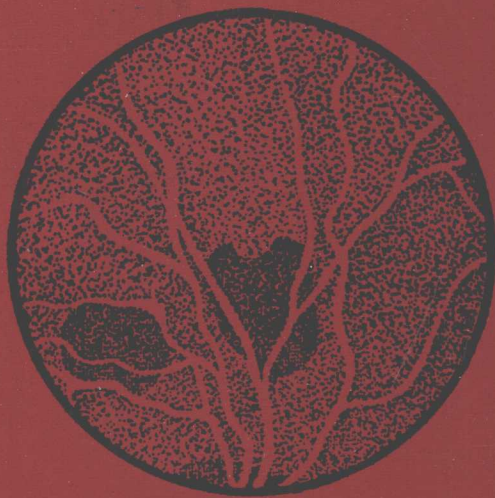

INHERITED RETINAL DISEASES

A Diagnostic Guide

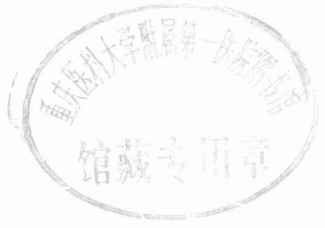


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Thomas E. Ogden
Gretchen B. Van Boemel

NOT FOR RESALE

INHERITED RETINAL DISEASES

A Diagnostic Guide
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FOREWORD

Inherited retinal diseases, with the exception of retinitis pigmentosa, are rare. Most ophthalmologists encounter only a few of the 72 diseases discussed in this book during their careers. Although the diseases are studied during training, once in practice the distinctions are soon lost to memory. When an unusual retinal degeneration is seen, the first thought might be to refer the patient for diagnosis to someone specializing in retinal diseases. However, a retinal specialist may not be readily available. This guide will help the general ophthalmologist meet the ensuing diagnostic challenge. The unique format of this guide will suggest the category of disease and possible diagnosis and will provide useful information to impart to the patient.

The authors have successfully devised a logical approach to the diagnosis of retinal disease based on anatomic abnormality and electrophysiologic tests. They provide a brief summary of the cardinal findings, inheritance, and natural history of each disease in an easily assimilated format. The work is extensively illustrated, and references to the original descriptions of most of the diseases are provided. Because recognition of the inheritance pattern is basic to diagnosis of these conditions, a practical summary of patterns of inheritance is provided. This is a valuable addition to a book intended for the practitioner.

The authors have accomplished their aims; they have provided a very useful guide to diagnosis. The text, because of its brevity and clarity, should receive an enthusiastic welcome from those in training as well as from those in practice.

Stephen J. Ryan

PREFACE



Every ophthalmologist occasionally sees a patient with an obscure retinal abnormality that seems inherited. The diagnosis may not be obvious, even to those who specialize in the retina and can summon from memory the 70 or so diseases that might be considered in the differential diagnosis. It is especially frustrating for the general ophthalmologist; many of these diseases are rarely seen, and the diagnostic possibilities swirl in dimly recalled memories from that period of cramming for board examinations. Only 15 to 20 of the more common of these diseases are even mentioned in general textbooks of ophthalmology, and those mentioned are given only as representatives of a class of diseases. The basic information is usually buried within the text of a large reference book, and developing a proper differential diagnosis requires time-consuming research.

Residents and fellows in ophthalmology have a similar problem. There is no convenient source for quick review of the salient features of the inherited retinal diseases. It is this void that this text seeks to fill. In many cases the original photographs of a condition are reproduced so that looking up the original articles describing the more rare diseases is unnecessary. Every disease is well illustrated; thus the text is also an atlas.

We hope that the general ophthalmologist will use this text to achieve a more definitive diagnosis for those patients with inherited retinal abnormalities, and we particularly hope the ophthalmologist will feel more comfortable in ordering the electrophysiology tests on which a final diagnosis may be based. There is also a more subtle motive for producing the text. Electrophysiology officially came of age in ophthalmology when the American Academy of Ophthalmology formally required all approved residency training programs to provide facilities for such tests. Laboratories for visual electrophysiology have become more common, and many practitioners have installed the equipment in their offices. Yet there is widespread confusion about the proper use of these tests for the diagnosis of inherited retinal diseases. These tests are reviewed in general terms in the appendices, and appropriate tests are clearly indicated for each of the diseases presented. We hope that this information will encourage more general use of the tests.

Treatment is not available for most of the inherited retinal diseases, but genetic and prognosis counseling may be very helpful to the patients and their families in coping with the disease. Such counseling depends entirely on accurate diagnosis and identification of inheritance patterns. The latter are fully explained and are an important feature of the text.

This manual was written by Dr. Jiménez-Sierra while he was a visiting scholar at the Doheny Eye Institute. He has a large practice in inherited retinal diseases in Mexico City, and most of the fundus photographs are of his patients' eyes. Dr. Ogden, who edited the manuscript and provided the appendix on electrophysiology, has been a visual electrophysiologist since 1962. His experience with clinical testing includes over 12,000 tests.

Ms. Van Boemel, who contributed the appendix on psychophysical testing, is a graduate student in psychology at the University of California, Irvine, and is an experienced electrophysiology and psychophysics technician.

For many of us, diagnosis of a rare and perhaps obscure condition in a patient is a cause for excitement and pleasure and perhaps for a feeling of pride. It can brighten an otherwise routine day. We hope this text will help the reader achieve some of these gratifying experiences.

Juan M. Jiménez-Sierra

Thomas E. Ogden

Gretchen B. Van Boemel

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The outstanding artwork represents the considerable talents of Patricia Chevez, M.D. We also wish to thank Ann Dawson for helpful suggestions and editorial assistance, as well as Eugenia A. Klein and Barbara S. Menczer of the C.V. Mosby Co. for their constant encouragement and support.

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Part I

INTRODUCTION

Classification of Disease

Inheritance Patterns

Genetic Counseling

Anatomic Basis of Disease Classification

Organization of the Manual

This manual was written with a very specific goal in mind. It is designed to help the general ophthalmologist arrive at diagnoses for patients with conditions rarely seen in the office, but for whom a correct diagnosis is vital if they are to understand the hereditary implications of their disease. Certain assumptions are made concerning the level of knowledge of the reader. It is assumed that there is familiarity with the basic ophthalmologic examination but lack of familiarity through disuse with quantitative methods of color vision testing, clinical electrophysiology, and dark adaptometry. It is also assumed that expressions common to the general practice of ophthalmology are familiar.

Most of the diseases presented in this manual are progressive, bilateral, and symmetric. It is likely that several listed as different are only different expressions of the same disease (macular pattern dystrophies). Some diseases (e.g., Leber's amaurosis) have a widely varying presentation and may actually represent several different but unidentified diseases. We use standard terminology for the diseases, but we group them by anatomic, clinical, and laboratory criteria in a way we hope will facilitate diagnosis. We have not generated a new classification.

Most of the diseases considered are properly referred to as dystrophies because they are hereditary, symmetric, and progressive; with onset after birth. Other nonhereditary, progressive diseases that are not always symmetric and bilateral are called degenerations. A third general category of stationary, bilateral, and symmetric diseases are present at birth (e.g., congenital stationary night blindness). We also present a small group of nonhereditary diseases (e.g., vitamin A deficiency) that may be mistaken for hereditary disorders.

CLASSIFICATION OF DISEASE

Classification of posterior pole diseases has been based on several different criteria. No classification is entirely satisfactory because the pathology of many of the diseases is incompletely understood. Previous classifications in the literature have been based largely on the following points, which are usually combined to arrive at a correct diagnosis:

Appearance of the predominant lesion. Many disease groups are recognized immediately from the appearance of the retina. These include the flecked retina diseases, the pigmentary retinopathies, and pattern dystrophies of the macula.

Topographic distribution of the disease in the posterior pole varies among diseases and may be localized (regional) or diffuse. The pattern of involvement provides important clues to the disease process.

Age at onset provides an additional basis for differentiation. Diseases may be present at birth (congenital), or they may develop during the first decade (infantile), during the second decade (juvenile), during or after the third decade (adult), or after the seventh decade (senile).

Progression is an important distinguishing characteristic among the degenerations that are progressive and, for instance, the stationary nyctalopias, which are present from birth but not progressive.

Symptoms are the basis of distinguishing the night-blinding disorders and color vision defects.

Inheritance pattern is the basis for separating a number of diseases whose clinical appearance may be virtually identical but whose progression and prognosis vary greatly according to inheritance pattern.

INHERITANCE PATTERNS

Most inherited retinal and choroidal diseases are not treatable. Once the diagnosis is established, the most important services an ophthalmologist can provide to the patient are genetic counseling and discussion of the probable prognosis for visual function. The disorders follow any of the Mendelian inheritance modes, depending on whether the involved genes are located on the autosomal or on the sex (X) chromosomes.

Autosomal Dominant Inheritance (AD)

Every generation is affected. Males and females are affected with equal frequency. The trait is transmitted only by an affected individual. Those without the trait do not transmit it. Autosomal dominant diseases are as a group more variable in expression, milder, and later in onset than recessive diseases. The risk to offspring of an affected parent is 50% because the defect involves one member of a chromosome pair and only one member of the pair is transmitted.

Conclusive evidence of autosomal dominant inheritance requires that there be affected individuals of both sexes in each of three successive generations.

Autosomal Recessive Inheritance (AR)

Only members of the same generation are affected. Usually the trait is only present in siblings, not parents. The trait is transmitted from asymptomatic carrier parents who each have one affected chromosome. Expression of the trait requires that both members of a chromosome pair be affected. The probability of receiving an affected chromosome from one parent is 50%, and the probability of disease from receiving two affected chromosomes, one from each parent, is 25%. Consanguinity is common in the families of patients with autosomal recessive diseases. Males and females are affected with equal frequency. These diseases are less variable in expression, are more severe, and begin at an earlier age than the dominantly inherited diseases. Every child of an affected person is a carrier of the trait. Obviously, if both parents are affected, all of their children will also be affected.

Sex-Linked Recessive Inheritance (X-L)

With this pattern of inheritance only males are affected. The father of an affected male is never affected; neither are the sons of an affected male. The trait is transmitted through the mother, who is normal but is a carrier, with the abnormal gene on one of her two X-chromosomes. The probability of transmission of the trait to her sons is 50% because males obtain their X-chromosomes from their mothers. The probability of transmission of the affected X-chromosome to a daughter from a carrier mother is also 50%. The affected male has only one X-chromosome and this is transmitted, along with the abnormal gene, to 100% of his daughters. Sex-linked recessive diseases are earlier in onset, show less variability in expression, and are more severe than diseases with AD inheritance.

The female carriers of X-L diseases often have mild fundus and electrophysiological abnormalities.

GENETIC COUNSELING

The goal of genetic counseling is to provide accurate information to a family concerning the prognosis of affected members and the probability that they will transmit the defect to their offspring. Because there is no treatment for most of these diseases, the only possibility for their control is through family planning.

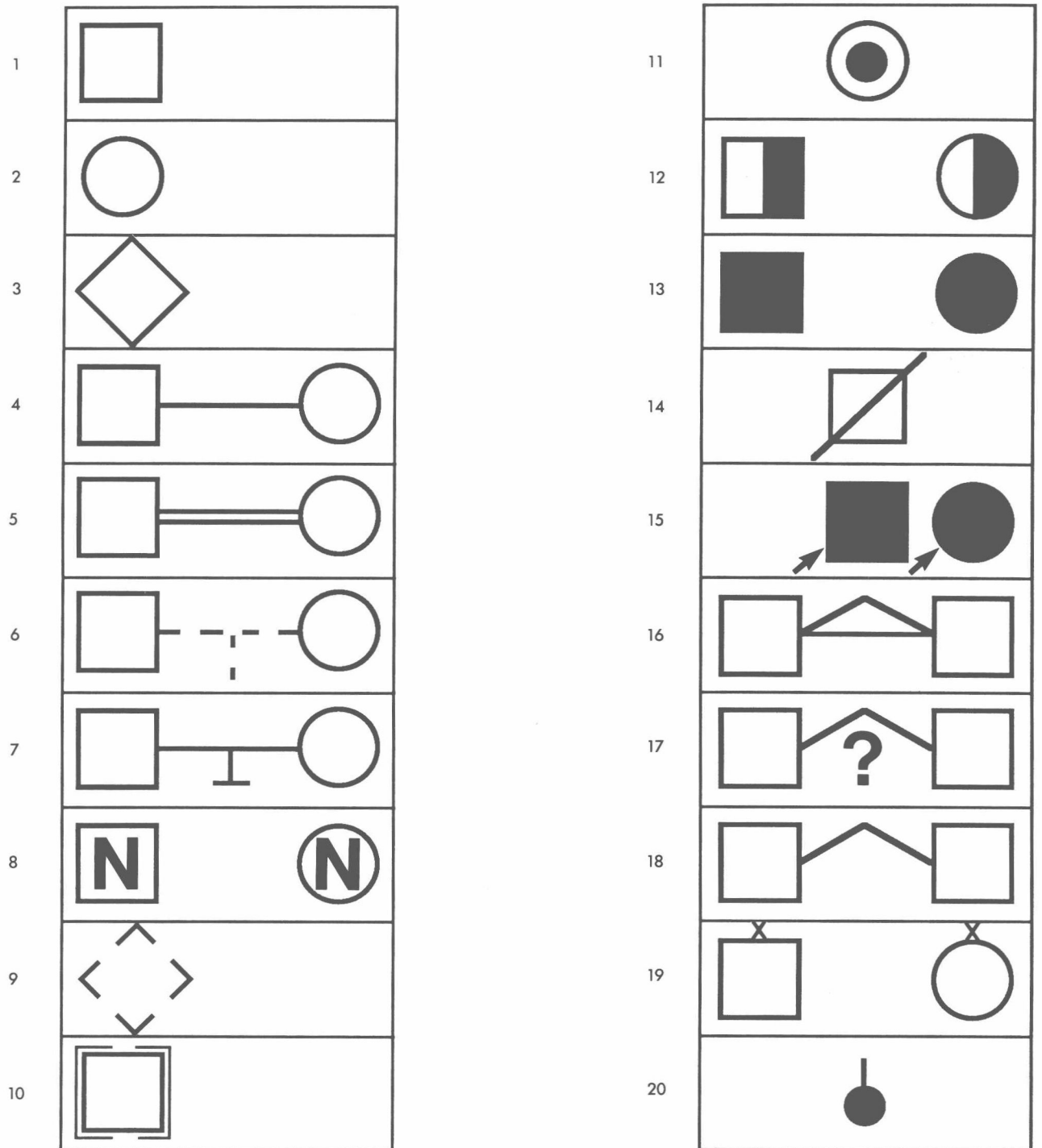
Genetic counseling is based on an accurate diagnosis and a correctly analyzed pedigree. The diagnosis alone is insufficient because some of the diseases have more than one mode of inheritance. For example, retinitis pigmentosa occurs sporadically and can be inherited as an autosomal dominant, autosomal recessive, or sex-linked recessive trait. Careful family histories should be obtained from these patients to cor-

roborate the diagnosis and to identify family members who may have the disease with incomplete expression or who may be carriers. Examination of the family is also essential to identify affected members and carriers. Diseases such as choroideremia (X-L) and Best's disease (AD) have only one mode of transmission, which is established with the diagnosis.

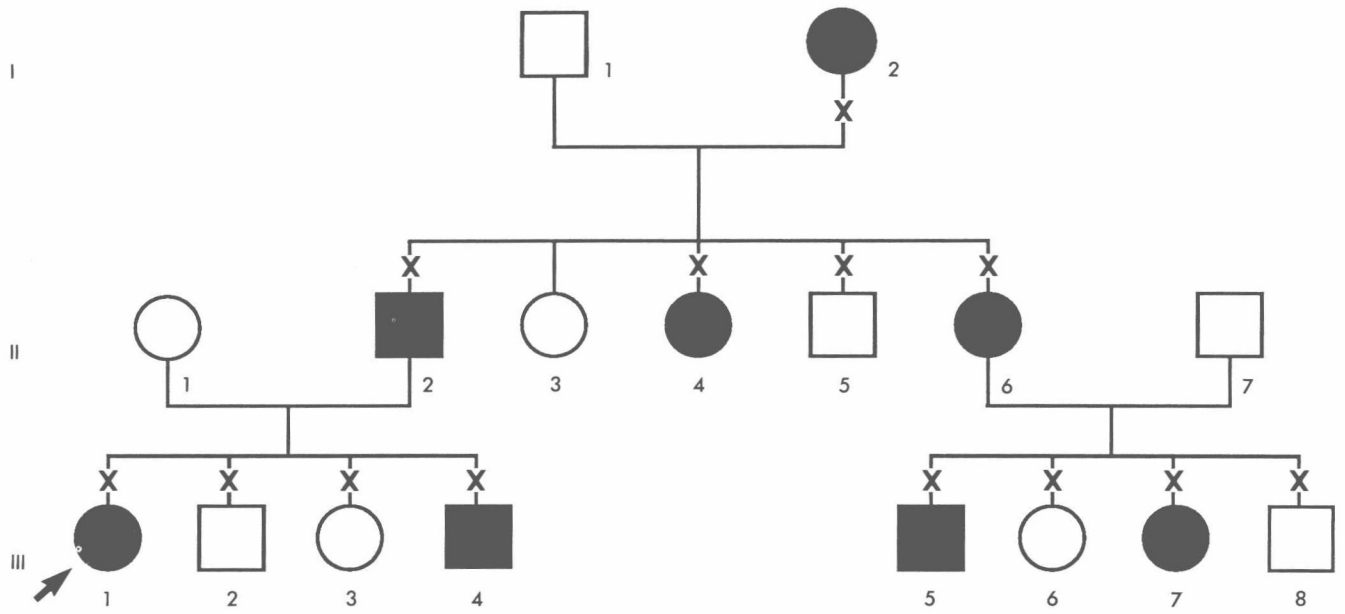
Particular attention should be paid to consanguinity when the history is taken. Consanguinity is common in small communities and suggests the possibility of autosomal recessive disease.

Diseases are sometimes referred to as genetically simplex or multiplex. Simplex inheritance implies that no other affected family members have been identified. The disease is assumed to represent a mutation of the affected gene. Multiplex inheritance implies that siblings of the affected patient are also affected, but no members of another generation have the trait. These terms are used when it is suspected that the disease has occurred for the first time in that generation. A subject with an inherited disorder born to normal parents, without family history or suggestions of consanguinity, may represent a gene mutation. The siblings are not at risk for the disease in this case. The children of the mutant may inherit the disease by any of the Mendelian modes of inheritance.

Successful recognition of different inheritance patterns is greatly facilitated by construction of an accurate pedigree chart. The diagrams on pages 5-7 show the symbols used to designate different familial status and typical pedigrees illustrating autosomal dominant, autosomal recessive, and X-linked recessive inheritance.

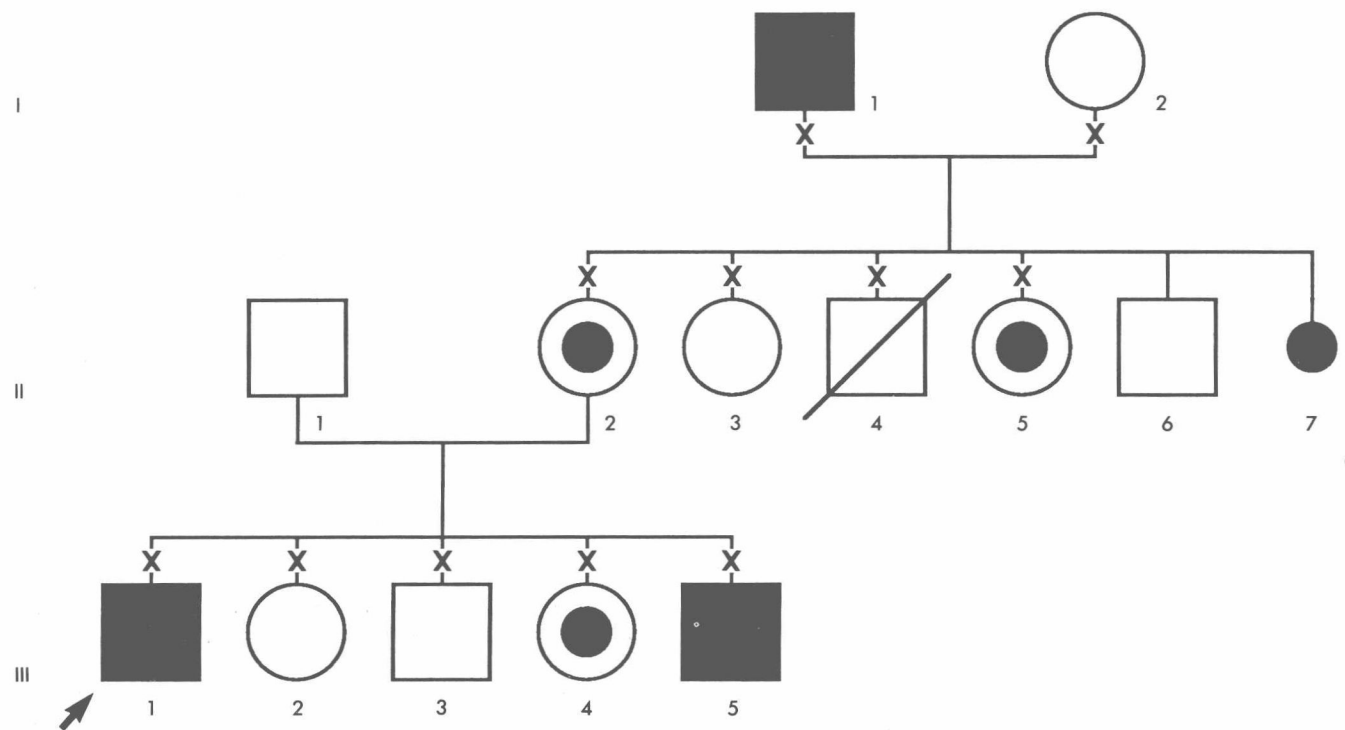


Pedigree symbols commonly used. 1, male; 2, female; 3, sex unknown; 4, marriage; 5, consanguineous marriage; 6, born out of wedlock; 7, childless marriage; 8, number of children (N) of sex indicated; 9, pregnancy; 10, adopted; 11, carrier of X-linked recessive trait; 12, heterozygotes for autosomal recessive trait; 13, affected individuals; 14, death; 15, proband, proband or index case; usually the patient, male or female; 16, monozygotic or identical twins; 17, twins of unknown zygosity; 18, dizygotic or fraternal twins; 19, X indicates that the patient was examined; 20, abortion or stillborn, sex unknown.



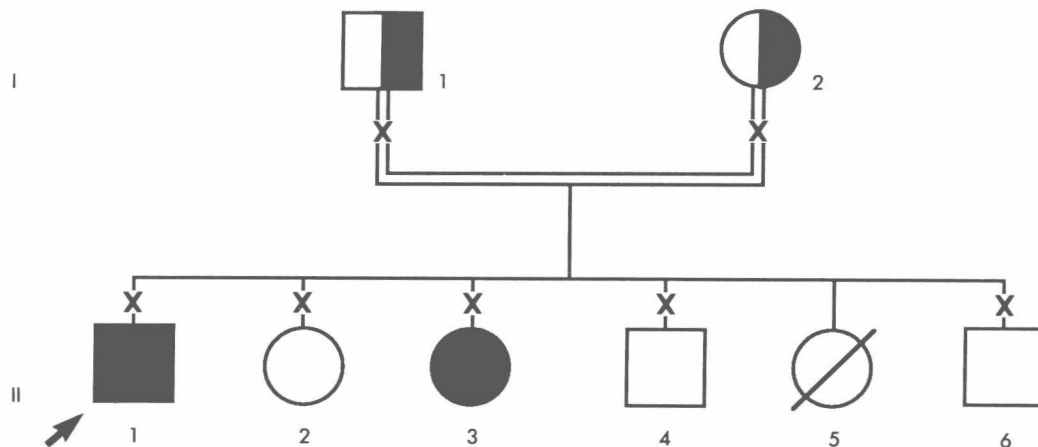
Autosomal Dominant Inheritance (AD)

I-2, II-4, II-6, III-7: Affected females; III-4, III-5: affected males; II-2: affected male (father of propositus); and III-1: affected female, propositus.



Sex-Linked Recessive Inheritance (X-L)

I-1: Affected male; II-2: female carrier, mother of propositus; II-4: Deceased male; II-5: female carrier (fundus abnormal); II-7: affected female; III-1: propositus, affected male; III-4: female carrier (fundus abnormal); and III-5: affected male.



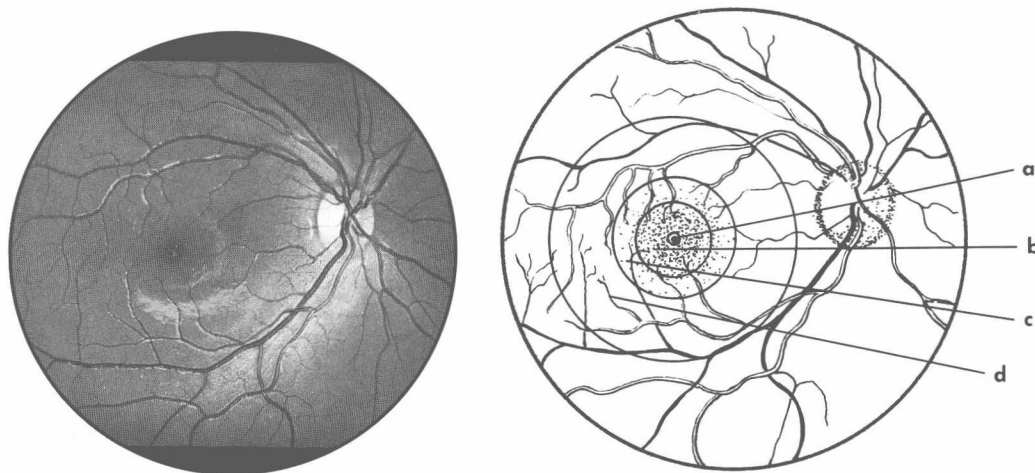
Autosomal Recessive Inheritance (AR)

I-1 and I-2: A consanguineous marriage of carriers; II-1: propositus; II-3: affected female; and II-5: deceased female.

ANATOMIC BASIS OF DISEASE CLASSIFICATION

Anatomic localization of the primary abnormality to a retinal layer or the choroid provides the best basis for classification, when this information is available. The inherited retinal and choroidal disorders presented in this book are grouped on the basis of retinal layer and area of the posterior pole primarily involved. The following section briefly reviews retinal anatomy and its clinical applications. Important terms are defined. Our definitions are, for the most part, standard but need to be stated to prevent misunderstanding.

Central retina is the retina of the posterior pole within about 3 mm of the fovea. The macula lutea is an area of yellow pigmentation extending about 1 mm laterally and 0.5 mm above and below the fovea. The macula is divided into the fovea or clinical macula (b), with its central foveola or pit (a), and a surrounding parafovea (c) that in turn is surrounded by the perifovea (d). The entire area within the outer circle is considered central retina. It should be recalled that the foveola and central fovea



Normal fundus photograph. The central retina is well defined about the fovea (b), corresponding to the clinical macula, with its central foveola (a). The region surrounding the fovea is the parafovea (c). Surrounding the parafovea is the perifovea (d).

are rod free; the maximum density of rods, and therefore the greatest retinal sensitivity to light, occurs at an eccentricity of 18 to 20 degrees of visual angle.

Peripheral retina is divided into near periphery, midperiphery, and far periphery, together extending about 14 mm from the macula. Beyond the far periphery is the 2 mm wide ora serrata.

The **choroid** is a thin, highly vascular membrane that is the posterior extension of the uveal tract. All of the capillaries of the choroid are arranged in a single layer on its inner surface, the choriocapillaris. This location provides for efficient transfer of metabolites to and from the retina. The choriocapillaris vessels are unusual in being fenestrated; many small membrane covered holes occur on the membrane of the endothelial cells. The fenestrations are permeable to fluorescein dye, which freely leaves the vessels to account for the “choroidal flush” seen in the angiogram.

Bruch’s membrane is a multilayered, noncellular basement membrane separating the choriocapillaris and the retinal pigment epithelium (RPE). It is freely permeable to metabolites passing into and out of the retina. It effectively separates the retina from the choroid. Breaks in Bruch’s membrane occur in many disease processes and result in a breakdown of this separation and growth of choroidal vessels into the subretinal space, that is, subretinal neovascularization.

The **retinal pigment epithelium (RPE)** is a monolayer of epithelial cells that are the metabolic pathway and service facility for the receptors. The basal surface of the RPE is specialized for metabolite transfer, and the apical surface is adorned with microvilli in contact with the receptors. A major function of the RPE is phagocytosis of the ends of the photoreceptors, and abnormality of this function may be involved in some of the pigmentary retinopathies.

The **photoreceptor layer** consists of the outer segments of the receptors, in other words, the part of the cell containing the photopigments. Outer segments grow continuously during life but maintain a proper length by shedding their outer tips, which are phagocytosed by the RPE. In the absence of proper relations between the outer segments and the RPE, for instance, in retinal detachment, the outer segments are lost; they regenerate when proper conditions are restored.

The **external limiting membrane** and **outer nuclear layers** are specialized parts of the receptors without clinical significance. These and the receptor layer are avascular and dependent on the choriocapillaris for nourishment.

The **outer plexiform layer** contains synaptic processes of receptor, bipolar, and horizontal cells and the axons of foveal receptors that course laterally, forming Henle’s layer in the macula. Henle’s layer may be the site of schisis or splitting of layers.

The **inner retina** is considered that part of the retina nourished by the retinal circulation. It consists of the inner nuclear, inner plexiform, ganglion cell, and nerve fiber layers and the vitreoretinal interface.

The **inner nuclear layer** contains the cell bodies of the horizontal, bipolar, amacrine, and Müller cells. It is nourished by a capillary network of retinal origin.

The **inner plexiform layer** contains processes of the bipolar, amacrine, and ganglion cells, processes of Müller cells, and many microglial cells. It may be a site of retinal schisis.

The **ganglion cell layer** contains the cell bodies of the ganglion cells and displaced amacrine cells. It is very thick in the parafoveal region because of the accumulation of cells displaced away from the fovea.

The **nerve fiber layer** contains the axons of the ganglion cells and astrocytes. It is absent in the fovea and increases greatly in thickness as the optic disc is approached. Retinal nerve fibers from the periphery that arch above and below the fovea are called arcuate fibers. A lesion in the nerve fiber layer causes a blind spot or sco-