognizable deformity is required.

The pharmacological impact of the glutamate family, including L-dopamine, on the neural system is discussed in **Section 8.6.4**.

18.8.1.3.1 Vitamin deficiencies can cause a variety of medical problems

Deficiencies in vitamin B1 are frequently associated with cataract and other problems of the lens system of vision. Vitamin B1 deficiencies have also been associated with the performance of the CNS; such problems have been specifically identified with regard to Broca's area and Wernicke's area. A deficiency in Broca's area appears to inhibit *ab initio* production of words in response to instructions from the cognitive engines of the prefrontal lobe. In the case of Wernicke's area, the situation is more complicated. These observations focus attention on the Pallidum in the case of Broca's area and in the combined striatum/pallidum in the case of Wernicke's area. See the figure reproduced in both **Figures 4.6.3-1 & 12.5.1-1** and the discussion of this figure in **Appendix S** of "[Processes in Biological Hearing](#)." The inhibition may be in decoding the words received prior to the presentation of their meaning to the cognitive engines. Such symptoms are frequently associated with early dementia. A dosage of 50-100 mg/day of vitamin B1 in the case of the elderly frequently results in observable improvement in word production within days in the above context.

A variety of pharmaceuticals, including digoxin and furosemide (Lasix®) can interfere with the vitamin B1 level in the blood.

18.8.1X Color blindness and its diagnosis

Many patients with abnormal color vision have not received a thorough evaluation of their condition before a diagnosis is presented. As shown in [**Figure 8.1.5-1**], the potential number of failure sites (modes) is high but an orderly evaluation can clarify many points and more clearly define various conditions. Interestingly, most color blind sufferers do not have a clear understanding of the extent of their disease. They frequently treat the problem as a nuisance more than a significant disease. A shortfall in the color performance affecting wavelengths shorter than 437 nm is seldom recognized at all because of its dependence on high color temperature illumination.

Abnormal color perception can occur in many forms. Its severity can be a function of light level. It can occur in

²¹⁷Vilipuru, A. & Glasser, A. (2002) Dynamic accommodation in rhesus monkey. *Vision Res.* vol. 42, pp 125-141

either or both eyes. It can affect either the central field of vision (nominally 1.2 degrees in diameter about the point of fixation) or either the left or right peripheral fields of vision. It can affect any one or all of the three chrominance channels of the neural system. It can appear suddenly as the result of an embolism (stroke). It can be temporary due to medication or other causes.

The color performance of peripheral vision is quite limited. While the color sensitivity of the retina is adequate out to angles of 90 degrees²¹⁸, the perception of color at these large angles is quite limited. Subjects normally rely upon the searching of the visual scene by the fovea to establish the location and color of major targets in the scene. This information is stored in the saliency map of the subjects external environment (**Section xxx**). After that, the color of objects in the peripheral can only be poorly identified prior to the re-examination of the object by foveal imaging.

A comprehensive evaluation would examine each of the above conditions in order to achieve a truly descriptive diagnosis. Each eye should be evaluated separately. The tests should be performed under daylight conditions (alternately a 6500 Kelvin light source is needed). Unfortunately, the Farnsworth D-15 and Farnsworth-Munsell H-100 tests are both designed for coarse screening. They use large diameter caps with colors that are unsaturated. As such, they do not stress the individual chrominance channels of vision. A more demanding test is frequently administered to production workers in the electronics industry. The test involves reading the color bands on a group of 1/2 watt resistors. Each band is 1/16 inch wide and about 5/32 inch high in profile. The only effective evaluations would involve use of a two axis anomaloscope probing the wavelengths from 400 to 650 nm (see **Section 18.1.8.2**).

18.8.1X.1 Colorblindness and the strong psychotic drug, Zyprexa

Recently, a colorblind subject was found to regain normal color perception after treatment with Zyprexa (**Section 18.8.6.5.1**).

18.8.2 Aura

Aura is an ancient, loosely defined, subjective term usually associated with visual symptoms. It is frequently associated with migraine headaches and similar conditions. Aura is in a sense narrower than the term hallucination. Hallucinations can be associated with all of the senses, although primarily with the visual and auditory modalities. The source of a hallucination can be found virtually anywhere in the nervous system. It includes the perception of tingling in the toes of an amputee and the ringing in the ears of one with tinnitus. Visual hallucinations have been defined by Lessell as a "symptom in which the patient claims to see something or behaves as if he sees something that the observer cannot see"²¹⁹." By this definition, dreams may be considered a special form of primarily visual hallucination. The definition clearly separates perceived, or conscious hallucinations, from unconscious hallucinations. The following material will concentrate on consciously perceived visual hallucinations.

Sacks has recently published a book called Hallucinations²²⁰. It is largely anecdotal, although reported by a true expert in the art of observing neurological events and behaviors. He reports on several hundred situations. More significantly, more than a dozen of the reports are both first hand and carefully documented. Sacks does provide some useful deterministic information concerning the approximate origin of certain hallucinations within the cerebral cortex. He also notes the multiple limitations of the MRI and fMRI in both observing neurological events and probably interfering with many such events due to the imposing character of the machines.

A wide variety of aura can be related to psychotic conditions rather than organic sources of disease. Along with a variety of hallucinations, this category also includes drastic spatial distortions in the representations of common elements of scenes. Some of these spatially distorted representations have been related to a psychotic condition and described as spatial metamorphopsia or spacial metamorphopsia.

Metamorphopsia is a type of distorted vision in which a grid of straight lines appears wavy and parts of the grid may appear blank (Wikipedia).

²¹⁸Lachenmayr, B. & Vivell, P. (1993) Perimetry and its Clinical Correlations. NY: Thieme page 296

²¹⁹Lessell, S. (1975) Higher disorders of visual function: positive phenomena *In* Glaser, J. & Smith, J. eds. Neuro-ophthalmology, vol. 8. St Louis, MO: C. V. Mosby pp 27-44

²²⁰Sacks, O. (2012) Hallucinations. NY: Knopf

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Dorr and family²²¹ have described to me the breadth of their aura;

I received a telephone call yesterday, May 2011, from Jerilyn S. Dorr concerning her 40 year old husband, Jerry Dorr and their 15 year old son. She is a special education teacher of considerable experience.

The discussion centered on the enhanced sensitivity of the sensory modalities during periods she describes as "keyed up. She also described a variety of electromagnetic properties of these two individuals that are beyond the scope of this report.

She reported, with Jerry and son in the background, that they suffer from a variety of visual and auditory peculiarities.

+ At least Jerry reports an unusual change in color for leaves etc from green to red during these periods.

+ At least Jerry reports being able to see heat image lasting several second from a hand print left on a wall, foot prints on a sidewalk, etc.

+ They also report an apparent "shimmering" associated with asphalt, similar to an earlier subject in England reported. An effect of this type was also reported by a man with a "lesion" of the posterior thalamic reticular nucleus that he described as an atrial/ventricular malformation..

+ At least Jerry reports an image persistence problem where he seems to have the unusual ability to see individual rain drops during a heavy shower.

+ Frequent and persistent migraine and aura during these intervals of heightened sensitivity.

+ They both report high sensitivity to sound, high sensitivity to odors and an apparent high sensitivity to barometric pressure or other meteorological conditions..

+ Measured high glucose levels during these intervals.

+ They tend to withdraw and go into a dark area during the migraine and aura episodes.

+ They have tried a wide range of medical tests and a wide range of prescription medicines, including melatonin, based on multiple clinical investigations.

+ They have retreated from all pharmaceuticals at this time, due to their lack of significant help.

Jerilyn is very familiar with ADHD and its recent subdivision into a series of categories. She is also conversant in autism. She sees a variety of common symptoms between these diseases and her relatives conditions, but no clear association with either.

Based on the above reports, I suggested the problem is most likely associated with the confluence of the lateral geniculate nucleus (LGN), the medial geniculate nucleus (MGN) and the thalamic reticular nucleus (TRN) at the posterior of the thalamus. It is probably caused by a chemical imbalance affecting the electrical performance of a very small number of neurons. Locating the problem area remains very far beyond the imaging capabilities of

²²¹Dorr, J. (2011) Personal Communication on scope of aura in family [xxx in vision file]

modern medicine, typically achieving pixel sizes of a few millimeters on a side. The problem area can probably be described as a few thousandths of a millimeter on a side.

As they have found, treatment with pharmaceuticals is largely a "shot in the dark" at this time. It is possible the problem involves the creation of a hormone, derived from glucose, at unusual concentrations. This hormone could be modulating the sensitivity of the sensory modalities as a group, and also affecting the assembly of the image information (leading to the aura). The hormones action is likely centered on the signal manipulating neurons of the above confluence of the TRN, LGN & MGN.

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Auras (nee hallucinations) can be divided into at least four categories related to their duration and onset. The International Headache Society²²² suggests the first two and the last of the following categories:

1. A typical aura is one that develops over more than 4 minutes, lasts less than one hour, and precedes, accompanies, or follows a headache.
2. A prolonged aura lasts more than 60 minutes but less than or up to 7 days.
3. An extended aura lasts from 7 days to several months and is frequently associated with the use of narcotics.
4. Some permanent aura are found that appear to be of developmental origin.
5. Apparently permanent aura arising during life are usually associated with an infarction that may be located and confirmed radiographically.

More specifically, the Society has described "migraine with aura as: an idiopathic, recurring disorder manifesting with attacks of neurological symptoms unequivocally localizable to cerebral cortex or brain stem usually gradually developed over 5-20 minutes and usually lasting less than 60 minutes. Headache usually follows neurological symptoms but may be completely absent."

²²²Headache classification committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders. . . *Cephalgia* vol. 8, suppl 7, pp 1-96

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Richards has provided a description of aura for a general audience based on close second hand observations related to his wife²²³. Liu, et. al²²⁴, and Sacks²²⁵ have provided a wide variety of case studies involving visual hallucinations. Wilkinson & Robinson have provided a compendium of aura²²⁶. Additional material is provided in Wilkinson²²⁷. Sacks has recently published a book on hallucinations²²⁸.

Relja et al. have recently reported on a “persistent aura” and efforts to establish a relationship between its presence and inadequate blood flow to regions of the brain²²⁹. Their results appear compatible with the propositions of this work, however the resolution of their 1.5 T MRI may not be adequate. Chen et al. have also provided a case report²³⁰. They suggested Lamotrigine was useful in aura, possibly affecting the utilization of glutamate. However, Relja et al. did not confirm the efficacy of Lamotrigine in aura. The molecular structure of the anti-convulsant drug Lamotrigine (CAS #84057-84-1) does not immediately suggest any role in glutamate-to-GABA utilization within the brain.

18.8.2.1 Definitions pertinent to this discussion

The usage of words in the medical and popular contexts is important in this subject. The differences between intermittent, persistent and chronic are important. For this section, the following distinctions will be made:

Acute— Having a rapid onset and following a short but severe course. Not a recurring condition.

Chronic— Lasting for a long period of time or marked by frequent recurrence.

Intermittent— Stopping and starting at intervals, either periodically or aperiodically.

Persistent— Existing or remaining in the same state for an indefinitely long time, enduring.

As a general rule, auras involving geometric patterns in the field of vision, with or without associated migraine, are intermittent and generally aperiodic. As a general rule, auras involving patterns of fine dots, and described as a snowy pattern or “TV-like static,” are persistent after an initial onset. Both of these conditions can generally be considered chronic. Some of the intermittent events involving geometric patterns can be overwhelming and are followed by incapacitation. Therefore, they can be considered acute.

This author is subject to intermittent aura generally associated with very heavy mental work loads. Each aura is of the fortification type (jagged straight lines forming an arc of about 240 degrees) that moves slowly toward the perimeter of the upper left quadrant of the field of vision. The aura remains nominally constant in size relative to the perceived field of view. Whether its velocity is constant has not been determined. The aura can be, and normally is, eliminated by physical and mental rest for periods of 10-20 minutes. No migraine has been associated with the aura. The author has seldom if ever experienced a headache (in the absence of physical trauma).

While Liu et al., Chen et al., and Relja all use the term “persistent” in the title of their papers, they all describe patients where the aura is intermittent. Chen et al. differentiate between *typical* events that last less than 60 minutes and *prolonged* auras lasting from 60 minutes to seven days. The same above authors use the term “positive” in the titles of their works to indicate the presence of a visual perception, as opposed to an absence of perception, or functional blindness, in part or all of the visual field. The term does not refer to the polarity of the neural signals or the relative brightness of the perception.

²²³Richards, W. (1971) The fortification illusions of migraines *Sci Am* vol 224, pp 88-96

²²⁴Liu, G. et. al. (1995) Persistent positive visual phenomena in migraine, *Neurology*, vol. 45, pages 664-668

²²⁵Sacks, O. (1992) Migraine. Berkeley, CA: University of California Press

²²⁶Wilkinson, M. & Robinson, D. (1985) Migraine art *Cephalgia* vol 5, pp 151-157

²²⁷Wilkinson, F. (2004) Auras and other hallucinations: windows on the visual brain *Prog Brain Res* vol 144, pp 305-320

²²⁸Sacks, O. (2012) Hallucinations NY: Alfred A. Knopf

²²⁹Relja, G Granato, A. Ukmari, M. et al. (2004) Persistent aura without infarction: description of the first case studied with both brain SPECT and perfusion MRI *Cephalgia* vol 25, pp 56-59

²³⁰Chen, W-T. Fuh, J-L. et al. (2001) Persistent migrainous visual phenomena might be responsive to lamotrigine *Headache* vol 41(8), pp 823-825

18.8.2.2 Visual hallucinations as spatially correlated extraneous images

Hallucinations can generally be separated into spatially correlated and uncorrelated forms. This section will only address the spatially correlated form. This form can be described by the patient in graphical terms that frequently suggest a complex geometric pattern. In severe cases, the graphical description may involve the significant geometrical distortion of the intrinsic scene itself.

An additional class of functional blindness's are those related to migraine headaches. These vary over a wide range and may or may not be related to the pain associated with a headache. They include migrainous hallucinations. In this context, a hallucination is any false sensory impression, ranging from unformed light (patterns) to complex cinematic visions (sometimes described as dreaming with the eyes open). This class includes a large number of minor functional problems frequently related to degrees of fatigue. These include the appearance of several sets of zigzag lines, circular forms surrounding the foveola or fovea, spoked patterns emanating from the foveola, etc. These patterns are often shimmering or oscillating in brightness and moving in various directions. Some of these patterns are associated with the merging of information processed via different signaling channels. A ring is frequently observed between the foveola and the periphery of the retina as shown in **Figure 18.8.2-1** reproduced from figure 7-28 of Glaser. Vertical and horizontal lines are frequently observed emanating from this ring (or its location). These effects are directly related to the failure of the brain to merge information received via alternate paths. The vertical and horizontal lines do not emanate from the center of the foveola since there is no segmentation in this region that could lead to improper merging of signals.

In the authors experience, these aura due to migraine headaches are primarily related to the retinotopic field of view, not the visuotopic field. This is demonstrated by rotating the eyes a few degrees and noting the movement of the aura within the visuotopic field but its relatively fixed location relative to its position on the retina. This characteristic aids in determining the location of these disturbances within the system. While this type may occur within either retina, it appears that it can occur in the input circuitry of the lateral geniculate nucleus and ay be related to the formation of the composite stereographic image prior to the propagation of the composite image to the visual cortex.

The author has observed a recent migraine pattern as a semicircle of a few degrees diameter at a radius of about 12 degrees from the point of fixation. The author has also noted the fact the migraine pattern remains in place whether the eyelids are open or not.

The circular character of the aura shown may be explained based on the data of Bunt et al²³¹ who reported the ganglion cell data of the retina sent to the LGN are duplicated within a region of 0.5 degrees each side of the vertical meridian. They also note a larger degree of duplication in the region of the foveola. "This strip expands to a width of 3° at the fovea, since mixing of horseradish peroxidase-labeled and unlabeled ganglion cells was found in a band approximately 0.5° wide along both the nasal and temporal rims of the foveola." Their data would suggest the circular aura shown is due to an improper merging of the foveola imagery from the high resolution PGN/pulvinar couple and the lower resolution LGN/occipital couple.

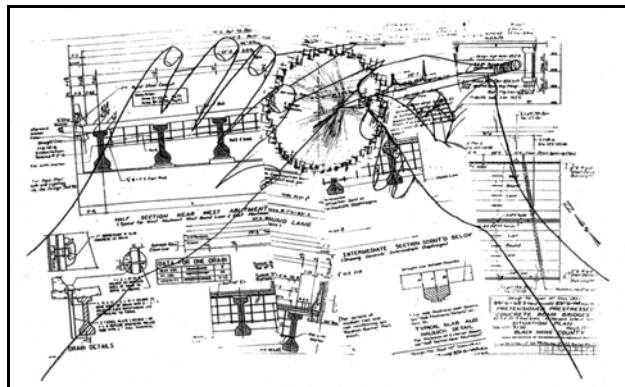


Figure 18.8.2-1 CR Migrainous hallucination. Drawing by a 42-year-old draftsman of his migraine aura. A central scotoma is surrounded by a ring border of sparkling colored lights. From Glaser, 1999.

²³¹Bunt, A. & Minckler, D. (1977) Foveal Sparing: New Anatomical Evidence for Bilateral Representation of the Central Retina *Arch Ophthalmol* vol 95(8), pp 1445-1447

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Using the examples in Sacks, three distinct orders of spatially coherent hallucinations can be defined.

The first order visual hallucination is the spatially coherent positive hallucination that is essentially independent of and appears as an overlay to the scene in object space; **Figure 18.8.2-2**. The pattern is frequently geometric in character and largely independent of the real-world image obtained from object space. It frequently occurs within one quadrant of the field of view and may move outward toward the periphery of the field.

The author has personally observed this visual hallucination during periods of severe mental fatigue. In the authors case, the pattern was always confined to a single quadrant, generally occurred about 45 degrees from the line of sight and drifted further toward the periphery over a period of seconds to tens of seconds. The hallucination could still be observed with the eyes closed. By closing the eyes and resting the visual system for a few minutes, the hallucination disappeared.

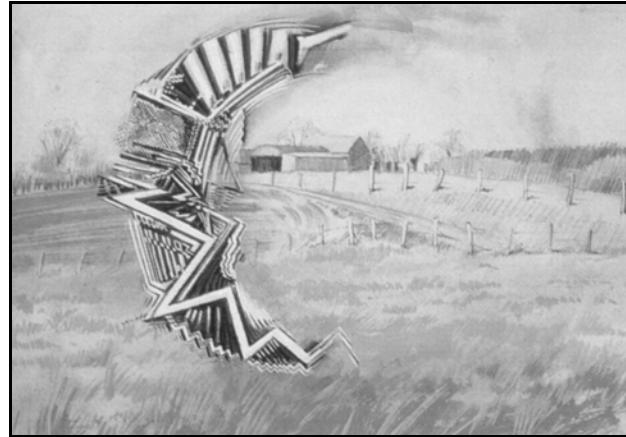


Figure 18.8.2-2 Proposed first order visual hallucination originating in the visual cortex. It shows the complex structure frequently reported for these phenomena. This is an artist's drawing. Such aura are usually restricted to one quadrant of the visual field, unless of the type described above. From Sacks, 1992.

Tanenbaum has recently reported his interpretation of the syndrome as a time sequence on the Facebook/Visual Snow Group, **Figure 18.8.2-3**. The hallucination apparently did not close. He did not indicate its size to allow comparison with the above figures. When asked whether it actually involved more than 180 degrees of angle, thereby crossing either the horizontal or vertical axes, he said;

The last Aura I had was over 18 weeks ago & none of my Auras were anywhere near 180 degrees. They normal start in my central vision as a small arc, & then start to slowly migrate to the left & at the same time, start increasing in size. Within 15-30 minutes, she goes into my peripheral and becomes no more.

Brude et al. have provided a time-lapse caricature of a similar hallucination (page 168).

These aura are frequently traceable to the blood flow associated with the posterior superior cerebral artery serving the lateral surfaces of the occipital lobe of the CNS. S. H. has described a similar set of arcs originating at the outer edges of the peripheral field and proceeding toward the intersection between the foveola and the peripheral fields of view before they disappear (personal communications, 25 July, 2015). These arcs appear traceable to the blood flow associated with the posterior inferior cerebral artery serving the medial surfaces of the occipital lobe of the CNS.

The second order visual hallucination is the spatially coherent positive hallucination that is intimately associated with the major object perceived in object space; **Figure 18.8.2-4**. These two-of-three images were produced by a psychotic artist (Louis Wain) during a very acute psychosis. The third illustrates a more complex situation that will be discussed below. In the image on the left, the artist described the background as consisting of swarming brilliant star-like figures. In the image on the right, the

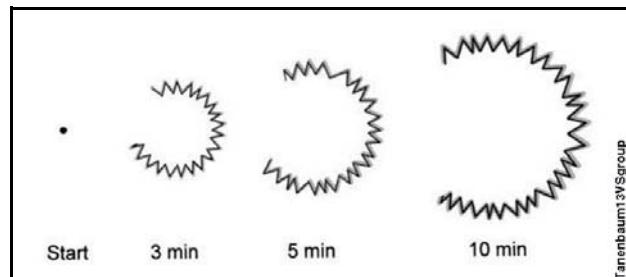


Figure 18.8.2-3 Appearance of aura with time. Whether the illustrated situation at the "Start" was actually observed is open to question. These aura's typically start at the intersection of the foveola and the peripheral retina. They frequently occupy only one quadrant, avoiding the vertical and horizontal meridians. See text. From Tannenbaum.

artist described his perception as concentric shimmering waves expanding from the point of fixation (but obviously keyed to the contours in the original image in object space). Both interpretations were described as dynamic in character.

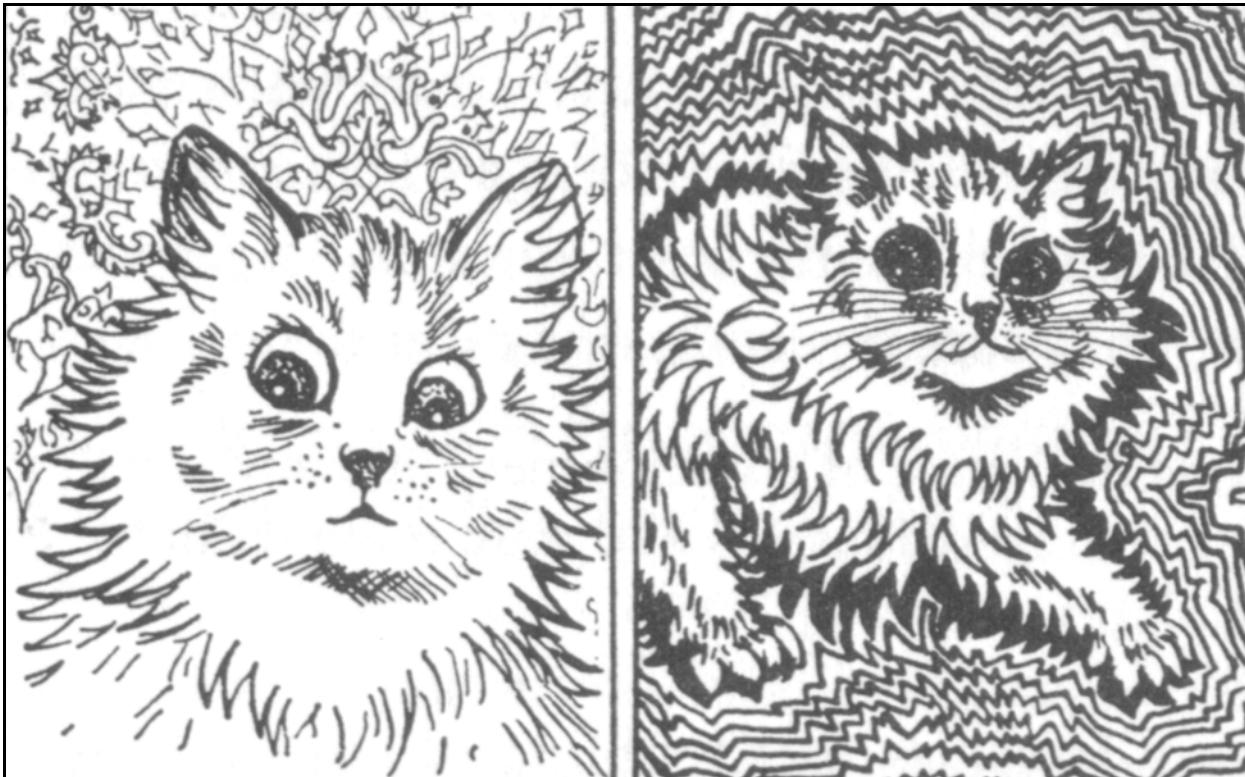


Figure 18.8.2-4 Proposed second order visual hallucination arising from errors in reading the saliency map in area 7. Produced sequentially by a schizophrenic artist. See text. From Sacks, 1992.

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The third order visual hallucination is that perceived as spatially coherent, on a local scale, but largely incoherent on a large scale, disruption of the entire visuotopic space; **Figure 18.8.2-5**. This hallucination is frequently described as a mosaic hallucination. This is the most severe form of visual hallucination short of loss of the visual function completely. In a severe psychotic, this type of hallucination may come on in a sequence of identifiable stages and may be spatially dynamic when fully developed. Some of the dynamic changes may occur so quickly as to be described as violent.

A recent e-mail communication has provided a substantive case in a 65 year old man, FH, that is more complicated than most. Many of the features described above, particularly as they were documented by artists like Picasso, Salvatore Dali, and the author of Alice in Wonderland, Lewis Carroll, are found in the following description, although the rate of onset may have been more rapid in this case;

"He experiences white-outs, snowy vision, everything is viewed through checkerboard in red and blue, he is unable to use his computer or read because he doesn't see the whole word, lately he has been seeing objects like gargoyles, that also transforms to a deer head. Besides the checkerboard always being there the vision is framed with green foliage in which the figures appear. When he looks at people he will see only one eye, the nose looks like nostrils and the teeth look like chicklets, all are outlined in black. Once in a great while he will be able to see almost normal. He has been experiencing this type of vision for about a year now."

In a more detailed telephone and email interview, the subject was diagnosed with glaucoma long ago. The acuity of his left eye is very low; he sees shapes but is unable to identify even large objects. His right eye exhibits good acuity but has a very limited spatial ability to read letters (typically only about three letters of a word are perceivable at once when looking at the label on a tire at six feet). Currently, his checkerboard is perceived as totally rectilinear and covering all four quadrants of his entire field of vision, which suggests its origin is not associated with either his retina, the sensory circuits of his thalamus or his occipital lobe. He perceives no difference when closing one eye or the other. The individual squares appear as about 2.5 inches on a side at a distance of six feet. The checkerboard can be perceived at high contrast and frequently appears "frosted" at high contrast. The foliage also frequently appears as "frosted."

He notes that he encounters white out due to bright headlights, and his HDTV tends to appear as only black and white when operating normally. While the checkerboard is always present, the white out condition can frequently be ameliorated for a short interval by blinking his eyes.

Although accustomed to considerable reading as part of his research activities in the past, he did not indicate any likelihood of the onset of his aura due to mental exhaustion. He did not indicate any propensity toward headaches during our entire discussion, either before or after a specific phase of his hallucinations.. Most of his hallucinations appeared to be persistent to permanent with only limited temporal variation and infrequent short intervals of relatively improved vision.

FH clearly exhibits a variety of both persistent and shorter term hallucinations that effectively prevent his operating

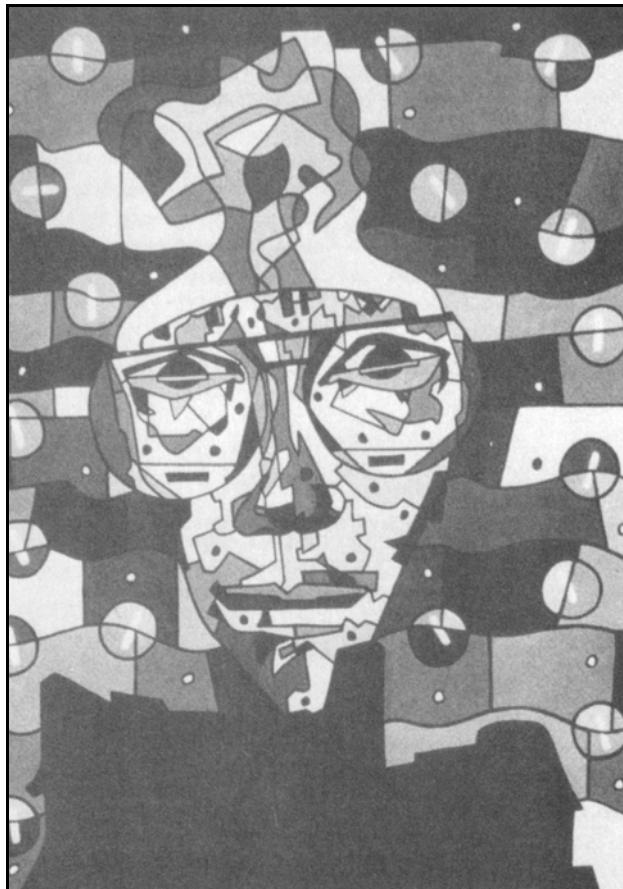


Figure 18.8.2-5 Proposed third order visual hallucination related to the interpretation of data, acquired from the saliency map of area 7, in the frontal visual areas of the cortex. Reproduced in Sacks, 1992 with permission from British Migraine Association..

in the conventional environment. His aura associated with foliage tends to progress until it fills his entire field of view. He has given up driving and reading and encounters considerable difficulty due to bumping into items around the house, even walls.

A subheading of this paragraph might discuss perceived geometrical distortions in normal imagery. These appear to occur in both long-term, transient and severe forms.

Some researchers have assigned the name “Alice in Wonderland symptom” to the basic condition of perceived geometric distortions, particularly when they relate to portions of the subjects own body(mycropsia). Its frequency of occurrence is quite low and probably qualifies as an orphan disease, except where it is induced by psychedelic drugs. Think of Sgt Pepper’s Marching Band and the psychedelic Volkswagen vans painted during the 1960’s. The condition almost certainly does not arise in the eyes or even the occipital lobe of the brain. It could arise in the thalamus region of the brainstem or parietal lobe but most likely arises in the prefrontal lobe. In the elderly, it is probably the result of a minor infarct (minor stroke) or other abnormality of the arterioles in these areas of the brain. It may or may not be identifiable using MRI technology.

Salvador Dali painted a variety of surrealistic scenes that are generally associated with what he actually perceived. However, the style became a money-maker for him and it becomes difficult to determine what he actually perceived on the first occasion and what he redrew repeatedly for profit. His simple “melting clock” shown in **Figure 18.8.2-6** is an example. In subsequent paintings, he included as many as four different melting clocks. These paintings are sometimes associated with an abnormality known as persistence of vision. However, they may have been of more monetary value to Dali than of scientific value related to a neurological condition. His 1931 variant was named “Persistence of Memory.”

His paintings frequently show gross geometric distortions from real world scenes as well as the insertion of objects into a scene totally out of context. The latter configuration may be due to recalling imagery from memory while also perceiving other imagery in real time.

The above symptoms cause one to focus on the area of the brain between the thalamus of the upper brainstem, the areas of the parietal lobe (as defined here) associated with multi-sensor signal correlation, and the prefrontal lobe of the cerebral cortex. The signals passed between these regions appear to involve multiple individual neural paths projecting information in a bit-parallel/word-serial format. In this format, the failure of one, or only a few neural paths can cause a significant error in the perception of a signal received at the prefrontal cortex. On the other hand, the difficulty FH has encountered in visualizing full words suggests a failure in the visual servomechanism located within, or immediately adjacent to, the thalamus (See the sections in **Chapter 19** on the operation of the servomechanisms involved in reading).

V. M. [xxx Vero Mango in VS group on 13 Jan 13] has spoken of her condition, heat wave vision, that appears to be a disturbance of the geometric fidelity of her perceived images. Such a condition might constitute a transient (and possibly less developed) version of Dali’s melting clock condition.

In all of the potential failures associated with these areas, it is only necessary to have a very few damaged neurons, out of 10-100 billion, to cause the symptoms

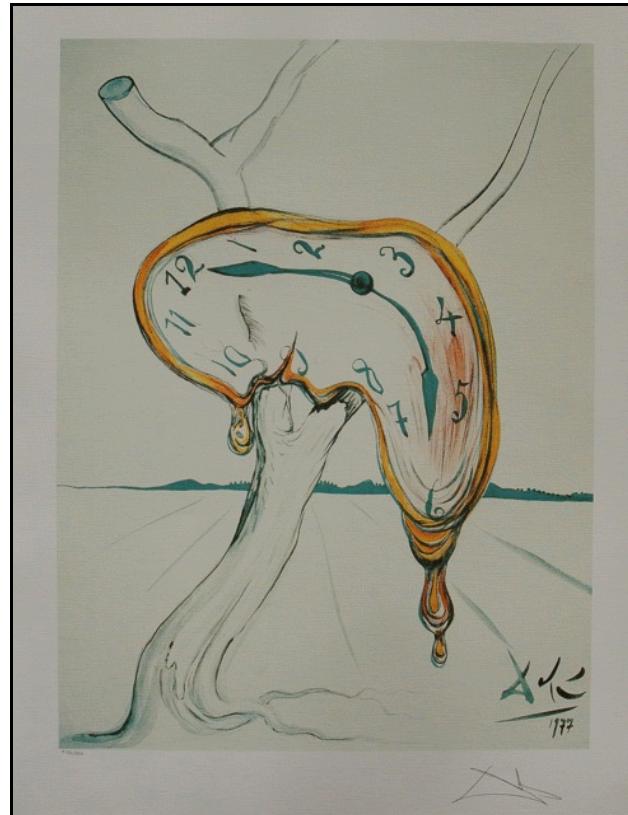


Figure 18.8.2-6 Melting Clock by Salvador Dali (1904-1989). Painted originally during his surrealistic period of the 1930's. A theme reproduced endlessly in subsequent paintings; this variant dated 1977. He described these materials as representing an unreal “dream” space. But the strangely hallucinatory characters of his imagery probably defined his neurological problems.

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encountered. The damage can be the result of necrosis of the critical neural tissue or just pressure on the critical nerves due to very minor internal bleeding in the immediate area. Both these situations make it highly unlikely any medical imaging technology of the next ten years can identify the problem area. Other than for the diagnosis of glaucoma, the symptoms are compatible with either the necrosis or abnormal physical pressure condition. The occurrence of brief periods of relatively improved vision is suggestive of the pressure condition associated with a variation in arteriole leakage or local blood pressure. While the cerebral cortex is amenable to a certain amount of reprogramming to accommodate such failures, this ability is generally believed to deteriorate with age, almost certainly after the 40's or 50's.

18.8.2.2.1 Sources of spatially correlated hallucinations

Several sketches have appeared in the literature related to the sources of either hallucinations or aura that have reflected the concepts of the author. No diagram has been located that appears adequate based on this work. The sources of spatial visual hallucinations are multiple and appear to depend on the nature of the hallucination.

Liu et. al. demonstrate that the source of these hallucinations and aura cannot be determined using the conventional diagnostic techniques available in 1994²³². They noted in particular “unremarkable” results from MRI, EEG, transcranial Doppler, carotid ultrasound electroretinogram (ERG), and single-photon emission computed tomography (SPECT). This continues to be the case in 2004. They did note parietal white matter lesions in two cases that might be suggestive of the source of the problem (potential pressure on some of the white matter neurons). However, they did note the full visual field involvement in the majority of their ten cases. The condition appears to be related more to the chemical and hydraulic parameters associated with different areas of the brain than anything else. However, the degree and the spatial extent of the abnormalities in these parameters is far below those levels normally measured in the laboratory. An additional review of the Liu et al. 1995 paper, and probably all of the Liu et al materials cited in this chapter, is warranted after reviewing the following material. The 1995 paper includes extensive lists of anecdotal symptoms as well as citations to patients reporting use of digoxin, alcohol, cocaine, LSD, marijuana and mescaline. More recently, the widespread use of oxycontin and Vicodin are likely to result in additional reports of hallucinations.

The typical circular aura limited to one quadrant of the visual field is almost certainly associated with the visual cortex. As a result of this computational feature, straight lines along the projected surface of the cortex correspond to circular segments in object space as shown in **Section 15.2.5**. **Figure 18.8.2-7** provides a caricature highlighting the features related to this type of hallucination. Note the right visuotopic field is reproduced on the left in the visual cortex and the center of the visual field is imaged at the temporal extremes of the occipital lobes of each hemisphere of the visual cortex. The occurrence of these quadrant related aura can be correlated with the hydraulic flow of blood plasma or other fluid components near the ends of the vascular system supporting each quadrant of area 17 of the cortex.

The fully circular pattern appears to be due directly to the computational anatomy found between the LGN and PGN or in the assembly of the pulvinar portion and the cortical portions of the complete visual representation returned to the TRN by the TRN, or the storage of this representation in the parietal lobe.

A hallucination appearing as a jagged line along a fixed radius in object space, corresponding to 5.4 degrees from the point of fixation, is imaged as a nominally straight line on the visual cortex

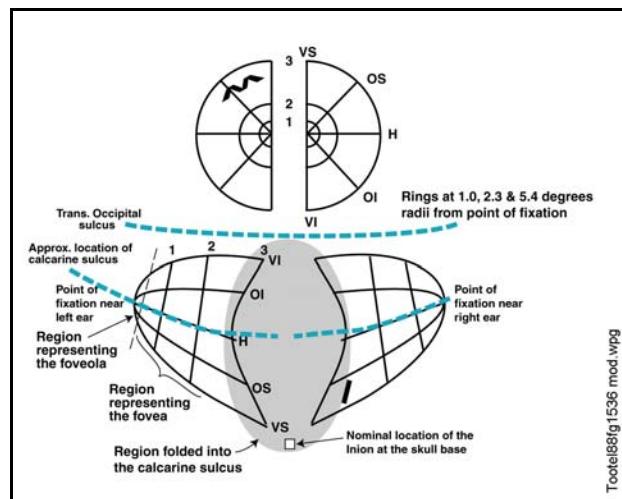


Figure 18.8.2-7 Caricature of the first order hallucination and the image topography of the visual cortex highlighting its relationship to the first order visual hallucination. Top; object space projected on retina. Bottom; map of object space on visual cortex. VS; superior pole of vertical axis. VI; inferior pole of vertical axis. H; horizontal meridian. OS & OI; oblique superior and oblique inferior rays. See text. Dashed line defines the limit of the foveola.

²³²Liu, G. Schatz, N. Galetta, S. et al. (1995) Persistent positive visual phenomena in migraine *Neurology* vol 45, pp 664-668

representation near the line where the surface of the cortex turns inward due to the longitudinal cerebral fissure. The two horizontal axes parallel the two calcarine sulci in this fissure. Most of the area of the occipital lobe affected by this type of hallucination, 5 degrees from fixation to the perimeter of the field of vision, appears to lie along the walls of the fissure. In **Section 15.2.5**, it is suggested that the topography may fold into the fissure in the region of 11 degrees from the point of fixation. However, there are no markers to define this point definitively.

Note the natural division of the occipital lobes by the longitudinal cerebral fissure. This feature tends to limit this type of hallucination to the left or right field if its source is associated with the topography of the occipital lobes.

The second order spatially correlated visual hallucination does not appear to respect the natural division caused by the two occipital lobes. It appears the source of this aura occurs later in the visual system. It is proposed that this hallucination originates after the two halves of the perceived field of view have been correlated and stored in the saliency map associated with area 7 of the cerebral cortex. The error may be associated with either the writing of the information into the saliency map or the reading of that information. While these errors are significant, the underlying integrity of the visuotopic image is not destroyed.

In the case of the third order hallucination, the very integrity of the visuotopic image is destroyed. It is proposed that this effect is due to a major error in either reading the saliency map or in interpreting the data read in the frontal visual areas of the cerebral cortex.

All of the orders of hallucination described above are commonly found in patients suffering from HPPD (Hallucinogen Persisting Perception Disorder) as well as those susceptible to migraine headaches.

All of these source locations and errors are compatible with the suspected chemical or hydraulic imbalances within the system. They would also be compatible with these types of imbalances resulting from injury or infarction. The motion frequently associated with the first order hallucination is particularly compatible with the concept of a wave of imbalance moving along the walls of the calcarine sulcus. On the other hand, the third order hallucination does not exhibit this wavelike motion. The temporal progression associated with mosaic hallucinations are illustrated in Sacks (page 74).

18.8.2.2.2 Computational models of aura

Several investigators have attempted to develop computational models explaining the generation of aura based on very little physiological evidence. These have frequently assumed the thin neural layer of the cerebral cortex acted as an excitable membrane subject to multiple vibratory modes. They have not concerned themselves with the rigidization of the cortex provided by its folding. Such analyses appear superficial to this investigator. These computational models have generally been based on very simple models of the spatial transform between object space and the surface of V1 (area 17)^{233,234}. The “complex logarithmic transform” suggested by Schwartz²³⁵ does not result in a mapping similar to that demonstrated in detail by Tootel et al. eleven years later²³⁶. Schwartz proposed the complex logarithmic transform on largely conceptual grounds and his analyses is somewhat superficial in that it suggests infinite magnification at the point of fixation and the horizontal lines in his Table 1 do not fit his cortical hemisphere in Figure 1C. The area of Figure 1C in the region of the dashed lines is not correctly portrayed. An alternate parabolic transform is used in the previous figure and conforms to Tootel et al in detail (**Section 15.2.5**).

18.8.2.2.3 After images and other imagery related hallucinations—scintillations

While commonly reported in the medical literature, see **Section 18.7**, after images and the generation of a compound image consisting of a series of superimposed prior images have not been reduced to a practical explanation from a physiological perspective in the academic literature. The apparent sampling interval between such a series of images may be important. Very short sampling intervals would lead to the perception of trails associated with high contrast objects in the visual field.

²³³Bressloff, P. Cowan, J. et al. (2002) what geometric visual hallucinations tell us about the visual cortex *Neural Computations* vol 14(3), pp 473-491

²³⁴Dahlem, M. & Chronicle, E. (2004) A computational perspective on migraine aura *Prog Neurobiol* vol 74, pp 351-361

²³⁵Schwartz, E. (1977) Spatial mapping in the primate sensory projection: analytic structure and relevance to projection *Biol Cybernetics* vol 25, pp 181-194

²³⁶Tootel, R. et al. (1988) Functional anatomy of macaque striate cortex (in five parts) *J Neurosci* vol 8(5), pp 1500-1624

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Both positive and negative trails have been reported in the anecdotal literature.

Several subjects have reported scintillations (sparkles) typically associated with high contrast edges in high luminance visual scenes. These appear to be associated with some form of saturation and/or circuit overload within the neural system of the visual modality. [xxx see Becker in Visual Snow survey folder][xxx See Shandara Mizil in Vision.com email folder for April 2008 [shandara_mizil@yahoo.com] who also exhibits significant UV vision through her normal biological lenses.]

18.8.2.2.4 Artificially induced hallucinations

Hallucinogens (psychedelics) are psychoactive substances that powerfully alter perception, mood and a host of cognitive processes. They consist primarily of the tryptamines and the phenethylamines. The stereochemistry and other properties of these materials have been studied in considerable detail but their precise interaction with the neural system is yet to be determined²³⁷.

18.8.2.2.5 Hallucinations in other modalities

Greenberg has provided a paper discussing hallucinations in the olfactory modality²³⁸. The cases described are as complex as those in vision. The source of some perceived odors is clearly at the perceptual level while the source of others appears to be at the PNS level, sometimes even localized to one or the other nostril. The perceived odor can be equivalent to a known odor or something totally unrecognized.

18.8.3 Achromatopsia as a complex visual syndrome

This section was designed to develop most of the potential features and causes of achromatopsia beginning about 1996. After the technical discussion, a report is provided on a study performed on about 30 achromatopes and presented at the Dallas 2008 National Convention of the Blind. Since about 2000, very significant improvements in the instrumentation available for studying achromatopsia have appeared, and a very significant set of second generation instruments have now appeared leading to what can be described as a halcyon period of research in this area. **Section 18.8.3.7** will focus on the results of merging this new data with the theoretical models of the system developed in this work.

Up until the 2008 time period, it was generally assumed that achromatopsia was primarily a neural disorder. Much of this major section was prepared under that assumption. Since 2008, the data has strongly suggested a non physiological (neither neural or morphological) cause for this syndrome. The cause appears to be homeostatic, i.e., primarily a chemical processing error based on one or more genetic mutations. The neural irregularities discussed here remain relevant but their basic cause may not be; the basic cause may originate in stage 0, the RPE and its interfaces rather than in stage 1, the sensory neurons. The symptoms of achromatopsia, and the apparent cause of the primary symptom, hemeralopia, appear to vary in degree; a variation in degree is not normally associated with a simple genetic mutation, as suggested by the labeling of genetically malformed “knockout” mice.

Achromatopsia (with an s) is a stationary congenital disease that is easily recognized in the clinic. Unfortunately, the disease is inappropriately named based on the fact that at least 80% of the subjects do exhibit color vision and are not achromats. Thus it is more appropriately named dyschromatopsia. The recent clinical text by Bradley et al. describes the condition imprecisely as an impairment of color perception²³⁹. The initial diagnosis is frequently based on a failure to perform adequately when observing the Ishihara pseudoisochromatic plates (designed as an initial clinical screen), amblyopia, frequently nystagmus, and invariably hemeralopia/photophobia. **Figure 18.8.3-1** provides a tabulation of these symptoms.

²³⁷Nichols, D. (2004) Hallucinogens *Pharmacol Therapeutics* vol 101, pp 131-181

²³⁸Greeberg, M. (xxx) Olfactory hallucinations In Wolstenholme, G. & Knight, J. eds. *Taste and Smell in Vertebrates*. London: J. & A. Churchill

²³⁹Bradley, W. Daroff, R et al. (1996) *Neurology in Clinical Practice*, Vol 1 Oxford: Butterworth-Heinemann pg 604

ITEM	SYMPTOM	CLINICAL DESIGNATION	CAUSE(S)
1.	Sensitivity to bright light	Photophobia	Saturation in Stage 0 or Saturation in Stage 1
2.	Loss of color contrast performance	Deutanopia	Saturation in Stage 1 or Saturation in Stage 2
3.	Loss of long wavelength sensitivity	Protanopia	Pre-natal fever is primary non-genetic candidate
4.	Loss of mid wavelength sensitivity	(?) Pentanopia	Undocumented in literature
5.	Loss of short wavelength sensitivity	Tritanopia	Very low incidence/Undocumented in literature
6.	Non-correctable loss of visual acuity	Amblyopia	Failure in Precision Optical Servomechanism
7.	Loss of version control	Nystagmus	Failure in Precision Optical Servomechanism
8.	Loss of pupil control	Paradoxical pupil	Failure in Precision Optical Servomechanism

Figure 18.8.3-1 Frequent symptoms of the Achromatopsia syndrome. The behavioral characteristic, photophobia, is usually a result of the underlying hemeralopia, the loss of perceived visual contrast at high light levels. This condition is frequently described as a visual “wash-out.”

It typically presents four different individual symptoms:

- + Hemeralopia (and Photophobia as a behavioral response)
- + Nystagmus
- + Amblyopia
- + Achromatopsia (without an s)

However, the severity of these individual symptoms may vary from very severe (complete) cases to less severe (incomplete) cases. The incomplete cases can vary widely. Blackwell & Blackwell have provided a large amount of spectral data on patients with achromatopsia²⁴⁰. In some cases, the achromatopsia can be evaluated precisely using the technique of Lakowski²⁴¹. The individual symptoms may also be acquired.

A fifth symptom has also been reported. In some patients, the iris opens in the presence of higher light levels rather than closes. The condition has been described as a paradoxical pupil. It is basically due to the loss of neural signals during visual washout. The neural system assumes the light level is below nominal and commands an opening of the iris.

The etiology of achromatopsia leads to hemeralopia as the first order symptom of the syndrome with the actions of the subject, photophobia, the first characteristic noted by the parent or clinician. The disease causing the symptom of hemeralopia is due to a failure of the adaptation amplifiers within the photoreceptors of the retina (regardless of their spectral sensitivity). See **Section 18.2.2**.

An excellent summary of the features of achromatopsia is available at a government funded site, <http://www.genetests.org/query?dz=achm>. Unfortunately, the site is also populated by a large amount of confusion related to other forms of achromatic vision and extraneous material based on the archaic rod/cone concept.

Longer popular descriptions of achromatopsia, from the viewpoint of the subject or a parent, have been provided by Futterman, herself a subject. The Futterman material is available at www.achromatopsia.org although it has not been updated since her passing away in 2001. The major discussion group is at Achromatopsia-Group@yahoogroups.com. A large percentage of the comments in this forum relate to people exhibiting only one or two of the symptoms of the complete achromatopsia syndrome. Many are simply achromats.

²⁴⁰Blackwell, H. & Blackwell, O. (1961) Rod and cone receptor mechanisms in typical and atypical congenital achromatopsia. *Vision Res.* vol. 1, pp 62-107

²⁴¹Lakowski, R. (1969) Op. Cit.

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The author presented an extended discussion of Achromatopsia to the above Achromatopsia-Group at their first national convention in Dallas in July, 2008. It is available on the web in PowerPoint format at <http://neuronresearch.net/vision/ppt/achromatopsia.ppt>

As the fields of molecular biology (and genetics) moves forward, cures for the physical aspects of achromatopsia may be visible on the horizon (at least ten years out). However, significant neurological problems may remain as discussed in **Section 18.8.3.9.**

18.8.3.1 A well-studied achromat with normal luminosity functions

A technically trained researcher named Nordby has been studied over many years. A recent paper by Hess, Waugh & Nordby provides access to the available material²⁴². That paper does not explore the definition of Nordby's condition but concentrates on the temporal response of his vision. Nordby, Stabell & Stabell explores the luminous efficiency function for this subject and finds it to be normal at photopic illumination levels²⁴³. They also give the clinical description of his condition:

"Author K. N., who displays all signs of congenital, *complete achromatopsia with reduced visual acuity OR rod monochromacy*, . . . (emphasis added). Earlier examinations showed *Achromatopsia totalis* based on the Nagel anomaloscope and the Wright colorimeter. He was also found to have reduced visual acuity, chronic horizontal pendular nystagmus, a small central scotoma, and moderate, painless photophobia. The observation was made that all structured vision is abolished at retinal illuminations above about 1500 scotopic Trolands."

Although labeled as showing rod monochromacy in these papers, he is not a rod monochromat in the language of this work.

Lewis writing in Newsome (page 119) gives the following definition. "Rod monochromacy is characterized by a total absence of color discrimination, by reduced central visual acuity (equal to or less than 20/200), by photodysphoria (that is, discomfort in daylight, and by congenital nystagmus which ranges from pendular to occasionally jerky and of relatively low amplitude.

Writing in the same reference, Lewis lists the following as synonymous with rod monochromacy;

Achromatopsia with reduced visual acuity
Complete (typical) congenital achromatopsia
Day blindness
Hemeralopia
πο monochromacy

This listing clearly includes conflicting descriptions related to a variety of retinal and neurological diseases. In the context of this work, achromatopsia is a complicated syndrome, whereas hemeralopia (day blindness) is a single symptom that a clinician frequently observes as photophobia.

K. Nordby exhibits a luminous efficiency function typical of any person with three fully functional spectral channels when measured at low photopic illumination levels and with the spectral filters typical of those in the Wright colorimeter of the 1930-40's. When measured at lower levels, 1800 scotopic Trolands, he exhibits the expected scotopic function. The foveal response shows a slight inflection point between 590 and 600 nm but does not show an inflection near 475 nm ala the Judd equivalent curves. This is the expected situation based on this work when using that instrumentation. The tests were carried out 9 degrees temporally of the fovea.

Baseler et al. have said Nordby had the CNGA3 genetic mutation²⁴⁴. This mutation is most often found in the Jewish population with historical origins in Iran and Iraq.

The conclusion of this work is that he is an intrinsic achromat by virtue of failures in both of the chrominance channels of perception or in a failure within the cortex. Nordby does present an unusual dark adaptation function typical of a subject with poor support for the adaptation amplifiers of the photoreceptor cells. This could be associated with the IPM or the vascular system performance on the choroid side of the retina. Specifically, his response is the same, regardless of the spectral range of the test wavelength, after adaptation to a 3100 Kelvin lamp

²⁴²Hess, R. Waugh S. & Nordby, K. (1996) Rod temporal channels. *Vision Res.* vol. 36, no. 4, pp. 613-619

²⁴³Nordby, K. Stabell B. & Stabell, U. (1984) *Vision Research*, vol 24, no. 8, pp. 841-849

²⁴⁴Baseler, H. Brewer, A. Sharpe, L. et al. (2002) Reorganization of human cortical maps caused by inherited photoreceptor abnormalities *Nature Neurosci* vol. 5(4), pp 364-370

(correlated color temperature using a Wright colorimeter, vintage 1946) at an intensity of 143,200 scotopic Trolands for three minutes.

The dark adaptation characteristic can be interpreted as exhibiting a nominal three and 10 minute time constants associated with the hydraulics of the vascular system. However, the three second time constant associated with the collector impedance of the adaptation amplifiers appears to be closer to a full minute or more. This is indicative of a high viscosity IPM with respect to the transfer of metabolics or some other impediment in close proximity to the surface of **all** of the dendrites associated with the three spectral types of Outer Segments. It is possible that the lemma of his dendrites is not completely specialized in the area required for the electrostenolytic process.

He does present a normal threshold sensitivity after complete dark adaptation. This suggests that his adaptation amplifiers are achieving nominal gain under low illumination intensities. This is as true at 440 nm as at 650 nm. The authors point out the dark adaptation curves have been adjusted vertically so they coincide at full dark adaptation. What they do not show is the full dark adaptation curve for the normal subject. This curve should start at the 143,200 Troland level and show a three second time constant associated with the normal adaptation amplifier load impedance. For lower pre-adaptation levels, the performance of Nordby at 490 nm, approaches and then equals that of the normal trichromat. Nordy, Stabell & Stabell take pains in their paper to justify their position relative to conflicting findings in the contemporary literature.

Hess & Nordby²⁴⁵ explore the spatial/temporal performance of Nordby in considerable detail. Most of the findings appear to be compatible with this work. Figure 1 of that paper is troubling in that they did not show the contrast sensitivity versus spatial frequency of R. F. H for the same illumination intensity as for Nordby. It appears this figure would tell a different story if one more line was added. The spatial/temporal performance with respect to "white" light of Nordby appears normal.

The 1988 paper by Nordby & Sharpe²⁴⁶ cast further doubt on the absence of "cone" photoreceptors in Nordby. The introduction of a discussion of "day rods" shows the continuing difficulty with the adaption of the morphological concept of rods and cones to the functional arena. In their conclusions, they indicate: "the duplexity is perhaps better understood, not in terms of two types of photoreceptors, but in terms of two independent pathways for rod signals: one which is slow and sensitive, functioning in dim light, and another which is rapid and less sensitive functioning in mezotopic light." If the word rod in the last sentence is replaced with photoreceptor, their conclusion is in consonance with this work, although the two pathways are not entirely independent but due to separate mechanisms affecting the one pathway.

In 1991, an expanded team of Stockman, Sharpe, Zrenner & Nordby²⁴⁷ explored the response to flicker of Nordby and Sharpe. Section D of their RESULTS says: "The psychophysical results for the achromat are similar to those for the normal observer." Their subsequent DISCUSSION focuses more intensely on the previous finding that the achromat and the normal both exhibited a duplexity in the signaling channel. In this work, that duplexity is founded in the adaptation amplifiers of the photoreceptor cells. As part of the laboratory work, those authors obtained electroretinograms using external electrodes in contact with the conjunctiva. They concluded that the recordings were predominantly b-wave responses. This is completely in agreement with the predictions of this work.

The 1996 paper referenced above concludes the series with some relevant observations. It does not provide a model of the system it describes as exhibiting temporal characteristics that are a function of the illumination intensity everywhere except in the cortex. This work presents the alternate proposal that the temporal properties of all signals subsequent to the adaptation amplifiers are independent of the illumination intensity throughout the precisely defined photopic region. However, it supports their proposition that there are at least "three temporal mechanisms" active at all illumination levels. They do not directly address the variable time constants of the P/D equation when discussing their findings relative to low pass and high pass filter characteristics of vision. They do reference a finding by Conner²⁴⁸ that the response becomes more low pass in character as the illumination is reduced. The 1996 paper did not present a conclusions section but contains considerable graphic data that could be reanalyzed.

²⁴⁵Hess, R. & Nordby, K. (1988) spatial and temporal properties of human rod vision in the achromat. *J. Physiol* vol. 371, pp. 387-406

²⁴⁶Nordby, K. & Sharpe, L. (1988) The directional sensitivity of the photoreceptors in the human achromat. *J. of Physiol.* vol 399, pp. 267-281

²⁴⁷Stockman, A. Sharpe, L. Zrenner, E. & Nordby, K. (1991) Slow and fast pathways in the human rod visual system: electrophysiology and psychophysics. *J. Opt. Soc. Am. A.* vol. 8, no. 10, pp 1657-1665

²⁴⁸Conner, J. (1982) The temporal properties of rod vision. *J. Physiology*, vol 332, pp. 139-155

18.8.3.1.1 Suggested followup tests

It would have been very enlightening to determine the luminous efficiency function of Nordby using spectral filters of less than 10 nm, using center wavelengths that were not multiples of 10 nm, at both photopic and scotopic levels. It would have been even more interesting to repeat the tests at photopic levels using differential adaptation ala Wald. These tests would have confirmed the obvious. Nordby had a complete set of fully operational, S-, M- and L-channel photodetectors in the Outer Segments. Each of these channels exhibits the normal spectral response as confirmed through psychophysical tests involving his luminance channel and cortical perception apparatus. He was a true intrinsic achromat by virtue of the failure in his chrominance channels proximal to the photoreceptor pedicels. He had an impediment associated with the adaptation amplifiers of the photoreceptors that is obvious in his dark adaptation functions.

The determination of the exact source and location of his chrominance channel failures is more challenging. As discussed in Section 18.4, the failure can involve signal manipulation in stage 2, signal projection in stage 3 or cortical perception in stage 4. It may be possible to confirm the correct operation of the chrominance channels of his system through the output of stage 3 using specifically tailored flicker tests. The object would be to present two narrow band illuminations to his retina that are carefully tailored to appear equally luminous but one of which is located at the wavelength generating a peak signal in the Q-channel and the other is at a wavelength generating a minimal signal in the same chrominance channel. Suggested wavelengths would be 572 nm. and 640 nm. Normal trichromats have a problem in this test because the chrominance signal and the luminance signal are antagonistic within the cortical system at the 640 nm. wavelength. If Nordby is deutanopic due to a problem distal to the point of decoding the projection signals at level 16, he will not exhibit any difference between these two test conditions at low flicker frequencies. The test can be repeated using 494 and 420 nm. to determine if he is tetartanopic. If he does show differences during these tests, the failure causing his problem is most likely cortical.

18.8.3.2 The people of Pingelap

A disproportional percentage, 5%, of the population of this isolated Pacific atoll (6.15 N, 160.40 E in the Senyavin Islands of the Caroline Island group) exhibit a set of vision disorders that have been studied clinically²⁴⁹ and genetically²⁵⁰. Sacks provided a popular description of these people in 1997²⁵¹.

The genetic analysis of the history of this population has been carried out in great and convincing detail. However, the statistical analysis of the presence and level of impairment of each symptom of the disease on the population and the inference as to the source of the problem has been less thorough. Use of the label complete achromatopsia as the initial words in the introduction of Sundin, et. al. is probably not appropriate. The initial tests documented in the literature and referenced in these documents were cursory measurements in the field employing a Snellen E-chart, Ishihara color discrimination plates, crude finger confrontation tests (to check peripheral vision) and fundoscopy. It may be unfortunate that the Hussels & Morton paper used the word "blind" so freely to describe people with 20/70 vision and who failed Ishihara tests for color discrimination. Two girls in the group described as colour-blind had 20/20 vision. In 1972, Hussels & Morton noted that people among this group were able to maintain clerical jobs²⁵². Based on these tests, the authors describe the disease as "consisting of horizontal pendular nystagmus, photophobia, amaurosis, colour-blindness, and gradually developing cataracts." They also noted that pupillary reaction to light and convergences were frequently sluggish, and dilatation was irregular. Based on these symptoms, they diagnosed the disease as "a form of achromatopsia or tapetoretinal degeneration with primary involvement of the cones." In the context of this work, the description of the disease and the diagnosis are less than precise. Brody, et. al. specifically called for more comprehensive and extensive ophthalmological testing. More extensive clinical tests were performed in 1970 and reported in 1972²⁵³. While more comprehensive, the tests remained largely qualitative and did not include spectrographic tests or anomaloscope tests. They did define the range of certain symptoms found in different subjects (6 out of 26 showed no nystagmus, ERG b-wave amplitude values varied widely—both + and – the norm) and surfaced the fact that most of the subjects (85%) were significantly myopic. They also noted that most of the subjects did not wear sunglasses routinely although they did tend to avoid open sunlight. Jimenez notes that the

²⁴⁹Brody, J. Hussels, I. Brink, E. & Torres, J. (1970) Hereditary blindness among Pingelapes People of Eastern Caroline Islands. *The Lancet* vol 1, pp 1253-1257

²⁵⁰Sundin, O. et. al. (2001) Op. Cit.

²⁵¹Sacks, O. (1997) The Island of the Colorblind. NY: Knopf

²⁵²Hussels, I. & Morton, N. (1972) Pingelap and Mokil Atolls: Achromatopsia *J. Hum. Genet.* vol. 24, pp 304-309

²⁵³Carr, R. Morton, N. & Siegel, I. (1971) Achromatopsia in pingelap islanders. *Am. J. Ophthalmology*, vol. 72, no. 4, pp 746-756

color tests used by Carr, et. al. are known to be unreliable for myopic patients with acuity of 20/100 or worse²⁵⁴.

The conventional clinical view has been that these people suffer from a lack of, or poor performance of, chromatic photoreceptors. However, in similar cases, autopsy has normally not shown any morphological problems in the retina. In these cases, fundoscopy showed little irregularity. To date, no precise evaluation of the luminosity functions or any anomaloscope measurements of the affected population could be located in the literature. The combination of symptoms, hemeralopia, complete achromatopsia and pendular horizontal nystagmus, and the variation of these symptoms among individual subjects, indicates a more complex situation. They point to a failure in the signal processing of the visual system. Such a failure is most definitively localized using electrophysiological tests.

18.8.3.2.1 Suggested followup tests

A critical test in the diagnosis of these people is to measure their luminosity function as a function of irradiance level using a constant photon flux level as a function of wavelength (using a 6500 K {preferably 7050 K} light source with a quartz bulb if incandescent). It is likely that this test will confirm a normal luminosity function at the lower end of the photopic illumination level. See the results for Nordby in **Section 18.8.3.1**. If the luminosity function is normal, this test would rule out any photosensitivity malfunction in the photoreceptors. The next set of tests would be those involving an anomaloscope to determine bias errors. Even though the subjects are described as complete achromats, this test can be performed as discussed in **Section 18.1.5.7.3 & 4** if their luminosity functions are nominal.

18.8.3.2.2 Anticipated results for the Pingelap people

It is expected that their luminosity functions will be normal up through a low photopic illumination level. Above this level, it is expected that their luminosity functions will be distorted by flattening. This is the normal result when the hypertopic operational regime is encountered in those with normal vision. The question then becomes, are the Pingelapese operating in the hypertopic regime when exposed to normal photopic illumination level because of a DC bias error or because of excessive gain in the adaptation amplifiers. This question can only be answered by the tests of **Section 18.1.5.7**.

18.8.3.3 The impact of genetics on Achromatopsia

Recent research activity has begun to relate specific genetic abnormalities to specific visual abnormalities. At this time, the relationship is still inferential since there has been no cause and effect relationship established at the detailed mechanism level. The current relationship is one of a symptom (or group of symptoms) and an individual genetic difference found in the same individual or small group of individuals. Kohl, et. al. have provided a current article on the state of the research²⁵⁵. Another paper was published by Sundin, et. al²⁵⁶. This paper was focused on a complex genetic problem involving a disproportionate percentage, 5%, of the population on the Pacific atoll of Pingelap. They presented with not only hemeralopia, but also poor acuity, nystagmus and complete loss of color discrimination. Although assigned the broad designation of achromatopsia by the initial investigators, their clinical evaluation was performed in the field and cursory. The paper by Kohl, et. al. recognized the limitations in the Sundin paper in a Note Added in Proof. Kohl, et. al. presented a more comprehensive genetic study. However, their inference that the genetic failure they traced resulted in a failure in “encoding the putative β-subunit of the cone photoreceptor cGMP-gated channel” is not supported by this work. They did develop the fact that the Pingalepese population exhibited a different genetic mutation than other European populations.

The above two papers have isolated two separate genetic failures related to the syndrome known as achromatopsia. However, they have not demonstrated how either of these failures are related to the putative cGMP-gated channel or how either failure can cause each of the symptoms of achromatopsia. While both of these papers furnish useful definitions of genetic terminology, the clinical terminology used in their introductions should not be relied upon. Achromatopsia (with an s) does not equate to either the archaic term rod monochromacy or to total color blindness in isolation (achromatopsia without an s). The references to electroretinography should reflect normal ERG's at low

²⁵⁴ Jimenez, J., Ogden, T. & Van Boemel, G. (1989) Inherited retinal diseases. St. Louis, MO: C. V. Mosby pg 256

²⁵⁵ Kohl, S. et. al. (2000) Mutations in the *CNGB3* gene encoding the β-subunit of the cone photoreceptor cGMP-gated channel are responsible for achromatopsia (*ACHM3*) linked to chromosome 8q21. *Human Mol. Gen.* Vol. 9, no. 14, pp 2107-2116

²⁵⁶ Sundin, O., Yang, J-M., Li, Y., Zhu, D., Hurd, J., Mitchell, T., Silva, E. & Maumenee, I. (2001) Genetic basis of total colourblindness among the Pingelapese islanders. *Nature Genetics*, vol. 25(3) pp 289-293

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light levels but reduced amplitude ERG's under levels higher than some point in the mesotopic range, rather than speaking of rods and cones. It is proposed that the discussion of cone density in the fovea is superfluous and at best based on morphological grounds rather than functional (generally electrophysiological) grounds.

Two teams have recently presented comprehensive results localizing the genetic defects related to achromatopsia²⁵⁷²⁵⁸. The results have clearly established there are at least two mutations that cause the disease. The two mutations were isolated in distinctly separate populations. The results are summarized in **Figure 18.8.3-2**.

Sundin, et. al. did not explore the relationship between these two genes and the related physiology of the visual system. Paraphrasing Sundin, et. al., they conclude that the presence of correct copies of the two genes is essential for phototransduction in all three spectral classes of photoreceptors.

Kohl, et. al. attempted to go farther and related the genetic mutations directly to the cytology of the photoreceptor cells based more on the conventional wisdom than on comprehensive research.

While both groups describe the mutations as impacting the α - and β -subunits of the cGMP-gated channel through the wall of the plasma membrane surrounding the Outer Segment, neither demonstrates nor references evidence that such a plasma membrane exists. See **Section 4.3.4** for evidence to the contrary.

Kohl, et. al. base their inference that the mutations impact the α - and β -subunits of the cGMP-gated channel on their supposition that subjects with achromatopsia do not have functional “cone type” photoreceptors. This assumption appears based on the further assumptions that subjects with achromatopsia do not exhibit normal photopic luminous efficiency functions, V_y and that an abnormal photopic ERG is indicative of failure in the transduction process of the photoreceptors. The clinical evaluations of subjects with achromatopsia have not normally included determinations of V_y . Tests, and the literature, have usually focused on the scotopic illumination range and the scotopic luminous efficiency function, V_y' . While Kohl, et. al. reference an overview of the subject of achromatopsia presented by Sharpe & Nordby²⁵⁹, they did not reference the specific report by Nordby, Stabell & Stabell²⁶⁰. The latter authors demonstrated that Nordby did in fact demonstrate a normal photopic luminous efficiency function, presumably near the low end of the normal photopic illumination range. The conclusion from that work was that the spectral photoreceptors of Nordby were functional.

While subjects with achromatopsia do exhibit abnormal ERG's over most of the photopic range associated with a subject with normal vision, these abnormalities can be assigned to specific causes within the visual system. As discussed in **Section 17.6.2**, the a-wave, or early potential is usually associated with the earliest response of the visual system to light. It can be correlated with the transduction process. The b-wave can be correlated with later signal manipulations within the visual system. In this work, the b-wave is complex and associated with both the waveforms at the output of the photoreceptor cells and the output of the signal processing neurons of the retina. In achromatopsia, the a-wave is usually present and relatively normal in size. Its presence indicates the transduction process is normal. It is the b-wave that is usually absent or of low amplitude. This is indicative of a failure after transduction. Depending on its form, this wave can be associated with failures in the output circuitry of the photoreceptor cells or in signal processing failures in Stage 2 of the visual process.

ACHROMATOPSIA			
Disease	CNGB3	CNGA3	GNAT2
Gene			
Populations	Pingelapese, Irish	Denmark From Jews of Iraq, Iran & Morocco	Europeans of Italy & Denmark
File Number	MIM 262300	MIM 216900	MIM 139340
Chromosome	8q21	2q11	1p13
Locus	ACHM3	ACHM2	
Prevalence	40-50%	20-30%	~2%
Similar form in:	Dogs		Mice
Investigators	Kohl et al. (2000) Sundin et al. (2000)	Kohl et al. (1998) Chang et al. (2006)	Kohl et al. (2002) Sundin et al. (2000)
Transmission Mode	Autosomal recessive inherited and congenital		

Figure 18.8.3-2 Genetic characteristics of achromatopsia.

²⁵⁷Sundin, O. et. al. (2000) Genetic basis of total colourblindness among the Pingelapese islanders. *Nature Genetics*, vol. 25, July pp 289-293

²⁵⁸Kohl, S. et. al. (2000) Mutations in the *CNGB3* gene encoding the b-subunit of the cone photoreceptor cGMP-gated channel are responsible for achromatopsia (*ACHM3*) linked to chromosome 8q21. *Human Mol. Gen.* vol. 9, no. 14, pp 2107-2116

²⁵⁹Sharpe, L. & Nordby, K. (xxx) Op. Cit.

²⁶⁰Nordby, K. Stabell, B. & Stabell, U. (1984) Op. Cit.

If Kohl, et. al. had developed or relied upon a more detailed model of the photoreceptor cell, it can be assumed they would have arrived at different conclusions as suggested in the previous Section. Their leap of faith inferring the mutations were directly related to cGMP appears to be inappropriate.

18.8.3.3.1 More recent work through 2008

The Kohl-Wissinger team has provided two papers describing an additional number of mutations related to the syndrome of achromatopsia^{261,262}. Gene expression was accomplished using Kidney cells rather than photoreceptors.

Cideciyan et al. have recently reported field results involving gene therapy on three subjects suffering from a congenital human blindness known as Leber congenital amaurosis (LCA)²⁶³. The therapy appears to have restored the production and release of chromophores from the RPE within a thirty day period.

18.8.3.3.2 Alstrom syndrome and other diseases related to achromatopsia

The availability of genetic testing has greatly increased the scope of knowledge concerning achromatopsia and related conditions. However, at the same time, the wider panorama of knowledge has surfaced additional problems. In both vision and other fields of medical research, the number of potential genetic problems has multiplied greatly. Wissinger et al. have reported on seventeen patients from 13 families suffering from what they define as a single condition “cone dystrophy with supernormal rod response” (CDSRR)²⁶⁴. “Ten of the eleven identified mutations were novel, including three missense and six truncating mutations and one gross deletion.” Similarly in the field of cancer research, Winstein reports in the Wall Street Journal, “The genetic mutations in cancer cells may vary in every patient, a study found, suggesting that drugs will need to be tailored more finely to small groups.²⁶⁵”

The following studies show that hemeralopia (and the accompanying photophobia) and nystagmus are not in any way limited to achromatopsia and a broader genetic mapping will be needed to create a comprehensive understanding of the origins of hemeralopia (due to photoreceptor output saturation) and nystagmus.

Malm et al. have recently reported on Alstrom syndrome, a complex condition first characterized in 1959 in Sweden²⁶⁶. Approximately 500 cases of the disease have been documented. It is characterized by occurrence recognized shortly after birth, hemeralopia, nystagmus, 40-70 dB loss of hearing in the first decade, significant childhood obesity and many problems associated with the internal organs.

The visual system exhibits highly abnormal ERG's. Progressive photoreceptor damage (typically described as Cone-rod dystrophy occurs within the first year of life. The symptoms are suggestive of progressive saturation problems in the neural output of the photoreceptors.

Alström syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

ALMS1 is the only gene currently known to be associated with Alström syndrome. Molecular genetic testing of the ALMS1 gene is estimated to detect mutations in 25%-40% of individuals.

Wissinger et al. have reported a type of “cone dystrophy with supernormal rod response” characterized by reduced visual acuity, color vision defects and specific alterations of ERG responses. The Wissinger team included Kohl and Zrenner. Their “supernormal rod response” may be due to the subjects being protanopes. Their conclusions indicate the scope of the mutations uncovered in their study. “Whereas no mutations were detected in the PDE6H gene, mutations in KCNV2 were identified in all patients, in either the homozygous or compound heterozygous state. Ten of the 11 identified mutations were novel.”

18.8.3.3.3 2012 discussion of determinism vs probabilistics in genetics

²⁶¹Koeppen, K. Reuter, P. Kohl, S. et al. Functional analysis of human CNGA3 mutations associated with colour blindness suggests impaired surface expression of channel mutants A3(R427C) and A3(R563C) *Eur J Neurosci* vol 27(9), pp 2391-2401

²⁶²Reuter, P. Koeppen, K. Ladewig, T. Kohl, S. et al. (2008) Mutations in CNGA3 impair trafficking or function of cone cyclic nucleotide-gated channels, resulting in achromatopsia *Human Mutat* vol 0, pp 1-9 Epub 2 June

²⁶³Cideciyan, A. Aleman, T. Boye, S. et al. (2008) Human gene therapy for RPE65 isomerase deficiency activates the retinoid cycle of vision but with slow rod kinetics *PNAS* vol 105(39), pp 15112-15117

²⁶⁴Wissinger, B. Dangel, S. Jagle, H. et al. (2008) Cone dystrophy with supernormal rod response is strictly associated with mutations in KCNV2 *Invest Ophthalmol Vis Sci* vol 49(2), pp 751-757

²⁶⁵Winstein, K. (2008) Study: More complexity in tailoring cancer drugs *WSJ* 26 February 2008, pg B1

²⁶⁶Malm, E. Ponjavic, V et al. (2008) Full-field electroretinography and marked variability in clinical phenotype of Alstrom syndrome *Arch Ophthalmol* vol 126(1), pp 51-57

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Kolata has provided a very useful report on the effect of genetic mutations on the organism in general²⁶⁷. The article is based on a paper by Roberts et al. that investigated the genome of 53,666 identical twins in registries from the United States, Sweden, Finland, Denmark and Norway²⁶⁸. The study showed the genome was probabilistic and not deterministic with respect to diseases as currently defined. It also included a discussion of the impact of various probabilistic estimates on the general population versus those at risk of a particular disease.

18.8.3.4 An alternate and more detailed explanation of Achromatopsia

Whereas Sundin, et. al. inferred their gene mutations resulted in transduction errors in vision, they did not define transduction. Whereas Kohl, et. al. inferred the same mutations resulted in a specific transduction error involving ion transport through a putative plasma membrane surrounding the Outer Segment, they did not reference research showing the existence of such a membrane. **Section 4.2.1** develops the fact that the Outer Segments of both *Mollusca* and *Chordata* are capsules associated with but external to their associated photoreceptor cells. **Section 4.3.4** of this work presents evidence that there is no such membrane based on high resolution electron microscopy.

In this work the general term transduction has been subdivided into four separate specific terms to more clearly denote the mechanisms involved in the operation of the photoreceptor cell. These terms are specifically defined as:

- + Photosensing—The excitation of an exciton into the π^* energy level of a chromophore of vision when in the liquid crystalline state and deposited on the opsins substrate existing external to the photoreceptor cell.
- + Transduction—The de-excitation of an exciton in the p^* energy level of a chromophore of vision and the simultaneous generation of an electron-hole pair in the base region of the Activa forming the adaptation amplifier within a dendrite of the photoreceptor cell.
- + Translation—The conversion of the energy related to the above electron-hole pair into a free electron current flowing in the cytoplasm of the photoreceptor cell.
- + Distribution—Conversion of the free electron current flowing within the axon of the second Activa within the photoreceptor cell into an electrical potential at the pedicle of that cell.

These terms do not rely upon the flow of ions or charges through a membrane surrounding the Outer Segment.

This work has isolated two separate and distinct variants of a single point failure in the visual system that can account for all of the symptoms of the typical patient with achromatopsia (with an s). These single point failures affects both of the chrominance channels (resulting in achromatopia—without an s), the luminance channel (causing hemeralopia) and the Precision Optical System (resulting in amblyopia and/or nystagmus). The fundamental failure consists of a bias error. The bias is formed by taking the difference between two electrical potentials. Each of these potentials is formed by a separate electrostenolytic process associated with the distribution amplifier stage of each photoreceptor cell. These two variants may reflect the genetically different errors reported in the literature for two different populations and discussed above.

The source of the problem among these people is best explored in terms of the Overall Block Diagram of the Visual System in [Figure 15.2.3-1] and some of the simplified figures and discussion in [Section 18.1.5.4]. To cause all of the above symptoms, interference with the POS (nystagmus), loss of color perception (achromatopsia) and excessive sensitivity to light (hemeralopia, at mesotopic illumination levels, that is normally associated with hypertropic operation), the most likely failure is a bias problem associated with the transfer of signals at an early part of Stage 2. It probably involves a bias error within the photoreceptor cells or between the photoreceptor cells and the initial signal processing neurons, the bipolars and horizontal cells, of the 1st lateral processing matrix. Such an error is always a risk in DC coupled signaling systems. It could be characterized as a saturation in the signaling channel causing a complete loss of information contrast. One subject described this condition as a complete wipeout of vision. This error would cause a significant failure in the encoding of signals prior to their transmission along the optic nerve.

Alternately, the error could be in a failure of the adaptation amplifiers to reduce their gain under conditions of high irradiance. This would cause a saturation in the signaling channels irrespective of any bias errors. This error would

²⁶⁷Kolata, G. (2012) Study Says DNA's Power to Predict Illness Is Limited NY: *NY Times* 2 April 2012

²⁶⁸Roberts, N. Vogelstein, J. Parmigiani, G. Kinzler, K. Vogelstein, B. & Velculescu, V. (2012) The Predictive Capacity of Personal Genome Sequencing *Sci Translational Med* published on line 2 April

also cause an abnormal encoding of the signals prior to transmission.

Figure 18.8.3-3 illustrates the critical location of this error. Since the proposed error occurs in the DC biasing of the distribution amplifiers at the output of the photoreceptor cells (instead of at the putative cGMP-gated channels), the visual system operates normally under scotopic and mesotopic conditions. However, as the signal level increases at the output of these amplifiers, their DC coupling to the following signal processing stages causes them to cause saturation in the following circuits. This saturation causes failure in the chrominance channels, the luminance channels and the appearance channels. Thus, this single point failure will cause all of the symptoms normally associated with Achromatopsia. It may be caused by two distinct genetic failures. The first would cause an error in supply (3) and the second would cause an error in supply (4). It is important to realize that these two power supplies are thought to be unique to the distribution amplifiers of the photoreceptor cells. They are not used in other neural cells known to be associated with vision.

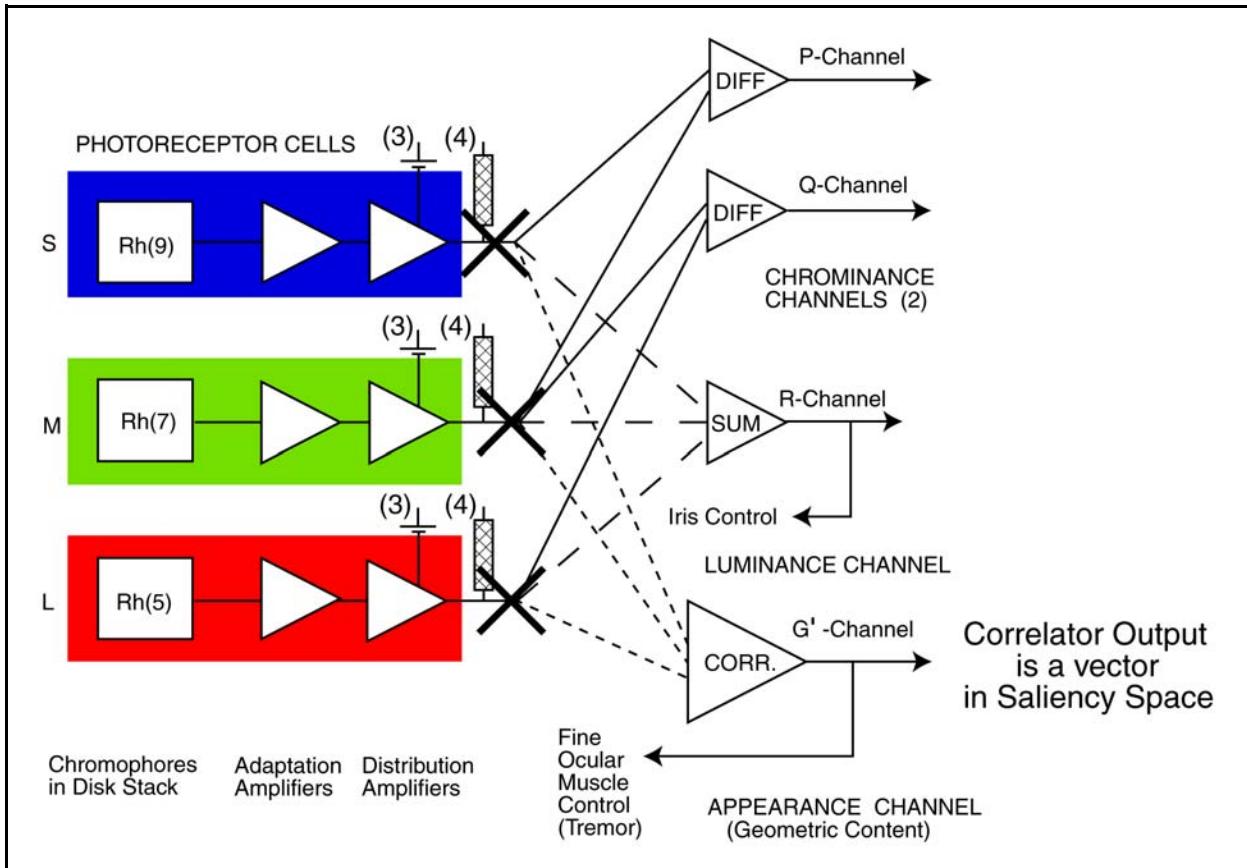


Figure 18.8.3-3 Single point failure mode in achromatopsia. The failure actually is the result of a difference in potential between two electrical power sources, (3) and (4). At high signal levels (the photopic regime), this error causes saturation in the subsequent signal processing channels. The chromatic circuits are unable to calculate P- and Q- values that can be passed to the cognitive brain. The luminance channels are unable to provide high resolution R-values that define the edges of objects in the optical field. The POS channel becomes an open feedback loop resulting in nystagmus. At low signal levels (the scotopic regime) the photoreceptors work normally (however, the chrominance manipulation channels do not present P- and Q- values for cognition because they are below the noise threshold level).

Figure 18.8.3-4 describes the operation of the photoreceptor circuitry under both normal and photophobic conditions. The solid herring bone at lower left shows the output signal at the emitter of the **adaptation amplifier when operating normally**. The mean of the herring bone describes the average output current and the ribs represent the signal variation caused by the contrast in the original scene. At low level, the mean is changing rapidly with input light level. This provides maximum sensitivity in the system. However, as the input illumination rises, the adaptation mechanism decreases the gain of the circuit. The result is an average output current that remains constant

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as the illumination increases. Under this condition, the output current is transformed into an output voltage by the distribution amplifier as shown. Both the DC and AC components of the output voltage correctly represents the input scene contrast at all light levels.

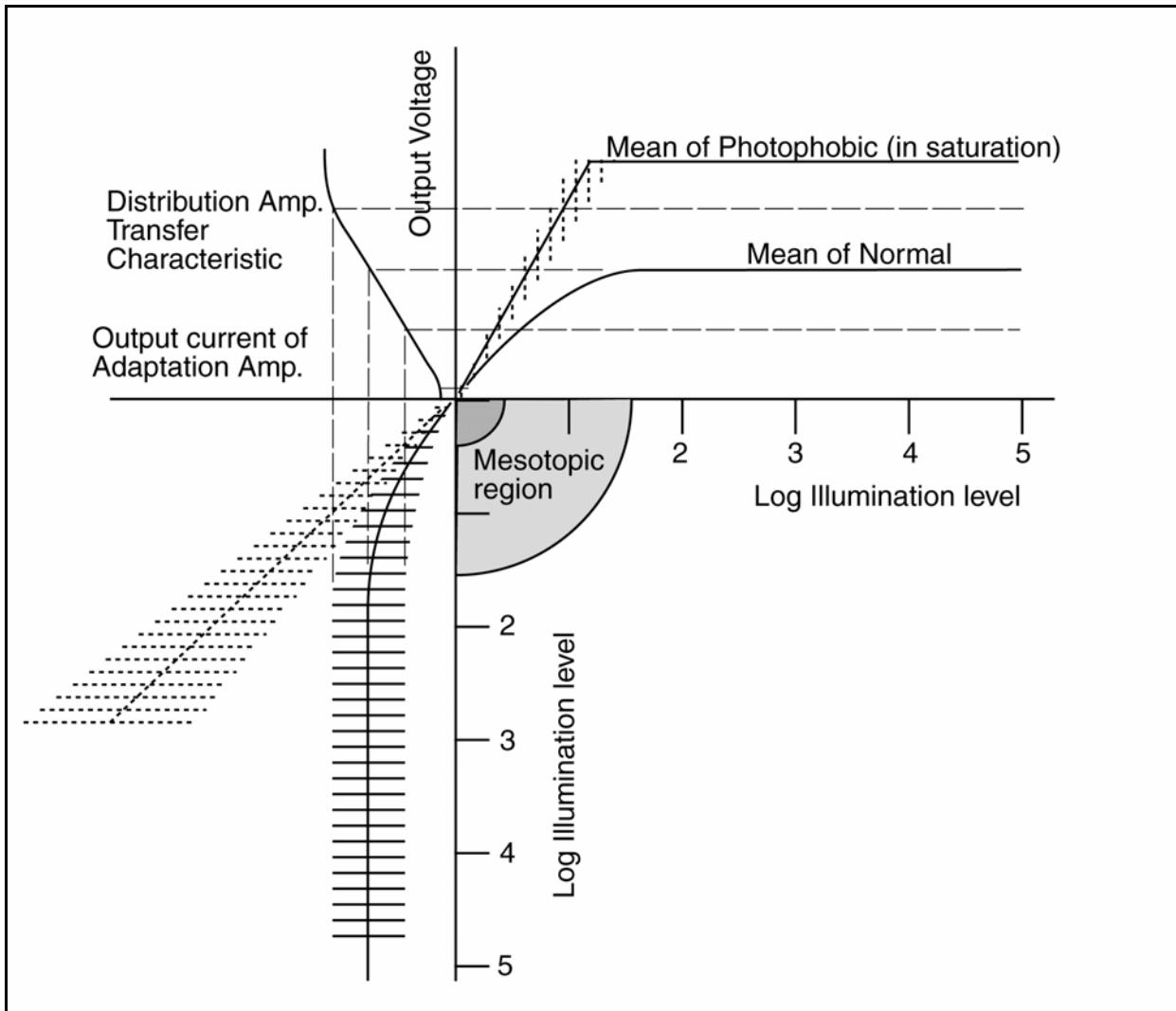


Figure 18.8.3-4 Faulty operation of the photoreceptor cells. See text.

Two failure modes can still be identified in this situation. First, if the adaptation mechanism fails, the average and deviation in the signal current is shown by the straight dashed herring bone on the left. As a result of this failure, the output current of the amplifier is no longer compatible with the transfer characteristic of the distribution amplifier. As a result, the output voltage of the distribution amplifier resulting from this failure rises rapidly at first but reaches a saturation level. As the illumination continues to rise, the saturation in the transfer characteristic essentially erases all information associated with the scene (a condition described as wipe-out).

The second potential failure would relate to the battery labeled (3). If this battery voltage was reduced, the shape of the transfer characteristic would change. This would change the operating voltage range at the pedicle and the input current range at the emitter of the distribution amplifier Activa. It may be important to note that the electrostenolytic process represented by battery (3) is apparently unique to the photoreceptor cells.

Either of these failures can cause the subject to exhibit a total loss of visual acuity at light levels above the mesotopic level. As a result, the subject exhibits hemeralopia under photopic or higher light levels but is perfectly happy when exposed to mesotopic light levels.

Figure 18.8.3-5 shows the predicted peaks in the portion of the b-wave due to the photoreceptor cells under these two failure scenarios. The s-shape traces represent the maximum and minimum excursion of the b-wave for a stimulus varying in contrast by about 2:1 at the specified light level. The solid lines represent the normal operation of the photoreceptor cell versus illumination level. The dashed lines represent the operation under the neuropathies described. While the s-shaped characteristic cannot be achieved easily using a single excitation pulse shape, it is easy to create graphically from a series of stimuli varying by only a factor of 2 about the nominal illumination level.

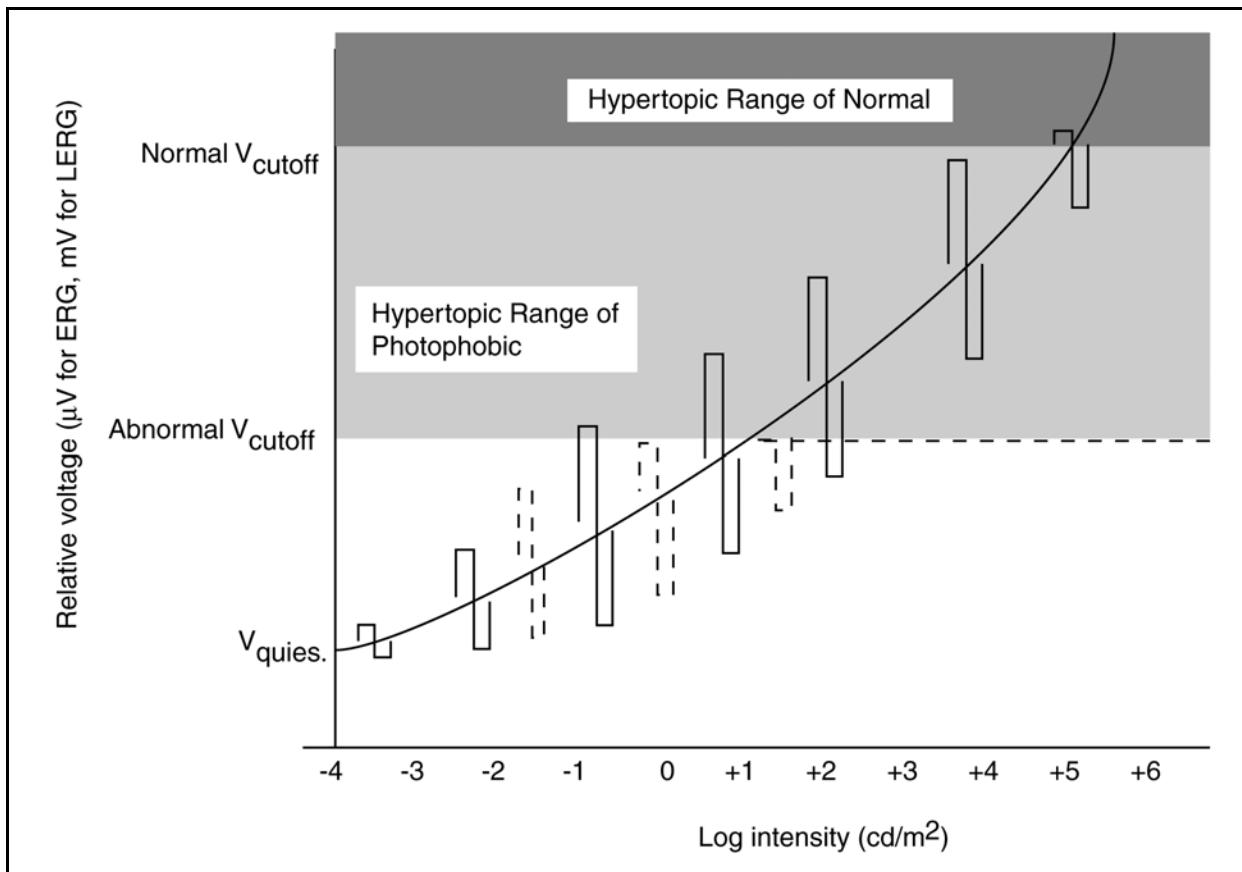


Figure 18.8.3-5 The predicted ERG b-wave due to a bias error within the photoreceptor cell. See text. The figure shows relative voltages using the quiescent value as a reference point for clarity. In the actual case, it is the normal cutoff voltage that should be used. Two different quiescent voltages would be shown based on the difference in bias potentials within the circuitry.

For the normal subject, the maximum difference between V_{cutoff} and $V_{\text{quiescent}}$ is normally about 20 mV measured by LERG (less using the noninvasive ERG). For a contrast of 2:1, the voltage amplitude of the resulting signal is small in the scotopic range, becomes constant over the normal photopic range and encounters limiting in the hypertopic range. For the photophobe, the signal follows the dashed lines. The voltage swing for a 2:1 contrast scene initially rises as in the normal case until saturation is reached. The voltage swing begins to decrease with illumination amplitude until a point is reached (the horizontal dashed line) where no output voltage swing is generated for any higher illumination level. Wipeout has occurred. The photophobe is blind based on his visual acuity even though all previous and subsequent vision circuits are operating normally. No information is available to create signals for the chrominance channels, the luminance channel, or the geometry channel. No information is available to close the oculomotor servomechanism or to control the pupillary servomechanism. The subject has all of the symptoms of achromatopsia.

Biel, et. al. have recently provided data on the ERG recorded from mice in which they had induced the mutation associated with Achromatopsia. The form of these ERGs is most informative. While their test protocols can be assumed to be similar to normal clinical practice, they did not specify the duration of their test stimuli. They provided a series of ERGs from both the diseased mice and a series of related but disease free mice. Their figures 2a

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and 2b displayed these waveforms (and the data from figure 2a appears in **Section 17.6.2.5**. From that data, they created two figures related to the a-wave and the b-wave of these ERGs. They referenced the position of Penn & Hagins²⁶⁹ that the a-wave is predominantly related to the response of the photoreceptors and the position of Stockton & slaughter²⁷⁰ that the b-wave reflects bipolar cell activity. **Section 17.6.2** provides more specific information with regard to these waveforms, including the fact the a-wave generally precedes the b-wave by 15-20 ms. Based on this analysis, alternate and more specific information can be provided. The a-wave represents the current passing through the adaptation amplifier of the photoreceptor cell and the initial part of the b-wave represents the voltage at the pedicle of the photoreceptor cell. The remaining portion of the b-wave is related to the voltages found within the lateral processing matrix as described in Section xxx.

Figure 18.8.3-6 shows their data. The mixed group of four normal and four diseased mice exhibited a-waves that fell well within the 5 and 95% quantiles over the entire stimulus range. This suggests that the major component of the a-wave, the Class C waveform emanating from the microtubules (dendrites) of the Outer Segment, was entirely normal. This fact, in turn, suggests that the photosensing, transduction and translation mechanisms were all operating normally in both the diseased and wild mice. The disease is not the result of an error in transduction prior to the adaptation amplifier. The b-waves, which typically occur 15 to 20 ms later in these animals, and clearly occur subsequent to the mechanism sited above, show distinct abnormality at high stimulus levels. The ERG shows an essentially flat response to the right of the open triangle. This clamping of the voltage level of the b-wave is suggestive of an out-of-range condition in an electrolytic amplifier within the system. The form of their abnormal curve is identical to the predicted form in the previous figure.

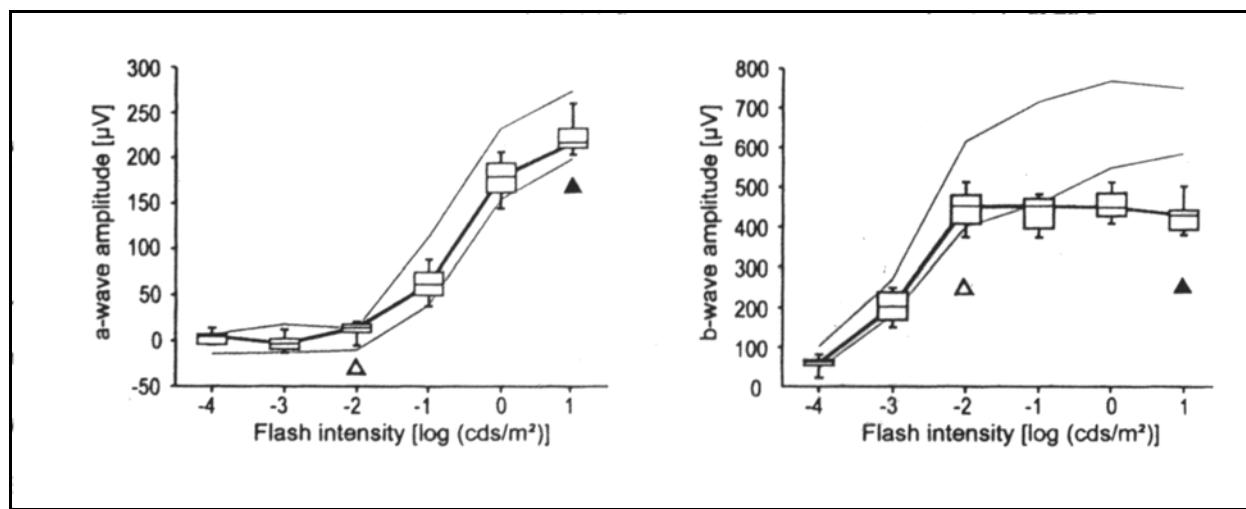


Figure 18.8.3-6 The a-wave and b-wave of mice with the mutation, CNG3^{-/-}. Left; a-wave amplitude from a group of four CNG3^{+/+} and four CNG3^{-/-} littermates as a function of the logarithm of the integrated luminance of the flash. Right; b-wave amplitude from a group of four CNG3^{+/+} and four CNG3^{-/-} littermates. [xxx ?] The boxes indicate the 25-75% quantile range, the bars indicate the 5 and 95% quantiles and the central bar indicates the median of the CNG3^{-/-} data. The thin lines represent the 5 and 95% quantiles for the total population of wild mice.

Looking at the block diagram presented above, an error of type (2) could be present in any one of the four signal processing channels, P, Q, R or G. An error in any of these individual channels results in one of the symptoms associated with Achromatopsia but not all of them. Only an error of type (1) can cause an error in all four of the signal processing channels. This error could be due to an inappropriate quiescent (dark) pedicle voltage, or to an inappropriate intrinsic (cutoff) pedicle voltage. Either of these two conditions would result in all of the symptoms of Achromatopsia.

18.8.3.4.1 Proposed specific cause of Achromatopsia

²⁶⁹Penn, R. & Hagins, W. (1969) xxx *Nature (London)* vol. 223, pp 201-205

²⁷⁰Stockton, R. & Slaughter, M. (1989) xxx *J. Gen. Physiol.* vol. 93, pp 101-122

It is proposed that the disease of Achromatopsia is caused by one of two failures related to the output, not the input, stage of the individual photoreceptor cell. These two potential failures are shared by all of the photoreceptors of that animal. More precise LERG tests can determine which of these candidates is actually the cause of achromatopsia. The proposed failure involves an incorrect battery potential at one of the bias points of the distribution amplifier in each photoreceptor cell. Such an incorrect potential can be caused by several different failures at the mechanism level. The mechanisms involved are discussed in **Section 8.6**.

The most likely cause of the failure is a missing battery source (of about -20 mV or less) applied to the base terminal [labeled (3) in the above block diagram] of the distribution amplifier of each photoreceptor cell. It is proposed that this erroneous potential is due to a transcription error due to mutations in the CNGB3 gene of chromosome 8q21 or the CNGA3 gene of chromosome 2q11 in accordance with Sundin, et. al. and Kohl, et. al. The result would be a faulty electrostenolytic mechanism at that point. Careful comparative chemistry between sufferers and normals can probably define this error in detail. The chemistry of the area of the inter photoreceptor matrix near the outer limiting membrane and adjacent to the inner segment of the photoreceptors is of interest. The expected error would be an abnormality in the concentration of the chemicals used in the electrostenolytic mechanism generating the required potential. The details of this reaction and the transport of these chemicals is discussed in Section xxx.

This analysis suggests that the particular electrostenolytic mechanism used at the base terminal is not used anywhere else in the visual system and may not be used anywhere else in the neural system. A confirmation of the conclusion of Sundin, et. al.

18.8.3.4.2 Iris control to aid achromatopsia patients

Merin, Ronen & Nawratzki²⁷¹ have noted that the typical achromatopsia sufferer is most comfortable at light levels below 1.0 log milliLamberts (3.18 cd/m^2) which is equivalent to feeble interior lighting (**Section 2.1.1**). They found pilocarpine 2% was an effective treatment. It causes/maintains constriction of the pupils at the lower photopic light levels and thereby allowed the patients to operate at light levels about one order of magnitude higher than previously (up into the twilight range).

18.8.3.5 Recent (2000-2007) applied research results concerning Achromatopsia

18.8.3.5.1 Recent press release

The following press release summarizes the work reported by Jackson Laboratories of Acadia, Maine. A short (3 page) "Brief Communication" provides the details supporting these claims²⁷². Hopefully a more complete paper will appear soon. The work is focused on a mutation described as occurring in the guanine nucleotide α -transducin (GNAT2) gene. This is either a different gene or different terminology than that discussed above for the Europeans and the Pingelapese sufferers of this disorder. The condition Alexander et al. are discussing probably relates to achromatopsia (without the s) in the terminology of this work since no mention of hemeralopia/photophobia or nystagmus appears in either document.

Vision Cells Light Up in Blind Mice 21 May 2007

Bar Harbor, Maine — Gene therapy has been used to restore sight in mice with achromatopsia, a form of hereditary blindness also seen in human patients, researchers at the University of Florida (UF) and The Jackson Laboratory report.

In a paper published online in today's (May 21) edition of *Nature Medicine*, the UF scientists, in collaboration with the laboratory of Jackson research scientist Bo Chang, M.D., the scientists described their use of a harmless virus to deliver corrective genes to mice with a genetic impairment that robs them of vision. The discovery shows that it is possible to target and rescue cone cells — the most important cells for visual sharpness and color vision in people.

"Cone vision defines whether someone is blind or not," said William W. Hauswirth, Ph.D., the Rybaczki-Bullard

²⁷¹

Merin, S. Ronen, S. & Nawratzki, I. (1981) Management of patients with congenital cone deficiency (achromatopsia with amblyopia) in Zauberman, H. ed. Proc Conf Subretinal space. Jerusalem (Documenta Ophthalmologica Proceedings Series volume 25) Page 244

²⁷²Alexander, J. Umino, Y. et al. (2007) Restoration of cone vision in a mouse model of achromatopsia Nature Med vol xxx, pp xxx

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professor of ophthalmic molecular genetics and a member of the UF Genetics Institute. “If you can usefully deliver a gene specifically to cone cells, there are implications for all blinding diseases, not just inherited ones. Even in two very common types of blindness, age-related macular degeneration and diabetic retinopathy, if you can target cones you might be able to rescue that vision.”

The mice had a hereditary form of blindness called achromatopsia, which affects about 1 in 30,000 Americans by silencing cone photoreceptors in the retina. The disease results in nearly complete color blindness and extremely poor central vision.

According to Dr. Chang, “We discovered the achromatopsia mouse about three years ago in the course of screening many strains of mice for vision problems,” as part of The Jackson Laboratory’s program to develop new mouse models for human eye conditions. He and Jackson colleagues then identified the genetic mutation that caused achromatopsia; meanwhile, scientists at other institutions were zeroing in on the analogous human mutation.

Within two months of the gene therapy injection into the subretinal space of the mouse eyes, scientists measured the electrical activity in the retinas, finding that 19 of the 21 treated eyes positively responded to therapy, and 17 of those 19 had electrical readings from their retinas on par with those taken in normal mice.

When the mice were between 6 and 7 months old, tests showed 18 of the 21 treated eyes continued to respond normally.

In addition, a separate, smaller group of treated mice were evaluated using an exam akin to an eye test at the doctor’s office.

In experiments overseen by Robert B. Barlow, Ph.D., a professor of ophthalmology at State University of New York Upstate Medical University, the mice were surrounded by four computer monitors that simulated the appearance of being inside a moving drum that had vertical stripes on the walls.

Scientists knew the mice could see the stripes because sighted animals naturally move their heads in the same direction as the moving stripes. By making the stripes ever-narrower — similar to how the letters get smaller toward the bottom of an eye chart — researchers could assess the mice’s visual abilities.

As a group, all of the mice displayed normal visual acuity in their treated eyes.

“People can talk and tell us what they see,” said lead researcher John J. Alexander, Ph.D., a postdoctoral fellow in the department of ophthalmology at UF. “Animals are much more difficult. What makes this test so fantastic is that it involves an animal’s natural response, and the results tell us that the animals’ brains are involved in the process; that they are actually seeing something.”

In addition to cones, which number about 6 million in the retina, the eye’s rod cells are important for low-light and peripheral vision and exist in much greater amounts, with populations of more 100 million. But treating cones could play a role in diseases that begin with the destruction of rods, such as retinitis pigmentosa, which affects about 1 in 3,000 Americans.

“This is the first to my knowledge of a cone-targeted gene therapy that restores function in an animal model where cones are the primary defect,” said Richard Weleber, Ph.D., a professor of molecular and medical genetics at Oregon Health & Science University who was not involved in the research. “This validates the concept that it is possible to deliver a gene therapy targeting the cone system, and that is incredibly important for a number of degenerative diseases.”

The research was supported by grants from the National Institutes for Health, the Foundation for Fighting Blindness, the Juvenile Diabetes Research Foundation, the Macula Vision Research Foundation, the Lions of Central New York, Research to Prevent Blindness, Fight for Sight and NASA.

“UF and Hauswirth have an interest in a biotechnology company that may seek to market some of the research technology.”

For information on automatic e-mail delivery of news releases (journalists only), please send an e-mail request for details to pubinfo@jax.org.

Office of Public Information

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 600 Main Street
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18.8.3.5.2 Technical update of achromatopsia occurrence figure

The work of Alexander et al. can be combined with the recent work of Kohl et al^{273,274}., Johnson et al²⁷⁵., Deeb²⁷⁶, & Chang et al²⁷⁷. to provide a broader and also more detailed understanding of the genetic and physiological features of achromatopsia. The major finding during this period was a new genetic source of achromatopsia affecting a small percentage (~2%) of the total cohort. This form was the source of the news release from the Jackson Laboratory.

Figure 18.8.3-7 updates the previous [Figure 18.8.3-1] to ca. 2007. It identifies the third form of achromatopsia and indicates its low prevalence based on the current estimates in Kohl et al. (2002). While the methods used to tie the genetic information to the physiology of the subject remains crude (primarily broadband luminance stimulation), a set of ERG's by Chang et al. (2006) are important.

²⁷³Kohl, S. Baumann, B. et al. (2002) Mutations in the cone photoreceptor G-protein A-subunit gene *GNAT2* in patients with achromatopsia *Am J Hum Genet* vol 71, pp 422-425

²⁷⁴Kohl, S. Varsanyi, B. et al. (2005) CNGB3 mutations account for 50% of all cases with autosomal recessive achromatopsia *Eur J Hum Genet* vol 13, pp 302-309

²⁷⁵Johnson, S. Michaelides, M. et al. (2004) Achromatopsia caused by novel mutations in both CNGA3 and CNGB3 *J Med Genet* vol 41, pp e20-e24

²⁷⁶Deeb, S. (2004) Molecular genetics of color-vision deficiencies *Visual Neurosci* vol 21, pp 191-196

²⁷⁷Chang, B. Dacey, M. et al. (2006) Cone photoreceptor function loss-3, a novel mouse model of achromatopsia due to a mutation in GNAT2 *Invest Ophthalmol & vis sci* vol 47(1), pp 5017-5021

Disease	ACHROMATOPSIA		
Gene	CNGB3	CNGA3	GNAT2
Populations	Pingelapese, Irish	Denmark From Jews of Iraq, Iran & Morocco	Europeans of Italy & Denmark
File Number	MIM 262300	MIM 216900	MIM 139340
Chromosome	8q21	2q11	1p13
Locus	ACHM3	ACHM2	
Prevalence	40-50%	20-30%	~2%
Similar form in:	Dogs		Mice
Investigators	Kohl et al. (2000) Sundin et al. (2000)	Kohl et al. (1998) Chang et al. (2006)	Kohl et al. (2002) Sundin et al. (2000)
Transmission Mode	Autosomal recessive inherited and congenital		

Figure 18.8.3-7 The achromatopsia universe as of 2007 with prevalence. The most recently identified form has a low prevalence compared to the other forms. Speculation in the literature suggests a fourth form is yet to be identified.

The data of Chang et al. is shown in **Figure 18.8.3-8**. It provides important evidence that the distribution amplifiers of the photoreceptor cells are normal in achromatopes of the GNAT2 form. This evidence shifts the search for the precise source of the physiological problem forward to the adaptation amplifier circuit. The search is advanced considerably by the discovery that the genetic error is interfering with the generation of aspartate (Chang, page 5021). Chang asserts (in a sentence containing typesetting errors) the miscoding in GNAT2 causes the generation of asparagine instead of aspartic acid. In the Merck Index, 8th Ed., asparagine is described chemically as an amino-acid derivative of aspartic acid. However, aspartic acid is itself a negatively-charged amino acid. Because of potential inter-language translation difficulties between German and English, care is required. In this work aspartic acid is described as CH(NH₂)COOH. Asparagine is described as NH₂COCH₂CH(NH₂)COOH. Asparagine is also described as α -aminosuccinic acid in the Merck Index. It is not clear that Chang distinguished between aspartic acid and glutamic acid in his identification. The relationship between glutamic acid and aspartic acid are so close, additional study will be needed to insure that the production of both materials are not affected by the GNAT2 mutation. In any case, glutamic acid and aspartic acid are the primary sources of electrolytic power in the nervous system based on this work. They are the only two negatively charged amino acids. The failure to produce these materials within the inter-photoreceptor matrix (IPM) between the outer limiting membrane and the RPE would have serious consequences for the adaptation amplifier of the photoreceptor cells. An inadequate supply of this material would cause the adaptation amplifiers to exhibit a high impedance in their collector circuit. This impedance would limit the current capability of the circuit under high stimulus conditions. Since on the order of 1% of this current

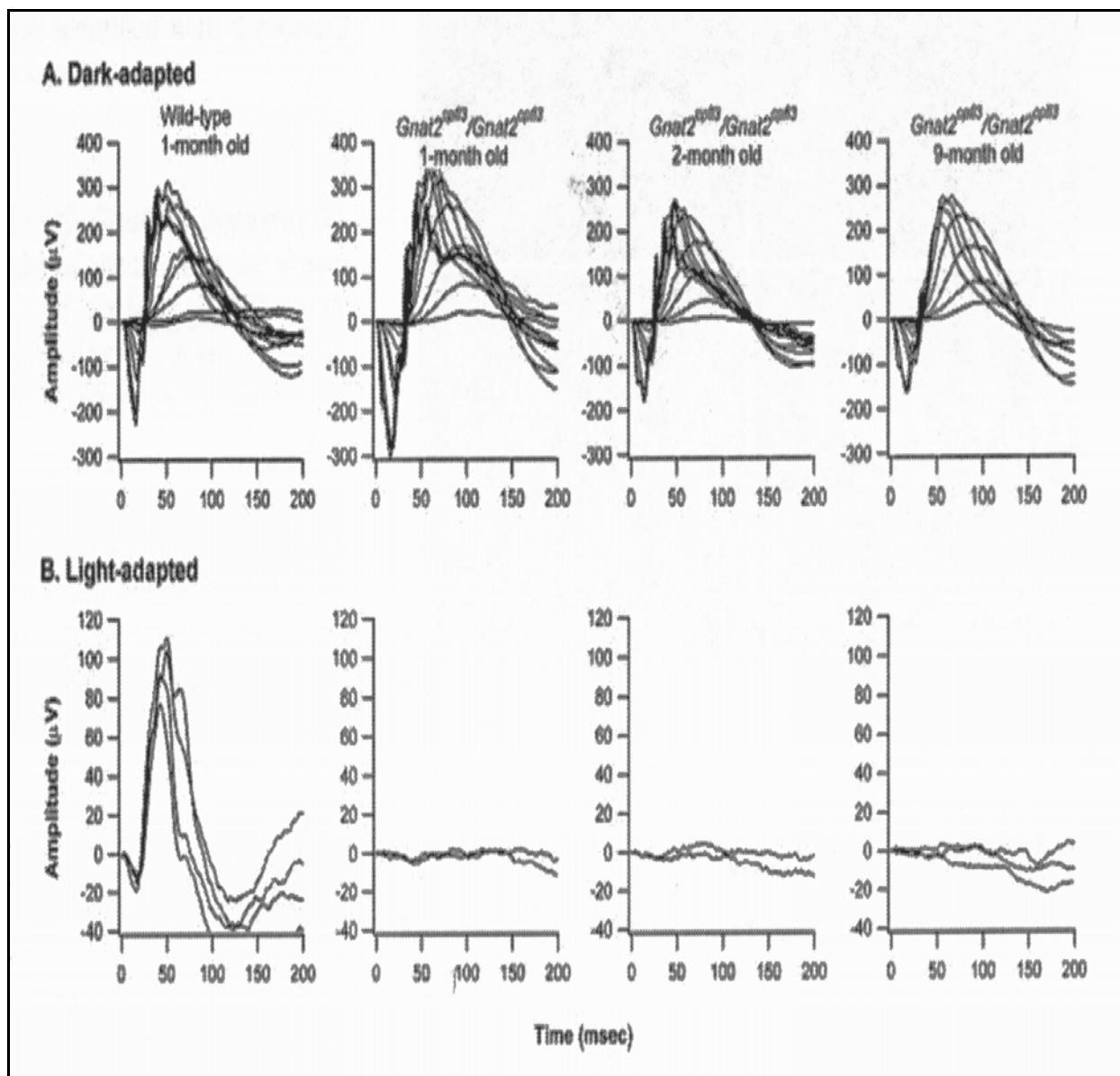


Figure 18.8.3-8 Electretoretinogram of $GNAT^{cpl13}$ mice at 1, 2, and 9 months and a normal mouse (an ALR/Lt at 30 weeks). Shown are intensity response tracings under (A) dark-adapted and (B) photopic conditions. The dark-adapted condition in (A) confirms the ability of the distribution amplifiers of the photoreceptors in GNAT type achromatopes to achieve normal output amplitudes. The loss in output signal in the right-hand frames of (B) are the result of a shift in DC potential of several millivolts at the pedicles not shown in these figures. From Chang, 2006.

appears at the base of the adaptation amplifier Activa, a limitation on this current would limit the current available at the base of this circuit. The average value of this base-current is used to discharge the excitons formed within the photosensitive material (Rhodopsin) on the surface of the outer disks. Failure to discharge this exciton level at a rate proportional to the stimulus level results in a build up of bleached chromophore and the lowering of the hypertopic performance level into the photopic and even mesotopic performance level. This is precisely the condition represented by achromatopsia. The result is achromatopsia, nystagmus and hemeralopia. The hemeralopia is the result of the greater degree of bleaching of the chromophores than normal. This greater bleaching causes more light to reach the substrate behind the photoreceptor outer segments.

Based on this analysis, **Figure 18.8.3-9** modifies [Figure 18.8.3.2] to more specifically identify the location of the

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failure in vision associated with the GNAT2 mutation. The failure is in the electrical path from the IPM to the collector of the Activa within the adaptation amplifier of all of the photoreceptor cells. The precise failure appears to be due to the lack of glutamic acid and/or aspartic acid reaching the electrostenolytic site on the surface of the lemma of the cell within the IPM. The result is the normal operation of the cells under low light level conditions but the failure of the cells to discharge the excited state (observed as the phenomenon of bleaching) of the chromophores coating the outer disks. The only observable abnormality of the retina due to this failure is the excessive bleaching of the retina during high illumination conditions. This failure causes multiple orthodromic signaling failures. These are observed as the syndrome known medically as achromatopsia:

1. Achromatopsia (with no s) due to the loss of signal at the input to the differencing circuits of the P & Q channels
2. Nystagmus due to the failure of the correlation circuits of the POS to receive appropriate signals
3. Hemeralopia due to the excessive bleaching of the chromophores allowing light to reach the RPE

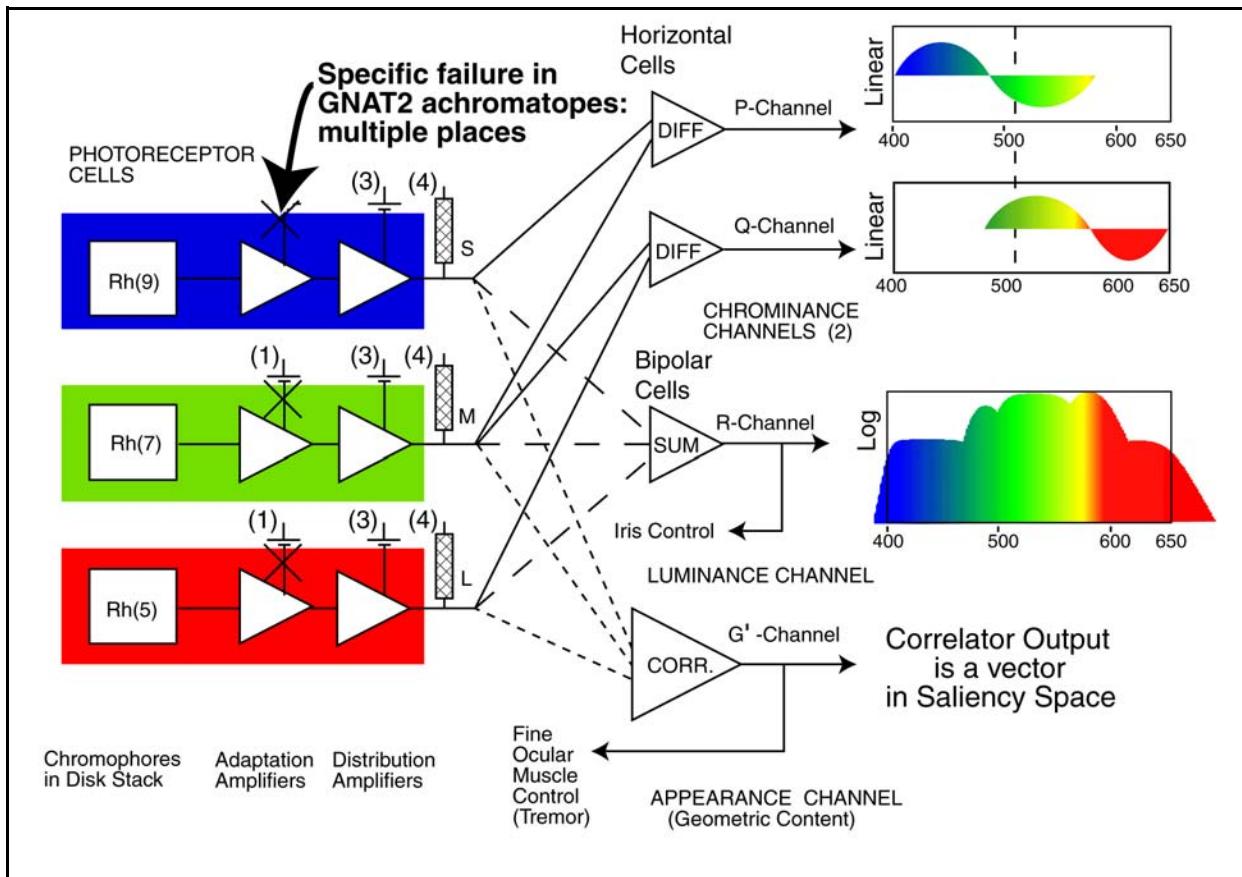


Figure 18.8.3-9 The specific location of the physiological failure resulting from the genetic miscoding in the GNAT2 form of achromatopsia. The failure in the electrolytic power supplied to the collector of the adaptation amplifier Activa results in lowering the hypertopic regime of vision to the lower levels of the photopic regime or into the mesotopic regime. The result is achromatopsia (due to loss of signal to the difference amplifiers), nystagmus (due to loss of signal to the correlator of the POS) and hemeralopia (due to excessive bleaching of the chromophores).

This analysis (based on the theory of this work) provides a far more direct, and observable, interpretation of the failure underlying at least this one form of achromatopsia than does the G-protein cascade hypothesis.

18.8.3.5.3 Introduction of the *in-vivo* OCT imaging technique

Optical coherent tomography is rapidly becoming a major imaging tool in diseases of the cornea, retina and uvea.

Arevalo has recently edited a major atlas of conditions imaged with OCT²⁷⁸. The work is invaluable for understanding macular conditions in detail for the first time. The book does not include the latest spectral domain (Fourier Domain) OCT or SDOCT techniques. The book also avoids discussing the clinical treatment of diseases of the macular. Only a few cases were tracked in the preparation of the book.

The team at University of Rochester has just submitted an article for 2014 publication, including two videos, showing that they have successfully married the technologies of AOSLO and OCT with the stabilization of the retinal image in their instrumentation and providing resolutions of less than one-third the diameter of an individual photoreceptor²⁷⁹. As anticipated in this work, they reported the subjects vision fading over a few seconds interval due to the Troxler Effect. See **Section 3.2.3.2**.

The team led by Roorda has issued a major series of papers resulting from the implementation of an AOSLO with tremor canceling circuitry, thereby achieving a much higher level of performance when imaging the surface of the human retina. Their work omits any activity related to the UV-signaling channel (because of the transmission of the lens) and most activity related to the S-signaling channel (under the assumption the S-receptors play a minimal role in color vision). They do question the long held view that the foveola is S-receptor free. See **Section 3.2.3.6**.

Mohan presented a very well formulated webcast on the history and utility of OCT in angiography of the retina as of 2016²⁸⁰. He used the term Fourier OCT instead of the spectral domain OCT used below.

During the last decade, a new non-invasive method of imaging the individual layers of the *in-vivo* retina in three dimensions has been developed. It has become an important tool in ophthalmology. The technique is Optical Coherence Tomography (OCT), a very sophisticated marriage of interferometric and conventional imaging. An in-depth discussion of the theory of the technique and its various siblings is given by Fercher et al²⁸¹. Putnam et al. described the configuration and performance of the University of Rochester OCT in 2005²⁸². A piece describing the capability of the OCT technique during the next decade is provided by Chen et al²⁸³. Their configuration is described as a spectral domain (Fourier Domain) OCT or SDOCT. While the configuration of Chen et al shows remarkable resolution potential, a stabilizing technique demonstrated by Ferguson et al²⁸⁴. will probably be married to it to obtain a truly excellent imaging capability in a living eye. The Ferguson et al. modification is integrated into a widely distributed Stratus OCT3 manufactured by Carl Zeiss. The OCT3 uses 800-850 nm light from a special low time-coherence source. Addition of the Chen et al. features requires a different light source.

The technique relies upon the backscatter from a semitransparent multilayer medium illuminated by a very small spot of light from a unique light source built into an interferometer configuration. When stabilized, the merged Chen & Ferguson configurations will be capable of 3.5 micron resolution over areas of 3 x 3 mm and 1 mm thick. This is sufficient to image the entire volume of the foveola and nearly all of the fovea of the human eye (except for possible limitations due to the natural curvature of the retina). Each layer of the retina is well defined in depth in current images and major anomalies are easily recognized. However, the transverse resolutions appear to be limited by motions of the living eye during the exposure interval (even in the SDOCT technique without stabilization).

²⁷⁸Arevalo, J. ed. (2009) Retinal Angiography and Optical Coherence Tomography. NY: Springer

²⁷⁹Yang, J-Z. Nozato, K. Saito, K. Williams, D. & Roorda, A. (2014) Closed loop optical stabilization and digital image registration in Adaptive Optics Scanning Laser Ophthalmoscopy *Biomed Optics Exp* vol 5(9), pp. 3174-3191 <https://doi.org/10.1364/BOE.5.003174>

²⁸⁰Mohan, N. (2016)

http://event.lvl3.on24.com/event/11/65/53/7/rt/1/documents/resourceList1461684407497/webcast_oct_angiography_final.pdf also C:///vision/ref papers.pdf

²⁸¹Fercher, A. Drexler, W. et al. (2003) Optical coherence tomography-principles and applications *Rep Prog Phys* vol 66, pp 239-303

²⁸²Putnam, N. Hofer, H. Doble, N. et al. (2005) The locus of fixation and the foveal cone mosaic *J Vision* vol 5(7), article 3

²⁸³Chen, T. Cense, B. Pierce, M. et al. (2005) Spectral domain optical coherence tomography *Arch Ophthalmol* vol 123, pp 1715-1720

²⁸⁴Ferguson, R. Hammer, D. et al. (2005) Three-dimensional retinal maps with tracking optical coherence tomography (TOCT) *SPIE Photonics West*, 22-27 Jan 2005.

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The best use of the technique to date related to achromatopsia is by Barthelmes et al²⁸⁵. They note a major change in the back-scatter from the region between the outer and inner photoreceptor segments in patients with at least one type of achromatopsia. They did not spatially resolve the histological elements adequately in this region. They speculate the change may be due to a change in the composition of the ovoid (nee ellipsoid) region within the cell. This region is known to be rich in mitochondria and likely to be generating specific proteins required for normal photoreceptor operation (other than the proteins of the disks). However, this plane is occupied by several other important structures that may be relevant. There are glia immediately adjacent to the photoreceptors in this area. Their components may also be affecting the expected back-scatter from the region. The photoreceptor cells have their peditic terminals and adaptation amplifier Activa in this area also ([Figure 4.3.3-1]). In any case, the images are compatible with the proposal of this work that a failure to produce the proteins necessary to support electrostenolysis at various locations on the surface of the photoreceptor cells leads to a bias error between the photoreceptors and their associated synapses. If so, the failure mode for the GNAT2 mutation can be expected to occur in the area of the ovoid as shown in block diagram form in [Figure 18.8.3-8] and in histological form in Figures 4.3.2-1, 4.3.3-1, 4.3.3-2 etc in Chapter 4. Efforts are under way to determine if the subjects in the Barthelmes et al. experiments harbor GNAT2 mutations.

It is worth noting that areas of electrostenolysis are frequently associated with areas of high reflectance due to the concentration of metallic ions in the vicinity. Failure of the electrostenolytic process would lead to an absence of these metallic ions. Alternately, the presence of the undissolved electrostenolytic byproduct CO₂ could lead to very high reflectance in this region for healthy subjects. Failure of the process would lead to the absence of these “bubbles.”

In 2011, Merino et al. reported on a new OCT incorporating second generation adaptive optical (AO) system that appears to offer significantly improved resolution in all three dimensions²⁸⁶. It is in routine clinical use at this time. Results obtained with this system will be addressed in **Section 18.8.3.6**.

Figure 18.8.3-10 provides a reference for the appearance of the retina via OCT²⁸⁷. The figure was obtained using a clinical OCT that did not incorporate the advanced techniques of Fourier Transforms, etc. but it does provide annotation of the features that can be observed with the OCT technique. The stated resolution was nominally ≤10 microns axially and 20 microns transversally. This figure does omit the disease conditions typically displayed using this technique. Gupta, et al. have provided an Atlas using the same OCT instrument²⁸⁸. It illustrates a variety of inclusions that can form within the retina along with tears and other conditions not illustrated in Kanski & Bowling. While the work is rapidly becoming dated compared to the imagery obtainable with the later machines, it is extremely valuable to the clinician and ocular surgeon. The Atlas does not address the retinal abnormalities typically associated with achromatopsia. It does include a brief description of all of the operating modes of the Stratus™ OCT Model 3000 of Carl Zeiss Meditec, Inc.

The field of OCT has been advancing rapidly and the OSA provided a special journal issue in 2011 summarizing all of the work under way in the field. Several high resolution images of the retina in plan view were contained in papers therein. See **Section 3.1.5.1 et al.** The Dubra et al paper (pp 1757-1768) requires careful analysis because they did not demonstrate any spectral data for their claimed “rod” photoreceptors, relying entirely on the spatial eccentricity of their images to speculate on the type of cells investigated. See also **Section 18.8.3.6.5l**.

²⁸⁵Barthelmes, D. Sutter, F. et al. (2006) Quantitative analysis of OCT characteristics in patients with achromatopsia and blue-cone monochromatism *IOVS* vol 47(3), pp 1161-1166

²⁸⁶Merino, D. Duncan, J. Tiruveedhula, P. & Roorda, A. (2011) Observation of cone and rod photoreceptors in normal subjects and patients using a new generation adaptive optics scanning laser ophthalmoscope *J Opt Soc Am* (in press)

²⁸⁷Kanski, J. & Bowling, B. eds (2011) Clinical Ophthalmology. NY: Elsevier page 612

²⁸⁸Gupta, V. Gupta, A. & Dogra, M. (2004) Optical Coherence Tomography of Macular Diseases. NY: Taylor & Francis

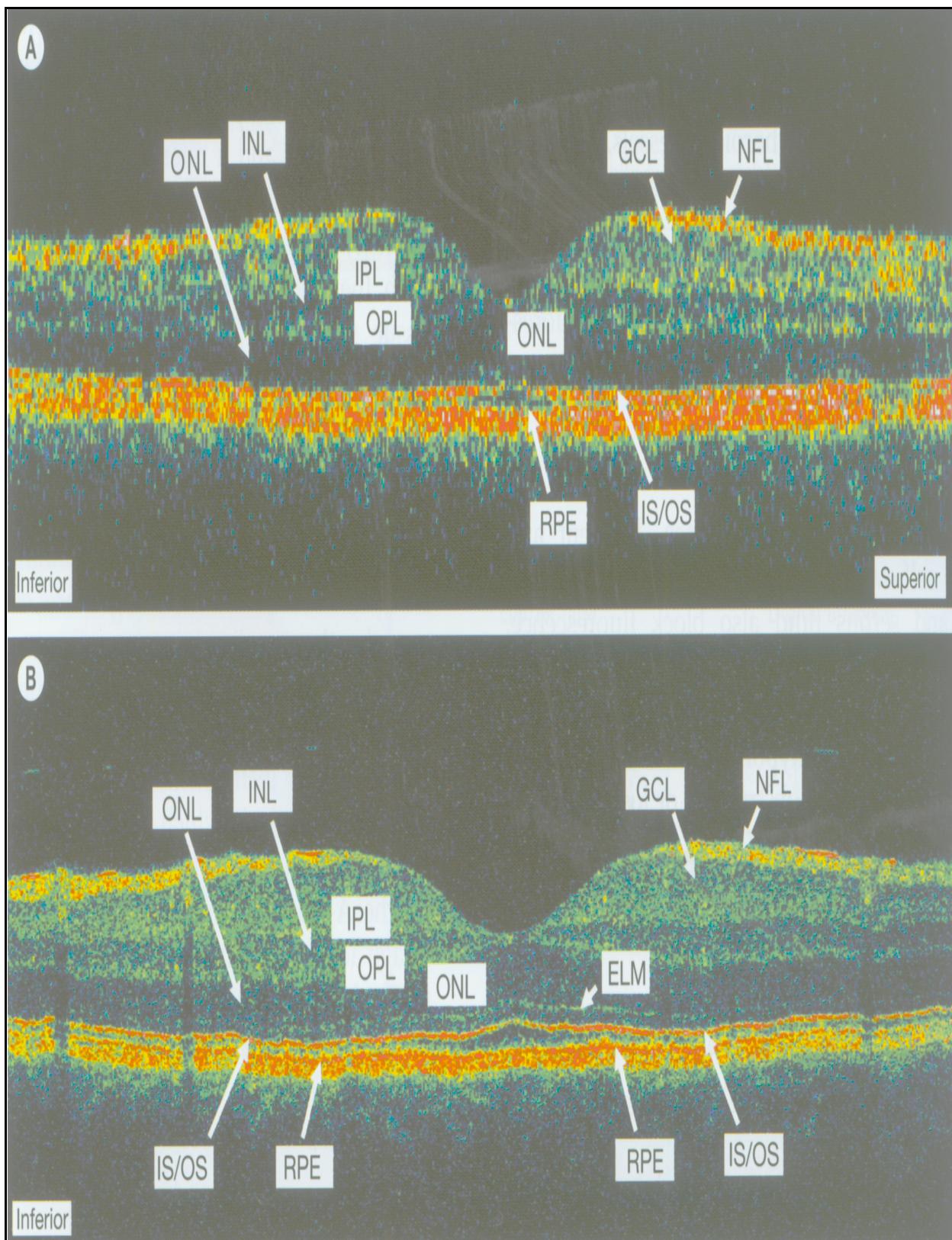


Figure 18.8.3-10 Annotated OCT image of a human retina. From Kanski, 2011

In 2015, three medical doctors, Spaide et al²⁸⁹, introduced another form of OCT, optical computer-aided tomography angiography (OCTA) using apparatus distributed by Optovue. Their figure 1 indicates the technique is very effective for retinal structure near the vitreous humor of the eye. The technique provides an unsurpassed level of detail for the vascularization in this volume of the retina, **Figure 18.8.3-11**. The resolution is less than that provided by the AOSLO approach discussed in **Section 18.8.3.6** that is used to image the individual photoreceptors of the eye.

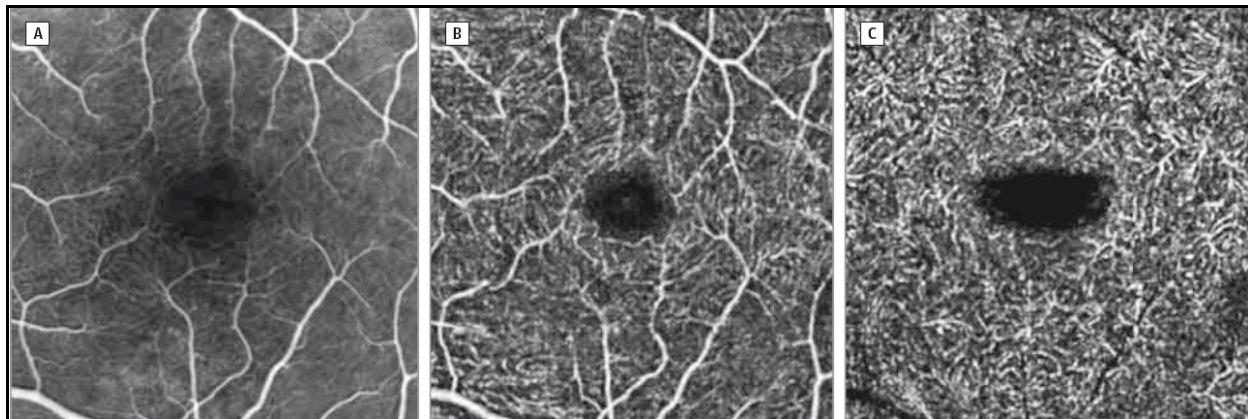


Figure 18.8.3-11 Comparison Between the Fluorescein Angiographic Image and OCTA of the Macula. A, Fluorescein angiographic image of the central macular region. B, Optical coherence tomography angiography image of the inner retinal vascular plexus. C, Optical coherence tomography angiography image of the outer plexus. The capillaries around the foveal avascular zone are included in the segmentation of the inner layer. From Spaide et al., 2015.

18.8.3.6 Additional clinical cases associated with a diagnosis of achromatopsia

DG recently came to the attention of this author. He had been previously diagnosed clinically as an autosomal recessive achromat (or alternately a rod monochromat) in 1992. The diagnosis was based primarily on his failure in interpreting Ishihara type plates, the loss of the ERG signal at high light level as frequently associated with achromatopsia, on a fluorescein dye examination of his retinas and a measurement of his visibility function as a function of wavelength (V-lambda) under both scotopic and mesotopic conditions. A test of his critical flicker frequency appeared normal (compared to W & S, page 558). Since a personal examination by this author was not immediately practical in 2007, a series of simple tests were designed to evaluate the visual performance of the subject remotely.

The first test was to determine if the subject exhibited residual color vision, particularly at low light level. A test was designed using common objects under well calibrated illumination conditions. The subject was asked to examine a series of readily available colored papers available at any office supply store under a full moon in October of 2007 at latitude 37° 47' North. The subject reported he could readily identify the red and yellow paper as colored under this illumination. This test confirmed that the Q-channel (red/green color contrast) of DG's visual system was working properly and his threshold for color vision was in accordance with **Figure 2.1.1-1** of this work (near the bottom of the mesotopic illumination regime).

The second test was to determine DG's color perception and color interpretation capabilities. This test consisted of **Figure 18.8.3-12** presented on a conventional computer monitor without any hints as to what it consisted of. While the color graphics were prepared using a Dell E773c CRT-based monitor and Adobe Illustrator software, DG used his personal laptop driving a 15" MAG Innovision LT501 LCD display. He repeated his tests on his office monitor, a

²⁸⁹Spaide, R. Klancnik Jr, J. & Cooney, M. (2015) Retinal Vascular Layers Imaged by Fluorescein Angiography and Optical Coherence Tomography Angiography *JAMA Ophthalmol* vol 133(1), pp 45-50 doi:10.1001/jamaophthalmol.2014.3616

DG expanded the test on his own initiative by varying the brightness of his LCD display on his laptop computer. He reported correctly on the color of each of the solid color patches at the brightness levels he routinely used for his laptop. In fact, he noted patches 2 and 7 were not saturated greens. I responded to him with two comments. He was correct, and the peak sensitivity of the human eye was at a wavelength of 532 nm which corresponded to what is more aptly described as a lime-green. DG also noted patch 3 did not appear to be a "pure" blue. Here again, the peak sensitivity of the human eye occurs at 437 nm, a wavelength described as a purplish-blue by most normals. DG repeated his tests at the office using a 17" Dell 1908FP CRT display without surfacing any additional information.

The fact that he correctly identified patch 4 further corroborated his ability to see yellow using the Q-channel (red/green contrast) of his visual system. It also confirmed that DG was not a deutanope. The fact he correctly identified patch 5 corroborated his ability to see azure using the P-channel (purple/yellow contrast) of his visual system and that he was not a tetartanope (See Section 18.1.5).

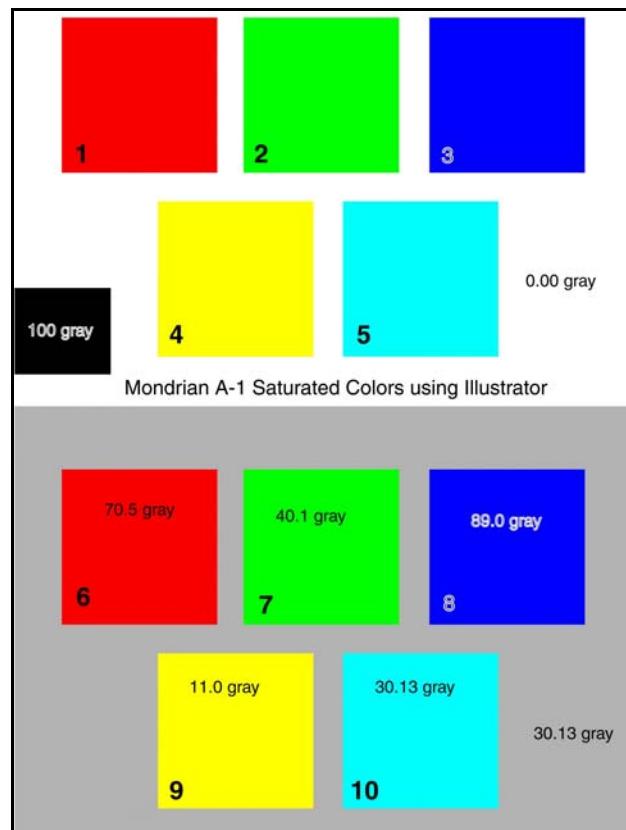


Figure 18.8.3-13 provides a graph prepared from this meager exploratory experiment. It is not meant to be statistically relevant but may suggest that saturation in the short wavelength channel occurs first due to his hemeralopia. The exclamation marks are used to highlight values requiring additional tests to confirm their statistical relevance. In this set of tests, purple corresponds to a wavelength of about 437 nm, blue is about 460 effective nm and azure about 490 effective nm. The term effective is used because the wavelengths were obtained using a monitor to mix peak wavelengths near 437 nm and 532 nm to obtain the perceived colors. Green is centered on 532 nm, red is the response due to the 645 nm phosphor of the monitor, yellow is typically near 580 effective nm and orange is typically near 610 effective nm.

The sloping lines, other than the 45 degree diagonal are suggestive of the saturation of the short wavelength channel before the medium wavelength channel as the light level is raised.

The fact that he correctly identified the three primary colors demonstrated clearly that all three spectral channels of his retina were working properly. The normal spectral performance of DG at low light levels was confirmed by his visual luminosity function, his spectral radiant sensitivity as a function of wavelength. His responses are shown in **Figure 18.8.3-14**. While truncated at 500 nm by the administering physician (probably due to an abundance of caution), the mesotopic radiance response appears completely normal peaking near 532 nm.. It shows the logarithmic summation of the long wavelength and medium wavelength spectral responses shown in color at the bottom of the figure. It would have included the short

Figure 18.8.3-12 Mondrian of the color spectrum with both white and gray backgrounds. For diagnostic purposes, this mondrian should be presented at a size to fill the vertical dimension of the display device.

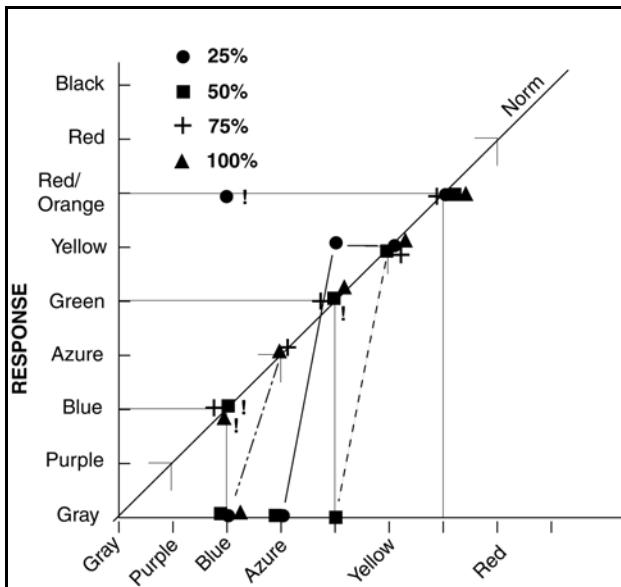


Figure 18.8.3-13 A preliminary color stimulus-response diagram for DG. The data is not statistically relevant but may show correct trends. See text.

wavelength response if the test had been extended to 420 nm. Similarly, the low radiance responses show the typical scotopic response peaking near 505 nm (a logarithmic summation of the short and medium wavelength spectral responses). This response (in the absence of any longer wavelength response) is usually used to define a “rod-monochromat” clinically. The fact that differential adaptation can separate this response into two separate responses is ignored (or overlooked historically).

The conclusion is unmistakable. The color performance of DG’s visual system is nominal in every respect at scotopic and mesotopic light levels. DG’s response to this test clearly confirmed that he is not achromatic, nor is he a protanope, nor a tritanope nor a pentanope (See **Section 18.1.5**). As noted above, his ability to discriminate shades of color between red and green insures he is not a deuteranope and his discrimination ability in the azure region insures he is not a tetartanope. It is doubtful that he is anomalous in any of these areas. He can not be considered a monochromat under any rational definition of that term.

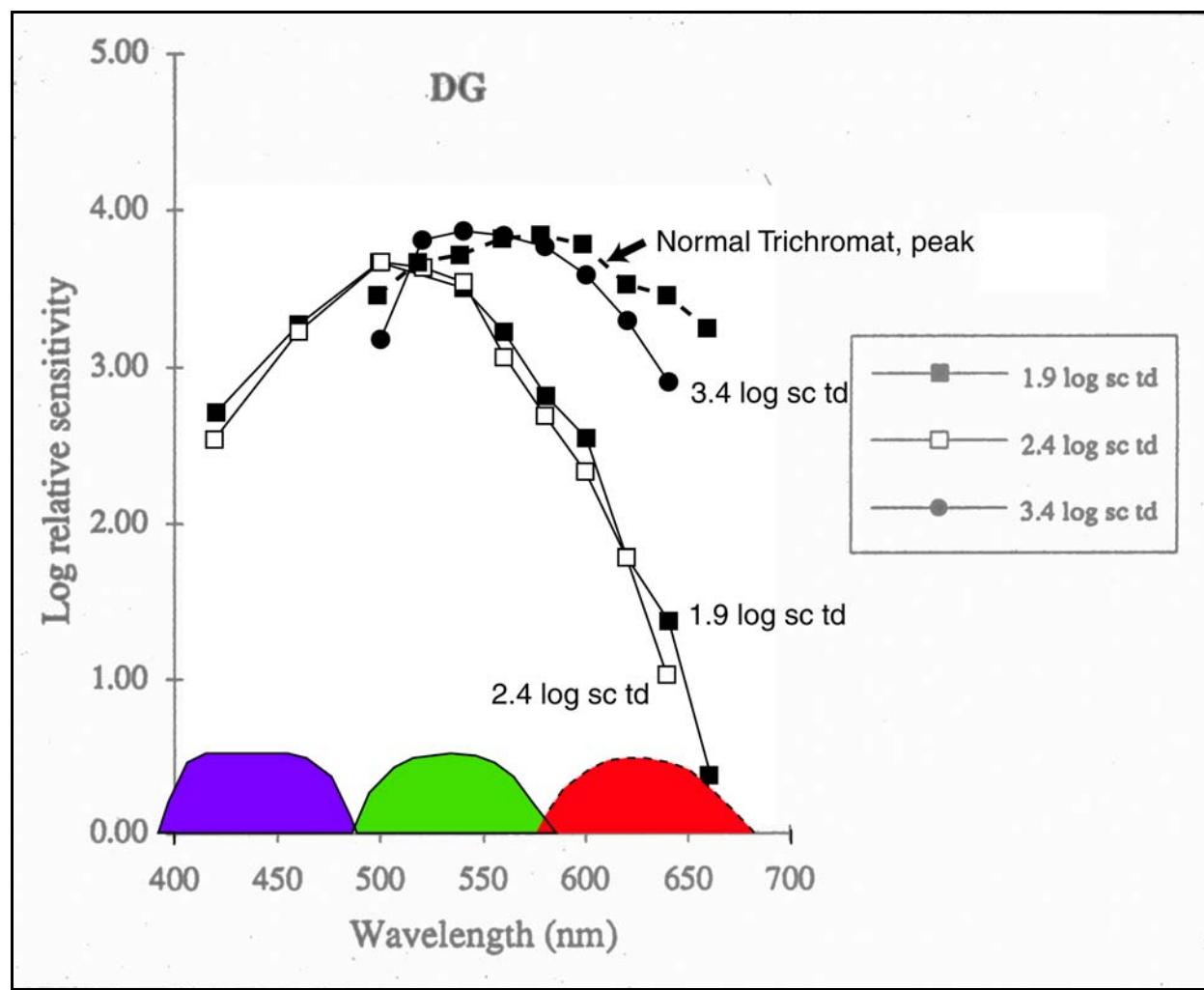


Figure 18.8.3-14 The spectral radiance sensitivity of DG as a function of wavelength and stimulus intensity. The high level tests were truncated at 500 nm by the administering physician. The two low intensity responses are the typical scotopic response of a normal. The high intensity response approaches the normal response. It would be expected that the long wavelength response would more closely match the typical trichromatic response at still higher intensity levels.

As DG raised the brightness of his computer display, the character of his disease became abundantly clear. As the brightness increased, he is able to differentiate more and more large-area color swatches, expanding into shorter wavelength regions. On the other hand, his acuity, the ability to resolve small-areas decreases with the saturation of

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the neurons accompanying higher brightness levels (see pages 160-163). DG exhibits a limited photopic sensitivity range. At normal brightness ranges, DG's eyes enter the hypertopic operating regime in accordance with **Figure 2.1.1-1**. Because of this saturation within his neural system, DG takes precautions, typical of a photophobe, to avoid such light levels.

A second test was performed to confirm the above situation. **Figure 18.8.3-15** was presented to DG without any comments. With the brightness level of his laptop set at optimum, DG could read all of these lines of text and correctly identify the background colors. However, as he raised the brightness level, the samples labeled C-2 and C-3 began to become unreadable. The characters lost definition. Individual strokes became distorted and changed dimensions. He also noted the distortion was not uniform along an individual line.

DG made an interesting comment at this point. He felt the use of characters with serifs would increase the legibility of the characters. This is of course the very purpose of serifs in printing.



Figure 18.8.3-15 Text on mondrians test chart. For diagnostic purposes, this mondrian should be presented at a size to fill the vertical dimension of the display device.

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A cursory attempt was made to determine the extent of the saturation occurring within DG's visual system. Initially, this was performed by asking him to estimate the width of the dysfunctional area of his retina using the text provided and displayed above. DG suggested a more definitive experiment based on his familiarity with the brightness and contrast controls on his laptop. He, and many others with his condition, routinely operate their laptops at reduced luminance to avoid their intrinsic visual saturation problems. He prepared a grid that allowed this estimate to be made in two dimensions. The test consisted of a series of gray dots on a white background as shown in **Figure 18.8.3-16**. The dot array covered the entire face of his monitor and was observed from a nominal distance of 12 inches. As a result the entire array approximated a visual field on the order of forty-five degrees. Only a segment of the overall field of view is reproduced here. The letters within the dots have been added for discussion purposes and were not present during the test. The optic disk is outside of the region portrayed.

The circles represent the field of view in object space. The oval will described below.

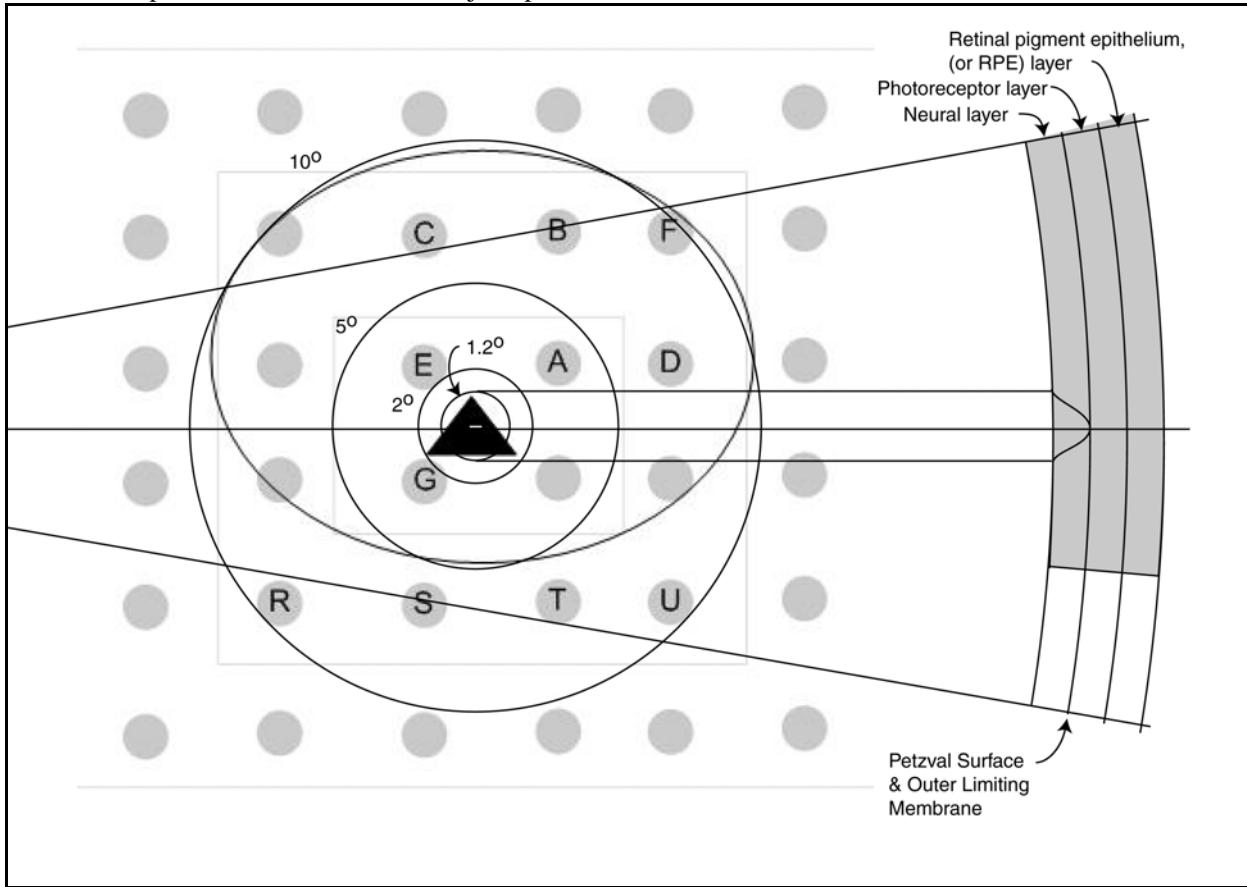


Figure 18.8.3-16 Approximate perimetry of the saturating area of the retina for DG. Poor resolution copy from a JPEG. The outer circle approximates ten degrees in object space and approximately the same angle relative to the back focal point of the eye. The nominal retina is shown on the right. The diagonals from the left converge at the back focal point of the lens of the eye. The focal plane is the nominal surface of best focus for the optical system of the eye. The foveola is shown by the 1.2 degree diameter circle on the left and the depression in the neural layer on the right. The five degree circle represents a frequently quoted diameter of a nominal macula (a poorly defined region observed optometrically through the pupil).

The unedited comments of DG resulting from this test as a function of monitor illuminance with both eyes as wide open as possible were as follows. The abbreviation b/c refers to the settings of the brightness and contrast on an internal computer calibration scale of 0 to 255.

b/c 0

- all dots perfectly visible and durable.

b/c 32

- all dots visible although after a few seconds dots A, B, and C have a tendency to fade or become muddled but any slight eye movement makes them all reappear

b/c 64

- all dots visible although A, B, C, D, and E tend to fade or distort fairly quickly. slight eye movement makes them visible again for a moment

b/c 96

- all dots visible initially but A-F are hidden by scotoma, with G soon disappearing entirely. eye movement makes them come back vaguely and not for long.

b/c 128

- all dots visible except those indicated by oval. the scotoma itself quickly becomes visible as a sort of light blob covering dots indicated by oval. R, S, T and U are a bit vague. Actually most of the dots in the grid are a bit vague at this light level

b/c 160

- all dots are vague, with dots in lower half of screen becoming hardly visible at all (LCD viewing angle issue?). scotoma covers dots indicated by oval same as before. Triangle easily becomes hidden.

b/c 192

- most dots very vague except those hidden entirely by scotoma. Dots along upper edge and in upper corners still reasonably visible

b/c 224

- entire picture appears white with only a couple dots near upper corners visible faintly

b/c 255

- complete washout

These comments can be summarized and interpreted using the theory presented in this work. However, the short-term transient performance described is beyond the scope of the current discussion. DG's luminance contrast sensitivity is normal at very low and low light levels. However, it deteriorates with increasing illuminance. The deterioration is described as a scotoma that is most profound within an elliptical area with a vertical (minor) axis of 5-7 degrees and a horizontal (major) axis of about 10 degrees centered about two degrees above his point of fixation. The scotoma is not symmetrical about his point of fixation. The increasing luminance of the local surround significantly reduces the legibility of the individual dots. The effect is particularly severe within the area defined as the scotoma but it occurs throughout the visual field culminating in what DG describes as a complete washout. Even the black triangle disappears due to the luminance of the local surround. The scotoma is not a physical absorber ahead of the photoreceptors. It is a spatial function of the performance of the photoreceptors themselves.

The above test was repeated with gray dots on a black background (and a white triangle for fixation) to discover any effect related to the local surround. **Figure 18.8.3-17** shows the observed situation.

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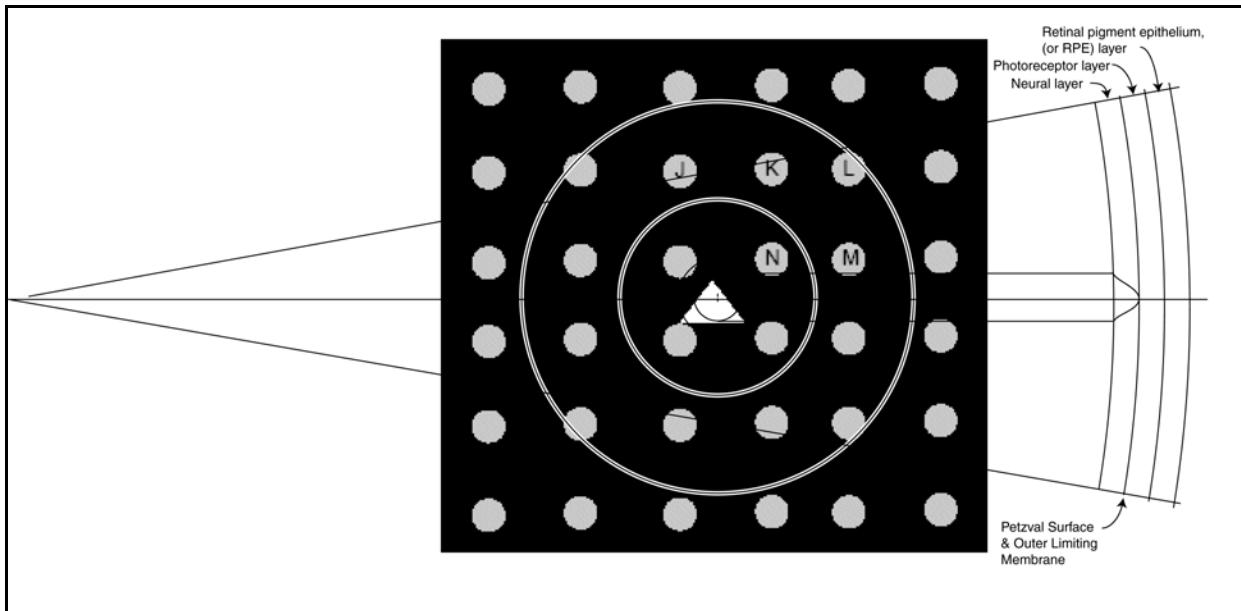


Figure 18.8.3-17 Approximate location of scotoma of DG in the presence of a black background. The grid is too coarse to provide a definitive outline of the scotoma but the responses do correspond to the scotoma of the previous figure. See text.

The results of this test as a function of monitor illuminance with both eyes as wide open as possible were as follows:

b/c 0

only element visible is durable gray triangle. Dots invisible due to low contrast with black background

b/c 32

all dots and triangle visible and durable upper portion of screen dots are dimmer (LCD effect) interior of triangle vaguely dimmer than edges

b/c 64

dots have a tendency to blink darker centers on and off but this is a well-known optical illusion, no special talent of mine. Triangle still clearly visible and its interior slightly dimmer than edge. Main news is that sometimes after a few seconds dim spots or clouds appear in the vicinity of J and K

b/c 96

dots are all clear, bright, and distinct, however triangle is starting to show a certain fuzziness or blurriness. Sometimes after a few seconds, dot K starts to become fuzzy or blurry sometimes with a few small spots nearby All dots are quite durable

b/c 128

triangle is not quite triangular anymore but rather an approximately triangular glowing and slightly morphing patch. as for the dots, they are all there bright and crisp except for K (which sometimes looks like it is getting fuzzy) or L (which also looks like it might be getting a bit fuzzy too) No scotoma per se though.

b/c 160

triangle is now more of an amorphous glare than a triangle. dots are still reasonably sharp but dots K and sometimes L seem to sometimes want to fuzz out and become amorphous

b/c 192

triangle is again kind of a diffuse glare or glow. dots are still clear and sharp but dots K and L still tend to fuzz out or sometimes merge into a sort of oblong. Dot M also tends to become diffuse after a few seconds. Dots are a bit bright for my taste.

b/c 224

triangle same as before. It kind of starts out triangular at first glance but soon becomes a diffuse glare or glow. dots

J, K, N, and M seem especially prone to quickly becoming diffuse and becoming surrounded by 'clouds' but other dots are still distinct. entire scene is bright and unpleasant.

b/c 255

triangle is a fuzzy glow/glare and larger now. dots J, K, L, M, and N have a tendency to quickly become indistinct or merge, with clouds or glows are similar brightness to dots. Entire scene even with black bg is unpleasantly bright.

As in the above case, these comments can be summarized and interpreted using the theory presented in this work. However, the short-term transient performance described is beyond the scope of the current discussion. DG's luminance contrast sensitivity is normal at very low light levels. Whereas the high luminance local surround encroached on the lower brightness in the above case, the higher illuminance dots spread into the *perceived areas* of the lower illuminance image in this case. The high luminance triangle is the first feature to result in the spreading of the *perceived image* into the local dark surround. The spreading of the *perceived sensation* destroys the form of the triangle. This spreading is large scale. It involves an area on the retina containing thousands of individual photoreceptors. As the luminance and contrast settings are increased, the *perceived sensation* for each individual dot begins to encroach on the local dark surround. This encroachment is most severe within the oval defined as the scotoma by DG (even though no perimeter definable as a scotoma is perceived in this second experiment). As the brightness/contrast is increased, the spreading of the perceived dots becomes sufficient to cause overwhelming of the local dark surround and the entire visual field becomes a uniformly bright image. The subject has essentially become blind to any detail in the scene (even the relatively large dots in this experiment). At this luminance level, his visual system is operating in his hypertopic illumination regime.

Figure 18.8.3-18 illustrates the performance of DG's visual system using an extended threshold versus radiance (TVR) diagram. The change from the lower to the higher sloping line in this presentation is a result of the spectral sensitivity of the eye changing while the spectral response of the radiance measuring instrumentation does not. The slope of the diagonal line is consistent with a dynamic range in his visual system of 200:1 (46 dB or 4.5 log units).

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The figure demonstrates that DG suffers from premature saturation in the luminance response of his visual system. This is confirmed by the fact that DG wears a pair of dark sunglasses outdoors with a transmission of 7%. He

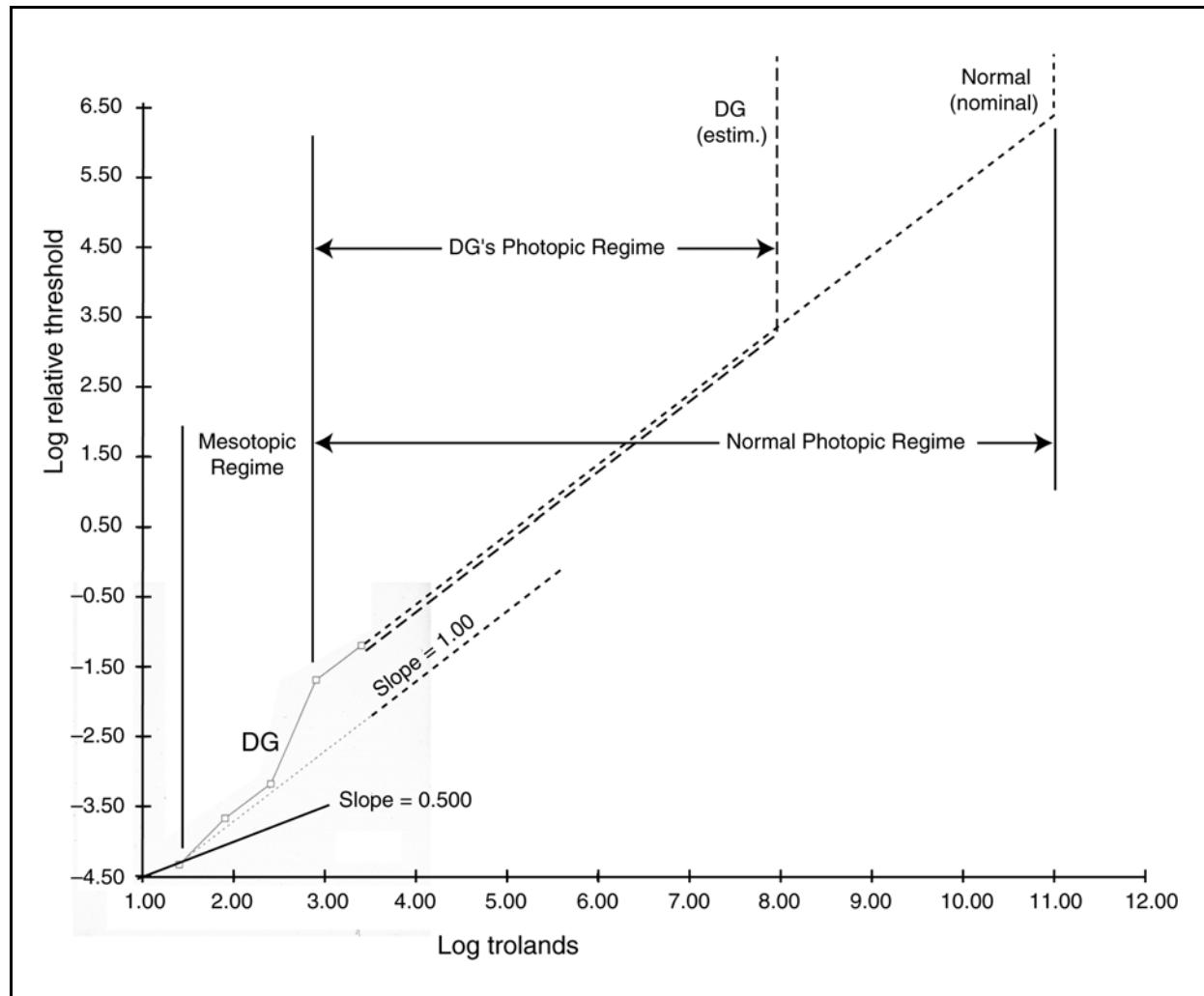


Figure 18.8.3-18 An extended TVR diagram for DG. A slope of 0.5 is indicative of the scotopic (noise limited) operating regime. A slope of 1.00 is indicative of operation in a regime limited by the dynamic range of the neural system. Entry into the hypertopic (saturation) regime is indicated by the vertical dashed lines. A threshold criteria is meaningless and all visual acuity is lost in the hypertopic region.

indicates that he would prefer an even darker pair at 5% transmission. At these levels, DG exhibits nearly normal color vision, except he is tetartanomic (exhibiting poor blue-green differentiation).

When combined with the earlier chromatic tests, the saturation in both his luminance and chrominance channels demonstrates that DG suffers from premature saturation in the output of the spectral channels of his vision prior to the formation of distinct luminance and chrominance channels (as described in **Figure 18.8.3-9**). The fact that the saturation occurs on a global basis within his field of view suggests the problem is not related to specific photoreceptors but is a function of the metabolic and/or metabotropic support to these photoreceptors.

The large signal circuit diagrams of **Figure 17.1.4-2** et al. are instructive in this situation. Both the distribution amplifier (AD) and the initial synapses (BS) are saturable circuits. Either of these individual circuits could introduce the limitation on the dynamic range encountered by DG. In addition, these are direct coupled circuits and a minor shift in the electrical potential of the electrodes of these circuits could cause an additional cutoff condition. The circuit in frame B of the figure also shows the signal forwarded to the precision optical servomechanism (marked to

Z channels).

18.8.3.6.1 Diagnosis of the disease suffered by DG ca. 2007

DG can be described as suffering from dyschromatopia characterized by hemeralopia (day-blindness) and tetartanomalia under mesotopic conditions. The tetartanomalia, a lesser form of tetartanopia, is characterized by an abnormality in distinguishing blues from yellows. The brief descriptions of the problems encountered by DG lead to a more specific diagnosis.

The above summaries of the operation of DG's visual system under opposite contrast conditions can be used to interpret the physiological operation of his retinas using the cross section of a retina shown on the right of both of the above figures. Each retina consists of four major layers. Beginning from the surface facing the pupil, it consists of the complex neural laminate, the more ordered photoreceptor layer, the retinal pigment epithelium layer, and finally the scleral layers (not shown explicitly) behind the RPE.

The first point to observe is that in the case of DG, the scotoma is not symmetrical about the point of fixation and is therefore not directly relatable to any optically observed macular region centered on the point of fixation. Further, the scotoma is not directly relatable to the foveola surrounding the point of fixation (the smallest circle essentially covered by the triangle in these experiments). In addition, the scale of the dysfunction is far larger than the scale of the individual photoreceptors. In previous experiments, the photoreceptors of DG have been shown to be operating correctly at levels below his hypertopic regime. If located within the retina, the dysfunction most likely involves the metabolic and/or metabotropic processes associated with the retina. There appear to be four principle possibilities.

1. The processes between the arterio-vascular system and the tissue of the scleral laminates can be dysfunctional.
2. The processes within the RPE laminate, and the associated inter-photoreceptor matrix (IPM) surrounding the outer segments of the photoreceptors, can be dysfunctional.
3. The interface between the disks of the outer segment and the neurites of the adaptation amplifier of the photoreceptor cell within the IPM space could be abnormal.
3. The processes found within the photoreceptor layer between the Outer Limiting Membrane (OLM) and the remainder of the neural laminate (surrounding the inner segments of the photoreceptor neurons) may be dysfunctional.
4. The processes between the arterio-vascular system and the tissue of the neural laminate providing support to the photoreceptor layer may be dysfunctional.

As noted below, DG's dark adaptation function appears to be normal. This situation strongly suggests DG's RPE laminate is operating normally with respect to the photo-detection process. The demands on this laminate actually decrease with increasing illumination level, suggesting dysfunction of the processes assigned to the RPE are not the source of the disease. However, it is possible the porosity of the RPE laminate may affect the metabolic and metabotropic operation of the outer segments of the photoreceptors. The remaining sources of dysfunction are centered on the metabolic and metabotropic processes associated with the scleral laminate and the neural laminate, and the porosity of these laminates to the constituents involved in these processes.

A fluorescein dye test was performed to confirm there was no obvious dysfunction of the major cardio-vascular structure associated with the neural laminate.

The recently introduced optical computer-aided tomography (OCT, **Section 18.8.3.5.3**) offers a capability of exploring physical distortions in the layers of the retina non-invasively. This technique may offer a method of isolating the cause of DG's disease.

Current Diagnosis:

It can be concluded that DG suffers from an autosomal recessive genetic disorder resulting in an electrical bias error at the axon of the visual sensory neurons (the trait) resulting in a dynamic range dysfunction (premature photopic to hypertopic operating regime transition). This dysfunction is most likely caused by a metabotropic error involving the electrostenolytic conversion (**Section 8.6**) of glutamic acid to gamma-amino-butyric acid (GABA) on the surface of the inner segment of the sensory neurons within the neural laminate of the retinas. This dysfunction affects the luminance and chrominance signalling channels and the precision optical servomechanism (POS) of the visual system. The primary symptom of this disease is loss of all spatial acuity at high stimulus levels due to the loss of signal amplitude to, and therefore interruption of operations within, the POS. The major clinical symptom associated with this underlying dysfunction is total amblyopia (including all luminance and chrominance contrast performance) at high light levels. The subject becomes photophobic in order to avoid this condition.

Within the scotopic, mesotopic and lower photopic regime, the subject is capable of near-normal visual performance when wearing conventional eye glasses. His work involves considerable reading of detailed technical texts. One of his hobbies is star gazing. Under full moon conditions, he is able to perceive at least the color red on a reflective test sheet.

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The condition is not organic and does not involve any physical malformation of the visual system. The chromophores of vision are not directly involved in this disease. The condition is a dominant form of agnosia at high stimulus levels.

This diagnosis can be confirmed by the administration of an ERG with a peak intensity of 2-5% of normal as suggested by **Figure 18.8.3-19**. The ERG response at the intermediate level would be near normal in amplitude if the level corresponded to the effective photopic level in the subject.

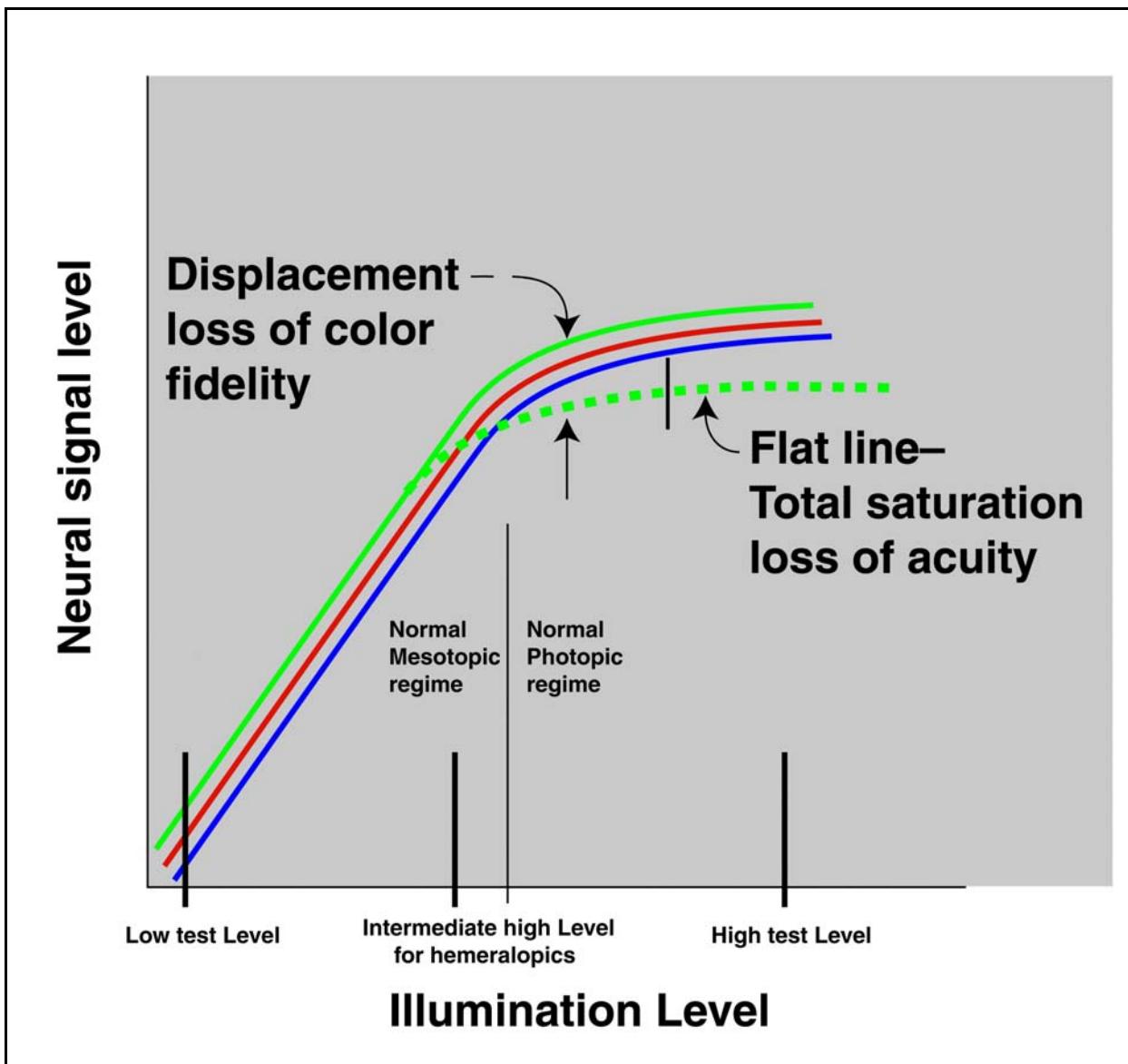


Figure 18.8.3-19 Modified ERG protocol appropriate for sufferers of Achromatopsia and hemeralopia in general.

Current Prognosis:

There is no immediate therapeutic treatment for this condition. A potential treatment would involve increasing the availability of glutamic acid and aspartic acid near the outer nuclear layer (the inner segment of the photoreceptor cells) of the neural laminate of the retina (**Figure 3.2.1-1**).

DG believes his dark adaptation function is normal. His ability to see stars in the night sky after a reasonable period

of dark adaptation (**Section 18.8.5.2.2**) demonstrates that he does not suffer from Oguchi's disease or "night blindness."

18.8.3.6.2 Alternate diagnosis of the disease suffered by DG

The analysis above was based on the assumption that the photo transduction process involving the chromophores was a linear constant gain mechanism and adaptation occurs within the neural portion of the photoreceptors. More recent analyses presented in this work is based on the liquid crystalline chromophores providing the adaptation mechanism and the neural circuits act as linear constant gain devices. Based on this change in understanding of the adaptation mechanism, an alternate analysis was performed in December 2008 relating to the symptoms associated with DG. A more complete analysis of the "visual cycle related to the RPE/IPM/photoreceptors was developed. The conclusion of that analysis was in support of assumption three above.

Figure 18.8.3-20 shows a schematic focused on the RPE/IPM/PC region of the retina along with a list of failure modes in this region.

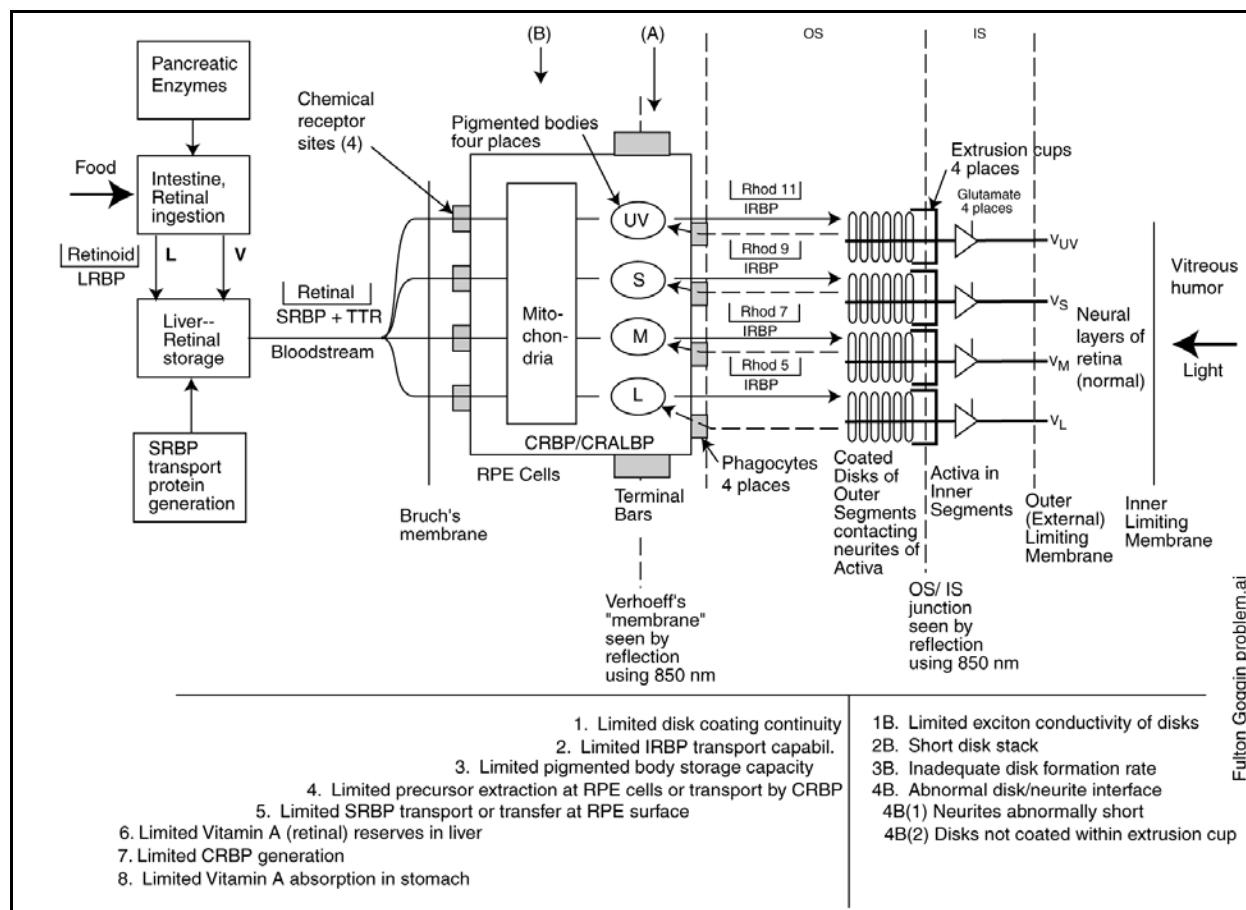


Figure 18.8.3-20 Schematic of the visual cycle under homeostasis and total dark adaptation with a list of potential failure modes. The presence of four distinct chromophoric channels is significant if the mosaic character of the retina is to be considered. Similarly, the two channels of transport between the intestine and the liver should be recognized, the lymph (L) path and the vascular (V) path. The liver itself appears to harbor two different types of cells important with respect to vision. Multiple failure modes from the list can exist simultaneously. See text.

The figure describes the overall flow of the retinols and chromophores (rhodones) in the eye, where they are stored and how they interact with the neural system. Below the figure is a two column listing of possible problems leading to various retinal disease conditions. Initial clinical trials designed to treat some of these diseases have occurred. The most widely discussed in 2015 involved a semi-porous plastic capsule inserted into the vitreous humor (on the

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right) containing modified human RPE cells. The goal was for these cells to release a factor, CNTF, that would migrate through the various impervious barriers (at least the inner and outer limiting membranes) and impact the region to the left of the OS/IS junction. See **Section 18.8.3.8.**

In further reading of the literature, several enzymes produced in the pancreas play major roles in preparing the various forms of vitamin A (provitamin A's in some contexts) for ingestion. One enzyme may be critical to the absorption of retinoic acid (used in non-visual applications) and another enzyme may be critical to the absorption of retinyl esters (used in visual applications). A third enzyme may be needed to aid absorption of beta carotene (a precursor of vitamin A). It also appears that the retinoids absorbed from the intestinal tract (see upper left of the figure and comment #8 of the lower text) are most likely transported to the liver via the lymphatic system rather than the vascular system (**Section 7.1.1.2.3** and the 1994 update from Ong). Ong notes, "This suggests CRBP(II), a.k.a. LRBp in this context, is uniquely suited for participating in the trafficking and metabolism of vitamin A that occurs in the enterocyte during absorption, but CRBP, apparently unsuited for that task, is the better choice for all other cells of the body that deal with the retinoic acid form of vitamin A." A significantly different caricature of an RPE cell is needed to reflect the functions of the retinoids in vision (**Section 18.8.3**, specifically **Figure 18.8.3-19.**)

Another case of possible retinoid absorption problems appeared in 2017. Dr. A. LaSalle is treating a female patient, SdR-58 years old, who is not utilizing some retinoids properly, whether administered orally or by injection. Dr. LaSalle described her situation as similar to a black hole, no matter how the retinoid is administered, the serum level would indicate it is disappearing almost immediately. The patient exhibits thinning and even fusion of the RPE and outer segment layers in her OCT scans that appears to be diagnostic of a problem related to the above figure. The patient is currently reporting a loss of vision in dim light and night blindness in her right eye, with less left eye impairment.

Section 7.1.2 addresses many aspects of the SdR case. A case study by Perlman et al²⁹⁰. provides data on a potentially similar situation, that may be an exemplar for night blindness and early macular dystrophy. Their figure 2 shows a very significant restoration of dark adaptation capability (a return to the norm) within seven months based on a 2° diameter 500 nm test light for the right eye at a 15° temporal location. A carotene in the blood test showed a nominal level (127 units/dl) after the seven months of treatment compared to 31 units/dl upon initial evaluation. The case also involved intramuscular injections of an unspecified form of vitamin A (**Section 7.1.2**) and a surgical reversal of an old "jejunooileal bypass operation (end to side) about 11 years prior to admission."

DG participated in an exploratory investigation of his retina using an advanced form of optical computer tomography (OCT). OCT was described briefly in **Section 18.8.3.5.3.** The initial results from this test indicated an anomaly in the region described as Verhoeff's "membrane" as seen as a reflection of 850 nm light coming from the right. The limiting axial resolution of the OCT was no better than two microns. Verhoeff's membrane is believed to be generated by the combined reflection of the "terminal bars," and the pigment bodies shown, storing precursors of the chromophores and labeled UV, S, M & L. There is controversy in the literature whether the "terminal bars" consist of a perforated membrane or just a lot of cells (cells frequently described as astrocytes or Mueller cells) surrounding the RPE cells. The weight of evidence seems to favor just a group of cells. No more definitive analysis of the source of this reflection can be given at this time.

Looking at the retina from the right would show that one RPE cell supports a group of individual photoreceptors. A group of deficient RPE cells could result in the scotoma reported by DG in figures 18.8.3-14 & -15 and the dark region of the fovea reported by Merino et al.

Nearly all of the potential problems listed on the right in the above tabulation can be eliminated in the case of DG except for 4B. The most interesting possibility is 4B(1). It appears the neurites forming a chalice enclosing the disks of the outer segment may be too short. This is illustrated in **Figure 18.8.3-21.** On the other hand, failure of the RPE to provide adequate chromophores (problems 3, 4 & 5 on the left in the tabulation) to coat the newly formed disks completely could cause a similar functional problem. An overall photoreceptor cell is shown at lower right. It is shown in exploded form in the rest of the figure. The neural chalice is shown on the left. The interesting feature is highlighted in the two small graphs on the right.

²⁹⁰Perlman, I. Barzilai, D. haim, T. & Schramek, A. (1983) Night vision in a case of vitamin A deficiency due to malabsorption *Brit J Ophthal* vol 67, pp 37-42

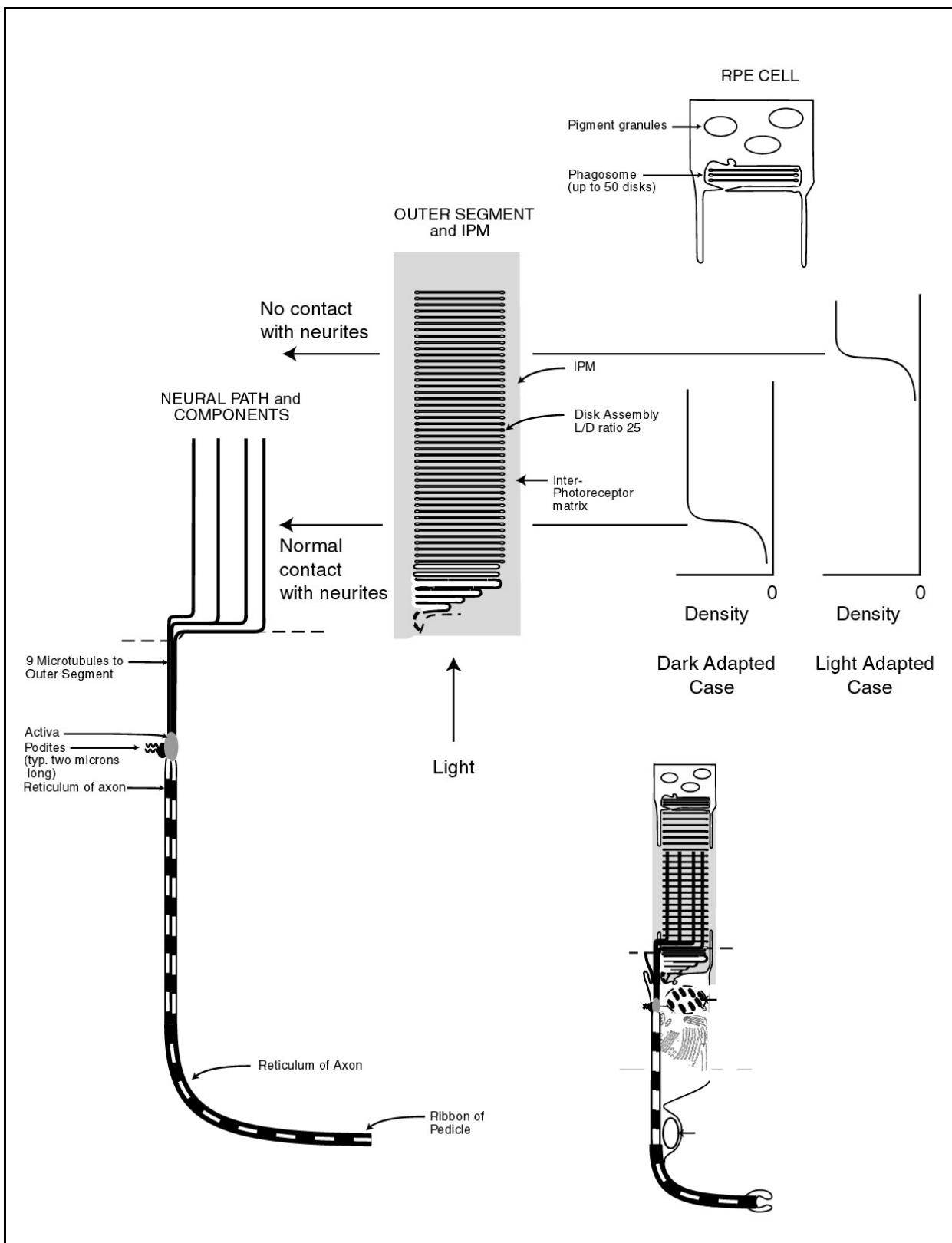


Figure 18.8.3-21 ADD Details of a photoreceptor exhibiting the loss of ERG signal at high light levels. See text.

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Under dark adaptation, nearly all of the disks are highly opaque and sensitive to light. Most of the light is absorbed in the first few disks in the OS stack (where the density increases rapidly) and generates excited electrons in the individual disks. The resulting excited electrons are transferred in the plane of the disks to the neurites shown on the left. Everything works according to plan under low light conditions. Color vision is essentially normal in the mesotopic illumination regime.

In the case of DG, it appears the neurites are shorter than normal and do not extend up to near the top of the disk stack. At low light level, everything works fine. However, at higher light levels, the initial disks have already been excited and are virtually transparent and the majority of the absorption and excited electron generation occurs higher in the stack (near where the density increases rapidly). The excited electrons are constrained to their own disk. Unless they can travel horizontally to and transfer to a neurite, they are not functional in the visual process. This appears to be where the problem arises. The retina will appear "bleached" under high light conditions but the subject will complain of going blind at that light level because no signal is being generated in the neurites connecting to the Activas and the rest of the neural system. The observed effect will be a loss of contrast as the light level is raised and a washing out of image detail. The loss of the electrical signal at the neurites will be observed by the clinician as a loss in the ERG at photopic light levels. This loss occurs in normal patients under hypertopic conditions (snow-blindness is a typical example). It is not known whether anyone has ever documented the ERG under snow-blindness conditions. But it appears to be a good analog of what happens in cases like DG.

The density gradients shown on the right of the figure are caricatures. Turning these into theoretical responses will require more analysis that presented in **Section 7.2**. It is important to recognize the independence of each disk in the outer segment as illustrated in **Section 4.3.4**. The question that must be answered is whether space charge effects in the excitation band of the photoreceptors, or other effects, can cause the density profile of the outer segment to be steeper than a first order exponential function and delayed as suggested?

This proposed alternate mechanism to explain DG's condition would be genetically caused but no attempt has been made to describe the gene(s) involved in determining the OS/neurite interface. DG found on 10 April 2009 that he exhibits the genetic defect of the CNGB3 variety (the variety affecting 50% of those diagnosed). How this genetic defect relates to the physiology of DG is not clear.

Experiments must be defined to verify this hypothesis. If correct, DG's retina will take a longer time to regain its normal appearance, as observed with an ophthalmoscope, after bleaching with a bright light. DG may or may not be aware of the longer time to achieve dark adaptation of the complete stack of disks in each photoreceptor outer segment because he is only using the disks closest to the inner segment.

A potential name for the condition described above might be;

- + OS/neurite interface neuropathy of the photoreceptor cells
- + Neuropathy of the photoreceptor cells
- + Photoreceptor cell dystrophy

These names become simpler, but less descriptive, in descending order.

18.8.3.6.3 Additional potential tests related to the disease of DG (EDIT)

There are at least two additional investigatory paths available. One would involve performing a series of ERG tests starting from different states of adaptation and/or different stimulation strengths. The other would be to develop a set of stair step luminance patterns that could be used to evaluate the curvature of the saturation characteristic. Both paths would be designed to ascertain more clearly the shape of the saturation portion of the luminance transfer characteristic and thereby more information as to the specific location of the dysfunction.

18.8.3.6.4 Other recent reports

The group at Tubingen University has continued their focus on clinical achromatopsia. Varsanyi, Wissinger, Kohl et

al. have recently reported on achromatopsia in nine Hungarian families²⁹¹. They describe the complete achromatopic condition and ascribe its original definition to Galezowski in 1868 who proposed that visual function in complete achromats is mediated wholly by rods, the “pure rod theory.” The subjects ability to perceive color was based on the use of Ishihara plates and the Farnsworth Dichotomous D15 test, rather than asking the subjects if they perceived color. Their subjects exhibited unmeasurable ERG’s under high light level stimulation (as would be expected in photoreceptor output saturation). The clinical work was not supported by a detailed model of the visual system elements being addressed.

Khan, Wissinger, Kohl & Sieving have recently reported extensively on achromatopsia occurring in two otherwise unidentified families²⁹². This study relies upon two references from the 1960's to define achromatopsia.

“Achromatopsia is an autosomal recessive congenital trait characterized by the absence of color discrimination with reduced visual acuity, nystagmus and hemeralopia.” However, their data shows these subjects exhibited considerable color perception when observing Ishihara test plates (page 3866). “The affected subjects could correctly discriminate and identify numbers on plates beyond the test plate. All four affected subjects correctly identified two to four plates in addition to the test plate.” In their discussion, they noted the extensive phenotyping “showed several surprising features.” Their last paragraph shows their conceptual model does not adequately differentiate between the responses of the various photoreceptors.

18.8.3.6.5 Recent AOSLO examination of DG

Merino et al. have recently published a major report including a detailed examination of the retina of DG with a new generation of adaptive optics augmented scanning laser ophthalmoscope (AOSLO) or alternately using adaptive optics augmented Optical computer-aided tomography (AO-OCT)²⁹³.

As part of the examination, the genetic code of DG in the area of the suspected CNGA3 and CNGB3 genetic mutations was examined. It was found that he exhibits one homozygous sequence variation in the coding sequence of the CNGB3 gene, a homozygous 1 base pair deletion of C at codon 283, “predicted to result in a high-penetrance disease-causing sequence variation.” This places DG in the most common cohort of this disease, the Pingelapse and a small group of people living in or descendants of people from Ireland.

²⁹¹Varsanyi, B. Wissinger, B. Kohl, S. Koeppen, K. & Farkas, A. (2005) Clinical and genetic features of Hungarian achromatopsia patients *Mol Vis* vol 11, pp 996-1001

²⁹²Khan, N. Wissinger, B. Kohl, S. & Sieving P. (2007) CNGB3 achromatopsia with progressive loss of residual cone function and impaired rod-mediated function *Invest Ophthalmol Vis Sci* vol 48(8), pp 3864-3871

²⁹³Merino, D. Duncan, J. Tiruveedhula, P. & Roorda, A. (2011) Observation of cone and rod photoreceptors in normal subjects and patients using a new generation adaptive optics scanning laser ophthalmoscope *J Opt Soc Am* (in press)

Figure 18.8.3-22 shows a series of retinal photographs taken with the new AOSLO equipment. The softness of the images of the achromatopsia eye appears to be significant. In addition, the size of the photoreceptors of the achromatopsia eye at 0.5 degrees is almost surely significant. It suggests the photoreceptors are not achieving the close-packed character of the photoreceptors of the normal eye in the area of the foveola (within 0.6 degrees of the point of fixation). As a result, DG can be expected to show a limited acuity of the uncorrectable type, in the absence of magnification in his glasses. The corrective prescription for this eye is -4.5 sph , $+0.50\text{ cyl}$, axis 105 deg.

The limiting spatial resolution, and the relative density of the photoreceptors, except at 0.5 degrees, of the two images appears to be similar, in spite of the softness of the images of the achromatopsia subject.. At one point in their discussion, Merino et al indicated dark spots in the appearance of the retina for the achromatopsia sufferer. This actually appears to be the case for both subjects in the 11 degree eccentricity images, and potentially the 4 and 7 degree images as well.

In Sec. 5.1, Para 7, Merino et al. state, “Also, the fovea in the AOSLO montage appeared darker than what is typically observed in normal subjects.” This could be a very important observation if the dark spots are essentially the result of a fractal distribution of dark spots across the retina, with one spot including the fovea of an achromatopsia sufferer. This will be addressed further below. It is not clear if this observation related to the 830 nm illumination of the apparatus or under observation of the retina with conventional light by the eye of the experimenter.

xxx add

Merino et al. also published cross sections of the retina of a normal and an achromatopsia sufferer in the vicinity of the foveola (recently confirmed to be DG by personal communication) reproduced here as **Figure 18.8.3-23..**

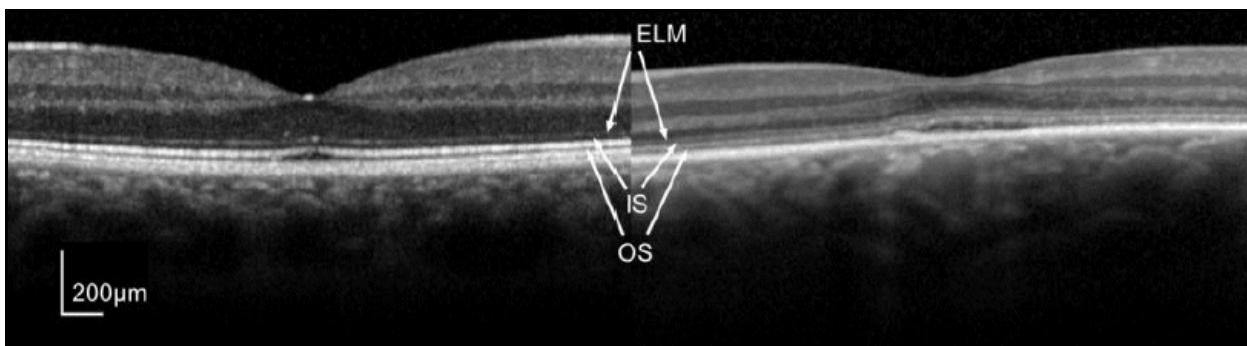


Figure 18.8.3-23 OCT image from a normal subject and someone reported to be suffering an undefined achromatopsia. Left; normal cross section. Right; cross section of achromatopsia patient. The image shows ELM (bright), IS (dark) and OS (dark) layers visible through both images. ELM; external limiting membrane. IS; inner segment of photoreceptors. OS; outer segment of photoreceptors.. From Merino et al., 2011.

The ELM is labeled the Outer Limiting membrane (OLM) in the notation of Dowling, 1969. The Merino et al. paper does not use the word adaptation, or any similar expression to describe the state of adaptation of their subjects during these measurements. The state of adaptation is critically important in the interpretation of these cross sections and also in the evaluation of the performance of these subjects.

Figure 18.8.3-24 shows a blowup of just the labels in the above figure. It is difficult to be positive about the features being labeled in this figure. It appears the ELM is a light line and the IS is a dark line. The OS is then also a dark line with the IS and OS separated by a broader unlabeled light line. Below the OS is a broad light line that is less

bright in the case of the normal retina (A), a poorly defined dark line and finally a very broad and poorly delineated light line (B). Assuming the same magnification, the neural tissue above the ELM (OLM) is 50% thicker in the case of the normal retina compared to the achromatopsia retina, suggesting both the lower (inner) nuclear layer and the upper (ganglion) cell layer are thinner in the case of the achromatopsia retina.. The optic fiber layer above the ganglion cell layer appears thicker in the normal retina, as does the outer fiber layer (using figure 3.2.1-1 in my vision book, from Dowling, 1969 as the reference).

[Xxx add words re DG layer thickness.]

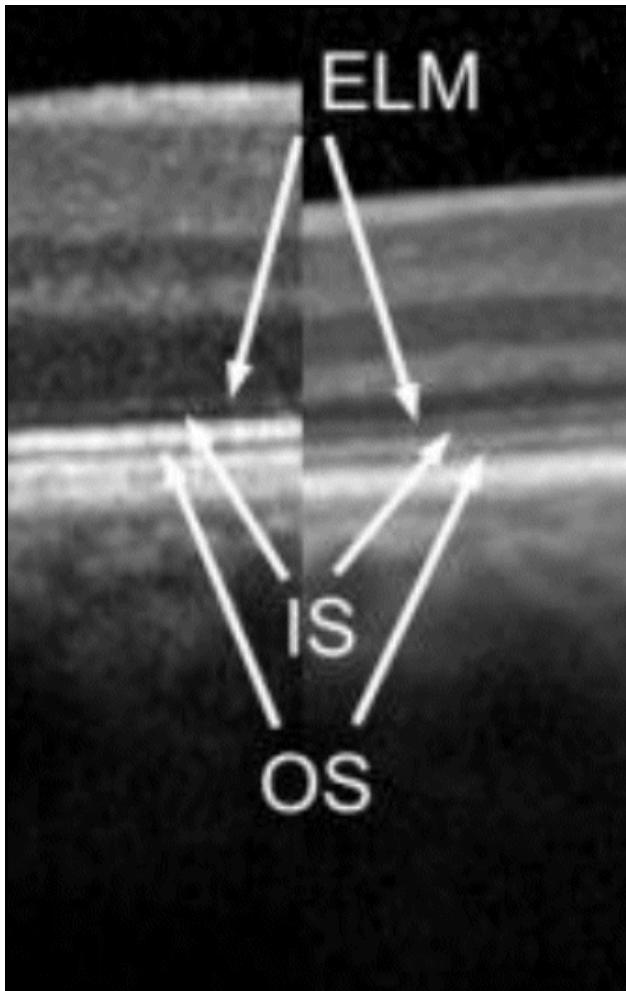


Figure 18.8.3-24 Labeled areas in figure 6 of Merino et al., 2011. See text.

Figure 18.8.3-25 shows a composite of the retina of DG, left and right with a normal retina in the center frame. The imagery on the left and right were from an earlier generation of OCT equipment. The center is from Merino et al. figure 6 (left).

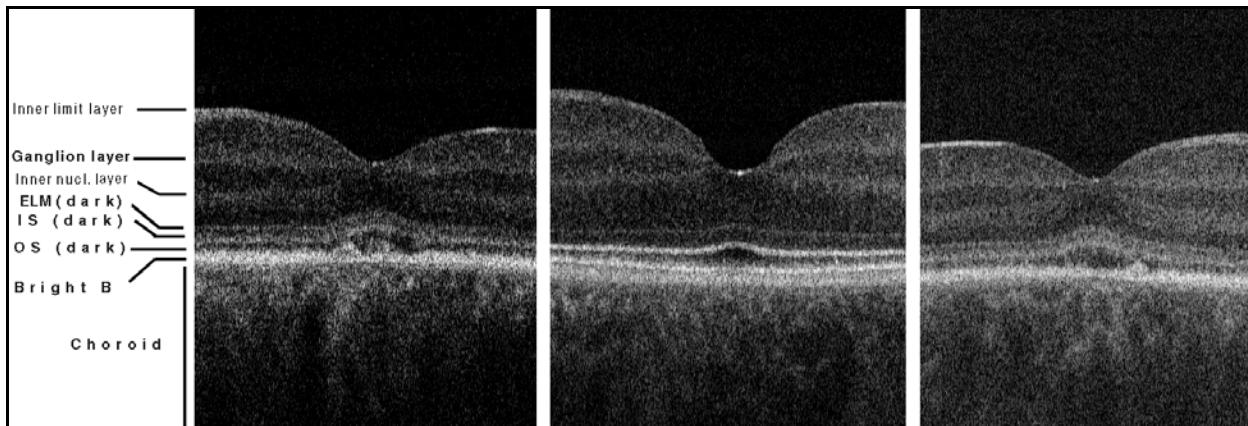


Figure 18.8.3-25 The left and right OCT images of DG with a normal retina shown in the center frame. Personal communication. Layers identified as in previous figure.

Being accurate with regard to these lines is crucial to understanding achromatopsia. As noted earlier, the outer segments of DG's retina appear to be of normal length compared to the same region of the normal. However, based on the following figure, there is some interruption in the uniformity of this dark band within the foveola. Also based on the following figure, the lack of a line (A) in DG's retinal cross section is significant. These two conditions are probably diagnostic for his condition. It is likely the line (A) is the repository of fully formed chromophores. The Rhodinines, are stored prior to their introduction into the inter-photoreceptor matrix (IPM). This leaves the bright line (B) as the region of the RPE in which the retinal received from the bloodstream is converted into the Rhodinines in a multiple step process. It may involve the mitochondria and/or it may involve enzymatic activity at the surface of the RPE adjacent to Bruch's membrane.

The images suggest the pit associated with the foveola of DG is shaped normally in depth and width, although some minor loss in magnification could be expected due the reduced curvature of the boundary between the neural tissue and the vitreous humor. This minor change appears to account for the performance of some normals reaching 20/15 (~6/4.5) while the greater majority average out at 20/20 (6/6). This change would leave DG at closer to 20/25 as best corrected vision. See **Figure 18.8.5-4**.

Of greater importance is the thinness of the bright line between the IS and OS in the case of DG, and the largely absent bright line between the OS and the diffuse line that will be labeled the

- - -

The Merino et al. paper "presents data related to images of cone photoreceptors and structures that appear consistent with rod photoreceptors." This is an unusual syntax in this subject area. They provide no definition or citation for delineating the difference between cones and rods. It is a fundamental principle of this work that there is no distinction; that the outer segments (the active receptor portion of all photoreceptors) in mammals are cylindrical shaped due to their production by an extrusion process. The specific shape of the inner segments is essentially irrelevant to the visual process, although they are also typically cylindrical. The only conical outer segments are associated with immature, non-functional new photoreceptor cells ("C" in upper left and immature cells in upper right of figure 4.3.5-4) of [Chapter 4](#).

18.8.3.6.6 Seeking the source and extent of the Achromatopsia of DG ca. 2011

It is now known that DG shares one genetic code error, as a minimum, with a cohort of Pingelapse and Irish people with visual modality sensory problems generally associated with the term achromatopsia. However, about 95% of the genetic code of DG and other humans with this condition has yet to be explored.

Achromatopsia is a complex syndrome consisting of about five describable medical conditions plus the behavioral characteristic known as photophobia. DG's condition does not involve all of these aspects of the syndrome, nor does his condition suggest total losses of capabilities in any of these areas as suggested by a major genetic code failure.

Achromatopia or dyschromatopia— total loss of or irregularities in color perception. DG exhibits near normal color vision within a limited scene brightness range. As shown in Figures 18.8.3-11 & 18.8.3-12, his visibility function is near normal as is his range of color perception over a limited scene brightness range.

Amblyopia— lower than normal corrected resolving power (aka lazy eyes). DG is an accomplished amateur astronomer. However, he requires several times the magnification of the typical astronomer to resolve pairs of adjacent stars under scotopic conditions and very low contrast imagery. This is suggestive of either a retinal or a neural (including ocular feedback) cause to his amblyopia. Efforts are being made to quantify this inadequacy (**Section 18.8.5.2.2**). This need for magnification is probably not correctable at this time.

Hemeralopia— a loss in visual performance at high light levels. DG does suffer significant hemeralopia at high light levels tolerated by visual normals. As discussed with respect to Figure 18.8.3-14, DG also suffer a transient form of hemeralopia at reduced light levels. This hemeralopia appears to involve a scotoma that can probably be associated with a region of his fovea that appears darker than normal in the words of Merino et al.

Because of the hemeralopia, DG exhibits considerable photophobia, although he does function outdoors with the aid of dark glasses. Under restricted maximum illumination, DG functions well at the computer and within his living environment. His night vision appears to be nominal, with the expected loss in long wavelength sensitivity compatible with normal subjects.

Nystagmus— uncontrolled motions of the eyes (aka wandering eyes). DG and his mother assert firmly that he has never suffered from this condition.

Strabismus— abnormal pointing of the eyes. DG and his mother assert firmly that he has never suffered from this condition.

Based on the above summary, it is difficult to diagnose DG as suffering from the syndrome of achromatopsia of the type and scope suggested in the popular press, or the type reported casually in introductory biological and/or medical texts. DG suffers primarily from an insufficiency in the dynamics of the sensory receptors of vision. The condition is not uniform retina wide, and although similar, it is not necessarily the same in both eyes. DG can identify a scotoma that is at least affected first as the light level is increased. DG's primary disease is one of hemeralopia that results in dyschromatopia under high light level conditions as a secondary condition. It also results in a transient loss of visual contrast as a secondary condition, which becomes stationary as the light level rises to the level resulting in total loss of contrast (frequently described as wash-out) across larger and larger portions of his visual field.

Based on the available OCT imagery, it appears that the retina pigmented epithelium (RPE) of DG is under sized and lacks the ability to generate (line B in the OCT imagery) or to store (line A in the OCT imagery) sufficient amounts of the visual chromophores, the Rhodonines, to release the chromophores into the inter-photoreceptor-matrix (IPM) and completely coat the disks of opsin secreted by his sensory neurons (Figures 18.8.3-18 & 18.8.3-19). The disks, when properly coated, are replaced on a weekly basis, requiring a continuous supply of the Rhodonines of each spectral type (although much of the material is reprocessed within the RPE rather than being disposed of). The dynamics of the RPE/OS interface are developed in detail in Section 4.6.2 of [Chapter 4](#).

There remains an un-demonstrated potential for the hemeralopia to be associated with the dendrites of the sensory neurons (surrounding and electrolytically accessing the coated disks of the outer segments) being abnormally short. If abnormally short, they would be unable to totally discharge (reconstitute) the chromophoric material in place after its quantum-mechanical excitation by the stimulating photons of light. The retina would then appear unusually transparent (bleached) under nominal adaptation conditions compared to normal retinas. The condition could probably not be recognized by an optometrist under the light adaptation conditions usually associated with a retinal examination.

It is entirely possible for both an inadequacy of chromophore production and release, and an abnormal formation of the dendrites of the inner segments of the photoreceptors to be present simultaneously. It is also possible that the disks secreted by the IS are being produced, and reabsorbed (phagocytosis) at an abnormally high rate that the RPE cells cannot adequately support. The outer segments appear to be of normal length in both the foveola and periphery of his retinas, but their rate of turnover is not easily assessed.

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The change in the character of the triangle and spots when presented along with a white background suggests the inadequacy of RPE performance and resulting disk coating by the chromophores is probably the dominant problem in the case of DG. The chromophore coating problem is a more diffuse spatial problem than would be the equivalent photoreceptor by photoreceptor problem of ineffective dendritic tissue.

It is proposed that DG, like anyone suffering from hemeralopia, will exhibit an absence of an ERG under illumination conditions resulting in wash-out but will exhibit a conventional ERG at optimal light levels. The conventional ERG is a global test that may be difficult to record at the necessarily reduced light levels. A local ERG (a.k.a. LERG) may be called for. A multi-focal ERG performed at appropriate light levels may characterize his scotoma more completely.

Color vision tests to date have confirmed that the S-, M – and L– spectral channels of DG are operating appropriately under reduced light levels (figure 18.8.3-12). Confirmation of his UV– spectral channel performance cannot be performed using kinescope monitors or incandescent light sources with a color temperature significantly below 6500 K. However, a test alternating between two area light sources of wavelengths near 410-420 nm and 432 nm (at a rate of about 0.1 to 1.0 Hertz) would quickly demonstrate the presence of the UV–channel photoreceptors functioning in his visual system.

It appears highly unlikely that the disease suffered by DG is due to a single genetic error associated with the CNGB3 gene. His disease cannot be associated with achromatopsia due to this CNGB3 mutation. It is more likely that several genes are involved, some present in the currently unexplored regions of the genome.

18.8.3.6.6 Appearance of the retina during examination

The test protocol used during AOSLO, or any OCT, examination is critically important. A primary consideration is the wavelength of the energy used in the test set. The chromophores of the visual system are highly absorbtive at the peak of their intended absorption spectrum, quite absorbtive at their intrinsic absorption centered on 500 nm, and quite transparent far from those two regions. It is known that the L–channel chromophores are quite transparent at wavelengths in the 800 to 900 nm region. It is reasonable to assume the other chromophores are even more transparent in that wavelength region. Little is known about the absorption of other specific types of tissue of the retina at 800 to 900 nm.

The appearance of the retina at wavelengths within the visual range from 300 nm to 700 nm varies considerably depending on its state of adaptation. When fully dark adapted, the single-pass bulk absorption efficiency of the outer segments (even away from their nominal peak wavelength), is normally 100% due to the multiple layers of chromophore present on the surfaces of the disk stack. The two-pass absorption efficiency including the reflection at the RPE interface if any, suggests no light can be observed reflecting from the RPE interface. The only light observed from the retina will be the few percent that may be reflected at the OS/IS interface within the extrusion cup of the IS.

On the other hand, under photopic adaptation conditions, the “bleaching” of the chromophores is the principle mechanism of neural saturation control and prevention. At stimulation levels four orders of magnitude above dark adaptation,(presumed to be in the photopic regime for this discussion) the single-pass absorption of the disk stacks falls to about 0.01%. As a result, the single and double pass absorption of the incident light is minimal and reflections can be expected to be observed from both the OS/IS interface and the RPE/OS interface. In many cases, it will be the RPE/OS interface that is most clearly observed.

If the retina is adapted on a spectrally selective basis, and the properly chosen wavelengths are used in this process, it should be possible to obtain imagery highlighting the sensor neurons of a specific spectral class (containing a specific chromophore). By using light chosen to suppress the S– and L– spectral channels (432 nm and >625 nm respectively), the photoreceptors associated with the UV– and M–channels should be accentuated. Note, this process requires the experimenters to recognize and anticipate involvement of all four spectrally selective channels of chordate vision, not just the conventional wisdom related to the three S–, M – and L–channels.

18.8.3.7 Current research results on achromatopsia (2008-2012)

As noted in **Section 18.8.3**, the achromatopsia community has entered a halcyon period where the theoretical and operational understanding of the visual system can be merged with the work of the clinical and genetic communities to converge on actual treatments for this disorder/disease within the next ten years. This section will address only superficially the results of several recent studies. Greater attention to these papers is warranted but will be left to specialists with more time available to focus on these areas. The convergence synopsized below demands a re-

evaluation of our specific goals, next steps, and protocol revisions/development needed to move closer to our goals.

Section 18.8.3.7.5 will suggest the root cause of the disease is associated with its hemeralopia symptom, which is a stage 0, homeostatic disorder rather than a stage 1 neural disorder. The other neurological symptoms of achromatopsia flow from the underlying stage 0 homeostatic disorder.

As noted above, an initial necessity is to redefine which patients exhibit complete achromatopsia and which only exhibit specific symptoms associated with this syndrome. Many of the subjects investigated as part of the Dallas study (**Section 18.8.3.6**) did not exhibit the principle symptoms of the syndrome. This came as a considerable surprise to some of the more vociferous subjects in the survey. One of those was shocked to find out that she was one of the few in the room who were actually achromats (totally color blind). Most of the participants had significant color vision at intensity levels marginally above sunset conditions. A number of the participants did not exhibit any nystagmus and many exhibited visual acuity at this light level equal to that of control subjects. Thus most of the subjects were in fact dyschromatopes of various types.. The tests used in the Dallas study are shown in **Section 18.8.3.6**.

A group of very recent papers are discussed in the following sections. A characteristic of these papers is the lack of a physical or functional model of the portion of the visual system they are exploring. To overcome this major shortcoming, figures drawn from earlier chapters of this work will be used to annotate some of the recent laboratory work in order to highlight the potentialities available. The reader is reminded to review the overall morphological situation as discussed in Section 4.3.5 of this work, PBV, and in Section 7.2 of the Guide. At a more detailed level, Figures 5.1.1-1 and 5.4.1-1 of the Guide (4.2.2-1 and 4.6.2-8 in PBV) are of interest. Of particular significance is Figure 4.6.2-9 of this work reproduced here as **Figure 18.8.3-26**

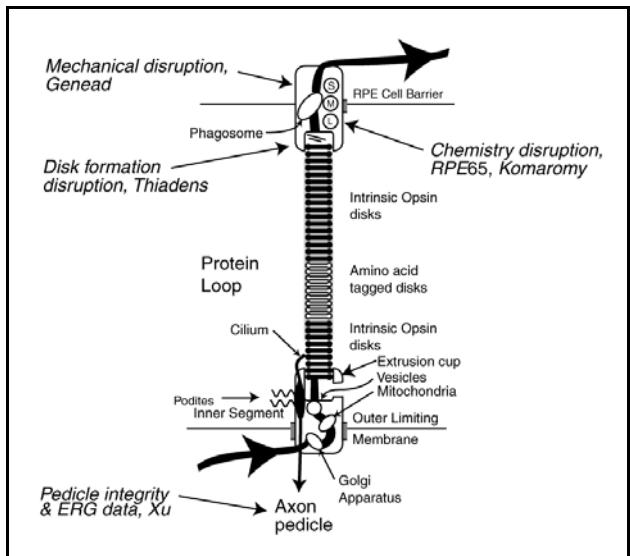


Figure 18.8.3-26 Caricature of the replacement of protein disks in the outer segment by the sensory neuron, based on isotope tagging of the amino acids in the protein. The disks are extruded by the vesicles shown and shaped into a disk stack in the extrusion cup. The cilium plays no role in the protein replacement loop. See text.

illumination at scotopic and mesotopic illumination levels only.

As is so common, the introductions to the following papers show a superficial knowledge of the operation of the overall visual system in the human and in their models. Discussions of genetic changes back to the time of the dinosaurs appear less than substantiated when virtually no soft tissue is available for creatures of that era. To make assertions that dogs are dichromats, after decades when all non-humans were claimed to be achromats, and in spite of the popularity of red and green bowls for dog food in pet supply stores, and their common use to feed sibling dogs who clearly differentiate between the bowls, seems unwarranted.

It is appropriate to review some terminology. Xu et al. have recalled the origins of the labels CNGB3 etc. These terms were originally acronyms based on the assumption of putative cyclic nucleotide-gated channels associated with the sensory neurons. It will become clear that the diseases investigated by Genead et al and Thiadens et al. have little to do with any putative nucleotide-gated channels. The disease originates at locations unrelated to the neural portions of the sensory neurons. As a result, the expressions based on the prefix letters CNG must be disconnected from the operation of the neural aspects of transduction.

It will be noted again below, Thiadens et al. identify one of the layers of the retina as associated with the connecting cilium (CC) rather than the Extrusion cup (EC), the more important structure in this discussion. The Thiadens paper is the first to provide a statistically relevant, though still limited, sample size, 40 eyes. Of the eyes examined, only a small group (7/40) exhibited RPE atrophy. All examples of RPE atrophy were found in the 40-70 age groups. The Xu et al. paper focuses on the electroretinography of mice presumed to be suffering from achromatopsia, without detailing the properties of achromatopsia. They also examined the structures of the pedicles of involved sensory neurons at high magnification using conventional electron microscopy. Microscopy gives greater detail regarding the structure of the photoreceptor IS elements but less appreciation of the overall mechanisms and their function.

The Komaromy et al. paper focuses on a mutation affecting the RPE layer specifically, (RPE65). It is a very excellent report on early results of using recombinant adeno-associated virus (rAAV)-mediated gene replacement therapy in dogs to correct a basically chemical processing defect. Their follow-up period lasted up to 2.5 years.

The variety of abnormalities illustrated in these papers do not correlate well with the four or five genes highlighted in the discussions; this is a conclusion shared explicitly with the Thiadens et al. paper.

This figure shows any one of the four spectral types of photoreceptors sensory neurons at the bottom of the figure supported by a single RPE cell at the top (shown harboring only the conventional three chromophores of vision (the UV chromophore has been overlooked).

The following discussion from Genead et al. focuses on the physical disruption of the orderly cells of the RPE layer extending into the physical disruption of the disks of the outer segment, which are intimately associated with the RPE during phagocytosis of the disks. Genead et al. employed a higher performance OCT than did Merino in the above discussion.

Like the Genead et al. paper, the Thiadens et al. paper focuses on the disruption of the RPE layer and the RPE/OS interface in humans, but employs a more advanced spectral domain optical coherence tomography (SD-OCT) instrument. They assert it provides 50 times higher depth resolution than earlier devices, such as that of Genead et al. Note, they use images of opposite contrast to that of Genead et al. and many others. The Komaromy et al. papers focus on the chemical malfunction of the RPE and its associated interfaces rather than any identifiable morphological hypoplasia. The Xu et al. paper focuses primarily on the morphology of the axon pedicles and the ERG recorded from the whole retina under Ganzfeld

18.8.3.7.1 High resolution examination focused on the RPE/OS interface– Genead et al.

Genead et al have recently provided a report using most of the latest available imaging techniques to study achromatopsia²⁹⁴. The paper is extensive but contains only a very few graphics. The many authors are scattered among many research centers. Twelve patients were involved, but some tests were only performed on a subset. The conclusion section indicates the exploratory nature of the program; “The current approach of using high-resolution techniques to assess photoreceptor structure and function in patients with achromatopsia should be useful in guiding selection of patients for future therapeutic trials as well as monitoring therapeutic response in these trials.”

The overall protocol used was that of clinicians, as opposed to researchers. They focused on the brand names of their instrumentation as opposed to the actual psychophysical parameters (such as light intensity and color temperature) used. The graphic results are not statistically adequate. However, they do show examples of several cases involving disruption of the RPE at the foveola, in some cases due to mottling of the entire RPE.

The twelve subjects were described superficially of different races and nationalities, rather than by their precise genomic ancestry as in their table 1 (**Figure 18.8.3-27**) Cursory examination suggests the earlier discussions of tracking the entire achromatopsia population back to only a few source individuals is probably archaic. Additional strains originating in India and China can be anticipated. It is unlikely that the subjects exhibiting a CNGA3 mis-coding share many relatives within the last few generations. It is interesting to note the two Jordanians do exhibit the same allele 1 and allele 2 coding errors. Based on their CNGA3 mis-coding and **Section 18.8.3.5.2**, it is likely that they and the Lebanese subject share relatives identified in that section as originating in Iraq. These are political subdivisions that did not exist in their current form prior to the British mandates of the 1920's.

Those with a CNGB3 mis-coding are all described as Caucasian, but there is no data suggesting they share a common ancestor based on the paper. The one Afro-American, one Lebanese and one Hispanic were not characterized further. Based only on the genetic data, the Hispanic may actually have Moslem relatives from the Eastern Mediterranean area dating from the middle ages. It should also be noted subject 2, a 15 year old male described as Caucasian, probably has relatives in the Eastern Mediterranean based on his genetic coding error.

This data appears worthy of a multidimensional analysis to identify the subgroups more effectively, although the number of data samples is too small for statistical accuracy.

²⁹⁴Genead, M. Fishman, G. Rha, J. et al. (2011) Photoreceptor Structure and Function in Patients with Congenital Achromatopsia IOVS Papers in Press. Published as Manuscript *iovs.11-7762* In journal as vol 52(10), pp 7298-7308

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Patient No.	Age (yrs)/ Sex	Race/Ethnicity	Gene	Allele 1	Allele 2
1	13/F	Hispanic	No mutations found		
2	15/M	Caucasian	<i>CNGA3</i> exons 6 and 7, heterozygous	c.661C>T - Arg221Stop, exon 6	c.830G>A - Arg277His, exon 7
3	30/F	Caucasian	<i>CNGB3</i> exon 10, heterozygous	c.1148delC - Thr383 del1aC	Not found
4	50/M	Lebanese	<i>CNGA3</i> exon 7, homozygous	c.1709G>T- Ser570Ile	c.1709G>T- Ser570Ile
5	15/M	Caucasian	<i>CNGB3</i> exon 10, homozygous	c.1148delC - Thr383 del1aC	c.1148delC - Thr383 del1aC
6	17/F	Jordanian	<i>CNGA3</i> exon 7, heterozygous	c.985G>T - Gly329Cys	c.1306C>T - Arg436Trp
7	27/F	Caucasian	<i>CNGB3</i> exon 10, homozygous	c.1148delC - Thr383 del1aC	c.1148delC - Thr383 del1aC
8	49/M	Caucasian	<i>CNGB3</i> exon 10, homozygous	c.1148delC - Thr383 del1aC	c.1148delC - Thr383 del1aC
9	33/M	Hispanic	<i>CNGA3</i> exon 7, heterozygous	c.1228C>T - Arg410Trp	c.1541A>T - Asp514Val
10	55/M	Caucasian	<i>CNGB3</i> exon 10, heterozygous	c.1148delC - Thr383 del1aC	Not found
11	52/F	African American	<i>CNGA3</i> exon 7, heterozygous	c.848G>A - Arg283Gln	c.1306C>T - Arg436Trp
12	14/M	Jordanian	<i>CNGA3</i> exon 7, heterozygous	c.985G>T - Gly329Cys	c.1306C>T - Arg436Trp

M=Male; F=Female.

DNA numbering is based on cDNA sequence (GenBank: AF065314.1); nucleotide +1 is the A of the start codon (ATG).

Figure 18.8.3-27 Summary of Genetic Mutations Screening Results in the Study Cohort. See text. Table 2 of Genead et al., 2011.

Figure 18.8.3-28 shows the significant variation in the retinal abnormalities they encountered using the SD-OCT technique to image the retina in cross section. Note the lack of a foveal pit in frame 5 and the significant slope relative to the optical axis in frames 4, 6, 8 & 10. Note the minimal or reversed curvature of the RPE in frames 2, 3 & 7. These are signs of problems not associated with achromatopsia as defined in **Section 18.8.3**. Note also the significant hypoplasia of the choroid, as well as the RPE and OS/IS in frame 8.

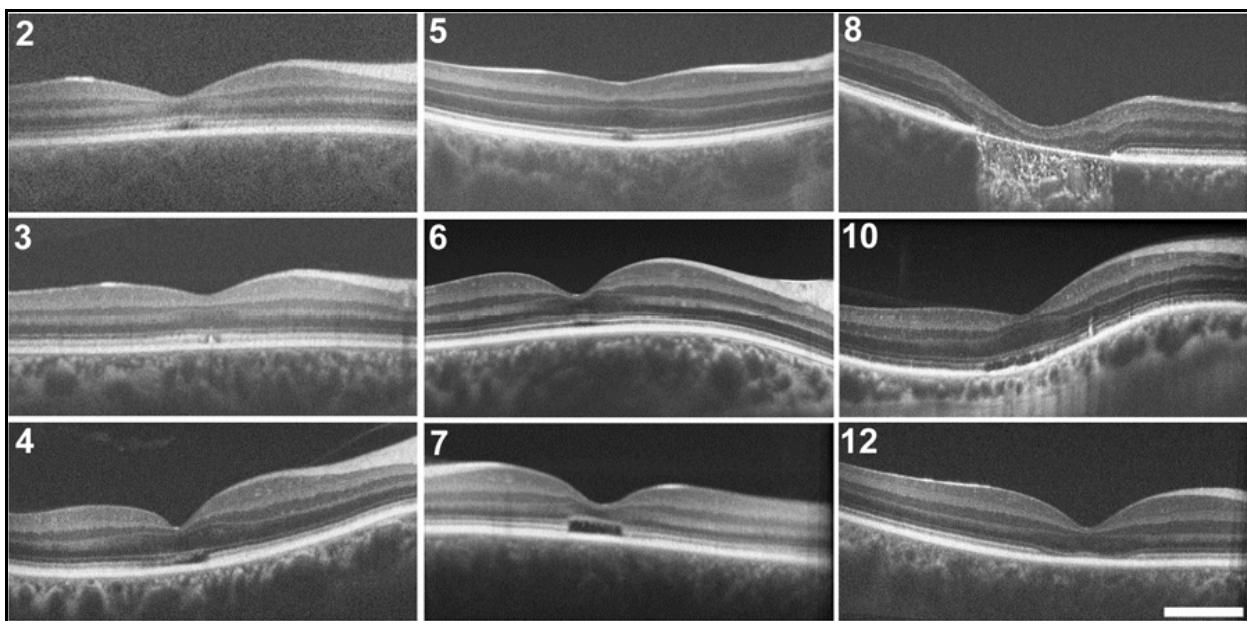


Figure 18.8.3-28 High-resolution SD-OCT scans through the fovea. The bright line farthest from the foveal pit is generally described as the area of the RPE. The voids immediately adjacent to the RPE are generally described as involving the outer segments (first dark layer) and the junction between the inner and outer segments (first light layer). Note the lack of a foveal pit in frame 5 and the significant slope in frames 4, 6, 8 & 10. Scale bar is 1mm. See text. From Genead et al., 2011.

The extended caption for this figure is;

“Scans were acquired using the Bioptigen SD-OCT and foveal location was confirmed using accompanying volume scans. Panel numbers correspond to subject numbers in Table 1. Note the variable appearance of the IS/OS disruption in these individuals, even in subjects with the same genotype (subjects 5, 7, 8 and subjects 6, 12).”

The investigators used the term “bubble” to identify a void in their cross sections behind the foveal pit near the RPE layer.

Some of these subjects (4, 6, 8, 10 and potentially 12) showed significant asymmetries relative to the optical axis through the foveal pit that would indicate significant focus limitations leading to acuity problems in the clinical setting (although they may be able to compensate by looking askew at the acuity chart..

Subject 8 exhibits a significantly more complex abnormality (hypoplasia) to the foveal area than the other subjects.

Figure 18.8.3-29 shows the significant variation in the retinal abnormalities they encountered using the AOSLO technique to image the retina. The relevance of these images is subject to considerable interpretation, based on the examiners previous training or knowledge of the retina.

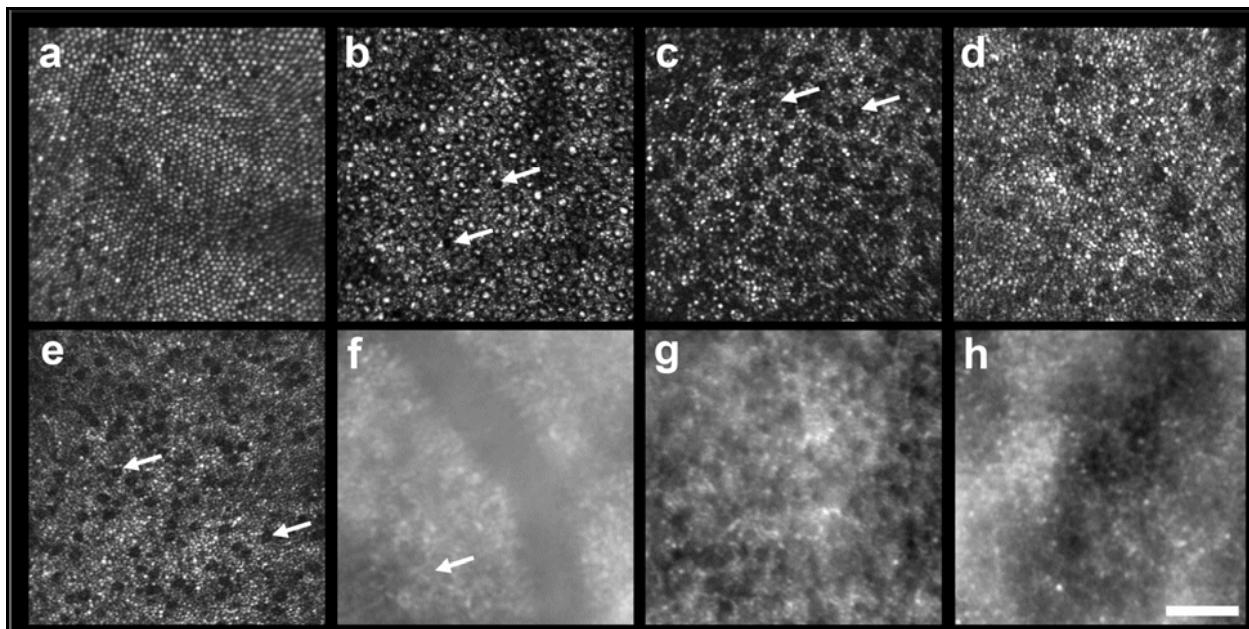


Figure 18.8.3-29 Images of the photoreceptor mosaic in achromatopsia. Scale bar is 50 μm . See text. From Genead et al., 2011.

The extended caption for this figure is;

"Images of the foveal cone mosaic (a) and peripheral (~10 degrees) rod and cone mosaic (b) obtained with the AOSLO for a normal subject are shown for comparison. In the peripheral image, the dark ring associated with each cone is presumably the boundary of the inner segment, while the central reflective core is from the outer segment or IS/OS junction. Note the variable appearance of the cones in the normal retina (b), with some cones being devoid of a central reflection (arrows in b). The images in panel c-e represent individual frames from the AOSLO, while f-h are from the AO flood-illuminated camera. All subjects had evidence of residual cone structure, though to a variable degree. Panel c and g are from subject 5, d is from subject 8, e is from subject 12, f is from subject 10, and h is from subject 6. Panels c-f demonstrate the presence of multiple cone inner segments that still retain a central reflective core (arrows), though it is diminished in its reflectance compared to normal."

The description of the central reflective core as indicative of an outer segment, OS, is likely correct on optical grounds. However, the absence of such a reflective central core is highly correlated with the spectral character and the state of adaptation of the photoreceptor involved. It is also a strong function of the $f/\#$ of the optical instrumentation based on the Stiles-Crawford Effect (**Section 17.3.7**). This variability is captured in the last sentence of the extended caption above.

Figure 18.8.3-30 shows their Table 1, summarizing the visual performance of the individual subjects. It is useful to note that 5 of the 12 subjects matched the complete chromatic range explored by the (apparently one-dimensional) anomaloscope. In the study of a similar but larger group reported at Dallas in 2008, the majority of these subjects were not color blind (achromatopes) but exhibited normal chromatic range under the reduced light intensity used for the tests (the screen of a laptop or desktop computer rather than of clinical instrumentation). This leads to the conclusion that these subjects were primarily affected by saturation in their photoreceptors at high light intensities leading to the condition of hemeralopia (day blindness), that is generally associated with the behavioral symptom of photophobia. Hemeralopia involves a failure in transduction as a function of illumination intensity that is largely independent of the chromatic performance of the individual sensory neuron. There is a gradual transition in the performance of the full-field ERG between the scotopic illumination level and the photopic illumination level used in the clinic. It can be caused by the inadequate de-excitation of the excited chromophore(s) on the disks by the neural system. The de-excitation must be accomplished within seconds to avoid at least localized hemeralopia. The condition can be exacerbated by an inadequate supply of chromophoric material originating in the RPE layer and deposited on the disks of the outer segment over a longer time interval.

Patient No.	Visual Acuity (log MAR)		Fundus Macular Appearance	Color Vision (anomalouscope)	Full-Field ERG			SD-OCT	AO Cone Structure	MP (dB)	
					Scotopic	Photopic					
	OD	OS				single-flash b-wave amplitude	32-Hz flicker				
1	0.92	0.90	wnl (OU)	Matched (0-73)	Normal	ND	ND	Normal OS/IS in the fovea	N/A	N/A	
2	0.94	0.92	blunted FR (OU)	Matched (47-73)	Normal	Severely reduced	ND	Focal OS/IS disruption (small bubble) in the fovea	Minimal cone IS structure, no visible OS reflection	OD=10.0 OS=11.3	
3	0.46	0.44	blunted FR (OU)	Matched (0-73)	Normal	Severely reduced	ND	Focal OS/IS disruption in the fovea +foveal hypoplasia	Moderate cone IS structure, no visible OS reflection	OD=11.4 OS=12.2	
4	0.78	0.80	blunted FR (OU)	Matched (48-73)	Mildly reduced amplitude	Severely reduced	ND	OS/IS loss and disruption (large bubble) in the fovea	Minimal cone IS structure, no visible OS reflection	N/A	
5	0.94	0.90	blunted FR (OU)	Matched (0-73)	Normal	ND	ND	Focal OS/IS disruption in the fovea (small bubble) +foveal hypoplasia	Substantial cone IS structure, frequent dim OS reflection	N/A	
6	0.92	0.90	wnl (OU)	Matched (35-73)	Normal	Severely reduced	ND	Normal OS/IS in the fovea	Moderate cone IS structure, no visible OS reflection	OD=11.6 OS=12.5	
7	0.92	0.96	central foveal hypopigmentation with mild RPE mottling (OU)	Matched (0-73)	Normal	Severely reduced	ND	OS/IS loss (large bubble) in the fovea	No visible cone IS structure	N/A	
8	0.80	0.72	atrophic macular lesion (OU)	Matched (46-73)	Normal	Severely reduced	ND	Loss and disruption of OS/IS and RPE loss and thinning in the fovea+foveal hypoplasia	Minimal cone IS structure, no visible OS reflection	N/A	
9	0.86	0.88	blunted FR (OU)	Matched (0-73)	Normal	Moderately reduced	ND	Loss and disruption of OS/IS (large bubble) in the fovea	N/A	N/A	
10	0.94	0.82	hypopigmented lesions with mild RPE mottling, ,punctate drusen (OU)	Matched (49-73)	Moderately reduced amplitude	Severely reduced	ND	Focal loss and disruption of OS/IS and mild RPE thinning in the fovea +foveal hypoplasia	Minimal cone IS structure, occasional dim OS reflection	N/A	
11	0.92	0.94	atrophic macular lesion (OU)	Matched (10-73)	Moderately reduced amplitude	Severely reduced	ND	Loss of OS/IS and RPE loss and thinning in the fovea +foveal hypoplasia	N/A	N/A	
12	0.92	0.90	wnl (OU)	Matched (41-73)	Normal	Severely reduced	ND	Focal loss of OS/IS +foveal hypoplasia	Substantial cone IS structure, occasional dim OS reflection	OD=13.5 OS=13.2	

Figure 18.8.3-30 Summary of Structural and Functional Findings in the Study Cohort. ND; non detectable. See text. Table 1 from Genead et al., 2011.

On page 16, the authors noted;

“The single flash light-adapted response was non-detectable in 2 patients (16.7 %) while 10 patients (83.3%) showed a markedly reduced b-wave response with average amplitude of 34.9 μ V (lower limit of normal is 132.8 μ V). All patients showed non-detectable responses to a 32-Hz flicker stimulus.”

The reduced response at normal photopic intensities is expected among hemeralopia (day blindness) patients. It would be most interesting if these tests were repeated at a light intensity ten times lower but still within the photopic

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range (**Table 2.1.1-1**). **Figure 18.8.3-16** illustrates the performance of DG's visual system using an extended threshold versus radiance (TVR) diagram.

18.8.3.7.2 High resolution examination focused on the RPE/OS interface– Thiadens et al.

The Thiadens et al. paper²⁹⁵ generally follows that of Genead et al. They associate an additional gene with achromatopsia, PDE6C but do not pursue its role further. There assertion that achromatopsia is not stationary appears too strong based on the statistical size of their cohort (40 eyes). Asserting that Achromatopsia normally appears during the first decade in humans appears unsupportable based on the commonality of the condition among babies, sometimes as young as a few months old. Their youngest patient was eight years old. Their observation of al hypoplasia among the elements of the photoreceptors of the foveola parallels that of Genead et al. While their SD-OCT apparatus exhibited significant new features and better axial resolution than that used in the Genead et al. study, the assertion of 50:1 better axial resolution does not appear to have been achieved. The lateral resolution does not appear to be significantly better than in Genead et al although their scale bars indicate a 2.5:1 higher magnification in their images. The resolution of the earlier imagery by Wojtkowski et al., using Fourier Domain Optical coherent tomography (FD-OCT) appears better than that of both of these groups²⁹⁶. In the Wojtkowski et al. imagery, CC represents the choriocapillaris structure behind the RPE rather than connecting cilium as used in Thiadens et al. (See **Section 3.2.2**) . In the work of both teams, and generally in this type of work, the RPE appears prominently, probably because they are a storage site for the retinoid-based chromophores of vision. In both works, the hypoplasia of the foveola, the very center of the retinal fovea, appears to begin in the region of the RPE/OS interface and/or the OS/IS interface. The Thiadens et al. paper suggest more clearly than the Genead et al. paper that the origin of the hypoplasia begins near the extrusion cup of the IS/OS interface and expands symmetrically until it is constrained by the RPE in one direction. It is possible the condition actually begins in the glia (Mueller Cells) between the photoreceptors at the level of the OS/IS interface. The Thiadens et al. figures show the hypoplasia extending into the outer nuclear layer (ONL), and possible into the inner nuclear layer (INL).

The longer OS found within the foveola is suggested in figure1A of Thiadens et al and clearly defined in Wojtkowski et al.

Thiadens et al use the term foveal reflex without further definition. Definitions vary in the literature. However, they generally converge on the foveal reflex as the center of the foveola (the fovea centralis), the small central point of the fovea generally at the center of the foveal pit. It generally appears as a yellow-white shiny reflection through the ophthalmoscope. Some ophthalmology material treats it as the center of a corner reflector formed by the sloping outer limiting membrane of the retina, and not a specific surface area.

The hypoplasia of the choroid encountered in both papers does not appear to have been discussed.

Thiadens et al. use an undefined term, ETDRS, formed from a Early Treatment Diabetic Retinopathy Study by a large committee. This study was designed to create a system for grading the severity of diabetic retinopathy. It was quite complex, involved nine specific zones of the observed retina, and simpler alternatives were discussed subsequent to 1985.

Thiadens et al. noted all of their subjects exhibited pendular nystagmus, hemeralopia (photophobia) and reduced acuity. They commented, All OCT parameters correlated highly between the right and left eyes ($R^2 \geq 0.90$). They made an important assertion;

“We did not find a genotype-phenotype correlation (i.e., the genes were equally distributed among those with and without OCT abnormalities).”

18.8.3.7.3 High resolution examination focused on the pedicles– XU et al.

The experiments of Xu et al. cover a wide field and employ a variety of mice with known genetic defects. They employed full field Ganzfeld electroretinography and dilated eyes rather than the generally more definitive, but

²⁹⁵Thiadens, A. Somervuo, V. van den Born, L. et al. (2010) Progressive Loss of Cones in Achromatopsia: An Imaging Study Using Spectral-Domain Optical Coherence Tomography IOVS vol 51(11), pp 5952-5957

²⁹⁶Wojtkowski, M. Srinivasan, V. Ko, T. et al. (2004) Ultrahigh-resolution, high-speed, Fourier domain optical coherence tomography and methods for dispersion compensation *Optics Express* vol 12(11), pp 2404-2422

difficult to record, small light field electronretinography.

They provide considerable information but it is not clear how their experiments are affecting the various mice strains. They do focus on the mislocation of opsin in the OS disks, but do not report on their evaluation of that mislocation with the electron microscope. They note mislocation of opsin is encountered in both CNGA3^{-/-} and CNGB3^{-/-} mice suggesting they have not located the mechanism associated with these individual mutations. Their discussion infers the presence of retinol in the IS is associated with chromophore creation and its delivery through the connecting cilium to the outer segments. The cilium does not deliver opsin to the OS. Its function is entirely neural and well documented in **Section 4.2.2**. The processing of retinol into chromophores (the Rhodinines) occurs within the RPE with the actual delivery of the individual chromophores to the disks via IRBP transporters.

Speaking of opsin alone, they note, “although the channel-deficient [photoreceptors] are able to synthesize opsins they failed to transport or retain the protein properly into the outer segments.” They continue, “suggesting that the reduction in the opsin protein level is likely due to enhanced degradation rather than decreased synthesis.” These assertions are compatible with the more detailed discussion of complex process of opsin disk formation in **Chapter 4**.

Xu et al. examined electron microscope images of the pedicle regions of the sensory neurons and proclaimed they appeared normal and unaffected. It is noted their examination was strictly histological; they did not address the charge density associated with these regions nor did it explore the electrical biasing of these synaptic areas.

Xu et al. also define several conditions not recognized in this work and will result in difficulty in relating their work to other work in the future. They note the mutation notation CNG relates to the putative cyclic nucleotide-gated channels of photoreceptors. The letters A & B following this labeling refer to presumed subunits of the CNG and the numbers 1 & 3 designate presumed rod and cone types of photoreceptors respectively. This work has shown the rod/cone designation is archaic and there are no wide spectral band rod photoreceptors. All photoreceptors are operationally and functionally alike, and can be separated into one of four narrow spectral bands.

Xu also follow the recent trend to define several proteins as spectrally selective materials. Rather than adopt a name like rhodopsin, they are using the label m-opsin and S-opsin for the medium and short wavelength “cone transducin units instead of the terminology Rhodone(7) Rhodone(9) to identify the actual medium short wave non-protein chromophores respectively. The term opsin properly refers to the protein forming the substrates (disk) supporting these chromophores.

Xu et al. employed an unusual electroretinography (ERG) procedure. They measured the full-field ERG for Ganzfeld illuminated and dialated eye using a constant intensity flash stimulus level under both dark adapted and light adapted conditions. They labeled the dark adapted condition, the scotopic condition and the light adapted condition the photopic condition. While describing the light adapted eye as pre-exposed to light for 5 minutes, they did not specify how long the eye was dark adapted before their measurements. While frequently encountered in the literature, their protocol does not quantify the dark-adapted state used and it does not account for the change in the sensitivity of the eye to different signal levels. This sensitivity is designed to vary over a range of about 1000:1 inversely with stimulus level within the photopic range. Their photopic sensitivity was only reduced by a factor of about 2:1 from their measured scotopic value (their figure 1B & 1E). This small variation is consistent with their constant amplitude test stimulus intensity falling in the mesotopic range. Their test protocol leads to difficulty interpreting their measurements in figure 1A, 1C & 1D.

Their processing chemistry was quite complex and even included using plain milk (of unspecified heterogenous character).

Their conclusions remained general, “These findings are consistent with an early-onset, slow progression of cone functional defects and cone loss in CNGB3^{-/-} mice, with the cone signaling deficits arising from disrupted phototransduction and cone loss rather than from synaptic defects.” While their conclusion is specifically related to mice, the implication that achromatopsia is a slowly progressive disease in humans should be avoided. As noted, they only addressed the morphology of the synaptic interface.

Xu et al. do note at least 70 mutations had been identified by May 2011 encoding the human CNGA3 and CNGB3 subunits, with mutations in CNBG3 alone found in more than 50% of patients with achromatopsia Citing Kohl et al., 2005)

18.8.3.7.4 High resolution examination focused on the RPE/OS interface– Komaromy et al.

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Unlike the above papers, Komaromy et al. focused on a mutation affecting the ability of the RPE to produce the chromophores required for color vision in mammals. The mutation has been named RPE65. Komaromy et al. begin by noting over 150 mutations have now been identified relating to the visual system (and presumably most of these with the retina). They note the retinal disease data bank, RetNet, at <http://www.sph.uth.tmc.edu/RetNet/>, supported by the Red Cross and several foundations at The University of Texas-Houston Health Science Center, maintains a listing and interpretation of these mutations. It notes for RPE65;

"candidate gene; accounts for 2% of recessive RP and 6 to 16% of LCA; same as RPE65-/- Swedish Briard-Beagle dog; protein is necessary for production of 11-cis-vitamin A; 9-cis-retinal restores visual function in mouse model; successful gene therapy in dog; in same pathway as LRAT; dominant mutation in large Irish family with several members diagnosed with choroideremia."

RetNet includes a massive list of citations to workers supporting research in specific mutation areas.

Komaromy et al. note the RPE65 mutation is fundamentally different from those causing physical disruption of the morphology of the retina. They also note "the RPE65 mutation is currently understood to be rare and complex in that loss of visual function and eventual photoreceptor degeneration is secondary to a biochemical blockade of the RPE visual cycle." On the other hand, based on this work, its treatment may be more straight-forward. It appears to be associated with the transport of retinol to the RPE and its conversion into the four chromophores of vision. This process is examined in detail in **Section 4.6.2** of this work.

Gene therapy to overcome the RPE65 mutation appears to be the farthest along with initial treatments found to be safe in trials involving human retinal degeneration. The therapy appears designed to solve a transport error associated with the multiple pathways associated with Rhodopsin formation in the RPE.. The overall transport process involves seven major steps and a number of sub-steps in the pathway described as "in same pathway as LRAT" in the above quotation . These are discussed in **Section 4.6.2.3** of this work. Initially, retinol is ingested in the form of Vitamin A. Finally, it is delivered to the disks of the outer segments in one of four spectrally specific forms of Rhodopsin, Rhodopsin(5), Rhodopsin(7), Rhodopsin (9) and Rhodopsin(11), the long wave, medium wave, short wave, and ultraviolet wave chromophores of vision..

Interpreting the Komaromy et al. paper is difficult because they change focus from the RPE65 mutation to a CNGB3 mutation. As noted earlier in this section, **Section 4.6.2** addresses the chromogen fabrication paths and **Section 7.1** addresses the dynamics of chromogen processing in more detail. Mammals employ four chromophores, and (contrary to the past literature in the field) they are virtually all functioning tetrachromats except for the larger mammals, beginning with humans, who are trichromats due to absorption of most ultraviolet light wavelengths (below 400 nm) by the lens of the eye. Dogs as a group are tetrachromats, although they have frequently been labeled dichromats due to test instrumentation problems in earlier years (low light source color temperature and glass bulbs and lenses rather than quartz in their instrumentation). The net spectral performance of dogs (*Canis lupus familiaris*) should be evaluated on a case-by-case basis because of their variation in lens size (due both to breed and significant lens size changes during maturation).

The question raised by the results of Komaromy et al. is whether the mutation they identified as RPE65 affects the transport of the retinoids as a group through the blood/RPE cell interface or whether it affects a subgroup of the four chromogens created at this boundary. It is also possible RPE65 affects the release of the retinoids at the RPE/IPM interface as a group, or on a more individual basis. Those suffering hemeralopia generally exhibit a full visual spectrum at mesopic light levels, but there are a significant fraction who exhibit poor performance in the short wavelength spectral area (and no data is known concerning their UV channel spectral sensitivity. If RPE65 suppresses the efficient transfer from the blood to the RPE on a group basis, both a shortage of chromogen storage should be demonstrable using the techniques employed to create [**Figure 4.6.2.6**] and a shortage of chromophore covering the disks should be demonstrable. Alternately, if it is the discharge of chromophores into the IPM that RPE65 is affecting, the storage of the chromogens should appear normal or enhanced in the RPE and a shortage of chromophores covering the disks should be observable. Further, and more detailed research is obviously warranted.

Komaromy et al. employed an injection method that delivered their vector to the subretinal space of the eye, forming a bleb in the language of surgery. This space and technique is defined more precisely in a 2006 paper by Komaromy, Varner et al²⁹⁷. Aguirre Komaromy et al. have provided more information on their techniques as they relate to amaurosis (total loss of sight not due to physically identifiable problems in the visual system²⁹⁸. Amaurosis

²⁹⁷Komaromy, A. Varner, S. et al. (2006) Application of a new subretinal injection device in the dog. *Cell Transplant* vol 15(6), pp 511-519

²⁹⁸Aguirre, G. Komáromy, A. Cideciyan, A. et al. (2007) Canine and Human Visual Cortex Intact and Responsive Despite Early Retinal Blindness from RPE65 Mutation *PLoS Medicine* vol 4(6), page e230+

typically involves all of the chromogens and/or chromophores described above. Thus, it is likely that a mutation in RPE65 affects all of the chromogens at the blood/RPE border or farther along the processing leading to the IPM and the photoreceptors.

A 2008 paper by Komaromy, Alexander et al. at least partially resolved the dichotomy related to the 2010 paper²⁹⁹. They noted that, subretinal injection of their materials was more effective than sub RPE injection. This suggests the utility of their method involved the RPE/IPM interface rather than the blood/RPE interface. Their goal had been to;

“to evaluate various human cone opsin promoters for their specificity and efficacy to target gene expression to the canine cone photoreceptors.”

They worked with a series of putative “promoters” and well known “reporters” and obtained good, although sometimes unexpected, research results. The paper clearly involved exploratory research as some of their results were “surprising.” it used the term promiscuous when the materials did not perform according to their conceptual model. Their summary conclusion reflects its exploratory character;

“We successfully proved the principle of cone-specific gene targeting in a large animal model. Our results open the door for cone-specific gene therapy in canine models of primary and secondary cone disease.”

In some cases, their results were inconsistent with their assumption of a conceptual L/M cone in a dichromatic dog retina. Why they expected a genetic derivative related to the human red or L photoreceptor to be effective in the putative dog L/M photoreceptor is unclear.

It is likely that future experiments can determine whether the RPE65 therapy was effective in mediating increased production of all four chromophores within the RPE, or only selected chromophores. This determination will aid in determining which of the transport proteins of **Table 4.6.2-1** have been most favorably affected.

²⁹⁹Komaromy, A. Alexander, J. et al. (2008) Targeting gene expression to cones with human cone opsin promoters in recombinant AAV *Gene Therapy* vol 15, pp 1049-1055

18.8.3.7.5 Analysis of Achromatopsia after reviewing 2008-2012 inputs.

[The figure and section numbers appearing in bold face are found in the online text “Processes in Biological Vision,” PBV, unless accompanied by the notation in the Guide. The Guide is a synopsis of the PBV published under the title, Biological Vision: A 21st Century Tutorial. Both are available at the website, <http://neuronresearch.net/vision/>. The individual chapters of the PBV are available by clicking on the label [Download Chapters](#) in the left navigation bar. The first numeric following the word section of figure indicates the chapter number where it is found.]

The papers within **Section 18.8.3.7** contribute considerably to our knowledge of the morphological aspects of achromatopsia. They lead to both better understanding and additional questions. The papers highlight the number of genetic mutations involved may be considerably higher than believed ten years ago. They suggest the actual mutations causing achromatopsia require additional sub designations at the allele level be associated with the principle named mutations at the gene level historically associated with achromatopsia. The following material will be subdivided into two distinct sections.

Morphology and homeostasis

The use of AOSLO apparatus has continued to show the retina is mottled when the natural rotary vibration of the retina is compensated for. Whether this mottled appearance is related to the images showing hypoplasia behind the foveola (fovea centralis) is not clear since the images in these papers were obtained from subjects who were known to exhibit poor performance in the area of the foveola. Similar hypoplasia at points away from the foveola might be present, even in normal eyes, but be compensated for within the central nervous system just as the blind spot is.

The statistics of Thiadens et al. that foveal hypoplasia is only present in 24/40 cases and RPE atrophy is only present in 7/40 cases suggests morphologically identifiable hypoplasia is at best one aspect of complete achromatopsia. The Komaromy et al. paper suggests an additional factor related to the hemeralopia in these subjects is a mutation in the RPE65 gene. The fact the Komaromy et al therapy was most effective when in contact with the RPE/IPM (alternately the RPE/OS) interface, through subretinal injection, introduces several possibilities.

1. The most obvious is that their treatment may affect the surface of the RPE initially controlling the release of *all* of the chromophores required for normal color vision (**Sections 4.6.2 & 7.1.1.1**).
2. Alternately, the S-photoreceptors may be preferentially, but not exclusively, affected by a genetic mutation leading to hemeralopia. The S-photoreceptors appear to be more frequently missing, or misreported by the neural system, in subjects when examined under mesotopic conditions (**Figure 18.8.3-11**). In that case, their treatment may affect the release of chromophores from the RPE preferentially with respect to spectral type.
3. The RPE surface is normally in intimate contact with both the IPM and individual OS of the sensory neurons. It has a routine function of phagocytizing the disks of the OS at the end of their normal life. An OS typically grows at a rate such that a specific disk is usually replaced after nominally one week in humans. See **Figure 4.5.1-1** of PBV (**Figure 7.2.1-1** of the Guide). The processes instigating and involving phagocytosis are not well documented (See **Section 4.6.1** and **4.6.2**, specifically **Figure 4.6.2-4** from Hogan et al³⁰⁰). The 1970's concept of Young that the OS employs a lemma enclosing the disks is not supported here. The existence of such a lemma, (b) in Hogan, has never been documented. The thick “sheaths” labeled (a) in **Figure 4.6.2-4** are integral elements of the RPE enveloping the OS and critically involved in the phagocytosis process.
 - A. One possibility is that the chromophores coating the individual disks are removed as a specific disk approaches the RPE/OS interface by “finger like” villous structures (c) in Hogan, and the opsin (protein) substrate becomes susceptible to phagocytosis by the RPE cells following chromophore removal. The recovered chromophore material, (d) and (e), is typically reprocessed and stored in the RPE cells prior to its reuse (but not on a short term, less than one minute, basis).
 - B. If the disks have not been adequately coated with the non-protein chromophore material initially they may become susceptible to phagocytosis at a greater distance from the RPE interface. The chromophore material is a retinoid, but not a retinal. The significant absence of the chromophore retinoid material from

³⁰⁰Hogan, M. Alvarado, J & Weddell, J. (1971) Histology of the Human Eye, An Atlas and Text. Philadelphia: W. B. Saunders

the root of the OS (within the extrusion cup of the IS) may lead to phagocytosis extending into the IS extrusion cup, and even into the now unprotected lemma of the IS portion of the sensory neuron itself.

C. In the case of B, the situation might be described as an auto-immune disease where the mutation in the RPE65 (or similar gene) might prevent the release of the chromophores in their protected state (coupled to a CRABP or other transport protein, **Section 4.6.2**), and their subsequent coating of the opsin disks and the opsin extrusion mechanism. This situation would allow the villous structures (c) of the RPE defined by Hogan to attack the exposed protein materials prematurely resulting in the voids (bubbles) observed in the SD-OCT imagery.

D. The degree of hypoplasia described in this scenario could vary based on a number of factors. The statistics of Xu et al. are not sufficient to provide confidence that age of the subject is one of them. But other genetic mutations might provide a controlling function.

E. In this scenario, the neurological aspects of the sensory neurons would not play a role, and questions related to putative cyclic nucleotide gated (CNG) channels are irrelevant. The microvilli passing through the connecting cilium would not be in contact with usable chromophore and the transduction process would not occur, regardless of the health of the microvilli.

4. The IPM normally fills an oxygen-free compartment between the RPE and the IS portions of the sensory neurons. The RPE cells are typically tightly packed to form a barrier between the vascular matrix. Some investigators have defined a separate barrier which the RPE cells penetrate. This putative barrier is known variously as zonulae occludens, terminal bars, and Verhoeff's membrane. The IPM and the sensory neurons are aided by Mueller cells in forming a similar barrier between the IPM and the outer nuclear layer, ONL, of the retina.

A. If any genetic mutation should allow oxygen, or oxygenated species into the IPM compartment, the retinoid chromophores would be deactivated as far as transduction is concerned, and might be deactivated as far as any protective role related to phagocytosis. Such a mutation could be at the RPE/IPM interface or at the OLM/IPM interface populated by Mueller cells (glia).

5. The cause of the localization and limited size of the hypoplasia is not addressed in the above scenario. The size is typically less than the diameter of the foveal pit (nominally 350 microns; **Figure 3.2.2-1**) and generally less than one millimeter.

6. The operation of the neural system in achromatopes is compatible with the above model.

7. The involvement of the choroid in hemeralopia (figure 1F of Thiadens et al. and particularly Figure 2(8) of Genead et al.) is not addressed in this analysis. It is clearly relevant to an understanding of the more severe hypoplasia leading to hemeralopia.

Neuroscience/neurology

The morphology and chemistry of the achromatope retina suggests the neural system is not actually involved in the syndrome as a disorder. This conclusion is based on several conditions described below. Initially, it is important to review the transduction process. Transduction in mammals involves the application of light energy to the disks of the outer segments closest to the inner segments, after its passing through the IS and other neural layers. The purpose of the foveal pit is to minimize the light scatter of the neural layers, and to provide a minimal amount of image magnification at the foveola/fovea centralis. The disks of each OS are effectively in series with respect to light energy but in parallel with respect to their stimulation of the neural system. It is the chromophores coating the passive opsin of the disks, in the form of a continuous liquid crystalline monolayer, that absorb the light energy, are converted into a quantum mechanical excited state, and are de-excited in the process of stimulating the microtubules within the OS connecting the dendritic structure of the sensory neuron within the IS via the connecting cilium. The absorption of the chromophores of a specific disk is very high in the dark adapted (unexcited) state and virtually zero in the fully light adapted (excited) state.

The absorption of the UV-chromophore and the performance of its signaling channel will not be addressed here because of lack of empirical data.

1. Under dark adapted conditions, most of the light is absorbed by the first few coated disks of the OS closest to the IS. The effective sensitivity of these initial coated disks is very high (peak conversion efficiency in the 90% or higher category).

2. As the initial coated disks become excited, the light passes through the initial disks and is passed to the following disks before absorption.

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3. If the initial disks are not completely coated with chromophore material or subsequent disks are less than fully coated with chromophore, the cumulative amount of light absorbed per unit time, and the stimulus applied to the microtubules/dendrites is reduced.
4. The de-excitation of the excited chromophore material is controlled by the ability of the microtubules/dendrites to provide electrical charges to the chromophore/microtubule interface.
5. At scotopic through mesotopic light levels, the typical achromatopsia patients exhibit nominal ERG's for each of the spectral channels of the visual system (except possibly for the short wavelength channel). Xu et al. showed a variation on the order of 2:1 or less in this area with light level. The ERG amplitude begins to decrease rapidly as the light level increases above a nominal mesotopic level. As the rate of photon absorption, exceeds the ability of unexcited chromophore molecules to be excited, the ERG amplitude goes to zero, and the sensitivity of the overall sensory neuron becomes zero as a function of light intensity as shown in **Figure 18.8.3-17**. The subject exhibits photopic (day) blindness in spite of nominal scotopic/mesotopic vision (including color vision, although not color constancy).
6. A potential major cause of the above photopic (day) blindness is the lack of chromophoric material coating the disks of the OS.
7. A potential major cause of the above photopic (day) blindness is the lack of sufficient electrical current at the disk/microtubule interface to discharge the excited chromophore material.
8. Based on the preceding discussion of homeostasis, the most likely cause of hemeralopia is the inadequate supply of chromophoric material to the individual disks of the OS or its premature removal from active light absorption by the premature phagocytosis of the disks.

The tentative conclusion of this section, based on the available evidence, is the underlying cause of achromatopsia in the majority of cases is the lack of adequate chromophore coating a sufficient number of disks in individual OS to support vision under photopic conditions. The resulting condition is an extension of the condition known as snow-blindness into the photopic regime resulting in day-blindness or hemeralopia (and the resulting behavioral response of photophobia.). Based on this analysis, the condition is related primarily to gene mutations affecting the RPE and its operation rather than to putative gene mutations associated with the neural system.

The data is inconclusive with regard to whether the achromatopsia is congenital or early onset in character, with congenital being the more likely descriptor. If progressive, the rate of progression is very low.

It is proposed that one potential cause of amaurosis, or total blindness in the absence of neural or morphological disorders (no known physiological cause), is the extension of hemeralopia due to total loss of chromophoric coating of the disks of the OS.

The following sections will suggest how the absence of neural electrical signals under photopic illumination in hemeralopia patients can result in a variety of other symptoms of achromatopsia based on the overall block diagram of the visual system as shown in **Figures 1.5.2-2 or 15.2.5-3 of PBV (Figure 8.1.1-1 of the Guide)**.

The genetic inference that achromatopsia is caused by failures related to one or more types of putative cyclic nucleotide gates (CNG) is not supported.

Figure 18.8.3-7, based on earlier knowledge, needs broadening if the role of the RPE65 mutation in hemeralopia is confirmed.

18.8.3.8 Recent clinical experiments to cure achromatopsia & related diseases

Several clinical trials have recently been performed to evaluate proposed treatments for achromatopsia with less than desired results. A wide variety of similar studies are in preparation or under way. Similar results appear to be likely when seeking to treat a variety of related diseases. Their status is supported by an NIH website, <https://www.clinicaltrials.gov/>. The current achromatopsia trial is described on this site by “its ClinicalTrials.gov

identifier: NCT01648452. Several papers have been released on this study^{301,302}. The title of the first paper cited summarizes the results to date. It is not likely the reduced rod pathway responses were statistically relevant.

18.8.3.8.1 Introduction of CNTF into the vitreous humor

Neurotech, of Cumberland Rhode Island, has been carrying out a set of clinical trials. “NT-501 ECT consists of encapsulated human cells genetically modified to secrete therapeutic doses of ciliary neurotrophic factor (CNTF) into the back of the eye for the treatment of retinal degenerative diseases. Neurotech is currently conducting several clinical trials in subjects with retinitis pigmentosa (RP) and macular telangiectasia (MacTel). Neurotech also collaborates with research ophthalmologists in investigator-initiated clinical trials for other neurotrophic ocular diseases.

A total of 184 subjects have been enrolled in three separate Phase 2 studies in the US, with some subjects reaching past 50 months post-implantation.” Less positive reports have indicated some initial results requiring immediate removal of the encapsulated human cells due to inflammation problems.

The Neurotech procedure is described on a website, <http://www.neurotechusa.com/ect-platform.html>.

The Neurotech concept does not appear well suited for treating of diseases of the photoreceptors, RPE or IPM (inter photoreceptor matrix) because of the large number of virtually impregnable membranes between the vitreous humor and the target areas. See **Section 18.8.3.6.2.**, specifically Figure 18.8.3-19. Introduction of CNTF into the vascular circulation between the sclera and the RPE (a much more restricted area) might provide better results.

18.8.3.9 Residual neurological problems related to achromatopsia

With the advances in genetics and molecular biology of the last two decades, it is possible that gene therapy will become available to cure the electrolytic problems associated with achromatopsia. However, there are indications that such treatment will expose a significant neurological deficit. The plasticity of the brain allows and supports the reorganization and reuse of parts of the cerebral cortex when they are not being used in their conventional role. Recent laboratory experiments and human experiences have documented this situation. Although it is early work, Baseler et al. have provided some fMRI experiments describing apparent re-allocations of part of the occipital lobe in patients with achromatopsia³⁰³. Kurson has recently provided a record of the continuing problems encountered by Mike May following restoration of his sight lost at the age of three years in an accident significantly damaging his corneas³⁰⁴. Mike still travels with a guide dog even though his acuity has been restored to near normal. As the Kurson website shows, Mike still has problems. Although having normal vision up to the age of three, he has significant problems recognizing faces and other common objects more than one year after his surgical repairs were completed. Thus a cure for the physical aspects of achromatopsia may leave behind significant neurological stumbling blocks.

18.8.4 Achromatopia as a simple symptom of high diagnostic utility

Exploring the literature of the simple symptom involving the loss of chromatic perception alone, achromatopia, has led to several insights into the visual modality. These insights will be explored in this section.

18.8.4.1 The (simple) achromatopia sufferers examined by Damasio et al.

[xxx cite this analysis in Section 15.10.6.7 ? When complete]

Damasio et al. (a group of practicing medical doctors) used a wide range of tools to clinically evaluate two subjects suffering from achromatopia. They reported their results in 1980³⁰⁵. Their thoroughness prevents endless

³⁰¹Zein WM, Jeffrey BG, Wiley HE, et al. (2014) CNGB3-achromatopsia clinical trial with CNTF: diminished rod pathway responses with no evidence of improvement in cone function. *Invest Ophthalmol Vis Sci* 2014 Sep 9;55(10):6301-8. doi: 10.1167/iovs.14-14860.

³⁰²http://clinicalstudies.info.nih.gov/cgi/detail.cgi?B_2012-EI-0167.html

³⁰³Baseler, H. Brewer, A. Sharpe, L. et al. (2002) Op. Cit.

³⁰⁴Kurson, R. (2007) Crashing Through. www.robertkurson.com

³⁰⁵Damasio, A. Yamada, T. Damasio, H. Corbett, J. & McKee, J. (1980) Central achromatopsia: behavioral, anatomic, and physiologic aspects *Neurology* vol 30, pp 1065-1071

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speculation about what other conditions might have accompanied their patients disease.

In case 1, the subject was diagnosed as suffering from “left central hemiachromatopsia due to infarction in the territory of the right posterior cerebral artery, possibly on the basis of mechanical disturbance of the vertebrobasilar system” (the subject had massaged his neck vigorously immediately prior to onset of the condition).

In case 2, the subject was diagnosed as suffering from bilateral infarction in the territory of the posterior cerebral arteries.” “In addition to achromatopia, the subject suffered from prosopagnosia.” A diagnosis of bilateral infarction appears statistically unusual; but was well documented in this case.

It was probably the result of a single hemorrhage as documented by the CT scan. The CT scan also indicates a more central area of damage

Damasio et al. employed and documented a series of standard tests to arrive at the above diagnoses including Goldman perimetry, CT scans, EEG's and ECG's.

In case 1 (a 49 year old man), the Goldman perimetry showed a small scotoma in the left upper quadrantal area. However, the primary complaint was his inability to perceive, “recognize or identify any color in any portion of the left field of either eye, including bright reds, blues, greens, and yellows. As soon as any portion of the colored object crossed the vertical meridian, he was able to instantly recognize and accurately name its color. When an object such as a large red flashlight was held so that it was bisected by the vertical meridian, he reported that the hue of the right half appeared normal while the left was gray. Except for the achromatopia, he noted no other disturbance in the appearance of objects (i.e., objects did not change size or shape, did not move abnormally and appeared in correct perspective.” No other symptoms of the broader syndrome defined here as achromatopsia (with an s) were reported or observed! Even depth perception in the colorless field was normal. The defect remained stable and a CT scan revealed a low-density area suggestive of infarction in the right occipital lobe.

In case 2 (a 60 year old woman), the subject awoke one morning and noted that although she was able to see details of objects and people, colors appeared “drainee out” and “not true.” She had no other complaint and did not consult a physician, but an oculist told her that her vision was good, 20/20 in each eye. The difficulty with color perception persisted. Eight weeks later she noted the sudden onset of prosopagnosia. She quickly adapted by using other cues such as voice timber, etc for identifying people. She did identify a dimming of her vision in the right field of view beginning at this time. No other complaints surface and her past history was unremarkable. She noted that everything appeared in shades of gray, occasionally black or “whitish,” but that true color was absent. Goldman perimetry revealed a dense right superior homonymous wedge defect. In addition, there ws a left superior quadrantic homonymous scotoma. Visual evoked responses were abnormal for colored stimuli. CT scan showed bilateral areas of low density in the occipitotemporal junction.

18.8.4.1.1 Analysis of the achromatopia cases presented by Damasio et al.

The two cases documented by the same medical team, Damasio et al., can be represented graphically using two figures. **Figure 18.8.4-1** shows a figure adapted from Tootel (1988) and discussed in **Section 15.2.5**. The losses in chromatic vision and related symptoms can be correlated with this image. In case 1, the subject exhibited normal full color vision in his right visual field that was supported by signals from both eyes. His left visual field became achromatic within minutes of his vigorous massaging of his neck. The precision of the measurements of the medical team did not support the expected result that a loss of chromatic performance in either field would result in a vertical demarcation that was actually one degree short of the vertical meridian. The academic literature would limit the remaining chromatic vision to a left or right visual field extending approximately one degree beyond the nominal vertical meridian (the region enclosed by the black box). In case 1, the subject reported no difficulties associated with prosopagnosia, a phenomenon related to the PGN/pulvinar pathway and the 1.2 degree central disc shown surrounding the point of fixation. The reported symptom is consistent with a loss of chromatic signals (typically labeled parvocellular pathway signals) due to an infarction in the right right occipital lobe interfering with the chromatic signals from that lobe reaching the association areas near BA 36 & 37.

In case 2, the subject reported a different set of symptoms as time progressed. She initially reported the sudden onset of achromatopia over her entire field of vision. Such a situation is correlatable with a loss of chromatic signals (the P- and Q-channels, or parvocellular pathways of vision) from both lobes of the occipital lobe near or after the arrival of these signals at the association areas near BA 36 & 37. The subsequent onset of prosopagnosia is also compatible with a loss of precision information from the 1.2 degree diameter foveola as passed to the association areas near BA 36 & 37 via the PGN/pulvinar pathway. These symptoms are correlatable with an infarction in the vicinity of the occipitotemporal junction. It is not clear that a bilateral infarction is necessary to disrupt the

performance of the association areas in this way.

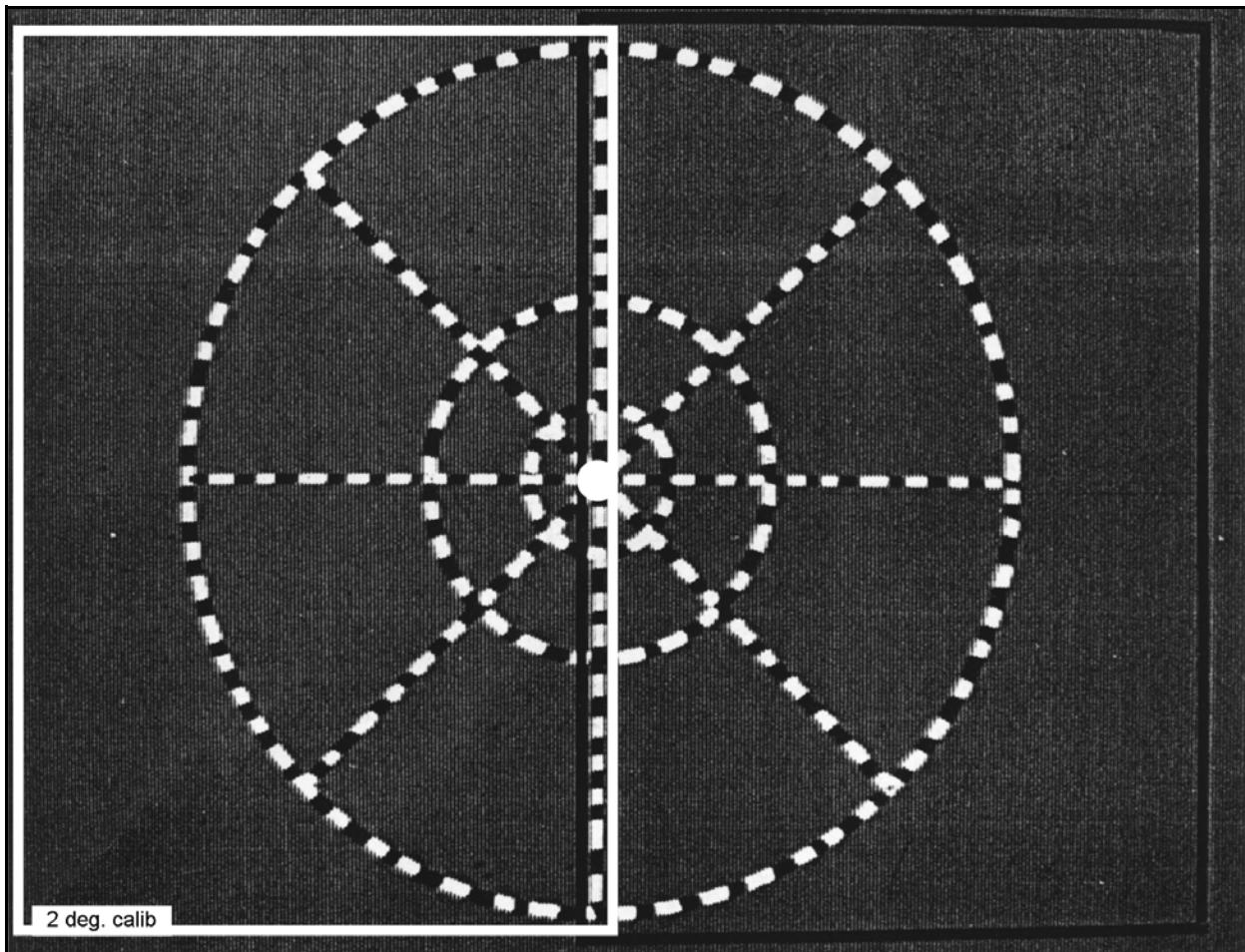


Figure 18.8.4-1 The nominal visual field of primates using radiographic techniques. The diameter of the dashed circles in object space are 2.0 , 4.6 and 10.8 degrees centered on the point of fixation as accurately as possible. The white box shows the field presented to area V1 of the ipsilateral hemisphere of the occipital lobe. A similar black box is also shown. These boxes overlap by about 2 degrees along the vertical meridian. Also shown is the foveola of the retina represented by a 1.2 degree diameter disk also centered on the point of fixation. See text. Modified from Tootel, 1988.

Unfortunately, the visual evoked responses employed red/green checkerboards of undefined spectral characteristics and an undefined light source, making the VEP responses unreliable from the academic perspective. See **Section 18.1.2.1**. No VEP measurements employing a blue/yellow checkerboard were referred to or provided. Tests with both of these color combinations are required to electrophysiologically confirm complete achromatopia (although in this case, the subjects presentation and affirmations confirm this condition..

Figure 18.8.4-2 provides a flow diagram for signals in the areas of the cerebrum of interest. The diagram suggests the areas V2, V3 & V4 can be considered to be wired in parallel with a contribution from each to the M and P paths shown projecting to visual areas 36, 37. All of the stage 4 information extraction engines of the visual modality are actually connected in a star configuration with their output contributions projecting to many currently functionally unidentified locations. While it is possible to continue using the labels M & P for the pathways shown, it is likely the method of signal propagation over these paths has changed from word serial/bit serial to word serial/bit parallel as suggested by the label at lower left. This change supports a much higher information transfer rate over a limited number of multiple neuron nerves. A dotted area defines the predicted functionally damaged areas based on this

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work. The medical work up for Case 1 describes the functional loss of chrominance information (parvocellular pathway shown as P paths) traveling from area V4, BA 19 to the visual association area (probably BA 37) without other functional damage. The CT scan shows the damage is focused on the ventral portion of area 19 of the right occipital hemisphere. The CT scan as annotated would suggest the damage was primarily to the ventral portion of area 19. The damage is likely to involve the stage 4 output neurons of the engine located nearest the area 19-area 37 border and or the stage 3A encoding neurons of stage 3 projection neurons emanating from the same area.

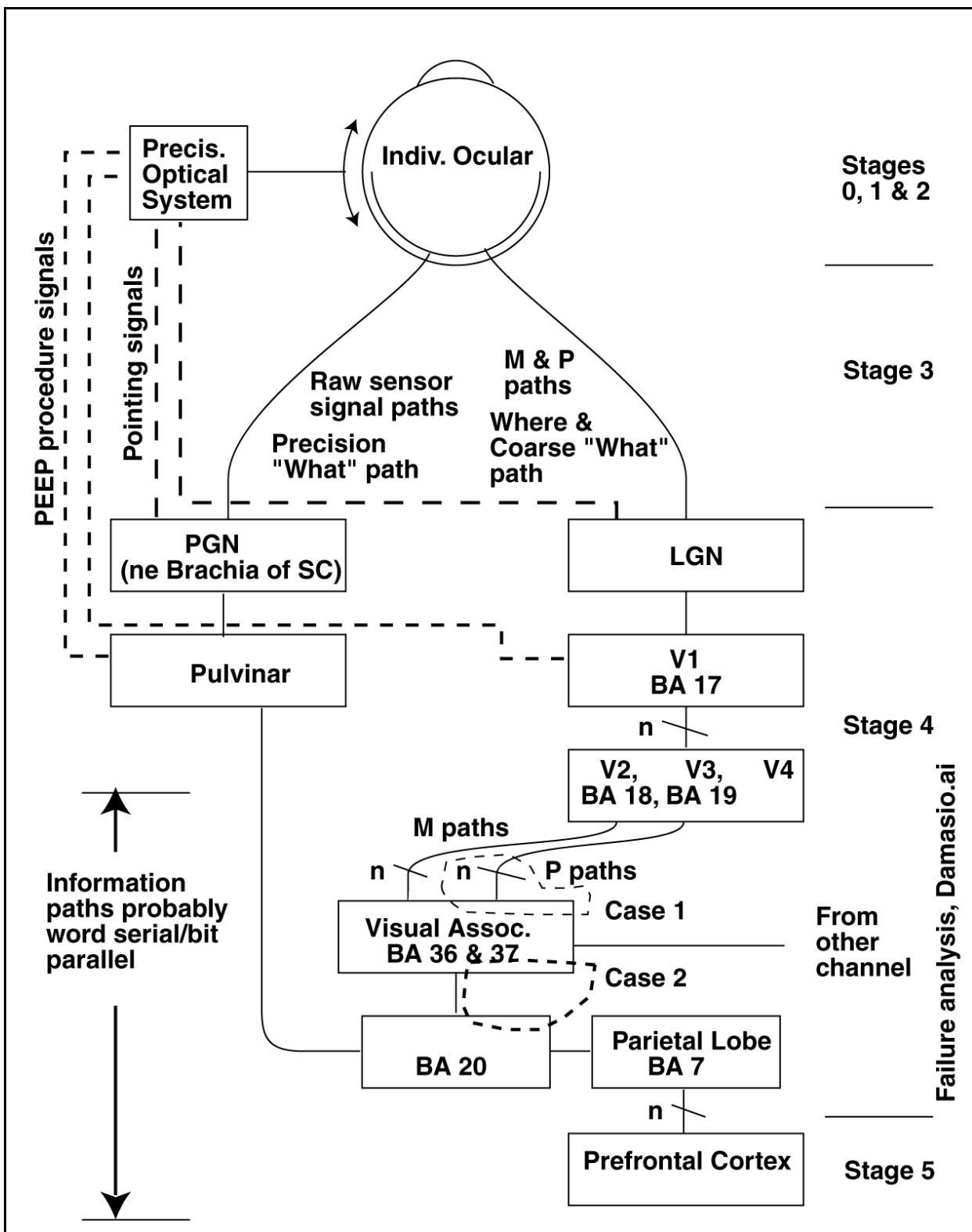


Figure 18.8.4-2 High level information combining in two symptom-level achromatopes as reported by Damasio et al., 1980. Areas V2, V3 & V4 are shown in parallel, but they are actually a part of a star network that is not currently detailed. REFINE AREAS OF CASE 1 AND CASE 2. See text.

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The medical work up for Case 2 indicates slightly different area of damage. The damage is focused bilaterally on the ventral portions of BA 20, BA 21 and BA 37 of both hemispheres of the cerebrum based on the CT scans. The CT scans also suggest the damage may have involved tissue of the interior ventral cerebrum adjacent to BA 20 as well as that typically associated with the more external portions of the cerebrum. The initial damage resulting in achromatopsia appears to have been focused on the ventral portions of area BA 37 of both hemispheres of the cerebrum. Specifically, the damage is to the circuits (or engines) supporting the P paths. These circuits are located within one or more engines and as in case 1 may involve either stage 4 engines or stage 3 neural (chrominance only) pathways. Subsequent damage appears to have been to the portion of BA 20 where merging of the precision "What" information from the pulvinar is combined with all of the information from the two association areas.

Neither of the subjects, case 1 or case 2, presented with any of the other symptoms usually associated with the syndrome known as achromatopsia (with an s) documented in **Section 18.8.3** of this chapter. These two subjects have fully functional oculars and retinas. The use of the terms monochromats or dichromats as they typically refer to the sensory neurons of the retinas are totally inappropriate in these two cases.

18.8.5 Ametropia and other errors of the accommodation servomechanism

The condition of ametropia includes a broad range of diseases related to both the physiological optics and the neurological processing of the images in the far field presented to the eyes. The most common is the class known as myopia (hypometropia) or near-sightedness. For technical reasons to be developed below, the opposite class, hypermetropia or far-sightedness, is less significant in the comfort and performance of the human. Because of its greater prominence in the human condition, several other classes of ametropia have been closely linked to or lumped into myopia. These can be divided into three subclasses; refractory based myopia, neural based myopia and pathological myopia. The subclass of neural based myopia is limited to neural properties related to ametropia. There is another significant class of neural disorders related to the dynamic aspects of the oculomotor system of vision. These include the nystagmias and the strabismias. These are addressed in a different section of this chapter. **Section 7.3.2** addresses the physiological and neural aspects of ametropia, other than pathological myopia.

Many patients have expressed lack of satisfaction with the description of their ametropia presented to them by clinicians. It is the goal of this section to provide a more structured description of the condition. One of the primary areas of concern relates to the simplistic description of the myopic condition as due to an excessively long axial diameter of the eyeball. It is claimed that this excessive length, or an insufficient physiological optical system that is the source of their problem. There is considerable data showing that the primary correlates of axial diameter of the eyeball are the sagittal diameter and the transverse diameter. That is to say long axial diameters are most closely correlated with "Big Eyes." There are two other features that correlate highly with the axial diameter of the eye. One is the depth of the eye between the position of the lens and the retina. This might be described as the vitreous depth. The second is the depth of the eye between the position of the lens and the surface of the cornea. This may be called the anterior depth. Either an increase in the physiological depth or a decrease in the optical depth results in myopia. The first is directly related to an extra long "eyeball." The second is directly related to a higher optical power in the physiological optics. Both of these conditions contribute about equally to the overall myopia³⁰⁶. Grosvenor & Flom provide statistics in this area. The bottom line is the axial diameter of the eye, relative to a tabular value, is not a specific indication or cause of myopia.

Many patients also are uncomfortable with the described course of their condition with time. This section will provide a more illustrative discussion of this scenario.

There is an inherent error of 0.17D when an optometrist measures your far-field vision using a Snellen Chart at a distance of 20 feet. He normally compensates for this in his calculations. While small, the number is significant at the theoretical level.

As noted by Goldschmidt at the close of a large symposium in 1990³⁰⁷: "A large number of studies on the effects of various (pharmaceutical) agents on the progression of myopia in childhood have been published." They went on to say: "The final conclusion of our work is that there does not appear to be any simple method by which we can delay or reduce the rate of progression of myopia." This situation appears to remain correct today.

³⁰⁶Grosvenor, T. & Flom, M. (1991) Op. Cit. pg 46-53

³⁰⁷Goldschmidt, E. (1990) Myopia in humans: can progression be arrested? In CIBA Myopia and the Control of Eye Growth. NY: John Wiley & Sons pp 222-234

18.8.5.1 Refractory ametropia including myopia

Refractory ametropia may result in either hypometropia (myopia) or hypermetropia (far-sightedness). [xxx see section 18.2.4]

18.8.5.1.1 Time course of refractory ametropia

Figure 18.8.5-1 reproduces a figure from **Section 7.3.2** that is informative. It describes the normal progression of the performance of the refractory system with time beginning at ten years of age. Prior to age ten, the system is in such a random state of development, with respect to the growth rate of individual elements of the physiological optics, it is difficult to generalize about it.

The gray band in the figure represents the range from zero to plus 4 diopters. This is the normal range required for focusing from 25 cm (10 inches) to infinity and includes the range of most human activity. The properly functioning accommodation system has more than sufficient range to cover this zone. However, the accommodation system is not symmetrical. The system proceeds from a fully relaxed condition to a condition of accommodation some 10 diopters more positive.

Two problems arise in the visual process. First, if the relaxed accommodation level (called the basal accommodation level here) of an individual is already positive, the eye cannot accommodate to zero diopters. This is the condition shown by the solid triangle. The bottom of the triangle intersects the basal accommodation scale on the right of the figure. Such a person is considered near sighted, refractively myopic, and will normally require glasses of at least minus one diopters to achieve proper distant vision. For a serious myope, a basal accommodation level of plus five is not unusual. Anyone with a basal accommodation level exceeding plus four will require glasses with a negative diopter rating at all ranges throughout his lifetime.

Most subjects with a basal accommodation level that is negative do not have a need for glasses during their early years. The accommodation level of such individuals will almost always include the shaded zone as shown by the dashed triangle. However, if he should have a basal accommodation level more negative than minus 5, he may require glasses for reading, and other close work, beginning at an early age.

In this discussion, the the basal accommodation level is an operational level found when the eye is relaxed by the subject. It is not the level of relaxation achievable by pharmacological means.

Most people exhibit an accommodation range of at least ten diopters at age ten. This range decreases monotonically with age as shown, for both hypermetropes and hypometropes (myopes). The results are the same but occur at different times as shown. For the myopic subject, he will require glasses for far vision from an early age. He will begin to suffer a loss of accommodation and require glasses at short range beginning somewhere around 45 years of age. This point will depend on both his basal accommodation level and his initial accommodation range at age 10. The hypermetrope will not be able to achieve as high a level of absolute peak accommodation as the typical myope, because of the offset introduced by his basal accommodation level. Therefore, the hypermetrope will tend to lose his ability to focus at short range somewhat earlier than the myope. This frequently happens around 40 years of age. These people are the ones that need “reading glasses,” particularly for menus in dark restaurants, etc. As his accommodation capability continues to decline, he will begin to have difficulty seeing at a distance. This occurs when his accommodation range becomes numerically less than his basal accommodation level. This latter phenomenon appears to equate to Donder’s “distance hyperopia.” At an age of 45-50, the typical hypermetrope will need positive lenses for seeing both near and distant objects. Bifocals become the order of the day for hypermetropes over 50 years of age.

There is considerable argument in the literature as to the changes in the visual accommodation plant resulting in

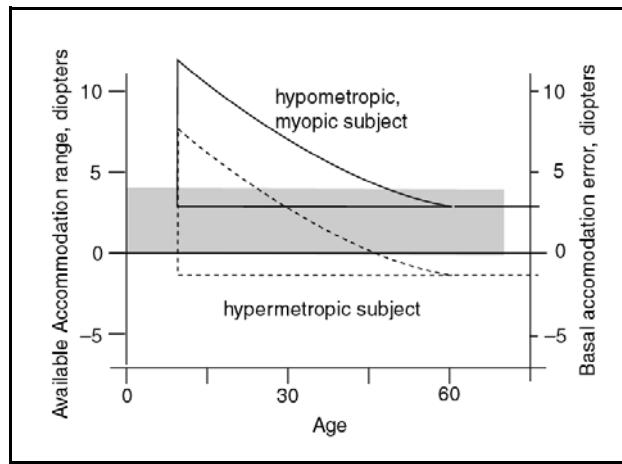


Figure 18.8.5-1 Presbyopia as a normal process of aging. The gray band shows the normal range of accommodation needed to properly image from 25 cm to infinity. This range includes the zero line. See Text.

presbyopia. The reply to Weale by Glasser & Campbell provides an introduction to the debate and references³⁰⁸. Figure 1 from that paper is accepted here as evidence that it is the lens (not the cornea) that is changing and not the capability of the ciliary muscle. It is reproduced in **Figure 18.8.5-2** without modification or analysis. They claim in the paper that their data explains the accommodation paradox discussed in **Section 7.3.2.1**. It shows that the accommodation range of the eye related to the lens is essentially zero after the age of 60. Thus, a determination of the basal refractive accommodation error can be easily performed for subjects in this classification without fear of error.

18.8.5.1.2 Lasik surgery as a cure for myopia

Data is beginning to collect concerning the highly successful use of laser surgery to change the profile of the cornea and thereby overcome the disease of hypometropia. The case of S. M. is illustrative.

"I was fitted with -2.0 glasses at the age of 14 although I distinctly remember that I had been having great difficulty reading the classroom blackboard since at least the age of 9. Myopia runs fairly rampant in the father's side of my family, and, as an aside, nearly all these myopes have weaker right eyes.

I was a very heavy reader during all these years and spent nearly all my waking hours in near-work. I started wearing soft contacts at the age of 18, as my myopia progressed over the years. . . .

By the age of 36, I was wearing -8.25L and -9.75R soft contact lenses. At this time I underwent Lasik surgery. My vision was corrected to 20/20R and 20/25L. This was absolutely incredible. Since I do a very large amount of computer work and reading each day, I was prescribed +0.75 reading glasses which I use for all near-work now. I have noticed that things don't look as blurry through these glasses as they did when I first started wearing them. . . .

Over the next two years, I started losing some of my sharpness of vision and decided to research the alternative vision improvement methods. My sight was at about -0.25 at day and -0.75 at night at this time. I am now 39 and have seen some improvement in my sight as a result of following some of the Bates' exercises (palming, sunning, eye exercises) and other advice on these groups."

S. M. did not quantify his early myopia. However, **Figure 18.8.5-3** plots the available data of S. M. on the previous graph. In this plot, it is assumed that S. M. was a typical myopic and the quoted values apply to the upper part of the myopic wedge. S. M. also did not appreciate completely that he was no longer myopic after surgery. Apparently, the surgeons hit their targets and reduced the optical power of his corneas by almost precisely the errors he suffered with. They left S. M. requiring negligible correction for distant vision and minimal correction for close work. That is, he was mildly hypermetropic following surgery and appears to be following a typical presbyopic profile (the short dashed line). He now requires a positive lens (not a negative lens) for close work. In the future, if his lens continues to harden, he may need a weak positive lens for far work.

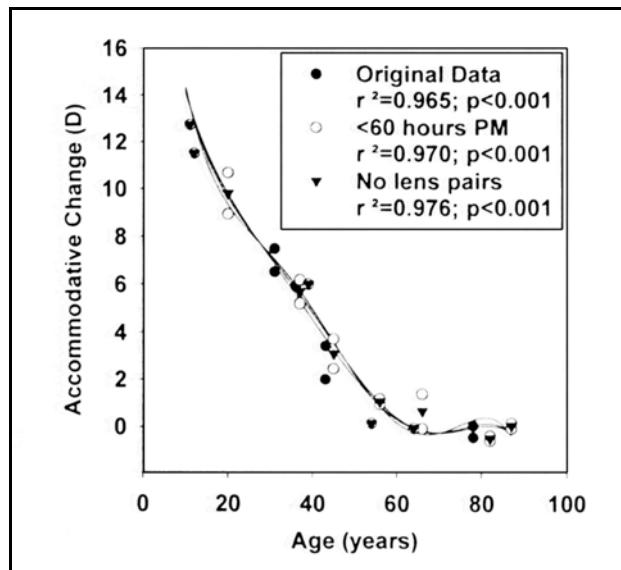


Figure 18.8.5-2 CR Change in focal length with stretching as a function of age of human lenses. From Glasser & Campbell, 1999.

³⁰⁸Glasser, A. & Campbell, M. (1999) On the potential causes of presbyopia. Vision Res. vol. 39, pp 1267-1272

18.8.5.1.3 Therapeutic treatment of refractive myopia

Curtin has dedicated a chapter to the management of myopia. He addresses both correction and methods to prevent progression in the disorder³⁰⁹. He discusses the frequently disappointing results of the various exercise and hygiene regimes proposed over the last century. Grosvenor & Flom have dedicated several pages to the subject (pp 345-350). This includes some background on the Bates Method.

18.8.5.2 Neural myopia, including amblyopia

Based on the block diagram of the analytical mode of operation of the human visual system (See **Section 15.xxx**), there are several diseases represented by errors in the lens accommodation servomechanism. These include errors in extraction of the accommodation error signal from the signals acquired at the retina (largely related to the pretectum) and errors in the transmission of the error signals back to the ciliary muscle.

18.8.5.2.1 Amblyopia

The clinical condition of amblyopia has been studied and analyzed entirely on the basis of the eye as a pixel limited imager. The eye is in fact a change detector supported by a special capability of the Precision Optical System and the oculomotor muscles. The result is a more sensitive system that gives the superficial impression of being an imager.

Amblyopia has traditionally been divided into two clinical conditions, anisometropia and strabismus. The literature associates different underlying causes to these two conditions. Levi has presented an excellent lecture on the subject³¹⁰. However, the Levi analysis depends on the eye being considered a pixel based imager and the subsequent signal processing containing a series of fixed spatial frequency, narrow-band, filters. His paper struggles with the dichotomy between the measured performance of the eye and the putative cutoff spatial frequency associated with a mosaic of stationary photoreceptors. This work concurs in his position "that the visual performance and, by inference, the underlying neural losses of strabismic and anisometric amblyopia are fundamentally different." Levi reported only on psychophysical aspects of the diseases. The specific neural signaling errors introducing these losses will be discussed in the following sections. This discussion relies upon the change detection capabilities of the eyes and tremor to avoid the need for discrete spatial frequency filters entirely. Under this hypothesis, the "grain" of the two-dimensional correlator within the pretectum is specified in terms of an "effective spatial velocity" rather than a spatial distance. This mechanism negates the need for discreet spatial frequency filters.

The effect of neural amblyopia can be illustrated using **Figure 18.8.5-4**. The figure shows the normal eye can accept a diopteric error in the physiological optics of ± 0.1 without even noticing it. The performance of the eye is normally limited neurologically to about 20/20, even though the on-axis optical system is capable of higher performance. The amblyopic limit is shown arbitrarily at 20/70. Individual cases have suggested this limit may typically be near 20/100 to 20/200. See **Section 18.3.4.1.2**.

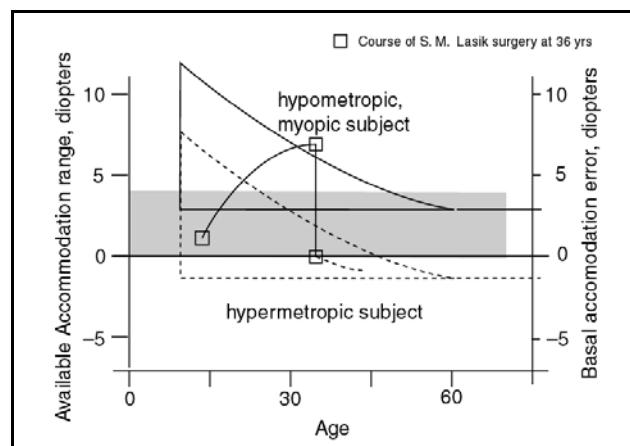


Figure 18.8.5-3 History of S. M. following LASIK surgery overlaid on the generic course of hypometropia, hypermetropia and presbyopia.

³⁰⁹Curtin, B. (1985) Op. Cit. Chapter 9

³¹⁰Levi, D. (1988) The "spatial grain" of the amblyopic visual system. *Am. Jour. Opt. Physiol. Optics.* vol. 65, no. 10, pp 767-786

18.8.5.2.2 Calibration of the amblyopia of DG

Recently the subject DG, last seen in [Section 18.8.3.6](#) has performed a double star resolution experiment of considerable interest. The experiment is reported below in unmodified form.

I have finally set up my artificial double star setup. To do this, I took a (LED) flashlight and covered the end with a card, blackened with felt pen so it completely blocks the light, and then bored two 2mm holes spaced 20 mm apart. Due to the design of the flashlight with a convex lens, when viewing the apparatus you can place your head so that the light from the two holes is either nearly equal or with one brighter than the other.

Tonight, with all the lights off, hence somewhat dark adapted, I obtained the following results. All results are as seen with my right eye, glasses on and an additional 2mm aperture stop placed behind my glasses. The two 'stars' are oriented left to right as I notice that they are easier to resolve this way - perhaps a bit of uncorrected astigmatism? they are of nearly equal brightness (which I verify with a peek through my 4x monoscope before each observation)

At 1.22 meters: two 'stars' are obvious and distinct - no challenge at all (56 arcminutes separation)

At 2.44 meters: two 'stars' are clearly visible as two separate points with wide dark space between (28 arcminutes separation)

At 3.65 meters: two 'stars' are visible, although not easily, and appear stretched in the vertical direction. dark space between stars is rather narrow compared to star size (19 arcminutes separation)

At 4.26 meters: two 'stars' have almost merged into a single horizontal strip. Intermittently a very narrow dark 'thread' is visible indicating their separation (16 arcminutes separation)

At 4.87 meters: two 'stars' appear merged into a single horizontal strip, shaped like a hyphen, but occasionally, especially when eyes are relaxed a dark flyspeck or thread appears in the middle to reveal them as separate points (14 arcminutes separation)

At 5.48 meters: two 'stars' appear merged into a single, slightly horizontally elongated dot, which is somewhat unsteady and never shows any evidence of being two separate points, except very occasionally for just an instant they look like they "want" to resolve. (12.5 arc minutes separation)

The latter parts of this report highlight the fact that the limiting resolving power of the eye involving "point sources" occurs when the two points are effectively focused on two distinct photoreceptors of the eye or are focused on points between the photoreceptors and the very fine intrinsic scanning pattern (tremor) is causing the perceived pattern to vary with time. Using DG's numbers, it is suggested that his corrected visual acuity (remaining amblyopia) during these tests was on the order of 20/65 (3.8/12.5). This value is consistent with [Figure 18.8.5-4](#).

However, DG's retina appears to exhibit normal size photoreceptors. This puts the concept of the two point sources falling on adjacent photoreceptors as unlikely. It may suggest that some of the spectrally specific photoreceptors may not be participating in the process. In the case of DG, he has poor performance in the blue-green portion of the color spectrum. This area will require additional study.

DG performed a similar test on 27 August 2008 using the moons of Jupiter which provides traceable intensity data. He used his 10X monoscope to correct for his organic myopia. [Figure 18.8.5-5](#) shows the close position of the two moons Gannymede and Callisto on the right. He claimed they were somewhat dimmer than the points created by his flashlight. He was able to resolve them clearly at 13.3 minutes of arc separation.

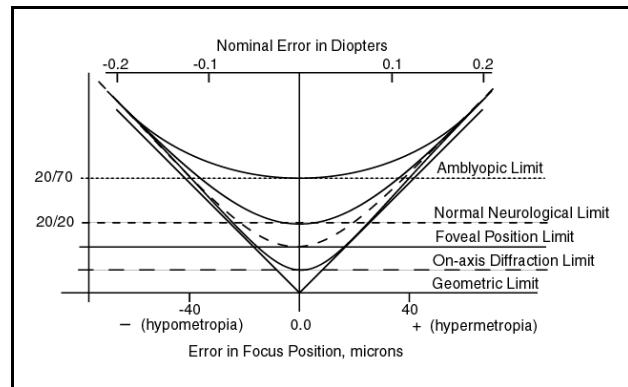


Figure 18.8.5-4 Error sources and best acuity performance available.

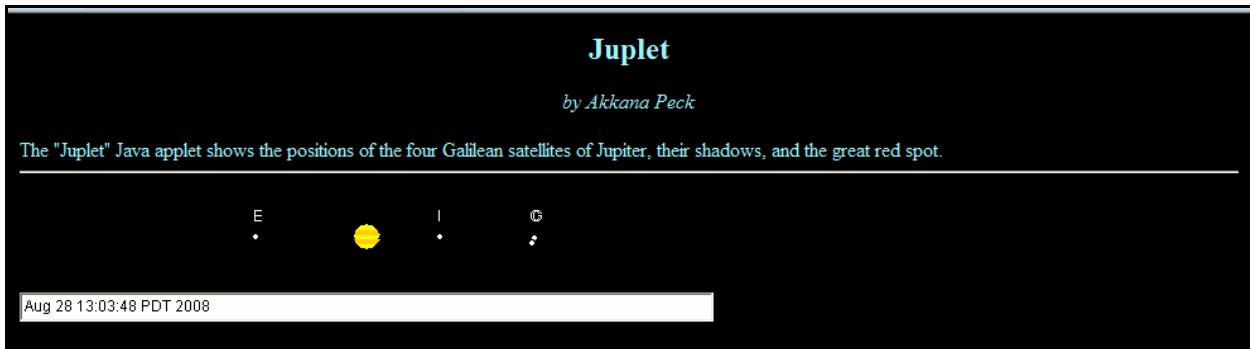


Figure 18.8.5-5 The moons of Jupiter as observed by DG on 28 August 2008. He was able to resolve Gannymede and Callisto at an effective spacing of 13.3 minutes of arc.

18.8.5.2.3 Anisometropia

As its name suggests, this is a condition of different degrees of ametropia in the two eyes. The condition can be due to either differences in the refractive state of the two eyes or due to errors in the neurological signals provided to the two oculomotor subsystems. The overall effect is that the two eyes are not focused simultaneously. The subject would be expected to routinely favor the eye achieving best focus.

Anisometropia does not specify but clinical discussion appear to usually refer to one eye being hypometropic, i. e., myopic (rather than hypermetropic) with the other eye being emmetropic (or closer to this condition).

There are several potential causes of this condition. One would be a refractive difference that cannot be corrected by a single neurological accommodation signal. This would suggest an inadequate system design since individually tailored accommodation signals would provide a greater ability to achieve an optimum accommodation condition. One error condition would involve a single signal being generated by the pretectum and an offset error being introduced into one of the commands generated in the Edinger-Westphal complex. An alternate situation would involve the generation of two signals by the pretectum with one of them containing an offset error. In this case, both channels of the Edinger-Westphal complex would be working normally. In both of the above cases, a simple offset could be replaced by a random noise source. More tailored clinical experiments should be able to determine the specific cause of this medical condition.

The effect on overall performance of both eyes simultaneously can be best characterized in the spatial frequency plane. In this plane, it can be described in terms of a low pass characteristic in addition to those due to the MTF of the optical system. The mechanism would be very similar to an aberration in the physiological optics. Levi presents the differences associated with strabismus and anisometropia using "visuograms"—i. e., a plot showing the ratio of the contrast sensitivities of the preferred to the amblyopic eye (N/A) or strabismic eye. If this ratio were inverted (A/N), the additional loss associated with the amblyopic and strabismic eye would be shown relative to the better performing eye as an MTF component. The impacts of both strabismus and anisometropia would then be multiplicative in the spatial frequency plane.

18.8.5.2.4 Flashes of clear vision

A numerically small group of subjects, primarily myopes, have consistently reported seeing scenes in better focus immediately after opening their eyes than one half to one second later³¹¹. These "flashes of clear vision" are repeatable. Interestingly, subjects reporting this phenomenon were tested for refractive error during the transient event and no changes in refraction were reported (It would be interesting to know the precision employed). The subjects say they attempt to focus on infinity before opening their eyes. For a myope, this is equivalent to going to their basal accommodation level. However, there is a problem. This experiment is suggestive of a significant computational or transmission error involving a DC offset in the analog signal before it is converted to a stream of action potentials and sent to the lens. It is necessary to define two components of the basal accommodation level, the refractive and the neural. The basal refractive accommodation level is that assumed by the physiological optics

³¹¹Grosvenor, T. & Flom, M. (1991) Op. Cit. pg 346

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of the eye. It is the level reached with the eyes closed and relaxed. Upon opening the eyes, the neural system evaluates the distance to the scene and provides an erroneous signal that constitutes the basal neurological accommodation error. The total basal accommodation level is now in error by an amount that is time dependent. It remains at the basal refractive error level for approximately 200 ms and then transitions to the total error level in another 100-200 ms depending on the light and contrast level of the stimulus. See **Section 7.3.2.1.2**.

The basal neurological accommodation error, like other neurological errors is not correctable by refractive optics, although some optometrists may attempt to compensate for it by over prescribing the refractive correction. The success of this approach is based on overwhelming the limited available range of accommodation in the subjects eye.

18.8.5.2.5 Initial transient periods of amblyopia resulting in poor acuity

The author, 80 years old and having cataract surgery on both eyes, notes two situations. The left eye achieves nominal 20/20 vision at a distance. The right eye exhibits a 0.25 diopter poorer performance and quantifiable astigmatism. Both eyes require correction of about 1.50 diopters for optimal reading.

The author routinely reads the Wall Street Journal within 20 minutes of arising in the morning under photopic conditions (either sunlight or 5000 K LED illumination). A condition is encountered roughly one day per week where the two eyes are not able to discern the text on the page (with appropriate glasses in place) even though the major and minor headlines can be perceived adequately. The condition typically clears within a few minutes and normal visual acuity is achieved thereafter.

The initial transient loss of visual acuity can not be due to loss of accommodation by either or both eyes. The initial transient loss of visual acuity is attributed to the failure of the oculomotor system to achieve appropriate tremor performance upon awakening (**Section 7.3**). The tremor performance may be limited in amplitude or frequency bandwidth (**Section 7.3.1.3**). In either case, the acuity achieved appears to be in the 20/70 to 20/200 range (see figure in **Section 18.8.5.2.1**).

18.8.5.3 Dark accommodation

While it may be intuitive that the eyes would relax to focus at infinity when in the dark (or with the eyelids closed), this is not the case. Chapter 19 of Grosvenor & Flom provides considerable data showing the eyes typically accommodate to a mean distance of between 25 and 100 cm (depending on the study). This distance can be considered the resting accommodation. However, it may be determined based on a value in short term memory related to the most common accommodation to be expected when the eyes begin imaging again. A consequence of this preprogrammed condition may be seen in the difficulty of locating a high flying aircraft against a clear sky. Unless something in the scene is found to cause accommodation to go to infinity, it may remain at a nominal value between 25 and 100 cm indefinitely, and the aircraft will not be imaged.

The dark accommodation level should be differentiated from the basal accommodation level defined in this work, where the subject is attempting to focus at infinity.

18.8.6 Vergence and other oculomotor errors

Many of the problems addressed in this section can be defined in considerable detail based on the electrolytic theory of the Neuron. However, in most cases, medical science is not yet able to provide a cure to the problem.

The literature frequently groups strabismus (a stable error in vergence between the two eyes) and amblyopia (a residual loss in visual acuity after correction prostheses have been provided, **Section 18.8.5.2**). However, the more sophisticated studies suggest separate causes for these conditions. Siepmann, Reinhard & Herzau have provided a paper illustrating the interplay between these two conditions as well as their independence in some cases³¹². They assert that strabismic amblyopia is always unilateral. They defined three types of strabismic amblyopia.

18.8.6.1 Strabismus

³¹²Siepmann, K. Reinhard, J. & Herzau, V. (2006) The locus of fixation in strabismic amblyopia changes with increasing effort of recognition as assessed by scanning laser ophthalmoscope *Acta Ophthalmol Scand* vol 84, pp 124-129

Strabismus is the pathological failure of the two eyes to converge on a given target in the visual field. It is found in horizontal, vertical and torsional situations. Functionally, Strabismus can be considered a stationary form of nystagmus. It involves the failure to achieve normal convergence by the two eyes when observing a scene at a given distance. As shown in **Section 18.8.6.2.3**, the convergence mechanism can introduce an error in the signals provided to the two eyes. This error may contain a DC offset, and result in strabismus, or it can contain an AC term, resulting in a continually varying error in convergence with time. The mechanism appears to employ two input signals in the preparation of the vergence commands. One coarse signal appears to be created in the LGN in the process of merging the peripheral and foveal fields of vision. A second fine signal appears to be created in the pretectum, using the coarse signal as a starting point. This fine signal is required to point the eyes with an accuracy of less than a fraction of a pixel diameter on the retina (on the order of 6-10 arc seconds). As in the case of nystagmus, at very small error values, strabismus may be a considered a form of or contribute to amblyopia.

18.8.6.2 Nystagmus

Nystagmus is used variously to describe both normal and pathological conditions related to the oculomotor system. The normal conditions include the ability to hold fixation on a stationary scene for sufficient periods of time without the eyes making uncontrolled large or small saccades. Pursuit nystagmus, generally not exhibited until several month post-partum in humans and probably learned, is the ability to maintain the image of a smoothly moving object on the point of fixation of the retina. If the velocity of the moving object is too large, the eye will fail in this endeavor and adopt optokinetic nystagmus. Optokinetic nystagmus allows the eye to track successive points in a continuously moving scene. It is characterized by a slow component of angular movement matched to the velocity and direction of scene movement during observation and a fast component in the opposite direction as the line of fixation jumps to a different location in the scene. This appears to be a learned capability in man. Each of the above types of nystagmus involve different amounts of computation within the brain to maintain the image on the foveola. For the moving scenes, the computations involve a predictive element. This element is related to the derivative of the angular motion of the scene in inertial space relative to the eyes, head and/or body. Sometimes computations are required to prepare commands for angular movement of each of these bodily components relative to the others. Errors in these calculations can result in a variety of unusual body movements related to pathological forms of nystagmus.

The pathological conditions of nystagmus can be associated with failure to maintain nominal performance in the above tasks. The nature of nystagmus has remained enigmatic to this day based on the conventional wisdom³¹³. Dell'Osso & Darnof have begun to describe nystagmus from a functional perspective, using terms like high gain instability, vestibular tone imbalance and integrator leakage. When addressed in terms of the actual circuit diagrams of the visual system, these terms can be quite useful. They will appear below in slightly different nomenclature. Gross nystagmus can be described as a pathological condition involving an uncontrolled oscillatory movement of the axes of the eyes during which the amplitude of oscillation is tens of hundreds of times greater than the amplitude of the tremor, while the frequency of the nystagmus is tens of times lower than the frequency of the tremor. (Yarbus pg 120) More broadly, it can be described as any uncontrolled or oscillatory movement of the body or eyes in the process of attempting to maintain a line of fixation on a fixed or moving scene element. Under this broader definition, the source of the problem is frequently traced to the neurons of the superior colliculus used to generate commands to both the oculomotor subsystem and the general skeletal motor subsystem. These commands rely upon the vestibular subsystem for critical reference conditions related to the motions being experienced by the head and a short term memory to explain which of those motions were instigated by the subject internally. If the internal memory does not agree with the references provided by the vestibular subsystem, the subject is subject to vertigo. If information from the eyes is able to correct these inconsistencies, the vertigo may be suppressed.

Based on the above broader definition and description, and the schematics diagram of the oculomotor system in [**Sections 15.2.4 & 15.2.5**], the source of many of the forms of nystagmus listed by Glaser can be more clearly defined. Note that the figures in the above section are only shown for one of the two orthogonal planes parallel to the line of fixation of one eye. The eyes are also capable of limited rotation about the line of fixation via the oblique muscle system. While the signal paths between the LGN and the pretectum, related to vergence, are not shown in [**Figures 15.2.5-1 & -2**], they are shown in [**Figure 15.2.5-3**]. Note that the latter figure also shows an input from the auditory subsystem. These diagrams are in total disagreement with "A hypothetical scheme for the cortical control of saccades" discussed in connection with his figure 10-4 and credited to Pierrot-Deseilligny, et. al³¹⁴. Most

³¹³Dell'Osso, L. & Daroff, R. (1999) Nystagmus and saccadic intrusions and oscillations. In Glaser, J. ed. Neuro-ophthalmology, 3rd ed. pg 369

³¹⁴Pierre-Deseilligny, C. Gaynard, B et. al. (1995) Cortical control of saccades. *Ann Neurol.* vol. 35, pg 557+

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of the pointing operations related to the eye are autonomous and performed within the POS (which does not include areas of the cerebrum). Only those pointing operations commanded by the engines of the cerebrum (labeled volition movements here) involve the cerebrum.

When discussing nystagmus, the terms circular, pendular, oscillatory, etc. are references to observed errors most notably associated with errors in the gain parameters of the closed-loop servomechanisms serving the affected eye muscles. These gain errors can be aggravated by a discontinuity in the initial stages of the loop which create the necessary reference signal for the loop. They can also be caused by a significant phase error within the loop. Such errors in vision are usually associated with an inappropriately long signal processing time within one of the engines processing the servomechanism signals. Once the rates of motion are measured, the source of these errors can be quantified using a Bode Diagram. Similarly, when the terms diagonal, circular, elliptical and oblique are used, these are frequently caused by errors early in the individual servo-loops where the reference signals are created. They are suggestive of errors in the superior colliculus since it is there that a common signal is formed that should be separated into components driving the individual oculomotor muscle groups of the eye. Failure to separate the signals into the correct components will result in synchronous movement by two or more muscle groups (either in phase or out of phase).

Using the above material, nystagmus can be divided into a group of functional types based on observation that relate to specific signal paths within the visual system. They can then be further subdivided and assigned characteristics associated with pharmacology, hereditary and ontogenesis if appropriate. Using the following material and the discussion in Dell'Osso & Daroff, concerning the recording of eye movements, nystagmus can be defined to a finer degree than previously³¹⁵. Note that recording down to levels below one arc minute amplitude will be necessary to diagnose some nystagmatic conditions approaching amblyopia (and generally associate with poor reading skills).

18.8.6.2.1 Nystagmus associated with and limited to one eye

These types of nystagmus can be generally associated with neurological failures in the superior colliculus, the oculomotor nuclei and any neurological nodes between the nuclei and the eye muscles associated with the affected eye. Such errors can induce horizontal, vertical or rotational nystagmus. There are several types of failures. Total failure of the eye to move in response to movements in the scene suggest disruption of the neural pathway near the oculomotor muscles. Continual random movements of the eye suggest a failure in the summing/switching circuit where the signals from the vestibular subsystem are combined with the preliminary command signal to form the complete signal. Such movements are common in a disrupted closed-loop servomechanism that has lost its input signal. The motions may be pendular or oscillatory depending on the gain of the remaining functional part of the servomechanism.

A failure of the one eye to track an object “looking straight at it” may suggest several causes, a displaced foveola, either physically or neurologically, an abnormality in the appropriated ocular muscles, or a DC bias error in the appropriate oculomotor servomechanism. These types of errors can be identified in the clinic without undue difficulty.

18.8.6.2.2 Nystagmus associated with both eyes

One of the primary requirements of good vision is the convergence of the lines of fixation of the two eyes onto a common point in object space so the images projected on the two foveola can be processed (largely) as one image. Although not well documented, it appears there are two convergence error signals presented to the convergence servomechanism . One is a coarse signal obtained from the LGN, probably from the magnocellular (luminance channel) region. The LGN has an advantage in creating this signal because of the mechanical leverage of using signals from areas in the fovea and inner peripheral retina. Once this signal is used by the superior colliculus to form the appropriate pointing signals that include a convergence component, there may be a second signal generated by the pretectum. The desired convergence accuracy is better than a fraction of the diameter of a single photoreceptor within the foveola. This can be achieved within the two-dimensional correlator of the pretectum without difficulty based on its edge detection capabilities. Thus the pretectum is able to provide a fine convergence signal to the superior colliculus to use in the calculation of the final convergence signals. As noted elsewhere, in many repetitive tasks, the superior colliculus calls on temporary memory to provide initial convergence signals related to a given scene.

³¹⁵Dell'Osso, L. & Daroff, R. (1999) Nystagmus and saccadic intrusions and oscillations. In Glaser, J. ed. Neuro-ophthalmology, 3rd ed. chapter 11, pp 369-380

A failure of the eyes to converge adequately based on the fine convergence signal may be very difficult to notice in the clinical situation. The magnitude of the motions involved are very small. The amplitude of these motions may be less than a minute of arc. In this situation, the diagnosed or reported symptom may be the same as in amblyopia.

Errors in convergence associated with both eyes are traceable to the LGN or the pretectum. They may be further isolated if the errors vary significantly in magnitude. Failures to achieve convergence are more likely traceable to the superior colliculus or to the neural paths from the LGN or pretectum to the superior colliculus.

18.8.6.2.3 Nystagmus associated with both eyes and other associated sensory systems

There are a broad range of nystagmatic conditions observed clinically in association with other sensory or motor subsystems. As noted earlier, the oculomotor commands are created in combination with a series of optional head and skeletal motor commands in order to control the line of fixation while the body is performing other tasks. These complex computations introduce the possibility of errors affecting the line of fixation but not due solely to the visual subsystem. As in the case of simple motions relating to the two eyes, temporary memory and other sensory channels (such as the auditory and somatosensory systems for alarm signals) are continually relied upon to calculate the desired oculomotor commands in the presence of other bodily activity. If the signals presented to the superior colliculus are not processed properly, a large group of induced nystagmatic conditions can result.

Signals from the above associated systems can be presented to the superior colliculus with errors in amplitude or time delay. The results can be observed clinically as eye movements not associated directly with vision. Many of these signals are alarm signals that are defensive in nature and designed to override the normal operation of the eye. If they override the normal operation unduly or unexpectedly, they are considered a disease.

18.8.6.3 Meares-Irlen syndrome

While nystagmus and strabismus are large signal errors within the oculomotor servomechanism, a series of small signal errors have been described by Meares³¹⁶, and somewhat later by Irlen³¹⁷. The large signal problems were first described in a clinical optometry setting. The small signal problems were described as a result of psychologists exploring reading problems.

Meares first reported improvements in reading ability in dyslexic individuals when glare was reduced by covering the text with colored overlays. Irlen extended the discussion to include a constellation of imaging problems and proposed that the use of colored transparent overlays aided the subjects. The methodology is explored in Wilkins³¹⁸. It is clearly exploratory in nature. Color filters are generally selected from a circle about the white point on the CIE 1975 UCS (u' v') color space. There may be an editorial problem in Wilkins. His figure 9.11 reports on the per cent reflectance of the filter samples. Of more relevance is the transmission factor of the filters. Where he shows 100% reflectance, such as in his yellow example, no light would reach the subject from the underlying page. It is likely his measurements represent the per cent transmission of the samples. Simmers, et. al. have recently explored the subject systematically and found the use of overlays statistically insignificant in their trials³¹⁹. They did not explore the psychological aspects of the method. Wilkins reports an extensive but largely unscientific literature exists concerning color in sunglasses and a recent resurgence in activity related to dyslexia.

The use of colored filters in the optical path of the visual system is compensated for by the adaptation system within a few seconds. After adaptation, the subject will still see a checkered table cloth in its correct colors, including white. The major effect of the colored filter is to lower the contrast slightly in the luminance, R, channel associated with non-foveola vision. It has little effect on the signals from the photoreceptors of the foveola since they are not processed like the more peripheral photoreceptors. As long as the illumination of the reading material is in the photopic range, the effect on the spatial analysis performance of the subject should be minimal to negligible due to using colored filters.

Irlen has established a website that attempts to characterize her constellation of imaging problems³²⁰. The dominant

³¹⁶Meares, O. (1980) Figure/background, brightness/contrast and reading disabilities *Visible Language* vol 14, 13-29

³¹⁷Irlen, H. (1991) *Reading by Colours*. NY: Avery

³¹⁸Wilkins, A. (1995) *Visual Stress*. NY: Oxford University Press pp 132-158

³¹⁹Simmers, A. Bex, P/ Smith, F. & Wilkins, A. (2001) Spatiotemporal visual function in tinted lens wearers *Invest Ophthal Vis Sci* vol. 42, no. 3, pp 879-884

³²⁰http://www.irlen.com/index_sss.html

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themes of these simulation are the double imaging and the displacement of lines of text. Both of these phenomena are associated with errors in the version servomechanism. Although not explicitly addressed, it is likely that subjects with these problems may also report depth perception deficits. Differentiation between these two diseases would further aid in localizing the source of the problem. Although Arlen has associated this syndrome with the scotopic sensitivity of the visual system, this label appears inappropriate. Wilkins agrees the term is inappropriate (pg 132). This syndrome is not directly associated with the scotopic illumination range or the mechanisms in the visual system that relate to scotopic vision.

Most of the examples can be accounted for by errors within either or both the vertical and horizontal version servomechanisms (See Sections 7.3 & 7.4). These errors can be localized as shown in **Figure 18.8.6-1**. Note that the figure only shows the servomechanisms as a group. It does not separate the vertical and horizontal version and/or vergence circuits. However, it highlights the most likely error sites, beginning with the semicircular canals and the vestibular system and including the LGN and PGN. The shaded path to the magnocellular portion of the LGN may extend on back to the parasol ganglion cells of the first luminance processing matrix.

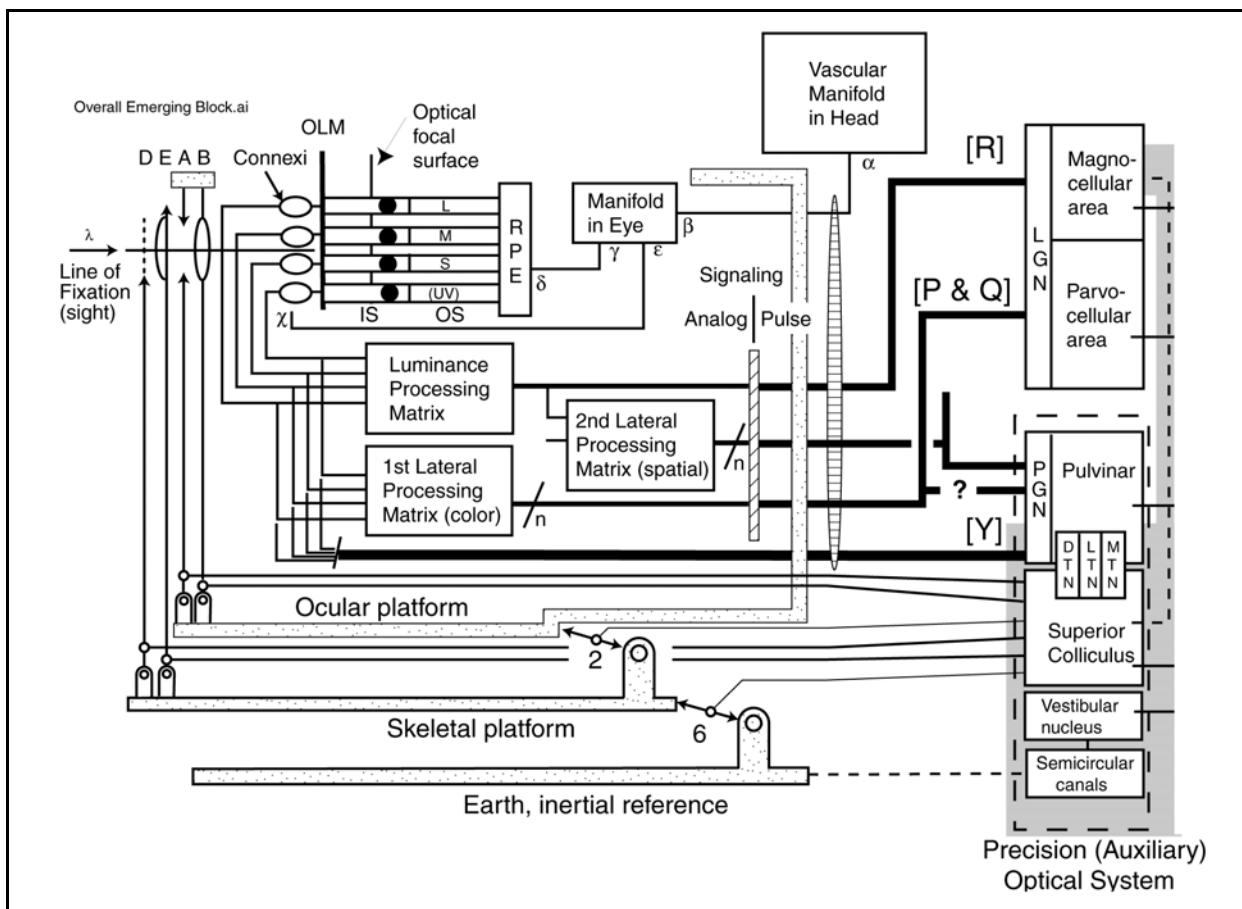


Figure 18.8.6-1 Error sources associated with Meares-Erlin Syndrome. The shaded area indicates the likely location of the signaling errors within the oculomotor servomechanism of the visual system.

18.8.6.4 Servomechanism errors and role of L-Dopa

Besides errors in the performance of individual circuits, there are cumulative errors more easily described in terms of the overall performance of the servomechanism of vision (and also the skeletal-motor system). These errors result from an accumulation of phase shifts that can lead to oscillation. They are generally described in terms of a Bode Diagram in linear servomechanism theory. In sampled-data systems, the situation is more complicated and it is usually described by reverting to the underlying Nyquist Diagram.

The situation often found in Nystagmus, as well as Parkinson's Disease of the motor system, is summarized in Truxal; "If the cutoff frequency [of the linear circuits] is higher [than the sampling frequency], the smoothing properties of the system are poor, and the output waveform is not a smooth function but instead changes rapidly in the vicinity of the sampling instants."³²¹ The system tends to oscillate at a frequency in the vicinity of the sampling frequency. To calculate the specific frequency of the oscillation requires detailed knowledge of the completer servomechanism, including any internal local loops associated with specific circuits. Such detailed knowledge is not yet available about the oculomotor system.

18.8.6.4.1 Experience in man-made systems

Several points concerning such servomechanism oscillations can be drawn from experience with man-made systems. Such oscillations near the sampling frequency are frequently described as "hunting" in tracking systems and as "motor boating" in audio systems. In a well designed system, these effects are usually found to be due to aging of the power supply components. A particular problem is the loss in performance of the low pass filter in the power supply. As a result, the impedance of the power supply becomes higher with age and an inherent tendency to oscillation becomes more apparent. The same tendency to oscillate can also appear due to changes in the power supply impedance due to other causes than ageing. In man-made systems, the tendency to oscillate can be suppressed by increasing the time constant of the power supply circuit. This can be done by increasing the value of either the filter capacitive or resistive impedance.

18.8.6.4.2 Similar degradations in biological systems

With the dispersed nature of the power supply circuits of the neural system, it is difficult to isolate a particular cause of oscillation in a given system. However, as noted above, the phase error resulting in a tendency to oscillate is a cumulative one. The error is typically due to a decrease in the time constant of the hydraulic circuit providing reactant (glutamate) to the electrostenolytic sites. This can be thought of as a reduction in the size of the available pool of glutamate at an electrostenolytic site relative to the demand for glutamate to maintain the potential of the related plasma. Several medical solutions are theoretically available. The obvious solution is to increase the availability of glutamate at the site. The other solution is to restrict the demand by raising the impedance of the electrostenolytic process itself. This can be done by reducing the effective area of the electrostenolytic site.

18.8.6.4.3 Role of L-Dopa in alleviating servo-motor diseases

L-Dopa has been found to be particularly effective in treating oscillatory tendencies in the motor system. It has been effective in applications involving both the peripheral and central nervous systems. The moving narrative by Oliver Sacks concerning patients suffering from a form of Parkinson's disease known as sleeping sickness, *encephalitis lethargica*, makes compelling reading³²². It demonstrates the major impact of L-Dopa on both the motor and intellectual aspects of the neural system. It should be noted that Sacks administered L-Dopa on a global basis based on ingestion. This global application led to a wide variety of side effects and eventual complications that suggested other regimens were needed. The following material will suggest other pharmaceuticals that may affect the neural system more efficiently than global treatment with L-Dopa.

There are references in the literature that suggest that L-Dopa can pass from the blood stream into the CNS without difficulty. Through this ability, L-Dopa is able to affect the oculomotor system as well as the more remote PNS neural systems. However, the fact that **Sacks required dosages measured in multiples of full grams per day** to achieve significant results suggests L-Dopa does not pass easily through the blood-brain-barrier. Zillmer & Spiers address the use of L-Dopa in the current time period³²³, noting the use of a decaboylase inhibitor can raise the amount of L-Dopa passing through the blood-brain-barrier before it is converted into dopamine which does not pass through this barrier readily. They also review the significant side effects associated with this drug.

The primary question is how does L-Dopa affect the neural system.

While biological electrostenolytic systems have not been widely studied, they involve a substrate and the accumulation of specific chemical(s) on that substrate. The *in-vivo* specificity is almost always due to stereo-

³²¹Truxal, J. (1955) Automatic Feedback Control System Synthesis. NY: McGraw-Hill pp 527-528

³²²Sacks, O. (1999) Awakenings, latest edition. NY: Vintage Books

³²³Zillmer, E. Spiers, M. & Culbertson, W. (2008) Principles of Neuropsychology, 2nd Ed. NY: Barnes & Noble pp 59 & 391-392

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chemical relationships between the substrate and the target chemical. In the case of the normal electrostenolytic mechanism, the chemical glutamate is attached to the substrate in such a way that it can release CO_2 in the process of becoming GABA. **Figure 18.8.6-2** explores the stereo-chemistry of the glutamate family associated with electrostenolysis further.

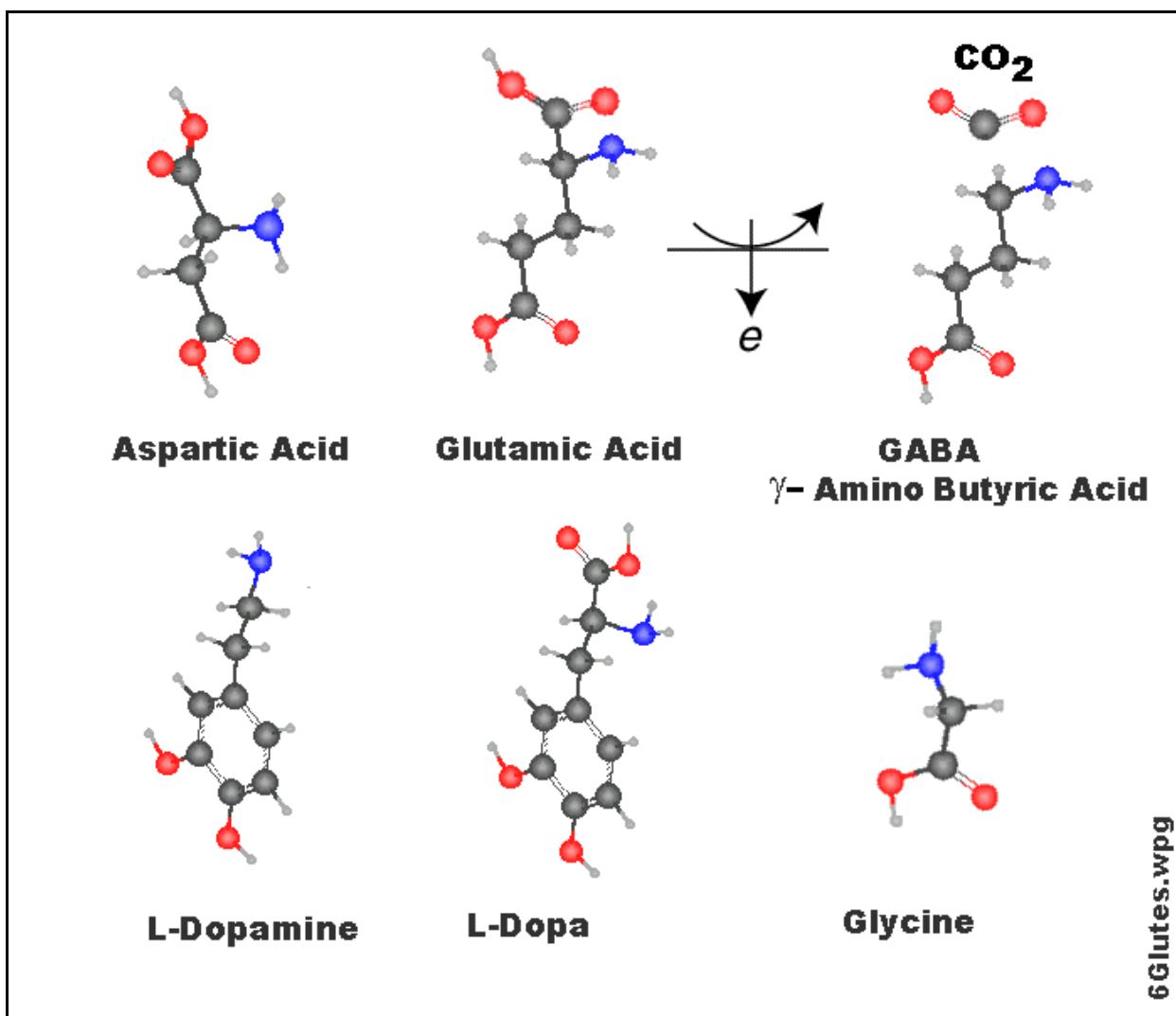


Figure 18.8.6-2 The stereo-chemistry of the glutamate family. All of the chemical shown are amino acids. Both aspartic and glutamic acids are negatively charged in the form shown. The normal electrostenolytic process of powering the neural system is represented by the symbol at upper right. See text for a discussion of the features of the other materials.

The normal electrostenolytic process powering biological neurons is shown by the symbol at the upper right and discussed in **Section 7.7.2**. Glutamic acid is decomposed into GABA and carbon dioxide while simultaneously transferring an electron through the lemma forming the substrate. GABA is a butyric acid that no longer exhibits an amino acid group at the α -carbon (based on the standard naming convention). The name is misleading to the casual reader. Amino is used as an adjective describing the presence of an amine group attached to the gamma carbon of butyric acid. In this form GABA does not qualify as an amino acid based on a strict structural interpretation. At best, GABA is an isomer of valine, a non-polar amino acid. The decomposition of the amino acid group of glutamate in the electrostenolytic reaction would suggest this group was not involved in the associated stereochemical mechanism attaching glutamic acid to the substrate.

If the amino acid group is not involved in the stereo-chemical relationship with the substrate, several observations

can be made. Three other chemicals are shown in the above figure (omitting L-dopamine for the moment). They are all known to impact the performance of neurons when applied topically. They all contain a similar structural form at their non-amino end, particularly if the L-Dopa is shown in an ionized form. In addition, if the resonant group in the L-Dopa can be considered equivalent to two carbon atoms in series, its ionized structure becomes chemically identical to that of glutamic acid (although some bond angles may be different). This similarity would suggest that the carboxyl group at the end of each of these molecules can form a stereo-chemical relationship with the substrate. Under this assumption, several other features become important. First, Aspartic acid is known to be an effective stimulant to nervous activity, particularly *in-vitro*. It appears that, although aspartic acid has one less carbon than glutamic acid, it can participate fully in the electrostenolytic process. Instead of GABA, the resulting reaction would produce β -alanine. While β -alanine might be a satisfactory reactant *in-vitro*, its hydrophobic character might cause problems *in-vivo*.

Glycine is typically found to retard nervous activity. Because of its stereo-chemical configuration, it appears glycine could form a stereo-chemical bond with the substrate. However, it could not disassociate and release carbon dioxide. Therefore, it would clearly hinder the electrostenolytic process by occupying stereo-chemical sites on the substrate. Alternately, the presence of high concentrations of glycine might inhibit the diffusion of GABA away from the substrate.

The role of L-dopa is of particular significance because of its known medical value. L-dopa is known to reduce the physical oscillations associated with Parkinson's Disease. It appears that it can do this by replacing glutamic acid in the stereo-chemical relationship with the substrate and then impact the electrostenolytic reaction in one of several ways. First, it could participate in the complete reaction, including the injection of an electron into the plasma of the cell. If it took longer than glutamate to complete the reaction and release from the substrate, this would have the effect of raising the impedance of the power source of the neuron, and thereby damp the tendency of the associated servomechanism to oscillate.

Second, the size of the L-dopa molecule might shadow the adjacent sites of the stereo-chemical substrate. In this case, L-dopa would slow the rate of electrostenolytic reaction at the substrate, whether it participated in the reaction or not. If it did not react and release from the substrate, L-dopa could impact the performance of the associated neuron (and thereby the associated servomechanism) for some period of time. This may be one of its features when used medicinally.

L-dopa is normally prescribed in massive dosage, 1-8 grams/day. This volume would suggest two conditions. First, L-dopa does not pass from the vascular system to the brain easily. Second, what does pass into the neural system of the brain is consumed in the electrostenolytic reaction powering the neurons.

McGeer, et. al. note that in about 15% of cases, L-Dopa will produce agitation, excitement and even psychosis, presumably from stimulation of receptors in the cortex or limbic system. They also note that the compound carbidopa is useful in controlling the concentration of L-Dopa by location. Carbidopa is a cyclic compound that does not cross the blood/brain barrier. It can only inhibit the decarboxylation of L-Dopa in the peripheral nervous system. Thus the effective ratio of L-Dopa applied to the peripheral and central nervous systems can be controlled in one direction. Puil offers an alternate structure for carbidopa, which he labels cycloglutamic acid, that isolates the carboxyl group from the ring structure and is more compatible with the stereochemical requirements of the electrostenolytic substrate.

Note the potential for L-dopamine, a naturally occurring species frequently found associated with neural tissue. While it is unable to participate in a stereochemical reaction requiring the presence of an amino acid configuration, it can be modified to such configuration (L-dopa) by the addition of a carboxyl group. L-dopamine, as a precursor to L-dopa, can potentially participate in the same reactions induced by the clinical introduction of L-dopa. Thus, the control of either L-dopamine or the carboxylation of L-dopamine may be important in controlling the stability of the neural system.

Serotonin has also been found medically effective in treating some patients with various aura, including snowy vision. It occurs naturally in the blood. Serotonin has a stereochemical configuration consisting of two rings instead of the one ring of L-dopamine. If carboxylated, serotonin would also exhibit the stereo-chemistry of the amino portion of L-dopa. When carboxylated, it could be expected to interfere with the operation of the glutamate to GABA conversion just as L-dopa does.

The carboxylation of both L-dopamine and serotonin could be accomplished by the same or similar process to that routinely performed in the glutamate shunt of the citric acid cycle supporting neuron operation.

18.8.6.5 The larger role of pharmacology in neurology

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Puil has provided an extensive review of the pharmacology associated with neuron operation³²⁴. Bradley has provided an introductory text on Neuropharmacology that fails to appreciate how most pharmaceuticals actually affect the nervous system³²⁵. It should not be relied upon. His statement in the introduction to Chapter 4 has led to considerable ridicule. It is shown here with the strikeout form added. “~~There are no synapses outside the central nervous system (CNS) so the only peripheral junction is the neuroeffector junction with the muscle cell, the neuromuscular junction.~~”

18.8.6.5.1 The temporary effect of Zyprexa on color vision

An optometrist, Sandra Jones of Lincoln, Ill., has recently reported the case of a male subject who was diagnosed and evaluated as red-green color blind. Following a psychotic episode, he was hospitalized and prescribed the strong psychotic drug, Zyprexa (olanzapine). Zyprexa is approved for the treatment of schizophrenia, acute bipolar mania, and bipolar disorder.

Lilly was recently involved in a lawsuit wherein it agreed not to promote Zyprexa in connection with Alzheimer's disease. It had not obtained approval to use the drug in connection with that disease.

Following administration of Zyprexa, the subject regained normal red-green color vision for an interval sufficient for a confirming evaluation after discharge from the hospital. With time, his red-green colorblindness reappeared. Several years later, the cycle was repeated but apparently without further visual evaluation.

Zyprexa has been reported to cause unspecified visual side effects. It is also recognized as antagonizing the effects of levodopa (L-dopa) and dopamine agonists. It can also affect the control of glucose in the system. It is a sulphide containing pharmaceutical as shown in **Figure 18.8.6-3**. Its structure does not suggest it can occupy a receptor site in place of L-dopa (or glutamate). It is likely it affects the availability of L-dopa in the vicinity of the glutamate receptor sites. These sites are frequently reported to be occupied by L-dopa within the CNS.

18.8.6.5.2 Probable action of Zyprexa in relation to red-green colorblindness

Red-green color blindness may result from a variety of abnormalities in the visual system. It can be best understood using the block diagram of **Figure 17.1.4-1** and the table in **Figure 18.1.5-5**.

Red-green colorblindness may be caused by protanopia (the failure of the L-channel chromophore generating mechanism to be formed prenatally). This condition is more common in men. It is frequently suggested that it is caused by a fever in the mother during pregnancy. It is epitomized by the subject equating red with black in most visual situations. Protanopia results in induced deuteranopia because of the lack of one required signal at the input to the differencing (horizontal) neurons of the retina. This results in failure to create a meaningful Q-channel signal.

Deuteranopia involves the loss of perception via the Q-channel of vision (one of the two chrominance channels within the neural system). Intrinsic deuteranopia can be caused by anomalies anywhere in the visual system beyond the outer segments of the photoreceptor neurons. Intrinsic deuteranopia is epitomized by most subjects seeing red objects as bright but colorless objects. Some subjects may report any object normally associated with the red-orange-yellow-green spectrum as yellowish compared to other objects which appear bluish or purplish.

18.8.7 Visual symptoms related to Alzheimer's Disease

Alzheimer's Disease is associated with a series of visual symptoms that are progressive. The frequently noted early

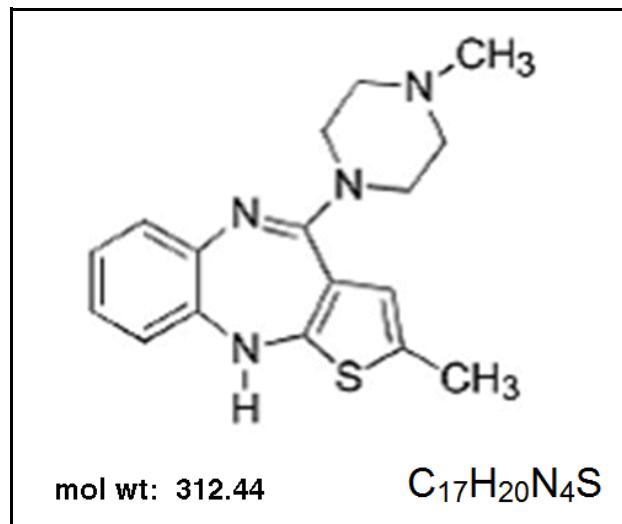


Figure 18.8.6-3 The chemical structure of Zyprexa (olanzapine). From the Lilly data sheet.

³²⁴Puil, E. (1981) S-glutamate: its interactions with spinal neurons *Brain Res. Rev.* vol. 3, pp 229-332
(Section 4.2 specifically)

³²⁵Bradley, P. (1989) Introduction to Neuropharmacology. London: Wright

visual symptom is the inability to recognize close friends and familiar objects and an apparently uncomprehending stare. The disease frequently terminates with the subject in a state of blindness due to the total failure of the tremor mechanism of the eyes. Such patients may respond to moving objects under some circumstances. However, their other cognitive facilities are usually greatly impaired by this stage.

The primary cause of visual failure related to Alzheimer's Disease relates to the tremor (microsaccades) and minisaccades generated by the POS. The failure to recognize familiar objects is caused by the failure of the analytical functions of the POS feedback loop to provide correlated vertical and horizontal microsaccades to the twitch portion of the oculomotor system. In the absence of these signals, the more primitive parts of the POS will generate essentially random signals that can be used by the oculomotor twitch system to insure motion of scene elements across the photoreceptors of the retina. The photoreceptors will continue to forward signals to the thalamus. However, the PGN and pulvinar will not be able to decode this information in order for the analytical mode of vision to recognize objects. The situation will resemble the condition where a normal person "stares off into space."

As the subject continues to degenerate, a point will be reached where the subject will begin to lose vision altogether. This is caused by the failure of the perturbation generator nerves to generate any microsaccades of sufficient strength to cause any microsaccades (tremor) to activate the twitch muscles of the eyes. Under those conditions, the subject will be able to see motion introduced artificially into his visual field. However, the effect will be that he will only see contrast edges. This condition in a more healthy person is described as seeing ghosts moving in their visual field (a form of blindsight).

During the later period, the eyes of the subject will appear as in a dead person. The loss of tremor causes the eyes to appear in higher contrast by an observer, and they will appear to stare aimlessly unless sufficient stimulus is introduced to distract them via signals reaching the POS.

18.8.8 Epilepsy and other neural conflict diseases

Section 15.2.xxx has illuminated new relationships that appear to be relevant to the understanding and possible treatment of epilepsy and other disorders involving conflicts between different parts of the brain. Historically, it has been assumed that the corpus callosum, the large group of commissure connecting the two parts of the brain, was the principle neural path based on morphology. As shown in the above section, recent research has begun detailing another corpus of smaller size but potentially greater importance. The corpus principia is part of the internal capsule connecting the two halves of the thalamus, a major component of the diencephalon. This corpus provides a pathway for exchanging abstract (machine language) signals between the two symmetrical portions of the thalamic reticular nucleus, TRN. These nuclei, the TRN, are proposed to be the fundamental control point for the exchange of signals within the brain. Normally, they exchange signals processed by other areas of the nervous system. These areas include the feature extraction engines in the parietal, temporal and occipital lobes of the cerebral hemispheres. Many of these areas communicate with their mirror image via the corpus callosum in order to prepare a coherent picture of their portion of the external environment. There are significant time delays between these various engines and the TRN. Because there are two similar signal paths between the various engines of the two hemispheres, it is possible for the signals to cause a conflict when they arrive at certain points. The result can be oscillatory conditions with regard to the implementation of commands issued by the anterior lobe and/or implemented by the motor system under TRN control. This is typically called a race condition. It appears to be the fundamental condition underlying many epileptic, and possibly some Parkinson type, conditions.

18.8.9 Other diseases of the visual system

A large class of diseases of vision are recognized in the clinical environment. Frequently however and particularly before the turn of the 21st Century, the symptoms of these diseases are only conceptually related to the underlying causes.

Macular degeneration is a particular example of a poorly defined disease. It is more appropriately designated a syndrome encompassing a wide variety of symptoms and historically identified by ophthalmological observation. Frequently, the underlying cause of the problem is some form of arteriosclerosis/atherosclerosis occurring in the arteries of the eye. This condition can be clarified by comparing the observed necrosis of the photoreceptors with the mapping of the arterial flow serving both the neural tissue and the RPE tissue associated with the retina.

The above mapping will frequently indicate that foveola degeneration is not due to retinal conditions but to neural problems within the CNS.

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Merin has noted on page 11, "Often two or more genotypes lead to the same abnormal phenotype." This is the situation encountered in many diseases labeled either retinitis pigmentosa or macular degeneration. The same situation is encountered in many other diseases of the visual modality, particularly those involving the photoreceptors and mislabeled by the ophthalmology community.

In 1991, Hargrave & O'Brien³²⁶ described, "Retinitis pigmentosa as a group of diseases characterized by night blindness and loss of mid-peripheral visual field. Progression of the disease may result in complete loss of photoreceptor cells in the retina. Retinitis pigmentosa is genetically heterogeneous and is caused by mutant alleles at a variety of loci with the human genome." The definition is obviously quite limited.

The linking of the diseases of vision to their underlying cause(s) is at the beginning of a revolution based on the recent introduction of computerized imaging systems for examining the in-vivo neural system. As noted in **Section 18.1**, the pedagogical view that diseases of vision can be satisfactorily observed with an ophthalmoscope is truly and terribly archaic. The advent of computer-aided optical coherence tomography (OCT) has caused a revolution in the ability of an ophthalmologist to observe what is actually going on within the layers of the retina. The use of CAT, PET and various MRI imaging systems have allowed the crude (from a spatial and temporal resolution perspective) imaging of the neural responses to visual stimulation.

Although difficult to adhere to, due to the way diseases have been observed and named in the past, this work will seek to categorize diseases according to the definitions in **Section 8.6.1.2.5**, specifically for the following terms;

Dystrophy— The degeneration of tissue, due to disease, malnutrition or genetic inheritance.

Neuropathy— Any of numerous *functional disturbances and pathologic changes* in the peripheral nervous system. The term is also used to designate noninflammatory lesions in the peripheral nervous system, in contrast to inflammatory lesions (neuritis).

Neuritis— Inflammation of a peripheral nerve or nerves, usually causing pain and loss of function.

Neuralgia— an intense burning or stabbing pain caused by irritation of or damage to a nerve.

Note the progression in terminology beginning with the very general term dystrophy; neuropathy typically relates to a functional problem (which may or may not be associated with subsequent pain), neuritis typically relates to an inflammation of neural tissue (which may or may not be associated with subsequent pain), and neuralgia which is the generic term for the pain associated with the above conditions. Different dictionaries define these terms slightly differently, and medical personnel do not necessarily use these terms with precision when speaking with lay persons, or even among themselves; thus leading to the long term confusion.

Retinitis— Historically a painless physical distortion or change in the retina leading to a loss in function. More appropriately a retinopathy.

Wikipedia has provided a useful categorization of a group of medical terms -plasia and -trophy;

Anaplasia (structural differentiation loss within a cell or group of cells)

Aplasia (organ or part of organ missing)

Hypoplasia (congenital below-average number of cells, especially when inadequate)

Hyperplasia (proliferation of cells)

Neoplasia (abnormal proliferation)

Dysplasia (change in cell or tissue phenotype)

Metaplasia (conversion in cell type)

Prosoplasia (development of new cell function)

Desmoplasia (connective tissue growth)

Atrophy (reduced functionality of an organ, with decrease in the number or volume of cells)

Hypertrophy (increase in the volume of cells)

Dystrophy (any degenerative disorder occurring due to improper or faulty nutrition)

³²⁶Hargrave, P. & O'Brien, P. (1991) Speculations on the molecular basis of retinal degeneration in retinitis pigmentosa In Hollyfield, et. al. Retinal Degenerative Diseases and Experimental Therapy, NY: Plenum Publishers pp 517-528

Diseases of the visual system can generally be divided into six categories;

- Neural diseases not associated with the pathology of the oculi,
- Vitreoretinal diseases of the oculi,
- Diseases affecting the optical path, including neuro-muscular diseases and cataracts,
- A variety of cardiovascular failures involving the visual cortex,
- A variety of cardiovascular failures involving the retina, and
- External pressures applied to the neural pathways typically by the development of tumors.

The number of documented diseases of the visual modality is very large (endless). Zauberman edited a comprehensive proceedings focused on vitreoretinal diseases³²⁷. Steidl & Hatnett have also provided a much more recent comprehensive description and methodology for diagnosing a wide variety of vitreoretinal diseases prior to the employment of OCT technology³²⁸. Much of their material is in the form of tables and most of it is qualitative in character based on acquisition by ophthalmoscope observation. **Figure 18.8.9-1** provides one of their introductory tables developed by Meredith. He notes that the initial complaint on first presentation is almost always “blurred vision.” The rest of the Steidl & Hatnett text includes a large number of diagnostic “fault trees” accompanied by color retinal images for the use of the clinician (even though many of the conditions can be due to conditions unrelated to what the ophthalmologist can observe).

	<i>Blurred vision</i>	<i>Central scotoma</i>	<i>Metamorphopsia</i>	<i>Image size change</i>	<i>Color vision change</i>	<i>Floater</i>	<i>Photopsia</i>	<i>Visual field loss</i>
Vitreous detachment	X					X	X	
Vitreous hemorrhage	X					X		
Retinal detachment	X					X	X	X
Vitreitis	X					X		
Retinitis	X					X		X
Tumor	X						X	X
CSR	X	X		X	X			
Epiretinal membrane	X		X	X				
SRNVM	X	X	X			X		
Macular hole	X	X						
CME	X		X					
BRVO	X		X					
CRVO	X		X				X	X
Cone dystrophy	X				X			

X, indicates possible symptoms associated with diagnosis; CSR, central serous retinopathy; SRNVM, subretinal neovascular membrane; CME, cystoid macula edema; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion.

Meredith03Table5_1.wpg

Figure 18.8.9-1 Usual symptom complexes for common posterior ocular (retinal) disorders. Note the qualitative nature of these observations. The first complaint is almost always blurred vision. Many of these complaints in the left column (such as blurred vision) may arise from problems not associated with the posterior oculus. See text. From Meredith, 2003.

Many of these diseases are inheritable and known to involve a wide selection of genetic problems. In this situation,

³²⁷ Zauberman, H. ed. (1979) Proc Conf Subretinal space. Jerusalem (Documenta Ophthalmologica Proceedings Series volume 25),

³²⁸ Steidl, S. & Hartnett, M. (2003) Clinical Pathways in Vitreoretinal Disease. NY: Thieme Chapter 5

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each individual disease can be tagged with an additional suffix indicating its genetic source.

The source of many of these diseases can best be defined using multidimensional analysis. Below are a series of figures designed to illuminate the source of these diseases employing different perspectives to view the results of such an analysis;

- an overview of diseases of the visual modality by their location within the modality,
- a description of major failure points within the neural system from the optic nerves to perception, and
- physical diseases of the retina exclusive of those intrinsic to the photoreceptors.

Figure 18.8.9-2 attempts to place these diseases into several major physiological categories. It is subject to continual updating. The key problem is the sandwich character of the retina. It consists of a series of laminar layers supporting neural signaling (stages 2 and 3), stage 1 sensory neuron receptors and retinal pigment epithelium (RPE) supporting the stage 1 sensory neurons. To optimize visual performance, these individual layers are not necessarily continuous over the whole surface of the retina observable by an ophthalmologist.

Many of the reported clinical diseases of the eye are based on ophthalmological observation; essentially involving a plan view of the multi-layered retina. This technique does not provide significant information concerning individual layers of the retina. The variations in these layers have become much better documented recently via the development of optical computerized tomography (OCT). See **Section 18.8.3.5.3**.

The clinical term, retinal dystrophy, is a particularly significant example of a poorly defined clinical disease. Individual investigators have associated this label with all of the three major categories defined in the figure. Merin (2005) has presented a clear overview of this group of diseases and a broad discussion³²⁹.

Merin has also discussed corneal dystrophy, a much more clearly defined disease focused on only the cornea.

³²⁹Merin, S. (2005) Inherited Eye Diseases. NY: Taylor & Francis

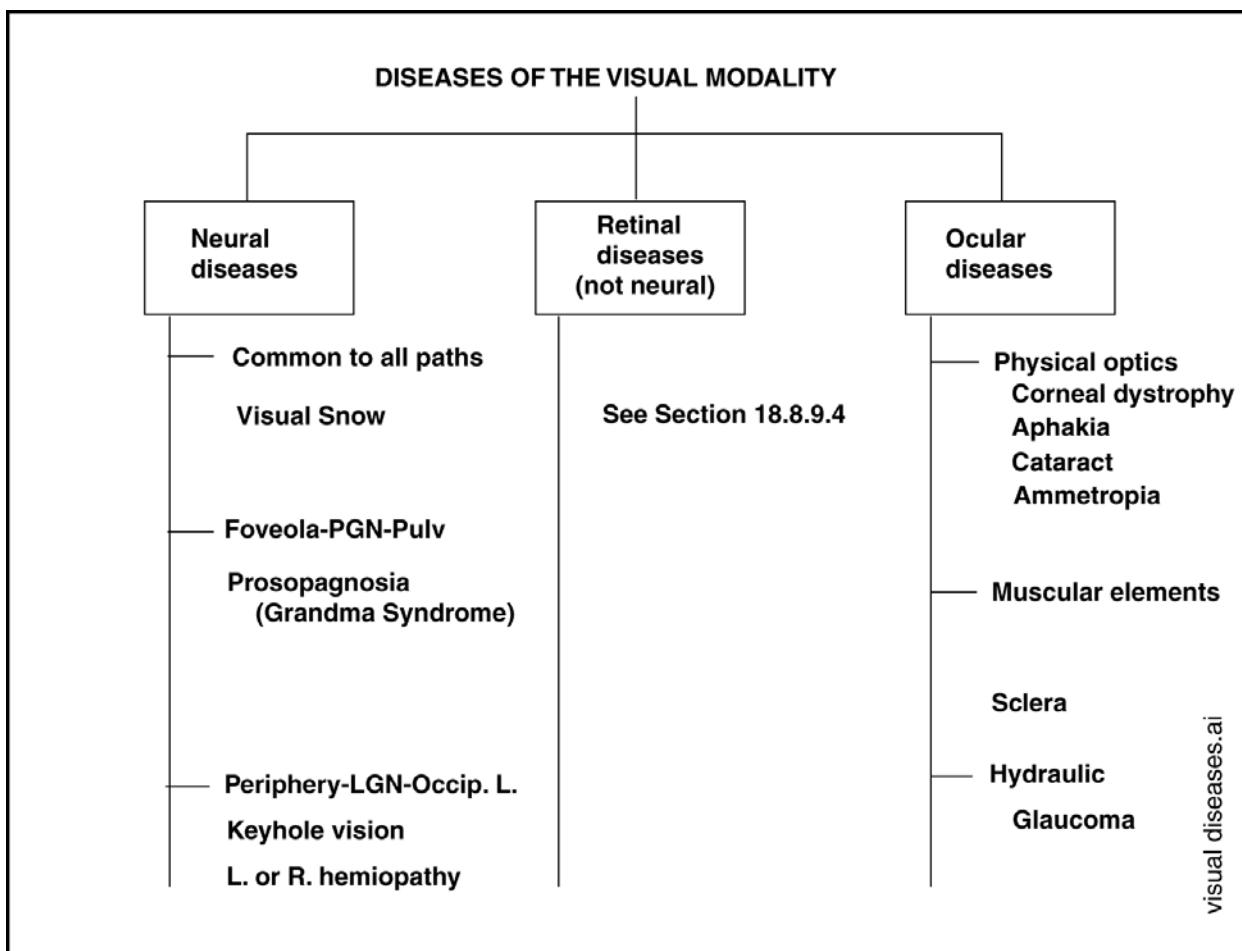


Figure 18.8.9-2 Superficial framework categorizing diseases of the visual modality. It is difficult to separate the diseases of the retina separately from the neural diseases of the stage 1 sensory receptor neurons. Each category is expanding rapidly due to currently continuing research. The figure is subject to continued expansion. See text.

Figure 18.8.9-3 provides a clear framework for the source of many visual diseases not observable visually by an ophthalmologist, and not observable directly using *in-vivo* imaging techniques (except where caused by failures in the associated cardiovascular system). These disruptions in signal flow are usually determined from the subjects description of the problem. Many of the losses in vision described on the right may occur in less complete form if only a portion of the pathway (examples E & F) is disrupted by a tumor or other physical pressures. Damage at G can result in a variety of ocular muscle control problems that are frequently observed by the ophthalmologist (nystagmus, etc) even if they do not recognize the associated loss in perceived precision imaging (prosopagnosia). This situation is sometimes reported as “nystagmus with loss of central acuity.” The representations of D, E & F showing small semicircular cutouts of the lost visual area are frequently not included in introductory pedagogical materials. Conversely, complete disruptions of both the left and right signal paths at D frequently result in what has been described as “keyhole vision.” This condition results from the loss of all of area 17 of the occipital lobe, frequently due to wounds in wartime, while the PGN/pulvinar pathway remains undamaged. In this case, the ophthalmologist may argue with the patient claiming he is totally blind while the patient argues back that he is not, and proceeds to read the newspaper for the doctor’s edification. The destruction of both paths labeled D also frequently cause the patient to be able to detect motions in the two fields outside of the keyhole because the cruder of such motion signals are developed in the LGN. The optometrist and/or ophthalmologist will insist such reporting must be a statistical error in his experiments because the statistics should show he is only guessing. This need not be so.

The representations on the right are not those described by an ophthalmologist based on his observation of chemical or cardiovascular effects interfering with, or supporting necrosis of, the photoreceptors. Note the very well defined

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vertical axis (except for the semi-circular notch). This sharp definition is characteristic of neural disease as opposed to macular degeneration. The semi-circular notch is less well defined in practice than suggested in the figure.

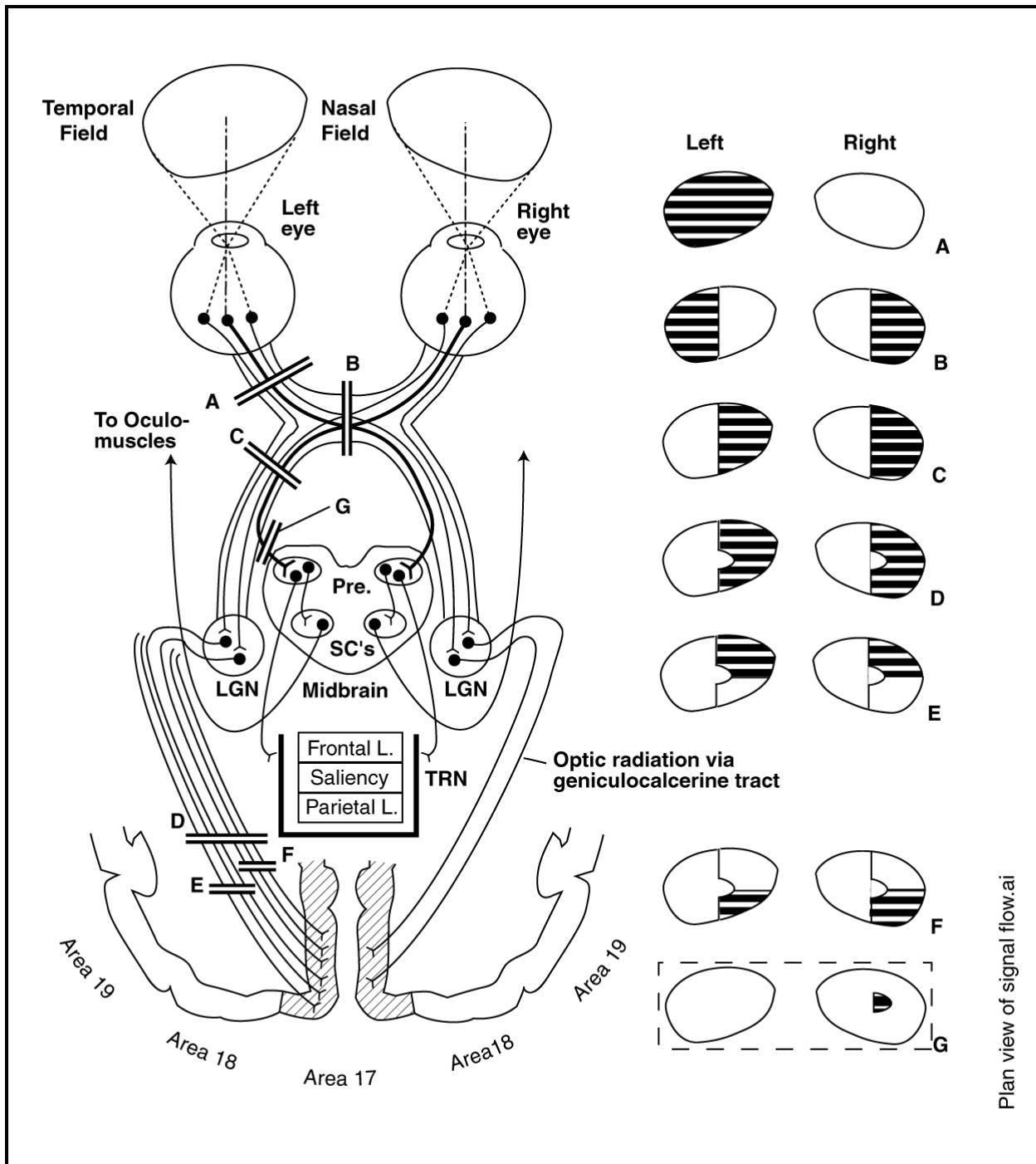


Figure 18.8.9-3 Plan view of visual signal flow & sources of disruption.

There are three distinct categories of degenerative diseases of the visual system focused on the retina. **Figure 18.8.9-4** provides an initial orientation to these diseases. Because of the long history of these diseases, their semantic categorization is very inconsistent. Most of the diseases listed in the figure do not involve physical pain and therefore should employ the suffix -opathy and not -itis. The discomfort related to most of these diseases is more psychological than physical. The retina, like other major engines of the neural system, is typically internal somatosensory nerve free. There are indications there may be some somatosensory nerves in the retina associated with sensing the intensity of light entering the eye.

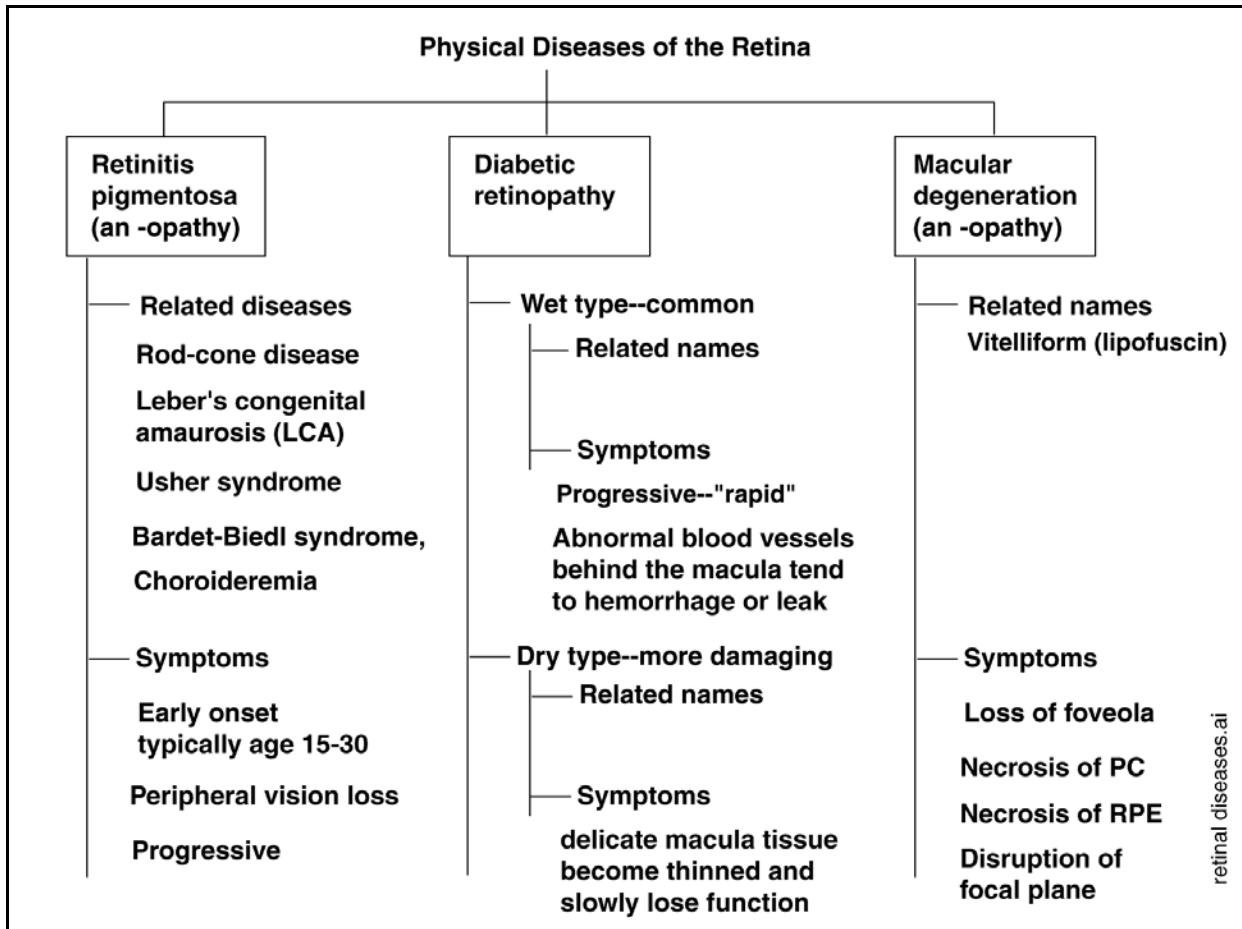


Figure 18.8.9-4 Initial orientation related to physical diseases of the retina not directly related to the photoreceptors. Describing diseases by their location with respect to the macula is particularly inappropriate. The macula is an apparent region based on looking through a multilayered structure. Merin 2005, pg 251 focuses on the problems of nomenclature in this area.

Generic symptoms frequently associated with these diseases include,

- Blurry vision
- Distorted vision
- Straight lines appear wavy
- Objects may appear as the wrong shape or size
- The loss of clear, correct colors
- Difficulty reading
- A dark, empty area in the center of vision

Such generic symptoms may be suggestive but clearly are not determinative. Some of these symptoms may not relate to these physical diseases of the retina. They may relate to other diseases of a neurological character. Straight lines appearing wavy & objects appearing as the wrong shape or size are generally considered psychotic diseases.

18.8.9.1 Inherited eye diseases

With the recent advances in genomics and its related off-shoots, great increases in understanding related to diseases of the visual system due to genetics has occurred. Merin has reviewed the complicated terminology related specifically to genetics before reviewing a wide range of inheritable eye diseases³³⁰.

18.8.9.1.1 Terminology in genetics related to inherited eye diseases

Only a few selected terms will be defined here.

Chromosome— A subpart of the human genome of ~3.2 billion nucleotides arranged in 22 pairs of autosomal chromosomes (chromosomes 1-22), and two sex chromosomes (X and Y). The chromosomes differ in sequence, gene content, size and structure.

Gene— All genes except on the X-chromosome of the male, are found in two copies in every person, each copy is an allele of the gene.

Allele— One of the two copies of DNA found in each gene except as noted above.

Genotype— A molecule of DNA defining a particular phenotype, animal.

Phenotype— **a.** The observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influences.
b. The expression of a specific trait, such as stature or blood type, based on genetic and environmental influences.
c. An animal resulting from epigenesis based on a specific genotype of DNA.

Epigenesis--The creation of an animal, a phenotype, based on a specific sample of DNA, a genotype.

“Most human traits and inherited diseases are controlled by more than one gene, this type of inheritance is called polygenic; each gene has an additive effect on the trait.

Figures 1 & 2 of Chapter 3 of Merin (2005) presents one of the clearest representations of a gene and the steps in the expression of a given protein.

Merin repeats on page 21, the current realization that “Most of the DNA is not arranged in functional units, and only 3% of the human genome encodes proteins. Noncoding DNA has been considered as ‘junk’ DNA in the past, but there is accumulative evidence indicating that it has many important functions including various regulatory roles.”

18.8.9.1.2 DNA mutations

Merin has a full chapter on DNA mutations and their consequences (beginning on page 23). His description of the state of DNA knowledge in his 2005 book differs significantly from the concepts frequently discussed in the last quarter of the 20th Century. He notes;

- Because only a small fraction of the human genome encodes proteins, most of the mutations do not have any effect on the phenotype and are designated as neutral mutations (or polymorphisms).
- The vast majority of germ line mutations disappear from the population within a few generations, and the likelihood that a mutation will both survive and have an effect on the protein function is slim.
- For the study of inherited human diseases we are usually interested in disease-causing mutations that occur within coding regions of genes.
- There is substantial evidence that many disease-causing mutations occur in noncoding regions within genes, as well as in intergenic regions.

An unusual type of mutation, expanding repeats, has been reported in many genes associated with autosomal dominant neurodegenerative disorders. Many of the neurodegenerative disorders contain an ocular phenotype; for example, expansion of CAG repeats in the SCA7 gene is a cause of dominant spinocerebellar atrophy with macular or retinal degeneration. Note the impact of this mutation on multiple disparate portions of the physiology.

³³⁰Merin, S. (2005) Inherited Eye Diseases. NY: Taylor & Francis

Merin has described the rapid growth in the interrogation of available genomic databases. He notes the central node for these databases is the National Center for Biological Information at 222.ncbi.nlm.gov. This front page leads to many useful databases for experienced users.

Corneal dystrophies are not a focus of this work but they were listed in the initial figure of this section.. They are defined by Merin as, "an inherited, bilateral, noninflammatory corneal opacification." This authors experience has been that the condition is not necessarily bilateral unless a window extending over 10 years is considered. At a more detailed level, they may involve a regional thickening of the corneal tissue that can cause loss of visual acuity without opacification. He notes the difficulty in describing and the difficulty in learning the consequences of corneal dystrophy. The introduction of laser surgery related to the cornea has greatly extended the interest in and the study of corneal dystrophies. Most of this surgery is focused on the aberrant shape of the cornea rather than any opacification.

Merin has noted the considerable confusion among the names associated with photoreceptor dystrophies, based on the now archaic chemically based conceptualizations of the visual modality. He includes a Table 1 that uses the old names showing columns for rods and cones separately that may be used for reference but should not be depended on for pedagogy or understanding in general. Note how the effect on the purported "rods" and "cones" are the "same" for both the rods and cones for congenital complete cone dystrophy of type 3 & 4. Most of the documented photoreceptor dystrophies are based on observable changes in the retina and not on the underlying cause of the disease. As will be developed here, many of the diseases listed in **Section 18.8.9.4** are actually due to cardiovascular failures leading to the necrosis of many of the photoreceptors, frequently beginning in the periphery of the retina. Figure 4 of Merin, Chapter 9 shows the emanation of the cardiovascular conduits from the blind spot by fundus angiography. It is easy to correlate the arrangement of these paths with the ophthalmoscope image of the fundus shown above. Clearly, any cause of a reduction of the flow of nutrients to, and waste products from, the retina will cause photoreceptor necrosis. If the reduction is progressive, the necrosis of the photoreceptors will be equally progressive.

18.8.9.2 Perimetry as a tool for categorizing diseases

Many diseases caused by cardiovascular failures in the visual cortex are identified using perimetry. However, their caricaturization usually requires additional observations. Perimetry was first introduced with some cautionary comments in **Section 2.2.1.1**. Several simple examples were presented in **Section 2.8.1.1.3** to introduce other subject matter. These sections should be reviewed before interpreting the following figures.

As commonly noted, perimetry can be used to identify a wide variety of diseases associated with the visual modality. By cutting various nerve bundles in animal models, it has been possible to define the particular parts of the field of view affected and to transfer that knowledge to the human situation. See **Figure 18.1.3-1**. It is reproduced above as **Figure 18.8.9-3**. Moving into a more diagnostic mode, deterioration of the cardiovascular system frequently results in more nuanced perimetry maps as shown later in this section.

Investigators before the 1980's frequently described nearly all diseases revealed by perimetry as having their source in the retina. More recently, it became obvious that many diseases were due to cardiovascular failures occurring later in the visual modality, particularly in the occipital lobe and V1. Many conditions could even be isolated to that part of an occipital hemisphere located within the longitudinal fissure as distinct from that located on the outer surface of the cerebrum. Failures of this type are frequently associated with the transition from the macular to the peripheral field of view (at a radius of about 7.2 degrees in the tangent board representation). Failures in the cardiovascular system occurring above or below the calcarine fissure, and frequently limited to only one hemisphere, of the occipital lobe also cause very distinct patterns in the perimetry representation.

Many of the diseases discussed in this section and observable by the ophthalmologist can be attributed to progressive failures in the cardiovascular system of the eyes, either to provide the appropriate nutrients or to carry away the waste products of normal neural operations.

A challenge at this juncture in to describe the medical nomenclature used traditionally in terms of the functional failures defined in this work.

18.8.9.2.1 Definition of the macula, fovea and foveola

Readers frequently have difficulty relating to the size of the various regions of the retina when projected into object space. **Figure 18.8.9-5** provides a coarse description of these features following Hogan et al. (1971).

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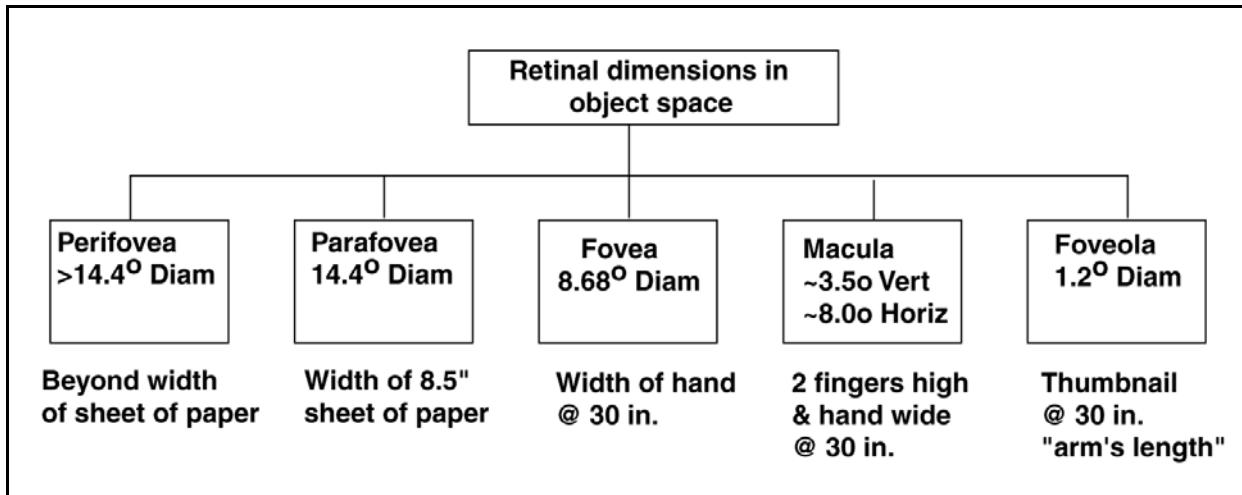


Figure 18.8.9-5 Retinal dimensions as they appear in object space. The sizes refer to an “arms’s length” in front of the viewer (nominally 30 inches). The diameters shown are centered on the point of fixation in object space. Note the macula is a highly variable size “object” that is frequently defined in terms of the observed variation in color of the retina. It is not generally an objectively defined dimension. See text.

When observing the retina with an ophthalmoscope, it is important to recognize that many of the layers of the retina are semitransparent under appropriate lighting conditions. Even the outer segments of the photoreceptors exhibit very low optical densities under normal room illumination. For daylight illumination, they are essentially transparent due to their bleaching (outer segment adaptation)

The layers of the retina of concern during diagnoses are listed in “The Standard Eye” presented in Appendix L and reproduced below. The list is long. INM refers to the Inter-Neural Matrix and IPM refers to the Inter-Photoreceptor Matrix (specifically the matrix surrounding the outer segments of the photoreceptors and extending to the surface of the retinal pigment epithelium (RPE). The retina involves three unique *membranes*; one separating the neural matrix from the vitreous humor, one separating the neural matrix (including the axons and nuclei of the photoreceptors) from the inter-photoreceptor matrix and Bruch’s *membrane* separating the RPE from the choroid enclosure. The IPM encloses both the inner and outer segments of the photoreceptor neurons for electrical circuit performance reasons and to restrict oxygen from the IPM fluid.

Retinal Cross Section (following Rodieck, 1973–vitreous humor to choroid)

Inner Limiting Membrane	chemical isolation: vitrea from INM
Inner cardio-vascular layer	support for neural operations
Optic fiber layer	axons of ganglion cells
Ganglion cell layer	ganglion cells
Inner plexiform layer	bipolar to ganglion connections/lateral cells
Inner nuclear layer	bipolar/lateral cells
Outer plexiform layer (synapse area)	dendrites of bipolar cells/lateral cells
Fiber layer	pedicels and spherules of photoreceptors
	axons of photoreceptors
Outer nuclear layer	photoreceptor cell nuclei
Outer limiting membrane	isolation; IPM from INM
Inner segment layer	translation region (Activa)
Outer segment layer	transduction region (Rhodopsin coated disks)
Retinal pigment epithelium layer	chromophore production & maintenance
Outer cardio-vascular layer	support for RPE operations
Bruch’s membrane	chemical isolation; retina from choroid
Choroid	structural support

Disease can involve changes to almost all of these layers including the introduction of extraneous material into these layers.

Figure 18.8.9-6 shows four tangent board presentations at an expanded scale (note the partially hidden 30 degree label at the left margin of each representation). A tangent board is a flat surface mounted perpendicular to the line of fixation with circles defining various angular fields of view. Only the central portions of the total field of view, delimited by the 30 degree radius, are shown. The presentations appear tailored to make a point. The areas of clear vision in the upper fields are not usually found to be as circular as indicated. Unfortunately, it has not always been possible to achieve adequate resolution in these experiments to always identify the macula, fovea and foveola as defined here. However, such figures make it perfectly clear that sectioning, or otherwise interfering with the nerves at different locations can have dramatically different effects on the subjects vision. These effects can often be documented using perimetry.

[xxx match angular values below to the above figure]

In the above expanded tangent board figures, three distinct areas of the retina are easily defined. The largest areas shown in the left hemifields of the upper frames from the same patient are defined here as constituting the macula (a.k.a., the parafovea). The radius of this feature is typically 7.2 degrees.

The smaller areas shown in the right hemifields of the upper frames are defined here as constituting the fovea. The radius of this area (the fovea) is typically 4.34 degrees (nominally 5 degrees).

The still smaller areas shown in both fields of the lower frames are defined here as constituting the foveola. Harrington labels these the fixation areas. The radius of this feature is typically 0.6 degrees (1.2 degrees diameter). This feature is difficult to measure in the typical optometry office because it is frequently smaller than the test probes used to acquire the individual isopters of the patient. These areas of "normal" visual processing are clearly indicated in expanded images of the lower fields in the figure. These minute areas are nominally 1.2 degrees in diameter.

If the upper fields were correctly diagnosed as double homonymous hemianopsia, an alternate explanation of the presence of the areas of normal vision is needed. In this work, these areas are associated with the PGN/pulvinar signal path that operates in parallel with the LGN/occipital signal path.

Harrington has described the major scotomas of the lower frames using the label 5 & 10/2000 to describe the spatial precision of his measurements. This means the data was collected using a 5 or 10 mm disc as the probe at a distance of 2 meters from the subjects eyes. The 5 mm probe represents an angle of 8.52 minutes of arc at 2 meters. The 10 mm probe would represent a 17 minutes of arc while the foveola is only 72 minutes of arc in total diameter.

The foveola can be represented by a 1.2 degree diameter disk. Such a disk can be described as 20/1000, a 20 mm disk at a distance of 1 meter. To define the edge of the foveola by the conventional perimetry method, the test object should be at a minimum 5 times smaller than the target, or about 4/1000 or smaller. Harrington (page 100) has provided a table of test object size versus maximum field of vision along the principle axes. The table does not address the small central features of the field of view.

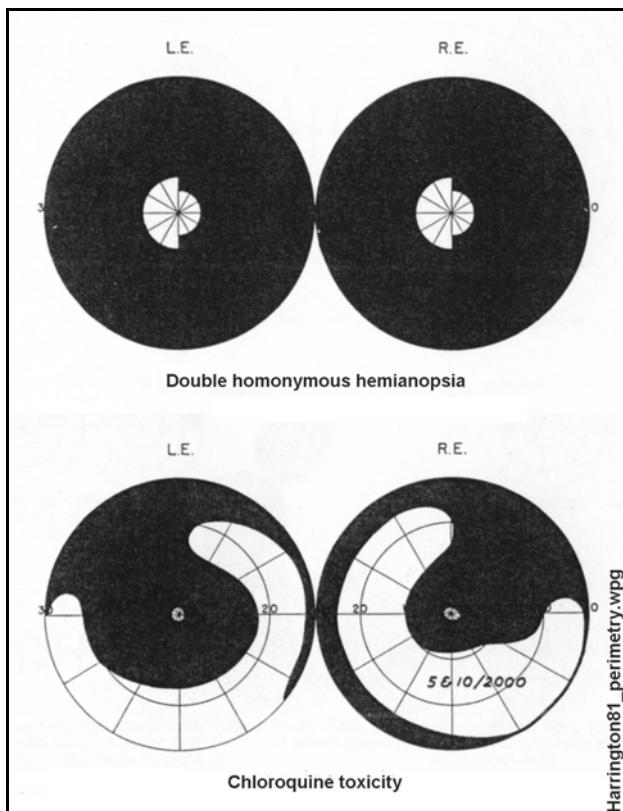


Figure 18.8.9-6 A comparison of the macula, fovea and foveola fields of view in human vision derived from tangent boards. The upper fields illustrate diseases typically associated with failures involving stage 4 & 5 (within the CNS) of the visual system. The lower fields show diseases typically associated with the stages 1 & 2 and involving the retina directly. However, they may also relate to stage 4 failures. The lower failures are typically associated with failures associated with the cardiovascular system. The loss of vision is frequently progressive after beginning at the outer edge of the field of view (at significantly larger angles than shown here). From Harrington, 1981.

Harrington attributes the large scotoma in the lower frames of the figure to “Pigmentary degradation of the retina following 4 months’ use of chloroquine in patient with lupus erythematosus.” In all likelihood, the condition shown involves much larger areas of the full visual field and is probably associated with significant cardiovascular failure and/or damage to the neurons of V1 of the occipital lobes. The signals from the fovea and macula are processed within V1 of the occipital lobe via the fovea-LGN-occipital lobe pathway. Harrington also notes, “Minute islands of central vision are retained surrounded by dense ring scotomas.” In reality, the minute islands are due to the signals from the foveola being processed separately in the CNS via the foveola-PGN-pulvinar pathway. Harrington also commented on the ability of patients with major scotoma due to damage to the occipital lobe to still sense motion in the otherwise blind visual field due to the processing of changes involving motion in the LGN of the fovea-LGN-occipital pathway (page 341).

Note the near mirror image symmetry in the lower fields of the figure. This symmetry suggests the loss of vision is most severe in the upper temporal quadrants and is related to the performance of the cardiovascular system, and that essentially all vision is lost at angles considerably larger than 30 degrees.

Many failures of the cardiovascular system of the retinas have also been identified and illustrated by Harrington. However, they exhibit quite different geometries (page 215). Similarly, diseases of the optic nerve show very distinctive patterns in perimetry presentations (page 231). Harrington speculates on the source of these diseases after noting the lack of utility of the ophthalmoscope in diagnosing problems of the optic nerve and beyond.

Harrington discusses complications in perimetry when subjects exhibit a “hysteria” in chapter 16. He also describes general technique useful in identifying subjects who are thought to be “malingering.”

Tasman has provided an even more detailed text focused on retinal diseases³³¹.

The so-called macula lutea, when identified, is usually identified with a discoloring of the retina itself, probably due to a foreign substance invading the neural layers of the retina.

18.8.9.2.2 Description of the cardiovascular system of the retina

Each eye is supported by one artery and one vein coursing through the optic nerve. Upon reaching the retina, the artery divides into one artery serving the layers of the retina adjacent to the choroid and one serving the neural portion of the retina near the inner neural matrix. Each of these arteries proceeds to divide further resulting in four sub-arteries with each serving a separate quadrant of the retina. Hogan et al. (1971, chapter 9) have provided detailed information about the character of these conduits, including the details of the conduit walls. He notes that a blockage of any of these conduits can result in the necrosis of adjacent functional tissue. He describes the parallel venous system as being very similar to the arterial system. Hogan et al. do not discuss the blockage of these conduits in disease situations. However, it is clear that the smaller conduits at the periphery of each quadrant of the retina are most likely to become blocked. Additional information related to the cardiovascular system appears in Section 3.3.

18.8.9.3 Generally age related (and progressive) macular diseases

A large number of visual diseases have been identified with the aging process. Many of these have been observed by the medical profession by visually examining the retina through the subject’s pupil. The result is that many of these diseases have been described as macular diseases based on a two-dimensional image. However, many of these can be more appropriately labeled using modern computer-aided optical coherence tomography (OCT). This technique provides a three dimensional mapping of the retina/choroid space with significant spatial resolution in three dimensions. The result is the isolation of a variety of diseases affecting only specific layers of the retina.

The macula is described variously in the literature. In general, it is defined as a disk centered on the point of fixation and generally with a diameter of about 5 degrees visual angle. The macula is frequently defined in terms of a subtle change in the color appearance of the retina when viewed through the pupil with an undefined light source and an inadequately defined state of adaptation involving the observer. Physiologically the macula can be described in terms of the representation on the occipital lobe of the CNS that is outside the longitudinal fissure of the brain (on the exposed surface of the occipital lobe at the rear of the brain. The blood flow to these two areas is relatively separate and distinct. The macula is significantly larger than the foveola of this work at 1.2 degrees diameter.

³³¹Tasman, W. ed. (1994) Clinical Decisions in Medical Retinal Disease. St. Louis, MO: Mosby

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The terms drusen and fuscin are also used variously. The preferred terms in this work are; drusen, a buildup of foreign matter between Bruché's membrane and the RPE; and fuscin, a buildup of foreign matter between the RPE and the photoreceptor cells. See **Section 7.1.2.2**. Figure 4.5.1-1 in **Section 4.5.1** illustrates these potential locations of drusen and fuscin buildup. Diabetic vascularization can also be located in this figure. It is associated with the interneuronal matrix between the retina and the viscous fluid of the ocular. Normal vascularization does not extend into the foveola.

A workshop dating from 2000 has provided an excellent overview of the subject of macular degeneration both as a progressive disease and an age-related disorder³³². As in other clinical diseases, standardization of nomenclature remains a difficult problem when discussing macular dystrophy. This problem is compounded by the desire to explain some of these conditions to the layman using only commonly understood concepts. The website for the pharmacological Lucentis, <http://www.lucentis.com/>, demonstrates this problem. The cartoons describing wet age-related macular degeneration (wAMD), macular edema following retinal vein occlusion (RVO), and diabetic macular edema (DME) are not scientifically traceable to any known facts concerning these conditions in the academic literature.

Macular dystrophy (colloquially degeneration) is a general term for a variety of diseases of the retina. The most commonly identified varieties include;

1. Stargardt's, *the most common type of macular dystrophy*, which usually occurs in childhood. A different form of Stargardt's, called fundus flavimaculatus, typically is found in adults. Stargardt's is characterized by formation of pigmented waste cells in the retina.
2. Vitelliform macular dystrophy (VMD), which generally is discovered first with the presence of a large, yellow oval lesion (vitelliform) in an egg yolk shape that shows up in the center of the macula. Many genetic mutations of this form of macular dystrophy have been identified, including Best's disease, which affects children and young people. A different version of the disease also can appear in adults, with macular lesions that vary in size and shape.
3. North Carolina macular dystrophy, which is an extremely rare form of the eye disease identified by a very specific genetic marker. While named for North Carolina family members who have this inherited form of macular dystrophy, the disease has been found in other locations worldwide.

Recently, the academic community has adopted a label Best vitelliform macular dystrophy that appears to merge the features of Best Disease and Vitelliform macular dystrophy. These variants will be discussed individually in **Section 18.8.9.4** after the following overview.

18.8.9.3.1 Age related macular degeneration

The Discovery Eye Foundation provided the following on their website as of 2015³³³. They note,

"Macular degeneration is a progressive eye condition affecting as many as 15 million Americans. The disease attacks the macula of the eye, where our sharpest central vision occurs, affecting reading, driving, identifying faces, watching television, safely navigating stairs and performing other daily tasks. Although it rarely results in complete blindness, it robs the individual of all but the outermost, peripheral vision, leaving only dim images or black holes at the center of vision."

They included a representation as shown in **Figure 18.8.9-7**. As illustrated, it appears to be the opposite of the Retinitis Pigmentosa representation.

Contrary to the Discovery Eye Foundation assertion, macular dystrophy (degeneration) is becoming recognized as frequently a disease involving vitamin A deficiency as its primary cause. It can be observed by examining the retina, but may not originate there. The disease frequently involves problems of retinoid

³³²Anderson, R. LaVail, M. & Hollyfield, J. eds. (2001) New Insights into Retinal Degenerative Diseases: The Proceedings of the IXth International Symposium on Retinal Degeneration Berlin: Springer-Science & Business Media

³³³Discovery Eye Foundation (2015) <http://discovereye.org/what-is-amd/>

absorption at the brush border of the intestine^{334,335} or insufficient enzymatic activity due to failures within the pancreas³³⁶. Dutta et al. have provided excellent clinical data for serum vitamin A levels and dark adaption thresholds during treatment for chronic alcoholic pancreatitis. The paper is dated relative to other papers. See **Section 7.1.2** for a broader analysis.

The loss of vision is concentrated in the area of the retina forming the foveola, with the rest of the fovea and perifovea spared at this stage. The disease is noted to be progressive. The commentary accompanying the discussion is open to discussion.

"As the disease progresses the area of color and central vision deteriorates and the gradual destruction of light sensitive cells continues until large areas are totally gone. Peripheral vision remains, but the ability to clearly see straight ahead and to see color is lost."

Their representation clearly shows color rendition remains vivid but at reduced resolution in the periphery.

The size of the macula varies dramatically among various investigators. Its most appropriate description is that of a region of the retina exhibiting an abnormal, usually yellowish coloration. As viewed through the pupil, it generally occupies an area 2.0 mm. wide (viewing angle ~8 degrees) and 0.88 mm. vertically (viewing angle ~3.5 degrees). These dimensions are significantly larger than shown in the two representations from the Discovery Eye Foundation.

They note, "For many people, the first sign of macular degeneration is something they notice themselves. Straight lines like doorways or telephone wires may appear wavy or disconnected. When you look at a person, her face may be blurred while the rest of her is in focus. Lines of print may be blurred in the center or the lines may be crooked. For some people, there is a sudden blurring or loss of sight in the center of vision." The perceptions noted appear to be due to different causes. The wavy lines appear to be neurological in origin.

They also note,

- "AMD is the number one cause of severe vision loss and legal blindness in adults over 60 in the U.S.
- There are two types of AMD – "wet" or neovascular and "dry" or atrophic.
- There is no cure for AMD, but new treatments are available for the wet form of the disease. There is currently no treatment for the dry form."

Section 7.1.2.1.2 places one potential cause of macular degeneration in context with other functions occurring within the retina. **Section 7.1.2.3** provides details relating to the buildup of drusen adjacent to Bruch's Membrane.

Section 7. 1.3.2.2 provides a new level of detail related to one hypothesis underlying macular degeneration.

18.8.9.3.2 Macular degeneration based on retinal changes

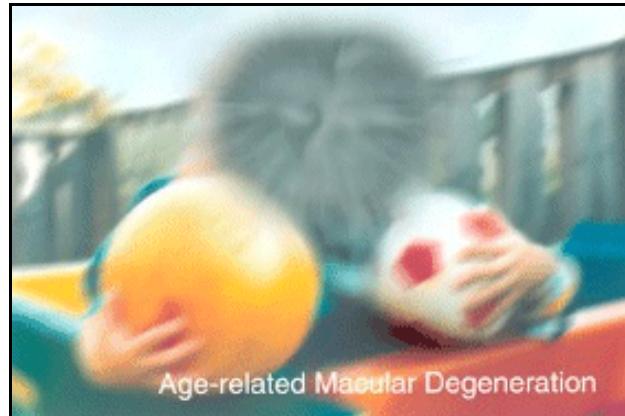


Figure 18.8.9-7 Representation of macular degeneration (more correctly foveola degeneration). No dimensions were given. It is suggested the diameter of the obscured region is nominally 1.2 degrees with the total image being approximately 5 by 3 degrees. As illustrated, macular degeneration is the nominal opposite of Retinitis Pigmentosa as represented above by the same source. From Discovery Eye Foundation, 2015

³³⁴Dew, S. & Ong, D. (1994) Specificity of the retinol transporter of the rat small intestine brush border *Biochem* vol 33(40), pp 12340-12345 *See also letters to the editor by Allen, Green & Green* concerning the short duration of the studies with the rat.

³³⁵Allen, L. Green, M. & Green, J. (1994) Letters to the Editor re: Dew et al.. vol 54, pp3319-3320

³³⁶Dutta S. Bustin, M. Russell, R. & Costa, B. (1982) Deficiency of fat-soluble vitamins in treated patients with pancreatic insufficiency *Ann Internal Med* vol 97(4), pp 549552

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Age related macular degeneration (ARMD) appears to be a syndrome of many components. In many diagnoses, the term macular only refers to the central portion of the retina and not to a specific layer. In many descriptions of ARMD, the author is referring to problems related to bleeding outside of the optical path between the aperture and the photoreceptor cells and ultimately flowing from the choroid artery. This can result in the disruption of the photoreceptor cell/IPM/RPE interface with subsequent loss of vision.

The Schepens Eye Res. Inst. in Boston has been aggressively exploring diagnostic techniques appropriate to this condition.

Gouras & Algyere have provided data on ARMD related to degeneration of the Eldred³³⁷. Their work has involved surgical replacement of some RPE tissue. They have also referenced early work leading to future surgical replacement of photoreceptor cells.

Nakanishi at Columbia University has been very active in this area from a medicinal perspective³³⁸.

Vander has provided a classification system for holes in the foveola arising from significant macular degeneration of either the wet or dry type³³⁹. His histological sketches predate the more recent OCT imagery of the type shown in **Section 18.8.3.6.5** and discussed at length in **Section 18.8.9.3.xxx**

Rahim et al. has provided the addresses to a large number of databases related to diabetic retinopathy and maculopathy as part of a program to automate the process of diagnosis of these conditions³⁴⁰. They note,

- “Diabetes mellitus produces damage to retinal capillaries and it can be visualized only in the retina.”
- “Microaneurysms, the earliest visible signs of diabetic retinopathy, appear as small red dots on the retina. There are other diabetic retinopathy signs, such as hemorrhages, i.e. red lesions caused by the rupture of the small blood vessels in the deeper layers of the retina. Exudates, which are yellow–white lesions caused by plasma leakage from the capillaries, are another type of common features of diabetic retinopathy. However, if the exudates are found within one disc diameter (1DD) of the fovea, they are called exudative maculopathy.”
- “Diabetic maculopathy affects the visual function through the macular ischaemia and increased retinal vascular permeability resulting in macular oedema.”

The program appears to be at an early stage and of limited utility based on a rapid reading. The paper contains a large number of images for comparison. “Although the proposed technique is not working well as an individual system variant in [7] for the microaneurysms detection, the technique has been working well in [8] for the diabetic retinopathy and maculopathy detection.”

Section 2.2.2, and particularly **Figure 2.2.2-5** reproduced from Vaughan & Asbury, illustrates on a flat surface the distribution of the cardiovascular system within the oculus. The cardio and vascular pathways are arranged like the cup of a goblet with their focus being on the optic disk and the visual artery from which they emerge/converge. The finer arteriole and venula structures are most susceptible to blockage or other problems related to the aging process. This fact suggests that many of the problems characterized as macular degeneration are actually caused by deterioration of the cardiovascular system leading to failure of the peripheral photoreceptors initially followed progressively by those receptors closer to the blind spot. Such degeneration is described by the Discovery Eye Foundation as a major problem associated with diabetic retinopathy. “Diabetic retinopathy is the most common diabetic eye disease and a leading cause of blindness in American adults caused by changes in the blood vessels of the retina.” The figure they present on their website does not clearly describe the characteristics of diabetic retinopathy, although the dark curved area at upper right is suggestive of the progression of the opathy. The demarcation between normal acuity vision and macular degeneration is usually quite well defined and abrupt. The foundation does suggest a new treatment is becoming available, “New Treatments are here now . Vascular endothelial growth factor (VEGF) is elevated when the retina becomes ischemic and neovascularization occurs. A new therapy is available that lowers or blocks the effects of VEGF.” They do not describe how this neovascularization impinges on normal vision. The website contains a variety of typographical errors.

³³⁷Gouras, P. & Algyere, P. (1996) Retinal cell transplantation in the macula: new techniques. *Vision Res.* vol. 36, no. 24, pp. 4121-4125

³³⁸www.columbia.edu/cu/chemistry/groups/nakanishi/vision/Slide1.GIF (case sensitive address)

³³⁹Vander, J. (1994) Idiopathic macular holes *in Tasman, W. ed. (1994) Clinical Decisions in Medical Retinal Disease.* St. Louis, MO: Mosby Chapter 6

³⁴⁰Rahim, S. Palade, V. Shuttleworth, J. & Jayne, C. (2016) Automatic screening and classification of diabetic retinopathy and maculopathy using fuzzy image processing *Brain Informatics*
DOI 10.1007/s40708-016-0045-3

18.8.9.3.3 Macular degeneration based on neural changes

While the name macular degeneration as a syndrome suggests changes in the macular, it can also be associated with the ability of the analytical mode of the visual system to perform to a norm. Many neural conditions can arise that degrade the subjects ability to see fine detail and eventually see at all using the central region of the fovea (the 1.2 degree diameter foveola) of the eye. The cause of such losses can be traced to neural changes in the perigeniculate nucleus (a.k.a. pretectum), pulvinar, possibly the cerebellum and area 7 of the cerebrum.

18.8.9.3.4 Entopic imagery due to abnormal photoreceptor stimulation

The transduction mechanism of vision employs a phono-acoustic element. The energy of the photons is first converted to a quantum mechanical form before that form stimulates the sensory element of the individual sensory neuron. This stimulation appears to be acoustic in character. As such, any abnormal mechanical force applied to the head, eye or retina can generate a neural response. These responses are typically called phosphenes and the phenomenon has been labeled photopsias. Ashtari et al. have documented one method of generating these phosphenes on a large scale using fMRI technology³⁴¹.

Figure 18.8.9-8 illustrates a condition encountered by the author at age 64. There were two obvious symptoms. Flashes of light were perceived in bed at night when the head was moved suddenly. Most of these were of very short duration and located at the extreme periphery of my field of vision. See Records for details³⁴².

During a walk in bright sunlight, on at least two and probably only two occasions, bleeding occurred at points within the foveola that caused a black trail to be formed like smoke from a chimney. Its contrast and concentration fell with time and distance from the source location. The trail swirled as the blood mixed with the fluid surrounding it in response to normal saccades of the eye. It has been suggested that this fluid is much less viscous than the normal vitreous humor. This condition is quite distinct from the previous section which involved disease not in the optical path of vision.

Marzi et al. have also addressed the response times (RT) of signals introduced into the vision portions of the occipital lobe and the parietal lobe of humans by transcranial magnetic stimulation (TMS) and resulting

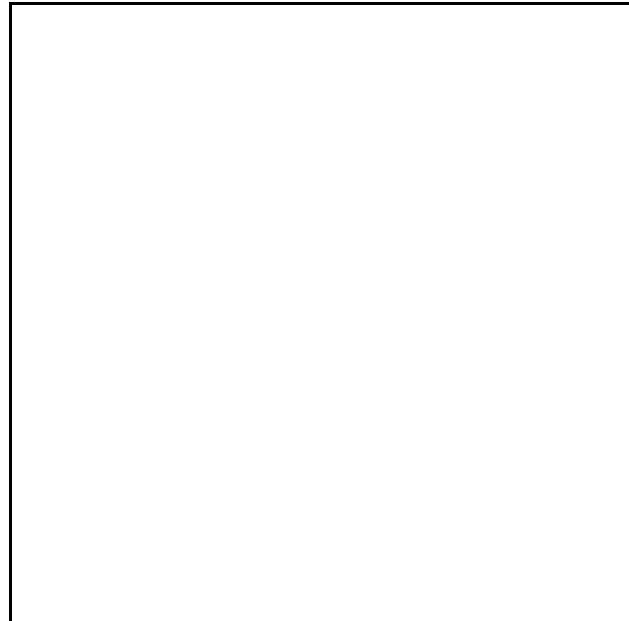


Figure 18.8.9-8 Phosphene generation due to vitreous detachment EMPTY.

³⁴¹Ashtari M, Cyckowski L, Yazdi A, Viands A, Marshall K, et al. (2014) fMRI of Retina-Originated Phosphenes Experienced by Patients with Leber Congenital Amaurosis. PLoS ONE 9(1): e86068. doi:10.1371/journal.pone.0086068

³⁴²Records, R. (1979) Physiology of the Human Eye and Visual System NY: Harper & Row pp 493-495

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in the perception of phosphenes³⁴³. They compared these time delays with those associated with visual stimulation using a similar protocol. (See Section 15.xxx). Transcranial magnetic and electrical stimulation appears to be of increasing value in evaluating the temporal performance of the visual system.

18.8.9.3.5 Wet and Dry forms of macular dystrophy

When speaking of macular degeneration, it is frequently divided into the “wet” type and the “dry” form. Wet macular degeneration (exudative form) is characterized by blood vessels that grow under the retina in the back of the eye, leaking blood and fluid. Dry macular degeneration is the more common form of the disease. Dry macular degeneration (The nonexudative form), cellular debris called drusen accumulates between the retina and the choroid, and the retina can become detached. Both types are generally associated with the central field of vision out to a 5 degree diameter visual angle (encompassing the macula, or the more specifically defined fovea of this work). A distinctly different disease frequently associated with the dry type may also involve neurological problems resulting in reduced visual acuity as well as scotoma.

Maguire & Annesley have provided an extensive although dated discussion of age-related macular degeneration³⁴⁴ (ARMD). They focused on the lipids of the retina rather than the glycoproteins. They noted that the Amsler grid was an effective tool for exploring spatial distortions within the central 20 degrees of the retina. They also provided sketches of holes developing in the foveola of the retina based on histological examinations. In recent years, the definitions associated with macular degeneration have improved considerably. Lim has provided an extensive analysis of age related macular degeneration (ARMD or AMD) with excellent graphics based on the latest OCT and other techniques³⁴⁵.

Mogk³⁴⁶ has discussed the pharmacological treatment of wet-type MD. [xxx expand]

18.8.9.3.6 Loss of optokinetic performance

There is a significant loss in optokinetic performance as a function of aging. Kennard & Rose have illustrated this quite graphically. The loss amounts to a reduction of 25% in slewing speed at age 60 relative to age 20³⁴⁷. A specific transient loss in optokinetic performance, specifically interruption of the tremor phenomenon is reported in Section 18.xxx [xxx visual acuity]

18.8.9.4 Named forms of macular dystrophy

Because of the prevalence of some form of macular dystrophy, many forms were reported long ago in the clinical literature and those names have persevered ever since (even when poorly delineated from other similar conditions).

18.8.9.4.1 Stargardt's macular dystrophy

Stargardt's macular dystrophy is described in Li et al. of 2001³⁴⁸. “This condition, now termed Stargardt's macular dystrophy, presents insidiously within the first two decades of life with a gradual loss of central vision. In the early course of the disease, fundus abnormalities on ophthalmoscopy may be minimal despite a marked reduction in visual acuity. Visual acuities often deteriorate to range between 20/200 to 20/400. *It is the most common form of*

³⁴³Marzi, C. Mancini, F. & Savazzi, S. (2009) Interhemispheric transfer of phosphenes generated by occipital versus parietal transcranial magnetic stimulation *Exp Brain Res* (2009) vol 192, pp 431–441

³⁴⁴Maguire, J. & Annesley, Jr. W. (1994) Age-related macular degeneration *In Tasman, W. ed. (1994) Clinical Decisions in Medical Retinal Disease.* St. Louis, MO: Mosby Chapter 3

³⁴⁵Lim, L. Mitchell, P. Seddon, J. Holz, F. & Wong, T. (2012) Age-related macular degeneration *Lancet* vol 379, pp 1728–38

³⁴⁶Mogk, L. (2016) What treatments are available for wet macular degeneration?

<http://www.visionaware.org/info/your-eye-condition/age-related-macular-degeneration-a-md/treatments-for-wet-macular-degeneration/125>

³⁴⁷Kennard, C. & Rose, F. (1988) *Physiological Aspects of Clinical Neuro-Ophthalmology.* Boca Raton, FL: Year Book Medical Publishers. pp 279-281

³⁴⁸Li, Y. Lam, L. Yu, Z. Yang, Z. et al. (2001) Clinical Spectrum in Autosomal Dominant Stargardt's Macular Dystrophy with a Mutation in *Elovl4* Gene *in Anderson, LaVail & Hollyfield eds., op cit.*

hereditary macular dystrophy, and accounts for 7% of all retinal dystrophies. The estimated incidence of Stargardt's macular dystrophy is 1 in 10,000. Classic ophthalmoscopic findings associated with Stargardt's macular dystrophy are bilateral atrophic macular lesions and yellow-white flecks at the level of the retinal pigment epithelium at the posterior pole." It is proposed in this work that the "flecks" are post-holo-SRBP residues that are not effectively removed by the vascular system (**Section 7.1.2**). "Franceschetti later coined the term "fundus flavimaculatus" to describe a fundus morphology characterized by the presence of white-yellow retinal flecks, which were scattered throughout the posterior pole and may extend out to the midperiphery." "In fundus flavimaculatus, midperipheral flecks are more prominent than the central macular flecks. Both Stargardt's macular dystrophy and fundus flavimaculatus have been found to exhibit much clinical variation in phenotypic expression and rates of progression." All recent efforts have been directed at a single gene mutation as the cause of these diseases. However, little justification for this assumption has been presented.

Li et al assert, "On fluorescein angiography, patients with Stargardt's macular dystrophy most often reveal a dark, or silent choroid with a variable central region of hypofluorescence that correlates with the severity of the disease. It is believed that choroidal fluorescence is blocked by lipofuscin in RPE in Stargardt's macular dystrophy. Also hyperfluorescent spots in the posterior pole are observed on angiography, whose locations do not always correspond precisely to those seen on ophthalmoscopy^{12,13,14}. At onset of visual loss, the results of ERG or EOG are often normal. However, as the disease progresses, ERG abnormalities may be observed ranging from mildly diminished photopic "b" wave amplitudes to markedly decreased photopic and scotopic "b" waves. Abnormal EOG ratios have also been described in patients with advanced Stargardt's and fundus flavimaculatus disease." These findings also appear to support the blockage of the finer vascular channels by drusen, affecting a larger surrounding area. While the data provided is excellent, the conceptual conclusions related to genes in the article are not supported by this work. It involves too many inferences to be relied upon. Li et al. note, "Historically, clinicians have often inferred the pathological basis of a disease from its phenotype. However, in recent years it has become evident that it is not possible to correlate a retinal dystrophy based on its ophthalmoscopic phenotype alone. Retinal flecks have been correlated with numerous disorders. Moreover, it is possible that patients with one phenotype may have another distinct phenotype at an earlier disease stage. Our classification into four phenotypes was not intended to denote a strict segregation of the different groups but rather a means to denote the wide morphological variability that was found in our cohort. A number of hereditary and toxic diseases could present with a fundus appearance similar to that found in Stargardt's macular dystrophy, including dominant progressive foveal dystrophies, progressive dominant cone dystrophy, pattern dystrophy, and toxic retinopathies. The wide phenotypic variation among family members indicates that a classification scheme based on morphological features alone would be insufficient in the diagnosis of retinal dystrophies such as in Stargardt's macular dystrophy."

As a general statement, it can be said that as of the early part of the 21st Century, "screening gene pools" to determine their relationship to a specific medically or clinically identified disease has not reached the threshold to be considered a science. There remain too many 2nd and 3rd order mechanisms that have not been identified. As a result, the screens are typically inadequate and specific conclusions are at best conceptual and can not be relied upon.

This assertion appears to be supported by the findings of Bowne et al. among others, when they note in connection with their retinitis pigmentosa investigations³⁴⁹, "The RP1 gene appears to tolerate a large degree of variation since 25 different benign variants have been identified (Table 2). Seven of these variants alter the amino acid sequence of RP1 and occur at polymorphic levels in the population. It is possible that these amino acid variants play a modifier role in the wide range of clinical phenotypes seen among adRP patients with RP1 mutations. Further research is needed to test this hypothesis."

18.8.9.4.2 Vitelliform macular dystrophy

Vitelliform macular dystrophy is not well understood. It is conventionally recognized as a genetic disease. It occurs in both childhood and adult onset forms.

Children born with VTM are considered legally blind (vision poorer than 20/400). The historical wisdom has been because of a sparseness of photoreceptors in their foveola. These diagnoses have been based primarily on anecdotal evidence obtained post mortem on elderly subjects. More recent evidence suggests some sparseness but also disruption of the Petzval surface due to the presence of drusen in between the RPE and the photoreceptor layers of the retina. Alternately, the drusen may occur between the RPE and Bruché's

³⁴⁹Bowne, S. Daiger, S. Malonel, K. et al. (2001) RP1 mutation analysis *In* Anderson, LaVail & Hollyfield eds., op cit.

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membrane, probably as a result of a breakdown in the delivery cycle of retinene to the RPE for conversion to the Rhodopins. (Pers. comm. Dr. C. Eifrig, Retina Assoc of Orange County). See Section xxx.

Lachenmayr & Vivell have provided an illustrated description of the concept of legally blind from the perspective of the authorities issuing driver's licenses³⁵⁰.

An unidentified author in Wikipedia describes the VTM condition as "causes a fatty yellow pigment (lipofuscin) to build up in cells underlying the macula. Lipofuscin is more often described as drusen in ophthalmology. Over time, the abnormal accumulation of this substance can damage cells that are critical for clear central vision. As a result, people with this disorder often lose their central vision and may experience blurry or distorted vision. Vitelliform macular dystrophy does not affect side (peripheral) vision or the ability to see at night." The discussion suggests it primarily disrupts the operation of the five degree diameter macula (which includes the much more significant 1.2 degree diameter foveola). The implication is that this is a dry type of macular degeneration that creates fuscus in the space between the RPE and the photoreceptors. It can thereby disrupt the spatial structure of the foveola thereby causing the photoreceptors to be displaced from their correct location (forming the Petzval surface) relative to the focal plane of the optical system. The result is a defocus and possibly a distortion of the imagery recorded by these sensory neurons.

18.8.9.4.3 Best's disease within macular dystrophy

The American Academy of Ophthalmology offers an internet site related to Best Disease from a clinical perspective³⁵¹. **Figure 18.8.9-9** illustrates the condition. As noted in the caption, the satellite lesions are probably not identifiable by the subject, but the center left lesion is centered on the point of fixation and generally fills the area behind the macula. The size of the lesions in Best Disease are usually given as 0.5 to 5.0 mm diameter. It is the fact that this lesion can involve the 1.2 degree diameter foveola that can result in serious loss of visual acuity and possibly local spatial distortion. The typical ophthalmological image of the type shown in the figure only encompasses a 25 to 40 degree diameter disc. These dimensions are developed in **Section 2.2.2** of Chapter 2.

³⁵⁰Lachenmayr, B. & Vivell, P. (1993) Perimetry and its Clinical Correlations. NY: Thieme Chapter 8

³⁵¹American Academy of Ophthalmologists (2014) http://eyewiki.aao.org/Best_Disease



Figure 18.8.9-9 Best disease with satellite lesions. Only the large lesion left of center is of concern here. It underlies the five degree diameter macula (which includes the 1.2 degree diameter foveola) and can cause a major loss in visual acuity and possibly local spatial distortion in vision. The lesion at right center is associated with the “blind spot” of vision and is of little concern. The other satellite lesions probably cannot be identified by the subject as a vision problem. From AAO website, 2014.

High performance OCT is a valuable tool for evaluating the character of macular dystrophy. It can now provide more precise descriptions of the form(s) of macular dystrophy such as vitelliform. See examples in **Section 18.8.3.5.3.**

18.8.9.4.4 Best's– vitelliform macular dystrophy ala Spaide et al., etc.

Kramer et al³⁵², have provided a broad paper on the forms of vitelliform MD. [xxx some good data but no imagery.] “In summary, this study demonstrates that mutations in the VMD2 gene are associated with both Best disease and

³⁵²Kramer, F. White, K. Pauleikhoff, D. et al. (2000) Mutations in the VMD2 gene are associated with juvenile-onset vitelliform macular dystrophy (Best disease) and adult vitelliform macular dystrophy but not age-related macular degeneration *Euro J Human Genetics* vol 8, pp 286-292

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AVMD but not AMD. Furthermore, AVMD appears to be a genetically heterogeneous condition and may include patients with a mild form of Best disease. This study provides an example of the use of genetic analysis to aid in the classification and clinical diagnosis of the retinal dystrophies.”

Spaide et al. have recently provided a study of a form of macular dystrophy with the purpose “To investigate and integrate the photographic, angiographic, and tomographic findings from a group of patients with various stages of vitelliform macular dystrophy type 2³⁵³. The paper includes many images of retinas assembled using the above techniques. Many images are only available through the supplemental material³⁵⁴ or the online version of the paper.. They examined nine patients in their private practice.

While their assertion, that chemically sensitive channels within the cells of the retina are involved is not supported within the paper or in this work, their overall introductory statement is useful,

“Vitelliform macular dystrophy type 2 (VMD2; also known as Best’s disease) is an autosomal-dominant disease caused by mutation in the gene coding for bestrophin, a Ca^{2+} -sensitive Cl^- channel protein located on the basolateral membrane of retinal pigment epithelial cells. Vitelliform macular dystrophy type 2 has a highly variable phenotypic expression, but complete penetrance of abnormalities in the rise of light current as measured during the electro-oculogram, which is related to defective Cl^- conductance from the flawed bestrophin protein.¹⁻⁵ In affected individuals, VMD2 is characterized by the variable deposition of yellowish material, often attributed to lipofuscin in the retinal pigment epithelium (RPE).”

They define a type 2 vitelliform macular dystrophy (VMD2) as specifically Best’s disease. They also note this type 2 has a highly variable phenotypic expression. *This statement indicates their efforts have not completely demonstrated the direct relationship between their presumed causal gene and the observed result among patients.*

Their conclusions described briefly in their abstract: “Similar to that seen in chronic central serous chorioretinopathy (CSC), patients with VMD2 have an accumulation of material on the *outer retina*, which may represent shed photoreceptor outer segments in association with subretinal fluid.” No formal Conclusion section was included in the paper but their Discussion section does discuss this finding in more detail. The term outer retina is shown in italics above as their discussion does not define this area as adjacent to the vitreous humor, or to the choroid.

Querques have commented on the above Spaide et al. paper³⁵⁵.

In a subsequent paper, Querques et al³⁵⁶. noted, “The exact locations of the vitelliform material in VMD, whether below, above, or inside the RPE, has not yet been conclusively determined, either by clinical or histological assessment. In most cases the yellow lesions slowly are absorbed, progressing to retinal atrophy. Visualizing exact intraretinal details with the higher imaging quality and resolution are essential to better understand macular diseases. In a recent study, using OCT, we described in adult onset VMD the location of yellowish material as under the sensory retina, but above the retinal pigment epithelium.” [xxx expand good imagery]

[xxx edit and expand]

Gamze Men et al³⁵⁷. have noted, “Best’s vitelliform macular dystrophy (bvmd) is an autosomal dominant disorder of the retina that presents with variable clinical appearance. Pseudohypopyon is the typical lesion of stage III BVMD. Few studies¹⁻³ on BVMD have employed optical coherence tomography (OCT) as the main observation procedure. We analyzed cross-sectional OCT images of a macular lesion in a case with stage III BVMD.”

³⁵³Spaide, R. Noble, K Morgan, A. & Freund, K. (2006) Vitelliform macular dystrophy *Ophthalmology* vol 113(8), pp 1392-1400

³⁵⁴<http://aojournal.org>

³⁵⁵Querques, G. & Noci, N. (2006) Vitelliform macular dystrophy xxx

³⁵⁶Querques, G. Regenbogen, M. Soubrane, G. et al. (2009) High-resolution spectral domain optical coherence tomography findings in multifocal vitelliform macular dystrophy *Surv Ophthalmol* vol 54(2), pp 311-316

³⁵⁷Men, G. Batioglu, F. Ozkan, S. Atilla, J. et al. (2004) Best’s vitelliform macular dystrophy with pseudohypopyon: an optical coherence tomography study *Am J Ophthalmology* vol 137(5), pp 963-965

Even in 2004, Men et al. note, "The site of the material accumulation in BVMD is a subject of debate."

"In the inferior part, however, broadening of the outer-retina-choroid-complex (ORCC) signal under retinal elevation was observed (Figure 2)."

Marmorstein et al. report, "Our understanding of bestrophin function, how mutations in bestrophin cause BMD, and how bestrophin may contribute to the transepithelial potential of RPE cells, requires knowledge of its tissue-specific expression patterns and its localization within the cell." Their imagery shows the build up of debris at the RPE/choroid interface (figure 5) and not at the RPE/OS interface as in the above discussions.

"Finding bestrophin on the plasma membrane by biochemical means is not sufficient to conclude that the protein is in fact a resident plasma membrane protein. Furthermore, if bestrophin is a resident plasma membrane protein, determining its polarity is critical to formulating models of bestrophin function."

[xxx review further.]

18.8.9.4.5 Chemical identification of the lipofuscin of macular dystrophy

Before reviewing the following literature, the mis-interpretation by the empiricists of the vision community concerning the use of red "safety lights" in the laboratory must be noted. This practice was introduced based on the practice followed in the photographic laboratory prior to 1940. At that time black and white photography was dominant and it became common following development of the original film image to wash the film to stop all development and then print the images using a second chlorine or bromine based photographic medium that was not sensitive to light at wavelengths longer than 500 nm (Mees, 3rd Ed., 1966, page 199). Thus a red "safety light" could be used effectively. With the advent of color photography in the late 1930's, the use of safety lights could no longer be used in dark rooms without detection of the light by the long wavelength sensitive film layers.

A search of the literature demonstrates the term fuscin is often used to label various molds or their byproducts (and in connection with mitochondria). The term lipofuscin is more appropriate when discussing the diseases of vision. The description of lipofuscin as a fatty yellowish compound is compatible with its potential to be a residue of a retinine that has not been properly absorbed by RPE cells prior to phagocytosis.

There is an active community (located primarily at Columbia University) seeking to identify the lipofuscin of macular dystrophy. No independent team has appeared that has corroborated the work of this community. It has apparently defined the structural character of the fuscin of macular dystrophy found between the RPE and outer segments (OS) of the retina. This end product appears to be a poly-retinoid probably involving an epoxide element interconnecting the individual retinoid molecules. Based on the conventional wisdom related to rhodopsin, the community has defined several potential paths leading to the creation of this material. The Electrolytic Theory of the Neuron, developed in this work leads to a much simpler path to the creation of this material.

The literature frequently uses the label lipofuscin to imply a lipid structure to this fuscin. Lipids can be saturated or unsaturated and there are many more precise chemical designations assigned to both types of lipids. In the case at hand, the materials are generally unsaturated, and in fact long chain conjugated carbon molecules. They are generally described as retinoids (**Chapter 5**; specifically **Sections 5.1.1, 5.2.3, 5.3.3, 5.5.1 and 5.5.4**) but can be described more specifically as retinines when the conjugated carbon molecule is in the diol condition (the presence of two oxygen atoms in a conjugated condition separated by conjugated carbon atoms).

Liu et al³⁵⁸. and Sparrow et al³⁵⁹. have provided valuable information concerning the "lipofuscin" associated with the aging retina, the accumulation of residue from the incomplete phagocytosis of the outer segments of sensory neuron receptors. Liu et al. have defined a material, A2E. "The major lipofuscin fluorophore, A2E, is a pyridinium bisretinoid." They propose, "A2E is generated from all-trans-retinal and ethanolamine, the former being released from photoactivated rhodopsin, and the latter being the head group of phosphatidylethanolamine (PE), an abundant

³⁵⁸Liu, J. Itagaki, Y. Ben-Shabat, S. et al. (2000) The Biosynthesis of A2E, a Fluorophore of Aging Retina, Involves the Formation of the Precursor, A2-PE, in the Photoreceptor Outer Segment Membrane *J. Biol Chem* vol 275(38), pp2935-29360

³⁵⁹Sparrow, J. Fishkin, N. Zhou, J. et al. (2003) A2E, a byproduct of the visual cycle *Vision Res* vol 43, pp 2983-2990

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membrane phospholipid. Nevertheless, the mechanism of production of A2E has not been demonstrated. Similarly, the site of its formation, whether within phagolysosomal compartments of the RPE cell or within the photoreceptor outer segment membrane before phagocytosis, remains unknown." They go on, "Evidence of a fluorophore being generated from reactions between phosphatidylethanolamine and all-trans-retinal was provided by Katz and co-workers who observed that incubating all-trans-retinal with isolated rod outer segments (ROS) resulted in the production of an orange-colored pigment with spectral and chromatographic properties similar to the product generated when retinal was reacted with synthetic liposomes containing PE. Nevertheless, the structure of this orange-colored fluorophore remained unknown." This is weak evidence in the light of modern investigative chemical techniques.

The analyses of the Columbia University group routinely assume the reaction between the presumed chromophore of vision, all-*trans*-retinal, and the lemma of RPE involves phosphatidylethanolamine, PE, rather than phosphatidylcholine, PC. PE is normally found on the interior leaf of the external lemma while PC usually constitutes the external leaf. Both molecules provide a nitrogen atom associated with the head group of the phospholipid. Reaction with PE would likely result in the fuscin collecting inside the RPE. Reaction with PC would likely result in the fuscin collecting in the IPM. The interior of the RPE is occupied by a variety of chromogens that are generally also fluorophores (**Section 4.6.2**).

[xxx expand these two excellent sources based on rhodoneine What is proof of a di-retinalyidine rather than a di-retinoid based on rhodoneine?] The introduction to the paper by Sparrow et al. is useful but many of the assertions are not supported by data at the detail level. As an example, does the accumulation of the di-retinoids occur within the RPE cell or on the external surface of the RPE in the Inter Photoreceptor Matrix? Light microscopy is not likely to be adequate to answer this question. The definition of A2-PE appears to be assumed based on conventional wisdom dating from the 1940's. Phosphatidylethanolamine (PE) is ubiquitous in cell (and specifically neuron) lemma. However, Parish et al. (1998) still notes, "The genesis of A2E, although speculative, could involve initial Schiff base formation between al-*trans*-retinal and ethanolamine or phosphatidylethanolamine to give a [1,6] proton tautomerization the enamine followed by Schiff base generation with a second molecule of retinal. This intermediate would undergo a [3,3]-sigmatropic rearrangement and subsequent autoxidation to yield fluorescent pigment A2E . ." The process appears overly complex!

Liu et al. observe, "The reaction of NRPE with a second all-*trans*-retinal to form a molecule of A2-PE (Liu et al., 2000; Parish et al., 1998), is likely to occur very infrequently and probably only when circumstances, including high levels of illumination (Saari et al., 1998), increase the availability of all-*trans*-retinal. Accordingly, the observation that exposure to bright light favors A2-PE formation, is perhaps explained by light-driven release of all-*trans*-retinal and supports the concept of a relationship between cumulative light exposure and the accretion of A2E by RPE." This is little more than the logical extension of a simpler concept from long ago. Their figure 4 incorporates a variety of epoxides that are more likely due to the rhodones (where oxygen is typically present at some of these locations) than the rhodopsins. "Investigations of the photochemical events that trigger the cell death have revealed that upon blue light irradiation, A2E self-generates singlet oxygen. The latter then proceeds to react with A2E at carbon-carbon double bonds along the retinoid-derived side-arms of the molecule to form epoxides." Their Section six asserts, "Whether other fluorophores in addition to A2E and its photoisomers contribute to RPE lipofuscin is not yet clear." "Yet, studies aimed at forging a link between the incidence of AMD and life-time light exposure have yielded inconsistent findings (Cruickshanks, Klein, & Klein, 1993; Darzins, Mitchell, & Heller, 1997; Taylor et al., 1992; West et al., 1989). Mounting evidence for the role of light in driving the formation of the RPE lipofuscin fluorophore A2E, together with the knowledge that this lipofuscin fluorophore can confer a susceptibility to blue light damage, begs a re-examination of this issue."

Fishkin et al³⁶⁰. of Columbia University have reported a slightly different synthesis leading to the formation of A2E. In their structural formula of figure 1, **P** represents the majority of the phosphatidylethanolamine (PE) and not just the phosphorous atom of that chemical. Their formulation would suggest the process of forming the fuscin is anchored to the phosphatidylethanolamine forming the inner surface of the RPE until the A2E is finally released from the modified PE. However, in another paragraph they assert the fuscin A2E is initially generated within the putative membrane of an ROS. This would involve the fuscin generation in a more complex relationship with the phagocytosis process.

The phosphatidylethanolamine residue remains a lipid but may not remain a functional portion of the RPE inner lemma. Thus, conglomerates of both A2E and the residue of PE must be examined as possible fuscin within the RPE. If the process involved PC rather than PE, the A2E and PC residue could accumulate within the inter-

³⁶⁰Fishkin, N. Jang, Y-P. Itagaki, Y. et al. (2003) A2-Rhodopsin: a new fluorophore isolated from photoreceptor outer segments *Org Biomol Chem* vol 1, pp 1101-1105

photoreceptor-matrix IPM.

Fishkin et al. have noted, “NMR and total chemical synthesis revealed A2E to consist of an unprecedented pyridinium polar head group and two hydrophobic retinoid tails (a pyridinium bis-retinoid). A2E is generated synthetically by the condensation of two molecules of all-trans-retinal adduct (vitamin A aldehyde) and a molecule of ethanolamine, hence the name A2E. However, within the retina, A2E biosynthesis (see Fig. 1) is initiated in the photoreceptor outer segment (ROS) membrane by a reaction between phosphatidylethanolamine and a single molecule of all-trans-retinal that generates a Schiff base conjugate (N-retinylidene-phosphatidylethanolamine, NRPE).” Note the use of the word unprecedented in the opening sentence. They did not demonstrate that A2E was the result of decomposition of any natural biological material. The NMR analysis may not normally surface the difference between rhodoneine and all-trans-retinal, because of the small difference in structure and molecular weight, unless the investigator was expecting the difference.

The Liu et al. paper relies upon the earlier Parish et al. paper³⁶¹ of 1998, from the same laboratory, to further describe the detailed structures of A2E and/or iso--A2E. They assert, “A2E is generated from all-trans-retinal and ethanolamine, the former being released from photoactivated rhodopsin, and the latter being the head group of phosphatidylethanolamine (PE), an abundant membrane phospholipid. Nevertheless, the mechanism of production of A2E has not been demonstrated. Similarly, the site of its formation, whether within phagolysosomal compartments of the RPE cell or within the photoreceptor outer segment membrane before phagocytosis, remains unknown.” Their figure 2 allows a more general procedure for obtaining a man-made equivalent of the naturally recovered material, particularly if one of the actual chromophores of vision is used as the starting material. A third option would be for the material to be generated within the inter-photoreceptor-matrix (IPM).

Mata et al. have studied the lipofuscin of the retina on the assumption it accumulates inside the RPE cells³⁶². Their experiments involved knock-out mice. They have also determined “A major fluorophore of lipofuscin is the toxic bis-retinoid, N-retinylidene-N-retinylethano-lamine (A2E).” They also note, “Lipofuscin accumulation in the RPE is also associated with Stargardt’s disease (STGD1) and fundus f lavimaculatus (FFM), recessive forms of macular degeneration that affect children. These allelic disorders are caused by mutations in ABCR. Heterozygous mutations in the ABCR gene may also predispose to AMD in a subset of cases.

Most of the above investigations involve both *homogenization* of retinas from animals, the believed synthesis of all-trans-retinal from stock chemicals and the intermixing of the presumed retinoid resulting from the homogenization step and the all-trans-retinal from the synthesis step. There was no demonstration that any of the recovered or synthesized retinoids were the actual chromophores of vision identified in Chapter 5 of this work, peak light sensitivity at 437, 532 or 625(610) nm when present in liquid crystalline form and illuminated by a light beam perpendicular to the surface of the liquid crystal.

Eldred & Katz³⁶³ provided a paper in 1988 at an earlier stage of exploration. It described a variety of miceles within RPE cells of donor eyes (ages 52-98 yr). Their data showed both absorbance spectra and fluorescent spectra. Eldred & Katz were unaware of the functional roll of the various micelles in RPE. The absorbance spectra indicated the micelles stored in the RPE were primarily chromogens lacking the precise structural chemistry required of active chromophores as developed in Chapter 5. Some of the micelles may have been fuscin, but they were not able to confirm that assumption at that time. Their data can be compared to the data of Wolken in Section 4.6.2.3.3. Eldred & Katz did describe a simpler structural chemistry for their potential A2E dating from the early 1980's; it called for the combining of two retinoids via a aliphatic conjugated chain containing two nitrogen atoms. They indicated their work did not support this hypothesis; and, “Alternative explanations for these spectra are difficult to put forth. Absorbance at 280 nm is typically associated with a substituted aromatic ring, as in the aromatic amino acids. Amino acids do not seem to be involved in these structures, however, based on the lack of reactivity with spray reagents designed for their detection (i.e. ninhydrin), and on the lack of any apparent amine or imine absorbance in FTIR analysis of the most prominent, orange fluorophore.”

Eldred & Lasky³⁶⁴ provided additional good background in 1993. It discussed the similarity between the natural

³⁶¹Parish, C. Hashimoto, M. Nakanishi, K. et al. (1998) The biosynthesis of A2E, a fluorophore of aging retina, involves the formation of the precursor, A2-PE, in the photoreceptor outer segment membrane *PNAS* vol 95, pp 14609-14613

³⁶²Mata, N. Wong, J. & Travis, G. (2000) Biosynthesis of a major lipofuscin fluorophore in mice and humans with ABCR-mediated retinal and macular degeneration *PNAS* vol 97(13), pp 7154 -7159

³⁶³Eldred, G. & Katz, M. (1988) xxx *Exp Eye Res* vol 47, pp 71-86

³⁶⁴Eldred, G. & Lasky, M. (1993) Retinal age pigments generated by self-assembling lysosomotropic detergents *Nature (London)* vol 361, pp 724-726

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miceles and potentially lipofuscin miceles within RPE molecules. Their figure 4 is particularly instructive. It shows thin-layer chromatogram for a variety of natural and synthetic fluorophores. Note they called them fluorophores rather than fuscin. They note the different migration rates for their synthetic fluorophores (in tracks 8 & 9) compared to the native orange-emitting fluorophores in lanes 1, 4 & 11. They also show (figure 2) a simpler structural form for their A2E, without a pyridinium ring containing a heterocyclic nitrogen. They propose a general structure of two retinoids attached to a single nitrogen contained within an aliphatic chain. In the concluding paragraph, they speculate, “Zinc is a cofactor to the retinol oxidoreductases. Disturbance of this enzyme activity *could* swing the balance of retinol/retinaldehyde toward retinaldehyde excess, which *could* then favour reaction with phosphatidylethanolamine.” This appears to be the first appearance of the concept of a combination of retinoids with PE. The use of “could” multiple times was italicized by this writer.

PE is usually present on the interior leaf of the bileaf external lemma of RPE. However, a closer look at phagocytosis is needed to ascertain how the retinoids of the disks can come into contact with this inner leaf.

A new term appeared during this time period. Autofluorescence is the natural emission of light by biological structures such as mitochondria and lysosomes when they have absorbed light, and is used to distinguish the light originating from artificially added fluorescent markers (fluorophores). Natural fluorescence would appear to be a more appropriate term, since autofluorescence suggests the material emits light *without* the benefit of stimulation by another light source.

Also of interest was the appearance of a second Eldred paper during the mid 1990's.

Eldred³⁶⁵ provided a paper in 1995 involving more exploratory research in a supplemental issue of Gerontology (vol 41, Supplement 2). It asserts that “One of the autofluorescent compounds that accumulates within the lipofuscin granules of the human retinal pigment epithelium (RPE) has now been identified as a quaternary nitrogen-containing cationic amphiphile (the bis-retinoid pyridinium salt, A2-E).” Under the label, “Role of the retinal pigment epithelium in the retina:” it provides a discourse on the operation of the retina in text form, unsupported by any graphical representation. While rational, the discourse is not justified in terms of continuity and contiguousness, merely citing a variety of individual authors contributing one concept or another. It does not address the normal function of the RPE in storing the chromogens of vision prior to their dispersal through the external lemma of the RPE into the IPM. These chromogens are stored as individual micelles within the RPE envelope (**Section 4.6.2**)

Under the label, “Accumulation of lipofuscin granules in the RPE,” Eldred does not recognize the normal function of the RPE in receiving chromogens from the choroid blood stream and their storage as micelles within the RPE until needed. Contrary to any assertions in the 1984 paper by Feeney-Burns et al., this function accounts for the buildup in micel volume within the RPE up to about age 50. One form of the disease macular dystrophy, appears to be due to the aggragation of non-chromogen micelles, within the RPE. These aberrant micelles are labeled fuscin or lipofuscin. Eldred appropriately labels these aberrant micelles in their observation, “RPE age pigments arise largely as a consequence of the photoreceptor outer segment renewal process.” Their key point is, “For reasons not previously known, the dismantling is occasionally not complete and as a consequence, there arise residual bodies, that in the course of time accumulate as lipofuscin granules in the cytoplasm.”

Eldred cites three of his earlier papers, and one paper submitted for publication, to support the conclusion that the aberrant micelles contain A2E or A2-PE. The submitted paper has not been indexed by Google Scholar as of 2016 under either the submitted title, or the submitted principle authors. In 2009, Giove et al³⁶⁶, including a W. Eldred, investigated the potential role of nitric oxide, NO, in macular dystrophy. Their findings focused on diabetic retinopathy and particularly vascularization failures as well as neural dysfunctions related to the stage 3 ganglion neurons. This subject will be reviewed in greater detail in **Section 18.8.9.5.2**. Eldred Discusses the “Mechanism of formation of A2-E” in this paper. Recognizing the presence of PE as the inner leaf of the external bileaf of the external lemma of RPE, he stresses, “Only upon disruption of the bilayer is it seen to be capable of reacting with the ethanolamine of phosphatidylethanolamine. Thus the reaction is likely to proceed only under rare conditions in the POS if disc membrane disruption occurs (as in the decomposing photoreceptor outer segment debris. . . More likely, the reaction occurs after phagocytosis and the membrane begins to be disassembled within the acidic environment of the RPE lysosome.”

Eldred discusses the rare conditions under which A2E is likely to form, thereby supporting this contribution to

³⁶⁵Eldred, G. (1995) Lipofuscin fluorophore inhibits lysosomal protein degradation and may cause early stages of macular degeneration *Geron* vol 41(suppl 2), pp14-28

³⁶⁶Giove, T. Deshpande, M. Gagen, C. & Eldred, W. (2009) Increased neuronal nitric oxide synthase activity in retinal neurons in early diabetic retinopathy *Mol Vis* vol 15, pp 249-2258

macular dystrophy as likely to be a disease of mid life and later. "That it takes years for the age-pigments to form is not surprising." Eldred concludes, "The structure of A2-E represents a new class of retinoid that has never before been described. . . Finally, this represents the first time that a potential direct biochemical link has been discovered between lipofuscin granule accumulation and an age-related disease process."

Gaillard et al³⁶⁷. have studied the photophysical properties on human lipofuscin. Their focus was on decay times, etc., of the natural and potential synthetic fluorophores. While useful exploratory research, the data does not relate to a specific model of the vision modality. They do identify their orange emitting fluorophore (OF) as radiating maximally, although weakly, at *ca.* 615 nm. This is an important wavelength associated with the L-channel chromophore of vision when present in liquid crystalline form. They note a stronger peak at ~490 nm. This wavelength can be compared to the omnidirectional peak absorption of both the retinene and retinine families when in dilute form. A related study by Reszka et al. focused on the photophysical properties of natural and potentially synthetic lipofuscin has been reported during the same time period³⁶⁸. Their work appeared to confirm the earlier work of one of the team members (G. Eldred) suggesting the lipofuscin contained a heterocyclic ring of nitrogen.

18.8.9.4.6 Alternate paths to the production of the lipofuscin of MD

This work proposes the lipofuscin labeled A2E arises from a significantly different series of events beginning with an actual chromophore of biological vision (a retinine) that is present on the surface of the opsin substrate rather than a retinene incorporated into the opsin.

As noted in **Section 5.1.1**, no demonstration of the spectral properties of all-*trans*-retinol or the broader family of the retinenes has ever occurred. It is the diol form of these conjugated retinenes, the retinines, that are the chromophores of biological vision. On the other hand, the retinenes and retinines are all natural fluorophors (autofluorophors).

----- Introduction

In order to discuss the dynamics involved in recycling the chromophoric material of the OS, it is mandatory to have a clear model of the physiological materials and processes involved. **Section 4.3.5** reviews the relevant data based on electronmicrographs. These clearly show the caricatures of R. W. Young from 1970 should be ignored (**Section 4.2**). There is no external cell membrane surrounding the disks of the outer segments. **Figure 18.8.9-10** is reproduced from **Section 4.3.5** and presents a proposed cross-section of that portion of the disk-chromophore-dendrite complex found in the Outer Segments after fabrication of the disks within the cup and calyx of the Inner Segment and their travel to the point just prior to phagocytosis of the farthest disks from the IS. The figure is idealized to show both the structure of the disk stack and the interface with the dendrite of the neuron found within the photoreceptor cell. Because of the aspect ratio of the individual disks, only a small fraction of an entire disk can be shown at this scale. The chosen fraction is that associated with the dendrite interface. The dendrite is shown at an expanded scale to highlight the internal elements of interest. It is virtually impossible to section both the disks and the dendrite (microtubule) in order to obtain a single electron micrograph capturing the detail shown here.

³⁶⁷Gaillard, E. Atherton, S. Eldred, G. & Dillon, J. (1995) Photophysical studies on human retinal lipofuscin *Photochem Photobiol* vol 61(5), pp 448-453

³⁶⁸Reszka, K. Eldred, G. Wang, R-H. et al. (1995) The photochemistry of human retinal lipofuscin as studied by EPR *Photochem Photobiol* vol 62(6), pp 1005-1008

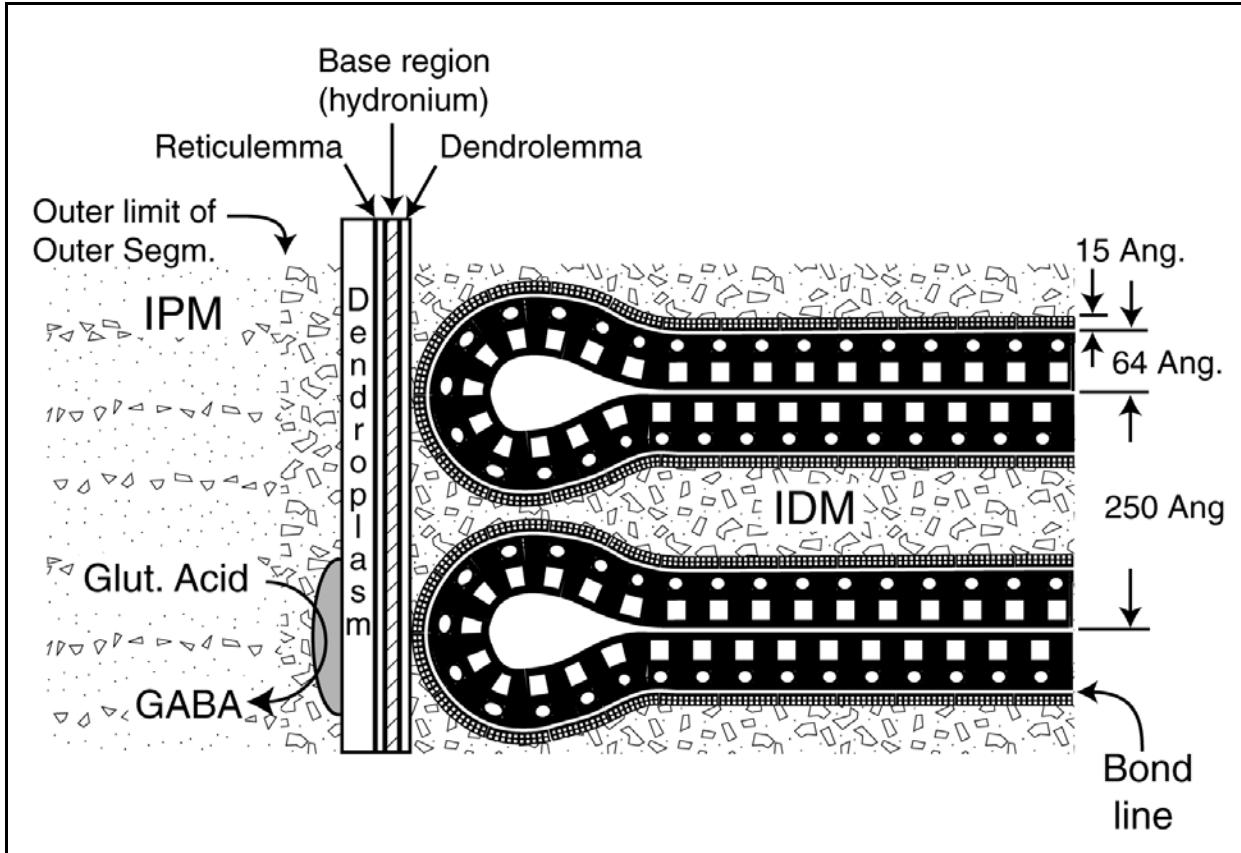


Figure 18.8.9-10 Details of the disk-chromophore-dendrite interface. The dendroplasm shown is that of the individual dendrite (microtubule). It does not surround the disks. The electrostenolytic process providing electrical potential to the dendroplasm is shown in the lower left. A molecule of glutamic acid is reduced to GABA and an electron is injected into the dendroplasm in this process. Diagram not to scale, see text.

The disks of the “fundamental photoreceptor complex,” shown in Section 4.5.1, are taken from the middle of a mature disk stack, from positions greater than #51 relative to the extrusion apparatus of the inner segment (IS) of the photoreceptor neuron. Each of these disks consists of two circular liquid crystalline films of the protein opsin (aka, rhodopsin although the retinal within the opsin is not involved in vision) merged along their periphery by a fold designed to isolate the hydrophobic ligand (shown as squares) of the molecules from the surrounding water-based solution. The large molecules of opsin result in a coarse structure containing only one molecule of retinal per opsin molecule. This retinal is not oriented properly for application as a photoreceptor, nor is it in the proper form, a conjugated diol form of retinine with the axis of each molecule parallel to the incident irradiation. On the outer surface of each opsin disk is a liquid crystalline coating of such a diol (ex. rhodonine(7) serving the M -channel sensory receptors). This coating is very densely packed and all chromophore molecules have their axis parallel to the incident irradiation, thus providing the high absorption cross section attributed to each molecule of the chromophore of each disk.

Following their useful life of nominally one week (two weeks as cited by Parish et al.), the liquid crystalline coating of the opsin substrates forming the outer segments of sensory neuron receptors of the retina must be recycled in some manner. There are several options at this point as shown in the following flow diagram, **Figure 18.8.9-11**.

[xxx expand text]

phagocytosed along with the protein-based substrate. This calls for the complete solubilization of the liquid crystal and the reuse of the chromophores to form new coatings on new substrates formed at the OS/IS interface or the transfer of the chromophore molecules through the RPE cell walls for temporary storage as micelles before their reuse as above.

The chromophores of the OS are normally solubilized and either returned to the IS/OS interface for re-application to a new disk or are transferred through the RPE cell lemma for temporary storage before reuse. Any process that causes the chromophore molecules of the OS to cross-link could result in the formation of a residue unsuitable for normal phagocytosis and further recycling of the retinines within the interphotoreceptor matrix (IPM). They would then require phagocytosis along with the remainder of the disks, primarily opsin, within the RPE.

If the RPE are unable to remove the cross-linking associated with the bi-retinines, and restore their normal chromogen configuration, the residue would constitute lipofuscin within the RPE.

The normal process of phagocytosis involves decomposition of the opsin material to a variety of peptides and one molecule of a retinene used in the formation of the opsin disks. If any of these materials cannot be returned to the bloodstream, they could constitute additional fuscus within the RPE.

18.8.9.5 Retinitis pigmentosa & diabetic retinopathy

Anderson and colleagues have long been associated with a symposia dedicated primarily to retinitis pigmentosa³⁶⁹ (RP). Later volumes rotate the name of the principle editor. In the 1991 edition, several authors have described RP as a broad group of diseases that are largely inherited. Genetically, McWilliams et al. (page 369) describe them as X-linked, autosomal recessive and autosomal dominant forms. Bhattacharya et al. (page 375) provide more details within these broad labels. The 1991 volume is based on historical views based on the chemical theory of the sensory neurons and depend largely on the 1970's morphological representation by Young.

In discussing “Isolated (non-syndromic) retinitis pigmentosa,” Merin³⁷⁰ offers the following definition (page 283); *Retinitis pigmentosa* has been defined as “a set” of progressive hereditary disorders that diffusely and primarily affect photoreceptor and pigment epithelial function. The term *rod-cone dystrophies* is often synonymously used to stress that rod function is affected earlier than cone function in most cases. The term *cone-rod dystrophies* (adjectives reversed) relates to another group of diseases in which cone function is primarily and earlier affected, although in late stages rod function may be affected to such an extent xxx.” These are not distinct, explicit and satisfying definitions.

Merin has noted that the first genetic mutation associated with retinitis pigmentosa was found exclusively in North America. “About 8% of that population with autosomal dominant retinitis pigmentosa have a mutation in which codon 23 codes for histidine (His), which is polar, rather than proline (Pro), which is nonpolar.” He does not address why a polar or nonpolar amino acid at a specific location in the subject’s DNA should affect the retina by causing retinitis pigmentosa. Retinitis pigmentosa is more a loosely defined syndrome than a single identifiable disease.

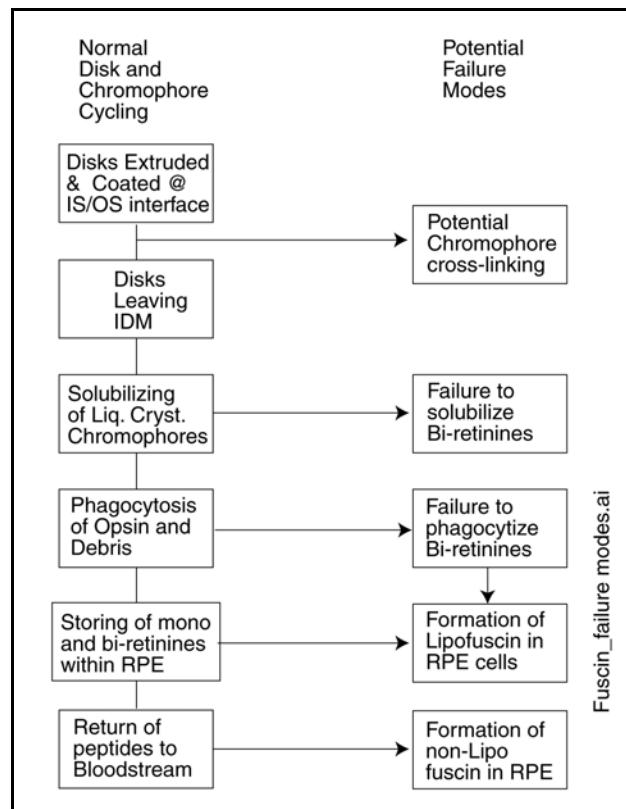


Figure 18.8.9-11 Operating and failure modes associated with lipofuscin in RPE cells. See text.

³⁶⁹Anderson, R. Hollyfield, J. & LaVail, M. (1991) Retinal Degenerations. Boca Raton, FL: CRC Press

³⁷⁰Merin, S. (2005) Inherited Eye Diseases. NY: Taylor & Francis

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18.8.9.5.1 Retinitis pigmentosa—Dry and Wet types

Merin has noted (page 11), “Often two or more genotypes lead to the same abnormal phenotype. In isolated retinitis pigmentosa, many genes are known to be involved, and a mutation of any of them may cause the disease. Some of these genes are dominant, others recessive, autosomal, or X-linked, and often the clinical picture does not allow one to differentiate among these different genotypes. In some cases, only the family history gives the clue for the type of inheritance involved.”

Retinitis is inherently a pain free disease and could be more appropriately named retinopathy pigmentosa. However, this label is more difficult to pronounce in English and retinitis pigmentosa (RP) has a long history. Retinitis pigmentosa is a collection of diseases not clearly defined in the literature. It is generally divided into two physical types, a wet type and a dry type. Clinically, the wet type is not precisely defined. In many cases, 1) it is generally associated with the build up of fluid between the photoreceptor cell (PC) layer of the retina and the RPE (located between the PC layer and Bruch's membrane adjacent to the sclera). It tends to cause major distortion of the PC layer with respect to the optical axis of the illumination reaching the PC layer. While the condition is traditionally described as pigmented, the pigmentation may not be due to the foreign fluid itself. In other cases, 2) it is associated with the growth of new small vascularization in the neural layer on the viscous fluid side of the retina. This vascularization can proceed rapidly and cause loss of useful vision in the periphery of the retina. The new vascularization is frequently frail and may result in hemorrhage into the viscous fluid.

The second class of wet-type retinitis pigmentosa is currently treated by photocoagulation applied to the peripheral retina with the intent of destroying both PC and RPE cells demanding oxygen for their sustenance, thereby reducing the demand of the vascular system. This treatment ignores the role of the peripheral retina in providing awareness mode and alarm mode information concerning the external environment as well as some binocular vision capability related to motion in the lateral far field of the eyes. An alternate treatment is becoming available involving injectables into the retina that suppress vascularization. The latter treatment is much preferred from a functional perspective and should be pursued within the medical community. Photocoagulation is a gross medical method that is incompatible with attempts to cure other forms of macular degeneration by expediting the removal of drusen and/or fuscin from the retina.

The dry type retinitis pigmentosa is generally associated with the build up of foreign material, debris, at one of several potential points within the retina, with different labels assigned to the debris. When found as small particles (>25 microns in diameter and observable with an ophthalmoscope) between the RPE and Bruch's membrane, they are labeled “drusen.” When similar size particles are found between the PC layer and the RPE layer, they are frequently described as “fuscin.”

The Discovery Eye Foundation provided the following on their website as of 2015³⁷¹. It reflects the common beliefs about the operations of the eye (particularly the concept of rods and cones). Where they speak of rods, they are generally speaking of the peripheral retina and the LGN-occipital lobe pathway. When they speak of cones, they are generally speaking of the photoreceptors found in the foveola and supporting the foveola-PGN-pulvinar pathway.

“Retinitis pigmentosa (RP) refers to a group of inherited diseases causing retinal degeneration.

The cell-rich retina lines the back inside wall of the eye. The cells within the retina capture and process images which are then transmitted through the optic nerve to the brain. People with RP experience a gradual decline in their vision because retinal photoreceptor cells (rods and cones) die. Forms of RP and related diseases include Usher syndrome, Leber's congenital amaurosis (LCA), rod-cone disease, Bardet-Biedl syndrome, and choroideremia, among others.

RP is typically diagnosed in adolescents and young adults. It is a progressive disorder. The rate of progression and degree of visual loss varies from person to person. Most people with RP experience loss of their peripheral vision but maintain their central vision until late in the disease.

What are the symptoms?

Symptoms depend on whether rods or cones are initially involved. In most forms of RP, rods are affected first. Because rods are concentrated in the outer portions of the retina and are triggered by dim light, their

³⁷¹Discovery Eye Foundation (2015) <http://discovereye.org/what-is-retinitis-pigmentosa/>

degeneration affects peripheral and night vision. When the more centrally located cones – responsible for color and sharp central vision – become involved, the loss is in color perception and central vision.

Night blindness is one of the earliest and most frequent symptoms of RP. People with mainly cone degeneration, however, first experience decreased central vision and ability to discriminate color.

RP is typically diagnosed in adolescents and young adults. It is a progressive disorder. The rate of progression and degree of visual loss varies from person to person. Most people with RP are legally blind by age 40, with a central visual field of less than 20 degrees in diameter. It is a genetic disorder and, therefore, is almost always inherited.”

The Discovery Eye Foundation attached **Figure 18.8.9-12** to their description. This figure is not a useful representation of the subject matter under discussion. The figure is more closely associated with a failure within the neural circuitry of the brain than with the retina. This figure resembles “keyhole vision” as frequently described as the result of major damage to the occipital lobe (frequently its complete destruction in warfare). As a result, the subject depends entirely on the foveola_PGN-pulvinar pathway for vision, including normal color perception. The diameter of the field of view is typically on the order of 1.2 degrees and represents the signals from only about 23,000 visual receptors (175 receptors in diameter).

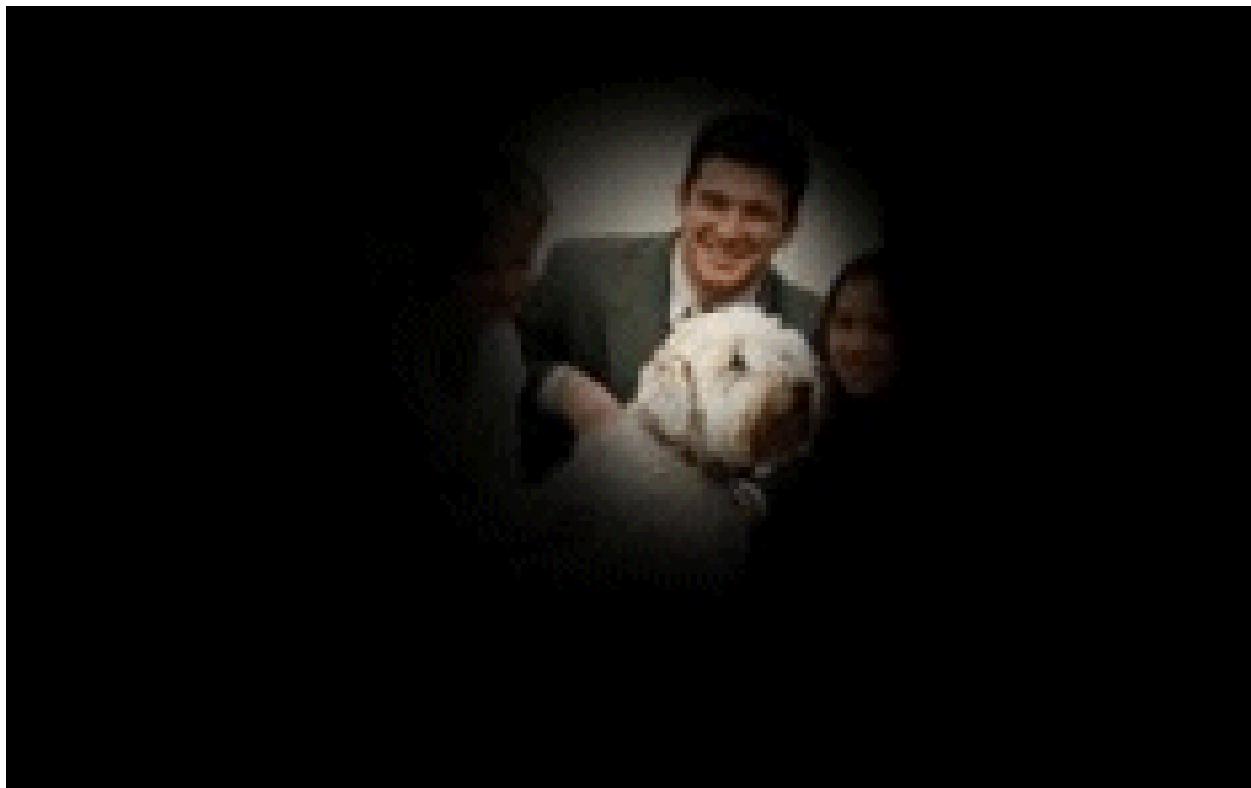


Figure 18.8.9-12 Common perception of Retinitis Pigmentosa. No dimensions relating to this representation were given. It is suggested here that the diameter is nominally 1.2 degrees. Alternate interpretations of the disease are common. From Discovery Eye Foundation, 2015.

Retinitis pigmentosa(RP) is a condition generally described as caused by over-activity of the pigmented retinal epithelial cells, leading to damage and occlusion of photoreceptors and blindness. Marmor has asserted that RP is

not a homogeneous disease³⁷². He reviewed a large number of his own patients and concluded; there was little correlation between RP and age of onset, little correlation between RP and the electroretinogram, and most importantly there was a shortening of the outer segments of the photoreceptors as RP progressed. The latter recognizes indirectly that the RPE is the source of the chromophores of vision that coat the disks of the outer segments (**Section 4.6.2.3**). Heckenlively, although dated, is the definitive work in this area³⁷³. He considers the disease a family of generally degenerative and frequently hereditary diseases. An anomalous ERP recorded as part of the ERG is frequently an early clinical sign of this disease. Schmidt categorizes this disease as one of tapetoretinal degeneration as opposed to the associated tapetochoroidal degeneration (choroideremia). Within the context of this work, the Outer Segments are probably affected by the irregular operation of the RPE.

Figure 18.8.9-13 shows the data of Marmor related to the age distribution of retinitis pigmentosa.

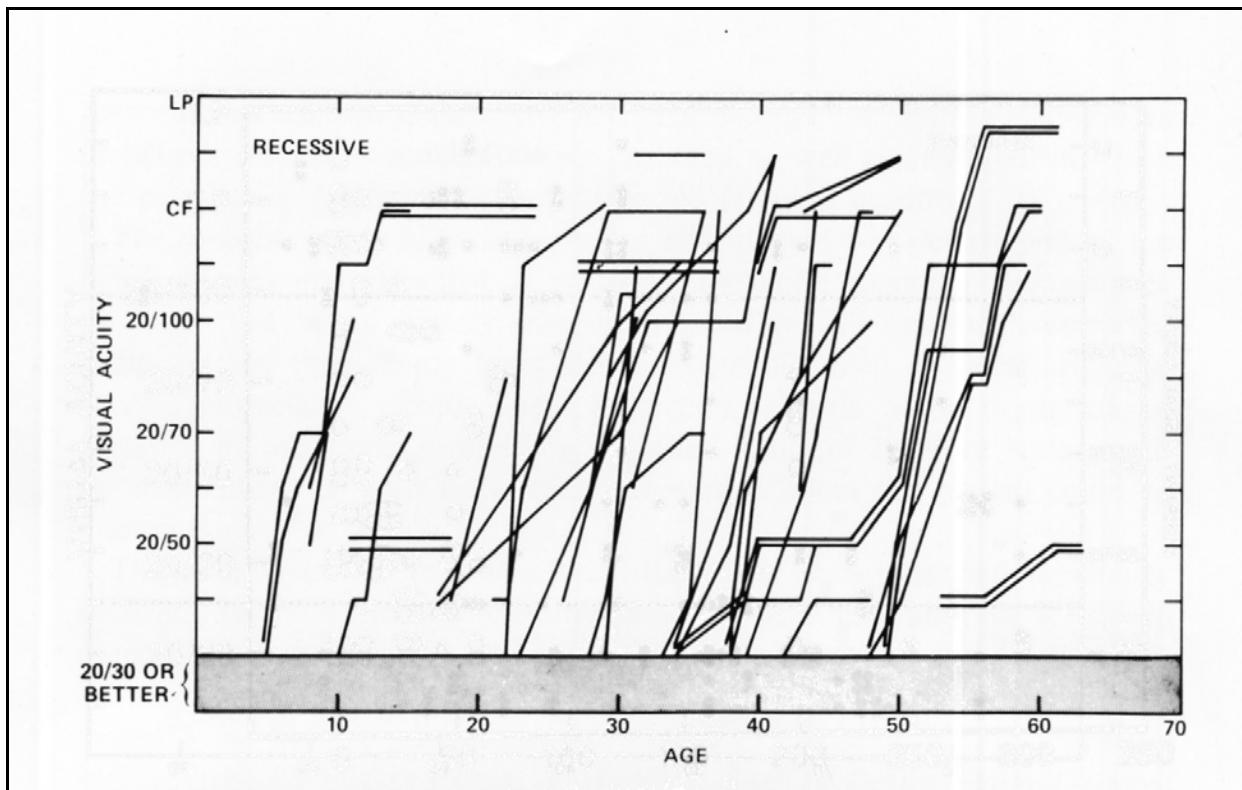


Figure 18.8.9-13 Visual history of eyes with recessive RP which could be traced over at least 5 years or a 3-line change in acuity. Each line connects all recorded acuities for one eye. Acuities of 20/30 or better are not discriminated. From Zauberman, 1979.

The description of Retinitis Pigmentosa as a family of diseases is supported by the variety of genetic abnormalities associated with this syndrome. See **Section 18.1.3.3**.

The disease is characterized by a circular mid-equatorial scotoma with foveal sparing. This characteristic suggests, and is consistent with, the unique nature of the foveola in the overall architecture of the visual system.

Leber congenital amaurosis (LCA) is a family of congenital (usually autosomal recessive) retinal dystrophies that results in severe vision loss at an early age. Patients present usually with nystagmus, sluggish or near-absent

³⁷²Marmor, M. (1979) Classification and prognosis in retinitis pigmentosa In Zauberman, H. ed. Proc Conf Subretinal space. Jerusalem (Documenta Ophthalmologica Proceedings Series volume 25) page 247

³⁷³Heckenlively, J. (1988) Retinitis Pigmentosa. NY: J. B. Lippincott.

pupillary responses, severely decreased visual acuity, photophobia and high hyperopia. These symptoms strongly suggest neuropathy of the neural engines in the region of the diencephalon controlling eye motions. Currently, there are 14 genetic mutations known to cause LCA. See **Section xxx.** and the EyeWiki provided by the AAO.

Usher syndrome is a relatively rare genetic disorder caused by a mutation in any one of at least 11 genes resulting in a combination of hearing loss and visual impairment, and is a leading cause of deafblindness. Usher syndrome is incurable at present. Wikipedia presents the most developed definition of this disease; however its description is the result of too many authors contributing to it.

Bardet-Biedl syndrome (BBS) is a ciliopathic human genetic disorder that produces many effects and affects many body systems. It is characterized principally by obesity, retinitis pigmentosa, polydactyly, hypogonadism, and renal failure in some cases.

Choroideremia (CHM) is a rare inherited disorder that causes progressive loss of vision due to degeneration of the choroid and retina. Choroideremia occurs almost exclusively in males. The first symptom, most commonly noticed in childhood, is night blindness. As the disease progresses, there is loss of vision, frequently starting as an irregular ring that gradually expands both in toward central vision and out toward the extreme periphery. Loss of acuity, depth perception, color perception and an increase in the severity of night blindness may also occur during this progression. The actual vision loss is caused by degeneration of several layers of cells essential to sight. These layers, which line the inside of the back of the eye, are called the choroid, the retinal pigment epithelium (RPE) and the retina.

18.8.9.5.2 Diabetic retinopathy

The terminology used in discussing this disease is not very consistent and of limited precision. The dimensions of the macula are seldom defined precisely. In this work, it is nominally 2.0 mm wide (~8 degrees) and 0.88 mm vertically (~3.5 degrees) centered on the point of regard (**Appendix L**). Some authors, particularly clinicians describe it as synonymous with the area within the 2.85 mm diameter of the parafovea (14.4 degree field). These are substantially different areas and are far greater than the 0.35 mm diameter (1.8 degree field) of the foveola associated with high resolution vision.

In 2009, Giove et al³⁷⁴, including a W. Eldred, investigated the potential role of nitric oxide, NO, in macular dystrophy. Their findings focused on diabetic retinopathy and particularly vascularization failures as well as neural dysfunctions related to the stage 3 ganglion neurons. [xxx expand]

The Discovery Eye Foundation provided the following on their website as of 2015³⁷⁵. The presentation included two short video clips. They note several forms of this retinopathy,

“Non-proliferative diabetic retinopathy can range from very mild which has small balloon-like defects in the retinal vessels (microaneurysms) to severe which has blockage of the retinal vessels which causes poor nutrition to the retina (ischemia).

Proliferative diabetic retinopathy occurs when the lack of blood flow becomes so severe that abnormal new blood vessels are stimulated to grow on the surface of the retina. These new blood vessels, called neovascularization, are fragile and can leak blood into the posterior chamber of the eye and cause what is known as a vitreous hemorrhage. As long as it is present, the blood can block the patient’s vision. Proliferative diabetic retinopathy is diagnosed by examination and fluorescein angiography.

Diabetic vascularization can also be located in **Figure 4.5.1-1** showing a cross section of the retina. Neovascularization is associated with the interneuronal matrix between the retina and the vitreous humor of the ocular. However, normal vascularization does not extend into the foveola. It is not clear whether neovascularization can extend into this area.

Macular edema occurs when the blood vessels leak fluid and the retinal tissue swells causing blurry vision. Clinically significant macular edema (CSME) can be associated with non-proliferative or proliferative retinopathy and is diagnosed by examination and optical coherence tomography (OCT). ”

³⁷⁴Giove, T. Deshpande, M. Gagen, C. & Eldred, W. (2009) Increased neuronal nitric oxide synthase activity in retinal neurons in early diabetic retinopathy *Mol Vis* vol 15, pp 249-2258

³⁷⁵Discovery Eye Foundation (2015) <http://discovereye.org/any-new-treatments-2/>

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The National Institute of Health has provided a bit more detail³⁷⁶; “Diabetic retinopathy may progress through four stages:

Mild nonproliferative retinopathy. Small areas of balloon-like swelling in the retina’s tiny blood vessels, called microaneurysms, occur at this earliest stage of the disease. These microaneurysms may leak fluid into the retina.

Moderate nonproliferative retinopathy. As the disease progresses, blood vessels that nourish the retina may swell and distort. They may also lose their ability to transport blood. Both conditions cause characteristic changes to the appearance of the retina and may contribute to DME.

Severe nonproliferative retinopathy. Many more blood vessels are blocked, depriving blood supply to areas of the retina. These areas secrete growth factors that signal the retina to grow new blood vessels.

Proliferative diabetic retinopathy (PDR). At this advanced stage, growth factors secreted by the retina trigger the proliferation of new blood vessels, *which grow along the inside surface of the retina* and into the vitreous gel, the fluid that fills the eye. The new blood vessels are fragile, which makes them more likely to leak and bleed. Accompanying scar tissue can contract and cause retinal detachment—the pulling away of the retina from underlying tissue, like wallpaper peeling away from a wall. Retinal detachment can lead to permanent vision loss.

Rahim et al. have provided extensive clinical data on the appearance and progression of diabetic retinopathy³⁷⁷. The condition is distinctly different from the appearance of “dry” macular degeneration. The imagery suggests blockages of blood flow within the retina on a much larger scale than involved in dry macular degeneration.

18.8.9.6 Augmented vision as an aid in retinal degeneration

There is significant interest in using augmented vision techniques (undergoing rapid development in the gaming, drone and general entertainment industries) to aid sufferers of retinal degeneration. The general approach would be to provide an expanded image of the image constituting the foveola, or a slightly larger diameter zone, above the actual field of view using electronics. This approach might provide a short term ability of the subject to continue living an independent life during the progression of a variety of retinal degeneration scenarios. The key to the success of this approach relies upon the viability of the central field of view, even in the presence of prosopagnosia. **Figure 18.8.9-14** illustrates this augmented vision approach when the subject suffers from prosopagnosia specifically. This prosthetic approach can only be considered as expedient as it does not cure the condition.

³⁷⁶<https://nei.nih.gov/health/diabetic/retinopathy>

³⁷⁷Rahim, S., Palade, V., Shuttleworth, J., & Jayne, C. (2016) Automatic screening and classification of diabetic retinopathy and maculopathy using fuzzy image processing *Brain Inform DOI* 10.1007/s40708-016-0045-3

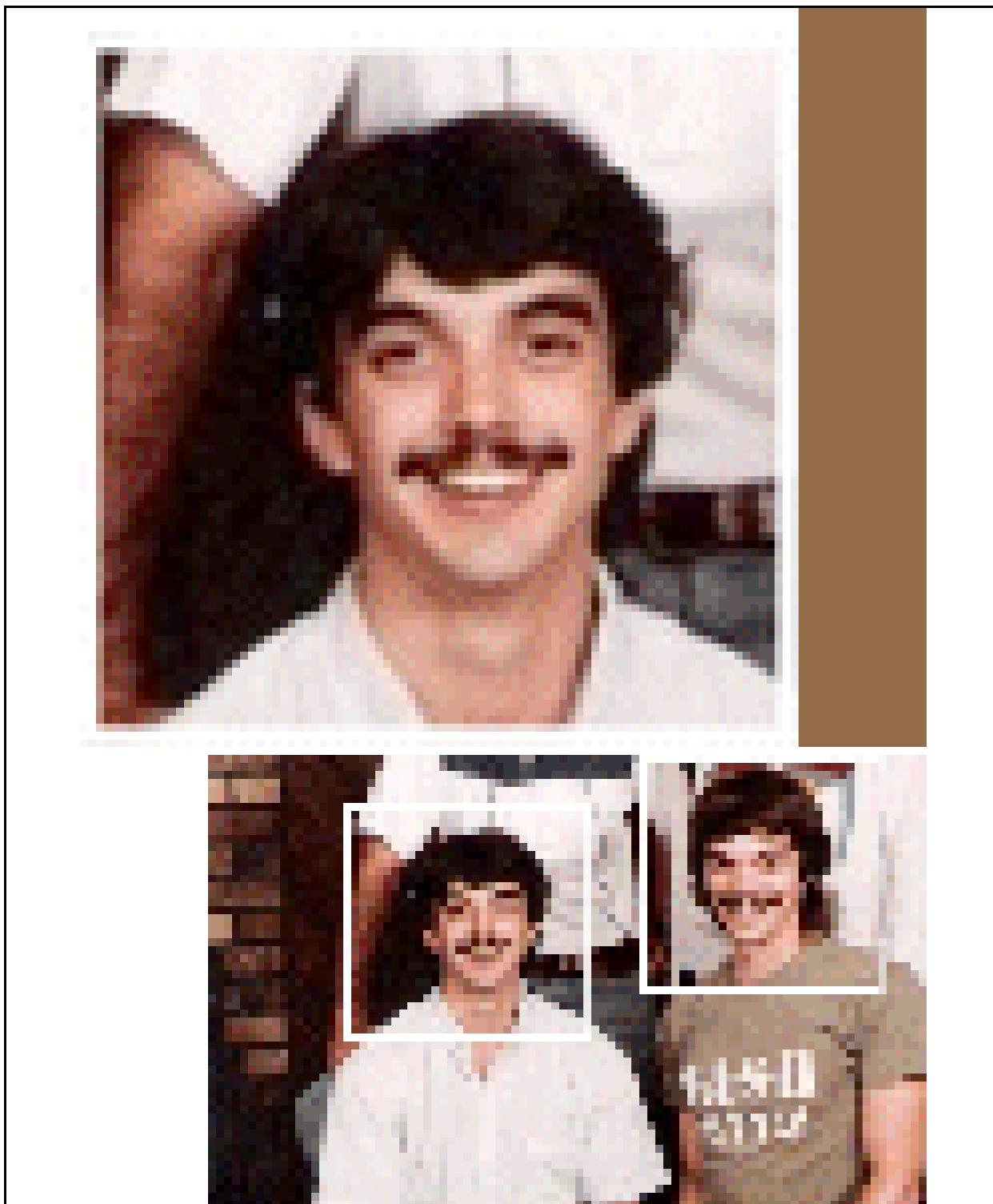


Figure 18.8.9-14 Augmented vision approach to overcoming prosopagnosia. The initial point of fixation is on the lower left frame where the subject can not differentiate between the lower two frames. The augmented image reproduces the region surrounding the initial point of fixation at a magnification of about 3:1 in a little used area of the visual field. By changing his point of fixation, the subject can identify the missing features associated with the central image associated with loss of performance in the PGN/pulvinar couple associated with the normal foveola. The subject still centers his line of fixation on the expanded picture presented in about a 5 x 5 degree field.

18.8.9.6.1 Implanted augmented vision devices

Da Cruz et al. have reported on the 5-year safety and performance of their Argus II Retinal Prosthesis System³⁷⁸. This system employs a multiple contact electronic array implanted at the retinal surface as an overlay to the terminus of the optic nerve. The array is provided with signals from an external video sensor mounted on a set of glasses and observing the scene ahead of the patient.

18.8.9.7 Aura, psychoses and other neural conditions ADD

18.8.9.7.1 Hallucinations related to fatigue & other migraine conditions EDIT

[coordinate with section 18.8.2.1]

Figure 18.8.9-15 illustrates a common condition encountered when the subject is under stress. Glaser describes the condition within the ring as a scotoma. The condition is quite variable, frequently the number of spokes within the ring is only 4, 5 or 6. The ring is frequently in the area of 2-8 degrees in outer diameter. It may be temporary, a matter of minutes if the visual system is taken away from work by sleep. Alternately, one subject had the problem for more than six months following surgery that involved extending his neck and possibly causing a blood inadequacy to his brain for a period of time sufficient to cause significant neural damage.

A related condition, macular sparing, is discussed briefly in **Section 18.8.1.2**. It is also discussed in **Section 2.8.1** related to the signal pathways of the visual system. These conditions help to define the size of the various signal processing regions of the visual system.

The hallucinations due to fatigue are not related only to various obvious areas of data merging within the visual system. In the case of the author and many others, shimmering tears appear occasionally in various areas of the field of view. They may be stationary or they sometimes float across an area of the retina. A few minutes of rest will frequently cause them to disappear.

18.8.9.7.2 Failures in geometric interpretation EDIT

McClosky has reported on a subject who has difficulty reading and grasping articles due to an apparent error in the signals representing stationary objects in her saliency map³⁷⁹. Misinterpretations of this type are considered a form of hallucination, particularly spatially correlated hallucinations (**Section 18.8.2.2**). This form can be described by the patient in graphical terms exhibiting significant geometrical distortion of the intrinsic scene itself. Some of the famous paintings of Dali (particularly the liquid clock) appear to be examples of this disease.

18.8.9.8 General misalignment of the photoreceptor of the retina

Normally, all of the photoreceptors of the retina are aligned to point toward the center of the aperture and exhibit an acceptance cone angle large enough to avoid any performance deficit relative to the location of individual optical

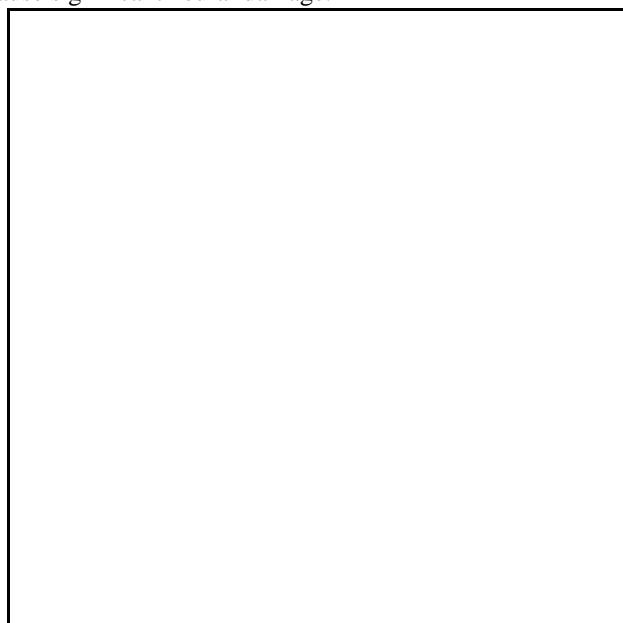


Figure 18.8.9-15 Failure modes related to inertial and hydraulic conditions within the eyes EMPTY.

³⁷⁸Da Cruz, L. Dorn, J. Humayun, M. et al. (2016) Five-Year Safety and Performance Results from the Argus II Retinal Prosthesis System Clinical Trial *Ophthalmology* vol 123(10), pp 2248-2254
[http://www.aaojournal.org/article/S0161-6420\(16\)30579-6/fulltext](http://www.aaojournal.org/article/S0161-6420(16)30579-6/fulltext)

³⁷⁹McClosky, M. (2009) Visual reflections: A perceptual deficit and its implications. New York: Oxford.
Also <http://web.jhu.edu/cogsci/people/faculty/McCloskey/> & McClosky perception.pdf in this folder xxx

rays emanating from the lens. If there is some reduction in overall visual performance due to the acceptance of off-axis rays by the photoreceptors, it is difficult to separate it from the loss in optical performance of the physiological optics alone in the Stiles-Crawford Effect.

Bedell & Enoch³⁸⁰ have reported a syndrome in one eye of a subject involving the misalignment of the photoreceptors relative to the entrance pupil. In this case, the photoreceptors are all pointing toward a point closer to the center of the eye than to the center of the aperture. The measurements were made in two orthogonal planes. Apparently the photoreceptors were aligned much more nearly perpendicular to the surface of the retina than was found in the other eye and in all eyes of close family members.

18.8.9.8.1 Tears in the retina causing gross mis-positioning of the photoreceptors EDIT

18.8.9.9 Failures associated with the pupillary function

Failures related to the pupillary function are distinctly benign because of the second order role the pupil plays in the overall operation of the visual system. Ellis has provided a schematic of the complete servomechanism associated with the pupil³⁸¹. Although noting that the signal source appears to be delivered to a specific set of ganglion cells in the retina, he does not describe the detailed location or characteristics of this source. Bremner has provided the best information on the operation and mis-operation of this servomechanism³⁸². His figure 10.1 is excessively brief and does not recognize failures in the retina and retinal path to the tectum that affect pupillary operation. Specifically, saturation in the photoreceptor cells (commonly found in hemeralopia and achromatopsia) can eliminate any signals from these cells needed by the midbrain to control the pupils. Similarly, a failure in the Pretectal nucleus can also result in faulty pupillary operation. Bremner does note the “OR logic” used within the midbrain when preparing the motor commands aimed at the sphincter muscle of the pupils. He also notes that defects in the afferent pathways may only be detected by observing the reactions [or lack thereof] of the pupils to light.

18.8.9.10 Floaters in the field of vision

Individuals have long reported “floaters” within their field of vision, with only anecdotal explanations of their cause from the clinical community. **Figure 18.8.9-16** provides a realistic representation of the two types of floaters commonly observed. The central squiggly line represents the leakage of blood between photoreceptors of the foveola. These are rarely observed in this form. They appear suddenly at the thick end of the line as they begin to shadow the adjacent photoreceptors. As the blood moves away from the foveola, it appears to narrow because the shadowing becomes less effective. The mechanism is like the deep shadow, or umbra, of the moon on the earth during a total eclipse versus the weaker shadowing within the penumbra during a partial eclipse. After leaking into the vitreous humor, the blood tends to form a spherical ball after which it appears as at upper right when it is near the retinal surface. When the blood drop is more than about six diameters from the retinal surface, no umbra or penumbra is observed. The presence of the blood drops in the vitreous humor can only cause a scattering of light and a slight reduction in the observed scene contrast. These floaters are defined as vitreous floaters. It is noteworthy that the natural desire to bring the dot at upper right to the line of fixation by rotating the eyeball is totally ineffective. The dot is immersed in the gelatinous vitreous humor and moves with the retina. It does not move under the force of gravity but does move with the minimal flow of the vitreous humor. This flow is approximately one degree per second in a perceived downward direction, that corresponds to an upward flow at the surface of the retina.

³⁸⁰Bedell, H. & Enoch, J. (1980) An apparent failure of the photoreceptor alignment mechanism in a human observer. *Arch. Ophthalmol.* vol. 98, Nov. pp. 2023-2026

³⁸¹Ellis, C. (1991) Disorders of the pupil *In* Swash, M. & Oxbury, J. Ed. Clinical Neurology, vol. 1 NY: Churchill Livingstone pp 432+

³⁸²Bremner, F. (1999) Disorders of pupillary function *in* Acheson, J. & Riordan-Eva, P. Fundamentals of Clinical Ophthalmology. London: BMJ Books pp 183-192

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In the lower center and lower right of the image are shown the second type, the lacrimal floaters. These floaters are very low contrast when viewed against a flat field, typically— but not necessarily— a blue sky. They are due to small dust particles, or even proteinaceous material, immersed in the lacrimal fluid (tears) lubricating the external surface of the cornea. These particles are out of focus because they are very near one of the principle points of the optical system. At this location, their image at the retina is their Fourier transform. As a result, the points appear as low contrast circles when their image is projected onto the retina. Because the lacrimal floaters are outside of the eyeball, they are subject to the force of gravity. They slowly drift toward the bottom of the field of view. If the subject tries to bring one of these floaters to the line of fixation by rotating the eyes, the floaters appear to lag behind the motion of the eyes because of their inertia and independence from the rotating eyeball. The floaters are actually moving in the opposite direction relative to the surface of the eyeball. In the absence of any rotation of the eyeball, these lacrimal floaters are perceived as moving downward at several degrees per second.

18.8.9.11 Night blindness

Merin (page 493) describes “Decreased night vision, usually referred to as night blindness or nyctalopia, comprises conditions in which the rod (low light level) vision mechanism is absent or subnormal. There is no parallel involvement of the cone (high light level) vision mechanism.” The two parentheses have been added for clarity as this work does not recognize the existence of functionally identifiably different rods and cones. He goes on to list five disorders potentially associated with nyctalopia;

“First, it may result from a nutritional factor, such as vitamin A deficiency and acquired or inherited visceral and gastrointestinal diseases.

Second, nyctalopia can result from inherited retinal dystrophies that primarily affect the rod system.

Third, decreased night vision can be related to the physiologic process of aging.

Fourth, other ocular disorders can reduce night vision by the selective involvement of the rod system.

Fifth, congenitally inherited disorders of scotopic vision, which are discussed in this chapter, affect the largest group of patients living in developed countries without serious malnutrition problems. They suffer from severe reduction or total absence of night vision.”

These five statements comprise a shopping list of anecdotal complaints rather than a functional description of a disease.

Merin does provide two distinct descriptions of dark adaptation in his chapter on night vision disorders. The one on page 495 looks remarkably normal and is reproduced as **Figure 18.8.9-17**. This figure should be compared with the normal human dark adaptation response in **Section 16.4.2** and the information in **Section 17.2.4**. The information on pages 508-511 provides more insights into possibly related diseases.

The figure from Merin indicates a significant problem in the electrostenolytic power supply to the photoreceptors of vision in this patient (**Section 8.4.6**) **Section 8.6.1.2** addresses how the common power supply to the photoreceptors provided via the RPE and choroid can account for the abnormal night vision performance of this patient.

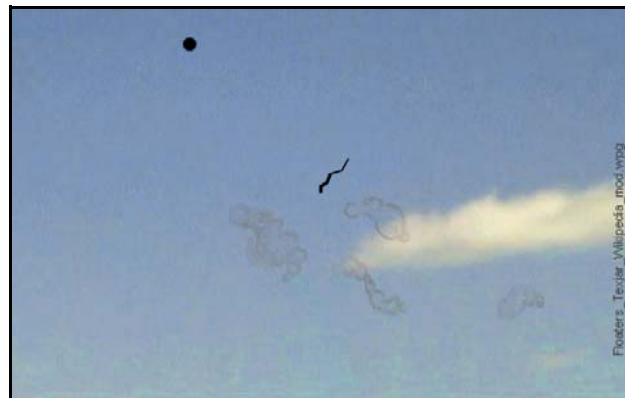


Figure 18.8.9-16 Floaters in the visual field. The black dot at upper left is a typical blood drop in the vitreous humor casting a shadow on the retina. The squiggly line is a rare image of a vascular leak from within the foveola. Below the squiggly line are the dust based floaters on the outer surface of the cornea. See text.

18.8.9.12 Unusual fluorescence of the retina

Unusual fluorescence of the retina is a sign of degeneration of the interface between the Outer Segment and the dendrites of the photoreceptor cell. The excited molecules of the chromophores are not able to return to their unexcited state through transfer of their energy to the base region of the Activas within the dendrites. See comments in Smith & Pokorny 1975, pg 163

18.8.10 Conditions following trauma to the visual system

18.8.10.1 Blindsight and other mind-blindness's

There is active debate relative to residual vision following significant trauma in the visual field^{383,384,385,386}. Cowey & Stoerig has presented a very well researched and convincing discussion (including nomenclature) followed by Stoerig & Cowey with additional details (perception of color). Zeki, et. al. provides a short summary of the clinical observations concerning this effect. Zeki, et. al. provides a thorough review of the Riddoch syndrome, including a series of definitions³⁸⁷. Zeki, et. al.(2) give a detailed account of one patient in a more recent paper³⁸⁸. A broad review of the psychology literature related to blindsight appears in Campion, Latto, & Smith³⁸⁹. Much of the material in that literature lacks specific calibration of the illumination and other parameters. There is also a frequent assumption that a scotoma is due to a failure in the photoreceptors of the retina. There is also frequent lack of definition of the extent of the cortex, with the pre-cortical area referring to the midbrain. In Campion, Latto & Smith, blindsight is defined as "visually guided behavior mediated by neural tissue other than striated cortex. They also recognize the multiple signaling paths from the retina to the cerebrum, and even provide physical proportions relative to these paths.

Stoerig published a very useful paper discussing the various clinical forms of blindness³⁹⁰. It includes an attempt to categorize the various forms. This categorization is consistent with, and can be considered a clinical interpretation of the material in this work. It also includes the picture of the monkey Helen grasping a raisin even though she suffered complete cortical blindness as a result of surgery³⁹¹. Stoerig was quite clear in one of his conclusions. "The exact role that the primary visual cortex plays in phenomenal vision (images containing both color and spatial cues) has not been studied sufficiently."

In 1997, Weiskrantz published an entire book centered on blindsight³⁹². It includes considerable material of a psychophysical nature. The book makes minimal reference to the analytical channel of vision or the critical role played by the PGN/pulvinar in vision (even in monkeys, pg 16). He does provide one figure, attributed to Rodman,

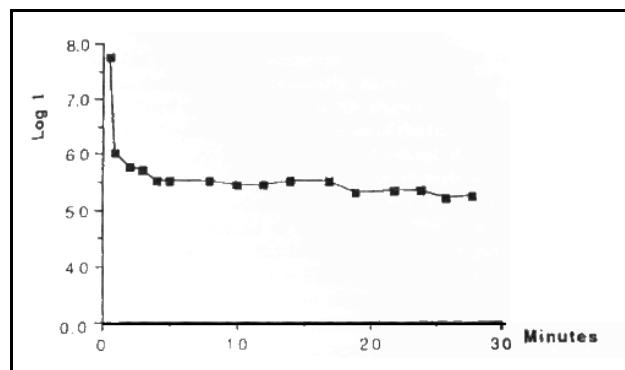


Figure 18.8.9-17 Dark adaptation curve of a patient with congenital nyctalopia and normal fundus. Note the exposine function of this response. "The monophasic curve has a cone level slightly higher than normal. There is no further decrease in threshold with time. No cone transition is apparent." See text. From Merin, 2005.

³⁸³Cowey, A. & Stoerig, P. (1991) The neurobiology of blindsight *TINS* Vol 14(4), pp 140-145

³⁸⁴Stoerig, P. & Cowey, A. (1992) Wavelength discrimination in blindsight *Brain* Vol 115, pp 425-444

³⁸⁵Miller, N. & Newman, N. (1998) Walsh & Hoyt's Clinical Neuro-Ophthalmology. Baltimore, MD: Williams & Wilkins pp 147-148 & 392-404

³⁸⁶Zeki, S. (1993) A Vision of the Brain. London: Blackwell Scientific Publications pp 347-350

³⁸⁷Zeki, S. Ffytche, D. (1998) The Riddoch syndrome: insights into the neurobiology of conscious vision. *Brain*, vol 121, pp 25-45

³⁸⁸Zeki, S. Aglioti, S. McKeefry, D. & Berlucchi, G. (1999) The neurological basis of conscious color perception in a blind patient. *Proc. Nat. Acad. Sci.* vol. 96, no. 24, pp 14124-14129

³⁸⁹Campion, J. Latto, R. & Smith, Y. (1983) Is blindsight an effect of scattered light, spared cortex, and near-threshold vision? *Behav. Brain Sci.* vol. 3, pp 423- 447

³⁹⁰Stoerig, P. (1996) Varieties of vision: from blind responses to conscious recognition *TINS* vol. 19, no. 9, pp 401-405

³⁹¹Humphrey, N. (1974) xxx *Perception* vol. 3, pp 241-255

³⁹²Weiskrantz, L. (1997) Consciousness Lost and Found. NY: Oxford Press

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et. al. on page 129, showing an alternate path from the retina through the superior colliculus to the pulvinar and then other areas of the cerebral cortex. Another similar figure on page 141 is useful and attributed to Karten & Shimizu (1991). The author restricts “terminology and other boring matters” to a four-page appendix addressing only four terms of interest here. He also notes the word “found” in the title should more precisely be “founded” as in foundation. While the data provided is very useful, no substantive model of the visual system is presented to account for these parameters and characteristics. Kenridge, Heywood & Weiskrantz have also published a brief paper³⁹³.

The overall discussion in the literature is limited in value due to two primary points. First, the term scotoma is not rigorously defined. A scotoma is a loss or reduction in the quality of perceived vision, generally surrounded by an area of normal performance. The failure resulting in the scotoma can occur anywhere in the visual system. Second, the discussion is poorly focused, primarily due to a lack of recognition of the role of the PGN/pulvinar couple and the pulvinar pathway in the visual system. The most notable features of blindsight involve continuing perception in the cortex anterior to area 7 in spite of major damage or resection of areas 17-18 and/or areas 19 through 22. Another major feature is the ability of the subject to track a visual image following damage to the above areas. Clearly, these two capabilities are centered on the analytical mode and the alarm mode respectively. The analytical mode is centered on the PGN/pulvinar couple and the alarm mode is centered on the combined LGN and POS. These are all elements of the thalamus. The occipital lobe (V1, V2, etc) is not involved in these tasks.

Campion, et. al. define the attributes of blindsight as; unconscious, subcortical and mediated by stimuli presented within the scotoma. This definition does not localize the scotoma, nor does it support visual functions in the cerebrum independent of the posterior occipital lobe. The Zeki school takes a broader view of blindsight. It will be addressed below.

The explanation of blindsight is relatively straightforward based on the theory of this work. The **awareness mode** of vision is dependent on the posterior cortex. However, the **alarm mode** and **analytical mode** are largely independent of this region. The tracking function occurs almost completely within the POS and is controlled by the TRN. The cerebrum is not significantly involved in this function except with respect to volition. The posterior cortex is not involved in this function at all. In the case of the **alarm mode** of vision, the LGN transmits signals to the TRN that again do not involve the posterior cortex. The perceptual function related to the foveola is also largely independent of the posterior cortex. It is primarily a function of the PGN/pulvinar and area 7 of the cerebrum. See **Section 15.2.2** and **Figures 15.2.2-2 & 15.2.2-3**.

The discussion of the locus of perception versus recognition becomes important in discussions of blindsight. Ptito, et. al³⁹⁴. have come closest to the correct interpretation when they suggested that neither striate nor extrastriate cortex is necessary for conscious perception, because their hemispherectomized patients retained some awareness of stimuli and were able to detect targets.

As a result of these mechanisms, patients frequently report residual vision to the consternation of the internist who have relied upon the conventional wisdom that all visual activity involves the posterior cortex. Weiskrants reported forced-choice experiments on his patient, involving small points of flashing lights, resulted in correct scores in more than 90% of the cases. The performance of his subject involved the normal operation of elements of the diencephalon and not the missing occipital hemisphere. **Figure 18.8.10-1** shows his convincing data originally from 1983.

³⁹³Kentridge, R. Heywood, C. & Weiskrantz, L. (1997) Residual vision in multiple retinal locations within a scotoma: implications for blindsight *J Cogn Neurosci* vol. xxx pp

³⁹⁴Ptito, A. et. al. (1991) Target detection and movement discrimination in the blind field of hemispherectomized patients. *Brain*, vol. 114, pp 497-512

Bennett & Hacker correctly noted the problem with Weiskrantz' explanation for blindsight, "The meticulous experimental work is impressive. But the conceptual apparatus which Weiskrantz invokes to describe the phenomena is defective³⁹⁵."

The performance related to the reporting of motion and direction, as well as color variation within the blindsight field is obviously due to the lateral geniculate nuclei reporting that information to the TRN and the insertion of that information into the saliency map. It is inserted into the saliency map alone in the absence of correlated information from the occipital lobe. Thus, the subject reports an awareness of these characteristics but is unable to associate these characteristics with any perceived shape associated with the external environment.

Confirmation of the signaling geometry proposed above is provided by a discussion of blindsight in Bridgeman & Staggs³⁹⁶. They report on a 27 year-old who suffered a severe traffic accident. He suffered a bilateral subdural hematomas over the occipital lobe (apparently excepting a small area of the left hemisphere within the calcarine sulcus). He was left with bilateral vision limited to a nine degree hemi-circle to the right, centered on the point of fixation. Yet, he was able to sense both moving and transient, but stationary, test targets introduced into his horizontal field of view over a range of ± 45 degrees. He also experienced some macular sparing. The investigators did not define this condition. However, it usually constitutes a 1.2 degree circle of vision centered on the line of fixation and representing the operation of the foveola and analytical mode of visual operation.

This subject appears to offer a well documented case of nearly complete failure of the awareness channels (except for the hemi-circle) yet normal operation of the alarm mode and apparently the analytical mode. The test protocol called for the subject to use a manual device to point to the target rather than let the POS reposition the line of fixation to the target. As a result, a learning process was introduced beyond that normally associated with the alarm mode. The data must be interpreted in this light. The POS was fully functional and the investigators rejected data where the subject responded by realigning his line of fixation by more than two degrees.

Additional informative comments related to blindsight appear in Stone³⁹⁷ and in Kennard & Rose³⁹⁸.

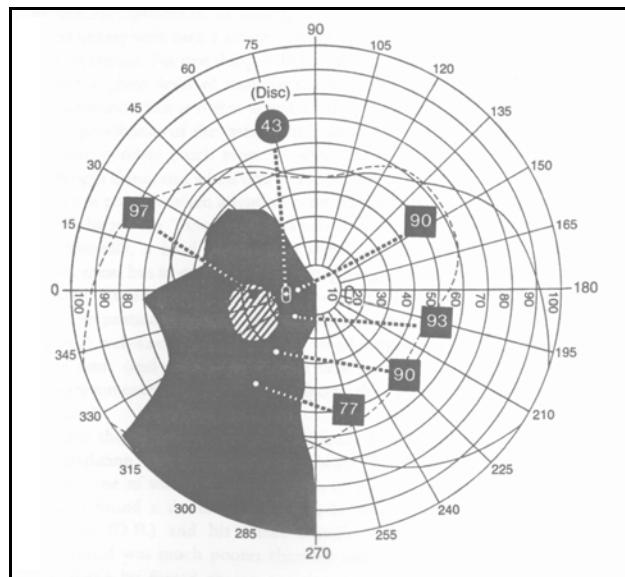


Figure 18.8.10-1 Blindsight results with D.B. when small lights were presented either in his blind field or on the genuinely blind optic disc. Numbers in the insets show the per cent correct values during 30 trials when the subject was required to guess whether a light had been presented (Chance = 50%). The hatched area represents the area in which D.B. had a feeling that something had been presented. From Weiskrantz, 1997.

³⁹⁵Bennett, M. & Hacker, P. (2003) Philosophical Foundations of Neuroscience. NY: Blackwell page 394

³⁹⁶Bridgeman, B. & Staggs, D. (1982) Plasticity in human blindsight. *Vision Res.* vol. 22, pp 1199-1203

³⁹⁷Stone, J. (1983) Parallel Processing in the Visual System NY: Plenum Press pg 355

³⁹⁸Kennard, C. & Rose, F. (1988) Physiological Aspects of Clinical Neuro-Ophthalmology Boca raton: FL: Year Book Medical Publishers pg 126

18.8.10.1.1 Trauma induced prosopagnosia

Caldara et al. have provided excellent information drawn from a constrained set of experiments and a good review of the literature of prosopagnosia³⁹⁹. The protocol used in the 2005 paper assumes the visual system is able to subdivide an image presented to the retina based on a set of octave-wide bandpass spatial frequency filters followed by further filtering of the data using a Gaussian spatial filter to sample the data within each frequency band. They provide no information as to how the neural system accomplishes the spatial band selection, which would normally require the use of transcendental functions that are foreign to the calculations within her deficit truly appears to be restricted to the category of faces. With faces, PS is able to categorize a face as a face, . . ." However, "this is in stark contrast with her inability to recognize previously seen or familiar faces and to match unfamiliar faces." neural system. They also assume the visual modality is able to sample an image using a Gaussian window because it is an easy spatial filter to use in the protocol. Their protocol was heavily focused on face recognition to the exclusion of other imagery. In fact, each subject was given a set of stylized facial images to study before participating in the experiments.

The important point is that there experiments were focused on a specific subject, PS, a 54 year old woman who sustained a closed head injury in 1991. The trauma primarily affected her ventral occipitotemporal cortex. They stressed that her "low level vision is almost perfect, her visual acuity being 8/10 in both eyes (August 2003), with a full visual field, apart from a small left paracentral scotoma. She reads normally (although slowly) and , crucially, does not present any problem at object perception and recognition, even for subordinate-level discriminations. Her deficit truly appears to be restricted to the category of faces. With faces, PS is able to categorize a face as a face, . . ." However, "this is in stark contrast with her inability to recognize previously seen or familiar faces and to match unfamiliar faces."

These investigators did not recognize the critical importance of the PGN/pulvinar couple in performing the recognition task. However, their work does suggest the stage 4 process of assembling the extracted information concerning a face may occur in the region of the ventral occipitotemporal cortex. This may also be the region associated with at least the visual portion of the saliency map. This subject is addressed more comprehensively in Section 19.10.1.

Their observation that "PS was more impaired in extracting information in high spatial frequencies, but did not differ from normals for low spatial frequency bands." strongly suggests difficulties related to her stage 4 information extraction mechanisms related to the PGN/pulvinar couple or the output from that couple.

18.8.9.8 Failures in geometric interpretation EDIT

18.8.10.2 Sudden complete loss of color vision

The condition of sudden complete loss of color vision following trauma is being reported more commonly⁴⁰⁰. Acquired achromatopia (without an s) is the appropriate clinical description. It is frequently associated with other forms of blindsight. A combination of forms of blindsight all point to damage to the feature extraction engines of the cortex.

18.8.10.2.1 Sudden changes in color perception

It is being reported more commonly that during a stroke (cerebral accident generally related to a blood clot), the subjects color perception may change significantly. Frequently, he reports a uniform color shift over a large part of the field of view (often the semi-circular field to the right or left of the point of fixation). This type of shift is easily reconciled with a change in the metabolic supply to the decoding stellate cells of the cortex associated with the

³⁹⁹Caldara, R. Schyns, P. Mayer, E et al. (2005) Does prosopagnosia take the eyes out of face representations? Evidence for a defect in . . . *J Cogn Neurosci* vol 17(10), pp 1652-1666

⁴⁰⁰Kandel, E. Schwartz, J. & Jessell, T. (2000) Principles of Neural science, 4th ed. NY: McGraw-Hill pp. 586-587

projection neurons of stage 3. Any such change can cause a change in the neutral point of the recovered chrominance signals compared to the expected quiescent value. A perceived uniform shading of the visual field is the result.

18.8.10.2.2 Sudden changes in color cognition

A researcher at Harvard (Jill) has reported her personal experience with a significant stroke. She struggled mightily following a significant size hemorrhage to regain her vision. After relearning to read, she continued having difficulty analyzing objects until someone suggested she use color as a cue. Her mind suddenly recognized that the visual system was providing color information and had been for some time. However, the mind was not using the information. She had to teach the cognitive part of her brain to use the perceptual information already available.

18.8.10.3 Detachment of the retina

Simple trauma can result in detachment of all or part of the retina from its normal association with the RPE. This detachment may appear as a simple tear or a more significant dislocation. Section 4.5 illustrates the overall photoreceptor-IPM-RPE complex and how tearing can occur.

Anderson, et. al. have provided significant laboratory information related to retinal detachment and re-attachment in cats⁴⁰¹. Their data stresses the importance of rapid repair of such damage. Due to the sensitivity of the chromophores of vision to attack by oxygen, it is suggested their use of air to aid in retinal repositioning relative to the RPE is unwise. The use of dry nitrogen or other unreactive gas would be preferred.

It has become common to surgically repair damage due to retinal detachment in human subjects. The repair should be done as soon as possible. The residual problems are discussed briefly in Anderson, et. al. and additional references are provided.

18.8.10.4 Loss of the lens of the eye, aphakia

Stark (having one aphakic eye) has reported extensively on his condition (<http://starklab.slu.edu>). Much of the information was used in **Section 17.2** to describe the difference between the tetrachromatic performance of the human retina versus the largely trichromatic (except for a cusp in sensitivity near 300 nm) performance of the overall human eye⁴⁰². Data has been presented for both the fovea and a position 5.5 degrees temporally. The conditions were both dark and chromatically adapted.

A caution is offered concerning the pair of before-and-after pictures presented on the above website of Professor Stark. These paintings of a lily pond were drawn by Monet before and after cataract surgery. They hang at Giverny. First, there is a question of where the artist obtained paints appropriate for reproducing the ultraviolet on canvas. Second, it must be noted that neither the typical printing press or the typical cathode ray display device can reproduce a picture containing colors found within the ultraviolet region. Nor can the eyes of the normal reader sense such colors.

Another description of aphakic vision has been offered by Anderson, a medical surgeon but not an ophthalmologist or optician. His report is analyzed more completely in **Section 17.2.2**.

18.8.11 Surgical repair of significant retinal damage/disease

18.8.11.1 Surgery for repair of retinal damage

This area is beyond the scope of this work. An introductory discussion of this subject is found at <http://www.surgeryrmh.unimelb.edu.au/FSM/Surgery/Diploma%20Modules/resources/eye.htm>

18.8.11.2 Surgical implants to circumvent retinal damage

The period, beginning in the late 1980's, saw the first surgical attempts to circumvent blindness in living human subjects. Prior to 2000, the activities were entirely research oriented. Several approaches have now reached the

⁴⁰¹Anderson, D., Guerin, C., Erickson, P., Stern, W. & Fisher, S. (1986) Morphological recovery in the reattached retina. *Invest. Ophthal. & Visual Sci.* Vol. 27, pp 168-183

⁴⁰²Stark, W., Wagner, R. & Gillespie, C. (1994) Ultraviolet sensitivity of three cone types in the aphakic observer determined by chromatic adaptation. *Vision Res.* vol. 34, no. 11, pp 1457-1459

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clinical demonstration stage but as Dowling noted in 2009, “the restoration of some vision using these devices will be a great achievement. However, none of these retinal prosthesis systems will restore anything resembling normal vision in the near future.”

Early work at the University of Utah focused on the assumption that there was a detailed spatial map of object space formed on the rear surface of the occipital lobe. Although the map was not conformal, it was assumed that specific areas could be located that could be excited electrically to cause perception of an object within the field of view of the eyes in object space. Work involving this approach has slowed following several experiments implanting wires contacting the cortex for purposes of excitation.

A group at the University of Louisville in Kentucky has been working on the physical replacement of retinal tissue, of both the RPE and of the photoreceptor layers. <http://www.louisville.edu/medschool/ophthalmology/aramant.htm>

The most innovative work going on currently is a cooperative effort between Johns Hopkins University and North Carolina State University. <http://www.irp.jhu.edu> This effort has advanced to the insertion of a photosensitive silicon chip into the eye for the purpose of sensing light and directly stimulating neurons of the retina on their way to the optic nerve.

Section VI of Hollyfield, Anderson & LaVail provides a recent survey of some of the exploratory activity in this field (mostly in Europe)⁴⁰³.

Jason Dowling has provided an excellent update as of 2009 on the status of retinal implants, both epiretinal and sub-retinal (in the space between the RPE cells and the biological sensory receptors)⁴⁰⁴.

18.9 Deficiencies related to reading and object recognition EDIT

The interpretation of reading problems is difficult in the absence of an extensive model of the visual system. Many authors have attempted to categorize the potential problems associated with reading. Newell has provided an outline of reading deficiencies three levels deep and containing over 25 headings but with less than two pages of discussion⁴⁰⁵. **Section 7.5.3** contains some information on the dynamics of the oculomotor system in the context of reading. **Section 17.8** addresses the fundamental performance of the visual system associated with reading. A brief summary of the function and disabilities associated with reading appear on the web page, www.sightresearch.net/reading/

Section 19.10.4 has recently been expanded considerably based on recent research related to reading and the PEEP procedure used to control the detailed movement of the eyes during reading.

Newell's list is a thoroughly mixed one based on clinical observations of a great number of reading deficiencies. He notes, part of the mixing may be due to the lack of clear terminology. His major categories are Learning disabilities, Sociopsychologic, Psychophysiological and Psychologic. These headings clearly suggest a multidimensional matrix of deficiencies. Newell did segregate reading deficiencies into two time domains compatible with this work.

Learning disabilities is a generic term for a broad range of symptoms related to reading, writing, mathematical and reasoning skills. This work will concentrate only on the reading aspects of this category. Furthermore, this work will focus on reading deficiencies where a clear internal functional shortcoming can be defined that is not due to shortcomings in maturation, physiologic optics, oculomotor subsystem operation or external forces. Thus, it will concentrate on Newell's categories of Psychophysiological and the two subheadings of language disabilities under Learning disabilities. This condenses the list of discussion points to include;

- I Learning disabilities
 - B. Specific (or primary) language disability
 - 1. Reading
 - 2. Spelling
 - 3. Word recognition

⁴⁰³Hollyfield, J., Anderson, R. & LaVail, M. (1999) Retinal degenerative diseases and experimental therapy. NY: Kluwer Academic/Plenum Publishers, pp 463-508

⁴⁰⁴Dowling, J. (2009) Current and future prospects for optoelectronic retinal prostheses *Eye* vol 23, pp 1999-2005

⁴⁰⁵Newell, F. (1986) Ophthalmology, 6th ed. St. Louis, MO: C. V. Mosby, pp 151-152.

- C. General language disability
 - 1. Arithmetic (dyscalculia)
 - 2. Writing recognition (dysgraphia)

III Psychophysiology

- B. Cerebral palsy
- E. Progressive neurologic disorders
- F. Acquired alexia (right hemiplegia, left hemisphere lesions)

The subject matter will not be treated in this order or constrained to these topics (as defined). In addition, this work will discuss the initial learning cycle that leads to the nominal reading capability of the subject.

In the context of Newell, the process of reading involves two short-term time intervals plus a permanent memory. His description of these time intervals is not consistent with this work. Modifications of his terminology will be used here. His *visual information storage interval* of about 0.25 seconds corresponds to the time interval required for the two-dimensional correlator of the midbrain to prepare an interp of the scene imaged upon the foveola. His *short-term storage interval* is undefined in duration but involves the mechanisms he describes as “encoding, organizational, or retrieval skills. . .” He notes that this interval appears not to involve verbal and linguistic processes primarily, although inability to recognize and pronounce words follows from the reading defect.” This interval corresponds to interval required for the mechanisms related to converting interps into percepts. Since these processes occur continually in a recurring time sequence, it is difficult to assign a finite number to this interval without a very clear definition of each and every mechanism. However, values should soon be available from fMRI tests related to this interval.

18.9.1 Alexia BRIEF

Alexia, the inability to read, can be described in degree as well as source. If partial, the condition is described as either neurological dyslexia or acquired dyslexia. An example of these problems is the ability to read large type letters but not small type. The same situation can arise in recognizing fine patterns that are not symbolic. In this discussion, the term dyslexia is not limited to those subjects who see symbols reversed. Such performance is suggestive of a broader difficulty centered on the failure of the two-dimensional correlator to provide concise interps or the cerebellum to accept generic interps and create low level percepts.

See also **Section 18.1.3.1.2.**

18.9.1.1 The condition of “Mr C”

Dehaene presents a long textual report on “Mr C” following trauma in 1887 (an infarct involving the left posterior cerebral artery confirmed at autopsy in 1892)⁴⁰⁶. The text makes it clear that the condition did not lead to blindness in the conventional sense. It did result in the loss of his ability to read. The loss involved the reading of individual letters as well as full words. Interestingly, it did not involve the loss of ability to read numbers and groups of numbers (even when presented in the same font).

The condition indicated a loss of performance related to the signal paths from the perigeniculate nucleus (PGN) and pulvinar as he reported a loss of high resolution vision particularly as it related to reading. From this background, Darjerine proposed “that Mr. C’s brain lesion had disconnected the fibers that fed visual information to a region that he called the “visual center for letters.” This work would suggest an alternative situation. That the information bearing path from the “visual center for letters” within the pulvinar was disconnected as it reached the association area. This left the “visual center for numbers” and the visual centers for extracting information concerning other elements of a scene (recognizing faces) within the pulvinar undamaged.

“To fully explain how the lesion of some visual areas could selectively alter reading, Dejerine (the physician) appealed to a concept of ‘disconnection’ . . . he emphasized that Mr. C;s lesion partially encroached on the ‘white matter’— the vast fiber tracts that connect distant areas of the brain.” The white matter was formed of the stage 3 signal distribution axons from the PGN & pulvinar. Confirmation that the damage resulted in the loss of signals from the PGN/pulvinar resulted from the assertion, “On Mr C;s right, the visual world seemed to be blurred.” Dehaene did not provide any finer description of the right field.

⁴⁰⁶Dehaene, S. (2009) Reading in the Brain. NY: Viking pgs 54-65

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The cases discussed by Dehaene resulted in a clarification of terminology related to the performance of the central region of the field of view surrounding the line of fixation..

Pure alexia– Inability of the visual portion of the pulvinar to extract textual information from letters and letter groups (words) *alone* from a scene and deliver the information to the association areas near the junction of the left parietal-temporal-occipital lobes. This phenomenon is frequently referred to as “alexia without agraphia.”

Pure agraphia– Inability of the visual portion of the pulvinar to extract graphical information (as opposed to textual and numeric information) *alone* from a scene and deliver the information to the association areas near the junction of the left parietal-temporal-occipital lobes.

Pure anumeria– Inability of the visual portion of the pulvinar to extract numerical information from numbers and number groups *alone* from a scene and deliver the information to the association areas near the junction of the left parietal-temporal-occipital lobes.

These definitions are precise enough to support Mr. C’s ability to perceive characters, numbers and shapes drawn on the surface of the palm of his hand (scene data entered via his somatosensory modality). Mr C exhibited a visual condition most aptly labeled “alexia without anumeria *or* agraphia.”

Care must be taken in expanding or using analogies for these terms. Dehaene incorrectly associates pure alexia with what he calls “aptly termed verbal blindness.” Verbal blindness more precisely describes a subjects inability to report, via the oral modality, the output of the pulvinar–association pathway his alexia or agraphia etc.. Verbal blindness may be due to a failure between this junction area (BA 22, 41–42) and the portion of the CNS dedicated to the production of speech (Broca’s speech area, BA 44–45). These BA numbers are currently being refined using the data gathering capability of MRI imaging.

Deheane went on (page 61) to note that MRI analysis has allowed other areas of traumatic damage near the left parietal-temporal-occipital junction to be defined that inhibit the proper processing of color, motion, etc. However, his definition of a portion of this area (on page 62) as the “letter box area” would not have been asserted if his top level schematic of the neural system isolated damage to the stage 3 decoding neurons in this area from the actual stage 4 association neurons in this area. Dehaene does delineate the variety of failure modes more carefully at the bottom of page 62 although his assertion that the outcomes are the same is imprecise (verbal blindness as an example). His cartoons on page 63 need updating. The discussion and illustration on page 64–68 appear to need updating and clarification also. Broca’s area is not shown although some of the areas orthodromic to it are (the premotor and motor areas of speech). Wernicke’s area (BA 22,41–42) is not discussed or illustrated appropriately

18.9.2 Symptoms of autism impacting reading and object recognition BRIEF

It is appropriate to incorporate a short discussion here because of the recognized ability of some savants, particularly those suspected of being somewhere on the autism spectrum of social impairment. Some of these people exhibit extraordinary memory capacities associated with both/either reading and text memorization or memory and object recognition related to extremely complex scenes. Both of these symptoms frequently appear at about age three when the brain is still plastic. The social interaction difficulties may signal the onset of autism at a time when the brain, primarily the TRN, is allocating the available neural surface of the cerebrum and pulvinar to different stage 4 information extraction functions. Allocation of a greater percentage of the available neural surface to functions and memory required for reading and object recognition could relate to autism.

There are many videos now on the internet illustrating the capabilities of various savants and frequently their autistic tendencies.

Stephen Wiltshire is known to be able to draw street scenes and maps with spectacular levels of detail. following only brief viewing of the material. Unfortunately, the term brief is only used in the anecdotal sense at this time. His life is focused on his drawing almost to the exclusion of speech. Does this suggest a greater allocation of neural surface to the visual senses than to speech generation?
<http://www.stephenwiltshire.co.uk/>

Alonzo Clemons is a very talented artist capable of rendering animals in remarkable detail using moldable materials very rapidly, using his bear hands almost exclusively . Like many others on the autistic spectrum, he loves spending time with his animals, particularly horses, but speaks and interacts sparingly with other humans.

http://www.artsales.com/ARTists/Alonzo_Clemons/

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$R(E) = C_S' \ln \int (E \times S) dl + C_M' \ln \int (E \times M) dl + C_L' \ln \int (E \times L) dl$	Eq. 18.1.3-1	47
$P(E) = \pm C_P'' (C_S' \ln \int E \times S dl - C_M' \ln \int E \times M dl)$	Eq. 18.1.3-2	47
$Q(E) = \pm C_Q'' (C_M' \ln \int E \times M dl - C_L' \ln \int E \times L dl)$	Eq. 18.1.3-3	47

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