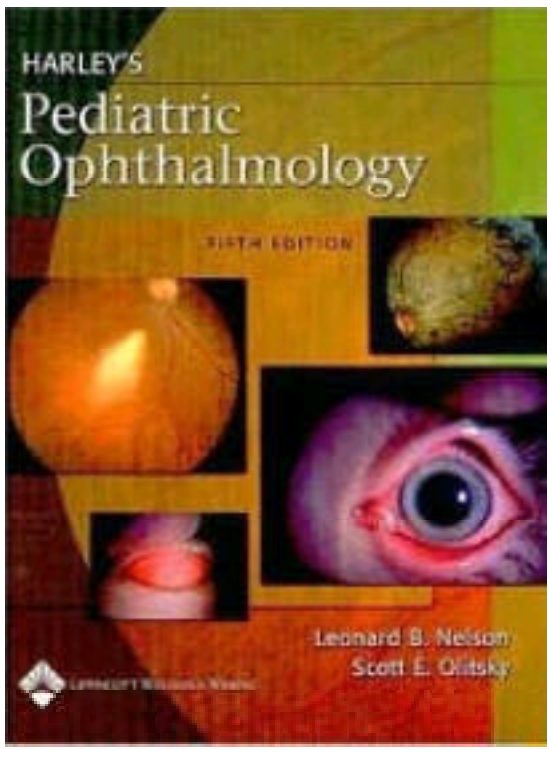
HARLEY'S
Pediatric
Ophthalmology
FIFTH EDITION
Leonard B. Nelson
Scott E. Olitsky

Editors: **Nelson, Leonard B.; Olitsky, Scott E.**
Title: ***Harley's Pediatric Ophthalmology, 5th Edition***

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Dedication

This book is dedicated to our wives, Helene and Andrea, and our children, Jen, Kim, Brad, Jenna, Ellie, and Peri, for their love, support, and understanding.

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Preface

The fifth edition of *Harley's Pediatric Ophthalmology* brings several changes to the textbook which have served as a benchmark in the subject for three decades. Since the publication of the first edition, edited by Dr. Harley in 1975, the field of pediatric ophthalmology and strabismus has changed markedly. Initially regarded as an unnecessary subspecialty within the field of ophthalmology, pediatric ophthalmology gained initial acceptance as a fundamental component of the field due to the efforts of early visionaries such as Drs. Parks, Costenbader, and Harley. Today, it is regarded as an essential and vital part of both clinical and academic ophthalmology.

The latest edition reflects changes seen in the specialty as a whole. New chapters have been added including a chapter on the growing medical legal concerns of treating infants and young children. The growing knowledge in the field of genetics and the ability to diagnose and treat diseases at an earlier age has been incorporated into the updates of each chapter. The reliance on evidence based medicine to prove the efficacy of our treatments is also included in the new edition. New contributors represent some of the recent leaders in the field and symbolize a “passing of the torch” from one generation of pediatric ophthalmologists to another. Dr. Scott Olitsky joins Dr. Leonard Nelson as co-editor of the textbook. Dr. Olitsky, a former fellow under Dr. Nelson at Wills Eye Hospital, now serves as Chief of Pediatric Ophthalmology at Children's Mercy Hospitals and Clinics in Kansas City. His clinical and academic expertise is a welcome addition to *Harley's Pediatric Ophthalmology*.

We thank all of our outstanding authors for their knowledge and assistance in the preparation of this book. In addition, we are grateful to the publishers at Lippincott, Williams & Wilkins who, as new publishers of this textbook, will participate in the fourth decade of a tradition begun by Dr. Harley. Lastly, no textbook in the field of pediatric ophthalmology could exist today if not for the vision and effort of Dr. Marshall Parks. Dr. Parks' early efforts in establishing the field of pediatric ophthalmology paved the way for all of us in that field. His insight into the ocular problems that occur in children as well as his unique ability to teach those insights to others have benefited generations of ophthalmologists as well as the patients we treat.

Leonard B. Nelson MD, MBA

Scott E. Olitsky MD

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Foreword

It has been thirty years since the first textbook on Pediatric Ophthalmology was published. Since that time there has been an explosion of new developments and procedures for the management and understanding of this subspecialty. Research laboratories in molecular genetics are advancing our knowledge, especially in the areas of primary and secondary glaucoma with associated anomalies and childhood metabolic disorders. The surgical management of infantile and other pediatric cataracts with intraocular implants has become more successful as well as refractive surgery for marked refractive errors. Techniques for caring for infants and children with problems associated with ocular tumors, vitroretinal disorders, retinopathy of prematurity, neuro-ophthalmological dysfunction, and amblyopia continue to present a significant challenge. There have also been a number of other distinctive changes in pediatric ophthalmology as technology and our knowledge broaden. We are especially grateful for the expertise of the contributors, the editors, and the publisher for bringing this splendid volume to our profession and other eye care practitioners as well as pediatricians.

Robinson D. Harley MD, PhD, FACS

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1

Genetics of Eye Disease

Terri L. Young

Leila M. Khazaeni

In 1903 Sutton noted parallels between chromosome behavior and Mendel's laws, thus identifying genes with chromosomes and marking the beginning of genetics as a science (1). One hundred years later, April 25, 2003 marks the fiftieth anniversary of the publication of the proposed double helical structure of DNA by Watson and Crick (2). The human genome sequence was also completed in 2003. The Human Genome Project is a joint initiative of the Department of Energy (Washington, DC) and the National Institutes of Health (Bethesda, MD), and was formed with the major goal of sequencing the DNA that defines the human genome. The ultimate goal of the project, the complete sequencing of human DNA, has been completed as first draft both by the public project and by the privately funded effort of Celera Genomics. An account of the progress of the Human Genome Project in its quest to sequence the entire human genome from its inception can be accessed at: http://www.doegenomics.org. The public version of the current sequence is accessible at several web sites including the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov) and the genome browser at the University of California at Santa Cruz (http://genome.ucsc.edu). Medicine has benefited immensely from this evolution in scientific discovery. A paradigm shift has occurred in the way diseases are classified, with less emphasis on clinical features as categorical constructs and greater emphasis on gene protein dysfunction due to associated DNA sequence alterations.

Genetics is a universal science that embraces all of biology. Lenz wrote in 1936: “Rules that are obeyed the same way in peas and snapdragons, in flies and butterflies, in mice and rabbits, of course also apply to humans” (3). This has repeatedly played out with the increasing pace of gene discovery in the latter part of the twentieth century, and into the twenty-first century, in large part due to genetic defects found in lower species that were then found to be associatively consistent in humans. Modern genetics has allowed the characterization of mutations that cause congenital human disorders and their comparison to mutations in model organisms. The worm (*Caenorhabditis elegans*), fruit fly (*Drosophila melanogaster*), zebrafish, and mouse all are serving the medical community with modules of evolutionary conserved ontogenetic mechanisms that aid in establishing developmental and functional models of human disease (4). With the advent of modern molecular genetics, the medical community has acquired a common language and a new paradigm.

The present statistics of ophthalmogenetic disorders is impressive, and growing. Searching the Online Mendelian Inheritance in Man (OMIM) database (http://www.ncbi. nlm.nih.gov/omim) for the term “eye” yields more than 647 entries (5). Winter's diagnostic London Dysmorphology Database (LDDB) lists under the general term “eyes, globes” more than 1,800 syndromes and still unclassifiable single case reports (6). Specific defects found in nearly 150 genes are associated with corneal and retinal dystrophies, eye tumors, retinitis pigmentosa, cataracts and glaucoma (http://www.sph.uth.tmc.edu/Retnet/disease.htm). The characterization of gene mutations in specific eye diseases has aided in the identification of the abnormal proteins that cause disease, and expanded definitions of pathologic processes.

Gene mutations have now been identified for several ophthalmic and systemic disorders with significant sightthreatening ophthalmic consequences. Ophthalmologists, and in particular pediatric ophthalmologists, are often on the frontline in assessing patients and families with such disorders. Knowledge of clinical and molecular features of the disease—such as developmental age of onset, heritable probability, DNA testing parameters, and customized treatment options based on molecular insights and strategies—is paramount to excellent patient care.

DATABASES FOR CLINICAL USE

Much of the information collected and discussed in this chapter will no doubt be dated even at publication because of the rapid evolution of research discoveries in genetics. For this reason, it is recommended that inquiries regarding specific clinical entities be made consulting online databases that are updated more quickly than any textbook chapter. As mentioned above, the OMIM database is without question the reference of choice of geneticists and genetic counselors for information regarding syndromic and nonsyndromic clinical entities for which a genetic basis has been discovered. OMIM's delay of comprehensive coverage of the scientific literature is less than 2 weeks. The LDDB is structured by the symptoms, anatomical sites, or tissues involved. There is a list of 14 diagnostic categories under the term “eyes, globes,” and a list of seven under the term “eyes, associated structures.” Many genetic and clinical centers also use the Australian Pictures of Standard Syndromes and Undiagnosed Malformation (POSSUM) database at http://www.possum.net.au/, which was launched in March 1987. Similar to LDDB, this program uses a hierarchic trait search list. The syndrome descriptions include the OMIM number, a list of synonyms, pictures of different patients at different ages, clinical and genetic comments, references, and trait lists. The program is continuously updated. The Human Gene Mutation Database (http://www.hgmd.org) at the Institute of Medical Genetics in Cardiff, Wales, curated by Cooper and colleagues since 2000, is at present the most useful general mutation database (7). It covers the scientific literature, references genes (at this writing more than 1,500 genes), and mutations discovered to date of those genes (more than 29,000), with links to approximately 250 open locus-specific databases, such as the retinoblastoma gene *RB1* (http://www.d-lohmann.de/Rb/). The web site of the HUGO (Human Genome Organisation) Mutation Database Initiative (8) at http://www. ebi.ac.uk/mutations/ contains a great number of links to locus-specific, central, general, national, and ethnic mutation databases.

BASIC GENETICS CONCEPTS

The eye is affected relatively early in the course of many genetic metabolic diseases; for some disorders, the ocular manifestations are unique and diagnostic. The eye is a complex organ with unique and specialized structures and biochemical functions related to vision. For these reasons, it is particularly vulnerable to genetic mishaps and inborn errors of metabolism.

The hereditary bases of diseases that affect the eye include several broad categories: single-gene mutations consistent with Mendelian inheritance patterns, chromosomal aberrations, cytoplasmic mitochondrial inheritance, and multifactorial inheritance; monogenic disorders can be divided into those that affect only the eye and ocular adnexa, and those that affect other systems in addition to the eye.

The term phenotype is defined as “the entire physical, biochemical, and physiological nature of an individual, as determined by his genetic constitution and the environment in which he develops; or, in a more limited sense, the expression of some particular gene or genes, as classified in some specific way” (9), and usually refers to either a physical feature or features of the individual or the biochemical assay of a gene product. It is a measurable physical or biochemical parameter that is determined by the interaction of the genetic constitution (genotype) with the environment. A wild-type phenotype is considered the normal or standard clinical (physical or biochemical) feature. The genotype may refer to the sum total of an individual's hereditary material (genome) or it may specify a single gene or gene pair.

At the biochemical level, the basic genetic unit for the orchestration of cellular function and transmission of traits from one generation to the next is a macromolecule consisting of deoxyribonucleic acid (DNA); it is self-reproducing and determines the composition of amino acids to form proteins. With rare exceptions, each cell of an organism contains the same DNA as every other cell, and this material encodes the information for the synthesis of proteins that catalyze enzymatic reactions, function as support structures, regulate intra- and intercellular functions, and determine the fate of a cell. The gene is a sequence of DNA that encodes for a single, specific protein or regulates the expression of a gene; just as the DNA is arranged like beads on a necklace, the genes are similarly aligned. The information contained in the DNA is transcribed to ribonucleic acid (RNA), an intermediary template, which is in turn translated to the protein (Fig. 1.1). The four types of RNA that have been identified are messenger RNA (mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), and heterogeneous RNA

(hnRNA). mRNA, which forms the template for protein synthesis in the cytoplasm, is formed in the nucleus of the cell from the DNA; tRNA transfers amino acids from the cytoplasm to the specific positions along the mRNA template. The functions of rRNA and hnRNA are less well understood. rRNA is associated with protein in the ribosomes and carries limited genetic information; hnRNA is an intranuclear RNA that may play a regulatory role. In eukaryotic cells (those with a nucleus and nuclear membrane, including human, plant, and protozoan cells but not bacteria), the DNA segments encoding a protein are interspersed with DNA that does not code for that protein; the coding portions are called exons and the noncoding portions introns. During the processing steps, the introns are removed and the exons are fused to form the mature mRNA, which is translated into the protein.

Both DNA and RNA are arranged in a linear fashion and consist of nucleotides, each of which is a base, pentose (five-carbon sugar—deoxyribose in the case of DNA and

ribose in the case of RNA), and phosphoric acid (Fig. 1.2). The bases are either purines (adenine or guanine) or pyrimidines (cytosine or thymine in DNA, and cytosine or uracil in RNA). The pentose sugar and the phosphoric acid form the macromolecular support. The precise order of the bases within the exons of a gene determines the amino acid sequence of the protein for which it encodes. For each amino acid, a triplet of DNA bases (codon) provides the necessary information for the identification of the amino acid in the protein; many amino acids have several codons that encode for them. For example, the amino acid phenylalanine is encoded by either the triplet base sequence uracil-uraciluracil or uracil-uracil-cytosine.

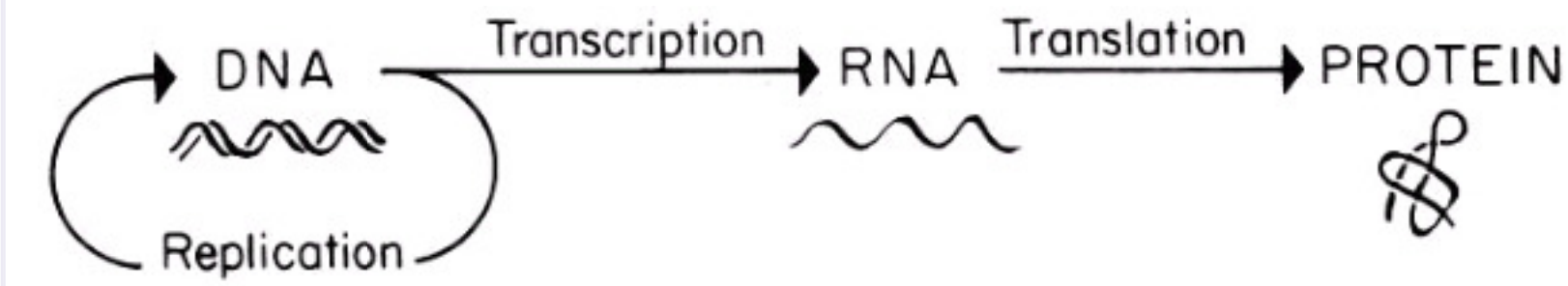
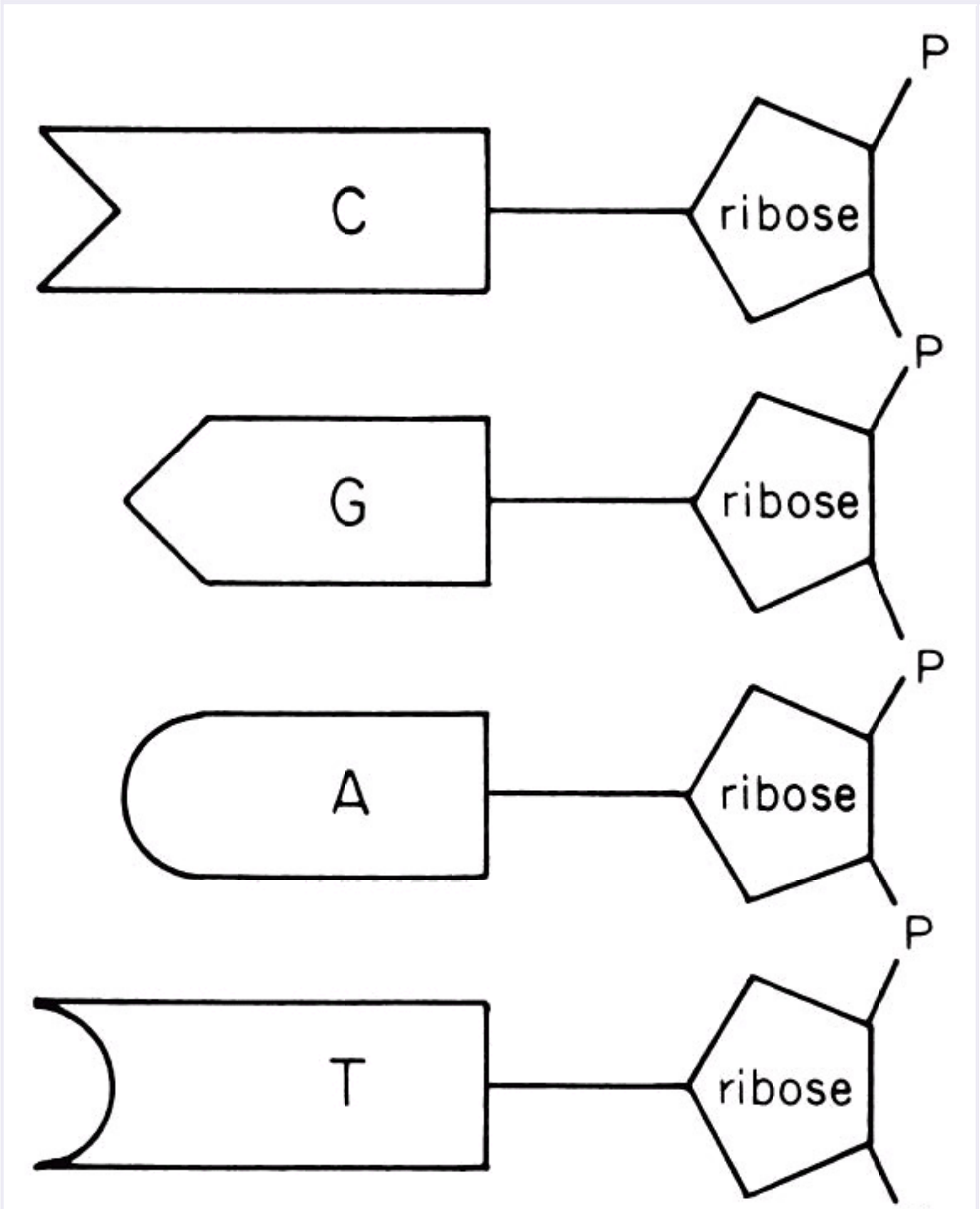


Figure 1.1 Relationship of transcription, translation, and replication.



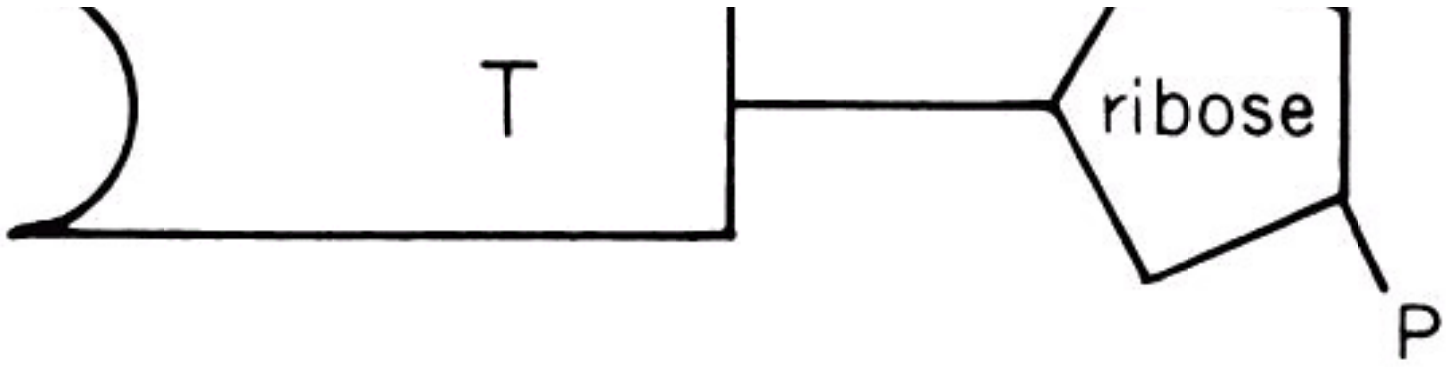


Figure 1.2 Nucleic acid structure.

Genetic disorders may be roughly categorized into those caused by single-gene defects, chromosomal or large DNA abnormalities such as duplications or deletions of large segments, or the effect of more than one gene. For each species, a gene occurs at a particular position (locus) on a specific chromosome. Humans are diploid organisms with two pairs of 22 autosomal chromosomes and two sets of genes—one member of each pair is inherited from each parent. The remaining two chromosomes, X and Y, determine gender. An individual is *homozygous* for a gene pair if the information specified by each member is identical, and *heterozygous* if the two encode for different polypeptides. Alternate forms of a gene are called *alleles.* Some alleles represent common variations not associated with disease (called *polymorphisms*), others represent disease-producing mutations (alterations of the DNA sequence that cause a change in amino acid sequence which alters the actual protein translated), and others are advantageous to the host under certain conditions. For example, the blood serotypes A, B, and O are common alleles; a normal individual may have AA, AO, BO, AB, or BB blood type. As another example, the genes coding for hemoglobin A (normal), S (sickle), and C are alleles, the hemoglobins S and C being mutations; the end products differ from each other by one amino acid in a chain of 146. Hemoglobin A has the amino acid glutamic acid in the position where valine is found in hemoglobin S and lysine in hemoglobin C. The substitution of glutamic acid alters the function of the protein. Allelism is the source of genetic variation in humans.

Most of the DNA is arranged in discrete chromosomes within the nucleus. A small fraction is within the mitochondria in the cytoplasm of the cell. Different species of animals and plants have different numbers of chromosome pairs; for example, a mouse has 20 pairs and a tomato 12 pairs. As mentioned above, humans have 23 pairs, of which two, X and Y, determine gender. The chromosomes are *homologous*: there are two of each type (autosomes) except the X and Y (sex chromosomes). Each nucleated cell of the organism has the same DNA as every other cell unless a mutation or chromosomal rearrangement occurred after conception.

The chemical bonds of DNA bind each linear strand to the linear strand of the same sequence positioned in the reverse direction. Hydrogen bonding between adenine (A, a purine) from one strand and thymine (T, a pyrimidine) from the other, or guanine (G, a purine) and cytosine (C, pyrimidine) maintains the alignment of the two strands. The tertiary structure of the double strand is a double helix. Since the pairing of A with T and G with C is essential to the secondary and tertiary structures, the two strands are complementary.

During the process of cell division (*mitosis*), all DNA is duplicated and each daughter cell receives the same information from the parent unless a mutation or chromosomal rearrangement occurs. The process of gamete (spermatozoa or ova) formation (*meiosis*) involves a halving of the number of chromosomes. During meiosis, a single cell forms four gametes, each of which has half the number of chromosomes (haploid). Crossing over (exchange of DNA or *recombination*) occurs during the duplication process between homologous chromosomes (a pair with the same gene loci in the same order), and genetic material is exchanged (Fig. 1.3). This process changes the order of the alleles on a chromosome and increases genetic variability. During fertilization, the two haploid cells (egg and sperm) fuse to form a diploid cell, restoring the normal number of chromosomes.

Single-gene defects may be caused by a point mutation that causes an alteration of an amino acid in the sequence of the protein product or by a deletion or duplication of DNA within the locus of a single gene. Point mutations of functional significance to the organism usually occur in an *exon* or regulatory sequence. Chromosomal abnormalities involve deletions (loss of material) or duplications (extra material) of DNA and can sometimes be identified microscopically. Such abnormalities involve a larger segment of DNA or an entire chromosome. *Haploinsufficiency* is a gene-dosage effect that occurs when a diploid requires both functional copies of a gene for a wild-type phenotype. An organism

that is heterozygous for a haploinsufficient locus does not have a wild-type phenotype.

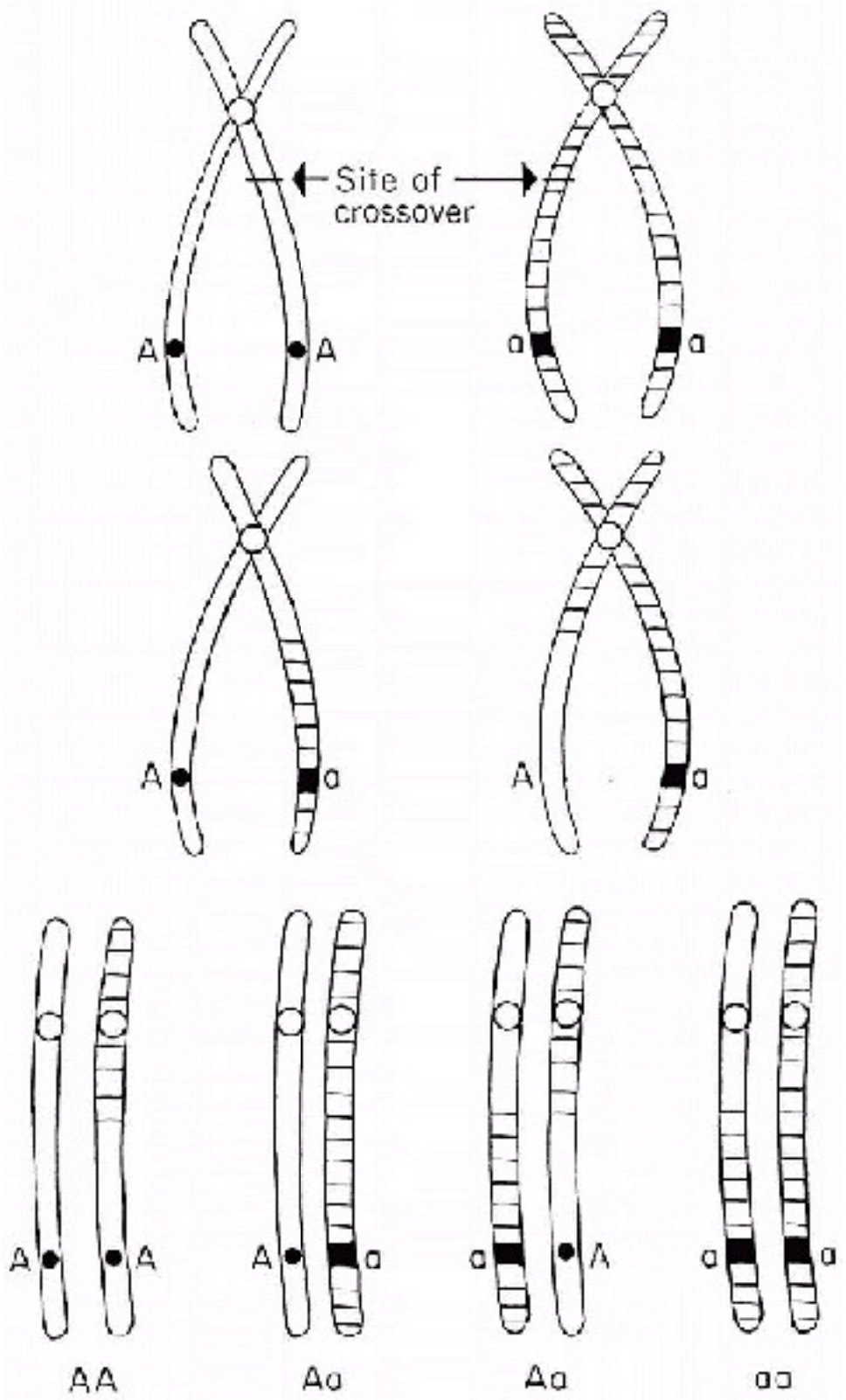


Figure 1.3 Crossing over (exchange of genetic material) between homologous chromosomes during meiosis.

Tjio and Levan (10) identified the correct number of human chromosomes as 46; previously the total was thought to be 48. The normal human 22 pairs of autosomal chromosomes and one pair of gender-determining chromosomes (XY for male and XX for female) are divided into seven groups on the basis of length and centromere position. In 1960 the initial Denver classification was developed at a meeting in Colorado and was based on the overall length and centromere position; seven groups, labeled A to G, were created. In 1971 the Paris nomenclature was created, and each chromosome was identified by length, centromere position, and banding. Chromosomes 1, 2, and 3 constituted group A; 4 and 5, group B; 6 to 12 and X, group C; 13 to 15, group D; 16 to 18, group E; 19 and 20, group F; and 21, 22, and Y, group G (Fig. 1.4).

Changes of chromosome structure can involve single chromosomes or an exchange of material between chromosomes. A piece of a chromosome may be lost by deletion or may be duplicated. The former results in *monosomy* for a group of genes and the latter results in *trisomy* for the genes. Chromosome segments can also be *inverted*—flipped 180 degrees from their normal orientation. If no material is gained or lost, the changes may not have a phenotypic effect. There are vast amounts of genetically inert DNA between groups of genes so usually these breaks cause no change in phenotype. Rarely, a gene may be disrupted by the chromosome breakage involved in the inversion. Another intrachromosomal rearrangement is the formation of a *ring*. This usually arises from breakage of the two ends and their subsequent fusion into a ring structure. There may be phenotypic consequences from deletion of chromatin from the two ends, and also from mitotic instability of the rings, resulting in trisomic or monosomic cells.

Translocation involves the exchange of material between chromosomes. Usually, translocations arise as reciprocal exchanges. If no material is lost or gained, the translocation is said to be balanced. Balanced translocations—and inversions for that matter—are occasionally found as variants in the general population. It is estimated that approximately 0.2% of individuals carry an asymptomatic rearrangement. If one comes to medical attention, it is usually because the unbalanced offspring of an individual with a translocation has congenital anomalies, or the individual has a history of spontaneous abortions.

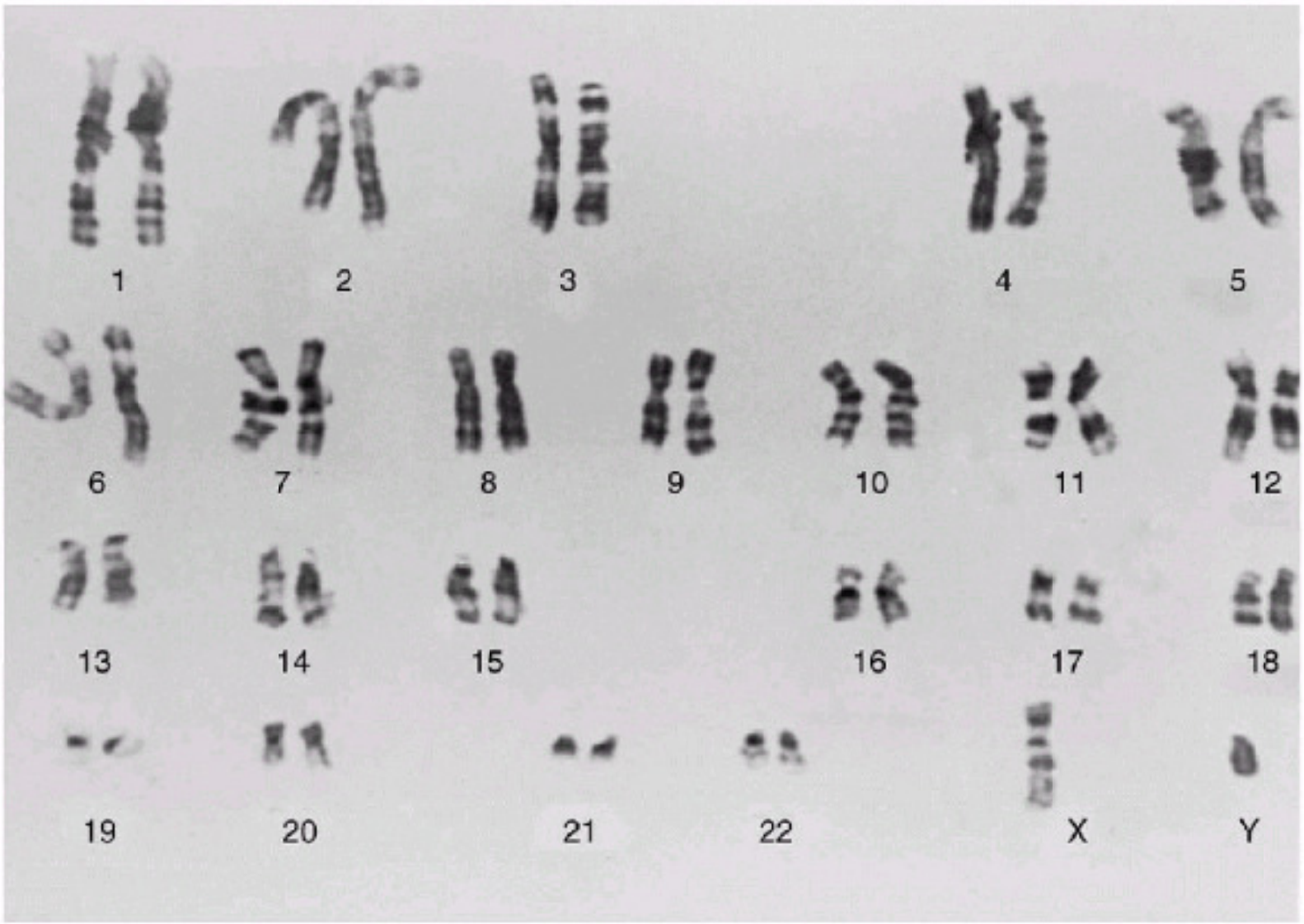


Figure 1.4 Karyotype of a normal male, showing banding produced by trypsin treatment of Seabright (11). (Courtesy of Robert S. Sparkes, MD.)

CYTOGENETIC TESTS

Karyotyping

By synchronizing the reproductive cycle of a group of cells and arresting the progression of the mitotic process, the chromosomes can be visualized microscopically, and specific chromosomal identification can be made on the basis of length and the use of stains such as trypsin-Giemsa (Gbanding; Fig. 1.4; 11), quinacrine mustard (Q-banding; 12), “reverse” or R-banding (Giemsa staining following controlled denaturation by heat), silver (staining of nucleolar organizing regions), and C-banding (staining of the condensed chromosome material near the centromere and regions with heterochromatin). All methods identify bands or specific regions and are useful for studying the specific structure of chromosome(s). The number of chromosomes can be counted and the bands of each studied for deletions, duplications, and other rearrangements. This technique is called karyotyping.

Relatively new techniques for arresting the progression of mitosis earlier in the cell cycle have been developed. In late prophase or early metaphase, the chromosomes are longer and less condensed and bands are further sub-divided; smaller deletions and/or duplications can be detected. Extended chromosome analysis, termed *high-resolution banding,* is much more time consuming but is particularly useful if a specific chromosomal abnormality or rearrangement is suspected. As the method is more labor intensive and expensive, one would not order high-resolution banding for a routine sample.

A cytogenetic nomenclature system has been adopted to describe the human chromosomal complement and indicate deviations from normal. An extra chromosome is indicated by a plus (+) and a missing one by a minus (-); thus 47,XX, + 21 is a female with trisomy 21 (three chromosomes 21). The short arm of a chromosome is called p and the long arm is q. Chromosomal bands are numbered according to landmarks starting from the centromere up the short arm and down the long arm. Chromosomal rearrangements are described by noting the rearrangement and indicating the breakpoint(s). For example, a female with a deletion of the short arm of chromosome 4 with breakpoint at band p15 has the karyotype: 46,XX,del(4)(p15). A ring is indicated as r (e.g., 46,XY,r[13]male with a ring chromosome 13) and translocation as t (e.g., 46,XX,t[3;9][p14; q21]female with a translocation between chromosomes 3 and 9 with breakpoints at band p14 on chromosome 3 and band q21 on chromosome 9). An inversion is indicated as inv (e.g., 46XY,inv[2][p12q12]male with an inversion of chromosome 2 with breakpoints at p12 and q12).

Fluorescent In Situ Hybridization

Recently DNA probes have become available for all human chromosomes—greatly expanding the field of molecular cytogenetics. If the origin of a duplication or translocation is unknown, the DNA probes can be fluorescently labeled and “painted” onto the metaphase spread or interphase nuclei chromosomal preparation, a technique called fluorescent *in situ* hybridization (FISH); chromosomal abnormalities can be readily identified under the microscope.

Telomeres, the physical ends of linear eukaryotic chromosomes, are specialized nucleoprotein complexes that have important functions, primarily in the protection, replication, and stabilization of the chromosome ends. In most organisms studied, telomeres contain lengthy stretches of tandemly repeated simple DNA sequences composed of GC-rich strands (called terminal repeats). These terminal repeats are highly conserved; in fact, all vertebrates appear to have the same simple sequence repeat in telomeres: (TTAGGG)n. Often sequences adjacent to the telomeric repeats are highly polymorphic, are rich in DNA repetitive elements (termed subtelomeric repeats), and in some cases, genes have been found in the proterminal regions of chromosomes.

Telomerase is the reverse transcriptase enzyme responsible for the extension of telomeric repeat sequences in most species studied. If telomerase activity is diminished or absent, telomeres will shorten. Shortened telomeres appear to lead to cell senescence (13). Eventually telomeric sequences can shorten to the point where they are not long enough to support the telomere-protein complex protecting the ends and the chromosomes become unstable. These shortened ends become “sticky” and promote chromosomal rearrangements (14,15). Some rearrangements may contribute to the development of cancers (16,17). Telomere

testing has been shown to identify alterations in 7% to 10% of cases with moderate/severe mental retardation and cases of multiple congenital anomalies with mental retardation in the setting of normal karyotype testing (18). The analysis involves the detection of deletions, duplications, or cryptic translocations using subtelomere FISH probes on each chromosome (15).

Comparative Genomic Hybridization

Comparative genomic hybridization (CGH) was developed to screen the entire genome for DNA content differences by comparing a test sample to a control (19,20). Because metaphase chromosomes are used as the substrate for analysis, the detection of unbalanced alterations is limited to the resolution of the metaphase target (at the level of a 450-band karyotype, approximately 5- to 10-Mb change). DNA microarray CGH is a powerful new technology capable of identifying chromosomal imbalance at a high resolution by cohybridizing differentially labeled test and control DNA samples to a microarray chip (21,22,23). The chip (small metallic platform with applied spots of known largeinsert DNA clones such as bacterial artificial chromosomes) technology offers higher resolution, is faster, and is highly sensitive. Because the DNA clones have a known map location and information, detected alterations are immediately linked to known genetic markers (pieces of DNA with a known chromosomal location and sequence), and the genetic location of a chromosomal abnormality such as a deletion or duplication can be determined by the map distances between known markers or by the length of the clones used.

SINGLE-GENE MUTATIONS

The substitution, addition, or deletion of one or more of the bases in an exon alters the DNA sequence and results in the formation of a protein with an abnormal amino acid at a specific site or the absence of the protein. Such abnormalities are believed to be common, and each human being is estimated to have three to five such mutations (24). If such a point mutation occurs in a portion of the protein that is not critical to function, the abnormality goes undetected (because it is not evident phenotypically) and does not affect the individual. If the codon error results in an amino acid substitution that changes the formation or function of the protein or truncates the product, the mutation is evidenced by reduced or (rarely) improved function, which would be advantageous to the organism from an evolutionary standpoint.

Autosomal Recessive Inheritance

For some mutations, the loss of a functional protein product from one of the chromosomes is asymptomatic because the gene on the homologous chromosome produces a normal product. If 50% activity of a protein is sufficient for normal function, the individual with one mutation is called a *carrier;* the signs and symptoms of the disease would be evident only in those who have two abnormal genes. Such a disorder is called *autosomal recessive* and is evident in some (statistically 25%) of the offspring of two carriers (Fig. 1.5). In general, there is a higher incidence of parental consanguinity associated with rare autosomal recessive disorders. For some diseases, carriers probably have a common ancestor because nearly all affected individuals have the identical mutation; an example of this founder effect is Tay-Sachs disease (OMIM 272800: infantile developmental delay, paralysis, dementia, blindness with lipid-laden ganglion cells leaving a central “cherry-red” spot funduscopically, premature death before the age of 5 years). Mutations of the implicated gene, the enzyme hexosaminidase, occur more commonly in the Ashkenazi Jewish population.

Autosomal Dominant Inheritance

When the protein is structural or the organism requires 100% activity for normal structure or function, phenotypic abnormalities are evident with a mutation of only one of the two homologous chromosomes. Such a disorder is termed *autosomal dominant* because the presence of a mutation on one of the chromosomes results in a phenotypically identifiable disease state. An affected individual with an autosomal dominant trait has a 50% chance of passing the gene to each offspring (Fig. 1.6). Examples of autosomal dominant disorders include Marfan syndrome (OMIM 154700: dislocated lenses, dilated aortic root, increased height, disproportionately long limbs and digits, anterior chest deformity, joint laxity, narrow arched palate, scoliosis due to connective tissue disorder; caused by mutations of the fibrillin-1 gene); neurofibromatosis type 1 (OMIM 162200: consistent features of café-au-lait spots, Sakurai-Lisch nodules of the iris, fibromatous skin tumors, occasional hamartomatous tumors found systemically; due to mutations in the neurofibromin gene); and Best disease (OMIM 153700: mutations in the bestrophin gene cause juvenile-onset and adult vitelliform macular dystrophy with collections of lipofuscin-like material in the subretinal space creating macular lesions which resemble an egg yolk). Disease-causing genes located on the autosomes occur equally in males and females, regardless of dominant or recessive inheritance.

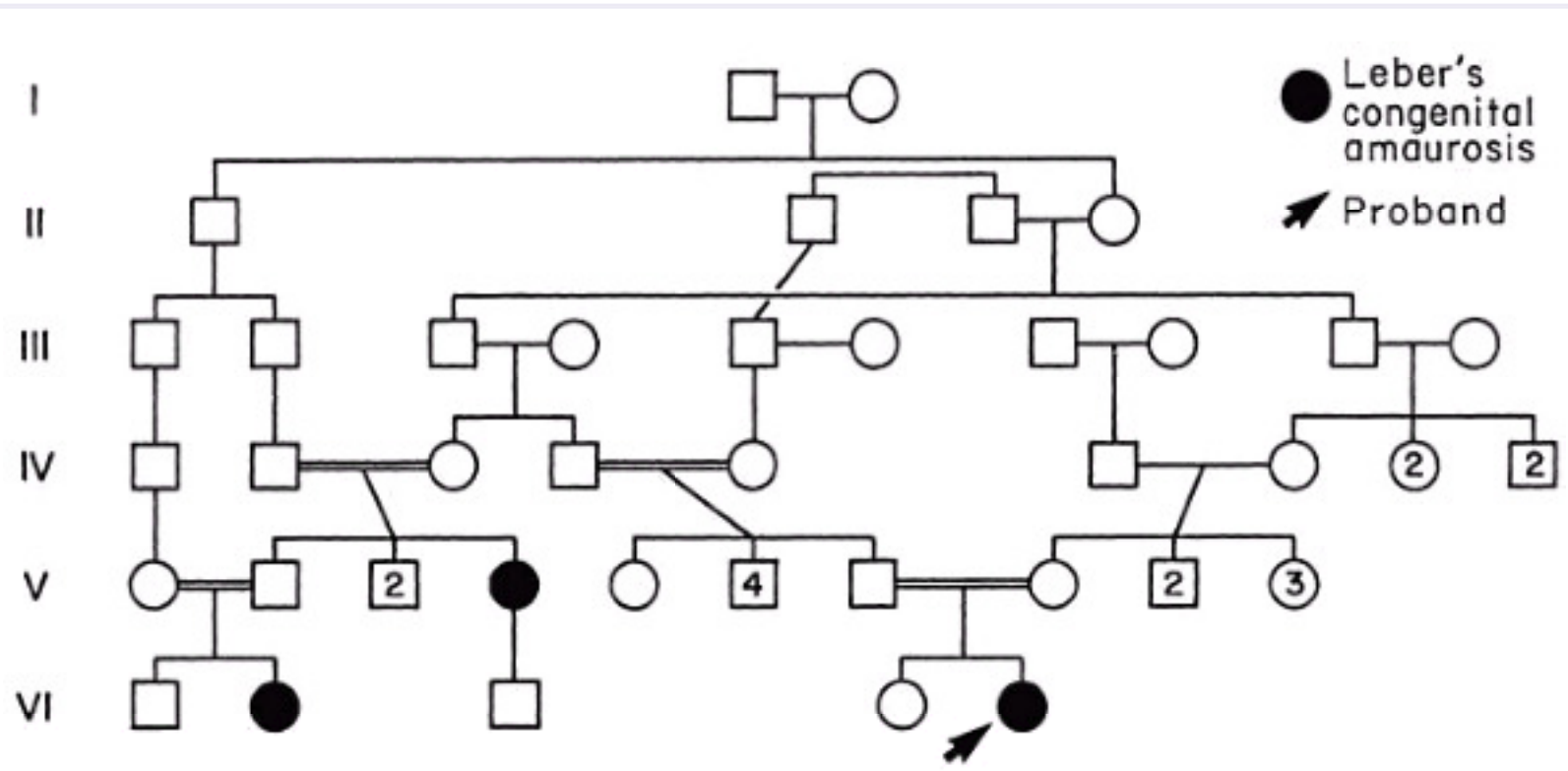


Figure 1.5 Pedigree of a family in which Leber congenital amaurosis was inherited as an autosomal recessive disorder. Consanguineous matings are indicated by double lines.

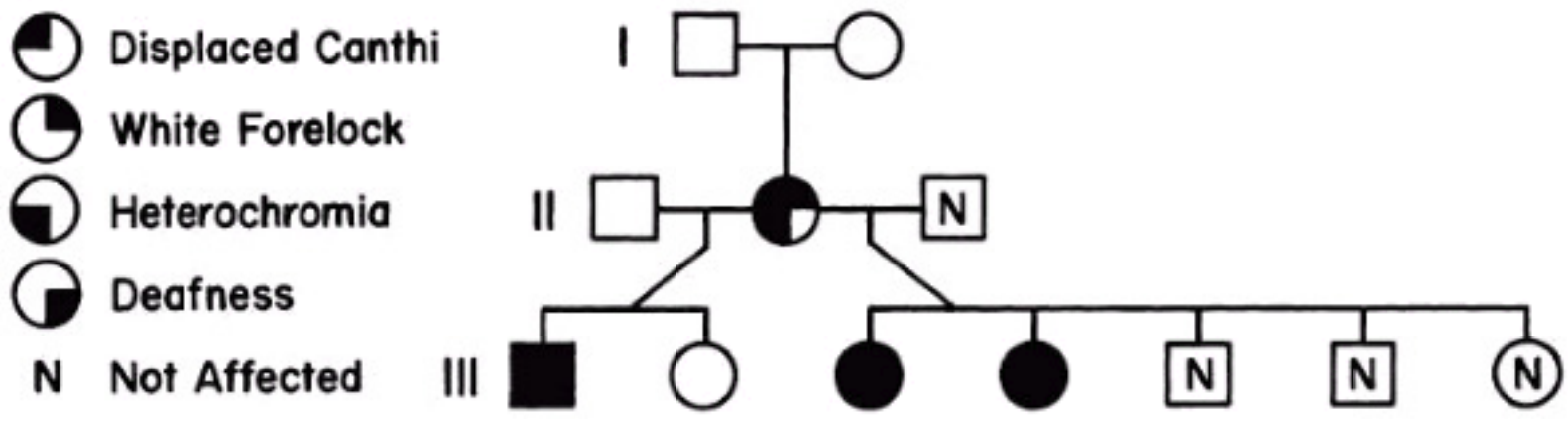


Figure 1.6 Pedigree illustrating the autosomal dominant transmission of Waardenburg syndrome. (Adapted from DiGeorge AM, Olmstead RW, Harley RD. Waardenburg's syndrome. A syndrome of heterochromia of the irides, lateral displacement of the medial canthi and lacrimal puncta, congenital deafness, and other characteristic associated defects. *J Pediatr* 1960;57:649-669.)

X-Linked Inheritance

Mutations on the X chromosome are unique because normal females have a pair, and normal males have only one X chromosome along with an unpaired Y chromosome. X-linked diseases may be recessive or, much less frequently, dominant. Therefore, one abnormal gene for which an individual requires only some of the protein product usually would not cause disease in a female, who is a heterozygote, but would in a male, who is a *hemizygote*. Such disorders are termed X-linked recessive and become evident in the male because he has only one copy of the X chromosome. Occasionally a heterozygous female carrier exhibits some manifestations of an X-linked recessive disease. The expression of the single recessive gene on the X chromosome in a female has been explained by the X inactivation theory, or Lyon hypothesis (25). During the second week of embryonic life, one of the two X chromosomes in each cell of the female fetus randomly becomes the “inactive X”; this X chromosome becomes condensed during interphase and appears as a darkly stained mass at the nuclear membrane

(Barr body or sex chromatin; Fig. 1.7). Most of the genes on the inactive X are not expressed. Once this differentiation occurs, the same X chromosome continues to be the inactive one in all the linear descendants of that cell. Thus, the female is a mosaic of two cell lines, those in which the genes on the maternally inherited X are active and those in which the paternally inherited X are active. The Lyon hypothesis is invoked to explain the splotchy pigment epithelium and choroidal pigmentation in the fundus of a female carrier of ocular albinism, or the tapetal reflex in the carrier of X-linked retinitis pigmentosa. X-linked disorders of the eye for which phenotypic evidence of the carrier state may be present in females include choroideremia (OMIM 303100: degeneration of the choriocapillaris and retina due to mutations in the Rab escort protein-1 gene [*REP1*]); Nance-Horan or cataract-dental syndrome (OMIM 302350: affected males have dense nuclear cataracts and frequent microcornea, and carrier females show posterior Y-sutural cataracts with small corneas and only slightly reduced vision; caused by mutations in the *NHS* gene) (26,27); blue cone monochromatism (OMIM 303700: affected males have poor central vision and color discrimination, infantile nystagmus, and nearly normal retinal appearance due to mutations in the locus control region upstream to the red and green cone pigment gene array) (28); and Lowe syndrome (OMIM 309000: affected males have cataracts, developmental delay, vitamin D-resistant rickets, and aminoaciduria, and carrier females have peripheral cortical lens opacities) (29). A carrier female has a 50% chance of passing a mutant gene on the X chromosome to any offspring; thus, the daughters have that same chance of being carriers and the sons of being affected with the disease (Fig. 1.8). Examples of X-linked recessive disorders include Duchenne muscular dystrophy (OMIM 310200: due to mutations of the dystrophin gene, affected males display progressive proximal muscular dystrophy with characteristic pseudohypertrophy of the calves and severe cardiomyopathy; there is massive elevation of creatine kinase levels in the blood, myopathic changes by electromyography, and myofiber degeneration with fibrosis and fatty infiltration on muscle biopsy); and X-linked juvenile retinoschisis (OMIM 312700: affected males with *RS* gene mutations have intraretinal splitting due to degeneration). If the X-linked gene is dominant, both the heterozygous female and hemizygous male manifest the mutant phenotype. It has been observed in the few X-linked dominant traits that a heterozygous female is more likely to have female offspring, and it has been postulated that there is fetal wastage of males. Presumably, the hemizygous state of the mutation may be lethal. Examples of X-linked dominant disorders include familial incontinentia pigmenti type II (OMIM 308300: mutations in the IKK-gamma gene causing skin defects of perinatal inflammatory vesicles, verrucous patches, dermal scarring, and retinal vascular anomalies) and Aicardi syndrome (OMIM 304050: affected females have flexion spasms and lacunar lesions of the choroid and retina).

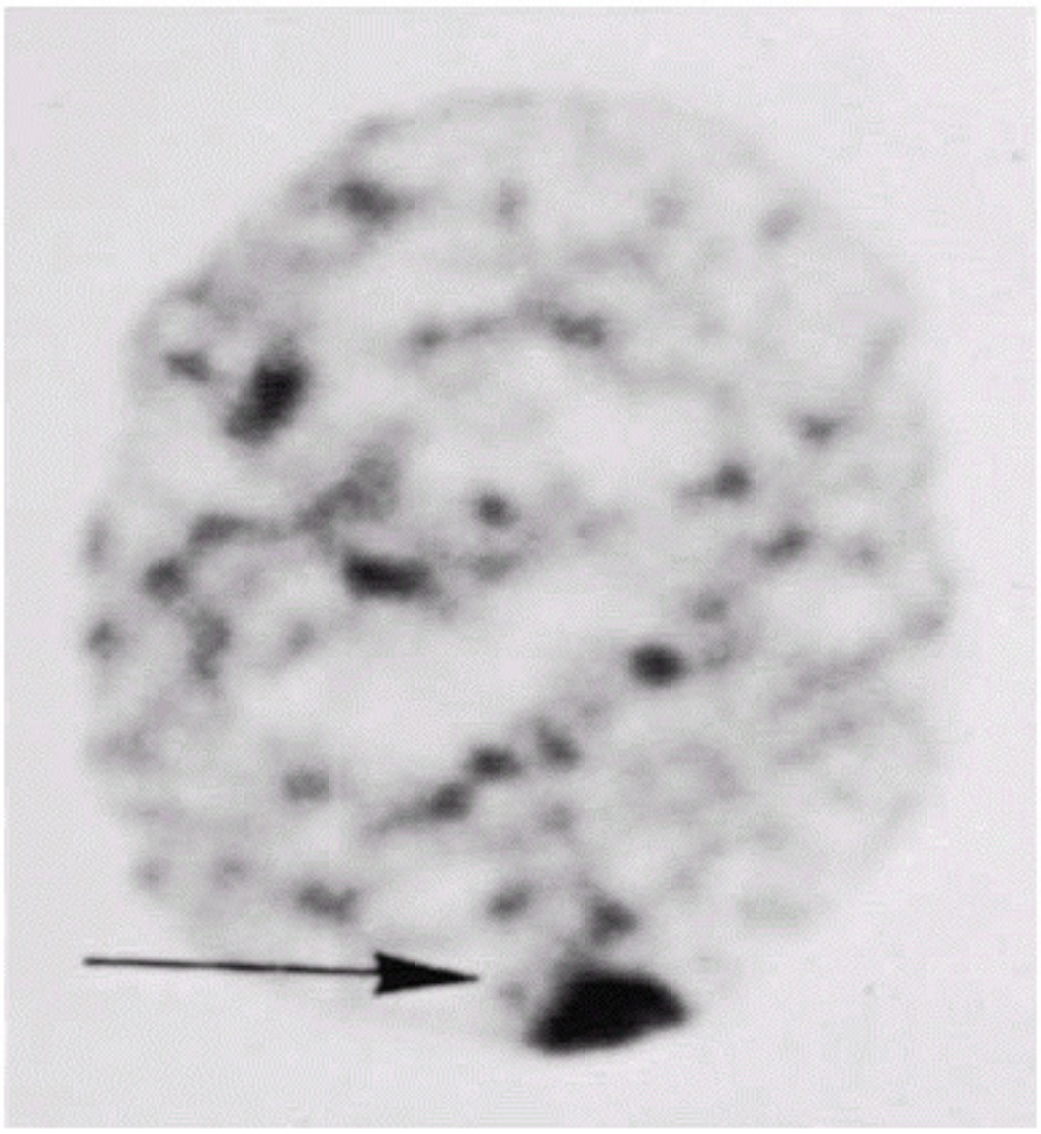


Figure 1.7 Barr body (sex chromatin) at the nuclear membrane in a cell from buccal mucosa of a normal female.

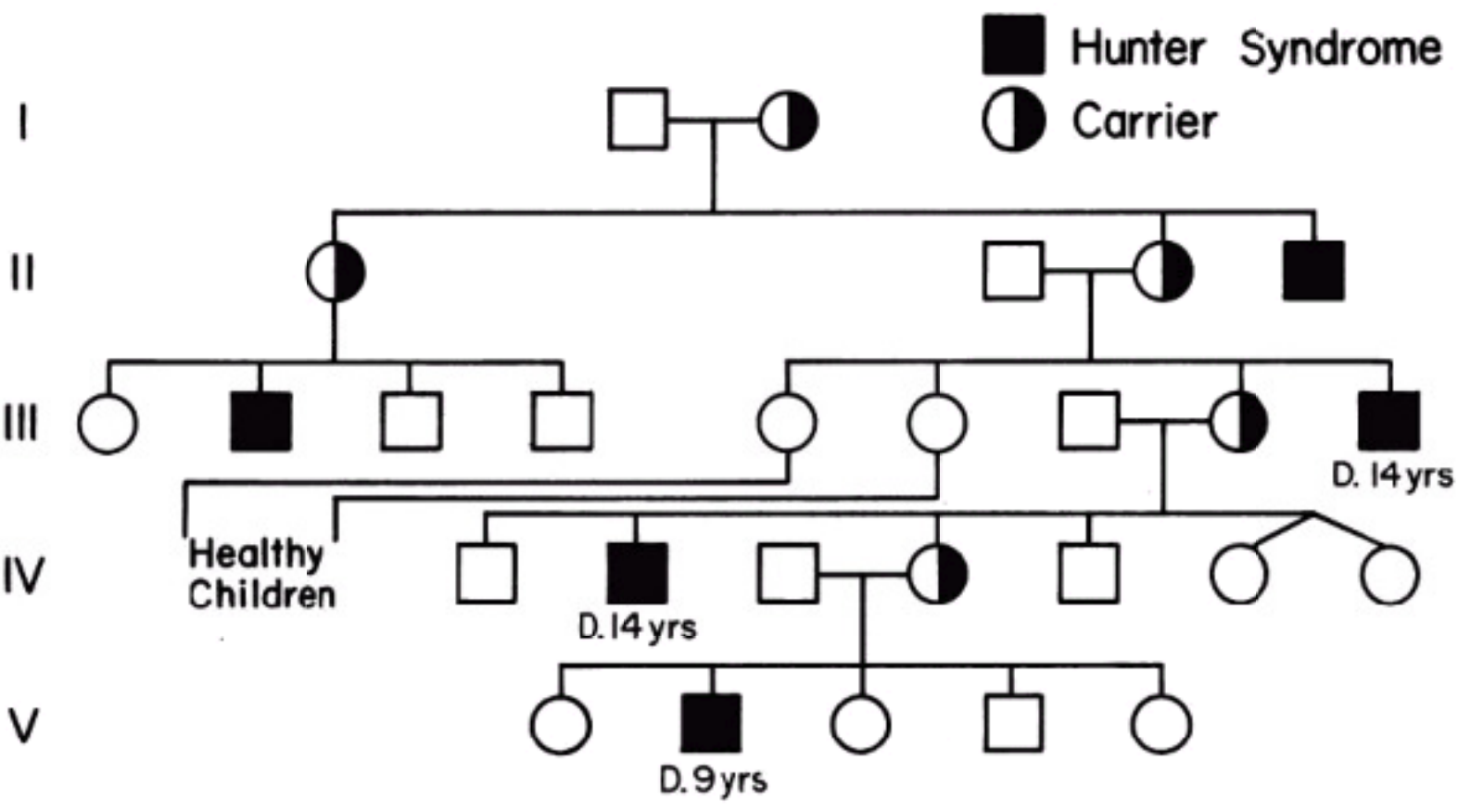


Figure 1.8 Pedigree showing X-linked inheritance of Hunter syndrome. Note that affected males are related through their mothers.

Mitochondrial Genetics

An additional source of genetic information in the cell lies in the mitochondria (30). Each cell contains hundreds of mitochondria, each of which contains multiple copies of a 16,569-base pair circular, double-stranded DNA molecule. This DNA encodes 13 peptides that are subunits of proteins required for oxidative phosphorylation. In addition, there is a complete set of 22 tRNAs and two rRNAs. These RNAs are involved in translation of mitochondrial-encoded proteins within the mitochondrion. Mitochondria are responsible for the generation of ATP via aerobic metabolism. Most mitochondrial proteins are encoded by nuclear genes;

however, some are encoded by mitochondrial genes, and mutations can lead to energy failure. The mitochondrial genome is subject to a number of peculiarities of inheritance including maternal transmission and a phenomenon known as *heteroplasmy*, resulting in distinctive patterns of familial disease. Heteroplasmy determines expression variability of the disease within a family. Different cells in an individual and different individuals in a family contain different proportions of mutant and wild-type mitochondria (31).

Mitochondrial mutation disorders display maternal genetic transmission. There may be the appearance of transmission directly from generation to generation, suggesting dominant inheritance. Both males and females may be affected, but men never transmit the disorder to any of their offspring. Women, on the other hand, pass the trait to all of their children, although expression may be more severe in some than in others. At the time of fertilization, the

sperm sheds its tail, including all of its mitochondria. Only the sperm head, containing nuclear DNA, enters the egg. Therefore, all the mitochondria for the next generation are contributed by the egg cell. Hence, mitochondrial genes are exclusively maternally derived, explaining the pattern of maternal transmission.

Major mitochondrial gene mutation syndromes include Kearns-Sayre (OMIM 530000: external ophthalmoplegia, pigmentary retinopathy, heart block, ataxia, increased cerebrospinal fluid protein); myoclonic epilepsy with ragged red fibers or MERRF (OMIM 545000: myoclonic epilepsy, myopathy, dementia); mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes or MELAS (OMIM 540000: lactic acidosis, stroke-like episodes, myopathy, seizures, dementia); Leber hereditary optic neuropathy (OMIM 535000: blindness, cardiac conduction defects); and Leigh syndrome (OMIM 256000: movement disorder, respiratory dyskinesia, regression) (32,33,34,35,36).

Penetrance

The clinical features of single-gene mutations vary from one individual to another. *Penetrance* is the percentage of known carriers manifesting the phenotype and reflects our ability to identify an individual with a mutant gene; reduced penetrance means that some individuals with the gene may not exhibit clinical evidence of the disease. Nonpenetrance is defined as the absence of phenotype in a person known to carry a specific mutant gene. Nonpenetrance has been demonstrated to occur with many genetic traits and can be most easily inferred when a grandparent and child have a disorder that does not appear to be expressed in the parent. For example, some individuals without evidence of colobomatous microphthalmia have an affected ancestor and an affected child (Fig. 1.9). The only potential explanation is that the apparently unaffected individual has the mutant gene in his or her genome but that the clinicians cannot find the evidence by ocular examination. If four family members descended from the same affected ancestor had affected progeny but one was free of the disease, the gene would be 75% penetrant.

Expressivity

Expressivity refers to the degree of phenotypic expression of a genetic trait. A disease may exhibit different manifestations among individuals in the same family. Such variable expressivity is common, particularly in autosomal dominant disorders. For example, some individuals with Marfan syndrome (OMIM 154700), an autosomal dominant disease of the connective-tissue gene fibrillin, may be tall and have dislocated lenses; others may be of normal stature and show no evidence of a dislocated lens but have an aneurysm of the ascending aorta.

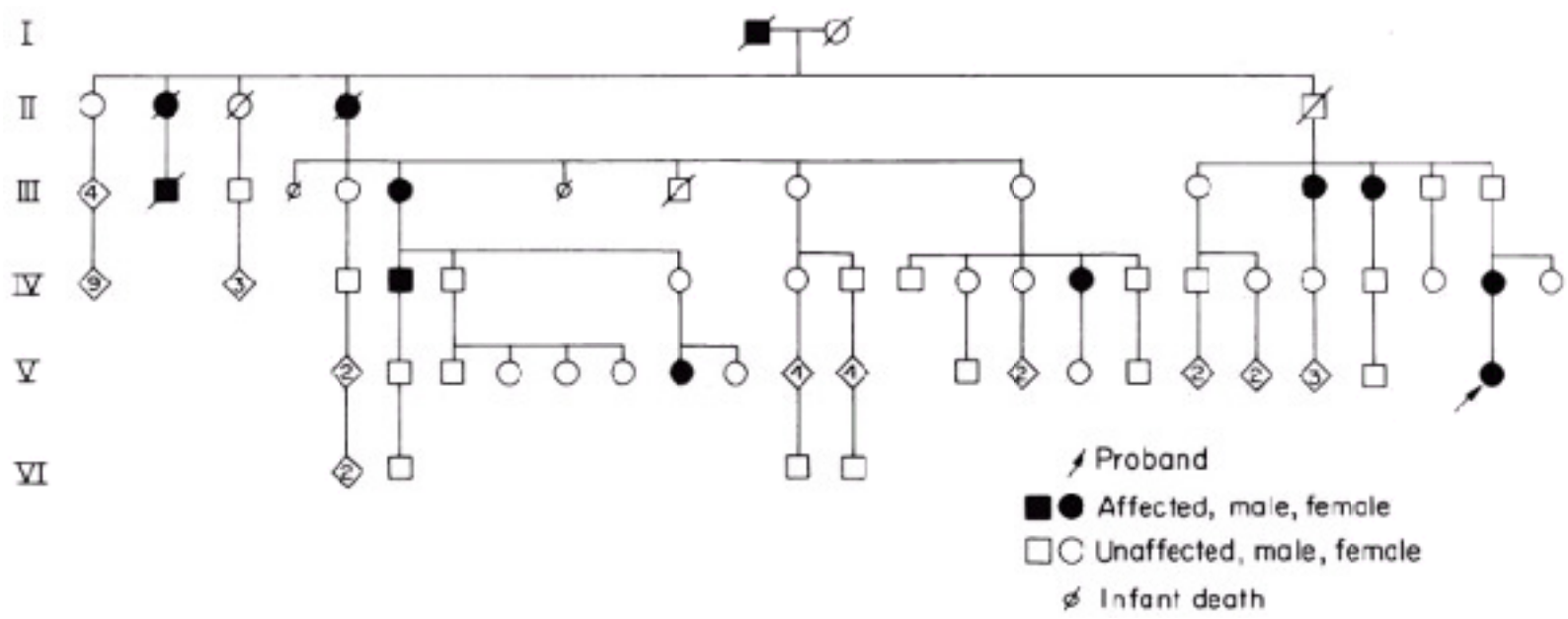


Figure 1.9 Multigenerational family with autosomal dominant colobomatous microphthalmia. The proband's (arrow) maternal grandfather was examined and showed no evidence of colobomata or microphthalmia. Thus, in this family the gene for colobomatous microphthalmia exhibits reduced penetrance.

Autosomal recessive disorders can exhibit variable expressivity, particularly if the mutation occurs at different sites in the protein. For example, there are numerous hemoglobinopathies with distinctive clinical manifestations that are caused by different mutations of the hemoglobin gene.

Genetic Heterogeneity

Different gene defects, modes of inheritance, and chromosomal abnormalities can produce similar clinical phenotypes, a phenomenon termed *genetic heterogeneity*. Examples of genetic heterogeneity are common in ophthalmology. Classification of diseases is thus most reliably made on the basis of specific gene mutations or chromosomal aberrations; doing so allows for directed therapies.

Mucopolysaccharidosis

The autosomal recessive Hurler syndrome or mucopolysaccharidosis type IH (OMIM 607014: corneal clouding, coarse facies, developmental delay, hepatosplenomegaly, and hernia) and X-linked recessive Hunter syndrome or mucopolysaccharidosis type II (OMIM 309900: no corneal clouding, coarse facies, dwarfism, hepatosplenomegaly, and deafness) may be difficult to differentiate clinically on the basis of physical findings in a young boy with no family history. As the inheritance patterns are different, the gene defects are distinctive. Conversely, the clinical features of the Hurler and Scheie (OMIM 607016: stiff joints, clouding of the peripheral cornea, and aortic regurgitation) syndromes can be differentiated by the mental retardation and early death that are features of the Hurler syndrome. Life expectancy in the Scheie form is nearly normal and mental retardation is very rare. Originally the two were classified as different diseases. With the identification of the enzymatic defect, it became clear that the disorders were allelic as the same gene is mutated in both, causing a deficiency in the enzyme alpha-L-iduronidase.

Leber Congenital Amaurosis

Leber congenital amaurosis (LCA; OMIM 204000) is a group of autosomal recessive retinal dystrophies. It is the most common genetic cause of congenital retinal disorders in infants and children. Its incidence is 2 to 3 per 100,000 births and it accounts for 10% to 18% of cases of congenital blindness. At least seven genes contribute to this disorder (*GUCY2D, RPE65, CRX, AIPL1, RPGRIP1, CRB1*, and *TULP1*) (37). The observed genetic heterogeneity is the result not only of the number of genes that have been implicated in LCA, but also the consequences of the different mutations in these genes. Mutations in at least two of these genes—*RPE65* and *CRX*—not only cause an LCA clinical presentation, but also lead to other late-onset retinal dystrophies such as retinitis pigmentosa and cone-rod dystrophy (38,39). Recently, gene therapy was used to successfully recover vision in a canine model of LCA (40). The researchers designed an adeno-associated virus vector to use in retinal transgene delivery. This vector was used to carry wild-type canine *RPE65* complementary DNA and was injected into the subretinal space of dog eyes. The LCA dogs showed visual recovery in performing visual function and behavioral tests. A gene therapy trial is in progress to treat humans with the same genetic disease.

Albinism

Albinism comprises a group of heterogeneous inherited abnormalities of melanin synthesis characterized by a congenital reduction or absence of melanin pigment associated with specific developmental changes of the visual system. Oculocutaneous albinism (OCA) involves two regions of the body: the skin and hair and the optic system, including the eye and optic nerves. Ocular albinism (OA) has similar changes in the visual system by reducing mainly the pigment in the retinal pigment epithelium (RPE) of the eye, usually with no clinical difference in the color of the skin and hair. Ophthalmologic signs, although variable, include nystagmus, hypopigmentation of the uveal tract and RPE, iris transillumination, foveal hypoplasia, and abnormal decussation of the optic nerve fibers at the optic chiasm.

The formation of melanin pigment is a complex event requiring several enzymes and proteins and the pigmentcontaining subcellular organelle, the melanosome. Melanin pigment is produced in the melanocyte, which is found in the skin, hair follicles, iris, and RPE of the eye. Melanin biosynthesis begins with hydroxylation of the amino acid L-tyrosine to dihydroxylphenylalanine (DOPA) and the oxidation of DOPA to DOPA quinone by the copper-containing enzyme tyrosinase, resulting in either black-brown eumelanin, or in the presence of sulfhydryl compounds, redyellow pheomelanin. The resulting pigment polymer is deposited on a protein matrix within the melanosome. In the skin and hair follicles, the melanosome is then transferred to keratinocytes via the dendrites of the melanocyte.

At present, four genetic loci responsible for human albinism have been mapped (OCA1: OMIM 203100, OCA2: OMIM 203200, Hermansky-Pudlak syndrome: OMIM 203300, and OA1: OMIM 300500); three of the genes have been isolated and pathologic mutations identified (*OCA1, OCA2*, and *OA1*). The classic “tyrosinase-negative” albinism results from tyrosinase gene mutations that inactivate the encoded enzyme and is categorized as OCA1 (41). Mild forms of OCA1, initially described as autosomal recessive ocular albinism, result from mutations of the tyrosinase gene that produce an enzyme with residual activity. OCA in which hairbulbs form melanin upon incubation in DOPA or tyrosine (tyrosinase-positive OCA) can be caused by mutations at several loci, including *OCA1*; *OCA2*, which is associated with the human homologue (P) of the mouse p gene—a melanosomal transport protein (42); and the rare Hermansky-Pudlak syndrome (OCA with platelet dysfunction).

MRI size and configuration comparisons of the optic pathways in normal versus albinism phenotypes revealed significantly smaller optic nerves and tracts, smaller chiasmatic widths, and wider angles between nerves and tracts in the albino group than in the control group (43). The chiasms of the albinos are shaped like an X, whereas the chiasm in the controls was shaped like two back-to-back parentheses, i.e.,)(. These differences reflect the atypical crossing of optic fibers. MRI can be an important diagnostic tool in patients with equivocal albinotic presentations.

X-linked OA1 is caused by mutations in the *OA1* gene at chromosome Xp22.3-p22.2, which encodes a membrane glycoprotein localized to melanosomes. Approximately 48% of the reported mutations in the *OA1* gene are intragenic deletions and about 43% are point mutations. Faugere and associates (44) report three *OA1* unrelated families with an initial diagnosis of congenital nystagmus. They identified three novel *OA1* mutations consisting of two intragenic deletions and a point mutation. Direct testing of carrier females is advocated and can be performed by direct sequencing or by scanning methods such as denaturing gradient gel electrophoresis or denaturing high performance liquid chromatography. The real-time fluorescent PCR gene-dosage assay is an accurate, nonradioactive, and fast method for gene carrier assessment that can be applied to any type of *OA1* gene deletion. A similar two-tiered diagnostic test strategy for mutation screening for *OA1* has been proposed (45).

Examples of Pleiotropic Disorders with Ophthalmic Considerations

A single-gene mutation that is expressed in many different tissues or can affect more than one organ system is termed *pleiotropic.* Waardenburg syndrome is an example of a disorder in which the mutation of one gene has multiple organ effects. This dominantly inherited disorder includes displaced canthi, heterochromia of the irides, white forelock, broad nasal root, and deafness (Fig. 1.6); the syndrome is divided into four types (I, II[A, B, and C], III, and IV) with the most severe being associated with upper limb defects (type III; OMIM 148820) and aganglionic megacolon (type IV; OMIM 277580). Dystopia canthorum, the lateral displacement of the inner canthi, distinguishes type I (OMIM 193500) (which shows this clinical phenotype) from type II. Types I and III (OMIM 148820) are caused by mutations in the *PAX3* gene, which was first identified in *Drosophila*

(46,47). Mutations in the transcription factor *MITF* have been implicated for Waardenburg syndrome type IIA (OMIM 193510) (48,49,50); digenic inheritance of type IIA and autosomal recessive ocular albinism has been proposed (51). Type IV or Waardenburg-Shah syndrome is a disorder of the embryonic neural crest that combines clinical features of Waardenburg syndrome and Hirschsprung's disease with colonic aganglionosis.

Alagille Syndrome

Alagille syndrome (OMIM 118450) is an autosomal dominant disorder characterized by cholestatic liver disease, pulmonic valvular and peripheral arterial stenosis, “butterfly” vertebrae, posterior embryotoxon with retinal pigmentary changes in the eye in some individuals, and unusual facies with broad forehead, pointed mandible, and bulbous nose tip. The syndrome is due to mutations in the Notch signaling *JAG1* gene on chromosome 20p12 (52,53).

Cornelia de Lange Syndrome

Cornelia de Lange syndrome (CDLS; OMIM 122470) is a dominantly inherited multisystem developmental disorder characterized by growth and cognitive retardation, abnormalities of the upper limbs, gastroesophageal dysfunction, hirsutism, cardiac and genitourinary anomalies, and characteristic facial features (54,55,56). Ophthalmic features include ptosis, nasolacrimal duct obstruction, arched eyebrows with synophrys, long eyelashes, refractive error, and infrequent glaucoma (57). The prevalence is estimated to be as high as one in 10,000. Gene mutations in the *NIPBL* gene on chromosome 5p13.1 have recently been associated with this disorder (58,59). The *fly* homolog of *NIPBL*, Nipped-B, facilitates enhancer-promoter communication and regulates Notch signaling and other developmental pathways in *Drosophila melanogaster* (60).

Marfan Syndrome

Marfan syndrome (OMIM 154700) is an autosomal dominant connective-tissue disorder with an estimated incidence of one in 5,000 with approximately 25% being sporadic cases. Three systems are predominantly involved: the skeleton, heart, and eye. Common and major manifestations of the disease include subluxation of the crystalline lens; dilatation of the aortic root and aneurysm of the ascending aorta; and skeletal abnormalities such as pectus excavatum and kyphoscoliosis and an upper segment/lower segment ratio of two standard deviations below the mean for age. Other criteria such as myopia, mitral valve prolapse, arachnodactyly, joint laxity, tall stature, pes planus, pneumothorax, and dural ectasia are also contributory. The diagnostic criteria have been recently revised, requiring involvement of three systems with two major diagnostic manifestations (61). The gene defect has been identified: Fibrillin (*FBN1*) maps to chromosome 15q15-q21.1. It is a large gene of more than 230 kb and highly fragmented with 65 exons. The protein is a 350-kDa glycoprotein and is the principal structural component of connective-tissue microfibrils found ubiquitously in all extracellular matrices. Fibrillin structures serve as scaffolds for the deposition of elastin in

elastic tissues (61).

To date, more than 500 mutations have been identified in the *FBN1* gene in Marfan syndrome patients and related diseases (61). Presently, no definite genotype/phenotype correlations have been identified except for neonatal mutations. An association with a subset of mutations in exons 24 to 32 and neonatal MFS appears correlative, thus molecular diagnostic testing can be performed (62). With a few exceptions, almost all mutations found in fibrillinopathies other than classic Marfan syndrome have been unique to one affected individual or family, which has hampered the delineation of potential genotype-phenotype correlations (62).

Comeglio and associates (63) characterized the incidence and class of *FBN1* mutations in the largest series reported to date, a group of 11 consecutive British patients affected predominantly by ectopia lentis (EL). The investigators identified six causative mutations in the fibrillin 1 gene (*FBN1*)—three mutations are novel and one was recurrent in two patients—thus establishing an *FBN1* mutation incidence of 63% (7/11). These results are within the 23% to 86% range of mutation identification rate in Marfan syndrome and related patients in recent investigations. All mutations were within the first 15 exons of the fibrillin gene, while database citations of Marfan mutations are distributed throughout the gene. A different type of *FBN1* mutation presents in this group of patients, with arginine to cysteine substitutions appearing frequently. The authors recommend that patients with predominant EL be screened for *FBN1* mutations. They also recommend echocardiography initially and at regular intervals throughout the patients'lifetimes, as there is a tendency for late-onset aortic dilatation and/or dissection to develop.

Lens subluxation is the diagnostic ocular abnormality in this disease. It is present in 65% to 70% of patients and varies from a mild superotemporal displacement of the lens seen only in postpupillary dilation to significant subluxation that places the equator of the lens in the pupillary axis. Subluxation of the lens due to stretched or absent zonular fibers is slowly progressive in the first two decades of life. Further displacement at a later age is uncommon. Total dislocation into the vitreous cavity is uncommon and may be complicated by phacolytic uveitis and glaucoma. Anterior displacement of the lens into the anterior chamber or within the pupillary space is rare in Marfan syndrome with EL. Premature cataracts are common, developing 10 to 20 years earlier in patients with Marfan syndrome than in the general population.

MASTER CONTROL GENES

The mature eye is a highly complex organ that develops through a highly organized process during embryogenesis. Alterations in the genetic programming of the eye could lead to outcomes of severe eye disorganization that are apparent at birth or shortly thereafter.

For the past decade, several master control genes that direct developmental and differential pathways have been identified. *PAX6, SOX2,* and *RX* are at the top of the eye developmental hierarchy; mutation or loss of these genes leads mainly to loss of the entire eye. Other genes, such as *FOX, PITX,* and *MAF* are important for the development of particular regions of the eye and are thought to be downstream of the top level of regulation in eye development. These genes are expressed during embryogenesis and initiate a cascade of gene expression responsible for specific cell-lineage commitments. Most genes at the top of the hierarchy of eye development code for transcription factors, although a few code for signaling molecules. The mutant phenotypes that are associated with some of these genes are described below, along with the genetic and molecular interactions that have been inferred between their products.

Paired Box Gene 6

Paired box gene 6 (*PAX6*) is the prototype for an eye master control gene. It is one of a family of genes that encode transcription factors with a homeodomain and a paired domain. Loss of function leads to the eyeless (ey) phenotype in *Drosophila* and also causes severe ocular defects in many other animals (64). Interestingly, ectopic (at a different location other than normal) expression of *Pax6* in *Drosophila*, mouse, and frog *(Xenopus)* causes the formation of a functional eye. This supports two concepts: (a) homologous genes in different species have the same function—to “switch on” eye development; (b) there is only one way to make the eye, by a cascade of signals initiated by *Pax6* expression (65).

In humans, *PAX6* mutations mainly cause aniridia (OMIM 106210), which is a panocular disorder, and less commonly cause isolated cataracts and macular hypoplasia (failure of retinal foveal development; OMIM 136520), keratitis (OMIM 148190), and Peters' anomaly (central corneal opacity which is frequently associated with adhesion between the cornea and the lens; OMIM 603807) (66). As in the mouse, the homozygous loss (both parental alleles have mutations) of *PAX6* function in humans affecting all expressing tissues is lethal.

Targets of *PAX6* encode other transcription factors or structural proteins of the lens (crystallins) and cornea (keratins 1-12). Many *PAX6*-regulated transcription factors (such as *SIX3*, *FOXE3*, *MAF*, *MITF*, *PROX1*, *LHX2*, and *PITX3*) are involved in the formation of the cornea and lens; others (such as *PAX2*, *CHX10*, and *EYA1*) are involved in retina and optic nerve development (67).

Only a few transcription factors or signaling molecules (e.g., *BMP4*, *BMP7*, *RX*, and *SHH*) are known to regulate *PAX6*. Among them, *SHH* might be highest in the hierarchy: knockout mice and humans with mutations in *SHH* suffer from holoprosencephaly with ocular manifestations that range from microphthalmia to cyclopia, which indicates a disruption in the earliest event in eye development, separation of the central eye field (68).

Genotype and phenotype information for human *PAX6* mutations is freely available from the *PAX6* mutation database (http://pax6.hgu.mrc.ac.uk).

Sex-Determining Region Y-Related High Mobility Group-Box Gene 2

Sex-determining region Y-related high mobility group box gene 2 (*SOX2*) is expressed in the developing lens placode, lens pit, optic cup, neural retina, lens, brain, and ear; heterozygous mutations of the gene result in anophthalmia in humans. Interestingly, all of these mutations seem to occur *de novc* (spontaneously) and are inherited as dominant alleles (69).

Retina and Anterior Neural Fold Homeobox Gene

The retina and anterior neural fold homeobox gene (*RX*) encodes a homeodomain transcription factor and is one of the first retinal patterning genes to be expressed during development (70). Rx-deficient mouse embryos lack eye anlagen (simple preliminary organ structures in the embryo) and do not express *Pax6* in the eye field, which indicates that *Pax6* upregulation in these tissues is dependent on functional *Rx* expression (71). It has recently been shown that the spontaneous mouse mutant *eyeless* (analogous to anophthalmia in humans) is caused by a point mutation in an alternative translation-initiation codon of *Rx* (72).

ISOLATED OCULAR AND PERIOCULAR SYNDROMES

Microphthalmia and Anophthalmia

Microphthalmia (OMIM 309700), a term derived from the Greek *micrc* (“small”) and *ophthalmos* (“eye”), refers to a congenital malformation in which the volume of the eye is reduced; the spectrum ranges from mild reduction in the anteroposterior axis to histologically documented anophthalmia (OMIM 206900). Nanophthalmia (OMIM 600165 and 605738) is used to describe microphthalmia with normal intraocular structures. Although microcornea or high hyperopia may be a useful clinical clue, the diagnosis frequently can be made by inspection alone; however, as microcornea can occur in the absence of microphthalmia (73,74) and conversely, microphthalmia in association with a normal-sized cornea (75,76,77), the clinical diagnosis may be inaccurate. As the spectrum of microphthalmia varies from slightly reduced axial length to histologically documented anophthalmia, ultrasonography with precise measurement of the anteroposterior axis is essential for the diagnosis. Since most normal adult eyes range from 21.50 to 27.00 mm, an adult axial length of less than 20 mm should be considered abnormal (78,79). Despite the use of this technologically advanced tool, extreme microphthalmia may be difficult to distinguish from anophthalmia.

Microphthalmia appears to be a relatively common ocular malformation in all races. The high prevalence, which would be unusual for a disorder caused by a

single gene, suggests multiple causes. Few studies have documented the prevalence in the general population. In a prospective study of more than 50,000 pregnancies in the United States in the late 1960s, the incidence of anophthalmia or microphthalmia was found to be 0.22 per 1,000 births and that of coloboma to be 0.26 per 1,000 (80). Prevalence among blind adults varies from 0.6% to 1.9% (81,82). In the pediatric age group, it accounts for 3.2% to 11.2% of cases of blindness (82,83,84). These differences are not readily explainable but may reflect the race or population studied; the highest prevalence (11.2%) was found in the 1980 survey on the causes of blindness among Japanese schoolchildren.

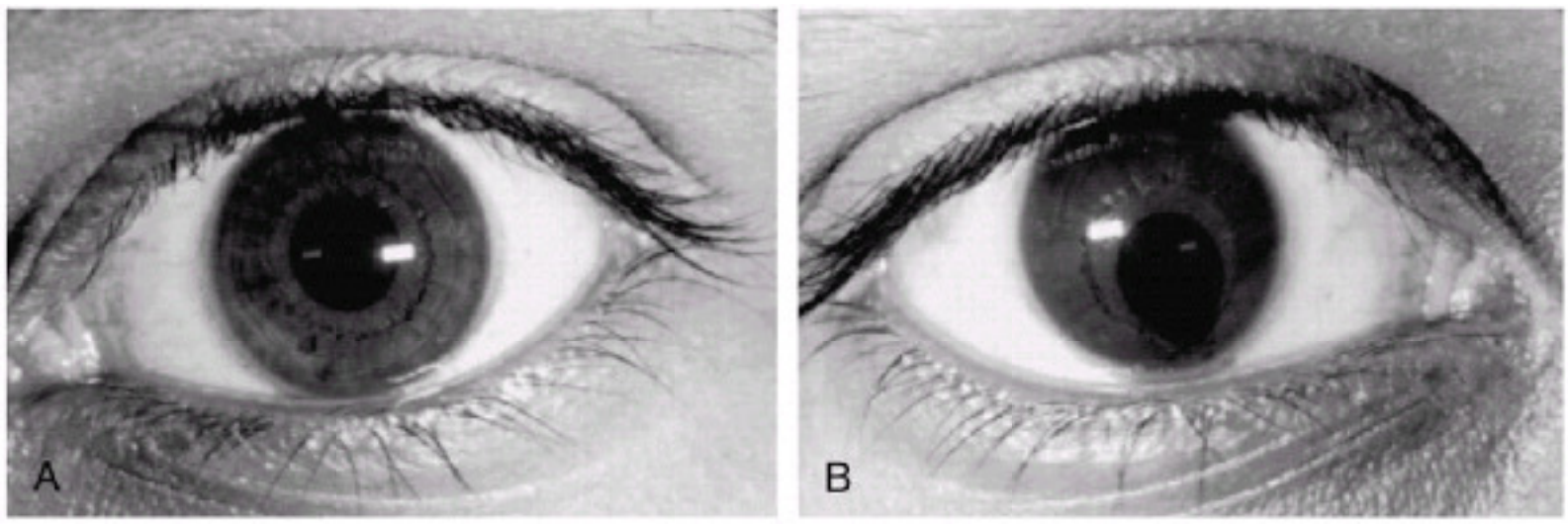


Figure 1.10 Right **(A)** and left **(B)** irides of a young man with mental retardation and deletion of the long arm of chromosome 18. Note the asymmetry.

Visual impairment in microphthalmia varies from little or no loss to absence of vision, as would be found in cases of anophthalmia. The degree of visual loss best correlates with the associated abnormalities and degree of microphthalmia; cataracts, optic nerve hypoplasia, and/or colobomata of the macula or optic nerve may cause significant visual impairment.

Cases of microphthalmia may be divided into two general forms: colobomatous and noncolobomatous. Although uveal colobomata may occur in the absence of microphthalmia, the two are frequently associated and presumably etiologically related. A coloboma may occur in the iris, choroid, optic nerve, or any combination thereof (Figs. 1.10 and 1.11). The colobomata result from incomplete closure of the fetal fissure, a process normally completed by the sixth week of gestation (85). The embryonic processes that determine the size of the eye are poorly understood. Congenital cystic microphthalmia and anophthalmia are extreme forms of this dysembryogenesis (86,87). As extreme microphthalmia may be difficult to distinguish from anophthalmia, serial sectioning of the orbit may be necessary to differentiate them. The malformation may be unilateral or bilateral, and asymmetry is common.

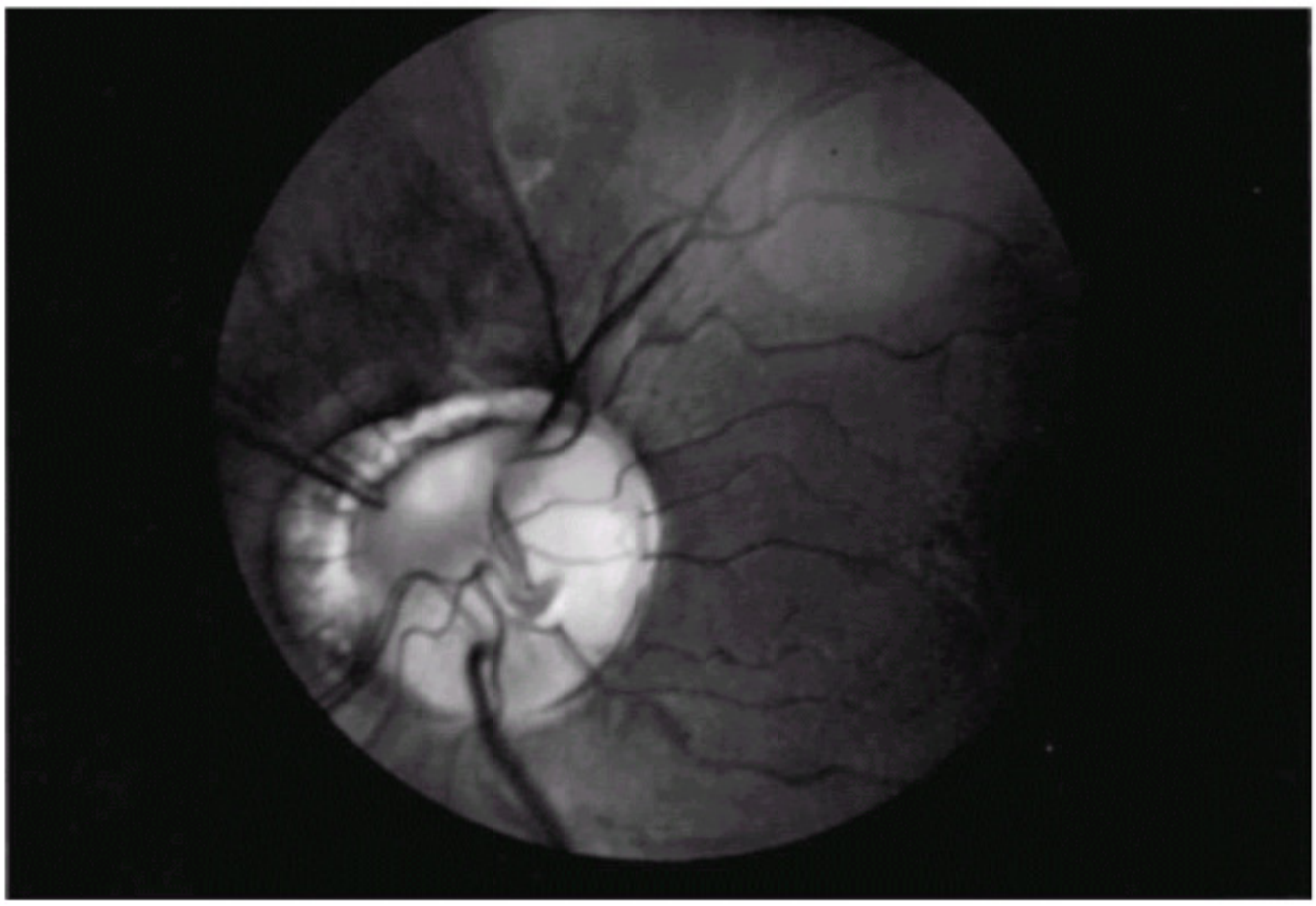


Figure 1.11 Coloboma of the right optic nerve in an eye with 20/20 vision.

Microphthalmia, with or without colobomata, may be a manifestation of many different disorders: genetic, environmental, and those of unknown cause. The evaluation of a patient is interdisciplinary. Aside from a complete ocular examination, all patients should have a careful history, including a genetic pedigree, and

physical examination. In certain cases, family members should also be examined.

Isolated colobomatous microphthalmia (OMIM 300345) may occur as an autosomal dominant disorder with incomplete penetrance; expressivity varies from small colobomata of the eye to microphthalmia and even anophthalmia (Fig. 1.9). Microphthalmia without colobomata also may be inherited as an autosomal dominant disease; more commonly, associated congenital cataracts or other ocular malformations are present (88,89). Microphthalmia with congenital retinal detachment or congenital cataracts may be inherited as an autosomal recessive disorder (90,91).

Microphthalmia (Mi) was one of the first mouse mutant genes to be described in which the development of the retina is affected. An interesting allelic series ranging from weak recessive to severe dominant phenotype has been compiled and genetically characterized. The eyes of the mutants develop poorly because of the defects in the RPE. The mutated gene, microphthalmia-associated transcription factor (*Mitf*) is a member of the basic-helix-loop-helix leucine zipper family of transcription factors. Mutations in the human homologue *MITF* (OMIM 156845) cause 20% of cases of Waardenburg syndrome type IIA (OMIM 193510) (92).

Human mutations in *SIX3* lead to holoprosencephaly; in some cases, the phenotype is milder and manifests as microphthalmia and iris coloboma (93). Several reports indicate that *SIX3* might function as a repressor of some developmental processes in the eye (94,95). In the mouse,

Six3 is activated by *Pax6* and *Prox1* (a transcription factor that is important for the differentiation of lens fiber cells and alpha crystalline expression) but is regulated by its own negative feedback loop (96). Transgenic mouse experiments have shown that *Pax6* and *Six3* regulate the transcription of each other (97).

The CHARGE syndrome (OMIM 214800) is characterized by the nonrandom association of colobomatous microphthalmia, heart defects, atresia choanae, retarded growth, genital anomalies, and ear anomalies or deafness; at least two of the features are necessary for the diagnosis (98,99,100,101,102,103,104). The ocular malformation is a common feature; the cardiac defects described in the syndrome are varied and may be lethal. The phenotypes of the chromosomal trisomy syndromes (13,18), 4p- (Wolf-Hirschhorn; deletion of the short arm of chromosome 4) syndrome, and cat-eye syndrome may be similar to the features of CHARGE association, and chromosomal analysis may be necessary to clarify the diagnosis (see the section on Chromosomal Rearrangements).

Two genetic loci have been identified in conjunction with isolated high hyperopia, autosomal dominant nanophthalmos (NNO1; OMIM 600165) on chromosome 11p (105) and NNO2 (OMIM 605738), which maps to chromosome 15q12-15. The phenotype for NNO2, however, is not of isolated, nonsyndromic high hyperopia. Rather it is that of unilateral or bilateral microphthalmos with variable expressivity such as corneal clouding and iridocorneal synechiae resembling Peters' anomaly or no microphthalmia with optic nerve agenesis.

Ocular Adnexa and Eyelid Abnormalities

The development of the eyelids and ocular adnexal structures is closely related to the formation of the eyes themselves. Complete failure of the eyelids to form results in cryptophthalmos (OMIM 123570), a condition in which the skin extends from the forehead to the cheeks uninterrupted, but attached to a usually malformed globe underneath. It may occur in isolation or as part of Fraser syndrome (OMIM 219000), which is autosomal recessive. A review of 27 cases of isolated cryptophthalmos revealed 11 of those to be familial, inherited in a dominant fashion (106). A gene has not yet been identified. Treatment depends upon the functional capability of the underlying globe, and this can be measured using imaging modalities in conjunction with visually evoked response and electroretinogram testing. If visual potential can be demonstrated, surgery may be attempted with the goal of creating a clear visual axis, possibly via a keratoprosthesis, as well as creating functioning lid structures.

Eyelid formation during development requires the eyelid folds to initially fuse and then to separate into upper and lower lids. The failure of this separation results in ankyloblepharon (OMIM 106250 and 106260), a condition in which the eyelids are completely or partially joined. Filiforme adnatum is a unique condition characterized by multiple strands of tissue connecting the two eyelids.

Structural maldevelopment of the eyelid may result in an eyelid coloboma or a disruption in the margin of the eyelid. Isolated eyelid colobomata range from a near total absence of the lid to the appearance of a small notch in the lateral aspect of the lid. Colobomata of the eyelid may also be part of a syndrome such as Treacher Collins syndrome (OMIM 154500) or Goldenhar syndrome (OMIM 164210) or may occur in association with cleft palate, dermoid, cleft lip, microphthalmia, iris colobomata, brow colobomata, and osseous facial clefts.

Congenital ptosis is due to a deficiency of the striated muscle fibers in the levator muscle. This abnormality may occur in three main forms: simple hereditary ptosis, with external ophthalmoplegia, and in the blepharophimosis syndrome (horizontal narrowing of the palpebral fissure; OMIM 110100). Simple congenital ptosis, unilateral or bilateral, may be inherited in an autosomal dominant fashion with incomplete penetrance (107). A gene for hereditary congenital ptosis type 1 (OMIM 178300) has been mapped to 8q21.12 (108). A case of bilateral isolated ptosis was also reported in a male patient found to have a *de novo* balanced translocation t(1;8)(p34.3;q21.12). The cytogenetic breakpoints were refined, and the chromosome 8 breakpoint was found to disrupt a gene homologous to the murine *zfh4* gene, which encodes for a transcription factor expressed in muscle and nerve tissue. This suggests the human *ZFH4* may be a candidate gene for congenital bilateral isolated ptosis (109). Analysis of a large white English pedigree revealed an X-linked dominant form of congenital isolated ptosis that mapped to chromosome Xq24-q27.1. This was named hereditary congenital ptosis type 2 (OMIM 300245) (110). Treatment for isolated congenital ptosis is surgical and may be performed on patients at any age; however, if the ptosis is significant, early surgery is necessary to prevent occlusion amblyopia. The choice of surgical procedure is dictated by the degree of ptosis, amount of levator muscle function, and clinical response to 2.5% phenylephrine ophthalmic solution. Patients who have a mild to moderate amount of ptosis which improves within 5 minutes after the administration of 2.5% phenylephrine ophthalmic drops into the upper eyelid fornix may benefit from a Mueller's muscle resection, while those with minimal response may require a levator muscle resection. In the absence or near absence of levator muscle function, a frontalis sling procedure is performed.

The association of blepharophimosis with ptosis and epicanthus inversus (BPES) is usually inherited in an autosomal dominant pattern (111). There are two types of BPES—type I is associated with ovarian failure and type II is not. The gene, *FOXL2*, is a winged helix/forkhead transcription factor and maps to chromosome 3q22-q23 (112,113,114). *FOXL2* is mutated to produce truncated proteins in type 1 families and larger proteins in type II. In this disorder, the palpebral fissures are narrowed both horizontally and vertically, and the ptosis is characterized by poor levator muscle function and the absence of a lid crease. Treatment involves correcting the ptosis with a frontalis sling procedure due to the poor levator muscle function. Surgical repair of the epicanthus inversus may also be undertaken in some cases.

Fibrosis of the extraocular muscle syndrome (FEOM) is a congenital disorder of innervation to the extraocular and eyelid muscles, which in turn affects muscular development (115). Affected individuals have a nonprogressive inability

to move some or all of the extraocular muscles due to fibrotic and scarred muscles, adhesions between muscles and Tenon's capsule, and adhesions between Tenon's capsule and the globe. The eyes are usually fixed in a downward gaze, and as a result the patient assumes a chin-up head posture. The adhesions may involve the levator muscle, resulting in bilateral ptosis. FEOM1 (OMIM 135700) is caused by a mutation in the *KIF21A* gene (116), typically maps to chromosome 12q12, and shows neuropathologic changes suggesting a primary defect in the development of the superior division of the oculomotor nerve (117,118). FEOM2 (OMIM 602078) is associated with bilateral ptosis, with the eyes fixed in an exotropic position. This autosomal recessive phenotype maps to chromosome 11q13.3-q13.4 and results from mutations of the *ARIX* gene (119). In families with FEOM3 (OMIM 600638), one or more affected individuals do not have the classic findings of the disorder. Their eyes may be not be infraducted or may elevate above midline, or the individual may be unilaterally affected. Ptosis may not be present (120).

Congenital entropion and ectropion refer to a malposition of the eyelid where the eyelashes are rotated towards and away from the globe, respectively. Congenital entropion results from imbalances in preseptal and pretarsal orbicularis. Congenital ectropion may result from inflammatory conditions such as *Chlamydia* infection and may be associated with noninflammatory conditions such as Down syndrome and ichthyosis.

Distichiasis, an anomaly in which two rows (instead of one row) of lashes are present at the lid margin, may be autosomal dominant. During development, eyelashes differentiate in association with the glands of Zeis in the eyelids during the invagination of ectoderm to form pilosebaceous units. Distichiasis results from maldevelopment in which cilia formation occurs in association with Meibomian glands. Treatment is directed toward protecting the corneal epithelium. If the lashes do not touch the epithelium, no treatment is required. Electrolysis, cryotherapy, or a surgical eyelid-splitting procedure to remove the hair follicles may be

performed when the lashes contact the corneal epithelial surface.

Conjunctiva

Many genetic disorders manifest themselves in the conjunctiva. Patients with ataxia telangiectasia (OMIM 208900: progressive cerebellar ataxia of childhood, oculomotor apraxia, absent optokinetic nystagmus, oculocutaneous telangiectases, immune defects, and malignancy predisposition) have significant dilatation and tortuosity of the conjunctival vessels. A characteristic oculomotor apraxia, i.e., difficulty in the initiation of voluntary eye movements, frequently precedes the development of the telangiectases. The ataxia telangiectasia mutated gene on chromosome 11 q23.3 (121) encodes a large protein kinase that regulates the cell cycle (122,123).

Congenital or early adult pterygium of the conjunctiva and cornea (OMIM 178000) is inherited as a dominant trait with 70% penetrance (124,125).

Pingueculae are evident in all forms of Gaucher disease (OMIM 230800, 230900, and 231000), one of the glycogen storage disorders (126).

Cornea

Developmental Corneal Abnormalities

Developmental abnormalities of the cornea include cornea plana, sclerocornea, microcornea, megalocornea, and keratoconus.

Cornea plana (CNA1; OMIM 121400, and CNA2; OMIM 217300) is a condition in which the cornea is flat, with a radius of curvature less than 43 diopters. A cornea with the same radius of curvature as the adjacent sclera is pathognomonic. This condition results from a failure of formation of the limbus by the second wave of neural crest cells during development. Cornea plana may be associated with microcornea or sclerocornea, as well as cataracts, anterior or posterior colobomata, and Ehlers-Danlos syndrome. Glaucoma may develop as a result of angle abnormalities (open-angle glaucoma) or due to a morphologically shallow anterior chamber (angle-closure glaucoma). Cornea plana has two subtypes distinguished by their inheritance pattern and severity. CNA1 is autosomal dominant, whereas CNA2 is autosomal recessive and the more severe of the two. Keratocan (*KERA*) mutations are associated with both types, although none were found in the original CNA1 families (127,128). *KERA* codes for a keratin sulfate proteoglycan and is important for the development and maintenance of corneal transparency and structure. *KERA* has restricted expression in early neural crest development and later expression in corneal stromal cells. Treatment includes neutralization of refractive errors and glaucoma management. If central clarity is lost, penetrating keratoplasty may be considered.

Sclerocornea (OMIM 269400) is also characterized by a flat cornea; however, it differs from cornea plana by the partial or complete loss of transparency of the cornea. The limbus may be ill-defined and scleral, episcleral, and conjunctival vessels extend across the cornea. Half of sclerocornea cases are sporadic, while the other half are either dominant or recessive (129).

Microcornea (OMIM 116150) is a condition in which the cornea is clear and of normal thickness; however, it measures less than 10 mm in diameter (9 mm in a newborn). It is thought to result from either fetal arrest of growth of the cornea or from overgrowth of the anterior tips of the optic cup leaving less space for the cornea to develop. It exists in both autosomal dominant and recessive forms, with the former occurring more commonly. Treatment includes correction of refractive errors and monitoring for the development of glaucoma due to shallow chambers or angle abnormalities.

Megalocornea (OMIM 249300) is a condition in which the corneal diameter is large (13.0 to 16.5 mm), but the cornea is clear and of normal thickness. The enlargement is not a result of congenital glaucoma. This condition represents either a failure of the anterior tips of the optic cup to close, allowing more room for the cornea to grow, or an overgrowth of the cornea in relation to the rest of the eye.

It may be associated with a number of ocular abnormalities including miosis, microcoria, goniodysgenesis, cataract, ectopia lentis, central cloudy dystrophy of Francois, and glaucoma. Furthermore, it is associated systemically with disorders of collagen synthesis. It is usually X-linked recessive and located in the Xq21.3-q22 region. There are reports of sporadic, autosomal dominant and recessive cases. A syndromic form of megalocornea, termed megalocornea and mental retardation syndrome (OMIM 249310), was first reported by Neuhauser and associates (130). Children are hypotonic and show mild frontal bossing, antimongoloid slant of the eyes, epicanthal folds, and broad nasal base. Iris hypoplasia may accompany the megalocornea.

Keratoconus (OMIM 148300) can be sporadic or autosomal dominant. The onset is around puberty with a progressive ectatic dystrophy leading to corneal thinning, with induced irregular myopic astigmatism which may be markedly asymmetrical. In advanced cases, anterior corneal scarring is present and hydrops may occur when Descemet's membrane ruptures with subsequent epithelial and stromal edema. Either circumstance may require a corneal graft to attain visual clarity. Keratoconus has been associated with several chromosomal anomalies including trisomy 21, Turner syndrome, ring chromosome 13, and chromosomal 7; 11 translocation; connective-tissue disorders such as Ehlers-Danlos, Marfan, and osteogenesis imperfecta syndromes; mitral valve prolapse; Leber congenital amaurosis; and atopy (131,132). Mutations in the *VSX-1* transcription factor gene were identified in 4.7% of patients with isolated keratoconus. This gene also plays a role in posterior polymorphous dystrophy (see below) (133).

Corneal Dystrophies

Hereditary dystrophies affecting all layers of the cornea are numerous; most are rare, and ophthalmologic evaluation is required to distinguish among them. Most of the corneal dystrophies are of Mendelian inheritance with some phenotype diversity and a variable degree of penetrance. The dystrophies involving enzymatic processes tend to be of autosomal recessive inheritance. Corneal clouding may be present at birth or is acquired (Fig. 1.12). Presenting signs and symptoms of the corneal dystrophies include cloudiness of the cornea, nystagmus due to poor vision, and photophobia. Corneal transplantation may be performed if vision is seriously reduced.

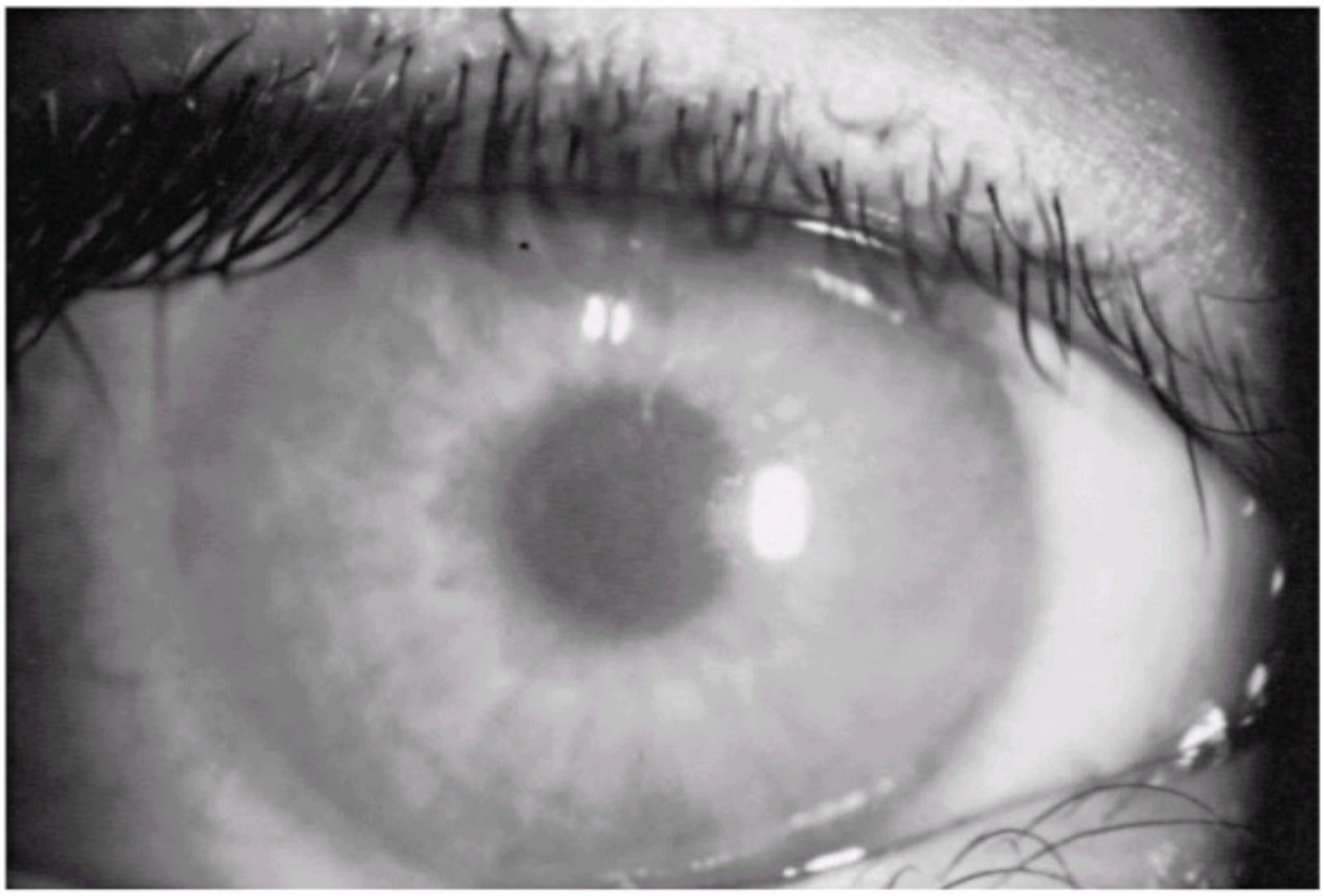


Figure 1.12 Opacification of corneal stroma in a 10-year-old patient with Maroteaux-Lamy syndrome (mucopolysaccharidosis VI).

Meesmann corneal dystrophy (OMIM 122100) has an autosomal dominant inheritance with an onset in early childhood (at approximately 12 months). Formed intraepithelial vesicles and microcysts, which contain periodic acid Schiff-positive “peculiar substances” suggestive of keratin, increase in number throughout life. The symptoms are variable, ranging from asymptomatic to pain and lacrimation associated with corneal erosions. Mutations have been identified in both keratin 12 (OMIM 601687) on chromosome 12q12-q13 and keratin 3 (OMIM 148043) on chromosome 17q12. Both genes, which are expressed in the anterior corneal epithelium, contain a highly conserved helix boundary motif, which plays a role in corneal structural integrity and keratinocyte filament assembly (134).

Defects in the human transforming growth factor ß-induced gene (*TGFßI* or ß*IGH3*) (135) are associated with multiple “classic” corneal dystrophies: lattice (OMIM 122200), non-classic LCDIIIa, intermediate-type LCDI/LCDIII, and LCD-deep dystrophies; granular (OMIM 121900) and non-classic granular dystrophies GCDII and GCDIII; Reis-Buücklers (OMIM 608470); Thiel-Behnke dystrophy (OMIM 602082); and Avellino corneal dystrophy. All of the corneal dystrophies show autosomal dominant hereditary transmission with variable penetrance and map to chromosome 5q31 (136,137,138,139). *TGFßI* is expressed in keratocytes and encodes for keratoepithelin, a highly conserved 683-amino acid protein. This protein contains an N-terminal secretory signal, four domains of internal homology, and an arginine-glycine-aspartame (RGD) motif at the carboxy terminus, which is found in many extracellular matrix proteins. The RGD motif modulates cell adhesion and acts as a recognition sequence for integrin binding. Gene mutations result in progressive accumulation of keratoepithelin corneal deposits. Aggregation of abnormal isoforms of keratoepithelin is associated with amyloid or other nonfibrillar deposits depending on the type of mutation (140).

The different subtypes of macular dystrophy, MCDI (OMIM 217800), MCDIa, and MCDII, are genetically and biochemically determined. The dystrophy is inherited in an autosomal recessive fashion, with onset in the first decade of life. Early on, the fine opacities have indistinct edges which start axially in the superficial stroma. The intervening stroma has a ground-glass appearance. Later, the opacities extend peripherally and into the deep stroma. The characteristic accumulation of glycosaminoglycans stains with Alcian blue and colloidal iron. MCDI is characterized by the absence of keratin chain sulfation (KCS) in cornea and cartilage and no appreciable serum KCS. In MCDII, serum and corneal keratin sulfate are detectable. MCD was mapped to chromosome 16q22 and mutations were noted in *CHST6* (OMIM 603797). *CHST6* encodes an enzyme, carbohydrate sulfotransferase, which is expressed in the cornea, spine, and trachea. The gene product initiates sulfation of keratin sulfate in the cornea. Mutations in this gene result in an inactive enzyme with the synthesis and secretion of proteoglycans (corneal structural genes) substituted with

polylactosamine instead of keratin sulfate (141,142,143).Gelatinous drop-like corneal dystrophy (GDLD; OMIM 204870) is an autosomal recessive disorder with clinical onset in the first decade of flat subepithelial nodular deposits similar to early band keratopathy. There is a gradual increase in number and depth of deposits which eventually become raised yellow-gray gelatinous masses with a mulberry configuration and surrounding dense subepithelial opacities. Recurrent lamellar keratoplasty or penetrating keratoplasty may be required. The gene, *M1S1*, maps to chromosome 1p31 and encodes for a gastrointestinal tumor-associated antigen. The abnormal *M1S1* gene product may affect epithelial cell junctions, resulting in increased cell permeability in GDLD corneas (144,145).

Posterior polymorphous corneal dystrophy (PPCD; OMIM 122000, 120252, and 605020) is an autosomal dominant disorder which shows variable expression and variable age of onset. Although it is usually a disease of adulthood, PPCD can be severe and present at birth. The disorder manifests as variable degrees of vesicular endothelial lesions with or without basement membrane thickening. This may be localized or diffuse, and may be associated with corneal edema. There is an increased risk for glaucoma and keratoconus. The abnormal anterior banded layer of Descemet's membrane is lined posteriorly by an abnormal posterior collagenous layer. PPCD is genetically heterogeneous with mutations identified in the transcription factor *VSX1* (chromosome 20p11.2-20q11.2) and the alpha 2 subunit of type VIII collagen *COL8A2* (chromosome 1p34.3-p32). PPCD is an allelic variant of keratoconus (OMIM 148300) and Fuchs' endothelial dystrophy (FECD; OMIM 136800), as VSX1 appears to play a role in approximately 9% of PPCD cases and 4.5% of keratoconus cases, and *COL8A2* appears to play a role in approximately 6% of PPD cases and 3.4% of FECD cases, respectively (133,146).

Congenital hereditary endothelial dystrophy (CHED1; OMIM 121700) is of autosomal dominant inheritance with onset at birth or in the first few months of life up to 8 years of age. CHED2 (OMIM 217700) is of autosomal recessive inheritance with an early onset of signs and symptoms at birth or within the first few weeks of life. The cornea has a ground-glass appearance, and the corneal epithelium may be roughened. There is no guttatae and the corneal sensitivity is normal. The decrease in vision is moderate to severe, and nystagmus is uncommon. The basement membrane is more thickened in CHED2. CHED is genetically heterogeneous, with CHED1 linked to a 2.7-cM locus at chromosome 20p11.2-20q11.2, and CHED2 linked to a chromosome 20p13 locus. No genes have been

identified as of yet (147,148).

Anterior Segment Dysgenesis

Malformations of the iris and anterior chamber angle may involve the region responsible for aqueous humor outflow and predispose patients to glaucoma.

As an isolated ocular malformation, aniridia (OMIM 106200) is an autosomal dominant disorder (Fig. 1.3). Visual impairment, which is unrelated to the degree of iris hypoplasia, is caused either by glaucoma or the frequent concomitant malformations of macular or optic nerve hypoplasia. Clinical expressivity can be variable within and among families (149,150). There are multiple reports of aniridia, developmental delays, genitourinary malformations, and Wilms' tumor associated with a deletion of the short arm of chromosome 11 (151,152,153,154); one patient had aniridia and Wilms' tumor without a microscopically detectable deletion (155) (see the section on Chromosomal Rearrangements). Autosomal dominant aniridia is due to a mutation in the *PAX6* gene (156,157). Mutations of this gene can cause other disorders, including congenital cataracts, anophthalmia and central nervous system defects (158), Peters' anomaly (159), and keratitis (160).

Axenfeld-Rieger syndrome (OMIM 602482 and 180500) is a spectrum of anterior segment and systemic structural change combinations which may be characterized by a prominent Schwalbe line, iris strands to the cornea, iris hypoplasia, dental abnormalities, characteristic facies, and umbilic defects; it is generally inherited in an autosomal dominant fashion. Associated ocular abnormalities include glaucoma, corectopia, iris pigment epithelial defects, microcornea, corneal opacities, and cataracts (161,162,163,164,165,166). Uncommonly, chromosomal rearrangements may cause Rieger syndrome, in which case there is usually developmental delay (167,168,169,170,171,172,173,174). Mutations of the eye developmental genes *FOXC1*, a forkhead box transcription factor, and *PITX2*, paired-like class of homeobox transcription factors, cause Axenfeld-Rieger syndrome (175,176,177,178,179). *FoxC1*-knockout mice also have anterior segment abnormalities that are similar to those reported in humans. The penetrance of the clinical phenotype varies with the genetic background, which indicates the influence of modulator genes.

In humans, mutations in *PITX3* cause anterior segment mesenchymal dysgenesis (180). In the mouse embryo, *Pitx3* is first expressed in the developing lens, initially in the lens vesicle and later in the anterior epithelium and lens equator. Deletions in the *Pitx3* promoter, which abrogate *Pitx3* expression in the eye, cause the phenotype of the *aphakia (ak)* mouse mutant, which lacks lenses and pupils (181).

Peters' anomaly may result from incomplete separation of the cornea and lens during embryogenesis; although evidence supports an autosomal recessive form of inheritance, chromosomal and nongenetic forms may exist (182,183,184,185). Mutations in the eye development genes *PAX6*, *PITX2*, *FOXC1*, and *CY1B1* have all been associated with Peters' anomaly (159,178,186,187).

Glaucoma

Glaucoma describes a heterogeneous group of optic neuropathies that lead to optic nerve cell damage, visual field loss, and permanent visual acuity deficits. It is the second most prevalent cause of bilateral blindness in the Western world, and it affects more than 60 million people world-wide. The hereditary forms of glaucoma are genetically heterogeneous. At least eight loci have been linked to glaucoma (GLC1A-F, GLC3A/B), and three genes have been identified to date: *MYOC, CYP1B1,* and *OPTN*.

Primary congenital glaucoma (PCG; OMIM 231300) is defined by onset before 3 years of age. It is often characterized

by buphthalmos, or an enlarged eye, as a result of increased intraocular pressure during intrauterine life or infancy when the elasticity of the scleral wall and cornea are greatest. Structurally, these eyes have a normal Schlemm's canal and normal episcleral veins; however, the trabecular meshwork is thought to be abnormal, impeding the drainage of aqueous humor from the anterior chamber. Infants with congenital glaucoma present with the classic triad of epiphora, photophobia, and blepharospasm. On examination, their corneal diameters may be markedly enlarged (greater than 12 mm during the first year of life), and the eye may be buphthalmic. Corneal edema may develop due to increased intraocular pressure, and acute stretching of the cornea may lead to Haab's striae (tears in Descemet's membrane). Inheritance is thought to be recessive with incomplete penetrance, and two loci have been mapped: one to chromosome 2p22-p21 (188,189) and the second to chromosome 1p36.2-p36.1 (190). Mutations of the gene *CYP1B1* (OMIM 601771) on chromosome 2p21 are associated with PCG (191). The gene encodes a 543-amino acid drug-metabolizing enzyme of the cytochrome P450 gene superfamily, subfamily I, which is a monooxygenase that is capable of metabolizing various endogenous and exogenous substrates, such as steroids and retinoids. It is expressed in the iris, trabecular meshwork, and ciliary body. Congenital glaucoma has also been reported to occur in association with deletions of chromosomes 10, 13, and 18; a pericentric inversion of chromosome 11; partial trisomy of chromosomes 3 and 14; and trisomies 13, 18, and 21 (192,193). Treatment is primarily surgical for congenital glaucoma, via a trabeculotomy or goniotomy.

Juvenile-onset open-angle glaucoma (JOAG; OMIM 137750) is defined as glaucoma acquired after birth and thus unaccompanied by buphthalmos. It is dominantly inherited and typically has its onset during the second or third decade of life. There is an association with myopia reported to be as high as 87% (194). Mutations in the myocilin gene (*MYOC*; also known as trabecular meshworkinducible glucocorticoid response gene; OMIM 601652) are associated with autosomal dominant JOAG (33% of patients) and with primary open-angle glaucoma (POAG; OMIM 137760) (2% to 4% of patients) (195,196). *MYOC* has been mapped to a locus (GLC1A) on chromosome 1q24.3-q25.2. *MYOC* is expressed in almost every ocular tissue, including the optic nerve (197); however, despite considerable effort, the function of MYOC remains obscure.

POAG is a chronic, progressive optic neuropathy characterized by cupping of the optic nerve head and is associated with visual field loss. Intraocular pressure may be elevated. It is insidious in onset and often progresses without symptoms since central visual acuity is relatively unaffected until late in the disease. Inheritance is thought to be multifactorial. In addition to the myocilin gene-associated GLC1A locus on chromosome 1q23-24, POAG has been mapped to several other loci: GLC1B on chromosome 2cen-q13, GLC1C on chromosome 3q21-24, GLC1D on chromosome 8q23, and GLC1F on chromosome 7q35-q36. Recently, mutations in the optineurin gene (*OPTN*), a locus previously designated GLC1E on chromosome 10p14-p15, have been demonstrated in 16.7% of patients with POAG (198). The pathogenic mechanism for glaucoma development due to mutations in *OPTN* is not fully understood—it is speculated that OPTN is operating through an apoptosis (cell death) pathway, playing a neuroprotective role in the eye and optic nerve (198).

Pigment dispersion syndrome (OMIM 600510) is a form of open-angle glaucoma which is characterized by pigment deposition on the corneal endothelium (Krukenberg spindle), trabecular meshwork, and lens periphery. Spoke-like loss of the iris pigment epithelium occurs, resulting in characteristic transillumination defects in the iris midperiphery. This loss of pigment is thought to be due to direct contact between the zonules and iris. Affected individuals are usually myopic men aged 20 to 50 years. Fluctuations in intraocular pressure (IOP) are usually wide, and patients are symptomatic with headaches, haloes, intermittent visual blurring, and pain. Medications are often helpful in controlling IOP; laser iridotomies are often attempted in cases of “reverse pupillary block,” and laser trabeculoplasty and filtering surgery are useful in treatment. Inheritance is autosomal dominant (199), and the gene has been mapped to chromosome 7q35-q36 (200).

Lens

Abnormalities of the lens of the eye may be divided into two broad categories: dislocations and opacities. A lens is subluxed if it is not in its proper anatomic location but still retains some zonular attachments to the ciliary body; in a complete dislocation, the lens floats free in the eye. Lens opacities, or cataracts, may occur in different layers of the lens and with varying severity.

The causes of subluxed and dislocated lenses are numerous. Dislocation or subluxation of the lens is a common manifestation of both Marfan syndrome (OMIM 154700) (Fig. 1.13) (201) and homocystinuria (OMIM 236200). Common manifestations in Marfan syndrome include lens subluxation superotemporally, dilatation of the aortic root, aneurysm of the ascending aorta, and skeletal abnormalities such as pectus excavatum, kyphoscoliosis, and an upper

segment: lower segment ratio two standard deviations below the mean for age. Pneumothorax, pes planus, dural ectasia, joint laxity, arachnodactyly, and mitral valve prolapse may also occur. The diagnostic criteria require involvement of three systems with at least two major manifestations. As mentioned previously, the

basis of Marfan syndrome is a mutation of the fibrillin gene, which maps to chromosome 15q15-q21.1 (202,203,204,205,206,207,208).

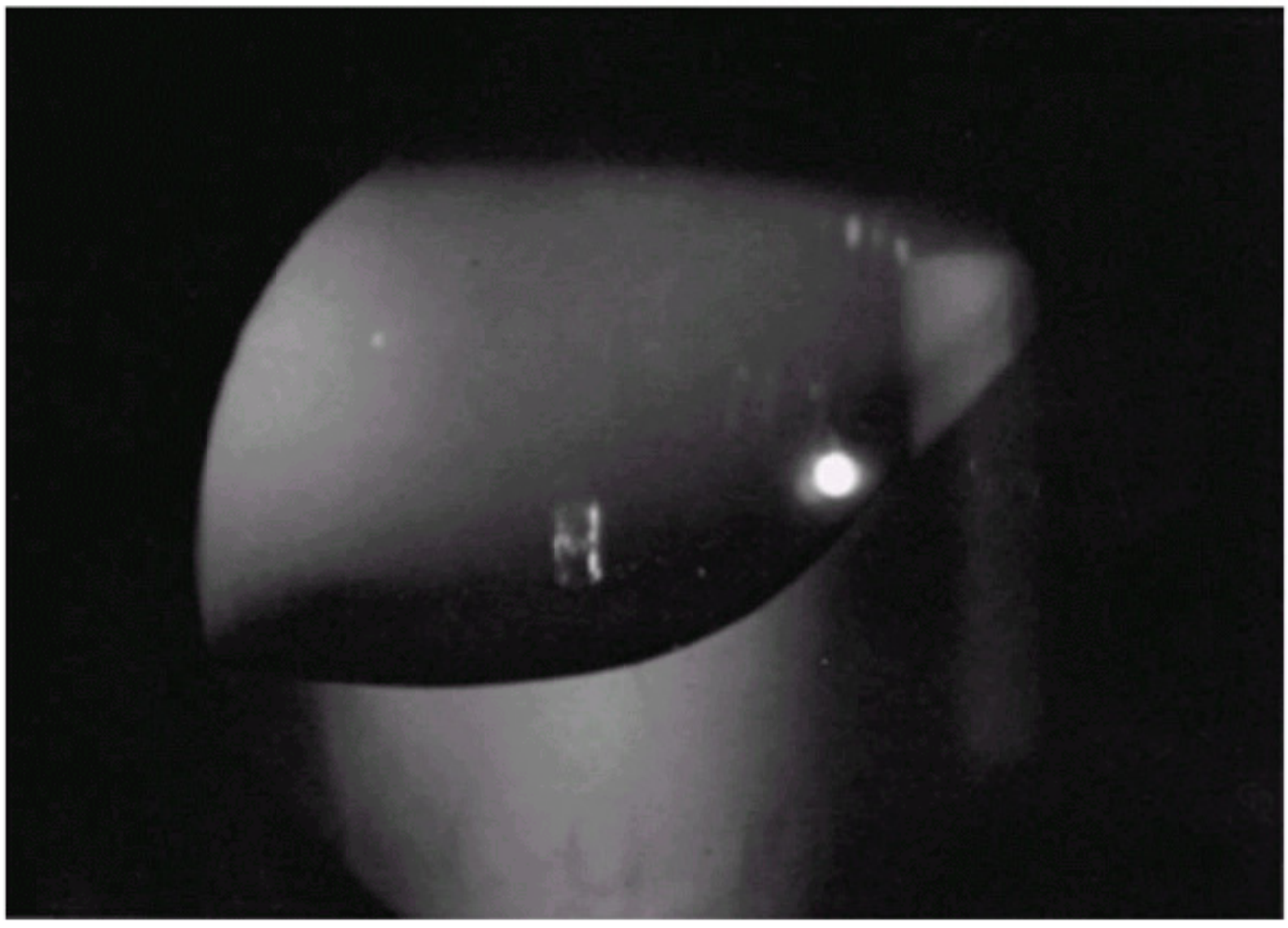


Figure 1.13 Superior dislocation of the lens in a young girl with Marfan syndrome.

Homocystinuria is characterized by a deficiency of the enzyme cystathione-ß-synthase, resulting in accumulation of homocysteine. Untreated patients present with mental retardation, unusually tall stature, coarse fair hair, cardiac murmurs, and thromboembolic diathesis. These patients have an increased anesthetic risk due to their tendency to develop thrombotic vascular occlusions. Ocular findings include blue irides and progressive myopia, which may be the first sign of lens dislocation. All untreated patients develop inferior or inferonasal dislocation of lenses bilaterally due to deficient zonular fibers. Diagnosis is confirmed by measurement of the serum homocysteine level. Surgery should be avoided if possible, and treatment consists of dietary management (low methionine and high cysteine) and supplementation of vitamin B6. The gene for cystathione-ß-synthase has been mapped to 21q22.3 (209), and it is transmitted in an autosomal recessive fashion.

Ectopia lentis et pupillae (OMIM 225200), an autosomal recessive disorder, is characterized by an eccentric pupil and subluxed lens (usually the lens is dislocated in a direction opposite the pupil) and is slowly progressive (210). Isolated lens subluxation or dislocation is rare, and most reports antedate careful definition of the Marfan syndrome and homocystinuria.

Isolated hereditary cataracts are usually transmitted in an autosomal dominant pattern, although autosomal recessive and X-linked forms have been reported. They may be present at birth or develop over time. Although the severity may vary within a family, the position and patterns are generally consistent. This variability within the same family suggests the importance of additional genes modifying the expression of the primary mutation. Conversely, cataracts with similar or identical clinical presentations can result from mutations in quite different genes. Currently, 27 isolated or primary cataract loci have been identified by linkage analysis or mutational screening, and 13 are associated with specific gene defects. For some a- and ß-crystallin mutations, inherited congenital cataracts are associated with microcornea and even microphakia. There are currently no identified developmental lesions causing isolated cataracts. Of those families for whom the mutant gene is known, about half have mutations in crystallins (structural components of the lens nucleus), about one-fourth have mutations in connexins (constituents of gap junctions on which the avascular lens depends for nutrition and intercellular communication), and the remainder are evenly split between aquaporin 0 (an enzyme involved in water channel activity) and the gene for the beaded filament protein *BFSP2* (structural filament unique to the lens fiber cells that combines with ß-crystallin) (158,211,212,213,214,215,216,217,218,219,220,221,222,223).

Cataracts are known to occur in association with a large number of metabolic diseases and genetic syndromes. Nance-Horan syndrome (OMIM 302350) is an X-linked recessive congenital cataract-dental disorder associated with microcornea, anteverted and simplex pinnae, brachymetacarpalia, and various dental anomalies; carriers exhibit distinctive sutural opacities (26,27). An isolated X-linked cataract has recently been mapped to chromosome Xp and is possibly allelic with the Nance-Horan syndrome (224).

Galactosemia (OMIM 230400) is an autosomal recessive disorder characterized by the inability to convert galactose to glucose, resulting in the accumulation of galactose and its conversion to galactitol. Classic galactosemia, which is the most common of three forms of the disease, involves a defect in galactose-1-phosphate uridyl transferase (*GALT*) and results in cataract formation during the first few weeks of life in 75% of untreated patients. Two other, less severe forms of the disease involve defects in two other enzymes, galactokinase and UDP-galactose-4-epimerase. Patients with classic galactosemia present with malnutrition, hepatomegaly, jaundice, and mental deficiency within the first few weeks of life. The cataract has a very characteristic “oil droplet” appearance on retroillumination due to accumulation of galactose and galactitol within the lens cells causing increased intracellular osmotic pressure and fluid influx into the lens. Diagnosis can be confirmed by testing the urine for reducing substances and demonstrating the presence of the nonglucose reducing substance, galactose. Treatment includes elimination of milk and milk products from the diet. *GALT* has been mapped to chromosome 9p13 (225,226,227).

Wilson disease, or hepatolenticular degeneration (OMIM 277900), is an autosomal recessive disorder of copper metabolism that results in a characteristic “sunflower cataract” which is not visually significant. This inborn error of metabolism results in excess copper deposition in the liver, kidney, and central nervous system. Systemic features include cirrhosis, renal tubular damage, and a Parkinsonlike defect of motor function. Ocular findings include the characteristic sunflower cataract as well as the KayserFleischer ring, a golden brown discoloration around the perilimbal cornea due to copper deposition in Descemet's membrane. The cataract results from the deposition of cuprous oxide in the anterior lens capsule and subcapsular cortex in a stellate pattern resembling the petals of a sunflower. Diagnosis may be confirmed by measuring the serum copper and ceruloplasmin levels, and treatment includes a copper-chelating agent as well as zinc in some cases to preserve hepatic function. Since the cataracts are usually not visually significant, patients may be monitored without the need for surgical intervention. The *WND* gene, in which mutations lead to Wilson disease, has been mapped to chromosome 13q14.3-q21.1 (228) and is a putative

copper-transporting P-type ATPase enzyme (229).

Myotonic dystrophy (OMIM 160900) is an autosomal dominant disorder in which patients may develop a characteristic “Christmas tree cataract” due to the deposition of polychromatic iridescent crystals in the lens cortex. Systemic findings usually develop in middle age and include delayed relaxation of contracted muscles, weakness of the facial musculature, frontal balding, and cardiac conduction defects. In addition to the crystalline lens deposits, patients with myotonic dystrophy may develop progressive posterior subcapsular cataract leading to complete cortical opacification.

Involvement of the facial muscles and extraocular muscles may lead to ptosis, weakness of eye closure, and ocular motility deficits. Inheritance is autosomal dominant with variable penetrance, and the disease has been mapped to chromosome 19q13.2-q13.3 (230). Boucher and associates (231) identified the gene for myotonic dystrophy type 1, called DM locus-associated homeodomain protein.

Vitreous, Retina, and Choroid

Hereditary vitreoretinal and choroidoretinal malformations and degenerations are numerous, and a complete description is beyond the scope of this chapter. Categorization can be difficult, as all three adjacent anatomic regions of the eye (vitreous, retina, and choroid) can be abnormal; classifications are based on clinical features such as funduscopic appearance, color vision tests, electrophysiologic tests, fluorescein angiography, and hereditary patterns. Selected clinical entities will be reviewed in this section.

Color Vision Genetics

Color vision defects are probably the most common abnormality of retinal function and can present at birth or can be acquired. Hereditary congenital color deficiencies are almost always X-linked recessive red-green abnormalities and predominantly affect males. The genes encoding the red and green photopigments are arranged in a head-totail tandem array on chromosome Xq28. The normal X-chromosome-linked color vision gene array is composed of a single red pigment gene followed by one or more green pigment genes. The high degree of homology between these genes predisposes them to unequal recombination, leading to gene deletions or the formation of red-green hybrid genes that explain the majority of the common red-green color vision deficiencies. Gene expression studies suggest that only the two most proximal genes of the array are expressed in the retina. The expression of the genes of the array is controlled by a highly conserved sequence of DNA, referred to as the locus control region (LCR), located approximately 3.5 kb upstream of the red pigment gene. Deletion of the LCR was shown to be associated with loss of expression of all the genes of the array, resulting in blue cone monochromacy (BCM; OMIM 303700). The severity of the color vision defect is roughly related to the difference in absorption maxima of the photopigments encoded by the first two genes of the array. The blue pigment gene is located on chromosome 7 (232).

There is wide variation in both normal and defective color vision among humans. The inherited forms of color vision deficiencies are classified into four main categories: (a) the common red-green defects that include the protan type caused by lack of red cones (protanopia) or by replacement of red cones with ones that contain anomalous pigments (protanomaly), and the deutan type caused either by lack of green cones or by replacement of green cones with ones that contain anomalous pigments (deuteranomaly); (b) the blue-yellow or tritan color vision due to non-functional blue cones; (c) loss of red and green cone function (BCM); and (d) complete color blindness due to loss of function of all three classes of cone (achromatopsia [ACHM]). The red-green deficiencies, which are inherited as X-chromosome-linked recessive traits, are by far the most common, reaching an incidence of as high as 8% among males of northern European extraction, and approximately 5% among other ethnic groups. The other forms are rare.

BCM, also known as X-chromosome-linked incomplete achromatopsia, is a rare X-linked ocular disorder, characterized by poor visual acuity, infantile nystagmus (which diminishes with age), and photophobia, together with severely reduced color discrimination capacity. It is sometimes associated with progressive macular atrophy. Deletions encompassing the LCR or point mutations which inactivate both the red and green pigments are responsible for BCM (233,234).

Tritan or blue-yellow color vision deficiency is due to defective blue cones and is characterized by blue-yellow color confusion. It is a rare (less than one in 1,000) autosomal dominant trait with severe (tritanopia) and mild (tritanomaly) forms. Mutations in the blue pigment gene on chromosome 7 have been implicated for this disorder (235,236).

ACHM, which is also referred to as total colorblindness or rod monochromacy, is an autosomal recessive congenital and stationary ocular disorder with a prevalence of one in 30,000. It is characterized by severe photophobia and nystagmus within the first months of life. Visual acuity is significantly reduced, and there is complete absence of color discrimination. In electroretinogram recordings, rod function is normal, but cone function is absent or strongly reduced. It is due to a genetic dysfunction of all three cone pigment genes. Three genes have been implicated with achromatopsia—two are channel-forming modulatory subunits of the cone photoreceptor cGMP-gated channel *CNGA3* (a subunit) (OMIM 600053) at the ACHM2 (OMIM 216900) locus on chromosome 2q11, and *CGNB3* (ß subunit) (OMIM 605080) at the ACHM3 (OMIM 262300) locus on chromosome 8q21. Mutations in the *CGNA3* gene account for 20% to 30%, and mutations in the *CNGB3* gene account for 40% to 50% of all achromatopsia patients. Recently, mutations in the cone-specific a subunit of the transducin G-protein (*GNAT2*) gene (OMIM 139340) on chromosome 1p13 (ACHM4 locus) were shown to account for approximately 2% of this rare disorder (237,238,239,240,241).

Vitreoretinal Degenerations

Diseases that involve the vitreous and retina predominantly include the X-linked recessive disorder congenital retinoschisis (OMIM 312700). Both the macula and retinal periphery exhibit splitting of the retina, which may be slowly progressive; vision usually is minimally impaired into middle age (242). The gene has been mapped to Xp22.2-p22.1. Familial foveal retinoschisis (OMIM 268080) has been described as an autosomal recessive disorder in one family; macular abnormalities resembled those of congenital retinoschisis (243).

Familial exudative vitreoretinopathy (FEVR; OMIM 133780 and 305390) is a hereditary ocular disorder characterized

by a failure of peripheral retinal vascularization. There is abrupt cessation of growth of peripheral capillaries. This can then lead to compensatory retinal neovascularization, which can secondarily proceed to exudative leakage and bleeding, cicatrization, and tractional retinal detachments. Early diagnosis is essential. FEVR is inherited as an autosomal dominant (244,245) or X-linked recessive condition (246,247). Loci associated with FEVR map to chromosomes 11q13-23, Xp11.4, and 11p13-12. Robitaille and associates (248) confirmed linkage to the chromosome 11q13-23 locus for autosomal dominant FEVR in a large multigenerational family, refined the disease locus, and identified mutations in the frizzled-4 gene (*FZD4*) as causative for this disorder. FZD genes encode Wnt receptors, which are implicated in development and carcinogenesis. Wnts are secreted signaling molecules implicated in various developmental processes, and frizzled proteins are the receptors for these ligands. These processes range from embryonic dorsal-ventral patterning, neural-tube patterning, and limb formation to kidney development. A neovascular inflammatory vitreoretinopathy (OMIM 193235) has been assigned to chromosome 11q13-23 (249).

The gene (norrin) for Norrie disease (OMIM 310600), an X-linked recessive syndrome of congenital retinal detachment, developmental delay, and hearing loss, has been mapped to the short arm of the X chromosome (250,251,252,253,254,255,256,257,258) and encodes a nuclear protein (259,260).

Retinal-Choroidal Dystrophies

The term *retinitis pigmentosa* (OMIM 268000) is very general and is applied to conditions in which the retinal deterioration is progressive and characterized by visual field loss, night blindness, and an abnormal or nonrecordable electroretinogram. Ophthalmoscopically, clumping of pigment frequently is present in the retina or adjacent to narrowed retinal vessels, giving rise to a “bone-spicule” appearance. The forms of retinitis pigmentosa may be broadly divided into those that affect the cones of the retina initially or predominantly and those that affect the rods initially or predominantly; inheritance may follow autosomal recessive or dominant or X-linked recessive patterns (261). Initial symptoms, progression, and ophthalmoscopic features are not consistent within a given hereditary pattern.

Autosomal dominant retinitis pigmentosa (adRP) may be caused by mutations of the candidate genes for rhodopsin (RP4) (262), peripherin/RDS (RP7) (263), and ROM1 (264); the disease has been linked to loci on chromosomes 7p (RP9) (265), 7q (RP10) (266), 8qll-21 (RP1) (267,268), 17p13.1 (RP13) (269,270), 17p22-24 (271), and 19q13.4 (RP11) (272). Mutations of the peripherin gene can result in a variety of clinical disorders including adRP, retinitis pigmentosa punctata

albescens, and macular dystrophy (273,274,275). Digenic inheritance of a mutation in both peripherin/*RDS* and *ROM1* has been implicated as another mechanism (276,277).

Autosomal recessive forms of the disease may be caused by mutations of genes encoding for RP4 (278,279), a subunit of rod phosphodiesterase (280), ß subunit of rod phosphodiesterase (281,282), and a subunit of the cGMP-gated channel CNCG1 (283); additional loci have been mapped to chromosomes 1p13-21 (284), 1q31-q32 (274,285), and 6p (286,287).

At present, there are three X-linked forms of retinitis pigmentosa at chromosomes Xp1l (RP2) (288), Xp21 (RP3) (289,290), and Xp21 (RP6). The gene for RP3 has been identified as having homology with the guanine-nucleotide exchange factor *RCC1* (289,290).

The term *cone-rod degeneration* refers to cases in which central vision is reduced early in the course of the disease; abnormalities in photopic electroretinogram precede alterations in the scotopic response. Mutations of the peripherin/*RDS* gene may cause an autosomal dominant form of the disease (291,292,293). Genes have been identified on chromosomes 6q16 (294,295), 6q25-q26 (296), 17p (297,298), 17q11 (299), 18q21 (300), 19q13.3-13.4 (301), as well as Xp21.1-p11.3 (302,303) and Xp22.13-11 (304).

Sorsby fundus dystrophy (OMIM 136900) is an autosomal dominant disease with complete penetrance. It is characterized by macular and extramacular chorioretinal neovascularization typically occurring in the fourth and fifth decades of life. Early features consist of small drusenoid lesions (referred to as colloid bodies), pigmentary clumping, and pigment epithelial atrophy, which may extend into the periphery. Visual loss progresses initially peripherally and may deteriorate to hand motion. Color anomalies, night blindness, and diminished electroretinogram responses (rod and cone) are common (305). The disorder is caused by mutations in the tissue inhibitor of metalloproteinases-3 (*TIMP3*) (306). The TIMP3 protein belongs to a family of secreted proteins that play a role in regulating extracellular matrix metabolism. They inhibit matrix metalloproteinases, and thereby determine the extent of matrix degradation during normal tissue remodeling processes.

Dominant Stargardt-like macular dystrophy (OMIM 600110) is an autosomal dominant disorder. Visual loss without apparent fundus lesions is a common first presentation of this disorder, usually in the first or second decade of life. The subtle early changes consist of RPE mottling and slight pallor of the optic nerve. Later, atrophy of the macular RPE occurs, which may or may not be accompanied by yellow flecks. Final visual acuity generally ranges from 20/40 to 20/200, the presence of yellow flecks predicting a more severe visual outcome. The “dark choroid” seen in recessive Stargardt disease is not seen in the dominant form. A photoreceptor-specific gene called *ELOVL4* (elongation factor of very-long-chain fatty acids) was identified as the responsible gene by Zhang and associates in 2001 (307). It has been hypothesized that the ELOVL4 protein is involved in synthesis of the polyunsaturated fatty acids present in the outer segments, thus playing a critical role in membrane composition and photoreceptor health (308).

Stargardt macular dystrophy (STGD; OMIM 248200) is the most common macular dystrophy with an estimated frequency of one in 8,000 to 10,000 in the United States. The age of onset and clinical course are variable. One-third of those affected present in the first decade of life, and they generally have a more progressive course than those with later onset. Fundus abnormalities include pigmentary changes in the macula, RPE atrophy giving a “bull's eye” appearance, a “beaten bronze” look of the posterior pole,

and yellow “fishtail” flecks at the level of the RPE. The latter manifestation is also called fundus flavimaculatus. In a large fraction of STGD patients, a “dark” or “silent” choroid is seen on fluorescein angiography which reflects accumulation of lipofuscin. Electroretinogram findings vary. The causal gene, ATP-binding cassette-transporter *ABCA4* or *ABCR*, was cloned in 1997 and maps to chromosome 1p13-p22. The ABCR protein translocates a precursor of lipofuscin; thus, in a defective state, abnormally high levels of lipofuscin accumulate in the RPE, triggering RPE cell death and causing secondary photoreceptor degeneration (309,310).

Best vitelliform macular dystrophy (OMIM 153700) maps to chromosome 11q13 (311,312), and the gene, *VMD2*, encodes a protein known as bestrophin, which has been localized to the basolateral plasma membrane of the RPE. Bestrophin is a chloride channel (313,314). The classic clinical presentation is an “egg yolk” appearance of the macula. A diagnostic hallmark is an abnormal electroocu-logram with an Arden ratio of less than 1.5, which indicates a lower change in the electric potential derived from the RPE than normal when light is cast on the fundus. Visual symptoms such as blurred vision and metamorphopsia may occur in the first decade, but significant visual decline usually does not happen until the third and fourth decades of life, when subretinal neovascularization and central atrophy may develop.

Gyrate atrophy (OMIM 258870), an autosomal recessive chorioretinal dystrophy associated with hyperornithinemia, is caused by a deficiency of the enzyme ornithine aminotransferase; the gene maps to chromosome 10 (315).

Some retinal dystrophies are relatively stable over time. Congenital stationary night blindness (CSNB; OMIM 310500, 163500, and 300071) is usually divided into complete and incomplete forms; inheritance is autosomal dominant, autosomal recessive, and X-linked recessive. Affected persons have decreased visual acuity and myopia; the defect is related to altered neurotransmission between bipolar cells and photoreceptors (316,317). Autosomal dominant CSNB has been associated with mutations in the rhodopsin (chromosome 3p) (318,319) and ß subunit of the rod phosphodiesterase genes (chromosome 3p) (320). The X-linked form has been linked to the Xp11.2-Xp11.23 (321,322); the gene may be allelic with one form of X-linked retinitis pigmentosa (288). A second locus on the X chromosome has been described (323); a third locus near the *RP3* gene region has been reported (324). Aland Island eye disease is a clinical variant of congenital stationary night blindness (325,326). Oguchi disease, a recessively inherited form of stationary night blindness, is caused by defects in the enzyme rhodopsin kinase (327).

Optic Nerve

Congenital Anomalies

Optic nerve hypoplasia (OMIM 165550) is a bilateral or unilateral developmental anomaly characterized by a reduced number of axons in a nerve which otherwise contains the appropriate supportive mesodermal tissue. This abnormality is present at birth and has a clinical spectrum ranging from a subtle segmental reduction in nerve head size to severe, diffuse loss of axons resulting in a small nerve head surrounded by a normal-sized optic canal, the “double-ring sign.” Superior segmental optic nerve hypoplasia has been reported in children of insulin-dependent diabetic mothers. Males and females are equally affected, and bilateral disease is more common than unilateral.

Autosomal dominant inheritance of optic nerve hypoplasia has been reported in one family (328). Recently, Azuma and associates reported mutations in the *PAX6* gene of patients with bilateral optic nerve hypoplasia and aplasia (329). Patients with bilateral, severe optic nerve hypoplasia may present with nonprogressive poor vision and nystagmus. Alternatively, patients with a mild form of optic nerve hypoplasia may be asymptomatic with normal visual acuity, or have only visual field defects in the presence of good visual acuity. Bitemporal visual field defects are commonly found, and these may indicate the presence of midline central nervous system abnormalities. Septooptic dysplasia (OMIM 182230), or De Morsier syndrome, consists of optic nerve hypoplasia and absence of the septum pellucidum or corpus callosum; other associations exist and children with this syndrome are mentally retarded and often have pituitary dysfunction. Magnetic resonance imaging of the brain is indicated in cases of optic nerve hypoplasia to evaluate associated central nervous system abnormalities.

Optic nerve coloboma (OMIM 120430) is a congenital abnormality resulting from incomplete closure of the embryonic fissure (Fig. 1.11). There is a spectrum of diseases ranging from a small notch inferotemporally to a large excavation of the inferior optic nerve. The superior portion of the nerve is usually unaffected, reflecting the inferotemporal position of the embryonic fissure. Serous detachments of the retina extending to the macula are a common complication. Although most appear to be sporadic, autosomal dominant inheritance has been described in some bilateral cases (330). Azuma reported the association of optic nerve coloboma with a mutation in the *PAX6* gene in a 1-year-old boy with iris anomaly, large coloboma of the optic nerve, retina, and choroid, persistent hyperplastic primary vitreous bilaterally, and growth and mental retardation (329). Mutations in the *PAX2* gene have been reported by several authors in patients with bilateral optic nerve colobomata and renal disease (331,332,333).

Optic nerve pits are congenital excavations of variable size, shape, depth, and location in the substance of the nerve head. They affect males and females equally and may be bilateral or unilateral, single or multiple. A visual field defect often exists corresponding to the location of the pit. Visual acuity is usually unaffected in the absence of a serous detachment of the retina in the macula, a possible complication which typically occurs in the third or fourth decade of life. Autosomal

dominant inheritance has been reported (334).

Hereditary Optic Neuropathies

Dominant optic atrophy (OPA1; OMIM 165500) is a hereditary optic neuropathy with early onset and autosomal dominant inheritance; visual impairment is variable and

may be progressive (335,336). Patients typically present with onset of bilateral, although sometimes asymmetric, vision loss in the first decade of life. Progression usually does not occur beyond the second decade of life. A gene was initially localized to chromosome 3q (337) and later identified as *OPA1*, a gene in the optic atrophy-1 candidate region 3q28-3q29; mutations in this gene were identified as the cause of dominant optic atrophy (338,339). A recessive form of optic atrophy also exists, either in isolation or as part of a syndrome. The affected phenotype is more severe than that of dominant optic atrophy.

Wolfram syndrome (OMIM 222300), or DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness), may present in early childhood or adolescence. Other neurologic abnormalities may also be associated. A gene has been identified, the *WFS1* gene, coding for wolframin on chromosome 4p16.1 (340). This disease may be sporadic or autosomal recessive in inheritance; a mitochondrial inheritance has also been suggested.

Leber optic atrophy (OMIM 535000) presents as a sudden loss of vision in the second or third decade of life and is characterized by hyperemia of the optic nerve head. The condition predominates in males, most commonly during teenage years or young adulthood. There is no transmission of the disease or the carrier state to the offspring of an affected male; however, female carriers have at least a 50% chance of transmitting the disease to their sons, and most of their daughters are carriers. Some 10% to 20% of female carriers manifest the disease (341). Although nearly all of an individual's DNA is located in the 46 chromosomes in the cell nucleus, a very small amount lies within mitochondria in the cytoplasm and is termed *mtDNA* (see the section on Mitochondrial Genetics). A point mutation of the mtDNA encoding NADH dehydrogenase has been demonstrated in multiple cases of Leber optic atrophy; mutations have been identified as either primary or secondary (342,343). Mutations at codon positions 11778, 14484, or 3460 are considered pathogenic (34,344,345,346,347,348,349,350). Secondary mutations, particularly those at 13708 and 15257, appear to contribute to the disease (351,352,353); these mutations may also occur in the normal population (354,355,356). An X-linked gene may contribute to the clinical features (357,358).

CHROMOSOMAL REARRANGEMENTS

Chromosomal aberrations were first identified in the late 1950s. The bases of Turner syndrome (359), Klinefelter syndrome (360), and Down syndrome (361) were established shortly after Tjio and Levan (10) identified the correct number of human chromosomes. Many other chromosomal diseases have since been delineated. Chromosome studies are now a major diagnostic tool for evaluation of children with congenital malformations, mental retardation, and ambiguous external genitalia. Approximately one in every 200 liveborn children and more than half of spontaneously aborted fetuses carry a chromosome abnormality.

Most numerical chromosomal anomalies originate during gametogenesis in a parent (usually the mother) and are due to nondisjunction or anaphase lag. During the first meiotic division, homologous duplicated chromosomes pair and then segregate, migrating to opposite poles independently of their parental origin; two cells, each with 23 duplicated chromosomes, are the result. This is followed by a second division of the duplicated chromosomes. Failure of separation of homologous chromosomes may occur in the first division, or failure of chromatid separation of the duplicated chromosomes may occur in the second (Fig. 1.14). In either case, complementary gametes with 24 chromosomes (one present in duplicate) and 22 chromosomes (one missing) result. If the former were fertilized by a normal gamete (23 chromosomes), the zygote would have 47 chromosomes, one being present in triplicate (trisomy); if the latter, the zygote would have 45 chromosomes with one missing (monosomy). The autosomal trisomies compatible with term gestation are those of chromosomes 13, 18, and 21. Full trisomies of other chromosomes are usually lethal in utero and are identified in spontaneous abortions. Autosomal monosomy also is usually lethal, although monosomy 21 has been reported. Mosaicism can occur in such cases.

Nondisjunction of sex chromosomes has less severe consequences. Monosomy X is the basis of Turner syndrome, and females with XXX and XXXX have been identified. Males with XXY (Klinefelter syndrome) and XYY are not uncommon and increasing numbers of X and Y to XXXXY or XXYY have been reported.

If nondisjunction occurs after fertilization in an early division of the embryo, mosaicism results. Cell lines with trisomies or monosomies in addition to normal cells may persist in a fetus or an individual. In general, cells with autosomal monosomies are nonviable, but monosomic 9 or X cells may survive. Three cell types—45,X; 46,XX; and 47,XXX—can coexist in females who presumably began life

as XX zygotes and developed a single mitotic nondisjunction, producing the X and XXX cells.

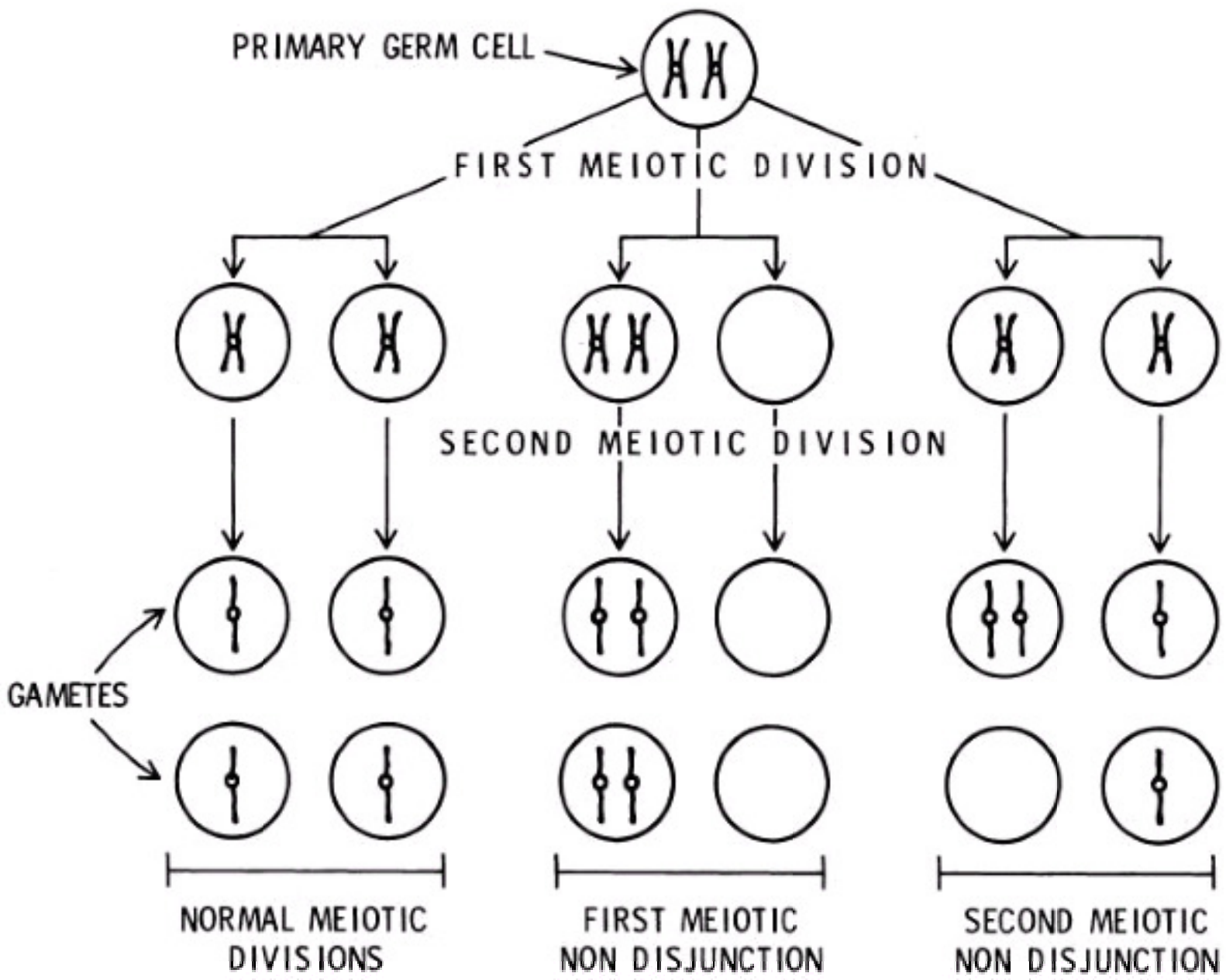


Figure 1.14 Diagram of meiosis for one pair of homologous chromosomes. Trisomy and monosomy resulting from nondisjunction in the first and second divisions are shown. (From Nelson WE, Vaughn VC, McKay RJ, eds. *Textbook of pediatrics*, 9th ed. Philadelphia: WB Saunders, 1969.)

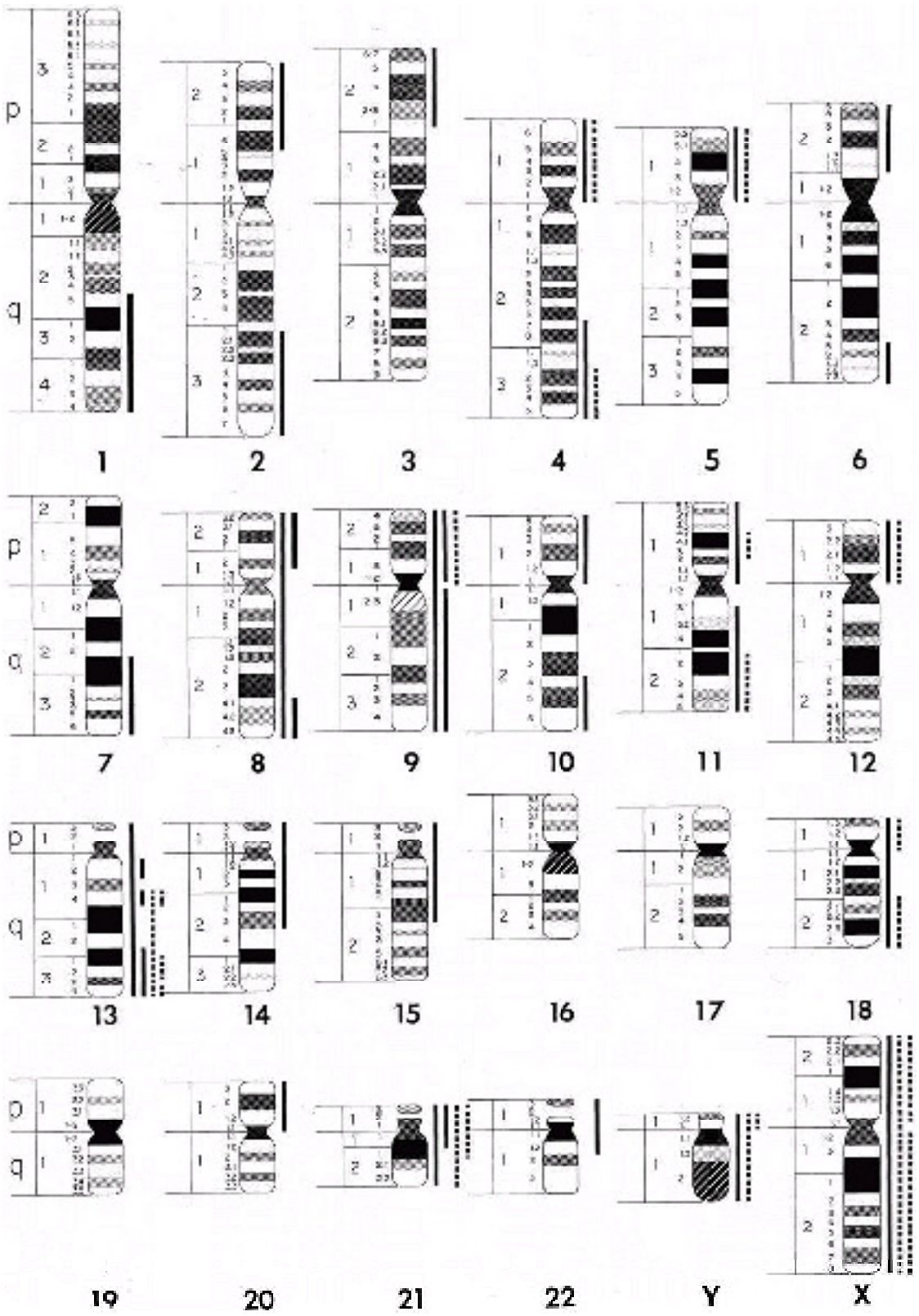


Figure 1.15 Chromosomal syndromes. Schematic representation of high-resolution banding of the human karyotype. Sub-bands are represented by the decimal system recommended by the Paris Conference in 1971. Numbers 1 to 22 represent autosomes, and X and Y sex chromosomes. Letters p and q on the left side of each chromosome row refer to short and long arms, respectively. The variable heterochromatic band q12 of chromosomes 1, 9, 16, and Y is represented with diagonals. To the right of each chromosome, presently known syndromes are represented: trisomic (duplication) syndromes by solid vertical lines and deletion (monosomy) syndromes by dotted lines. (Adapted from previously unpublished figures, courtesy of Jorge J. Yunis, MD.)

The first identified human translocations were centric fusions between two acrocentric chromosomes (centromere near one end of the chromosome), which reduced the chromosome count by one; the nonessential short arms were lost. Most of the translocations causing Down syndrome and trisomy 13 are due to centric fusions. Reciprocal translocations between biarmed chromosomes alter arm ratios without changing the chromosome number. Carriers of reciprocal translocations are clinically normal and are usually detected because of unbalanced offspring; such carriers may produce a child with multiple anomalies or have a history of spontaneous abortions.

Case reports of familial translocations, deletions, and duplications in which identification of structural abnormalities was possible by use of high-resolution chromosome banding techniques have led to the delineation of many syndromes of partial monosomy or trisomy. Figure 1.15 indicates schematically the chromosome regions involved in some syndromes that have been identified. Many identifiable chromosomal syndromes exhibit ocular manifestations.

Many chromosomal aberrations have ocular involvement, the most common manifestations being hypertelorism, epicanthus, antimongoloid lid slant, ptosis, strabismus, and microphthalmia; however, any and all structures of the eye can be abnormal in a patient with a chromosomal rearrangement. Of the more common manifestations, microphthalmia, a malformation in which the volume of the eye is reduced, is most visually significant; it has been reported to be associated with a variety of chromosomal rearrangements. Usually, an associated coloboma of the uvea (the iris in Fig. 1.10 or the choroid) is evident and is caused by incomplete closure of the fetal fissure; the typical position is inferonasal. Visual impairment may be severe if the eye is significantly decreased in size or completely absent, or if the coloboma involves the macula (the portion of retina responsible for the sharpest vision) or optic nerve. An isolated iris coloboma does not cause significant visual impairment. Table 1.1 summarizes the chromosomal rearrangements that have been reported in association with colobomatous and noncolobomatous forms of microphthalmia; Table 1.2 describes the associations of cyclopia.

Aneuploidy

Aneuploidy is a state of having a complete diploid set of chromosomes with one or more extra or missing chromosomes. The major chromosomal aneuploidy syndromes compatible with live birth include trisomy 13, 18, and 21 and monosomy X (Turner syndrome), XXY (Klinefelter syndrome), XXX, and XXY. Cat eye syndrome is partial trisomy 22.

Trisomy 13 (Patau Syndrome)

Infants with trisomy 13 (362) usually have normal birth weight and are hypotonic. About half have a cleft lip or palate (Fig. 1.16A). Those without clefts have a characteristic face with sloping forehead and bulbous nose (Fig. 1.16B). Perinatal death is common, and survivors are severely retarded; 90% die by 1 year of age.

TABLE 1.1 CHROMOSOMAL ABERRATIONS

Colobomatous Microphthalmia

Condition	Reference
Triploidy	Cogan 1971 (454)
Trisomies	
13	Cogan et al 1964 (455)
18	Mullaney 1973 (456)
Duplications	
4q+	Wilson et al 1970 (457)
7q+	Vogel et al 1973 (458)
9p+	Rethore et al 1970 (459)
9p+q+	Schwanitz et al 1974 (460)
13q+	Hsu et al 1973 (461)
22q+	Walknowska et al 1977 (462)
Deletions	
3q-	Alvarado et al 1987 (463)
4p-	Wilcox et al 1978 (174)
4r	Carter et al 1969 (464)
7q-	Taysi et al 1982 (465)
11q-	Ferry et al 1981 (466);
	Bialasiewicz et al 1987 (467)
13q-	O'Grady et al 1974 (468)

13q-	O'Grady et al 1974 (468)
13r	Saraux et al 1970 (469)
18q-	Schinzel et al 1975 (470)
18r	Yanoff et al 1970 (471)
Microphthalmia	
Duplications	
10q+	Yunis et al 1976 (472)

Anomalies include cardiovascular malformations, polycystic renal cortex, biseptate uterus in females, undescended testes and abnormal insertion of the phallus in males, polydactyly of the hands and feet, hyperconvex nails, capillary cutaneous defects, and cutaneous scalp defects. The central nervous system is markedly affected, degrees of defects ranging from cyclopia (Fig. 1.16C) with absence of rhinencephalon, union of ventricles and thalami, and defects of

the corpus callosum, falx cerebri, and commissures to simple arrhinencephaly with absence of olfactory nerves and lobes.

TABLE 1.2 CHROMOSOMAL REARRANGEMENTS WITH CYCLOPIA AND SYNOPHTHALMIA

Trisomy 13	Howard 1977 (473)
Trisomy 18	Lang et al 1976 (474)
18r	Cohen et al 1972 (475)
18p-	Nitowsky et al 1966 (476); Faint et al 1964 (477)
3p+	Gimelli et al 1985 (478)

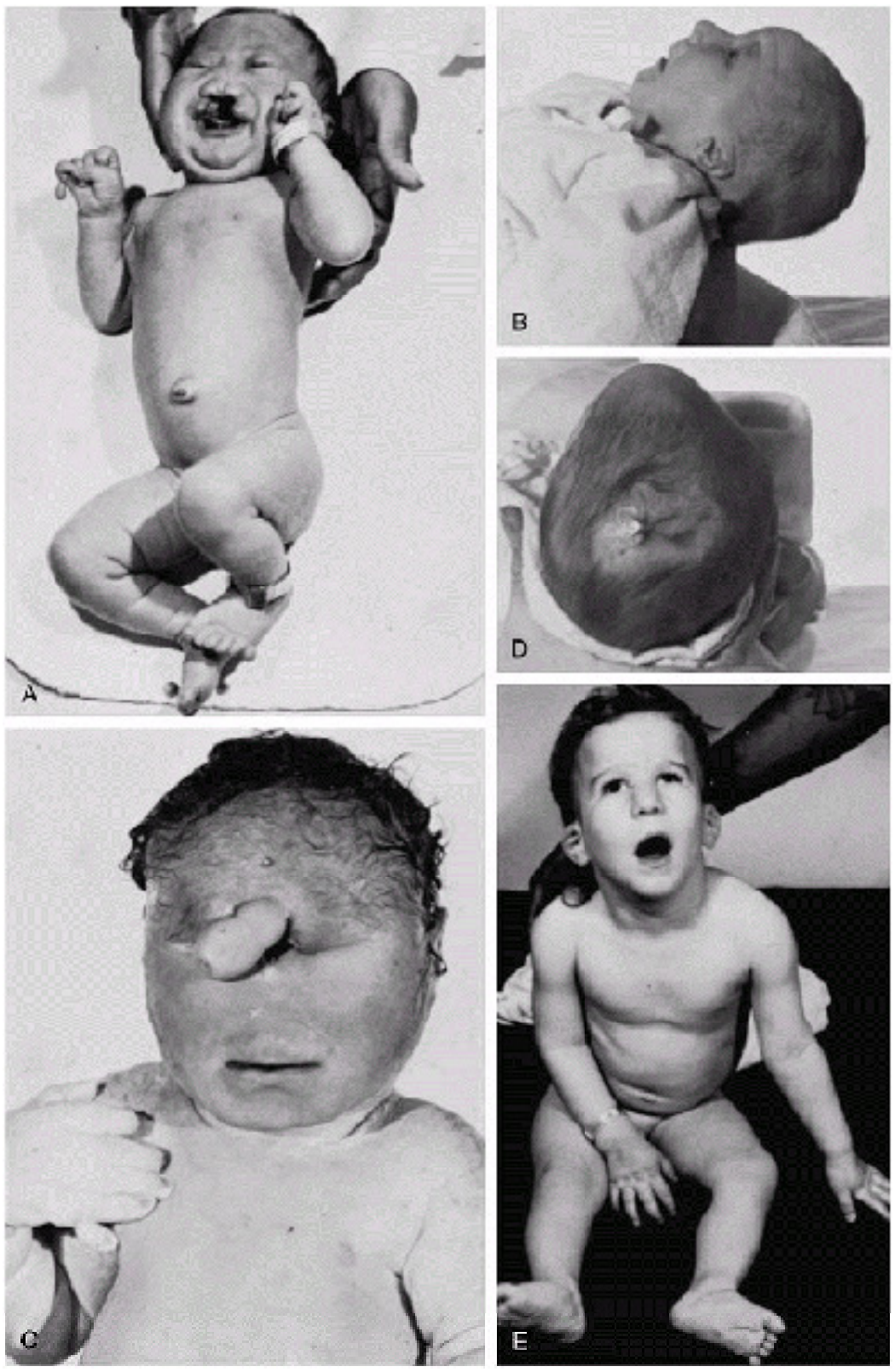


Figure 1.16 Trisomy 13. **A:** Newborn infant. Note the cleft lip and palate, sloping forehead, and supernumerary digits on all four extremities. **B:** Characteristic profile in an infant without clefts, showing bulbous nose, sloping forehead, anomalies of the external ear, and micrognathia. **C:** Cyclopia with an extra digit. **D:** Scalp defect. **E:** A 2.5-year-old severely retarded boy with mosaicism for trisomy 13. Characteristic face, with microphthalmia on the left; low-set, abnormal ears; and tapering fingers with hyperconvex fingernails.

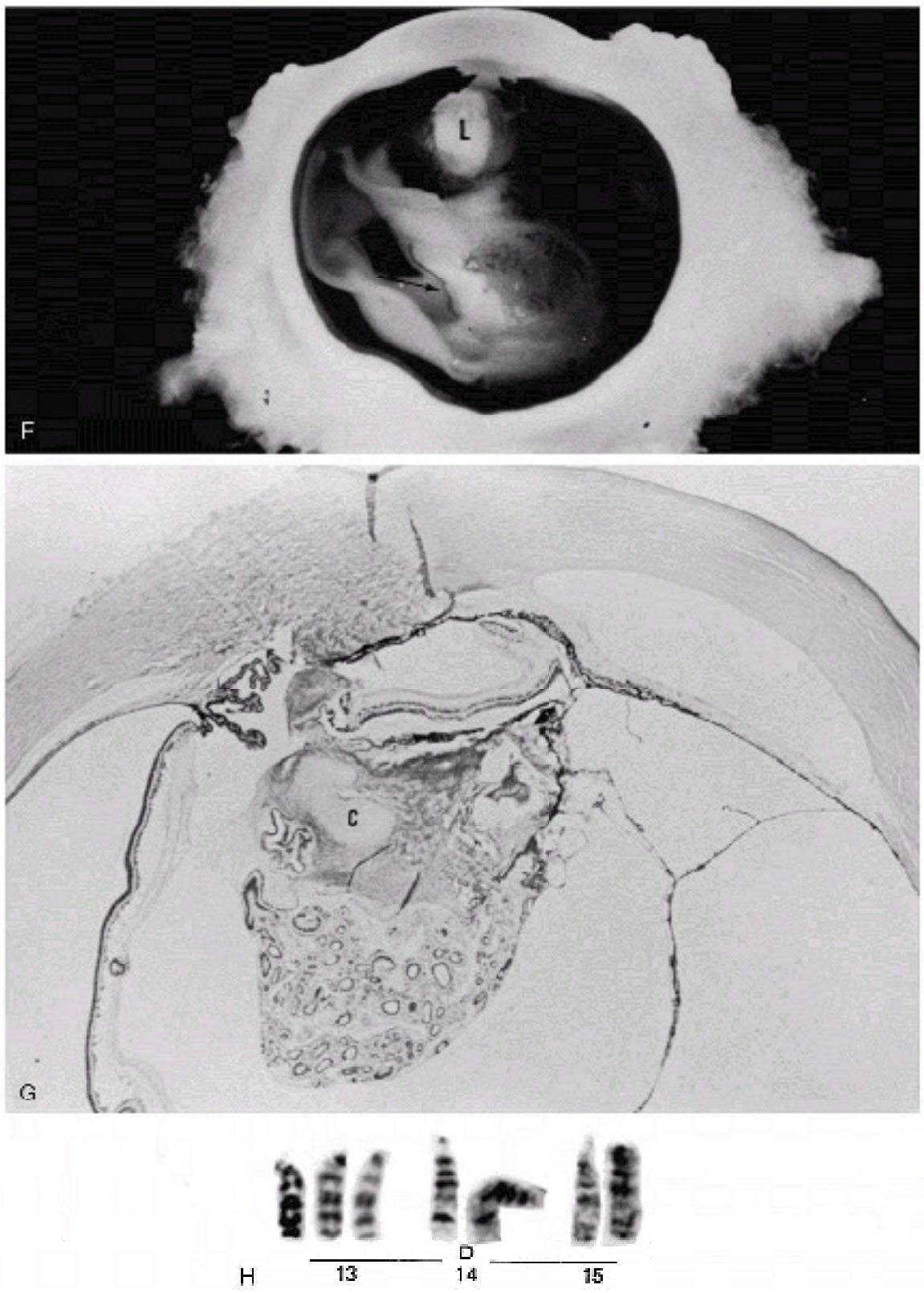


Figure 1.16 *Continued.* **F:** Microphthalmic left globe with microcornea. The cataractous lens (L) lies anterior to the detached retina. The persistent hyaloid artery (*arrow*) is surrounded by persistent hyperplastic primary vitreous. **G:** The island of intraocular hyaline cartilage (C) lies in the plane of a uveal coloboma and is surrounded by persistent hyperplastic primary vitreous. Centrally, the embryonal retina shows numerous dysplastic rosettes (H & E, original magnification ×4). (From Rodrigues MM, Valdes-Dapena M, Kistenmacher M. Ocular pathology in a case of 13 trisomy. *J Pediatr Ophthalmol* 1973;10:54, reproduced from the *Journal of Pediatric Ophthalmology* by permission of the publisher, Charles B. Slack, Inc.) **H:** The group D chromosomes, with trisomy 13.

Ocular abnormalities are a cardinal feature of trisomy 13 and include colobomatous microphthalmia, cataracts, corneal opacities, glaucoma, persistent hyperplastic primary vitreous, intraocular cartilage, and retinal dysplasia (Figs. 1.16F and 1.16G). Most children with trisomy 13 have 47 chromosomes, but a few have 46 chromosomes with a translocation of two of the D category chromosomes, which usually occurs *de novo* but rarely is inherited from a carrier parent. Males and females are equally affected.

Trisomy 18 (Edwards Syndrome)

The clinical findings of trisomy 18 are normally related to the presence of an extra chromosome 18 (363). Rarely, an unbalanced translocation involving chromosome 18 may cause the syndrome.

The features that help to differentiate trisomy 18 clinically are microcephaly, characteristic facies (Fig. 1.17), low birth weight for gestational age, hypertonicity with limbs in flexion, limited hip abduction, apneic spells, and marked failure to thrive. The facial characteristics include a prominent occiput, with narrow bifrontal diameter; receding chin, micrognathia, and high-arched palate; and low-set, large, malformed ears with poor helical development. The hand is usually flexed, with overlapping of the second and fifth fingers and failure of development of interphalangeal creases. Rocker-bottom feet, webbing of toes, and dorsiflexion of a short great toe are common. Arch dermatoglyphic patterns are seen on most fingertips. These babies have hypoplasia of adipose tissue and poor muscle development.

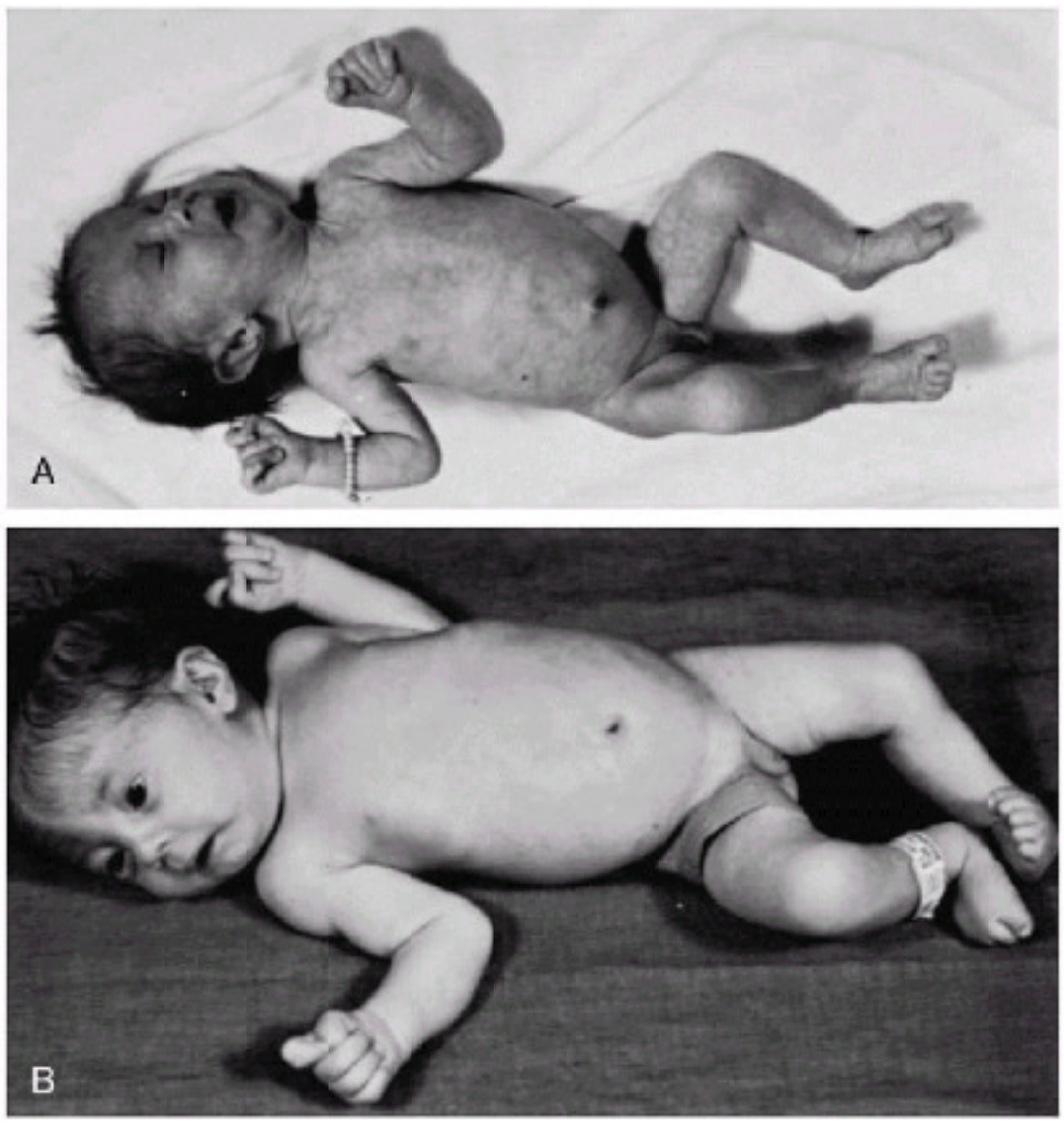


Figure 1.17 Trisomy 18. **A, B:** Two newborn female infants with the characteristic appearance of micrognathia, low-set ears, hypoplastic helix, and flexion deformity of the fingers. Note the slightly enlarged clitoris and club feet in **(B). C:** Dorsiflexion of the short great toe.

Renal anomalies and congenital heart disease occur in more than 65 % of cases. Pyloric stenosis, eventration of the diaphragm, and Meckel's diverticulum are found in 25% to 50% of cases. The majority (90%) die before 1 year of age.

The most common eye anomalies are orbital and palpebral, including hypertelorism and hypoplastic supraorbital ridges. The less common ocular features of this syndrome include colobomatous microphthalmia, corneal opacities, cataract, microcornea, retinal depigmentation, and congenital glaucoma.

Pathologic studies of the eye in trisomy 18 are limited. In the two cases reported by Ginsberg and coworkers (364), the most significant abnormalities affected the cornea, uveal tract, lens, and retina. Corneal opacities reflected retrograde changes (lamellar disorganization and fibrosis) of stroma. Anomalies of the ciliary process, breaks in the iris sphincter, posterior subcapsular cataract, and muscle abnormalities were described. Rodrigues and colleagues (365) observed abnormalities of the RPE in the patient with trisomy 18 and XY/XXY mosaicism (Figs. 1.17D and 1.17E). No abnormalities were seen in the eyes of one other patient (46,XX/47,XX, + 18) studied by Green (366).

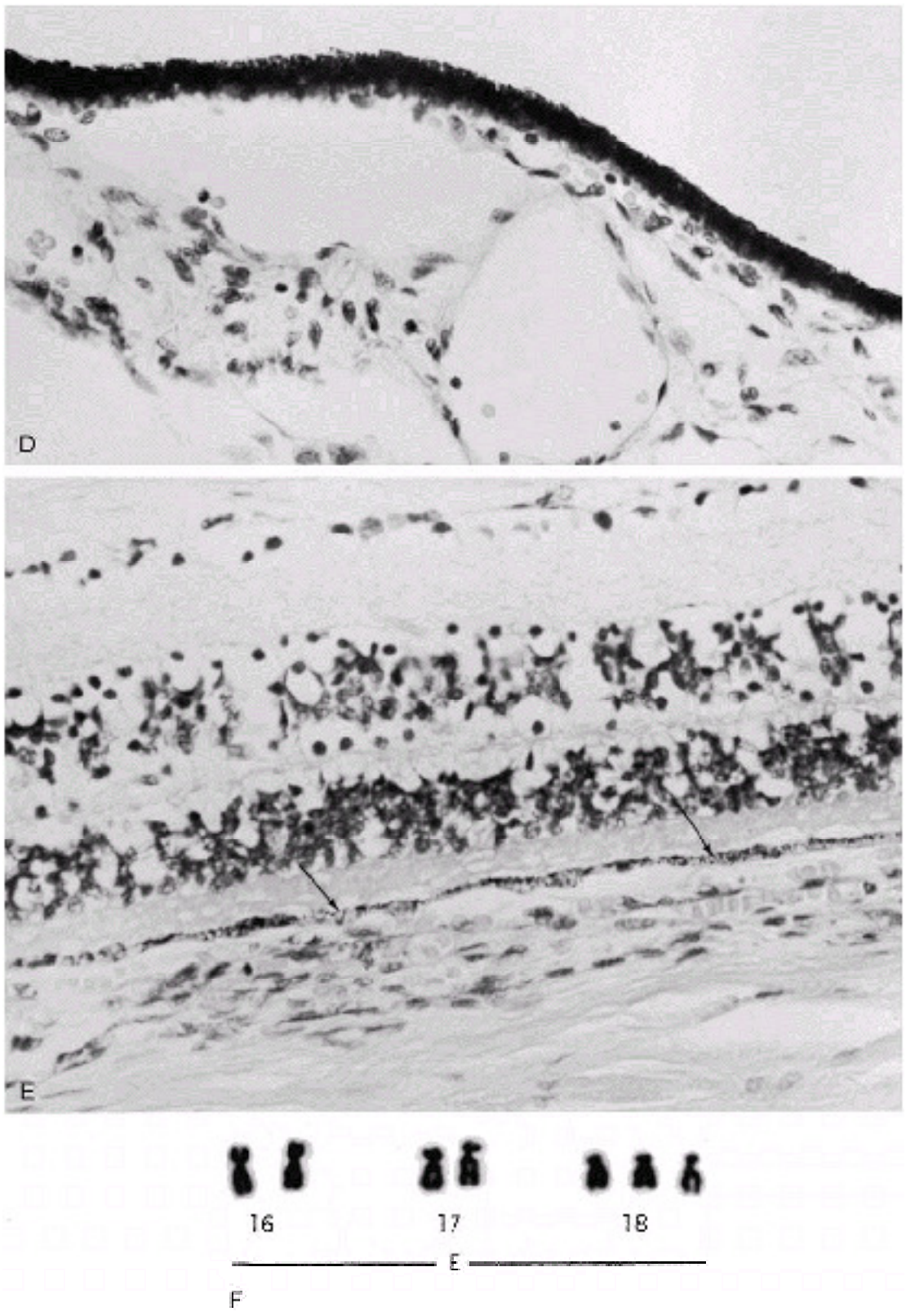


Figure 1.17 *Continued.* **D:** Retinal pigment epithelium displaying marked thickening and hyperpigmentation at the periphery (H & E, original magnification ×256). **E:** Hypopigmentation of the retinal pigmentation (arrows) at the posterior pole (H & E, original magnification ×256). **F:** E group chromosomes, with trisomy 18. (D and E reprinted from Rodrigues MM, Punnett HH, Valdes-Dapena M, et al. Retinal pigment epithelium in a case of trisomy 18. *Am J Ophthalmol* 1973;76:265-268, with permission from Ophthalmic Publishing Company.)

Trisomy 21 (Down Syndrome)

The most common autosomal abnormality in live births is Down syndrome (OMIM 190685), named for Langdon Down, who first described the condition in 1866 (367) (Fig. 1.18). Most children with Down syndrome have 47 chromosomes with an extra chromosome 21 (361); the parents usually have normal chromosomes. Approximately 6% of children with Down syndrome have 46 chromosomes, one of which represents the centric fusion of chromosome 21 and a D or G group chromosome. The translocation may have been inherited from a normal parent who has 45 chromosomes (the translocation replacing one 21 and either one D or one G) or may have developed *de novo*. There is no clinical difference between children with a trisomy and with translocation Down syndrome. The incidence of Down syndrome is one in 700 live births and is age dependent. The risk increases with maternal age to 1 in 40 for women over age 44. The risk of having a second child with Down syndrome for chromosomally normal parents is 1% to 2%. In the case of a parental translocation, the risk of Down syndrome offspring is 10% to 15% if the mother is the carrier, but only 1% to 2% if the carrier is the father. In the rare case of a 21;21 translocation in a parent, all offspring have Down syndrome (Fig. 1.19).

Mosaicism for trisomy 21 is not uncommon. The clinical manifestations may vary from a normal phenotype to that of typical Down syndrome. Physically normal persons with mosaicism are usually detected after the birth of a child with trisomy 21, when chromosomal investigation reveals an abnormal 47,+21 cell line in one parent. The risk of having other children with trisomy 21 may be as high as 50%, but it cannot be calculated with any precision since it depends on knowing the proportion of trisomic cells in the gonad.

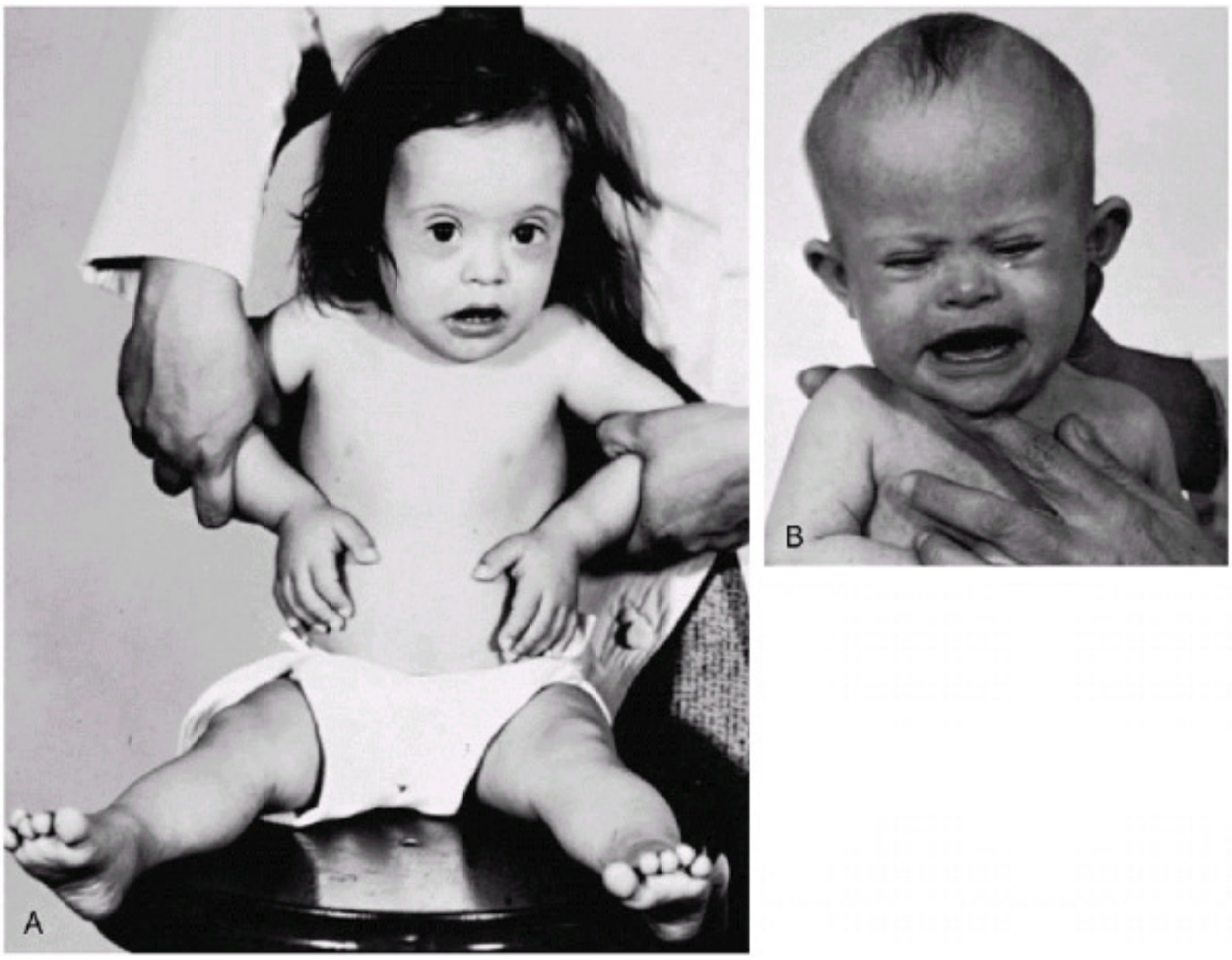


Figure 1.18 Down syndrome. A: An 11-month-old boy with typical facies, stubby hands, and prominent sandal gap of the feet. B: Ectropion of all four eyelids in an infant with Down syndrome.

Systemic findings of Down syndrome include hypotonia; mental retardation; brachycephaly; large, protruding tongue; small nose with a low, small bridge; small, often poorly defined, ears; short, thick neck; stubby hands with a single palmar crease; clinodactyly of the fifth digit with hypoplasia of the middigital phalanges; short, stubby feet with a wide gap between the first and second toes; and congenital heart disease. Males are usually sterile; females are fertile. Of 21 reported children born to women with Down syndrome, 13 were normal and 8 had trisomy 21 (368).

The characteristic ocular findings are epicanthal folds, mongoloid slant of the eye, hypoplasia of the iris, Brushfield spots, myopia, keratoconus, esotropia, cataracts, and blepharitis. Ectropion of all four eyelids may occur (Fig. 1.18B).

Cat Eye Syndrome

Cat eye syndrome (OMIM 115470), or Schmid-Fraccaro syndrome, is characterized clinically by the combination

of coloboma of the iris and/or choroid, anal atresia with fistula, downslanting palpebral fissures, preauricular tags and/or pits, frequent occurrence of heart and renal malformations, and normal or near-normal mental development. A small supernumerary chromosome (smaller than chromosome 21) is present, frequently has two centromeres, is bisatellited, and represents an inv dup(22)(q11) (369). The origin of the extra chromosome was identified by DNA probes and is from within the long arm of chromosome 22 (q11 band); there are three or four copies of this region in affected persons (370).

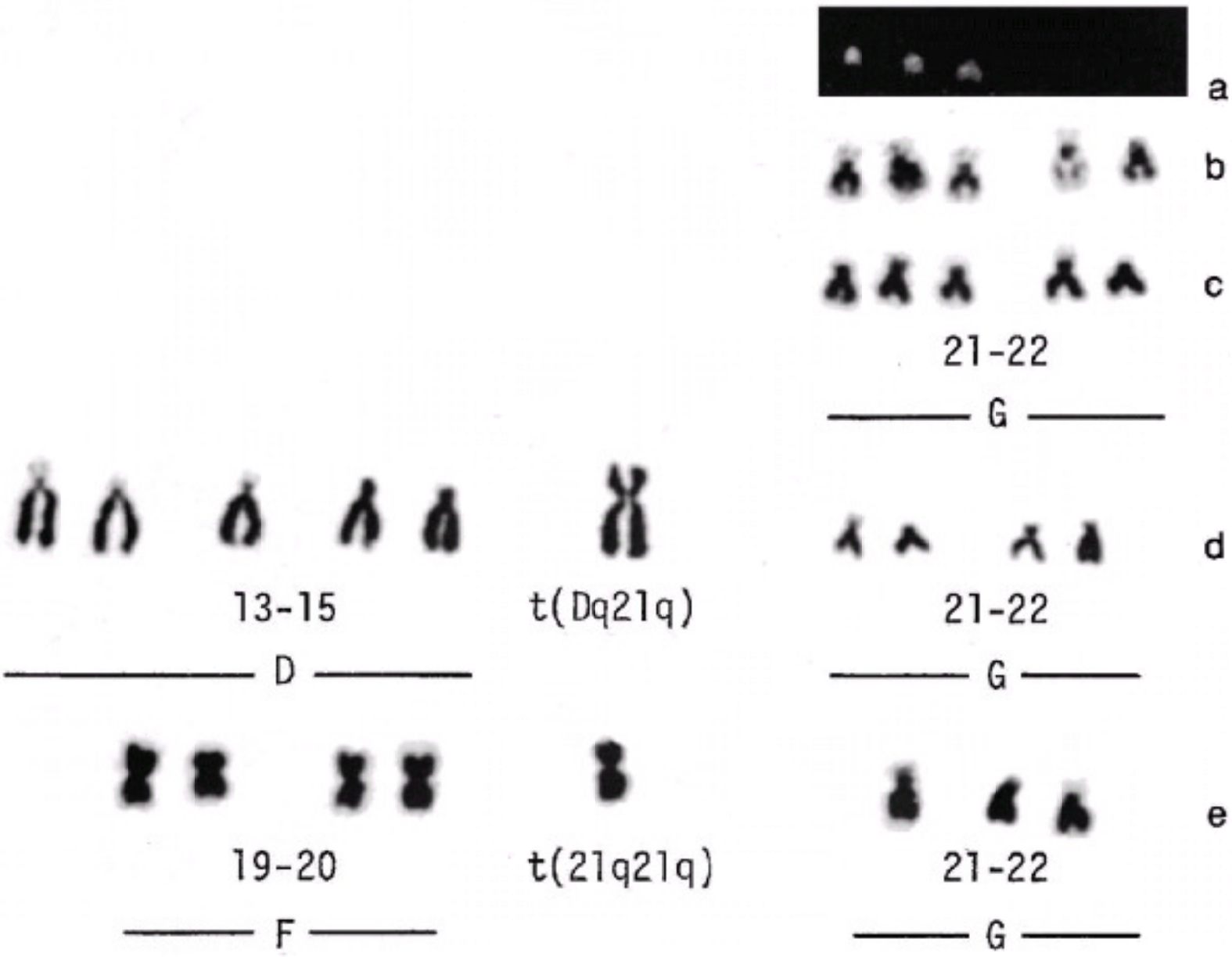


Figure 1.19 Chromosomal variations in Down syndrome. Trisomy 21 proved with fluorescent banding (*a*) and trypsin banding (*b*). Centric fusion translocations involving the D and 21 (*d*) and two chromosomes 21 (*e*). In each case the genetic information of chromosome 21 is present in triplicate.

The additional chromosome 22 generally arises *de novo* from one of the parents. Since cat eye syndrome is a rare chromosome disorder in which transmission is possible through both sexes, chromosome examination should be performed if one of the parents displays characteristic features such as a preauricular pit or downslanting palpebral fissures. Even in nonsymptomatic parents, mosaicism for an extra chromosome is possible.

Cytogenetic Structural Abnormalities

The second group of clinically recognizable chromosomal syndromes have deletions resulting from breaks in a chromosome, usually with loss of a terminal portion. If the deletion occurred *de novc* in an egg or sperm, only a single child in a family will be affected. Deletions can also be inherited as the unbalanced form of a translocation for which a normal parent has an abnormal but balanced chromosome constitution. Ring chromosomes are formed when the ends of chromosomes break and fuse to each other, forming a ring. There is a loss of chromatin (DNA) from both ends, and such children may resemble those with simple deletions of the same chromosome. Many partial deletions occur frequently enough to be considered a syndrome.

Deletion 4p- (Wolf-Hirschhorn Syndrome)

The physical findings in partial deletion of the short arm of chromosome 4 (Wolf-Hirschhorn syndrome; OMIM 194190) include severe mental retardation, seizures, prominent glabella, midline scalp defect, preauricular dimple, cleft lip and palate or high-arched palate, deformed nose, hemangiomas of the forehead, internal hydrocephalus, and undescended testes and hypospadias in males (371). Colobomatous microphthalmia is very common, as are ocular hypertelorism, exophthalmos, and strabismus (174). The chromosomal anomaly may be a *de novo* deletion or may result from an unbalanced segregation in the gamete of a carrier parent (Fig. 1.20).

Deletion 5p- (Cri-du-Chat Syndrome)

Partial deletion of the short arm of chromosome 5 (Cri-du-Chat syndrome; OMIM 123450) was originally described by Lejeune and colleagues (372). Children with this syndrome usually have low birth weight and a slow growth rate neonatally. They are hypotonic. The infant's cat-like cry that gives the syndrome its name is attributed to an abnormality in laryngeal structure, which is striking in infancy but usually disappears with age. There is severe mental deficiency. Physical findings include microcephaly with a very round face in infancy, micrognathia, low-set ears, and congenital heart disease (Fig. 1.21). Ocular findings are antimongoloid slant, hypertelorism, epicanthal folds, exotropia, myopia, and optic atrophy. Like the syndrome of 4p-, 5p- may represent a new event or be inherited from a carrier parent.

Deletion 11p- (WAGR Syndrome)

WAGR syndrome (OMIM 194072) involves aniridia, mental retardation, and genitourinary anomalies and has been

associated with a predisposition to Wilms' tumor. Deletion of the short arm of chromosome 11 involving the llp13 band accounts for this syndrome (151,152,153,154) (Fig. 1.22); one patient had aniridia and Wilms' tumor without a microscopically detectable deletion (155). The deletion may occur *de novo* or as a consequence of meiotic events in a normal carrier parent. Although Wilms' tumor has been the embryonal tumor associated with this triad, benign gonadoblastoma was found in a child with deletion 11p13, aniridia, and mental retardation but who had no evidence of Wilms'tumor on postmortem examination at

age 21 months (154). The gene for catalase is near the aniridia locus in band p13 on the short arm of chromosome 11 (373), and production of this enzyme may be reduced in the presence of some deletions (151). All children with aniridia and this deletion should be followed carefully by abdominal ultrasonography for the first 4 to 5 years of life to facilitate early detection of Wilms'tumor.

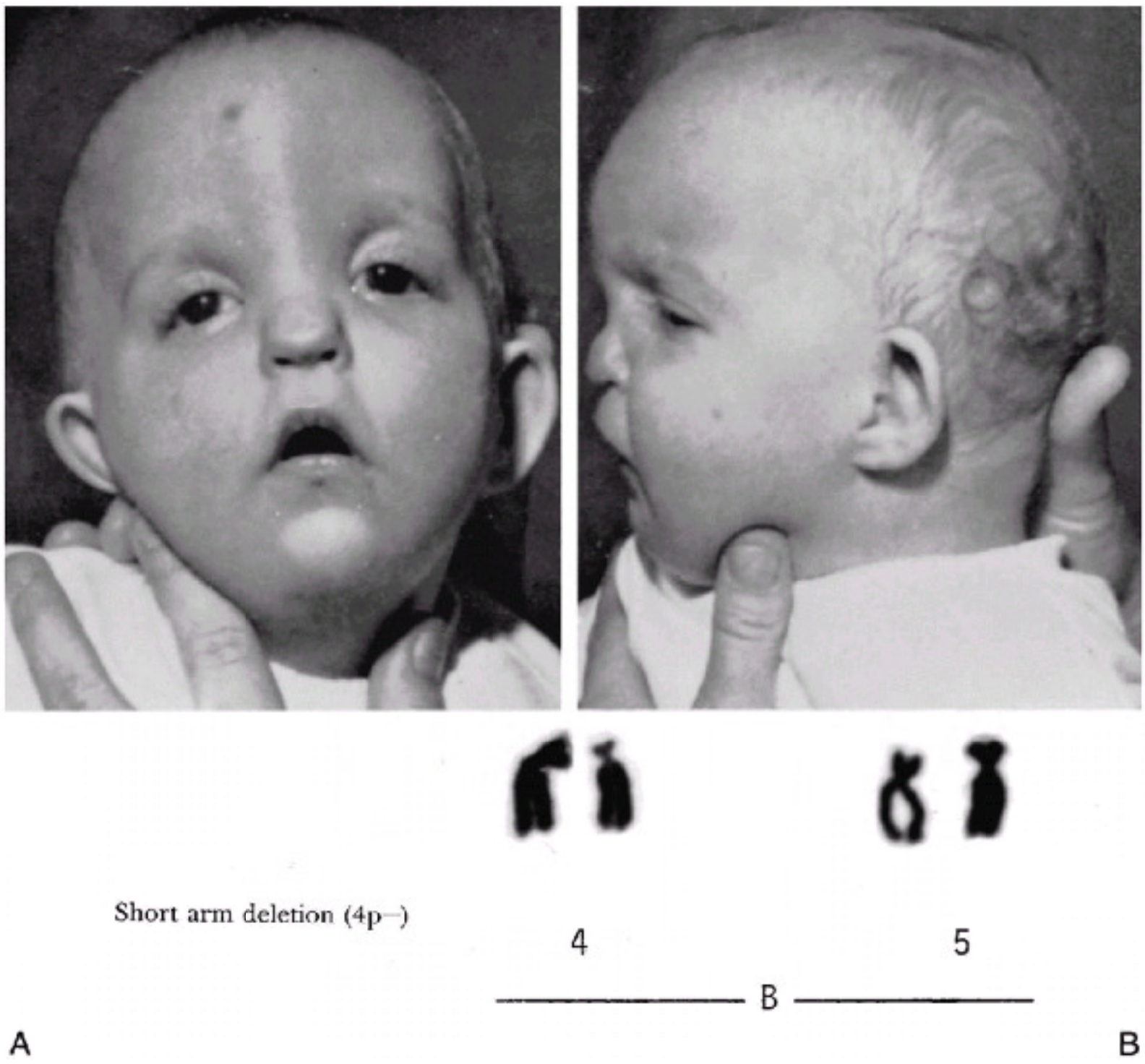


Figure 1.20 A: A 1-year-old boy with deletion of the short arm of chromosome 4 (4p-). (From Nelson WE, Vaughn VC, McKay RJ, eds. *Textbook of pediatrics*, 9th ed. Philadelphia: WB Saunders, 1969, with permission.) **B:** Chromosomes of B group with deletion of part of the short arm of 4.

Deletion 13q-

Partial monosomy for chromosome 13 may be due either to deletion of part of the long arm or to a ring 13. The phenotypes are similar and include microcephaly with trigonocephaly; prominent bridge of the nose; small chin; large, low-set, malformed ears; and facial asymmetry (Fig. 1.23). These children are profoundly retarded. Males have hypospadias and undescended testes. Absent or hypoplastic thumbs are frequent. Ocular findings include hypertelorism, narrow palpebral fissures, epicanthal folds, ptosis, colobomatous microphthalmos, cataract, and retinoblastoma.

In some cases of sporadic retinoblastoma, a deletion of band 13q14 of the long arm of chromosome 13 has been demonstrated; many children with this deletion have dysplastic features and developmental delay. In a few patients, the chromosome deletion was inherited as a consequence of a rearrangement involving chromosome 13 in a parent (374). Most cases arose *de novo*.

Sporadic retinoblastoma due to deletion of band 13q14 is estimated to account for approximately 2% of all retinoblastomas. The gene for the expression of human esterase D (a ubiquitous enzyme whose biologic function is unknown) is also located at band 13ql4. Measurement of esterase D levels is potentially useful for identifying patients with retinoblastoma who have deletions too small to detect cytogenetically.

Deletion 18

Deletions of chromosome 18 may occur in either the short (18p-) or long (18q-) arm, or in both, through ring formation (r18) following fusion of broken chromosome ends with the loss of terminal portions of both arms. Therefore, physical findings of r18 may overlap both the short and

long arm deletion syndromes and are not described separately here (Fig. 1.24) (375).

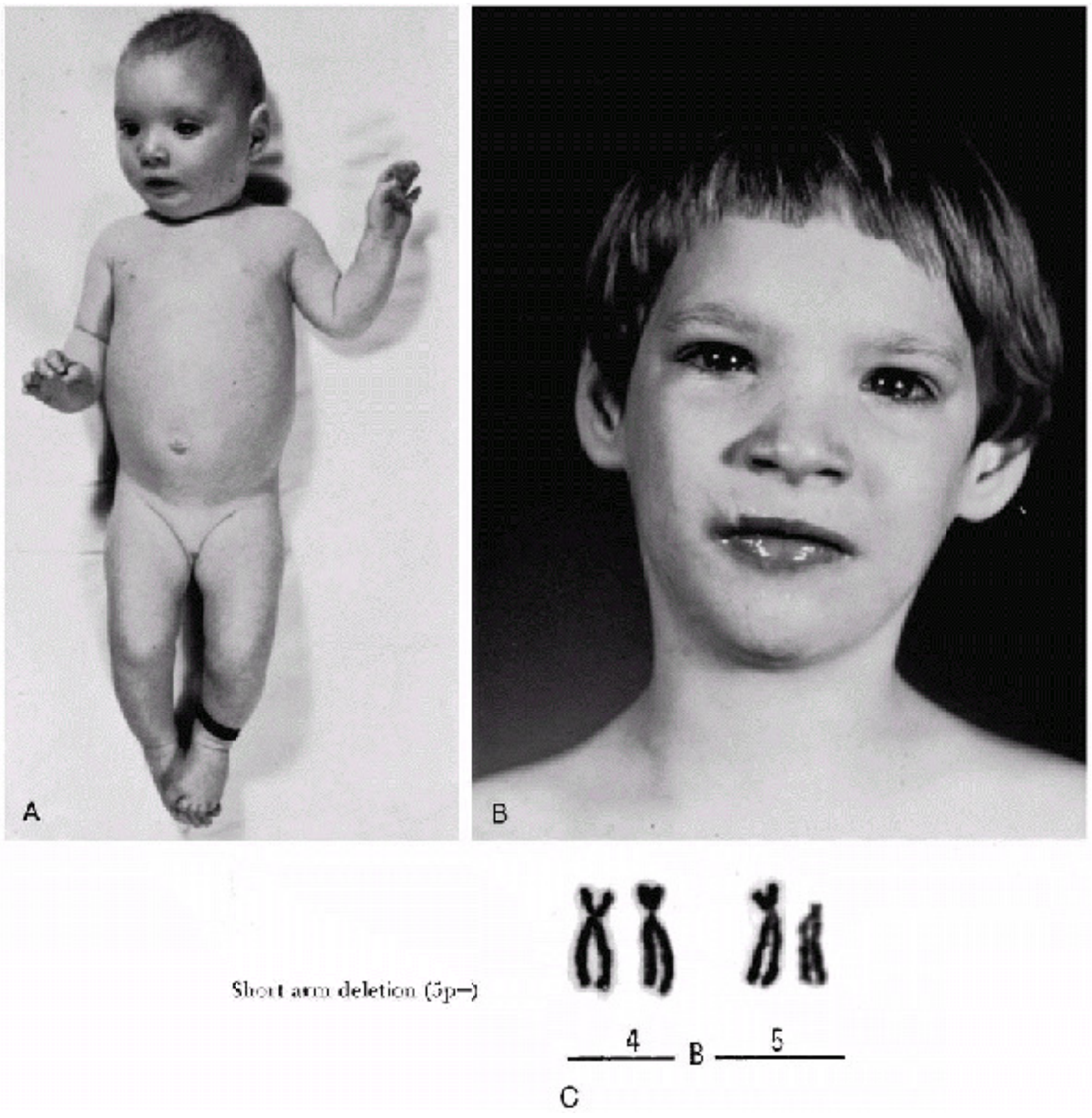


Figure 1.21 Child with deletion of the short arm of chromosome 5 (5p-). **A:** At age 3 months. **B:** At 4 years. She has microcephaly, hypertelorism, epicanthal folds, and severe mental retardation. C: Chromosomes of B group with deletion of most of the short arm of 5.

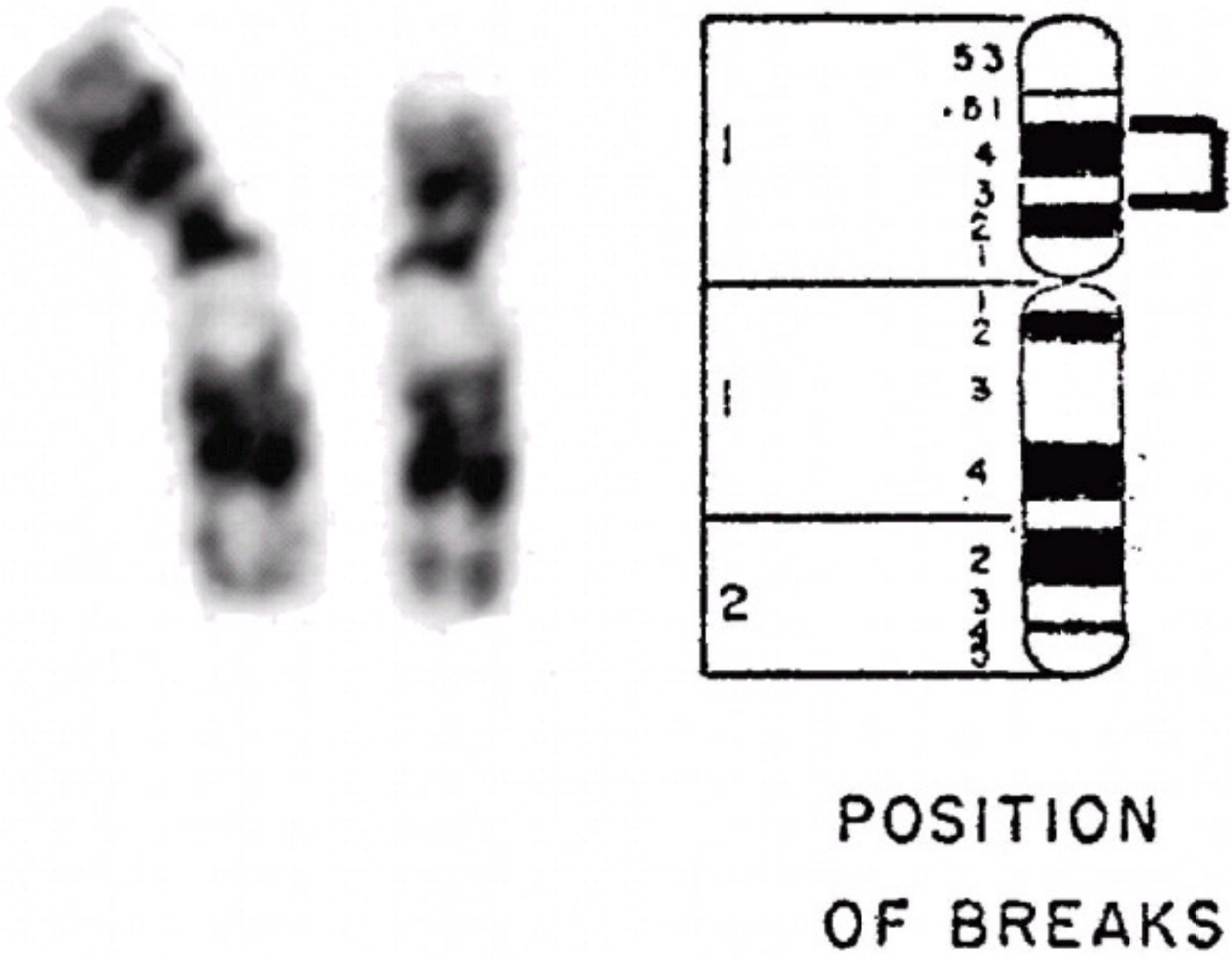


Figure 1.22 Chromosomes 11 in a child with aniridia, hypogonadism, and Wilms' tumor. An interstitial short arm deletion including bands p13-p14 is apparent in the chromosome on the right. The position of breaks giving rise to the deletion is shown schematically. (Courtesy of Laurel Marshall.)

Deletion 18p-

The physical findings associated with the deletion (total or partial) of the short arm of chromosome 18 show a wide range. The mildest expression encompasses microcephaly, mental retardation, short stature, webbed neck, and immunoglobulin abnormalities (Fig. 1.25) (376).

In its most severe form, the syndrome mimics trisomy 13, with the median facial dysplasia of cebocephaly or cyclopia and incomplete morphogenesis of the brain. Cardiac, renal, and gastrointestinal abnormalities are rarely seen in 18p- syndrome. The eye anomalies of mildly affected children consist of hypertelorism, epicanthal folds, ptosis, and strabismus. Microphthalmia and cyclopia have been reported in the cebocephalic patients.

The only histopathologic study of the eye in an 18p deletion was reported by Yanoff and colleagues (375) in a

case of cebocephaly with a ring 18. Bilateral microphthalmia with cyst, intrascleral cartilage, intrachoroidal smooth muscle, and other anomalies were seen. No recognizable components of the optic system could be identified.

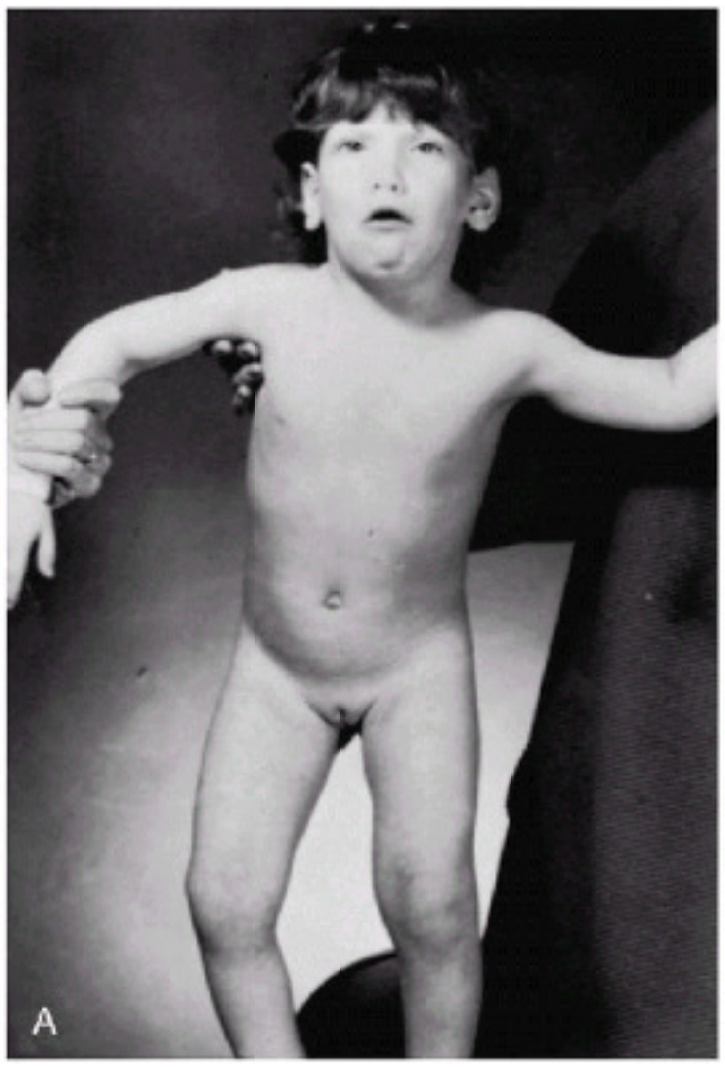


Figure 1.23 A: A 3-year-old girl with ring chromosome 13, micrognathia, hypertelorism, esotropia, bilateral colobomata of the irides, epicanthal folds, and mongoloid slant of the eyes. (From Kistenmacher ML, Punnett HH. Comparative behavior of ring chromosomes. *Am J Hum Genet* 1970;22: 304-318, with permission.) **B:** Chromosomes of the D group, showing long arm deletion (13q-) (*above*) and ring (13r) (*below*).

Deletion 18q-

Partial deletion of the long arm of chromosome 18 (377) produces a syndrome marked by failure of growth and development.

The facies is striking: microcephaly, midface hypoplasia, and a carp-like mouth. The ears have a prominent anthelix and/or antitragus. There is a narrow or atretic ear canal and hearing loss.

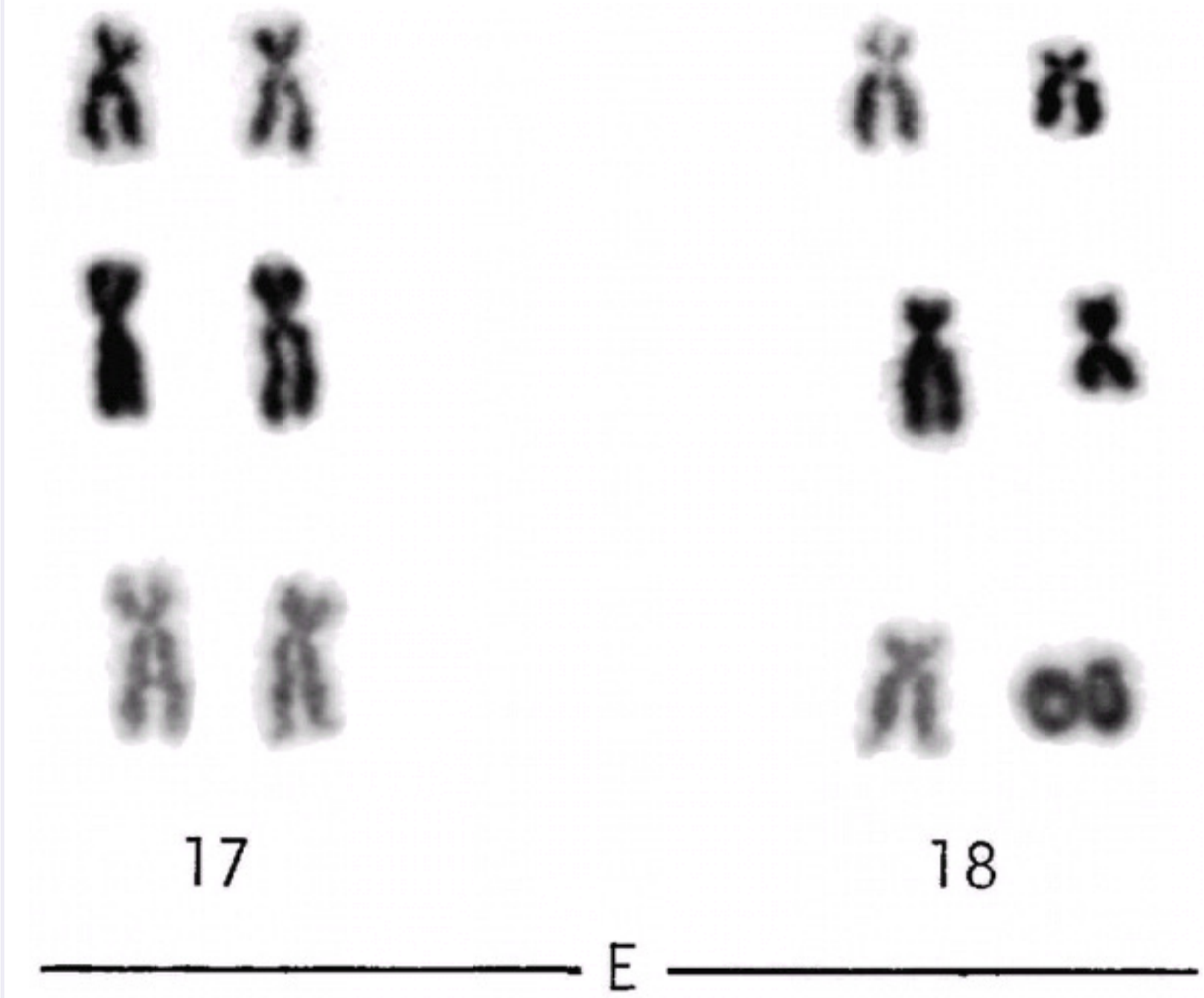


Figure 1.24 E group chromosomes, showing chromosome 18 with short arm deletion (18p-), long arm deletion (18q-), and ring (18r).

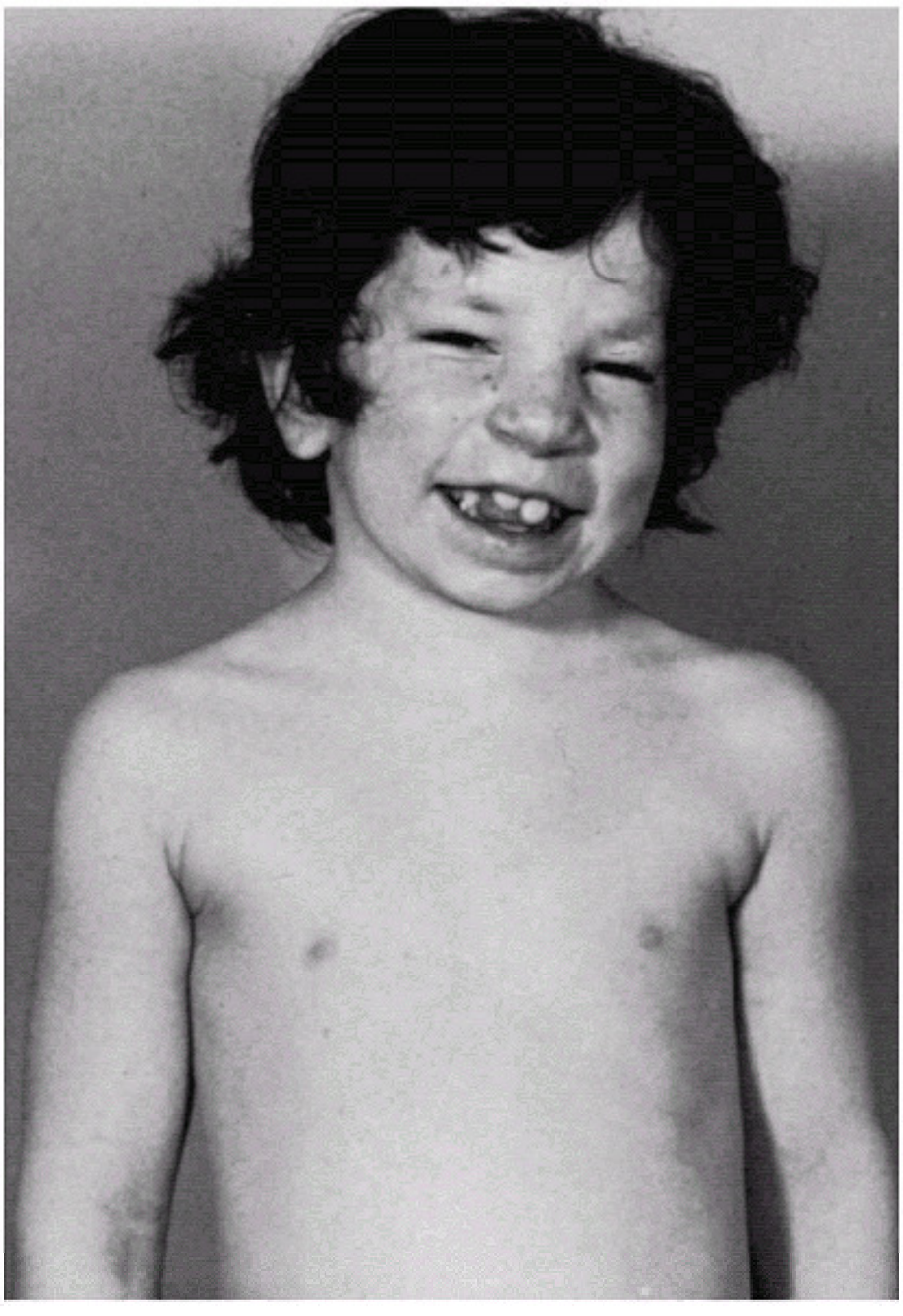


Figure 1.25 An 8-year-old girl with deletion of the short arm of chromosome 18, bilateral congenital ptosis, diabetes, and thyroiditis.

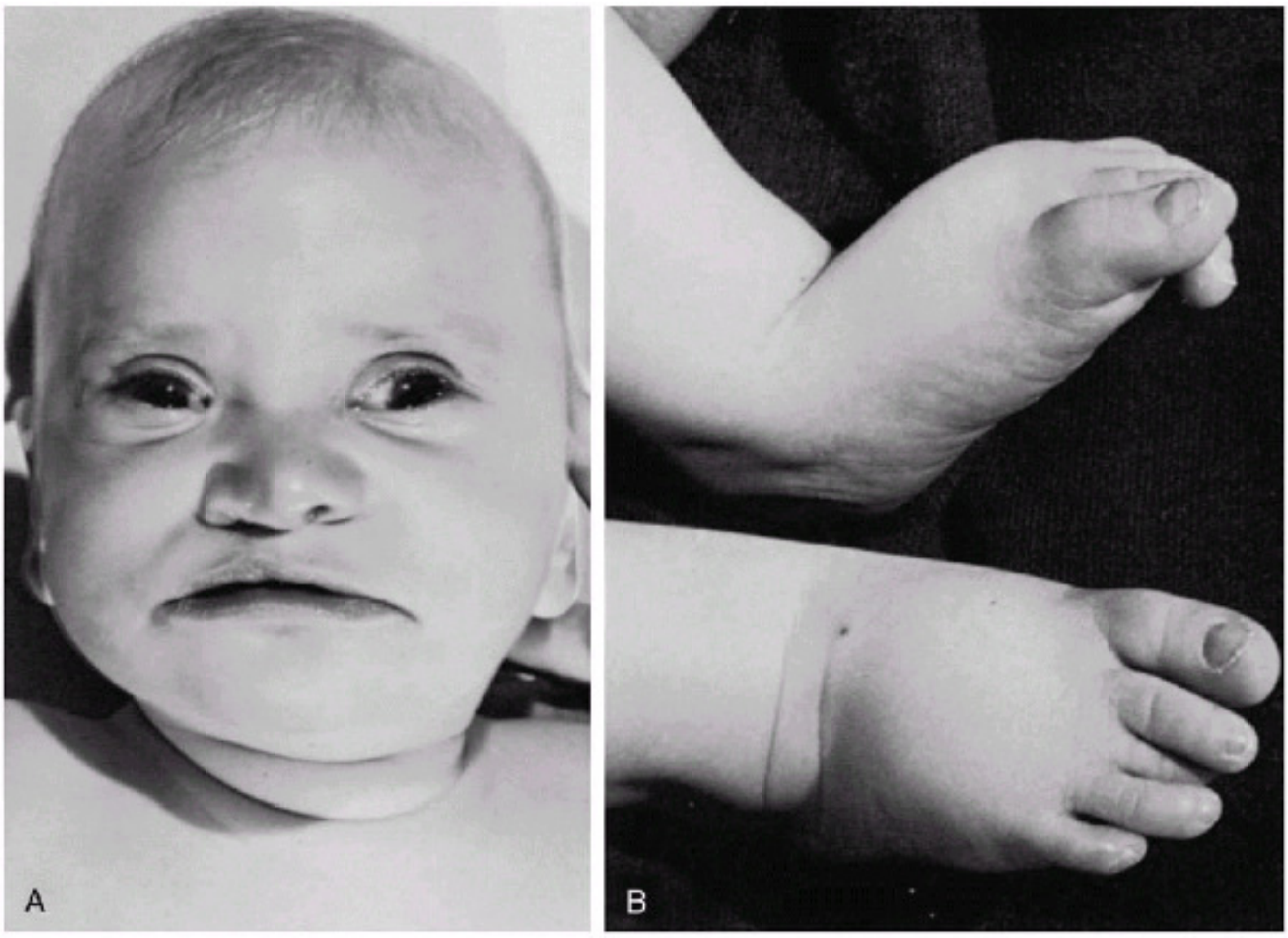


Figure 1.26 A: A 10-month-old infant with deletion of the long arm of chromosome 18, cleft lip (repaired) and palate, nystagmus, exotropia, bilateral optic atrophy, and macular anomalies. **B:** Abnormal insertion of the third toe and fat pads on the dorsal aspect of the feet.

The fingers taper markedly and have many whorl patterns. Single palmar creases are seen. Toes have abnormal placement, with the third toe placed above the second and fourth. Unusual fat pads occur on the dorsa of the feet. Dimples are prominent on knuckles, knees, elbows, and shoulders (Fig. 1.26). Eye abnormalities include epicanthal folds, slanted palpebral fissures, nystagmus, hypertelorism, microphthalmia, corneal abnormalities, cataracts, and abnormal optic discs. Most cases are sporadic partial deletions of the long arm of chromosome 18, but occasionally a parent carries a balanced translocation.

The ocular features of the trisomy and deletion/duplication syndromes are summarized in Tables 1.3, 1.4, and 1.5.

Sex Chromosomes

The syndromes due to aneuploidy of the sex chromosomes were described before the development of modern cytogenetic techniques.

Turner Syndrome

Turner (378) described several patients with infantilism, webbed neck, and cubitus valgus, establishing as a clinical syndrome a previously described endocrine disorder. The absence of sex chromatin (Barr bodies) in most Turner syndrome (OMIM 163950) patients was reported independently by three groups in 1954 (379,380,381). The first published 45,X karyotype (359) was confirmed by many laboratories in the same year. Approximately 80% of girls with Turner syndrome have 44 autosomal chromosomes, a single X, and no sex chromatin. The remaining 20% have other chromosomal variants. The unifying cytogenetic characteristic is the presence of a cell line that does not have two normal X chromosomes. It may lack the second X completely or have an abnormal second X (ring, fragment, deletion). The few patients who have Barr bodies are mosaics (45,X/46,XX) or have a long arm isochromosome—46,X,-i(Xq)—an abnormal chromosome with duplication of one arm forming two arms of equal length.

The typical findings in Turner syndrome, which is now called Noonan syndrome, are sexual infantilism, short stature, webbed neck, broad shield chest with widely spaced nipples, increased carrying angle, small uterus, and multiple pigmented nevi (Fig. 1.27). Recurrent ear infections are common. The ovaries consist of fibrous streaks with few or no follicles, and failure to feminize may be the presenting problem in older girls who have few of the physical stigmata. Coarctation of the aorta is common and may account for some of the early childhood deaths. Autoimmune diseases, particularly Hashimoto thyroiditis and diabetes, have been associated with the syndrome. Turner syndrome in some newborn infants is characterized by lymphedema of the hands and feet, which may persist into adulthood.

Ptosis and strabismus are the most common ocular lesions

encountered. Congenital cataracts may occur, as well as those of later onset, particularly in association with diabetes. Refractive errors, corneal scars, blue sclera, and a variety of other anomalies have been reported (382).

TABLE 1.3 OCULAR MANIFESTATIONS IN TRISOMY SYNDROMES

	Trisomy 13[a]	Trisomy 18[b]	Trisomy 21[c]
Epicanthus	+	+	+
Hypertelorism	+	+	
Hypotelorism			+
Mongoloid lid slant			+
Strabismus	+	+	+
Ptosis		+	
Microphthalmia/anophthalmia	+	+	
Coloboma	+		
Cataracts			
Juvenile			+
Congenital	+	+	
Corneal opacity	+	+	
Congenital glaucoma	+	+	+
Other			
Brushfield spots			+
Cyclopia	+		
Intraocular cartilage	+		
Absent eyebrows	+		
Congenital retinal detachment	+		

[a] Hoepner et al 1972 (479); Keith 1966 (480)

[b] Huggert 1966 (481); Rodrigues et al 1973 (482); Ginsberg et al 1968 (364)

[c] Ginsberg et al 1980 (483); Shapiro et al 1985 (484); Caputo et al 1989 (485)

TABLE 1.4 CHROMOSOMAL DUPLICATION SYNDROMES

	4q +	5p +[c]	9p +[d]	10p +[e]	12p +[f]	10q +[g]	11p +[h]	13q +[i]	14q +[j]	18pi[k]	22q +[m]	4[b]p +[a]
Epicanthus			+		+							
Blepharophimosis	+		+	+								
Ptosis				+							+	
Hypertelorism	+	+		+		+	+				+	
Hypotelorism												
Mongoloid lid slant												
Antimongoloid lid slant							+			+		
Strabismus	+	+		+		+	+			+		
Microphthalmia	+		+	+		+		+	+		+	
Coloboma	+	+		+	+		+	+		+	+	
Cataracts												
juvenile												
Congenital				+							+	
Corneal opacity								+				
Congenital glaucoma									+			
Brushfield spots												+

[a] Gustavson et al 1964 (486);

[b] 4q+: Wilson et al 1970 (457);

[c] Monteleone et al 1976 (487);

[d] Rethore et al 1970 (488);

[e] Yunis et al 1976 (472);

[f] Rethore et al 1975 (489);

[g] Orye et al 1975 (490), Yunis et al 1974 (491);

[h] Falk et al 1973 (492);

[i] Hsu et al 1973 (461);

[h] Falk et al 1973 (492);

[i] Hsu et al 1973 (461);

[j] Raoul et al 1975 (493);

[k] supernumery isochromosome 18, Condron et al 1974 (494);

[m] cat eye syndrome, Zellweger et al 1976 (495)

TABLE 1.5 CHROMOSOMAL DELETION SYNDROMES

	4r[b]	5p -[c]	10p-[d]	11p-[e]	11q-[f]	13q-[g]	15q-[h]	18p-[i]	18q-[j]	4p-[a]
Epicanthus	+	+		+	+	+		+	+	
Blepharophimosis										
Ptosis	+				+	+		+		
Hypertelorism	+	+				+		+	+	
Hypotelorism					+					
Mongoloid lid slant					+					
Antimongoloid lid slant									+	
Strabismus	+			+	+				+	
Microphthalmia	+	+				+			+	
Coloboma	+	+	+		+				+	
Cataracts										
Juvenile	+									
Congenital		+		+						
Corneal opacity					+					
Congenital glaucoma		+	+	+						
Aniridia				+						
Retinoblastoma						+				
Ocular albinism									+	

[a] Wolf-Hirschhorn syndrome, Wilcox et al 1978 (174);

[b] Carter et al 1969 (464);

[a] Wolf-Hirschhorn syndrome, Wilcox et al 1978 (174);

[b] Carter et al 1969 (464);

[c] Cri-du-Chat syndrome, Breg et al 1970 (496), Farrell et al 1988 (497);

[d] Broughton et al 1981 (498);

[e] Riccardi et al 1978 (153);

[f] Bateman et al 1984 (183), Lee et al 1981 (499);

[g] Allderdice et al 1969 (500);

[h] Prader-Willi syndrome, Ledbetter 1981 (501), Hittner et al 1982 (29), Ledbetter et al 1982 (502), Mattei et al 1983 (503);

[i] Schinzel et al 1974 (504);

[j] Schinzel et al 1975 (470)

The incidence of color blindness in females with 45,X Turner syndrome equals that seen in normal males, since only one X chromosome is present. In informative families, this easily recognized defect may identify the origin of the single X. If the girl with Turner syndrome and her father are discordant (if the child is color blind and the father is normal, or vice versa), the single X must have come from the mother, assuming correct paternity. If both child and father are color blind and the mother is normal, the X may be assumed to be from the father.

Ambiguity of the external genitalia is not a feature of Turner syndrome, but it is seen in children with 45,X/46,XY mosaicism in whom the physical findings of Turner syndrome may be combined with varying degrees of masculinization of the genitalia. Some may resemble typical Turner syndrome; others are phenotypic males. Frequently a unilateral streak gonad is found with a contralateral abdominal testis.

Klinefelter Syndrome

Klinefelter and coworkers (383) described a syndrome of gynecomastia, small testes with hyalinization of seminiferous tubules, absent spermatogenesis but normal Leydig cell complement, and elevated urinary gonadotropins. Patients with this clinical syndrome were shown by Plunkett and Barr (384) to be chromatin positive and by Jacobs and Strong (360) to have 47,XXY chromosome complement. Boys with more severe forms of Klinefelter syndrome (OMIM 278850) may have XXXY sex chromosomes and two Barr bodies, or XXXXY and three Barr bodies. Increasing numbers of X chromosomes cause greater physical and mental impairment. Males with XXXY are mentally retarded and may have radioulnar synostosis, scoliosis, microcephaly, congenital heart disease, and prognathism (Fig. 1.28). The ocular findings include epicanthal folds, hypertelorism, upward slant of the palpebral fissures, strabismus, Brushfield spots, and myopia.

The extra X chromosome may be either maternal or paternal in origin. Mosaicism (46,XY/47,XXY/48,XXXY or 48,XXXY/49,XXXXY) is common and may be explained by two successive nondisjunctions, the initial one in parental gametogenesis and the second in the zygote.

Considerable overlap with Klinefelter syndrome has been seen in boys with 48,XXYY karyotypes. They are unusually tall with eunuchoid proportions and exhibit some degree of mental retardation. Some males have also exhibited the aggressive or bizarre behavior attributed to men with 47,XYY karyotypes. No phenotypic characteristics other than tall stature have been reported with the latter.

The physical or behavioral characteristics attributed to XYY males are variable. The first XYY males reported were identified during surveys of persons in British maximum-security hospitals, and their aggressive personalities received considerable publicity. Other XYY males have been identified on the basis of hypogonadism or infertility and are otherwise normal. Structural eye anomalies are not usually seen in the XYY syndrome, although myopia, dislocation of the lens, and bilateral retinal detachments have been reported.

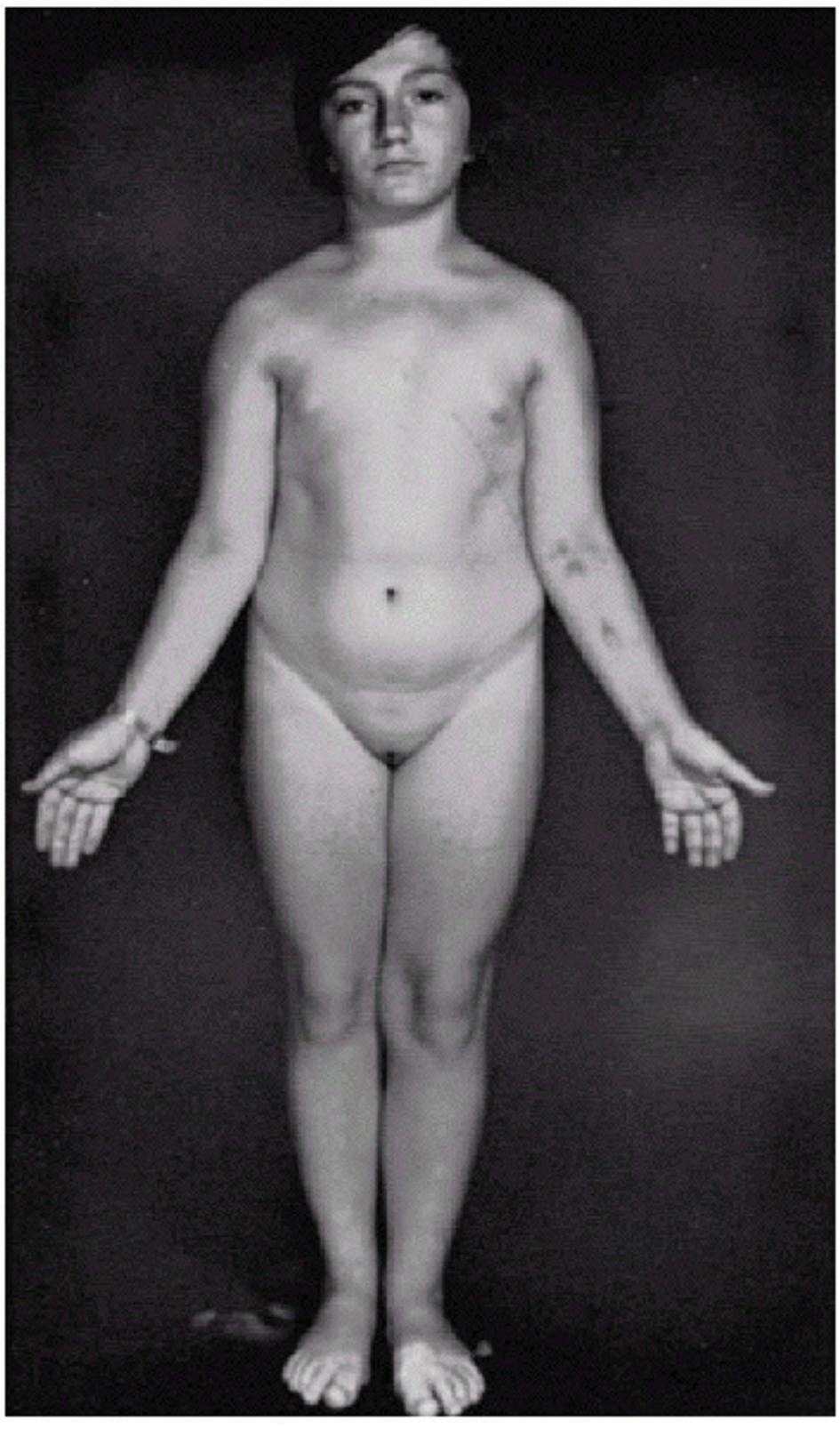


Figure 1.27 Turner syndrome in a 15-year-old girl with short stature, cubitus valgus, and a goiter. Her karyotype is 45,X/46,XX. (From Behrman RE, Vaughan VC III, Nelson WE, eds. *Nelson textbook of pediatrics*, 13th ed. Philadelphia: WB Saunders, 1987, with permission.)

POLYGENIC AND MULTIFACTORIAL INHERITANCE

The concepts of polygenic and multifactorial inheritance provide an explanation for disorders that tend to cluster in families but do not conform to single-gene Mendelian inheritance. The expression of a disease may depend on the presence of a critical number of genes that are inherited independently. Such a disorder would be *polygenic*, and the genetic risk factors would be additive. If environmental factors affect the outcome, the term *multifactorial* is used. The genetic threshold value may differ for the two genders for polygenic and multifactorial disorders. For example, pyloric stenosis occurs more frequently in males than in females, and the risk factors must be greater if a female is to express the anomaly. Therefore, the likelihood of an affected female having affected children is higher than that for an affected male. The gender relationship is reversed for congenitally dislocated hip, which is more common in females. Examples of diseases that cluster in families but are not proven to be single-gene defects and are not purely environmental include refractive error, strabismus, diabetes, cleft lip, and spina bifida as examples. We will briefly discuss the genetics of myopic refractive error and strabismus below.

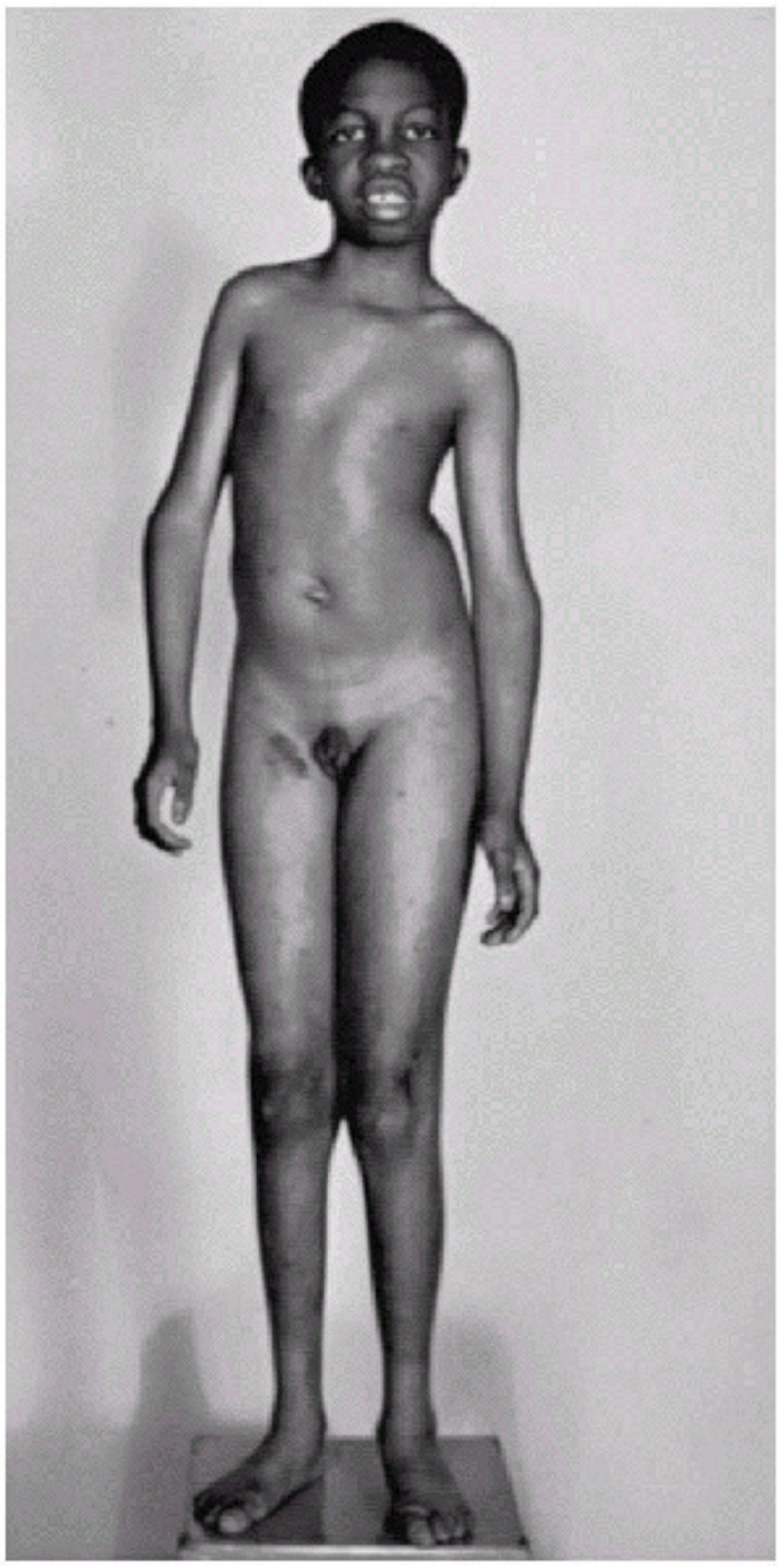


Figure 1.28 A 12-year-old boy with 48,XXXY/49,XXXXY mosaicism. He has prognathism, epicanthal folds, scoliosis, hypogonadism, severe mental retardation, clinodactyly, and radioulnar synostosis. (From Behrman RE, Vaughan VC III, Nelson WE, eds. *Nelson textbook of pediatrics*, 13th ed. Philadelphia: WB Saunders, 1987.)

Myopia

Myopia is a condition in which the eye is too long for the combined corneal and lens focal lengths, and the plane of sharp focus of the image is therefore in front of the retina. The growth of the eye is controlled by an image-processing feedback mechanism commandeered by the retina. There is no doubt that an environmental component is involved in myopic development, and extended near work appears to be the major risk factor. Inheritance also plays a role, since myopic parents are more likely to have myopic children. Myopia is far more frequent in Asian populations than in the United States or Europe, even if groups are compared that have performed similar amounts of near work.

There are multiple genetic syndromes with systemic findings that have myopia as a consistent clinical feature. For example, Stickler syndrome type 1 (OMIM 108300) is

an autosomal dominant, type IIa collagen gene mutation, connective-tissue disorder characterized by ocular, orofacial, and skeletal abnormalities. Associated ocular manifestations include high myopia, glaucoma, cataracts, vitreoretinal degeneration, and retinal detachment (385,386). Marfan syndrome (OMIM 154700) is an autosomal dominant, fibrillin-1 gene mutation, connective-tissue disorder with clinical features of myopia, lens dislocation, tall body habitus, and increased aortic wall distensibility (202,387). Knobloch syndrome (OMIM 267750) has an autosomal recessive high myopia presentation with vitreous degeneration and encephalocele, and is due to mutations in the collagen type 18A1 gene on chromosome 21q22.3 (388). Unlike these syndromes, however, the vast majority of individuals with myopia—moderate or severe—have no associated defects.

Determining the role of genetic factors in the development of nonsyndromic myopia has been hampered by the high prevalence, genetic heterogeneity, and clinical spectrum of this condition. The existence of a genetic contribution to any disease is based on evidence of familial aggregation and twin studies (389). In the past, several modes of inheritance for myopia were proposed, with no clear agreement among studies of pedigrees (389,390,391). Goss and associates (392) reviewed a number of studies, some of which proposed an autosomal dominant mode of inheritance, others autosomal recessive, and still others, an X-linked pattern of inheritance for myopia. More recently, Naiglin and associates (393) performed segregation analysis on 32 French families with high myopia and determined an autosomal dominant mode of inheritance. The ?s for myopia (the increase in risk to siblings of a person with a disease compared to the population prevalence) has been estimated to be approximately 20 for siblings for high myopia, compared to approximately 1.5 for low myopia, suggesting a strong genetic

basis for high myopia (394).

Twin studies provide the most compelling evidence that myopia is inherited. Multiple studies note an increased concordance of refractive error and refractive components (axial eye length, corneal curvature, lens power, anterior chamber depth) in monozygotic twins compared to dizygotic twins (390,395,396,397). Twin studies estimate a notable heritability value, the proportion of the total phenotypic variance that is attributed to the genome, of between 0.5 and 0.96 (395,396,398).

Many studies report a positive correlation between parental myopia and myopia in their children, indicating a hereditary factor in myopia susceptibility (399,400,401,402,403). Children with a family history of myopia had on average less hyperopia, deeper anterior chambers, and longer vitreous chambers even before becoming myopic. The odds of children with two myopic parents becoming myopic were 6.4 times those of children with one or no myopic parents. The odds of developing myopia for children who had refractions in the lower half of the distribution at 6 to 12 months were 4.3 times those of children who had refractions in the upper half. A pedigree analysis indicated that 63% of individuals at risk for developing juvenile-onset myopia actually became myopic, with an equal number of affected males and females. This implies a strong role for genetics in the initial shape and subsequent growth of the eye in myopia. Assessing the impact of genetic inheritance on myopic development may be confounded by children adopting their parents'behavioral traits, such as higher than average near-work activities (e.g., reading) (404).

In addition to genetics, moderate myopic development can be influenced by environmental factors. This is exemplified by experimental modulation of refractive error in the developing eyes of several mammalian and avian models (405,406,407), and the development of myopia in young children with media irregularities that prevent a focused retinal image (408,409,410). Moreover, the prevalence of myopia in some populations appears to have increased dramatically from one generation to the next in increasingly industrialized settings or with increased levels of educational achievement (411,412,413,414,415). The identification of myopia genes may therefore provide insight into geneticenvironmental interactions.

The notion that multiple genes may be involved in the pathogenesis of myopia has been supported by the results of recent mapping investigations for high myopia of greater than -6.00 diopters of spherical refractive error. Three genomic regions on chromosome Xq28 (MYP1 locus; OMIM 310460) (416,417) and autosomal dominant loci on chromosome 18p11.31 (MYP2 locus; OMIM 160700) (418) and chromosome 12q23.1-24 (MYP3 locus; OMIM 603221) (419) have been shown to segregate with myopia in a small number of independent families. The MYP2 locus has been confirmed by two independent laboratories (420,421). Recently, a new locus for autosomal dominant high myopia has been mapped to chromosome 17q21-22 (MYP5; OMIM 608474) (422). A suggestive fourth locus for autosomal dominant high myopia has been reported on chromosome 7q36 (MYP4; OMIM 608367) (423).

An investigation of factors that regulate the rate and duration of eye growth in the mouse has also revealed two loci (Eye1 and Eye2) that may be responsible for genetic factors influencing myopia (424,425). The human homologous regions (*synteny)* are at chromosomes 6p, 16q13.3, and 19q13 for Eye2, and chromosome 7q for Eye1.

Some forms of severe myopia may be inherited as Mendelian autosomal dominant or recessive traits. However, the majority of myopic individuals have a moderate refractive error that is more likely to be the result of a combination of genetic and environmental influences. Studying the nature of the genes that confer susceptibility for high myopia may provide insights for the development and progression of the common form of myopia, as well as address the interaction of genetic and environmental factors.

Consensus opinion regarding common, juvenile-onset myopia of moderate amounts is that its etiology is influenced by both genetic and environmental factors (403). As a multifactorial, common, complex trait, genes or gene loci for this type of myopia have yet to be identified. Susceptibility loci contributing to common, juvenile-onset myopia may be difficult to map by classic linkage analysis because of the limited power to detect genes of intermediate or small effect using independent pedigrees.

Strabismus

Strabismus (misalignment of the eyes; also referred to as “squint”) is one of the most common ocular disorders in

humans, affecting 1% to 4% of the population (426). The familial clustering of strabismus has been recognized since antiquity. For example, Hippocrates stated that “children of parents having distorted eyes squint also for the most part” (426). The causes of the common forms of nonsyndromic strabismus, such as concomitant esotropia and exotropia, are likely to be multiple and confounding, and no single malfunction, environmental agent, or gene mutation has been identified (427,428).

Strabismus tends to cluster in families. Population studies support a hereditary component with a sibling prevalence ranging from 11% to 70% (429,430). Francois (431) reported four pedigrees with members affected with esotropic strabismus. He concluded that autosomal dominant inheritance with reduced penetrance accounted for the disease. Dufier and coworkers (432) retrospectively studied the families of 195 persons with isolated esotropia. They found an affected family member of the proband by history or examination in more than 50% and vertical transmission from parents to child in 35%. They performed segregation analysis using a strabismus frequency of 3% in the general population and concluded that an autosomal dominant model with incomplete penetrance was most likely for esotropia and that an autosomal recessive model was most compatible with esotropia with amblyopia.

In a segregation analysis study of 173 pedigrees with infantile nonaccommodative esotropia, Maumenee and colleagues (433) found that the disease best fit a model with either two autosomal dominant genes with incomplete penetrance or multifactorial inheritance. Not included in this analysis are the many genetic conditions that are associated with strabismus via their effect on the development and function of the central nervous system or the anatomy of the eye and orbit. With respect to overall heritability, the relative risk for first-degree relatives of an affected individual is estimated to be between 3 and 5 (434). Hu (435) found a 9% incidence among first-degree relatives and a 2.2% incidence among second-degree relatives, versus a population incidence of 0.6%. Richter (436) examined and studied the siblings and parents of patients (probands, 697; total, 1509) and children with strabismus (probands, 136; total, 344) whose condition was ascertained at the time of vaccination. She found that the incidence of strabismus or the various strabismus-associated ocular anomalies among siblings of an affected proband was approximately 20%if both parents were unaffected and 30% to 40% if one or both parents were also affected, versus a population frequency of 4%. Strabismus affects males and females equally.

Studies of families with probands with exotropia are less numerous. Waardenburg (437) reported 18 families who had more than one member with exotropia; 13 exhibited vertical transmission from parent to child. He postulated autosomal dominant inheritance with reduced penetrance.

Twin studies further support the concept of a hereditary component predisposing to the development of strabismus (438). Waardenburg (437) combined previous reports of esotropia in twins with his cases and found the concordance rate of strabismus in monozygotic pairs to be approximately 80% (69 sets) and in dizygotic pairs, approximately 12% (101 sets). DeVries and Houtman (439) studied 17 pairs of monozygotic twins in whom one of the two developed esotropia within the first year of life, and found concordance in eight. Rubin and coworkers (440) questioned 50 ophthalmologists and compiled results on 22 sets of twins, one of whom had exotropia, and 122 pairs, one of whom had esotropia; concordance was 77% in monozygotic sets and 50% in dizygotic for exotropia, and 75% in monozygotic and 53% in dizygotic for esotropia, with a heritability of 0.54 for exotropia and 0.47 for esotropia. The authors analyzed esophoria and exophoria separately and found the concordance to be relatively low for both forms of strabismus. Richter (436) also studied strabismus (combining both esotropia and exotropia) in twins and found concordance in 11 or 12 monozygotic pairs and 7 of 27 dizygotic pairs; on the basis of her frequency and twin studies, she concluded that strabismus was multifactorial. If genetic factors alone accounted for strabismus, the concordance of monozygotic twins should be 100% conversely, if environmental influences alone cause the condition, 4% or less (the prevalence in the general population) of the dizygotic twins of affected persons should be similarly affected.

In 1972 Niederecker and coworkers (441) found that parents of probands with either esotropia or exotropia were less able than controls to maintain ocular alignment (fusional amplitudes). In an assessment of ocular deviation and the relationship of accommodative convergence to accommodation ratio, Mash and coworkers (442) found that certain vergence amplitudes had higher heritability values than others and differed significantly among the strabismus populations.

In a series of large quantitative genetic studies, ocular alignment and other parameters in a group of strabismus patients and their families from Iowa were studied (442,443). The studies assessed the heritability of ocular measurements that might predispose patients to strabismus. They found that ocular alignment

(esodeviation or exodeviation) tended to be consistent within a family, with substantial heritability from the female parent at 0.42. Thus, relatives of patients with esodeviations tended also to have esodeviations, and relatives of patients with exodeviations tended to have exodeviations. The mother's ocular alignment correlated best with that of the offspring. These authors calculated the heritability of the relationship of the accommodative convergence to accommodation ratio at 0.38.

A recent study by Parikh and associates (444) identified the linkage of a presumptive strabismus susceptibility locus to chromosome 7p22.1 with a multipoint logarithm of odds score of 4.51 under a model of recessive inheritance in one large family. They also demonstrated the failure to observe significant linkage to chromosome 7p in six other multiplex families, consistent with genetic heterogeneity among families. Their findings suggest that it will be possible to localize and ultimately identify strabismus susceptibility genes by linkage analysis and mutation screening of candidate genes.

In conclusion, isolated strabismus is a common disease in the general population and the causes are poorly understood. Strabismus does not appear to develop as a result of a single gene mutation; however, all forms cluster in

families and there is little evidence to support an environmental cause. Although the evidence is not conclusive, a polygenic and/or multifactorial model is likely with a “threshold” level of many factors such as interpupillary distance, fusional ability, refractive error, and others, with strabismus becoming manifest if the individual has a combination of abnormalities.

GENETIC COUNSELING AND PRENATAL DIAGNOSIS

The recurrence risk for a single-gene disorder depends on whether the mutant gene is located on an autosome or on a sex chromosome, on whether it is manifested in the heterozygous state, and on the penetrance. An individual with a dominantly inherited disease may have a parent with the disorder and a family history of affected individuals in several generations (vertical transmission; Fig. 1.6). An individual with an autosomal dominant disorder mated to a normal partner will pass the gene on to approximately half of his or her offspring, regardless of gender; the other half of the children will receive the normal allele. Thus, the expectation for a child who does not carry the mutation will be 50% for each pregnancy, and the expectation for a child with the abnormal allele will also be 50%, regardless of the outcome of the preceding pregnancies. The likelihood that a child with the abnormal allele will express the disease is a function of its penetrance.

A child with a disorder inherited in a dominant manner may represent a new mutation if the penetrance is high and there is no family history. The recurrence risk for future pregnancies of the mother would be close to zero because most detectable mutations occur in a single gamete. However, a mutation in a tissue sector that includes germ cells could lead to the birth of more than one affected offspring. Documentation of such rare somatic mutations of germ cell lines exists in the case of two achondroplastic children born to normal parents (445). The subsequent birth of an achondroplastic child to one of the affected individuals demonstrated the dominant inheritance of the disorder in this family.

In a mating of two carriers of an autosomal recessive disorder, the probability is equal that each parent will contribute either a normal or an abnormal allele to the zygote for each pregnancy. There are three possible genetic combinations: (a) the homozygous normal child who receives a normal allele from each parent, (b) the heterozygote who receives a normal allele from one parent and the abnormal allele from the other parent, and (c) the affected child who receives an abnormal allele from each parent. The expected ratio is one homozygous clinically normal to two heterozygous clinically normal to one homozygous clinically abnormal (affected) offspring. The probability is 3:1 that the embryo will have received at least one normal allele and be phenotypically normal. Thus, there is a 25% risk of an affected child with each pregnancy.

When the enzyme defect is known and measurable in a recessively inherited metabolic disorder, it is possible to identify which relatives of an affected individual are carriers. The affected individual usually has reduced or absent enzyme activity, whereas the heterozygote has approximately half that of the normal homozygous individual. For example, the clinical manifestations of galactosemia are due to lack of activity of the enzyme galactose-l-phosphate uridyl transferase and accumulation of galactose-l-phosphate. Heterozygotes for galactosemia have approximately half the enzyme activity (as measured in white cells and tissue culture fibroblasts) of individuals with two normal alleles. It is possible to diagnose galactosemia and many other metabolic disorders in utero by measuring the enzyme level in tissue cultures of fetal cells obtained by chorionic villus sampling or by amniocentesis; however, DNA analysis is rapidly supplanting traditional biochemical methods.

In the case of rare recessive disorders, there is an increased incidence of consanguinity between the parents of affected individuals, both parents having received the mutant gene from the same common ancestor (Fig. 1.5). A gene may be relatively rare in one population but common in another. For example, the incidence of oculocutaneous albinism in the United States is approximately 1 in 20,000; among the San Blas Indians of Panama, it is 1 in 132. Assuming both diseases are due to a defect in the same gene, the carrier state is more common in the San Blas inhabitants. The genes for Tay-Sachs disease and familial dysautonomia are extremely rare except among Jews who trace their ancestry to Eastern Europe. Cystic fibrosis is almost exclusively a disease of white populations. The high frequency of some recessive genes is attributed to genetic drift within an isolated population, termed the founder effect (as in the San Blas Indians). For other genes, heterozygosity may convey a selective advantage. The increased ability of sickle cell heterozygotes to survive an episode of malaria creates a selective advantage, and the carrier (heterozygous) state is more frequent in Africa where malaria is more common. It has also been suggested that heterozygosity for Tay-Sachs disease conveys resistance to pulmonary tuberculosis (446).

In the case of an X-linked recessive disorder, the heterozygous female carrier transmits the abnormal allele to half her daughters (who are carriers) and to half her sons, who manifest the disease because they have only one X chromosome (Fig. 1.8). The other 50% of sons and daughters are normal. Affected males transmit their single X chromosome to all their daughters, who are obligate carriers for the X-linked recessive gene and affected for the X-linked dominant gene. Male-to-male transmission of an X-linked gene rarely occurs, since the male transmits his Y chromosome to his son; this phenomenon could occur if a gene were on the X and Y chromosomes. In an X-linked dominant disorder, half the children of an affected female will be affected; usually there is a predominance of females and presumed fetal wastage of males.

In genetic counseling, population genetics is useful for the calculation of a coefficient of inbreeding and a recurrence risk. The coefficient of inbreeding can be calculated for a couple on the basis of their consanguineous relationship. The recurrence risk for a particular disease may be calculated using Bayes'theorem, and is based on the ancestral risk and the affected status of the offspring of the individual at risk for being a carrier.

The field of prenatal diagnosis has advanced rapidly in the past decade. The diagnostic use of chorionic villus sampling, amniocentesis, ultrasonography, fetoscopy, and other procedures has dramatically altered the nature of genetic counseling for families with a disease amenable to prenatal detection. Parents now may make a decision whether or not to continue a pregnancy based on the knowledge of an affected fetus rather than on a statistical risk.

In amniocentesis, amniotic fluid and suspended fetal cells are aspirated transabdominally. Usually this procedure is performed in the second trimester after the fifteenth week of gestation. Recently, sophisticated ultrasonography has enabled amniocentesis to be performed as early as 11 to 12 weeks after the last menstrual period.

Chorionic villus sampling involves the removal of cells that are destined to become the placenta from outside the pregnancy sac; these cells are from the fertilized egg from which the embryo develops. The cells are obtained transcervically or transabdominally, using ultrasound monitoring. The procedure is usually performed between the ninth and twelfth weeks after the last menstrual period. The cells can be grown in culture and used for chromosomal analysis and biochemical assay.

The general indications for prenatal diagnostic chorionic villus sampling are (a) an increased risk of having a child with a chromosomal abnormality (i.e., maternal age 35 years or older, previous child with a chromosomal abnormality, or the mother is a known carrier of a chromosomal rearrangement); (b) carrier status in the parents for a diagnosable biochemical disorder; and (c) carrier status of a serious X-linked disorder in the mother. For amniocentesis, the indications are identical. In addition, only amniocentesis is useful for the detection of a neural tube defect such as anencephaly, spina bifida, and encephalocele, and may be indicated if a parent or previous child has been so affected.

Chromosomal abnormalities are detectable by cytogenetic studies. Biochemical disorders are diagnosable in utero if they are expressed in cultured cells or amniotic fluid. Neural-tube defects in the fetus may be detected by elevated alpha-fetoprotein levels in amniotic fluid and altered pseudocholinesterase in the amniotic fluid; pregnancies at high risk are identified by screening of maternal serum. Generally, the neural-tube defect can be characterized by second-trimester

ultrasonography. For X-linked diseases, determination of fetal gender is followed by the appropriate diagnostic test. If no test is available, the decision to continue pregnancy may be based solely on the information that a male fetus has a 50% risk of being affected.

Both chorionic villus sampling and amniocentesis have become accepted medical procedures with little risk to the mother or fetus. Ocular trauma to the fetus is an unusual complication. Unilateral hazy cornea with changes suggestive of perforation have been documented and attributed to midtrimester amniocentesis (447,448,449,450,451). This complication should be avoidable by the use of ultrasound-guided procedures.

Prenatal diagnosis is feasible for many diseases with ocular manifestations. Techniques for analysis include ultrasound testing of fetal anatomy and analysis of fetal cells or amniotic fluid. Significant ocular malformations have been diagnosed prenatally by ultrasonography (452,453) as fetal ocular biometry has been established.

REFERENCES

1. Sutton WS. The chromosomes in heredity. *Biol Bull* 1903;4: 231-251.

2. Watson JD, Crick FHC. Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. *Nature* 1953;171: 737-738.

3. Lenz W. Zukunftsperspektiven in der humangenetik. In Hammerstein W, Lisch W, eds. *Ophthalmologische genetik*. Stuttgart, Germany: Enke, 1985:384-390.

4. Shin JT, Fishman MC. From zebrafish to human: modular medical models. *Ann Rev Genomics Hum Genet* 2002;3:311-340.

5. McKusick VA. *Mendelian inheritance in man: a catalog of human genes and genetic disorders*, 11th ed. Baltimore: Johns Hopkins University Press, 1994.

6. Winter R, Baraister M. *London Dysmorphology Database*. Version 3.0. Oxford: Oxford University Press Electronic Publishing, 2001.

7. Krawczak M, Ball EV, Fenton I, et al. Human gene mutation database—a biomedical information and research resource. *Hum Mutat* 2000;15:45-51.

8. Cotton RGH, McKusick V, Scriver CR. The HUGO mutation database initiative. *Science* 1998;279:10-11.

9. Thompson JS, Thompson MW. *Genetics in medicine*, 3rd ed. Philadelphia: WB Saunders, 1980:356.

10. Tjio JH, Levan A. The chromosome number of man. *Heredias* 1956;42:1-6.

11. Seabright M. A rapid banding technique for human chromosomes. *Lancet* 1971;2:971-972.

12. Caspersson T, Zech L, Johansson C. Differential binding of alkylating fluorochromes in human chromosomes. *Exp Cell Res* 1970; 60:315-319.

13. Prescott JC, Blackburn EH. Telomerase: Dr. Jekyll or Mr. Hyde? *Curr Opin Genet Dev* 1999;9:368-373.

14. Bouffler SD. Involvement of telomeric sequences in chromosomal aberrations. *Mutat Res* 1998;404:199-204.

15. Krejci K, Koch J. An in situ study of variant telomeric repeats in human chromosomes. *Genomics* 1999;58:202-206.

16. Abdulla S. Telomerase as a marker for cancer. *Mol Med Today* 1997;3:187.

17. Albanell J, Lonardo F, Rusch V, et al. High telomerase activity in primary lung cancers: association with increased cell proliferation rates and advanced pathologic stage. *J Natl Cancer Inst* 1997; 89:1609-1615.

18. Gendrot C, Ronce N, Raynaud M, et al. X-linked nonspecific mental retardation (MRX16) mapping to distal Xq28: linkage study and neuropsychological data in a large family. *Am J Med Genet* 1999;83:411-418.

19. Lichter P, Joos S, Bentz M, et al. Comparative genomic hybridization: uses and limitations. *Sem Hematol* 2000;37:348-357.

20. Jeuken JWM, Sprenger SHE, Wesseling P. Comparative genomic hybridization: practical guideline. *Diagn Mol Pathol* 2002;11: 193-203.

21. Pinkel D, Segraves R, Sudar D, et al. High resolution analysis of DNA copy number variation using comparative genomic hybridization to microarrays. *Nat Genet* 1998;20:207-211.

22. Pollack JR, Perou CM, Alizadeh AA, et al. Genome-wide analysis of DNA copy-number changes using cDNA microarrays. *Nat Genet* 1999;23:41-46.

23. Snijders AM, Nowak N, Segraves R, et al. Assembly of microarrays for genome-wide measurement of DNA copy number. *Nat Genet* 2001;29:263-264.

24. Morton NE, Crow JF, Muller HJ. An estimate of the mutational damage in man from data on consanguineous marriages. *Proc Natl Acad Sci USA* 1956;42:855-863.

25. Lyon MF. Gene action in the X-chromosome of the mouse (Mus musculus L.) *Naturwissenschaften* 1961;190:372-373.

26. Bixler D, Higgins M, Hartsfield J Jr. The Nance-Horan syndrome: a rare X-linked ocular-dental trait with expression in heterozygous females. *Clin Genet* 1984;26:30-35.

27. Lewis RA, Nussbaum RL, Stambolian D. Mapping X-linked ophthalmic diseases. IV. Provisional assignment of the locus for X-linked congenital cataracts and microcornea (the Nance-Horan syndrome) to Xp22.2-p22.3. *Ophthalmology* 1990;97:110-120.

28. Berson EL, Sandberg MA, Maguire A, et al. Electroretinograms in carriers of blue cone monochromatism. *Am J Ophthalmol* 1986; 102:254-261.

29. Hittner HM, Kretzer FL, Antoszyk JH, et al. Variable expressivity of autosomal dominant anterior segment mesenchymal dysgenesis in six generations. *Am J Ophthalmol* 1982;93:57-70.

30. Shoffner JM, Wallace DC. Mitochondrial genetics: principles and practice. *Am J Hum Genet* 1992;51:1179-1186.

31. Wallace DC. Mitochondrial DNA variation in human evolution, degenerative disease, and aging. *Am J Hum Genet* 1995;57: 201-223.

32. Bindoff LA, Desnuelle C, Birch-Machin MA, et al. Multiple defects of the mitochondrial respiratory chain in a mitochondrial encephalopathy (MERRF): a clinical, biochemical and molecular study. *J Neurol Sci* 1991;102:17-24.

33. Moraes CT, DiMauro S, Zeviani M, et al. Mitochondrial DNA deletions in progressive external ophthalmoplegia and Kearns-Sayre syndrome. *N Engl J Med* 1989;320:1293-1299.

34. Wallace DC, Singh G, Lott MT, et al. Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. *Science* 1988;242:1427-1430.

35. DiMauro S, Moraes CT. Mitochondrial encephalopathies. *Arch Neurol* 1993;50:1197-1208.

36. Shapira AHV, DiMauro S, eds. *Mitochondrial disorders in neurology*. Oxford: Butterworth-Heinemann, 1994.

37. Fazzi E, Signorini SG, Scelsa B, et al. Leber's congenital amaurosis: an update. *Eur J Paediatr Neurol* 2003;7:13-22.

38. Morimura H, Fishman GA, Grover SA, et al. Mutations in the RPE65 gene in patients with autosomal recessive retinitis pigmentosa or Leber congenital amaurosis. *Proc Natl Acad Sci USA* 1998;95:3088-3093.

39. Sohocki MM, Sullivan LS, Mintz-Hittner HA, et al. A range of clinical phenotypes associated with mutations in CRX, a photoreceptor transcription-factor gene. *Am J Hum Genet* 1998;63: 1307-1315.

40. Acland GM, Aguirre GD, Ray J, et al. Gene therapy restores vision in a canine model of childhood blindness. *Nat Genet* 2001;28: 92-95.

41. Tomita Y, Takeda A, Okinaga S, et al. Human oculocutaneous albinism caused by a single base insertion in the tyrosinase gene. *Biochem Biophys Res Commun* 1989;164:990-996.

42. Rinchik EM, Bultman SJ, Horsthemke B, et al. A gene for the mouse pink-eyed dilution locus and for human type II oculocutaneous albinism. *Nature* 1993;361:72-76.

43. Schmitz B, Schaefer T, Krick CM, et al. Configuration of the optic chiasm in humans with albinism as revealed by magnetic resonance imaging. *Invest Ophthalmol Vis Sci* 2003;44:16-21.

44. Faugere V, Tuffery-Giraud S, Hamel C, et al. Identification of three novel OA1 gene mutations identified in three families mis-diagnosed with congenital nystagmus and carrier status determination by real-time quantitative PCR assay. *BMC Genet* 2003;4:1.

45. Hegde M, Lewis RA, Richards CS. Diagnostic DNA testing for X-linked ocular albinism (OA1) with a hierarchical mutation screening protocol. *Genet Test* 2002;6:7-14.

46. Farrer LA, Arnos K, Asher JH Jr, et al. Locus heterogeneity for Waardenburg syndrome is predictive of clinical subtypes. *Am J Hum Genet* 1994;55:728-733.

47. Zlotogora J. X-linked albinism-deafness syndrome and Waardenburg syndrome type II: a hypothesis. *Am J Med Genet* 1995;59: 386-387.

48. Nobukuni Y, Watanabe A, Takeda K, et al. Analysis of loss-offunction mutations of the MITF gene suggests that haploinsufficiency is a cause of Waardenburg syndrome type IIa. *Am J Hum Genet* 1996;59:76-83.

49. Tassabehji M, Newton VE, Liu XZ, et al. The mutational spectrum in Waardenburg syndrome. *Hum Mol Genet* 1995;4:2131-2137.

50. Tassabehji M, Newton VE, Read AP. Waardenburg syndrome type 2 caused by mutations in the human microphthalmia (MITF) gene. *Nat Genet* 1994;8:251-255.

51. Morell R, Spritz RA, Ho L, et al. Apparent digenic inheritance of Waardenburg syndrome type 2 (WS2) and autosomal recessive ocular albinism (AROA). *Hum Mol Genet* 1997;6:659-664.

52. Rand EB, Spinner NB, Piccoli DA, et al. Molecular analysis of 24 Alagille syndrome families identifies a single submicroscopic deletion and further localizes the Alagille region within 20p12. *Am J Hum Genet* 1995;57:1068-1073.

53. Li Y, Bollag G, Clark R, et al. Somatic mutations in the neurofibromatosis 1 gene in human tumors. *Cell* 1992;69:275-281.

54. De Lange C. Sur un type nouveau de degeneration (typus Amsteledamensis). *Arch Med Enfants* 1933;36;713-719.

55. Jackson L, Kline AD, Barr MA, et al. de Lange syndrome: a clinical review of 310 individuals. *Am J Med Genet* 1993;47:940-946.

56. Ireland M, Donnai D, Burn J. Brachmann-de Lange syndrome. Delineation of the clinical phenotype. *Am J Med Genet* 1993;47: 959-964.

57. Levin PS, Green WR, Victor DI, et al. Histopathology of the eye in Cockayne's syndrome. *Arch Ophthalmol* 1983;101:1093-1097.

58. Krantz ID, McCallum J, DeScipio C, et al. Cornelia de Lange syndrome is caused by mutations in *NIPLB*, the human homolog of *Drosophila melanogaster Nipped-B*. *Nat Genet* 2004;36: 631-635.

59. Tonkin ET, Wang T-J, Lisgo S, et al. *NIPBL*, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome. *Nat Genet* 2004;36:636-641.

60. Rollins RA, Morcillo P, Dorsett D. Nipped-B, a Drosophila homologue of chromosomal adherins, participates in activation by remote enhancers in the *cut* and *Ultrabithorax* genes. *Genetics* 1999;152:577-593.

61. Collod-Beroud G, Boileau C. Marfan syndrome in the third millennium. *Eur J Hum Genet* 2002;10:673-681.

62. Robinson PN, Booms P, Katzke S, et al. Mutations of FBN1 and genotype-phenotype correlations in Marfan syndrome and related fibrillinopathies. *Hum Mutat* 2002;20:153-161.

63. Comeglio P, Evans AL, Brice G, et al. Identification of FBN 1 gene mutations in patients with ectopia lentis and marfanoid habitus. *Br J Ophthalmol* 2002;86:1359-1362.

64. Gehrig WJ. The genetic control of eye development and its implications for the evolution of the various eye-types. *Int J Dev Biol* 2002;46:65-73.

65. Halder G, Callaerts P, Gehring WJ. Induction of ectopic eyes by targeted expression of the eyeless gene in Drosophila. *Science* 1995;267:1788-1792.

66. Van Heyningen V, Williamson KA. *PAX6* in sensory development. *Hum Mol Genet* 2002;11:1161-1167.

67. Ashery-Padan R, Gruss P. Pax6 lights up the way for eye development. *Curr Opin Cell Biol* 2001;13:706-714.

68. Chiang C, Litingtung Y, Lee E, et al. Cyclopia and defective axial patterning in mice lacking Sonic hedgehog gene function. *Nature* 1996;383:407-413.

69. Fantes J, Ragge NK, Lynch SA, et al. Mutations in SOX2 cause anophthalmia. *Nat Genet* 2003;33:461-463.

70. Mathers PH, Grinberg A, Mahon KA, et al. The Rx homeobox gene is essential for vertebrate eye development. *Nature* 1997; 387:603-607.

71. Zhang L, Mathers PH, Jamrich M. Function of *Rx*, but not *Pax6* is essential for the formation of retinal progenitor cells in mice. *Genesis* 2000;28:135-142.

72. Tucker P, Laemle L, Munson A, et al. The *eyeless* mouse mutation (*ey1*) removes an alternative start codon from the *Rx/Rax* homeobox gene. *Genesis* 2001;31:43-53.

73. Young HB. Microcornea without microphthalmos. Report of a case. *Ann Ophthal* 1904;13:753.

74. Judisch GF, Martin-Casals A, Hanson JW, et al. Oculodentodigital dysplasia. Four new reports and a literature review. *Arch Ophthalmol* 1979;97:878-884.

75. Boynton JR, Purnell EW. Bilateral microphthalmos without microcornea associated with unusual papillomacular retinal folds and high hyperopia. *Am J Ophthalmol* 1975;79:820-826.

76. Spitznas M, Gerke E, Bateman JB. Hereditary posterior microphthalmos with papillomacular fold and high hyperopia. *Arch Ophthalmol* 1983;101:413-417.

77. Uemura Y, Morizane H. The fundus anomalies in high hypermetropic eyes, with particular reference to the interpapillo-macular retinal fold. *Rinsho Ganka* 1970;24:15.

78. Francois J, Goes F. Ultrasonographic study of 100 emmetropic eyes. *Ophthalmologica* 1977;175:321-327.

79. O'Malley PF, Allen RA. Peripheral cystoid degeneration of the retina. Incidence and distribution in 1,000 autopsy eyes. *Arch Ophthalmol* 1967;77:769-776.

80. Heinonen OP, Slone D, Shapiro S. *Birth defects and drugs in pregnancy*. Littleton, Mass: Publishing Sciences Group, 1977.

81. MacDonald AE. Causes of blindness in Canada: an analysis of 24,605 cases registered with the Canadian National Institute for the Blind. *Can Med Assoc J* 1965;92:264-279.

82. National Society to Prevent Blindness. *Vision problems in the U.S*. (A statistical analysis prepared by the operational research department). New York: National Society to Prevent Blindness, 1980.

83. Fraser GR, Friedman AI. *The causes of blindness in childhood. A study of 776 children with severe visual handicaps*. Baltimore: Johns Hopkins Press, 1967.

84. Fujiki K, Nakajima A, Yasuda N, et al. Genetic analysis of microphthalmos. *Ophthalmic Paediatr Genet* 1992;1:139-149.

85. Mann I. *The development of the human eye*. London: British Medical Association, 1964:277.

86. Pagon RA. Ocular coloboma. *Surv Ophthalmol* 1981;25: 223-236.

87. Bateman JB. Microphthalmos. *Int Ophthalmol Clin* 1984;24: 87-107.

88. Capella JA, Kaufman HE, Lill FJ. Hereditary cataracts and microphthalmia. *Am J Ophthalmol* 1963;56:454-458.

89. Usher CH. A pedigree of microphthalmia with myopia and corectopia. *Br J Ophthalmol* 1921;5:289.

90. Phillips CI, Leighton DA, Forrester RM. Congenital hereditary bilateral non-attachment of retina. A sibship of two. *Acta Ophthalmol (Copenh)* 1973;51:425-433.

91. Temtamy SA, Shalash BA. Genetic heterogeneity of the syndrome: microphthalmia with congenital cataract. *Birth Defects Orig Artic Ser* 1974;10:292-293.

92. Steingrimsson E, Moore KJ, Lamoreux ML, et al. Molecular basis of mouse microphthalmia (mi) mutations helps explain their developmental and phenotypic consequences. *Nat Genet* 1994; 8:256-263.

93. Wallis DE, Roessler E, Hehr U, et al. Mutations in the homeodomain of the human *SIX3* gene cause holoprosencephaly. *Nat Genet* 1999;22:196-198.

94. Zhu CC, Dyer MA, Uchikawa M, et al. Six 3-mediated auto repression and eye development requires its interaction with members of the Groucho-related family of co-repressors. *Development* 2002;129:2835-2849.

95. Lengler J, Krausz E, Tomarev S, et al. Antagonistic action of Six3 and Prox1 at the ?-crystalline promoter. *Nucl Acids Res* 2001;29: 515-526.

96. Lengler J, Graw J. Regulation of the human SIX3 promoter. *Biochem Biophys Res Commun* 2001;287:372-376.

97. Goudreau G, Petrou P, Reneker LW, et al. Mutually regulated expression of *Pax6* and *Six3* and its implications for the *Pax6* haploinsufficient lens phenotype. *Proc Natl Acad Sci USA* 2002; 99:8719-8724.

98. Chemke J, Czernobilsky B, Mundel G, et al. A familial syndrome of central nervous system and ocular malformations. *Clin Genet* 1975;7:1-7.

99. Hall BD. Choanal atresia and associated multiple anomalies. *J Pediatr* 1979;95:395-398.

100. Hittner HM, Hirsch NJ, Kreh GM, et al. Colobomatous microphthalmia, heart disease, hearing loss and mental retardation—a syndrome. *J Pediatr Ophthalmol Strabismus* 1979;16:122-128.

101. Ho CK, Kaufman RL, Podos SM. Ocular colobomata, cardiac defect, and other anomalies: a study of seven cases including two sibs. *J Med Genet* 1975;12:289-293.

102. Hussels IE. Midface syndrome with iridochoroidal coloboma and deafness in a mother: microphthalmia in her son. *Birth Defects Orig Artic Ser* 1971;8:269.

103. Pagon RA, Graham JM Jr, Zonana J, et al. Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr* 1981;99:223-227.

104. Warburg M. Microphthalmos and colobomata among mentally retarded individuals. *Acta Ophthalmol (Copenh)* 1981;59: 665-673.

105. Othman MI, Sullivan SA, Skuta GL, et al. Autosomal dominant nanophthalmos (NNO1) with high hyperopia and angle-closure glaucoma maps to chromosome 11. *Am J Hum Genet* 1998;63: 1411-1418.

106. Thomas IT, Frias JL, Felix V, et al. Isolated and syndromic cryptophthalmos. *Am J Med Genet* 1986;25:85-98.

107. Briggs HH. Hereditary congenital ptosis with report of 64 cases conforming to the Mendelian rule of dominance. *Am J Ophthalmol* 1919;2:408-417.

108. Engle EC, Castro AE, Macy ME, et al. A gene for isolated congenital ptosis maps to a 3-cm region within lp32-p34.1. *Am J Hum Genet* 1997;60:1150-1157.

109. McMullan TFW, Crolla JA, Gregory SG, et al. A candidate gene for congenital bilateral isolated ptosis identified by molecular analysis of a de novo balanced translocation. *Hum Genet* 2002; 110:244-250.

110. McMullan TFW, Collins AR, Tyers AG, et al. A novel X-linked dominant condition: X-linked congenital isolated ptosis. *Am J Hum Genet* 2000;66:1455-1460.

111. Kohn R, Romano PE. Blepharoptosis, blepharophimosis, epicanthus inversus, and telecanthus—a syndrome with no name. *Am J Ophthalmol* 1971;72:625-632.

112. Amati P, Chomel JC, Nevelon-Chevalier A, et al. A gene for blepharophimosis, ptosis, epicanthus inversus maps to chromosome 3q23. *Hum Genet* 1995;96:213-215.

113. Small KW, Stalvey M, Fisher L, et al. Blepharophimosis syndrome is linked to chromosome 3q. *Hum Mol Genet* 1995;4:443-48.

114. Crisponi L, Deiana M, Loi A, et al. The putative forkhead transcription factor FOXL2 is mutated in blepharophimosis/ptosis/epicanthus inversus syndrome. *Nat Genet* 2001;27:159-166.

115. Engle EC, Goumnerov B, McKeown CA, et al. Oculomotor nerve and muscle abnormalities in congenital fibrosis of the extraocular muscles. *Ann Neurol* 1997;41:314-325.

116. Yamada K, Andrews C, Chan W-M, et al. Heterozygous mutations of the kinesin *KIF21 A* in congenital fibrosis of the extraocular muscles type 1 (CFEOM1). *Nat Genet* 2003;35:318-321.

117. Engle EC, Kunkel LM, Specht LA, et al. Mapping a gene for congenital fibrosis of the extraocular muscles to the centromeric region of chromosome 12. *Nat Genet* 1994;7:69-73.

118. Engle EC, Marondel I, Houtman WA, et al. Congenital fibrosis of the extraocular muscles (autosomal dominant congenital external ophthalmoplegia): genetic homogeneity, linkage refinement, and physical mapping on chromosome 12. *Am J Hum Genet* 1995;57:1086-1094.

119. Nakano M, Yamada K, Fain J, et al. Homozygous mutations in *ARIX*(*PHOX2A*) result in congenital fibrosis of the extraocular muscles type 2. *Nat Genet* 2001;29:315-320.

120. Mackey DA, Chan W-M, Chan C, et al. Congenital fibrosis of the vertically acting extraocular muscles maps to the FEOM3 locus. *Hum Genet* 2002;110:510-512.

121. Gatti RA, Berkel I, Boder E, et al. Localization of an ataxia-telangiectasia gene to chromosome 11q22-23. *Nature* 1988;336: 577-580.

122. Savitsky K, Bar-Shira A, Gilad S, et al. A single ataxia-telangiectasia gene with a product similar to PI-3 kinase. *Science* 1995;268: 1749-1753.

123. Savitsky K, Sfez S, Tagle DA, et al. The complete sequence of the coding region of the ATM gene reveals similarity to cell cycle regulators in different species. *Hum Mol Genet* 1995;4: 2025-2032.

124. Hecht F, Shoptaugh MG, Winglets of the eye: dominant transmission of early adult pterygium of the conjunctiva. *J Med Genet* 1990;27:392-394.

125. Jacklin HN. Familial predisposition to pterygium formation: report of a family. *Am J Ophthalmol* 1964;57:481-482.

126. Cogan DG, Chu FC, Gittinger J, et al. Fundal abnormalities of Gaucher's disease. *Arch Ophthalmol* 1980;98:2202-2203.

127. Tahvanainen E, Villanueva AS, Forsius H, et al. Dominantly and recessively inherited cornea plana congenital maps to the same small region of chromosome 12. *Genome Res* 1996;6;249-254.

128. Pellegata NS, Dieguez-Lucena JL, Joensuu T, et al. Mutations in *KERA*, encoding keratocan, cause cornea plana. *Nat Genet* 2000;25:91-95.

129. Bloch N. [The different types of sclerocornea, their hereditary modes and concomitant congenital malformations.] *J Genet Hum* 1965;14:133-172.

130. Neuhauser G, Kaveggia EG, France TD, et al. Syndrome of mental retardation, seizures, hypotonic cerebral palsy and megalocorneae, recessively inherited. *Z Kinderheilk* 1975;120:1-18.

131. Rabinowitz YS. Keratoconus. *Surv Ophthalmol* 1998;42:297-319.

132. Edwards M, McGhee CN, Dean S. The genetics of keratoconus. *Clin Exp Ophthalmol* 2001;29:345-351.

133. Heon E, Greenberg A, Kopp KK, et al. VSX1: A gene for posterior polymorphous dystrophy and keratoconus. *Hum Mol Genet* 2002;11:1029-1036.

134. Irvine AD, Corden LD, Swensson O, et al. Mutations in corneaspecific keratin *K3* or *K12* genes cause Meesmann's corneal dystrophy. *Nat Genet* 1997;16:184-187.

135. Munier FL, Korvatska E, Djemai A, et al. Keratoepithelin mutations in four 5831-linked corneal dystrophies. *Nat Genet* 1997; 15:247-251.

136. Gregory CY, Evans K, Bhattachary SS. Genetic refinement of the chromosome 5q lattice dystrophy type 1 locus to within a 2cM interval. *J Med Genet* 1995;32:224-226.

137. Eiberg H, Kjer B, Kjer P, et al. Dominant optic atrophy (OPAL) mapped to chromosome 3q region. *Hum Mol Genet* 1994;3: 977-980.

138. Small KW, Mullen L, Barletta J, et al. Mapping of Reis-Bücklers' corneal dystrophy to chromosome 5q. *Am J Ophthalmol* 1996; 121:384-390.

139. Stone EM, Mathers WD, Rosenwasser GO, et al. Three autosomal dominant corneal dystrophies map to chromosomes 51. *Nat Genet* 1994;6:47-51.

140. Munier FL, Frueh BE, Othenin-Girard P, et al. ßIGH3 mutations in type IIIA and intermediate type I/IIIA of lattice corneal dystrophies are Fas4-specific. *Invest Ophthalmol Vis Sci* 2002;43: 949-954.

141. Hassell JR, Newsome DA, Krachmer J, et al. Corneal macular dystrophy: a possible inborn error in corneal proteoglycan maturation. *Fed Proc* 1980;39:2120.

142. Vance JM, Jonasson F, Lennon E, et al. Linkage of a gene for macular corneal dystrophy to chromosome 16. *Am J Hum Genet* 1996;58:757-762.

143. Akama TO, Nishida K, Nakayama J, et al. Macular corneal dystrophy type I and type II are caused by distinct mutations in a new sulphotransferase gene. *Nat Genet* 2000;25:237-241.

144. Kinoshita S, Nishida K, Dota A, et al. Epithelial barrier function and ultrastructure of gelatinous drop-like corneal dystrophy. *Cornea* 2000;19:551-555.

145. Tasa G, Kals J, Muru K, et al. A novel mutation in the M1S1 gene responsible for gelatinous drop-like corneal dystrophy. *Invest Ophthalmol Vis Sci* 2001;42:2762-2764.

146. Biswas S, Munier FL, Yardley J, et al. Missense mutations in COL8A2, the gene encoding the a2 chain of type VIII collagen, cause two forms of corneal endothelial dystrophy. *Hum Mol Genet* 2001;10:2415-2423.

147. Toma NM, Ebenezer ND, Inglehearn CF, et al. Linkage of congenital hereditary endothelial dystrophy to chromosome 20. *Hum Mol Genet* 1995;4:2395-2398.

148. Hand CK, Harmon DL, Kennedy SM, et al. Localization of the gene for autosomal recessive congenital hereditary endothelial dystrophy (CHED2) to chromosome 20 by homozygosity mapping. *Genomics* 1999;61:1-4.

149. Elsas FJ, Maumenee IH, Kenyon KR, et al. Familial aniridia with preserved ocular function. *Am J Ophthalmol* 1977;83:718-724.

150. Hittner HM, Riccardi VM, Ferrell RE, et al. Variable expressivity in autosomal dominant aniridia by clinical, electrophysiologic, and angiographic criteria. *Am J Ophthalmol* 1980;89:531-539.

151. Bateman JB, Sparkes MC, Sparkes RS. Aniridia: enzyme studies in an 11p- chromosomal deletion. *Invest Ophthalmol Vis Sci* 1984; 25:612-616.

152. Smith ACM, Sujansky E, Riccardi VM. Aniridia, mental retardation and genital abnormality in two patients with 46,XY,11p-. *Birth Defects Orig Artic Ser* 1977;13:257.

153. Riccardi VM, Sujansky E, Smith AC, et al. Chromosomal imbalance in the aniridia-Wilm's; tumor association: 11p interstitial deletion. *Pediatrics* 1978;61:604-610.

154. Warburg M, Mikkelsen M, Anderson SR, et al. Aniridia and interstitial deletion of the short arm of chromosome 11. *Metab Pediatr Ophthalmol* 1980;4:97-102.

155. Riccardi VM, Hittner HM, Strong LC, et al. Wilms tumor with aniridia/iris dysplasia and apparently normal chromosomes. *J Pediatr* 1982;100:574-577.

156. Glaser T, Walton DS, Maas RL. Genomic structure, evolutionary conservation and aniridia mutations in the human *pax6* gene. *Nat Genet* 1992;2:232-239.

157. Jordan T, Hanson I, Zaletayev D, et al. The human *PAX6* gene is mutated in two patients with aniridia. *Nat Genet* 1992;1: 328-332.

158. Glaser T, Jepeal L, Edwards JG, et al. *PAX6* gene dosage effect in a family with congenital cataracts, aniridia, anophthalmia and central nervous system defects. *Nat Genet* 1994;7:463-471.

159. Hanson IM, Fletcher JM, Jordan T, et al. Mutations at the *PAX6* locus are found in heterogeneous anterior segment malformations including Peters' anomaly. *Nat Genet* 1994;6:168-173.

160. Mirzayans F, Pearce WG, MacDonald IM, et al. Mutation of the PAX6 gene in patients with autosomal dominant keratitis. *Am J Hum Genet* 1995;57:539-548.

161. Alkemade PPH. *Dysgenesis mesodermalis of the iris and the cornea: a study of Rieger's syndrome and Peters' anomaly*. Assen, The Netherlands: Van Gorcum, 1969.

162. Awan KJ. Peters-Rieger's syndrome. *J Pediatr Ophthalmol* 1977; 14:112-116.

163. Crawford RAD. Iris dysgenesis with other anomalies. *Br J Ophthalmol* 1967;51:438-440.

164. Dark AJ, Kirkham TH. Congenital corneal opacities in a patient with Rieger's anomaly and Down's syndrome. *Br J Ophthalmol* 1968;52:631-635.

165. Falls HF. A gene producing various defects of the anterior segment of the eye. *Am J Ophthalmol* 1949;32:41.

166. Henkind P, Sigel IM, Carr RE. Mesodermal dysgenesis of the anterior segment: Rieger's anomaly. *Arch Ophthalmol* 1965;73: 810-817.

167. Akazawa K, Yamane S, Shiota H, et al. A case of retinoblastoma associated with Rieger's anomaly and 13q deletion. *Jpn J Ophthalmol* 1981;25:321-325.

168. Ferguson JG Jr, Hicks EL. Rieger's anomaly and glaucoma associated with partial trisomy 16q. Case report. *Arch Ophthalmol* 1987; 105:323.

169. Heinemann M, Breg R, Cotlier E. Rieger's syndrome with pericentric inversion of chromosome 6. *Br J Ophthalmol* 1979;63:40-44.

170. Herve J, Warnet JF, Jeaneau-Bellego E, et al. [Partial monosomy of the short arm of chromosome 10, associated with Rieger's syndrome and a Di George type partial immunodeficiency.] *Ann Pediatr (Paris)* 1984;31:77-80.

171. Ligutic I, Brecevic L, Petkovic I, et al. Interstitial deletion 4q and Rieger syndrome. *Clin Genet* 1981;20:323-327.

172. Stathacopoulos RA, Bateman JB, Sparkes RS, et al. The Rieger syndrome and a chromosome 13 deletion. *J Pediatr Ophthalmol Strabismus* 1987;24:198-203.

173. Tabbara KF, Khouri FP, der Kaloustian VM. Rieger's syndrome with chromosomal anomaly (report of a case). *Can J Ophthalmol* 1973;8:488-491.

174. Wilcox LM Jr, Bercovitch L, Howard RO. Ophthalmic features of chromosome deletion 4p- (Wolf-Hirschhorn syndrome). *Am J Ophthalmol* 1978;86:834-839.

175. Murray JC, Bennett SR, Kwitek AE, et al. Linkage of Rieger syndrome to the region of the epidermal growth factor gene on chromosome 4. *Nat Genet* 1992;2:46-49.

176. Mears AJ, Mirzayans F, Gould DB, et al. Autosomal dominant iridogoniodysgenesis anomaly maps to 6p25. *Am J Hum Genet* 1996;59:1321-1327.

177. Priston M, Kozlowski K, Gill D, et al. Functional analyses of two newly identified PITX2 mutants reveal a novel molecular mechanism for Axenfeld-Rieger syndrome. *Hum Mol Genet* 2001; 10:1631-1638.

178. Nishimura DY, Searby CC, Alward WL, et al. A spectrum of FOXC1 mutations suggests gene dosage as a mechanism for developmental defects of

the anterior chamber of the eye. *Am J Hum Genet* 2001;68:364-372.

179. Panicker SG, Sampath S, Mandal AK, et al. Novel mutation in *FOXC1* wing region causing Axenfeld-Rieger anomaly. *Invest Ophthalmol Vis Sci* 2002;43:3613-3616.

180. Semina EV, Ferrell RE, Mintz-Hittner HA, et al. A novel homeobox gene *PITX3* is mutated in families with autosomal-dominant cataracts and ASMD. *Nat Genet* 1998;19:167-170.

181. Semina EV, Murray JC, Reiter R, et al. Deletion in the promoter region and altered expression of Pitx3 homeobox gene in aphakia mice. *Hum Mol Genet* 2000;9:1575-1585.

182. Boel M, Timmermans J, Emmery L, et al. Primary mesodermal dysgenesis of the cornea (Peters' anomaly) in two brothers. *Hum Genet* 1979;51:237-240.

183. Bateman JB., Maumenee IH, Sparkes RS. Peters' anomaly associated with partial deletion of the long arm of chromosome 11. *Am J Ophthalmol* 1984;97:11-15.

184. Kivlin JD, Fineman RM, Crandall AS, et al. Peters' anomaly as a consequence of genetic and nongenetic syndromes. *Arch Ophthalmol* 1986;104:61-64.

185. Mondino BJ, Shahinian L Jr, Johnson BL, et al. Peters' anomaly with the fetal transfusion syndrome. *Am J Ophthalmol* 1976;82: 55-58.

186. Doward W, Perveen R, Lloyd IC, et al. A mutation in the REIG1 gene associated with Peters' anomaly. *J Med Genet* 1999;36: 152-155.

187. Vincent A, Billingsley G, Priston M, et al. Phenotypic heterogeneity of CYP1B1: mutations in a patient with Peters' anomaly. *J Med Genet* 2001;38:324-326.

188. Plasilova M, Ferakova E, Kadasi L, et al. Linkage of autosomal recessive primary congenital glaucoma to the GLC3A locus in Roms (gypsies) from Slovakia. *Hum Hered* 1998;48:30-33.

189. Sarfarazi M, Akarsu AN, Hossain A, et al. Assignment of a locus (GLC3A) for primary congenital glaucoma (buphthalmos) to 2p21 and evidence for genetic heterogeneity. *Genomics* 1995;30: 171-177.

190. Akarsu AN, Turacli ME, Aktan SG, et al. A second locus (GLC3B) for primary congenital glaucoma (buphthalmos) maps to the 1p36 region. *Hum Mol Genet* 1996;5:1199-1203.

191. Stoilov IR, Akarsu AN, Sarfarazi M. Identification of three truncating mutations in cytochrome P_{450}1B1 (CYP1B1) as the principal cause of primary congenital glaucoma (buphthalmos) in families linked to the GLC3A locus on chromosome 2p21. *Hum Mol Genet* 1997;6:641-647.

192. Broughton WL, Rosenbaum KN, Beauchamp GR. Congenital glaucoma and other ocular abnormalities associated with pericentric inversion of chromosome 11. *Arch Ophthalmol* 1983;101: 594-597.

193. Chrousos GA, O'Neill JF, Traboulsi EI, et al. Ocular findings in partial trisomy 3q. A case report and review of the literature. *Ophthalmic Paediatr Genet* 1989;9:127-130.

194. Wiggs JL, Del Bono EA, Schuman JS, et al. Clinical features of five pedigrees genetically linked to the juvenile glaucoma locus on chromosome 1q21-q31. *Ophthalmology* 1995;102: 1782-1789.

195. Stone EM, Fingert JH, Alward WLM, et al. Identification of a gene that causes primary open angle glaucoma. *Science* 1997;275: 668-670.

196. Shimizu S, Lichter PR, Johnson AT, et al. Age-dependent prevalence of mutations at the GLC1A locus in primary open-angle glaucoma. *Am J Ophthalmol* 2000;130:165-177.

197. Karali A, Russell P, Stefani FH, et al. Localization of myocilin/trabecular meshwork—inducible glucocorticoid response protein in the human eye. *Invest Ophthalmol Vis Sci* 2000;41: 729-740.

198. Rezaie T, Child A, Hitchings R, et al. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Science* 2002; 295:1077-1079.

199. Scheie HG, Cameron JD. Pigment dispersion syndrome: a clinical study. *Br J Ophthalmol* 1981;65:264-269.

200. Andersen JS, Pralea AM, DelBono EA, et al. A gene responsible for the pigment dispersion syndrome maps to chromosome 7q35-q36. *Arch Ophthalmol* 1997;115:384-388.

201. Maumenee IH. The eye in the Marfan syndrome. *Trans Am Ophthalmol Soc* 1981;79:684-733.

202. Dietz HC, Cutting GR, Pyeritz RE, et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature* 1991;352:337-339.

203. Dietz HC, Pyeritz RE, Hall BD, et al. The Marfan syndrome locus: confirmation of assignment to chromosome 15 and identification of tightly linked markers at 15g15-121.3. *Genomics* 1991;9: 355-361.

204. Kainulainen K, Pulkkinen L, Savolainen A, et al.: Location on chromosome 15 of the gene defect causing Marfan syndrome. *N Engl J Mea* 1990;323:935-939.

205. Lee B, Godfrey M, Vitale E, et al. Linkage of Marfan syndrome and a phenotypically related disorder to two different fibrillin genes. *Nature* 1991;352:330-334.

206. Magenis RF, Maslen KL, Smith L, et al. Localization of the fibrillin (*FBN*) gene to chromosome 15, band q21.2. *Genomics* 1991;11:346-351.

207. Maslen CL, Corson GM, Maddox BK, et al. Partial sequence of a candidate gene for the Marfan syndrome. *Nature* 1991;352: 334-337.

208. Tsipouras P, Del Mastro R, Sarfarazi M, et al. Genetic linkage of the Marfan syndrome, ectopia lentis, and congenital contractural arachnodactyly to the fibrillin genes on chromosomes 15 and 5. *N Engl J Mea* 1992;326:905-909.

209. Munke M, Kraus JP, Ohura T, et al. The gene for cystathionine beta-synthase (CBS) maps to the subtelomeric region on human chromosome 21q and to proximal mouse chromosome 17. *Am J Hum Genet* 1988;42:550-559.

210. Diethelm W. Über ectopia lentis ohne arachnodaktylie und ihre beziehungen zur ectopia lentis et pupillae. *Ophthalmologica* 1947;114:16-32.

211. Brakenhoff RH, Henskens HAM, van Rossum MWPC, et al. Activation of the gamma E-crystallin pseudogene in the human hereditary Coppock-like cataract. *Hum Mol Genet* 1994;3:279-283.

212. Lubsen NH, Renwick JH, Tsui LC, et al. A locus for a human hereditary cataract is closely linked to the gamma-crystallin gene family. *Proc Natl Acad Sci USA* 1987;84:489-492.

213. Rogaev EI, Rogaeva EA, Korovaitseva GI, et al. Linkage of polymorphic congenital cataract to the ?-crystallin gene locus on human chromosome 2q33-35. *Hum Mol Genet* 1996;5: 699-703.

214. Kramer P, Yount J, Mitchell T, et al. A second gene for cerulean cataracts maps to the crystallin region on chromosome 22. *Genomics* 1996;38:539-542.

215. Litt M, Carrero-Valenzuela R, LaMorticella DM, et al. Autosomal dominant cerulean cataract is associated with a chain termination mutation in the human ?-crystallin gene CRYBB2. *Hum Mol Genet* 1997;6:665-668.

216. Eiberg H, Lund AM, Warburg M, et al. Assignment of congenital cataract Volkmann type (CCV) to chromosome lp36. *Hum Genet* 1995;96:33-38.

217. Renwick JH, Lawler SD. Probable linkage between a congenital cataract locus and the Duffy blood group locus. *Ann Hum Gene* 1963;27:67-84.

218. Eiberg H, Marner E, Rosenberg T, et al. Marner's cataract (CAM) assigned to chromosome 16: linkage to haptoglobin. *Clin Genet* 1988;34:272-275.

219. Marner E, Rosenberg T, Eiberg H. Autosomal dominant congenital cataract. Morphology and genetic mapping. *Acta Ophthalmol (Copenh)* 1989;67:151-158.

220. Richards J, Maumenee I, Rowe S, et al. Congenital cataract possibly linked to haptoglobin. *Cytogenet Cell Genet* 1984;37:570.

221. Berry V, Ionides ACW, Moore AT, et al. A locus for autosomal dominant anterior polar cataract on chromosome 17p. *Hum Mol Genet* 1996;5:415-419.

222. Padma T, Ayyagari R, Murty JS, et al. Autosomal dominant zonular cataract with sutural opacities localized to chromosome 17q11-12. *Am J Hum Genet* 1995;57:840-845.

223. Armitage MM, Kivlin JD, Ferrell RE. A progressive cataract gene maps to human chromosome 17q24. *Nat Genet* 1995;9:37-40.

224. Francis PJ, Berry V, Hardcastle AJ, et al. A locus for isolated cataract on human Xp. *J Med Genet* 2002;39;105-109.

225. Shih LY, Rosin I, Suslak L, et al. Localization of the structural gene for galactose-1-phosphate uridyl transferase to band p13 of chromosome 9 by gene dosage studies. (Abstract) *Am J Hum Gene* 1982;34:62A.

226. Shih LY, Suslak L, Rosin I, et al. Gene dosage studies supporting localization of the structural gene for galactose-1-phosphate uridyl transferase (GALT) to band p13 of chromosome 9. *Am J Med Gene* 1984;19:539-543.

227. Kondo I. Nakamura N. Regional mapping of GALT in the short arm of chromosome 9. (Abstract) *Cytogenet Cell Genet* 1984;37:514.

228. Kooy RF, Van der Veen AY, Verlind E, et al. Physical localisation of the chromosomal marker D13S31 places the Wilson disease locus at the junction of bands q14.3 and q21.1 of chromosome 13. *Hum Genet* 1993;91:504-506.

229. Bull PC, Thomas GR, Rommens JM, et al. The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. *Nat Genet* 1993;5:327-337.

230. Harley HG, Brook JD, Floyd J, et al. Detection of linkage disequilibrium between the myotonic dystrophy locus and a new polymorphic DNA marker. *Am J Hum Genet* 1991;49:68-75.

231. Boucher CA, King SK, Carey N, et al. A novel homeodomainencoding gene is associated with a large CpG island interrupted by the myotonic dystrophy unstable $(CTG)_n$ repeat. *Hum Mol Genet* 1995;4:1919-1925.

232. Deeb SS, Motulsky AG. Molecular genetics of human color vision. *Behav Genet* 1996;26:195-207.

233. Nathans J, Thomas D, Hogness DS. Molecular genetics of human color vision: the genes encoding blue, green, and red pigments. *Science* 1986;232:193-202.

234. Nathans J, Davenport CM, Maumenee IH, et al. Molecular genetics of human blue cone monochromacy. *Science* 1989;245: 831-838.

235. Weitz CJ, Miyake Y, Shinzato K, et al. Human tritanopia associated with two amino acid substitutions in the blue-sensitive opsin. *Am J Hum Genet* 1992;50:498-507.

236. Weitz CJ, Went LN, Nathans J. Human tritanopia associated with a third amino acid substitution in the blue-sensitive visual pigment. *Am J Hum Genet* 1992;51:444-446.

237. Arbour NC, Zlotogora J, Knowlton RG, et al. Homozygosity mapping of achromatopsia to chromosome 2 using DNA pooling. *Hum Mol Genet* 1997;6:689-694.

238. Wissinger B, Jagle H, Kohl S, et al. Human rod monochromacy: linkage analysis and mapping of a cone photoreceptor expressed candidate gene on chromosome 2q11. *Genomics* 1998;51: 325-331.

239. Kohl S, Marx T, Giddings I, et al. Total colourblindness is caused by mutations in the gene encoding the a-subunit of the cone photoreceptor cGMP-gated cation channel. *Nat Genet* 1998;19: 257-259.

240. Kohl S, Baumann B, Broghammer M, et al. Mutations in the *CNGB3* gene encoding the ß-subunit of the cone photoreceptor cGMP-gated channel are responsible for achromatopsia (ACHM3) linked to chromosome 8q21. *Hum Mol Genet* 2000; 9:2107-2116.

241. Aligianis IA, Forshew T, Johnson S, et al. Mapping of a novel locus for achromatopsia (ACHM4) to 1p and identification of a germline mutation in the a-subunit of cone transducin (GNAT2). *J Med Genet* 2002;39:656-660.

242. Condon GP, Brownstein S, Wang NS, et al. Congenital hereditary (juvenile X-linked) retinoschisis. Histopathologic and ultrastructural findings in three eyes. *Arch Ophthalmol* 1986;104:576-583.

243. Lewis RA, Lee GB, Martonyi CL, et al. Familial foveal retinoschisis. *Arch Ophthalmol* 1977;95:1190-1196.

244. Criswick VG, Schepens CL. Familial exudative vitreoretinopathy. *Am J Ophthalmol* 1969;68:578-594.

245. Gow J, Oliver GL. Familial exudative vitreoretinopathy: an expanded view. *Arch Ophthalmol* 1971;86:150-155.

246. Clement F, Beckford CA, Corral A, et al. X-linked familial exudative vitreoretinopathy. *Retina* 1995;15:141-145.

247. Fullwood P, Jones J, Bundey S, et al. X-linked exudative vitreoretinopathy: clinical features and genetic linkage analysis. *Br J Ophthalmol* 1993;77:168-170.

248. Robitaille J, MacDonald MEL, Kaykas A, et al. Mutant frizzled-4 disrupts retinal angiogenesis in familial exudative vitreoretinopathy. *Nat Genet* 2002;32:326-330.

249. Stone EM, Kimura AE, Folk JC, et al. Genetic linkage of autosomal dominant neovascular inflammatory vitreoretinopathy to chromosome 11q13. *Hum Mol Genet* 1992;1:685-689.

250. Bleeker-Wagemakers LM, Friedrich U, Gal A, et al. Close linkage between Norrie disease, a cloned DNA sequence from the proximal short arm, and the centromere of the X chromosome. *Hum Genet* 1985;71:211-214.

251. Bleeker-Wagemakers EM, Zweije-Hofman I, Gal A. Norrie disease as part of a complex syndrome explained by a submicroscopic deletion of the X chromosome. *Ophthalmic Paediatr Genet* 1988; 9:137-142.

252. Gal A, Stolzenberger C, Wienker T, et al. Norrie's disease: close linkage with genetic markers from the proximal short arm of the X chromosome. *Clin*

Genet 1985;27:282-283.

253. Kivlin JD, Sanborn GE, Wright E, et al. Further linkage data on Norrie disease. *Am J Med Genet* 1987;26:733-736.

254. Ngo JT, Spence MA, Cortessis V, et al. Recombinational event between Norrie disease and DXS7 loci. *Clin Genet* 1988;34: 43-47.

255. Ngo J, Spence MA, Cortessis V, et al. Duplicate report crossing over in Norrie disease family. *Am J Med Genet* 1989;33:286.

256. Ngo JT, Bateman JB, Cortessis V, et al. Norrie disease: linkage analysis using a 4.2-kb RFLP detected by a human ornithine aminotransferase cDNA probe. *Genomics* 1989;4:539-545.

257. Ngo JT, Bateman JB, Spence MA, et al. Ornithine aminotransferase (OAT): recombination between an X-linked OAT sequence (7.5 kb) and the Norrie disease locus. *Genomics* 1990;6:123-128.

258. Sims KB, Ozelius L, Corey T, et al. Norrie disease gene is distinct from the monoamine oxidase genes. *Am J Hum Genet* 1989;45: 424-434.

259. Berger W, Meindl A, van de Pol TJ, et al. Isolation of a candidate gene for Norrie disease by positional cloning. *Nat Genet* 1992; 1:199-203.

260. Chen ZY, Hendriks RW, Jobling MD, et al. Isolation and characterization of a candidate gene for Norrie disease. *Nat Genet* 1992; 1:204-208.

261. Heckenlively JR. The hereditary retinal and choroidal degenerations. In: Rimoin D, Emery A, eds. *Principles and practice of medical genetics.* Edinburgh: Churchill Livingstone, 1983.

262. Kumar-Singh R, Wang H, Humphries P, et al. Autosomal dominant retinitis pigmentosa: no evidence for nonallelic heterogeneity on 3q. *Am J Hum Genet* 1993;52:319-326.

263. Shastry BS. Retinitis pigmentosa and related disorders: phenotypes of rhodopsin and peripherin/RDS mutations. *Am J Med Genet* 1994;52:467-474.

264. Bascom RA, Heckenlively JR, Stone EM, et al. Mutation analyses of the ROM1 gene in retinitis pigmentosa. *Hum Mol Genet* 1995; 4:1895-1902.

265. Inglehearn CE, Keen TJ, Al-Maghtheh M, et al. Further refinement of the location for autosomal dominant retinitis pigmentosa on chromosome 7p (RP9). *Am J Hum Genet* 1994;54:675-680.

266. Jordan SA, Farrar GJ, Kenna P, et al.: Localization of an autosomal dominant retinitis pigmentosa gene to chromosome 4q. *Nat Genet* 1993;4:54-58.

267. Blanton SH, Heckenlively JR, Conttingham RW, et al. Linkage mapping of autosomal dominant retinitis pigmentosa (RP1) to the pericentric region of human chromosome 8. *Genomics* 1993; 15:376-386.

268. Sadler LA, Gannon AM, Blanton SH, et al. Linkage and physical mapping of the chromosome 8 form of autosomal dominant retinitis pigmentosa (RP1). *Cytogenet Cell Genet* 1993;64:144.

269. Greenberg J, Goliath R, Beighton P, et al. A new locus for autosomal dominant retinitis pigmentosa on chromosome 17p. *Hum Mol Genet* 1995;3.962-965.

270. Kojis TL, Heinzmann C, Flodman P, et al. Map refinement of locus RP13 to human chromosome 17p13.3 in a second family with autosomal dominant retinitis pigmentosa. *Am J Hum Genet* 1996;58:347-355.

271. Bardien S, Ebenezer N, Greenberg J, et al. An eighth locus for autosomal dominant retinitis pigmentosa is linked to chromosome 17q. *Hum Mol Genet* 1995;4:1459-1462.

272. Al-Maghtheh M, Inglehearn CF, Keen J, et al. Identification of a sixth locus for autosomal dominant retinitis pigmentosa on chromosome 19. *Hum Mol Genet* 1994;3:351-354.

273. Kajiwara K, Sandberg MA, Berson EL, et al. A null mutation in the human peripherin/RDS gene in a family with autosomal dominant retinitis punctata albescens. *Nat Genet* 1993;3: 208-212.

274. Van Soest S, Vandenborn LI, Gal A, et al. Assignment of a gene for autosomal recessive retinitis pigmentosa (RP12) to chromosome 1q31-q32.1 in an inbred and genetically heterogeneous disease population. *Genomics* 1994;22:499-504.

275. Weleber RG, Carr RE, Murphey WH, et al. Phenotypic variation including retinitis pigmentosa, pattern dystrophy, and fundus flavimaculatus in a single family with a deletion of codon 153 or 154 of the peripherin/RDS gene. *Arch Ophthalmol* 1993;111: 1531-1542.

276. Goldberg AFX, Molday RS. Defective subunit assembly underlies a digenic form of retinitis pigmentosa linked to mutations in peripherin/rds and rom-1. *Proc Natl Acad Sci USA* 1996;93: 3726-3730.

277. Kajiwara K, Berson EL, Dryja TP. Digenic retinitis pigmentosa due to mutations at the unlinked peripherin/RDS and ROMI loci. *Science* 1994;26:1604-1608.

278. Kumaramanickavel G, Maw M, Denton MJ, et al. Missense rhodopsin mutation in a family with recessive RP. *Nat Genet* 1994; 8:10-11.

279. Rosenfeld PJ, Cowley GS, McGee TL, et al. A null mutation I the rhodopsin gene causes rod photoreceptor dysfunction and autosomal recessive retinitis pigmentosa. *Nat Genet* 1992;1: 209-213.

280. Huang SH, Pittler SJ, Huang XH, et al. Autosomal recessive retinitis pigmentosa caused by mutations in the alpha subunit of rod cGMP phosphodiesterase. *Nat Genet* 1995;11:468-471.

281. McLaughlin ME, Sandberg MA, Berson EL, et al. Recessive mutations in the gene encoding the beta-subunit of rod phosphodiesterase in patients with retinitis pigmentosa. *Nat Genet* 1994;4: 130-134.

282. McLaughlin ME, Ehrhart TL, Berson EL, et al. Mutation spectrum of the gene encoding the beta subunit of rod phosphodiesterase among patients with autosomal recessive retinitis pigmentosa. *Proc Natl Acad Sci USA* 1995;92:3249-3253.

283. Dryja TP, Finn JT, Peng YW, et al. Mutations in the gene encoding the alpha subunit of the rod cGMP-gated channel in autosomal recessive retinitis pigmentosa. *Proc Natl Acad Sci USA* 1995;92: 10177-10181.

284. Martinez-Mir A, Bayes M, Vilageliu L, et al. A new locus for autosomal recessive retinitis pigmentosa (RP19) maps to 1p13-1p21. *Genomics* 1997;40:142-146.

285. Leutelt J, Oehlmann R, Younus E, et al. Autosomal recessive retinitis pigmentosa locus maps on chromosome lq in a large consanguineous family from Pakistan. *Clin Genet* 1995;47: 122-124.

286. Knowles JA, Shugart Y, Banerjee P, et al. Identification of a locus, distinct from RDS-peripherin, for autosomal recessive retinitis pigmentosa on chromosome 6p. *Hum Mol Genet* 1994;3: 1401-1403.

287. Shugart YY, Banerjee P, Knowles JA, et al. Fine genetic mapping of a gene for autosomal recessive retinitis pigmentosa on chromosome 6p21. *Am J Hum Genet* 1995;57:499-502.

288. Thiselton DL, Hampson RM, Nayudu M, et al. Mapping the RP2 locus for X-linked retinitis pigmentosa on proximal Xp: a genetically defined 5-cM critical region and exclusion of candidate genes by physical mapping. *Genome Res* 1996;6:1093-1102.

289. Meindl A, Dry K, Herrmann K, et al. A gene (*RPGR*) with homology to the RCC1 guanine nucleotide exchange factor is mutated in X-linked retinitis pigmentosa (RP3). *Nat Genet* 1996;13: 35-42.

290. Roepman R, van Dujnhoven G, Rosenberg T, et al. Positional cloning of the gene for X-linked retinitis pigmentosa 3: homology with the guanine-nucleotide exchange factor RCC1. *Hum Mol Genet* 1996;5:1043-1046.

291. Nakazawa M, Kikawa E, Chida Y, et al. Asn244His mutation of the peripherin/RDS gene causing autosomal dominant cone-rod degeneration. *Hum Mol Genet* 1994;3:1195-1196.

292. Nazawa M, Naoi N, Wada Y, et al. Autosomal dominant cone-rod dystrophy associated with a Val200Glu mutation of the peripherin/RDS gene. *Retina* 1996;16:405-410.

293. Wells J, Wroblewski J, Keen J, et al. Mutations in the human retinal degeneration slow (*RDS*) gene can cause either retinitis pigmentosa or macular dystrophy. *Nat Genet* 1993;3:213-218.

294. Small KW, Weber JL, Roses AD, et al. North Carolina macular dystrophy is assigned to chromosome 6. *Genomics* 1992;13: 681-685.

295. Small KW, Weber JL, Roses AD, et al. North Carolina macular dystrophy (MCDR1): a review and refined mapping to 6q14-q16.2. *Ophthalmic Paediatr Genet* 1993;14:143-150.

296. Milosevic J, Kalicamin P. Long arm deletion of chromosome 6 in a mentally retarded boy with multiple physical malformations. *J Ment Def Res* 1975;129:139-144.

297. Balciuniene J, Johansson K, Sandgren O, et al. A gene for autosomal dominant progressive cone dystrophy (CORDS) maps to chromosome 17p12-p13. *Genomics* 1995;30:281-286.

298. Kelsell RE, Evans K, Gregory CY, et al.: Localisation of a gene for dominant cone-rod dystrophy (CORD6) to chromosome 17p. *Hum Mol Genet* 1997;6:597-600.

299. Kylstra JA, Aylsworth AS. Cone-rod retinal dystrophy in a patient with neurofibromatosis type 1. *Can J Ophthalmol* 1993;28: 79-80.

300. Warburg M, Sjo O, Tranebjaerg L, et al. Deletion mapping of a retinal cone-rod dystrophy. Assignment to 18q-211. *Am J Med Genet* 1991;39:288-293.

301. Evans K, Fryer A, Inglehearn C, et al. Genetic linkage of cone-rod retinal dystrophy to chromosome 19q and evidence for segregation distortion. *Nat Genet* 1994;6:210-213.

302. Bartley J, Gies D, Jacobson D. Cone dystrophy (X-linked) (COD1) maps between DXS7 (11.28) and DXS206 (Xj1.1) and is linked to DXS84 (754). *Cytogenet Cell Genet* 1989;51:959.

303. Hong H-K, Ferrell RE, Gorin MB. Clinical diversity and chromosomal localization of X-linked cone dystrophy (COD1). *Am J Hum Genet* 1994;55:1173-1181.

304. McGuire RE, Sullivan LS, Blanton SH, et al. X-linked dominant cone-rod degeneration: linkage mapping of a new locus for retinitis pigmentosa (RP15) to Xp22.13-p22.11. *Am J Hum Genet* 1995;57:87-94.

305. Felbor U, Suvanto EA, Forsius HR, et al. Autosomal recessive Sorsby fundus dystrophy revisited: molecular evidence for dominant inheritance. *Am J Hum Genet* 1997;60:57-62.

306. Weber BH, Vogt G, Pruett RC, Stohr H, Felbor U. Mutations in the tissue inhibitor of metalloproteinases-3 (TIMP3) in patients with Sorsby's fundus dystrophy. *Nat Genet* 1994;8:352-356.

307. Zhang K, Kniazeva M, Han M, et al. A 5-bp deletion in ELOVL4 is associated with two related forms of autosomal dominant macular dystrophy. *Nat Genet* 2001;27:89-93.

308. Stone EM, Nichols BE, Kimura AE, et al. Clinical features of a Stargardt-like dominant progressive macular dystrophy with genetic linkage to chromosome 6q. *Arch Ophthalmol* 1994;112: 765-772.

309. Kaplan J, Gerber S, Larget-Piet D, et al. A gene for Stargardt's disease (fundus flavimaculatus) maps to the short arm of chromosome 1. *Nat Genet* 1993;5:308-311.

310. Allikmets R, Singh N, Sun H, et al. A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. *Nat Genet* 1997;15:236-246.

311. Forsman K, Graff C, Nordstrom S, et al. The gene for Best's macular dystrophy is located at 11q13 in a Swedish family. *Clin Genet* 1992;42:156-159.

312. Stone EM, Nichols BE, Streb LM, et al. Genetic linkage of vitelliform macular degeneration (Best's disease) to chromosome 11q13. *Nat Genet* 1992;1:246-250.

313. Petrukhin K, Koisti MJ, Bakall B, et al. Identification of the gene responsible for Best macular dystrophy. *Nat Genet* 1998;19: 241-247.

314. Sun H, Tsunenari T, Yau KW, et al. The vitelliform macular dystrophy protein defines a new family of chloride channels. *Proc Natl Acad Sci USA* 2002;99:4008-4013.

315. Barrett DJ, Bateman JB, Sparkes RS, et al. Chromosomal localization of human ornithine aminotransferase gene sequences to 10q26 and Xpll.2. *Invest Ophthalmol* 1987;28:1037-1042.

316. Kato M, Aonuma H, Kawamra H, et al. Possible pathogenesis of congenital stationary night blindness. *Jpn J Ophthalmol* 1987;31: 88-101.

317. Rao VR, Cohen GB, Oprain DD. Rhodopsin mutation G90D and a molecular mechanism for congenital night blindness. *Nature* 1994;367:639-642.

318. Dryja TP, McGee TL, Reichel E, et al. A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. *Nature* 1990;343:364-366.

319. Dryja TP, Berson EL, Rao VR, et al. Heterozygous missense mutation in the rhodopsin gene as a cause of congenital stationary night blindness. *Nat Genet* 1993;4:280-283.

320. Gal A, Orth U, Baehr W, et al. Heterozygous missense mutation in the rod cGMP phosphodiesterase beta-subunit gene in autosomal dominant stationary night blindness. *Nat Genet* 1994;7: 64-68.

321. Aldred MA, Dry KL, Sharp DM, et al. Linkage analysis in X-linked congenital stationary night blindness. *Genomics* 1992;14: 99-104.

322. Bech-Hansen NT, Moore BJ, Pearce WG. Mapping of locus for X-linked congenital stationary night blindness (CSNB1) proximal to DXS7. *Genomics* 1992;12:409-411.

323. Bech-Hansen NT, Pearce WG. Manifestations of X-linked congenital stationary night blindness in three daughters of an affected male: demonstration of homozygosity. *Am J Hum Genet* 1993;52:71-77.

324. Bergen AAB, Brink JB, Riemslag F, et al. Localisation of a novel X-linked congenital stationary night blindness locus: close linkage to the RP3 type

retinitis pigmentosa gene region. *Hum Mol Genet* 1995;4:931-935.

325. Glass IA, Good P, Coleman MP, et al. Genetic mapping of a cone and rod dysfunction (AIED) to the proximal short arm of the human X chromosome. *J Med Genet* 1993;30:1044-1050.

326. Schwartz M, Rosenberg T. Aland island eye disease: linkage data. *Genomics* 1991;10:327-332.

327. Yamamoto S, Sippel KC, Berson EL, et al. Defects in the rhodopsin kinase gene in the Oguchi form of stationary night blindness. *Nat Genet* 1997;15:175-178.

328. Hackenbruch Y, Meerhoff E, Besio R, et al. Familial bilateral optic nerve hypoplasia. *Am J Ophthal* 1975;79:314-320.

329. Azuma N, Yamaguchi Y, Handa H, et al. Mutations of the PAX6 gene detected in patients with a variety of optic-nerve malformations. *Am J Hum Genet* 2003;72:1565-1570.

330. Savell J, Cook JR. Optic nerve colobomas of autosomal-dominant heredity. *Arch Ophthalmol* 1976;94:395-400.

331. Schimmenti LA, Pierpont ME, Carpenter BLM, et al. Autosomal dominant optic nerve colobomas, vesicoureteral reflux, and renal anomalies. *Am J Med Genet* 1995;59:204-208.

332. Narahara K, Baker E, Ito S, et al. Localisation of a 10q breakpoint within the PAX2 gene in a patient with a de novo t(10;13) translocation and optic nerve coloboma-renal disease. *J Med Genet* 1997;34: 213-216.

333. Amiel J, Audollent S, Joly D, et al. PAX2 mutations in renalcoloboma syndrome: mutational hotspot and germline mosaicism. *Eur J Hum Genet* 2000;8:820-826.

334. Stefko ST, Campochiaro P, Wang P, et al. Dominant inheritance of optic pits. *Am J Ophthalmol* 1997;124:112-113.

335. Kjer P. Infantile optic atrophy with dominant mode of inheritance: a clinical and genetic study of 19 Danish families. *Acta Ophthalmol* 1959;164(Suppl 54):1-147.

336. Brown J Jr, Fingert JH, Taylor CM, et al. Clinical and genetic analysis of a family affected with dominant optic atrophy (OPAl). *Arch Ophthalmol* 1997;115:95-99.

337. Eiberg H, Maoller HU, Berendt II, et al. Assignment of granular corneal dystrophy Groenouw type I (CDGG1) to chromosome 5q. *Eur J Hum Genet* 1994;2:132-138.

338. Alexander C, Votruba M, Pesch UEA, et al. OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28. *Nat Genet* 2000;26: 211-215.

339. Delettre C, Lenaers G, Griffoin J-M, et al. Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy. *Nat Genet* 2000;26:207-210.

340. Hardy C, Khanim F, Torres R, et al. Clinical and molecular genetic analysis of 19 Wolfram syndrome kindreds demonstrating a wide spectrum of mutations in WFS1. *Am J Hum Genet* 1999; 65:1279-1290.

341. Rogers JA. Leber's disease. *Aust J Ophthalmol* 1977;5:111-119.

342. Brown MD, Wallace DC. Spectrum of mitochondrial DNA mutations in Leber's hereditary optic neuropathy. *Clin Neurosci* 1994; 2:138-145.

343. Howell N. Primary LHON mutations: trying to separate “fruyt” from “chaf.” *Clin Neurosci* 1994;2:130-137.

344. Howell N, Bindoff LA, McCullough DA, et al. Leber hereditary optic neuropathy: identification of the same mitochondrial ND1 mutation in six pedigrees. *Am J Hum Genet* 1991;49:939-950.

345. Huoponen K, Vilkki J, Aula P, et al. A new mtDNA mutation associated with Leber hereditary optic neuroretinopathy. *Am J Hum Genet* 1991;48:1147-1153.

346. Johns DR, Neufeld MJ, Park RD. An ND-6 mitochondrial DNA mutation associated with Leber hereditary optic neuropathy. *Biochem Biophys Res Commun* 1992;187:1551-1557.

347. Johns DR, Heher KL, Miller NR, et al. Leber's hereditary optic neuropathy: clinical manifestations of the 14484 mutation. *Arch Ophthalmol* 1993;111:495-498.

348. Mackey D, Howell N. A variant of Leber hereditary optic neuropathy characterized by recovery of vision and by an unusual mitochondrial genetic etiology. *Am J Hum Genet* 1992;51: 1218-1228.

349. Singh G, Lott MT, Wallace DC. A mitochondrial DNA mutation as a cause of Leber's hereditary optic neuropathy. *N Engl J Mea* 1989;320:1300-1305.

350. Vilkki J, Savontaus ML, Kalimo H, et al. Mitochondrial DNA polymorphism in Finnish families with Leber's hereditary optic neuroretinopathy. *Hum Genet* 1989;82:208-212.

351. Brown MD, Voljavec AS, Lott MT, et al. Mitochondrial DNA complex I and III mutations associated with Leper's hereditary optic neuropathy. *Genetics* 1992;130:163-173.

352. Johns DR, Berman J. Alternative, simultaneous complex I mitochondrial DNA mutations in Leber's hereditary optic neuropathy. *Biochem Biophys Res Commun* 1991;174:1324-1330.

353. Johns DR, Smith KH, Savino PJ, et al. Leber's hereditary optic neuropathy: clinical manifestations of the 15257 mutation. *Ophthalmology* 1993;100:981-986.

354. Kellar-Wood H, Robertson N, Govan GG, et al. Leber's hereditary optic neuropathy mitochondrial DNA mutations in multiple sclerosis. *Ann Neuro* 1994;36:109-112.

355. Oostra RJ, Bolhuis PA, Wijburg FA, et al. Leber's hereditary optic neuropathy: correlations between mitochondrial genotype and visual outcome. *J Med Genet* 1994;31:280-286.

356. Oostra RJ, Bolhuis PA, Zorn-Ende G, et al. Leber's hereditary optic neuropathy: no significant evidence for primary or secondary pathogenicity of the 15257 mutation. *Hum Genet* 1994;94: 265-270.

357. Chen JD, Cox I, Denton MJ. Preliminary exclusion of an X-linked gene in Leber optic atrophy by linkage analysis. *Hum Genet* 1989; 82:203-207.

358. Harding AE, Sweeney MG, Govan GG, et alP. Pedigree analysis in Leber hereditary optic neuropathy families with a pathogenic mtDNA mutation. *Am J Hum Genet* 1995;57:77-86.

359. Ford CE, Jones KW, Polani PE, et al. A sex-chromosome anomaly in a case of gonadal dysgenesis (Turner's syndrome). *Lancet* 1959;1:711-713.

360. Jacobs, PA, Strong JA. A case of human intersexuality having a possible XXY sex-determining mechanism. *Nature* 1959;183: 302-303.

361. Lejeune J, Gautier M, Turpin R. [Human chromosomes in tissue cultures.] *C R Hebd Seances Acad Sci* 1959;248:602-603.

362. Patau K, Smith DW, Therman E, et al. Multiple congenital anomaly caused by an extra autosome. *Lancet* 1960;1:790-793.

363. Edwards JH, Harnden DG, Cameron AH, et al. A new trisomic syndrome. *Lancet* 1960;1:787-790.

364. Ginsberg J, Perrin EV, Sueoka WT. Ocular manifestations of trisomy 18. *Am J Ophthalmol* 1968;66:59-67.

365. Rodrigues MM, Punnett HH, Valdes-Dapena M, et al. Retinal pigment epithelium in a case of trisomy 18. *Am J Ophthalmol* 1973;76:265-268.

366. Green WR. Personal communication, 1970.

367. Down JLH. Observations on an ethnic classification of idiots. *Clin Lect Rep Lond Hosp* 1866;3:259-262.

368. Reiss JA, Lovrien EW, Hecht F. A mother with Down's syndrome and her chromosomally normal infant. *Ann Genet* 1971;14: 225-227.

369. Schachenmann G, Schmid W, Fraccaro M, et al. Chromosomes in coloboma and anal atresia. *Lancet* 1965;19:290.

370. McDermid HE, Duncan AM, Brasch KR, et al. Characterization of the supernumerary chromosome in cat eye syndrome. *Science* 1986;232:646-648.

371. Wolf U, Reinwein H, Porsch R, et al. [Deficiency on the short arms of a chromosome No. 4] *Humangenetik* 1965;1:397-413.

372. Lejeune J, Lafourcade J, Berger R, et al. [3 cases of partial deletion of the short arm of a 5 chromosome.] *C R Hebd Seances Acad Sci* 1963;257:3098-3102.

373. Junien C, Turleau C, de Grouchy J, et al. Regional assignment of catalase (CAT) gene to band 11p13. Association with the aniridia-Wilms'tumor-gonadoblastoma (WAGR) complex. *Ann Genet* 1980;23:165-168.

374. Strong LC, Riccardi VM, Ferrell RE, et al. Familial retinoblastoma and chromosome 13 deletion transmitted via an insertional translocation. *Science* 1981;213:1501-1503.

375. Yanoff M, Rorke LB, Niederer BS. Ocular and cerebral abnormalities in chromosome 18 deletion defect. *Am J Ophthalmol* 1970; 70:391-402.

376. Gorlin RJ, Yunis J, Anderson VE. Short arm deletion of chromosome 18 in cebocephaly. *Am J Dis Child* 1968;115:473-476.

377. De Grouchy J, Royer P, Salmon C, et al. Partial deletion of the long arms of the chromosome 18. *Pathol Biol (Paris)* 1964;12: 579-582.

378. Turner HH. A syndrome of infantilism, congenital webbed neck, and cubitus valgus. *Endocrinology* 1938;23:566-574.

379. Decourt L, Sasso WS, Chiorboli E, et al. [Genetic sex in Turner's syndrome patients.] *Rev Assoc Med Bras* 1954;1:203-206.

380. Polani PE, Hunter WF, Lennox B. Chromosomal sex in Turner's syndrome with coarctation of the aorta. *Lancet* 1954;2:120-121.

381. Wilkins L, Grumbach MM, van Wyk JJ. Chromosomal sex in ovarian agenesis. *J Clin Endocrinol Metab* 1954;14:1270-1271.

382. Chrousos GA, Ross JL, Chrousos G, et al. Ocular findings in Turner syndrome. A prospective study. *Ophthalmology* 1984;91: 926-928.

383. Klinefelter HF Jr, Reifenstein EC Jr, Albright F. Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism, and increased secretion of follicle-stimulating hormone. *J Clin Endocrinol Metab* 1942;2:615-624.

384. Barr ML, Plunkett ER. Testicular dysgenesis affecting the seminiferous tubules principally, with chromatin-positive nuclei. *Lancet* 1956;271:853-856.

385. Knowlton RG, Weaver EJ, Struyk AF, et al. Genetic linkage analysis of hereditary arthro-ophthalmopathy (Stickler syndrome) and the type II procollagen gene. *Am J Hum Genet* 1989;45: 681-688.

386. Richards AJ, Yates JRW, Williams R, et al. A family with Stickler syndrome type 2 has a mutation in the COL11A1 gene resulting in the substitution of glycine 97 by valine in alpha-1(XI) collagen. *Hum Mol Genet* 1996;5:1339-1343.

387. Nijbroek G, Sood S, McIntosh I, et al. Fifteen novel FBN1 mutations causing Marfan syndrome detected by heteroduplex analysis of genomic amplicons. *Am J Hum Genet* 1995; 57:8-21.

388. Sertie AL, Sossi V, Camargo AA, et al. Collagen XVIII, containing an endogenous inhibitor of angiogenesis and tumor growth, plays a critical role in the maintenance of retinal structure and in neural tube closure (Knobloch syndrome). *Hum Mol Genet* 2000;9:2051-2058.

389. Goldschmidt E. On the etiology of myopia: an epidemiological study. *Acta Ophthalmol Suppl* 1968;98:1-172.

390. Teikari JM, O'Donnell J, Kaprio J, et al. Impact of heredity in myopia. *Hum Hered* 1991;41:151-156.

391. Ashton GC. Segregation analysis of ocular refraction and myopia. *Hum Hered* 1985;35:232-239.

392. Goss DA, Hampton MJ, Wickham MG. Selected review on genetic factors in myopia. *J Am Optom Assoc* 1988;59:875-884.

393. Naiglin L, Clayton J, Gazagne C, et al. Familial high myopia: evidence of an autosomal dominant mode of inheritance and genetic heterogeneity. *Ann Genet* 1999;42:140-146.

394. Guggenheim JA, Kirov G, Hodson SA. The heritability of high myopia: A re-analysis of Goldschmidt's data. *J Med Genet* 2000; 27:227-231.

395. Teikari JM, Kaprio J, Koskenvuo M, et al. Heritability of defects of far vision in young adults—a twin study. *Scand J Soc Med* 1992;20:73-78.

396. Sorsby A, Sheriden M, Leary GA. Refraction and its components in twins. *Medical Research Council Special Report*. HMSO London. Series 303, 1962.

397. Lyhne N, Sjolie AK, Kyvik KO, et al. The importance of genes and environment for ocular refraction and its determiners: a population based study among 20-45 year old twins. *Br J Ophthalmol* 2001;85:1470-1476.

398. Hammond CJ, Snieder H, Gilbert CE, et al. Genes and environment in refractive error. The twin eye study. *Invest Ophthalmol Vis Sci* 2001;42:1232-1236.

399. Goss DA, Jackson TW. Clinical findings before the onset of myopia in youth: parental history of myopia. *Optom Vis Sci* 1996; 73:279-282.

400. Gwiazda J, Thorn F, Bauer J, et al. Emmetropization and the progression of manifest refraction in children followed from infancy to puberty. *Clin Vis Sci* 1993;8:337-344.

401. Zadnik K, Satariano WA, Mutti DO, et al. The effect of parental history of myopia on children's eye size. *JAMA* 1994;271: 1323-1327.

402. Zadnik K. The Glenn A. Fry Award Lecture (1995). Myopia development in childhood. *Optom Vis Sci* 1997;74:603-608.

403. Pacella R, McLellan J, Grice K, et al. Role of genetic factors in the etiology of juvenile-onset myopia based on a longitudinal study of refractive error. *Optom Vis Sci* 1999;76:381-386.

404. Wallman J: Parental history and myopia: taking the long view. *JAMA* 1994;272:1255-1256.

405. Wallman J, Turkel JI, Trachtman J. Extreme myopia produced by modest change in visual experience. *Science* 1978;201: 1249-1251.

406. Weisel TN, Raviola E. Myopia and eye enlargement after neonatal lid fusion in monkeys. *Nature* 1977;266:66-68.

407. Sherman SM, Norton TT, Casagrande VA. Myopia in the lidsutured tree shrew (Tupaia glis). *Brain Res* 1977;124:154-157.

408. Hoyt CS, Stone RD, Fromer C, et al. Monocular axial myopia associated with neonatal eyelid closure in human infants. *Am J Ophthalmol* 1982;91:197-200.

409. Von Noorden GK, Lewis RA. Ocular axial length in unilateral congenital cataracts and blepharoptosis. *Invest Ophthalmol Vis Sci* 1987;28:750-752.

410. Twomey JM, Gilvarry A, Restori M, et al. Ocular enlargement following infantile corneal opacification. *Eye* 1990;4:497-503.

411. Lin LLK, Hung PT, Ko LS, et al. Study of myopia among aboriginal school children in Taiwan. *Acta Ophthalmol Suppl* 1988;185: 34-36.

412. Zylberman R, Landau D, Berson D. The influence of study habits on myopia in Jewish teenagers. *J Pediatr Ophthalmol Strabismus* 1993;30:319-322.

413. Young FA. Myopia and personality. *Am J Optom Physiol Opt* 1987; 64:136-143.

414. Young FA. Reading, measures of intelligence, and refractive errors. *Am J Optom Physiol Opt* 1963;40:257-264.

415. Rosner M, Belkin M. Intelligence, education, and myopia in males. *Arch Ophthalmol* 1987;105:1508-1511.

416. Schwartz M, Haim M, Skarsholm D. X-Linked myopia. Bornholm eye disease. *Clin Genet* 1990;38:281-286.

417. Young TL, Ronan SM, Alvear AB, et al. X-linked high myopia associated with cone dysfunction. *Arch Ophthalmol* 2004;122: 897-908.

418. Young TL, Ronan SM, Drahozal LA, et al. Evidence that a locus for familial high myopia maps to chromosome 18p. *Am J Hum Genet* 1998;63:109-119.

419. Young TL, Ronan SM, Alvear A, et al. A second locus for familial high myopia maps to chromosome 12q. *Am J Hum Genet* 1998; 63:1419-1424.

420. Lam DSC, Tam POS, Fan, DSP, et al. Familial high myopia linkage to chromosome 18p. *Ophthalmologica* 2003;217:115-118.

421. Heath SC, Robledo R, Beggs W, et al. A novel approach to search for identity by descent in small samples of patients and controls from the same Mendelian breeding unit: a pilot study on myopia. *Hum Hered* 2001;52:183-190.

422. Paluru P, Heon E, Devoto M, et al. A new locus for autosomal dominant high myopia maps to the long arm of chromosome 17. *Invest Ophthalmol Vis Sci* 2003;44:1830-1836.

423. Naiglin L, Gazagne Ch, Dallongeville F, et al. A genome wide scan for familial high myopia suggests a novel locus on chromosome 7q36. *J Med Genet* 2002;39:118-124.

424. Zhou G, Williams RW. Mouse models for the analysis of myopia: an analysis of variation in eye size of adult mice. *Optom Vis Sci* 1999;76:408-418.

425. Zhou G, Williams RW. Eye1 and Eye2: gene loci that modulate eye size, lens weight, and retinal area in the mouse. *Invest Ophthalmol Vis Sci* 1999;40:817-825.

426. Von Noorden, G. *Binocular vision and ocular motility: theory and management of strabismus*, 5th ed. St. Louis: Mosby Year Book.

427. Cross HE. The heritability of strabismus. *Am Orthopt J* 1975;25:11-17.

428. Spivey BE. Strabismus: factors in anticipating its occurrence. *Aust J Ophthalmol* 1980;8:5-9.

429. Chimonidou E, Palimeris G, Koliopoulos J, et al. Family distribution of concomitant squint in Greece. *Br J Ophthalmol* 1977;61: 27-29.

430. Simpson NE, Alleslev LJ. Association of children's diseases in families from record linkage data. *Can J Genet Cytol* 1972;15: 789-800.

431. Francois J. Affections of the ocular muscles. In: Francois J, ed. *Heredity in ophthalmology*. St. Louis: CV Mosby Co, 1961: 239-269.

432. Dufier JL, Briard ML, Bonaiti C, et al. Inheritance in the etiology of convergent squint. *Ophthalmologica* 1979;179:225-234.

433. Maumenee IH, Alston A, Mets MB, et al. Inheritance of congenital esotropia. *Trans Am Ophthalmol Soc* 1986;84:85-93.

434. Podgor MJ, Remaley NA, Chew E. Associations between siblings for esotropia and exotropia. *Arch Ophthalmol* 1996;114: 739-744.

435. Hu DN. Prevalence and mode of inheritance of major genetic eye diseases in China. *J Med Genet* 1987;24:584-588.

436. Richter S. [On the heredity of strabismus concomitans] *Humangenetik* 1967;3:235-243.

437. Waardenburg PJ. Squint and heredity. *Doc Ophthalmol Proc Ser* 1954;7:422-494.

438. Reynolds JD, Wackerhagen M. Strabismus in monozygotic and dizygotic twins. *Am Orthopt J* 1986;36:113.

439. De Vries B, Houtman WA. Squint in monozygotic twins. *Doc Ophthalmol* 1979;46:305-308.

440. Rubin W, Helm C, McCormack MK. Ocular motor anomalies in monozygotic and dizygotic twins. In: Reinecke R, ed. *Strabismus: proceedings of the 3rd meeting of the international strabismological association*, Asilomar, CA, 1978. New York: Grune & Stratton, 1978:89.

441. Niederecker O, Mash AJ, Spivey BE. Horizontal fusional amplitudes and versions. Comparison in parents of strabismic and nonstrabismic children. *Arch Ophthalmol* 1972;87:283-285.

442. Mash AJ, Hegmann JP, Spivey BE. Genetic analysis of vergence measures in populations with varying incidences of strabismus. *Am J Ophthalmol* 1975;79.978-984.

443. Mash AJ, Spivey BE. Genetic aspects of strabismus. *Doc Ophthalmol* 1973;34:285-291.

444. Parikh V, Shugart YY, Doheny KF, et al. A strabismus susceptibility locus on chromosome 7p. *Proc Natl Acad Sci USA* 2003;100: 12283-12288.

445. Bowen P. Achondroplasia in two sisters with normal parents. *Birth Defects Orig Artic Ser* 1974;10:31-36.

446. Myrianthopoulos NC, Aronson SM. Population dynamics of Tay-Sachs disease. II. What confers the selective advantage upon the Jewish heterozygote? In: *Proceedings of fourth international symposium on sphingolipidoses*. New York: Plenum Press, 1972:561.

447. Cross HE, Maumenee AE. Ocular trauma during amniocentesis. *Arch Ophthalmol* 1973;90:303-304.

448. Broome DL, Wilson MG, Weiss B, et al. Needle puncture of fetus: a complication of second-trimester amniocentesis. *Am J Obstet Gynecol* 1976;126:247-252.

449. Isenberg SJ, Heckenlively JR. Traumatized eye with retinal damage from amniocentesis. *J Pediatr Ophthalmol Strabismus* 1985; 22:65-67.

450. Karp LE, Hayden PW. Fetal puncture during midtrimester amniocentesis. *Obstet Gynecol* 1977;49:115-117.

451. Merin S, Beyth Y. Uniocular congenital blindness as a complication of midtrimester amniocentesis. *Am J Ophthalmol* 1980;89: 299-301.

452. Elej alde BR, de Elejalde MM, Hamilton PR, et al. Prenatal diagnosis of cyclopia. *Am J Med Genet* 1983;14:15-19.

453. Lev-Gur M, Maklad NF, Patel S. Ultrasonic findings in fetal cyclopia. A case report. *J Reprod Med* 1983;28:554-557.

454. Cogan DG. Congenital anomalies of the retina. *Birth Defects Orig Artic Ser* 1971;7:41-51.

455. Cogan DG, Kuwabara T. Ocular pathology of the 13-15 trisomy syndrome. *Arch Ophthalmol* 1964;72:246-253.

456. Mullaney J. Ocular pathology in trisomy 18 (Edwards' syndrome). *Am J Ophthalmol* 1973;76:246-254.

457. Wilson MG, Towner JW, Coffin GS, et al. Inherited pericentric inversion of chromosome no. 4. *Am J Hum Genet* 1970;22: 679-690.

458. Vogel W, Siebers JW, Reinwein H. Partial trisomy 7q. *Ann Genet* 1973;16:277-280.

459. Rethore MO, Larget-Piet L, Abonyi D, et al. [4 cases of trisomy for the short arm of chromosome 9. Individualization of a new morbid entity.] *Ann Genet* 1970;13:217-232.

460. Schwanitz G, Schamberger U, Rott HD, et al. Partial trisomy 9 in the case of familial translocation 8/9 mat. *Ann Genet* 1974; 17:163-166.

461. Hsu LYF, Kim HJ, Sujansky E, et al. Reciprocal translocation versus centric fusion between two no. 13 chromosomes. A case of 46,XX,-13, +t(13;13)(p12;q13) and a case of 46,XY,-13, +t(13; 13)(p12;p12). *Cytogenet Cell Genet* 1973;12:235-244.

462. Walknowska J, Peakman D, Weleber RG. Cytogenetic investigation of cat-eye syndrome. *Am J Ophthalmol* 1977;84:477-486.

463. Alvarado M, Bocian M, Walker AP. Interstitial deletion of the long arm of chromosome 3d: case report, review, and definition of a phenotype. *Am J Med Genet* 1987;27:781-786.

464. Carter R, Baker E, Hayman D. Congenital malformations associated with a ring 4 chromosome. *J Med Genet* 1969;6:224-227.

465. Taysi K, Burde RM, Rohrbaugh JR. Terminal long arm deletion of chromosome 7 and retino-choroidal coloboma. *Ann Genet* 1982;25:159-161.

466. Ferry AP, Marchevsky A, Strauss I. Ocular abnormalities in deletion of the long arm of chromosome 11. *Ann Ophthalmol* 1981; 13:1373-1377.

467. Bialasiewicz AA, Mayer UM, Meythaler FH. [Ophthalmologic findings in 11 q-deletion syndrome.] *Klin Monatsbl Augenheilk* 1987;190:524-526.

468. O'Grady RB, Rothstein TB, Romano PE. D-group deletion syndromes and retinoblastoma. *Am J Ophthalmol* 1974;77:40-45.

469. Saraux H, Rethore MO, Aussannaire M, et al. [Ocular abnormalities of phenotype DR (ring D chromosome).] *Ann Ocul (Paris)* 1970;203:737-748.

470. Schinzel A, Hayashi K, Schmid W. Structural aberrations of chromosome 18. II. The 18q- syndrome. Report of three cases. *Humangenetik* 1975;26:123-132.

471. Yanoff M, Rorke LB, Niederer BS. Ocular and cerebral abnormalities in chromosome 18 deletion defect. *Am J Ophthalmol* 1970; 70:391-402.

472. Yunis E, Silva R, Giraldo A. Trisomy 10p. *Ann Genet* 1976;19: 57-60.

473. Howard RO. Chromosomal abnormalities associated with cyclopia and synophthalmia. *Trans Am Ophthalmol Soc* 1977;75: 505-538.

474. Lang AF, Schlager FM, Gardner HA. Trisomy 18 and cyclopia. *Teratology* 1976;14:195-203.

475. Cohen MM, Storm DF, Capraro VJ. A ring chromosome (no. 18) in a cyclops. *Clin Genet* 1972;3:249-252.

476. Nitowsky HM, Sindhvananda N, Konigberg UR, et al. Partial 18 monosomy in the cyclops malformation. *Pediatrics* 1966;37: 260-269.

477. Faint S, Lewis EJW. Presumptive deletion of the short arm of chromosome 18 in a cyclops. *Hum Chromosome Newsl* 1964;14:5.

478. Gimelli G, Cuoco C, Lituania M, et al. Dup(3) (p2-pter) in two families, including one infant with cyclopia. *Am J Med Genet* 1985;20:341-348.

479. Hoepner J, Yanoff M. Ocular anomalies in trisomy 13-15: an analysis of 13 eyes with two new findings. *Am J Ophthalmol* 1972; 74:729-737.

480. Keith CG. The ocular manifestations of trisomy 13-15. *Trans Ophthalmol Soc UK* 1966;86:435-454.

481. Huggert A. The trisomy 18 syndrome. *Acta Ophthalmol (Copenh)* 1966;44:186.

482. Rodrigues MM, Valdes-Dapena M, Kistenmacher M. Ocular pathology in a case of 13 trisomy. *J Pediatr Ophthalmol* 1973;10: 54.

483. Ginsberg J, Ballard ET, Buchino JJ, et al. Further observations of ocular pathology in Down's syndrome. *J Pediatr Ophthalmol Strabismus* 1980;17:166-171.

484. Shapiro MB, France TD. The ocular features of Down's syndrome. *Am J Ophthalmol* 1985;99:659-663.

485. Caputo AR, Wagner RS, Reynolds DR, et al. Down syndrome. Clinical review of ocular features. *Clin Pediatr (Phila)* 1989;28: 355-358.

486. Gustavson KH, Finley SC, Finley WH, et al. A 4-5/21-22 chromosomal translocation associated with multiple congenital anomalies. *Acta Paediatr* 1964;53:172-181.

487. Monteleone P, Monteleone J, Sekhon G, et al. Partial trisomy 5 with a carrier parent t(5p-;9p+). *Clin Genet* 1976;9:437-440.

488. Rethore, MO Larget-Piet, L, Abonyi D, et al. [4 cases of trisomy for the short arm of chromosome 9. Individualization of a new morbid entity.] *Ann. Genet* 1970;13:217-232.

489. Rethore MO, Kaplan JC, Junien C, et al. [Increase of the LDHB activity in a boy with 12p trisomy by malsegregation of a maternal translocation t(12;14) (q12;p11).] *Ann Genet* 1975;18: 81-87.

490. Orye E, Verhaaren H, Samuel K, et al. A 46,XX,10q+ chromosome constitution in a girl. Partial long arm duplication or insertional translocation? *Humangenetik* 1975;28:1-8.

491. Yunis JJ, Sanchez O. A new syndrome resulting from partial trisomy for the distal third of the long arm of chromosome 10. *J Pediatr* 1974;84:567-570.

492. Falk RE, Carrel RE, Valente M, et al. Partial trisomy of chromosome 11: a case report. *Am J Ment Defic* 1973;77:383-388.

493. Raoul O, Rethore MO, Dutriliaux B, et al. [Partial 14q trisomy. I. Partial 14q trisomy by maternal translocation t(10;14) (p15.2; q22).] *Ann Genet* 1975;18:35-39.

494. Condron CJ, Cantwell RJ, Kaufman RL, et al. The supernumerary isochromosome 18 syndrome (+18pu). *Birth Defects Orig Artic Ser* 1974;10:36-42.

495. Zellweger H, Ionasescu V, Simpson J, et al. The problem of trisomy 22. A case report and a discussion of the variant forms. *Clin Pediatr (Phila)* 1976;15:601-606.

496. Breg WR, Steele MW, Miller OJ, et al. The cri du chat syndrome in adolescents and adults: clinical finding in 13 older patients with partial deletion of the short arm of chromosome no. 5(5p-). *J Pediatr* 1970;77:782-791.

497. Farrell JW, Morgan KS, Black S. Lensectomy in an infant with cri du chat syndrome and cataracts. *J Pediatr Ophthalmol Strabismus* 1988;25:131-134.

498. Broughton WL, Fine BS, Zimmerman LE. Congenital glaucoma associated with a chromosomal defect. A histologic study. *Arch Ophthalmol* 1981;99:481-486.

499. Lee ML, Sciorra LJ. Partial monosomy of the long arm of chromosome 11 in a severely affected child. *Ann Genet* 1981;24:51-53.

500. Allderdice PW, Davis JG, Miller OJ, et al. The 13q-deletion syndrome. *Am J Hum Genet* 1969;21:499.

501. Ledbetter DH, Riccardi VM, Airhart SD, et al. Deletions of chromosome 15 as a cause of the Prader-Willi syndrome. *N Engl J Med* 1981;304:325-329.

502. Ledbetter DH, Mascarello JT, Riccardi VM, et al. Chromosome 15 abnormalities and the Prader-Willis syndrome: a follow-up of 40 cases. *Am J Hum Genet* 1982;34:278-285.

503. Mattei JF, Mattei MG, Giraud F. Prader-Willi syndrome and chromosome 15. A clinical discussion of 20 cases. *Hum Genet* 1983; 64:356-362.

504. Schinzel A, Schmid W, Luscher U, et al. Structural aberrations of chromosome 18. I. The 18p-syndrome. *Arch Genet (Zur)* 1974; 47:1-15.

505. DiGeorge AM, Olmstead RW, Harley RD. Waardenburg's syndrome. A syndrome of heterochromia of the irides, lateral displacement of the medial canthi and lacrimal puncta, congenital deafness, and other characteristic associated defects. *J Pediatr* 1960;57:649-669.

506. Nelson WE, Vaughn VC, McKay RJ, eds. *Textbook of pediatrics*, 9th ed. Philadelphia: WB Saunders, 1969.

507. Kistenmacher ML, Punnett HH. Comparative behavior of ring chromosomes. *Am J Hum Genet* 1970;22:304-318.

508. Behrman RE, Vaughan VC III, Nelson WE, eds. *Nelson textbook of pediatrics*, 13th ed. Philadelphia: WB Saunders, 1987.

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2

Neonatal phthalmology: Ocular Development in Childhood

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Although the eye is one of the most fully developed sensory organs at birth, there are still profound growth and change in the composition of many of its structures. The visual system undergoes tremendous changes during the postnatal period and in the first few years of life. Rapid and fluid changes in the eye and brain allow the development of normal vision. Understanding this process is paramount to the appropriate care of children's eyes. This chapter focuses on the anatomic changes in the eye and orbit during infancy and through adolescence. Intraocularly, the anterior segment, retina, and optic nerve undergo rapid changes within the first year of life to allow the development of a clear refracted image on the retina. Neurologic development then allows the subsequent processing of the retinal image. Externally, the bony growth of the orbit and surrounding ocular structures are also influenced by the changes in the eye. The ophthalmologist caring for the pediatric patient must be aware of the normal developmental changes so as not to confuse them with pathologic states. In addition, disease states that interfere with development may require interventions during these critical periods to allow for normal growth of the eye and orbit. Premature infants present a special challenge to the ophthalmologist. The eye findings in premature infants that may be a part of embryonic development are consistent with the gestational age of infant. This has led to certain eye parameters being considered indicative of the gestational age of the neonate. This chapter will address the normal changes in the structures of the eye from findings in premature infants through to complete maturation of those structures, including the globe, anterior segment, pupil, retina, neurologic development, orbit, and refractive changes.

GLOBE DIMENSIONS

The weight of the term infant's eye varies between 2.3 and 3.4 grams (1,2,3). The volume of the globe varies between 2.20 cm^3 and 3.25 cm^3 (1,2). The axial length of the eye in term infants varies by the method of measurement. Ultrasonographic measurements tend to be shorter than measurements obtained through pathologic studies. Nevertheless, the average axial length is between 17.10 and 17.5 mm with the axial length being on average 0.2 mm longer in boys than girls (4). There is on average a 2.5- to 3.5mm increase in axial length in the first year of life (4,5), making the mean axial length 20.6 mm. The rate of increase then decreases in subsequent years, such that the mean axial length is 21.5 mm in the second year and 21.9 mm in the third year. The axial length reaches adult dimensions by approximately 5 years of age. There may be limited increases in the axial length between 5 and 15 years of age without the presence of a myopic refractive error, but the total increase is usually less than 1.0 mm (6,7). The gender differences seen in infancy are maintained throughout the growth period of the eye. The axial length remains longer in boys than girls throughout adolescence (5,8) (Table 2.1).

Measurements of axial length significantly influence intraocular lens selection in children undergoing cataract surgery. Expected estimates of growth have led some surgeons to piggyback intraocular lenses to allow more flexibility in adjusting to the changing refractive needs of the infant eye, whereas others prefer to use glasses or contact lenses in children less than 2 years of age (9). The selection of appropriate intraocular lens correction remains a controversial subject and may be dependent on the local resources available

(10). When amblyopia and glaucoma are controlled, there appear to be no significant differences in the growth of an aphakic globe, allowing for use of biometric data to estimate refractive needs in children undergoing cataract extraction (11).

TABLE 2.1 GLOBAL DIMENSIONS OF THE EYE

	Term Infants	Adults
Globe Diameter		
Sagittal (mm)	17.5	14.14
Axial (mm)	17.1	24.8
Volume (mL)	2.4	6.9
Weight (g)	3	7.5

Adapted from Goes F. Ocular biometry in childhood. *Bull Soc Belge Ophtalmol* 1982;202:159-193, with permission.

ANTERIOR SEGMENT

Cornea

The absolute dimensions in the term newborn eye are closer to the adult dimensions than nearly any other organ in the body. For example, the cornea undergoes

macroscopic and intracellular changes to allow transparency, as well as changes in refractive power postnatally, yet the corneal diameter undergoes only minimal growth. The cornea begins with sagittal and transverse diameters being equal with a shorter diameter vertically. In premature infants, the corneal diameter may be approximated at any gestational age because of its relationship to the child's weight in grams. It has been determined that the corneal diameter in mm equals 0.0014(weight in grams) plus 6.3 (12). At term, the average corneal diameter horizontally is 9.0 to 10.5 mm, with a mean of 9.8 mm (13,14). The vertical diameter may exceed the horizontal with a range of 9.9 to 10.5 mm. A macrocornea is defined as having a horizontal diameter greater than 2 standard deviations from the mean, or 11.0 mm in term infants. A microcornea has a diameter less than 9.0 mm (Fig. 2.1). This standard range of measurements may help identify children with corneal enlargement secondary to diseases such as infantile glaucoma.

The changes in corneal diameter are also accompanied by changes in corneal curvature. Since the cornea is instrumental in refraction, the changes in corneal radii of curvature influence the clarity of retinal images. To maintain emmetropia, changes in corneal curvature must be perfectly balanced with changes in the lens and axial length of the eye. The corneal curvature is much steeper in infants than in adults. This observation extends to premature infants as well. In premature infants with a mean gestational age of 36 weeks, the average keratometry of the cornea is 49.50 ± 1.82 diopters (D) (15). At term, the average keratometry is 47.00 ± 1.19 D. The corneal curvature continues to decrease rapidly in the first 2 to 4 weeks of life in term infants and then slows after 8 weeks of life. The average change from 2 weeks to 8 weeks is 4.41 D ± 2.00 D (15). At 12 weeks of age, the average keratometry is 44.05 ± 1.70 D, which is a change of only 0.5 ± 1.00 D from the 8-week measurement. Studies of the measurement of corneal curvature are complicated by differences in the method of measurement (16,17,18). Most studies, however, agree that there is a rapid decrease in corneal curvature in the first year of life. Keratometry values obtained for term infants range from 48.06 to 47.00 D. These corneal changes likely balance the rapid increase in axial length during the early postnatal period (19). The flattening of the cornea persists into the second and early third decades (20). The average keratometry at age 20 is 42.0 D. The horizontal meridian begins to steepen between the fourth and fifth decades of life and then continues to steepen with age. This results in a gradual change from with-the-rule astigmatism common in youth to against-the-rule astigmatism in 50- to 60-year-old individuals (20) (Table 2.2).

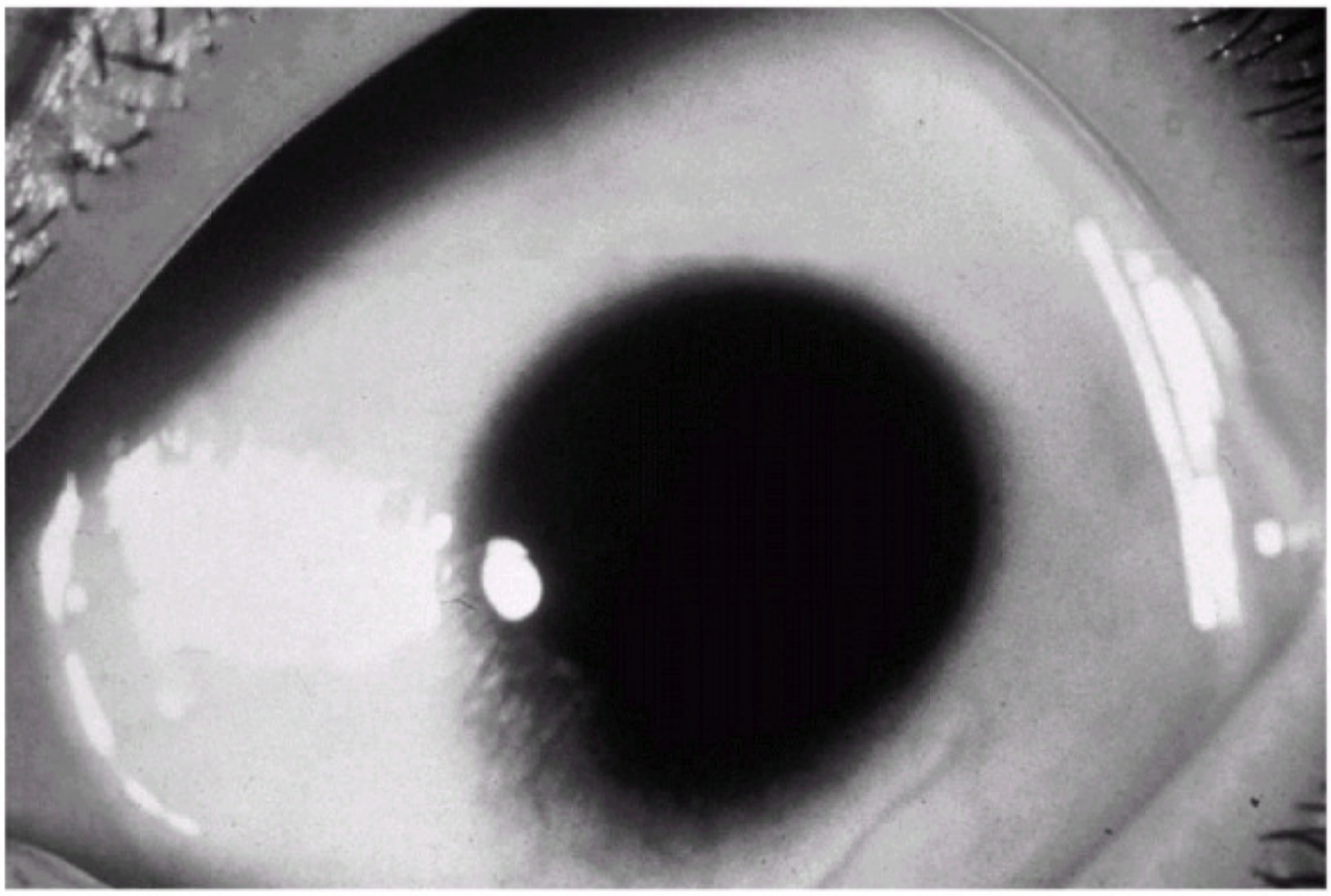

Figure 2.1 A microcornea in childhood has a diameter less than 2 standard deviations from the mean. In infants, a microcornea is less than 9.0 mm. Courtesy of Wills Eye Resident Collection.

Histologically the layers of the cornea develop to attain both the structure and function needed in mature corneas. The corneal epithelium thickens with successive cellular layers, and there is an increase in cell size within each layer. At 20 weeks' gestational age, the corneal epithelium has only two cell layers with the basal cells having a thickness of 20 µm (21). By 6 months of age, the basal cells reach their adult thickness of 18 µm. The desmosomes, which

are the intracellular junctions between the corneal epithelial cells, are present in a 20-week gestational-age cornea. They are more abundant in the superficial layer, although thinner and less regularly distributed. Corneal abrasions in the early gestational period would, therefore, be expected to occur more easily. In addition, given the lack of corneal cellular layers and reduced thickness, a corneal abrasion would likely require a greater amount of time for healing to occur. The epithelial basement membrane becomes thicker and more homogenous during this early gestational period. At the same time, the hemidesmosomes anchoring the basal cell layer of the epithelium to the basement membrane increase, and Bowman's layer becomes compact with more collagen fibrils.

TABLE 2.2 CORNEAL DIMENSIONS

	Newborn	Adult
Horizontal diameter (mm)	9.0 to 10.5	10.5 to 13.0
Vertical diameter (mm)	9.9 to 10.5	11.0 to 12.0
Keratometry (D)	48.06 to 47.0	42

Adapted from Goes F. Ocular biometry in childhood. *Bull* Soc *Belge Ophtalmol* 1982;202:159-193, with permission.

The corneal stroma also becomes thicker during the first several months of life, from 0.229 mm at 20 weeks' gestation to 0.490 mm at 6 months postnatally, at which time the adult thickness has essentially been reached (21). This change in thickness results from enlargement of the collagen fibrils themselves. Once mature, the collagen fibers no longer thicken during subsequent aging. The average diameter of a collagen fiber is between 250 and 300 å (22). There are small structural changes observed between adolescent collagen fibers and those from elderly individuals. There is increased interfibrillary distance in adolescent corneal stroma, compared with samples from elderly individuals, which also has greater breakdown of fibers and multiple small collagen-free spaces in electron microscopic analysis (22). The etiology of the increased cross-sectional area within the corneal collagen fibers has been investigated (23). On average, the cross-sectional area increases from approximately 3.04 nm^2 to 3.46 nm^2 over a 90-year timespan. In contrast, the interfibrillary distance decreases with age. It has been postulated that this change may be due in part to an increase in the nonenzymatic cross-linking between collagen molecules. Biochemical studies have revealed an increase in collagen glycation and its end products within elderly corneal stromal samples, leading to decreased interfibrillary spacing. Proteoglycans also play a role in regulating spacing between collagen fibrils, with a decrease in the ratio of proteoglycan to collagen found with aging (24). Counterbalancing the decrease in interfibrillary distance, there is an increased occurrence of water accumulation between collagen fibrils. These “lakes” contribute to light scatter which may diminish visual clarity with age, and largely account for the overall increased cross-sectional area.

The keratocytes in the corneal stroma decrease in thickness and density during development (25). One study found a keratocyte density of 6.22×10^4 keratocytes/mm^3 in the first decade of life, decreasing approximately 0.3% per year thereafter (25). This study also found that interindividual keratocyte density was quite variable, while intraindividual density was not. Keratocytes play an important role in corneal stromal wound healing. It has been postulated that the decrease in keratocyte density is due to a combination of environmental and predetermined genetic factors, although the exact mechanism is unknown. The decrease in keratocytes may be partially or completely responsible for the age-related changes within the cornea, including the decrease in central corneal thickness with age, steepening of the cornea with resulting refractive changes through childhood, and increased light scatter noted in the cornea with age. The decline in keratocyte density and the interindividual variability may be of particular importance to refractive procedures where corneal stromal wound healing may affect the outcome of the procedure. An inverse relationship has been noted between the vigor of wound healing with its effect on refractive regression and increasing age.

Like corneal keratocyte density, endothelial cell density also decreases with age. A cornea from a 12-week fetus has an endothelial cell density of 14,000 cells/mm^2 (25). At term, the average endothelial cell density is 6,800 cells/mm^2. This large decline during fetal development may be explained by rapid corneal growth. Yet the decrease from infancy to childhood is also rapid, ranging from 1.4% to 4.0%. As mentioned previously, corneal growth has essentially attained adult parameters by 2 years of age. The reason for this decrease is unknown. The annual rate of loss of endothelial cells slows in adulthood to approximately 0.3% per year. This rate of decrease emphasizes the importance of approximate age-match in donor corneas used in corneal transplants in newborns and infants with conditions such as Peters' anomaly or other visually limiting corneal opacities.

The endothelial cells contribute to the translucent nature of the cornea as well as the regular spacing of the collagen fibers. The cornea is an intransparent structure in fetuses up to 26 weeks' gestational age (26). The intransparency is mild to moderate, symmetric, and uniform with smooth corneal epithelium. The cornea becomes transparent within 4 to 6 weeks of birth. Most infants greater than 32 weeks' gestational age demonstrate corneal transparency, but any developmental intransparency clears within 1 to 2 days of delivery in term infants.

The etiology for the variability in the structural changes in the cornea has long been sought. Recent studies have identified proteins that may mediate cellular activities in corneal development (27). Tenascin-C (TN-C) mediates several important cellular activities, including cell adhesion, migration, and proliferation and differentiation of stem cells. TN-C is expressed widely in the preterm cornea. Restriction of expression begins to occur in the neonate, and by adulthood TN-C is expressed only in the limbus. Variants of TN-C caused by alternate splicing of the gene lead to the pleiotropic nature of TN-C. These variants also differ in their expression within the cornea and with age. Further studies of proteins that influence growth may lead to development of strategies to affect disease states.

In summary, the corneal diameter increases slightly, especially in the vertical diameter, and the corneal curvature flattens. In the beginning of the second decade of life, the corneal curvature steepens, especially in the horizontal meridians. The corneal layers also mature in the first decade, resulting in overall increased corneal thickness. There is an increase in the size of the epithelial and stromal layer in the early postnatal period, but the endothelial and stromal keratocyte density decreases in this same time period. Nevertheless, there is an increase in the overall corneal thickness. Corneal thickness influences the measurement of intraocular pressure (28). Intraocular pressure measurements

may be overestimated as corneal thickness increases. Therefore, thinner corneas in infants less than 6 months of age would be expected to show lower intraocular pressure with Goldmann or Schiotz tonometry. Since the Tono-Pen compresses a much smaller corneal area, it is slightly less affected by corneal thickness (29). The influence of corneal thickness on intraocular pressure measurements should be kept in mind in the ongoing treatment of infantile glaucoma. The method of intraocular pressure determination also significantly impacts the value of the intraocular pressure. General anesthetics tend to lower intraocular pressure, while infant distress with crying and squeezing of the lids elevates intraocular pressure. In normal children less than 5 years of age, the mean intraocular pressure is 6 mm Hg (30). Recent studies have found intraocular pressure to vary with age, until age 10, by the relationship, Ta equals 0.71(age in years) plus 10 (31,32). Applanation tonometry underestimates intraocular pressure under general anesthesia and generally underestimates intraocular pressure in childhood. Pneumometric tonometers may more accurately record intraocular pressure (30,31). The range of normal intraocular values in children also tends to be lower, which must be incorporated into the management of infantile glaucoma.

Anterior Chamber

The anterior chamber depth is influenced by the growth of the sclera, as well as by factors related to lens movement and thickness. At term, the anterior chamber averages 2.05 mm with a range of 1.8 to 2.4 mm in depth (19,33). The depth continues to increase until the end of adolescence, and then it progressively diminishes. During adolescence, the depth averages 3.25 mm. In emmetropic patients, the increase in anterior chamber depth appears to stop at an earlier age, compared to patients with myopia (14). This apparent difference is related to the continued changes in the lens and axial length in patients with myopia. The difference in the anterior chamber depth between the two eyes does not exceed 0.15 mm in normal individuals (14). The anterior chamber depth is slightly deeper in boys than girls. The volume of the anterior chamber is approximately 64 mm^3 in term infants and 116 mm^3 in adults (14). Adjustments during intraocular surgery in childhood may be necessary based upon these differences in anterior chamber depth.

Iris

The architectural crypts of the iris develop from gestation through the early postnatal period. The primary pupillary membrane forms early in gestation and atrophies near term (Fig. 2.2). The color of the iris results from pigmentation of the stromal mesodermal cells and iris blood vessels. At term, the mesodermal stromal cells of the iris continue to develop pigment, which accounts for the darkening of iris color observed in the first few months of life. There are at least 14 identified pigmentation genes which contribute to iris color. Researchers have also identified many pigmentassociated genes that reside on chromosome 15 which also contribute to iris color (34). The multiple genes and structural elements that contribute to iris pigmentation continue to make genetic predictions of iris pigmentation difficult.

Figure 2.2 Persistent pupillary membrane without visual sequela. Courtesy of Wills Eye Resident Collection.

Lens

The tunica vasculosa lentis is a plexus of blood vessels that is instrumental in the development and nourishment of the lens in embryonic life. The tunica vasculosa lentis completely regresses after 35 weeks of gestation (Fig. 2.3). The extent of regression can be used to estimate gestational age (35). At 27 to 28 weeks' gestational age, the entire lens surface is covered with vessels. Between 29 and 30 weeks, the central vessels of the tunica begin to atrophy. At 31 to 32 weeks, the central lens area is visible, with thinning of the peripheral vessels. Between 33 and 34 weeks of gestation, only thin peripheral vessels remain of the tunica vasculosa lentis.

The crystalline lens is the structure most responsible for adapting to the changing axial length of the eye and its subsequent influence on the refractive needs of the eye. The length of the eye increases rapidly until approximately 3 years of age, followed by a period of slow growth of approximately 1 millimeter in the next 10 years. The cornea loses approximately 3 to 5 D of power by flattening in the first year of life, leaving the majority of the dioptric change necessary to maintain emmetropia to the lens. A tremendous decrease in dioptric power occurs in the first year of life. The eye's power changes from approximately 90 D at birth to 75 D at 1 year (36). Despite the axial growth that necessitates this change, the majority of infants maintain emmetropia.

Several authors have attempted to study the structural, molecular, and geometric changes in the lens that allow it to change in power (37,38,39). There are two main methods to determine the power of the lens in infancy and childhood. The Gullstrand-Emsley schematic method requires no direct measurement of the lens parameters—it uses other measurable ocular parameters to determine the power of the eye and compares it to the cycloplegic refraction to calculate the power of the lens. Thus, by using varying

techniques to measure corneal keratometry, axial length, and refractive correction, the lens power may be calculated. The other method of lens power determination measures the lens surface curvature, thickness, and volume. It then requires estimates of the refractive index of the lens to calculate lens power. The established refractive index of an adult lens is 1.416. Yet this value is too low to allow agreement between the two methods of lens power determination in children. One study established that a refractive index of 1.427 allowed closer agreement of lens power calculations (37). In addition, this study showed that the exact geometric shape of the lens appeared to influence the index of refraction as well. The index of refraction can also vary throughout the lens. Therefore, this study employed a 10-shell model of the lens with a varying index of refraction in each shell (37). However, even this method was not reproducible in varying age groups. The refractive index decreases rapidly in childhood, accounting for the majority of the refractive power change in the lens. The decrease in refractive index then slows, and after age ten, the refractive index increases slightly. This variability of the refractive index contributes to the maintenance of emmetropia.

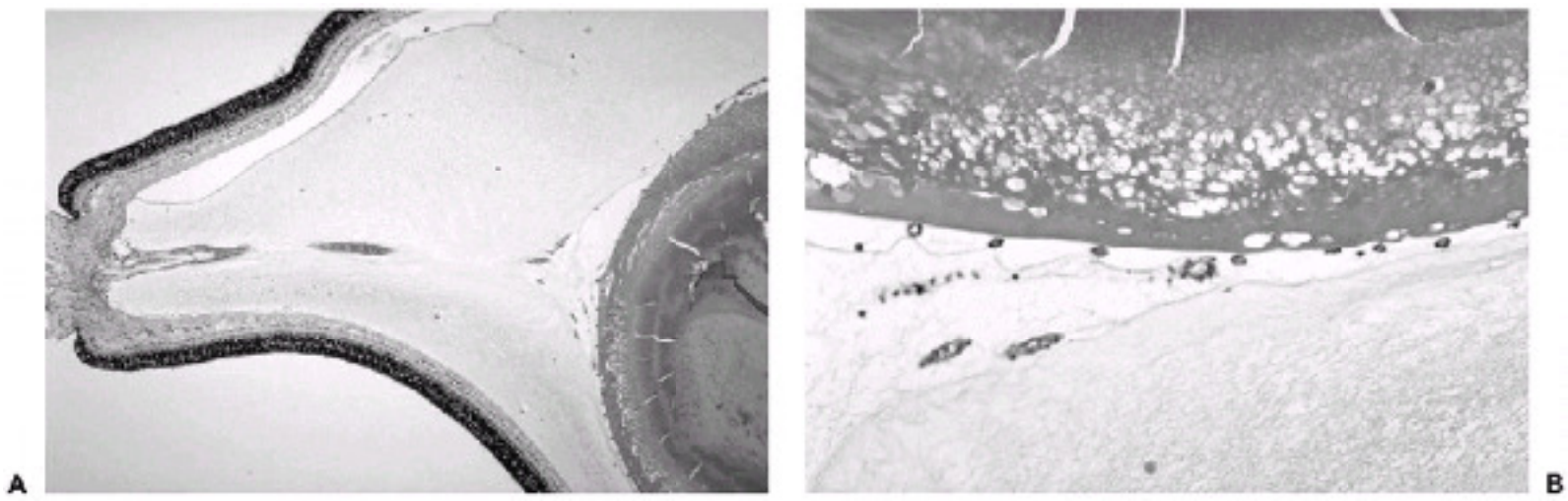

Figure 2.3 A: Tunica vasculosa lentis in a 20-week fetus. **B:** Histologic remnants of tunica vasculosa lentis along the posterior border of the fetus lens. Courtesy of Ralph Eagle, MD.

Given the constant production of new lens fibers throughout life, the axial thickness of the lens would be expected to increase continually. Yet there is actually a thinning of the lens by 0.5 mm in the first decade of life, most of it occurring in the first 3 years. Zadnik and associates (39) propose that the equatorial growth of the eye causes stretching of the lens that results in this thinning. Consistent with this theory, the anterior and posterior lens radii also increase in childhood by 1.0 mm and 0.2 mm, respectively (40). Equatorial growth would cause passive stretching of the crystalline lens with flattening of the lens surface curvature and reduction of the lens power. In this theory, myopia may result when either physical parameter prevents the lens from thinning appropriately, or the maximum thinning allowable has occurred but cannot compensate for axial length. In fact, children with myopia in this study were found to have thinner lenses than their hyperopic or emmetropic peers (39). Interestingly, the rates of increase of the anterior and posterior lens radii differ. The rate of increase of the anterior lens curvature slows after age 3, whereas the posterior lens curvature rate of increase remains constant in childhood. These both contribute to the overall flattening of the lens. The average lens thins until age 10 with little change thereafter. The lens thinning decreases to less than 0.5% compared to 4.1% thinning from ages 6 to 9. In the population studied, the onset of myopia occurred between 9 and 10 years of age in the majority of individuals. Myopia may result from a variety of factors. In one proposed, passive model, myopia may result from the disassociation of the axial length and biometric lenticular parameter changes. The source of this disassociation may be due to limited equatorial growth compared to axial growth. The discontinuation of equatorial growth could stop the flattening of the lens, decrease the reduction in refractive index, or by some other factor stimulate further axial growth which ultimately results in myopia.

Molecularly, the composition of the lens undergoes changes as well. Fetal lenses have a higher percentage of gamma crystalline protein (21%) compared to adolescents (13%) (41). The beta and alpha crystalline percentages are similar, although in the elderly, the alpha crystalline proportion increases further. The optical density of the lens also increases throughout life, increasing its absorption of light (42,43).

Sclera

The collagen in the sclera undergoes developmental changes in the early postnatal period. The sclera is four times as pliable in infants as in adults and has approximately one-half the tensile strength (44). This pliability explains the buphthalmos seen in infantile glaucoma with elevated intraocular pressures (Fig. 2.4). The structural changes in the sclera are due to the changing proteoglycan composition of the sclera. There are three major proteoglycans in the sclera: aggrecan, biglycan, and decorin (45). All three are increasingly expressed until the fourth decade. There is an increase in sclera thickness from 0.45 mm in neonates to 1.09 mm in adults. After the fourth decade, decorin and biglycan decrease in expression. Aggrecan has

the highest concentration in the posterior sclera and continues to show high expression throughout life. The different expression rates of these proteoglycans may result in the differential growth seen in various portions of the sclera (45). For example, growth of the posterior sclera may result in increases in axial length, which will be discussed in more detail in the refractive section. Certain anatomic relationships confirm the differing growth rates. The posterior portion of the sclera shows greater growth than the equatorial portion in the early postnatal period, resulting in the apparent forward migration of the extraocular muscle insertion sites relative to the equator of the eye (46).

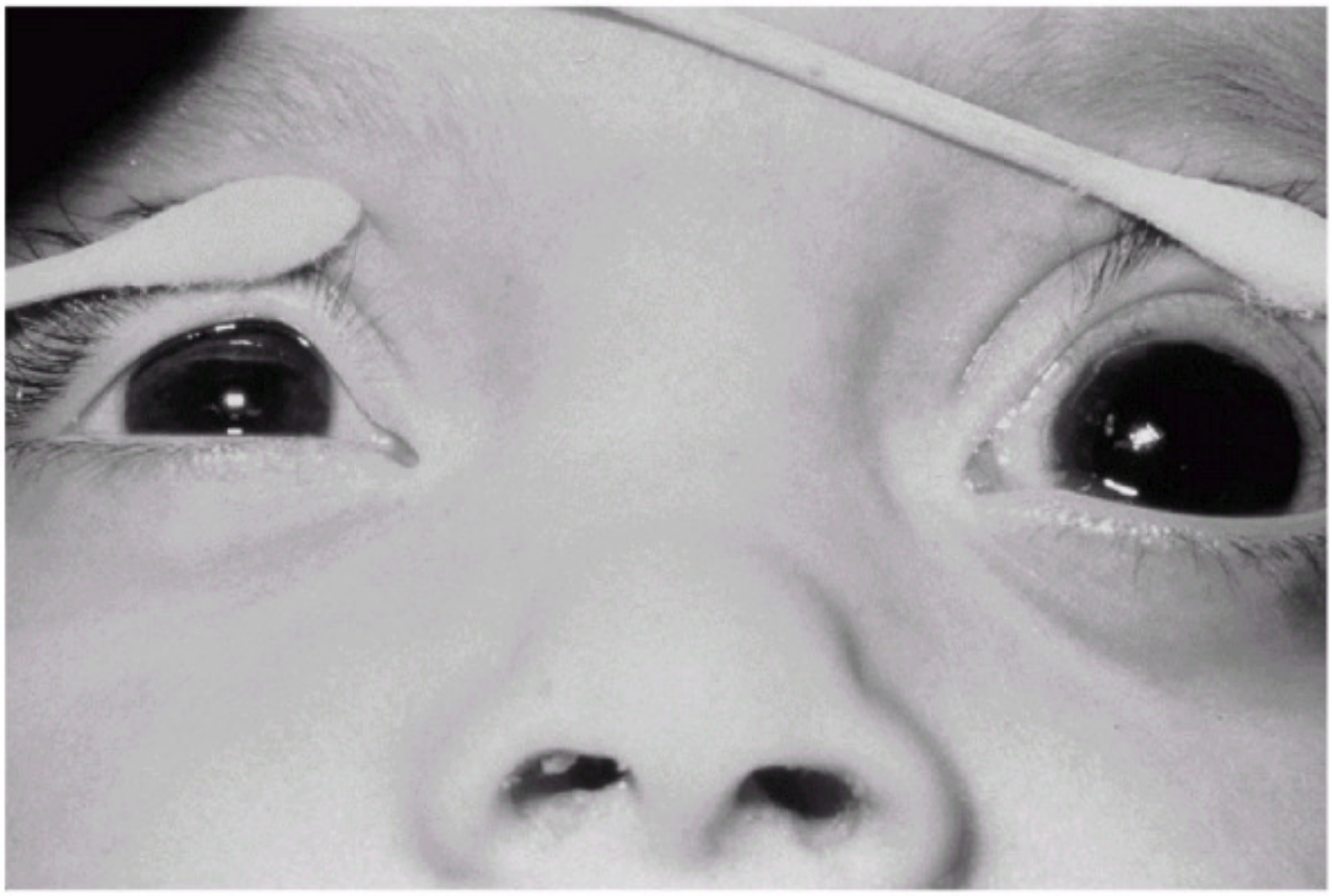

Figure 2.4 Buphthalmos in both eyes of child with congenital glaucoma. Courtesy of Wills Eye Resident Collection.

PUPIL

Isenberg and associates (47) found that the pupil is proportionally larger in premature infants less than 26 weeks' gestational age than in adults. This dilation may result from the more rapid maturation of the dilator muscle of the iris during gestation. The pupil does not respond to light until approximately 31 weeks' gestational age (48). The presence of the pupillary response may be due to the maturation of the neural pathways at this age, given evidence for retinal photoreceptor function in younger infants (48). It may also be related to the regression of the tunica vasculosa lentis. The average range for pupillary size in ambient light is between 1.8 mm and 5.4 mm (47).

RETINA

In keeping with the increases in equatorial and axial size of the eye, the retina of the infant eye undergoes significant change. A transverse shift in cells within the retina occurs during the neonatal period, which is accompanied by changes in the density of retinal pigment epithelium (RPE) cells (49,50). There is a geometric relationship between the total retinal surface area and the anatomic dimension of the eye, but the relationship is not linear. The ciliary body grows, displacing the anterior border of the retina posteriorly. In addition, the axial length is not directly correlated to the retinal surface area since the axial length includes the anterior segment. The lens also moves more posteriorly in the neonate, but not at the same rate as the ora serrata moves posteriorly. The retinal area has been shown to increase at a faster rate than the equatorial diameter of the globe (51). Between 6 months' gestational age and the second postnatal year, the retinal surface area and RPE surface area have been shown to increase by a factor of 2.69 (51). Nearly one-half of this increase occurs from 6 months' gestation to term. Mitotic activity in the retina has ceased by 6 months' gestational age (52). Therefore, the increase in surface area is accompanied by shifts in the distribution of the retinal ganglion cells and photoreceptors in the fovea.

Within the adult fovea, there are no inner retinal layers. This architecture creates a foveal pit with the surrounding retina having the highest concentration of ganglion cells (53). In addition, there are no rods within 350 µm of the center of the fovea; only cones are found in this area. The neural processing in the fovea happens such that each cone communicates through several bipolar cells and at least two ganglion cells (54). This allows for the high visual acuity present in the fovea. The fovea begins development very early in gestation, and cell division ceases there by 14 weeks' gestational age (55,56). The foveal pit is appreciable by 32 weeks' gestational age due to migration of the ganglion cells and subsequently the inner retinal layers (57). At term, the human fovea is immature with a single layer of ganglion cells and an inner nuclear layer still present (58). This process of migration is not complete until 11 to 15 months postterm, which may contribute to the relatively low visual acuity of neonates. The foveal cones increase in density by becoming thinner and longer. Rods are pushed peripherally. The cone outer segments develop slowly; this process of cone maturation is not complete until greater than 45 months postterm. The entire process of foveal maturation is not complete until 4 years postnatally. The significant postnatal development of the fovea has implications for the sensitivity in this period to amblyogenic conditions. The development of the vasculature of the retina will be discussed within the retinopathy of prematurity chapter (Chapter 3).

To evaluate the maturation of the retinal layers, electroretinogram (ERG) analysis in normal individuals at many different ages has been preformed (59). Gross ERG values differ between institutions, but in general a normal 5-month-old has longer implicit times and smaller amplitudes in dark-and light-adapted ERGs than adults. The dark-adapted b-wave amplitude increases with age, and the implicit time decreases. The mixed rod-cone b-wave amplitude reaches one-half maximum value by 1.2 months of age, whereas the rod-mediated responses reached one-half maximum value by 19 months of age. Maximum responses are reached by 37 months and 84 months, respectively (59). Oscillatory potentials show the least mature responses at birth. The dark-adapted oscillatory potentials reach the normal limits for adults by 21 months of age. Thus, despite slower initiation of development, the oscillatory potentials develop more rapidly than other ERG responses. Light-adapted ERG responses show similar

changes as dark-adapted ERG responses. The cone-isolated response reaches one-half maximum values by 1.9 months of age. In addition, the a-wave takes longer to develop than the b-wave (59,60). The development of the dark-adapted b-wave amplitude is similar to the a-wave development, although this time course is dependent on the intensity of light used during the study as well (59). The flash intensity required to achieve standard responses normalizes to adult values by 3 years of age (59).

In summary, the ERG a-and b-wave amplitudes and implicit times are sufficiently mature by 3 to 5 years of age to be compared to adult values. Similarly, oscillatory potential amplitudes are comparable by 2 years of age. This standard of comparison of data can prove useful in the evaluation of retinal disease, often in the absence of visible findings in the retina. In one evaluation of children with nystagmus with no known neurologic disease or visual pathway disease, 56% of children were found to have a sensory deficit resulting in nystagmus on ERG testing (61).

ERG responses mature at different rates depending on the components responsible for generation of the response. The relatively greater maturity of b-wave than a-wave development may be explained by the greater maturity of the photoreceptor-bipolar synapse and bipolar-Muller cell synapse than the maturity of the a-wave postreceptoral mechanisms (59). The more rapid development of the oscillatory potentials compared to the b-wave parameters may be explained by the different maturity of the components responsible for generation of the oscillatory potentials, which includes the bipolar, amacrine, and interplexiform cells. Receptoral mechanisms, which contribute to the a-wave amplitude and b-wave sensitivity, develop more slowly than the mechanisms for oscillatory potentials, which are generated by middle and proximal retinal cells (59).

The reduced sensitivity of the ERG in infancy may also be due to rod maturation. Rods are short and immature at birth with reduced outer segment lengths. Although the quality of infant rhodopsin has been shown to be the same as adults, the net concentration of rhodopsin does increase with age (62,63). Regeneration of rhodopsin seems to proceed at a similar rate in adults and children (64); however, responses of temporal and spatial summation differ significantly. These rod-mediated developmental changes are thought to occur due to the maturation of processing central to the photoreceptor (62). The elongation of the rod outer segment in infancy is accompanied by an increase in rhodopsin content. At 5 weeks' postterm, the rhodopsin content is 50% of the median adult amount (63). The number of rods in an adult retina varies from 78 to 107 million, allowing for a wide range in studies of the total rhodopsin content of an eye (65). In addition, an individual's long-term light exposure history affects rhodopsin content, such that individuals reared in bright habitats have shorter rod outer segments and less rhodopsin than those reared in dark habitats. Therefore, studies of the importance of rhodopsin content are difficult to analyze.

Rods located in different areas of the retina also have different sensitivities during testing. Maturation of the parafoveal rod outer segments (10 degrees eccentric to the fovea) is delayed compared to rod outer segments that are 30 degrees eccentric to the fovea (66,67). In fact, using forced preferential looking techniques and regional ERGs to compare parafoveal and peripheral rod responses, Fulton and associates (68) demonstrated concurrent maturation of rod outer segments and rod-mediated visual sensitivity.

NEUROLOGIC DEVELOPMENT

The quantification of visual acuity relies on three basic factors: optic, physiologic and psychologic (69). Often the techniques for assessing visual acuity in infants, such as forced preferential looking can be limited by psychologic development of the infant. The anatomic optic factors of the eye have been discussed in the preceding sections. The development of the neurologic connections to the eye also plays a vital role in visual function. Since the landmark work of Wiesel and Hubel (70,71), there has been an awareness of a critical period of visual development. Disruption of normal visual input during this critical window, whether by ocular media opacities, refractive errors, strabismus, or other visual anomalies, results in decreased visual acuity, or amblyopia. Normal development of the lateral geniculate nucleus is complete by 6 to 12 months of age, although minor alterations continue until 2 years of age (72). Amblyopia, on the other hand, induces anatomic changes in the lateral geniculate nucleus with underrepresentation and atrophy of neurons from the amblyopic eye (73). In the visual cortex, amblyopia causes a decrease in the number of binocularly driven neurons (74). The process of neural inhibition of input from the amblyopic eye has been shown in animal studies to be an active process (75). The nonamblyopic eye actively inhibits the amblyopic eye even after correction of the process that initiated the amblyopia. This inhibition appears to be mediated by norepinephrine, although pharmacologic treatment has not at the present time resulted in successful reversal of amblyopia (76). Amblyopia and its treatment are further covered in other chapters.

Snellen visual acuity is not the only factor reduced by periods of visual deprivation in infancy. Contrast sensitivity, stereopsis, and scotopic and photopic sensitivity are reduced as well (77). These different functions are postulated to have differing critical windows of development (77). The earlier in infancy that visual deprivation occurs, the more profound is the resultant decrease in contrast sensitivity in an animal model using macaque monkeys (77). Contrast sensitivity generally increases with binocular viewing, but in monkeys with visual deprivation, binocular viewing did not enhance contrast sensitivity. The critical period of contrast sensitivity development extended to 24 months of age in macaque monkeys. Stereopsis, which also requires binocular function, has been shown to decrease with early visual deprivation in one eye (77). This may be due to reductions in the population of binocularly driven cortical cells or specific unidentified factors associated with stereopsis. The binocularly driven cortical cells have been shown to become almost exclusively monocular in conditions of monocular visual deprivation (78). In nondeprived monkeys, 81% of cortical neurons are binocularly driven.

In contrast, only 25% of cortical neurons were binocularly driven in monocularly visually deprived monkeys. The critical window for this function was also shown to extend to 24 months of age in the monkey model (78). In addition, scotopic sensitivity was reduced in amblyopic monkeys, especially in cases of visual deprivation at less than 1 month of age. Interestingly, there was no detectable decrease in scotopic sensitivity if the visual deprivation occurred at greater than 3 months of age in these monkeys (78). The critical window for photopic sensitivity is longer, with no reductions detected if visual deprivation occurred after 5 months of age (78). These results demonstrate the different critical window period for different visual functions. The critical window for scotopic and photopic sensitivity is earlier than for Snellen acuity and stereopsis in monkeys. Further analysis of children with amblyopia should reveal if the critical window varies for different visual functions as well.

The etiology for amblyopia development can impact visual functions as well. For example, in amblyopia resulting from visual deprivation, enlargement of the receptive field occurs in retinal neurons (79). In contrast, in strabismic amblyopia, grating acuity may be preserved in the amblyopic eye due to spatial distortion that permits detection of the grating but cannot compensate to allow complex form recognition (80). The neurologic basis for these differences has not been identified.

The visual cortex may also be affected, primarily resulting in reduced visual function. Limited visual recovery can be demonstrated following visual cortex damage (81). Interestingly, the concept of recovery following damage to the cortex in early childhood has been thoroughly studied for other cortical modalities (82). This type of recovery is well documented in the motor (83), sensorimotor (84), and even association cortex (85). Evidence supporting spontaneous recovery in the visual cortex, on the other hand, has been limited. Confounding the problem of visual recovery following cortical damage has been evidence of rapid secondary degeneration of other visual structures following visual cortex damage, such as the neurons in the dorsal lateral geniculate nucleus (86) and even retinal ganglion cells (87). One study revealed limited recovery of the contralateral field following lesions to the visual cortex in monkeys during infancy (81). In contrast, animals sustaining injury to the visual cortex in adulthood did not demonstrate similar recovery. Possible mechanisms for recovery, assuming similar damage to the striate cortex was achieved in all animals (confirmed with magnetic resonance imaging analysis), include activation or unmasking of residual visual pathways stimulated by the retrograde degeneration known to occur after visual cortex damage. Since retrograde degeneration occurs more rapidly in childhood, the residual visual pathways may be stimulated earlier. The residual pathways may involve changes in both subcortical and cortical domains. One example of a residual visual pathway is projections between the retinal ganglion cells and superior colliculus (88). Another example is the pathway from the midbrain to the thalamic visual nuclei and extrastriate cortex (89). Further studies are needed to elucidate which pathways play important roles in visual recovery.

Another component of visual function is the interhemispheric integration of visual inputs. One study has shown that this integration occurs in humans after 24 months of age (90,91). Interhemispheric integration is controlled within the callosal fibers that allow the exchange of information between the left and right hemispheres. This contributes to the “bilateral advantage,” which allows increased computing skills when images are presented to both hemifields compared to unilateral hemifield presentation. Another study of infants under 6 months of age reveals some transfer of visual processing of shapes between the hemispheres, but the transfer of learned visual tasks was nonexistent in children under 10 months of age (90,92,93).

Yet another entity that results in decreased visual function and occurs in infancy is delayed visual maturation (DVM). Illingworth (94) first described this entity of limited response to visual stimuli in the absence of ocular pathology, cortical pathology, nystagmus, or any other developmental delays. Visual behavior normalizes in these infants by 8 months of age, and when tested in later childhood is within normal ranges (94,95). Subsequent descriptions of DVM have included children with delays in other developmental milestones. Fielder (96) divided DVM into three subtypes: isolated DVM, DVM associated with neurologic abnormalities, and DVM associated with ocular abnormalities. These differing entities have slightly different prognoses. Premature infants less than 37 weeks of gestation with DVM have a grimmer prognosis (97). Cerebral palsy and mental retardation were found much more commonly in preterm infants with DVM than in preterm infants without DVM. Nevertheless, even in this group, 14 of 16 children went on to have normal final visual acuity when tested at 3 to 5 years of age, despite their neurologic abnormality (97). The etiology of DVM remains unknown. Normal ERG and visually evoked potential studies suggest the absence of retinal pathology or visual cortex abnormalities. The visual association areas controlling visual attention may be involved in the development of DVM, but this is

only speculation (94). Further understanding of visual processing should help elucidate the abnormalities in DVM.

ORBITAL STRUCTURES

The eyes are a dominant aesthetic feature of the face and are significantly influenced by the dimensions of the structures of the orbit. Several studies have attempted to quantitate the volume and spatial dimensions of the orbit in childhood and adolescence to establish normal parameters. These parameters can then guide treatment for patients with facial alterations and deformities including enucleation (98). Technologic advances now allow three-dimensional analysis of the orbit to more accurately describe the facial dimensions of it. In one study, specific landmarks of the orbital region were marked on each subject, with a computerized electromagnetic digitizer obtaining the three-dimensional coordinates of these landmarks (99). The exact orbital length and height, intracanthal distance, binocular width from one lateral canthus to the other, and angle of the lid fissure relative to the true horizontal plane were all determined (Fig. 2.5). This study revealed that the

linear and angular measurements of the orbit continue to change, not only in childhood but also from adolescence to adulthood. Also a clinically significant difference was found between male and female orbits in all age groups in the linear distances measured. All linear differences were greater in males than in females except for the height of each orbit (Table 2.3). In addition, the age-related differences were more significant in male than in female subjects. For example, the binocular width increased by 4 mm between adolescence and adulthood in males, and by only 1.5 mm in females. Previous studies have reported that the binocular width has reached its adult value by 13 years of age (98). Yet, clearly in the more recent study substantial growth continued in male orbits (99). In male subjects, the greatest change in dimensions of the orbit took place between adolescence and early adulthood, whereas females had equally distributed changes from infancy throughout adulthood. Interestingly, the height to length ratio of the orbit, which grossly estimates orbital shape, was similar in both males and females despite the linear measurement differences. Farkas and associates (100) revealed that at 1 year of age, the intercanthal width had already reached 84% of its value at 18 years of age. The binocular width reached 85% of its adult value at 1 year of age. By 5 years of age, these respective linear measurements had reached 93% and 88% of their adult values, respectively. Therefore, Farkas recommended final corrective craniofacial surgery in this region at 5 years of age (100). The intercanthal width increased markedly between 3 and 4 years of age, and then showed very little subsequent growth. The binocular width, on the other hand, continued to show growth even after 5 years of age. The intracanthal width reached adult values by 8 years of age in females and 11 years of age in males. Binocular growth reached full maturation by 13 years of age in females and 15 years of age in males. With these types of measurements of the orbit, orbital surgeons can more accurately define facial relationships for any age and gender and understand their relative changes with growth. This allows better understanding of which surgical procedure can best affect a disease process.

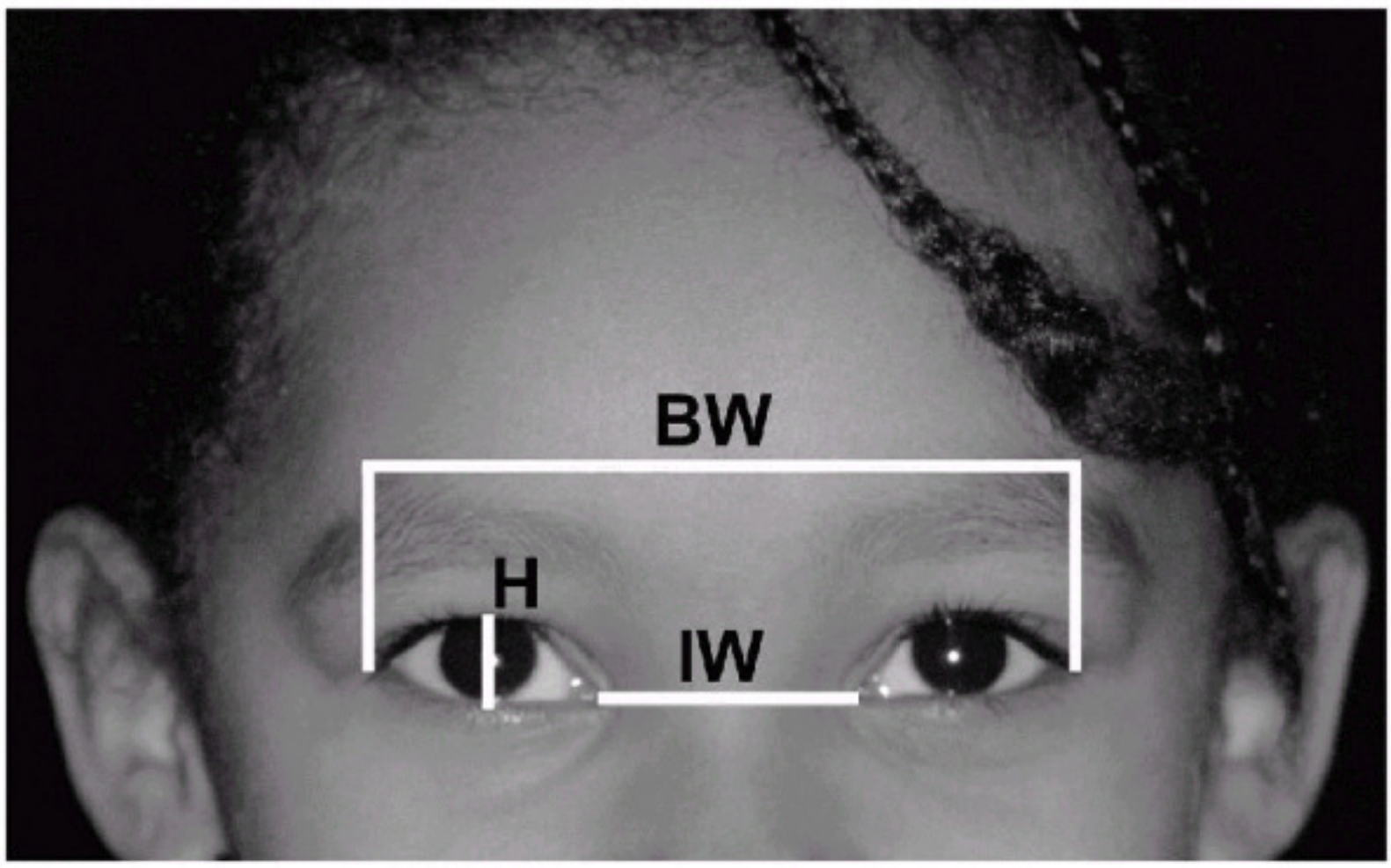

Figure 2.5 BW, binocular width in mm from lateral canthus of right eye to lateral canthus of left eye; IW, intracanthal width in mm from medial canthus of right eye to medial canthus of left eye; H, height of orbit in mm with eye in naturally open position; L, length of eye fissure in mm from lateral canthus to medial canthus.

In another study, the orbital volume was estimated using magnetic resonance imaging (101). In the first month of life, the orbital volume was found to be 15 cm^3 in males and 13 cm^3 in females. The orbital volume of males measured larger than in females at every age measured thereafter as well. The orbital volume grew in a linear pattern in both genders and reached 77% of its adult value by 5 years of age. In patients with craniosynostoses, the restriction on orbital volume loses its major effect within the first few months of life, allowing fronto-orbital advancement surgery to be delayed until the second half of the first year of life to maximize the effect of accelerated orbital growth (102).

Understanding of these data can also be helpful in planning for enucleation in children. It has long been acknowledged that enucleation during childhood causes retardation of further orbital growth, resulting in facial asymmetry (103,104,105). Tissue expanders and orbital implants have been proposed to limit the retardation of growth. The orbital volume difference between the unaffected orbit and anophthalmic orbit was minimized in patients with orbital implants or patients who used conformers with prompt replacement of the orbital prosthesis with growth (101). In patients with replacement of the prosthesis, the difference between the volume in the enucleated orbit and unaffected orbit ranged from 1.3 cm^3 to 2.5 cm^3. Without replacement, the difference in orbital volume ranged from 6.7 cm^3 to 7.1 cm^3, which represents a 20% to 37% difference in orbital volume. Even in patients without orbital implant placement at the time of enucleation, frequent prosthesis

replacement avoided marked growth retardation of the orbit in this study (101). In addition, Fountain and associates (106) found that even if the orbital implant at the time of enucleation was less than 50% of the volume of the globe as an adult, orbital growth was maintained without orbital implant replacement. Newer studies even question the effect of age at enucleation on volume reduction (107). Hintschich and associates (107) reported that reduction of orbital volume is continuous after enucleation, and the mechanism is related to volume adaptation more than retardation of growth. This study compared the orbital volume in

patients enucleated before 8 years of age to those enucleated between 15 and 53 years of age. All groups had a clinically significant reduction in orbital volume in the anophthalmic orbit. In those less than 8 years old at enucleation, the median reduction was 7.0%; in the older group, the median reduction was 3.8%. The difference between these groups was not statistically significant. Interestingly, the greatest reduction in orbital volume found in this study was 14.5%, which is less than that reported in similar studies (108). This difference was attributed to the method of orbital volume determination using high-resolution CT scans. Instead of age at enucleation as the main determinant, Hintschich found a clinically significant correlation between the time interval since enucleation and the orbital volume (107). Even after the orbit reached adult volumes, enucleation produced reduction of orbital bony volume (104,107,109).

TABLE 2.3 ORBITAL DIMENSIONS IN MALES AND FEMALES

	Adolescent male	Adolescent female	Adult male	Adult female
Binocular width (mm)	90.19	88.4	94.51	90.24
Intercanthal width (mm)	28.64	27.89	34.7	28.99
Height of orbit (mm)	30.99	31.63	34.5	33.48
Length of eye fissure (mm)	32.46	32.04	33.56	31.99

Adapted from Ferrario VF, Sforza C, Colombo A, et al. Morphometry of the orbital region: a soft-tissue study from adolescence to mid-adulthood. *Plast* Reconstr *Surg* 2001;108:285-292, with permission.

In addition to the orbital size and shape, the position of the eyelids relative to the pupil has a large impact on the aesthetics of the eye. The eyelids, for example, may be fused until the 28th week of gestation. If it is necessary to examine a child prior to the spontaneous resolution of this fusion, gentle downward pressure with the fingers on the lower eyelid accompanied by gentle upward pressure on the upper eyelid will break the epithelial bridge across the lids (110). The upper eyelid is in its lowest position relative to the pupil in the first three months of life. Most likely coincident with the development of muscle hyperactivity in the levator or in Muller's muscle, the upper lid achieves its highest position relative to the pupil between 3 and 6 months (111). There is a gradual decrease in the lid position thereafter. In contrast, the distance between the lower eyelid and center of the pupil linearly increases.

The upper eyelid crease is formed by the superior extension of the levator aponeurosis, which inserts on the pretarsal orbicularis. In non-Asian eyelids, the normal insertion is usually located at the superior margin of the tarsus. In a study of 33 white and African American children, the normal upper eyelid crease was one-third the distance from the lash line to the lower brow in children 1 year of age (112). In infants, the normal upper eyelid crease is only slightly less than one-third this distance. The mean distance from the lash line to the lid crease in children less than 4 years of age was 2.6 mm; in children greater than 4 years of age, it was 5.7 mm. In unilateral cases of ptosis with absent eyelid crease, a crease is created to match the contralateral eye; however, in bilateral cases, the general guideline established in this study may be helpful. In another study of more than 1,300 patients, the most rapid change in eyelid structure was during the first decade of life and thereafter, only minimal changes were observed (113).

There continues to be some controversy concerning the ability of newborn infants to produce tears. Sjögren (114) reported that only 35% of term infants had normal tear production, whereas Apt and Cullen (115) reported the percentage as 82% and found that it increased to 95% after the first week of life. A recent study of 96 term infants found that the mean total tear production was 16.3 mm by Schirmer test strips (116). In 22 preterm infants with a postconceptional age of at least 32 weeks, the mean total tear production was 7.4 mm (116). This study found that total tear production positively correlated with birth weight and postconceptional age in preterm infants. In term infants, the total tear secretion increased at 2 weeks of age to 18.1 mm and by 4 weeks of age to 19.5 mm (116). In an older study by Patrick (117), a similar percentage of term infants had normal tearing, but this study found no correlation between birth weight or postconceptual age and tearing. Isenberg and associates (118) also studied preterm infants and found a reduction in reflex and basal tearing rates, which gradually increased to reach normal levels at 40 weeks' postconceptional age. They found a positive correlation between increasing weight, postconceptional age and basal tear production. Although the reduction in the aqueous tear component of the preterm infant could put the infant at increased risk of corneal damage from prolonged exposure during exams such as retinopathy of prematurity screenings, the lipid content of the tear film was found to be much thicker than in adults and presumably protects against tear evaporation (119). In addition, the mean tear break-up time in newborns was 32.5 seconds (119). This is supported by the studies of Kaercher and associates (120) who found a more stable tear film, which lessened with age, in younger children. A more stable tear film with prolonged tear break-up time may also explain the prolonged staring of infants. The etiology of the thicker lipid component of the tear film is unknown; although since most other ocular features are immature, it is unlikely that the meibomian glands are hyperproductive. Neonates have a considerably smaller palpebral fissure, which may secondarily lead to a thicker lipid layer. Further studies are required to elucidate this issue.

REFRACTIVE ERROR

Refractive errors requiring correction are very common in developed countries. The most common refractive error in this category is myopia. The incidence of myopia ranges from 25% in childhood in the United States to as high as 40% to 60% in Asia (121,122). The incidence of hyperopia requiring refractive correction is approximately 10% to 15% (123). The distribution of refractive errors also varies with age. In premature infants less than 36 weeks of gestational age, there is a higher incidence of myopia than in full-term infants (124,125). The shorter the gestational period, the greater the myopia (124). The etiology of myopia in premature infants is due to steeper corneas, shortened axial lengths, and shallower anterior chamber depths than in

full-term infants (126,127). In addition, 70% of premature infants had greater than 1.00 D of astigmatism, which was in general against-the-rule (124). Fifty percent of these infants showed less than 1.00 D change in their refractive correction, and 32% showed progression of their myopia (125). These data justify the recommendation for screening of premature infants for large refractive errors.

In a cross-sectional study of healthy children less than 4 years old, the mean refractive error was + 1.4 D with 74% of the children having no significant astigmatism (128). Ninety-five percent of these children had less than 1.50 D of anisometropia, and the same percentage had greater than + 3.25 D of hyperopia (128). These data agree with studies by Atkinson (129) and Ottar (130) of similar populations of children). In another study in which refractive errors in 514 children were prospectively evaluated, hyperopia was found to decrease with age, as did the high degree of astigmatism found in infants (131). In the majority of children, emmetropia had not been achieved by 4 years of age. This study also reported 95% predictive limits of refractive error by age. At 1 year of age, the mean spherical equivalent was + 1.50 D. In 2-year-olds, the mean spherical equivalent decreased to + 1.25 D. It further decreased to approximately + 1.00 D by 3 years of age and remained at that level at 4 years of age. Interestingly, throughout this entire age group (1 to 4 years of age), the approximate 95% predictive limit of refractive error was from + 3.00 D to - 0.50 D. Only in children less than 6 months of age is the 95% predictive limit larger, between + 5.00 D and - 1.00 D.

Myopia of greater than - 0.50 D was found in only 3% of the study population of 514 children. By defining guidelines for normal refractive errors in young children, cross-sectional studies can establish reasonable guidelines for amblyopia screening programs as there is no accepted standard for the level of refractive error at which amblyopia develops. One survey of the refractive error prescribing practices of pediatric ophthalmologists found that 50% of physicians gave spectacles for hyperopia greater than + 5.00 D in children less than age 2, for hyperopia greater than + 4.00 D in children 2 to 7 years of age, for astigmatism greater than + 2.50 D in children less than age 2, and for astigmatism greater than + 1.50 D in children 4 to 7 years of age (132). Nevertheless, accepted standards have yet to be established for the different refractive screening methods (130).

Longitudinal studies of refractive error have shown that emmetropization occurs. One study of 1,246 children revealed a gradual decrease in refractive error from low hyperopia to emmetropia, resulting from decreased lens power and elongation of the globe as previously discussed in this chapter (133). The evidence for emmetropization lies in the non-Gaussian distribution of refractive errors in the population. Emmetropization appears to have both active and passive components. The growth of axial length; mild reduction in dioptric power of the cornea by lengthening of its radius; reduced power of the lens; and lengthening of the anterior chamber, which further reduces the effective power of the lens, constitute the passive components of emmetropization. The active mechanism of emmetropization hinges on the feedback of image clarity from the retina. The exact mechanism by which this alters growth is yet unknown (134). Even infants born with congenital myopia show evidence of emmetropization (135). The incidence of congenital myopia is approximately 4% to 6% (136). The incidence of myopia declines from birth to less than 2% at 5 years of age (126). In a prospective study of childhood myopia ranging from - 0.25 D to - 3.50 D, emmetropization was found to occur by 3 years of age (135). The rate of change in refractive error was relatively constant from 8.5 months to 38.5 months of age at +0.44 D per year. There was also greater astigmatism, which decreased with age, in the myopic infants. In premature infants without retinopathy of prematurity, myopia also decreased within the first 5 months of birth at a rate of + 0.30 to + 0.40 D per week (137).

Studies of the characteristics of children with myopia have led to several theories about the etiology of myopia. Myopia is most likely to occur between the ages of 8 and 14 in the United States (138). Myopic eyes have a prolate shape with greater axial length than equatorial diameter (139). There are two main theories of the etiology of myopia: the genetic predisposition theory and the increased demand of near work theory. The genetic theory is supported by similar ocular parameters and refractive errors in monozygotic twins (140,141). There is also an increased prevalence of myopia among children of myopic parents (142,143). Yet supporting the near work theory, studies have revealed a greater incidence of myopia in populations with increased near demand and higher education levels (144,145). Evidence concerning the near demand theory may also be confounded by children with a high accommodative convergence to accommodation ratio (AC/A). AC/A ratios were found to be greater in myopic children (146). If the AC/A ratio was greater than 5.84, the risk of development of myopia was 22 times greater. The Orinda longitudinal study (133) found that parental history of myopia was more predictive of myopia than the report of amount of near work.

Other factors that may be predictive of myopia development include the refractive correction in infancy. Several studies have suggested that cycloplegic refraction in early infancy may be suggestive but not accurately predictive of myopia in later childhood. Myopia in the first year of life correlated with myopia at 3 years of age (135). In later childhood, individuals with emmetropia or low myopia are more susceptible to myopic progression as they do not have a hyperopic buffer (147). Supporting this observation, Edwards and associates (148) found that children with greater than + 2.50 D of hyperopia at 11 weeks of age were less likely to become myopic at age 7 to 8. They were unable to show any other correlation between cycloplegic refraction at 11 weeks of age and future refractive error.

Clearly, an early childhood refractive error is not the only factor predictive of myopia. Myopia is more common in certain ophthalmic disorders known to distort visual input, such as infantile hemangiomas of the eyelid (149) and injuries to Descemet's membrane (150). Even distortion from astigmatism may be relevant. In one study, greater than 3.00 D of astigmatism was correlated with myopia (151). Even children with 1.00 D of astigmatism become more myopic with age than those children without astigmatism. It is unclear if correction of these astigmatic

errors in young children would lessen the overall degree of future myopia. Other factors may play a more important role, given the high percentage (50%) of children less than 3 years old with some astigmatism compared to the lower incidence of myopia in school-age children (151).

Animal models of myopia have been used to further evaluate the active feedback mechanism in emmetropization and the causes of ametropia. Several experimental studies have shown that distortion or opacification of visual input during development can result in myopia. For example, Hubel and Wiesel (152) demonstrated that image deprivation in the initial postnatal period resulted in reduced neural connections to the occipital lobe and the development of amblyopia. Wiesel and Raviola (153) also showed that the absence of a clear retinal image in macaque monkeys resulted in axial elongation, leading to form-deprivation myopia. Many other influences on refractive correction have been studied. For example, chicks reared in continuous illumination develop increased axial length, myopia, and astigmatism (154). In contrast, chicks, cats, and monkeys raised in continuous darkness developed hyperopia (155,156). The effect of greater accommodative demand has been simulated by confining animals to small chambers. This resulted in a slight myopia compared to control animals in both monkeys and cats (157,158,159). A rabbit model of scleral buckling effects on the eye demonstrated high myopia due to increased axial length in eyes with buckles (160). The axial length in this model increased for 2 weeks postoperatively and then was stabilized. Whether these animal studies are relevant to humans remains to be seen, but there is some evidence supporting the applicability (123).

In summary, there are a myriad of changes in the ocular features during infancy and early childhood. It appears that these changes are highly orchestrated to result in the appearance of clear retinal images, which are then properly processed to allow vision. Other ocular development proceeds in tandem with the refractive and neurologic changes to result in growth of the orbital features, in addition to the intraocular elements. Understanding these normal changes is vital to the care and management of young patients.

REFERENCES

1. Weiss L. Über das wachstum des menschlichen auges und über die veränderung des muskelinsertionen am wachsenden auge. *Arb Anat Inst Wiesbaden* 1897;8:191-248.

2. Scammon RE, Armstrong EL. On the growth of the human eyeball and optic nerve. *J Comp Neurol* 1925;38:165-210.

3. Isenberg SJ. Physical and refractive characteristics of the eye at birth and during infancy. In: Isenberg SJ, ed. *The eye in infancy,* 2nd ed. St. Louis: Mosby, 1994.

4. Delmarcelle Y, François J, Goes F, et al. [Clinical ocular biometry (oculometry).] *Bull Soc Belge Ophtalmol* 1976;172:1-608.

5. Abe S. [The sagittal growth of the eye.] *Nippon Ganka Gakkai Zasshi* 1979;83:1666-1678.

6. Gernet H, Hollwich F. [Oculometric results in infantile glaucoma.] *Bull Mém Soc Fr Ophtalmol* 1969;82:41-47.

7. Fledelius H. Prematurity and the eye. Ophthalmic 10-year follow-up of children of low and normal birth weight. *Acta Ophthalmol Suppl* 1976;128:3-245.

8. Larsen JS. The sagittal growth of the eye. 1. Ultrasonic measurement of the depth of the anterior chamber from birth to puberty. *Acta Ophthalmol (Copenh)* 1971;49:239-262.

9. Wilson ME, Bluestein EC, Wang XH. Current trends in the use of intraocular lenses in children. *J Cataract Refract Surg* 1994;20:579-583.

10. Wilson ME, Pandey SK, Thakur J. Paediatric cataract blindness in the developing world: surgical techniques and intraocular lenses in the new millennium. *Br J Ophthalmol* 2003;87:14-19.

11. Niederreiter P, Klemen UM, Leitner J. [Ultrasound biometry in childhood.] *Klin Monatsbl Augenheilkd* 1987;191:355-357.

12. Musarella MA, Morin JD. Anterior segment and intraocular pressure measurements of the unanesthetized premature infant. *Metab Ped Sys Ophthalmol* 1982;8:53-60.

13. Blomdahl S. Ultrasonic measurements of the eye in the newborn infant. *Acta Ophthalmol* 1979;57:1048-1056.

14. Goes F. Ocular biometry in childhood. *Bull Soc Belge Ophtalmol* 1982;202:159-193.

15. Inagaki Y. The rapid change of corneal curvature in the neonatal period and infancy. *Arch Ophthalmol* 1986;104:1026-1027.

16. Ehlers N, Sorensen T, Bramsen T, et al. Central corneal thickness in newborns and children. *Acta Ophthalmol* 1976;54:285-290.

17. York MA, Mandell RB. A new calibration system for photokeratoscopy. II. Corneal contour measurements. *Am J Optom Arch Am Acad Optom* 1969;46:818-825.

18. Akiba M. [Studies on the refractive status of the normal infant.] *Nippon Ganka Gakkai Zasshi* 1969;73:363-370.

19. Larsen JS. The sagittal growth of the eye. IV. Ultrasonic measurements of the axial length of the eye from birth to puberty. *Acta Ophthalmol (Copenh)* 1971;49:873-886.

20. Hayashi K, Hayaski H, Hayashi F. Topographic analysis of the changes in corneal shape due to aging. *Cornea* 1995;14:527-532.

21. Lesueur L, Arne JL, Mignon-Conte M, et al. Structural and ultrastructural changes in the developmental process of premature infants' and children's corneas. *Cornea* 1994;13:331-338.

22. Kanai A, Kaufman HE. Electron microscopic studies of corneal stroma: aging changes of collagen fibers. *Ann Ophthalmol* 1973; 5:285-292.

23. Malik NS, Moss SJ, Ahmed N, et al. Aging of the human corneal stroma: structural and biochemical changes. *Biochim Biophys Acta* 1992;1138:222-228.

24. Borcherding MS, Blacik LJ, Sittig RA, et al. Proteoglycans and collagen fibre organization in human corneoscleral tissue. *Exp Eye Res* 1975;21:59-70.

25. Møller-Pedersen T. A comparative study of human corneal keratocyte and endothelial cell density during aging. *Cornea* 1997; 16:333-338.

26. McCormick AQ. Transient phenomenon of the newborn eye. In: Isenberg SJ, ed. *The eye in infancy*, 2nd ed. St. Louis: Mosby, 1994.

27. Maseruka H, Ridgeway A, Tullo A, et al. Developmental changes in patterns of expression of tenascin-C variants in the human cornea. *Invest Ophthalmol Vis Sci* 2000;41:4101-4107.

28. Gordon MO, Beiser JA, Brandt JD, et al. The ocular hypertension treatment study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120:714-720.

29. Sullivan-Mee M, Pham F. Correspondence of Tono-Pen intraocular pressure measurements performed at the central cornea and mid-peripheral cornea. *Optometry* 2004;75:26-32.

30. Jaafar MS, Kazi GA. Normal intraocular pressure in children: a comparative study of the Perkins applanation tonometer and the pneumatonometer. *J Pediatr Ophthalmol Strabismus* 1993;30: 284-287.

31. Eisenberg DL, Sherman BG, McKeown CA, et al. Tonometry in adults and children. A manometric evaluation of pneumatonometry, applanation, and TonoPen in vitro and in vivo. *Ophthalmology* 1998;105:1173-1181.

32. Pensiero S, Da Pozzo S, Perissutti P, et al. Normal intraocular pressure in children. *J Pediatr Ophthalmol Strabismus* 1992;20: 79-84.

33. Jeanty P, Dramaix-Wilmet M, Van Gansbeke D, et al. Fetal ocular biometry by ultrasound. *Radiology* 1982;143:513-516.

34. Frudakis T, Thomas M, Gaskin Z, et al. Sequences associated with human iris pigmentation. *Genetics* 2003;165:2071-2083.

35. Hittner HM, Hirsch NJ, Rudolph AJ. Assessment of gestational age by examination of the anterior vascular capsule of the lens. *J Pediatr* 1977;91:455-458.

36. Luyckx J. [Measurement of the optic components of the eye of the newborn by ultrasonic echography.] *Arch Ophtalmol Rev Gen Ophtalmol* 1966;26:159-170.

37. Mutti DO, Zadnik K, Adams AA. The equivalent refractive index of the crystalline lens in childhood. *Vision Res* 1995;35: 1565-1573.

38. Wood IC, Mutti DO, Zadnik K. Crystalline lens parameters in infancy. *Ophthalmic Physiol Opt* 1996;16:310-317.

39. Zadnik K, Mutti DO, Fusaro RE, et al. Longitudinal evidence of crystalline lens thinning in children. *Invest Ophthalmol Vis Sci* 1995;36:1581-1587.

40. Mutti DO, Zadnik K, Fusaro RE, et al. Optical and structural development of the crystalline lens in childhood. *Invest Ophthalmol Vis Sci* 1998;39:120-133.

41. Dilley KJ, Harding JJ. Changes in proteins of the human lens in development and aging. *Biochim Biophys Acta* 1975;386: 391-408.

42. Hansen RM, Fulton AB. Psychophysical estimates of ocular media density of human infants. *Vision Res* 1989;29:687-690.

43. Wegener A, Muller-Breitenkamp U, Dragomirescu V, et al. Light scattering in the human lens in childhood and adolescence. *Ophthalmic Res* 1999;31:104-109.

44. Girard LJ, Neely W, Sampson WG. The use of alpha chymotrypsin in infants and children. *Am J Ophthalmol* 1962;54:95-101.

45. Rada JA, Achen VR, Penugonda S, et al. Proteoglycan composition in the human sclera during growth and aging. *Invest Ophthalmol Vis Sci* 2000;41:1639-1648.

46. Swan KC, Wilkins JH. Extraocular muscle surgery in early infancy: anatomical factors. *J Pediatr Ophthalmol Strabismus* 1984; 21:44-49.

47. Isenberg SJ, Dang Y, Jotterand V. The pupils of term and preterm infants. *Am J Ophthalmol* 1989;108:75-79.

48. Robinson J, Fielder AR. Pupillary diameter and reaction to light in preterm neonates. *Arch Dis Child* 1990;65:35-38.

49. Hendrickson A, Kupfer C. The histogenesis of the fovea in the macaque monkey. *Invest Ophthalmol Vis Sci* 1976;15:746-756.

50. Streeten BW. Development of the human retinal pigment epithelium and the posterior segment. *Arch Ophthalmol* 1969;81: 383-394.

51. Robb RM. Increase in retinal surface area during infancy and childhood. *J Pediatr Ophthalmol Strabismus* 1982;19:16-20.

52. Hollenberg MJ, Spira AW. Human retinal development: ultrastructure of the outer retina. *Am J Anat* 1973;137:357-385.

53. Curcio CA, Allen KA. Topography of ganglion cells in human retina. *J Comp Neurol* 1990;300:5-25.

54. Schein S. Anatomy of macaque fovea and spatial densities of neurons in foveal representation. *J Comp Neurol* 1988;269: 479-505.

55. Provis JM, van Driel D, Bilson FA, et al. Development of the human retina: patterns of cell distribution and redistribution in the ganglion cell layer. *J Comp Neurol* 1985;233:429-451.

56. Borwein B, Borwein D, Medeiros J, et al. The ultrastructure of monkey foveal photoreceptors, with special reference to the structure, shape, size and spacing of the foveal cones. *Am J Anat* 1980;159:125-146.

57. Mann I. *The development of the human eye*, 3rd ed. New York: Grune and Stratton, 1969.

58. Hendrickson A. A morphological comparison of foveal development in man and monkey. *Eye* 1992;6:136-144.

59. Westall CA, Panton CM, Levin AV. Time courses for maturation of electroretinogram responses from infancy to adulthood. *Doc Ophthalmol* 1999;96:355-379.

60. Breton ME, Quinn GE, Schueller AW. Development of electroretinogram and rod phototransduction response in human infants. *Invest Ophthalmol Vis Sci* 1995;36:1588-1602.

61. Cibis GW, Fitzgerald KM. Electroretinography in congenital idiopathic nystagmus. *Pediatr Neurol* 1993;9:369-371.

62. Fulton AB. The development of scotopic retinal function in human infants. *Doc Ophthalmol* 1988;69:101-109.

63. Fulton AB, Dodge J, Hansen RM, et al. The rhodopsin content of human eyes. *Invest Ophthalmol Vis Sci* 1999;40:1878-1883.

64. Fulton AB, Baker BN. The relation of retinal sensitivity and rhodopsin in developing rat retina. *Invest Ophthalmol Vis Sci* 1984; 25:647-651.

65. Curcio CA, Sloan KR, Kalina RE, et al. Human photoreceptor topography. *J Comp Neurol* 1990;292:497-523.

66. Hansen RM, Fulton AB. The course of maturation of rod mediated visual thresholds in infants. *Invest Ophthalmol Vis Sci* 1999; 40:1883-1885.

67. Hendrickson AE, Drucker D. The development of parafoveal and midperipheral retina. *Behav Brain Res* 1992;19:21-32.

68. Fulton AB, Hansen RM. The development of scotopic sensitivity. *Invest Ophthalmol Vis Sci* 2000;41:1588-1596.

69. Weymouth FW. Visual acuity of children. In: Hirsch MJ, Wick RE, eds. *Vision in children*. Philadelphia: Chilton Books, 1963: 119-143.

70. Wiesel TN, Hubel DH. Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *J Neurophysiol* 1965;28:1029-1040.

71. Hubel DH, Wiesel TN. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J Physiol* 1970; 206:419-436.

72. Fogarty TP, Reuben RN. Light-evoked cortical and retinal responses in premature infants. *Arch Ophthalmol* 1969;81: 454-459.

73. Wiesel TN, Hubel DH. Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. *J Neurophysiol* 1963;26:978-993.

74. Wiesel TN, Hubel DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J Neurophysiol* 1963;26: 1003-1017.

75. Kratz KE, Spear PD, Smith DC. Postcritical-period reversal of effects of monocular deprivation on striate cortex cells in the cat. *J Neurophysiol* 1976;39:501-511.

76. Kasamatsu T, Pettigrew JD, Ary M. Cortical recovery from effects of monocular deprivation: acceleration with norepinephrine and suppression with 6-hydroxydopamine. *J Neurophysiol* 1981;45: 254-266.

77. Crawford MLJ, Harwerth RS, Smith EL, et al. Keeping an eye on the brain: the role of visual experience in monkeys and children. *J Gen Psychol* 1993;120:7-19.

78. Crawford MLJ, von Noorden GK, Meharg LS, et al. Binocular neurons and binocular function in monkeys and children. *Invest Ophthalmol Vis Sci* 1983;24:491-495.

79. von Noorden GK. Experimental amblyopia in monkeys. Further behavioral observations and clinical correlations. *Invest Ophthalmol* 1973;12:721-726.

80. Hess RF, Campbell FW, Greenhalgh T. On the nature of the neural abnormality in human amblyopia; neural aberrations and neural sensitivity loss. *Pflugers Arch* 1978;377:201-207.

81. Moore T, Rodman HR, Repp AB, et al. Greater residual vision in monkeys after striate cortex damage in infancy. *J Neurophysiol* 1996;76:3928-3933.

82. Finger S, Wolf C. The “Kennard effect” before Kennard: the early history of age and brain lesions. *Arch Neurol* 1988;45: 1136-1142.

83. Kennard MA. Reorganization of motor function in the cerebral cortex of monkeys deprived of motor and premotor areas in infancy. *J Neurophysiol* 1938;1:477-496.

84. Carlson M, Burton H. Recovery of tactile function after damage to primary or secondary somatic sensory cortex in infant Macaca mulatta. *J Neurophysiol* 1986;55:1057-1075.

85. Bachevalier J, Brickson M, Hagger C, et al. Age and sex differences in the effects of selective temporal lobe lesions on the formation of visual discrimination in rhesus monkeys. *Behav Neurosci* 1990; 104:885-889.

86. Milhailovic LT, Dragoslava C, Dekleva N. Changes in the number of neurons and glia cells in the lateral geniculate nucleus of the monkey during retrograde cell degeneration. *J Comp Neurol* 1971; 142:223-230.

87. Weller RE, Kaas JH. Parameters affecting the loss of ganglion cells following ablations of striate cortex. *Vis Neurosci* 1989;3: 327-349.

88. Johnson MH. Brain and cognitive development in infancy. *Curr Opin Neurobiol* 1994;4:218-225.

89. Rodman HR, Gross CG, Albright TD. Afferent basis of visual response properties in area MT of the macaque. Effects of striate cortex removal. *J Neurosci* 1989;9:2033-2050.

90. Liégeois F, Bentejac L, de Schonen S. When does inter-hemi-spheric integration of visual events emerge in infancy? A developmental study on 19- to 28-month-old infants. *Neuropsychologia* 2000;38:1382-1389.

91. Lie´geois F, de Schonen S. Simultaneous attention in the two visual hemifields and interhemispheric integration: a developmental study on 20- to 26-month-old infants. *Neuropsychologia* 1997;35:381-385.

92. Deruelle C, de Schonen S. Hemispheric asymmetries in visual pattern processing in infancy. *Brain Cogn* 1991;16:151-179.

93. de Schonen S, Mathivet E. Hemispheric asymmetry in a face discrimination task in infants. *Child Dev* 1990;61:1192-1205.

94. Illingworth RS. Delayed visual maturation. *Arch Dis Chila* 1961;36:407-409.

95. Cole GF, Hungerford J, Jones RB. Delayed visual maturation. *Arch Dis Child* 1984;59:107-110.

96. Fielder AR, Russell-Eggitt IR, Dodd KL, et al. Delayed visual maturation. *Trans Ophthalmol Soc UK* 1985;104:653-661.

97. Kivlin JD, Bodnar A, Ralston CW, et al. The visually inattentive preterm infant. *J Pediatr Ophthalmol Strabismus* 1990;27: 190-195.

98. Farkas LG, Posnick JC, Hreczko TM, et al. Growth patterns in the orbital region: a morphometric study. *Cleft Palate Craniofac J* 1992;29:4:315-318.

99. Ferrario VF, Sforza C, Colombo A, et al. Morphometry of the orbital region: a soft-tissue study from adolescence to mid-adulthood. *Plast Reconstr Surg* 2001;108:285-292.

100. Farkas LG, Posnick JC. Growth and development of regional units in the head and face based on anthropometric measurements. *Clef Palate Craniofac J* 1992;29:301-302.

101. Bentley RP, Sgouros S, Natarajan K, et al. Normal changes in orbital volume during childhood. *J Neurosurg* 2002;96:742-746.

102. Bentley RP, Sgouros S, Natarajan K, et al. Changes in orbital volume during childhood in cases of craniosynostosis. *J Neurosurg* 2002;96:747-754.

103. Thomson WE. The determination of the influence of the eyeball on the growth of the orbit, by experimental enucleation of one eye in young animals. *Trans Ophthalmol Soc* 1901;21:258-268.

104. Pfeiffer RL. The effect of enucleation on the orbit. *Trans Am Acad Ophthalmol* 1945;49:236-239.

105. Osborne D, Hadden OB, Demming LW. Orbital growth after childhood enucleation. *Am J Ophthalmol* 1974;77:756-759.

106. Fountain TR, Goldberger S, Murphree AL. Orbital development after enucleation in early childhood. *Ophthal Plast Reconstr Surg* 1999;15:32-36.

107. Hintschich C, Zonneveld F, Baldeschi L, et al. Bony orbital development after early enucleation in humans. *Br J Ophthalmol* 2001; 85:205-208.

108. Kennedy RE. Bone changes in the adult anophthalmic orbit influencing oculoplastic reconstructive considerations. *Trans Am Ophthalmol Soc* 1976;74:237-248.

109. Weiss L. Ueber das verhalten der augenhöhle bei einäugigen. *Arch Augenheilk* 1892;25:423-446.

110. McCormick AQ. Transient phenomena of the newborn eye. In: Isenberg SJ, ed. *The eye in infancy,* 2nd ed. St. Louis: Mosby, 1994:67-72.

111. Paiva RSN, Minare-Filho AM, Cruz AAV. Palpebral fissure changes in early childhood. *J Pediatr Ophthalmol Strabismus* 1002; 38:219-223.

112. Zamora RL, Becker WL, Custer PH. Normal eyelid crease position in children. *Ophthal Surg* 1994;25:42-47.

113. Fox SA. The palpebral fissure. *Am J Ophthalmol* 1966;62:73-78.

114. Sjögren H. The lacrimal secretion in newborn premature and fully developed children. *Acta Ophthalmol* 1955;33:557-560.

115. Apt L, Cullen BF. Newborns do secrete tears. *JAMA* 1964;189: 951-953.

116. Toker E, Yenice Ö, Ögüt MS, et al. Tear production during the neonatal period. *Am J Ophthalmol* 2002;133:746-749.

117. Patrick RK. Lacrimal secretion in full term and premature babies. *Trans Ophthalmol Soc UK* 1974;94:283-289.

118. Isenberg SJ, Apt L, McCarty JA, et al. Development of tearing in preterm and term neonates. *Arch Ophthalmol* 1998;116: 773-776.

119. Isenberg SJ, Del Signore M, Chen A, et al. The lipid layer and stability of the preocular tear film in newborns and infants. *Ophthalmology* 2003;110:1408-1411.

120. Kaercher T, Mobius D, Welt R. Biophysical behavior of the infant Meibomian lipid layer. *Int Ophthalmol* 1994;18:15-19.

121. Sperduto RD, Siegel D, Roberts J, et al. Prevalence of myopia in the United States. *Arch Ophthalmol* 1983;101:405-407.

122. Lam CSY, Goh WSH. The incidence of refractive errors among school children in Hong Kong and its relationship with optical components. *Clin Exp Optom* 1991;74:97-103.

123. Meyer C, Mueller MF, Duncker GIW, et al. Experimental animal myopia models are applicable to human juvenile-onset myopia. *Surv Ophthalmol* 1999;44:S93-S102.

124. Dobson V, Fulton AB, Manning K. Cycloplegic refractions of premature infants. *Am J Ophthalmol* 1981;91:490-495.

125. Lavrich JB, Nelson LB, Simon JW, et al. Medium to high grade myopia in infancy and early childhood: frequency, course and association with strabismus and amblyopia. *Binocul Vis Eye Muscle Surg Q* 1993;8:41-44.

126. Baldwin WR. Refractive status of infants and children. In: Rosenbloom AA, Morgan MW, eds. *Principles and practice of pediatric optometry*. Philadelphia: Lippincott, 1990:104-152.

127. Cook A, White S, Batterbury M, et al. Ocular growth and refractive error development in premature infants without retinopathy of prematurity. *Invest Ophthalmol Vis Sci* 2003;44:953-960.

128. Kuo A, Sinatra RB, Donahue SP. Distribution of refractive error in healthy infants. *J AAPOS* 2003;7:174-177.

129. Atkinson J, Braddick O, Robier B, et al. Two infant vision screening programmes: prediction and prevention of strabismus and amblyopia from photo-and videorefractive screening. *Eye* 1996; 10:189-198.

130. Ottar WL, Scott WE, Holgado SI. Photoscreening for amblyogenic factors. *J Pediatr Ophthalmol Strabismus* 1995;32:289-295.

131. Mayer DL, Hansen RM, Moore BD, et al. Cycloplegic refractions in healthy children aged 1 through 48 months. *Arch Ophthalmol* 2001;119:1625-1628.

132. Miller JM, Harvey EM. Spectacle prescribing recommendations of AAPOS members. *J Pediatr Ophthalmol Strabismus* 1998;35: 51-52.

133. Zadnik K. Myopia development in children. *Optom Vis Sci* 1997; 74:603-608.

134. Brown NP, Koretz JF, Bron AJ. The development and maintenance of emmetropia. *Eye* 1999;13:83-92.

135. Ehrlich DL, Atkinson J, Braddick O, et al. Reduction of infant myopia: a longitudinal cycloplegic study. *Vision Res* 1995;9: 1313-1324.

136. Curtin BJ. The pathogenesis of congenital myopia. *Arch Ophthalmol* 1963;69:166-173.

137. Linfield PB. Myopia and the trend towards emmetropia in newborn premature babies. *Invest Ophthalmol Vis Sci* 1993;34:1353.

138. Blum HL, Peters HB, Bettman JW. *Vision screening for elementary school: the Orinda study*. Berkeley: University of California Press, 1959.

139. Mutti DO, Sholtz RI, Friedman NE, et al. Peripheral refraction and ocular shape in children. *Invest Ophthalmol Vis Sci* 2000;41: 1022-1030.

140. Minkovitz JB, Essary LR, Walker RS, et al. Comparative corneal topography and refractive parameters in monozygotic and dizygotic twins. *Invest Ophthalmol Vis Sci* 1993;34:1218.

141. Kimura T. Developmental change of the optical components in twins. *Acta Soc Ophthalmol Jpn* 1965;69:963-969.

142. Zadnik K, Satariano WA, Mutti DO, et al. The effect of parental history of myopia on children's eye size. *JAMA* 1994;271: 1323-1327.

143. Hui J, Peck L, Howland HC. Correlations between familial refractive error and children's non-cycloplegic refraction. *Vision Res* 1995;35:1353-1358.

144. Zadnik K, Mutti DO, Friedman NE, et al. Initial cross-sectional results from the Orinda longitudinal study of myopia. *Optom Vis Sci* 1993;70:750-758.

145. Wallman J. Nature and nurture of myopia. *Nature* 1994;371: 201-202.

146. Mutti DO, Jones LA, Moeschberger ML, et al. AC/A ratio, age, and refractive error in children. *Invest Ophthalmol Vis Sci* 2000; 41:2469-2478.

147. Curtin BJ. *The myopias: basic science and clinical management*. Philadelphia: Harper & Row, 1985.

148. Edwards MH, Shing FC. Is refraction in early infancy a predictor of myopia at the age of 7 to 8 years? The relationship between cycloplegic refraction at 11 weeks and the manifest refraction at age 7 to 8 years in Chinese children. *Optom Vis Sci* 1999;76: 272-274.

149. Robb RM. Refractive errors associated with hemangiomas of the eyelids and orbit in infancy. *Am J Ophthalmol* 1977;83:52-58.

150. Angell LK, Robb RM, Berson FG. Visual prognosis in patients with ruptures in Descemet's membrane due to forceps injuries. *Arch Ophthalmol* 1981;99:2137-2139.

151. Fulton AB, Hansen RM, Petersen RA. The relation of myopia and astigmatism in developing eyes. *Ophthalmology* 1982;89: 298-302.

152. Hubel DH, Wiesel TN. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J Physiol* 1970; 206:419-436.

153. Wiesel TN, Raviola E. Increase in axial length of the macaque monkey after corneal opacification. *Invest Ophthalmol Vis Sci* 1979;18:1232-1236.

154. Lauber JK, Schutze V, McGinnis J. Effects of exposure to continuous light on the eye of the growing chick. *Proc Soc Exp Biol Med* 1961;106:871-872.

155. Regal DM, Boothe R, Teller DY, et al. Visual acuity and visual responsiveness in dark-reared monkeys (Macaca nemestrina). *Vision Res* 1976;16:523-530.

156. Raviola E, Wiesel TN. Effect of dark-rearing on experimental myopia in monkeys. *Invest Ophthalmol Vis Sci* 1978;17:485-488.

157. Yinon R, Koslow KC, Goshen S. Eyelid closure effects on the refractive error of the eye in dark and in light reared kittens. The optical effects of eyelid closure on the eyes of kittens reared in light and dark. *Curr Eye Res* 1984;3:431-439.

158. Young FA. The effect of restricted visual space on the primate eye. *Am J Ophthalmol* 1961;52:799-806.

159. Rose L, Yinon U, Belkin M. Myopia induced in cats deprived of distance vision during development. *Vision Res* 1974;14: 1029-1032.

160. Choi MY, Yu YS. Effects of scleral buckling on refraction and ocular growth in young rabbits. *Graefes Arch Clin Exp Ophthalmol* 2000;238:774-778.

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3

Retinopathy of Prematurity

James D. Reynolds

Retinopathy of prematurity (ROP) is a complex disorder of the developing retinal vasculature in the immature retina of prematurely born infants. A relatively harmless and spontaneously resolving disease in the majority of affected infants, it unfortunately can threaten blindness in a significant minority and even today can still result in blindness despite the best medical care.

ROP was first described in 1942 by Terry. His initial, brief report referred to this new disease as possibly a “fibroblastic overgrowth of the persistent tunica vasculosa lentis” (1). His second report was more extensive and involved several colleagues, one of whom, Messenger, formulated the descriptive term retrolental fibroplasia (2). Although not completely endorsed by Terry, the name stuck and the disease was known as retrolental fibroplasia (RLF) for the next 40 years. The second report, containing several pathologic specimens in the cicatricial end stages of the disease with multiple complications, clearly misinterpreted the involved pathophysiology. Terry did not recognize the retina as the source of the problem and still linked it to the rare congenital birth defect of persistence of the hyaloid artery and tunica vasculosa lentis. But he did recognize the salient epidemiology—that “some new factor had arisen” and the condition was occurring much “more frequently in infants born extremely prematurely.”

Terry concluded the initial case report with an entreaty to determine the “frequency, cause, and full nature” of the condition to discover “prophylactic treatment and effective therapy.” More than half a century of intense clinical and laboratory research efforts have made great strides in developing “effective therapies” for severe stages of ROP, and the understanding of the “nature” of this condition has improved tremendously. But little progress has been made in truly understanding the “cause” of this disease and even less in developing effective “prophylactic treatment.” The central mysteries of this disease have not been adequately unraveled to effectively eradicate unfavorable visual outcomes.

Individuals with ROP-induced blindness are far fewer than those afflicted with blindness from macular degeneration or diabetic retinopathy. Nonetheless this is a significant disease to the affected children, their parents, and to society in general. Steinkuller and coworkers (3) analyzed childhood blindness in the 10 years preceding their 1999 report. They found the three leading causes of pediatric blindness in the United States were cortical visual impairment, ROP, and optic nerve hypoplasia. Cortical visual impairment results from a variety of brain insults, often *in utero*, and usually is associated with other global sequelae. Optic nerve hypoplasia is a birth defect in fetal development without a known cause. Neither condition presents an opportunity for treatment. Thus, the leading cause of preventable blindness in children in the United States is ROP. This ongoing problem of ROP-induced infant blindness in the United States is confirmed by the Blind Babies Foundation (4).

Expanding the scope outside the United States finds a worldwide epidemic rivaling the U.S. experience in the 1940s and 1950s. Gilbert and coworkers (5) analyzed ROP throughout the world. They divided the world into three groupings of ROP epidemiology which correlated highly with national wealth. In high-income countries like the United States, many extremely premature infants are saved, effective ROP treatments are universally applied, and ROP-induced blindness occurs but is limited. In low-income countries like most of those in Africa, extremely premature infants simply do not survive due to a lack of intensive care nursery technology. Hence, ROP blindness does not exist. However in middle-income countries, such as in Latin America or Asia, intensive care is available, premature infants survive, but adequate means for screening and/or treatment are not available and ROP blindness is epidemic. The World Health Organization (WHO) and various partnering agencies launched the VISION 2020 program which targeted childhood blindness and confirmed the need for ROP services, especially in middle-income countries (6).

One such middle-income country is Vietnam. A 1-year prospective series at a single maternity hospital in Ho Chi Minh City quantified the assessment of ROP risk (7). This study demonstrated an incidence of any ROP similar to that in the United States. But the incidence of severe ROP was considerably greater, and ROP was present in larger, older babies. Unfortunately, it also demonstrated a high rate of blindness from less than ideal management.

In addition to the quantity of the problem, the socioeco-nomic costs relate to the quality of the problem. Apart from the number of individuals affected, there is a qualitative difference between a lifetime of blindness and end-of-life blindness. Gilbert and Foster refer to this in terms of “blind years” and state that the worldwide number of blind years resulting from childhood blindness is similar to the quantity of blind years resulting from adult cataracts (8).

Another major socioeconomic issue relates to the form of ROP management. Our current understanding of ROP has limited any effective prevention. Treatment regimens are limited to high technology, high skill, and high-cost interventional therapy. This makes treatment expensive in high-income countries and unaffordable in middle-income countries.

HISTORY

The history of ROP in its early years as a public health epidemic and the scientific investigation involved in the search for answers is fascinating and holds lessons that are still relevant today. This disease seemed to come from nowhere when it burst on the nursery scene in the 1940s. As noted above, it was first described by Terry (1,2). Following this, RLF developed into a full-blown epidemic, blinding 10,000 babies between 1942 and 1954 (9). A frantic search for cause and effect and potential management was initiated. The only sure fact was that RLF occurred with an alarming frequency in premature infants whose lives were being saved for the first time by new approaches to caring for such infants in technologically advanced nurseries. But investigators were beginning to suspect supplemental oxygen administration (10,11).

Jacobson and Feinstein performed a postmortem on the clinical epidemiologic research attempt to solve the RLF puzzle (9). The authors painstakingly described and analyzed a “decade of errors” in this research. Poor methodology, misleading assumptions, reliance on small sample size, empirical methods, investigator bias, lack of controls, and lack of randomization all contributed to dead-ends. The story culminates in the success of the multicenter, randomized clinical trial, the National Cooperative Study, in definitively uncovering the correlation between increased exposure to supplemental oxygen and RLF (12,13). These supplementary oxygen revelations resulted in a curtailing of limitless oxygen administration in the nursery. An oxygen policy based on the least amount of inspired oxygen for survival dramatically lowered the incidence of blind babies. But it did not eliminate them. And unfortunately it did not minimize mortality and morbidity (14). The oxygen controversy, thought to be put to rest in 1955, still rages today. Silverman states in an editorial that “there has never been a shred of convincing evidence to guide limits for the rational use of supplemental oxygen in the care of extremely premature infants” (15).

In the last half century, in the continuing quest to answer the questions posed by Terry (1), researchers did not always learn from their mistakes. False passages illuminated by poor methodology continued to plague ROP research. Resurrection of perhaps prematurely discarded ideas came into vogue. It required the age of the multicenter randomized trial to arrive in conjunction with basic laboratory investigation to begin to characterize ROP. The rest of this chapter will concentrate on the last 25 years of ROP research, defining what is now known about Terry's “nature, cause, prophylaxis (sic), and therapy.”

CLASSIFICATION

An early difficulty in epidemiologic research was the lack of a universal classification of ROP. Investigators were not always speaking the same language, meaning that important elements of the disease could go unrecognized or unappreciated. This serious impediment was removed in 1984 with the publication of

the International Classification of Retinopathy of Prematurity (ICROP) (16). This was the key to opening the door to rigorous trials. Its relevance was immediately recognized, and clinicians and researchers alike embraced the classification. Its significance cannot be overstated. Overnight the epidemiology landscape changed dramatically.

Besides providing this crucial basis for further research, the classification had another, more subtle, much less recognized but still very important benefit. The process of its development and adoption brought many of the central investigators together. It served as a model of cooperation and collaboration and paved the way for the future multicenter trials that would so define this disease. So the classification provided both the scientific foundation and philosophic approach for subsequent investigations.

The core of the classification was defining the stages of the acute disease and presenting a topographic map upon which to locate the disease in the retina. Both have major clinical significance. Staging of ROP relied upon clearly definable and observable structural changes in the retina. The stages proceeded from mildest to most severe disease and were classified as stages 1 through 4. These stages were usually easily recognized by experienced examiners utilizing the indirect ophthalmoscope, which provides the important three-dimensional picture of this disease. The stages of ROP were agreed to be the following:

Stage 1: line of demarcation

Stage 2: ridge of elevated tissue

Stage 3: neovascularization with extraretinal fibrovascular proliferation

Stage 4: retinal detachment

4a: macula not involved

4b: macula detached

Stage 5: total retinal detachment

More descriptively, stage 1 is a circumlinear, whitish, thin, flat line distinctly separating normally vascularized retina from as yet unvascularized retina. Stage 2 is present

when this circumlinear line becomes thicker and more elevated and forms a true ridge extending out of the plane of the retina. The three-dimensional view of the indirect ophthalmoscope is crucial here. Stage 3 is extraretinal fibrovascular neovascularization. The fibrous component has a very different appearance than the neovascularization in diabetes or sickle cell disease. This neovascularization is more of a continuous sheet of solid pink tissue (Fig. 3.1). Fronds of individual vessels typical of other diseases are not seen in ROP. Stage 4 represents retinal detachment, small or large, shallow or high. The retinal detachment may be exudative, tractional, or both, but is not rhegmatogenous. Stage 5 is an addition to the International Classification used to denote a total retinal detachment, either open funnel or closed (17).

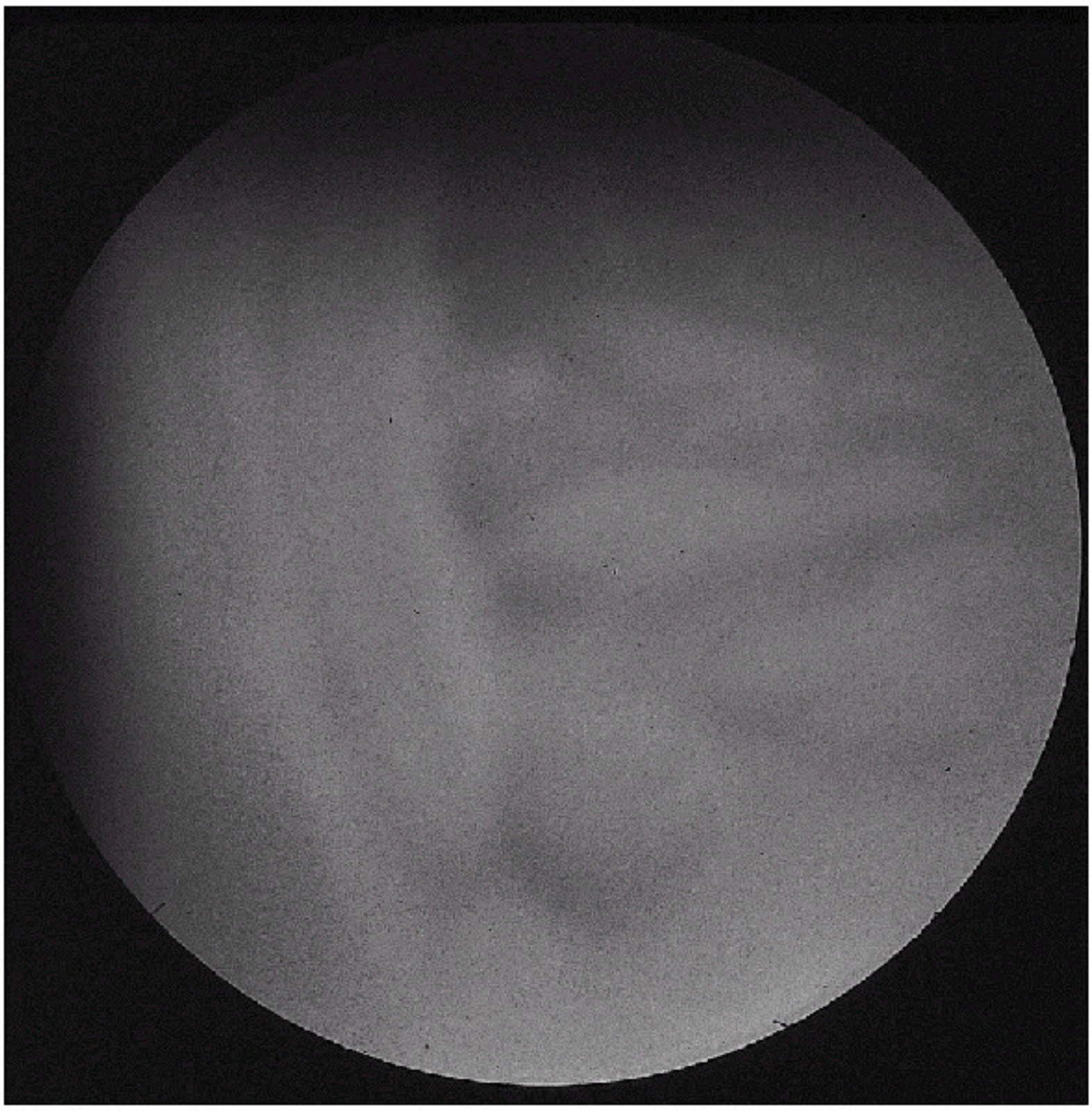

Figure 3.1 Typical, moderately severe stage 3 ROP. Note the continuous sheet of extraretinal, fibrovascular tissue. Even in this two-dimensional photo, the elevation is apparent.

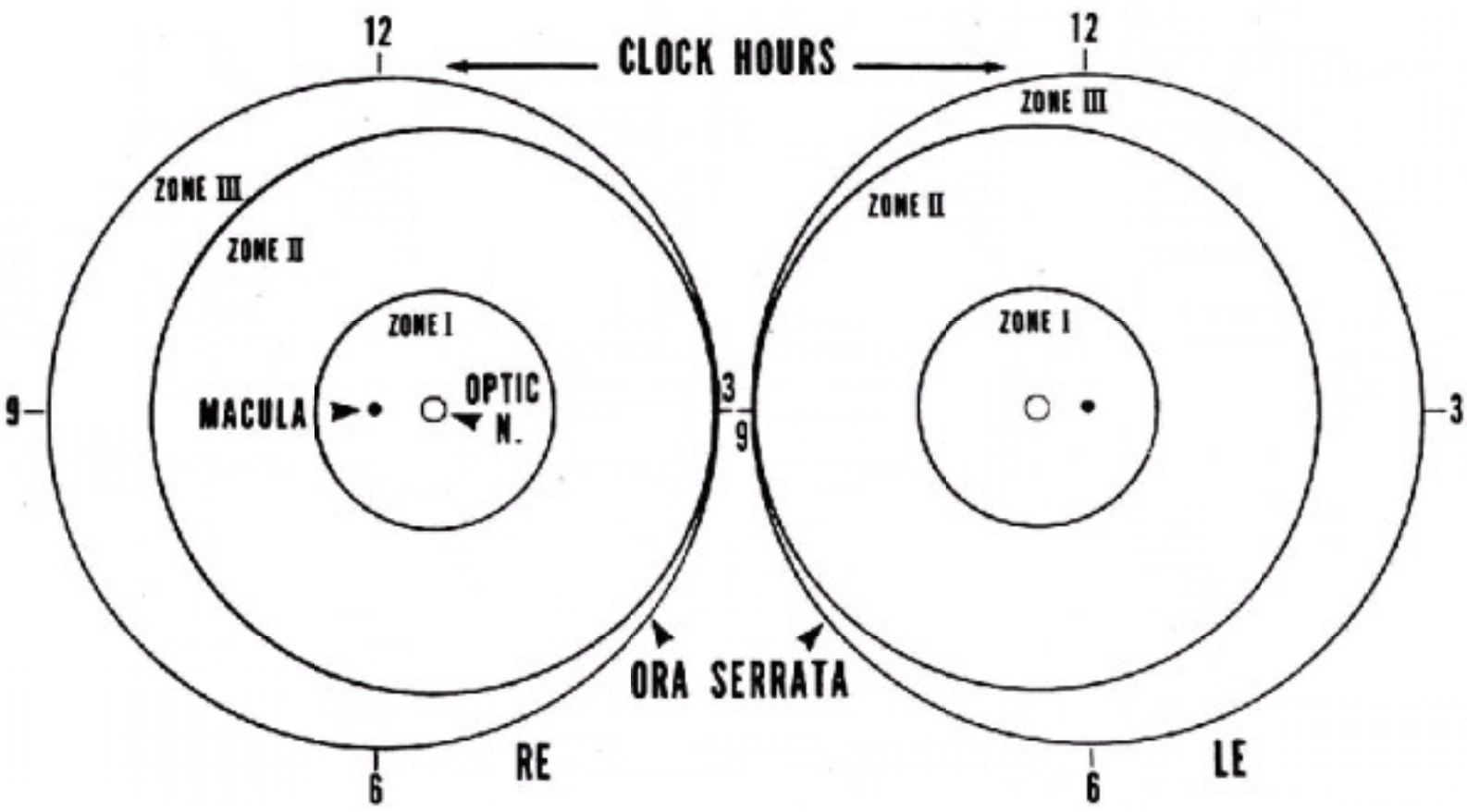

Figure 3.2 Schematic representation of the retinas divided into three zones, with the relevant anatomic landmarks. (Reprinted from the Committee for the Classification of Retinopathy of Prematurity: An international classification of retinopathy of prematurity. *Arch. Ophthalmol* 1984;102: 1130-1134. Copyright, American Medical Association, 1984. All rights reserved.)

The topographic map of the retina devised by the International Classification is shown in Figure 3.2. It divides each retina into three zones. The goal of these divisions was to be clinically relevant yet easily recognized. These zones are defined as follows:

Zone I: a concentric circle, centered on the optic nerve, with a radius of two times the distance from the center of the nerve to the center of the fovea

Zone II: diagrammatically a concentric annular area arising from the outer border of zone I and ending at the ora nasally and just beyond the equator temporally

Zone III: a large temporal crescent arising from the outer border of zone II and terminating at the temporal ora serrata

There are several very important points to understand about the location classification that have bearing on the way the natural history of this disease plays out on this topography. First, it is an arbitrary classification. The zones were picked to enhance ease of recognition. The optic nerve, macula, and nasal and temporal ora are all distinct and identifiable by indirect ophthalmoscopy. Recognition of the equator, which can be difficult, is irrelevant to the classification. Secondly, the macula is the true anatomic center of the eye, not the optic disc. But vascularization of the retina proceeds centrifugally from the optic disc to the ora. Since the optic disc is in the nasal retina, normal vessel development reaches the nasal ora first, leaving the as yet unvascularized temporal crescent. If observed at just the right moment in time, this temporal crescent can actually extend to well over 300 degrees of the peripheral retina. Thirdly, there is no defined border between zones II and III on the temporal side. Because there was no easily identifiable

midperipheral landmark to use as a reference, the temporal location is defined exclusively by the relationship of the normal vessel growth or ROP pathology to the nasal ora. No matter where the real location is temporally, if the vessels have not reached the nasal ora, the location is zone I or II. If the vessels have reached the nasal ora, then the location is defined as zone III. With normal, uninterrupted vascularization, the diagrammatic representation of a concentric zone II reflects reality. But when pathology supervenes, it is possible to have temporal disease in zone II that does not physically move but becomes arbitrarily classified as zone III when nasal vascularization is less impeded by pathology. In other words, nonconcentric ROP can exist in the presence of asymmetric location of disease onset, progression, or involution.

Although minor, it is a flaw in the classification that the three zones reflect the natural progression of normal vascularization but do not always accurately reflect the true location of temporal disease. A true representation would relate temporal disease to its anatomic proximity to the macula in zone II as it does in zone I. This would realistically predict its ability to impact the macula and central vision. But since temporal disease location is defined by nasal pathophysiology, temporal disease is always, at best, an estimated location. As will be shown in subsequent sections, this has an impact on natural history and screening guidelines. In summary, the location classification is grounded in normal physiology of vascularization, is easily identifiable, and is highly clinically relevant.

By convention, ROP is clinically classified by the highest stage and lowest zone. The retina is imaginarily divided into twelve equal radial segments, commonly referred to as clock hours, and this represents the extent of the disease. Disease can be present for as little as 1 clock hour or as many as 12. But the highest stage and lowest zone of just 1 clock hour determines the disease classification at that time. For example, 1 hour of stage 3, zone I and 11 hours of stage 2, zone II is diagnosed as stage 3, zone I disease.

Finally, the concept of plus disease was introduced (16). Plus disease refers to posterior pole large vessel engorgement and tortuosity. Plus disease occurs in response to a stimulation for increased blood flow. There is usually a neovascular shunt present, which itself has arisen due to ischemia signals within the retina. And plus is more likely to occur when the ROP is more posterior, possibly because the large vessels respond more to an anatomically nearer ischemic microenvironment. Along with flagrant plus disease comes vitreous haze, iris vessel engorgement, and iris resistance to mydriatics. This hemodynamic change is a threshold concept that requires a minimum degree of change before it can be termed plus. Its specific definition is:

Plus disease: posterior venous dilation and arteriolar tortuosity of at least a photographically defined minimum

But the process of developing plus disease is not all-ornone. Posterior pole vessel dilatation and tortuosity can be of gradual onset or to a level not recognized as full plus. Thus, plus disease requires the observer to make a quantifiable judgment of an inherently qualitative clinical sign. This is far different from the other portions of the classification. Stage and location are not a question of degree. Often this judgment is easy with flagrant plus disease being obvious. But borderline plus disease can be difficult. The very word borderline implies the difficulty involved. The minimum level of plus disease required has been traditionally taught to ROP examiners by way of a single standard photograph (16). It has never been put into a prose definition and never been objectively quantified. Various investigators have subdivided preplus changes, but they have not been widely accepted (18,19,20).

Another difficulty in judging plus disease is the impact that the examination has on the clinical picture. Scleral depression can impede blood flow by temporarily raising the intraocular pressure. Reduced blood flow results in reduced dilation. Prolonged examination, perhaps by multiple, sequential observers, can increase blood flow, a kind of rebound effect. Again, a crucial judgment is made more difficult and the observer must be cautious.

Finally, the ICROP II described and classified retinal detachments, as well as regression patterns of ROP. Special attention was given to peripheral versus central changes. Regression of acute ROP is synonymous with the onset of cicatricial disease development (17).

The International Classification, parts I and II, was an enormous step forward. It has an ease of use that allows reliable interobserver assignment of disease stage, location, extent, and presence or absence of plus disease. Equally important is its strong clinical relevance. The observer needs only some experience and an awareness of the above caveats.

Subsequent subsidiary classifications have become clinically universal. These do not alter or depart from the International Classification but have added clinically relevant subclassifications. The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) developed the concept of assigning clinical significance to a certain level of disease (21). Although arbitrary and developed as a definition to determine study intervention, the concepts proved so clinically useful that they were adopted to define the standard of care. These two ubiquitous definitions are prethreshold ROP and threshold ROP. Prethreshold was defined as a near intervention level of disease severity, and threshold, as the name implies, was a level of disease severity which triggered study intervention. These definitions are:

Prethreshold ROP: any stage ROP in zone I, stage 2 zone II plus, or any stage 3

Threshold ROP: at least 5 contiguous or 8 cumulative clock hours of stage 3 zone I or II with plus

These two concepts are ingrained in clinical parlance, and the terms are always used to mean the exact definitions above. They no longer define the standard of care for disease intervention, but they did so for 15 years.

The last clinical concept applied to help subdivide ROP further is that of rush disease. This is a well-known subdivision of ROP but is not well defined or universal. But the ROP examiner should be aware of the term. A close approximation of how it is commonly used is:

Rush disease: rapidly progressive ROP, usually in the posterior retina (zone I or posterior zone II), usually with rapidly evolving plus disease and neovascularization

Thus, the current clinical classification system utilizes the formally agreed upon International Classification and the clinically useful modifiers over the years and includes:

Stage

Location

Extent

Plus disease

Regression of disease (cicatricial pattern)

Prethreshold ROP

Threshold ROP

Rush disease

All examiners should be familiar and facile with these terms, their definitions, and most important, their clinical appearance and relevance.

SCREENING AND EXAMINATION

Screening for ROP is an essential element in the management of ROP. The cardinal rule is that the patient must be examined before the patient can be treated. The cardinal sin is failing to examine the patient within the window of treatment opportunity. Appropriate screening requires scientific evidence to outline the screening parameters but also requires appropriate administrative supervision in applying those screening parameters to each at-risk infant.

An ideal evidence-based screening protocol should detect serious disease in a timely fashion, consistently, reliably, and cost effectively. It should minimize the number of examinations required and maximize the opportunity for intervention. It does not have to account for every conceivable exception. In fact, screening programs by nature must have parameters based in population statistics, not in exceptional circumstance. Risk must be reasonably defined.

Examination of the entire premature infant retina requires a well-dilated pupil and indirect ophthalmoscopy with lid speculum and scleral depression. Minimizing examinations is especially important in premature infants undergoing the stress of pharmacologic pupillary dilation and scleral depression. These tiny infants are especially medically unstable in the early weeks of ROP screening examinations. Reported complications include cardiopul-monary arrest, apnea, bradycardia, tachycardia, alterations in blood pressure, decreased oxygen saturation, inadvertent extubation, gastric reflux, and infection (22,23,24,25,26,27). In addition, unnecessary examinations add to the expense of care and may inconvenience families and expose infants to infection risk when forced to attend unnecessary outpatient examinations. Thus, ROP screening guidelines should provide for when to appropriately begin examinations, how often to examine, and when to conclude examinations. In addition, the at-risk population needs to be reasonably defined.

Screening guidelines have been offered and updated many times from many sources. These sources include single-center experience, as well as political consensus documents. Three policy statements come from the Royal College of Ophthalmologists and British Association of Perinatal Medicine (28); American Academy of Pediatrics, American Association for Pediatric Ophthalmology and Strabismus, and American Academy of Ophthalmology (29); and Canadian Association of Pediatric Ophthalmology (30). Utilizing these three consensus recommendations, a reasonable conclusion as to the at-risk population would be all premature infants with a birth weight of less than or equal to 1,500 grams or with gestational ages of 31 weeks or less. Keep in mind that this represents the at-risk population in high-income countries. The Vietnam series would suggest that larger, older babies are at risk in middle-income countries (7). This is probably due to differences in the standard of care available in the neonatal intensive care nurseries.

The timing of ROP screening no longer needs to rely on single-center data or consensus policy statements. Reynolds and coworkers utilized the databases from the CRYO-ROP study (31) and the Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) study (32) “to define appropriate ages and retinal ophthalmoscopic signs for the initiation and conclusion of acute-phase ROP screening” (33). The goal was to examine the infant within the window of opportunity for ideal treatment intervention while minimizing exams. An additional goal was to provide for an evolving definition of the ideal point of intervention in the disease spectrum without

requiring alteration of the guidelines. Figure 3.3 shows the basic data used by the authors, and Figure 3.4 demonstrates the near identity of CRYO-ROP and LIGHT-ROP despite a decade of separation. This identity of disease onset validates the applicability of CRYO-ROP data to today's situation.

Analyzing this data and more, the authors recommended that the timing of the initial exam follow the guidelines in Table 3.1. Based on accurate assessment of

gestational age at birth, any infant can be plugged into the table, and the week of the initial exam can be definitively set in advance. Similar timing data, with the addition of prognostic retinal signs along with ROP involution data (34), can be used to determine a safe and appropriate time for the conclusion of screening.

TABLE 3.1 TIMING OF INITIAL EYE EXAM

Designed to detect at least 99% of serious ROP

Gestational age at birth (weeks)	Age at initial examination (weeks)	
	Postmenstrual	Chronologic
22[a]	31	9
23[a]	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4

[a] This guideline should be considered tentative rather than evidence based for 22- to 23-week infants owing to the small number of survivors in these gestational age categories.

ROP, retinopathy of prematurity.

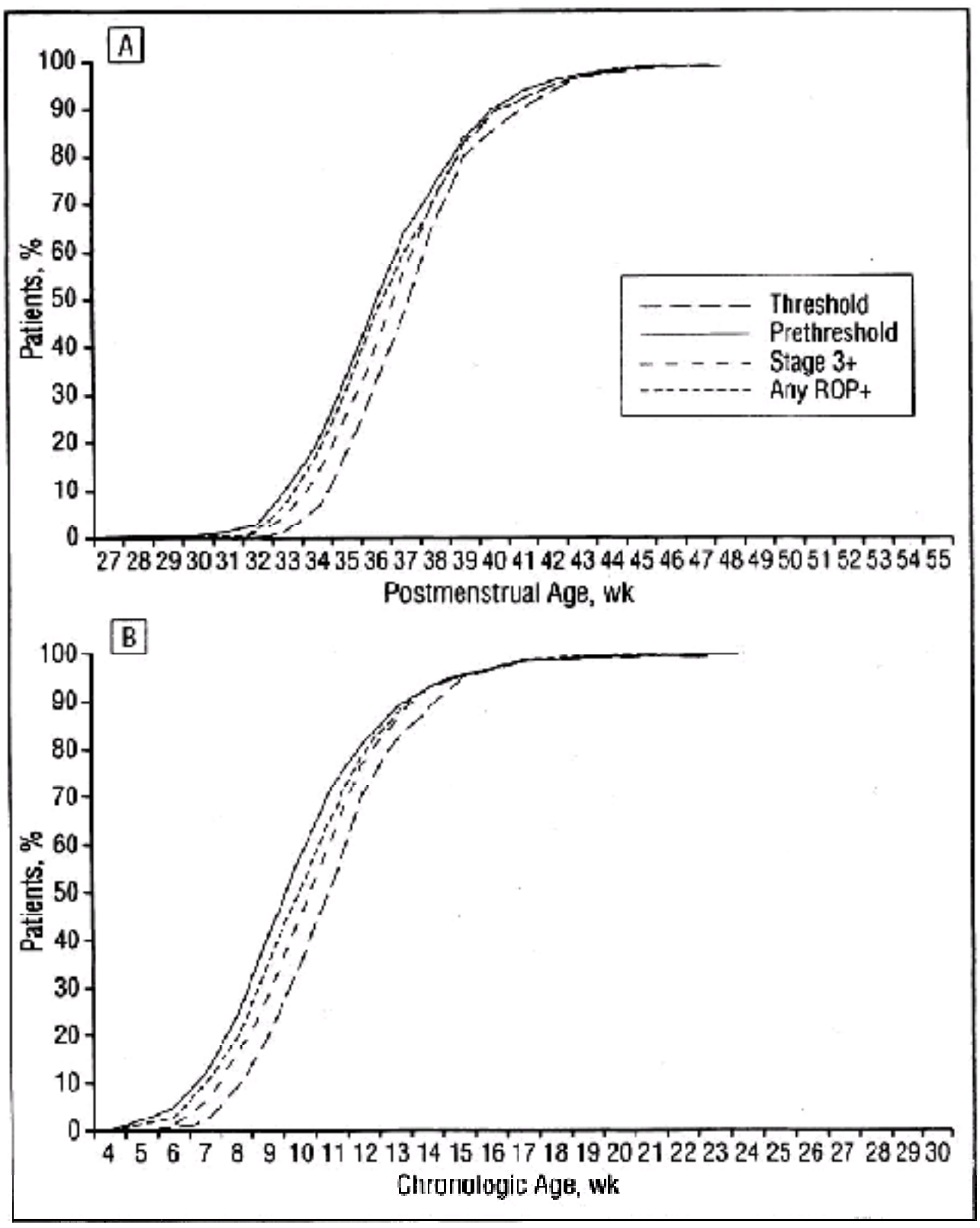

Figure 3.3 Timing of the onset of threshold, prethreshold, stage 3 plus, and any ROP with plus disease by postmenstrual age and chronologic age. (Reprinted from Reynolds JD, Dobson V, Quinn GE, et al, for the CRYO-ROP and LIGHT-ROP Cooperative Groups. Evidence based screening criteria for retinopathy of prematurity. *Arch Ophthalmol* 2002;120:1470-1476. Copyright American Medical Association, 2002. All rights reserved.)

In summary, the following guidelines should determine screening for acute-phase ROP:

1. Subjects: premature infants less than or equal to 1,500 grams birth weight or less than or equal to 31 weeks' gestational age
2. Screening initiation: Table 3.1
3. Screening conclusion
    a. Zone III retinal vascularization attained without previous zone I or II ROP, assuming no examiner error. If there is doubt about the zone or if the postmenstrual age (PMA) is unexpectedly young, confirmatory examinations may be warranted.
    b. Full retinal vascularization
    c. PMA of 45 weeks and no prethreshold ROP or worse present
    d. Definite disease regression signs in compatibly aged infants

In the section on ROP classification, a minor flaw in the system was noted that allowed temporal zone II ROP to be reclassified as zone III ROP without changing its true anatomic location. This is why the above screening conclusion guideline on zone III is qualified by excluding eyes with previous zone II ROP. These latter eyes probably represent most of the uncommon, unfavorable outcomes that occur with zone III ROP. In other words, the poor outcomes that rarely occur in zone III ROP probably had asymmetric temporal vs. nasal disease, and the nasal retina went on to vascularize while the temporal disease progressed without changing its real anatomic location. This is an important caveat for which the examiner must account.

Finally, although the initiation and conclusion of ROP screening exams in an appropriately at-risk population is now known, what about exam frequency and time to treatment? These latter two parameters are still consensus values arising from the conduct of multicenter trials. Exams are thought to be indicated every 2 weeks in infants with retinas

showing stage 2 or less disease but should probably be weekly for plus or nearly plus disease, stage 3 disease, zone I disease, rapidly progressive disease, or disease occurring in an atypically young infant. Time from observation of treatable disease to application of treatment should be within 3 days.

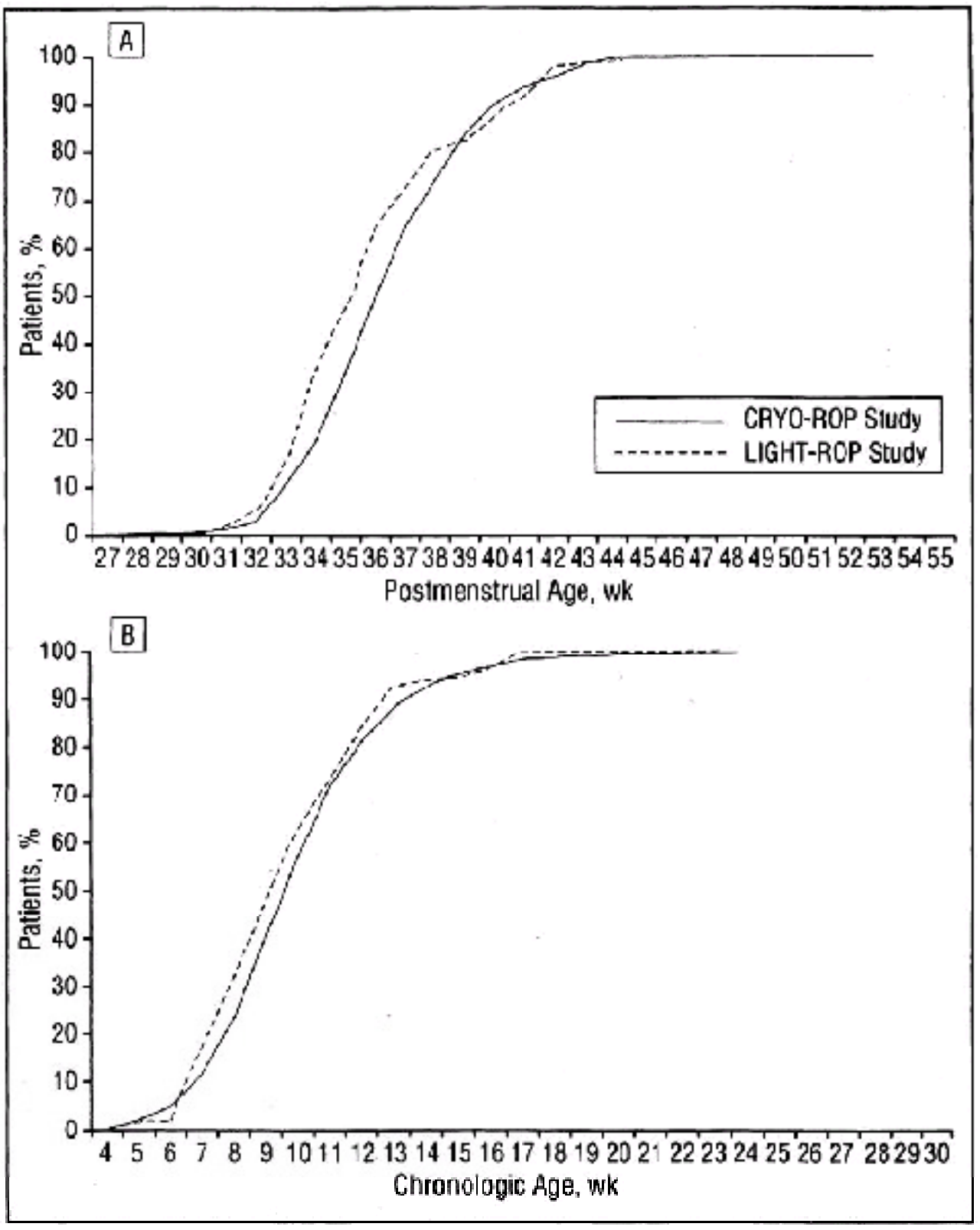

Figure 3.4 Timing of the onset of prethreshold ROP for CRYO-ROP and LIGHT-ROP patients less than 31 weeks gestational age at birth. Note the nearly identical curves. (Reprinted from Reynolds JD, Dobson V, Quinn GE, et al, for the CRYO-ROP and LIGHT-ROP Cooperative Groups. Evidence based screening criteria for retinopathy of prematurity. *Arch Ophthalmol* 2002;120:1470-1476. Copyright, American Medical Association, 2002. All rights reserved.)

This covers the scientific and disease-specific screening guidelines, but what of the administrative component? This is equal in importance. While the goal of evidence-based screening guidelines is to define the 99th percentile parameters, which appropriately exclude consideration of extraordinary events, the goal of the administrative component is the inclusion of 100% of the infants defined as at risk by the 99th percentile parameters. In other words, good science followed by good care. Such inclusive goals do not come easily or casually. All the interested parties must be involved in the attempt to set up a foolproof system of inclusion. Realistically no human activity is foolproof or perfect. But the goals should be set and clearly understood by all. System analysis is the operant process. It does not fall upon any nurse or any physician or any hospital employee to assure success. It is the system that is put in place, conscientiously adhered to by all, modified by the recognition and attempted correction of unforeseen events that will move toward perfection.

The involved parties include neonatologists, primary care pediatricians or family practitioners, nurses, social workers, discharge planners, ophthalmologists, quality assurance officers, clerical workers, and parents. Residents and fellows may also play a role but are appropriately peripheral in responsibility. No single party should accept full responsibility for ensuring inclusion. That is a recipe for disaster without checks and balances. Work as a team, institute the above scientifically based screening protocol, identify responsibilities and responsible parties, monitor progress, utilize system analysis, document the progress, communicate, and finally imbue all concerned with a sense of dedication and determination. The cost of failure is high, in more ways than one.

A useful mnemonic summarizes the above:

Delineate responsibility

Develop a process

Discuss frequently with all

Document the entire process

Do it

INCIDENCE

The prevalence of blindness from ROP in the United States appears to be growing despite effective treatments for severe ROP (3,4). The incidence of worldwide ROP blindness is unquestionably on the rise (5). But this could be related to a rise in the number of surviving premature infants and not to a change in the actual incidence or severity of ROP.

Several advances for the care of prematurely born infants have been instituted in neonatal intensive care units in high-income countries. These include surfactant administration, antenatal steroid use, pulse oximetry monitoring, improved nutrition, and others. Have these improvements in systemic care or other, as yet unknown, factors contributed to a change in incidence and severity of ROP as opposed to the prevalence of ROP blindness?

Some studies have suggested at least some type of decrease in ROP. However, these reports have serious flaws. The Vanderbilt experience compared 1995-1996 numbers with the years 1986-1987, when they were part of CRYO-ROP (35). It can be seen that the baseline years of 1986-1987 in Vanderbilt had threshold rates of 19% as compared with overall CRYO-ROP rates of 6%. The 1995-1996 numbers are much closer to both CRYO-ROP and LIGHT-ROP. Although the incidence of threshold ROP went down dramatically in Tennessee, the decrease was from an isolated exorbitant rate to a typical national rate. This study does not prove a decrease in incidence. Rather it proves the aberrations to which single centers with small numbers of babies are prone (36).

A study from an Australian center comparing data between 1988-1991 and 1991-1994 is subject to the same flaws (37). The threshold numbers were 25.0% versus 9.7%, respectively. The first number is extreme, and the second is still higher than the multicenter experience in the United States. This is also probably single-center aberration, but perhaps this is reflective of Australian nursery practices approaching U.S. standards. Conversely, a Denmark study found no difference in ROP in high-risk infants (38). Termote and coworkers (39) reported a decrease in ROP in all patients, but an increase in those smaller than 1,000 grams at birth.

No independent body of literature has addressed the effects of the previously noted medical advances on ROP incidence except for surfactant use. The prophylactic and therapeutic administration of exogenous surfactant to newborn premature infants has had a dramatic impact on lung disease and survival. Surfactant theoretically could increase severe ROP by increasing survival of low-birth-weight infants, decrease ROP by improving the general health of these infants, or impact ROP in other as yet unknown ways. Early studies found conflicting results.

The evidence now seems clear that surfactant does not reduce either the incidence or severity of ROP. In a study by Repka and coworkers (40), infants from two CRYO-ROP centers were evaluated in a randomized trial with prospective, serial eye exams. No difference in ROP outcome was noted. With this evidence, the authors postulate that the absolute number of babies with threshold ROP will rise as survival improves and birth-weight-specific incidence of ROP remains the same. Holmes and coworkers (41) also failed to find a statistically significant difference in their randomized trial.

TABLE 3.2 INCIDENCE AND SEVERITY OF ROP

CRYO-ROP vs. LIGHT-ROP

Patients	4,099	361
Any ROP	2,699 (65.8%)	251 (69.5%)
Prethreshold	731 (17.8%)	52 (14.4%)
Threshold	245 (6.0%)	18 (4.9%)

The best way to assess the incidence and severity of ROP over time is to compare multicenter randomized trials. Despite technologic and medical advances in the intervening years, it appears that the rates of ROP are very similar. The CRYO-ROP study enrolled and followed 4,099 patients. Of those, 2,699 (65.8%) developed at least some ROP; 731 (17.8%) developed at least prethreshold ROP and 245 (6.0%) developed threshold ROP (42). The LIGHT-ROP study enrolled and followed 361 patients. Of those, 251 (69.5%) developed at least some ROP (although only 202 developed the study minimum definition of at least 3 clock hours of confirmed ROP), 52 (14.5%) developed at least prethreshold ROP, and 18 (4.9%) developed threshold ROP (32). These two studies were conducted in 1986 through 1988 and 1995 through 1997. Table 3.2 shows that even though the enrollment periods were separated by almost a decade, the incidence and severity of ROP is very similar.

What of the more recent Early Treatment for Retinopathy of Prematurity (ET-ROP) randomized trial? Since this was a treatment trial that impacted the incidence of threshold, threshold ROP cannot be used for comparison. But again the rate of prethreshold ROP could be used for comparison purposes (43). Unfortunately neither the total number of enrolled infants nor the number with any ROP was published. However, 828 developed at least prethreshold ROP. Undoubtedly the rate of prethreshold ROP will be demonstrated not to have declined once the raw data is made public. It seems safe to conclude that ROP remains a major health issue.

The knowledge that ROP rates remain stable despite improvements in neonatal care has a major impact on the continuing need to be vigilant in screening for this condition. The knowledge that it continues to be a major contributor to childhood blindness despite current interventions is a major reason to continue the unfailing investigation into the basic pathophysiology of ROP and its prevention and treatment.

NATURAL HISTORY AND PROGNOSIS

ROP has traditionally been divided into an acute phase and a cicatricial phase. The acute phase is the period of development and progression of the stages of ROP in

ICROP. At some point the disease progression slows and stops, and a transitional period of disease involution or regression occurs. The cicatricial phase begins when the acute phase ends and what could be paraphrased as the regression or scarring phase begins. Most times this scarring phase is clinically insignificant, represented by permanent but minor or subtle changes in the peripheral retina. But occasionally acute fibrovascular severe ROP produces significant scarring and traction, which can ultimately lead to tractional retinal detachment with a fibrous or membranous component. This serious development is usually the definition for which cicatricial disease is reserved. The minor peripheral scarring is appropriately thought of simply as a regression pattern (17).

Attention will be focused on the natural history of acute disease. The empiric knowledge gained from experienced observers added much to the understanding of this disease. But it is the multicenter trials, especially the CRYO-ROP study, on the foundation of ICROP, that have contributed so much epidemiologic science to

the understanding.

The primary relevance of the CRYO-ROP study was its proof of the efficacy of cryotherapy in reducing unfavorable anatomic and visual outcomes in severe ROP. But an amazing secondary benefit from this study is the wealth of natural history data and analysis that it produced. It is a testament to the participants in this study that so much has been published on this. The control population and nonrandomized patients have contributed more to the clinical understanding of this disease than the treatment arm.

The natural history of a disease is the natural history of a population. It is the defining of the range of potential behaviors. It is governed by the rules of population statistics, i.e., bell curves, standard deviations, etc. As such, it can accurately determine the behavior of the disease in an entire group. But it is difficult to apply such statistics in individuals. Population statistics can predict what an individual's course may be, but the prediction can be right or wrong. Essentially one can predict how likely an individual patient is to behave in a certain pattern. But the exceptional circumstance is by definition not the likely course. Experienced examiners recognize ROP as a disease of individual surprises, and prediction for the individual is imprecise.

For all its twists and turns, ROP is a predictable disease that proceeds acutely in a linear fashion. The ROP screening guidelines are a direct result of this. A major finding of CRYO-ROP was the relation of ROP onset to retinal maturity (42). ROP has always been viewed as resulting from a complex interplay of forces set in motion by exposure of the premature retina to the extrauterine environment. But the length of exposure to this environment, the chronologic age of the infant, is less correlated with ROP onset and progression than the corrected age of the infant, the postgestational or postmenstrual age. The pathophysiologic reasons for this are discussed at length subsequently, but inherent activity in the retina determines the timing of disease expression. Put another way, the youngest infants at birth develop ROP at a later chronologic age, and the infants with the oldest gestational ages at birth develop ROP at an earlier chronologic age. For example, most infants who develop threshold ROP do so between 36 and 38 weeks' postgestational age whether they were born at 25 weeks' gestation and are more than 10 weeks old or they were born at 30 weeks' gestation and are only 6 to 8 weeks old.

We also know that each stage of ROP has similar correlations. So the disease has a natural linear progression, but its manifestations are clearly influenced by inherent retinal activity and not just environment. Stages 1 and 2 disease are common. More than half of infants in almost any series develop at least this much ROP. By and large these two stages behave similarly. Most regress without consequence. More serious disease can threaten unfavorable outcomes of macular fold, retinal detachment, or visual acuity of 20/200 or less.

ROP progression seems to have natural breakpoints between disease without risk of unfavorable outcome and disease with this risk. Escalating disease with very low risk includes:

Stage 1, zone II or III, no plus

Stage 2, zone II or III, no plus

Stage 3, zone II or III, no plus

The constants above are not stage but absence of zone I or plus disease. All of these have a less than 1% chance of a poor outcome (44).

Maximal observed disease with significant and increasing risk includes:

Stage 3 plus, 1-4 sectors, zone II

Stages 1 and 2, zone I

Stage 3 plus, 5-8 sectors, zone II

Stage 3 plus, 9-12 sectors, zone II

Stage 3, zone I

According to the natural history cohort of CRYO-ROP, the above risks of unfavorable outcome range from over 8% to 60% (44). The greatest risk of poor outcome was zone I threshold ROP. The unfavorable visual outcome in those patients was close to 90% whether treated or not (45).

The specific ROP factors that CRYO-ROP authors considered prognostic were zone, plus disease, stage, circumferential extent of neovascularization, and one not implied above, the rate of progression (42). But these five are not all equal. The presence or absence of plus disease and the presence of zone I disease seem to trump all others (44).

The recently published results from the ET-ROP trial essentially confirmed the opinions which arose from CRYO-ROP data analysis (43). Zone I disease and plus disease are the major drivers of unfavorable outcomes. One major difference in the statistics between CRYO-ROP and ET-ROP is appropriately part of the natural history discussion. Zone I disease was found to be much more common in the ET-ROP population and followed a more benign course. The ET-ROP authors appropriately pay special attention to this. They note it could represent a true change in the natural history of this disease, but more likely it represents observer bias. The heightened knowledge of the importance and relevance of zone I disease to ROP management in general and ET-ROP in particular altered the observational criteria of examiners between CRYO-ROP and ET-ROP. It may represent no more than an excellent example of how even carefully trained and/or instructed study participants can bring their bias to bear.

The natural history of regression or cicatricial disease is less well understood but involves fibrovascular proliferation, contraction, scarring, pigmentary changes, and permanent traction. The CRYO-ROP study again developed a simple but useful way of evaluating cicatricial disease. They used a macular scoring (MS) system, on the premise that the degree of macular damage was the most clinically relevant cicatricial event. They did not classify other changes noted by ICROP II. They classified that tractional damage as follows:

MS 0: normal macula

MS 1: macular heterotopia

MS 2: macular fold

MS 3: macular retinal detachment

In the presence of normal brain function, a normal macula means normal vision, and a retinal detachment including the macula means very poor vision (46). But macular heterotopia and macular folds yield a surprisingly wide range of visual acuities (47).

RISK FACTORS

Risk factors can be divided into several categories including epidemiologic population, systemic, ambient environment, and retinal signs. The latter are really prognostic natural history signs and were dealt with in the preceding section.

The overwhelming risk factors are birth weight and gestational age at birth. The lower the birth weight and the younger the gestational age, the greater the risk of both mild and severe ROP. In the CRYO-ROP study, for example, the risk of developing prethreshold ROP for the entire population of infants less than 1,251 grams was 17.8%. But divided by 250 gram increments the rates were: 1,000 to 1,250 grams equaled 7.3%; 750 to 999 grams equaled 21.4%; and less than 750 grams equaled 39.4%. Gestational age breakdowns were equally impressive. This was true across all subcategories of ROP (42). An additional risk factor in CRYO-ROP was white versus black race (20.5% vs. 13.1% prethreshold).

Over the years many other risk factors have been associated with ROP. McColm and Fleck (48) have reviewed and referenced many of these. Many of those risk factors were reported in single-center studies with small sample sizes and poor controls, utilizing historical and nonrandomized data. Such purported risk factors are not necessarily erroneous but certainly require rigorous confirmation. One of the confounding issues with the epidemiologic investigation of ROP is that it occurs in very sick babies. Their survival may be tenuous, they have multisystem failures, and they are kept alive by vigorous and varied interventions. It is difficult to isolate ROP within this milieu of multiorgan illness and multisystem support. Establishing adequately matched controls is a challenge.

An attempt to assess risk factors with adequately matched controls was reported by Biglan and coworkers (49,50). The group matched an ROP cohort to a no ROP or minimal ROP cohort, each with chronic lung disease, an indicator of how sick a baby gets. Although retrospective and from a single center, this attempt at controlling for a baby's acuity of illness level found very few differences between the two groups and hence very few risk factors. The authors suggested many previously reported risk factors were risk factors for severity of general illness level and not ROP. Risk factors that were found were the expected higher levels of inspired oxygen and longer duration of supplemental oxygen. In addition, two other markers of level of illness were also correlated: seizures and intraventricular hemorrhage. A logistic regression analysis by Hammer and coworkers (51) also found the expected oxygen duration risk factor and little else. These two trials, near the end of the single-center era of ROP, approached risk factors in a rigorous epidemiologic fashion and basically confirmed oxygen supplementation as a risk factor, as well as an increased level of general illness. In fact, in a somewhat facetious paraphrase of this reality, Enzenauer (52) noted that ROP correlated with the “smallest and sickest” and speculated that it would also correlate with the weight of the babies' charts.

The ever-present risk factor of oxygen deserves special consideration. All concerned appreciate that oxygen is involved in the pathophysiology of ROP. But how? In what way is it a risk factor? Is timing of administration important? Are fluctuations important? How does the fraction of inspired oxygen (FIO_2), arterial oxygen concentration (PaO_2), transcutaneous monitoring (TcO_2), or oxygen saturation by pulse oximeter relate to retinal tissue oxygen tensions and ROP?

Oxygen was linked to ROP when the work of Patz and the cooperative trial of Kinsey demonstrated that ROP was related to the administration of supplemental oxygen (11,13). This was confirmed repeatedly, but always with duration or with FIO_2, not PaO_2, a supposedly closer approximation to tissue oxygen. Flynn and coworkers (53) finally demonstrated a connection with PaO_2 utilizing TcO_2.

But the debate on the role of oxygen continues. In a dramatic role reversal, the theory that oxygen administration might actually help ROP, at least in its severe acute phase, was resurrected. Interestingly, this concept had been addressed in 1952 as part of the original search for RLF's cause (54). Even more enlightening, the Jacobson and Feinstein review (9) mentioned earlier as addressing the pre-Kinsey study activity ridiculed this concept. But Phelps and Rosenbaum (55) noted a positive effect on serious ROP in animals when the FIO_2 was raised. Gaynon (56) noted similar effects in humans. This led to the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial. Unfortunately this study failed to find a definitive therapeutic benefit for oxygen supplementation (57). However, the concept of oxygen manipulation is not dead. Other work has rekindled this idea (58,59,60), and a new clinical trial may begin (15,60).

Another risk factor that fueled a hot debate was ambient light exposure. Discussed as early as 1949 and 1952 (62,63) this debate returned with a vengeance following the 1985 work of Glass and coworkers (64). Supported by some but disputed by others, this question required another multicenter trial to answer (65,66,67). The LIGHT-ROP study definitively

found that ambient light reduction had no impact on ROP (32,68).

Vitamin E supplementation also has been considered and hotly debated, but this is covered in the later treatment section.

PATHOGEN ESIS

Recent investigation has shed considerable light on the basic pathogenesis of ROP. Although a cellular understanding of ROP is still lacking, much is known about what is happening at the tissue level. Proper understanding of pathogenesis requires a rudimentary knowledge of normal embryology and physiology of the retina. Not surprisingly, these two paths are deeply intertwined.

Blood supply of the mature retina comes from two distinct sources. The choroidal circulation supplies the outer retina, and the retinal circulation supplies the inner retina. For example, a central retinal artery occlusion destroys the electroretinogram's b-wave which arises from the inner retina but leaves the a-wave, generated from the photoreceptors, intact. Embryologically the choroidal circulation is complete prior to 20 weeks' gestational age and therefore prior to survivable premature birth. But the retinal circulation arising from the optic nerve head is just beginning to develop a vascular bed at this time. It is the retinal circulation that is intimately involved with ROP pathogenesis.

By definition, angiogenesis is the formation of endothelial-lined blood vessels. Arteriogenesis is the addition of smooth muscle cells that together with endothelium forms intact arterioles. Vascularization is the new arterialization of a tissue, and vasculogenesis is reserved for the formation of the vascular system, typically embryonic (69). Thus, vasculogenesis of the retinal circulatory system involves the formation of vessels, angiogenesis and arteriogenesis, and the spread of those newly formed vessels throughout the retina, vascularization.

Angiogenesis can occur in different patterns within mammalian systems. In humans, three patterns coexist, but the primary pattern in fetal development is via differentiation (70). A primitive mesenchyme spreads over the retina in a centrifugal fashion, originating at the optic nerve. These mesenchymal cells form angioblasts which mature into endothelial cells. These endothelial cells then coalesce into vessels. Periendothelial cells or pericytes add the smooth muscle. This peripherally advancing vascularization requires about 20 weeks of development, reaching the temporal ora at 40 to 42 weeks' gestational age.

The fetal vasculogenesis process is under the control of various factors. The molecule most discussed and widely investigated is vascular endothelial growth factor, VEGF, which is constructed by highly regulated VEGF mRNA (71,72,73,74). But this is not the only vasoactive element. VEGF itself comes in several different isoforms (75) and acts in concert with insulin-like growth factor 1 (76,77,78), basic fibroblast growth factor, and transforming growth factor (69). These various molecules create a complex cocktail of cytokines. Finally, changes in the extracellular matrix are an integral part of regulated cell migration and assembly (79,80,81,82). This entire process occurs simultaneously with the development of the structural and functional cells of the retina, some of which undoubtedly interact with the vasculogenesis process, e.g., astrocytes (83,84).

The development of the cellular elements of the retina follows a rigid time schedule in fetal life. It is a system designed to be fully active at or near term gestation. The last trimester is the period in which functional activity of the retina develops. Prior to 32 weeks, the photoreceptors and other cells are minimally electrically active, the retina is thin and immature, retinal metabolic demand is low, and the entire retina's nutrient requirements, both outer and inner, are supplied by the choroid. But on or about 32 weeks, the retinal cells establish connections, begin major metabolic activity, and mature rapidly. The choroid can now only supply the photoreceptors, and the inner retina begins to rely on the developing retinal circulation more and more. This is all evidenced by both anatomic studies and functional electroretinogram and visually evoked response testing (85,86,87,88,89). So anatomic development and a fully functional metabolism are perfectly and rigidly timed to coincide with retinal vasculogenesis.

VEGF production, and that of other regulatory cytokines, are themselves regulated by hyperoxia, normoxia, and hypoxia. The retina is incapable of significant hypoxia prior to the increasing oxygen requirements of very actively metabolizing cells. This connection among vasculogenesis, retinal maturation, and retinal metabolic demand, first hypothesized by Ashton and coworkers (90), interacting with the physiologic perturbations set in motion by premature birth explains the homogeneity of timing of ROP in relation to postgestational age noted in CRYO-ROP (42).

The pathogenesis of ROP begins with premature birth. Exposure to the extrauterine, technologically supportive environment coupled with the inability of the immature lungoxygen delivery system to adequately supply the needs of the developing retina is the true cause of ROP. The pathogenesis of ROP can be divided into two phases. Phase I is the initial reaction following premature birth and is called the hyperoxia-vasocessation phase. Phase II is the hypoxiavasoproliferation phase. Phase I is extremely common and ultimately harmless, but phase II can be anatomically and visually threatening. Although these phases are sequential, it is a mistake to think of the pathophysiology as linear. There may be extremely variable retinal oxygenation, especially in the unstable, extremely immature infant. Hyperoxia and hypoxia probably occur in many varied cycles. But for simplicity, they can be considered as single sequential events.

Phase I begins immediately after birth. The in utero retinal microenvironment is habituated to mixed venous blood and its lower PaO_2. At birth, mixed venous blood is transformed into arterial oxygenation levels by the switch from placental oxygenation to lung oxygenation. This alone does not necessarily create an

immediate hyperoxic state. The immature lung does not oxygenate efficiently, and the medical response of increasing the FIO_2 and/or utilizing ventilatory support does produce an initial relative hyperoxia. This relative hyperoxia is reinforced by the low metabolism of the retina in very immature infants. This failure

to utilize oxygen aids in keeping the initial tissue oxygen tension high.

This relative retinal hyperoxia results in downregulation and diminished production of VEGF. Retinal angiogenesis and retinal vascularization are impaired and vasocessation occurs. Kretzer and Hittner (91) failed to find any evidence of endothelial cell breakdown, which would be present if mature vessels and their endothelial cells were obliterated at the interface. Normal endothelial cell apoptosis would not produce the same degree of very localized endothelial destruction. So vasocessation seems logical and compatible with the evidence.

Phase I then may recede without incident. A more appropriately physiologic state may be achieved, VEGF may be produced in appropriate amounts, normal vasculogenesis is reestablished, and ROP either does not develop or mild ROP regresses and the retina is successfully vascularized. But phase II may supervene.

In phase II, the lungs become damaged and even more unable to oxygenate the blood properly, retinal metabolic demand rises precipitously, and this combination of poor supply and increased demand creates a relative tissue hypoxia. It is easy to understand how this process would be exacerbated in the most ill infants. A return to room air is not the essential element in retinal tissue hypoxia. Weaning high FIO_2 is universal, but only the sickest babies get ROP. A lower FIO_2 may contribute, but it is far too simplistic. VEGF is now upregulated and the vasculogenic system responds. But why doesn't the system respond normally and develop normal vessels? Why does an abnormal fibrovascular component develop? Is it just VEGF gone wild? Or is there an additional cellular component(s)? It is probable that there are other complex factors at work. Oxygen cytotoxicity, either directly or via free radicals, is a possibility, although there is little real evidence beyond speculation for this. It seems likely that increased levels of VEGF act upon somehow abnormal vasoformative elements, either mesenchyme or angioblasts, or perhaps damaged astrocytes or the extracellular matrix contribute. These abnormal elements respond to VEGF by forming abnormal fibrovascular tissue, i.e., neovascularization or stage 3 ROP.

The correlation with ROP onset and gestational age that was discussed in the natural history section has everything to do with the relative retinal hypoxia that can only be produced by poor supply coincident to all the changes wrought by premature birth and exacerbated by the normal increase in retinal metabolic demand, which is rigorously timed by embryologic exigencies. It is not just exposure to a harsh extrauterine environment. It is not just oxygen alternations. It is environment superimposed on the timing of retinal developments.

In summary, the phase I/vasocessation phase is very common in extremely low-birth-weight infants. It can be followed by phase II/revascularization if normal physiology prevails or phase II/vasoproliferation if abnormal physiology triumphs. All of this is mediated by VEGF and other cytokines being down-or upregulated by relative changes in tissue oxygenation levels determined by an interplay of supply and demand on possibly cell-damaged vasoformative elements. If these events are not purely linear but are cycled, as is likely, there is an even greater chance of serious ROP development (92,93).

MANAGEMENT

Management of ROP implies more than just treatment, and indeed there is much more involved with the management of this disease than just treatment intervention. One can divide ROP management into four basic categories: prevention; interdiction; correction; and mitigation.

Prevention involves any means by which ROP may be prevented. Interdiction implies an intervention aimed at halting the progress of ROP. Correction is involved with treatment of cicatricial or end-stage ROP after the acute disease has run its course. And last, mitigation involves appropriate management of all the associated sequelae of ROP, including blindness. Such a broad approach to management will necessarily involve a large variety of professionals but the ophthalmologist, especially the pediatric ophthalmologist, should be involved in every step—making decisions, aiding and advising decision making, and ensuring proper referrals.

Prevention

The ideal answer to the problem of ROP is complete prevention, and the single best way to achieve that is the prevention of premature birth. The number of premature births is staggering. In 2002 a stable 1.45% of births were very-low-birth-weight infants, i.e., birth weights less than 1,500 grams. This means well over 50,000 infants of 1,500 grams or less are born annually in the United States (94). All of those survivors are at risk for ROP and require screening. Support of the actions aimed at improving both access to prenatal care and improved obstetric care, via social programs and research, is an appropriate course of action. Reducing ROP in this fashion has the huge advantage of also reducing the other developmental disabilities associated with premature birth. From a public health perspective, this has a large return on investment.

Currently the next best option in preventing ROP is idealized intensive care. As noted previously in this chapter, many of the advances in intensive nursery care have not resulted in diminished ROP. However, as also noted, a rigorous evidence-based approach to infant oxygenation has never been developed. It may be possible, as an outcome of a large, randomized trial, to identify optimal ranges of oxygen saturation that would maximize survival and minimize ROP, cerebral palsy, and developmental disabilities.

Finally, less ideal for the whole patient but still preferable as ROP management is the prevention of ROP itself. This effort has so far been a complete failure. Two major previous attempts at preventing the development of any ROP and/or severe ROP centered on ambient light reduction and pharmacologic vitamin E supplementation. The role of light was discussed in detail in the Risk Factors section of this chapter. In short, the LIGHT-ROP cooperative trial found no benefit from ambient light reduction on ROP (32).

Vitamin E supplementation has also had a controversial past. Vitamin E is one of several antioxidant elements involved in normal physiology. One of its purported values is to neutralize free radicals. Acting on the premise that oxygen cytotoxicity, either directly or via free radical production, is an inherent part of the pathogenesis of ROP, vitamin E supplementation was theorized to be able to prevent or reduce such cytotoxic actions (95). Unfortunately, several randomized clinical trials of pharmacologic doses of vitamin E, as opposed to normal physiologic dose supplements, were contradictory (95,96,97,98). Few nurseries have instituted pharmacologic vitamin E protocols (99).

Inositol supplementation in formula may influence ROP. Inositol and phosphoinositides have multiple metabolic actions (100). Hallman and coworkers (101) initially noted a connection between serum inositol concentration and ROP. Detected from a subanalysis of a more global randomized neonatal study, the observation was followed up by subsequent, more focused series (100,102). Again conflicting results were obtained, and no consensus has been reached. A multicenter trial is probably necessary for a definitive answer.

Interdiction

Treatments aimed at interrupting the progression of ROP are currently the mainstay of ROP management and are centered around peripheral retinal ablation with either cryotherapy or laser photocoagulation. The theory behind peripheral retinal ablation is as follows. Applying cryotherapy or laser photocoagulation anterior to the ridge, in nonvascularized ischemic retina, kills the ischemic cells producing the regulatory signals for VEGF production as well as killing the producers of VEGF. This dual effect significantly lowers VEGF (103) and leads to ROP involution rather than progression. Two multicenter randomized clinical trials have fixed the standard of care for this type of intervention. CRYO-ROP was, of course, the landmark study that proved the efficacy of cryotherapy and set the standard for the first widely accepted and instituted interdictory therapy for ROP (21). ET-ROP was a subtle but meaningful refinement of treatment indications for peripheral retinal ablation, although an extra benefit was providing a more recent assessment of overall success rates for this treatment when applied in its now most common method, i.e., laser photocoagulation rather than cryotherapy (43).

The results of CRYO-ROP have been republished so many times in so many venues that repeating them here is redundant. But briefly, cryotherapy applied to the peripheral retina anterior to the fibrovascular ridge of neovascularization when threshold ROP had been reached reduced the unfavorable anatomic outcomes by

almost one-half and reduced the unfavorable visual outcomes by almost one-third (104). The difference between anatomic and visual outcomes is notable. This primarily relates to nonocular or subtle ocular differences that can make a significant visual impact (46).

Besides the message of efficacy, there are two important caveats regarding the CRYO-ROP primary results. First, despite application of cryotherapy according to protocol, unfavorable outcomes still occurred in a sizable minority. Second, cryotherapy was proven effective for zone II threshold ROP, but zone I threshold had a very poor response to protocol treatment, with an unfavorable outcome rate of nearly 90%.

During the decade following the publication of CRYO-ROP results, treatment evolved in two ways. Laser photocoagulation slowly gained widespread predominance over cryotherapy as a retinal ablative technique, and intervention earlier in the course of serious ROP was increasingly utilized, especially for zone I disease. In the first case, laser was simply substituted for cryo as an equivalent or improved way to kill nonvascularized retina (105,106,107,108,109,110). And in the second case, the shift to earlier treatment occurred because CRYO-ROP protocols did not succeed in zone I disease.

Despite single-center attention to these two evolutions, a multicenter randomized trial was necessary. ET-ROP provided that (43). ET-ROP was successful in its primary goals of refining the level of ROP disease which could benefit significantly from peripheral retinal ablation. Intervention may now be performed on ROP as follows:

Zone I, any stage ROP with plus

Zone I, stage 3 ROP

Zone II, stage 2 or 3 ROP with plus

As noted in the Natural History section, zone I ROP and plus disease are the main signals of poor outcome and were proven to result in better outcomes with early intervention. The extent or clock hours of ROP are irrelevant without plus disease.

But what of the comparison between cryotherapy and laser? Laser is more convenient, more easily applied, especially posteriorly, and better tolerated. But is it more effective? ET-ROP may be able to answer that question indirectly. ET-ROP patients received laser photocoagulation in the overwhelming majority of treated cases. However, the indications for treatment were clearly different. But there was a group of patients in the ET-ROP trial who received laser treatment according to CRYO-ROP guidelines—those with conventionally managed eyes. Comparing only those eyes of ET-ROP with CRYO-ROP can yield valid comparisons, especially since the visual acuity outcomes were tested using similar techniques. CRYO-ROP had an age 9 months unfavorable visual acuity outcome of 35%. ET-ROP had an unfavorable visual acuity outcome rate of 19.6%. The investigators did not address this issue with a separate analysis, the populations were not identical, especially with respect to frequency of zone I disease, and clearly other variables could be contributing. But from this simple comparison of published numbers, it seems that success rates for even conventionally managed ROP improved over 15 years, much as the single-center and anecdotal evidence had been claiming. Whether most of this improvement can be attributed to advantages of laser over cryo is debatable, but it probably is contributory.

While the interdictory treatments of laser and cryotherapy are undoubtedly worthwhile, they do have complications. Minor or transient complications of cryotherapy or laser include lid edema, conjunctival edema and inflammation, retinal or vitreous hemorrhage, diminished peripheral visual fields, and even choroidal or exudative retinal detachments.

More serious and vision-threatening complications include cataract, glaucoma, uveitis, anterior segment ischemia, hyphema, macular burn, and occlusion of the central retinal artery (43,45,111,112,113,114,115,116,117,118,119,120,121). Luckily these rates of serious complications are low and do not always produce a loss of vision. However, a reasonable estimate of the visually threatening complication rate from all causes is 2% to 3%.

Another attempt at interdictory therapy was the STOP-ROP trial (57). This trial was based on the theory that increasing the oxygen saturation when serious ROP develops would potentially diminish the relative retinal hypoxia, reduce VEGF levels, and hence prevent progression of serious ROP. Unfortunately, this was not found to be efficacious, although its theoretic potential remains (53). One indirect message from this study is the difficulty in translating clinical changes in oxygen delivery to the tissue and cellular events of the retina. Relative retinal hypoxia and all that entails undoubtedly is a much more complex series of events to impact than simply monitoring oxygen saturations.

Corrective Therapy

Unfortunately, current corrective therapy aimed at correcting visually significant cicatricial disease has been disappointing. The tractional retinal detachments and retinal folds that develop in ROP are difficult surgical problems. This is the most expensive, most heroic, most technically demanding treatment phase of ROP. Yet even hard-won anatomic success yields disappointingly little relevant improvement in vision. The published results on this phase of therapy in total retinal detachment patients in the CRYO-ROP trial were dismal (122,123). Patients reported by surgeons from single centers often fare better, but the results are still not good (124,125,126,127). However, newer, more sophisticated attempts continue to be made and perhaps will slowly improve results. One overriding logic governs almost all of these interventions, i.e., there is no real alternative hope. The key lies in prevention and interdiction, not correction.

Mitigation

This is the final phase of ROP management. It comes into play once the treatment phases for ROP have ended. Mitigation management is aimed at the treatment of all the sequelae that can arise from ROP. Such conditions, escalating in seriousness, include: myopia, anisometropia, amblyopia, strabismus, cataract, glaucoma, phthisis, and blindness. Indirect problems of ophthalmologic concern that result more from intracranial disease than ROP include nystagmus, optic atrophy, and cortical visual impairment. Late-onset rhegmatogenous retinal detachments also occur.

Myopia is by far the most common sequelae of ROP. It correlates highly with increasing severity of ROP. In the CRYO-ROP study, the myopia and high myopia rates were 20% and 5%, respectively, in all ROP eyes less than threshold, and a dramatic 80% and 54% in stage 3 plus with 9 or more clock hours of disease (128). Early and frequent cycloplegic refractions are essential in this group of patients.

Anisometropia, amblyopia, and strabismus are also common problems. Their incidence also increases with increasing severity of ROP (129,130,131,132). Again, early and frequent ophthalmologic exams are critical in detecting these problems. Management may require glasses, amblyopia therapy, possibly superimposed on organic disease, and surgery.

Cataract and glaucoma are thankfully much less common. As noted, each can occur as a complication of ROP treatment but are more common as disease sequelae from severe ROP, usually with visually significant cicatricial disease. Cataracts arise in a wide variety of severely altered ocular physiology states, and ROP cataracts are undoubtedly similar. ROP glaucoma can take various forms (133). Treatment of both of these conditions is complicated by the underlying ROP changes and age of the patient.

Finally, the management of uncorrectable visual impairment and blindness is a necessity. Although at times uncomfortable for the ophthalmologist, it can be of paramount importance to the individual. The role of the ophthalmologist here is often comfort and reassurance coupled with education and advocacy. Proper referral to low-vision specialists, early interventionists, community and government programs, and patient and family support and advocacy groups can make major differences in both the approach to and coping with a blindness disability.

Future management of ROP may involve methods to promote normal vasculogenesis or inhibit abnormal angiogenesis. However, the interwoven complexity of the various factors, e.g., multiple cytokines, extracellular matrix interaction, and different tissue specificity, leave many unanswered questions (69). Much more work is necessary as the surface has barely been scratched.

CONCLUSION

It is appropriate to conclude this review of ROP in the same manner as it began. There have been great strides made since Terry's description in 1942 (1).

Despite the epidemiologic pitfalls inherent in this disease and in scientific inquiry in general, progress has been dramatic. Basic research offers much promise for the future. But the irrefutable truth is that there are still babies who are blinded by ROP in the United States and throughout the world. There is still much to learn. So this chapter ends with the same plea that Terry made in 1942. Appropriate resources need to be brought to bear to determine the full cause of and discover a prevention for this enigmatic disease.

REFERENCES

1. Terry TL. Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens. I. Preliminary report. *Am J Ophthalmol* 1942;25:203-204.

2. Terry TL. Fibroblastic overgrowth of persistent tunica vasculosa lentis in premature infants. II. Report of cases—clinical aspects. *Arch Ophthalmol* 1943;29:36-53.

3. Steinkuller PG, Du L, Gilbert C, et al. Childhood blindness. *J AAPOS* 1999;3:26-32.

4. Tompkins C. A sudden rise in the prevalence of retinopathy of prematurity blindness? *Pediatrics* 2001;108:526-527.

5. Gilbert C, Rahi J, Eckstein M, et al. Retinopathy of prematurity in middle-income countries. *Lancet* 1997;350:12-14.

6. Pizzarello L, Abiose A, Ffytche T, et al. Vision 2020: the right to sight. A global initiative to eliminate avoidable blindness. *Arch Ophthalmol* 2004;122:615-620.

7. Hong Phan M, Nguyen PN, Reynolds JD. Incidence and severity of retinopathy of prematurity in Vietnam, a developing middle-income country. *J Pediatr Ophthalmol Strabismus* 2003;40: 208-212.

8. Gilbert C, Foster A. Childhood blindness in the context of VISION 2020—the right to sight. *Bull World Health Organ* 2001; 79:227-232.

9. Jacobson RM, Feinstein AR. Oxygen as a cause of blindness in premature infants: “Autopsy” of a decade of errors in clinical epidemiological research. *J Clin Epidemiol* 1992;45:1265-1287.

10. Campbell K. Intensive oxygen therapy as a possible cause of retrolental fibroplasia: a clinical approach. *Med J Aust* 1951;2: 48-50.

11. Patz A, Hoeck LE, de la Cruz E. Studies on the effect of high oxygen administration in retrolental fibroplasia. *Am J Ophthalmol* 1952;35:1248-1252.

12. Kinsey VE, Hemphill FM. Etiology of retrolental fibroplasia and preliminary report of the cooperative study of retrolental fibroplasia. *Trans Am Acad Ophthalmol Otolaryngol* 1955;59:15-24.

13. Kinsey VE. Retrolental fibroplasia: cooperative study of retrolental fibroplasia and the use of oxygen. *AMA Arch Ophthalmol* 1956; 56:481-543.

14. Bolton DPG, Cross KW. Further observations on cost of preventing retrolental fibroplasia. *Lancet* 1974;445-448.

15. Silverman WA. A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics* 2004;113:394-396.

16. Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Arch Ophthalmol* 1984;102:1130-1134.

17. International Committee for the Classification of the Late Stages of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. II. The classification of retinal detachment. *Arch Ophthalmol* 1987;105:906-912.

18. Wallace DK, Kylstra JA, Chesnutt DA. Prognostic significance of vascular dilation and tortuosity insufficient for plus disease in retinopathy of prematurity. *J AAPOS* 2000;4:224-229.

19. Freedman SF, Kylstra JA, Capowski JJ, et al. Observer sensitivity to retinal vessel diameter and tortuosity in retinopathy of prematurity: a model system. *J Pediatr Ophthalmol Strabismus* 1996;33: 248-254.

20. Saunders RA, Bluestein EC, Sinatra RB, et al. The predictive value of posterior pole vessels in retinopathy of prematurity. *J Pediatr Ophthalmol Strabismus* 1995;32:82-85.

21. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. *Arch Ophthalmol* 1988;106:471-479.

22. Young TE. Topical mydriatics: the adverse effects of screening examinations for retinopathy of prematurity. *Neo Previews* 2003; 4:163-166.

23. Kumar H, Nainiwal S, Singha U, et al. Stress induced by screening for retinopathy of prematurity. *J Pediatr Ophthalmol Strabismus* 2002;36:349-350.

24. Laws DE, Morton C, Weindling M, et al. Systemic effects of screening for retinopathy of prematurity. *Br J Ophthalmol* 1996; 80:425-428.

25. Mirmanesh SJ, Abbasi S, Bhutani VK. Alpha-adrenergic bronchoprovocation in neonates with bronchopulmonary dysplasia. *J Pediatr* 1992;121:622-625.

26. Palmer EA. How safe are ocular drugs in pediatrics? *Ophthalmology* 1986;93:1038-1040.

27. Isenberg S, Everett S. Cardiovascular effects of mydriatics in low-birth-weight infants. *J Pediatr* 1984;105:111-112.

28. Retinopathy of prematurity: guidelines for screening and treatment. The report of a joint working party of the Royal College of Ophthalmologists and the British Association of Perinatal Medicine. *Early Hum Dev* 1996;46:239-258.

29. Joint statement of the American Academy of Pediatrics, the American Association for Pediatric Ophthalmology and Strabismus, and the American Academy of Ophthalmology. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2001;108:809-811.

30. Canadian Association of Pediatric Ophthalmologists Ad Hoc Committee on Standards of Screening Examination for Retinopathy of Prematurity. Guidelines for screening examinations for retinopathy of prematurity. *Can J Ophthalmol* 2000;35:251-252.

31. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. 3 month outcome. *Arch Ophthalmol* 1990;108:195-204.

32. Reynolds JD, Hardy RJ, Kennedy KA, et al, for the Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. Lack of efficacy of light reduction in preventing retinopathy of prematurity. *N Engl J Med* 1998;338:1572-1576.

33. Reynolds JD, Dobson V, Quinn GE, et al, for the CRYO-ROP and LIGHT-ROP Cooperative Groups. Evidence-based screening criteria for retinopathy of prematurity. *Arch Ophthalmol* 2002; 120:1470-1476.

34. Repka MX, Palmer EA, Tung B, for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Involution of retinopathy of prematurity. *Arch Ophthalmol* 2000;118:645-649.

35. Bullard SR, Donahue SP, Feman SS, et al. The decreasing incidence and severity of retinopathy of prematurity. *J AAPOS* 1999; 3:46-52.

36. Reynolds JD, Hardy RJ, Palmer EA. Incidence and severity of retinopathy of prematurity. *J AAPOS* 1999;3:321-322.

37. Kennedy J, Todd DA, Watts J, et al. Retinopathy of prematurity in infants less than 29 weeks' gestation: 3 ½ years pre-and postsurfactant. *J Pediatr Ophthalmol Strabismus* 1997;34:289-292.

38. Fledelius HC. Retinopathy of prematurity in a Danish county. Trends over the 12-year period 1982-93. *Acta Ophthalmol Scand* 1996;74:285-287.

39. Termote J, Schalij-Delfos NE, Brouwers HAA, et al. New developments in neonatology: less severe retinopathy of prematurity? *J Pediatr Ophthalmol Strabismus* 2000;37:142-148.

40. Repka MX, Hardy RJ, Phelps DL, et al. Surfactant prophylaxis and retinopathy of prematurity. *Arch Ophthalmol* 1993;111:618-620.

41. Holmes JM, Cronin CM, Squires P, et al. Randomized clinical trial of surfactant prophylaxis in retinopathy of prematurity. *J Pediatr Ophthalmol Strabismus* 1994;31:189-191.

42. Palmer EA, Flynn JT, Hardy RJ, et al, for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991; 98:1628-1640.

43. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity. Results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol* 2003;121: 1684-1696.

44. Cryotherapy for Retinopathy of Prematurity Cooperative Group. The natural ocular outcome of premature birth and retinopathy. Status at 1 year. *Arch Ophthalmol* 1994;112:903-912.

45. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. One year outcome—structure and function. *Arch Ophthalmol* 1990;108:1408-1416.

46. Gilbert WS, Dobson V, Quinn GE, et al, for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. The correlation of visual function with posterior retinal structure in severe retinopathy of prematurity. *Arch Ophthalmol* 1992;110:625-631.

47. Reynolds J, Dobson V, Quinn GE, et al, for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Prediction of visual function in eyes with mild to moderate posterior pole residua of retinopathy of prematurity. *Arch Ophthalmol* 1993; 111:1050-1056.

48. McColm JR, Fleck BW. Retinopathy of prematurity: causation. *Semin Neonatol* 2001;6:453-460.

49. Biglan AW, Brown DR, Reynolds JD, et al. Risk factors associated with retrolental fibroplasia. *Ophthalmology* 1984;91:1504-1511.

50. Brown DR, Milley JR, Ripepi UJ, et al. Retinopathy of prematurity. Risk factors in a five-year cohort of critically ill premature neonates. *Am J Dis Child* 1987;141:154-160.

51. Hammer ME, Mullen PW, Ferguson JG, et al. Logistic analysis of risk factors in acute retinopathy of prematurity. *Am J Ophthalmol* 1986;102:1-6.

52. Enzenauer RW. Retinopathy of prematurity and weight of the baby's chart. *J AAPOS* 2001;5:198.

53. Flynn JT, Bancalari E, Snyder ES, et al. A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. *N Engl J Mea* 1992;326:1050-1054.

54. Jefferson E. Retrolental fibroplasia. *Arch Dis Child* 1952;27: 329-336.

55. Phelps DL, Rosenbaun AL. Effects of variable oxygenation and gradual withdrawal of oxygen during the recovery phase in oxygen induced retinopathy: kitten model. *Pediatr Res* 1987;22: 297-301.

56. Gaynon MD. Supplemental oxygen and photopic lighting in the management of retinopathy of prematurity. Presented at: Update on Retinopathy of Prematurity Conference; February 22, 1992; Los Angeles, California.

57. The STOP-ROP Multicenter Study Group. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. *Pediatrics* 2000;105:295-310.

58. Tin W, Milligan DWA, Pennefather P, et al. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;84: F106-F110.

59. Askie LM, Henderson-Smart DJ, Irwig L, et al. Oxygen-saturation targets and outcomes in extremely preterm infants. *N Engl J Mea* 2003;349:959-967.

60. Chow LC, Wright KW, Sola A for the CSMC Oxygen Administration Study Group. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics* 2003;111:339-345.

61. Cole CH, Wright KW, Tarnow-Mordi W, et al. Resolving our uncertainty about oxygen therapy. *Pediatrics* 2003;112: 1415-1419.

62. Hepner WR, Krause AC, Davis ME. Retrolental fibroplasia and light. *Pediatrics* 1949;3:824-828.

63. Locke JC, Reese AB. Retrolental fibroplasia. The negative role of light, mydriatics, and the ophthalmoscopic examination in its etiology. *Arch Ophthalmo* 1952;48:44-47.

64. Glass P, Avery GB, Subramanian KNS, et al. Effect of bright light in the hospital nursery on the incidence of retinopathy of prematurity. *N Engl J Mea* 1985;313:401-404.

65. Hommura S, Usuki Y, Takei K, et al. Ophthalmic care of very low birthweight infants. Report 4. Clinical studies on the influence of light on the incidence of retinopathy of prematurity. *Nippon Ganka Gakkai Zasshi* 1988;92:456-461.

66. Ackerman B, Sherwonit E, Williams J. Reduced incidental light exposure: effect on the development of retinopathy of prematurity in low birth weight infants. *Pediatrics* 1989;83:958-962.

67. Seiberth V, Linderkamp O, Knorz MC, et al. A controlled clinical trial of light and retinopathy of prematurity. *Am J Ophthalmol* 1994;118:492-495.

68. LIGHT-ROP Cooperative Group. The design of the multicenter study of light reduction in retinopathy of prematurity (LIGHTROP). *J Pediatr Ophthalmol Strabismus* 1999;36:257-263.

69. Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. *Nat Mea* 2000;6:389-395.

70. Casey R, Li WW. Factors controlling ocular angiogenesis. *Am J Ophthalmol* 1997;124:521-529.

71. Stone J, Itin A, Alon T, et al. Development of retinal vasculature is mediated by hypoxia-induced vascular endothelial growth factor (VEGF) expression by neuroglia. *J Neurosci* 1995;15:4738-4747.

72. Alon A, Hemo I, Itin A, et al. Vascular endothelial growth factor acts as a survival factor for newly formed retinal vessels and has implications for retinopathy of prematurity. *Nat Mea* 1995;1: 1024-1028.

73. Pierce EA, Foley ED. Smith LEH. Regulation of vascular endothelial growth factor by oxygen in a model of retinopathy of prematurity. *Arch Ophthalmol* 1996;114:1219-1228.

74. Aiello LP. Vascular endothelial growth factor. *Invest Ophthalmol Vis Sci* 1997;38:1647-1652.

75. Robinson CJ, Stringer SE. The splice variants of vascular endothelial growth factor (VEGF) and their receptors. *J Cell Sci* 2001; 114:853-865.

76. Hellstrom A, Engstrom E, Hard AL, et al. Postnatal serum insulin-like growth factor I deficiency is associated with retinopathy of prematurity and other complications of premature birth. *Pediatrics* 2003;112:1016-1020.

77. Hellstrom A, Perruzzi C, Ju M, et al. Low IGF-I suppresses VEG Fsurvival signaling in retinal endothelial cells: Direct correlation with clinical retinopathy of prematurity. *Proc Natl Acad Sci USA* 2001;98:5804-5808.

78. Smith LEH, Shen W, Perruzzi C, et al. Regulation of vascular endothelial growth factor-dependent retinal neovascularization by insulin-like growth factor-1 receptor. *Nat Med* 1999;5: 1390-1395.

79. McGuire PG, Jones TR, Talarico N, et al. The urokinase/urokinase receptor system in retinal neovascularization: Inhibition by A6 suggests a new therapeutic target. *Invest Ophthalmol Vis Sci* 2003; 44:2736-2742.

80. Majka S, McGuire PG, Das A. Regulation of matrix metalloproteinase expression by tumor necrosis factor in a murine model of retinal neovascularization. *Invest Ophthalmol Vis Sci* 2002;43: 260-266.

81. Majka S, McGuire PG, Colombo S, et al. The balance between proteinases and inhibitors in a murine model of proliferative retinopathy. *Invest Ophthalmol Vis Sci* 2001;42:210-215.

82. Das A, McLamore A, Song W, et al. Retinal neovascularization is suppressed with a matrix metalloproteinase inhibitor. *Arch Ophthalmol* 1999;117:498-503.

83. Chan-Ling T, Stone J. Degeneration of astrocytes in feline retinopathy of prematurity causes failure of the blood-retinal barrier. *Invest Ophthalmol Vis Sci* 1992;33:2148-2159.

84. Zhang Y, Stone J. Role of astrocytes in the control of developing retinal vessels. *Invest Ophthalmol Vis Sci* 1997;38:1653-1666.

85. Hendrickson AE, Yuodelis C. The morphological development of the human fovea. *Ophthalmology* 1984;91:603-612.

86. Johnson AT, Kretzer FL, Hittner HM, et al. Development of the subretinal space in the preterm human eye: Ultrastructural and immunocytochemical studies. *J Comp Neurol* 1985;233: 497-505.

87. Taylor MJ, Menzies R, Mac Millan LJ, et al. VEPs in normal full-term and premature neonates: Longitudinal versus cross-sectional data. *Electroencephalogr Clin Neurophysiol* 1989;68:76-80.

88. Norcia AM, Tyler CW, Piecuch R. Visual acuity development in normal and abnormal preterm human infants. *J Pediatr Ophthalmol Strabismus* 1987;24:70-74.

89. Harding GF, Grose J, Wilton A, et al. The pattern reversal VEP in short-gestation infants. *Electroencephalogr Clin Neurophysiol* 1989; 74:76-80.

90. Ashton NA, Ward B, Serpell G. Effect of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. *Br J Ophthalmol* 1954;38:397-430.

91. Kretzer FL, Hittner HM. In: Porter R, Whelan J, eds. *Biology of vitamin E*. London: Pittman Books, 1983:165-185.

92. Penn JS, Henry MM, Wall PT, et al. The range of PaO_2 variation determines the severity of oxygen-induced retinopathy in newborn rats. *Invest Ophthalmol Vis Sci* 1995;36:2063-2070.

93. Penn JS, Tolman BL, Lowery LA. Variable oxygen exposure causes preretinal neovascularization in the newborn rat. *Invest Ophthalmol Vis Sci* 1993;34:576-585.

94. Arias E, MacDorman MF, Strobino DM, et al. Annual summary of vital statistics—2002. *Pediatrics* 2003;112:1215-1230.

95. Hittner HM, Godio LB, Rudolph AJ, et al. Retrolental fibroplasia: efficacy of vitamin E in a double-blind clinical study of preterm infants. *N Engl J Med* 1981;305:1365-1371.

96. Phelps DL, Rosenbaum AL, Isenberg SJ, et al. Tocopherol efficacy and safety for preventing retinopathy of prematurity: a randomized, controlled, double-masked trial. *Pediatrics* 1987;79: 489-500.

97. Schaffer DB, Johnson L, Quinn GE, et al. Vitamin E and retinopathy of prematurity. Follow-up at one year. *Ophthalmology* 1985; 92:1005-1011.

98. Puklin JE, Simon RM, Ehrenkranz RA. Influence on retrolental fibroplasia of intramuscular vitamin E administration during respiratory distress syndrome.

Ophthalmology 1982;89:96-103.

99. Fielder AR. Retinopathy of prematurity: aetiology. *Clin Risk* 1997; 3:47-51.

100. Carver JC, Stromquist CI, Benford VJ, et al. Postnatal inositol levels in preterm infants. *J Perinatol* 1997;17:389-392.

101. Hallman M, Bry K, Hoppu K, et al. Inositol supplementation in premature infants with respiratory distress syndrome. *N Engl J Med* 1992;326:1233-1239.

102. Friedman CA, McVey J, Borne MJ, et al. Relationship between serum inositol concentration and development of retinopathy of prematurity: a prospective study. *J Pediatr Ophthalmol Strabismus* 2000;37:79-86.

103. Young TL, Anthony DC, Pierce E, et al. Histopathology and vascular endothelial growth factor in untreated and diode lasertreated retinopathy of prematurity. *J AAPOS* 1997;1:105-110.

104. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. Ophthalmological outcomes at 10 years. *Arch Ophthalmol* 2001; 119:1110-1118.

105. Ng EYJ, Connolly BP, McNamara JA, et al. A comparison of laser photocoagulation with cryotherapy for threshold retinopathy of prematurity at 10 years. Part 1. Visual function and structural outcome. *Ophthalmology* 2002;109:928-935.

106. Shalev B, Farr AK, Repka MX. Randomized comparison of diode laser photocoagulation versus cryotherapy for threshold retinopathy of prematurity: seven-year outcome. *Am J Ophthalmol* 2001; 132:76-80.

107. Paysse EA, Lindsey JL, Coats DK, et al. Therapeutic outcomes of cryotherapy versus transpupillary diode laser photocoagulation for threshold retinopathy of prematurity. *J AAPOS* 1999;4: 234-240.

108. McGregor ML, Wherley AJ, Fellows RR, et al. A comparison of cryotherapy versus diode laser retinopexy in 100 consecutive infants treated for threshold retinopathy of prematurity. *J AAPOS* 1998;2:360-364.

109. White JE, Repka MX. Randomized comparison of diode laser photocoagulation versus cryotherapy for threshold retinopathy of prematurity: 3-year outcome. *J Pediatr Ophthalmol Strabismus* 1997;34:83-87.

110. The Laser ROP Study Group. Laser therapy for retinopathy of prematurity. *Arch Ophthalmol* 1994;112:154-156.

111. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Effect of retinal ablative therapy for threshold retinopathy of prematurity. Results of Goldmann perimetry at the age of 10 years. *Arch Ophthalmol* 2001;119:1120-1125.

112. Fallaha N, Lynn MJ, Aaberg TM, et al. Clinical outcome of confluent laser photoablation for retinopathy of prematurity. *J AAPOS* 2002;6:81-85.

113. Lambert SR, Capone A, Cingle KA, et al. Cataract and phthisis bulbi after laser photoablation for threshold retinopathy of prematurity. *Am J Ophthalmol* 2000;129:585-591.

114. Gold RS. Cataracts associated with treatment for retinopathy of prematurity. *J Pediatr Ophthalmol Strabismus* 1997;34:123-124.

115. Simons BD, Wilson MC, Hertle RW, et al. Bilateral hyphemas and cataracts after diode laser retinal photoablation for retinopathy of prematurity. *J Pediatr Ophthalmol Strabismus* 1998;35: 185-187.

116. Noonan CP, Clark DI. Acute serous detachment with argon laser photocoagulation in retinopathy of prematurity. *J AAPOS* 1997; 1:183-184.

117. Christiansen SP, Bradford JD. Cataract following diode laser photoablation for retinopathy of prematurity. *Arch Ophthalmol* 1997;115:275-276.

118. Watanabe H, Tsukamoto Y, Saito Y, et al. Massive proliferation of conjunctival tissue after cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 1997;115:278-279.

119. Saito Y, Hatsukawa Y, Lewis JM, et al. Macular coloboma-like lesions and pigment abnormalities as complications of cryotherapy for retinopathy of prematurity in very low birthweight infants. *Am J Ophthalmol* 1996;122:299-308.

120. Christiansen SP, Bradford JD. Cataract in infants treated with Argon laser photocoagulation for threshold retinopathy of prematurity. *Am J Ophthalmol* 1995;119:175-180.

121. Pogrebniak AE, Bolling JP, Stewart MW. Argon laser-induced cataract in an infant with retinopathy of prematurity. *Am J Ophthalmol* 1994;117:261-262.

122. Quinn GE, Dobson V, Barr CC, et al, for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Visual acuity of eyes after vitrectomy for retinopathy of prematurity. Follow-up at 5½ years. *Ophthalmology* 1996;103:595-600.

123. Quinn GE, Dobson V, Barr CC, et al. Visual acuity in infants after vitrectomy for severe retinopathy of prematurity. *Ophthalmology* 1991;98:5-13.

124. Mintz-Hittner HA, O'Malley RE, Kretzer FL. Long-term form identification vision after early, closed lensectomy-vitrectomy for stage 5 retinopathy of prematurity. *Ophthalmology* 1997;104: 454-459.

125. Seaber JH, Machemer R, Eliott D, et al. Long-term visual results of children after initially successful vitrectomy for stage V retinopathy of prematurity. *Ophthalmology* 1995;102:199-204.

126. Fuchino Y, Hayashi H, Kono T, et al. Long-term follow-up of visual acuity in eyes with stage 5 retinopathy of prematurity after closed vitrectomy. *Am J Ophthalmol* 1995;120:308-316.

127. Hirose T, Katsumi O, Mehta MC, et al. Vision in stage 5 retinopathy of prematurity after retinal reattachment by open-sky vitrectomy. *Arch Ophthalmol* 1993;111:345-349.

128. Quinn GE, Dobson V, Repka MX, et al, for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Development of myopia in infants with birth weights less than 1251 grams. *Ophthalmology* 1992;99:329-340.

129. O'Connor AR, Stephenson TJ, Johnson A, et al. Strabismus in children of birth weight less than 1701 g. *Arch Ophthalmol* 2002; 120:767-773.

130. Bremer DL, Palmer EA, Fellows RR, et al for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Strabismus in premature infants in the first year of life. *Arch Ophthalmol* 1998; 116:329-333.

131. Summers G, Phelps DL, Tung B, et al, for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Ocular cosmesis in retinopathy of prematurity. *Arch Ophthalmol* 1992;110: 1092-1097.

132. Reynolds JD. Anisometropic amblyopia in severe posterior retinopathy of prematurity. *Binocul Vis Quarterly* 1990;5:153-158.

133. Reynolds JD. In: Wright KW, ed. *Pediatric ophthalmology and strabismus*. St. Louis: Mosby, 1995:404.

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4

The Pediatric Eye Examination

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One of the principal differences between examining children and adults is that children are not likely to participate willingly. They have learned that a trip to the doctor's office is typically associated with discomfort. As a result, ophthalmologists and technicians who attempt such examinations must learn something of the art of “courting” the child. There is no single correct approach, and different examiners must employ their own individual styles that are comfortable for themselves, as well as their patients. Additionally, different children, at different developmental stages and with different levels of anxiety, need to be approached individually.

Although it is important to be consistent and complete, it is even more important to be directed and adaptable in approaching the child. For example, children are typically most amenable to examination during the first moments of an encounter. They will often become bored or frightened if the examiner spends too much time taking marginally relevant histories or if threatening manipulations are performed initially. Experienced examiners suggest a number of specific strategies:

1. Review the chart before calling the child so that the priorities to be addressed are clear. If a young child is returning to determine if he or she has begun to alternate fixation, assess that issue first.
2. Remember that the encounter begins during the walk into the examining room. Establish eye contact with the child and greet him or her warmly. One trick is to comment favorably on an aspect of the child's attire: “Those sure look like fancy shoes you have on. I bet you can really run fast with those.”
3. Try to engage the child. One might induce the child to “slap me five,” a nearly universal greeting among children over age 2. Or ask the child how old he or she is. Once the child responds, he or she will likely begin to trust the examiner and participate in the examination.
4. Early in the encounter, even before reaching the examining chair, make note of any obvious abnormalities. In some cases, anomalous head postures, intermittent strabismus, nystagmus, discharge, light sensitivity, neurologic disorders, and structural eye defects can be recognized quickly so the history and examination can be better directed.
5. Allow the child and parent to determine if the child should sit in the chair alone or on a lap. This threshold is not strictly age dependent.
6. Avoid terminology which might be frightening to the child. We have “toys to play with,” not examining instruments. We play “peek-a-boo” rather than applying an adhesive occluder. We use “tickle eye drops” and ask the child to wipe them out quickly, before they start laughing.
7. Save the most threatening portions of the examination for the end. For example, the drops should be instilled after the visual acuity and motility have been assessed, and indirect ophthalmoscopy should be done at the very end of the encounter.

HISTORY

Although the chief complaint and history of the present illness are best addressed in the examining room, parents may be asked to supply historic data on a standardized form before the examination begins. Included should be: past medical history, including medications and allergies; birth and developmental history; previous health problems; previous surgeries; family history, especially of childhood eye disorders; social history, including with whom the child lives; and review of systems. The examiner may help to complete the form in the examining room.

Classically, the chief complaint is given by the parent in his or her own words. The older child may be asked for

his or her input as well. The history of the present illness should amplify the chief complaint, including factors such as location, onset, progression, duration, modifying influences, associated symptoms, and prior treatment. For example, if the chief complaint is that a 2-year-old girl's eye “crosses,” the history of the present illness may specify that it is the right eye, which turns “inward, toward the nose”; that the problem began 2 months ago and has increased in frequency, especially when the child is tired or looking at fine detail up close; that it is sometimes associated with closing or covering the eye; and that glasses were prescribed elsewhere without apparent effect. As mentioned above, it may be important to take only a directed history before beginning the examination, especially with young children whose attention and cooperation may be limited.

VISUAL ACUITY

Accurate assessment of (corrected) monocular visual acuity is the single most important element in the examination. It may also be the most difficult to accomplish. A parent pointing to the figures at the end of the room can help maintain the child's attention if needed. Literate children should be tested using the Snellen system, the letters presented on a distant TV monitor, projector screen, or wall mounted placard calibrated for the room size. Preliterate but verbal children should use the HOTV system (matching these four distant optotypes with a card held on the child's lap) or one of various picture systems, including Lea symbols and Allen pictures (Fig. 4.1). It is important to remember that pictures are easier than letters. Amblyopia is typically associated with the “crowding phenomenon,” wherein the visual acuity is better with single optotypes than with lines or full fields, or with single figures surrounded by “crowding bars.” It may be advisable to measure using the same system as at the last visit, even once the child has “graduated” to the Snellen letters. Therefore, the system used, if other than Snellen lines, should be specified.

Initially, visual acuities should be taken binocularly at distance, especially in young children who might be threatened by monocular occlusion. A marginally cooperative child may match the pictures using a near card before he will speak their names. Sometimes children will begin to participate if asked a question to which they know the answer: “Is that a fish or a bird on the TV screen?” Some young children will enjoy pushing the buttons controlling the video monitor and, if so rewarded, will name the pictures enthusiastically. Near visual acuity is taken binocularly in children who have poor distance vision or visual complaints at reading distance. After the binocular acuity is measured, a hand, occluder, or adhesive patch can be used to measure monocular acuities. It must be remembered that children are very adept at “peeking” by using the opposite eye if they cannot see the chart with the eye being tested. Observations such as “this child has eccentric fixation” suggest that he or she may have been peeking across the nose using the one good eye.

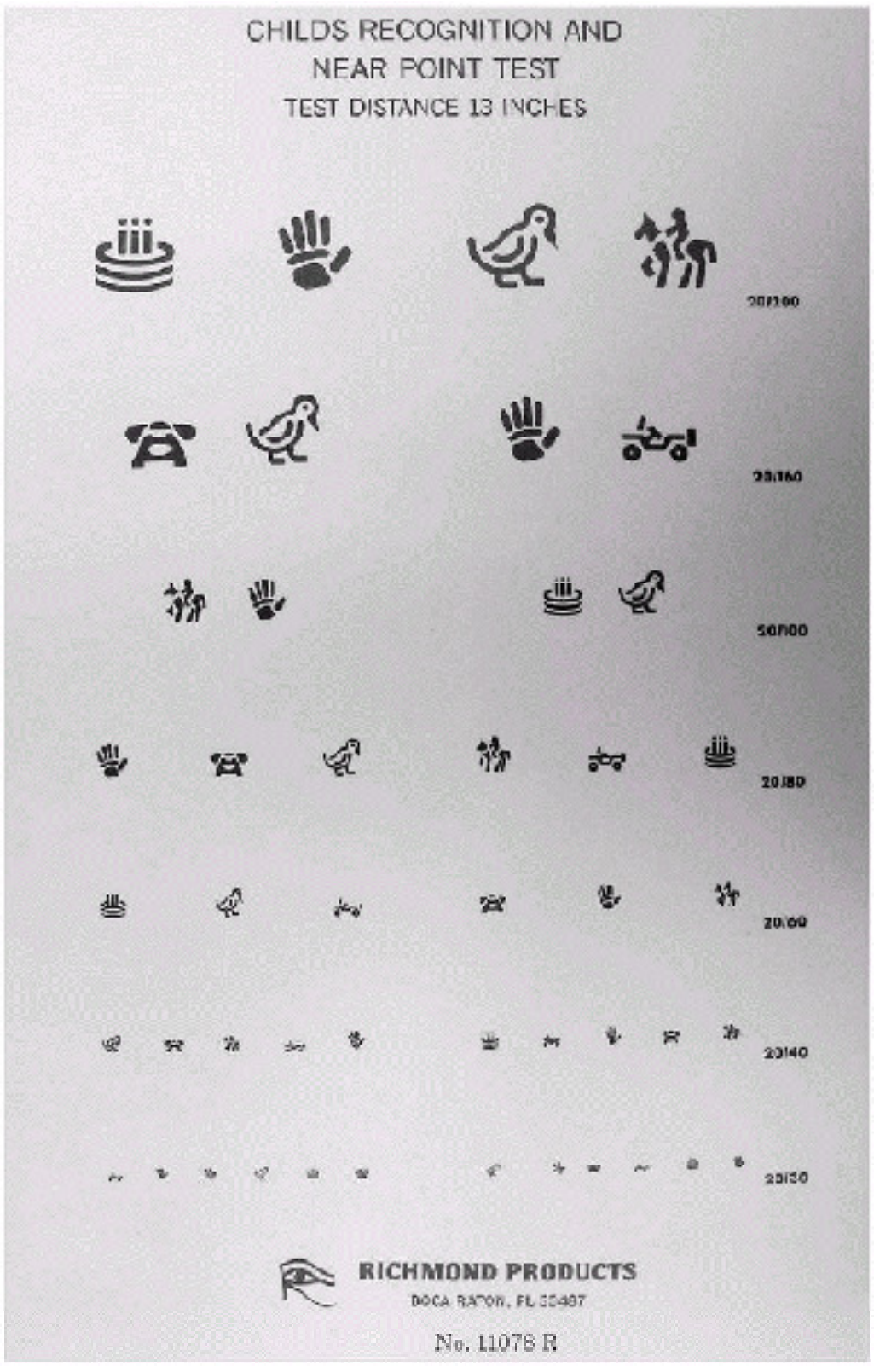


Figure 4.1 Allen pictures used for visual acuity measurement in preliterate children. The same pictures can be presented at the end of the room using a projector or video display.

Visual Acuity Assessment in the Preverbal Child

Assessing the vision of an infant clinically is something of an art form. The exercise begins by simply observing the child to determine his or her interest in the visual environment. Is the child even aware of faces and objects, or of bright lights directed into the eyes? Will the child demonstrate “eye popping,” i.e., opening his or her eyes widely in response to dimming of the room lights? Do the pupils react briskly and symmetrically to direct and consensual light? Is there nystagmus or roving eye movements? Does the child tend to rub his or her eyes forcibly (oculodigital reflex) to “overlook” faces and objects or explore objects by touch?

Preverbal children can sometimes be induced to reach for small objects held at near, such as a coin (or the edge of a coin between the examiner's fingers) or small candy sprinkles (nonpareils). Cooperative children can then be asked to fetch a coin or a small toy tossed across the room. If the test can be performed monocularly, it can dramatically demonstrate poor vision in one eye.

Monocular visual loss in infants is more classically detected by using a hand or thumb alternately over each eye while the child looks at an appealing object, such as a mechanical toy or movie at the end of the room. Testing with objects at near is less sensitive. If there is strabismus in any direction, intermittent or constant, the fixation preference for one eye may be obvious because only the other eye deviates. In the absence of discernible strabismus, the poor vision in one eye may become apparent when the child moves to avoid the hand or occluder held before the good eye. If he or she does not object to a cover in front of the right eye, but moves to look around the occluder in front of the left eye or demonstrates unsteady or uncentered fixation using the right eye, one can assume poor vision in the right eye.

The above observations have been codified in the “central, steady, maintained” (CSM) system of fixation assessment. An eye with normal vision fixates centrally, i.e., with the visual axis directed from the macula toward the object of regard. An eye which does not appear to be directed at the object when the other eye is covered is said to have noncentral fixation. Similarly, an eye with normal vision maintains steady fixation on the object of regard. An eye which demonstrates nystagmoid movements with the other eye covered is said to have unsteady fixation. An eye with normal vision will maintain fixation when the other eye is uncovered, as is the case with alternating strabismus. If an eye turns in any direction, even intermittently, so that it is the only eye which deviates, its fixation is said to be nonmaintained (NM). For example, a child with a left exotropia will likely have C, S, NM fixation in the left eye. Although this kind of fixation may be compatible with visual acuities nearly as good as 20/20, severely unsteady and, especially, noncentral fixation bespeaks substantially poorer vision.

Sometimes it may be difficult to detect strabismus, even using the cover test. For example, children with severe amblyopia may not reliably refixate using the

amblyopic eye when the good eye is covered. Strabismus may be more evident when the cover is first removed from the good eye. “Cross fixation” is the phenomenon associated with largeangle, infantile esotropia, wherein children look across the nose to either side, using the right eye when looking to the left and the left eye when looking to the right. Cross fixation is roughly equivalent to alternate fixation, especially if the change from one eye to the other occurs near the midline. Fixation preference is a sensitive test of amblyopia: if only one eye turns, that eye very likely sees more poorly than the fellow eye. On the other hand, alternate fixation suggests equal vision in the two eyes.

Quantifying the visual acuity of preverbal children is a challenge. There are two methods which can be used. Preferential looking is based on the natural preference for children to look at patterns rather than blank backgrounds. A card (e.g., Teller acuity cards [Fig. 4.2]) with stripes on one side will elicit a head and eye movement toward the side with the stripes which the examiner can see through a peep hole in the middle of the card. The stripes may next be presented on either side and made progressively smaller until the child can no longer see them. At that point, the head and eye movements are no longer consistent, and a measure of the visual acuity can be made.

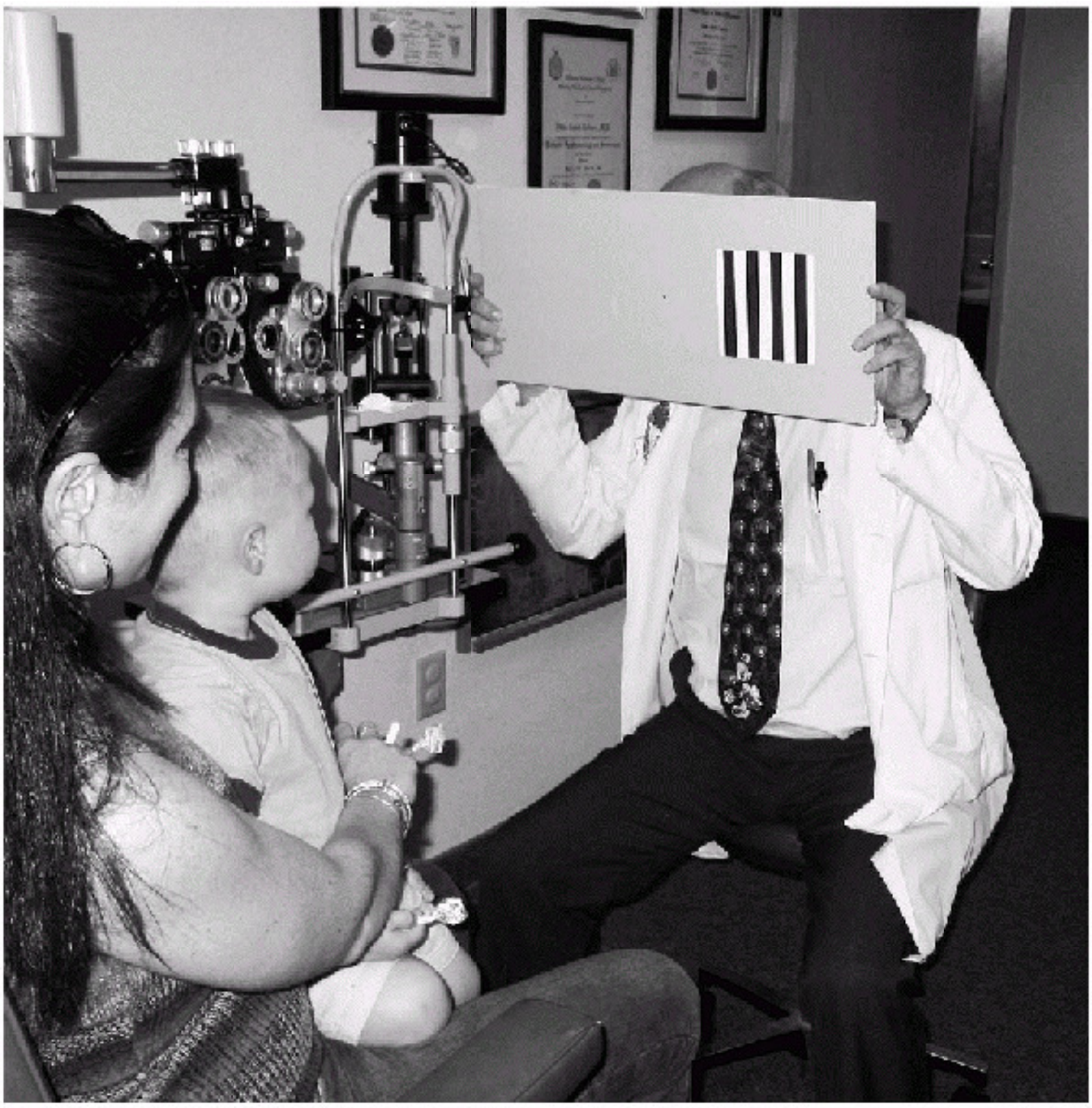


Figure 4.2 The Teller acuity card system can be used to measure the visual acuity of preverbal children.

Visual-evoked potentials are essentially occipital electroencephalograms recorded in response to repeated visual stimulation (Fig. 4.3). The repeated recordings are averaged

so that only the visual response is identified, generally about 100 milliseconds after stimulus presentation. As with preferential looking, the stripes in the stimulus are made sequentially smaller until they are hard to see and the cortical response begins to disappear. Again, the visual acuity measurement can be made by extrapolation at the stripe size corresponding to zero response. Both preferentiallooking and visual-evoked potentials require an experienced examiner and may be difficult to perform in a busy office.

Figure 4.3 Visual-evoked potentials can be used for measuring visual acuities in children too young to name letters or pictures.

OTHER TESTS OF VISUAL FUNCTION

Visual fields can be assessed by confrontation, if necessary without covering either eye. With the child fixating on a cartoon or mechanical toy at the end of the room, the examiner brings a toy into the temporal field from each side, looking for a head and eye movement to indicate that each hemifield is intact. Color vision is screened, especially in boys, using an age-appropriate color screening system, such as the Ishihara plates with numbers or shapes. Color screening is generally performed with both eyes open. More sophisticated color testing may be appropriate, including the Farnsworth D-15 and 100 hue tests, for patients who do poorly on screenings.

Binocularity is most often assessed using a test of stereoacuity, such as the Titmus (housefly) test (Fig. 4.4) or the Randot circles or animals. The housefly measures only gross stereopsis (3,000 seconds of arc), and the picture may be frightening to young children. The Randot circles test stereoacuity as fine as 20 seconds of arc and are preferred over the original 9 Wirt circles, which measure only to 40 seconds and are contaminated by monocular clues. Tests of stereopsis at distance, though more accurate in some circumstances, are used less often.

Figure 4.4 Stereoacuity is measured using the Titmus (housefly) test and Randot circles and animals. Polarized glasses are necessary for testing.

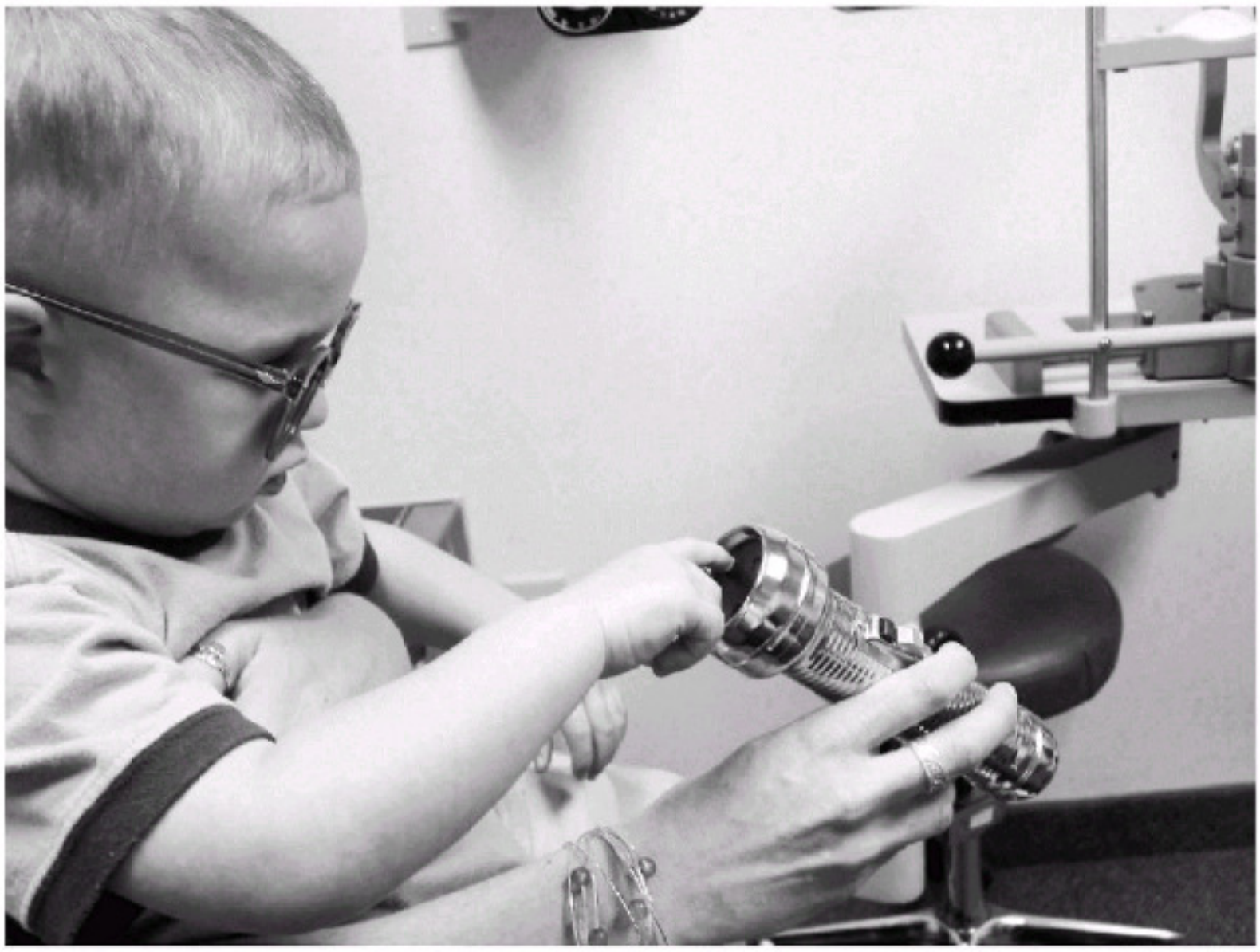


Figure 4.5 The Worth-4 system can be used even in young children to test binocular cooperation.

Children who test poorly on the stereo tests should be investigated for suppression of one eye during binocular viewing. The most commonly used test is the Worth-4 system, which includes four colored lights on a handheld flashlight and standard red (right)/green (left) glasses. Only the child who fuses will see four lights (one red, two green, one red-green rivalry) (Fig. 4.5). The child who suppresses the right eye will see three green lights; the child who suppresses the left eye will see two red lights. The flashlight can be held at varied distances to test different size suppression scotomas. Classically, the test is done at 1/3 meter, where it tests for gross suppression, and at 6 meters, where it tests for fine, central suppression. A polarized version of the Worth-4 test has been developed.

Other tests of suppression include the Bagolini and four prism-diopter base-out tests. The Bagolini has the distinction of testing for suppression in circumstances which most closely mimic normal binocular viewing. Striations marked in trial lenses are mounted diagonally at right angles to each other. A finger rubbed across a spectacle lens is a useful substitute if commercially supplied Bagolini lenses are not available. The subject is asked to view a point source of light (such as a muscle light), which will generate a streak image in each eye 90 degrees opposite in orientation to the striations. He or she can then describe the orientation and intersection of the two streak images.

Children with strictly normal (bifoveal) fusion will see a perfect cross (X). Children with suppression will see a gap in the streak corresponding to the deviating eye. Sometimes the examiner must call the child's attention to the break, especially in cases of exotropia. If there is total suppression, as in congenital deviations, the child will see only the streak corresponding to the fixing eye.

In the four prism-diopter base-out test, the patient is asked to view a distant target with both eyes while base-out prisms are introduced sequentially before each eye. With normal fusion, the prism will shift the image in either eye, inducing a version movement of both eyes toward the side of the prism apex. The same movement will be induced if the prism is held before the fixing eye even if the other eye

has a suppression scotoma. But if the prism is held before the eye which has the scotoma, the image will merely shift within the scotoma, and no movement will be elicited.

Ocular Motility Testing

This portion of the examination is often done early, perhaps even before visual acuity assessment in younger children, as it may be less threatening. An attractive toy is brought, at arm's length, into the six diagnostic positions of gaze: right, left, up and right, up and left, down and right, and down and left. A semiquantitative estimate of under- or overaction of the individual muscles (Table 4.1) can be made based on the number of millimeters of difference in the position of the limbus in each eye. For example, 2 + overaction of the left inferior oblique will cause 2 millimeters of exposed sclera inferior to the left limbus with the eyes up and to the right far enough so the right inferior limbus is tangent to the lower lid. Note that overaction of one oblique muscle (e.g., left inferior oblique) corresponds on version testing to underaction of the yoke muscle (e.g., right superior rectus), reflecting only a change in fixation (e.g., from the right to the left eye). The designations “overaction” or “underaction” do not imply the etiology of the deviation, which may represent a paresis, restriction, or other muscle pathology.

If versions are not full, ductions, or monocular rotations, should be tested in all diagnostic positions. Limited ductions can be characterized using the same semiquantitative system described above. Limited ductions are particularly important in third and sixth nerve palsies, double elevator palsy, Duane syndrome, and restrictive ophthalmopathies such as Graves' disease. In congenital esotropia, contraction of the medial rectus muscles may develop because of habitual cross fixation, causing limited abduction in one or both eyes. In some cases, abduction can be improved by occluding the opposite eye for several days. Sometimes, full abduction can be demonstrated using the “doll's eye” phenomenon or playing “peek-a-boo” in the abducted field.

The Cover Test

After versions and ductions are tested, alignment should be assessed using the cover test in primary (straight-ahead) position at distance and near, and where

applicable, in the six diagnostic positions of gaze (Figs. 4.6 and 4.7). Because downgaze is used for reading, the cover test may be performed at near in both primary position and about 30 degrees below primary position. With the child's attention securely fixed on an accommodative target, the examiner uses a hand or occluder to cover and uncover each eye sequentially, watching for movement of the uncovered eye. First the cover is placed over the right eye. If the left eye is straight, it will not move. If it is esotropic, it will move outward to pick up fixation, assuming the eye can see the object and the child is cooperative. Similarly, it will move inward if it is exotropic, downward if it is hypertropic, and upward if it is hypotropic. Because the deviation may be

in the right eye, the cover test must be repeated with the occluder over the left eye. It is important to remember that strabismus may be intermittent, and prolonged or repeated occlusion may be necessary to discern some deviations. Similarly, it may be important for the examiner to repeat testing in order to discern movements which are reliable, ignoring movements which are not reproducible.

TABLE 4.1 AVERAGE NORMAL FUSIONAL AMPLITUDES IN PRISM DIOPTERS

Testing distance	Convergence fusional amplitude	Divergence fusional	Vertical fusional amplitude
6 m	14	6	2.5
25 cm	38	16	2.6

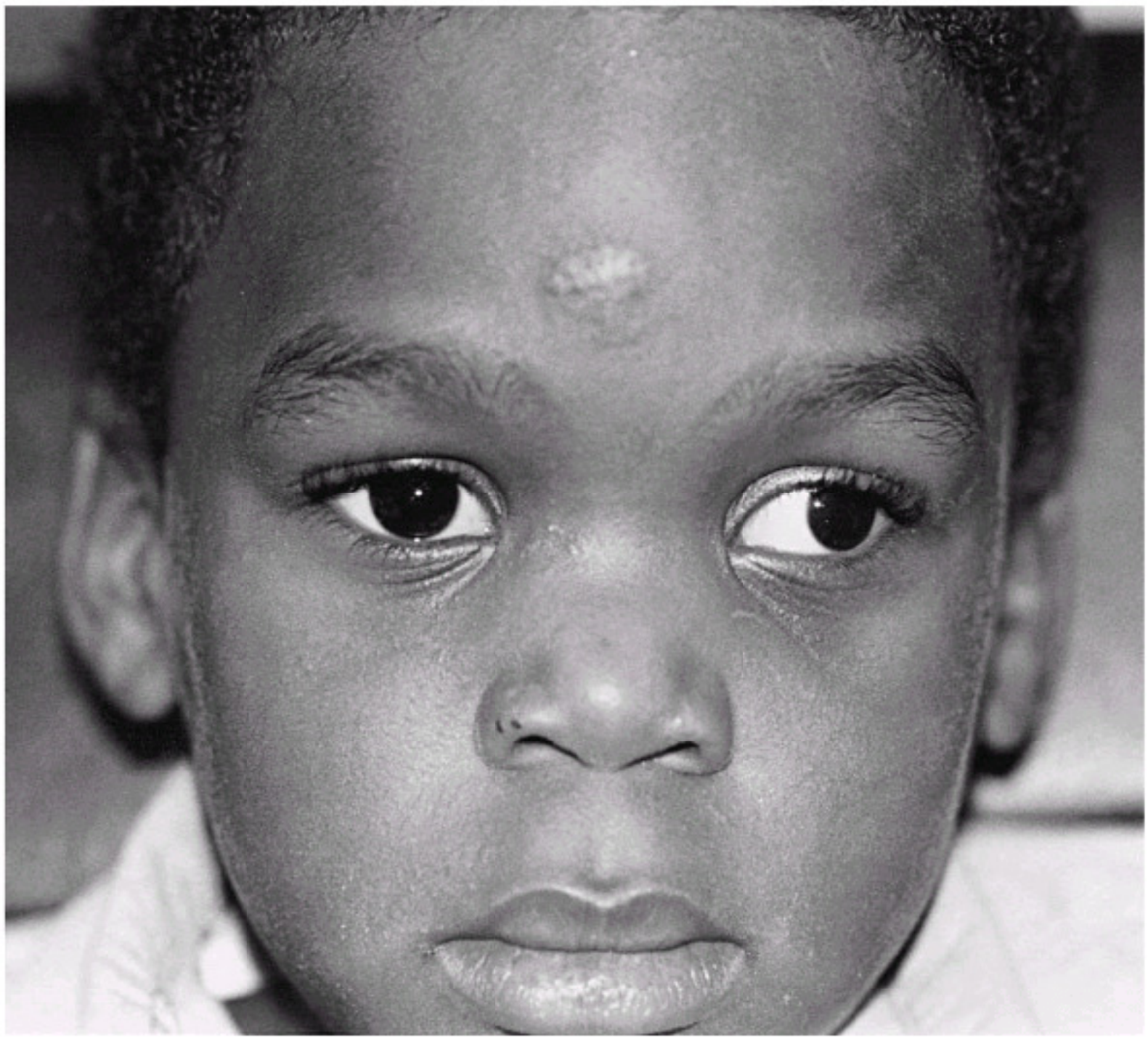


Figure 4.6 Cover test. Child with left exotropia.

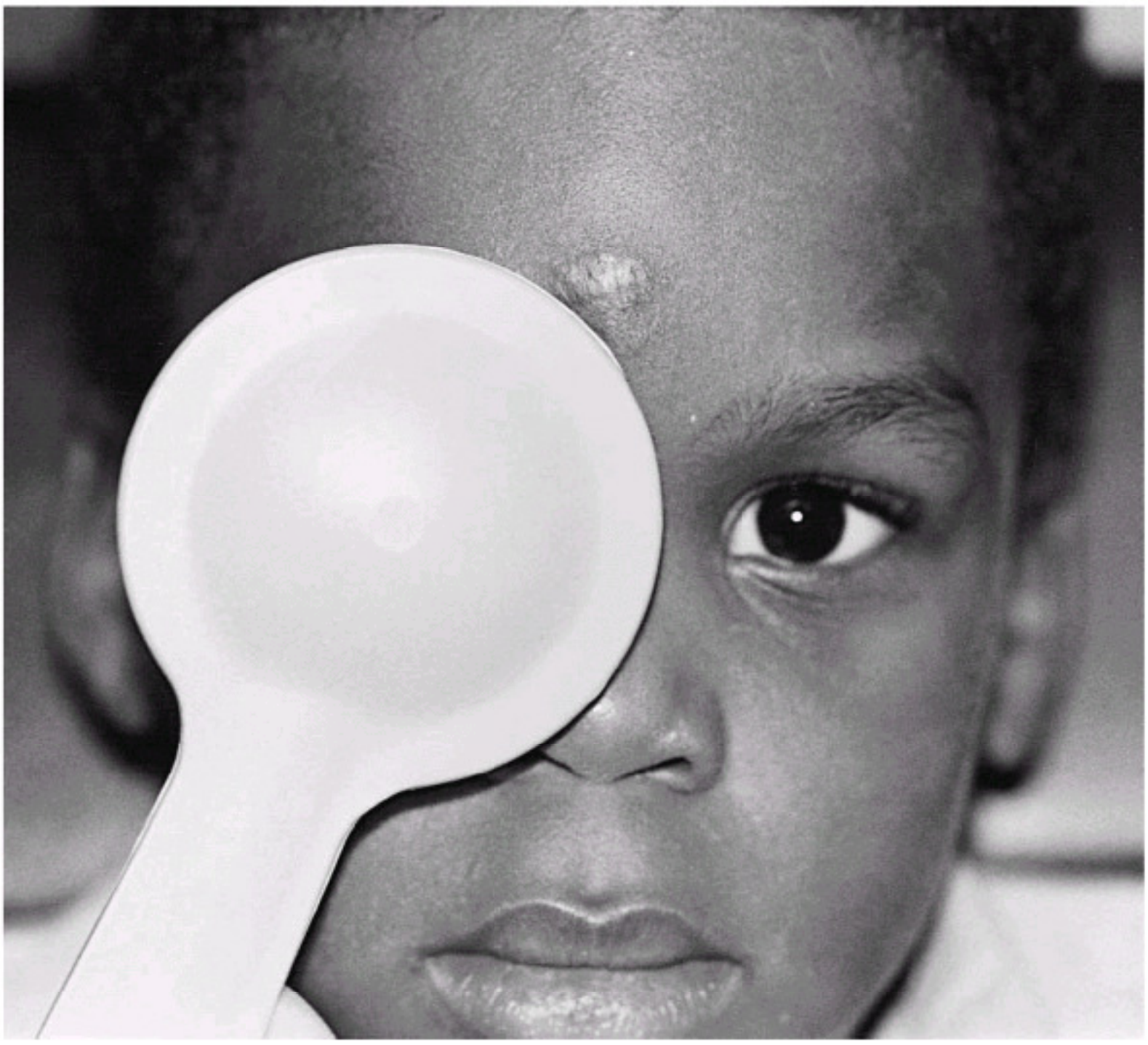


Figure 4.7 Cover test. With occluder placed before the right eye, the left eye has adducted to fixate. *, positive cover test.

The Alternate Cover Test

The alternate cover test is performed by moving the occluder directly from one eye to the other without allowing an interval for binocular viewing. Fusion is thus suspended throughout testing. If no movement is detected, the eyes are truly aligned, or orthophoric. On the other hand, if movement is detected, there is either a phoria (latent deviation controlled by fusion) or tropia (manifest deviation). In fact, the alternate cover test detects the total deviation. It is not necessary to move the occluder very quickly between eyes. Indeed, it is important to allow sufficient time for each eye, in turn, to fixate securely.

The Prism and Alternate Cover Test

The cover and alternate cover tests are used for the detection of deviations. Addition of prisms permits their measurement (Figs. 4.8 and 4.9). A prism is held before either eye, with the apex in the direction of the deviation. The alternate cover test is then performed. If a movement is detected, stronger or weaker prisms are chosen until the movement is eliminated. The neutralizing prism deflects the image of the target to the fovea of the deviating eye, such that no refixation movement is necessary. Individual prisms or the prism bar may be used, and prisms may be held before both eyes. Indeed, larger deviations are more accurately measured using “split prisms,” half held before each eye. Prisms should not be “stacked,” as they do not add arithmetically. Plastic prisms (such as those included in the bar) should be held with the posterior surface in the frontal plane. Glass prisms should be held with the posterior surface perpendicular to the visual axis.

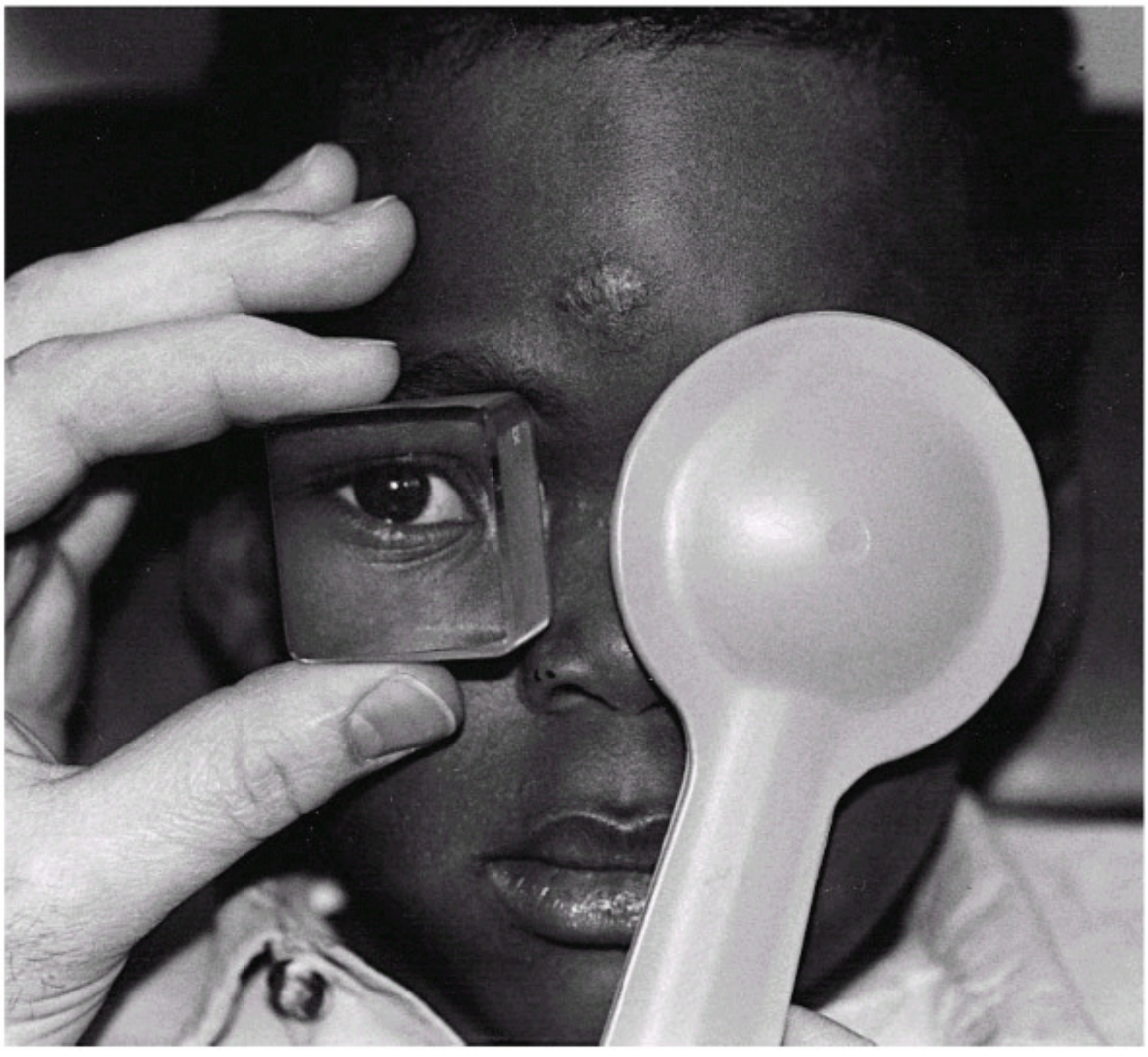


Figure 4.8 Prism and alternate prism cover tests with base-out prism held before the right eye in a child with exotropia.

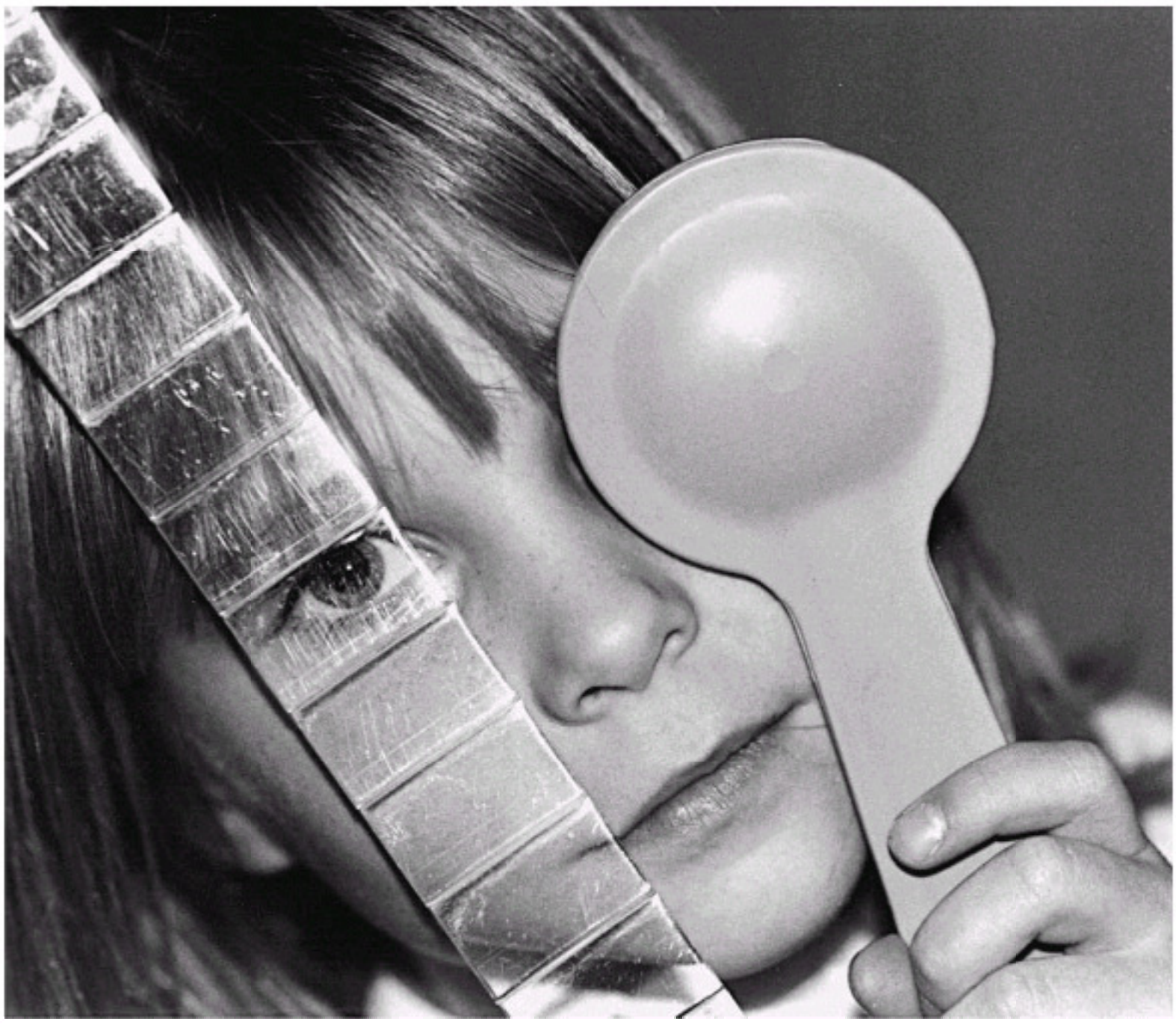


Figure 4.9 Prism and alternate prism cover tests performed with the head tilted toward the left shoulder for vertical strabismus.

Occasionally a larger deviation may be detected with the occluder moving from one eye to the other. This phenomenon may occur with a paretic or restrictive strabismus causing a larger, “secondary” deviation with the defective eye fixating. It may also pertain with uncorrected anisometropia, with more esotropia apparent when the more hyperopic eye is fixating. Similarly, cycloplegia will tend to increase esotropia, especially in hyperopic children, because of induced accommodative convergence. If a vertical deviation is detected, head-tilt testing should be performed to diagnose a cyclovertical muscle paresis, if one is present. It is emphasized that, as with the cover test, the child must be able to fixate securely using each eye on an accommodative target. Similar to the alternate cover test, the prism alternate cover test measures the total deviation, tropia plus phoria.

The Simultaneous Prism Cover Test

To measure only the manifest deviation, or tropia, a prism is introduced before the deviating eye at the same time as an occluder is introduced before the fixing eye (Fig. 4.10). The correctly chosen prism neutralizes the shift of the deviating eye. In most strabismus cases, the tropia is the same as the total deviation. In such cases, the simultaneous prism cover test will give the same measurement as the prism alternate cover test and is typically not used. However, in some patients, there is only a small tropia evident on cover testing but a larger total deviation evident on prism alternate cover testing. Such patients may have a large superimposed phoria. In these cases, simultaneous prism cover test measurement will be smaller.

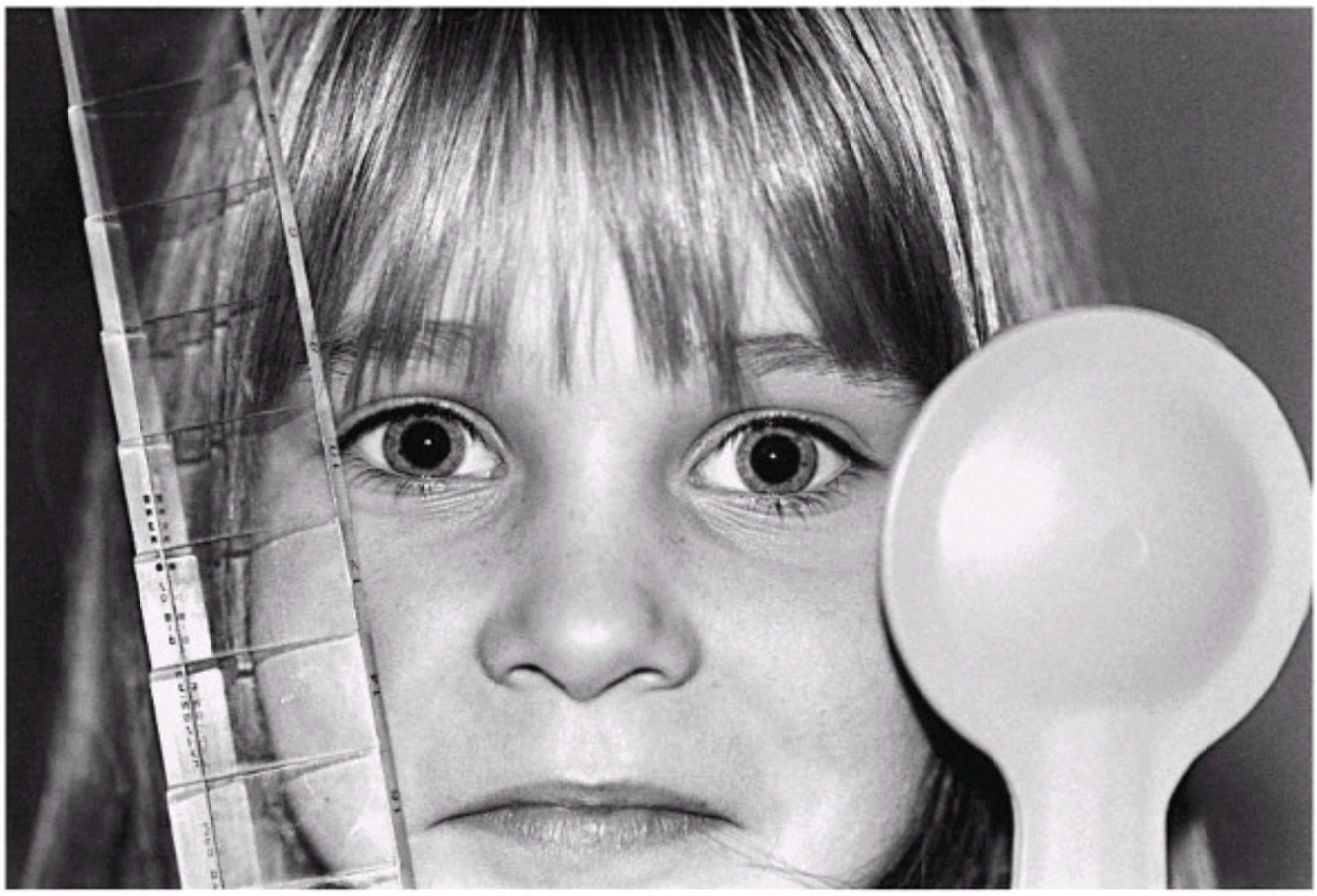


Figure 4.10 Simultaneous prism cover test.

Pupillary Light Reflex Tests

When cover testing is impossible because of poor vision, eccentric fixation, or lack of cooperation, very good estimates of ocular deviations can be made using the cover tests. Assuming the visual axis passes through the center of the pupil, the Hirschberg test estimates the deviation based on the number of millimeters the reflex is decentered in the deviating eye. With the test light directed at the nasal bridge, each millimeter is equivalent to 7 degrees. The decentration is temporal in esotropia, nasal in exotropia, downward in hypertropia, and upward in hypotropia. Just as prisms can be combined with the cover test, they can also be combined with the light reflex tests. In the Krimsky test, the prism is used to center the light reflex in each eye (Fig. 4.11).

The Krimsky method is considered more accurate than the Hirschberg test, but neither is as accurate as the prism alternate cover test. It is important to remember that the visual axis may not pass through the pupillary center. The angle kappa is the angle formed at the intersection of the visual axis and pupillary axis. It is considered “positive” when the pupillary light reflex falls slightly to the nasal side of the pupil, simulating exotropia (Fig. 4.12). In some cases, the angle kappa is quite large. It must be taken into account when measuring strabismus using both Hirschberg and Krimsky tests. Although both tests are classically performed using a penlight or “muscle light” at near, they can also be performed using a distant light source.

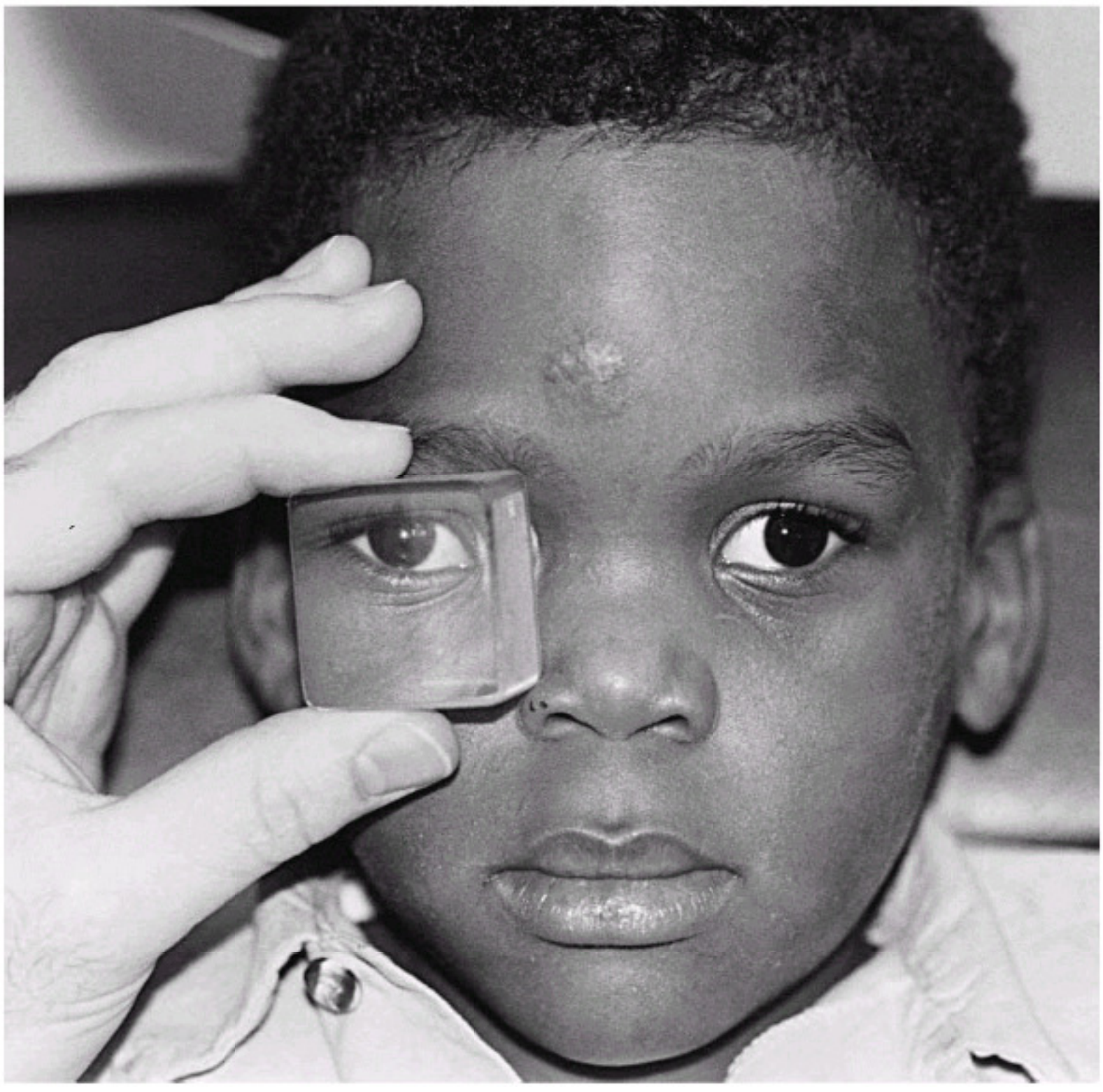


Figure 4.11 Krimsky test in a child with left exotropia.

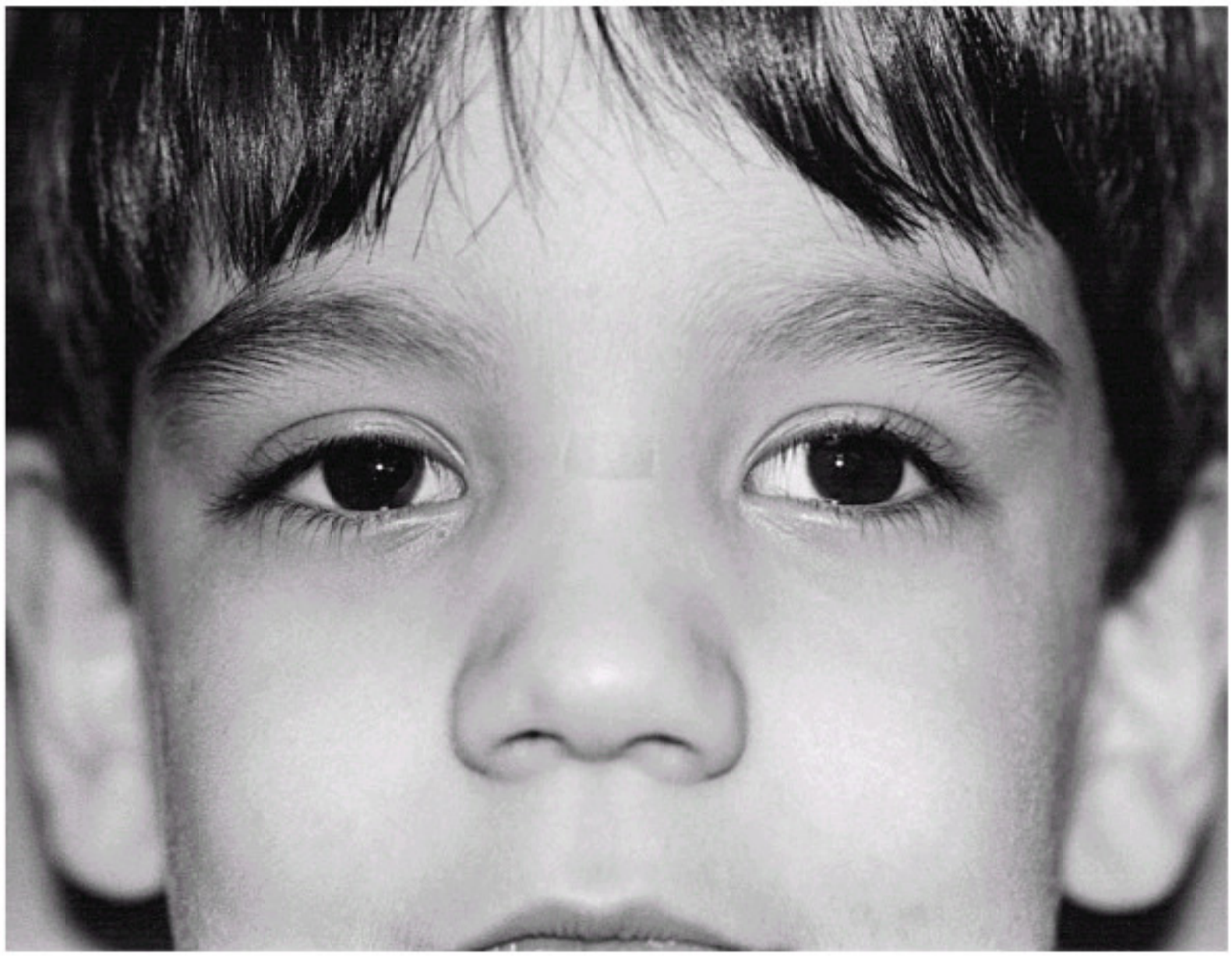


Figure 4.12 Positive angle kappa in the left eye simulating left exotropia.

Maddox Rod

This simple test, which uses either a red or a white Maddox lens to turn a point source of light into a line image, can be very useful for measuring small vertical deviations and ocular torsion (Fig. 4.13). For vertical deviations, the ridges are held vertically so the line image is horizontal. The subject identifies the vertical prism which subjectively aligns the light source and the horizontal line. For measuring torsion,

both red and white Maddox lenses are used in a trial frame. The subject is asked to identify the angle of the two lenses which make the red and white lines appear horizontal and parallel. Maddox lenses are not as useful in horizontal deviations because of the influence of variable accommodative and fusional vergence.

Figure 4.13 Double Maddox rod test in trial frame for measuring cyclotorsion.

Subjective Testing

In cooperative older children and adults, subjective measurement of strabismus angles can be most helpful in certain circumstances. If, for example, a patient reports diplopia which is relieved when the corrective prism is held before the eye(s) in free space, a valuable and precise measurement has been accomplished. In some patients, it is helpful to use a red lens before one eye to help identify which eye is associated with each image. Occasionally, a patient may simply be asked to “find the prisms which superimpose the two Es.” Those prisms can then be used in various positions and at various fixation distances to ensure that single binocular vision can be maintained. Often patients without diplopia can precisely identify their strabismic angle as larger prisms are introduced by noting diplopia as soon as the deviation is overcorrected.

Near Point of Convergence

Convergence is necessary for maintaining normal alignment at reading distance. The alignment at near should be tested using an accommodative target, and the near point of convergence should be estimated. If convergence is inadequate, an exotropia and diplopia will be noted as a light or small figure is brought closer to the patient. As a nonaccommodative target, the light may actually demonstrate this problem better. In convergence insufficiency, patients will complain of asthenopic symptoms after prolonged reading. In addition to the remote near point of convergence, they will demonstrate low fusional convergence amplitudes when tested with base-out prisms. Treatment with exercises (“pencil push-ups,” with or without base-out prism) can be helpful. Occasionally, base-in prisms are prescribed in separate reading glasses or in bifocals, but surgery is generally to be avoided because it can cause distance esotropia. Because accommodation may also be defective in patients with convergence insufficiency, their near point of accommodation should also be estimated using an accommodative target at near through distance glasses.

The opposite problem occurs with the high-accommodative-convergence-to-accommodation-ratio form of accommodative esotropia. In this condition, accommodative convergence is overactive, causing an esotropia at reading distance even if appropriate distance glasses are worn. Especially if the child has binocularity potential, bifocal glasses may be prescribed to supply the accommodation needed for reading so that the patient's accommodative convergence is not required. It is important to test the alignment at near using an accommodative target through both distance and bifocal lenses.

Fusional Vergences

Fusional vergences measure the ability of a patient to overcome the effect of variable prisms in order to maintain ocular alignment. If they are demonstrated, motor binocularity exists. Either a prism bar or a rotary (Risley) prism is used while the patient views an accommodative target. The prism power is slowly increased until a “breakpoint” is apparent, either by the observation of an ocular deviation in the direction of the prism base or by the subjective report of diplopia. Fusional vergence amplitudes are normally larger for convergence than for divergence, and are least for vertical vergence. They are larger for near than for distance, even with convergence insufficiency.

Fusional vergence amplitudes can be nearly normal despite subnormal sensory binocularity, as in the monofixation syndrome. As a result, children with this syndrome following surgery for infantile esotropia may have the ability to maintain close to normal alignment. Fusional vergences are characteristically larger than normal in patients with congenital fourth nerve palsies.

External Examination

As indicated above, general inspection of the child's overall appearance and body habitus may provide an immediate diagnosis in some circumstances. Obvious external features, such as ptosis, blepharophimosis, and eyelid or iris colobomata, should be noted. The pupils can be checked for reactivity to light and near targets and for the presence of afferent pupillary defects. The latter is diagnosed with the “swinging flashlight” test. As the light is directed from the normal eye to the eye with a defect in the afferent visual pathway, both pupils will dilate. It is essential to control the child's accommodation during testing, ideally with their attention directed to a distant target in a semidarkened room. In addition to the anterior ocular segment, the external examination should encompass, when appropriate, the eyelids and adnexae, periauricular lymph nodes, and tarsal surface.

Slit-Lamp Examination

Slit-lamp examination can be performed on very young children with the help of one or two assistants. Portable slit lamps may be necessary for some children, especially in an operating room setting (Fig. 4.14). In most routine cases, slit-lamp examination is not necessary in children, and it is important to remember that the instrument can be frightening for young children.

The slit lamp is especially useful in patients with ocular inflammation or irritability, in patients with nystagmus in whom albinism is suspected, and in following trauma. One parent holds the child, with the feet dangling if necessary, close to the chin rest. A second assistant brings the face into the instrument, and the examiner holds the eyelids open as needed. Children old enough to sit by themselves may be easier positioned either kneeling or sitting with their knees to the sides of the chair.

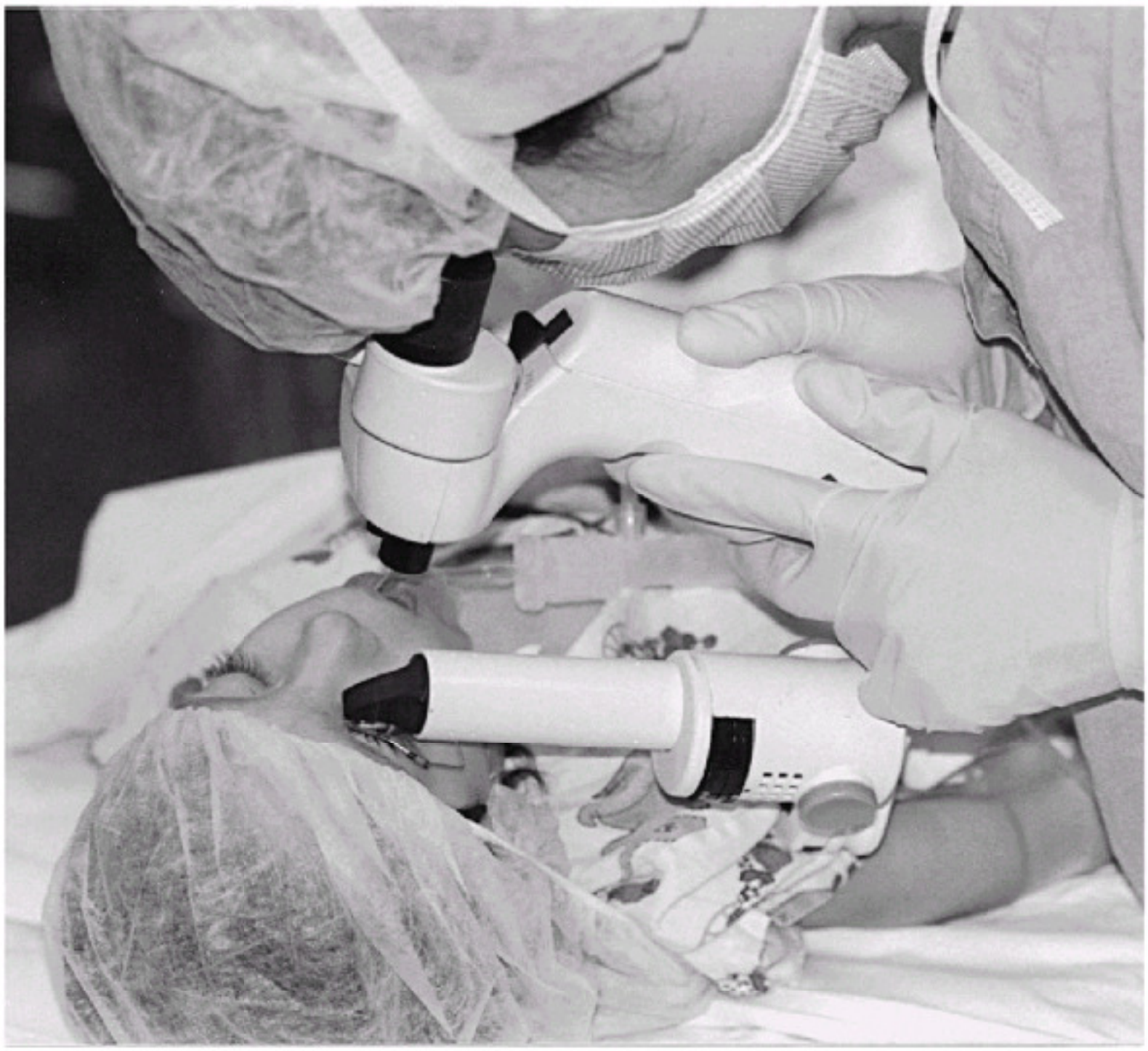


Figure 4.14 Portable slit-lamp examination in operating room during examination under anesthesia.

Tonometry

Tonometry is often difficult and frightening to young children and may be deferred as part of the routine examination unless glaucoma is suspected. In the neonatal period, intraocular pressure (IOP) measurement can often be accomplished in the office using a handheld applanator (e.g., Perkins tonometer) after topical anesthetic is instilled, especially while the child is taking a bottle (Fig. 4.15). The fluctuations in readings as the child inhales and exhales can induce movement of the mires. Though many examiners find the Tono-Pen easier to use, it may give erroneous readings. When the child reaches about 1 year of age, inability to cooperate may make examinations under anesthesia necessary. However, it is important to remember that there may be a significant decrease in IOP with the use of general anesthesia and muscle relaxants. Older children may be coaxed into the slit lamp for Goldman applanation tonometry, which remains the “gold standard.”

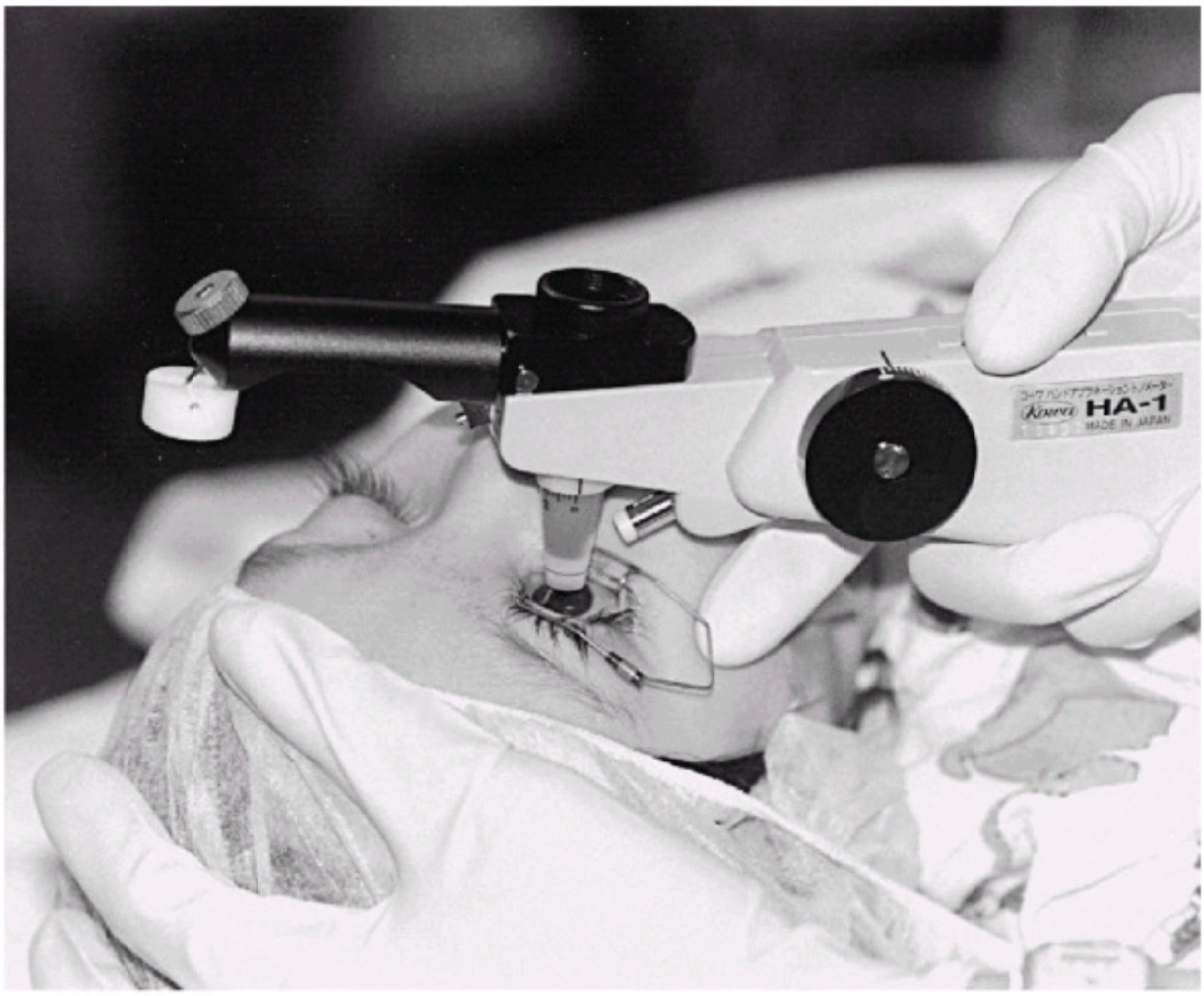


Figure 4.15 Applanation tonometry being performed during examination under anesthesia.

Ophthalmoscopy

This important part of the examination is usually performed last, as it is often done after cycloplegic/mydriatic eye drops are instilled, and both the drops and light source may be uncomfortable. If the child can cooperate, he or she can remain seated. However, uncooperative children may require restraint in the recumbent position, with the head on a parent's knees and the feet straddling the parent's waist. A lid retractor is rarely necessary.

The indirect ophthalmoscope is preferred for young children, as their cooperation is typically too limited for effective direct ophthalmoscopy (Fig. 4.16). Indirect ophthalmoscopy is also preferred with opaque media for retinopathy of prematurity and other peripheral retinal disorders and following trauma. On the other hand, the direct ophthalmoscope may yield a better view of the disc and posterior pole, may permit estimation of the severity of media opacities, and may demonstrate subtle nystagmus.

Refraction

As noted above, determination of the best corrected visual acuity in each eye is the single most important part of the eye examination, even if refraction is not the favorite for some practitioners. Manifest refraction is useful when prescribing glasses in older children, but a cycloplegic retinoscopy should be performed in every child at the initial visit (Fig. 4.17). It is not unusual to find an unsuspected refractive error requiring treatment in a young child presenting for an entirely unrelated reason. It is important to remember that refractive errors in children, as opposed to adults,

can lead to permanent visual loss from amblyopia if they are undiagnosed and uncorrected.

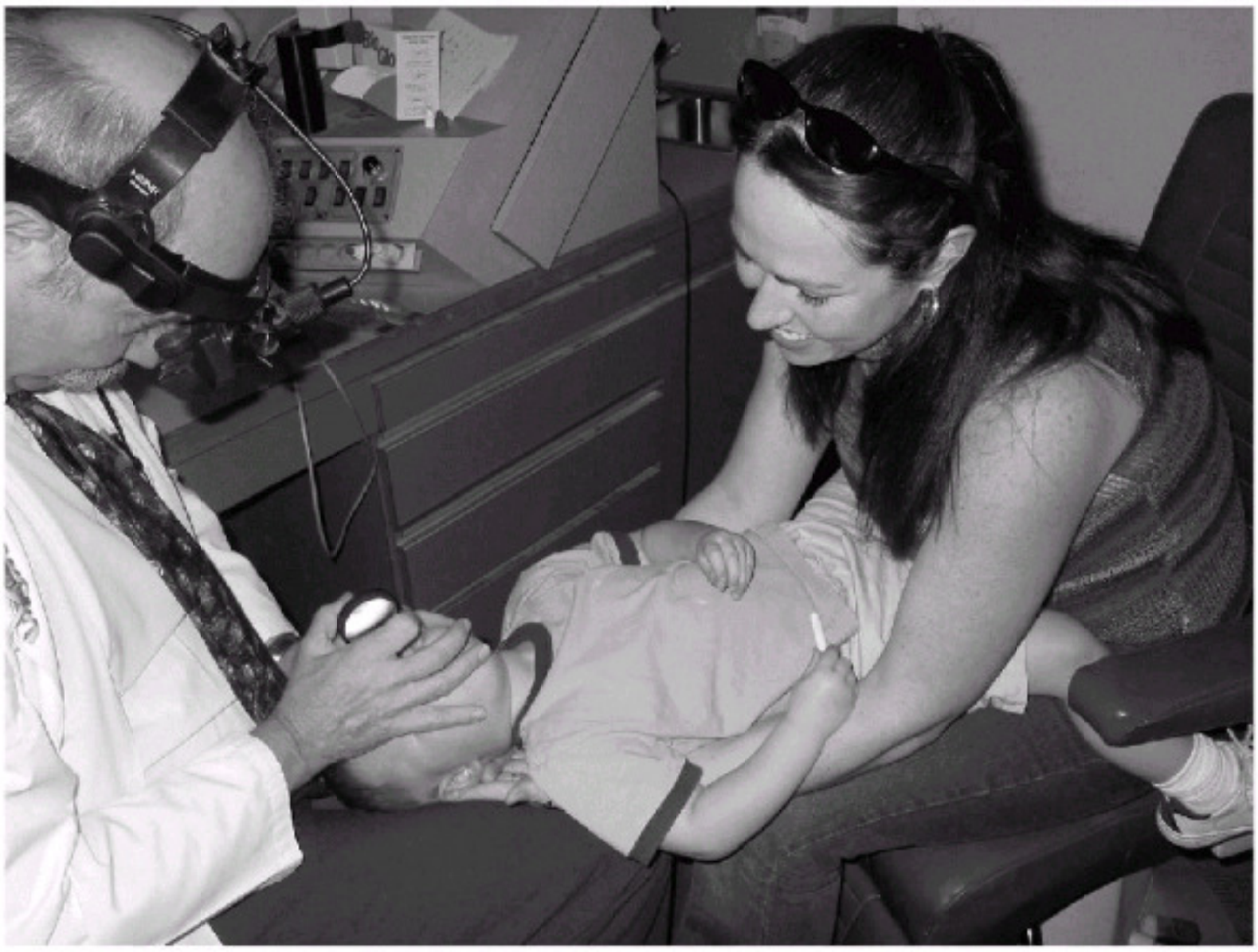


Figure 4.16 Indirect ophthalmoscopy can be performed with the child held on a parent's lap, if necessary.

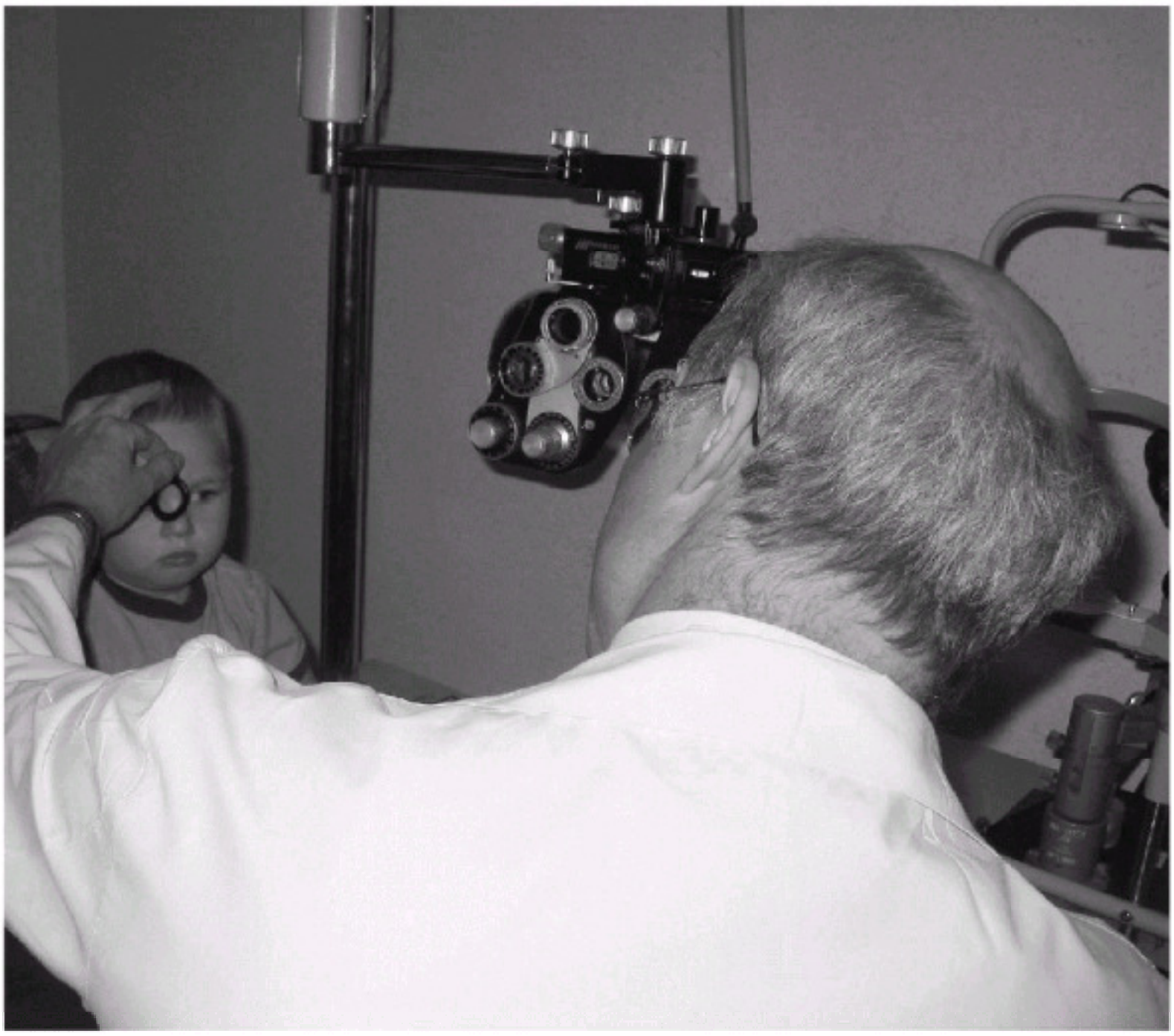


Figure 4.17 Cycloplegic retinoscopy is important to perform in every child on the initial visit.

Adequate cycloplegia can be accomplished with combinations of cyclopentolate and tropicamide; atropine is rarely required. Some practitioners instill a topical anesthetic before the cycloplegic to increase comfort, aid in penetration, and decrease tearing. Additional instillations, perhaps including phenylephrine 2.5% may be required, especially in darkly pigmented eyes. Young children do better with handheld trial lenses, though older children may accept the refractor ("phoropter"). Care must be taken to remain on-axis when performing retinoscopy, especially avoiding fixation with the other eye if it is strabismic. It is preferred that the child remain seated during retinoscopy, as the recumbent position allows the lens to be displaced posteriorly and may change the refraction.

Although some practitioners use autorefractors in older children, manifest refraction can require judgement. Children are easily "under-plussed" or "over-minused." Rather than asking "which is better," the examiner should demonstrate improvement in visual acuity with each increase in minus. Hesitant or inconsistent responses or unexpected changes in refraction are indications for cycloplegic refraction.

SUMMARY

Proper performance of the pediatric eye examination can be a challenge, but is well within the capabilities of any ophthalmologist. Examiners should remember the importance of engaging the child, establishing secure fixation, and maintaining a directed, flexible approach throughout the exam. In some cases, a repeat examination on a subsequent day may be necessary. Early diagnosis of treatable conditions is the reward for success.

SUGGESTED READING

Anderson WB, Freedman S, Shields MB, et al. *Atlas of ophthalmic surgery: strabismus and glaucoma*. St. Louis: Mosby Year-Book, 1995.

Calhoun JH, Nelson LB, Harley RD. *Atlas of pediatric ophthalmic surgery*. Philadelphia: WB Saunders, 1987.

Nelson LB, Harley RD, eds. *Harley's pediatric ophthalmology*, 4th ed. Philadelphia: WB Saunders, 1998.

Nelson LB, Catalano RA. *Atlas of ocular motility*. Philadelphia: WB Saunders, 1989.

Parks MM. Ocular motility and strabismus. In: Tasman W, Jaeger EA, eds. *Duane's clinical ophthalmology*. Philadelphia: Lippincott, 1993: 1-20.

Parks MM. The monofixational syndrome. *Trans Am Ophthalmol Soc* 1969;67:609-657.

von Noorden GK. *Binocular vision and ocular motility: theory and management of strabismus*, 4th ed. St. Louis: CV Mosby, 1990: 163.

von Noorden GK. *Atlas of strabismus*, 4th ed. St. Louis: Mosby, 1983: 149.

Wright KW. *Color atlas of strabismus surgery strategies and techniques*. Irvine, CA: Wright, 2000.

Wright KW, Spiegel PH, eds. *Pediatric ophthalmology and strabismus*, 2nd ed. New York: Springer, 2003.

Editors: **Nelson, Leonard B.; Olitsky, Scott E.**
Title: ***Harley's Pediatric Ophthalmology, 5th Edition***

5

Electrodiagnostic Tests of the Retina and Higher Centers

Ronald E. Carr

The availability of electrodiagnostic tests of visual function adds new dimensions to the diagnosis of retinal diseases, as well as disorders of the postreceptoral visual pathway. In adults, psychophysical or subjective tests of vision may clarify a diagnosis or add information to the study of a visual problem; however, such responses cannot be elicited in infants, and the answers of older children who are responsive may be questionable.

In the context of pediatric ophthalmology, the major groups in whom such tests would be diagnostically useful are (a) infants with nystagmus and poor vision from birth, (b) children with overt but nondiagnostic macular lesions, (c) children in whom a generalized retinal degeneration may be present or suspected, and (d) children with the onset of decreased vision of unknown cause.

BASIC CONCEPTS

Among the testing modalities that are useful diagnostically are the electroretinogram (ERG), electrooculogram (EOG), and visual-evoked response (VER). In order to better appreciate the information that can be derived from such tests, this section gives a short summary of the basic concepts inherent in each.

Electroretinography

It has been known for more than 100 years that a flash of light will elicit a distinctive electric response from the retina, but this test has been applied to humans only since the 1940s. At that time a contact lens which incorporated an electrode around its periphery was developed. Such an electrode produced a suitable conducting mechanism so that the retinal response could be easily recorded. Technologic advances over the past 40 years have led to improvements in recording and amplifying techniques, but the basic principles remain unchanged.

The ERG can be defined as the *transient* electric response from certain *outer* retinal layers to a *change in luminance.* Thus, in the clinical situation, an ERG response is noted as a rapid discharge to a flash of light that is not elicited again until a second light is flashed (Fig. 5.1). In a recording that is done in the light, the ensuing photopic ERG shows sharply delimited a-waves and b-waves. After a period of dark adaptation, the scotopic ERG represents a summation of cone plus rod responses. The addition of the large number of rod receptors accounts for the much greater response seen after dark adaptation. At the present time the standard clinical ERG is elicited by diffusely illuminating the entire eye so that the recording is a mass response—one that tests the viability of the entire retina. Thus, if only a small area of the retina is affected, as in macular degeneration, the ERG as recorded in this manner will be normal since most of the retinal receptors are still intact and capable of giving a normal response.

In the usual recording situation, a contact lens electrode is placed on the anesthetized cornea, and the responses are displayed on an oscilloscope. Either a diffuse light placed about 3.75 cm from the contact lens is used, or so-called Ganzfeld (full-field) stimulation is applied. In infants or younger children, ketamine has proved to be a satisfactory anesthetic since it does not affect the ERG responses and

is effective long enough (30 minutes) to complete an examination, including refraction, fundus evaluation, and ERG.

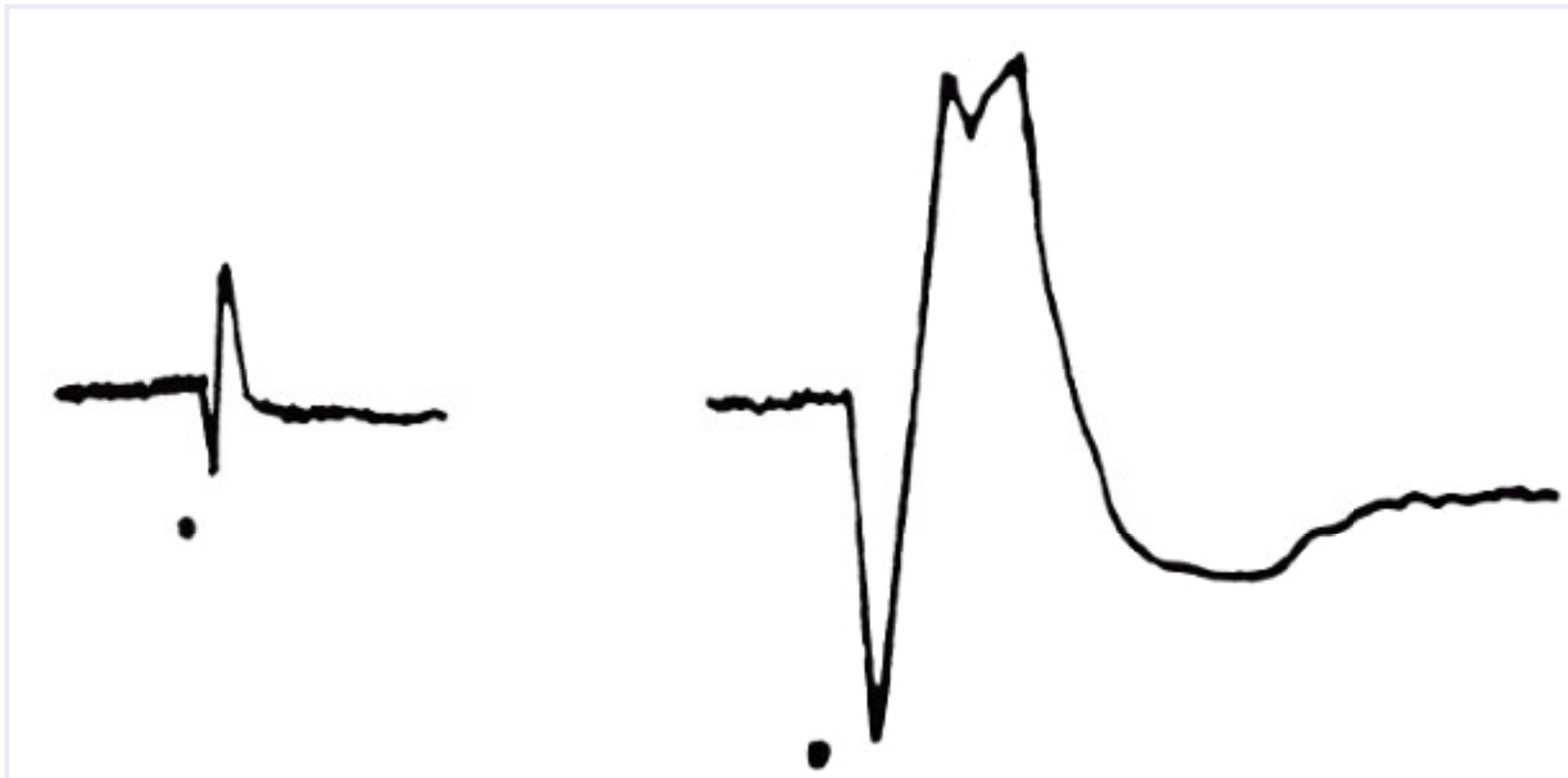


Figure 5.1 Left: Photopic (light-adapted) ERG response showing initial negative a-wave and second positive b-wave. **Right:** Scotopic (dark-adapted) ERG response showing the large increment due to the addition of the rod receptors to the photopic response. ERG, electroretinogram.

The ERG, as clinically used, consists of two major responses—an initial negative response called the a-wave and a second positive response called the b-wave (Fig. 5.1). Studies performed in animals, and in certain clinical situations in humans, have shown that the a-wave is derived from the inner segments of the photoreceptors, whereas the b-wave is derived from Muller cells and is indicative of activity within the bipolar cell region. Thus, the ERG provides methods of looking at specific retinal areas. Likewise, such knowledge indicates that the ganglion cell layer does not contribute at all to this response so that optic atrophy has

no effect on the ERG.

Certain recording techniques can be used to separate functions of the rod and cone systems (Fig. 5.2). The rod system is unable to respond to a light flickering at greater than 16 to 20 Hz; if a light is flickered at a faster rate (i.e., 30 Hz), the only receptors then able to respond are the cone receptors. This technique of using a high-intensity stimulus at 30 Hz is known as the flicker ERG, and such a response will look at the cone system alone. To differentially look at the rod system, it is important to understand that the rods are very sensitive to blue light but relatively insensitive to light from the red end of the spectrum. Conversely, the cones are quite insensitive to blue light stimuli and sensitive to red light stimuli. Thus, if a low-intensity blue-light stimulus is used following dark adaptation, the resultant response is virtually devoid of any cone contribution, and the ERG is that of rod function alone. Likewise, if a bright red-light stimulus is used, a biphasic response is seen. The initial response is from the more rapidly responding cones, whereas the second response is from the slower responding rods. The rod response is about the same as the cone response under such recording conditions, although there are 15 to 20 times as many rods as cones; this discrepancy merely reflects the relative lack of sensitivity of the rod system to stimuli of this wavelength.

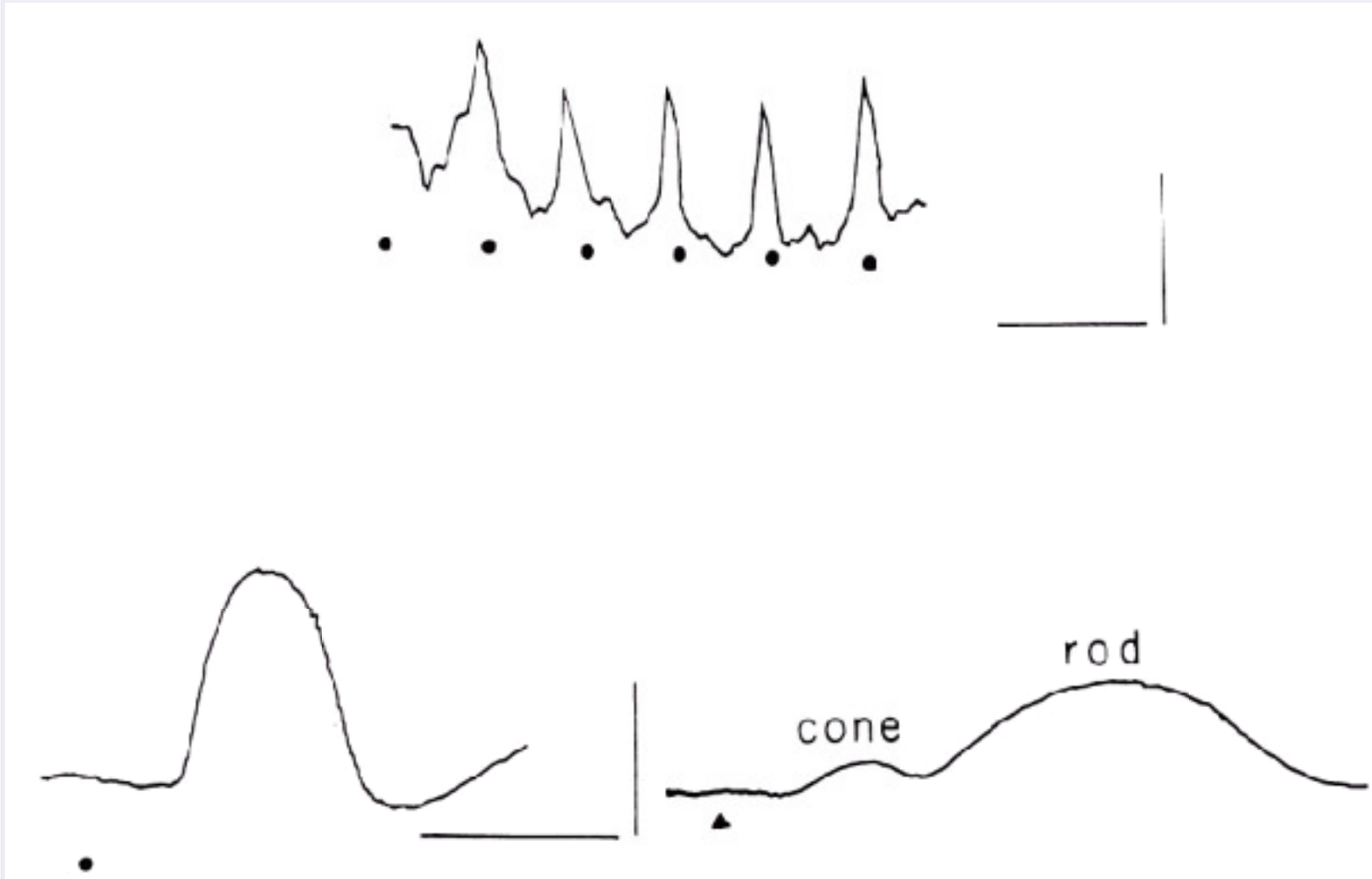


Figure 5.2 Top: Photopic flicker (30-Hz) response, indicative of cone function. **Lower left:** Scotopic response to a weak blue stimulus (S_1B). The relative insensitivity of the cones to this stimulus indicates that this is a response of the rod system virtually alone. **Lower right:** Scotopic response to a moderate red stimulus (S_8R). The two segments show the more rapid responding cones and slower rod responsiveness. This response allows comparative studies of rod and cone populations. Calibration: 0.3 sec; 0.1 mV.

In the clinical situation, the following test protocol has been used and found to be the least time consuming:

Under light-adapted conditions, a bright white single flash is elicited ($S_{16}W$)

The flicker response is then obtained ($S_{16}W$ flicker)

The patient is dark adapted for 15 minutes

A low-intensity blue stimulus is elicited (S_1B)

A moderate-intensity red stimulus is elicited (S_8R)

A bright white stimulus is elicited ($S_{16}W$)

Variations and more extensive protocols can be used in certain situations, and everyone conducting these studies should establish his or her own protocol. However, in most clinical situations, the protocol just noted provides sufficient information.

There are certain situations, particularly with young children, in which 15 minutes in darkness or a prolonged protocol may prove difficult. If this is true, one eye may be securely patched for 15 minutes while the patient is prepared for ERG testing. The contact lens should be inserted under red light, and all testing should be done in darkness. A low-intensity blue light (S_1B) will reveal the rod response, and a flicker recording ($S_{16}W$) may then be done to elicit

the cone response. The last response would then be a fullintensity single-flash white stimulus ($S_{16}W$). The total time for this ERG recording is thus reduced to several minutes.

At the present state of knowledge, all ERG recordings should be performed using some type of full-field stimulus and an oscilloscope. This enables recording of one other type of information—the measurement of the time elapsed between the onset of the stimulus and the peak of the response (implicit time) (Fig. 5.3). In certain disease entities, such a measurement may be extremely important in arriving at the correct diagnosis (1). A more detailed article on standardization of various ERG parameters and clinical protocols is now available for those setting up their own labs (2).

As noted previously, the full-field ERG is a mass response reflecting the electric activity of the entire retina. It has been recognized for many years, however, that it would be clinically useful to be able to record electric responses from discrete, local retinal regions, in particular the macular area. Two conditions are necessary to obtain such recordings. First, a method is needed for eliminating the effect of scattered light in producing responses from areas peripheral to those of interest

because even if a light is focused directly onto the optic nerve, such light will scatter and stimulate more peripheral retinal regions and give an ERG. To eliminate this and ensure that the light stimulates only the area of interest, the peripheral retinal response is eliminated by diffusely illuminating these retinal regions so that the scattered light is insufficient to elicit a response. The second requisite for recording such a response is the capability to summate a large number of such responses since each alone is so small that it cannot be individually discriminated. Present technology easily allows this to be done.

For recording the focal ERG, the stimulus is either a rapid flicker or rapid sinusoid located centrally within the surround used for background illumination (Fig. 5.4). One hundred to 200 responses are usually necessary to produce a good record and as with the standard ERG, both amplitude and implicit time (or phase shift) are the vital parameters. Because of the rapidity of the stimulus, the responses reflect cone activity alone.

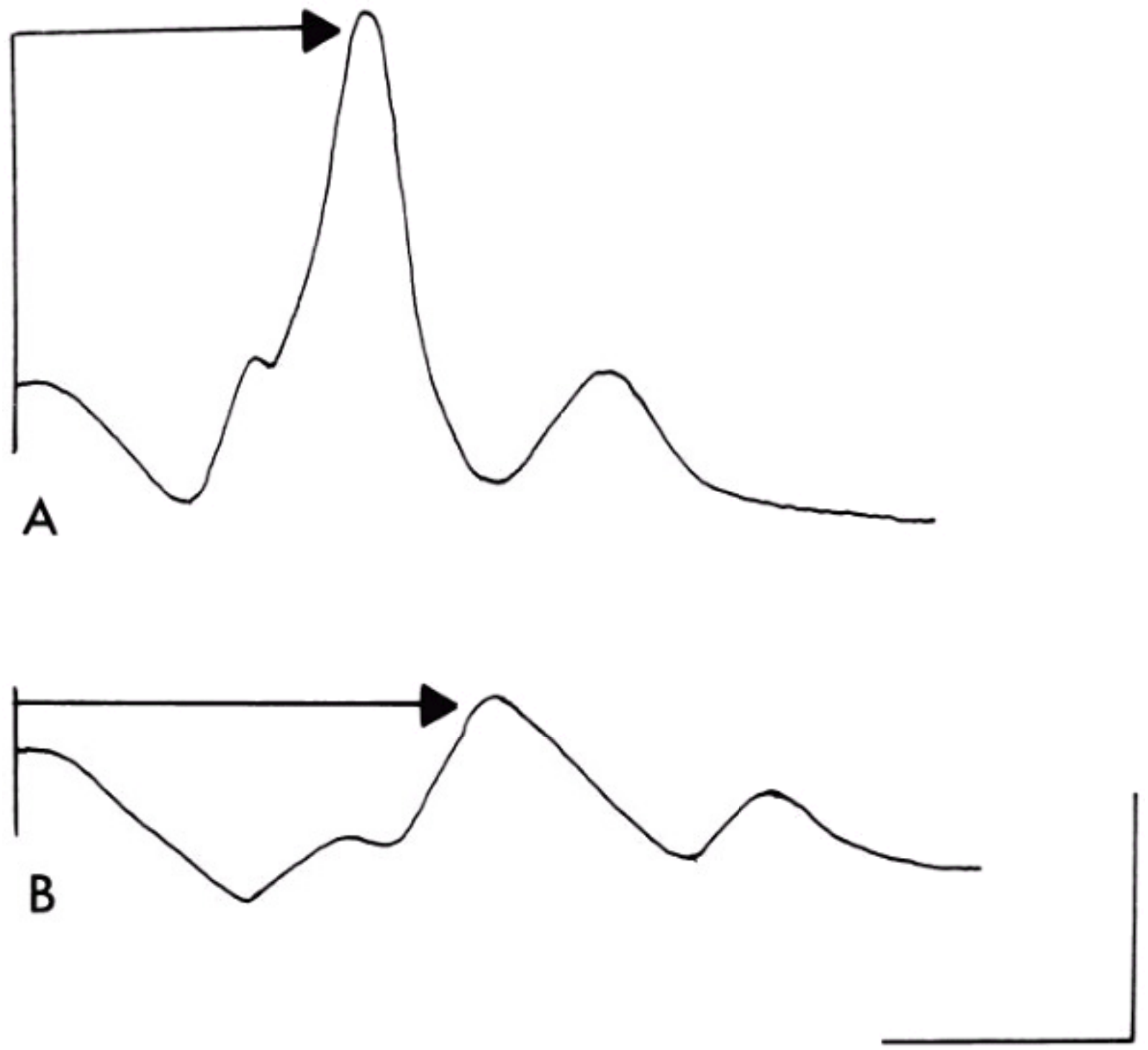


Figure 5.3 ERG latency measurement. **A:** Normal cone b-wave latency. **B:** Prolonged cone b-wave latency. The latency is measured from the onset of the stimulus to the peak of the response. Calibration: 25 msec; 50 μV. ERG, electroretinogram.

In 1992 Sutter and Tran (3) introduced a multifocal ERG (MERG) system in which multiple retinal areas are stimulated simultaneously and each response is independently detected. Thus, a topographic ERG map may be constructed of the entire posterior retina (Fig. 5.5). The area encompassed is approximately 50 degrees horizontally by 30 degrees vertically, within which 105 separate regions may be stimulated. Again, only cone function is being tested. Recently methods have been devised so that both amplitudes and implicit times may be measured for each response and compared to the age-adjusted normal population (4). Good fixation is needed because the MERG responses may be reduced in amplitude if fixation is eccentric. In such situations, the implicit times are shortened as opposed to pathologic conditions when implicit times are increased (5). Guidelines for the recording of the MERG have been established with standard protocols now in place (6).

Electrooculography

The principle of the EOG is based on the fact that there is a recordable potential across the retina, the transretinal potential. Indeed, in the vertebrate eye, if one electrode is placed on the internal limiting membrane and another placed posteriorly behind the sclera, a potential is recordable that is oriented so that the vitreal electrode is positive with regard to the scleral one. Since the eye is a moderately good conductor of electric responses, the same potential can also be recorded if one electrode is placed on the cornea and the other remains behind the sclera. Thus, the eye can be considered a dipole with the anterior surface (cornea) as the positive pole and the posterior portion as the negative pole.

Clinically, this response is recorded by putting electrodes on each side of a patient's eye and having the patient then move the eye from side to side over a fixed number of degrees. In so doing, the positive portion of the dipole (cornea) moves toward one electrode while the negative portion (posterior sclera) moves toward the other. In this way recordings between these two electrodes are made as the eyes move back and forth (Fig. 5.6).

The clinical efficacy of this test is based on the fact that the transretinal potential decreases during a period of dark adaptation and increases during a period of light adaptation. Thus, there is a dynamic function to the EOG that produces, under proper recording conditions, a *dark trough* and a *light peak* (Fig. 5.7). A ratio between these two values can be derived and expressed as a percentage. In humans, any value above 170% is normal, whereas any value below 145% is

abnormal.

In clinically recording this response, the skin electrodes are securely taped to the inner and outer canthi after ensuring good electrode-skin contact by cleaning and slightly abrading the area of skin to which they are attached. After

a short recording period under mesopic conditions to acquaint the patient with the test, the recordings are made during darkness for 15 minutes and then during a period of light adaptation for 15 minutes. A light of sufficient intensity must be used to ensure full development of the light peak (7). Recordings are made each minute, with the patient moving the eyes back and forth over a fixed excursion five to six times. The rate of eye movement can be rhythmically fixed by having a light source move back and forth across light-emitting diodes. The total time of recording is about 5 to 8 seconds each minute. Again, there are established clinical protocols for the recording of the EOG.

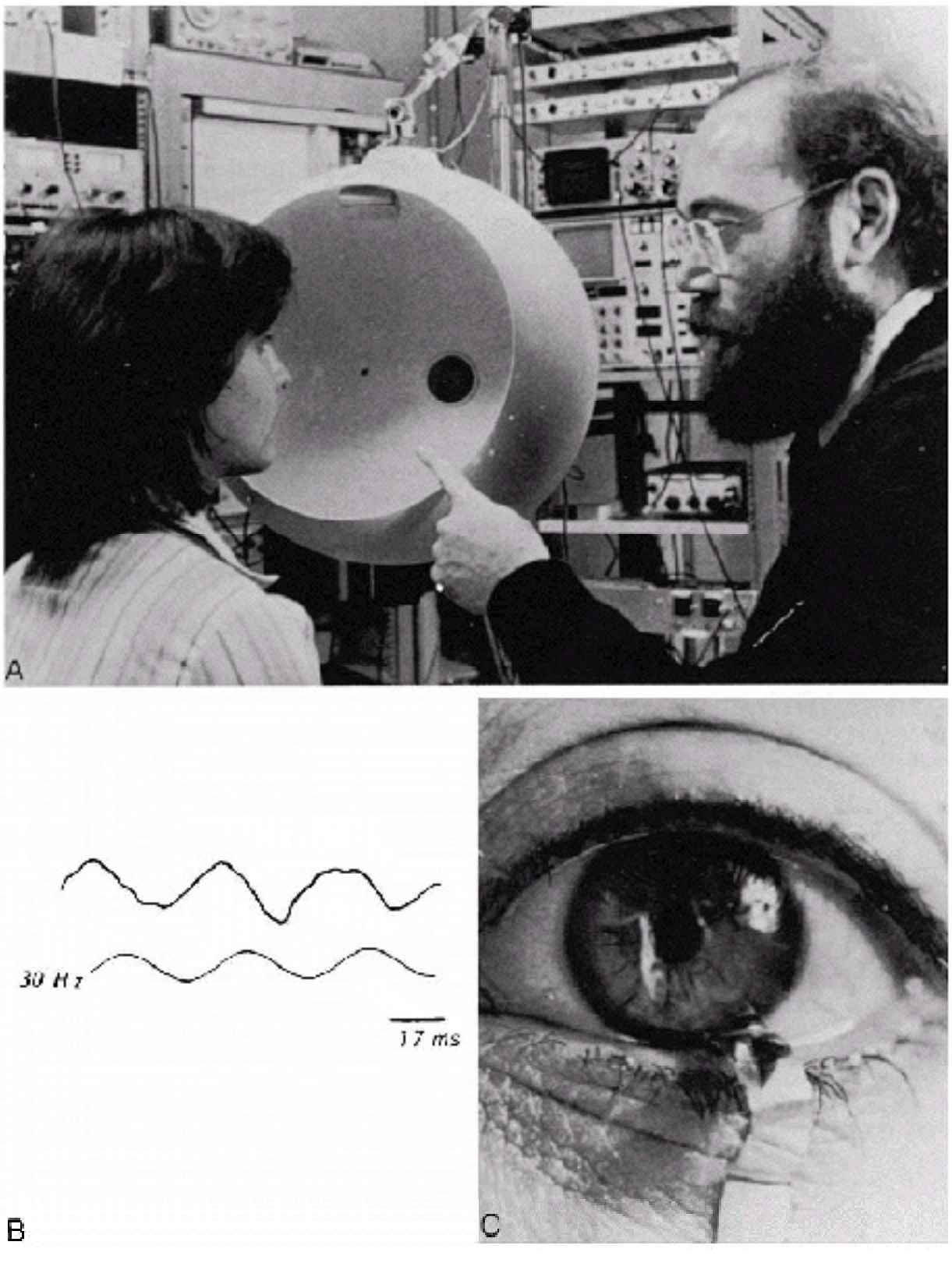


Figure 5.4 A: Apparatus for producing the focal ERG. An LED array is located in the center of a Ganzfeld bowl, which itself can be diffusely illuminated. **B:** The focal ERG in response to a 30-Hz, sinusoidally driven stimulus. **C:** A gold foil ERG electrode hooked over the lower lid. ERG, electroretinogram; LED, light-emitting diode.

Visual-Evoked Response

Although the VER has been studied for many years, new instrumentation has only recently made this test clinically more suitable for the detection of abnormalities along the visual pathway. The responses are clinically recorded over the occiput in a region over cortical areas 17 and 18. Because of the orientation of fibers in the superficial areas of the visual cortex, the retinal region mainly represented in such recordings is the macula. Thus, the test enables the examiner to look almost exclusively at macular function, although it is macular function that could be affected at any area along the visual pathway. However, methods are available that in most cases enable one to discriminate between abnormal function due to macular disease and abnormal function due to higher center disease.

The earliest type of human VER recording was made with a diffuse flash of light, a stimulus that is limited in its appeal since it gives tremendously variable interindividual VERs in terms of both waveform and amplitude. Its main clinical contribution at present is in comparing a normal eye with

one with abnormal vision. Since there is little intraindividual variability in comparing the eyes of the same individual, any major discrepancy can be considered diagnostic of an abnormality along the visual pathway of the affected eye (Fig. 5.8). Such a response is also of value in looking at the latency of the response. The

time period from the onset of the stimulus to the peak of the response is confined to fairly narrow limits and can easily be adapted to any clinical setting for the stimulus being used.

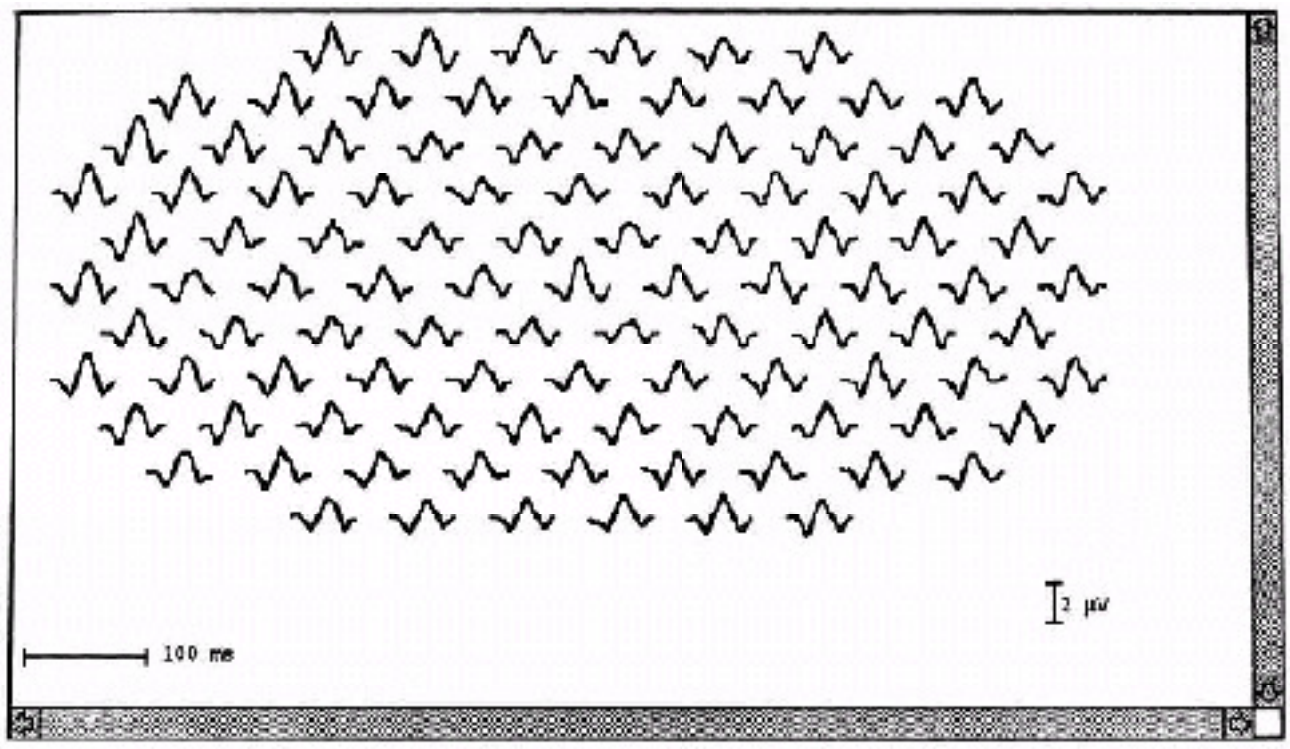


Figure 5.5 ERG tracings from a multifocal ERG system. **Top:** Tracing array or topographic ERG map. There are 103 separate areas represented within a 47-degree by 39-degree area. Stimulus frequency is -37 Hz. Number of summated runs is 4. Time of each run is 4 minutes. **Bottom:** Top trace represents the central response from the topographic map. Succeeding traces represent the average of ERG responses in rings around the central area. Trace 2 represents the six traces around the center, trace 3 represents the next 11 traces in a circle around the first ring, etc. The amplitudes are recorded relative to the central response. Implicit times are of major importance and can be easily obtained for both a- and b-waves. ERG, electroretinogram.

A much more productive light stimulus is one in which a checkerboard pattern is displayed to the eye. Since contrast and movement are the features that cause visual cortical cells to respond most vigorously, the use of such an alternating checkerboard pattern is a more controlled stimulus than a diffuse light flash. The checkerboard pattern produces responses that are much more easily compared between one person and another.

To escape the interindividual waveform differences found when doing slow repetitions of the stimulus, increasing the rate of pattern alternation leads to a smooth, sinusoidal

type of response and one in which there is an exquisite sensitivity to changes in pattern size and contrast (Fig. 5.9).

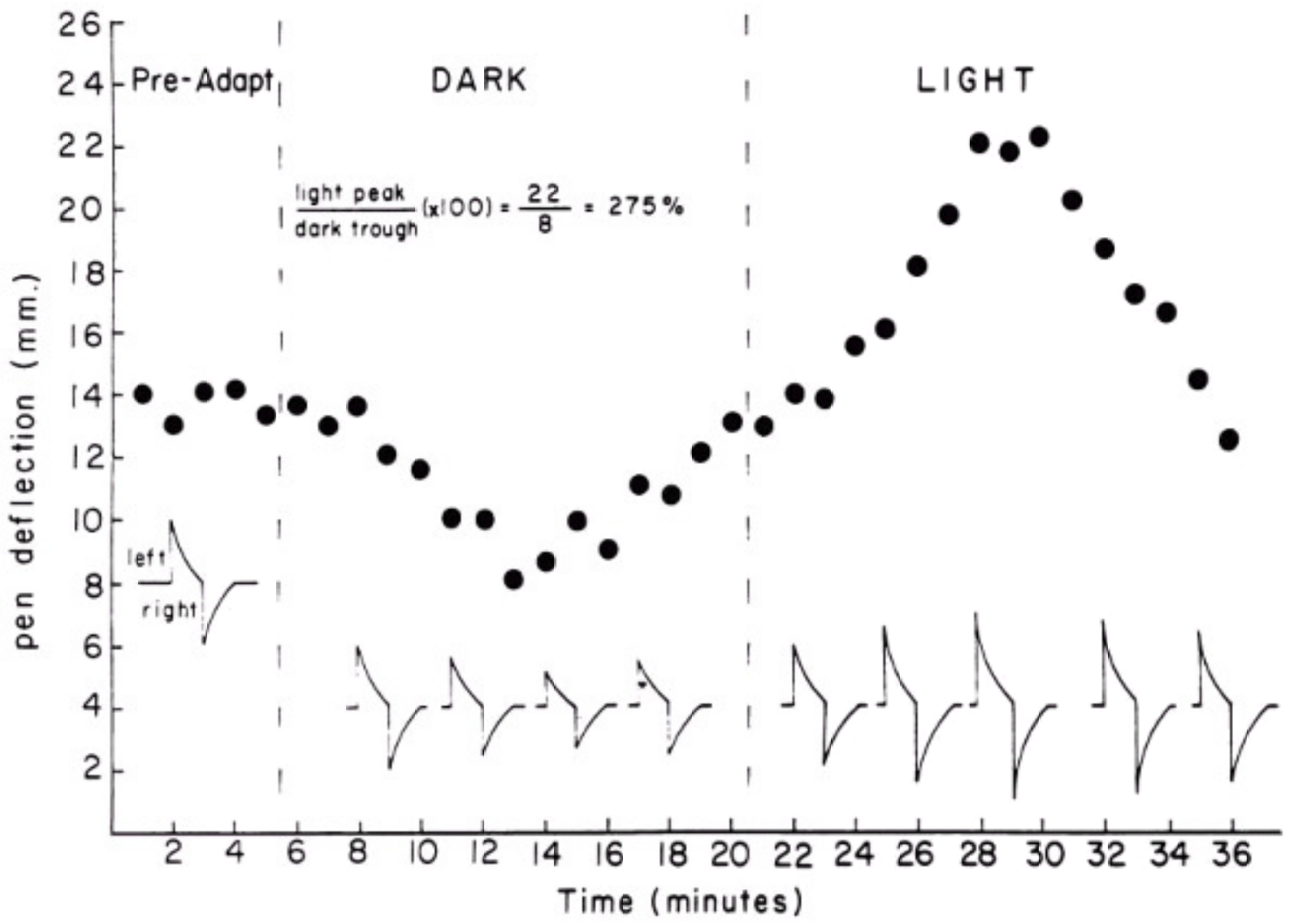


Figure 5.6 EOG. Black circles represent the averaged amplitude of five positive deflections measured each minute. Below the circles are representative tracings taken at different times and elicited by having the patient move the eyes with a tracking target. After a preadaptation period, the patient tracks in darkness for 15 min to elicit the *dark trough.* This is followed by a 15-min period under bright lights to derive the *light peak.* A ratio is then derived that represents the EOG ratio for that patient. EOG, electrooculogram.

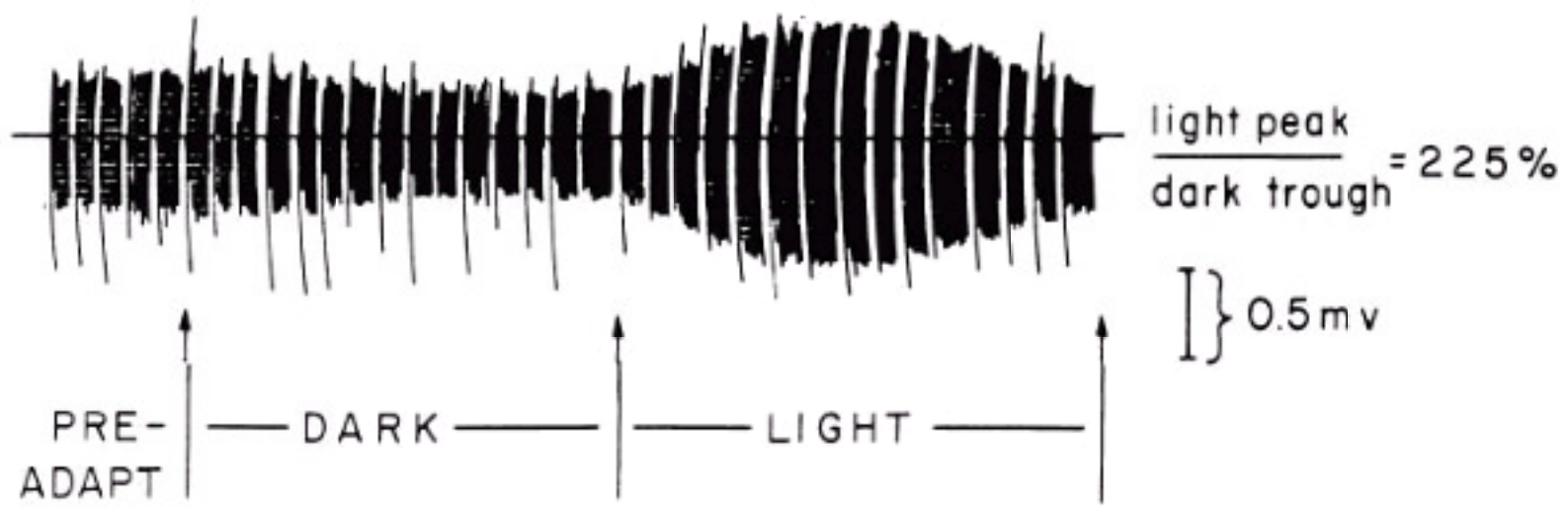


Figure 5.7 A simpler method of calculating the EOG ratio is derived by slowing the paper speed and obtaining a truncated response from which the light peak and dark trough can be easily measured. EOG, electrooculogram.

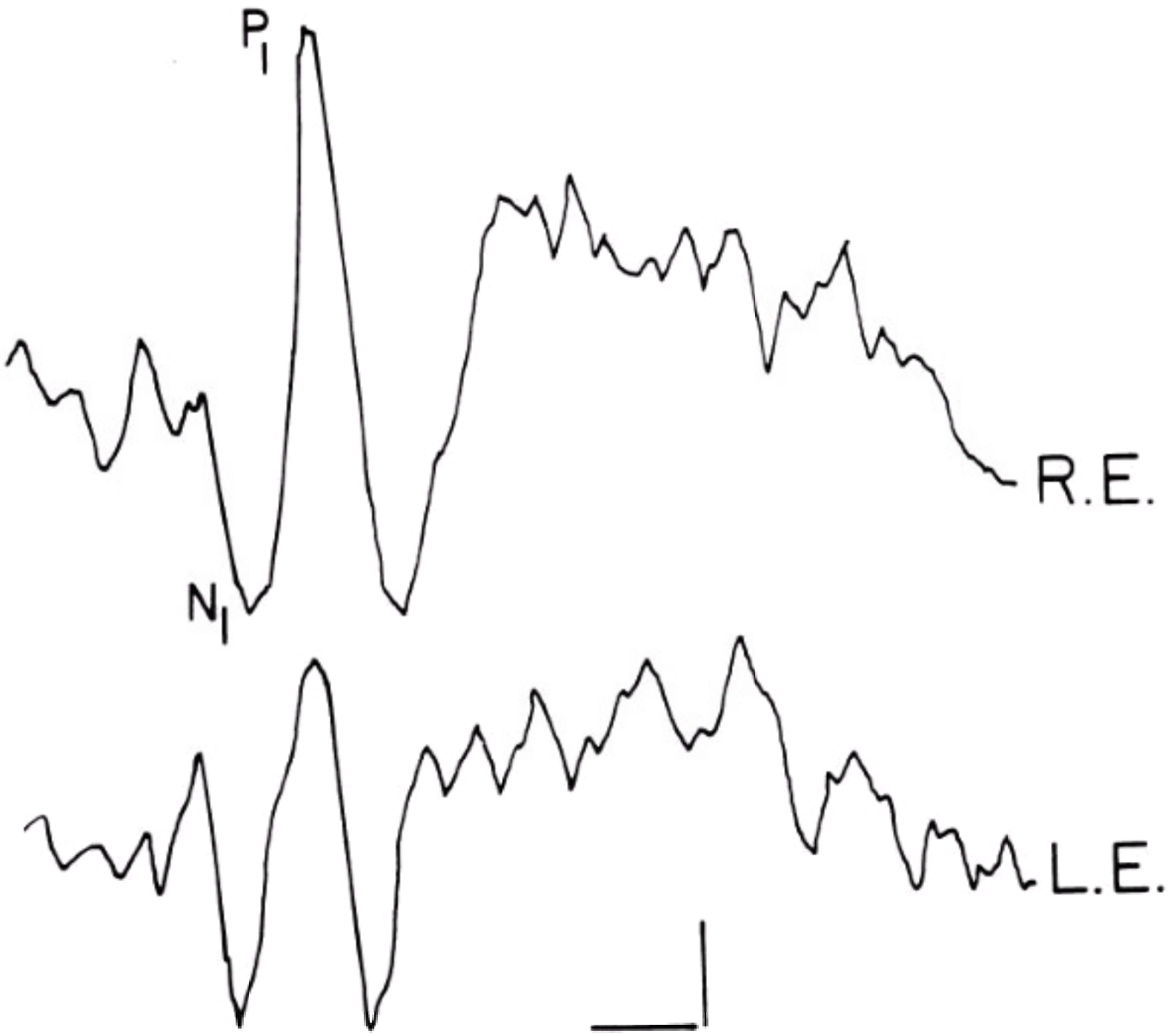


Figure 5.8 Flash VER. The patient is a 38-year-old white man with optic neuritis OS and a vision of 20/20 OD and 20/400 OS. Note the reduced amplitude of the P_1 response in the affected eye. Calibration: 30 msec; 1 µV. OD, right eye; OS, left eye; VER, visual-evoked response.

In the clinical situation, a scalp electrode is placed approximately 1 cm above the inion. If flash VERs are done, the stimulus is picked up with an oscilloscope. With checkerboard pattern stimulation, each laboratory usually sets up its own protocol for check size and percentage of contrast

reduction. One standard protocol is shown in Figure 5.9 and is used to measure latency abnormalities as well as abnormalities in contrast sensitivity. While there can be some variation from lab to lab, a standard protocol should be used since it enables one to compare results between labs (8).

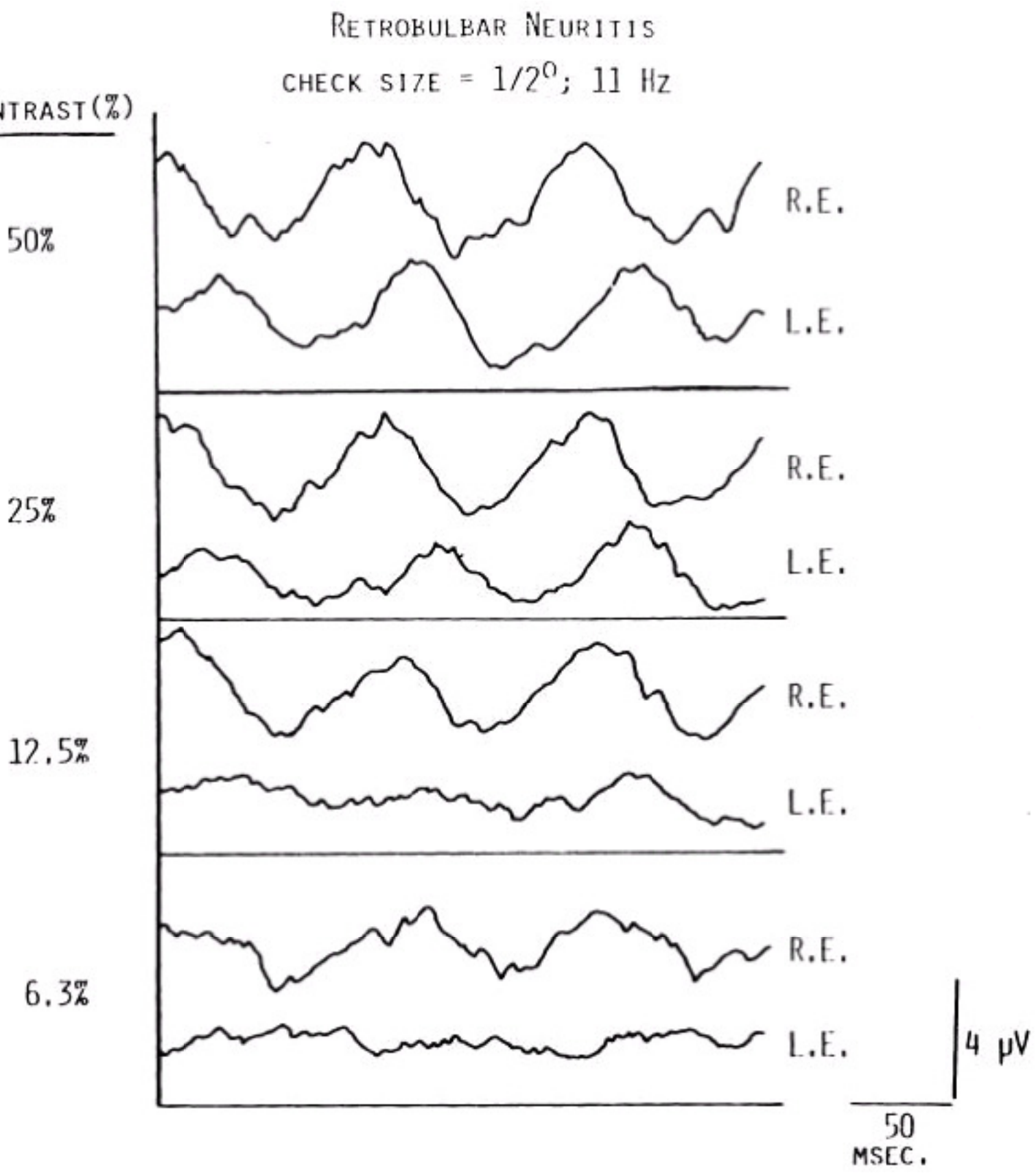


Figure 5.9 VER derived from an alternating checkerboard. The patient is a 22-year-old white woman with a history of optic neuritis OS. At the time of the recording, visual acuity was 20/20 OD and OS. Latencies are markedly affected at both 25% and 50% contrast. Likewise, amplitude measurements are reduced in the affected eye. The protocol, as listed here in terms of contrast percent, check size, and alternation rate, is satisfactory to compare both inter- and intraindividual abnormalities. Response number is 256. OD, right eye; OS, left eye; VER, visual-evoked response.

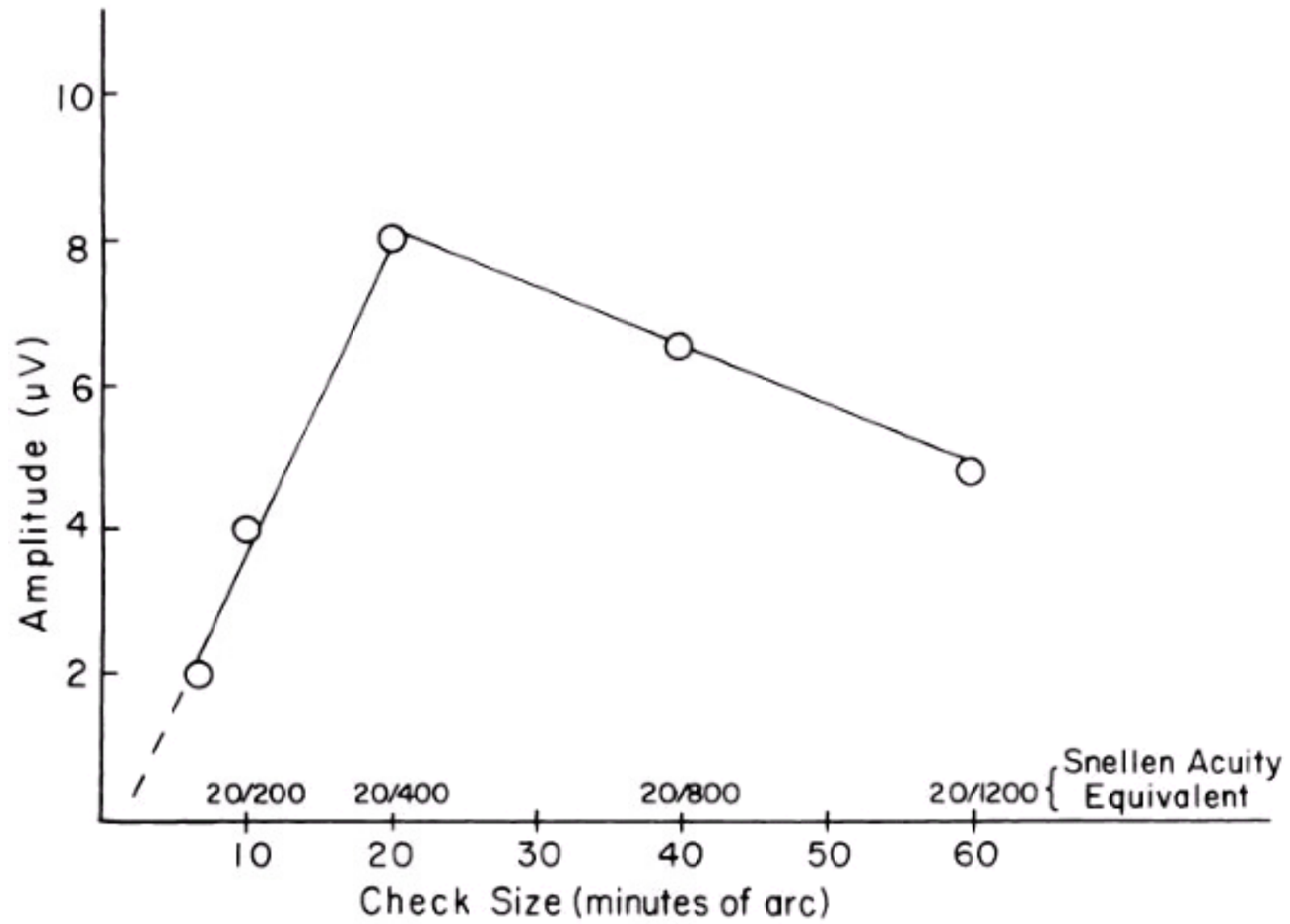


Figure 5.10 VER amplitudes at various check sizes. The Snellen acuity equivalent is noted above the check size in minutes of arc. The dashed line is an extrapolation to a zero amplitude (i.e., best visual acuity). VER, visual-evoked response.

In addition, by using specific amplification and computer techniques, it is possible to derive a VER function to correlate with subjective visual acuity (9).

Figure 5.10 shows such a curve as generated in a normal individual. The check sizes of approximately 20 to 30 minutes of arc give the largest VER amplitudes. Thus, a curve has to be derived and extrapolated to zero voltage where the objective acuity can be found. Innovations in presenting the stimuli and recording the data have served to reduce the test time to approximately 5 minutes (10).

CLINICAL USES OF ELECTRODIAGNOSTIC TESTS

Infants with Nystagmus and Poor Vision from Birth

A problem that every clinician faces at some time is when parents bring their child to the office or clinic with a history that the child has never seen well and has associated nystagmus. In such situations, electrodiagnostic tests may be invaluable in providing both a diagnosis and visual prognosis in certain diseases that may cause this symptom complex.

There are multiple causes for such a finding (Table 5.1), and a careful history and systemic ocular evaluation are sufficient in most cases to clarify the cause.

However, there are three retinal disorders in which the ophthalmoscopic changes may be so variable, or in which the retina may appear normal, that the diagnosis can be established only by the use of ancillary objective tests.

These disorders include Leber congenital amaurosis, rod monochromatism (achromatopsia), and one form of congenital stationary night blindness (CSNB).

TABLE 5.1 CAUSES OF NYSTAGMUS AND POOR VISION FROM BIRTH

I. Opacities of the media

Bilateral corneal opacities

Bilateral cataracts

II. Retinal disorders

A. Ophthalmoscopically visible

1. Optic nerve

a. Optic atrophy

b. Developmental anomalies

i. Hypoplasia

ii. Coloboma

2. Macular disease

a. Infections (“coloboma”)

b. Developmental

i. Hypoplasia

ii. Traction

3. Rare bilateral association (e.g., retinal dysplasia, PPHV)

B. Ophthalmoscopically variable

1. Achromatopsia (rod monochromatism)

2. Leber congenital amaurosis

3. Congenital stationary night blindness

a. X-linked with myopia

III. Systemic diseases

A. Neurologic disorders (e.g., hydrocephalus)

B. Metabolic disorders (e.g., Lowe syndrome)

C. Chromosomal abnormalities (e.g., Down syndrome)

D. Somatic malfunctions (e.g., De Lange syndrome)

	D.	Somatic malfunctions (e.g., De Lange syndrome)
IV.	Disturbances of higher centers (etiology unknown)	
	A.	Congenital nystagmus
	B.	Spasmus nutans
	C.	Latent nystagmus
	D.	Occlusion nystagmus

PPHV, persistent primary hyperplastic vitreous.

Leber Congenital Amaurosis

Leber congenital amaurosis, an autosomal-recessive disorder, is one of the generalized tapetoretinal degenerations. It is, however, one of marked variability in both ophthalmoscopic findings (Fig. 5.11) and the presence of systemic abnormalities. In a number of cases, the retina may appear essentially normal in the infant, profound abnormalities being seen in the older child as the disease progresses (11). Because of the relative normalcy of the retina in certain patients, the disorder may be difficult to diagnose. However, the ERG establishes the correct diagnosis because this disorder is similar to retinitis pigmentosa in that there is a generalized degeneration of the photoreceptors, and as such, the ERG responses are markedly reduced or absent.

Thus, this electrophysiologic evidence of widespread degeneration of the outer retinal layers provides the diagnosis even when retinal changes may not be evident.

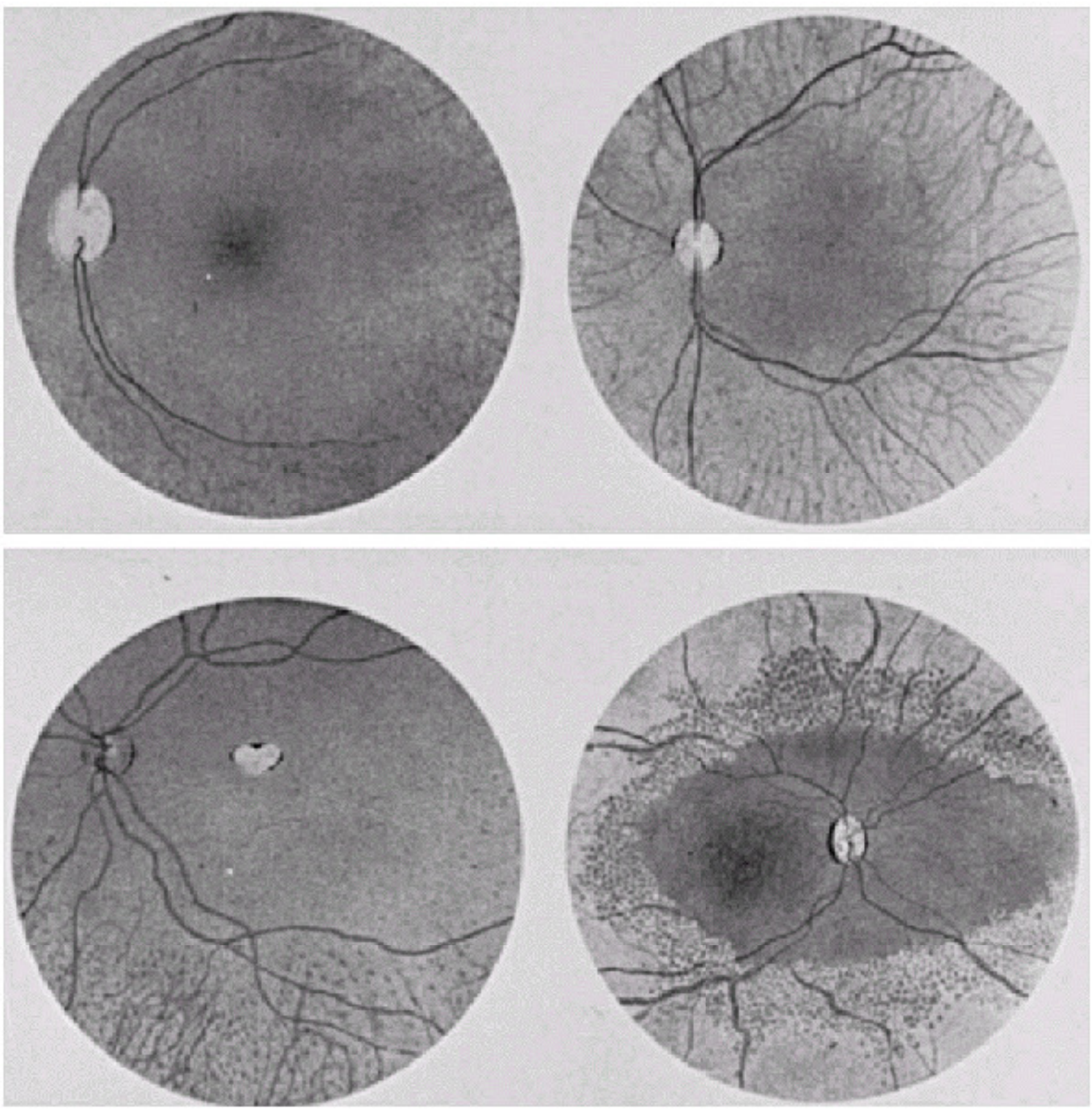


Figure 5.11 Leber congenital amaurosis (artist's representation). The marked difference in the fundus picture in these four cases is evident. All patients had poor vision at birth, nystagmus, and an extinguished ERG. ERG, electroretinogram.

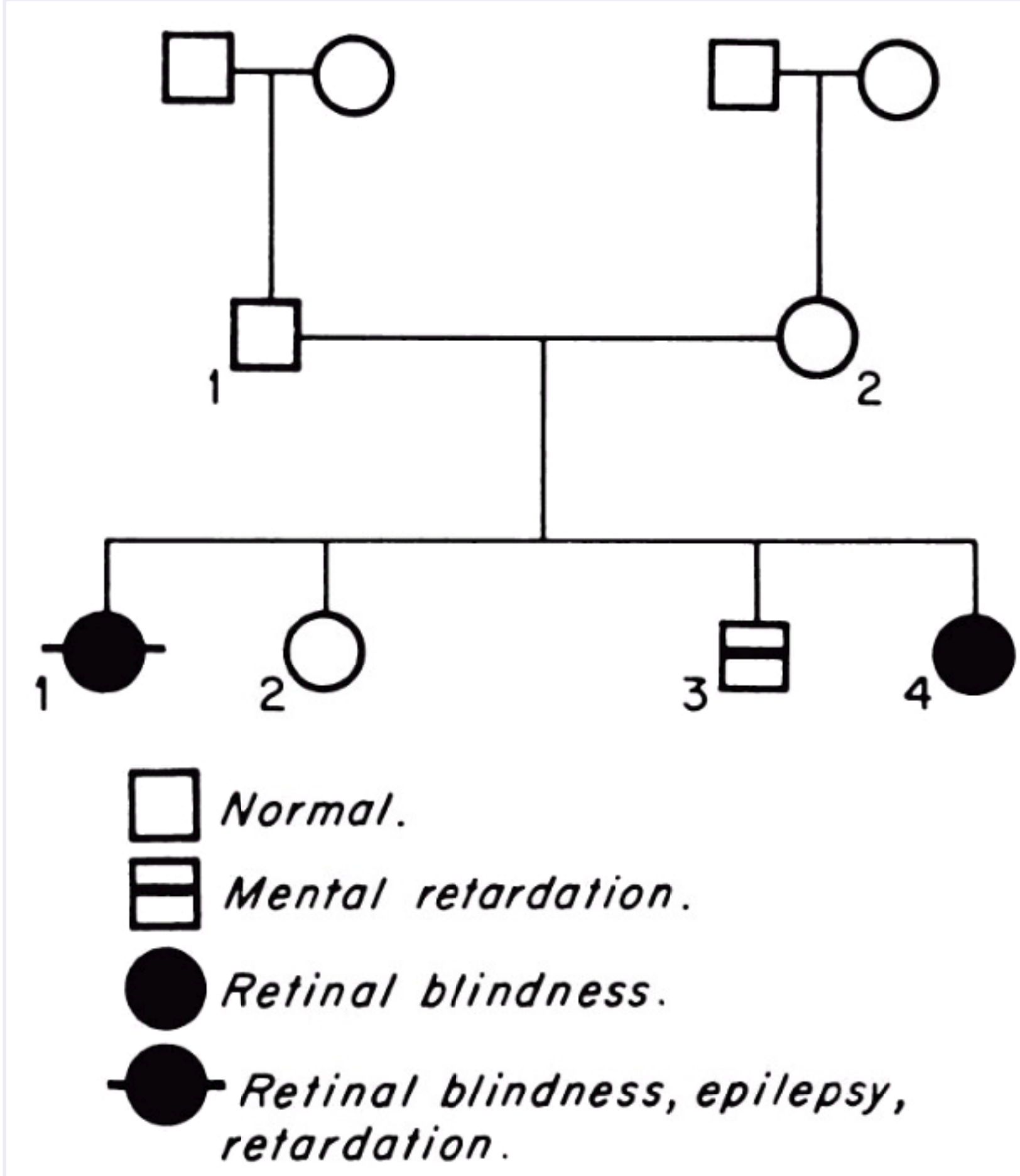
As noted earlier, associated neurologic abnormalities in a large percentage of the cases may likewise lead to confusion in diagnosis. Neuromuscular abnormalities, choreoathetoid movements, mental retardation, deafness, and epilepsy have all been reported in conjunction with the retinal problem (11). To further confuse the issue in some pedigrees, family members with only neurologic problems and no eye disorders have been described (Fig. 5.12).

This disorder is probably more common than suspected. Two large studies, one in Scandinavia (12) and the other in Holland (13), showed that the incidence of the disease was approximately 18% in schools for blind children. Histologic studies in the past have been confusing, but a study performed on a freshly acquired eye specimen showed subretinal deposits, possibly of photoreceptor outer segments, along with underdeveloped photoreceptors and pigment epithelium (14). This led to the consideration that progressive degenerative changes could give rise to a multitude of retinal abnormalities—the polymorphism that is so typical of the ophthalmoscopic presentation.

Achromatopsia

Achromatopsia is an autosomal-recessive disorder in which there is a congenital absence or near absence of the cone receptors, a suspicion confirmed by histologic studies (15). All affected individuals appear very much the same in that there is nystagmus and poor vision but also “photophobia.” This is not true photophobia in the sense that patients with iritis are sensitive to light, but rather an attempt by the affected individual to seek a mesopic level of illumination so that the intact rod system can function. This disorder

has been classified into two groups, complete and incomplete, the difference (as noted in Table 5.2) probably due to some cones being present in the latter group. The one invariant finding in both groups is that the photopic response is reduced and no photopic flicker follows on the ERG. The scotopic system is completely normal electrophysiologically (Fig. 5.13). The diagnosis is important to make because this is a stationary disorder that is compatible with normal schooling and in which there is no fear of worsening visual acuity.



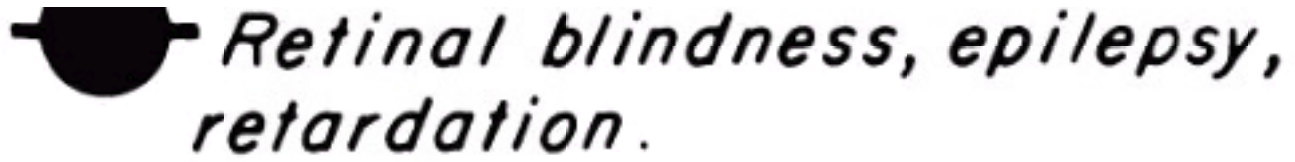


Figure 5.12 Leber congenital amaurosis pedigree. This autosomal-recessive disorder may show marked variability in its presentation, not only in fundus changes but also in the extent of systemic abnormalities.

TABLE 5.2 DIFFERENTIATION OF ACHROMATOPSIA (ROD MONOCHROMATISM)

	Incomplete	Complete
Visual acuity	20/60 to 20/200	20/200 to 20/400
Color vision	Present but abnormal	None
Macular changes	None	Common
Nystagmus	Present	Present
Photophobia	Present	Present
Electroretinogram	Reduced photopic response	Reduced photopic response
	Absent photopic flicker	Absent photopic flicker
	Normal scotopic response	Normal scotopic response
Heredity	Autosomal recessive	Autosomal recessive

Congenital Stationary Night Blindness

There are several forms of CSNB (Table 5.3) and most are associated with normal vision. The one variant that has the greatest diagnostic difficulty is usually inherited as an X-linked recessive and is associated with moderate degrees of myopia (-4 to -8 diopters) and nystagmus with concomitant poor vision. Again, the prime diagnostic tool is the ERG, for a specific pattern is evident (Fig. 5.14). In the older child in whom subjective tests can be performed, the presence of a normal visual field, a dark adaptation curve that has no rod segment and a normal cone segment, and the nonprogressive nature of the disorder point to the proper diagnosis and eliminate the diagnosis of a generalized heredoretinal degeneration.

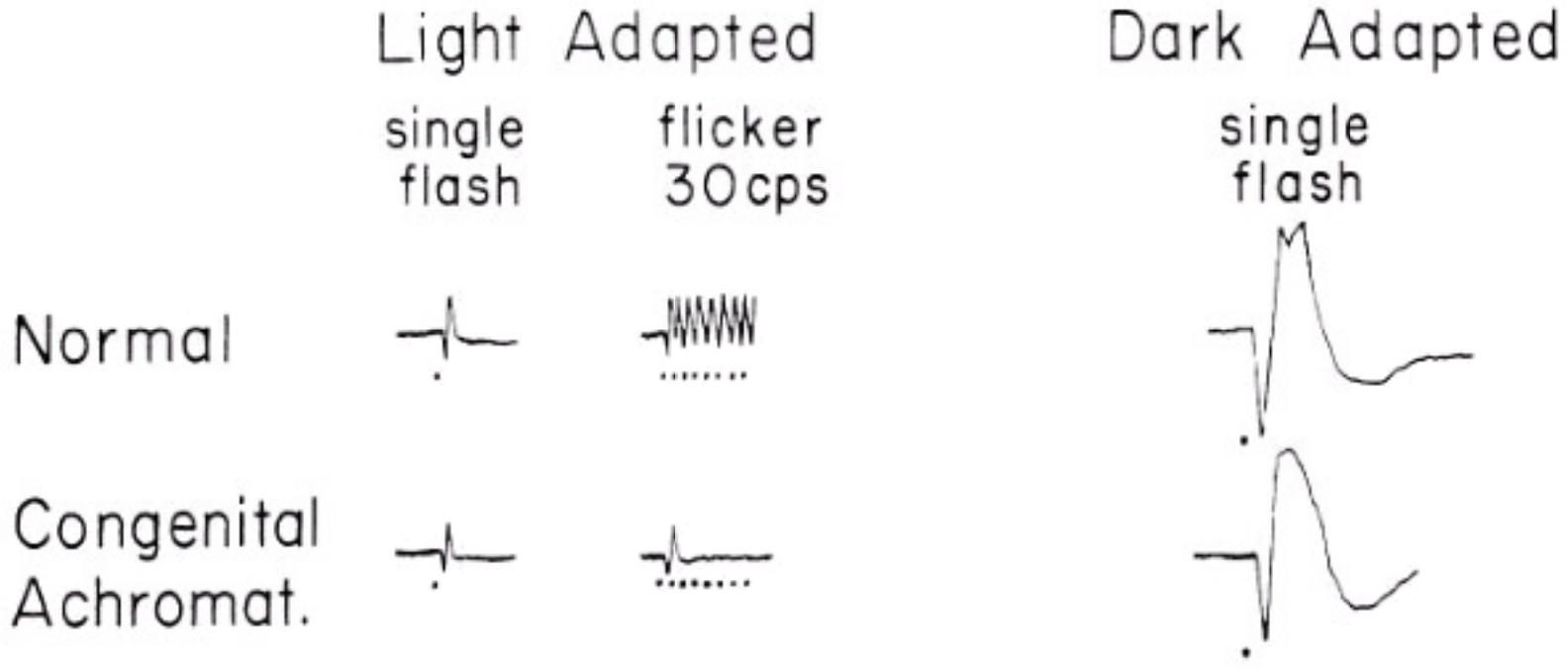


Figure 5.13 Congenital achromatopsia (rod monochromatism). The most reliable diagnostic test is the ERG, which shows an absent ERG flicker response and reduced photopic single-flash response. The scotopic response is normal. ERG, electroretinogram.

TABLE 5.3 FORMS OF CONGENITAL STATIONARY NIGHT BLINDNESS

I.	Normal retina	
	Autosomal recessive	
	Autosomal dominant	
	X-linked recessive	
	Often associated with nystagmus and decreased vision	
II.	Abnormal retina	
	Oguchi disease	
	Fundus albipunctatus	
	Fleck retina of Kandori	

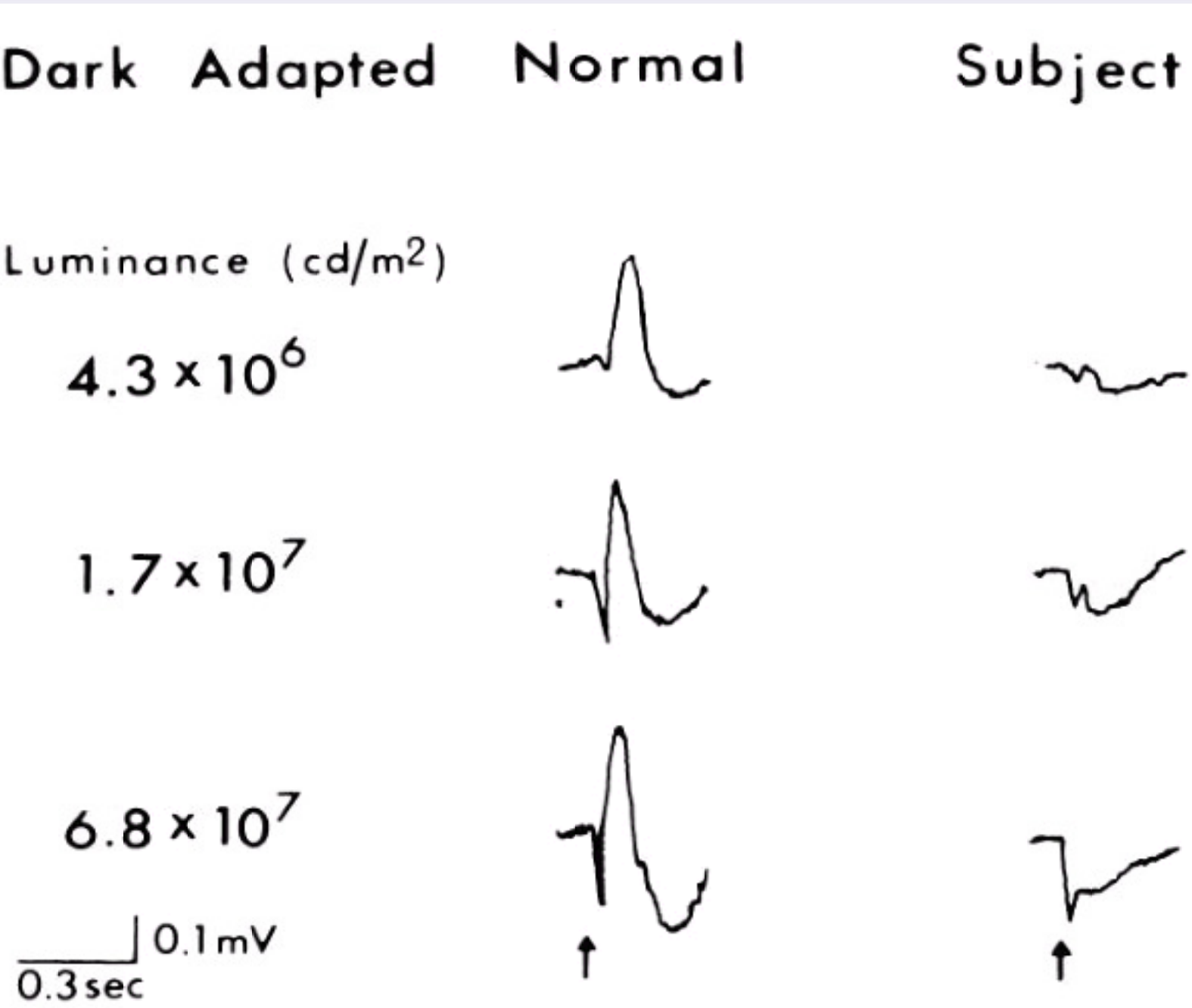


Figure 5.14 Congenital stationary night blindness: scotopic ERG at varying light intensities. The major abnormality is the absence of any positive response. The initial negative response is normal. The abnormality in this case is probably one of neural transmission in the bipolar cell region. ERG, electroretinogram.

Children with Overt but Nondiagnostic Macular Lesions

Macular degeneration in the young is not as variable as it is in the adult population. However, certain macular changes may be observed in the infant or child that may be nonspecific enough to require electrodiagnostic studies for their clarification. Among these are congenital retinoschisis with macular cystic changes, vitelliform macular degeneration (Best disease), macular degeneration with associated generalized retinal degeneration, and the most common entity in this group, juvenile macular degeneration (Stargardt disease; fundus flavimaculatus).

Congenital Retinoschisis (Congenital Veils of the Vitreous)

In the classic presentation of congenital retinoschisis, an X-linked recessive disorder, children show cystic macular changes (macular retinoschisis) and large diaphanous peripheral areas of schisis (Fig. 5.15). Within this same spectrum may be those patients who show only the macular changes, with the peripheral retina apparently free of any changes. The ERG may be helpful since there is a marked reduction in the b-wave of the ERG with complete normalcy of the a-wave in virtually all cases. Such a finding may be an indication of rather widespread changes in the Muller cells, the cells which give rise to the ERG b-wave.

Vitelliform Macular Degeneration (Best Disease)

Patients in the earliest stage of this disorder may present with the classic “egg yolk” in the macular area. This well-defined yellowish lesion no doubt lies beneath the pigment epithelium since vision is normal; likewise, the absence of any overt changes on fluorescein angiography would further support the normalcy of the pigment epithelium (Fig. 5.16). Not all young patients present in this manner, however. Patients have been seen with multiple cysts, nonspecific degenerative changes, partially resorbed vitelliform cysts, and normal retinas that may later develop macular lesions or may remain completely normal. This marked variability is not unusual for an autosomal-dominant disorder, but it may make the diagnosis somewhat confusing. However, the EOG light rise is markedly abnormal in this disorder, whereas the ERG is normal. This dichotomy between these tests is not usually seen and can be considered diagnostic for Best disease. This factor is particularly valuable in a patient with nonspecific fundus changes if other family members are unavailable for examination. This disorder may be underdiagnosed, principally because an EOG is often not performed in the absence of specific retinal changes (Fig. 5.17).

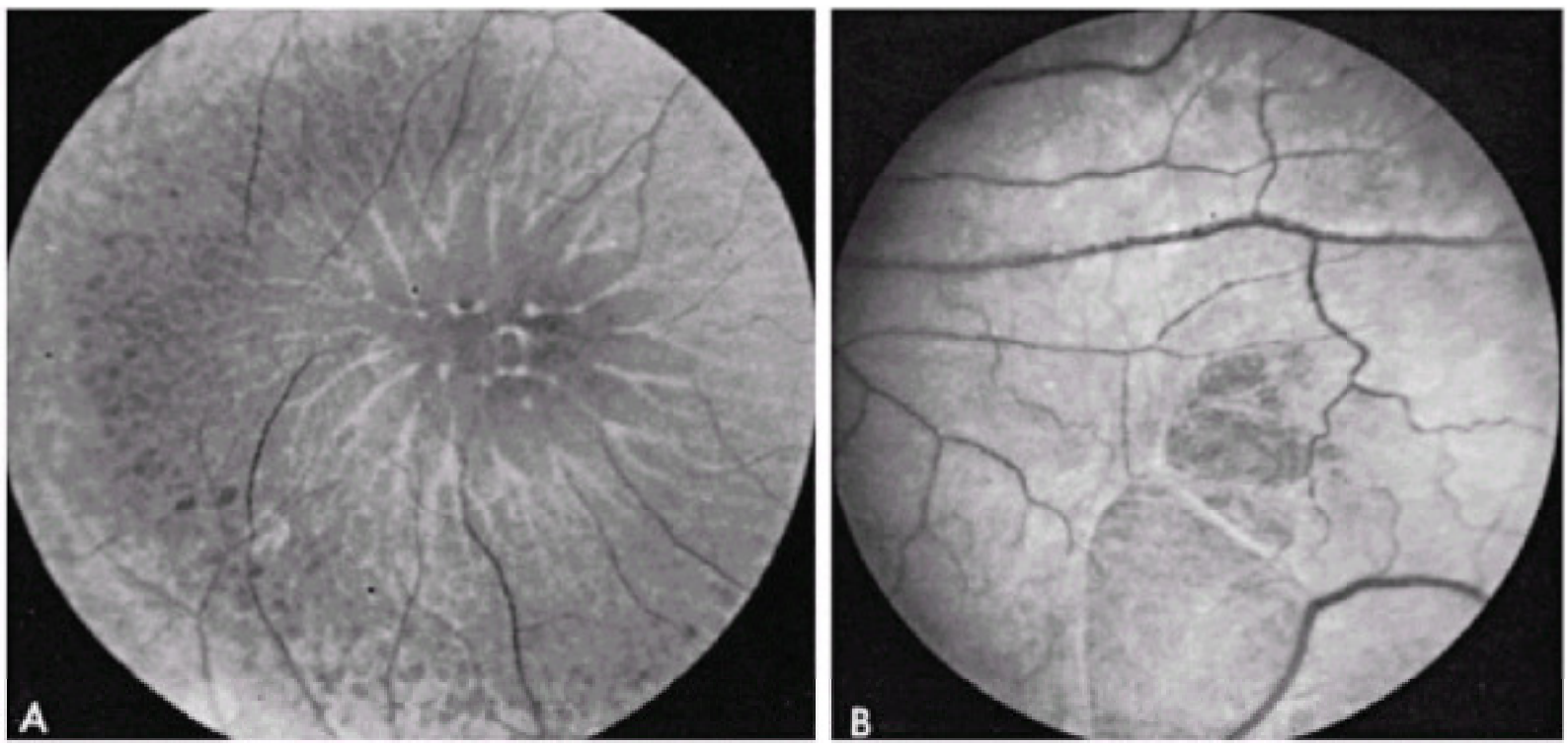


Figure 5.15 Congenital retinoschisis (X-linked retinoschisis, congenital veils of the vitreous). **A:** Macular cystic changes. **B:** Retinal periphery showing diaphanous areas of retinoschisis.

Macular Degeneration with Associated Generalized Retinal Degeneration

This is yet another variant of retinitis pigmentosa in that there is generalized degeneration of the entire photoreceptor system. The diagnosis may be difficult because patients may have complaints referable to the photopic and not scotopic system and there may be a relative paucity of peripheral retinal changes, certainly in comparison with the overt macular changes. The importance of differentiating this disease from that of macular degeneration alone is due to the visual future of each type of patient. The ERG remains the major diagnostic tool, showing the absent or near-absent response so typical of generalized degeneration. If, as noted earlier, only the macula is affected, the standard ERG recording would be normal, a fact attributable to the very small total number of receptors affected.

Juvenile Macular Degeneration (Stargardt Disease; Fundus Flavimaculatus)

Juvenile macular degeneration is the most common of the childhood macular degenerations. Although the typical

cases of this autosomal-recessive disorder are easy to diagnose because of the history and funduscopic changes (Fig. 5.18), there are certain cases in which the subjective symptoms of decreased vision may antedate any objective funduscopic changes. In such patients, it becomes the task of the ophthalmologist to determine whether a true visual loss is present. It is in such patients that the focal ERG has its greatest use. Such a test, which elicits responses from the central 3 to 6 degrees, will be markedly abnormal once the acuity has fallen below 20/40. Confirmatory data can be obtained with the pattern VER, which shows reduced contrast sensitivity and abnormal latencies in many instances.

The full-field ERG, as routinely performed, is normal since most photoreceptors are viable. The MERG can also be helpful in such cases with reduction of the central responses being noted. However, with good fixation being necessary in this test, the reliability of the responses in a child may be open to question.

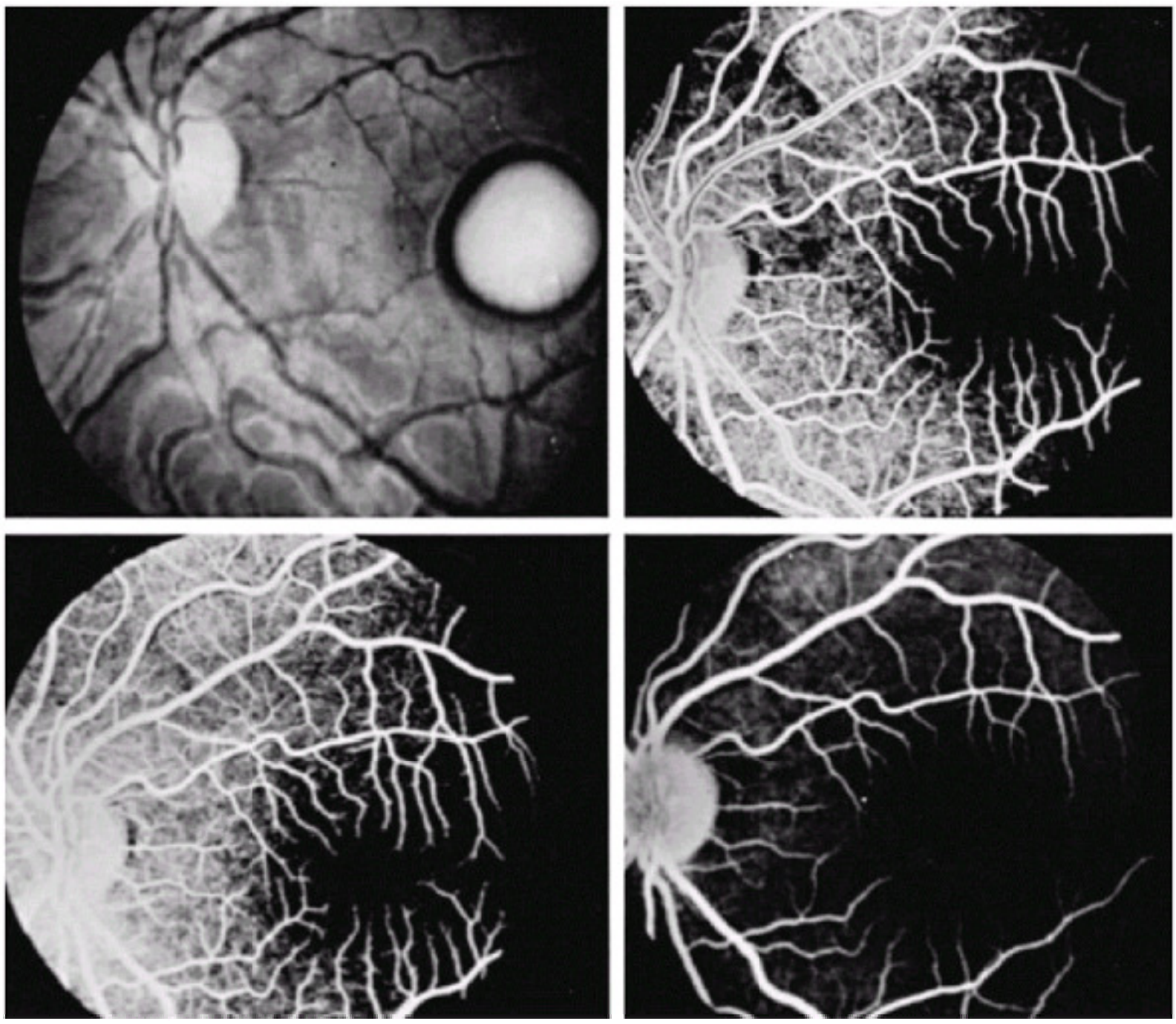
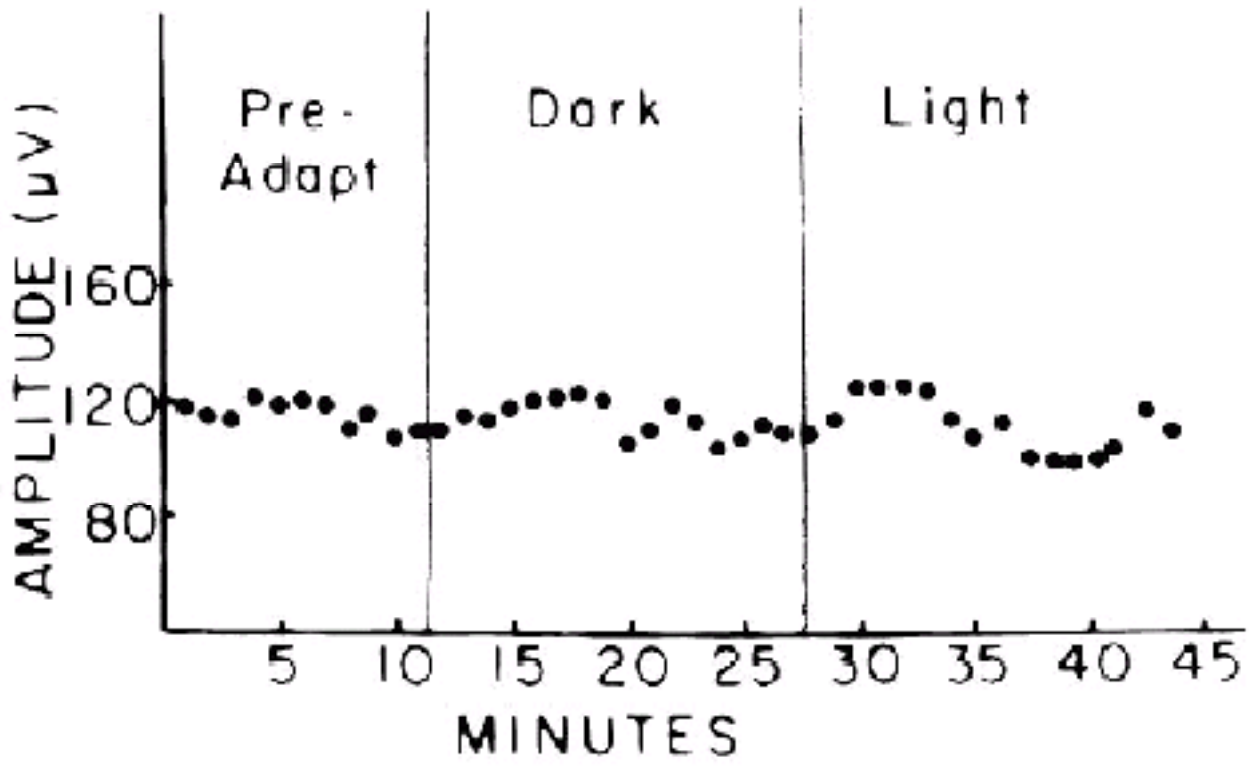


Figure 5.16 Best disease (vitelliform macular degeneration): the classic retinal change as seen in an 11-year-old white boy with 20/20 vision. The well-defined “egg yolk” lies beneath the pigment epithelium, and fluorescein angiography demonstrates no changes.



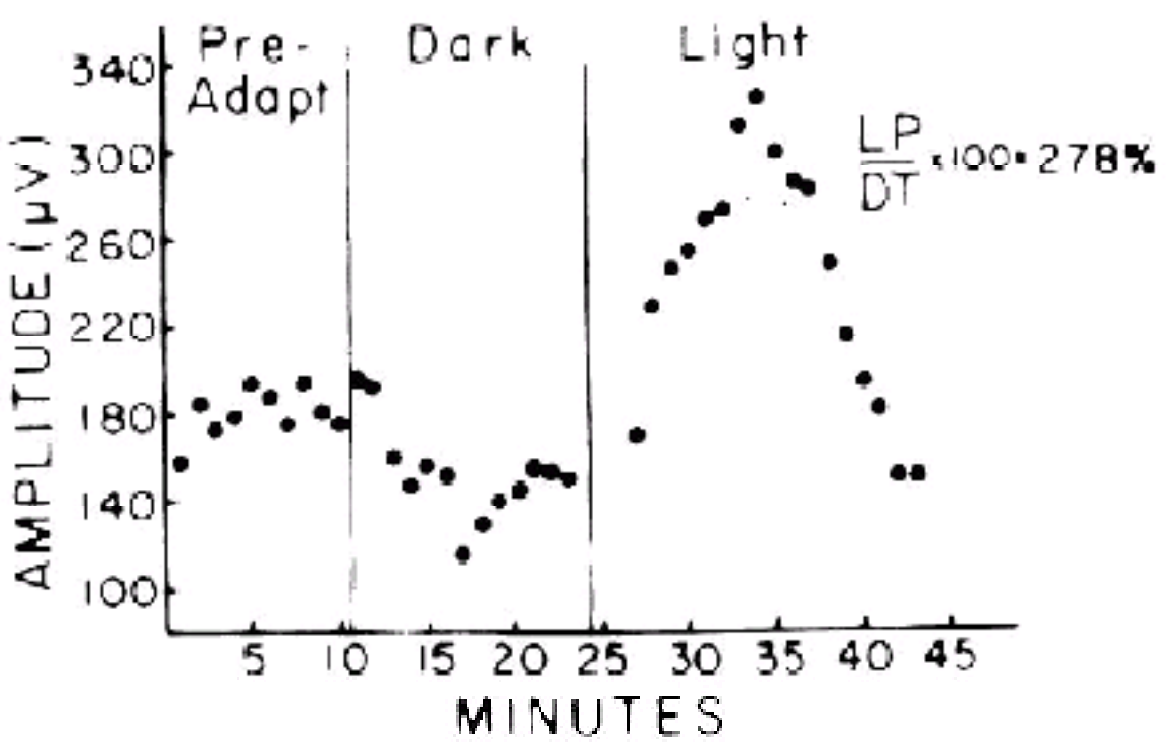


Figure 5.17 Top: EOG in a patient with Best disease. There is no EOG light rise or dark trough, only baseline oscillations. **Bottom:** EOG in an unaffected sibling showing a normal EOG ratio. EOG, electrooculogram.

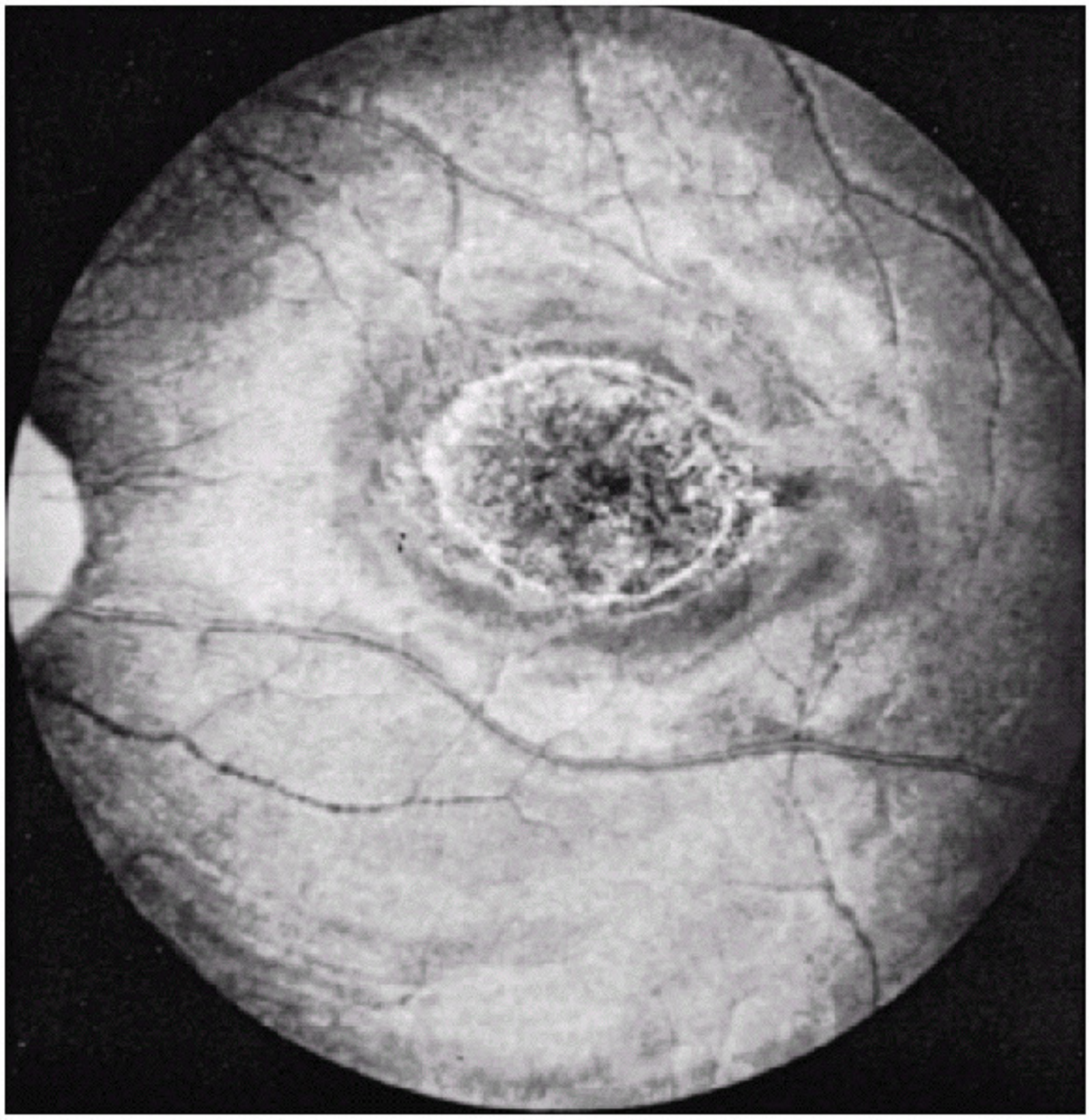


Figure 5.18 Stargardt disease. Macular area of an 11-year-old boy with 20/200 vision.

While fluorescein angiography is rarely needed to make a diagnosis, some abnormality of the retinal pigment epithelium is normally seen on the angiogram in patients with poor vision and normal-looking retinas.

Certain patients with Stargardt disease may have a number of atrophic-appearing spots, either scattered throughout the posterior pole or in a full or partial oval around the macula (Fig. 5.19). Association of macular degeneration and these nonpathologic retinal changes has been given the name *fundus flavimaculatus.* Fluorescein angiography may be helpful in elucidating these abnormalities since they invariably are better seen in this manner than ophthalmoscopically.

Children in Whom a Generalized Retinal Degeneration is Suspected

There are a number of widespread retinal degenerations in which poor night vision, reduction of visual fields, and generalized funduscopic abnormalities are noted, and retinitis pigmentosa may be considered the prototype of such a problem (Table 5.4). Except for Leber congenital amaurosis, the disorder usually is not suspected until later in childhood when difficulty in dim light is either experienced by the patient or suspected by the parents. Most patients show funduscopic signs typical of the disorder, but only electrodiagnostic studies suffice to make the diagnosis in some children. Virtually all patients show either a total or near absence of all ERG responses. There are, however, rare patients in whom reasonably good amplitudes may be recorded. In such cases, increased implicit times (Fig. 5.3) may lead to the correct diagnosis.

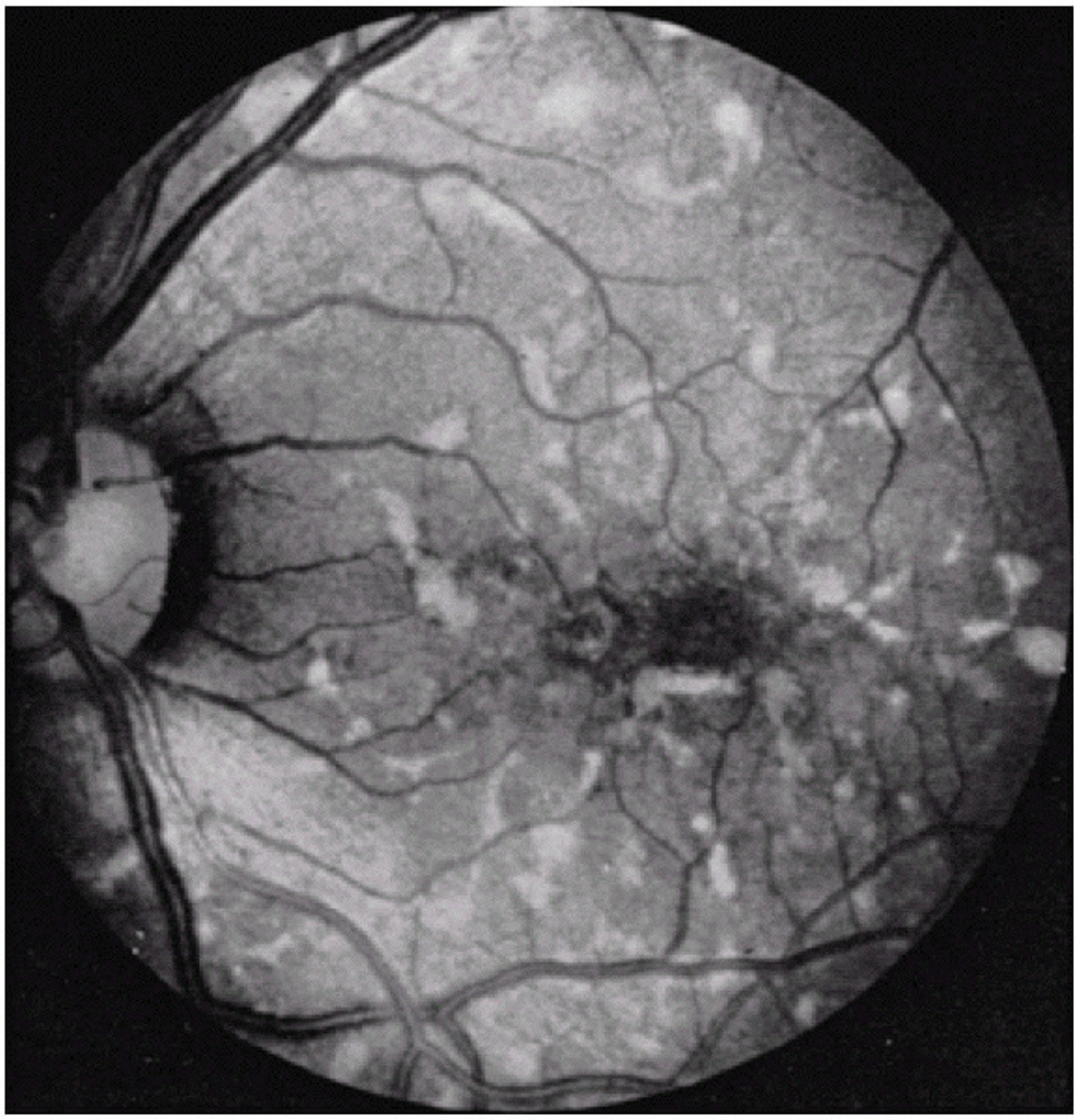


Figure 5.19 Stargardt disease. Mild macular degenerative changes with surrounding atrophic-appearing yellow-white spots. This is often called fundus flavimaculatus. Visual acuity 20/70.

TABLE 5.4 GENERALIZED HEREDODEGENERATIONS OF THE RETINA

I. Associated with primarily retinal abnormalities

A. Retinitis pigmentosa (AD, AR, XL)

B. Atypical retinitis pigmentosa

1. Retinitis pigmentosa sine pigmento (AR)

2. Retinitis punctata albescens (AD, AR)

3. Leber congenital amaurosis (AR)

4. Associated with macular degeneration

5. Associated with systemic diseases

II. Associated with primarily choroidal abnormalities

A. Choroideremia (XL)

B. Gyrate atrophy (AD, AR)

III. Associated with vitreous abnormalities and retinoschisis

A. Autosomal dominant (Wagner disease, Stickler syndrome)

B. Autosomal recessive (Favre disease)

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked recessive.

Because of the hereditary patterns involved in these disorders, it may be important to evaluate some children at a very young age, both to satisfy the family that a child does or does not have a familial problem and to determine the future visual prognosis. In these cases, the ERG becomes invaluable since fundus changes are often minimal and subjective responses cannot be obtained. Again, the ERG findings, even at the earliest stages of the disease, are indicative of widespread degenerative changes.

There are a large number of systemic disorders which have, as part of the syndrome complex, an associated generalized degeneration of the retina (Table 5.5). These disorders are described in other chapters, and a complete description of all of them is found in the review article by Weleber and Evans (16).

Of particular note in this group are the disorders classified as neuronal ceroid lipofuscinosis (Batten disease). This disorder should be suspected in a young child with previously good vision who shows a rapid visual loss and ERG indicative of generalized degeneration of the retina. The initial fundus finding may be an unusual macular “bull'seye” appearance with more generalized retinal changes being seen only later.

Because night blindness is the predominant symptom in the generalized heredoretinal degenerations, it may raise the possibility of such a diagnosis. However, it is important from a prognostic point of view to distinguish the progressive blinding degenerations from the relatively benign disorder of CSNB. There are several variants of CSNB (Table 5.3), which can most easily be classified as those with fundus abnormalities and those without any fundal changes. In the latter group, the hereditary pattern may be autosomal

recessive, autosomal dominant, or X-linked recessive. The X-linked recessive type, discussed earlier, is usually associated with myopia, nystagmus, and decreased vision. In the other hereditary variants, vision is normal. If subjective tests can be done, they show full peripheral fields as tested under mesopic conditions and a dark adaptation curve that shows no abnormality in attaining normal cone thresholds. Rod thresholds, however, are markedly elevated and do not change even with prolonged patching (Fig. 5.20).

TABLE 5.5 SYSTEMIC DISEASES ASSOCIATED WITH RETINITIS PIGMENTOSA

I. Metabolic disorders

A. Lipid abnormalities

1. Bassen-Kornzweig syndrome (abetalipoproteinemia)

2. Refsum disease (infantile and adult)

3. Ceroid lipofuscinosis (Batten disease)

a. Haltia-Santavuori disease (early infancy)

b. Jansky-Bielschowsky disease (late infancy)

c. Spielmeyer-Vogt disease (juvenile)

4. Miscellaneous rare associations

a. Hooft disease

b. Letterer-Siwe disease

c. Pelizaeus-Merzbacher disease

d. Mucolipidosis IV

B. Mucopolysaccharide (MPS) storage disorders

1. MPS I-H (Hurler)

2. MPS I-S (Scheie syndrome)

3. MPS I H/S (Hurler-Scheie syndrome)

4. MPS II (Hunter syndrome)

5. MPS III (Sanfilippo syndrome)

C. Miscellaneous rare associations

1. Oxalosis

2. Albinism

3. Cystinuria

II. Neurologic disorders

A. Laurence-Moon syndrome

B. Bardet-Biedl syndrome

B. Bardet-Biedl syndrome

C. Hereditary ataxias

1. Friedreich ataxia

2. Pierre-Marie ataxia

3. Spastic paraplegia

4. Pallidal degeneration

5. Cerebellar ataxia (AD)

D. Mitochondrial myopathy (Kearns-Sayre syndrome)

E. Usher syndrome

F. Alstrom disease

G. Miscellaneous rare associations

1. Cockayne syndrome

2. Charcot-Marie-Tooth syndrome

3. Flynn-Aird syndrome

4. Marinesco-Sjogren syndrome

III. Renal or hepatic disorders

A. Medullary cystic disease (juvenile nephronophthisis; Senior-Loken syndrome; Fanconi syndrome)

B. Alagille syndrome

C. Zellweger (cerebrohepatorenal syndrome)

D. Adrenoleukodystrophy

AD, autosomal dominant.

The ERG response can be of two types (Figs. 5.14 and 5.21). In the one usually seen in X-linked and autosomal-recessive disorders, there is a deep, normal negative response but no positive response. The latency of the negative response is likewise normal. The second type of response is the one most difficult to distinguish from that of retinitis pigmentosa since it is very markedly reduced in amplitude. However, latency measurements are normal, thus differentiating CSNB from heredoretinal degeneration. Studies of these types of CSNB show that they are due to abnormalities in neural transmission in the outer retinal layers (17).

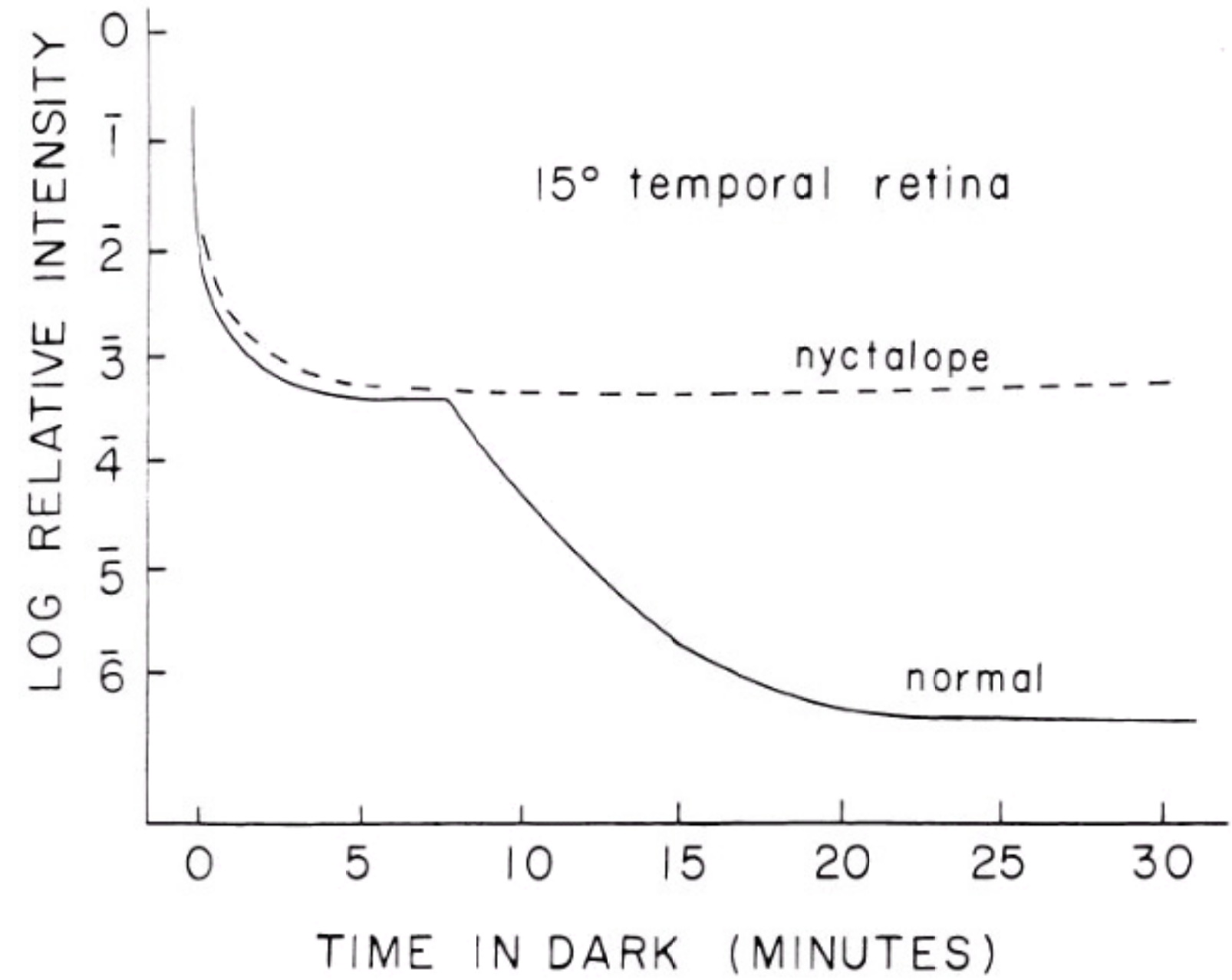


Figure 5.20 Peripheral dark adaptometry comparing a normal person with a patient with congenital stationary night blindness. The normal curve (*solid line*) is bipartite, the initial segment representing cone function and the second segment rod function. The curve of the nyctalope (*dashed line*) shows no rod adaptation.

Several types of CSNB are seen in which definitive retinal

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changes may be recognized and lead to a correct assessment of the clinical picture. One of these, Oguchi disease, is characterized by a peculiar metallic sheen to the retina, the background retina having an appearance like beaten silver and the retinal vessels standing out in high relief against this background. This retinal picture may be present either throughout the retina or only in the posterior pole. It is of interest that this peculiar retinal color disappears on prolonged dark adaptation (Fig. 5.22 top). Likewise, prolonged dark adaptation leads to a complete normalization of rod

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sensitivity (Fig. 5.22A and B). The ERG again leads to the correct diagnosis since a negative response occurs with only a short period of dark adaptation, similar to what was observed in one of the other variants of CSNB noted earlier (Fig. 5.14). However, unlike this group, after prolonged patching has led to normalization of the dark threshold, the ERG in Oguchi disease is also normal (Fig. 5.22C). This latter ERG response is difficult to repeat because such patients show exquisite sensitivity to light, and a single bright flash will again elevate their threshold for a prolonged period.

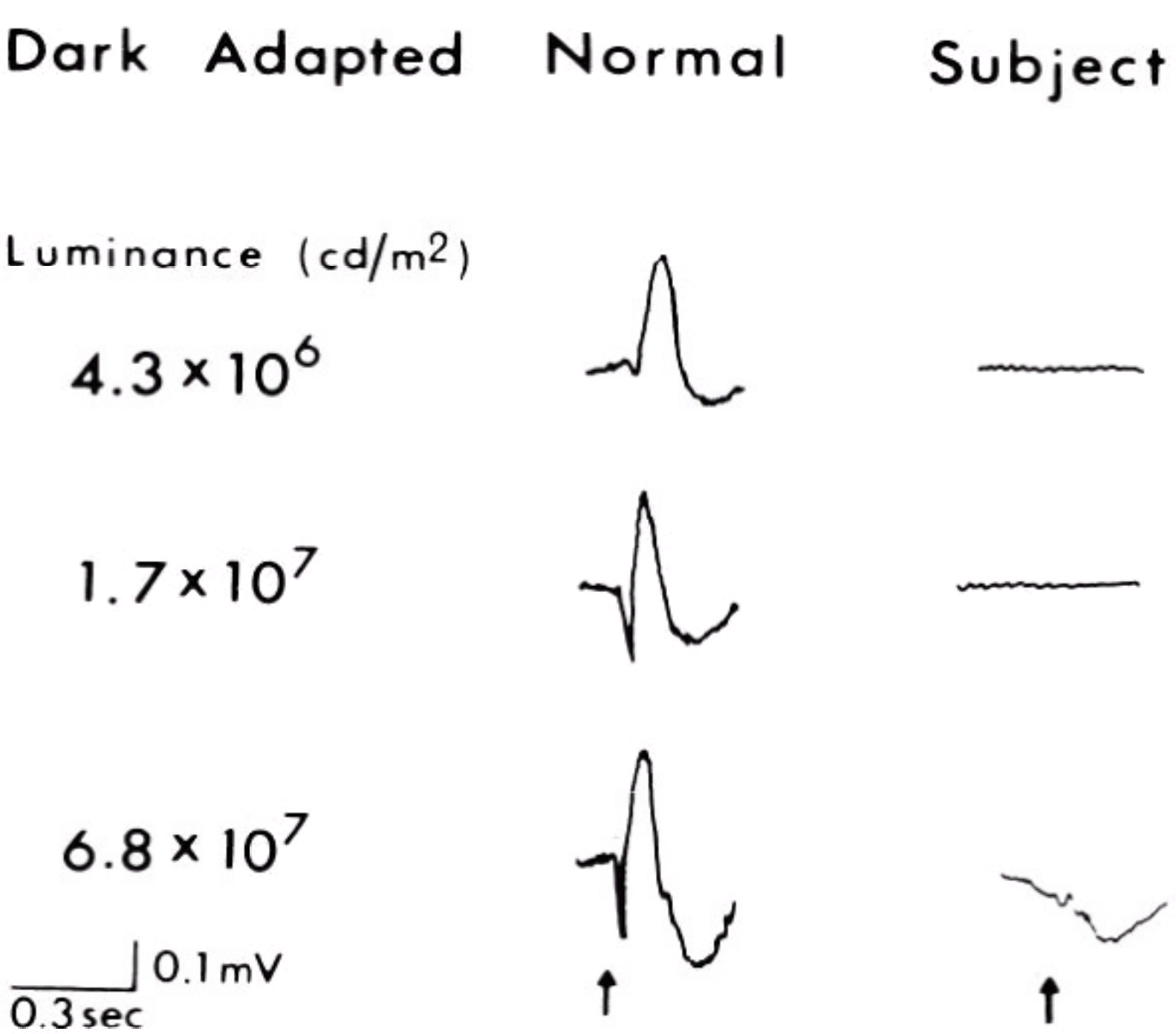

Figure 5.21 Congenital stationary night blindness. The scotopic ERG is shown at varying light intensities. There is virtually no response at even the brightest light intensity. Latencies, however, are normal. In this type of case, there is probably an abnormality of neural transmission in the region of the photoreceptor inner segments. ERG, electroretinogram.

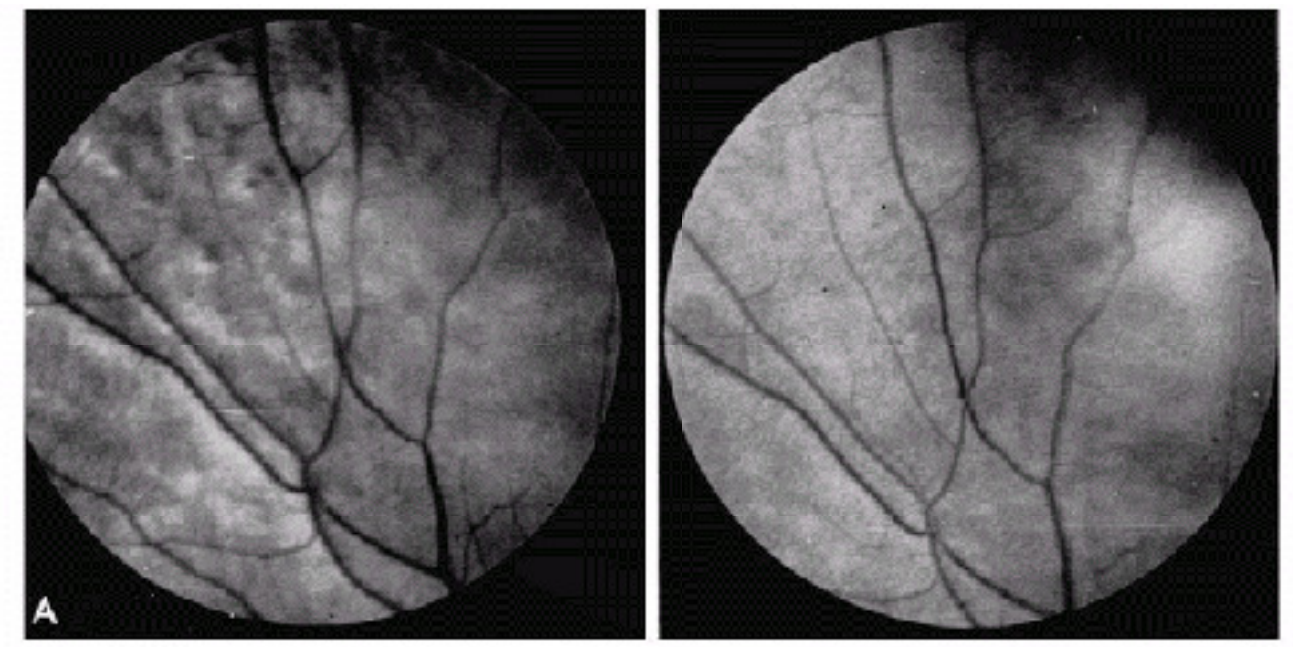

Figure 5.22 Oguchi disease. **A:** Fundus showing: (**left**) the peculiar metallic appearance of the retina against which the blood vessels stand out; (**right**) the same area of the retina after 4 hours of dark adaptation. The retinal appearance is now normal (Mizuo phenomenon). **B:** Dark adaptation comparing a normal individual with a patient with Oguchi disease (*open circles*). Note the prolonged course of adaptation until a normal final threshold is reached. **C:** ERG: (**left**) a normal response to both a weak and strong light stimulus after 30 min of dark adaptation; (**right**) after this same period there is no discernible second positive response in the patient. A normal response is apparent only after prolonged dark adaptation (4 hours). ERG, electroretinogram.

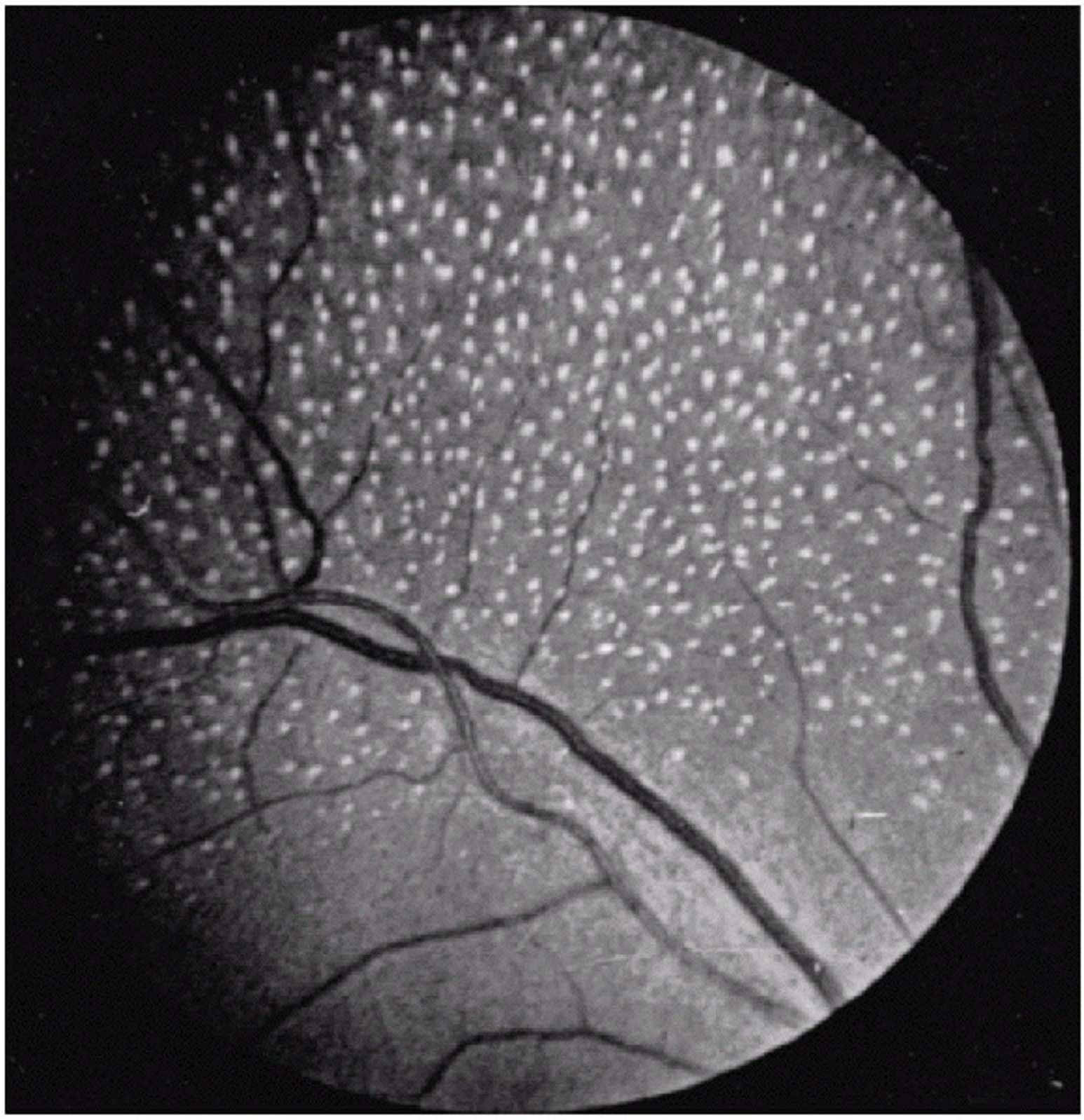

Figure 5.23 Fundus albipunctatus. A multitude of discrete yellow-white spots are seen throughout the retina but spare the posterior pole.

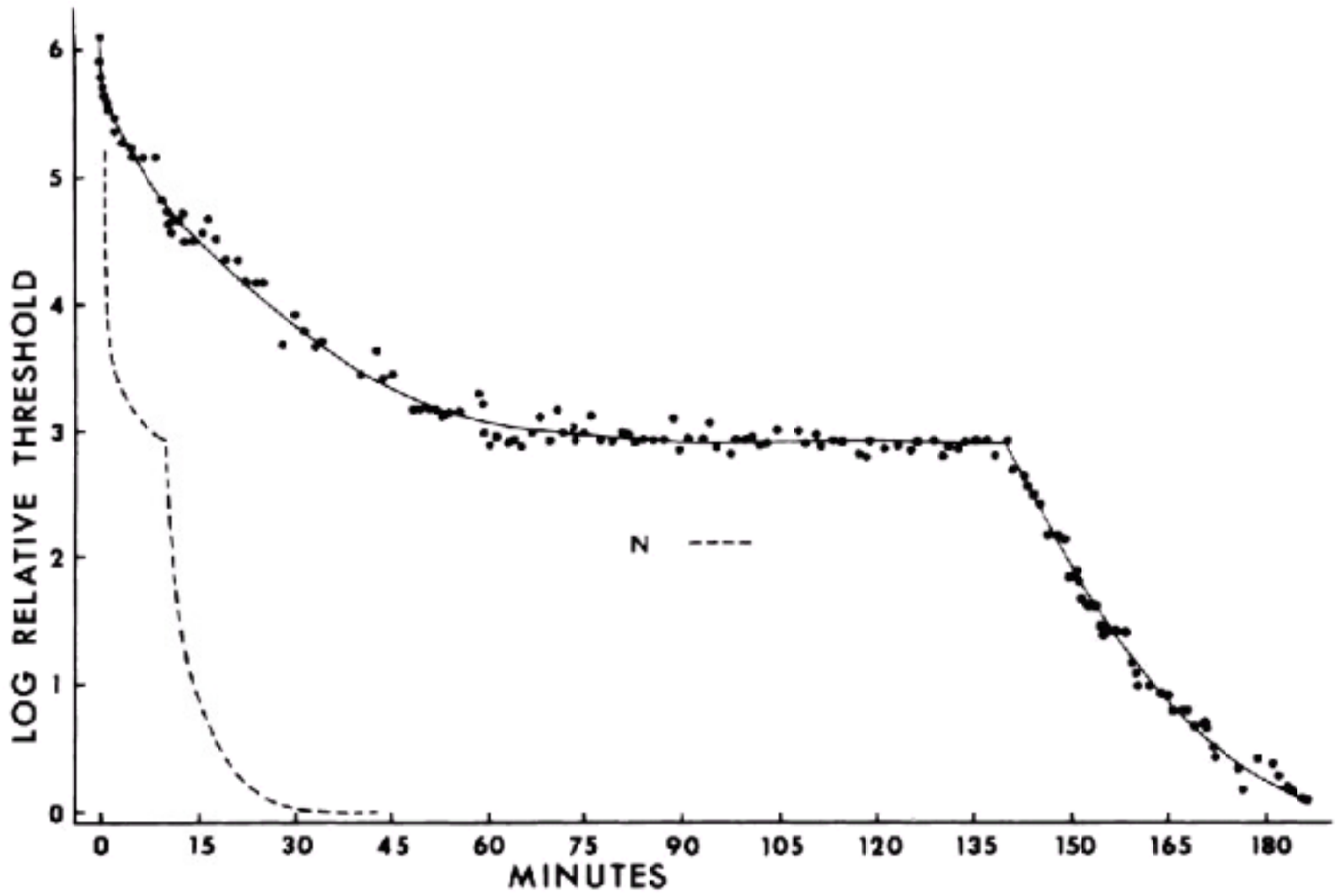

Figure 5.24 Fundus albipunctatus. Dark adaptometry comparing a normal individual (*dashed line*) with a patient with fundus albipunctatus. Note the slow fall to normal of both the cone and rod segments.

The second disorder of CSNB with fundus changes is fundus albipunctatus. Funduscopically, multiple white or yellow-white spots are scattered throughout the posterior pole but invariably spare the macular area (Fig. 5.23). The dark adaptation curve shows a certain similarity to the curve in Oguchi disease in that there is a very slow fall (several hours) to a final dark-adapted threshold. However, unlike Oguchi disease, the cone system shows a marked delay in reaching a normal final threshold (Fig. 5.24). The basic pathogenesis in this disease is a marked delay in regeneration of the visual pigments, which accounts for the abnormal psychophysical findings (18). The ERG also is delayed in reaching normal amplitudes, and the EOG requires several hours of dark adaptation before a normal light rise is elicited. Because of the delay in attaining normal values, dark-adapted thresholds and the ERG will be abnormal if recorded at the end of a standard time period (Figs. 5.24 and 5.25). If this disorder is not considered in the differential diagnosis, the physician may be misled into diagnosing a generalized degeneration of the retina on the basis of standard testing procedures.

Children with Onset of Decreased Vision of Unknown Cause

This last group may provide the most serious diagnostic problems for the ophthalmologist. In the absence of any overt funduscopic changes, the clinician must decide whether any abnormality is actually present along the visual pathway to account for the decreased vision. The major causes of this symptom may include macular disease, generalized degeneration of the cone system, optic nerve disease, higher center disease, and malingering. The last is obviously a diagnosis of exclusion once the other disorders have been ruled out.

Macular disease, in which there are no overt ophthalmoscopic signs, and *generalized degeneration of the photoreceptors,* again with an essentially normal retina, have been

mentioned previously. In both of these disorders, the ERG is important. In the former, the focal ERG points to a localized abnormality of the photoreceptors in the macula, while the abnormal full-field ERG points to a generalized receptor abnormality in the latter.

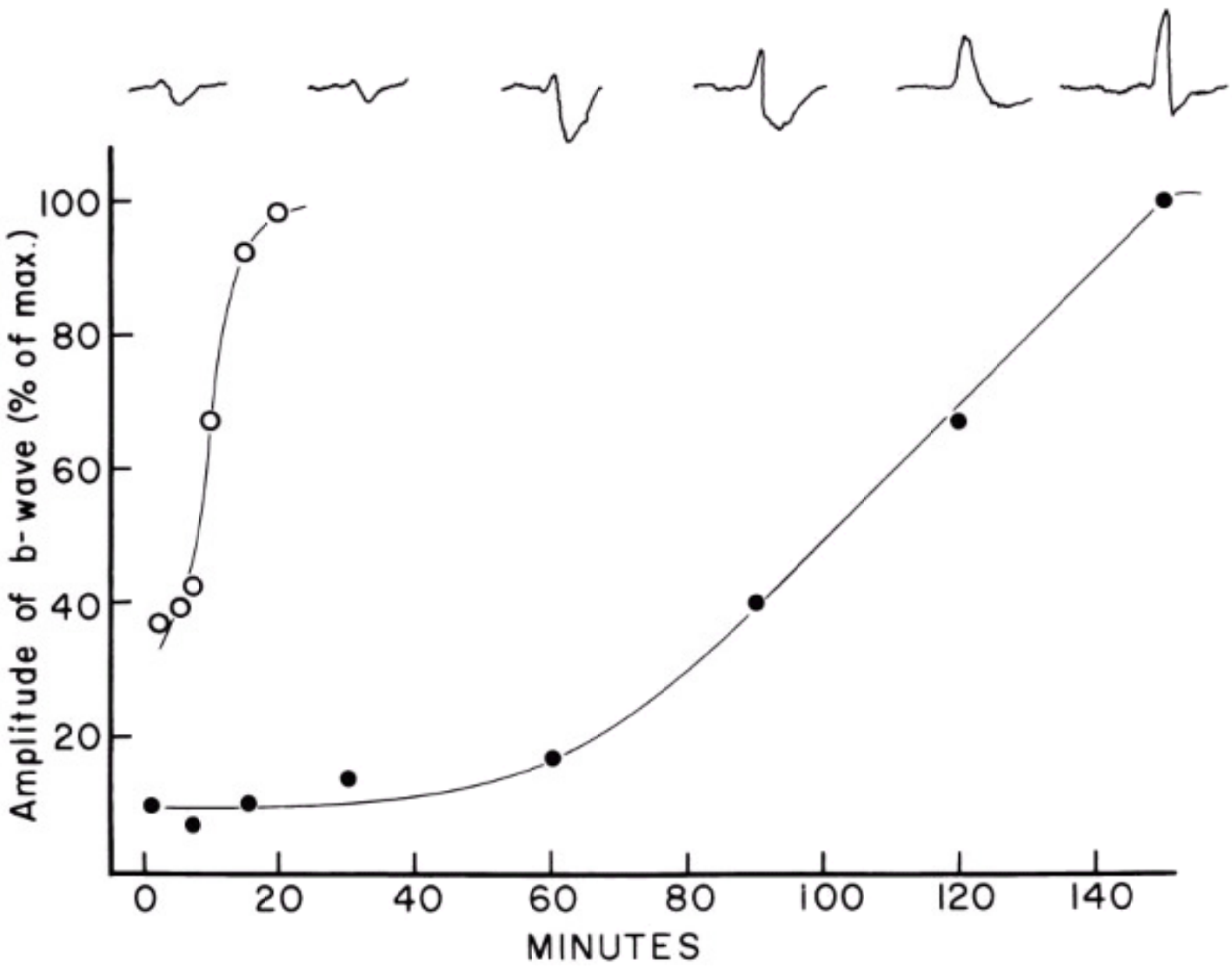

Figure 5.25 Fundus albipunctatus. Representative ERGs at various times after dark adaptation are shown. Note that it takes more than 2 hours for a normal response to be generated. The time course of b-wave regeneration in a normal individual (*open circles*) is compared with a patient with fundus albipunctatus (*closed circles*). ERG, electroretinogram.

Late-onset degeneration of the cones is a rare abnormality that can occur as an inherited disorder (autosomal dominant), as a result of certain drugs (19), or as an isolated entity. The presenting symptom may be either some loss in color perception or a loss in visual acuity. In the early stages, the retina may appear completely normal, and indeed color vision may likewise be normal if the foveal cones are spared. However, the ERG again provides the diagnostic measure needed to make the diagnosis for the widespread cone dysfunction leads to a marked reduction of the photopic response and an absence of any flicker follow. *Optic nerve disease* of all types shows abnormalities of the VER in terms of contrast sensitivity and latency, and if the test parameters are acute enough, of amplitude as well. The same is true of *higher center disease*.

To diagnose *malingering* in a child with poor vision requires ruling out all other possible causes of decreased vision. The normalcy of all electrodiagnostic studies would make such a diagnosis feasible. It is also in such situations that the objective measurement of acuity by the VER becomes helpful. Children who are malingerers usually claim vision of 20/200 or less, so the VER acuity test provides a rapid method of disproving the claim.

REFERENCES

1. Berson EL, Gouras P, Hoff M. Temporal aspects of the electroretinogram. *Arch Ophthalmol* 1969;81:207-214.

2. Marmor MF, Zrenner E, for the International Society for Clinical Electrophysiology of Vision. Standard for clinical electroretinography (1999 update). *Doc Ophthalmol* 1998;97:143-156.

3. Sutter EE, Tran D. The field topography of ERG components in man. I. The photopic luminance response. *Vision Res* 1992;32:433-446.

4. Seiple W, Greenstein VC, Holopigian K, et al. A method for comparing psychophysical and multifocal electroretinographic increment thresholds. *Vision Res* 2002;42:257-269.

5. Vrabec TR, Affel EL, Gaughan JP, et al. Voluntary suppression of the multifocal electroretinogram. *Ophthalmology* 2004;111:169-176.

6. Marmor MF, Hood DC, Keating D, et al. Guidelines for basic multifocal electroretinography (mfERG). *Doc Ophthalmol* 2003; 106:105-115.

7. Fishman GA, Young RSL, Schall SP, et al. Electrooculogram testing in fundus flavimaculatus. *Arch Ophthalmol* 1979;97:1896-1898.

8. Harding GFA, Odom JV, Spilleers W, et al, for the International Society for Clinical Electrophysiology of Vision. Standard for visual evoked potentials

1995. *Vision Res* 1996;36:3567-3572.

9. Tyler CW, Apkarian P, Levi DM, et al. Rapid assessment of visual function: an electronic sweep technique for the pattern visual evoked potential. *Invest Ophthalmol Vis Sci* 1979;18:703-713.

10. Nelson JI, Kupersmith MJ, Sieple WH, et al. The swept display technique: separation of x- and y-dominated evoked potentials. In: Nodar R, Burber C, eds. *Proceedings of the second international evoked potential symposium*. Cleveland,1983.

11. Dekaban A, Carr RE. Congenital amaurosis of retinal origin. Frequent association with neurological disorders. *Arch Neurol* 1966;14:294-301.

12. Alstrom CH, Olson O. Heredo-retinopathia congenitalis. Monohybride recessiva autosomalis. *Hereditas Genet Arkiv* 1957;43:1-177.

13. Schappert-Kimmijser J, Henkes HE, von den Bosch J. Amaurosis congenita (Leber). *AMA Arch Ophthalmol* 1959;61:211-218.

14. Mizuno K, Takei Y, Sears ML, et al. Leber's congenital amaurosis. *Am J Ophthalmol* 1977;83:32-42.

15. Glickstein M, Heath GG. Receptors in the monochromat eye. *Vision Res* 1975;15:633-636.

16. Weleber R, Gregory-Evans D. In: Ryan SJ, ed. *Retina*, 3rd ed, Vol 1. St. Louis: CV Mosby, 2001:362-460.

17. Carr RE. Congenital stationary nightblindness. *Trans Am Ophthalmol Soc* 1974;72:448-487.

18. Carr RE, Ripps H, Siegel IM. Visual pigment kinetics and adaptation in fundus albipunctatus. *Doc Ophthalmol Proc Ser* 1974;4:193-204.

19. Siegel IM, Smith BF. Acquired cone dysfunction. *Arch Ophthalmol* 1967;77:8-13.

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6

Refraction in Infants and Children

Michael X. Repka

The management of refractive error is the most common problem faced by the ophthalmologist when examining pediatric patients. Patients present with symptoms of blurred vision, inability to read, sitting too close to the television, squinting, or poor performance in school. They may have been referred by a pediatrician or, as is more often the case, after a failed school screening examination. In addition to subnormal vision, patients and their parents may complain of ocular fatigue, inability to study, letter reversal while reading and writing, and “dyslexia.” Many will have normal ocular examinations, and only reassurance is necessary. However, a substantial proportion has a refractive problem. Detection and management of refractive error are the subjects of this chapter.

DETERMINATION OF VISUAL ACUITY AND REFRACTIVE ERROR

The determination of refractive error is an essential component of every pediatric patient examination. The rapid changes of refractive error during childhood mandate frequent rechecks. For instance, an aphakic infant may require monthly examinations, whereas yearly checks are sufficient for most myopic teenagers. Refraction of a child cannot be rushed and should rely on objective techniques rather than on the subjective techniques used in adult practice. The examination is generally carried out with the parents present. It is best for young children, usually those under 4 or 5 years of age, to sit on a parent's lap. Older children may prefer to sit alone, as long as a parent or other familiar person remains in the examination room. The room should never be totally darkened, as this may provoke anxiety (Fig. 6.1).

Visual acuity was considered to be essentially absent at birth only 6 decades ago (1). Optokinetic nystagmus (OKN) measurements in the late 1950s showed this belief to be erroneous (2). Visual-evoked potential (VEP) acuities have been found to range from 20/200 to 20/100 at birth and to reach 20/20 by 1 year of age. Preferential looking techniques have demonstrated acuities of approximately 1 cycle per degree at birth (20/400), rapidly improving to adult levels of 30 cycles per degree by 30 months. Linear letter acuity is normally 20/40 by age 3 and 20/30 by age 4 or 5 years (3). By 6 years of age, most children have achieved 20/20 acuity.

Acuity in the Preverbal Child

Measurement of visual acuity is normally performed in the course of determining the refractive error. In most children less than 2.5 years of age, preverbal methods must be used (4). Clinical methods for infants involve an estimate of fixation and following behavior (Fig. 6.2). A penlight is never used as a target since it lacks the edge contours necessary for accurate detection. Instead, a test target should incorporate high-contrast edges, e.g., stripes or a checkerboard. Perhaps the best target for an infant is the examiner's face. An infant normally displays a visual preference for the human face. For the child of 6 months and older, an interesting toy should be used. Monocular fixation normally can be demonstrated at term and certainly should be present by the end of the first month of life. Following behavior refers to a qualitative assessment of the competence the infant demonstrates in following a moving target. The smoothness and amplitude of pursuit rapidly improves during the first 6 months of life. Careful observation for the presence of a fine nystagmus should be part of each examination. Some practitioners prefer to describe the quality of the fixation behavior with the terms “central,” “steady,” and “maintained.” Maintained fixation implies that the patient will still fixate with the same eye after a blink. No matter how fixation is described, the examiner also assesses the binocular fixation pattern to determine if

there is an eye preference. A difference suggests a problem in the nonpreferred eye. One potential scheme is listed in Table 6.1, adapted from Zipf (5), in which categories A and B are normal, while C and D suggest amblyopia. However, there is overlap between grades of these criteria, and the criteria will tend to overdiagnose amblyopia. In one study, optotype testing confirmed amblyopia in only 17 of 52 patients (33%) who had been diagnosed by fixation preference testing (6).

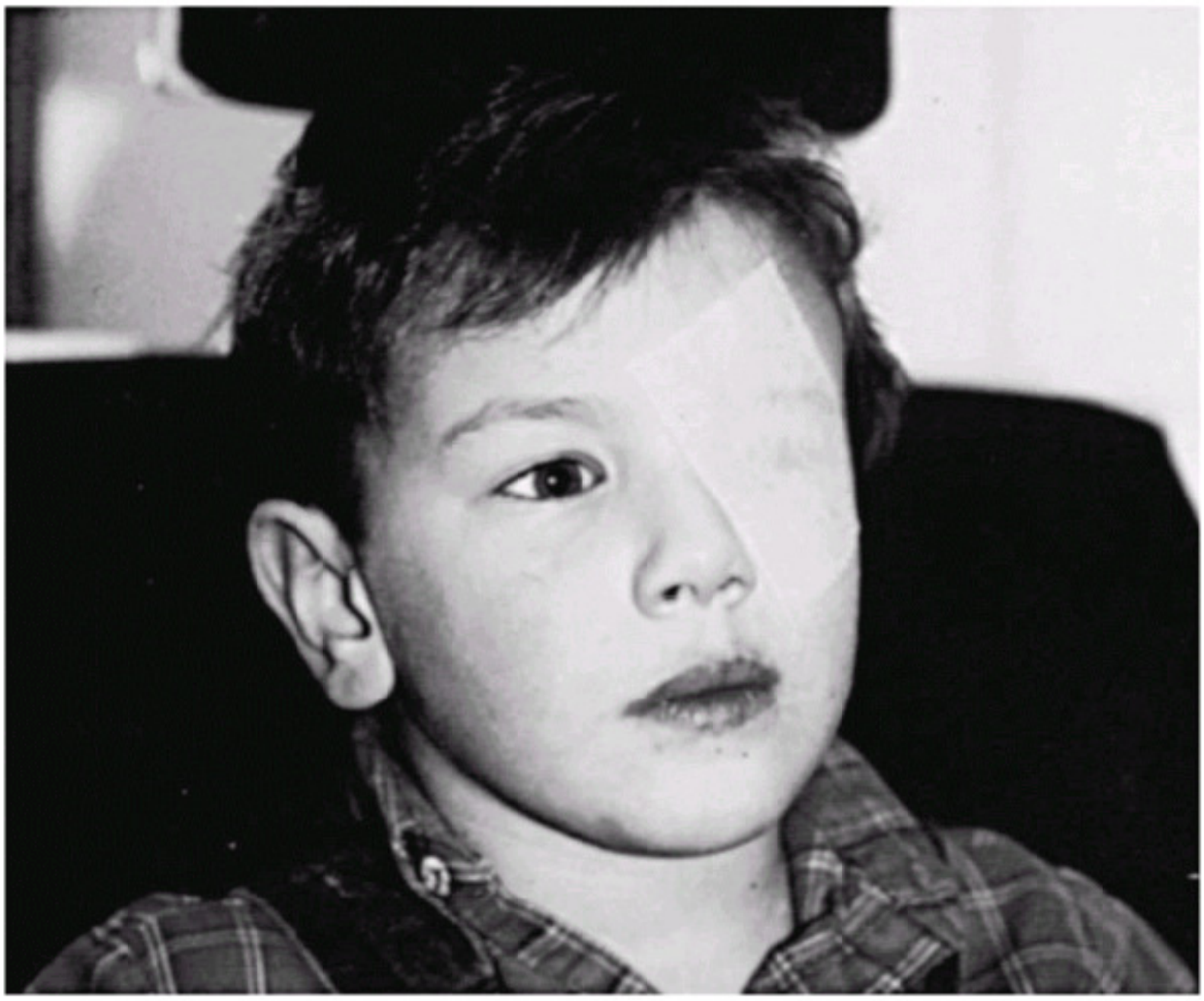

Figure 6.1 Examination of the preschooler. The patient is seated comfortably in a partially darkened room. The left eye is occluded with paper tape.

In an attempt to improve upon fixation preference testing with an objective and quantitative method of assessing visual function, techniques utilizing grating targets of varying spatial frequency (stripe width) have evolved. Such methods rely on detection of resolution acuity, a more sophisticated measure of visual performance than mere detection of a target as used for fixation assessment. There are three methods currently used for determining resolution acuity. They rely on preferential looking techniques, eliciting and detecting OKN, or recording a VEP.

Figure 6.2 Fixation preference. The examiner is testing the monocular fixation pattern of an infant by using an attractive toy.

TABLE 6.1 GRADING SCHEME FOR FIXATION PREFERENCE[a]

Grade	
A	Spontaneous alternation between the right and left eyes
B (holds well)	Fixation held with nonpreferred eye before refixation to preferred eye for: = 3 seconds during a smooth pursuit through a blink
C (holds momentarily)	Fixation held with nonpreferred eye for 1 to 3 seconds
D (does not hold)	Refixation with preferred eye occurs immediately (<1 sec) when the occluder is removed from the preferred eye

[a]12-16 prism diopter placed base-down before one eye to produce a strabismus in the orthotropic patient.

(Adapted from Zipf RF. Binocular fixation pattern. *Arch Ophthalmol* 1979;94:401-405, with permission.)

The most widely used test today is preferential looking. Forced-choice preferential looking (7), operant preferential looking (8), and current variations of the acuity card procedure (9,10) have been developed to provide a simple, efficient method of assessing visual acuity in infants, young children, and nonverbal patients (Fig. 6.3). Each of these methods assumes that the child prefers to look at an area of higher visual interest, the striped grating, rather than a neutral gray field. By determining the smallest width grating on which the patient will fixate, resolution acuity can be determined. Normative data for these tests can be used to translate these spatial resolution values to approximate Snellen acuity (11,12).

The preferential looking methods remain largely a research vehicle because of the time and specially trained personnel required. Acuity card testing, which is the fastest method, required 36 minutes for testing of the monocular and binocular acuity of one patient (10). The acuity card procedure, with more experience, may

become useful for amblyopia therapy in children with severe unilateral abnormalities (e.g., monocular aphakia). These methods are not suitable as screening tools.

Visual acuities in infants have also been measured with VEP recordings as well as by eliciting OKN by stripes of various widths. These two methods are handicapped by the complicated apparatus necessary for their performance. The OKN method is additionally handicapped by its reliance on a normal ocular motor system for end-point determination. The usefulness of VEP is diminished by its reliance on a dedicated technician. An additional concern with VEP is that acuities determined by it are typically much better than those determined by behavioral methods because VEP bypasses neural processing to determine a response end point.

All three resolution methods for assessing visual acuity (forced-choice preferential looking, VEP, and OKN) are further hampered by their overestimation of visual acuity in

amblyopic individuals (13). This is the largest group of patients for whom the development of this type of test is most important.

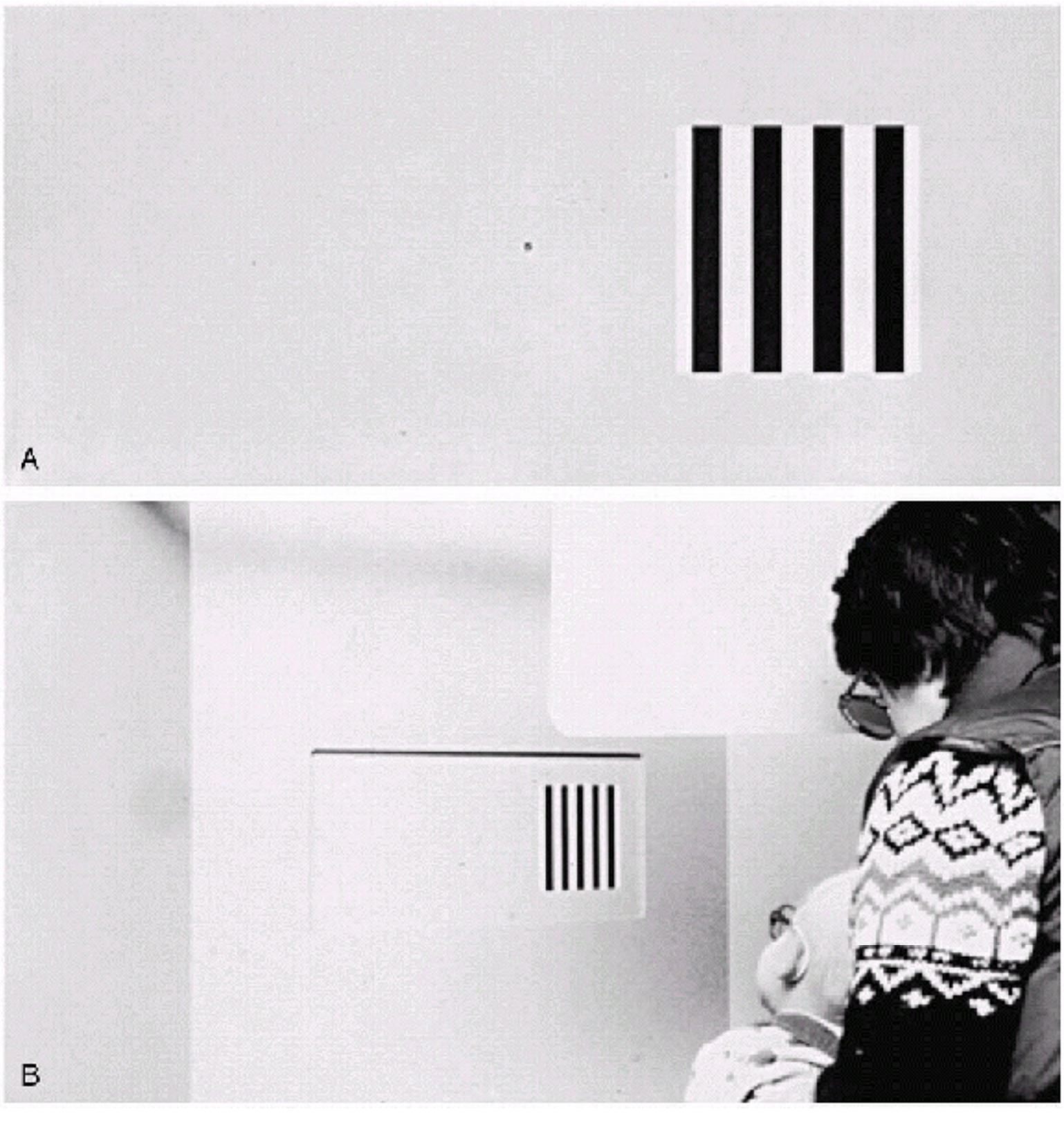

Figure 6.3 Teller acuity cards for preferential looking. A: Grating card with the largest striped pattern (0.32 cycles/degree) on one side and gray field on the other. B: An infant being tested in the Vistech apparatus.

From 1 until 2.5 years of age, visual acuity remains difficult to measure. Behavioral techniques are too time consuming to maintain an active toddler's interest, although limited success has been reported with the acuity card procedure (10). Other tests for this age range have been developed (14) and are reviewed by Simons (15) and McDonald (16). Most clinicians have found these tests to be insufficiently reliable, and they continue to rely on assessment of fixation behavior until the child is 2.5 years old.

Acuity in the Verbal Child

After the age of 2.5 years, many children will participate in a verbal determination of acuity. These tests measure recognition acuity: the ability to differentiate one stimulus from a group of similar stimuli.

The particular test used, as well as the method of presentation, should be the most complex to which the patient can respond consistently. Comparison of visual acuities from visit to visit must take into account the specific test performed as well as the child's reliability.

For any test of children's vision, the method of optotype

presentation will affect the measured acuity. Give adequate time and remove as much distraction from the exam room as possible. The testing distance should be 3 meters rather than 6 meters because of better testability. Whenever possible, presentation of a line of characters or surrounded single optotypes (Fig. 6.4) is preferable to displaying single letters. These two methods produce similar results (17). Singleletter presentation eliminates contour interactions around the test optotype, which results in improvement in the measured visual acuity in both normal and amblyopic eyes (15). This effect is clinically termed “the crowding phenomenon.” The effect is greater in amblyopic eyes; thus, a patient with amblyopia may not be detected when tested with single optotypes.

Figure 6.4 Letter with “surround” bars. A single letter is used to eliminate recognition confusion from multiple stimuli, while the bars produce the necessary edge interactions to produce good linear acuity. These are positioned one-half symbol width away from the optotype.

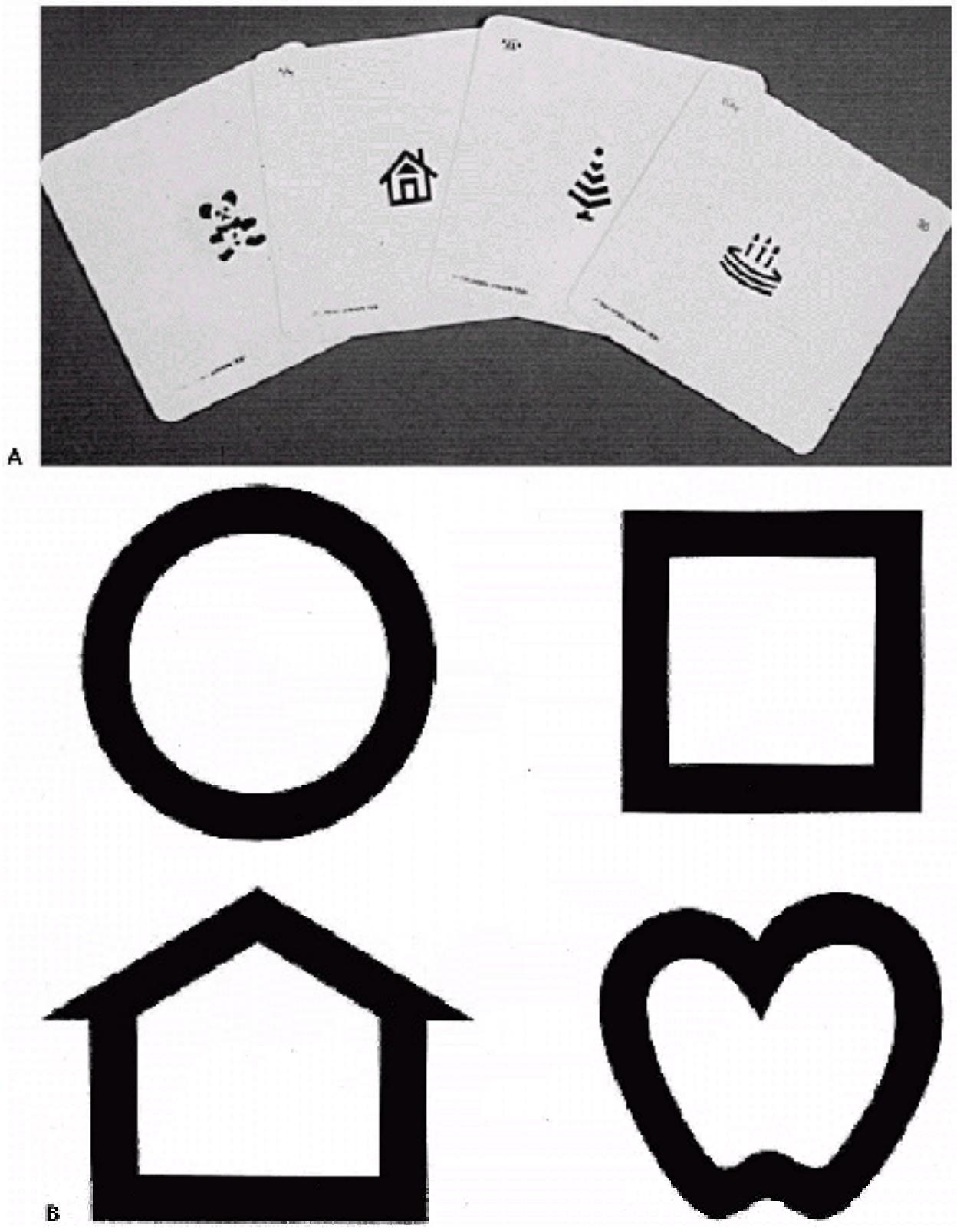

Figure 6.5 Picture optotypes. **A:** Traditional Allen pictures. **B:** Lea symbols.

The test most commonly used for the youngest children involves picture optotypes (Fig. 6.5A), as they are considered more easily tested in young children. However, these tests even with surround bars are less sensitive to intereye acuity disparity than letter optotypes, and thus may not detect all cases of decreased vision. Hyvärinen invented a set of symbols (house, square, apple, circle) modeled on the Landolt C (18)(Fig. 6.5B).

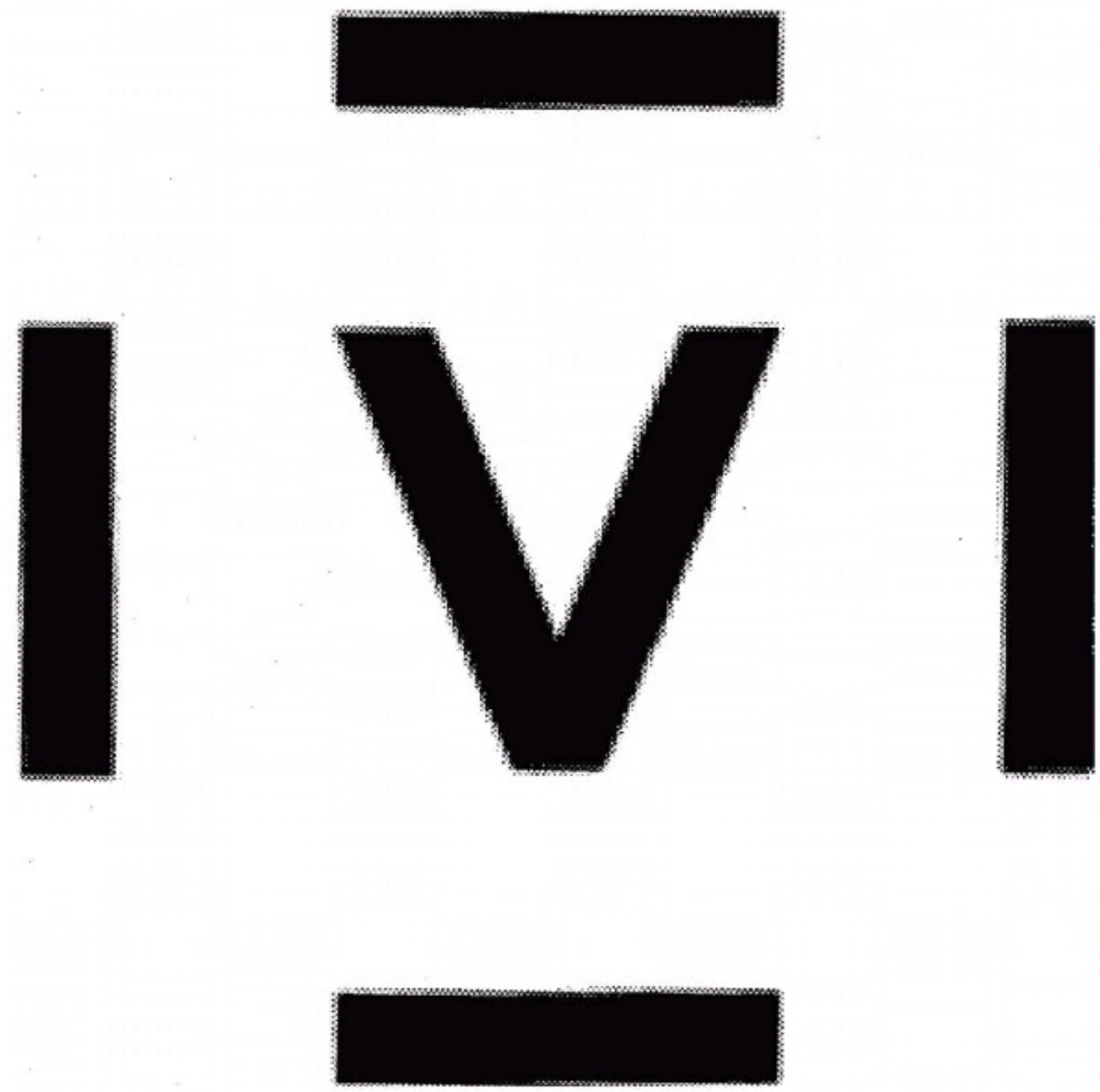

Figure 6.6 HOTV optotypes are presented in a single surrounded format in a random sequence on a computer monitor at 3 m. The child should be shown or even hold a matching card to facilitate the testing. Linear versions of the test are also available.

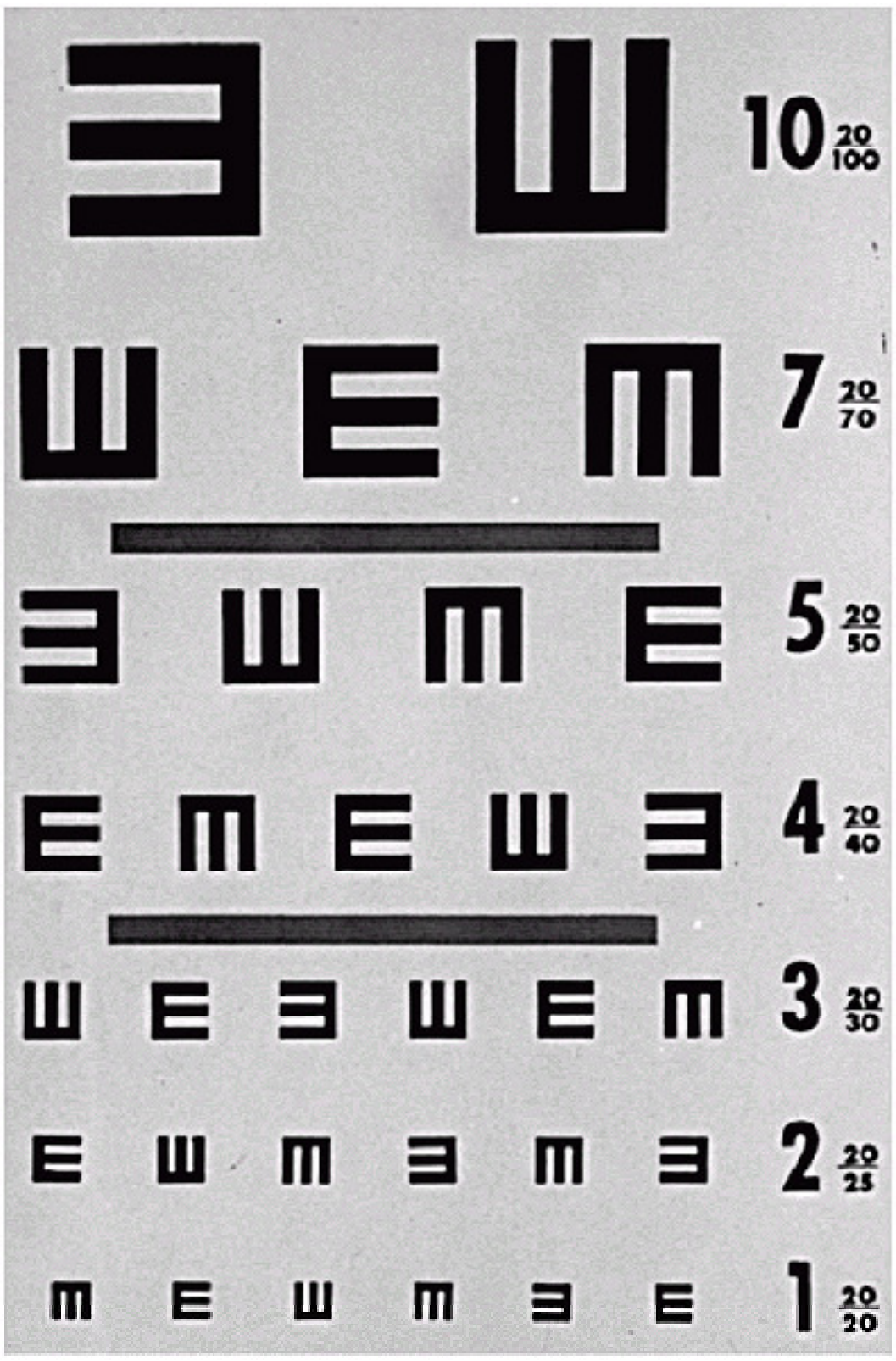

Figure 6.7 Tumbling-E test.

Single surrounded HOTV tests are of great utility in the 30- to 54-month age group. The patient matches the letter being displayed to one on a handheld card. Consequently, recognition but not literacy is required for this letter optotype test. The method of presenting the HOTV stimuli has been formalized in a protocol developed for the Amblyopia Treatment Studies (19). An automated version of the Amblyopia Treatment Study HOTV test is being used in many centers to provide consistent visual acuity determinations (20) (Fig. 6.6). The Lea symbols in a chart format have been compared to the automated HOTV test among children 3 to 3.5 years of age (21). Equally high proportions were successfully tested. However, children tested 2.5 lines better with the HOTV test, most likely because the multiline Lea chart was used. In clinical practice, the Lea symbols have fared much better when tested in a single crowded optotype format (22).

After 4 years of age, either the surrounded HOTV, letters, or tumbling-E test is used (Fig. 6.7). The E test was first devised by Snellen and is widely accepted as a standard. A line of Es is presented to the patient, who is asked to orient his or her fingers in the direction that the fingers of the E

are pointing or to hold a plastic E in the same orientation as the test E. When the patient holds the plastic E, the completion of this test is faster and more accurate. Use of the handheld E reduces the left-right confusion that children often experience while performing this test.

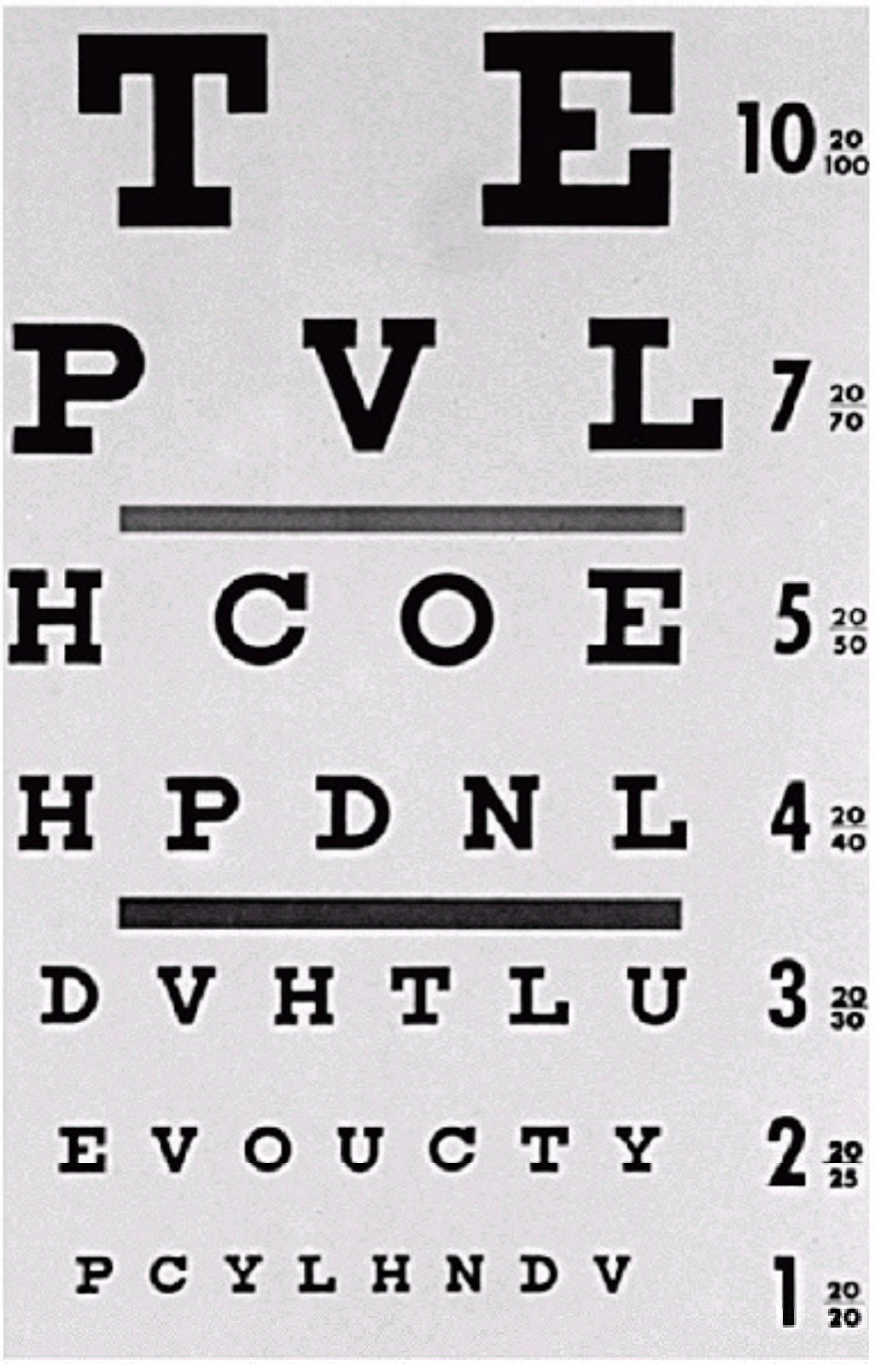

Figure 6.8 Snellen chart.

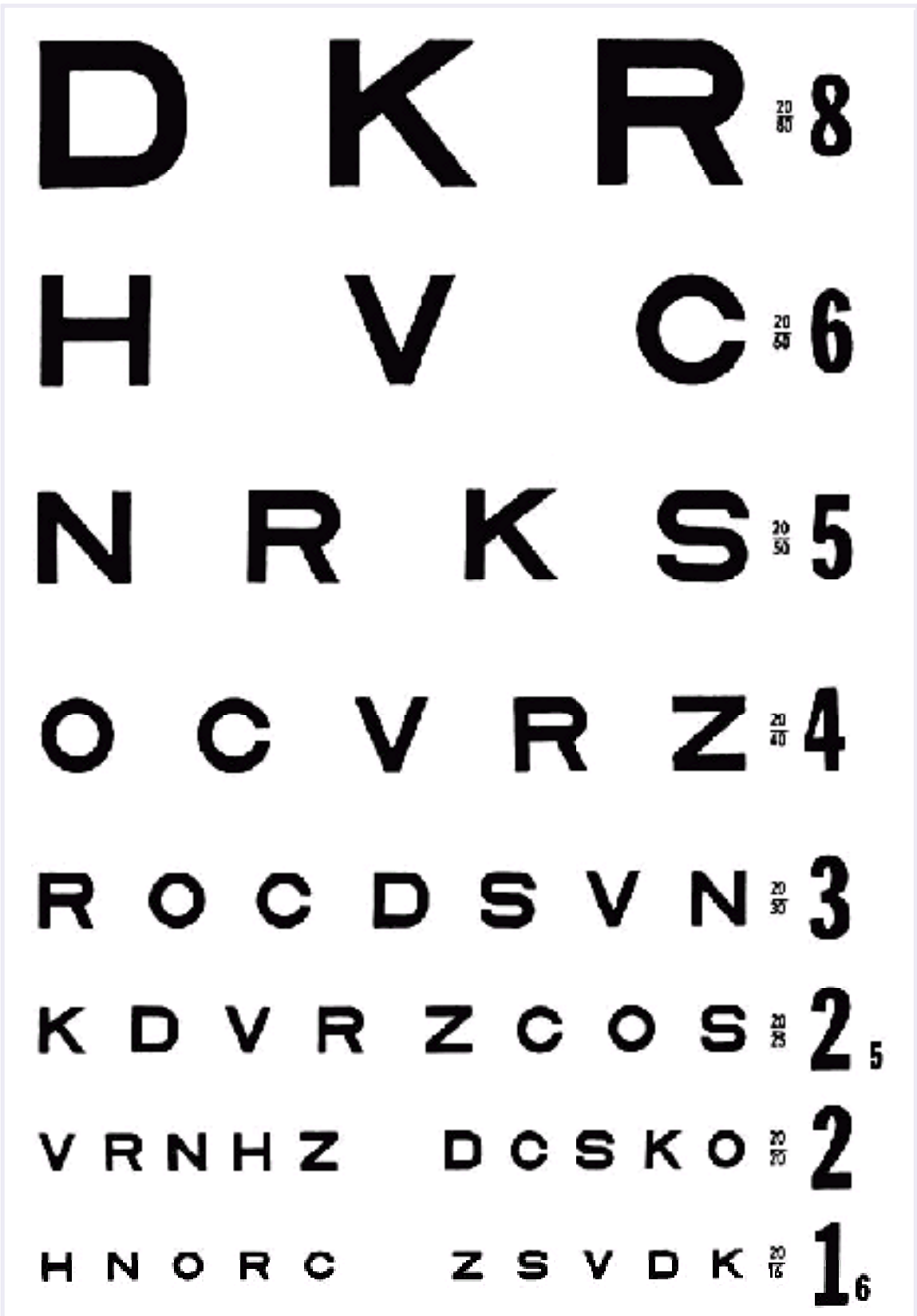

Figure 6.9 Sloan letter optotypes.

The most commonly used letter visual acuity test is one of the modifications of the Snellen chart (Fig. 6.8). The Snellen chart is not ideal since it employs letters of different legibility at the same visual angle. A better letter test was designed by Sloan (23), consisting of ten letters of approximately equal legibility (Fig. 6.9). These letters have been used in the Early Treatment of Diabetic Retinopathy Study acuity test (24).

The standard optotype test of visual acuity specified by the National Academy of Science-National Research Council Committee on Vision is the Landolt C (25) (Fig. 6.10). This test to date has met with clinical acceptance only in Japan.

TECHNIQUE OF REFRACTION

Refraction of children is difficult because of their apprehension and brief attention spans. Consequently, the refraction must be both rapid and accurate. Despite the development of numerous objective automatic refracting instruments, retinoscopy remains the best method of determining a child's refraction. The technique of objective retinoscopy is described elsewhere in detail (26,27,28,29,30). Retinoscopy is usually performed without sedation or a lid speculum. In rare instances, conscious sedation or even general anesthesia may be required to perform accurate retinoscopy.

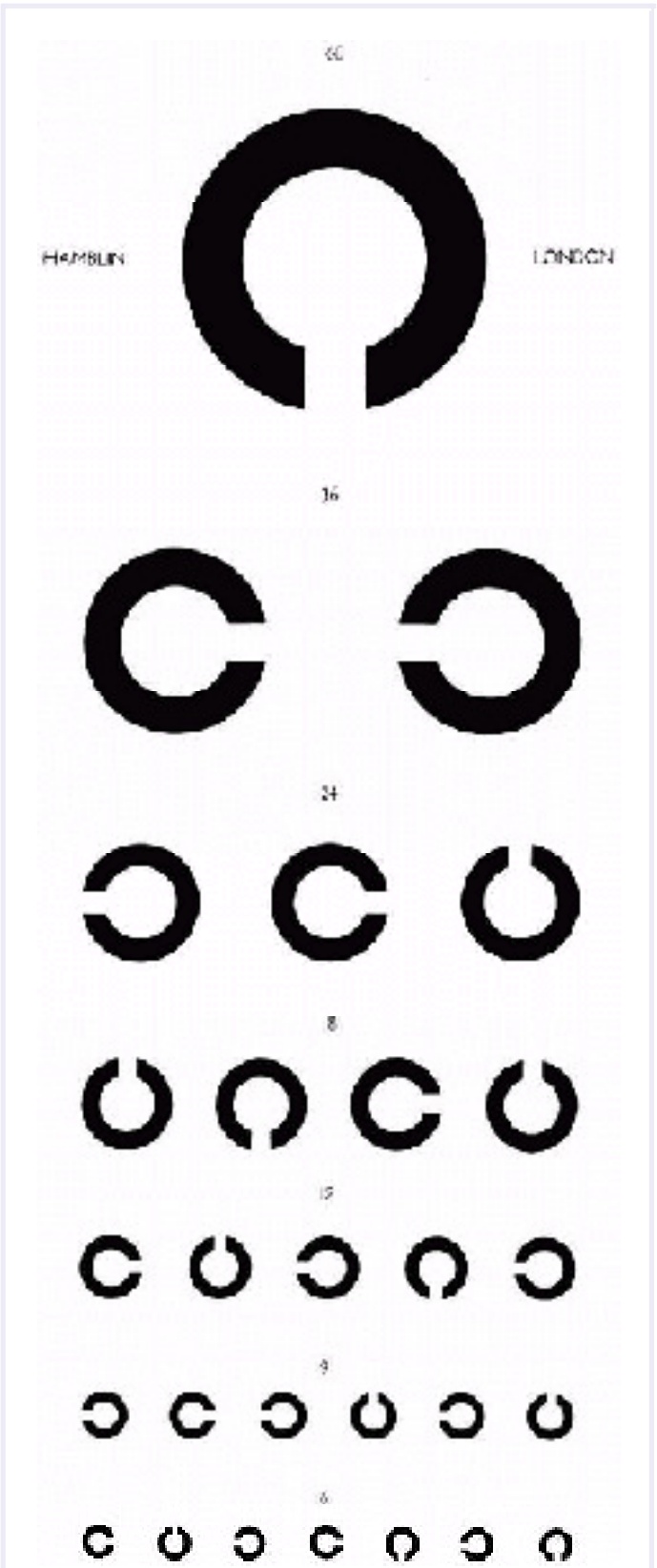

Figure 6.10 Landolt C optotype test.

Retinoscopy

The techniques of estimating refractive error taught by Copeland are used infrequently and rarely taught today. Most practitioners prefer neutralization methods using loose lenses in infants and young children, and trial frames or a phoropter (refractometer) in older children and teenagers.

Retinoscopy is best performed with cycloplegia. When no cycloplegic agent is used, the retinoscopic refraction is termed “manifest” or dry. For such a refraction to be accurate, patients' accommodation must be controlled, usually by having them view a distant, nonaccommodative target such as a target light. Optotypes are unsuitable targets since the accommodative mechanism will respond to retinal blur, constantly changing the level of accommodation in an attempt to focus the image.

It is useful to attempt a manifest refraction of school-age children and teenagers before dilation if there is evidence of undiagnosed hypermetropia. If a large hyperopic error is confirmed during the cycloplegic refraction, the examiner will know about how much hyperopic correction the patient will tolerate, and prescribe accordingly. This will eliminate the need for the patient to return for a postcycloplegic manifest refraction.

Cycloplegic Refraction

The cycloplegic refraction is an integral part of the examination of each pediatric patient. In addition to determining refractive error, the instillation of the cycloplegic agent allows a thorough retinal exam. Selection of the cycloplegic agent depends on the age of the patient as well as the pigmentation of the iris. Cycloplegia in children more than 4 months of age is obtained by placing one drop of proparacaine HCl 0.5% in the inferior fornix of each eye, followed by one drop of cyclopentolate 1%. The use of a topical anesthetic before instillation of the cycloplegic drug enhances the cycloplegic effect. This is due to either reduction of reflex tearing and lid squeezing or alteration of the corneal epithelial barrier (31). The refraction is performed 35 to 40 minutes later. For preterm infants, a weaker cycloplegic agent is recommended such as a combination of 0.2% cyclopentolate and 1% phenylephrine. For term to 4-month-old infants, 0.5% cyclopentolate is satisfactory, although phenylephrine is also needed with darker irides. Use of the weaker agents reduces the systemic side effects, especially vomiting. In the case of smaller babies in the neonatal intensive care unit, care should be taken to examine them shortly before a feeding when the stomach is empty.

Many examiners consider atropine the most complete cycloplegic agent for children, especially for those with accommodative forms of esotropia. In a series of 120 patients with accommodative esotropia, Rosenbaum and coworkers (32) found an average of 0.34 diopter more hyperopia with atropine 1% administered over 3 days compared with two drops of 1% cyclopentolate. They also noted that the difference between the cyclopentolate and atropine cycloplegic refractions tended

to be greater for esotropic patients with hypermetropia greater than 2.00 diopters. Nonetheless, most practitioners continue to reserve atropine for those patients who fail to be adequately cyclopleged, despite two or three doses of cyclopentolate (33). Because of the potential for undercorrection with cyclopentolate, any patient who inadequately responds to a hyperopic correction or whose refractive esotropia decompensates should undergo a repeat cycloplegic refraction. It is common to find more hyperopia at the second refraction.

If the examiner elects to use atropine, care should be taken. Atropine is administered by the parent or guardian usually as 1% ointment or solution twice daily for 3 days before the retinoscopic evaluation. It is important to instruct the parent not to instill the ointment the day of the evaluation, as the ointment vehicle will make retinoscopy nearly impossible. The parents should be instructed to store atropine, especially the solution, well away from children. Each drop of 1% solution contains 0.5 mg of atropine.

Symptoms of atropine toxicity include dryness of the mouth, tachycardia, fever, flushing of the skin, ataxia, disorientation, and even major motor seizures. If the ingestion is recent, milk or water should be administered, and emesis induced with syrup of ipecac. Gastric lavage should be performed if the ingestion is recent and emesis cannot be safely induced. Symptoms may persist for hours or even days. If the symptoms or signs are severe (arrhythmia, seizures), they are treated in children with repeated doses of physostigmine 0.25 mg subcutaneously or intramuscularly every 15 minutes (34). For children under 5 years of age, 0.02 mg/kg physostigmine IV (up to 0.5 mg) every 5 minutes with a maximal dose of 2.0 mg of physostigmine is recommended (35). Both the peripheral and central effects of atropine are antagonized by physostigmine.

Dynamic Retinoscopy

A retinoscopic technique not widely appreciated or used by ophthalmologists is dynamic retinoscopy, which allows a quick assessment of the patient's ability to accommodate without the need for cumbersome laboratory equipment. The examiner begins by neutralizing the refractive error while the patient fixates the distant target. The working distance lens is then removed. The patient is asked to look at a near, accommodative target held next to the retinoscope. If the patient is able to accommodate to the near target, the examiner should see the motion of the reflex change to neutralization. Patients with high hypermetropia, retinal disease, or amblyopia often have deficient amplitudes of accommodation. When symptomatic accommodative insufficiency is noted, it should be corrected by the prescription of a near correction, which may relieve asthenopic symptoms.

Photoscreening

Photoscreening, also called photorefraction, is a term describing a screening test designed to detect amblyopiogenic factors, including strabismus, media opacities, and refractive error. These techniques involve simultaneous photography of the corneal and fundus light reflexes.

Two basic methods have been described (36,37). They differ in the relationship of the flash source to the optical axis of the camera. The coaxial method (isotropic) requires three good pictures per patient (36). One is focused at the plane of the pupil, one defocused a fixed number of diopters anteriorly, and one an equal amount posteriorly. Spheric and cylindric refractive errors can be determined within 0.75 diopter over a range of +4 to -4 diopters. Detection of strabismus is made difficult by the defocus

necessary to measure the refractive error. This system has been largely supplanted by the off-axis system.

The off-axis system (eccentric photorefraction) provides a clearly focused image of the pupil, fundus red reflex, and corneal reflex (37). Since the strobe stimulus is linear, each photograph yields information only along the axis parallel to the flash axis. In the past, two photographs with the strobe oriented at 90 degrees to each other were necessary. More recently, modifications using two simultaneous flashes have been implemented, thereby requiring only one photograph (38,39,40,41). The sensitivity of off-axis photorefraction for detection of refractive error is usually greater than 80%, and it is better with cycloplegia and pupillary dilation. This technique can detect hyperopia greater than 1.0 diopter and myopia less than 2.5 diopters. Anisometropia of 1.0 diopter is routinely detected. The actual refractive error, however, can be determined only with cycloplegia because of variable levels of accommodation present during the examination. The corneal light reflex produced by the flash has made it possible to reliably detect strabismic angles as small as 2 degrees. One commercial photorefractor was found to have 91% sensitivity and 74% specificity for abnormal ocular status when tested on a group of patients known to have ocular abnormalities (42). This strategy seems to work well with children of kindergarten age or older (43). Another off-axis screener was tested on kindergarten students without cycloplegia (44). The photoscreener failed to identify only 1.6% of refractive errors thought to be significant by the authors. An off-axis instrument with an instant film record has undergone the most thorough evaluation (45). Pupil diameters of greater than 4 mm are recommended by the manufacturer. There were 35 of 949 patients screened who had false-negative results for significant refractive errors. These children were an average age of 29 months, ranging from 6 to 59 months of age. Each of the screening devices was superb for detecting strabismus. However, significant refractive error is far more common in the population, and the ability of the instrument to detect this problem reliably remains the primary goal of photoscreening.

Photoscreening is unlikely to replace an exam in the ophthalmologist's office since the standard exam would still be available. Of more interest is the role this technology could play in the school or pediatrician setting. To date, photoscreening has yet to be shown to be superior to optotype-based methods for use in the pediatrician's office (46,47,48). The accuracy of photoscreening methods without cycloplegia appears to result in underreferral since they do not measure refractive error exactly. Effective application of this technique as a population screen will require eliminating the need for cycloplegia, dealing with the cost of testing, and obtaining skilled technicians to administer the test in a screening setting (49). An important shortcoming remains the absence of a study showing effectiveness in children under 3 years of age who cannot be tested by existing methods. Morgan and Johnson (42) could not test 24% of their patients under 3 years of age. Donahue and colleagues (49) did not diagnose strabismus, anisometropia, or astigmatism in children under 2 years of age. Further refinement of this method, as well as development of other screening strategies, will ultimately produce an effective screening tool. Recent work found fully automated refractometry without cycloplegia to be superior to photoscreening (50).

Automated Refraction

Automated objective refraction of noncyclopleged children under 15 years of age has been difficult. This is because of substantial instrument and proximal myopia that is induced by peering into the instrument. Current instruments, which are smaller in size and less threatening, are highly testable and reliable when the testing is performed with cycloplegia. Subjective refractors have largely disappeared from the market. Their utility has been limited by patient cooperation and brief attention spans.

THE ANATOMIC COMPONENTS OF REFRACTION

The refractive state of the eye is determined by four variables: corneal curvature, lenticular power, depth of the anterior chamber, and axial length of the globe. Each of these components has been exhaustively studied in an attempt to correlate a particular component to evolution of refractive error. Curtin (51) suggested that axial length is the principal determinant of refraction. During the infantile growth phase of the eye (up to 3 years of age), adjustments of corneal curvature and lens power are capable of producing an emmetropic refraction through a large range of axial lengths. During the juvenile growth period (3 to about 14 years), it appears that corneal curvature and lens power cannot continue compensating for continued axial expansion, resulting in a myopic refractive error.

Each of the components of refraction changes throughout development. Ocular anterior segment growth during infancy is extremely rapid. The newborn cornea of 10 mm attains nearly adult proportions by the end of the second year. At term birth, the mean corneal power is 55.2 diopters, decreasing during the first year of life to 45 diopters (52,53). The cornea of a premature child is generally steeper than that of a comparable child born at term. The increased corneal power seems to correlate well with the myopic trend observed in premature children (54).

The lens, unlike the remainder of the eye, continues to grow throughout life. At birth, a newborn lens is spherical, with a thickness of approximately 4 mm; it doubles in size during the first year of life. Lens power declines from 3 to 14 years of age due to progressive flattening.

The axial length of the eye undergoes two different growth stages, an infantile stage ending at age 3 and a juvenile stage ending at age 14 years. The average axial length during the infantile stage of growth increases from 18.0 to 22.8 mm (55). During the juvenile growth phase, axial length increases only 1 mm. The eye

achieves its full adult size by age 13 years. No spurt of ocular growth has been detected during puberty.

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THE EVOLUTION OF REFRACTIVE ERROR

The natural history of refractive error has been the subject of numerous investigations (51). At birth, the eye is approximately 3 diopters hypermetropic. Cross-sectional studies found that hyperopia increased until 7 years of age, and then declined (56). More recent studies have suggested that Brown's well-known work may be flawed, showing a steady decline in hyperopic refraction throughout childhood (52,55,57,58). Among children wearing spectacles, the percentage with correction for hyperopia decreases with age from 66% at 4 to 5 years to 11% at 12 to 17 years (59). The prevalence of myopic correction increases from 30% in the younger group to 87% in the older group. The prevalence of myopia in the general population of the US approaches nearly 27% at 20 years of age.

Emmetropization

Emmetropic refractive error occurs more often than might be expected if refractive error simply followed a normal distribution. This process of emmetropization is a complex interaction of elements that produces near-emmetropia in 97% of the population (+ 4 to -4 diopters). A wide body of evidence suggests that both hereditary and environmental factors influence each of the components of refraction. Studies of the effect of environment on the refraction of laboratory animals, both primate and nonprimate, as well as humans, have shown that disruption of sensory input can produce an abnormal refractive state, most often myopia (51,60,61). However, hypermetropia can be induced by image defocus in the early postnatal period (62,63). More recently it has been shown that minimal image defocus early in infant nonhuman primate eyes induces a modification in the normal growth pattern of that eye which would eliminate the induced refractive error (64). Thus, emmetropization in some limited instances may be able to compensate for induced refractive error. If this is generalizable to older human children, early correction would not be in the best interest of the child. There is speculation about the theoretical adverse effect of correcting all refractive errors. Such treatment could eliminate the normal emmetropization process. Ingram and coworkers (65) studied fully corrected hypermetropic children with refractive esotropia. They found that children treated from 6 months of age had impaired emmetropization. These results need be viewed with caution as the study was uncontrolled.

Etiology of Myopia

Most theories continue to suggest a dominant role for genetic determination of refractive error. This belief is based on twin studies, as well as genealogic studies (51). No accepted mode of inheritance has been demonstrated. It is not known if each of the refractive components is inherited independently or if the combination of components is the inherited factor.

The role of the environment in producing refractive error has been suggested by the increased frequency of myopia among patients with high intellectual achievement. This finding has been reported multiple times since Cohn's observation in 1907, confirming a strong correlation between myopia and intellectual performance (66). These studies, although suggestive, do not determine if the genetic determination of myopia is expressed because of the superior performance on academic skills (nearwork theory). It may be that the myopia causes the superior performance, or simply that the two traits are closely linked genetically.

The best conclusion available concerning the etiology of myopia is that the environment alters the penetrance and expressivity of genes, thereby producing the ultimate refractive error.

ACCOMMODATION

Accommodation is the change in dioptric power of the crystalline lens produced by the alteration of its shape in response to ciliary muscle contraction. The neural innervation to the ciliary muscle includes parasympathetic and sympathetic fibers. The parasympathetic fibers stimulate ciliary muscle contraction, while the sympathetic fibers inhibit contraction. A patient typically maintains a “resting” level of accommodation at an intermediate focus, between no accommodation and full accommodation. The position of the resting state varies in response to many factors, including systemic and topical medication use and the amount of nearwork performed.

The amplitude of accommodation decreases from a high at birth (67). During the second decade of life, the loss of accommodation is very gradual, the patient losing only about 2 diopters. Studies of accommodation in infants, using dynamic accommodation, showed that infants 2 to 10 months of age accommodate in the appropriate direction for changes in target distance, and furthermore accommodate at speeds comparable with those of adults (4.6 diopters/second) (68).

Accommodation is primarily stimulated by retinal image blur. Other factors also play important roles in the control of accommodation, including chromatic aberration, stimulus size, target contrast, and target velocity. Accommodation in normal eyes has the highest gain at the fovea (69). Response amplitude decreases as more eccentric retinal areas are stimulated. This is particularly relevant in the amblyopic eye, in which the amblyopic foveal retinal receptors are less efficient at stimulating accommodation, producing reduced accommodative amplitudes in amblyopic eyes (70). Abnormalities persist in formerly amblyopic eyes (71,72). These investigators hypothesized that the unaffected peripheral retina, rather than the amblyopic fovea, was controlling the accommodative response. This resulted in an insufficient response.

Accommodation has also been found to be deficient in children with impaired vision and Down syndrome, as well as in children suffering damage to the ciliary muscle or ciliary ganglion (73,74). Bifocals should be considered for children with these medical conditions.

MANAGEMENT OF REFRACTIVE ERROR

Once the refractionist has determined the refractive error, with and without cycloplegia, a management decision must

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be made. Impact-resistant polycarbonate lenses should be prescribed. This material meets most industrial standards and is lightweight. Its drawbacks are that it scratches easily and currently costs more than other materials.

Glasses are generally worn full-time in school. This facilitates compliance and allows consistency on the part of the patient's teacher. Bifocals are most often prescribed for patients with an esotropia for control of a high accommodative-convergence-to-accommodation ratio and are worn full-time. Bifocals are indicated only if they provide the patient with the opportunity for fusion; bifocals are not usually employed if they only reduce the strabismic angle to an angle still too large for fusion (greater than 10 prism diopters). This matter is discussed in Chapter 7. It is standard practice to prescribe 30 mm to 35 mm flat-top-style bifocal lenses, positioned to bisect the pupil. Less commonly, children wear bifocals because of aphakia, premature presbyopia from an ocular injury, or tonic pupil.

Hyperopia is the normal refractive state of the eye in childhood. Hyperopic refractive error may be divided into manifest and latent portions. The latent portion of the hyperopic refractive error is corrected by the patient's tonic accommodation and is not detected during manifest refraction. The latent portion of the hyperopia is uncovered only with a cycloplegic refraction.

Manifest hyperopia is that portion of the hyperopia detected or found in the “dry” or noncycloplegic portion of the refraction. It may be subdivided into facultative and absolute portions. Facultative hyperopia is the portion that the patient can correct with extreme accommodative effort; such effort often causes asthenopia. Absolute hyperopia represents the portion for which the patient cannot compensate with maximal available accommodative effort, and presents with decreased vision.

Myopia is rare in infants except in those who develop retinopathy of prematurity or who have had severe visual deprivation (61). By late adolescence, nearly 27% of the population is myopic. Most have developed simple school-age or physiologic myopia. The only symptom is decreased vision at distance, often asymptomatic. Rarely, protracted squinting may cause asthenopic symptoms that bring the myopic patient to medical attention. Most, however, are detected by routine annual vision tests performed under the school system or by the primary care physician. This type of school-age-onset myopia tends to increase gradually

until the child stops growing.

A less common type of myopia presents with poor vision in the first several years of life. This congenital or infantile myopia is generally of large magnitude, 5 diopters and greater, and tends to remain stable throughout life. When this type of myopia is unilateral, it generally leads to amblyopia.

Many therapeutic regimens for relief of myopia have been suggested to prevent or retard the progression of school-age myopia. Since nearwork has long been considered the etiologic factor in production of myopia, these regimens typically have been aimed at blocking accommodation. These include long-term atropinization (75,76), the use of bifocals at near ranges, and removing myopic spectacles for nearwork. Excessive accommodation, according to the nearwork theory of myopia, produces increased refraction power of the anterior segment. This controversial theory remains unproved. A recently completed doublemasked randomized clinical trial compared the rate of myopic progression between groups treated with progressive add bifocals or single-vision lenses (77). These authors evaluated 469 children ages 6 to 11 years. The mean 3-year increases in myopia were -1.28 diopters with the bifocals compared with -1.48 diopters with single-vision myopic spectacles. This difference was statistically significant, but the small magnitude led the authors to conclude that a change in clinical practice to the use of bifocals was not warranted. A new agent, pirenzapine, has been identified and is undergoing clinical trials.

The third type of refractive error is astigmatism, which may be corneal or lenticular. It is important to correct astigmatism to avoid refractive or meridional amblyopia, a form of deprivation amblyopia, especially when the axis is oriented 15 or more degrees away from the vertical or horizontal (48). Although amblyopia usually occurs with large astigmatic errors, even 1.5 to 2 diopters may produce it. The full astigmatic correction oriented at the correct axis is prescribed (78). Irregular astigmatism produced by corneal scarring, keratoconus, or other corneal disease is best corrected with a rigid gas-permeable contact lens.

The last major concern in prescribing correction is anisometropia, for which careful attention must be paid to the visual acuity. Anisometropia of 1.0 diopter can produce anisometropic amblyopia in hyperopic patients (79). Myopic patients are more resistant to the development of amblyopia. Any spectacle corrections should take anisometropia into account. If considerable anisometropia is present, the monofixation syndrome may be found. When anisometropia is corrected by spectacles, it is usually well tolerated by children, whereas it would produce symptomatic aniseikonia in adults.

Guidelines

The following guidelines for the correction of refractive error in children should be modified to fit the needs of the individual patient. Usually such a correction will be worn happily by the child, at least part of the time. However, if glasses are not worn electively by the child, an error has been made somewhere. The error may be in the determination of the refractive state of the eye, but more likely is an error in judgment regarding the visual demands of the child.

Many children are perfectly content with some distance blur from uncorrected low myopia because so much of interest to them is close. Relatively low myopic corrections should be prescribed to be worn for school but may be optional at other times.

The blur from astigmatic errors is present at all distances, unlike the distance blur from uncorrected myopia. Astigmatic errors of more than 2 diopters should be corrected at least part-time to prevent the development of amblyopia. Oblique astigmatic errors of as little as 1 diopter may require correction because of symptoms or the presence of amblyopia. In the presence of hyperopia or myopia of sufficient magnitude to warrant correction, the astigmatism should be fully corrected.

The correction of hyperopic refractive error is dependent on the patient's demonstrated ability to accommodate and the presence of a strabismus. Children have very large amplitudes of accommodation, but they often experience asthenopic symptoms from extended periods of accommodation. Thus, it is not surprising that relatively low-power hyperopic corrections are frequently preferred for extended nearwork, even though the large amplitude of accommodation by the near-point method would suggest otherwise. In the absence of esotropia, children would be content to wear, at least some of the time, glasses to correct the hyperopia detected with cycloplegia reduced by about 2 diopters.

APHAKIA

Contact Lens

The most common method of correcting monocular aphakia in children uses an extended-wear contact lens. A silicon extended-wear lens is often used, which is available in a wide range of powers (up to + 36.0 diopters), base curves (7.3, 7.5, 7.7, 7.9, 8.1, 8.3), and diameter (11.3, 12.5 mm). High plus lenses (more than 20 diopters) are available only in a single 11.3-mm diameter and three base curves: 7.5, 7.7, 7.9. Most aphakic children can be suitably corrected with these lenses (80). Rigid gas-permeable lenses are a less costly alternative. Materials that allow extended wear are available, and gas-permeable lenses can be manufactured for especially steep base curves and high powers not available in the silicon extended-wear lenses. An infant contact lens should be adjusted to overcorrect the hypermetropia by approximately 2 diopters. For a toddler, the contact lens correction should be nearly emmetropic for distance or overcorrected by only 1 diopter. This patient should have bifocal spectacles prescribed when near tasks begin. Spectacles will also serve as protection for both eyes.

Epikeratophakia

Epikeratophakia is now largely of historic note as an alternative means of correcting aphakic or other large refractive errors in children (81,92). The correction attained with epikeratophakia in infants has been too variable for this technique to be widely used in the management of infantile aphakia. This approach has largely been abandoned in favor of intraocular lens implantation.

Intraocular Lens

The use of intraocular lens (IOL) implants for aphakia in childhood has become widely accepted for visual rehabilitation in older children and increasingly in infancy (83,84). These lenses are not designed to be interchanged and thus cannot keep pace with the myopic shift of the growing eye. In general, a small IOL implant with an optic diameter of 5.0 to 5.5 mm designed for capsular bag fixation is implanted (85,86). These lenses have been quite successful in the posttraumatic setting (87). The frequency of visual rehabilitation has been remarkable with the use of implants. The management of the posterior capsule should be planned in advance of the IOL implant surgery, as nearly every capsule opacifies quickly. Primary posterior capsulectomy and anterior vitrectomy is generally advocated for most children less than 5 years of age. The lens selected should be implanted with powers predicted to produce hypermetropia. The amount of hypermetropia recommended generally varies from 4 to 5 diopters at age 2 years to 2 diopters at age 6 years. In the hypermetropic or short eye, the SRK/T, SRK II, or Holladay formulae are preferred (88). The minimum age for implantation in normal children has continued to decline as more experience has been gained (84,89). Bilateral implantation is routinely considered for children 3 years of age and older, and monocular implants are offered after the first year of life or whenever contact lens use will not be easily achieved. The most frequently used implants are acrylic and often foldable.

LOW VISION

Children represent a small fraction of patients with low vision (90). The most prevalent causes of visual loss have been congenital cataract, optic atrophy, and albinism. Some experts believe that the impact of congenital cataract is waning, while that of retinopathy of prematurity is just beginning to be felt.

The physician examining children with impaired vision must perform the routine evaluation, as well as assessments of visual field, ambulatory ability, classroom function, and ability to perform other daily activities.

High refractive errors should be corrected. The use of special aids for infants and toddlers is rarely necessary. Early intervention programs for the visually disabled are generally available, and parents should be encouraged to make contact from the time the diagnosis is made. These are generally administered by the local school district. The intention of these programs is to minimize or eliminate any retarding effect on intellectual development that might be caused by subnormal

vision.

The print used in books intended for the first three grades is 18-point type (2M), 14- to 16-point type (1.6M) for the fourth grade, and 10- to 12-point type (1M) through high school. Because of a child's high accommodative reserve, the patient with subnormal vision can often gain adequate magnification simply by holding the object close to the eye and accommodating. The use of a hand magnifying lens can help with the occasional need for greater magnification. By having the child bring actual school work to the office or low-vision clinic, an assessment can be made of visual function.

Once approach methods are no longer successful, due to inadequate accommodative capacity, inadequate magnification, need to view distance targets, or the child's selfconsciousness, low-vision aids are necessary. These are identical to those available for adults. Spectacles are the first choice for constant use, providing good magnification and ample visual field, but greatly restricting the working distance of the patient. Closed-circuit television (up to

60×), stand magnifiers, and computer-generated electronic image magnification and/or enhancement are some of the other aids employed. For distant and intermediatedistance tasks, telescopes are necessary. These may be helpful not just for watching sports or catching a bus, but for viewing a computer screen or reading music.

The visually impaired child is most often educated today within the regular school system, rather than in the residential blind school system. Support for the classroom teacher comes from a specialist in education of the visually impaired, who will provide training and materials for the teacher. The physician should strive to keep the teachers apprised of prognosis, along with important facts about the examination. For example, a patient with a right homonymous hemianopia should be seated on the right side of the classroom so that most of the classroom is within the intact field.

For a complete review of the management of low vision, the reader is encouraged to consult several fine texts (91,92).

REFERENCES

1. Teller DY, Movshon JA. Visual development. *Vision Res* 1986;26:1483-1506.

2. Gorman JJ, Cogan DG, Gellis SS. An apparatus for grading the visual acuity of infants on the basis of opticokinetic nystagmus. *Pediatrics* 1957;19:1088-1092.

3. Friendly DS. Preschool visual acuity screening tests. *Trans Am Acad Ophthalmol* 1980;76:383-480.

4. Hoyt CS, Nickel BL, Billson FA. Ophthalmological examination of the infant. Developmental aspects. *Surv Ophthalmol* 1982;26:177-189.

5. Zipf RF. Binocular fixation pattern. *Arch Ophthalmol* 1979;94:401-405.

6. Atilla H, Oral D, Coskun S, et al. Poor correlation between “fix-follow-maintain” monocular/binocular fixation pattern evaluation and presence of functional amblyopia. *Binocul Vis Strabismus Q* 2001;16:85-90.

7. Teller DY. The forced choice preferential looking procedure: a psychophysical technique for use with human infants. *Infant Behav Dev* 1979;2:135-153.

8. Mayer DL, Dobson V. Visual acuity development in infants and young children, as assessed by operant preferential looking. *Vision Res* 1982;22:1141-1151.

9. McDonald MA, Dobson V, Sebris SL, et al. The acuity card procedure: a rapid test of infant acuity. *Invest Ophthalmol Vis Sci* 1985;26:1158-1162.

10. Preston KL, McDonald M, Sebris SL, et al. Validation of the acuity card procedure for assessment of infants with ocular disorders. *Ophthalmology* 1987;94:644-653.

11. McDonald MA, Sebris SL, Mohn G, et al. Monocular acuity in normal infants: the acuity card procedure. *Am J Opt Physiol Opt* 1986;63:127-134.

12. McDonald MA, Ankrum C, Preston K, et al. Monocular and binocular acuity estimation in 18- to 36-month-olds: acuity card results. *Am J Opt Physiol Opt* 1986;63:181-186.

13. Mayer DL. Acuity of amblyopic children for small field gratings and recognition stimuli. *Invest Ophthalmol Vis Sci* 1986;27:1148-1153.

14. Lithander J. Two techniques to evaluate visual acuity from the age of 18 months. *Strabismus* 1996;4:15-23.

15. Simons K. Acuity norms in young children. *Surv Ophthalmol* 1983;28:84-92.

16. McDonald MA. Assessment of visual acuity in toddlers. *Surv Ophthalmol* 1986;31:189-210.

17. Stager DR, Everett ME, Birch EE. Comparison of crowding bar and linear optotype acuity in amblyopia. *Am Orthoptic J* 1990;40:51-56.

18. Hyvärinen L, Nasanen R, Laurinen P. New visual acuity test for preschool children. *Acta Ophthalmol* 1980;58:507-511.

19. Holmes JM, Beck RW, Repka MX, et al. The amblyopia treatment study visual acuity testing protocol. *Arch Ophthalmol* 2001;119:1345-1353.

20. Moke PS, Turpin AH, Beck RW, et al. Computerized method of visual acuity testing: adaptation of the amblyopia treatment study visual acuity testing protocol. *Am J Ophthalmol* 2001;132:903-909.

21. Vision in Preschoolers (VIP) Study Group. Threshold visual acuity testing of preschool children using the crowded HOTV and Lea symbols acuity tests. *J AAPOS* 2003;7:396-399.

22. Becker R. Examination of young children with Lea symbols. *Br J Ophthalmol* 2002;86:513-516.

23. Sloan LL. New test charts for the measurement of visual acuity at far and near distances. *Am J Ophthalmol* 1959;48:807-813.

24. Early Treatment Diabetic Retinopathy Study Research Group. Early treatment diabetic retinopathy study design and baseline patient characteristics. ETDRS report number 7. *Ophthalmology* 1991;98:741-756.

25. National Academy of Science-National Research Council Committee on Vision. Report of working group 39: recommended standard procedures for the clinical measurement and specification of visual acuity. *Adv Ophthalmol* 1980;41:103-148.

26. Copeland JC. *A simplified method of streak retinoscopy*. Chicago: Optec, Inc., 1936.

27. Corboy JM. *The retinoscopy book: a manual for beginners*. Thorofare, NJ: Slack, Inc., 1979.

28. Guyton DL. *Retinoscopy: plus cylinder technique*. San Francisco: American Academy of Ophthalmology, 1986.

29. Guyton DL. *Retinoscopy: minus cylinder technique*. San Francisco: American Academy of Ophthalmology, 1986.

30. Guyton DL. *Subjective refraction: cross cylinder technique*. San Francisco: American Academy of Ophthalmology, 1987.

31. Apt L, Henrick A. Pupillary dilatation with single eyedrop mydriatic combinations. *Am J Ophthalmol* 1980;89:553-559.

32. Rosenbaum AL, Bateman JB, Bremer DL, et al. Cycloplegic refraction in esotropic children. *Ophthalmology* 1981;88:1031-1034.

33. Parks MM. Discussion of Raab EL: Hypermetropia in accommodative esodeviation. *J Pediatr Ophthalmol Strabismus* 1984;21:197-198.

34. Havener WH. *Ocular pharmacology*, 5th ed. St. Louis: CV Mosby, 1983:387-389.

35. Gunn VL, Nechyba C, Barone MA. *The Harriet Lane handbook: a manual for pediatric house officers*, 16th ed. Philadelphia: CV Mosby, 2002.

36. Howland HC, Howland B. Photorefraction: a technique for study of refractive state at a distance. *J Opt Soc Am* 1974;64:240-249.

37. Kaakinen K. A simple method for screening of children with strabismus, anisometropia, or ametropia by simultaneous photography of the corneal and the fundus reflexes. *Acta Ophthalmol* 1979;57:161-171.

38. Day SH, Norcia AM. Photographic detection of amblyogenic factors. *Ophthalmology* 1986;93:25-28.

39. Norcia AM, Zadnik K, Day SH. Photorefraction with a catadioptric lens. *Acta Ophthalmol* 1986;64:379-385.

40. Kaakinen K, Ranta-Kemppainen L. Screening of infants for strabismus and refractive errors with two-flash photorefraction with and without cycloplegia. *Acta Ophthalmol* 1986;64:578-582.

41. Kaakinen KA, Kaseua HO, Teir HH. Two-flash photorefraction in screening of amblyogenic refractive errors. *Ophthalmology* 1987;94:1036-1042.

42. Morgan KS, Johnson WD. Clinical evaluation of a commercial photorefractor. *Arch Ophthalmol* 1987;105:1528-1531.

43. Morgan KS, Kennemer JC. Off-axis photorefractive eye screening in children. *J Cataract Refract Surg* 1997;23:423-428.

44. Kennedy R, Schepps SB, Bagaric D. Field trial of the Otago photoscreener. *Can J Ophthalmol* 1995;30:193-197.

45. Ottar WL, Scott WE, Holgado SI. Photoscreening for amblyogenic factors. *J Pediatr Ophthalmol Strabismus* 1994;32:289-295.

46. American Academy of Pediatrics. Committee on Practice and Ambulatory Medicine and Section on Ophthalmology. Use of photoscreening for children's vision screening. *Pediatrics* 2002;109:524-525.

47. Wright MC, Colville DJ, Oberklaid F. Is community screening for amblyopia possible, or appropriate? *Arch Dis Child* 1995;73:192-195.

48. American Academy of Ophthalmology. *Pediatric eye evaluations. Preferred practice pattern*. San Francisco: American Academy of Ophthalmology,

2002.

49. Donahue SP, Johnson TM. Age-based refinement of referral criteria for photoscreening. *Ophthalmology* 2001;108:2309-2314.

50. Miller JM, Dobson V, Harvey EM, et al. Comparison of preschool vision screening methods in a population with a high prevalence of astigmatism. *Invest Ophthalmol Vis Sci* 2001;42:917-924.

51. Curtin BJ. The etiology of myopia. In: Curtin BJ, ed. *The myopias: basic science and clinical management*. Philadelphia: Harper & Row, 1985:113-124.

52. Grignolo A, Rivara A. Biometry of the eye from the sixth month of pregnancy to the tenth year of life. *Acta Facult Med Brun* 1968;35:251-257.

53. Grignolo A, Rivara A. [Biometric observations on the eyes of infants born at full term and of premature infants during their first year.] *Ann Ocul (Paris)* 1968;201:817-826.

54. Cook A, White S, Batterbury M, et al. Ocular growth and refractive error development in premature infants without retinopathy of prematurity. *Invest Ophthalmol Vis Sci* 2003;44:953-960.

55. Sorsby A, Benjamin B, Sheridan M, et al. Refraction and its components during the growth of the eye from the age of three. *Med Res Counc Annu Rep* 1961;301:1-67.

56. Brown EVL. Net average yearly changes in refraction of atropinized eyes from birth to beyond middle life. *Arch Ophthalmol* 1939;19:719-734.

57. Hirsch MJ. Refraction of children. *Am J Optom Arch Am Acad Optom* 1964;41:395-399.

58. Larsen JS. The sagittal growth of the eye. I. Ultrasonic measurement of the anterior chamber from birth to puberty. *Acta Ophthalmol (Copenh)* 1971;49:239-262.

59. National Center for Health Statistics. Refraction status and motility defects of persons 4-74 years, U. S. 1971-72. Hyattsville, Md: U.S. Department of Health, Education and Welfare, 1978.

60. Yinon URI. Myopia induction in animals following alteration of the visual input during development: a review. *Curr Eye Res* 1984;3:677-690.

61. Hoyt CS, Stone RD, Fromer C, et al. Monocular axial myopia associated with neonatal eyelid closure in human infants. *Am J Ophthalmol* 1981;91:197-200.

62. Kruther SG, Nathan J, Kiely PM, et al. The effect of defocusing contact lenses on refraction in cynomolgus monkeys. *Clin Vision Sci* 1988;3:221-228.

63. Smith EL III, Hung L, Harwerth RS. Effects of optically induced blur on the refractive status of young monkeys. *Vision Res* 1994;34:290-293.

64. Hung FL, Crawford MLJ, Smith EL. Spectacle lenses alter eye growth and the refractive status of young monkeys. *Nat Med* 1995;1:761-765.

65. Ingram RM, Arnold PE, Dally S, et al. Emmetropisation, squint, and reduced visual acuity after treatment. *Br J Ophthalmol* 1991;75:414-416.

66. Rosner M, Belkin M. Intelligence, education, and myopia in males. *Arch Ophthalmol* 1987;105:1508-1511.

67. Duane A. Studies in monocular and binocular accommodation with their clinical applications. *Am J Ophthalmol* 1922;5:865-877.

68. Howland HC, Dobson V, Sayles N. Accommodation in infants measured by photorefraction. *Vision Res* 1987;27:2141-2152.

69. Phillips SR. *Ocular neurological control systems: accommodation in the nearest mons triad* [dissertation]. Berkeley: University of California, 1974.

70. Urist MJ. Primary and secondary deviation in comitant squint. *Am J Ophthalmol* 1959;48:647-656.

71. Abraham SV. Accommodation in the amblyopic eye. *Am J Ophthalmol* 1961;52:197-200.

72. Otto J, Graemiger A. [On inexact accommodation of amblyopic eyes with eccentric fixation.] *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1967;173:125-140.

73. Lindstedt E. Failing accommodation in cases of Down's syndrome. A preliminary report. *Ophthalmol Paediatr Genet* 1983;3:191-192.

74. Lindstedt E. Accommodation in the visually impaired child. In: Woo GC, ed. *Low vision. Principles and applications*. New York: Springer-Verlag, 1986:424-435.

75. Swann AP, Hunter CD. A survey of amblyopia treated by atropine occlusion. *Br Orthopt J* 1974;31:65-69.

76. Brodstein RS, Brodstein DE, Olson RJ, et al. The treatment of myopia with atropine and bifocals: A long-term prospective study. *Ophthalmology* 1984;91:1373-1379.

77. Gwiazda J, Hyman L, Hussein M, et al. A randomized clinical trial of progressive addition lens versus single vision lens on the progression of myopia in children. *Invest Ophthalmol Vis Sci* 2003;44:1492-1500.

78. Guyton DL. Prescribing cylinders: the problem of distortion. *Surv Ophthalmol* 1977;22:177-188.

79. Ingram RM. Refraction as a basis for screening children for squint and amblyopia. *Br J Ophthalmol* 1977;61:8-15.

80. Levin AV, Edmonds SA, Nelson LB, et al. Extended wear contact lenses for the treatment of pediatric aphakia. *Ophthalmology* 1987; 94(Suppl):68-69.

81. Arffa RC, Mavelli TL, Morgan KS. Long-term follow-up of refractive and keratometric results of pediatric epikeratophakia. *Arch Ophthalmol* 1986;104:668-670.

82. Morgan KS, Stephenson GS, McDonald MB, et al. Epikeratophakia in children. *Ophthalmology* 1984;91:780-784.

83. Wilson ME. Intraocular lens implantation: has it become the standard of care for children? *Ophthalmology* 1996;103:1719-1720.

84. Lambert SR, Lynn M, Drews-Botsch C, et al. Intraocular lens implantation during infancy: perceptions of parents and the American Association of Pediatric Ophthalmology and Strabismus members. *J AAPOS* 2003;7:400-405.

85. Brady KM, Atkinson CS, Kiltey L, et al. Cataract surgery and intraocular lens implantation in children. *Am J Ophthalmol* 1995;119:1-9.

86. Crouch ERJ, Pressman SH, Crouch ER. Posterior chamber intraocular lenses: long-term results in pediatric cataract patients. *J Pediatr Ophthalmol Strabismus* 1995;32:210-218.

87. Koenig SB, Ruttum MS, Lewandowski ME, et al. Pseudophakia for traumatic cataracts in children. *Ophthalmology* 1993;100: 1218-1224.

88. Sanders DR, Retzlaff JA, Kraff MC, et al. Comparison of the SRK/T formula and other theoretical and regression formulas. *J Cataract Refract Surg* 1990;16:341-346.

89. Rosenbaum AL, Masket S. Intraocular lens implantation in children. *Am J Ophthalmol* 1995;120:105-107.

90. Hill AR, Cameron A. Pathology characteristics and optical correction of 900 low vision patients. In: Woo GC, ed. *Low vision. Principles and applications*. New York: Springer-Verlag, 1986:362-385.

91. Woo GC, ed. *Low vision. Principles and applications*. New York: Springer-Verlag, 1986.

92. Faye EE. *Clinical low vision*, 2nd ed. Boston: Little, Brown & Co., 1984.

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7

Amblyopia

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The term “amblyopia,” derived from Greek, literally means “dullness of vision.” von Noorden defined amblyopia as a “decrease of visual acuity in one eye when caused by abnormal binocular interaction or occurring in one or both eyes as a result of patterned vision deprivation during immaturity, for which no cause can be detected during the physical examination of the eye(s) at which in appropriate cases is reversible by therapeutic measures” (1).

Amblyopia is a functional reduction in the visual acuity of an eye caused by “disuse” or “misuse” during the critical period of visual development. Ophthalmologic examination of the eye typically reveals no organic abnormality. The mechanism of vision loss is not exactly known, but it is thought to originate in the visual cortex. Amblyopia results in reduced visual acuity, binocularity and depth perception, and contrast sensitivity. Fusion and stereopsis, the central formation of a three-dimensional image from the images perceived by each eye, are dependent upon receiving clear images from each eye simultaneously (2).

VISUAL DEVELOPMENT

At birth, the visual system is immature and visual acuity is estimated to be approximately 20/400 (3). Visual acuity improves and stereopsis develops during the first months of life. The retina, optic nerves, and visual cortex begin their maturation during the first weeks of life. Myelination of the optic nerves, development of the visual cortex, and growth of the lateral geniculate body occur during the first two years (3). The fovea, the most visually sensitive part of the retina, reaches maturity at approximately 4 years of age. Visual stimuli are critical to the development of normal vision. Development of the visual pathways in the central nervous system requires that the brain receives equally clear, focused images from both eyes (4). Any process that significantly interferes with or inhibits development of the visual pathways in the brain may result in amblyopia (2).

The period of visual maturation is a critical period during which the visual system is affected by outside influences. Most of the maturation of the visual system is thought to occur during the first 3 years of life, although some plasticity remains between 3 and 8 years of age, or perhaps even longer to some degree. One author describes three critical periods in the development of visual acuity and amblyopia (5):

The period of development of visual acuity (from birth to 3 to 5 years of age)

The period during which deprivation may cause amblyopia (from a few months to 7 or 8 years of age)

The period during which recovery from amblyopia can be obtained (from the time of deprivation to adolescence or possibly young adulthood)

Epidemiologic, Social, and Psychosocial Factors

The prevalence of amblyopia in the United States is estimated to be between 1% and 3% (6,7,8). Using a conservative prevalence estimate of 2%, there are approximately 5.9 million people with amblyopia presently living in the United States. Prevalence rates for amblyopia are higher in developing countries (9). The National Eye Institute has reported that amblyopia is the most common cause of unilateral visual loss in patients under the age of 70 years (10). Estimates of prevalence, however, are affected by the definition of reduced visual acuity and by the process of early screening and treatment in the population being studied (6,11,12,13). Prevalence is not affected by gender (14). In some series, the left eye was more commonly affected than the right, particularly in cases of anisometropic amblyopia (14). A recent population-based study evaluated 3,654 people age 49 and older in an area around Sydney, Australia. Amblyopia was diagnosed in 3.2% of this population, using a visual acuity criterion of 20/40 or less and 2.9% using a visual acuity criterion of 20/30 or less (15).

The mean age at presentation of amblyopia varies depending on its cause (14,16). In a series of 961 children with amblyopia, the mean ages at presentation for anisometropic, strabismic, and mixed amblyopia were 5.6, 3.3, and 4.4 years, respectively (14). The upper age limit for the development of amblyopia in children who are exposed to

an amblyopia-inducing condition (e.g., traumatic cataract) has been reported to be between 6 to 10 years (17,18). Individuals with amblyopia are at increased risk for loss of vision and blindness in the nonamblyopic eye (19,20). In one population-based study of 370 individuals with unilateral amblyopia, the projected lifetime risk of vision loss in the fellow eye was 1.2% (95% percent CI 1.1 to 1.4) (19). In 16% of patients, vision loss in the nonamblyopic eye was due to orbital or ocular trauma.

Detection and treatment of amblyopia is important for a variety of reasons. Affected patients may have reduced vocational and socioeconomic opportunities because normal vision in both eyes is required for many jobs (21). This may be even more critical now, in the computer age, when the inability to adequately function because of reduced stereopsis and/or reduced visual acuity is becoming increasingly important.

The psychosocial implications of amblyopia are tremendous. Significant psychosocial stress related to amblyopia therapy has been reported by amblyopic children and the families of amblyopic children during the treatment period (22). Even adults with a history of amblyopia treatment in childhood continue to have psychosocial difficulties related to the previous amblyopia therapy that can adversely affect self-image, work, education, and friendships (21).

Amblyopia treatment has been reported to be economically sound. In a recent study, Membreno and coworkers (23) utilized the concepts of time trade-off and money trade-off to compare amblyopia therapy with treatment of other medical conditions. Time trade-off involves patients reporting how many years of their remaining life expectancy would they be willing to give up to treat a given problem, while the money trade-off approach involves patients reporting how many months of their present income they would be willing to spend to cure a particular problem. These measures allow comparison of treatment of a diverse range of medical conditions against each other. These authors reported on the incremental cost effectiveness of therapy for amblyopia and calculated a savings of $2,281 per quality-adjusted life year with amblyopia treatment. They concluded that when compared to healthcare interventions for other medical conditions, amblyopia care is highly cost effective.

CLASSIFICATION OF AMBLYOPIA

Amblyopia is often defined as a difference in visual acuity of two lines or more (Snellen or equivalent) in a child with an otherwise healthy visual system. In reality, amblyopia may be present any time visual acuity is reduced, and the reduction of acuity cannot be explained by findings on clinical examination, even if the difference is one line or less.

A distinction must be made between *functional* (potentially reversible) *amblyopia* and *organic* (irreversible) *amblyopia*. Organic amblyopia is a term used to describe visual impairment due to obvious or nonobvious ocular pathology, commonly involving the retina or optic nerve. Examples include optic nerve hypoplasia,

optic atrophy, and foveal hypoplasia. Organic amblyopia is not the focus of this chapter. Functional amblyopia can occur concurrent with organic amblyopia and will be discussed later in this chapter. Functional amblyopia occurs in an eye that is anatomically normal.

Amblyopia is most commonly characterized by clinical associations which initiate the problem. Amblyopia can likewise be classified based upon the causal mechanism. Familiarity with both methods of classification is important for clinicians and can be useful in designing and implementing appropriate treatment strategies.

Clinical Classification

Strabismic Amblyopia

Strabismic amblyopia is one of the most common forms of amblyopia. It results from abnormal binocular interaction that occurs when the visual axes of the two eyes are misaligned. This abnormal interaction causes the foveae of the two eyes to be presented with different images. Diplopia and visual confusion result (Fig. 7.1). Visual confusion (simultaneous perception of the two different images from the foveas) stimulates active inhibition of the retinostriate pathways of visual input originating in the fovea of the deviating eye. The visual cortex suppresses the image from the deviating eye; long-term suppression during the sensitive period of visual development can result in amblyopia.

Any type of strabismus can be associated with amblyopia. As many as 17% to 40% of children with congenital esotropia develop amblyopia (24,25). Even intermittent exotropia, often erroneously thought to be associated with amblyopia only infrequently, has been associated with amblyopia. Paresis and palsy of cranial nerves 3, 4, or 6 may or may not be associated with amblyopia, depending upon severity of the defect and the child's ability to maintain fusion by adopting an anomalous head posture. Amblyopia

is unusual in congenital trochlear nerve paresis, for example, because affected children usually adopt an anomalous head tilt contralateral to the side of the affected muscle, thus providing protection against amblyopia. Amblyopia is so uncommon in congenital trochlear nerve palsy that its presence is highly suggestive of a missing or anomalous superior oblique tendon (26).

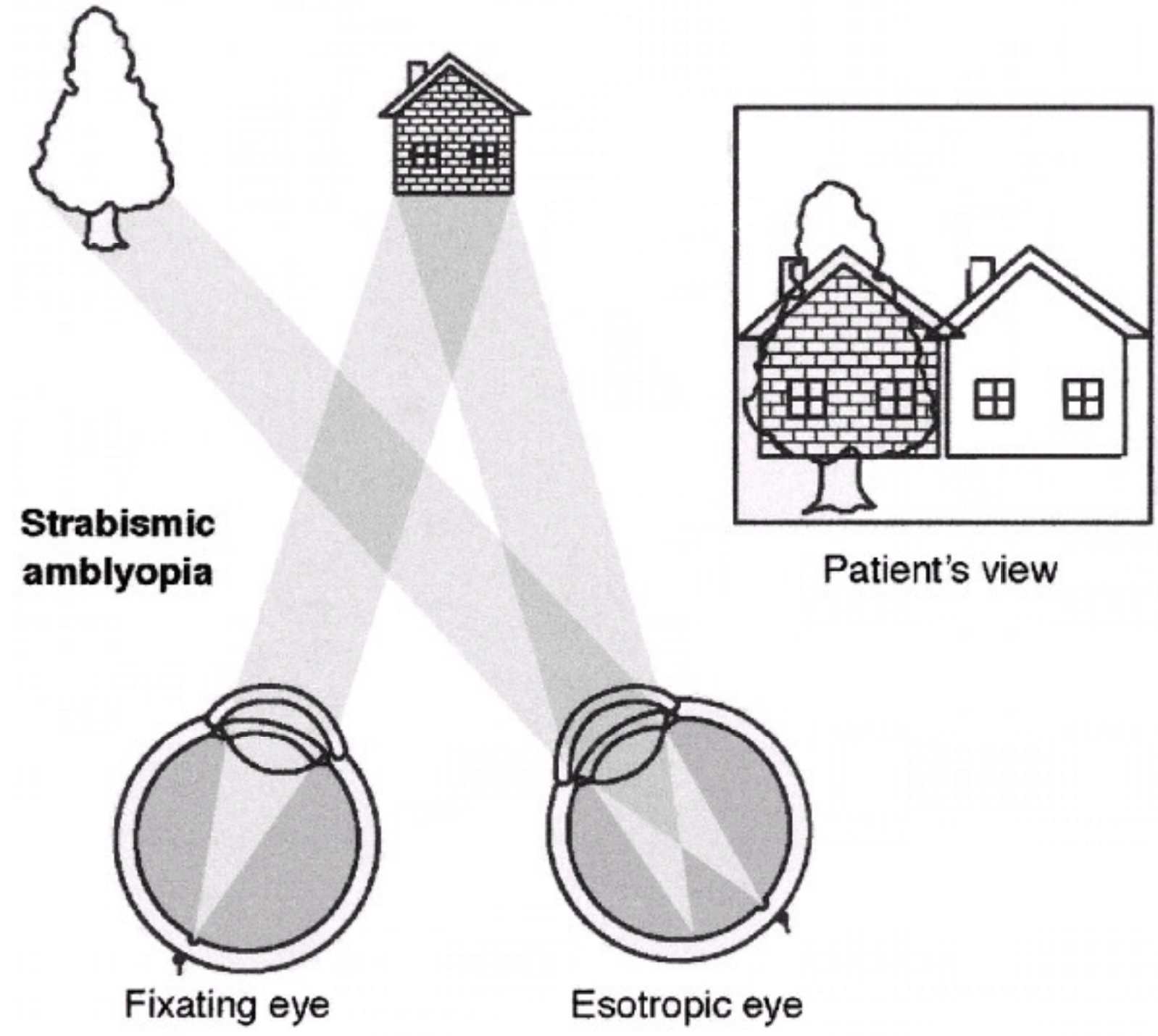

Figure 7.1 Abnormal binocular interaction causes diplopia and visual confusion.

Surgery to correct the strabismus is ineffective in the treatment of associated strabismic amblyopia. Strabismus surgery is generally deferred until the amblyopia has been maximally treated, though the success rate of surgery for esotropia has been reported to be unaltered by the presence of mild residual amblyopia (27).

Anisometropic Amblyopia

Anisometropia is another common cause of amblyopia. Anisometropic amblyopia occurs in hyperopic, myopic, or astigmatic children. As a general rule, anisometropic amblyopia occurs more frequently and to a worse degree in children with anisohyperopia (27,28). This occurs because the fovea of the more ametropic eye in a child with anisohyperopia never receives a clearly focused image when viewing binocularly. In mild to moderate anisomyopia, the more myopic

eye can be used for near work and the less myopic eye can be used for distance work, providing an important measure of protection against development of amblyopia. Weakley (29) studied refractive errors likely to produce amblyopia. He noted that anisohyperopia as small as 1.0 diopters, anisomyopia as small as 2 diopters, and anisoastigmatism as small as 1.5 diopters was sufficient to produce amblyopia. While there is significant latitude to decide when and how to treat an individual patient with anisometropia, these are excellent guidelines.

In contrast to the other types of amblyopia, anisometropic amblyopia may not be detected until the child is old enough to undergo vision screening performed by a pediatrician or school system. The typical child with anisometropic amblyopia lacks obvious external abnormalities of the eyes (e.g., cataracts, strabismus), and visual function appears normal because the child sees well with the fellow eye.

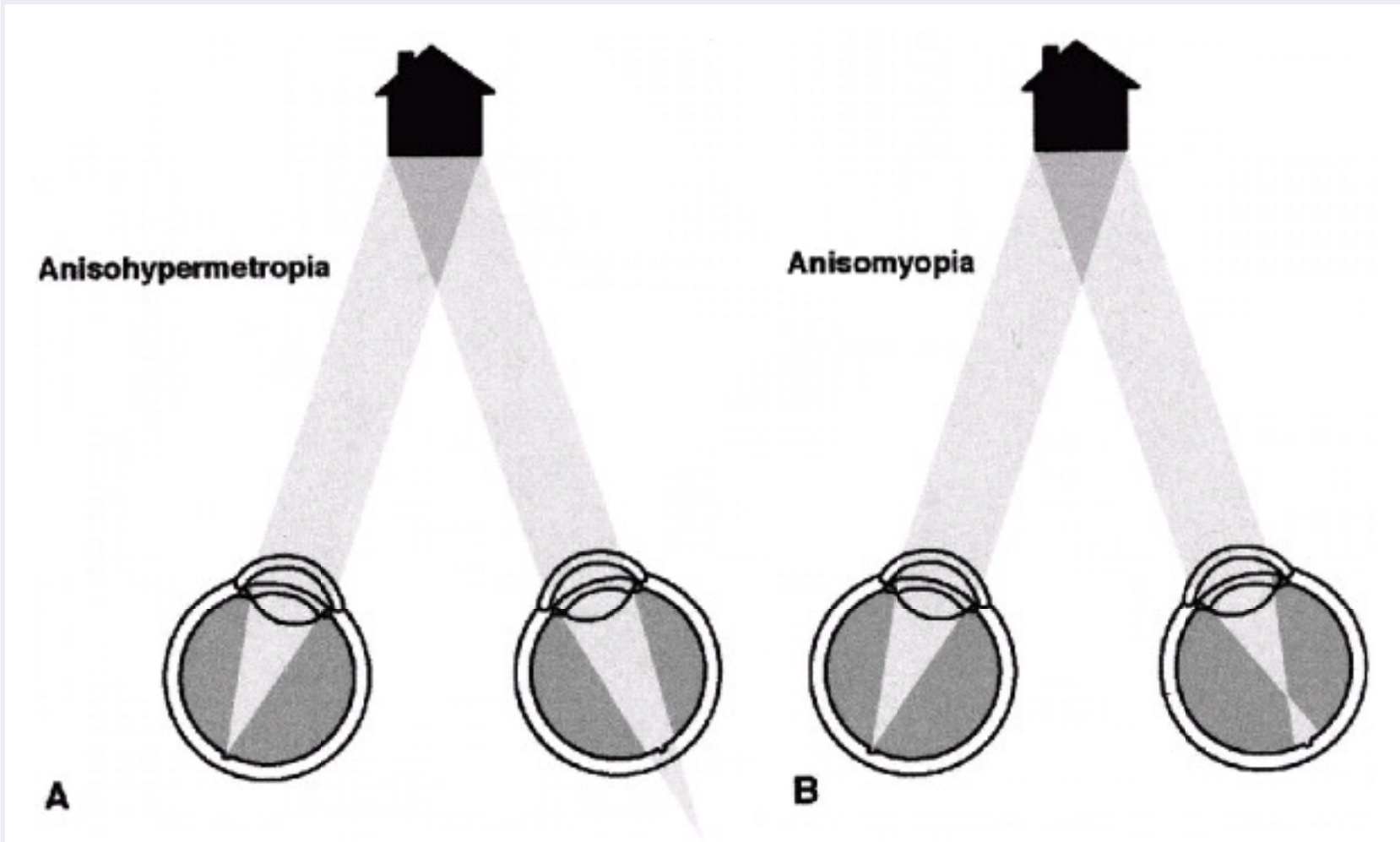

Figure 7.2 A: Anisohypermetropia. B: Anisomyopia, the image in the more ametropic to be defocused.

In a manner thought to be similar to strabismic amblyopia, there is active cortical inhibition of input from the fovea of one eye in a child with anisometropia. This inhibition occurs to eliminate sensory misperceptions due to having a focused image in one eye and defocused image in the other (Fig. 7.2).

Visual-Deprivation Amblyopia

Deprivation amblyopia is the least common and most serious form of amblyopia. Visual deprivation is caused by occlusion of the visual axis or severe distortion of the foveal image from refractive causes. Congenital cataracts, ptosis, congenital corneal opacities, vitreous hemorrhage, and severe refractive errors may cause deprivation amblyopia. Even temporary obstruction of the visual axis, such as that caused by a hyphema or temporary eyelid edema in a very young child can produce visual-deprivation amblyopia. Visual-deprivation amblyopia can be unilateral or bilateral (Fig. 7.3). Sensory strabismus often occurs in children with unilateral vision deprivation. Deprivation amblyopia can result in permanent visual impairment if it is not treated urgently in infancy. Visual-deprivation amblyopia can be iatrogenic such as that which can occur during patching of the sound eye for the treatment of amblyopia. Iatrogenic amblyopia from patching therapy (30,31) or prolonged unilateral atropinization (32) is known as occulsion amblyopia.

Special Forms of Amblyopia

Ametropic amblyopia is a term used to characterize amblyopia in both eyes due to bilateral uncorrected or improperly corrected high refractive errors. It is most common in children

with hyperopia, typically greater than 5 or 6 diopters (33). It can also occur with high astigmatism and high myopia, though it is typically less severe in such cases (34).

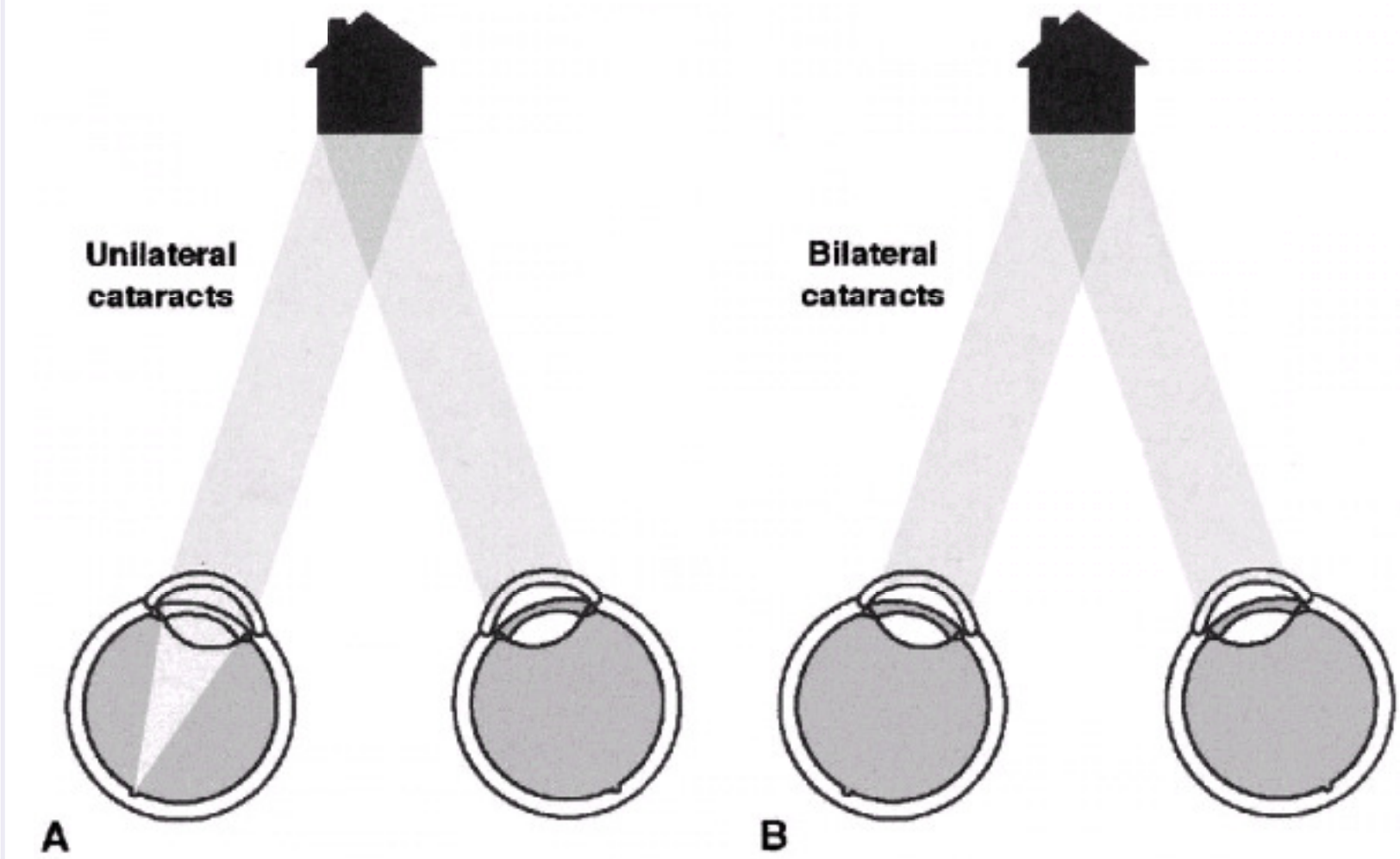

Figure 7.3 Reduced retinal input because of media opacity in one or both eyes can result in deprivational amblyopia.

Occlusion amblyopia, as mentioned earlier, is an iatrogenic condition caused by therapeutic patching of the eye with normal acuity. It usually occurs in the sound eye as a result of amblyopia treatment, but it is occasionally seen in young children after occlusion therapy to treat ocular pathology, such as a corneal abrasion. Concern for occlusion amblyopia is one of the most important reasons for routine follow-up of children being treated for amblyopia. Rapid development of occlusion amblyopia in the sound eye during therapy for amblyopia is a sign of continued visual system plasticity, and it is believed that it often portends a satisfactory visual outcome for both eyes of such patients if detected and corrected promptly.

Idiopathic amblyopia is occasionally diagnosed in retrospect when a child with a monocular reduction of visual acuity and no detectable cause responds with improved vision during a trial of treatment for amblyopia. Therefore, amblyopia treatment is often attempted when visual acuity is reduced and no cause can be found. Presumably, an amblyogenic process was present earlier in the child's life that has since resolved. Detailed history-taking will often identify a history of strabismus or previous occlusion of the visual axis, for example, from prolonged eyelid edema caused by an insect bite or infection of the lids as a young child. Equalization of a previous anisometropic refractive error is another possible explanation cause (35,36), although history is unlikely to be helpful in this situation.

Mechanistic Classification

From a mechanistic viewpoint, there are two causes of amblyopia. These include form-vision deprivation and abnormal binocular interaction (34,37). Each can occur in isolation or concurrently. Form-vision deprivation refers to amblyopia caused by poor image quality being projected onto the fovea. The visual cortex is thus never allowed to develop the capacity to process a sharply focused image and amblyopia results. Form-vision deprivation occurs from conditions that obstruct the visual axis such as cataract, vitreous hemorrhage, corneal opacity, or severe ptosis, but it can also be produced by severe anisometropia. For example, a child with an uncorrected refractive error of + 10.00 diopters in his right eye and + 1.00 diopter in the fellow eye can develop form-vision deprivation in the right eye due to pronounced image blur in the right eye.

Abnormal binocular interaction refers to the condition in which the image projected onto the fovea of each eye is dissimilar enough to preclude fusion, thus prompting suppression and ultimately amblyopia of the suppressed eye. While strabismus may be the most obvious cause of abnormal binocular interaction, unilateral media opacities and anisometropia may participate in this mechanism as well. For example, in a child with uncorrected unilateral high myopia, in addition to a blurred image, the size of the image projected onto the fovea of the myopic eye is distinctly different than that projected to the fovea of the contralateral eye, resulting in abnormal binocular interaction in addition to form-vision deprivation. Table 7.1 demonstrates the possible mechanisms of amblyopia development that strabismus, anisometropia, and visual deprivation may create.

TABLE 7.1 AMBLYOPIA MECHANISMS

	Mechanism	
	Form-vision deprivation	**Abnormal binocular interaction**
Strabismus	-	+
Anisometropia	+	+
Visual deprivation		
Unilateral	+	+
Bilateral	+	-

PATHOPHYSIOLOGY

The mechanism and pathogenesis of amblyopia is an area of vast interest, with hundreds of publications produced on the topic in the last 2 decades. A common question that still remains to be answered fully is the exact location of the disturbance within the visual system responsible for ultimately producing amblyopia. It has been shown that the amblyopic eye functions at its best in mesopic and scotopic conditions and at its worst under photopic conditions (38). Retinal receptive fields in amblyopic eyes have also been shown to be larger than normal (39). Contrast-sensitivity functions measured from the foveal region in strabismic amblyopes are similar to contrast-sensitivity functions measured from the peripheral retina of a normal eye (40).

While amblyopia is most often detected during visual acuity testing, reduction in Snellen visual acuity is not the only visual abnormality that is present in the amblyopic eye. The full range of abnormalities present in the amblyopic eye has probably yet to be identified. Known visual abnormalities include reduced contrast sensitivity (41), dark adaptation abnormalities (42,43), and visual field abnormalities (44,45). Even the “sound” eye has been shown to have abnormalities in patients with anisometropic amblyopia (46,47). Leguire (47) reported reduced contrast-sensitivity function in both the amblyopic and “sound” eye of amblyopic patients. Kandel (46) reported dark adaptation to be better in the nonamblyopic eye.

Some authors have proposed that most eyes with amblyopia actually have subtle, undiagnosed ocular pathology involving the optic nerves, such as mild optic nerve hypoplasia (48,49,50). Certainly, it is true that some children initially diagnosed with amblyopia are later found to have subtle eye pathology when cooperative enough in later life to undergo a more detailed examination. The possibility of occult optic nerve and/or retinal pathology should always be kept in mind during the management of children with amblyopia who are not responding to treatment as anticipated.

Amblyopia is associated with histologic and electro-physiologic abnormalities in the visual pathways. Hubel and Wiesel (51) pioneered methods of studying the effects of changing visual experience in kittens by suturing an eyelid closed. Similar findings have been found in a primate model (52). In these and other experiments, amblyopia can be produced by suturing the lids closed in one eye and by inducing experimental anisometropia in susceptible animals (53,54,55,56,57).

The layers of the lateral geniculate nuclei (LGN) corresponding to input from the amblyopic eye have also been shown to be attenuated in monkeys with strabismic, anisometropic, and visual deprivation amblyopia (4,58,59). Cells from the LGN travel through the parietal or temporal lobes to the visual cortex, located in the occipital lobes. Ocular dominance columns representing alternating input from the right and left eyes are present in all portions of the visual cortex that receive binocular input. Notable exceptions are input from retina corresponding to the position of the optic nerve in the fellow eye and the temporal crescent of retina, which are monocular in each eye. Amblyopia is associated with a decrease in the number of binocularly driven cells that exist in the striate cortex (52,60,61). In a monkey model with deprivation amblyopia, the ocular dominance columns associated with the amblyopic eye were shown to be markedly attenuated. These cortical changes presumably become irreversible over time. Recently Demer and coworkers (62) demonstrated significant reduction in relative cortical blood flow and glucose metabolism during visual stimulation of the amblyopic eye during a positron emission tomography scan.

VISION SCREENING AND AMBLYOPIA DETECTION

There are both obvious and nonobvious causes of amblyopia from the standpoint of parental perception. Obvious strabismus and dense cataracts are typically easily detected by parents and pediatricians, resulting in prompt diagnosis and treatment. Less obvious causes of amblyopia include anisometropia, microstrabismus, posteriorly located cataracts, and vitreous opacities. Amblyopic vision loss associated with these conditions is often not suspected by parents and is often not detected until routine vision screening when the child is mature enough to undergo formal psychophysical acuity testing.

While it is not the purpose of this chapter to discuss vision screening, a few thoughts on the process of vision screening are in order. While vision screening is recommended for 3- to 5-year-old children, it has been estimated that only 21% of children in the United States actually receive vision screening during the recommended time interval between 3 and 5 years of age. Snowdon and Smith (63) recently challenged the validity of recommendations on the timing of amblyopia screening, reporting that delay in diagnosis of mild amblyopia (20/40 or better) until age 5 years did not adversely affect the long-term visual outcome. Some recent studies have questioned the validity and effectiveness of vision screening programs in general.

EXAMINATION OF THE PATIENT WITH AMBLYOPIA

Visual acuity testing protocols used to diagnose amblyopia depend upon the age and abilities of each individual child. Children under the age of 5 years often fail to achieve 20/20 acuity with either eye, due to inability to concentrate/cooperate for testing with the smallest visual targets. Therefore, amblyopia should be suspected if the vision in the two eyes is unequal. While not the only visual abnormality, visual acuity testing is obviously the crux of the diagnosis of amblyopia. Unfortunately, those children most likely to respond to amblyopia treatment (i.e., younger children) are the most difficult to evaluate.

Assessment of Visual Behavior/Acuity

Assessment of visual behavior is the key critical element in the diagnosis of amblyopia in preverbal children. Assessment

of visual behavior begins with evaluation of the child's ability to fixate on and follow an accommodative visual target, such as the examiner's face or a small toy. A child who readily fixates on and follows a toy with one eye but fails to do so with the fellow eye most often has reduced vision in the eye that fails to fixate and/or follow. The examiner must recognize the limited attention span of a young child and assure that failure to fixate and follow the target is not merely due to lack of

interest. To guard against this possibility, a second accommodative target is often utilized to confirm the absence of equal fixation and following behavior. Inequality in fixation and following behavior does not necessarily indicate the presence of amblyopia, but may simply indicate the presence of an uncorrected refractive error or other correctable problem. In a young child, however, this finding is highly suspicious for amblyopia.

Fixation Behavior Testing

Fixation behavior testing involves moving a visual target through the child's visual space. Each eye is tested separately by occluding the fellow eye during testing. Occlusion of the fellow eye can be done with an occluder or the examiner's hand and rarely requires use of an eye patch. Accuracy is improved if the test is repeated several times. The eye movements of infants are expected to be somewhat uncoordinated. The ability to follow past midline develops at approximately 2 months of age; vertical eye movements typically develop around 3 months. Serious visual disorders may be indicated by any asymmetry or abnormality in the fixation reflex.

The Differential Occlusion Objection Test

The differential occlusion objection (DOO) test is a classic visual behavior test for moderate to severe amblyopia. The DOO test involves measuring the child's response to sequential occlusion of the eyes. Children with symmetric vision should respond equally, or not at all, to sequential occlusion of the eyes. Children with unequal vision typically become fussy or agitated when the eye with better vision is covered (Fig. 7.4). The test should be repeated several times to improve accuracy. A consistent strong preference for one eye, indicated by greater objection to occlusion of that eye, is highly suggestive of amblyopia in the fellow eye.

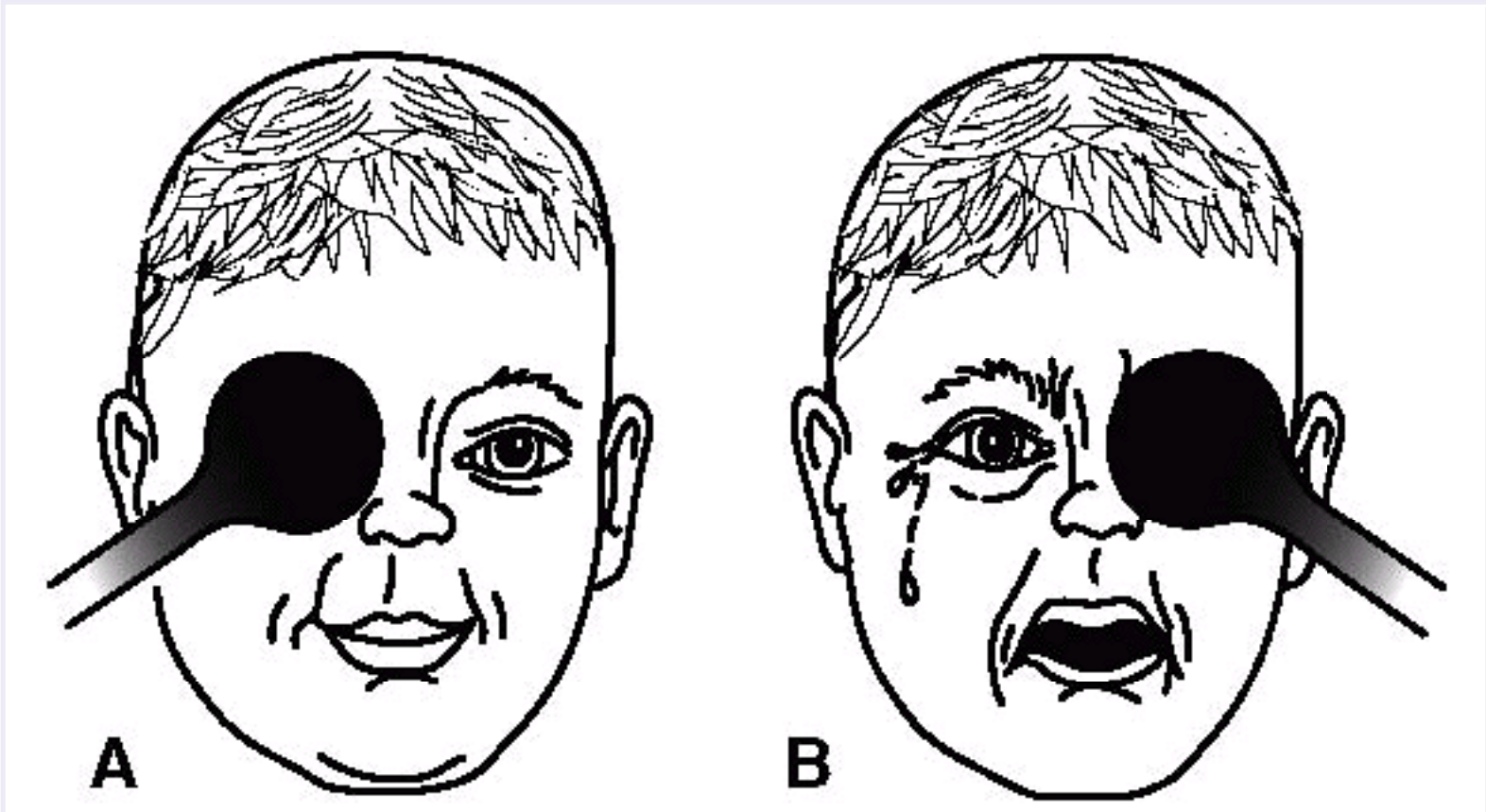

Figure 7.4 Strong objection to occulsion of the left eye in this infant suggests amblyopia in the right eye.

Fixation Preference Testing

Fixation preference testing is another commonly used procedure to identify amblyopia, especially in children too young to participate in formal psychophysical (quantitative) acuity testing. The test is simple to perform in a patient with strabismus. The examiner simply attempts to demonstrate the presence or absence of equability to maintain fixation with either eye by first occluding one eye and determining if the child can maintain fixation with the currently fixing eye upon removal of the occluder and then repeating the process for the contralateral eye. If the child is able to maintain fixation with either eye upon removal of the occluder, significant amblyopia is probably not present. On the other hand, if the child consistently demonstrates a preference for fixation with one eye when the occluder is removed, amblyopia should be suspected in the nonpreferred eye (Fig. 7.5).

The Vertical Prism Test

The vertical prism test uses a 10- or 12-prism-diopter vertical prism to induce vertical separation of the visual axis to facilitate detection of unequal vision in children with straight eyes (64). The test is performed by first holding the prism base down before the child's right eye, inducing a vertical tropia, shifting the image upward and producing vertical diplopia. The child must then make a decision as to which image he or she is going to fixate. The child with symmetric vision between the two eyes will typically exhibit one of two responses. The majority will show no change in eye position when the prism is sequentially introduced before each eye. Less frequently, a child with symmetric vision will demonstrate an upward movement of both eyes when the prism is placed before either eye as he or she attempts to fixate on the image that has been displaced by the base-down prism. The child with significant amblyopia, on the other hand, will usually have an asymmetric response to sequential placement of the prism before each eye. When the prism is placed before the sound eye, both eyes will move upward as the sound eye attempts to fixate the target that has been displaced upward by the base-down prism. No change in eye position will occur when the prism is placed before the amblyopic eye because the sound eye will continue to maintain fixation on the visual target. The accuracy of the vertical prism test is greatly enhanced by frequent practice and by repeating the test several times during each examination to assure a consistent response.

Visual acuity testing

Visual acuity testing should begin as early in life as practical. A child as young as 2 years of age can occasionally participate in psychophysical (quantitative) acuity testing. The examiner should use the most sophisticated psychophysical test possible when assessing a child's vision. Snellen acuity testing is considered optimal, while picture tests, such as Allen figures, are considered the least satisfactory, their use often resulting in overestimation of actual visual acuity. The HOTV, Tumbling E, and Landolt C tests are considered superior to Allen figure testing in this regard. A

difference in best-corrected visual acuity difference of two lines between fellow eyes (e.g., 20/20 in the left eye and 20/30 in the right eye) is clinically indicative of amblyopia, though amblyopia may still be present when the acuity difference between fellow eyes is only one line or less. This is an especially important consideration for Allen figure acuity testing. A child with one line difference on Allen figure testing may be found to have several lines of difference with a more

sophisticated test. As such, the Allen figure test should always be coupled with a fixation preference test.

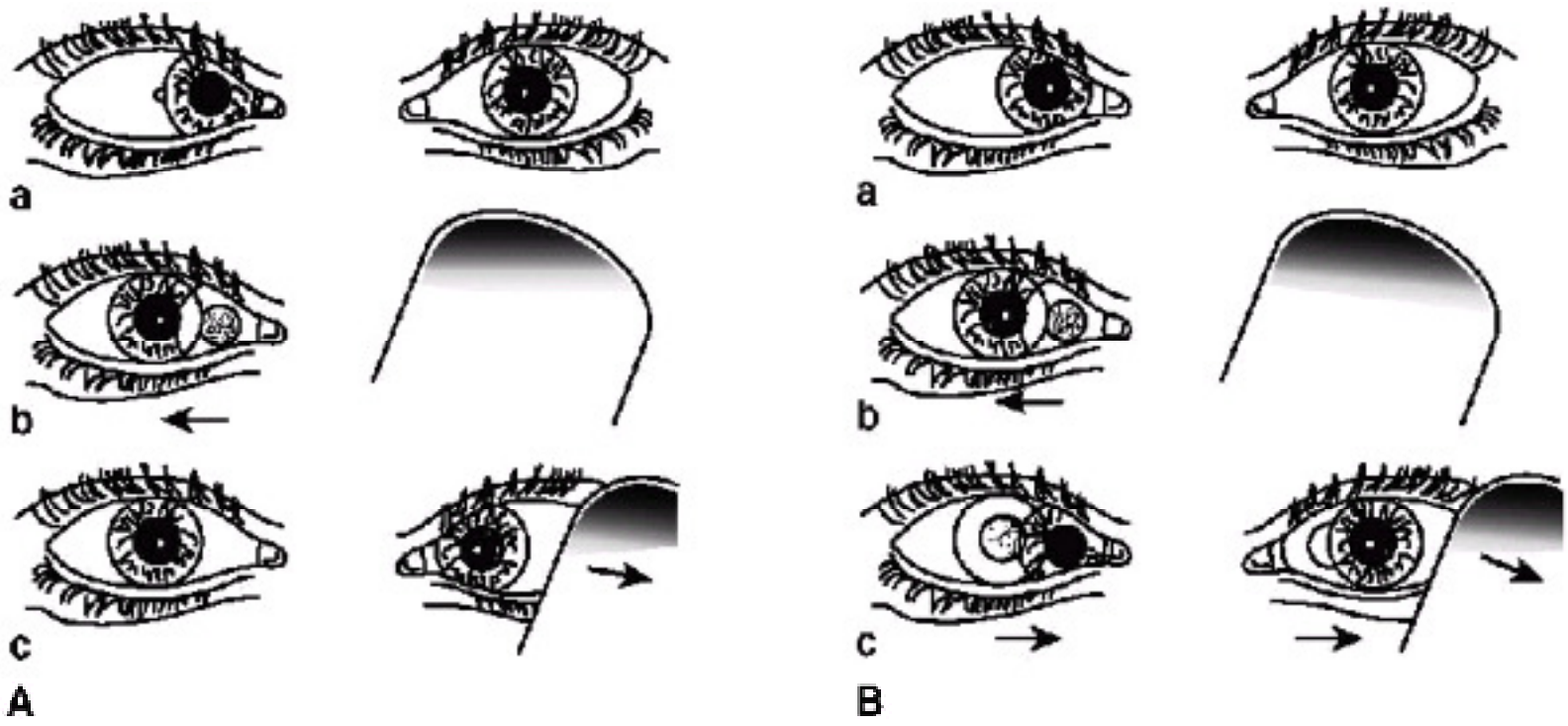

Figure 7.5 A: Alternating fixation. This demonstrates that either eye can maintain fixation and that amblyopia is unlikely. B: Fixation preference for the left eye. When the occluder is placed over the left eye, the right eye will fixate, but when it is removed the child immediately swtiches back to left eye fixation. This confirms amblyopia of the right eye.

Younger children rarely achieve a visual acuity of 20/20 on any test due to limited ability to concentrate. The young child's vision should be considered normal if the visual acuity is equal and not severely reduced (i.e., 20/40 to 20/50 or better). Thus, a 3-year-old child who has 20/40 vision in each eye with the Tumbling E test is considered to have normal vision, but a 3-year-old child with 20/70 vision in each eye, or 20/50 vision in one eye and 20/30 vision in the other eye should undergo further evaluation.

Patients with amblyopia often are noted to have a more severe visual acuity deficit when tested with a full line of optotypes than when tested with isolated optotypes. This phenomenon, known as the crowding effect, must be considered when testing visual acuity in patients who may have amblyopia. The crowding of visual targets can have a significant impact on visual acuity testing of the amblyopic eye (65). Ignoring the crowding phenomenon in an amblyopic child by presenting only single optotypes often results in erroneously good acuity scores. Thus, using a row of visual targets provides a more accurate assessment of visual acuity and improved detection of amblyopia.

Testing of isolated letters may have some value in selected situations. Some examiners believe that isolated letter acuity predicts ultimate visual potential after amblyopia therapy. Others have suggested that failure of acuity to improve with conversion to isolated letters is indicative of an organic cause for visual impairment.

VISUAL ACUITY TESTING TIPS

Children have an innate desire to perform well. This drive to do well and please adults stimulates memorization, peaking, and other unwanted behaviors during the vision testing process. To avoid these potential testing problems, an adhesive patch over the fellow eye is almost always used. Placement of an adhesive patch provides the examiner better control of fixation during the test and improves the accuracy of vision testing, essentially eliminating the artifact of peaking during vision testing.

The use of a computerized vision-testing device that has the ability to randomly present optotypes, is also highly desirable to reduce memorization artifact. Also, it is not uncommon for a child to perform poorly on vision testing of the first eye only to improve with vision testing of the second eye due to a learning-curve effect from practice. If the measured acuity is worse in the second eye, the first eye should be retested to guard against this learning-curve artifact.

It is not the purpose of this chapter to review the details of a comprehensive ophthalmologic examination. It is important to note, however, that a comprehensive ophthalmologic examination is required for all children suspected of having amblyopia. Organic causes of vision loss can be occasionally overlooked, especially in active or uncooperative children. Some of the most common causes of undetected organic vision loss include subtle optic nerve hypoplasia (by far the most common), mild optic atrophy, and subtle macular abnormalities. The presence of an afferent pupillary defect, often difficult to identify in the uncooperative child, may be the only clue to the presence of an optic nerve abnormality as the cause of vision loss in the child who is otherwise difficult to evaluate. It is important to consider the possibility of a subtle organic vision abnormality when a child who is compliant with treatment recommendations does not respond as expected to amblyopia therapy.

TREATMENT OF AMBLYOPIA

Management of the patient with amblyopia is less straightforward than the preceding discussions of etiology and detection might imply. The reality is that children are difficult to evaluate, inconsistent in their responses on examination, require continuous reassessment and modification of assessment techniques, and are often not fully compliant with treatment. The basic treatment recommendations for amblyopia have undergone little change. Treatment of amblyopia with occlusion therapy was described as early as 900 AD by Thabit Ibn Qurrah in Mesopotamia (66). Occlusion therapy and penalization therapy are the most commonly prescribed treatments for amblyopia. While few effective new treatments have been reported in recent decades, knowledge on timing and treatment strategies utilizing existing treatment methods has significantly expanded over the last decade.

The literature is replete with recommendations that children be treated as early in life as possible to achieve an optimal outcome. This recommendation has recently been challenged. Several studies have demonstrated less impact of age (up to 6 years) at onset of treatment for strabismic and anisometropic amblyopia of 20/400 or better than previously suspected (67,68,69,70). It is important, therefore, for the practicing clinician to remain open-minded about the treatment of amblyopia and be willing to implement new treatment recommendations that are scientifically validated as they become available.

The goal of amblyopia treatment is the achievement of the maximum visual acuity for an individual patient. In brief, treatment consists of removing media opacities, correcting significant refractive errors, encouraging the child to use the amblyopic eye, and monitoring for recurrence (Table 7.2). Use of the amblyopic

eye is encouraged by an occluding patch or via penalization using long-acting topical cycloplegic medications or optical blur of the sound eye (71,72,73,74). Certain therapies, including eye movement exercises, vision training, and methods designed to stimulate or suppress vision using flashing lights or rotating patterns, are not scientifically proven and are not recommended (75).

The cause of visual deprivation must be eliminated in children with deprivation amblyopia before use of the amblyopic eye can be successfully encouraged. Similarly, significant refractive errors must be corrected with glasses and/or contact lenses in all children with amblyopia, regardless of cause. After these first two steps are accomplished, the child must be encouraged to use the amblyopic eye. Use of the amblyopic eye is encouraged by occlusion therapy or penalization of the better-seeing eye with cycloplegic drops or spectacle blur.

TABLE 7.2 THE FOUR PRIMARY STEPS OF AMBLYOPIA TREATMENT

Correction of any visual abnormalities (i.e., cataracts, ptosis)
Treatment of significant refractive errors
Encouragement of use of the amblyopic eye
Observation for and treatment of recurrences

While there are a few exceptions, amblyopia treatment measures are usually implemented one at a time. This is done in order to assess each treatment individually. Perhaps an even more important reason to implement only one treatment at a time is to avoid overtaxing the amblyopic child with excessive treatment modalities, which can promote frustration in the child that may lead to compliance problems.

Optical Correction

The first step in the management of any child with amblyopia involves facilitating projection of a clear image onto the fovea of each eye. Without this prerequisite step, additional attempts to treat amblyopia are likely to be unsuccessful. Assuring that a clear image is projected onto the fovea requires removal of any significant media opacity and correction of any significant refractive error with spectacles and/or contact lenses. Anisometropic amblyopia frequently responds to refractive correction alone without the need to institute occlusion or penalization therapy (76,77).

Occlusion Therapy

Occlusion therapy has long been the mainstay of amblyopia treatment after the above measures have been carried out. It is preferred by many ophthalmologists because it lacks systemic side effects, is effective, and is inexpensive. Occlusion therapy involves patching the sound eye. This process forces the use of the amblyopic eye and can result in substantial and long-term visual improvement of the amblyopic eye. The major disadvantage to occlusion therapy is compliance difficulties. Children often remove or peel back their patches to allow peeking. Both of these behaviors may render treatment less effective or completely ineffective. Supervised inpatient occlusion treatment has been shown to be effective in the United Kingdom (78), but it is impractical and not done in the United States (78).

Occlusion therapy recommendations have significantly evolved in the past several years. The schedule of patching varies depending upon the age of the child and the physician's preference. Many physicians believe that younger children require less occlusion therapy than do older children. A common treatment recommendation for initial management of amblyopia in the child under 1 year of age was to patch 1 hour per month of life and follow-up initially every 1 to 2 weeks. There has, however, been no scientific validation of this recommended schedule (79). In older children, past recommendations typically included 6 or more hours of patching per day with initial follow-up at an interval of 1 to 2 weeks per year of life. Follow-up intervals were gradually increased as the child's response to therapy was determined and/or less patching per day was used. Children undergoing occlusion therapy should be followed closely because of the risk of occlusion amblyopia in the sound eye (80).

There is significant controversy regarding the number of

hours of occlusion that need to be prescribed for occlusion therapy on a day-to-day basis (79,81,82). Most studies on the success of occlusion therapy for amblyopia have been retrospective and not well controlled (71,78,81,83). A recent series of studies, known as the Amblyopia Treatment Studies, were conducted by the Pediatric Eye Disease Investigator Group (PEDIG) and have provided some much needed scientific insight on the treatment of amblyopia, challenging many long-held beliefs about amblyopia treatment.

Because of the controversy regarding the amount of occlusion therapy required to treat moderate amblyopia, PEDIG investigated the effectiveness of instructing patients to patch 2 hours per day versus 6 hours per day and found that these two recommended patching regimens resulted in essentially identical improvement in acuity at 4 months from the start of treatment (70). Many have interpreted these results as demonstrating that 2 hours of patching is equal to 6 hours of patching. This, however, is an erroneous conclusion as these investigators did not monitor the amount of occlusion therapy actually performed, but merely compared the effectiveness of “recommended treatment.” Despite this drawback, the study findings are both intriguing and important.

More recently, PEDIG investigated whether recommending 6 hours of patching was as effective as recommending full-time patching for severe amblyopia (20/100 to 20/400)(69). Similar to the previous study for moderate amblyopia, these two recommended treatment schedules resulted in almost identical levels of visual improvement at 4 months. So the question now arises as to whether 2 hours (or less) of patching per day could be enough for any level of amblyopia. Is there a maximum benefit response of occlusion per day that the visual system can assimilate?

There are several patching alternatives available to facilitate occlusion therapy. Adhesive patches remain the mainstay of treatment. Several commercially available patches have been devised which fully occlude the visual axis and periphery in spectacle-wearing amblyopes and may be preferable, especially in hot, humid climates.

In general, devices that clip onto the front of spectacle lenses without fully occluding the visual axis are not recommended. Such clip-on occluders allow the child to easily peak over or around the glasses and may not be as effective.

An occlusion contact lens is another option in poorly compliant children with amblyopia. This option is usually reserved for noncompliant children who have failed all other treatments or children who are aphakic in the amblyopic eye and have parents who are accustomed to inserting and removing contact lenses. It is imperative that the parents understand the potential complications of contact lenses, which include microbial keratitis, giant papillary conjunctivitis, corneal scarring, etc. (84,85,86). These potential complications render this option less desirable for most patients and are the major reason why this treatment modality is used sparingly.

Penalization

Penalization is a technique used to temporarily handicap the sound eye, thereby providing a visual advantage to, and encouraging use of, the amblyopic eye. Penalization causes blurring of vision in the sound eye through use of medication, spectacle manipulation, or both. Prolonged use of pharmacologic or optical blurring can result in long-term improvement in visual acuity of the amblyopic eye (73,87).

Pharmacologic penalization is used by some practitioners and is accomplished through the instillation of cycloplegic ophthalmic drops into the sound eye. Atropine 1% is the most commonly used agent, but homatropine and scopolamine are preferred by some ophthalmologists. All of these topical anticholinergic medications cause pupillary dilation, temporary paralysis of the ciliary body, and significantly reduced ability to accommodate. Reduction in ability to accommodation reduces the ability of the sound eye to focus, thereby providing the amblyopic eye with a competitive advantage and encouraging its use. Pharmacologic penalization is optimally used in hyperopic eyes, but can be effectively utilized in low myopia as well. In general, atropine penalization must be used in conjunction with proper spectacle correction for the amblyopic eye, especially in patients with refractive amblyopia.

Though infrequent, anticholinergic side effects do sometimes occur with use of atropine drops and should be discussed with parents when the drug is prescribed. The most common side effects include flushing of the skin and fever. Irritability, increased aggression, and seizures have rarely been reported.

Atropine penalization may now be gaining increased acceptance and use, following reports by PEDIG, demonstrating that atropine was essentially equally efficacious with regard to effect on visual acuity when compared with occlusion therapy following 6 months of therapy in a group of children with moderate strabismic or anisometropic amblyopia. In this large, prospective, masked, multicenter trial conducted by PEDIG, 419 children younger than 7 years with moderate strabismic or anisometropic amblyopia (visual acuity in the range of 20/40 to 20/100) were randomly assigned to receive one drop of 1% atropine sulfate or occlusion for a minimum of 6 hours per day (88,89). Improvement in visual acuity occurred slightly more rapidly in the occlusion group. After 6 months of treatment, however, visual acuity in the amblyopic eye improved by 3 lines or more in similar proportions of both groups (79% of the occlusion group and 74% of the atropine group). Compliance with treatment was better in the atropine group (78% versus 49% completed at least 76% of the prescribed treatment).

Optical penalization involves altering the spectacle or contact lens correction of the sound eye to produce image blur, potentially providing the amblyopic eye a competitive advantage. Optical penalization may be used alone, or more typically, in combination with pharmacologic penalization. The disadvantage to isolated optical penalization is that children may avoid the undesired blur by simply removing or looking over their spectacles in many cases. Optical penalization, however, when used in combination with cycloplegic agents, is a powerful adjunct in the management of amblyopia (73).

Care must be taken when reducing the optical correction of the sound eye when used in combination with pharmacologic penalization to assure that penalization amblyopia

does not occur in the sound eye. Follow-up should occur at frequent enough intervals to detect and manage penalization amblyopia. Loss of one line of vision in the sound eye was reported in 15% of eyes treated with atropine in the Amblyopia Treatment Study, compared with 7% of eyes randomized to occlusion therapy (89). In both treatment groups, discontinuation of therapy was associated with return of vision in most eyes.

Systemic treatments

Systemic therapies have been attempted for the treatment of amblyopia with limited success. Levodopa-carbidopa is an agent used to treat Parkinson disease. It works by centrally increasing dopamine availability. Some Parkinson patients coincidentally reported increased contrast sensitivity and visual acuity after starting levodopa-carbidopa, prompting testing of the agent for the treatment of amblyopia. Levodopa-carbidopa was found to produce short-term, mild improvement of visual acuity in both the amblyopic and sound eyes of amblyopic patients. The treatment was also mildly effective in older children who were beyond the standard age range for treatment response (90,91). However, the improvement in visual acuity was not sustained when the drug was discontinued. The addition of occlusion therapy to levodopa-carbidopa therapy has been shown to improve response and maintain improvement in visual acuity (92,93,94), although this claim has not been confirmed (95,96). Other pharmacologic agents, including citicoline (cytidine-5'-diphosphocholine), are being investigated for the treatment of amblyopia and may some day prove beneficial (97,98).

Maintenance therapy

Once visual acuity has been maximized by treatment, many ophthalmologists recommend maintenance therapy using occlusion therapy several hours per day or periodic penalization for several months to minimize the risk of recurrence (99,100,101). A typical protocol is to empirically recommend maintenance occlusion therapy 1 to 2 hours per day or maintenance atropine penalization once every 1 to 2 weeks for a period of 3 to 6 months prior to total cessation of therapy.

CESSATION OF THERAPY

Among the most difficult decisions that a physician must make is the decision to discontinue treatment of a chronic condition, especially when response to therapy has not been optimal. This is certainly true for amblyopia. When can the clinician feel both medically and medicolegally comfortable with discontinuing amblyopia therapy? Most of the visual recovery that occurs with amblyopia therapy occurs in the first several months of treatment (83,89). No validated scientific studies are available to advise clinicians as to when therapy can be safely discontinued. A common practice is to require three consecutive visits, separated by at least 6 to 8 weeks with good treatment compliance and without improvement before considering discontinuation of therapy (83). Both occlusion and penalization therapies, if applicable, are typically attempted before considering cessation of treatment. Practically speaking, this means that the child who has not equalized vision with treatment will receive 4 to 6 months of therapy with patching or penalization, followed by a similar trial of treatment with the alternate modality before treatment is abandoned. Exceptions are not uncommon and depend on a number of factors including compliance, school-related issues, and family stress. A frank discussion with parents prior to discontinuing therapy is recommended, and they should be advised that, although unlikely, continued therapy could result in further improvement. It is essential to have parents participate in the ultimate decision to discontinue therapy when residual amblyopia remains to alleviate current and future guilt parents may feel, believing that they did not do an optimal job in the detection and/or management of their child's amblyopia.

The decision to discontinue treatment of deprivational amblyopia is often the most difficult to make. Such patients are typically patched no more than 6 hours per day because stereopsis has been reported to be better with treatment of 6 hours or less (102) and because it is very difficult to get children with deprivational amblyopia to comply with more extensive patching. Because objective visual acuity cannot be accurately evaluated in preverbal children, amblyopia therapy should be continued until the child is old enough for psychophysical visual acuity testing. Generally a more sophisticated test than picture (Allen) testing is required before considering cessation of therapy unless the vision is so poor as to preclude ambulation or other activities of daily living when the sound eye is patched.

PROGNOSIS

The efficacy of the various treatments for amblyopia is difficult to measure and to compare because no standard, accurate, linear test of visual acuity that can be used for children of all ages exists (103). In addition, many cases are diagnosed and successfully treated before visual acuity can be accurately measured. Treatment that is initiated by the time the child reaches 4 to 5 years of age usually is at least partially successful (104).

In a study of 104 amblyopic children (105), several factors were identified that were associated with a high risk of treatment failure including poor compliance, age of at least 6 years, astigmatism of at least 1.5 diopters, and initial vision of 20/200 or worse. Beardsell and coworkers (103) retrospectively studied the outcome of occlusion treatment in 246 children, 167 with strabismic amblyopia and 79 with anisometropic amblyopia. Successful outcomes (linear acuity 6/12 or better) were achieved in 85% of the children with strabismic amblyopia and 100% of those with anisometropic amblyopia. Factors correlated with unsuccessful outcome included low visual acuity at the start of treatment, more than 1 diopter of anisometropia, hypermetropia of more than 3 diopters, and fair or poor compliance

with treatment recommendations. Neither age at presentation nor age at start of treatment were correlated with outcome in this study. Other studies, however, have shown better results with institution of therapy at a younger age (104).

Compliance with the treatment plan, more likely in younger children, is a critical factor in outcome (22,103, 105,106,107). Even older children have shown remarkable improvement with amblyopic therapies (108). In one series of 36 children between the ages of 7 and 10 years who were treated with full-time occlusion (standard occlusion, total penalization, or occlusive contact lens), final best-corrected visual acuity for all patients was between 20/20 and 20/30 (109).

Long-term outcome was studied in a cohort of 94 children who were successfully treated for unilateral amblyopia with occlusion and had 20/20 vision at the end of amblyopia treatment at age 9 years (110).The patients were examined an average of 6.4 years after cessation of therapy. Deterioration of visual acuity was greater (average deterioration of 1.5 versus 0.6 lines on the Snellen chart) and occurred more often in those with pretreatment visual acuity worse than 20/100 than in those with pretreatment visual acuity between 20/60 and 20/100 (63% versus 42%). Deterioration of visual acuity also was related to the type of amblyopia, with deterioration in mixed, strabismic, and anisometropic amblyopia occurring in 79%, 46%, and 36% of patients, respectively. Fifty-four of the patients from the study described above were reevaluated 21.5 years after cessation of therapy at an average age of 29 years (111). Amblyopia had recurred in approximately one-third of the patients.

Amblyopia may have long-term psychosocial consequences. In one survey of 25 patients with a history of amblyopia, approximately 50% responded that amblyopia interfered with their schooling, work, or lifestyle, and approximately 40% responded that it affected their play of sports and/or influenced their job choices (21). In addition, compared to control subjects, patients with amblyopia had a greater degree of somatization, obsessive-compulsive behavior, depression, and anxiety.

SPECIAL ISSUES

Older Children

Recent noncontrolled studies have questioned the belief that treatment of amblyopia beyond the age of 8 or 9 years is of little benefit (109,112,113). Mintz-Hittner and coworkers (109) reported a dramatic improvement in the Snellen visual acuity in children 7 to 10 years old. Full-time occlusion in compliant children resulted in substantial acuity gains. Unfortunately, this study cohort may have represented a self-selected group of children who were either likely to respond to therapy or did not perform well on initial visual acuity testing for reasons other than amblyopia. Furthermore, patients who did not comply well with treatment were not included, and there was no control group. PEDIG is currently conducting a prospective, randomized, controlled clinical trial on amblyopia treatment in older children aged 7 to 18 years. A pilot study demonstrated some improvement in acuity in this age group of children (114).

Concurrent Ocular Pathology

Amblyopia can coexist with anatomic abnormalities of the retina or optic nerve. Optic nerve hypoplasia, optic atrophy, and retinal colobomata are three examples. The clinician should always assume that there may be a reversible component of amblyopia in eyes with obvious pathology, and a diligent attempt should be made to improve any reversible component of visual impairment. Improvement occurs frequently enough that a treatment attempt should be made in all such cases, unless a severe, unequivocal abnormality of the fovea or optic nerve that is not compatible with better vision is present.

Children are admittedly difficult to examine. It is understandable, therefore, that subtle (and even overt) pathology can be overlooked in the small, uncooperative child. The most commonly overlooked abnormalities include mild optic nerve hypoplasia, subtle optic atrophy, and foveal hypoplasia. We recommend documenting the level of the child's cooperation during each examination. This alerts the clinician at follow-up visits that the previous examination may have been suboptimal and allows other clinicians to view the clinician's conclusions in the proper perspective. Careful assessment of the pupils for an afferent pupillary defect is recommended at all amblyopia checkups. When a child fails to respond to amblyopia therapy as expected, the refraction may have been made in error or important pathology may have been overlooked, prompting careful reevaluation. Usually the previous findings are confirmed upon reevaluation, but maintaining an attitude that facilitates careful reanalysis when the child is not responding as expected to therapy is prudent.

CONCLUSIONS

In conclusion, amblyopia is a common problem encountered by both pediatric ophthalmologists and practitioners of adult ophthalmology. It is clinically associated with strabismus, anisometropia, and media opacities in the vast majority of cases. Deprivational amblyopia from media opacities is the least common and most severe form of the disease. Amblyopia is a cortical phenomenon with anatomic and functional changes reported in the central nervous system, both in the lateral geniculate body and visual cortex. Detection is often difficult, particularly in preverbal and uncooperative children. The psychosocial and socioeconomic benefits of amblyopia treatment are significant. While there is certainly a period of highest response to treatment, the maximum age at which treatment is likely to be ineffective has yet to be determined.

The basic treatment paradigm for amblyopia includes removal of any significant media opacities and correction of any significant refractive errors, followed by treatment designed to encourage utilization of the amblyopic eye.

Long-term follow-up is needed to detect recurrence. Occlusion therapy and atropine penalization are the most common treatments. Optical penalization can be used in selected cases, usually in conjunction with pharmacologic penalization. No systemic treatments have gained widespread acceptance. Maintenance therapy to reduce the risk of recurrence may be important, though clear, scientific evidence has not documented the utility of maintenance therapy. When a child fails to respond to therapy, investigation for subtle retinal or optic nerve pathology should be considered. Significant and interesting strides have recently been made in the treatment of amblyopia through the Amblyopia Treatment Studies. These studies and hopefully others will eventually lead to improved treatment strategies and overall improved visual outcomes.

REFERENCES

1. von Noorden GK. Mechanisms of amblyopia. *Adv Ophthalmol* 1977;34:93-115.

2. Magramm I. Amblyopia: etiology, detection, and treatment. *Pediatr Rev* 1992;13:7-14.

3. Boothe RG, Dobson V, Teller DY. Postnatal development of vision in human and nonhuman primates. *Annu Rev Neurosci* 1985;8:495-545.

4. Headon MP, Powell TP. Cellular changes in the lateral geniculate nucleus of infant monkeys after suture of the eyelids. *J Anat* 1973;116:135-145.

5. Daw NW. Critical periods and amblyopia. *Arch Ophthalmol* 1998;116:502-505.

6. Thompson JR, Woodruff G, Hiscox FA, et al. The incidence and prevalence of amblyopia detected in childhood. *Public Health* 1991;105:455-462.

7. Preslan MW, Novak A. Baltimore vision screening project. *Ophthalmology* 1996;103:105-109.

8. Preslan MW, Novak A. Baltimore vision screening project. Phase 2. *Ophthalmology* 1998;105:150-153.

9. Rahi JS, Sripathi S, Gilbert CE, et al. Childhood blindness in India: causes in 1318 blind school students in nine states. *Eye* 1995;9:545-550.

10. National Eye Institute Office of Biometry and Epidemiology. *Report on the National Eye Institute visual acuity impairment survey pilot study*. Bethesda, Md: National Eye Institute, 1984:81-84.

11. Eibschitz-Tsimhoni M, Friedman T, Naor J, et al. Early screening for amblyogenic risk factors lowers the prevalence and severity of amblyopia. *J AAPOS* 2000;4:194-199.

12. Kohler L, Stigmar G. Visual disorders in 7-year-old children with and without previous vision screening. *Acta Paediatr Scanc* 1978;67:373-377.

13. Kvarnstrom G, Jakobsson P, Lennerstrand G. Visual screening of Swedish children: an ophthalmological evaluation. *Acta Ophthalmol Scanc* 2001;79:240-294.

14. Woodruff G, Hiscox F, Thompson JR, et al. The presentation of children with amblyopia. *Eye* 1994;8:623-626.

15. Attebo K, Mitchell P, Cumming R, et al. Prevalence and causes of amblyopia in an adult population. *Ophthalmology* 1998;105:154-159.

16. Sjostrand J, Abrahamsson M. Risk factors in amblyopia. *Eye* 1990;4:787-793.

17. Keech RV, Kutschke PJ. Upper age limit for the development of amblyopia. *J Pediatr Ophthalmol Strabismus* 1995;32:89-93.

18. Vaegan, Taylor D. Critical period for deprivation amblyopia in children. *Trans Ophthalmol Soc UK* 1979;99:432-439.

19. Rahi J, Logan S, Timms C, et al. Risk, causes, and outcomes of visual impairment after loss of vision in the non-amblyopic eye: a population-based study. *Lancet* 2002;360:597-602.

20. Tommila V, Tarkkanen A. Incidence of loss of vision in the healthy eye in amblyopia. *Br J Ophthalmol* 1981;65:575-577.

21. Packwood EA, Cruz OA, Rychwalski PJ, et al. The psychosocial effects of amblyopia study. *J AAPOS* 1999;3:15-17.

22. Holmes JM, Beck RW, Kraker RT, et al. Impact of patching and atropine treatment on the child and family in the amblyopia treatment study. *Arch Ophthalmol* 2003;121:1625-1632.

23. Membreno JH, Brown MM, Brown GC, et al. A cost-utility analysis of therapy for amblyopia. *Ophthalmology* 2002;109:2265-2271.

24. Calcutt C, Murray AD. Untreated essential infantile esotropia: factors affecting the development of amblyopia. *Eye* 1998;12:167-172.

25. Schiavi C, Benedetti P, Scorolli L, et al. Is there a cause-effect relationship between suppression and amblyopia and strabismus? In: Kaufmann H, ed. *Transactions of the 21st meeting of the European Strabismological Association*. Salzburg, Austria: European Strabismological Association, 1993:45.

26. Helveston EM, Giangiacomo JG, Ellis FD. Congenital absence of the superior oblique tendon. *Trans Am Ophthalmol Soc* 1981;79:123-135.

27. Weakley DR Jr, Holland DR. Effect of ongoing treatment of amblyopia on surgical outcome in esotropia. *J Pediatr Ophthalmol Strabismus* 1997;34:275-278.

28. Some points in anisometropia in discussion on problems in refraction. *Trans Ophthalmol Soc U K* 1939;59:119.

29. Weakley DR Jr, Birch E. The role of anisometropia in the development of accommodative esotropia. *Trans Am Ophthalmol Soc* 2000;98:71-76.

30. von Noorden GK. The etiology and pathogenesis of fixation anomalies in strabismus. *Trans Am Ophthalmol Soc* 1969;67:698-751.

31. Hardesty HH. Occlusion amblyopia: report of a case. *AMA Arch Ophthalmol* 1959;62:314-316.

32. von Noorden GK, Campos EC. Amblyopia. In: von Noorden GK, Campos EC, eds. *Binocular vision and ocular motility: Theory and Management of Strabismus*, 6th ed. St. Louis: Mosby, 2002:538-558.

33. Schoenleber DB, Crouch ER Jr. Bilateral hypermetropic amblyopia. *J Pediatr Ophthalmol Strabismus* 1987;24:75-77.

34. Mohindra I, Held R, Gwiazda J, et al. Astigmatism in infants. *Science* 1978;202:329-331.

35. Abrahamsson M, Fabian G, Sjostrand J. A longitudinal study of a population based sample of astigmatic children. II. The changeability of anisometropia.

Acta Ophthalmol (Copenh) 1990;68:435-440.

36. Abrahamsson M, Fabian G, Andersson AK, et al. A longitudinal study of a population based sample of astigmatic children. I. Refraction and amblyopia. *Acta Ophthalmol (Copenh)* 1990;68:428-434.

37. von Noorden GK, Campos EC. Examination of the patient, IV amblyopia. In: von Noorden GK, Campos EC. *Binocular vision and ocular motility: theory and management of strabismus*, 6th ed. St. Louis: Mosby, 2002:252.

38. Burian HM. The dissociation of form vision and light perception in strabismic amblyopia. *Am J Ophthalmol* 1944;27:950.

39. Hommer K, Schubert G. The absolute size of foveal receptive field centers and Panum's areas. *Albrecht Von Graefe's Arch Ophthalmol* 1963;166:205-210.

40. Thomas J. Normal and amblyopic contrast sensitivity function in central and peripheral retinas. *Invest Ophthalmol Vis Sci* 1978;17:746-753.

41. McKee SP, Levi DM, Movshon JA. The pattern of visual deficits in amblyopia. *J Vis* 2003;3:380-405.

42. Osman ZM, Abbas SR, Hefni W. Dark adaptation curve for different types of amblyopia. *Bull Ophthalmol Soc Egypt* 1978;71:327-338.

43. Williams C, Papakostopoulos D. Electro-oculographic abnormalities in amblyopia. *Br J Ophthalmol* 1995;79:218-224.

44. Fioretto M, Gandolfo E, Burtolo C, et al. Evaluation of amblyopic scotoma by electrophysiological examinations and computerized perimetry. *Eur J Ophthalmol* 1996;6:201-207.

45. Sireteanu R, Fronius M. [Visual field defects in strabismic amblyopes.] *Klin Monatsbl Augenheilkd* 1989;194:261-269.

46. Kandel GL, Grattan PE, Bedell HE. Are the dominant eyes of amblyopes normal? *Am J Optom Physiol Opt* 1980;57:1-6.

47. Leguire LE, Rogers GL, Bremer DL. Amblyopia: the normal eye is not normal. *J Pediatr Ophthalmol Strabismus* 1990;27:32-38.

48. Lempert P. The axial length/disc area ratio in anisometropic hyperopic amblyopia: a hypothesis for decreased unilateral vision associated with hyperopic anisometropia. *Ophthalmology* 2004;111:304-308.

49. Lempert P. Axial length-disc area ratio in esotropic amblyopia. *Arch Ophthalmol* 2003;121:821-824.

50. Lempert P. Optic nerve hypoplasia and small eyes in presumed amblyopia. *J AAPOS* 2000;4:258-266.

51. Hubel DH, Wiesel TN. Receptive fields and cells in striated cortex of very young, visually inexperienced kittens. *J Neurophysiol* 1963;26:994-1002.

52. Hubel DH, Wiesel TN, LeVay S. Plasticity of ocular dominance columns in monkey's striate cortex. *Philos Trans R Soc Lond B Biol Sci* 1977;278:377-409.

53. von Noorden GK, Crawford ML. Form deprivation without light deprivation produces the visual deprivation syndrome in Macaca mulatta. *Brain Res* 1977;129:37-44.

54. Smith EL 3rd, Chino YM, Ni J, et al. Residual binocular interactions in the striate cortex of monkeys reared with abnormal binocular vision. *J Neurophysiol* 1997;78:1353-1362.

55. Fankhauser F, Rohler R. The physical stimulus, the quality of the retinal image and foveal brightness discrimination in one amblyopic and two normal eyes. *Doc Ophthalmol* 1967;23:149-188.

56. von Noorden GK, Dowling JE, Ferguson DC. Experimental amblyopia in monkeys. I. Behavioral studies of stimulus deprivation amblyopia. *Arch Ophthalmol* 1970;84:206-214.

57. von Noorden GK, Dowling JE. Experimental amblyopia in monkeys. II. Behavioral studies in strabismic amblyopia. *Arch Ophthalmol* 1970;84:215-220.

58. von Noorden GK. Histological studies of the visual system in monkeys with experimental amblyopia. *Invest Ophthalmol* 1973;12:727-738.

59. von Noorden GK, Middleditch PR. Histology of the monkey lateral geniculate nucleus after unilateral lid closure and experimental strabismus: further observations. *Invest Ophthalmol* 1975;14:674-683.

60. Crawford ML, Blake R, Cool SJ, et al. Physiological consequences of unilateral and bilateral eye closure in macaque monkeys: some further observations. *Brain Res* 1975;84:150-154.

61. Baker FH, Grigg P, von Noorden GK. Effects of visual deprivation and strabismus on the response of neurons in the visual cortex of the monkey, including studies on the striate and prestriate cortex in the normal animal. *Brain Res* 1974;66:185-208.

62. Demer JL, von Noorden GK, Volkow ND, et al. Imaging of cerebral blood flow and metabolism in amblyopia by positron emission tomography. *Am J Ophthalmol* 1988;105:337-347.

63. Snowdon SK, Stewart-Brown SL. Preschool vision screening. *Health Technol Assess* 1997;1:1-83.

64. Wright KW, Walonker F, Edelman P. 10-Diopter fixation test for amblyopia. *Arch Ophthalmol* 1981;99:1242-1246.

65. Morad Y, Werker E, Nemet P. Visual acuity tests using chart, line, and single optotype in healthy and amblyopic children. *J AAPOS* 1999;3:94-97.

66. Qurrah TI. *Vision and perception*. Riyadh, Saudi Arabia: Obiekan Publishing House, 1991.

67. The clinical profile of moderate amblyopia in children younger than 7 years. *Arch Ophthalmol* 2002;120:281-287.

68. Pediatric Eye Disease Investigator Group. A comparison of atropine and patching treatments for moderate amblyopia by patient age, cause of amblyopia, depth of amblyopia, and other factors. *Ophthalmology* 2003; 110:1632-1637.

69. Holmes JM, Kraker RT, Beck RW, et al. A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children. *Ophthalmology* 2003;110:2075-2087.

70. Repka MX, Beck RW, Holmes JM, et al. A randomized trial of patching regimens for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2003;121:603-611.

71. Cleary M. Efficacy of occlusion for strabismic amblyopia: can an optimal duration be identified? *Br J Ophthalmol* 2000;84:572-578.

72. Mazow ML, Chuang A, Vital MC, et al. 1999 Costenbader Lecture. Outcome study in amblyopia: treatment and practice pattern variations. *J AAPOS* 2000;4:1-9.

73. France TD, France LW. Optical penalization can improve vision after occlusion treatment. *J AAPOS* 1999;3:341-343.

74. Simons K, Gotzler KC, Vitale S. Penalization versus part-time occlusion and binocular outcome in treatment of strabismic amblyopia. *Ophthalmology* 1997;104:2156-2160.

75. Amblyopia. American Academy of Ophthalmology (AAO), San Francisco.

76. Clarke MP, Wright CM, Hrisos S, et al. Randomised controlled trial of treatment of unilateral visual impairment detected at preschool vision screening. *BMJ* 2003;327:1251.

77. Moseley MJ, Neufeld M, McCarry B, et al. Remediation of refractive amblyopia by optical correction alone. *Ophthalmic Physiol Opt* 2002;22:296-299.

78. Dorey SE, Adams GG, Lee JP, et al. Intensive occlusion therapy for amblyopia. *Br J Ophthalmol* 2001;85:310-313.

79. Loudon SE, Polling JR, Simonsz B, et al. Objective survey of the prescription of occlusion therapy for amblyopia. *Graefes Arch Clin Exp Ophthalmol* 2004;242:736-740.

80. Simon JW, Parks MM, Price EC. Severe visual loss resulting from occlusion therapy for amblyopia. *J Pediatr Ophthalmol Strabismus* 1987;24:244-246.

81. Hug T. Full-time occlusion compared to part-time occlusion for the treatment of amblyopia. *Optometry* 2004;75:241-244.

82. von Noorden GK. Practical management of amblyopia. *Int Ophthalmol* 1983;6:7-12.

83. Keech RV, Ottar W, Zhang L. The minimum occlusion trial for the treatment of amblyopia. *Ophthalmology* 2002;109:2261-2264.

84. Wilhelmus KR, Robinson NM, Font RA, et al. Fungal keratitis in contact lens wearers. *Am J Ophthalmol* 1988;106:708-714.

85. Suchecki JK, Donshik P, Ehlers WH. Contact lens complications. *Ophthalmol Clin North Am* 2003;16:471-484.

86. Ahuja M. Contact lens wear and microbial keratitis. *J Indian Med Assoc* 2002;100:664-666.

87. Pediatric Eye Disease Investigator Group. The course of moderate amblyopia treated with atropine in children: experience of the amblyopia treatment study. *Am J Ophthalmol* 2003;136:630-639.

88. Foley-Nolan A, McCann A, O'Keefe M. Atropine penalisation versus occlusion as the primary treatment for amblyopia. *Br J Ophthalmol* 1997;81:54-57.

89. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2002;120:268-278.

90. Leguire LE, Rogers GL, Bremer DL, et al. Levodopa and childhood amblyopia. *J Pediatr Ophthalmol Strabismus* 1992;29:290-298.

91. Leguire LE, Walson PD, Rogers GL, et al. Levodopa/carbidopa treatment for amblyopia in older children. *J Pediatr Ophthalmol Strabismus* 1995;32:143-151.

92. Leguire LE, Rogers GL, Walson PD, et al. Occlusion and levodopa-carbidopa treatment for childhood amblyopia. *J AAPOS* 1998;2:257-264.

93. Mohan K, Dhankar V, Sharma A. Visual acuities after levodopa administration in amblyopia. *J Pediatr Ophthalmol Strabismus* 2001;38:62-67.

94. Gottlob I, Wizov SS, Reinecke RD. Visual acuities and scotomas after 3 weeks' levodopa administration in adult amblyopia. *Graefes Arch Clin Exp Ophthalmol* 1995;233:407-413.

95. Pandey PK, Chaudhuri Z, Kumar M, et al. Effect of levodopa and carbidopa in human amblyopia. *J Pediatr Ophthalmol Strabismus* 2002;39:81-89.

96. Leguire LE, Komaromy KL, Nairus TM, et al. Long-term follow-up of L-dopa treatment in children with amblyopia. *J Pediatr Ophthalmol Strabismus* 2002;39:326-330.

97. Campos EC, Bolzani R, Schiavi C, et al. Cytidine-5'-diphosphocholine enhances the effect of part-time occlusion in amblyopia. *Doc Ophthalmol* 1996;93:247-263.

98. Campos EC, Schiavi C, Benedetti P, et al. Effect of citicoline on visual acuity in amblyopia: preliminary results. *Graefes Arch Clin Exp Ophthalmol* 1995;233:307-312.

99. Oster JG, Simon JW, Jenkins P. When is it safe to stop patching? *Br J Ophthalmol* 1990;74:709-711.

100. von Noorden GK, Attiah F. Alternating penalization in the prevention of amblyopia recurrence. *Am J Ophthalmol* 1986;102:473-475.

101. von Noorden GK. Amblyopia: a multidisciplinary approach. Proctor lecture. *Invest Ophthalmol Vis Sci* 1985;26:1704-1716.

102. Birch EE, Stager D, Leffler J, et al. Early treatment of congenital unilateral cataract minimizes unequal competition. *Invest Ophthalmol Vis Sci* 1998;39:1560-1566.

103. Beardsell R, Clarke S, Hill M. Outcome of occlusion treatment for amblyopia. *J Pediatr Ophthalmol Strabismus* 1999;36:19-24.

104. Flynn JT, Woodruff G, Thompson JR, et al. The therapy of amblyopia: an analysis comparing the results of amblyopia therapy utilizing two pooled data sets. *Trans Am Ophthalmol Soc* 1999;97:373-390.

105. Lithander J, Sjostrand J. Anisometropic and strabismic amblyopia in the age group 2 years and above: a prospective study of the results of treatment. *Br J Ophthalmol* 1991;75:111-116.

106. Oliver M, Neumann R, Chaimovitch Y, et al. Compliance and results of treatment for amblyopia in children more than 8 years old. *Am J Ophthalmol* 1986;102:340-345.

107. Loudon SE, Polling JR, Simonsz HJ. A preliminary report about the relation between visual acuity increase and compliance in patching therapy for amblyopia. *Strabismus* 2002;10:79-82.

108. Pediatric Eye Disease Investigator Group. A prospective, pilot study of treatment of amblyopia in children 10 to 18 years old. *Am J Ophthalmol* 2004;137:581-583.

109. Mintz-Hittner HA, Fernandez KM. Successful amblyopia therapy initiated after age 7 years: compliance cures. *Arch Ophthalmol* 2000;118:1535-1541.

110. Levartovsky S, Oliver M, Gottesman N, et al. Factors affecting long term results of successfully treated amblyopia: initial visual acuity and type of amblyopia. *Br J Ophthalmol* 1995;79:225-228.

111. Leiba H, Shimshoni M, Oliver M, et al. Long-term follow-up of occlusion therapy in amblyopia. *Ophthalmology* 2001;108:1552-1555.

112. Wick B, Wingard M, Cotter S, et al. Anisometropic amblyopia: is the patient ever too old to treat? *Optom Vis Sci* 1992;69:866-878.

113. Moseley M, Fielder A. Improvement in amblyopic eye function and contralateral eye disease: evidence of residual plasticity. *Lancet* 2001;357:902-904.

114. Mohan K, Saroha V, Sharma A. Successful occlusion therapy for amblyopia in 11- to 15-year-old children. *J Pediatr Ophthalmol Strabismus* 2004;41:89-95.

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8

Sensory Adaptations in Strabismus

Marshall M. Parks

Before understanding the adaptations that occur in binocular vision after the onset of strabismus, one must first grasp the characteristics of binocular vision. Binocular vision is the cortical phenomenon gained by unifying the separate retinal images (1). Binocular vision is acquired, as is any conditioned reflex. Two of the three requisites for its development are straight eyes and similar images presented to each retina. Congenitally constant strabismic infants, and those with a high degree of anisometropia or with unilateral translucent or opaque media, are unable to develop the binocular vision reflex. The third requisite for its development is a temporal factor. Unless the first two requisites of straight eyes and similar retinal images are present before the third year of life, binocular vision will never develop. This fact has led to early treatment of congenital strabismus, anisometropia, and unilateral media opacities.

The earliest evidence that binocular vision has developed in a normal infant is the observation of a convergence response to an 8-prism diopter base-out prism slipped before one eye. The response can usually be observed by 4 to 6 months of age.

MACULAR VERSUS EXTRAMACULAR BINOCULAR VISION

Two distinct visual systems exist at both the monocular and binocular levels. This duality features the spatially small central vision served by the macular region of the retina fitted within the larger peripheral vision served by the extramacular retina. The perimeter of the macular visual system blends into the extramacular visual system without a distinct boundary. As a result, anatomists, researchers, and clinicians recognize the impossibility of precisely defining the dimension of the macula.

The macular visual system differs markedly from the extramacular visual system in cellular structure and physiology, from the retinal level through the visual pathways and including the visual cortex. The two systems also differ in the age at which they mature. For example, the extramacular visual system appears to be mature at birth. The newborn manifests pupillary responses to a light stimulus, protective blink responses to bright light or a threatening maneuver, optokinetic responses to a moving visual target, and visual evoked responses in the cortex. However, the macular visual system is not anatomically mature at birth: It first begins to function between 2 and 3 months of age. The sensorimotor reflex it serves is fixation. If the macular visual system is deprived of the opportunity to develop during the first 3 months of life, fixation never develops. Once developed, fixation requires constant reinforcement through use until approximately 9 years of age; otherwise, lack of function causes it either to decrease to a level below its full potential or to disappear entirely. Lack of reinforcement of the macular reflex does not affect the quality of the fixation after 9 years of age; thus, the amblyopic period extends until 9 years of age.

One is usually aware of only the small spatial area within the total visual field, called the “area of conscious regard.” Consequently, macular vision ordinarily receives our sole attention unless we consciously make ourselves aware of an extramacular image or an unusually exciting extramacular image attracts our attention away from the area of conscious regard. For the most part, however, extramacular vision is processed at a subconscious level, an arrangement permitting one to be relatively oblivious to the general environment while concentrating on the area of conscious regard.

As macular and extramacular monocular vision differ, so do macular and extramacular binocular vision. The cellular differences and extramacular monocular and binocular vision probably begin with the ganglion cells in the retina.

The ganglion cells of the retina are of two types, the smaller parvoganglion cells and the larger magnoganglion

cells. Each has its own retinal receptor field from which a parvoganglion cell receives input from a specific cone and a magnoganglion cell receives input from certain rods. The ganglion cell population nearest the fovea is almost exclusively parvoganglion cells. As retinal loci increasingly peripheral to the fovea are examined, the population of parvoganglion cells diminishes while the magnoganglion cell population increases. The parvoganglion cell receptor field size remains approximately unchanged while the magnoganglion cell receptor field size increases peripheral to the fovea.

The axons of the corresponding ganglion cell receptor fields for the two eyes come to lie in juxtaposition to one another in the optic tracks as they proceed to their synapse in the lateral geniculate bodies. The ventral two layers of cells in the lateral geniculate bodies contain the synapse of the parvoganglion cell system, and the dorsal four layers are occupied by the synapse of the magnoganglion cell axons. This arrangement is continued in the optic radiation to layer IV in the calcarine fissure of the occipital lobe. From there, the parvoganglion cellular pathways proceed higher in the cortex with multiple synaptic connections to the occipital temporocortical area, whereas the magnoganglion system feeds into the occipitoparietal area.

The parvocellular binocular vision system yields color perception, is slow processing, and is designed for studying fine contour. The magnocellular binocular vision system yields no color perception, is fast processing, and is designed to subconsciously process the information regarding the alignment of the eyes and dispatch the appropriate innervation to the oculomotor system to maintain the alignment for accomplishing fusion. The powerful fusional vergences are a product of the magnocellular system. The parvocellular system is also endowed with fusional vergence capability, but its power is weak compared with the power of the magnocellular system.

Both the parvoganglion and the magnoganglion systems process stereopsis. The stereoacuity, however, is enhanced within the parvocellular system because it exclusively serves the foveal binocular vision endowed with exquisite resolving power capable of detecting the most minimal horizontal retinal image disparity required to perceive stereopsis. The minimal retinal image disparity in humans that yields the perception of stereopsis is approximately 14 seconds of arc. Only parvocellular receptor fields can achieve this level of stereoacuity. Extrafoveal images that project onto retinal areas with less resolving power than the foveal images require greater retinal image disparity to perceive stereopsis. The best stereoacuity that magnoganglion receptor fields can accomplish is no better than 60 seconds of arc. The average stereoacuity for extrafoveal binocular vision is 200 seconds of arc.

The differences between macular and extramacular binocular vision are many and are discussed next.

Amplitude of Fusional Vergence

Extramacular binocular vision supplies the power to the fusional vergence, whereas macular binocular vision does the fine-tuning. This is illustrated by first measuring the horizontal fusional vergence amplitude, then eliminating the macular binocular vision temporarily by bleaching one macula with a sustained bright light from a euthyscope directed onto the macula of only one eye, while protecting the extramacular retina from the light. Repeating the fusional vergence amplitude measurement before macular function returns shows it to be unchanged. Repeating the procedure, except now bleaching the extramacular retina with the euthyscopic light for several seconds while protecting the macula, permits only the fusional vergence of the macular binocular vision to function for several minutes. This method, in contrast with the former, significantly reduces the amplitude of fusional vergence that is measurable.

Tolerance of Misalignment

The deviation of the visual axis that permits fusion is much greater for extramacular binocular vision than for macular binocular vision. The misalignment tolerance for macular binocular vision is approximately 0.5 prism diopter, which is fixation disparity (2), whereas the tolerance for extramacular binocular vision is 8 prism

diopters. Macular binocular vision is a tight and demanding fusion system compared with the loose and forgiving extramacular fusion system.

Tolerance of Dissimilarity of Retinal Images

Similar retinal images presented to each retina are required for fusion, yet the images are not required to be absolutely similar in size, contour, and clarity. However, the threshold of dissimilarity of retinal images that preclude fusion is much less for macular than for extramacular binocular vision. This is the cause of the commonly encountered amblyopic anisometrope with absence of macular binocular vision, but with essentially straight eyes because of the presence of extramacular binocular vision. The image disparity threshold was exceeded for macular binocular vision but not for the extramacular binocular vision.

An interesting phenomenon is observed in the laboratory by a nonstrabismic patient who has both macular and extramacular binocular vision capability regarding projection of dissimilar images that have no resemblance to one another. As the haploscope projects the dissimilar images to each eye, macular binocular vision immediately vanishes but extramacular binocular vision continues. The macular image of only one eye is seen at a time, but rapid alternation in the use of either macula produces rivalry of the images; never are both macular images simultaneously perceived. However, the extramacular dissimilar images are simultaneously perceived, although not fused. This is the laboratory correlate to strabismus, because deviation of the eyes causes dissimilar images to project onto the maculae and all corresponding extramacular retinal areas. As the eyes deviate into strabismus, macular binocular vision immediately ceases because dissimilar macular images cannot be perceived; a scotoma corresponding to the nonfixating macula can be plotted. The extramacular binocular vision continues registering visual confusion of the dissimilar images projecting onto the extramacular corresponding retinal areas and diplopia of the similar images projecting onto the

extramacular noncorresponding retinal areas. The object of regard projecting onto the macula of the fixating eye and the extramacular retina of the deviated eye will be diplopic.

Durability of Binocular Vision

What we learn from the foregoing is that the symptoms of visual confusion and diplopia encountered in strabismus result from the extramacular binocular vision reflex continuing to function even though fusion is impossible. However, the macular binocular vision reflex ceases to function when fusion is impossible and consequently causes no annoying symptoms in strabismus. This illustrates the difference in the durability of macular and extramacular binocular vision. Once extramacular binocular vision has developed, it will never completely vanish, but it can be altered in two ways. First, a patient with strabismus of greater than 8 prism diopters will develop a sensorial adaptation that adjusts the disparate retinal images to be perceived as though the eyes were straight; normal retinal correspondence is changed to anomalous retinal correspondence. However, the extramacular retinal area in the nonfixating eye, which receives the same image that is projected onto the macula of the fixating eye, is unable to undergo this adaptation of anomalous retinal correspondence. The symptoms of diplopia and visual confusion for this portion of the binocular visual field are eliminated by the sensorial adaptation of suppression. Suppression eliminates visual function in the restricted extramacular region of the nonfixating eye on which projects the macular image of the fixation eye. A second alteration in extramacular binocular vision occurs when the dissimilarity of retinal image clarity exceeds the threshold of fusion capability. A typical condition that causes this situation is an acquired monocular cataract. Even though strabismus follows, diplopia and visual confusion are absent because of the reduced visual function in the cataractous eye. Gradually, with absence of reinforcement of the extramacular binocular reflex over a few years, the motor component of fusion disappears, but the sensory component of normal retinal correspondence extramacular binocular vision persists. After cataract removal and optical correction of the aphakia, the symptoms of visual confusion and diplopia appear. Despite aligning the eyes either by surgery and/or prisms, the diplopia persists because of the absence of the necessary motor component of fusion that delivers the proper fusional vergence that automatically brings and holds the diplopic images together. The result is dancing of the images about one another. Gradually the motor component of fusion may restore over many months, but usually the dancing images are so troublesome that the patient elects to occlude one eye rather than persevere in the hope the diplopia will disappear. The redevelopment of fusional vergences is hopeless if one eye is occluded.

In contrast, after macular binocular vision develops, its continued function requires the critical stimuli of similar retinal images and straight eyes. Moreover, the reflex requires reinforcement throughout life; otherwise it rather quickly vanishes with disuse. In fact, the critical period in which the macular binocular vision reflex can withstand absence of reinforcement and not vanish is approximately 3 months. Absence of use for this period results in the macular binocular vision being lost forever. This is well illustrated in the intermittently exotropic patient who preoperatively reinforces the macular binocular vision reflex while the eyes are straight but postoperatively suffers because of surgical overcorrection, constant esotropia. Now, reinforcement of macular binocular vision is impossible, and within 3 months the macular binocular vision will be permanently lost. The acquired monocular cataract is another clinical model illustrating the same phenomenon. Furthermore, the critical period in which constant disuse of the macular binocular vision reflex can be withstood without resulting in its permanent loss seems not to be age related.

Adaptability of Binocular Vision

The adaptability of macular versus extramacular binocular vision is strikingly different. In fact, macular binocular vision is absolutely not adaptable. Instead of adapting to a misalignment of the eyes that exceeds 0.5 prism diopters, it ceases to function. This is not the case regarding extramacular binocular vision, which continues to function even though the misalignment exceeds 8 prism diopters, producing diplopia and visual confusion. However, the adaptable feature about extramacular binocular vision is what overcomes the diplopia and visual confusion. The diplopia generated from the area of conscious regard is eliminated by suppressing the visual stimuli dispatched to the visual cortex from the retinal region of the deviated eye that receives the images from this spatial area. A 5-degree absolute facultative scotoma in esotropia, but invariably a larger scotoma in exotropia, can be plotted during binocular perimetry to demonstrate the region of the suppression in the extramacular visual system. The suppression scotoma is transferred to the opposite eye if the fixation is switched to the opposite macula. Suppression well expresses the adaptability of the extramacular binocular vision system. The adaptation occurs in response to the visual stimuli emanating from the area of conscious regard. The phenomenon does not affect the macula of the fixating eye; it occurs in the extramacular binocular vision reflex and affects the opposite eye.

To further emphasize the adaptability of the extramacular visual system, the diplopia and visual confusion caused by visual stimuli emanating peripherally to the area of conscious regard are eliminated by another anomalous retinal correspondence. This adaptation involves inducing a change in the cortex of the innate directional values supplied from corresponding retinal areas to adjust for the deviation of the eyes. Extramacular fusion, rather than simultaneous perception, is now achieved despite strabismus, eliminating the peripheral diplopia and visual confusion.

The magnificence of adaptability of the extramacular binocular visual system is not fully appreciated until it is realized that the region of the suppression and the directional value of the anomalous retinal corresponding areas adjust to the changing eye alignment in noncomitant strabismus as rapidly as the eyes move. For example, A or V pattern strabismus, with vertical deviations that change on lateral gaze, is compensated for by the extramacular binocular vision sensorial adaptations changing as rapidly as the eyes move. Another dimension of the adaptability of the

extramacular binocular vision system is the ability to compensate one moment for the intermittent strabismus with suppression and anomalous retinal correspondence and the next moment restore to normal retinal correspondence without suppression when the phoria status returns. The intermittent exotropic patient illustrates this feature regarding the adaptability of the extramacular binocular vision.

A normal retinal correspondence extramacular binocular visual system offers strong fusional vergence with excellent amplitudes. However, in the anomalous retinal correspondence mode, fusional vergence amplitudes are nonexistent. Fusional vergence amplitudes serve the purpose of maintaining the eye alignment within 8 prism diopters, or so that extramacular normal retinal correspondence binocular fusion can occur. But while in the anomalous retinal correspondence mode, as the deviation changes in various positions of gaze, no benefit is derived from the fusional vergences, because the sensorial adaptation can adjust to any alignment as fast as the deviation changes.

Stereoacuity

Stereopsis is a binocular visual reflex that occurs for spatial targets within Panum's fusional space and is present only in a nonstrabismic setting during normal

retinal correspondence extramacular binocular vision. If the patient has macular binocular vision, the stereoacuity is superb, because the bifixating eyes with their exquisite minimum separable position can discern the most minute horizontal disparity of the similar images projected on their macular (3). The least horizontal disparity of the images that evokes the perception of stereopsis is the measure of stereoacuity. Because of the lack of macular binocular vision, a patient with extramacular binocular vision scores poorly in stereoacuity testing, making this a reliable test to determine the presence or absence of macular binocular vision. However, a strabismic patient fusing with anomalous retinal correspondence is devoid of stereopsis. By having the strabismic deviation reduced to within 8 prism diopters, the patient usually now appreciates stereopsis, but not always. The reason may be that the patient has congenital esotropia, and in this group of patients only 40% develop stereopsis. Sixty percent of congenitally esotropic patients surgically aligned to within 8 prism diopters who enjoy extramacular fusion have no stereopsis perception. Extramacular fusion apparently is the best sensory status obtainable for this group of patients.

DIAGNOSIS OF SUPPRESSION AND ANOMALOUS RETINAL CORRESPONDENCE

Multiple diagnostic methods prevail, but the Worth four-dot test and the Bagolini striated glasses test are the simplest. Both tests disclose suppression and anomalous retinal correspondence (1).

Worth Four-Dot Test

The Worth four-dot test is based on the fact that the cluster of four dots, some seen by one eye, some by the opposite eye, and one by both eyes, projects an image of a certain size on the retinas according to the distance the dots are from the patient. The suppression scotoma in esotropia is approximately 5 degrees, so the cluster must project a slightly larger image to be seen outside the scotoma. The near Worth dots project an image of 6 degrees at 0.33 m from the patient. As the light is advanced toward the patient from 2 m away, the suppression response suddenly changes to a fusion response, which in the presence of strabismus is possible only because of anomalous retinal correspondence. However, in exotropia the suppression scotoma is larger than in esotropia, including the temporal retina up to the hemiretinal line. The exotropic patient usually does not give a fusion response at 0.33 m to the Worth four dots, and another test must be used.

Bagolini Striated Glasses Test

The Bagolini striated glasses test permits viewing of the normal environment while fixating a light that is converted to streaks across the retinas; one streak is in the 135-degree meridian and the other is in the 45-degree meridian. If the strabismic patient manifesting a deviation of greater than 8 prism diopters sees an “X” with its center at the light being fixated, anomalous correspondence is present. Suppression is identified by a break in the streak on the nonfixating eye surrounding the muscle light. Again, as was the case with the Worth four-dot test, an exotropia may have such a large suppression scotoma that the ends of the streak beyond the scotoma may not be discerned.

Base-In Prism Test for Exotropia

A better test for suppression and anomalous correspondence in exotropia is the base-in prism test. Increasing base-in prism before the nonfixating eye causes sudden recognition of diplopia as the prism power moves the object of regard across the hemiretinal line onto the nasal retina. The diplopia is homonymous with the image seen by the deviated eye, appearing to be many feet away from the object of regard. This observation is possible only because of anomalous retinal correspondence, which causes the nasal retina adjacent to the macula to behave as though it were peripheral nasal retina.

TREATMENT OF SUPPRESSION AND ANOMALOUS RETINAL CORRESPONDENCE

The appropriate treatment is to straighten the eyes with glasses and/or surgery, or to compensate for the deviation with prism spectacles (4). Training directed toward having the patient forego the adaptation in the extramacular binocular visual system, which eliminates the annoying symptoms of diplopia and visual confusion, is unnecessary. By having the eyes straightened, the patient returns to normal retinal correspondence extramacular binocular vision spontaneously without having to be taught how to do this. It may take a few days or a few weeks to change from anomalous

to normal retinal correspondence, but it will happen. Until the change occurs, the patient may experience diplopia and visual confusion. Some children with esotropia and anomalous retinal correspondence do converge back to their pretreatment strabismic angle rather than allowing the anomalous retinal correspondence the time required to change back to normal retinal correspondence. This feature of anomalous retinal correspondence is illustrated in the positive response to the prism adaptation test in which the patient returns within hours to days to the same angle of deviation, while viewing through prisms that compensate for the original strabismic angle (5). Unfortunately, the same patient who responds positively to the prism adaptation test may respond similarly to surgery that normally would eliminate the strabismic angle.

Occlusion of an eye makes anomalous correspondence unnecessary to compensate for the symptoms of diplopia and visual confusion. Occlusion therapy continued for several weeks throughout the entire portion of the day that the patient is awake, alternating from eye to eye to prevent amblyopia if necessary, is an efficient method to reduce the depth of the anomalous correspondence.

MISCONCEPTION ABOUT SUPPRESSION AND ANOMALOUS RETINAL CORRESPONDENCE: MONOFIXATION SYNDROME

The multiple misconceptions about the sensorial adaptations in strabismus confuse the new student exposed to this subject and frighten the average clinician who must treat the patient.

Suppression is the sensorial adaptation within the extramacular binocular visual system that eliminates diplopia in the area of conscious regard. The macula of the fixating eye is never suppressed; only the extramacular region in the opposite eye is suppressed. A common misconception is to assume that the extramacular suppression may also affect the ipsilateral macula, suppressing it also, and produce amblyopia. However, this is impossible. Neither monocular macular nor binocular macular vision is ever suppressed. Macular monocular vision during the amblyogenic period, which extends through the first 9 years of life, requires constant use (reinforcement) to maintain its proficiency. The lack of monocular macular reinforcement that causes amblyopia is unrelated to the suppression occurring in the extramacular binocular visual system during binocular viewing in a strabismic patient.

The lack of monocular macular reinforcement that causes amblyopia also occurs in approximately two thirds of patients with monofixation syndrome (6). The patients have essentially straight eyes, and normal extramacular binocular vision without suppression, but they monofixate (macular binocular vision is absent, and they consequently do not bifixate). If they consistently prefer to fixate with the same macula, as is encouraged by anisometropia, the lack of reinforcement of the opposite monocular macular reflex results in amblyopia. Amblyopia can also be induced in either a strabismic or a nonstrabismic child simply by occluding the preferred eye for several days or weeks. The occlusion merely removes the necessary reinforcement of the monocular macular reflex required during the amblyogenic period to maintain normal visual acuity.

I previously alluded to the fact that the macular binocular visual system has no sensorial adaptations. If the critical stimuli of straight eyes and similar images are never present (as in congenital esotropia) the system simply does not function. Nothing is suppressed. Now the patient must monofixate in the absence of bifixation. Unless the fixation is alternated from macula to macula, the necessary reinforcement of the nonpreferred macular-cortical system required to maintain peak proficiency is lacking, and amblyopia becomes established. In summary, suppression occurs in neither the monocular macular-cortical system nor the macular binocular visual system. Thus, the concept that macular suppression is the cause of amblyopia is erroneous and misleading.

A direct outgrowth of the macular suppression amblyopia misconception is the prevalent thought that eccentric fixation and anomalous correspondence are related. Eccentric fixation expresses a profound degree of amblyopia and implies that the fixation reflex is nonexistent. The macular suppression amblyopia concept so tempted some authors to believe that an eccentric retinal point assumes the function of the macula that it received the name “pseudomacula.” The next step was to relate the macula of the fixating eye and the pseudomacula of the strabismic eye as having assumed a binocular linkage that replaced normal

retinal correspondence with anomalous retinal correspondence. Such a naive concept illustrates the lack of knowledge about suppression, which in fact eliminates all chances of binocular vision between the macula of one eye and the purported pseudomacula of the other eye. Instead of an anomalous fusion of the images on the macula and pseudomacula, the images from the area of conscious regard that project on the pseudomacula are suppressed.

Images projected onto the strabismic eye from the area of conscious regard are not involved in anomalous retinal correspondence. Only the spatial area outside of conscious regard, which projects onto disparate extramacular retina areas of the strabismic eyes, is involved in anomalous retinal correspondence. Anomalous retinal correspondence, like suppression, is a sensorial adaptation that is restricted to the extramacular binocular vision system.

Another misconception about binocular vision comes from an old definition stating that “fusion in the presence of a manifest deviation of the eyes is anomalous retinal correspondence” (7). This was once thought to be correct but is no longer tenable. It was formulated before the concept that the misalignment tolerance acceptable for fusion is different for macular binocular vision as opposed to extramacular binocular vision. The 0.5 prism diopter tolerated by macular binocular vision (fixation disparity) is not detectable by the observer, but the 8 prism diopters tolerated by extramacular binocular vision are detectable. The old definition made 50 years ago still today leads many to insist that the patient with monofixation syndrome with a manifest 8 prism diopters or less deviation is obtaining fusion by using anomalous retinal correspondence. They disregard the following facts:

1. The normal retinal correspondence phoria status in a patient with monofixation syndrome should be recognized on the reduction of an alternate cover measurement exceeding 8 prism diopters to the smaller angle of 8 prism diopters or less by cover-uncover testing.
2. The patient with anomalous retinal correspondence would not reduce the deviation to 8 prism diopters or less because fusional vergence is not present.
3. The patient with anomalous retinal correspondence would be unaware of any stimuli that would evoke a fusional vergence, such as diplopia and visual confusion.
4. The stereoacuity in a patient with monofixation syndrome remains unchanged whether the deviation by cover-uncover testing is 0 or 8 prism diopters, but stereopsis vanishes if the deviation exceeds 8 prism diopters.

REFERENCES

1. Parks MM. Sensory tests and treatment of sensorial adaptations. In: Duane TD, Jaeger EJ, eds. *Clinical ophthalmology*. Vol. 1. Philadelphia: JB Lippincott Co., 1990:1-13.

2. Ogle KN. Fixation disparity. *Am J Ophthalmol* 1954;4:35.

3. Parks MM. Stereoacuity, an indicator of bifixation. In: *Strabismus symposium*. New York: Karger, 1968:258.

4. Parks MM. Single binocular vision. In: Duane TD, Jaeger EJ, eds. *Clinical ophthalmology*. Vol. 1. Philadelphia: JB Lippincott Co., 1990.

5. Scott WE. Office use of prisms. Symposium on strabismus. *Trans New Orleans Acad Ophthalmol*. St. Louis: CV Mosby Co., 1978:96-99.

6. Parks MM. Monofixation syndrome. *Trans Am Ophthalmol Soc* 1969;67:609.

7. Burian HM. Sensorial retinal relationship in concomitant strabismus. *Trans Am Ophthalmol Soc* 1945;53:373.

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9

Strabismus Disorders

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Strabismus, or abnormal ocular alignment, is one of the most common eye problems encountered in children. The misalignment may be manifest in any field of gaze, constant or intermittent, and may occur at distant or near fixation or both. Strabismus affects between 2% and 5% of the preschool population and is an important cause of visual and psychological disability (1,2,3,4).

The word “strabismus” derives from the Greek *strabismos* (a squinting) and probably predates the geographer Strabo, whose “peculiarly horrible and unbecoming squint was famous in Alexandria during the Roman Empire.”

Strabismus involves a number of different clinical entities. Knowledge of the terms used to describe a strabismic deviation and the more common patterns of strabismus helps to predict the cause of the strabismus and to determine proper treatment.

Orthophoria is the condition of exact ocular balance. It implies that the oculomotor apparatus is in perfect equilibrium so that both visual axes always intersect at the object of visual regard.

Heterophoria is a latent tendency for the eyes to deviate. This latent deviation is normally controlled by fusional mechanisms that provide binocular vision or avoid diplopia. The eye deviates under certain conditions only, such as fatigue, illness, stress, or tests that interfere with the maintenance of these normal fusional abilities (such as covering one eye). If the amount of heterophoria is large, it may give rise to bothersome symptoms, such as transient diplopia or asthenopia.

Heterotropia is a misalignment of the eyes that is manifest. The condition may be alternating or unilateral, depending on the vision. In alternating strabismus, either eye may be used for definitive seeing, while the fellow eye deviates. Because each eye is used in turn, each develops similar vision. In unilateral strabismus, only one eye is preferred for fixation, while the fellow eye deviates consistently. The constantly deviating eye is prone to defective central vision during the visually immature period of life.

A convergent deviation, crossing or turning in of the eyes, is designated by the prefix “eso-” (i.e., esotropia, esophoria). Divergent deviation, or turning outward of the eyes, is designated by the prefix “exo-” (i.e., exotropia, exophoria). Vertical deviations are designated by the prefixes “hyper-” and “hypo-” (i.e., hypertropia, hypotropia). In cases of unilateral strabismus, the deviating eye is often part of the description of the misalignment (left esotropia). Most vertical deviations are described in terms of the hypertropic eye. An exception to this general rule occurs when the lower, or hypotropic, eye is restricted in its movement. The deviation is then named according to the hypotropic eye.

Ocular Alignment in Infancy

Ocular deviations during the first month of life do not necessarily indicate an abnormality. Because of oculomotor instability during this time, adequate assessment of alignment is usually not made until the patient is approximately 3 months of age and any angle of strabismus that is present is stable (5).

Infants are rarely born with their eyes aligned. During the first month of life, alignment may vary intermittently from esotropia to orthotropia to exotropia. Nixon et al (6) observed 1,219 alert infants in a newborn nursery in an attempt to discern whether esotropia is present at birth or develops later in infancy. They found that 593 (40%) infants seemed to have straight eyes, 398 (33%) had exotropia, and 40 (3%) had esotropia. Many had variable alignment, and 188 (7%) were not sufficiently alert to permit classification. Other large population studies have confirmed that strabismus is common in early infancy (7,8).

PSEUDOESOTROPIA

Pseudoesotropia is one of the most common reasons that an ophthalmologist is asked to evaluate an infant. Costenbader (9) found that, of 753 patients suspected by their parents to have esotropia, 47% actually had pseudoesotropia.

This condition is characterized by the false appearance of esotropia when the visual axes are aligned accurately. The appearance may be caused by a flat, broad nasal bridge;

prominent epicanthal folds; or a narrow interpupillary distance (Fig. 9.1). The observer sees less sclera nasally than would be expected, which creates the impression that the eye is turned in toward the nose, especially when the child gazes to either side. This might be especially noticeable in photographs taken from an angle. Pseudoesotropia can be differentiated from a true manifest deviation by use of the corneal light reflex and the cover-uncover test, when possible. Once pseudoesotropia has been confirmed, parents can be reassured that the child will outgrow the appearance of esotropia. As the child grows, the bridge of the nose becomes more prominent and displaces the epicanthal folds, so that the sclera medially becomes proportional to the amount visible on the lateral aspect. It should be stressed that it is the appearance of crossing that the child will outgrow. Some parents of children with pseudoesotropia erroneously believe that there is an actual esotropia that will resolve on its own. Because true esotropia can develop later in children with pseudoesotropia, parents and pediatricians should be cautioned that reassessment is required if the apparent deviation does not improve.

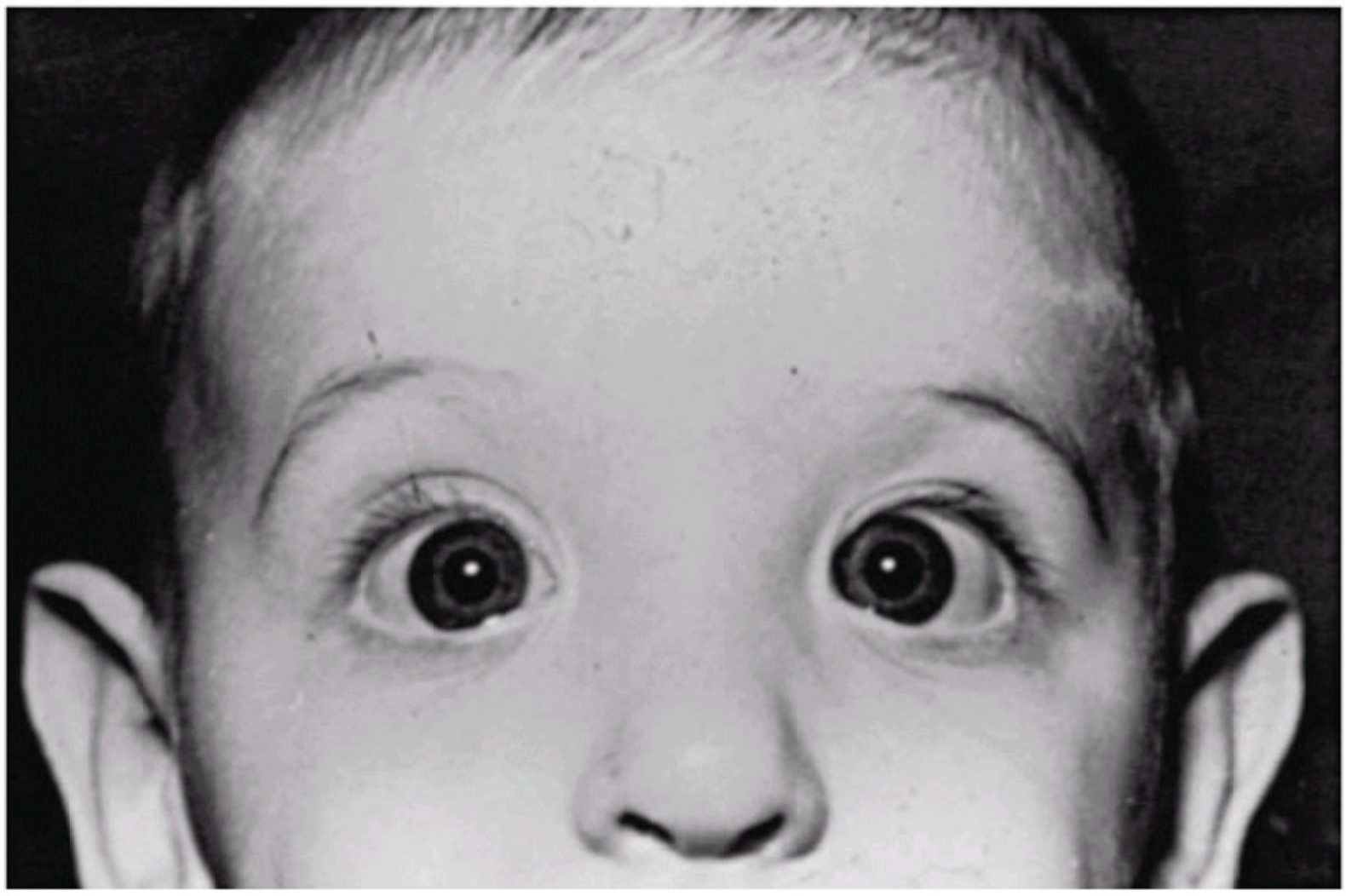

Figure 9.1 Pseudoesotropia caused by a wide nasal bridge and epicanthal folds. Note that the light reflex is centered in each pupil. (Courtesy of Steven Rubin, MD.)

CONGENITAL ESOTROPIA

Definition

The term *congenital esotropia* is a confusing one. Few children who are eventually diagnosed with this disorder are actually born with an esotropia. Although parents often give a history of their child's eyes crossing since birth, they rarely remember seeing the deviation in the newborn nursery and will often deny seeing it during the first few weeks of life. Ophthalmologists have also rarely found infants with esodeviations to have been born with the condition. In a prospective study of 3,324 infants, only 3 children developed findings characteristic of congenital esotropia. All of these children were either orthotropic or exotropic at birth (9). Most reports in the literature have therefore considered infants with confirmed onset earlier than age 6 months as having the same condition, which some observers have redesignated “infantile” or congenital-infantile esotropia (10,11). The differentiation between these terms may be important. A child born with a later-onset congenital esotropia may have a better prognosis for the development of binocular vision than a child with a true congenital deviation because he or she would have had an early period of ocular alignment, which could provide a stimulus for the early formation of binocular development (12). Although the merit of such terminology is recognized, the term *congenital esotropia* will be used in this discussion. Congenital esotropia remains a widely accepted designation, and other congenital ocular disorders, including cataracts, glaucoma, and nystagmus, may not become evident during the immediate postnatal period.

Epidemiology

Congenital esotropia is a common form of strabismus, with an incidence of 1% to 2%, in most series (13,14). The sex distribution of congenital esotropia is equal. Transmission in many families seems to be as an irregular autosomal dominant trait; in others it may be recessive. Others have found different results, and the reported incidence of affected family members has varied widely (15). It is common to find a history of strabismus in the parents or siblings of affected patients. Reduced binocular function has been reported in parents of patients with congenital esotropia and may represent a subthreshold effect of the genes that cause this disorder (16). The incidence of congenital esotropia is higher in patients with a history of prematurity, cerebral palsy, hydrocephalus, and other neurological disorders. Maternal cigarette smoking and low birthrate have also been linked to the development of esotropia (17).

Pathogenesis

Much clinical literature in this century has focused on the implications of two conflicting theories of pathogenesis for congenital esotropia. Worth's (18) sensory concept was that congenital esotropia resulted from a deficit in a supposed fusion center in the brain. According to his theory, the goal of restoring binocularity was considered hopeless, because there was no way to provide this congenitally absent neural function. Until the 1960s, results of surgical treatment almost universally supported this pessimistic view (19,20,21). Data on these patients were obtained at a time when surgery was rarely performed before age 2.

Chavasse (22) disagreed with Worth's theory. He suggested that normal binocular vision may be achieved through facilitation of conditioned reflexes that depend on early ocular alignment. To Chavasse, the primary problem was mechanical. In this view, most congenital esotropes were potentially curable, if the deviation could be fully eliminated in infancy. Only theoretical support was available for this motor theory, until Costenbader (9), Taylor (23), and Ing (24) began to report favorable binocular results in some infants operated on between ages 6 months and 2 years. These encouraging results became the basis for the theory of early surgery for patients with congenital esotropia.

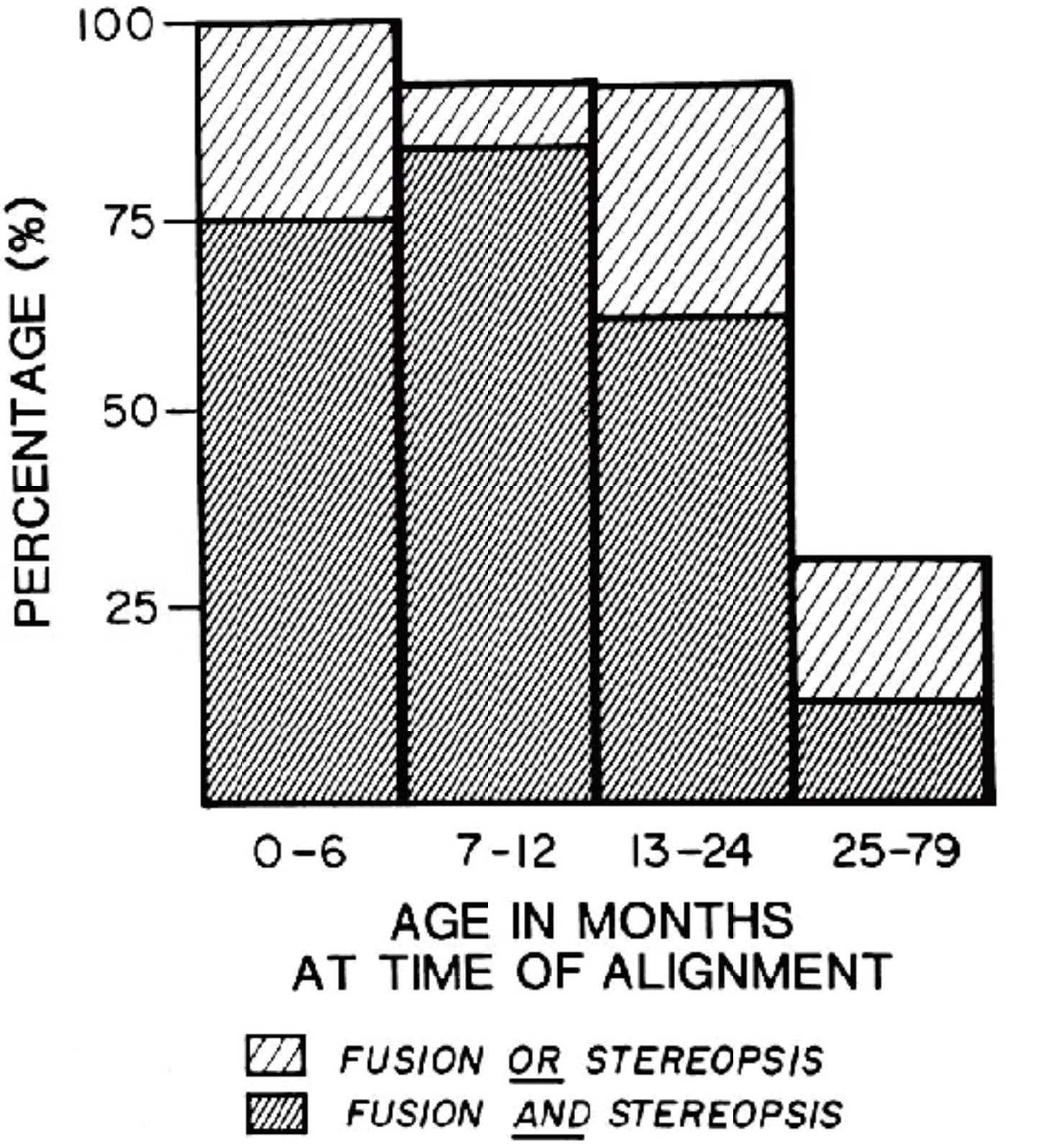

Figure 9.2 Binocularity results from surgical alignment in congenital esotropia. (From Ing MR. Early surgical alignment for congenital esotropia. *Trans Am Ophthalmol Soc* 1981;79:625, with permission.)

Even advocates of early surgery have generally found imperfect binocularity in their postoperative patients. Von Noorden (13) summarized the sensory results obtained by most investigators using various tests of binocularity by cautioning that “subnormal binocular vision must be considered an optimal result.” Parks defined *monofixation syndrome*, in which peripheral fusion and vergence amplitudes capable of maintaining alignment within approximately 10 prism diopters may exist, despite deficient stereopsis and a central suppression scotoma in one eye during binocular viewing (25). Many strabismus surgeons accept this sensory state as the goal of treatment (see “Treatment” in later text). Ing (26) used the Worth 4-Dot system and a gross test of stereopsis to compare the binocularity of 106 patients successfully aligned at various stages in infancy. His results, summarized in Figure 9.2, indicated that alignment earlier than age 2 was associated with fusion or stereopsis in 93%, as opposed to 31% after age 2.

Research in experimental animals by Hubel (27), Wiesel (28), von Noorden, and Tychsen and Burkhalter (29), among others, demonstrated that the structural and functional integrity of binocular cells in the lateral geniculate nucleus and visual cortex require early binocular experience. Also, Crawford et al (30) showed that only a brief period of binocular dissociation in infant monkeys can cause a permanent loss of stereopsis, in spite of subsequent prolonged periods of normal binocular visual input.

The pathogenesis of congenital esotropia remains unanswered. Helveston et al (11) reviewed their experience with 44 infants, whose esotropia was confirmed during the first 6 months. Of 13 patients surgically aligned before age 12 months, none achieved stereopsis. In contrast, 12 of 31 operated on after 12 months did develop at least gross stereopsis. Given this experience, these authors suggested that there are two forms of congenital esotropia. The first conforms to Worth's model and has no fusion potential, even with early surgical correction. In the second form, the concepts of Chavasse seem more valid: Binocularity begins to develop but is overcome by motor factors later in infancy. Even though surgery tends to be performed later in these patients, they are more likely to achieve stereopsis. Other authors have also supported the concept that congenital esotropia probably constitutes more than a single etiologic category (31).

Clinical Manifestations

Visual Acuity

The association of amblyopia and congenital esotropia is well known. Amblyopia may occur in a higher precentage of patients with congenital esotropia than was once thought. It is difficult to ascertain the exact incidence, however, especially in preverbal children. The incidence of amblyopia may be as high as 40% to 72%(8,32). Many infants spontaneously alternate their fixation and do not develop amblyopia. Others may “cross-fixate,” using alternate eyes in the opposite field of gaze, and appear to be protected as well (Fig. 9.3). Some children may develop a preference for one eye and fixate with the other, either in far side gaze or not at all (33). Studies using preferential looking as a

test of infant acuity suggested that amblyopia may develop several months after the onset of fixation preference (34,35).

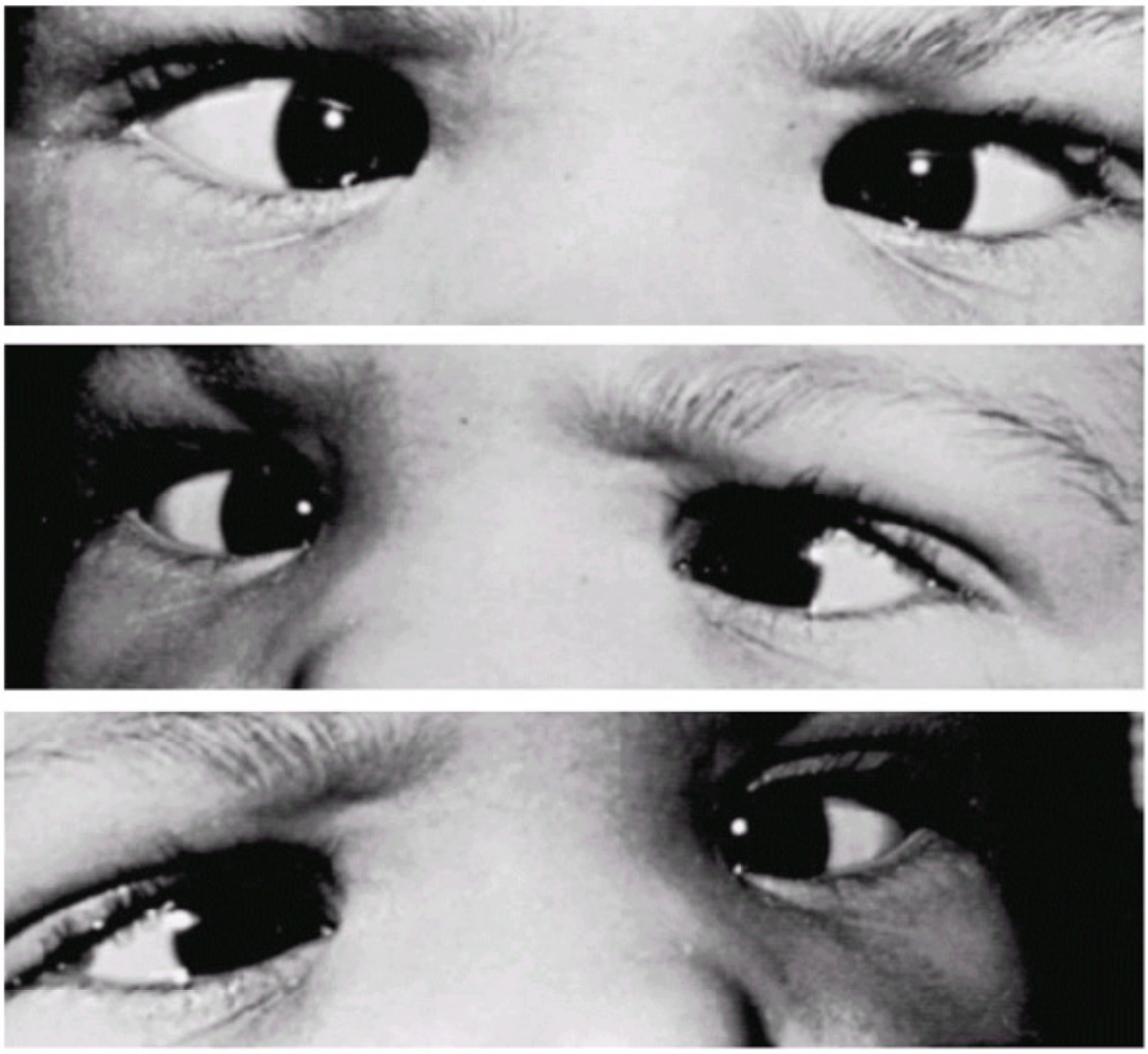

Figure 9.3 Congenital esotropia in the primary position. Note the large esodeviation (top). Cross fixation with the child using the right eye to gaze left (center); cross fixation with the child using the left eye to gaze right (bottom). (From Nelson LB, Brown GC, Arentsen JJ. *Recognizing patterns of ocular childhood diseases*. Thorofare, N**J:** Charles Slack, 1985, with permission.)

Figure 9.4 Large angle of esotropia in a 6-month-old child.

Size of Deviation

The characteristic angle of congenital esodeviations is considerably larger than those acquired later in life (Fig. 9.4). Helveston et al (11) found a mean of 40 prism diopters in 133 children. Hiles et al (33) and Costenbader (9) noted averages in the 50- to 60-prism-diopter range, some infants measuring 80 prism diopters or more. Measurements tend to be similar at distance and near, although accurate distant fixation is difficult to achieve in the examination of infants. Because the prism cover test is also difficult in most young infants, the Krimsky method is often substituted. In a commonly used adaptation of the Krimsky technique, two base-out prisms are used, apex to apex, to center the pupillary light reflexes in infants with larger angles (Fig. 9.5). It should be remembered that prisms held this way do not add linearly, and an error in measurement can be introduced, if this fact is not taken into account when measuring very large angles of deviation (36). There is little short-term variability in the deviation size; it is generally unaffected by accommodation from one moment to the next. Long-term changes may occur: Increases seem more frequent than decreases. Ing (37) found that a majority of patients showed an increase in their angle of deviation when followed over an average of 3 months. However, there have been some patients with both small and large angle esotropias that have resolved on their own (38,39).

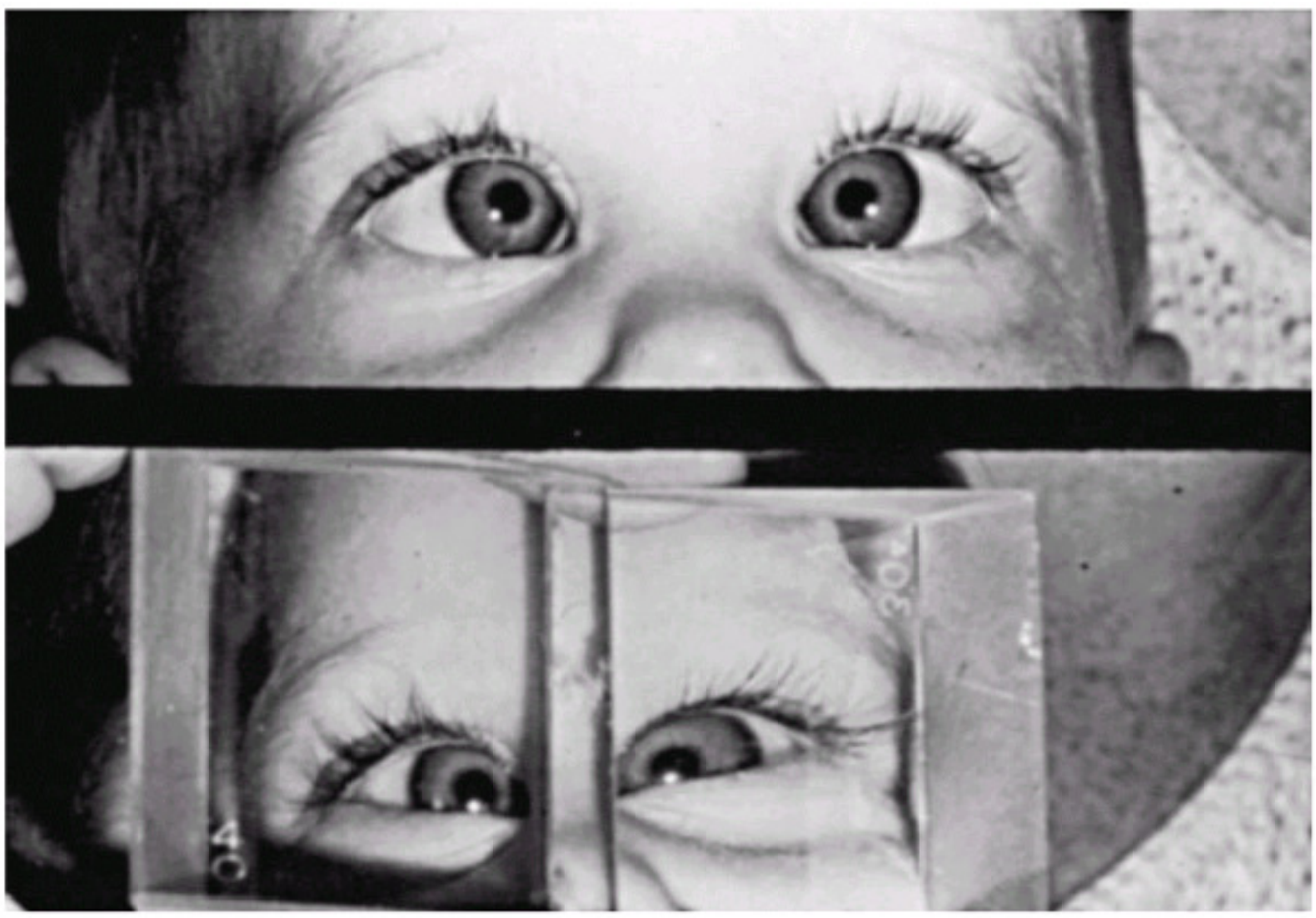

Figure 9.5 Congenital esotropia in the primary position (top). The modified Krimsky method to measure the large angle of esotropia (bottom). (From Nelson LB, Wagner RS, Simon JW, et al. Congenital esotropia. *Surv Ophthalmol* 1987;31:363, with permission.)

Refractive Errors

Children with congenital esotropia tend to have cycloplegic refractions similar to those of normal children of the same age (9,40,41). These observations contrast markedly with the characteristic hyperopia associated with accommodative esotropia, especially of the refractive types (42). Burian (43) emphasized that esodeviations tend to decrease with time in children with high hyperopia.

Ocular Rotations

Children with congenital esotropia will often appear to exhibit an apparent abduction deficit. This pseudoparesis is usually secondary to the presence of cross-fixation. If the child has equal vision, he or she will have no need to abduct either eye. The child will use the adducted, or crossed, eye to look to the opposite field of gaze. In this case, the child will show a bilateral pseudoparesis of abduction. If amblyopia is present, only the better seeing eye will cross-fixate, making the amblyopic eye appear to have an abduction weakness. A true unilateral or bilateral abducens nerve palsy is uncommon in infancy. To differentiate between a true abducens paralysis and a pseudoparalysis, two techniques may be used. The examiner can evaluate ocular rotations by rotating the infant's head, either with the infant sitting upright in a movable chair or using a doll's head maneuver. Abduction testing can also be examined after the infant has worn a patch over one eye for a period of time.

Associated Findings

Dissociated Vertical Deviation (DVD)

Dissociated vertical deviation (DVD) consists of a slow upward deviation of one or alternate eyes. Occasionally, excyclotorsion can be demonstrated on upward drifting of the eye and incyclotorsion on downward motion. DVD may be latent, detected only when the involved eye is covered or manifest, occurring intermittently or constantly (Fig. 9.6). It can be differentiated from a true vertical deviation, because no corresponding hypotropia occurs in the other eye on cover testing.

Bielschowsky's (44,45) phenomenon is another feature of DVD, characterized by downward movement of the occluded eye when filters of increasing density are placed before the fixating eye. Although the etiology of DVD is unknown, Guyton (46) suggested that it may be secondary to a cycloversion/vertical vergence that is produced to dampen a cyclovertical nystagmus that occurs in patients with an early onset defect of binocular function.

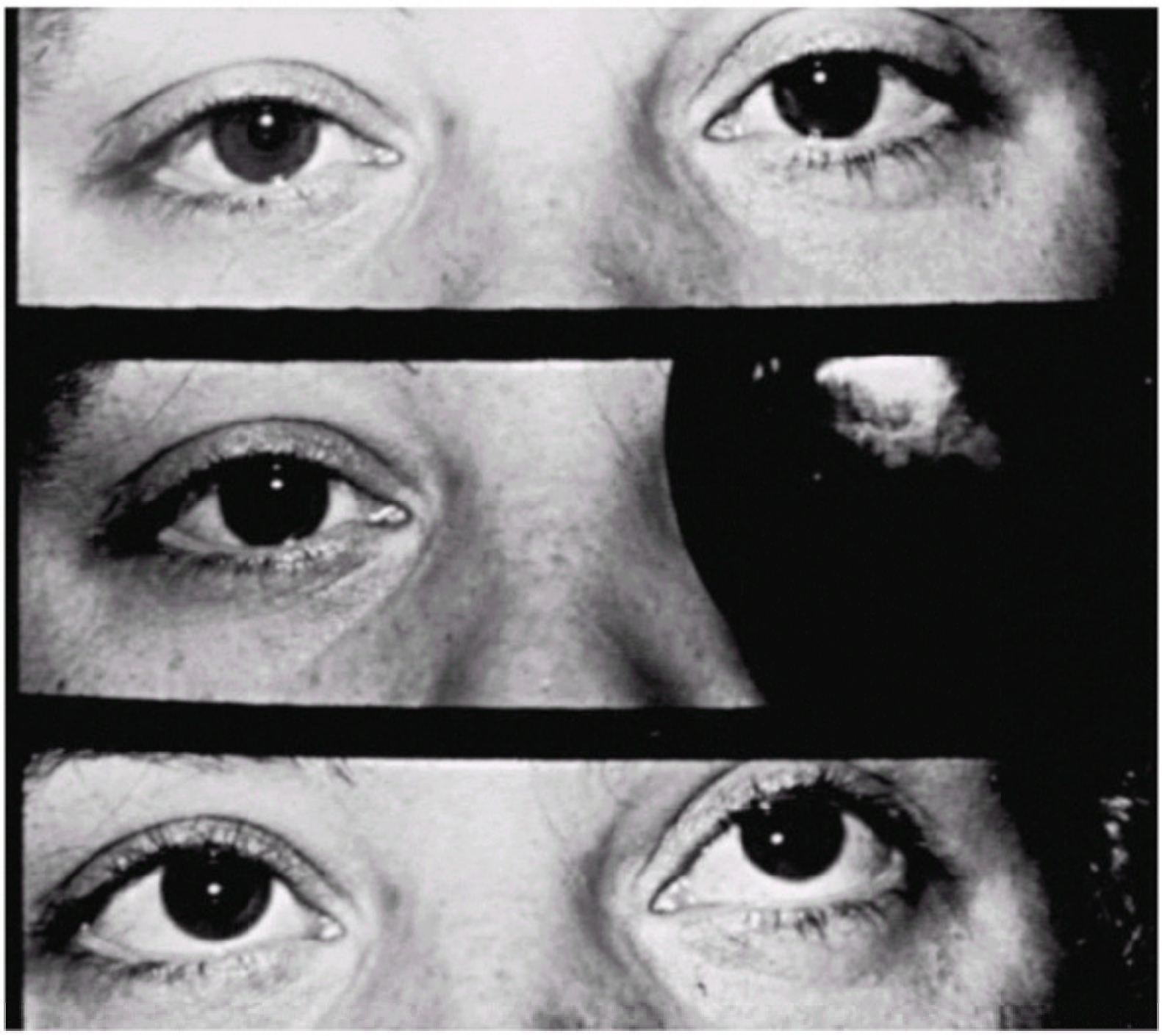

Figure 9.6 Dissociated vertical deviation. When the patient is fixating in the primary position, no deviation is noted (top). A cover is placed in front of the left eye (center). When the cover is removed from the left eye, it now elevates (bottom). (From Nelson LB, Wagner RS, Simon JW, et al. Congenital esotropia. *Surv Ophthalmol* 1987;31:363, with permission.)

The incidence of DVD in patients with congenital esotropia is high, ranging from 46% to 92% (33,44,47). Hiles et al (33) found DVD in 76% of their congenital esotropes, with onset greatest during the second year of life. After the third year, this occurred at a mean rate of 10% per year. Ing (10) reported a 63% incidence of DVD in his study of postoperative patients, and Neely et al (47) found an incidence of 92% by age 6. DVD appears to be a time-related phenomenon and is not related to successful initial surgery or the development of binocular vision (10,47,48).

DVD can be estimated by using the Hirschberg and Krimsky methods or the prism cover test (49). A base-down prism is placed over the involved eye. The strength of the prism is adjusted until no movement occurs as the cover is shifted from the involved to the fixating eye. Because prism cover measurement is difficult and may be inaccurate, some observers prefer to estimate DVD on a semiquantitative grading scale (1 to 4+) (44,50).

Inferior Oblique Overaction

The incidence of overaction of one or both inferior oblique muscles in patients with congenital esotropia has been reported to be as high as 78%. Hiles et al (33) noted the onset of inferior oblique overaction (IOOA) to be most frequent during the second year of life, with a mean rate of 33% per year; the greatest occurrence was during the third and seventh years. Wilson and Parks (51) found an incidence of IOOA of 72% in patients with a history of congenital esotropia. The average age of onset in their study was 3.6 years. There was no correlation between the development of IOOA and age at surgery, time from onset of strabismus to surgery, or decompensation of ocular alignment. The presence of fundus torsion at the time of surgery may help to predict which patients will develop IOOA (52). IOOA and DVD are both conditions that can cause excessive elevation of one or both eyes in adduction in patients with congenital esotropia. The differentiating features of these two conditions are listed in Table 9.1 (53). IOOA results in elevation of the involved eye as it moves nasally (Fig. 9.7). DVD may also result in elevation as the eye moves nasally because the nose acts as a cover, dissociating the eyes. However, the vertical misalignment in DVD usually occurs equally in abduction, adduction, and primary position. When the adducting eye in IOOA fixates, there is a corresponding hypotropia in the contralateral abducting eye. In DVD, contralateral hypotropia does not occur. IOOA and DVD frequently occur together in these patients. Hiles et al (33) noted an incidence of 59% of the two occurring concomitantly.

TABLE 9.1 DISTINGUISHING FEATURES OF DISSOCIATED VERTICAL DEVIATION AND INFERIOR OBLIQUE OVERACTION

Dissociated Vertical Deviation
1. Causes elevation in adduction and abduction
2. Usually comitant, i.e., same in adduction, primary, and abduction
3. Variability of hyperdeviation
4. Usually not associated with a pattern
5. Same amount of hyperdeviation in upgaze and downgaze
6. Hyperdeviation may be associated with torsional movement and abduction
7. No corresponding hypotropia in abducted eye
Inferior Oblique Overaction
1. Causes elevation in adduction, not abduction
2. Incomitant, more in field of action of inferior oblique
3. Not variable
4. Commonly associated with V pattern
5. More hyperdeviation in upgaze than downgaze

6. Hyperdeviation not associated with torsional movement

7. Corresponding hypotropia in abducted eye

Modified from Scott WE, Sutton VJ, Thalacker JA. Superior rectus recessions for dissociated vertical deviation. *Ophthalmology* 1982; 89:317-322, with permission.

IOOA can be classified as grades I to IV. Grade I represents 1 mm of higher elevation of the adducting eye in gaze up and to the side. Grade IV indicates 4 mm of higher elevation. These differences in elevation between the two eyes are measured from the 6 o'clock position on each limbus. A measurement of the degree of adduction that is required to elicit the overaction is also helpful when considering treatment. A moderate-size overaction that occurs with limited adduction may be more noticeable than a larger overaction that is seen in extreme side gaze only.

Nystagmus

Rotary nystagmus may occur in children with congenital esotropia. Hiles et al (33) found rotary nystagmus in 30%

of their patients with congenital esotropia; it tended to diminish during the first decade of life. In the authors' experience, the incidence of this type of nystagmus is much less.

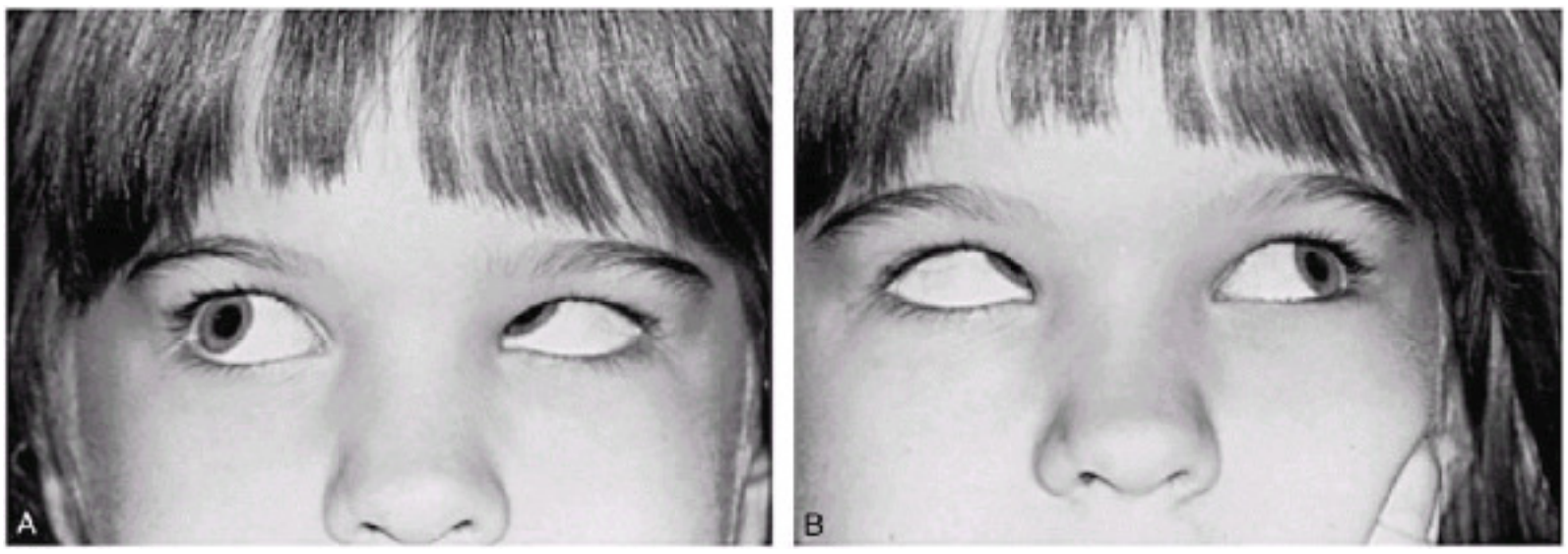

Figure 9.7 A: Overacting left inferior oblique. **B:** Overacting right inferior oblique.

Latent nystagmus is a predominantly horizontal jerk nystagmus elicited by occluding either eye. The slow phase is toward the side of the occluded eye. This type of nystagmus also tends to diminish with time. Measurement of visual acuity in the uncovered eye, while using opaque occlusion of the nonviewing eye, produces the maximal nystagmus and the poorest vision. Alternative methods for evaluating visual acuity that create a relative binocular state by partially occluding or blurring the image in the nonviewing eye include fogging lenses, double polarizing lenses, and the green filter in the Worth red-green glasses with the duochrome slide of the American Optical Project-O-Chart (54).

Latent nystagmus is more common than rotary nystagmus in congenital esotropia. If a significant latent nystagmus is present, amblyopia treatment, using occlusion therapy, may be less effective because the nystagmus will decrease the central vision stimulation. Other forms of amblyopia treatment may be more efficacious, if this occurs. There are conflicting reports as to whether the presence of nystagmus decreases initial success of surgery in patients with congenital esotropia (55,56).

Differential Diagnosis

During the first year of life, a number of conditions can simulate congenital esotropia and cause diagnostic difficulty (Table 9.2). Because the management of these conditions may differ from the treatment of congenital esotropia, their clinical recognition is important. In general, a relatively small angle deviation should raise doubt in assigning the diagnosis of congenital esotropia. Many of these other disorders can be ruled out following a thorough ophthalmologic evaluation. For this reason, all infants presenting with esotropia require a full evaluation, including a dilated funduscopic examination.

Treatment

Goals and Timing of Treatment

The primary goal of treatment in congenital esotropia is to reduce the deviation at distance and near to orthotropia, or as close to it as possible. Ideally, this results in normal sight in each eye, in straight-looking eyes, and in development of at least a rudimentary form of sensory fusion that will maintain motor alignment. One measurement of long-term success in these patients can be made by evaluating the number of surgeries required to maintain cosmetically acceptable alignment.

Classically, it has been taught that patients with congenital esotropia never develop bifoveal fixation, that is, they do not develop stereoscopic acuity of 40 seconds of arc, regardless of their age at surgical alignment (40). Clinical evidence suggests, however, that alignment within 10 prism diopters of orthotropia before age 2 is associated with the attainment of some degree of binocular vision and stereopsis (10,25,57). Recently, there have been reports of patients obtaining bifoveal fixation when operated on at a very young age (57). These reports are the basis for the theory of very early surgery in congenital esotropia. Conversely, although the chance of developing binocular vision decreases

with the patient's age at the time of surgical alignment, even older patients can develop some degree of binocularity later in life, once their eyes are aligned. Morris et al (58) found that 12 adult patients with a history of congenital esotropia, who had never been treated, achieved peripheral fusion after surgical alignment to

within 8 prism diopters of orthotropia. Eight of these patients also developed stereopsis.

TABLE 9.2 DIFFERENTIAL DIAGNOSIS OF CONGENITAL ESOTROPIA

Pseudoesotropia
Duane's retraction syndrome
Mobius' syndrome
Nystagmus blockage syndrome
Congenital sixth nerve palsy
Early-onset accommodative esotropia
Sensory esotropia
Esotropia in the neurologically impaired

The most often found sensory result in patients successfully aligned before age 2 is the monofixation syndrome, as described by Parks (Table 9.3) (10,11,25,59). The purported benefit derived from the monofixation syndrome, in which the horizontal deviation is less than 10 prism diopters, is the development of peripheral normal retinal correspondence and fusional vergence amplitudes. Parks (60) claimed that these attributes are instrumental in maintaining motor alignment in such patients for the remainder of their lives. Arthur et al (61) showed this to be true. In their study, 80 patients who had been treated for congenital esotropia were divided into two groups; those who had obtained monofixation syndrome and those who had not. Over 17.5 years, 74% of patients in the monofixation group had maintained alignment. Over 14 years, only 45% of patients without monofixation had achieved the same outcome. However, the prognosis for long-term alignment is not the same for all patients who achieve the monofixation syndrome. Kushner subdivided these patients into three categories: orthophoria, esotropia up to 8 prism diopters, and exotropia up to 8 prism diopters. He found that patients who were orthophoric showed the best long-term stability. Those children with a small-angle esotropia were less stable than those who were orthophoric but more stable than those with a small-angle exotropia. Because the role of binocular potential at birth could not be eliminated in predicting who would fall into each of these three categories, it is not known whether active intervention, that is, further surgery for small-angle deviations, has any role in improving the long-term success rate of maintaining ocular alignment (62).

Parents of children with congenital esotropia often report improvements in their child's fine motor development and visual function after surgery. Rogers et al (63) showed that early alignment is associated with improved fine motor skills and other visually directed tasks. The improved appearance of the child can enhance his or her psychological acceptance by the parents. This can be instrumental in the normal development of the parent-child relationship (64).

TABLE 9.3 CHARACTERISTICS OF THE MONOFIXATION SYNDROME

1. Manifest horizontal deviation is 8 prism diopters or less

2. Scotoma under binocular conditions

    a. Demonstrated by any of several tests: Worth 4 Dot, 4 base-out prism test, Bagolini lenses, binocular perimetry

    b. May also be present under monocular conditions, i.e., organic macula lesion

3. Normal fusional vergences

4. Stereo acuity is 67 to 3,000 sec of arc

5. May also be present:

    a. Amblyopia

    b. Superimposed phoria

    c. Anisometropia

In the past, some surgeons preferred to wait to operate on patients with congenital esotropia until they were 2 years of age or older because of the difficulty in obtaining sufficiently complete information in young patients, an unacceptably high incidence of reoperations, and the lack of proven functional benefit (65,66). Although Ing showed that surgery before age 2 gave a better chance for the development of binocular vision, Birch et al demonstrated that surgery prior to age 1 increased the level of the binocularity that was obtained (10,67). In their study, 73 children undergoing surgery for congenital esotropia were studied prospectively. The number of children achieving random dot stereopsis was not significantly different among patients who had undergone surgery prior to age 2. However, there was a statistical significance in the level of stereopsis between groups of these patients. The prevalence of foveal (less than 60 seconds) or macular (61 to 200 seconds) was 42% in patients who had surgery at ages 5 to 8 months and 55.6% at ages 9 to 12 months. No patient who underwent surgery at ages 13 to 24 months achieved this level of binocular vision (67). Some surgeons encourage surgery earlier than age 6 months, with the hope of achieving perfect binocular vision (57,68). Patients with a constant and stable esotropia of at least 40 prism diopters, who present between ages 2 to 4 months, are unlikely to improve spontaneously, providing another argument for even earlier surgery (69,70). Other surgeons continue to express concerns over operating at a very early age (71,72). These concerns include the documented spontaneous resolution of esotropia in some infants, anesthetic risks, and an unproven influence on long-term horizontal alignment and/or the development of IOOA and DVD.

Nonsurgical Treatment

Amblyopia

Early and rigorous amblyopia therapy is an essential component in the treatment of congenital esotropia. Treatment in older children is more difficult, more time-consuming, and less effective in restoring acuity in the amblyopic eye. Many clinicians, therefore, prefer to initiate nearly total daytime occlusion of the dominant eye early in the patient's infancy. Patching is continued with monitoring of fixation behavior or quantitative acuity measurements at intervals of 1 week per year of age.

A variety of clinical maneuvers have been helpful in cases of amblyopia when patching is difficult. Many children experience excoriation of the periocular skin related to the patch. Once the skin has healed, tincture of benzoin can be applied to protect the skin and increase the adhesiveness of the patch. For children who also require glasses, a clip-on or suction cup occluder can be attached to the back of the spectacle lens, preventing light from entering the dominant eye. Care must be taken that the child does not

“cheat” and look around the patch. Homemade elbow splints can be fashioned from cardboard and taped in place to prevent habitual removal of patches or glasses. This technique is usually required for only the first few days of occlusion. The use of atropine to penalize the fixating eye has been shown to be effective in treating amblyopia of older children with moderate amblyopia (73). Atropine has also been used in this younger population, sometimes as the first line of therapy. In a child with dense amblyopia and only a small amount of hyperopia in the fixating eye, it is unlikely that atropine will be effective.

Once alternate fixation in the midline can be demonstrated, the child is assumed to have no significant amblyopia, and patching is discontinued (Fig. 9.8). Evaluation for the presence of cross-fixation may also be useful in monitoring response to amblyopia treatment, although mild amblyopia may be present in patients who demonstrate this fixation pattern (74). However, continued monitoring remains necessary. Maintenance patching part time may be required for infants who revert to their original fixation preference, and patching of the previously amblyopic eye may be needed for those who switch fixation preference to the other eye. If occlusion has not been successful after several months, reexamination for subtle organic disorders (e.g., optic nerve hypoplasia) is indicated. More often, there has been noncompliance with recommended patching. Recurrent and new onset amblyopia is common in these children during the period of visual immaturity. Hiles et al found that an average of 31% of patients required some patching during each of the first 8 years (33).

Surgery is usually performed after amblyopia treatment is completed. Classically, it had been taught that surgery alone could not correct amblyopia and that amblyopia itself was an impediment to the development of binocular vision. However, Lam et al showed that there was no difference in motor or sensory outcome, if amblyopia therapy is postponed until after early surgery is performed (75). Some patients in this study showed resolution of their amblyopia after surgery, with no other form of therapy. The authors believe that it is best to first treat the amblyopia, if present. Amblyopia management in an infant is easier in the presence of a large esotropia. Judgment concerning fixation preference is difficult in a preverbal child with straight eyes. Occlusion therapy in children at this young age generally requires only a small amount of time to equalize vision and therefore does not delay surgical correction to a significant degree. Also, parental incentive to comply with the often arduous task of occlusion therapy is greatly diminished once the child's eyes are straight.

Refractive Errors

Because most children are hyperopic, it may sometimes be difficult to decide which children should be given a trial of antiaccommodative therapy before suggesting surgery. Accommodative esotropia in this age group is uncommon but does occur (Fig. 9.9). The amount of hyperopia relative to the angle of deviation should be considered. Even a moderate level of hyperopia would not be expected to be the cause of a very large esotropia, and children with a well-documented history of early crossing may not respond to treatment of even higher levels of hyperopia. Antiaccommodative therapy can be provided both pharmacologically and optically. Spectacles may be fitted in even very young infants, if necessary, and have the advantage of providing quantifiable antiaccommodative therapy. Miotics control accommodation less reliably than glasses. Bedrossian looked at the response to miotics in a population of patients who were all orthotropic with glasses. Only 42% showed the same response to pharmacologic therapy. Ten percent demonstrated no response to the miotic (76). Miotics have been associated with pupillary cysts and, in adults, with retinal detachment and cataract. In addition, miotics may result in prolonged apnea after anesthesia, if succinylcholine is used. At best, they only delay the inevitable trial of spectacles.

Surgical Treatment

Various surgical techniques have been used for the correction of congenital esotropia. Proponents of two-muscle surgery

advocate either symmetrical recession of both medial rectus muscles, or monocular medial rectus recession combined with lateral rectus resection, regardless of the size of the preoperative deviation (77,78,79,80). Both procedures are graded, with more millimeters of surgery performed for larger angles. If a second procedure is required, a resection of one or both lateral rectus muscles, or a recess-resect procedure in the fellow eye, is performed.

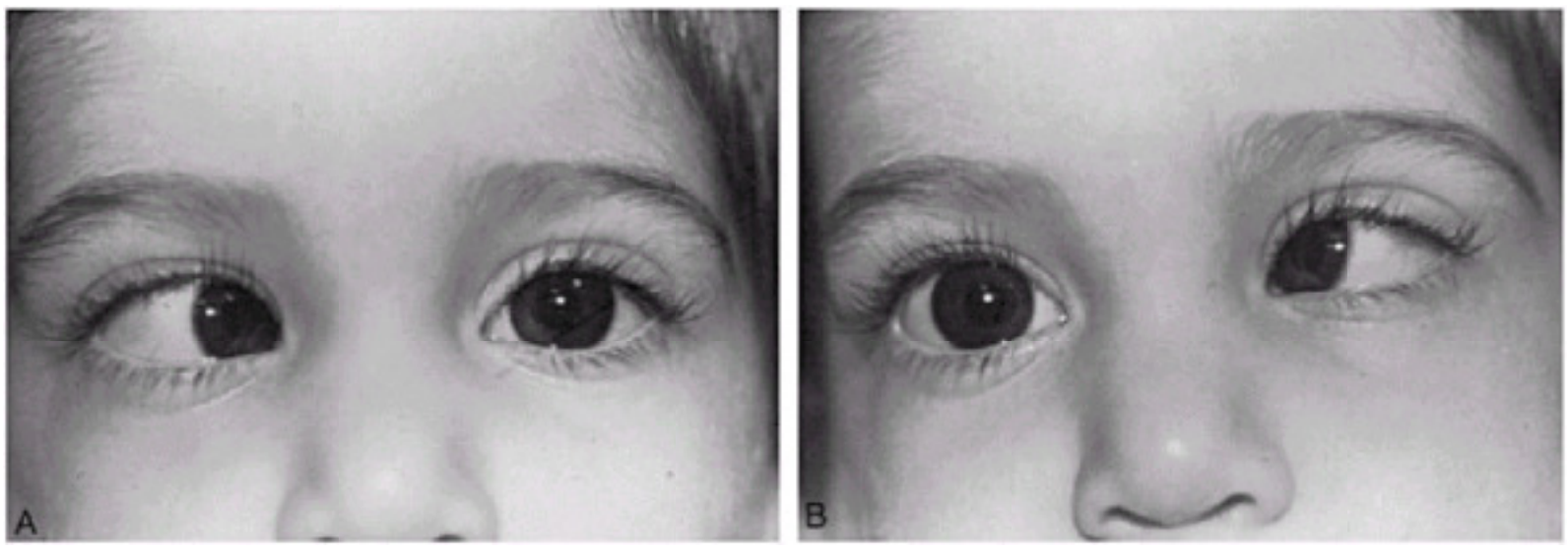

Figure 9.8 A: Congenital esotropia with the child fixating with the left eye. **B:** Alternate fixation with the child now using the right eye. (From Nelson LB, Wagner RS, Simon JW, et al. Congenital esotropia. *Surv Ophthalmol* 1987;31:363, with permission.)

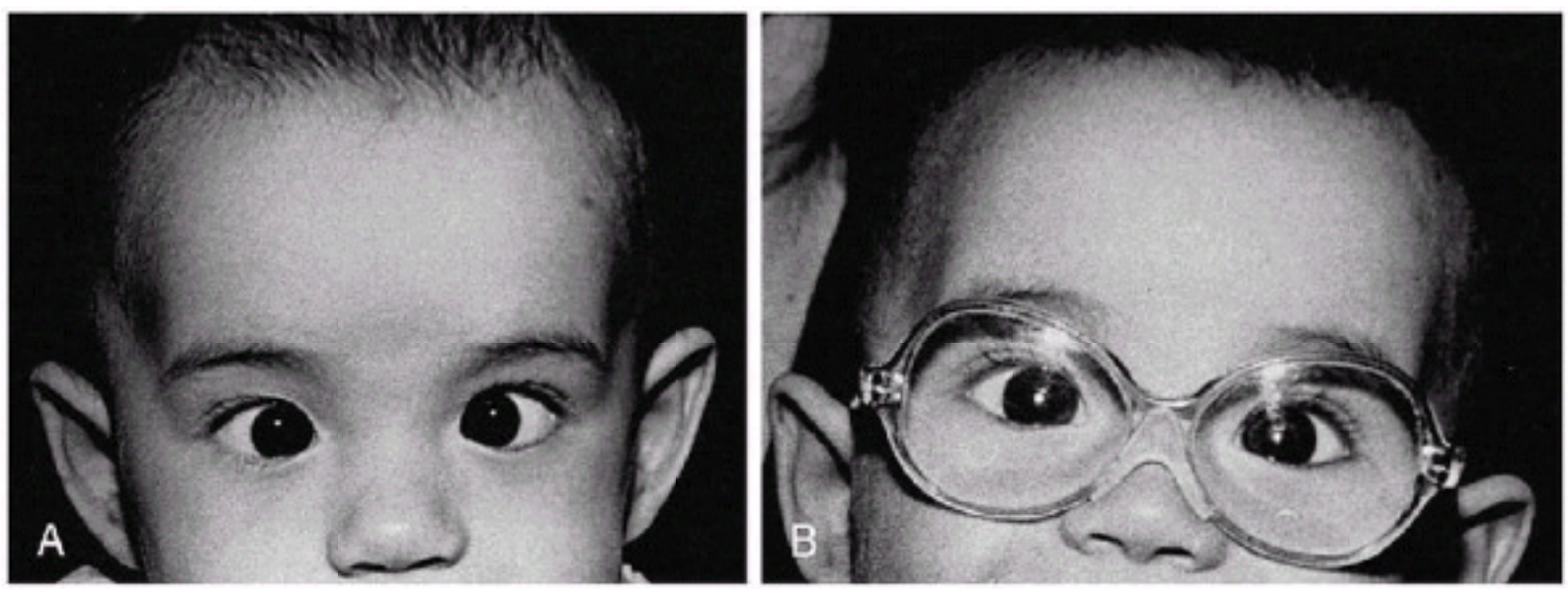

Figure 9.9 A: Accommodative esotropia in a 6-month-old child. There is a large-angle esotropia present. **B:** The esotropia resolves with the hyperopic spectacles. (From Steele MA, et al. Congenital esotropia in pediatric ophthalmology. *Ophthalmol Clin North Am*. In: Olitsky, Nelson, eds. Philadelphia: WB Saunders, 1996, with permission.)

Ing et al (24) corrected only 30% of patients with a deviation of at least 50 prism diopters. However, this was at a time when the maximum medial rectus recession was 5 mm. Greater amounts of recession were not done at this time due to a concern about less predictability and the creation of an adduction deficit.

To increase the success rate in patients with larger deviations, some surgeons operate on three or four horizontal recti muscles at one time (10,81,82,83,84,85). Other surgeons prefer to instead perform larger bilateral medial rectus recessions. These larger recessions provide good results and do not cause a postoperative adduction or convergence deficit (84,86,87,88). Two-muscle surgery is a quicker, simpler, and less traumatic procedure. It also leaves the lateral rectus muscle unoperated, if further surgeries are required. However, some surgeons feel that these large recessions may cause late overcorrections (89). Calhoun (90) feels

that late overcorrections are not caused by improper types or amounts of surgery. He suggests that an underlying defect in binocular function should be blamed for a late-onset exotropia, not the surgery that may have been performed months, years, or even decades earlier.

Botulinum toxin has been used by some investigators in the treatment of congenital esotropia (91,92). Multiple injections may be necessary, and it has not been shown to provide sensory results equal to incisional surgery (93).

Postoperative Management

Overcorrection and Undercorrection

Early successful alignment does not ensure long-term stability. Hiles et al underscored the instability of the alignment in patients operated on for congenital esotropia (33). The need for repeat observations throughout the first decade of life cannot be overemphasized.

An initial small-angle exotropia may be desirable in infants young enough to fuse (57,84). Parks and Wheeler, on the other hand, expressed concern regarding any overcorrection in children with congenital esotropia operated on after age 2. Because these children are likely to lack peripheral fusion, an increased exotropia ultimately may occur (40). Reduction of spectacle correction in hypermetropes and overcorrections in myopes has also been used to treat small overcorrections (94). A large overcorrection associated with an adduction weakness in the immediate postoperative period should alert the surgeon to the possibility of a slipped muscle. Exploration of the suspected muscle should be undertaken.

Consecutive exotropia greater than 15 prism diopters approximately 6 weeks after surgery usually requires a secondary procedure. In the presence of full ocular rotations, Cooper's dictum should be followed (95). He felt that “undoing what was done” is not always the best way to overcome overcorrections. Therefore, a patient with a significant exotropia after bilateral medial rectus muscle recession is a better candidate for lateral rectus muscle recession than for advancement of the previously recessed medial rectus muscles. If, however, significant underaction of one or both medial rectus muscles is demonstrated by a limitation of adduction or greater exotropia at near, the surgeon may need to advance and, perhaps, resect the “crippled” medial rectus muscle.

Undercorrections of greater than 10 prism diopters may respond to correction of hypermetropia greater than + 1.50 diopters, and a trial of spectacles is indicated (96). Patients with residual esotropia measuring greater than 15 prism diopters, unless the deviation is responsive to antiaccommodative therapy, should be evaluated for secondary surgery after 6 weeks' observation.

Accommodative Esotropia Following Congenital Esotropia

Accommodative esotropia may be present in children who were surgically corrected for congenital esotropia. Hiles et

al (33) reported that 65% of corrected congenital esotropes required spectacle correction of hypermetropia to control esotropia at some time postoperatively.

Freeley et al (96) found that 28% of 83 patients with congenital esotropia, who had been successfully aligned by age 18 months, subsequently redeveloped esotropia. In 78% of these patients the esotropia was corrected with a hyperopic correction. In some patients this correction was as little as + 1.50 diopters. Therefore, they advised correcting hyperopia in excess of + 1.50 diopters with spectacles before considering further surgery (96). These patients may be prone to the development of an accommodative esotropia secondary to their underlying poor binocular function (97,98).

Dissociated Vertical Deviation

Patients with DVD do not usually complain of diplopia and are often asymptomatic. DVD is less frequently noted in adults with strabismus than in children, suggesting that DVD tends to improve with time. Harcourt et al (99) disagreed with this impression, having followed patients with DVD for as long as 7 years without noting a significant decrease in the condition. If the disorder is entirely latent, detected by the examiner on cover testing only, surgery is not indicated. If it is intermittent, surgery is dictated by the size and frequency of the deviation as well as the patient's concern regarding its appearance.

Inferior Oblique Muscle Overaction

This rarely, if ever, causes symptoms; it is usually a problem due to its appearance only. Patients usually avoid the extreme lateral gaze necessary to elicit IOOA. Instead, they almost instantaneously turn the face to look laterally, minimizing the cosmetic appearance of IOOA. The thresholds for surgery for IOOA are different, depending on whether weakening the inferior obliques is the only surgery being contemplated, or whether weakening the inferior obliques in conjunction with horizontal strabismus surgery is being considered. If the inferior obliques alone are weakened, there should be a significant overaction present to justify surgery. When there is an obvious elevation of the adducting eye at about 30 degrees or less of lateral gaze, a reasonable cosmetic defect is present and the option of surgery could be offered. If, however, the elevation on adduction is evident on extreme lateral gaze only, this minor cosmetic defect might be best left alone. If horizontal strabismus surgery is being performed, smaller grades of inferior oblique overaction may be corrected at the same time.

Surgery for Dissociated Vertical Deviation and Inferior Oblique Muscle Overaction

Three surgical approaches have historically been advocated to correct DVD: recession of the superior rectus, recession of the superior rectus combined with a posterior fixation suture, and resection of the inferior rectus. The posterior fixation suture alone has not been effective (44,50, 100,101,102).

An overacting inferior oblique muscle may be effectively weakened by recession, disinsertion, myectomy, and denervation and extirpation, with equally good results (103,104,105,106). Inferior oblique recession, as popularized by Parks, is associated with low rates of complications and recurrences. The surgeon has the ability to grade the amount of recession, according to the extent of overaction.

Scott (107), using a computer model, described anterior transposition of the inferior oblique muscle. By placing the distal end of the muscle to a position near the lateral end of the inferior rectus insertion, he believed that the effective recession would be greater because the new anterior insertion would be closer to the origin. He also thought that this procedure could be done with better exposure than a standard recession. Elliot and Nankin compared anterior transposition with standard inferior oblique recession in 154 patients. They found less residual overaction and more normalization of motility in the eyes that underwent anterior transposition. This result was especially noteworthy because the authors had selected patients with greater overaction to undergo anterior transposition (108). Elliot and Parks compared anterior transposition to denervation and extirpation. In their study, patients with large, symmetrical bilateral inferior oblique overaction underwent denervation and extirpation in one eye and anterior transposition in the other. Anterior transposition was found to be more effective in eliminating the overaction. The authors also noted that the anterior transposition tended to limit elevation to some degree. This limitation of elevation, along with the creation of a primary position hypotropia, seems to be most significant in unilateral surgical cases (109).

Mims and Wood (110) compared patients undergoing anterior transposition to a control group of patients who had undergone standard recession. They also found anterior transposition to be more effective. A surprising finding in the study was that only 1 of 61 patients who had undergone anterior transposition later developed a DVD requiring surgery. In the control group, 9 of 61 patients eventually developed a similar DVD. The authors speculated that anterior transposition may decrease the risk for the development of DVD. However, the study groups were not comparable, and there may have been a degree of bias introduced into the study. Bacal and Nelson (111) showed that anterior transposition was effective in treating either DVD or IOOA or both, when concurrently present.

Many surgeons now perform anterior transposition of the inferior oblique, when either inferior oblique overaction or DVD occurs alone in patients with a history of congenital esotropia. The authors feel it is the procedure of choice when both motility disorders are present at the same time. It eliminates the need to operate on both the superior rectus and the inferior oblique.

Amblyopia

The possibility of amblyopia occurring postoperatively must always be considered. Ing found a 41% incidence of postoperative amblyopia in his group of 106 patients (10). Fixation preference testing should be performed at each postoperative visit, until the visual acuity can be measured. Unfortunately, it is more difficult to recognize a fixation

preference, the closer the eyes are to orthotropia. Wright et al (112) suggested using the 10 prism-diopter fixation test for preverbal children with small-angle or no deviation. A 10 prism-diopter vertical prism is placed in front of one eye to produce a vertical deviation, which facilitates the recognition of a fixation preference.

Once recognized, amblyopia should be treated promptly. Some patients may require maintenance therapy until visual maturity is reached, and susceptibility to amblyopia is eliminated when the sensitive period of visual development ends at approximately age 9.

NYSTAGMUS BLOCKAGE SYNDROME

The nystagmus blockage syndrome (NBS) is characterized by nystagmus that begins in early infancy and is associated with esotropia (113,114). The nystagmus is reduced or absent with the fixing eye in adduction. As the fixing eye follows a target moving laterally toward the primary position and then into abduction, the nystagmus increases and the esotropia decreases (115,116). A head turn develops in the direction of the uncovered eye when the fellow eye is occluded. This abnormal head posture allows the uncovered eye to persist in an adducted position.

Cuppers noted the NBS in 139 (10.2%) of 1,352 esotropic patients (117). There seems to be an increased incidence of hydrocephalus during infancy in patients with this condition (118).

A number of features distinguish primary infantile esotropia from the NBS. Although nystagmus may be noted in primary infantile esotropia, it occurs in all directions of gaze. If a child with NBS has one eye patched, he will turn his head in the direction of the uncovered eye to maintain the eye in adduction. When a patch is placed on either eye of a child with congenital esotropia, there is no compensatory head turn. Finally, when a base-out prism is placed before the fixating eye in a child with nystagmus blockage syndrome, the fellow eye will remain in adduction, and the esotropia will actually increase. This phenomenon does not occur in children with congenital esotropia.

Von Noorden and Wong (118) reported 64 patients with the nystagmus blockage syndrome who underwent surgery. Compared with a control group of congenital esotropia without nystagmus, patients with nystagmus blockage syndrome had more overcorrections and undercorrections and a higher number of reoperations.

ACCOMMODATIVE ESOTROPIA

Accommodative esotropia is defined as a “convergent deviation of the eyes associated with activation of the accommodative reflex” (40). Esotropia that is related to accommodative effort may be divided into three major categories: (a) refractive, (b) nonrefractive, and (c) partial or decompensated.

Refractive Accommodative Esotropia

Refractive accommodative esotropia occurs usually in a child between ages 2 and 3, with a history of acquired intermittent or constant esotropia. Occasionally, children age 1 or younger present with all of the clinical features of accommodative esotropia. Several investigators have demonstrated that the accommodative mechanism is capable of functioning within the first few months of life (119,120). Pollard (121) reported two patients, with onset of esotropia at ages 4 and one-half months and 5 months, whose hyperopic correction greater than 3 diopters resulted in resolution of the esodeviation. Baker and Parks (122) reported 21 patients with onset of accommodative esotropia before age 1 year. Approximately 50% of their patients whose esodeviation was initially controlled with glasses decompensated into nonaccommodative esotropia. However, Coats et al (123) reported that only 3 of their 17 patients who developed accommodative esotropia before age 1 year decompensated.

The refraction of patients with refractive accommodative esotropia averages + 4.75 diopters (124). The angle of esodeviation is the same when measured at distance and near fixation and is usually moderate in magnitude, ranging between 20 to 40 prism diopters (125). Amblyopia is common, especially when the esodeviation has become more nearly constant.

Pathogenesis

The mechanism of refractive accommodative esotropia involves three factors: uncorrected hyperopia, accommodative convergence, and insufficient fusional divergence. Donders (126) first described the close relationship between accommodation and convergence. When an individual exerts a given amount of accommodation, a specific amount of accommodative convergence is associated with it. An uncorrected hyperope must exert excessive accommodation to clear a blurred retinal image. This, in turn, will stimulate excessive convergence. If the amplitude of fusional divergence is sufficient to correct the excess convergence, no esotropia will result. However, if the fusional divergence amplitudes are inadequate, or motor fusion is altered by some sensory obstacle, an esotropia will result. Patients with lower levels of hyperopia, but with significant anisometropia, are also at an increased risk to develop an accommodative esotropia (127).

Treatment

In refractive accommodative esotropia, the full hyperopic correction, determined by cycloplegic refraction, is initially prescribed (Fig. 9.10). If the child is orthophoric, or has a small esophoria while wearing glasses, the child can be followed at regular intervals, as often as every 3 months or on a semiannual or annual basis, once the condition is stabilized (128).

Beginning around ages 4 to 5 years, the strength of the hyperopic correction can be reduced gradually to enhance fusional divergence and to maximize visual acuity. This can

be performed by manifest refraction instead of a cycloplegic refraction. Children with moderate levels of hyperopia may be capable of developing enough fusional divergence to be able to function without their glasses (129). Children with extreme levels of hyperopia are unlikely to ever “outgrow” their refractive error and will experience asthenopia without their correction. Aggressive reduction of the hyperopic prescription may not be warranted in these children.

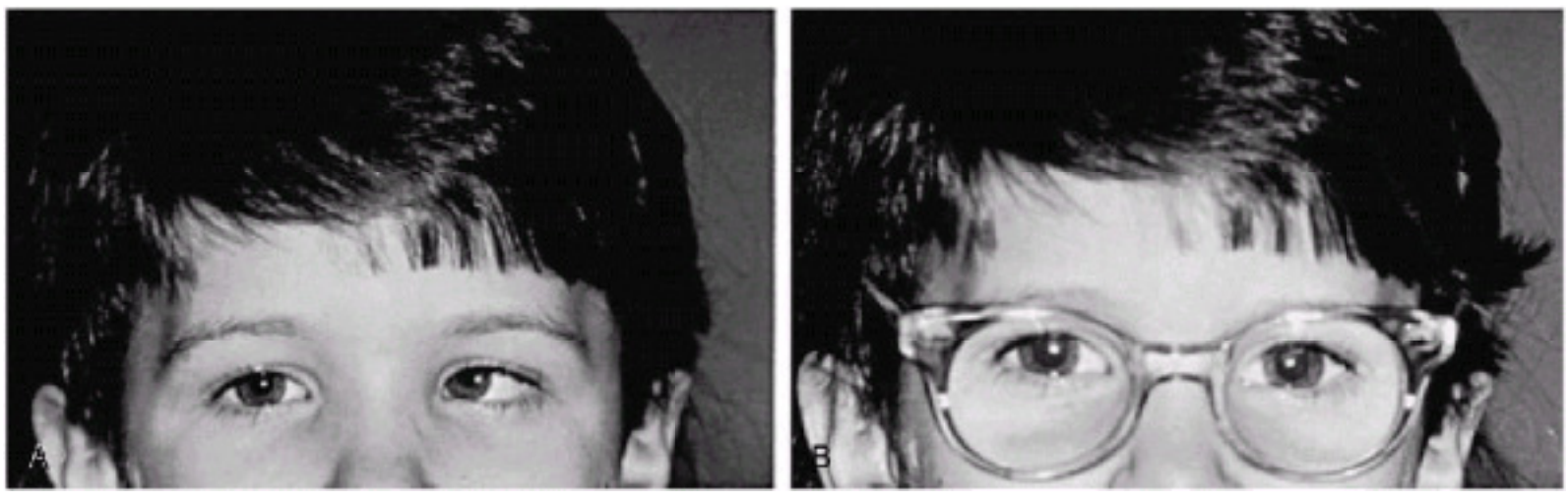

Figure 9.10 A: Accommodative esotropia in a child with similar distance—near measurements. Without glasses there is an esotropia of 30 prism diopters. **B:** With the appropriate hyperopic glasses, the eyes are straight.

It is important to warn parents of children with either refractive or nonrefractive accommodative esotropia that the esodeviation, without glasses, will appear to increase after the initial correction is worn. Parents frequently state that, before wearing glasses, their child had a small esodeviation, whereas after removal of the glasses the esodeviation is now quite large. Parents often blame the increased esodeviation on the glasses and note that their child has become dependent on them. This situation can best be explained on the basis of the child using the appropriate amount of accommodative effort after the glasses have been worn. When the child removes the glasses, he or she will continue to use an accommodative effort to bring objects into proper focus and increase the esodeviation. The strong desire these children have to wear their new glasses may be secondary to the relief of asthenopia, benefits of single binocular vision, or both. Explaining these phenomena to parents ahead of time is more effective than the same explanation after the fact.

Nonrefractive Accommodative Esotropia

Children with nonrefractive accommodative esotropia present usually between ages 2 and 3 years, with an esodeviation that is greater at near than at distance fixation. The refractive error in this condition may be hyperopic or myopic, although the average refraction is +2.25 diopters (40).

Pathogenesis

In nonrefractive accommodative esotropia, there is a high accommodative convergence to accommodation AC:A ratio—the effort to accommodate elicits an abnormally high accommodative convergence response. There are a number of ways of measuring the AC:A ratio—the heterophoria method, the fixation disparity method, the gradient method, and the clinical evaluation of distance and near deviation (42,130). Most clinicians prefer to assess the ratio using the distance-near comparison (42). This method allows the ratio to be evaluated more easily and quickly, because it employs conventional examination techniques and requires no calculations. The AC:A relationship is derived by simply comparing the distance and near deviation. If the near measurement in an esotropic patient is greater than 10 prism diopters, the AC:A ratio is considered to be abnormally high.

Treatment

The management of nonrefractive accommodative esotropia may involve a variety of modalities. Many pediatric ophthalmologists attempt to correct the esodeviation at near with bifocals, provided that the distance deviation is less than 10 prism diopters. Initially, a +2.50 executivetype bifocal, with the top of the lower segment crossing the lower pupillary border, is given (Fig. 9.11). In a follow-up, the child should wear the least amount of hyperopic bifocal correction to maintain straight eyes at near fixation.

Von Noorden et al studied the effect of bifocals on children with high AC:A ratios and found bifocals to be an effective method of controlling the near esodeviation (131). In this study, 37% of patients were able to reduce or remove their bifocals and maintain fusion at near, 46% continued to need bifocals for near fusion, and 17% deteriorated. Analysis of these data demonstrated a better prognosis for eventual normalization of the AC:A ratio in patients with an initial good response to bifocals and a high AC:A ratio.

Parks and Wheeler (40) noted that patients with both high AC:A ratios and a need for bifocals do not usually improve until after age 7 years. They found, in contrast to von Noorden, that the more severe the high AC:A ratio,

the greater the possibility of the patient deteriorating and developing a nonaccommodative esotropia.

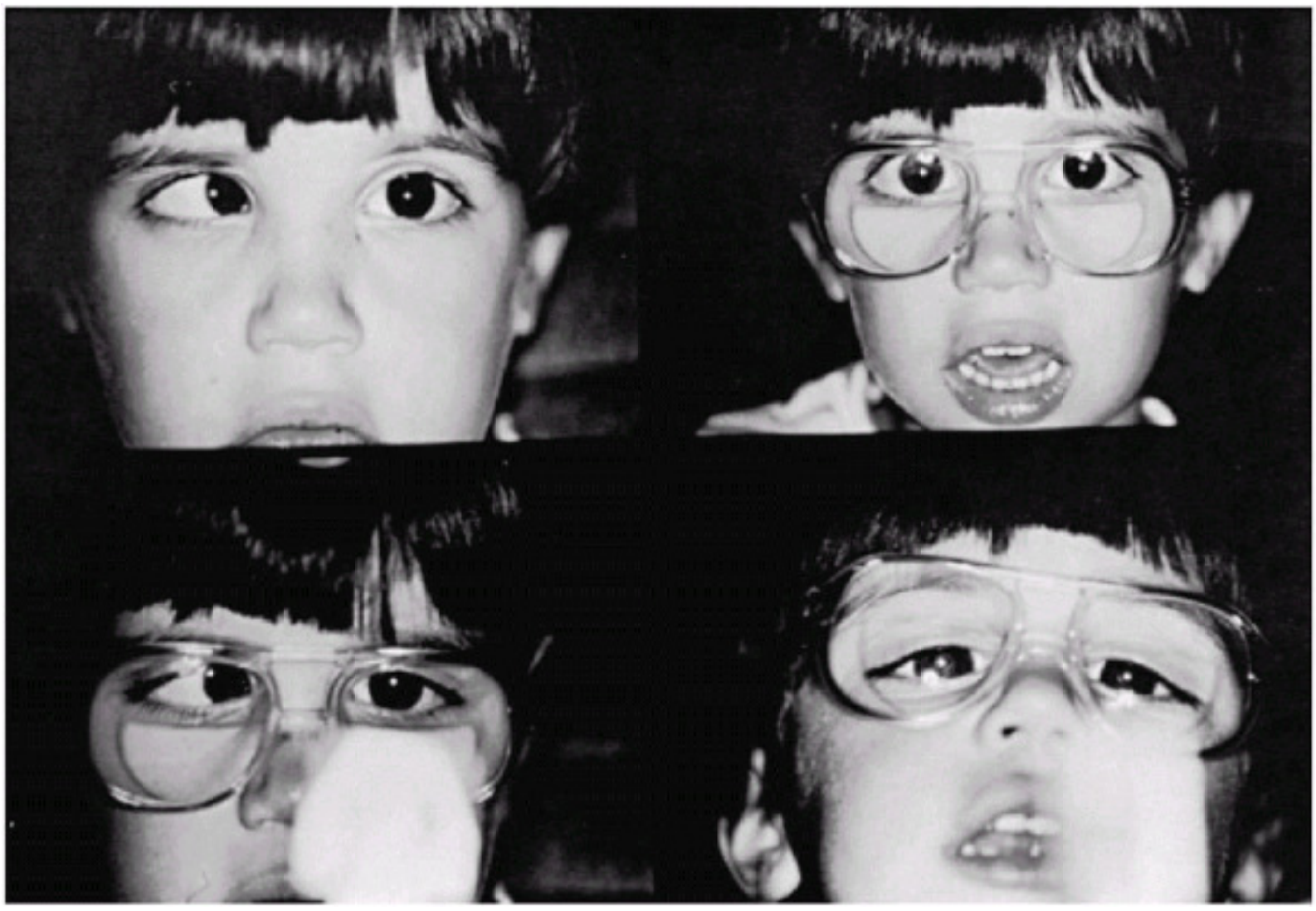

Figure 9.11 Child with high A**C:**A ratio. With the hyperopic glasses, the esotropia is reduced. Note the esotropia when the patient is looking above the bifocals at a near target. Through the bifocals the esotropia is reduced. (From Nelson LB, Catalano RA. *Atlas of ocular motility*. Philadelphia: WB Saunders, 1989, with permission.)

The use of bifocals in treating the esotropia at near is not without some controversy. Albert and Lederman (132) reported on 69 patients with excess esotropia at near. They found no difference in the natural reduction of esotropia in those patients wearing bifocals versus patients who had their bifocals discontinued. Only 12% of their group demonstrated bifoveal fixation, and none complained of diplopia at near. The reason for the initiation of treatment was the parents' observation of the crossing at near. Because the esotropia at near appeared to not be cosmetically noticeable, the authors questioned the energetic treatment of this disorder. Ludwig et al (133) reported on the deterioration rate of patients, based on the severity of their distance-near disparity. They found that the deterioration rate was proportional to the amount of excess esotropia at near. The authors speculated that these patients continue to experience esotropia at near, despite bifocal therapy. Pratt-Johnson and Tillson (134) reviewed the long-term sensory status in 99 patients with excess esotropia at near. Half were treated with bifocals, whereas the others were not. The authors found no difference in sensory status or deterioration rate between the two groups.

Miotics have been used successfully in patients with high AC:A ratios (76). Parks (124) observed that, although the AC:A ratio normalized on miotics, it reverted to pretreatment levels with discontinuation. Because miotics have a number of ocular and systemic side effects, their use is avoided by some ophthalmologists.

Surgery for high AC:A ratio is usually performed when the esodeviation at near fixation is no longer controlled with bifocals or the distance deviation is higher than an acceptable level. Surgery has been shown to decrease the AC:A ratio (132,135). There are two types of surgery that are commonly performed in patients with an excess esotropia at near. O'Hara and Calhoun (136) demonstrated favorable results when operating for the full amount of esotropia at near, even in patients with little or no distance deviation. Although many of their patients were orthotropic at distance, there were few overcorrections. However, the fear of producing an exotropia in the distance has led to the popularization of the posterior fixation, or Faden suture, in the treatment of these patients (131,137). Generally, the medial rectus recession is titrated for the distance angle, and a posterior fixation suture is performed to decrease convergence at near. Kushner et al (138) compared these two techniques in a prospective, randomized study. The authors found the use of augmented surgery, taking into account the near deviation, to be more effective than the posterior fixation suture technique. A higher percentage of patients in the augmented surgery group achieved satisfactory

alignment and were able to discontinue the use of their bifocals. The authors also found a trend in the same group toward complete elimination of the glasses. Fifteen years later, these same patients continued to demonstrate good alignment (139). The authors prefer to perform a bilateral medial rectus recession for the full amount of esotropia that is present at near. If the level of hyperopia is small, the near measurement without corrective lenses may be used in an attempt to eliminate the need for glasses.

Partial or Decompensated Accommodative Esotropia

Refractive or nonrefractive accommodative esotropias do not always occur in their “pure” forms. Patients may have a significant reduction in esodeviation, when given glasses. However, a residual esodeviation persists, in spite of full hyperopic correction, which is the deteriorated or nonaccommodative portion (Fig. 9.12). This condition commonly occurs when there is a delay of months between the onset of accommodative esotropia and antiaccommodative treatment. Sometimes the esotropia may initially be eliminated with glasses, but a nonaccommodative portion slowly becomes evident, in spite of the patient's wearing the maximal amount of hyperopic correction consistent with good vision (140).

The indications for surgery for partial or decompensated accommodative esotropia remain controversial. Some ophthalmologists believe that any esotropia greater than 10 prism diopters warrants surgery to reduce the deviation to less than 10 prism diopters, to enhance the development of the monofixation syndrome. These ophthalmologists believe that if the monofixation syndrome develops, the patient will function better because of the advantage of peripheral fusion. Also, the prognosis for the permanency of the surgically created alignment will be enhanced as a result of good motor fusional vergences associated with the monofixation syndrome.

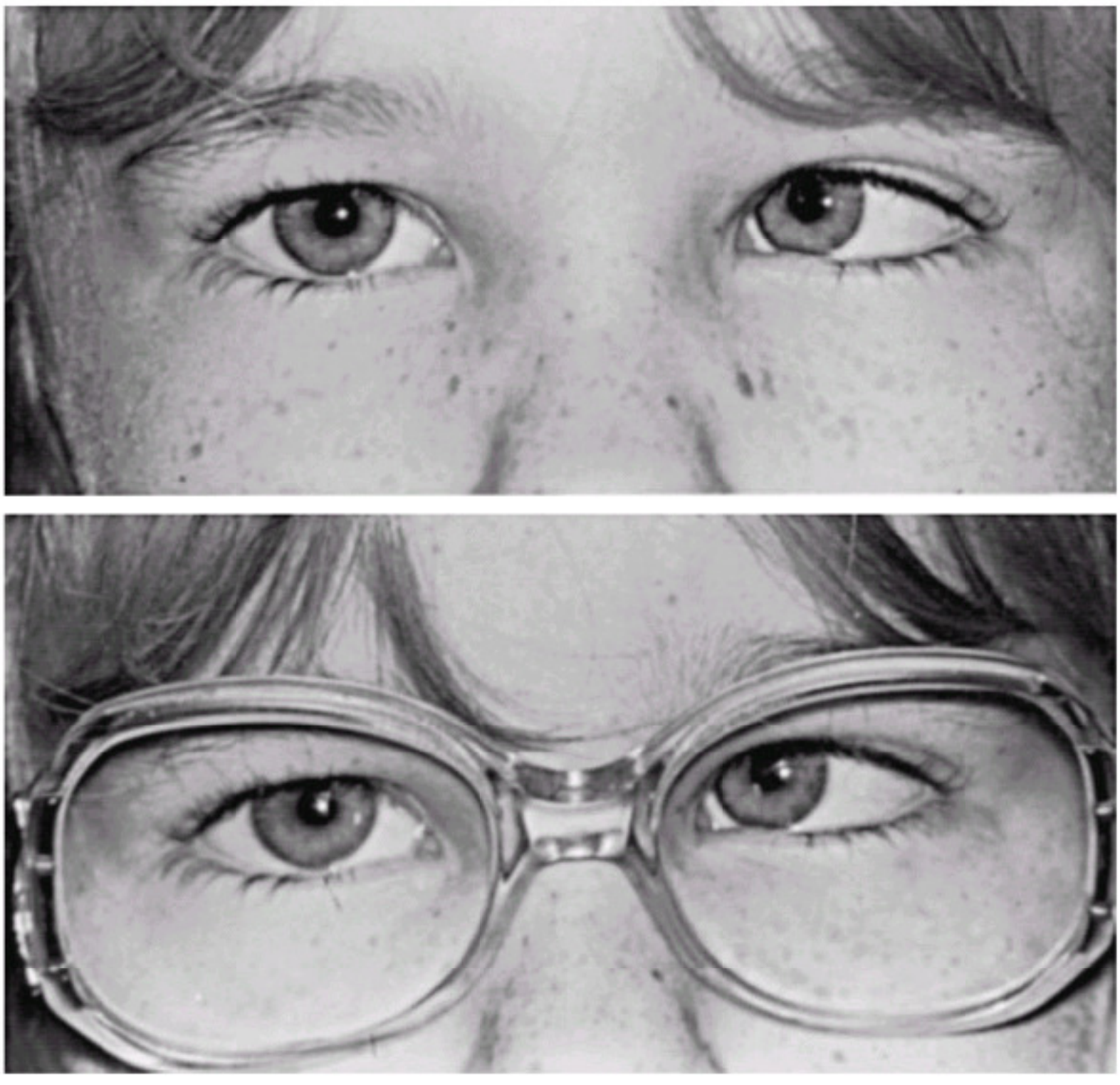

Figure 9.12 Child with esotropia in whom the appropriate hyperopic glasses did not reduce the deviation. (From Nelson LB, Catalano RA. *Atlas of ocular motility*. Philadelphia: WB Saunders, 1989, with permission.)

Other ophthalmologists consider that surgery should be performed on the nonaccommodative portion, only if it is cosmetically significant as determined by the patient or family or both. These ophthalmologists feel that there is no functional deficit that can be demonstrated consistently in a real-world situation in patients who do not have peripheral fusion, as would be present in the monofixation syndrome.

If surgery is elected, the amount of surgery to be performed is generally determined by the distance deviation, with the child's full hyperopic correction. When the near deviation is greater than the distance deviation, it is reasonable to operate for the near deviation. Because of an unacceptable number of undercorrections in some series of patients, other surgical formulas have been advocated. Wright et al showed that if patients underwent bilateral medial rectus recessions for a target angle halfway between the esotropia that was present at near with glasses and the esotropia that was present at near without glasses, 93% of patients would experience a reduction of their deviation to less than 10 prism diopters. This would be in contrast to a 74% success rate in a group receiving “standard” surgery. Few patients in the augmented study group required a change in their hyperopic prescription following surgery (141). Kushner looked at the effect of surgically overcorrecting patients and then decreasing their hyperopic prescription to maintain alignment. He found that this strategy worked for those patients with less than 2.5 diopters of hyperopia in their fixating eye. However, overcorrections were less likely to be reversible with postoperative reduction in the hyperopic correction in patients with greater than 2.5 diopters (142).

Another method for augmenting surgery is prism adaptation. In prism adaptation, the patient is given press-on base-out prism for any residual esotropia that remains after prescribing the full hyperopic correction. The patient then returns in 2 weeks and, if the esotropia has increased, a larger prism is then given. This process continues until the deviation remains stable. The surgeon then operates on the full “prism adapted” angle. The Prism Adaptation Trial was a multicenter, prospective, randomized study that looked at this technique. The study found that standard surgery results in approximately a 75% success rate. Patients undergoing prism adaptation showed an 85% success rate (143). Although prism adaptation does appear to increase surgical success, it has the disadvantage of being costlier and requiring more time. Some surgeons perform a “mini” prism adaptation by prism adapting the patient in the office. It is unknown whether this type of prism adaptation provides the same increase in surgical success.

Cyclic Esotropia

Cyclic strabismus is a relatively rare disorder of ocular motility that is reported to occur in one in 3,000 to 5,000 cases of strabismus (144,145). Cyclic strabismus was first

mentioned at the Strabismus Ophthalmic Symposium II and first described in a publication by Costenbader and Mousel (144,146). A thorough history and repeat examinations are often necessary to elicit the cyclic nature of the deviation. An awareness of the typical characteristics of cyclic strabismus may enable one to make the diagnosis more readily.

Cyclic strabismus is usually an acquired condition with onset at ages 3 to 4 years (147). Variable presentations with onset at birth and in adult life have been reported. Accidental or surgical trauma has been associated with cyclic strabismus in a few cases. The two cases of cyclic esotropia following intermittent exotropia were postsurgical (148,149).

The type of esodeviation is classically a large-angle esotropia alternating with orthophoria or a small-angle esodeviation on a 48-hour cycle (Fig. 9.13) (150). Variations include vertical deviations, incomitance, that may be manifest as a mild V pattern, and exotropia (147,151). Cycles of 1, 3, 4, and 5 days have been reported as well as cycles of 48 hours' esotropia and 24 hours' orthotropia (144,147,148,151). The duration of the cycle may be as short as 2 weeks, in which case the diagnosis can be missed, or it may persist for several years before becoming a constant deviation (148).

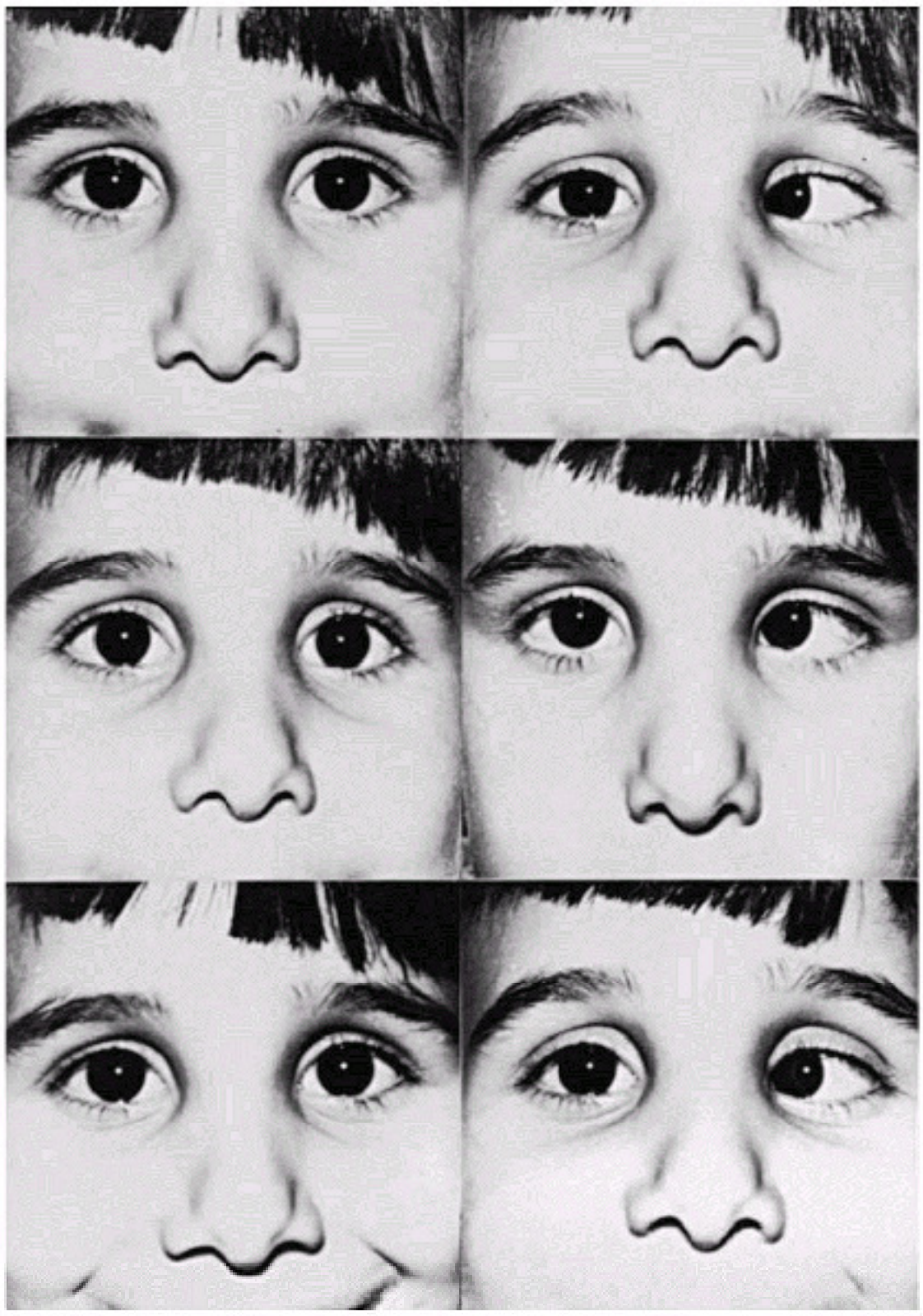

Figure 9.13 Cyclic esotropia. Photographs taken on 6 consecutive days. Note the esotropia on alternating days. (From Friendly DS, Manson RA, Albert DG. Cyclic strabismus—a case study. *Doc Ophthalmol* 1973;34:189, with permission.)

Patients with cyclic strabismus often have a family history of strabismus. The fact that most cases occur in the middle preschool may explain the frequency of the mild hyperopic refractive error.

Pathogenesis

Various theories have been proposed to explain cyclic strabismus. It may be the result of an aberration in the biological clock (144,152). Metz and Bigelow (153) described a patient with cyclic esotropia that underwent a change in the circadian pattern of her esotropia after rapid time travel through six time zones. This change would tend to support the biological clock theory. Gadoth et al (154), in an investigation of a patient with minimal brain dysfunction and cyclic esotropia, failed to establish the hypothalamic-hypophyseal axis as the site of an abnormal clock.

Fusion and binocular vision are usually absent or defective on the strabismic day, with marked improvement on the straight day. Windsor and Berg (145,151) suggested that the periodicity of the deviation may be beneficial in maintaining a fusional potential. Diplopia on strabismic days is unusual and has been a prominent symptom only in patients of a relatively later age who are unable to develop suppression. Windsor and Berg (151) also suggested that posttraumatic cyclic strabismus may be secondary to the unmasking of a previously latent cyclic deviation.

Treatment

Cyclic esotropia is noted for its unpredictable response to various forms of therapy, with the exception of surgery, which is usually curative (145,155). Occlusion

therapy has been shown to convert cyclic esotropia into a constant esotropia (151,156).

The effectiveness of giving a hyperopic refractive error to reduce the esodeviation is unpredictable. The first patient of Windsor and Berg (151) changed from a 24-hour to a 48-hour cycle, with correction of the hyperopia. Three of the 14 patients reported by Helveston (147) obtained fusion with glasses, two of which were bifocals. Therefore, correction of a hyperopia should be considered in a patient with cyclic esotropia before surgery is undertaken.

Surgical correction of the total esodeviation with either a bilateral medial rectus recession or a monocular medial rectus recession and lateral resection has been the most successful mode of therapy. Surgery may not result in immediate resolution of the deviation, and further surgery may be necessary in some cases (150,151).

ACUTE ACQUIRED COMITANT ESOTROPIA

Acute acquired comitant esotropia (AACE) is a rare condition that occurs in older children and adults (157,158). It is characterized by the dramatic onset of a relatively large angle of esotropia with diplopia and mild hyperopic refractive

error (159). Although there may be a brief period of intermittency, the esodeviation soon becomes constant.

Pathogenesis

Burian (159) was the first to describe AACE in 1945. He divided AACE into two types: type 1, which becomes apparent immediately after a period of occlusion, and type 2, which occurs without obvious exogenous cause.

Type 1 occurs after periods of interruption of fusion. It has been reported to follow occlusion therapy for amblyopia in patients in whom no deviation was initially noted (160). Other cases of type 1 AACE have occurred after brief occlusion from lid swelling secondary to blunt trauma.

Type 2 has no obvious exogenous cause precipitating the esotropia. Of Burian's eight patients, who ranged in age from 6 and a half to 72 years, only one had a preceding illness. None of his patients had any evidence of a neurological condition. Several patients underwent a brief period of intermittency before the deviation became constant. All had diplopia. The esotropia varied from 30 to 70 prism diopters, ocular rotations were normal, and refraction ranged from -5.50 to + 3.00 diopters.

Anderson and Lubow (161) reported a patient with an acute esotropia who was found to have an astrocytoma of the corpus callosum. Bilateral papilledema and hemiplegia were noted when the patient first presented, 2 weeks after the onset of the acute esotropia. This case of acute esotropia, secondary to an intracranial tumor, can be distinguished from AACE by the accompanying neurological signs and symptoms. Williams and Hoyt (162) described six patients with AACE who were found to have intracranial tumors. Four patients eventually had strabismus surgery, and none were able to reestablish ocular motor fusion.

Treatment

Children and adults who develop an acute esotropia must undergo a careful motility analysis to rule out a paretic deviation, in a search for lateral gaze incomitancy. If the ophthalmic examination is otherwise negative, and a neurological physical examination is normal, it is still unclear whether further workup, including computed tomography (CT) or magnetic resonance imaging (MRI) scanning, should be performed.

EXOTROPIA

Congenital Exotropia

Exotropia occurring under age 1 year in an otherwise healthy child is rare. In a review of 235 patients under age 19 years with exotropia, only 4 children had congenital exotropia (163). Although exotropia before age 1 year may go through a period of intermittency, many cases progress quickly to a constant alternating exotropia. The angle of deviation is often quite large, averaging 35 prism diopters or greater (Fig. 9.14). Patients with an exotropia of 50 prism diopters or greater often appear to have decreased adduction on side gaze; with gaze right or left, the abducting eye fixates while the opposite eye approaches midline and stops. This is similar to the cross fixation found in congenital esotropes. Occlusion or the doll's-head maneuver will demonstrate that good adduction is possible. Amblyopia is not common, because these children typically alternate fixation. The refractive error is similar to that of the general population.

Treatment

Patients with congenital constant exotropia are operated on early in life in the same manner as those patients with congenital esotropia (164). As with patients with congenital esotropia, early surgery can lead to gross binocular vision but not bifoveal fixation. In addition, these patients also tend to develop A and V patterns, DVD, and IOOA and should be followed closely for the development of these associated motility disturbances (165,166).

Intermittent Exotropia

Demographics

Intermittent exotropia is the most common divergent strabismus in childhood (163). The age of onset varies but is often between 6 months and 4 years (167).

Natural History and Characteristics

The natural history of intermittent exotropia is generally unknown because most patients inevitably receive therapeutic

intervention at some stage of the disease. Although the natural history of this disorder is not well delineated, many pediatric ophthalmologists consider that the frequency or magnitude of the deviation in children with untreated intermittent exotropia is unlikely to improve. An unknown proportion of children with intermittent exotropia decompensate into constant exotropia. Hiles et al (168) reported long-term observation for up to 22 years in 48 patients with intermittent exotropia. Forty patients (83%) remained within 10 prism diopters of their original distance measurements at the end of the study. This study was retrospective and included selective instead of consecutive patients with intermittent exotropia. Patients had either refused surgery or the fusional control of the exotropia was thought to be too good to require surgical intervention at that time. Therefore, many of the patients were mainly phoric rather than tropic, and temporization was utilized. Also, an unknown number of patients may have progressed and received surgery elsewhere.

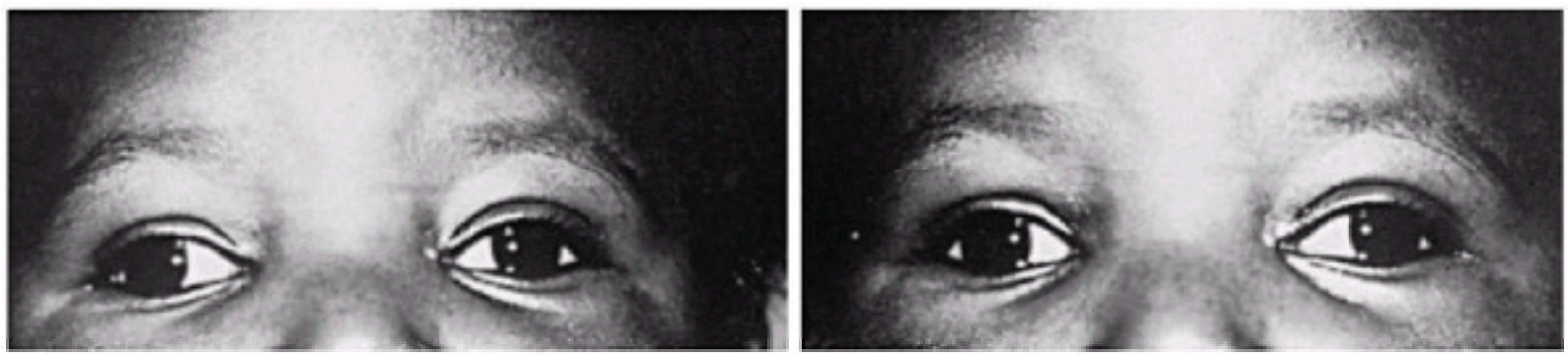

Figure 9.14 Large-angle exotropia in a child under age 1 year, who alternates freely.

Initially, the deviation is usually intermittent and greater at distance fixation; often, there is no deviation at near fixation in the early stages (Fig. 9.15). Because many nonophthalmologists examine children at near only, the question of strabismus may be dismissed when a parent first brings this problem to the attention of the pediatrician. Intermittent exotropia may be considered as possibly evolving through four phases that make useful divisions for discussion and comparison:

Phase I. Exophoria at distance, orthophoria at near.

Phase II. Intermittent exotropia at distance, orthophoria or intermittent exotropia at near.

Phase III. Exotropia at distance, exophoria or intermittent exotropia at near.

Phase IV. Exotropia at distance and near.

In Phase I, in which there is exophoria at distance only, children are asymptomatic and are rarely evaluated by ophthalmologists. In Phase II, an intermittent exotropia is noted by the family when the child views at distance during periods of inattentiveness or fatigue. During this phase, there is no suppression scotoma, so that child may report diplopia or infer it by closing one eye, especially in bright sunlight. When a child in Phase II is examined, the exotropia is easily elicited by the cover test, but the deviating eye returns quickly with a blink or a change of fixation. In Phase III, a suppression scotoma develops to avoid diplopia. Instead of making a correcting fusional convergent movement, the eye remains deviated for longer periods, even through a blink or change in fixation. In Phase IV the suppression scotoma is firmly set, with constant exotropia at distance and near fixation.

Amblyopia is not common in children with intermittent exotropia. The distribution of refractive errors is similar to that in the general population. Lateral incomitance is a decrease in the deviation when it is measured in extreme right or left gaze. Some authors have stressed the importance of reducing the amount of surgery in laterally incomitant exotropia to avoid an overcorrection (169,170). Though the incidence of lateral incomitance in exotropia has been reported to be 22%, Repka and Arnoldi (171) believe this to be falsely high due to measurement artifact. They showed that “lateral incomitance” could be induced by improper horizontal tilting of the neutralizing prism. Furthermore, they found that measurements in lateral gaze were often smaller when the prism was held over the abducting rather than adducting eye. This may occur because each eye must rotate farther from the midline when the neutralizing prism is held over the abducting eye. Because mechanical restriction at end gaze first affects the abducting eye, lateral incomitance appears to be present.

Pathogenesis and Classifications

Exodeviations probably result from a combination of mechanical and innervational factors. Bielschowsky (172) believed that an anomalous position of rest contributes to the occurrence of exodeviations. He believed that, when the impulses to the extraocular muscles were at rest, the

eyes tended to assume a divergent appearance. Duane (173) championed the view that exodeviations are caused by an innervational imbalance that upsets the reciprocal relationship between active convergence and divergence mechanisms. He proposed a classification system based upon his theory. According to Duane, an exodeviation greater at distance than at near fixation is caused by hypertonicity of divergence excess; a deviation greater at near than at distance is caused by convergence insufficiency; and a deviation that is equal at distance and near fixation, basic exotropia, is caused by a divergence excess combined with a convergence insufficiency.

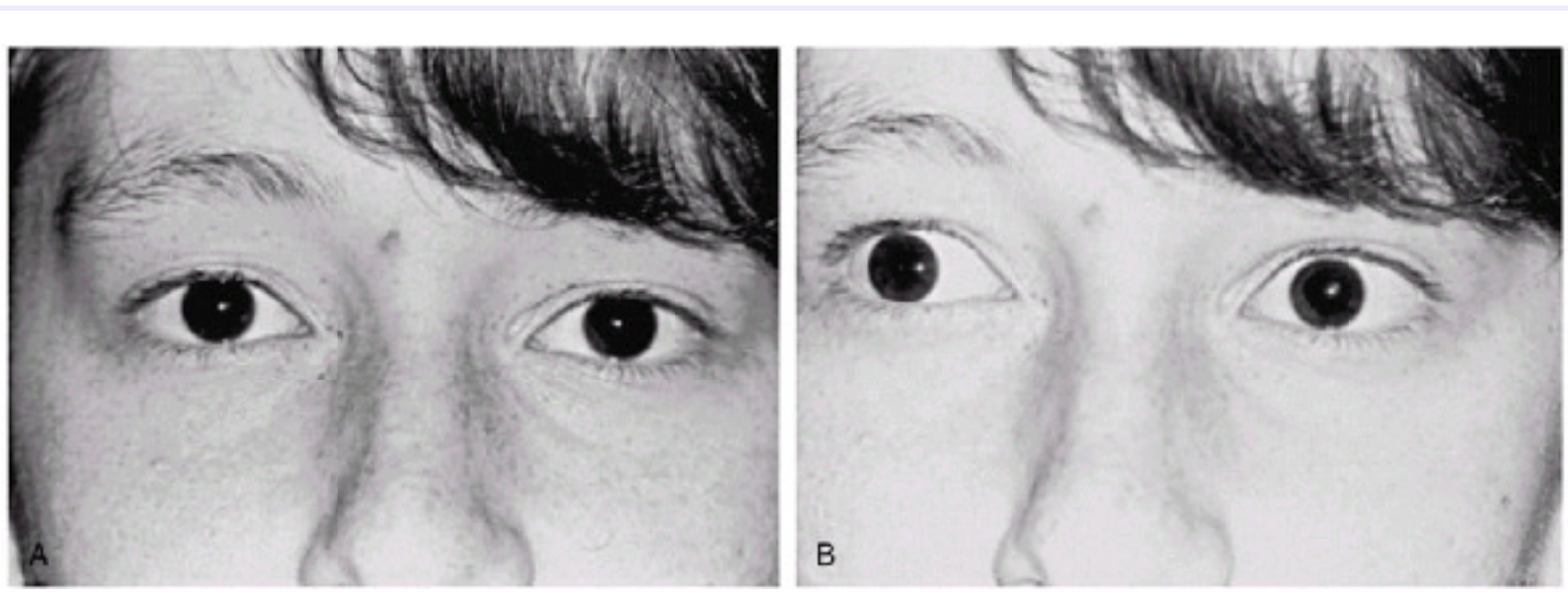

Figure 9.15 A: Intermittent exotropia in a patient with good binocular function. **B:** The right eye drifted out only with fatigue, illness, or daydreaming. (From Nelson LB, Catalano RA. *Atlas of ocular motility*. Philadelphia: WB Saunders, 1989, with permission.)

Burian (174) supported Duane's innervational theory to explain divergence. He believed that the horizontal vergences have both tonic and fusional components; however, convergence also involves accommodation, for which there is no corresponding mechanism in the divergence system. It is the accommodation mechanism in childhood that often obscures the near fixation exodeviations. Burian added a fourth category to Duane's classification. He introduced the term

“simulated divergence excess” for those patients with a divergence excess exodeviation, where the distance and near deviations become equal after monocular occlusion or when the patient fixates at near through a + 3.00 diopter lens. Kushner (175) introduced the concept of tenacious proximal fusion to describe patients who did not show an increase in their near deviation size through + 3.00 lenses but did so after a period of occlusion.

Intermittent exotropia is commonly a precursor to constant exotropia of both basic and divergence excess types. Therefore, it has been questioned as to whether entirely different factors are actually responsible for the various subtypes of exodeviation. Parks (176) argues that rather than assume that exodeviations that have a distance-near disparity are the result of a faulty divergence or convergence system, these patterns can be explained solely on the basis of the AC:A ratio. A patient with a convergence insufficiency exotropia would then be said to suffer from a low AC:A ratio, and a patient with a divergence excess exotropia would have a high AC:A ratio. This may be a compensatory high AC:A ratio, which a child develops to maintain fusion at near. This hypothesis would explain why patients with intermittent exotropia tend to have a high AC:A ratio, whereas patients with a constant exotropia usually have a normal AC:A. With a constant deviation, fusion is lost at distance and near, and there is no longer a reason to maintain a high AC:A ratio. Many clinicians find it difficult to neatly categorize all patients with intermittent exotropia into Duane's system. They find it easier to use the more fluid method of categorization that Parks has devised.

Treatment

Although most pediatric ophthalmologists agree that the treatment for intermittent exotropia is surgical, opinions vary widely regarding the timing of surgical intervention and the preoperative use of nonsurgical methods.

Timing of Surgical Intervention

This is a cause for considerable controversy because of the possible effects on both the immature visual and sensory systems during childhood. The concern is over early surgical intervention in a child with intermittent exotropia in which good preoperative visual acuity and stereopsis could be exchanged for a small-angle esotropia with the threat of amblyopia and decreased stereopsis. However, delaying surgery too long could allow for the development of a suppression scotoma, which could increase the risk for a recurrent manifest deviation later in life.

In a review of 208 patients with intermittent exotropia, Dunlap (177) noted a definite higher percentage of overcorrection requiring reoperations in children younger than age 5. He concluded that early surgery for intermittent exotropia did carry a greater risk of persistent esotropia that required correction.

Richard and Parks (178) noted that 12% of 41 patients under age 3 had an overcorrection, whereas only 2.6% of 78 patients over age 3 had an overcorrection. However, the authors reported that the age at the time of initial surgery for intermittent exotropia did not appreciably influence the overall percentage of satisfactory results.

Pratt-Johnson et al (179) found that surgery for intermittent exotropia performed at a median age of 2.5 years was associated with a higher cure rate than surgery performed 3 years later. These authors noted, however, that most patients with the postoperative monofixation syndrome were in the under-4-years age group. It is the potential for development of the monofixation syndrome, coupled with the observation by Hiles et al that many patients with intermittent exotropia can be followed for an extended period without a change that has caused some surgeons to prefer to delay surgery in young children. However, many, or most, patients with intermittent exotropia who are found to have monofixation syndrome after surgery may actually have had it prior to surgical intervention (180). However, age may not be the most important factor when addressing the timing of surgery. Abroms et al (181) found that surgery before age 7, before 5 years of strabismus duration, or while the deviation is intermittent gave the best sensory result.

Nonsurgical Management

Nonsurgical treatment of intermittent exotropia includes the use of cycloplegics, base-in prisms, overcorrecting minus lenses, occlusion therapy, and orthoptic exercises.

Cycloplegics

Theoretically, weak cycloplegics could be used to treat patients with intermittent exotropia by stimulating an increased accommodative effort and causing greater accommodative convergence. These agents are not commonly used because of the large individual variability of response and interference with near activities.

Prisms

The use of prisms in the treatment of exodeviations has been reported primarily in the optometric literature (182,183). The success rate of prism therapy varies as reported in these series. Prism therapy consists of two different strategies: “demand-reducing” prisms and full prismatic correction. Demand-reducing prisms correct for a portion

of the total deviation and may be useful for presbyopic patients with convergence insufficiency. Full prismatic correction neutralizes the total deviation and is commonly used in children to reestablish “normal” binocular conditions. If possible, the prism power is then gradually reduced as tolerated by the patient. Prism glasses can be very heavy and cause image distortion, which makes compliance a problem. Also, many patients with intermittent exotropia have large fusional convergence amplitudes. The use of full prismatic correction decreases these convergence abilities. If these patients proceed to surgery and are left slightly undercorrected, they may continue to experience symptoms of diplopia or asthenopia, which may require further surgery or long-term use of prism correction. In contrast to the support for prisms as an initial treatment in the optometric literature, most ophthalmologists employ the use of prisms in these patients only as a method of postponing surgery until the patient is older and at less risk for developing amblyopia in case of a surgical overcorrection.

Overcorrecting Minus Lenses

Overcorrecting with minus lenses to stimulate accommodative convergence has been successfully used by some investigators. Caltrider and Jampolsky (184) found that, by overminusing by 2.00 to 4.00 diopters, 25 (71%) of 35 children had an improvement in fusional status. Reynolds et al (185) found that overminus lens therapy helped to improve fusional control in those patients with a moderate-size deviation. However, only 12% of their patients were able to eventually discontinue use of their glasses. Limitations of overminus therapy are possible accommodative asthenopia and its usefulness only in young patients with large accommodative amplitude. Patients who do not require optical correction for improvement of their visual acuity may be less compliant with this therapy.

Occlusion Therapy

The objective of occlusion therapy in intermittent exotropia is to eliminate the need for suppression, which often occurs in the transition phase between an intermittent deviation and a constant one (182). There are several small series that evaluate the success rate of occlusion therapy. Most of these studies suffer from a lack of masking and control groups. In addition, most authors limit the use of occlusion to patients with relatively small deviations. Occlusion may have a role in the temporary improvement of fusional control. It does not appear to lead to a long-term benefit. Occlusion therapy may be useful to help postpone surgery in some younger patients until they reach an age when amblyopia following surgery is less likely.

Orthoptics

Although the theoretical basis of using orthoptics to improve fusional convergence amplitudes is appealing, most find the benefits to be limited (186,187). Generally, orthoptics consists of diplopia awareness training and improvement in fusional vergence amplitudes. Many patients with intermittent exotropia already experience diplopia, as evidenced by their closing of one eye or that the deviation is intermittent. Furthermore, in nearly all patients with intermittent exotropia, the fusional convergence amplitudes are already abnormally large. Many ophthalmologists limit the scope of orthoptic therapy to increasing fusional convergence in

patients with convergence insufficiency.

Surgical Management

Indications for Surgery

When the deviation is intermittent, is eliminated with a blink, and occurs only with fatigue, observation is warranted. In a younger child, if the condition is progressing from Phase II to Phase III, in which the deviation occurs during periods when the child is alert and lasts through a blink or change in fixation, surgery is indicated to try to prevent the development of a suppression scotoma. If the child closes or covers one eye for viewing, the exodeviation is too large for the fusional convergence mechanisms to control. This child has diplopia and compensates by closing or covering one eye. Surgery is indicated in this situation to correct the annoying symptom. In Phase III, with constant exotropia at distant fixation but an exophoria or intermittent exotropia at near, a suppression scotoma is present at distance fixation, because there is no awareness of diplopia or compensation to avoid it. At near, some degree of binocular function can usually be demonstrated with stereoacuity or Worth 4-Dot testing. Surgery should be offered at this stage to try and maintain whatever binocular function is present at near and, perhaps, regain what has been lost at distance.

In patients older than 10 years, symptoms of diplopia and asthenopia and social concerns are the main indications for surgery, because suppression is unlikely to develop, and postponement of surgery will not adversely affect the surgical outcome.

Choice of Surgical Procedure

Some surgeons use the classification system developed by Duane and Burian to decide what type of surgery to perform on patients with intermittent exotropia. They aim to weaken the apparently overacting or strengthen the apparently underacting muscles, based upon the distance and near measurements. Therefore, for a basic and “simulated” divergence exotropia, they perform a unilateral recession/resection procedure based upon the assumption that the resultant correction will be the same for both distance and near. A divergence excess deviation is treated with a bilateral lateral rectus recession, and convergence insufficiency is treated with a bilateral medial rectus resection. Kushner (188) found that patients with a basic type of exodeviation were more likely to respond well to a unilateral recess/resect procedure than a bilateral lateral rectus recession. He also found that a bilateral recession worked better in simulated divergence excess than it did in a basic type deviation. However, his study did not address the possibility of performing more surgery on those patients who underwent a bilateral recession with a basic exodeviation.

In contrast, Parks (176) feels that bilateral lateral rectus recessions and unilateral recess/resect procedures are equivalent in their effect. He feels that a surgeon's confidence in

a particular procedure should determine what technique is utilized. Many surgeons prefer doing symmetrical surgery and avoiding resections, if not necessary.

Although bilateral lateral rectus recessions are used by many ophthalmologists in the treatment of intermittent exotropia, unilateral lateral rectus recession has received recent attention. Several studies have shown similar results using a unilateral recession to those obtained with bilateral surgery (189,190,191). Unilateral surgery has the advantage of requiring less time under anesthesia and limiting the risk of surgery to just one eye. In addition, a unilateral recession may lower the risk of developing amblyopia from a small overcorrection because the patient can adopt a small face turn to maintain fusion (192).

Goals of Surgery

The surgical success rate in treating intermittent exotropia is difficult to discern from the literature. Reports in the literature are plagued by the variable nature of the disease, a lack of standardized success/failure criteria and study bias, depending on the type of intervention preferred by the authors. It is therefore not surprising that rates of success vary widely in the literature, ranging from 40% to 92% (189,193,194,195). Most authors define surgical success as a small residual exotropia less than 10 prism diopters or an exophoria/esophoria only.

Surgeons who perform bilateral lateral rectus recessions should anticipate a postoperative esotropia of 10 to 15 prism diopters that may last for the first 10 days to 3 weeks (196). Patients who display this initial overcorrection tend to have the best results once they are fully recovered from surgery, although a moderate initial overcorrection does not always predict a good outcome (197). It may be advisable to warn parents about an initial period in which their child's eyes will cross and that they may experience diplopia, which can be worse than what was present prior to surgery. Patients who undergo unilateral recess/resect procedures do not experience more than a few prism diopters of immediate postoperative overcorrection. Similarly, unilateral lateral rectus recessions show little, if any, initial overcorrection in the immediate postoperative period (198).

The goal for an adult with exotropia should be viewed somewhat differently. In these patients a persistent consecutive esotropia may cause intractable diplopia. Further surgery may be required to place the patient back into his or her original suppression scotoma. However, a small residual exodeviation will usually provide complete relief of symptoms and an improvement in appearance. An undercorrection, therefore, is much preferable to an overcorrection, in this instance.

CONVERGENCE INSUFFICIENCY

Convergence insufficiency is characterized by an exodeviation that is present only at near or greater than distance fixation. Complaints associated with convergence insufficiency include asthenopia and diplopia during periods of near work. Patients may also complain about blurring of their vision as they attempt to exchange accommodative convergence for fusional convergence and induce an artificial myopia. The symptoms of convergence insufficiency cover a large spectrum, from mild to very severe, and are often extremely annoying in the presence of a small exodeviation at near fixation.

Management

Orthoptic treatment of convergence insufficiency has been successful in improving fusional amplitudes and relieving symptomatology in most cases (199,200). The use of base-in prisms may also help alleviate the symptoms of convergence insufficiency.

There is a small, select group of patients whose symptoms do not respond to orthoptics, prisms, or any other form of medical ophthalmic therapy. These particular patients with intractable and debilitating symptoms may respond to medial rectus resection (201,202,203). An initial overcorrection with diplopia and a need for prismatic treatment may be required for the best long-term result (202,203). Other authors have had good results using a monocular recess/resect procedure in which the surgery was based upon the near angle, and the medial rectus resection was increased with a corresponding decrease in the lateral rectus recession (204).

A and V Patterns

A and V patterns are manifested by a horizontal change of alignment as the eyes move from the primary position to midline upgaze or downgaze. Although vertical incomitance was mentioned by Duane in 1897, its importance was not emphasized until the studies by Urretz-Zavalia and Urist (205,206). Albert (207) suggested the terms “A pattern” and “V pattern,” which have found worldwide acceptance.

Esotropia with V pattern increases in downgaze and decreases in upgaze (Fig. 9.16). The deviation in V exotropia increases in upgaze and decreases in downgaze (Fig. 9.17). In A esotropia, the deviation increases in upgaze and decreases in downgaze (Fig. 9.18). In A exotropia, the deviation increases in downgaze and decreases in upgaze (Fig. 9.19). Occasionally, a patient may have essentially no deviation or a small one in primary position, although exotropia X pattern is present in upgaze and downgaze. Also, exotropia may occur only in upgaze Y pattern or in downgaze ? pattern. The A and V patterns are demonstrated by measuring a deviation in primary position and in approximately 25 degrees of upgaze and downgaze, while the patient fixates on a distant object. An A pattern is said to exist, if divergence increases in downgaze by 10 or more prism diopters. A V pattern signifies an increase in divergence of 15 or more prism diopters in

upgaze. The smaller amount of change required to make a diagnosis of an A pattern is due to the greater effect of the downgaze deviation on reading and other near tasks. Anomalous head posture is common in patients with A and V patterns. Patients with A esotropia and V exotropia, who have fusion in downgaze, may develop a chin-up head posture. Conversely, V esotropia and A exotropia may cause chin depression.

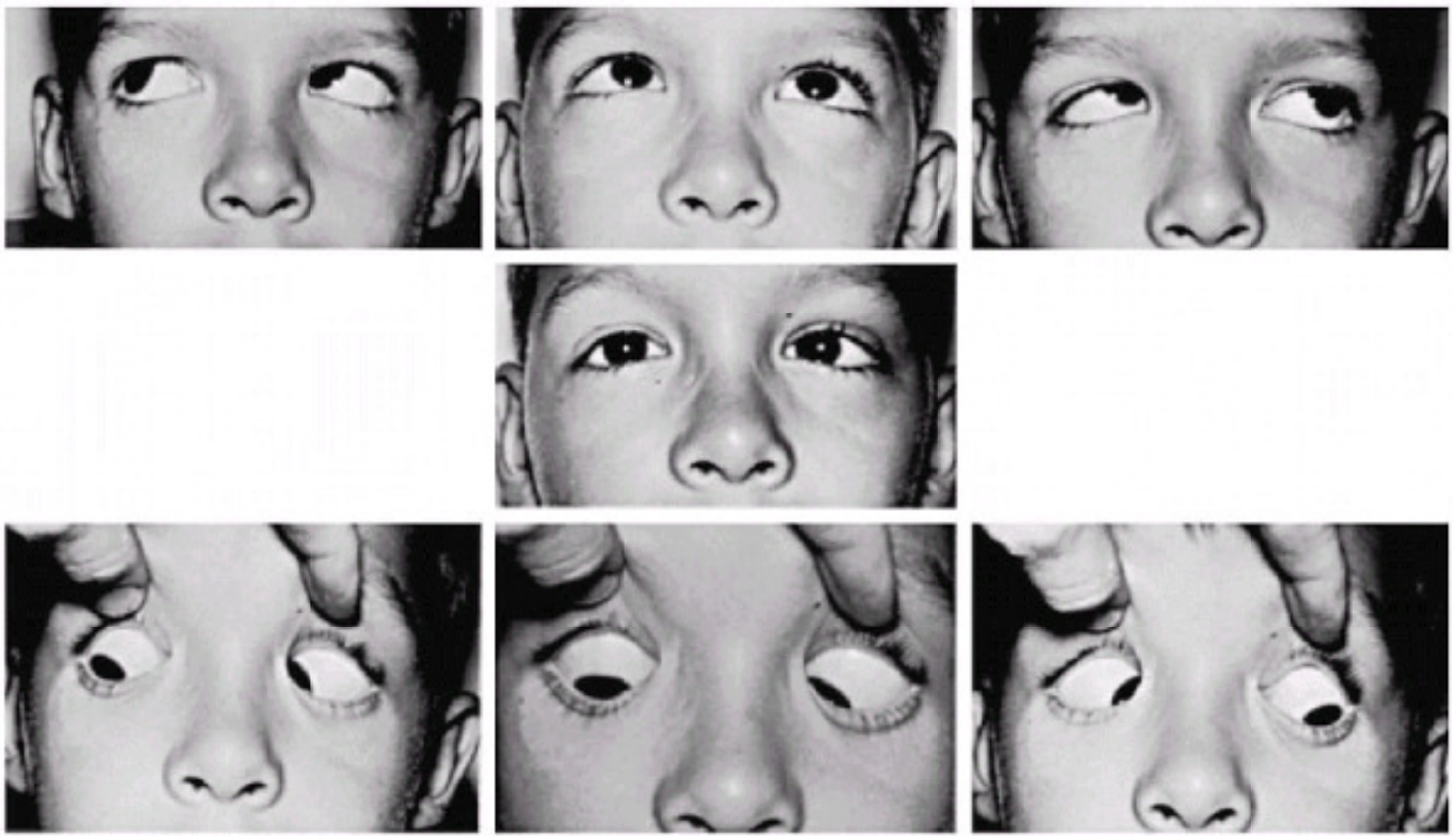

Figure 9.16 V pattern in esotropia; the esotropia increases in straight downgaze and decreases in straight upgaze. Overaction of both inferior oblique muscles causes greater abduction in upgaze. Underaction of both superior oblique muscles causes decreased abduction in downgaze. (From Harley RD. In: Manley DR. *Symposium on horizontal ocular deviations*. St. Louis: CV Mosby, 1971, with permission.)

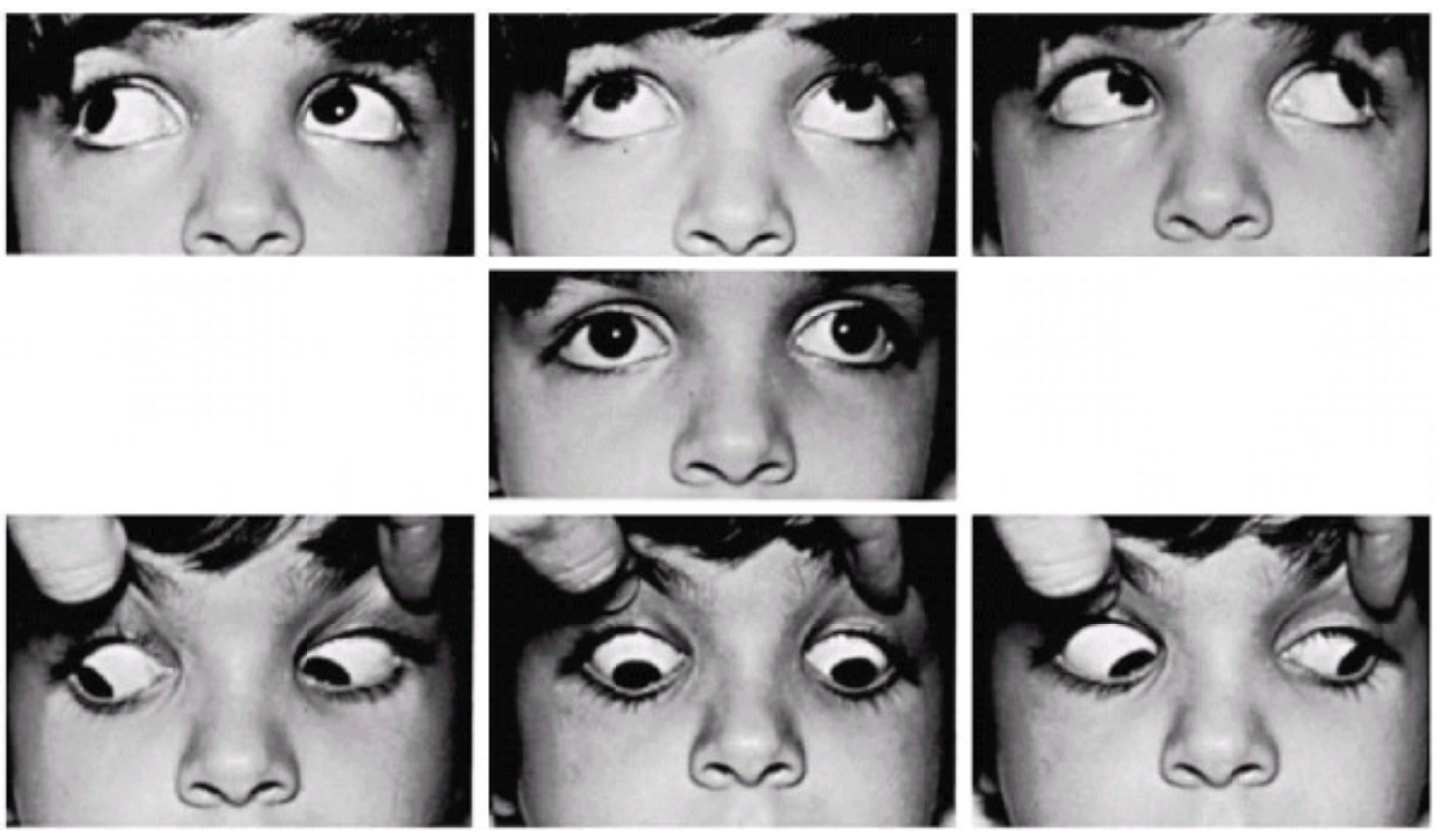

Figure 9.17 V pattern in exotropia; the exotropia increases in straight upgaze and decreases in straight downgaze. Overaction of both inferior oblique muscles causes increased abduction in upgaze. Underaction of both superior oblique muscles causes decreased abduction in downgaze.

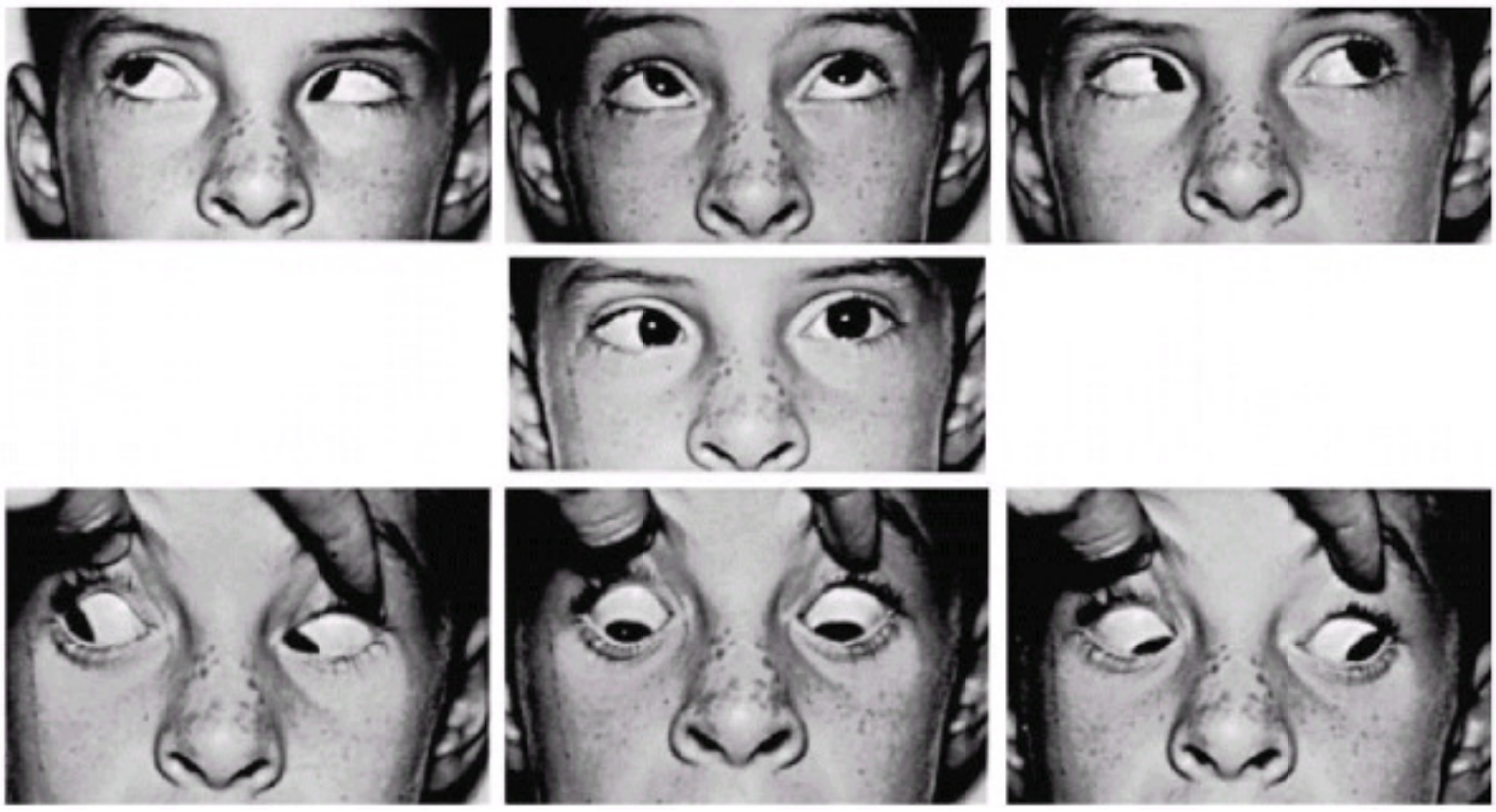

Figure 9.18 A pattern in esotropia; the esotropia increases in straight upgaze and decreases in straight downgaze. Underaction of both inferior oblique muscles causes decreased abduction in upgaze. Overaction of both superior oblique muscles causes increased abduction in downgaze. (From Harley RD. In: Manley DR. *Symposium on horizontal ocular deviations*. St. Louis: CV Mosby, 1971, with permission.)

Pathogenesis

A number of different theories have evolved to explain the etiology of A and V patterns. There is no universal agreement of their cause at this time.

Urist (206,208) was a proponent of the horizontal muscles as the cause of A and V patterns. He believed that in V esotropia, overaction of the medial rectus muscles causes the increased convergence in downgaze, and the overaction of the lateral rectus muscle results in increased divergence in upgaze. Conversely, increased divergence in downgaze A exotropia is thought to be caused by underacting medial

rectus muscles and, in A, esotropia by underacting lateral rectus muscles. There is some electromyographic evidence to support the contention that the horizontal rectus muscles are the cause of A and V patterns (209,210).

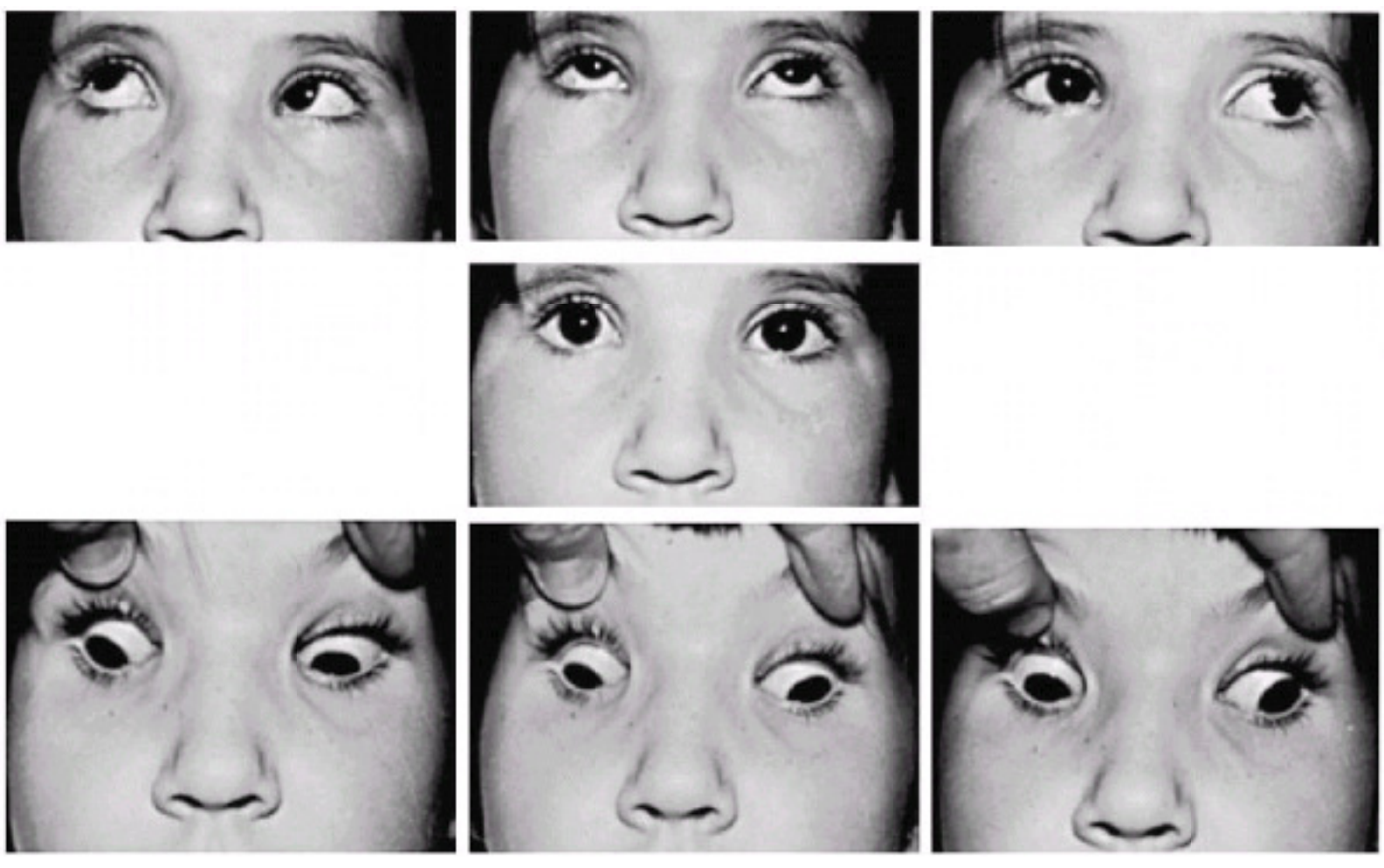

Figure 9.19 A pattern in exotropia; the exotropia increases in straight downgaze and decreases in straight upgaze. Overaction of both superior oblique muscles causes increased abduction in downgaze. Underaction of both inferior oblique muscles causes decreased abduction in upgaze.

Brown (211) believed that A and V patterns are caused by primary anomalies in the function of the vertical rectus muscle, in which adduction is the tertiary action. Brown's view is supported by the observation that secondary horizontal deviations with A and V patterns may develop following acquired paresis of the vertical rectus muscles and that surgery on the superior rectus muscles may help to treat both A and V patterns (212).

Another possible cause of A and V patterns is oblique muscle dysfunction. Since the oblique muscles have secondary abducting action, when the superior obliques are overacting, they may cause an A pattern; when the inferior obliques are overacting or the superior obliques are underacting, a V pattern often results. Many patients with oblique dysfunction demonstrate an A or V pattern. However, A and V patterns frequently exist in the absence of demonstrable oblique dysfunction.

Ocular torsion has also been proposed as the cause of A and V patterns (213,214). Torsion of the globe results in vertical displacement of the insertions of the horizontal recti and horizontal displacement of the vertical recti. These displacements would then be expected to alter the vectors of the forces exerted on the globe so that the horizontal recti become partial elevators or depressors, and the vertical recti become increasing abductors or adductors. This change in force vectors could then produce or enhance an A or V pattern. In the case of excyclotorsion, the superior recti would cause excessive abduction in elevation, and the inferior recti would cause adduction in depression, thus producing a V pattern. The cause of the initial torsion that leads to the secondary change in vector forces is unknown. Kushner felt that primary oblique dysfunction was the cause of the ocular torsion, whereas Guyton and Weingarten felt that a loss of fusion leads to secondary “sensory” torsion of the globe. In support of the sensory torsion theory, Miller and Guyton (215) observed that patients who were overcorrected following surgery for intermittent exotropia, thereby losing fusion, were more likely to later develop an A or V pattern than those patients who maintained fusion postoperatively. Ocular torsion may play a role in the A and V patterns of strabismus seen in children with craniofacial abnormalities.

Treatment

A and V patterns can be corrected in one of several ways: moving the insertions of the horizontal rectus muscles, weakening or strengthening of the inferior or superior oblique muscles, or moving the insertions of the vertical rectus muscles laterally or medially.

Vertical transposition of the horizontal rectus muscles is an effective method of treating A and V patterns (216). Moving or offsetting the horizontal rectus muscle insertion up or down weakens the action of that muscle when the eye is moved in the direction of the offsetting. For example, if the medial rectus muscles are moved up one-half tendon width, their horizontal action further decreases in upgaze. It follows that moving the medial rectus toward the apex of an A and V pattern is appropriate for correcting the incomitant deviation. Conversely, moving the lateral rectus muscle toward the open end of the A or V is also appropriate for correcting the incomitant deviation. This is true regardless of whether recession or resection is performed.

It is generally accepted that offsetting the muscle insertion up or down one-half tendon width, irrespective of whether it is performed on the medial rectus or the lateral rectus muscle, or whether it is combined with a recession or resection of that muscle, will correct approximately 15 prism diopters of the A or V pattern when the offsetting is performed on two horizontal rectus muscles (217,218). The amount of pattern correction is proportional to the amount of preoperative pattern that was present (219,220). Vertical transposition of the horizontal rectus muscles may be performed symmetrically and bilaterally, or may be confined to one eye, with appropriate vertical displacement of the medial and lateral rectus muscles (216,221). Slanting of the horizontal rectus muscles may also give the same result (222,223).

Surgery on the oblique muscles is another effective method of reducing the vertical incomitancy. Weakening both inferior obliques causes about 15 prism diopters of esoshift in upgaze, that is, a lessening of exotropia or an increase in esotropia in upgaze (224). Because this procedure has no effect on horizontal alignment in primary or downgaze, a V pattern esotropia with a large deviation in downgaze and underacting superior obliques can also be treated with a bilateral superior oblique tuck because this will increase the abducting force of the superior oblique, and decrease the esotropia, in downgaze. Weakening both overacting superior obliques causes about 25 to 45 prism diopters of convergence in downgaze, with up to 10 diopters of convergence in primary position and no effect in upgaze (225,226). The effect of a bilateral superior oblique weakening procedure on the downgaze deviation is proportional to the size of the preoperative pattern (227).

Overacting inferior obliques should not be weakened unless there is some degree of underaction of the superior obliques, and, conversely, the superior obliques should not be weakened unless the inferior obliques are underacting. If this advice is ignored, the opposite pattern is likely to develop not too long after surgery, with the unoperated oblique muscles overacting.

If a patient has good binocular function, even if it is intermittent, the superior obliques should be weakened with caution. Typically, this scenario involves a patient with an A pattern intermittent exotropia who demonstrates bifixation when the deviation is not present. Even with the best surgical technique, weakening of the superior obliques may lead to an asymmetrical result with a vertical or torsional deviation in primary position occurring postoperatively. This may result in a sustained head tilt to compensate for the induced tropia (228). If the superior obliques are to be weakened, a procedure that leaves the tendon available for reoperation may be helpful, if an iatrogenic ocular torticollis is produced. Because it may be impossible to reverse a free tenotomy of the superior oblique, some authors have advocated recession of the tendon, placement of an expander

between its cut ends, or a split Z-tendon lengthening (229,230,231).

Horizontal transposition of the vertical rectus muscles to correct A and V patterns was first proposed by Miller (232). The adduction component of the vertical rectus muscles is enhanced or reduced, respectively, by transposing the insertions nasally or temporally, usually one-half tendon width. This transposition does not interfere with the vertical duction of the operated vertical rectus muscles. Because most patients with A and V patterns require horizontal surgery for correction of strabismus in primary position, most pediatric ophthalmologists prefer to transpose the horizontal rectus rather than the vertical rectus muscles. Therefore, if a patient has an A or V pattern with or without fusion, and, if there is no oblique dysfunction, the horizontal muscles can be offset to correct the pattern. If there is oblique dysfunction, surgery on these muscles can be performed to correct the pattern. With inferior oblique overaction with a V pattern, these muscles can be weakened. If the V pattern is much larger than 15 diopters in upgaze, the horizontal muscles will need to be offset as well. A V pattern with a large esotropia in downgaze and superior oblique underaction may require a bilateral superior oblique strengthening procedure to adequately correct the downgaze deviation. Finally, if the patient has an A pattern with fusion, the superior oblique should be weakened with caution and, preferably, in a manner in which the cut ends of the tendon can be located again, if needed; offsetting the horizontal muscles alone may be the safest treatment in these patients.

CRANIAL NERVE PALSIES

Paralytic strabismus, a motor imbalance caused by paresis or paralysis of an extraocular muscle, is characterized by a deviation that varies according to the direction of gaze and fixation with the involved or uninvolved eye. The diagnosis of paresis of recent onset is suggested by a deviation greatest in the field of action of the paretic muscle, by double vision, and by an increase in the deviation when the patient fixates with the paretic eye. It is important to distinguish paresis or paralysis of one or several extraocular muscles from a comitant form of strabismus, not only because correct identification of the muscle or muscle groups helps the planning of proper therapy, but also because an acquired paresis or paralysis may indicate a systemic or neurological abnormality.

The treatment of paralytic strabismus, especially in adults with diplopia, can be the most challenging in the field of strabismus. Proper evaluation and treatment strategies are essential in the care of patients with these conditions. It is important that patient and physician alike maintain realistic expectations of the goals in the treatment of these often frustrating disorders.

The distribution and etiology of third, fourth, and sixth nerve palsies at the Mayo Clinic has been extensively reviewed by Richards et al (233). In their series of

4,278 cases, the abducens nerve was most commonly affected, followed by oculomotor nerve (26.8%) and trochlear nerve (15.4%) palsies. Thirteen percent of patients had multiple cranial nerve involvement. The most common etiologies included: undetermined, head trauma, neoplasm, vascular, and aneurysm. In a similar study limited to the pediatric population, the most common cranial nerve affected was the trochlear nerve (36%), followed by the abducens nerve (33%), and the oculomotor nerve (22%). Multiple nerve palsies accounted for 9% of cases seen. The most common cause was congenital for third and fourth nerve palsy, undetermined for sixth, and trauma for multiple nerve palsies (234).

Third Nerve Palsy

Third nerve palsies in children are frequently congenital (233,235,236,237). In children with an acquired third nerve palsy, trauma is the most common cause (238).

Congenital

The four extraocular muscles: medial rectus, inferior rectus, superior rectus, and inferior oblique innervated by the third nerve, are affected in various degrees. Typically, the involved eye is hypotropic and exotropic, with varied degrees of limitation of elevation, depression, and adduction (Fig. 9.20). The third nerve also innervates the levator muscle, so variable degrees of ptosis may also be present. The intraocular musculature is not usually affected in congenital third nerve palsy. However, pupillary constriction may occur on attempted adduction in some cases of aberrant regeneration (234,235,236,239).

Some patients with congenital third nerve palsy develop binocular vision by maintaining a compensatory head posture. Amblyopia may occur in either eye if the child does not maintain a head posture to compensate for the strabismus (240,241).

Congenital third nerve palsies are generally considered to be benign and isolated. However, Balkan and Hoyt (241) reported other focal neurological signs with congenital third nerve palsy, including pupillary involvement, oculomotor synkinesis, hemiplegia seizures, and developmental delays. They suggested that all patients with congenital third nerve palsies should be examined by a pediatric neurologist for other signs of focal neurological damage.

Pathogenesis

There are several possible causes of congenital third nerve palsy. Perinatal trauma to the peripheral oculomotor nerve has been considered the primary mechanism in the development of congenital third nerve palsies (234,240). Absence of other brainstem findings in the presence of aberrant regeneration in many patients supports this mechanism. However, Balkan and Hoyt (241) demonstrated that associated neurological anomalies and brainstem signs sometimes occur in patients with congenital third nerve palsies. Ischemic and hypoxic insults to the brainstem in utero have been shown to produce unilateral or bilateral nuclear aplasia (242). Therefore, a central brainstem lesion may account for some cases of congenital third nerve palsies.

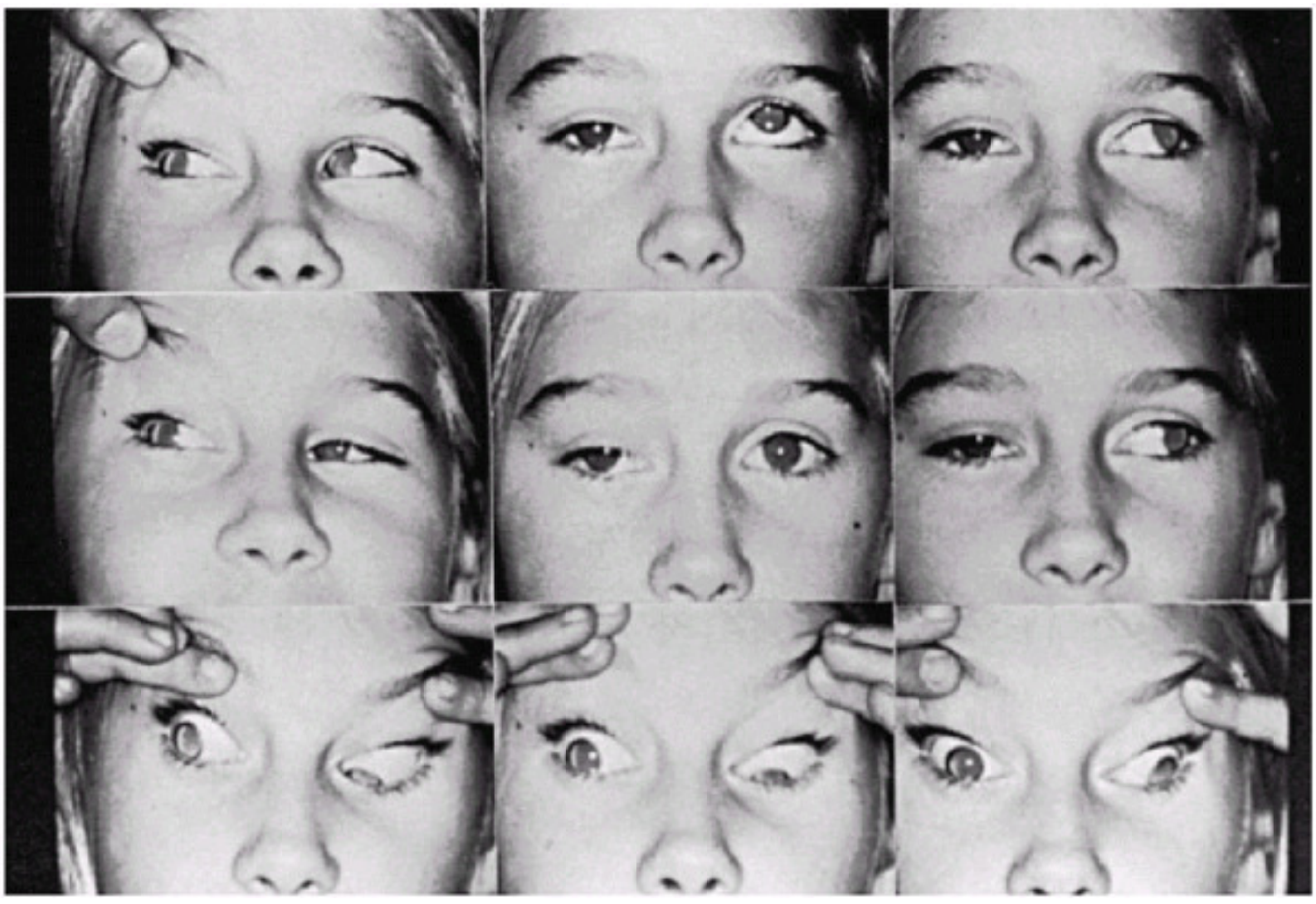

Figure 9.20 A child with right third nerve palsy with exotropia in the primary position and ptosis. There was an inability to depress, elevate, or adduct the right eye. (Courtesy of Robison D. Harley, MD.)

Acquired

Acquired third nerve palsy in children and adults is often an ominous sign. The palsy may be partial or complete and may involve only the extraocular muscles or both intraocular and extraocular muscles. Aberrant regeneration of the oculomotor nerve is thought to result from extensive and haphazard growth of the regenerated nerve fibers (243,244). Signs of aberrant regeneration include those listed in Table 9.4. The possible causes of acquired third nerve palsy are included in Table 9.5. Young children with cerebral aneurysms can present with an acute third nerve palsy with and without other neurological abnormalities (245,246).

TABLE 9.4 REGENERATION OF THE THIRD NERVE

1.	Retraction of the globe on attempted vertical gaze
2.	Adduction of the globe on attempted vertical gaze
3.	Lid retraction in downgaze pseudo-Graefe's sign
4.	Miosis on adduction pseudo-Argyll Robertson's pupil
5.	Eyelid elevates on adduction

Modified from Parks MM, Mitchell PR. Cranial nerve palsies. In: Duane TD, Jaeger EA, eds. *Clinical ophthalmology.* Philadelphia: JB Lippincott Co, 1987, with permission.

Treatment

Initial ophthalmic treatment for patients with acquired third nerve palsy involves relief of diplopia. If there is complete third nerve palsy, the associated complete ptosis will cover the pupil and prevent diplopia. However, in partial third nerve palsy, the lid may not cover the pupillary space, so diplopia may remain a problem. Occlusion therapy is then the best solution to the diplopia. Surgery to correct acquired third nerve palsy should be postponed until 6 months after the onset of the condition. Multiple procedures are often required to achieve alignment in primary position (247).

In congenital third nerve palsy, or an acquired palsy that has not resolved, surgical intervention is indicated to allow for the development of binocular vision or to relieve diplopia. If there is significant medial rectus muscle function, the eyes may be aligned in primary position with a large lateral rectus muscle recession combined with a medial rectus muscle resection (236,248). If ptosis surgery is necessary, a frontalis suspension procedure is required in patients with poor or absent levator function. Care must be taken not to elevate the lid too high because the cornea will be at significant risk for exposure, given the inability to elevate the globe. If aberrant regeneration has occurred so that the ptotic lid elevates on attempted adduction (Fig. 9.21), it may be possible to operate on the nonparetic eye to force the involved eye into this position and treat the ptosis as well as the strabismus with the same surgery.

TABLE 9.5 CAUSES OF ACQUIRED THIRD NERVE PALSIES

I. Brainstem lesion

A. Benedikt's syndrome

B. Weber's syndrome

II. Inflammatory conditions

A. Meningitis

B. Encephalitis

C. Polyneuritis from toxins, such as alcohol, lead, arsenic, and carbon monoxide and from diabetes

D. Herpes zoster

E. Echovirus infection

III. Vascular lesions, aneurysms

IV. Tumors

V. Demyelinating diseases

VI. Trauma

VII. Miscellaneous

A. Leukemia

B. Porphyria

C. Polyarteritis nodosa

D. Sarcoidosis

E. Infectious mononucleosis

F. Congenital toxoplasmosis

G. Myasthenia gravis

H. Temporal arteritis

I. Measles immunization

Modified from Parks MM, Mitchell PR. Cranial nerve palsies. In: Duane TD, Jaeger EA, eds. *Clinical ophthalmology.* Philadelphia: JB Lippincott Co, 1987, with permission.

In a complete third nerve palsy, the motility of the globe is severely limited, because only the lateral rectus and superior oblique muscles are functional. The eye is fixed in a characteristic down-and-out position. The goal of surgical intervention is to use the two remaining functional muscles in such a way as to achieve a straight-ahead eye with only limited movement of the globe (249). This goal should be carefully explained to the patient and parents to avoid unrealistic postoperative expectations.

In a patient with a complete third nerve palsy, the lateral rectus muscle should be recessed a minimum of 16 mm from its original insertion. Complete myectomy of the lateral rectus has also been performed with success (250). Resection of the paralyzed medial rectus may add little to the correction of the exotropia. The paralyzed medial rectus will often stretch and will not provide significant tension required to prevent the eye from drifting laterally. Transposition surgery in the treatment of a third nerve palsy is difficult because there are no vertical muscle forces to move nasally because the superior and inferior recti are also paretic.

Therefore, in the absence of significant medial rectus muscle function, a number of investigators have advocated using the superior oblique muscles as a means of exerting adducting forces to the globe (248,251,252,253,254). This technique involves fracturing the trochlea, removing the superior oblique tendon, and advancing and attaching it to the sclera near the insertion of the medial rectus muscle. However, this procedure may be technically difficult and the tendon easily severed, especially when the maneuver is attempted in an adult patient with a calcified trochlea.

Scott (255) advocated anterior transpositions of the superior oblique tendon without trochleotomy. The superior oblique tendon is first tenotomized at the medial border of the superior rectus muscle, advanced further through the trochlea, and resutured to the sclera 2 to 3 mm anterior to the medial end of the superior rectus muscle insertion. Saunders and Rogers (256) performed anterior transposition and advancement of the superior oblique tendon without trochleotomy with poor results, because of inadequate horizontal alignment, postoperative hyperdeviations, or paradoxical movements.

If transposition of the superior oblique is considered, it is imperative that the function of this muscle is normal. Many patients who have suffered traumatic third nerve

palsy may show involvement of the fourth nerve as well. If the medial rectus is paretic, it may be difficult to judge the function of the superior oblique because the globe will not be able to move into the down-and-in position. Two methods may be utilized to evaluate the integrity of the superior oblique. The examiner can look at a conjunctival blood vessel as the patient is asked to look into the field of action of the superior oblique. If the muscle is functioning, the blood vessel will rotate nasally as the superior oblique attempts to move the globe into this position and causes incyclorotation of the globe. Also, a funduscopic examination can be performed to look for evidence of excyclotorsion, which may be observed in the presence of a coexistent superior oblique palsy.

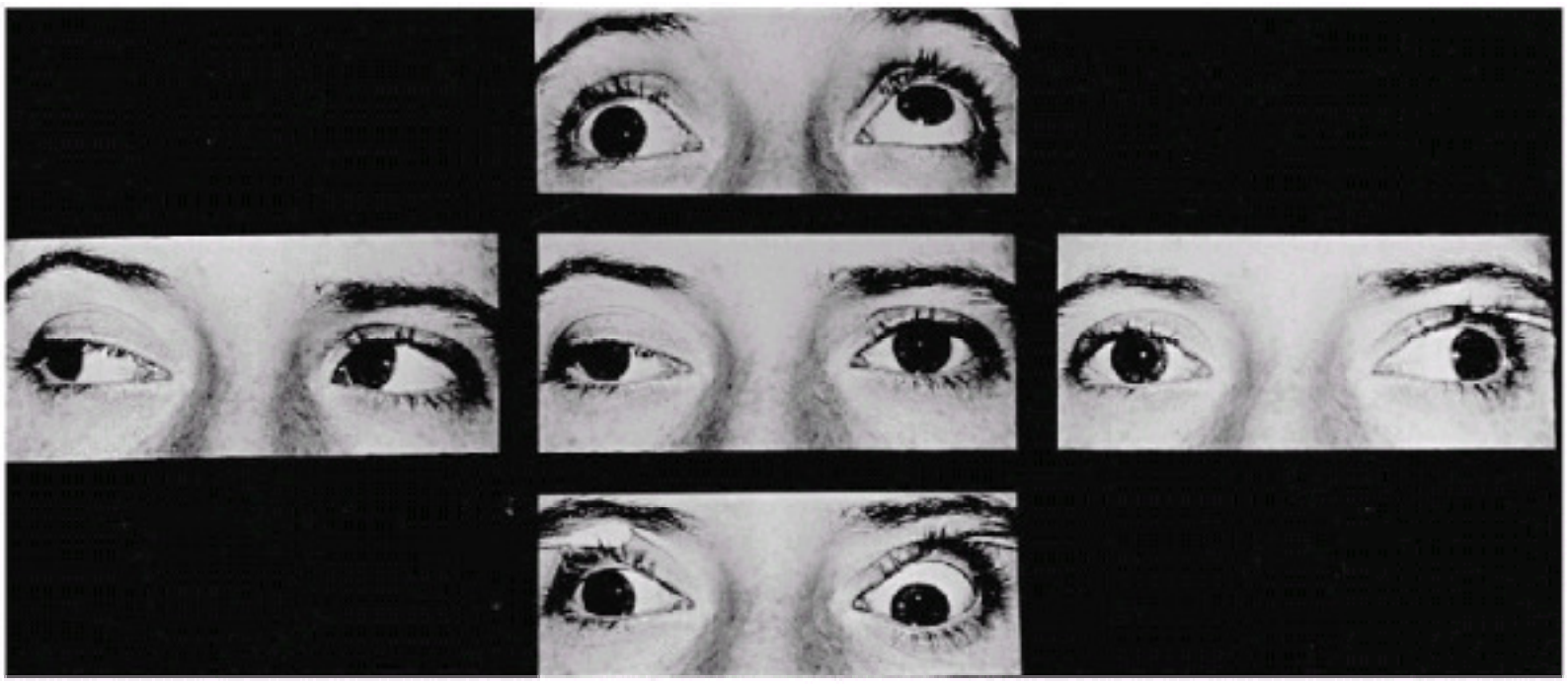

Figure 9.21 Right third nerve palsy with aberrant regeneration. Notice that the ptotic lid elevates with attempted adduction of the right eye.

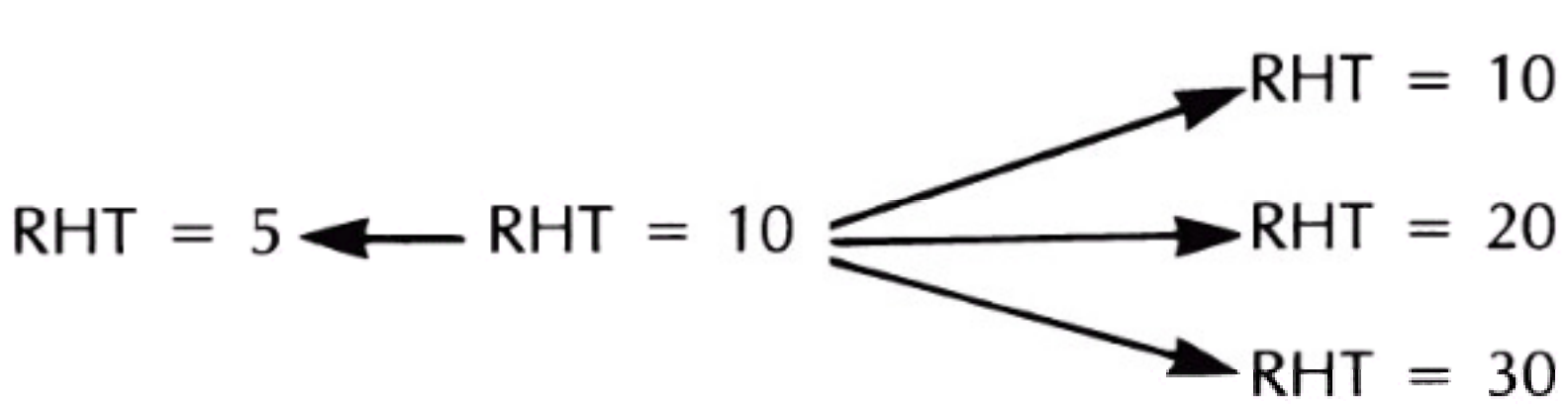

Figure 9.22 Diagram illustrating a fourth nerve palsy of recent onset.

Fourth Nerve Palsy

Fourth nerve palsy is the most common cause of an isolated cyclovertical muscle palsy (233,236). Paresis of the fourth nerve can be congenital or acquired. Closed-head trauma is the most common cause of fourth nerve palsy in most series and represents one third of all traumatic ocular motor palsies (257,258,259,260). Von Noorden (261) reviewed 270 cases of superior oblique paralysis and found that 40% were congenital, 34% were traumatic, 23% were idiopathic, and 3% were due to other causes, such as vascular disease, tumors, or myasthenia gravis.

Despite extensive clinical and laboratory testing, often no definitive etiology is identified in many cases of fourth nerve palsy (259). Harley (237) reviewed the

causes of paralytic strabismus in 121 children from birth to age 16 and found 67% of fourth nerve paralysis to be of undetermined origin.

A fourth nerve palsy is initially an incomitant hypertropia, greatest in the adducted depression position of the involved eye (Fig. 9.22). If the palsy continues, contracture of the ipsilateral inferior oblique occurs, and the maximal hyperdeviation is found in the field of action of this muscle. Another sign of contracture of the ipsilateral inferior oblique muscle is overelevation of the adducted palsied eye (Fig. 9.23). On the side in which the vertical deviation of the eyes is maximal, the hypertropia becomes incomitant in upgaze and downgaze (Fig. 9.24).

Patients with unilateral fourth nerve palsy often present with torticollis to reduce diplopia (Fig. 9.25). Head tilt to the side of the nonparetic eye is found in many patients. Because the superior oblique muscle is a depressor and intortor, its tone is diminished by upgaze, and by tilting the head to the shoulder opposite the palsied muscle, patients

with unilateral superior oblique palsy can maintain binocular vision. The absence of a head tilt is usually attributed to amblyopia or extremely large amplitude of vertical fusion (262). Some patients tilt their head to the side of the paretic eye to increase the vertical deviation and to make it easier to ignore the second image (259,263).

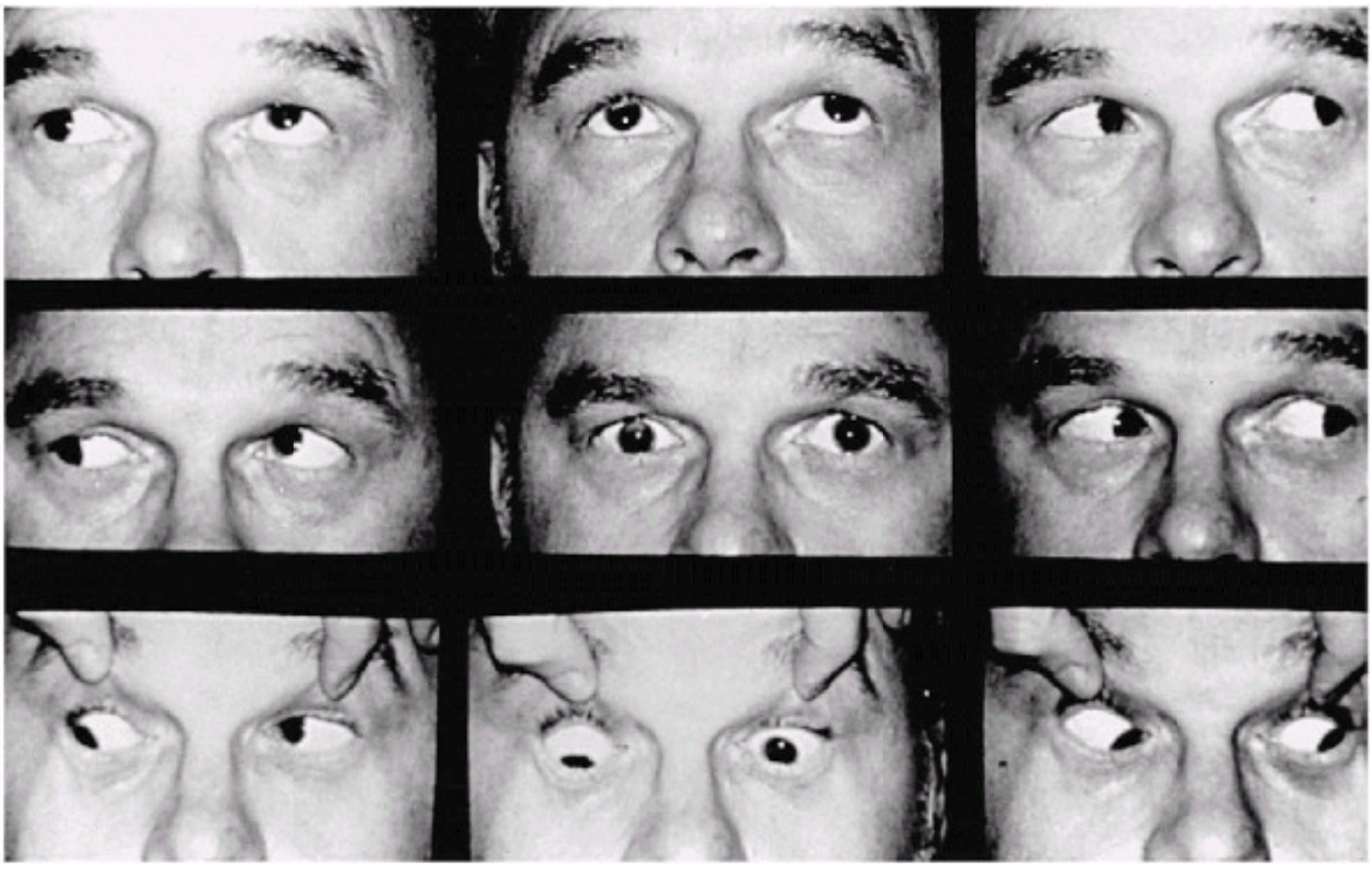

Figure 9.23 Adult with an acquired left superior oblique palsy. Note the left hypertropia, overacting of the left inferior oblique, and underacting of the left superior oblique.

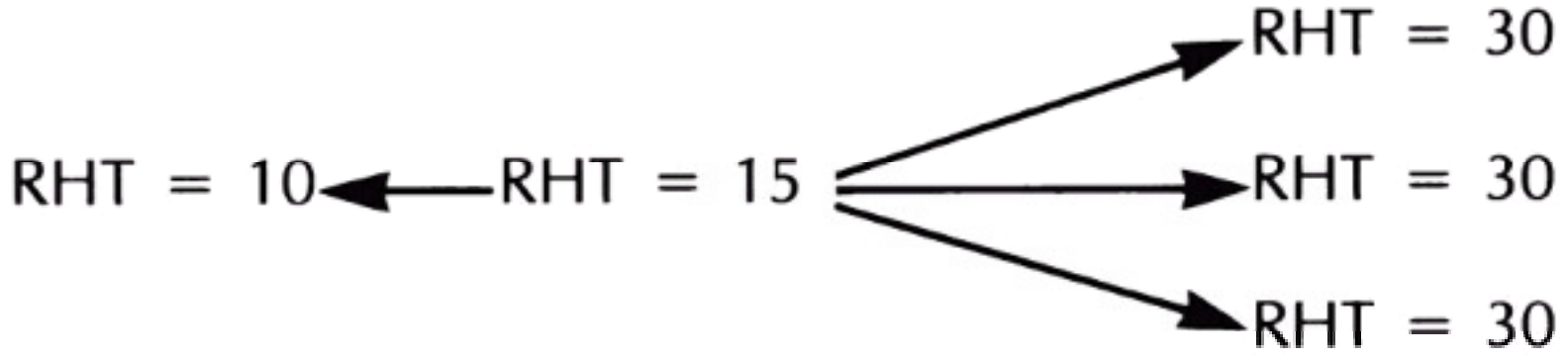

Figure 9.24 Diagram illustrating a fourth nerve palsy with the hypertropia comitant in upgaze and downgaze.

Facial asymmetry has been associated with congenital superior oblique palsy (264,265,266). Typically, this asymmetry is manifested by midfacial hemihypoplasia on the dependent side opposite the affected superior oblique. The nose deviates toward the hypoplastic side, and the mouth slants so that it approximates a horizontal orientation, despite the torticollis. It is thought that the facial asymmetry is secondary to the compensatory head tilt, which may lead to secondary gravitational effects, reduced blood flow through a compromised internal carotid artery, or deformational molding of the face and skull during sleep. In muscular torticollis, once facial asymmetry develops, it may persist, despite subsequent treatment (267,268). To prevent the facial asymmetry from developing, some authors recommend early surgery to correct the deviation (262,269).

Often an older patient presents with a new onset of diplopia secondary to a fourth nerve palsy. It is important to determine whether the palsy has only recently developed or whether it represents a congenital disorder that has decompensated. A newly acquired fourth nerve palsy may require further evaluation, including a detailed neurological examination and radiographic imaging. Several features may help to determine the acuteness of the deviation. A patient with a congenital superior oblique palsy will often have large vertical fusional amplitudes. If these amplitudes are measured and found to be large, or if the patient experiences only occasional diplopia in the presence of a large vertical deviation, the palsy is most likely long-standing or congenital. Examination of old photographs may show a compensatory head tilt (Fig. 9.26). The presence of facial asymmetry, as described previously, would also signify a previous motility disorder. Last, patients with

congenital superior oblique palsies may not experience subjective torsional diplopia, whereas patients with an acquired palsy generally do complain of tilting of the second image (259,270,271).

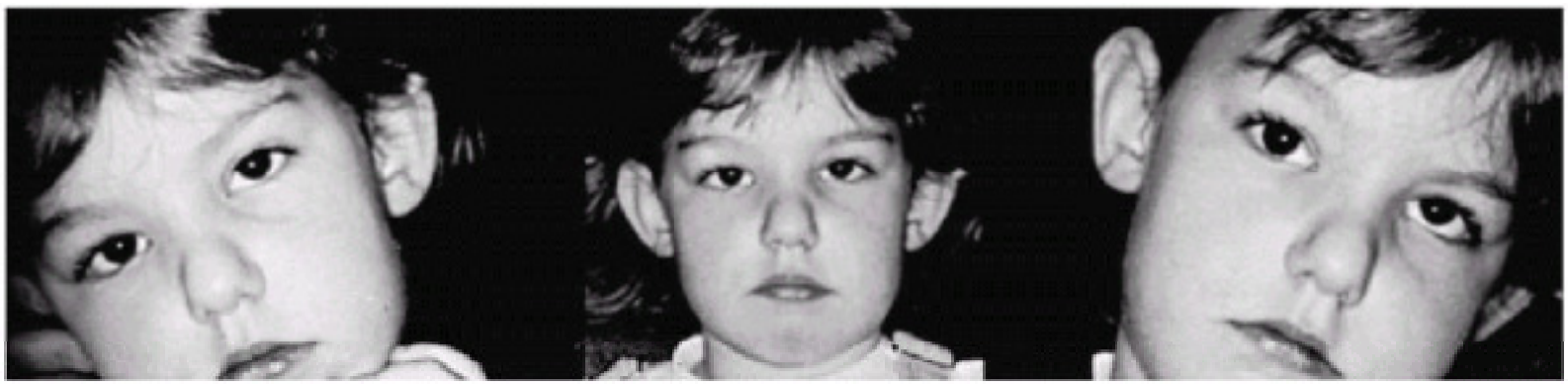

Figure 9.25 A child with a left superior oblique palsy. Note the increase in the left hypertropia, with the head tilting to the left. (From Nelson LB, Catalano RA. *Atlas of ocular motility*. Philadelphia: WB Saunders, 1989, with permission.)

Figure 9.26 A: A patient who presented with new onset diplopia. **B:** The same patient as seen in an old photograph approximately 40 years earlier demonstrating the same head tilt.

To evaluate logically any isolated cyclovertical muscle palsy, Parks devised a three-step test. Along with the latter, the double Maddox rod test should be performed to detect a torsional component. The three-step test is described in the following text (Figs. 9.27, 9.28 and 9.29).

Step One: Determining whether there is a right hypertropia or left hypertropia in the primary position eliminates four of the eight cyclovertical muscles as possibly palsied. For example, right hypertropia establishes that there is possibly:

A. Weak left elevator
    1. Left superior rectus
    2. Left inferior oblique
B. Weak right depressor
    1. Right inferior rectus
    2. Right superior oblique

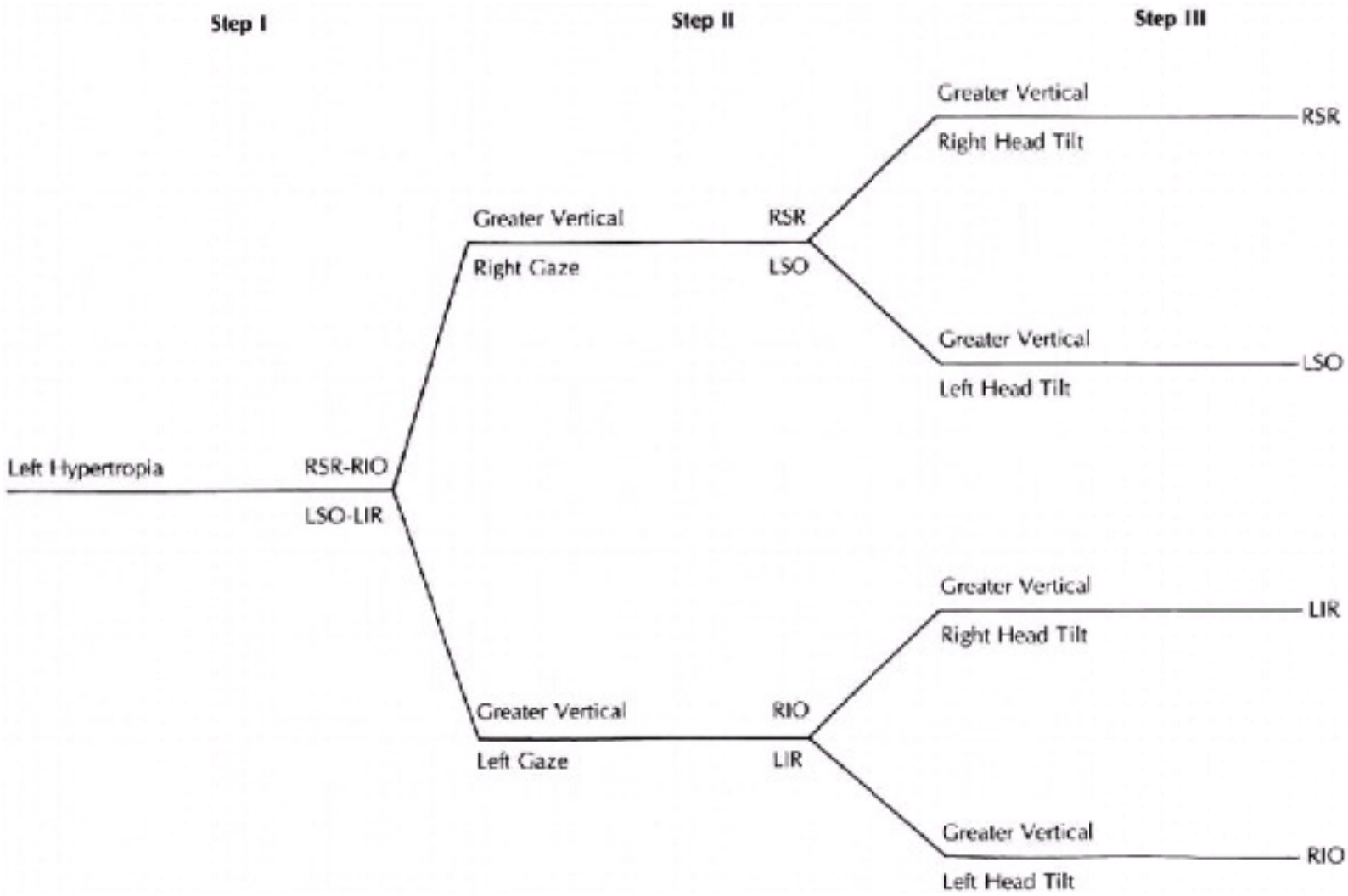

Figure 9.27 Three-step test for left hypertropia.

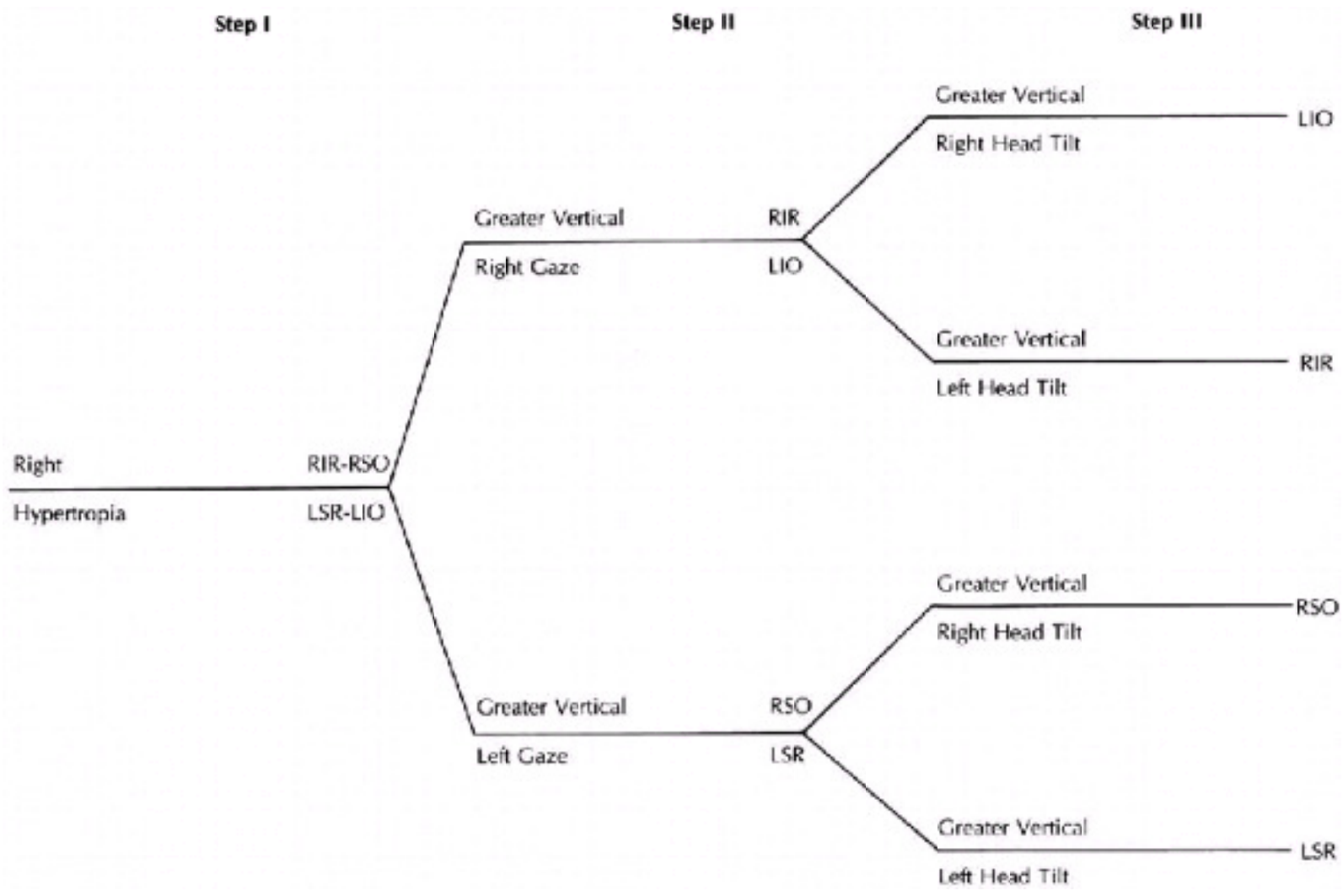

Figure 9.28 Three-step test for right hypertropia.

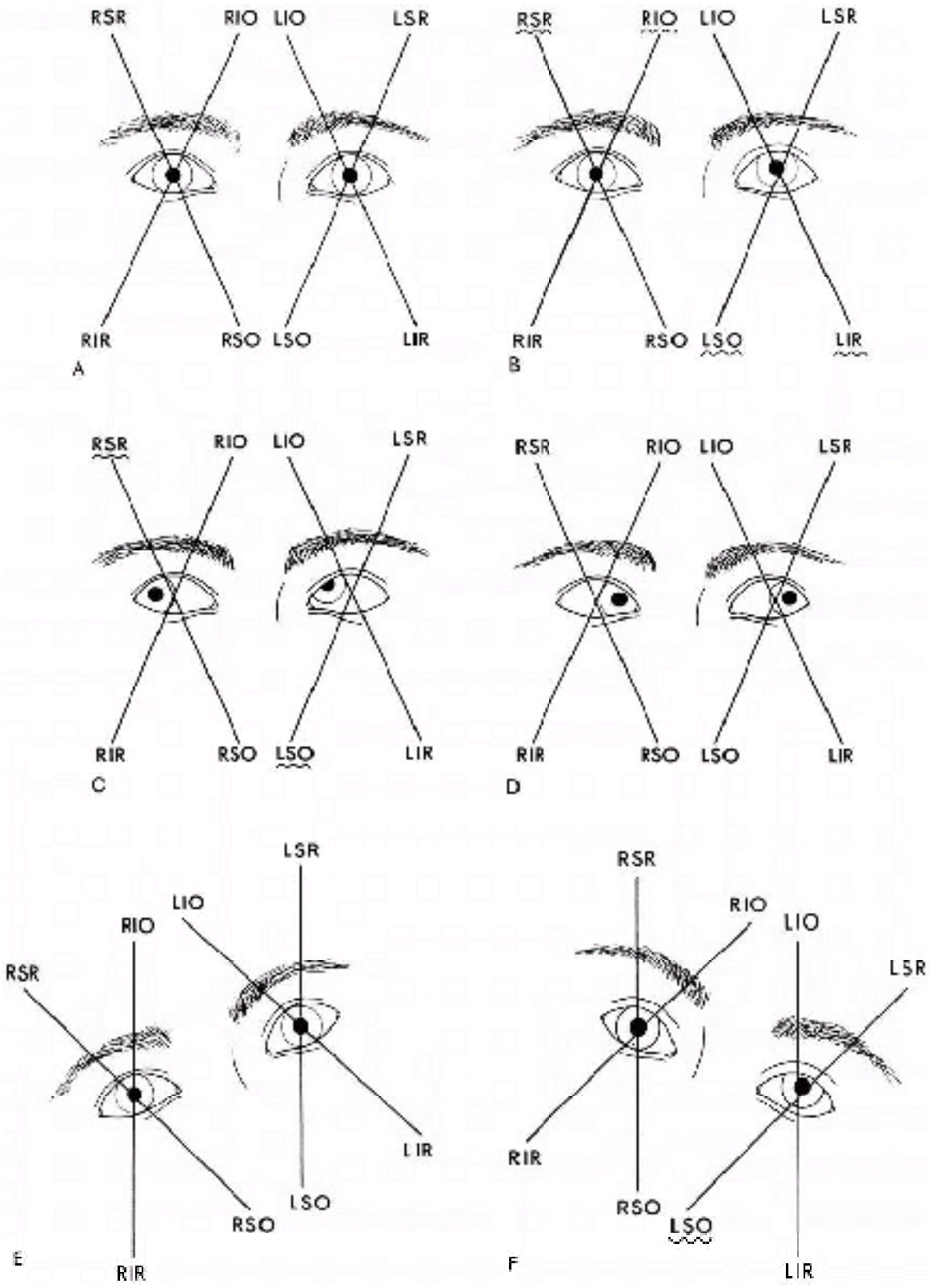

Figure 9.29 A: Primary position showing the positions of gaze in which the vertical actions of the cyclovertical muscles are maximal. **B:** Left hypertropia, which could be caused by a weakness of the LSO, LIR, RIO, or RSR. **C:** Left hypertropia greater in straight gaze LSO-RSR. **D:** No hypertropia in straight left gaze. **E:** No hypertropia on right head-tilt. **F:** Left hypertropia increases on left head-tilt LSO.

Step Two: Determining whether the vertical deviation increases on right or left gaze eliminates one of the two cyclovertical muscles in each eye. For example,

A. Right hypertropia that increases in left gaze indicates that either
    1. The right superior oblique is weak, or
    2. The left superior rectus is weak.
B. At the end of Step Two, the two possible palsied muscles are always either intortors or extortors.

Step Three: The Bielschowsky head-tilt differentiates which of the two muscles from Step Two is palsied.

The Bielschowsky head-tilt is based on the utricular reflex, which is stimulated by tilting the head. Tilting to the right causes the intortors of the right eye and extortors of the left eye to contract, while the opposite combination contracts on tilting to the left. Of the two extortors and two intortors that are stimulated by head-tilting, one muscle in each eye is an elevator and the other a depressor. This balance normally maintains vertical alignment on head-tilting. In weakness of a cyclovertical muscle, there is a vertical imbalance with head-tilting that is the basis for the Bielschowsky sign, on the third step of the three-step test. If, for example, the right superior oblique is palsied, tilting the head to the right should stimulate the two intortors of the right eye, the superior oblique, and superior rectus. Because the superior oblique is palsied, the right superior rectus will be stimulated and increase the right hypertropia.

In addition to Parks's three-step test, measurement of the deviation in the field of action of the superior oblique down-and-in and inferior oblique up-and-in should be done. This “fourth” step provides information in determining treatment options in patients with superior oblique palsy (see “Treatment” in later text).

In older children and adults who present with hypertropia, the double Maddox rod can be used to detect any torsional component (272,273). In children too young for the presence of excyclotropia to be evaluated with the double Maddox rod, indirect ophthalmoscopy and fundus photography are both useful for diagnosing cyclotropia objectively (275,276). Anatomically, the fovea is about one third of a disc diameter below the center of the optic nerve. If the fovea is lower than the expected normal relationship with the optic nerve, excyclotorsion of the retina exists (Fig. 9.30). It should be remembered that the indirect ophthalmoscope inverts and reverses the image of the retina seen by the observer so that the fovea will appear higher than the optic nerve during indirect ophthalmoscopy in the presence

of excyclotorsion.

Superior oblique palsy occurs bilaterally in 8% to 29% of cases (276,277,278). In bilateral superior oblique palsy, there is a left hypertropia in right gaze, a right hypertropia in left gaze, a right hypertropia on right head-tilt, a left hypertropia on left head-tilt, and V-pattern esotropia. The V-pattern esotropia is caused by deficient abduction of the palsied superior oblique muscles being offset by the adduction caused by the normally contracting inferior rectus muscles. When the palsies are symmetrical, there will be no vertical deviation in primary gaze because the effect of each side will “cancel” the other. However, excyclotorsion will exist and can be measured subjectively or objectively, as described previously (Fig. 9.31). If the palsy is asymmetrical, the paresis on the lesser affected side may be hidden by the large hypertropia of the more affected eye until after unilateral surgery is performed. The patient will then present postoperatively with a hypertropia of the untreated eye. This phenomenon has been termed a “masked” bilateral superior oblique palsy. To decrease the incidence of “unmasked” palsies, Jampolsky (279) stated that all superior oblique palsies should be considered bilateral until proven otherwise. Important signs of possible bilaterality include subjective torsion greater than 10 degrees, bilateral objective fundus torsion, any size reversal of the hypertropia in any gaze position, especially in the field of action of the inferior oblique, or an esodeviation in downgaze (280,281). Ellis et al (282) have suggested that a surgical overcorrection of a unilateral superior oblique palsy may sometimes masquerade as an unmasking of a bilateral palsy.

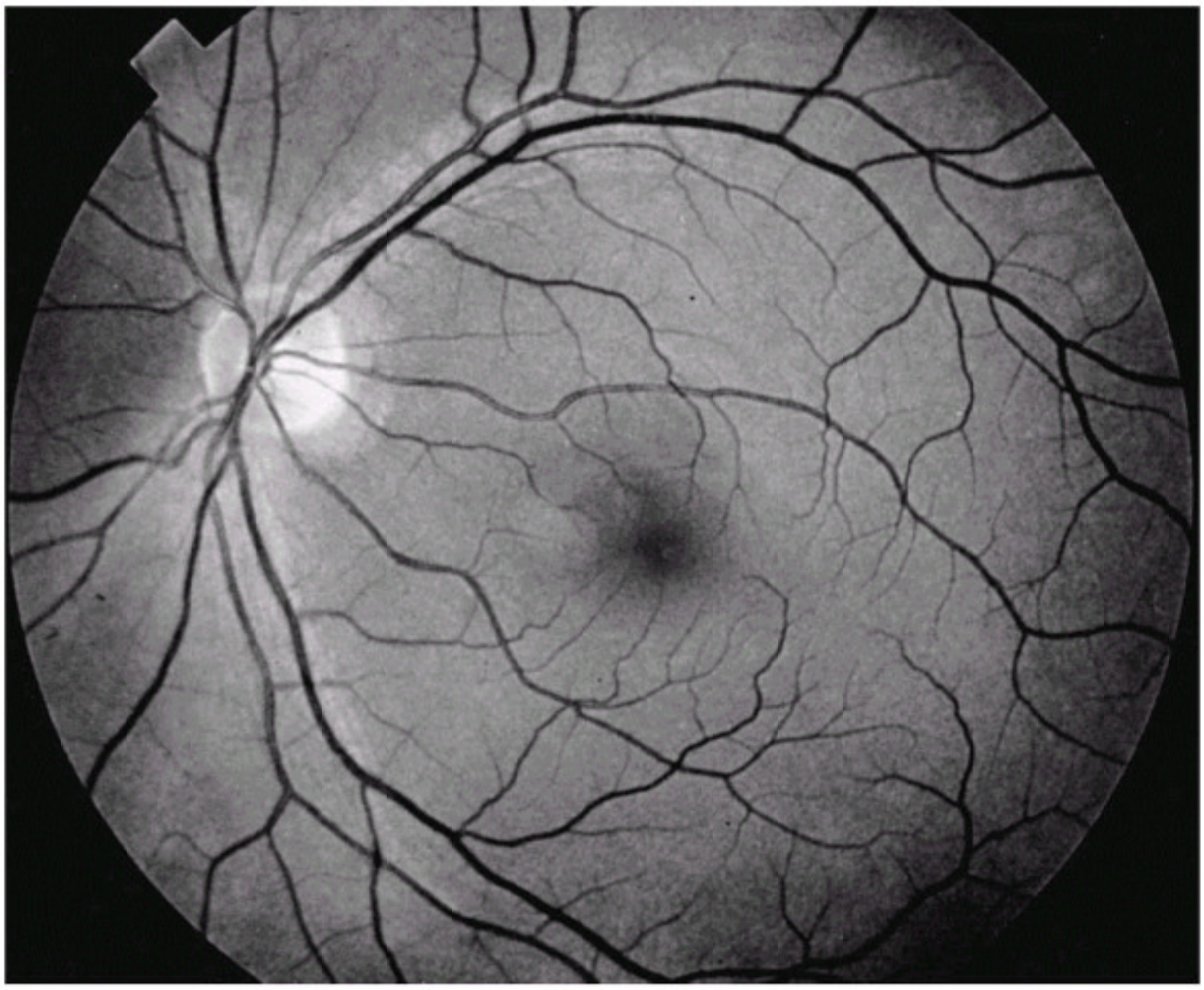

Figure 9.30 Fundus torsion secondary to excyclotropia. The fovea is below the lower one third of the optic disc.

Treatment

Except for an occasional patient with vertical deviation of 10 prism diopters or less when prism may be tolerated, most cases of superior oblique palsy require surgery. In general, surgery for superior oblique palsies should be directed to those muscles whose greatest action is in the field when the vertical deviation is the largest.

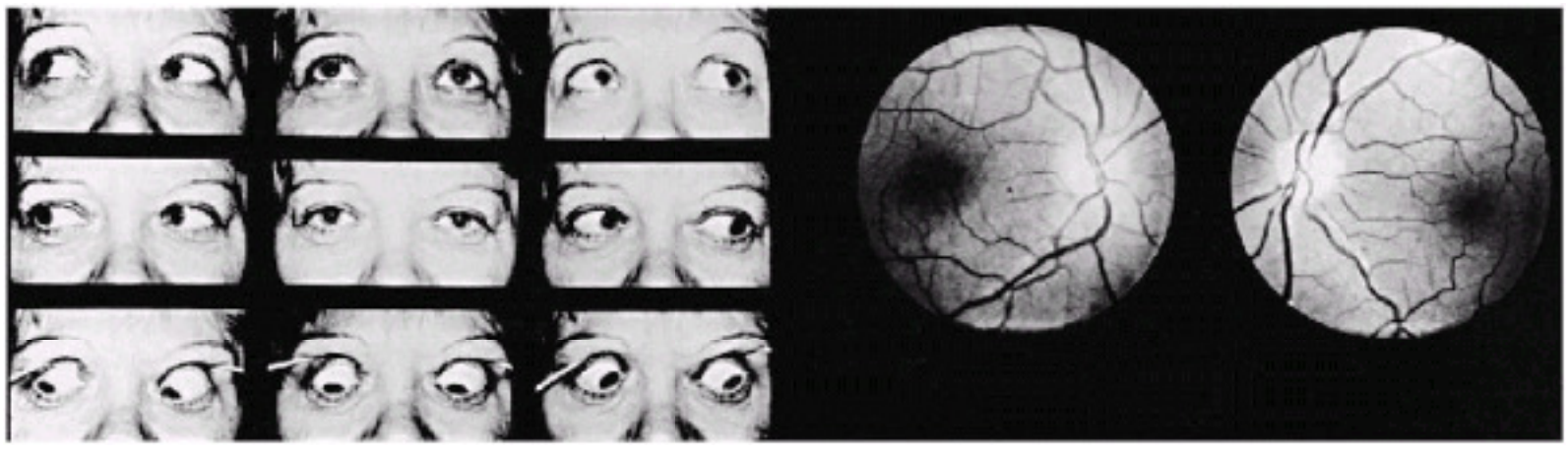

Figure 9.31 A: Bilateral fourth nerve palsy. Note the esotropia in downgaze and (B) the excyclotorsion of the left eye fundus.

Knapp (283) devised a classification and treatment scheme for superior oblique palsy (Table 9.6). Knapp's classification demonstrates the need for careful measurements in all diagnostic gaze positions. Although Gonzalez (284) found that many pediatric ophthalmologists use Knapp's surgical options as a general guideline, only 4% of those surveyed strictly adhere to them.

Young patients with congenital palsies will often have a floppy or anomalous superior oblique tendon (285). This can often be suggested with an exaggerated traction test at the time of surgery (286). If tendon laxity is demonstrated, a superior oblique tuck should be performed. A superior oblique tuck should also be performed when the greatest deviation exists in its field of action (Knapp class II). If the deviation is greatest in the field of action of the inferior oblique, this muscle should then be weakened. In general, weakening of the inferior oblique or strengthening of the superior oblique will correct up to 15 prism diopters of hypertropia. For deviations greater than this, surgery on a second muscle is necessary. A simultaneous superior oblique tuck and inferior oblique weakening procedure can be performed (287,288). Alternatively, either one of these procedures can be combined with a recession of the contralateral inferior rectus or the ipsilateral superior rectus. Care must be taken not to perform too large a recession on the superior rectus, if the inferior oblique is also weakened because a double-elevator palsy may result. Anterior transposition of the inferior oblique (ATIO) has also been used in the treatment of unilateral superior oblique palsy (289). However, Bremer et al (290) reported three cases of primary position hypotropia, after ATIO, that required reoperation. Other surgeons have obtained good results with ATIO in the treatment of superior oblique palsy with little risk of a postoperative hypotropia (291,292,293).

TABLE 9.6 KNAPP CLASSIFICATION OF SUPERIOR OBLIQUE PARESIS

Class I	Greatest hypertropia in field of action of ipsilateral inferior oblique
Class II	Greatest hypertropia in field of action of ipsilateral superior oblique
Class III	Greatest hypertropia in entire opposite field
Class IV	Greatest hypertropia in entire opposite field and across lower field
Class V	Greatest hypertropia across entire lower field
Class VI	Bilateral superior oblique palsy
Class VII	Traumatic palsy and ipsilateral Brown's syndrome

Bilateral superior oblique palsies are generally treated by strengthening procedures. If torsional diplopia is the primary problem, a Harada-Ito procedure is indicated. In this procedure, as modified by Fells (294,295), the anterior half of the superior oblique tendon is displaced to an anterior and temporal location. A standard displacement of the tendon is capable of correcting varying degrees of excyclotorsion (278).

Sixth Nerve Palsy

Sixth nerve palsy causes an esotropia in primary position, which increases in the field of action of the paretic lateral rectus muscle. The palsy may be unilateral or bilateral. Continuation of binocular vision is usually possible by maintaining the eyes in the lateral gaze position away from the palsied eye; this results in a compensatory horizontal face turn toward the palsied eye (Fig. 9.32).

Congenital

Congenital sixth nerve palsies are rare (236,248,296,297,298). In newborns, a transient lateral rectus paresis may be rarely noted, with resolution by 6 weeks of age (6,8). Most infants with a significant esotropia and reduced lateral gaze are congenital esotropes with a cross-fixation pattern. Others, who have a motility disorder resembling a sixth nerve palsy, may have Duane's retraction syndrome or Mobius' syndrome.

Acquired

The sixth nerve has a long intracranial course, and there are three anatomical areas where the sixth nerve is most susceptible to injury: (a) as it exits from the pontomedullary junction, where it may be compressed by the anteroinferior

cerebellar artery; (b) at its penetration of the dura (Dorello's canal), causing Gradenigo's syndrome below the petrous crest; and (c) within the cavernous sinus.

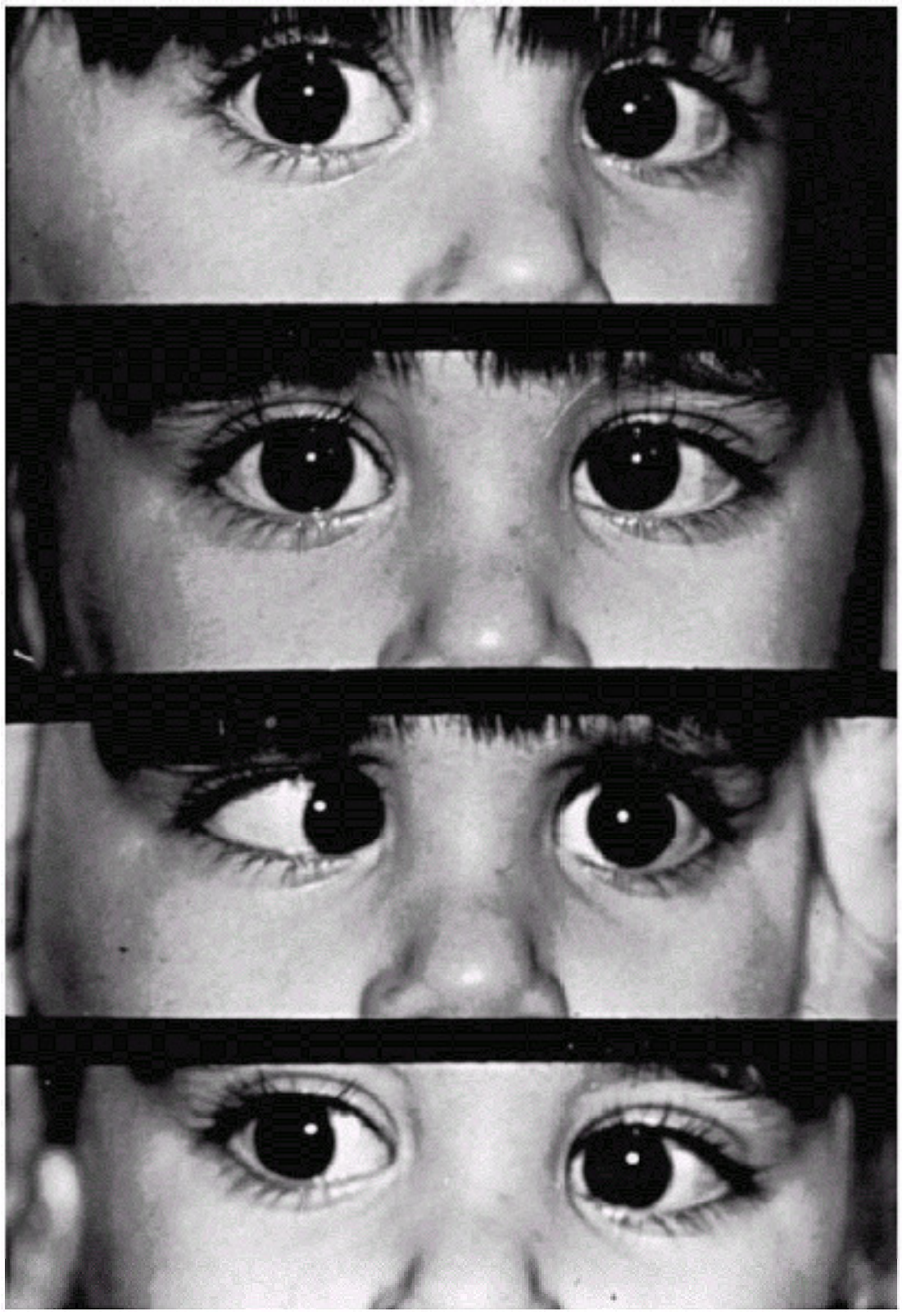

Figure 9.32 Congenital left sixth nerve palsy in an otherwise healthy child. Left face turn with orthotropia (top). Head straight demonstrating left esotropia (upper center). Gaze left demonstrating no abduction of the left eye past the midline (lower center). Gaze right showing no narrowing of the palpebral fissure, typically noted in Duane retraction syndrome (DRS) (bottom). (From Nelson LB, Wagner RS, Simon JW, et al. Congenital esotropia. *Surv Ophthalmol* 1987;31:363, with permission.)

Most studies of sixth nerve palsies in children have found that trauma and neoplastic disorders are the most common cause. Other causes include elevated intracranial pressure nontumor, congenital, inflammatory, miscellaneous, and idiopathic (236,299,300).

Acquired bilateral sixth nerve palsy is usually a manifestation of a serious intracranial abnormality or increase in intracranial pressure (Fig. 9.33). However, Knox et al (301) called attention to a group of children in whom a sixth nerve palsy followed nonspecific, probably viral, illness. Several investigators noted that benign sixth nerve palsy may be recurrent (302,303,304).

Middle ear infection associated with petrositis and edema of its dura, or possibly thrombosis in the contiguous venous sinuses, pinches the sixth nerve against the petrosphenoidal ligament (Gruber's ligament) as the nerve passes between the ligament and the dura Dorello's canal, causing Gradenigo's syndrome (305). This syndrome is characterized by painful paralysis of the sixth nerve with associated ipsilateral decrease in hearing. The duration of the sixth nerve palsy is typically brief, 3 to 6 weeks because of the effectiveness of antibiotic therapy. Gradenigo's syndrome is rare since the advent of antibiotics.

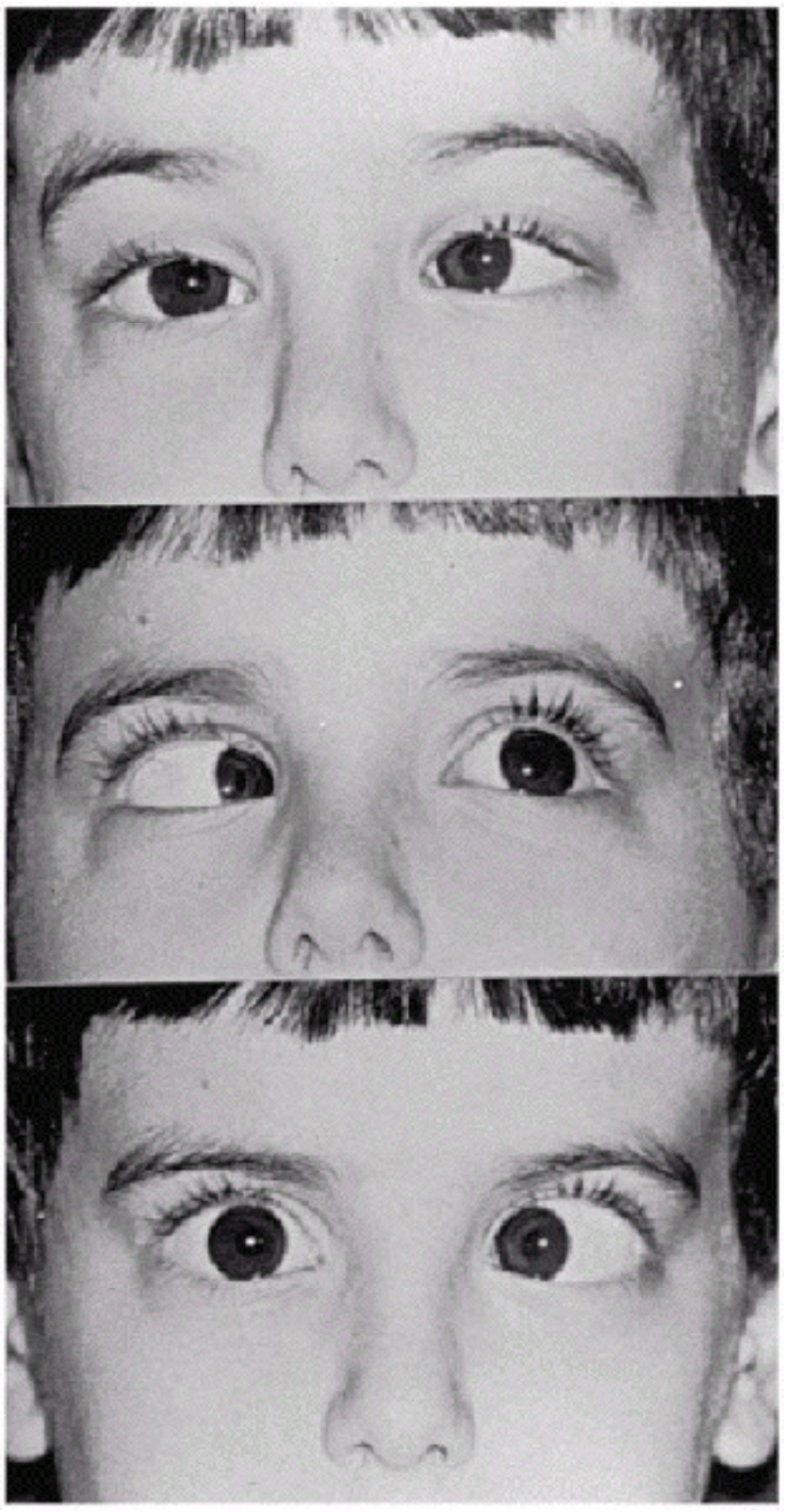

Figure 9.33 A child with an intracranial tumor who developed bilateral asymmetrical sixth nerve palsy. Note the greatest esotropia in right gaze.

Treatment

In a child with an isolated acute sixth nerve palsy without other neurological signs, including papilledema, headache, or ataxia, a neurological evaluation, including a CT or MRI scan, should be considered. If the workup is negative, they

should be reexamined at regular intervals and the parents advised to observe for new signs and symptoms.

Initial management of unilateral sixth nerve palsy should be conservative. A majority of patients will recover spontaneously within 6 months (306). Patients may adopt a compensatory face turn or simply occlude one eye to control the diplopia. Young children who do not develop a compensatory face turn should receive alternate occlusion to prevent the development of amblyopia and suppression. During alternate patching, they should be given full hyperopic correction to prevent accommodative esotropia from developing. In acute sixth nerve palsy, botulinum injection into the ipsilateral medial rectus may permit binocular vision in primary position during recovery (307,308,309,310). However, botulinum injection does not alter the recovery rate (311,312). Patients who initially present with bilateral palsies or a unilateral complete palsy with inability to abduct past the midline are less likely to recover within 6 months (313). After 6 months of waiting for possible return of sixth nerve function, surgical treatment is appropriate. A graded medial rectus recession and lateral rectus resection for the appropriate amount of esotropia can be performed. In an eye with a totally paralyzed lateral rectus and esotropia in the range of 50 prism diopters, the medial rectus should be recessed approximately 12 mm. Anything less than this amount will likely result in an eye that will become more esotropic with time, whereas any more than approximately 12 mm will cause substantial limitation of adduction (248). Resecting the lateral rectus may not give much additional benefit, if it is totally paralyzed.

A muscle transfer procedure may be necessary to keep the eye in the straight position and also obtain some abducting force. Several muscle transfer techniques have been popularized. The Hummelsheim procedure consists of transposing the lateral halves of the vertical recti to the lateral rectus (314). A resection of the transposed halves of the tendon can be radded to increase the effect of this procedure (315). The Jensen procedure involves splitting the vertical and lateral recti, tying the upper half of the lateral rectus to the lateral half of the superior rectus muscles, and doing the same with the inferior rectus (316,317,318). A full tendon transposition of the vertical rectus muscles is used by many surgeons. To augment the effect of a full muscle tendon transposition, Foster introduced the lateral fixation suture (319). In this procedure, a nonabsorbable suture is placed in the sclera 16 mm posterior to the limbus and adjacent to the lateral rectus muscle, incorporating one fourth of the transposed vertical rectus muscle. He found that the addition of a lateral fixation suture improved the tonic abducting force of the transposition procedure without compromising adduction..

In addition to the transposition procedure, weakening of the ipsilateral medial rectus is often required to decrease the adduction force. This could lead to anterior

segment ischemia, especially in an older patient with poor circulation. Partial tendon transfers (Jensen and Hummelsheim) may decrease this risk. However, anterior segment ischemia has been reported after their use, even in a young child (320). The use of intraoperative botulinum injection into the medial rectus combined with vertical rectus transposition surgery has been shown to be efficacious and eliminates the need to remove a third rectus muscle (321,322,323). Many patients can be treated successfully, although multiple surgeries and the use of postoperative prism correction is common (324). Management of bilateral sixth nerve palsy is very similar to that of unilateral sixth nerve palsy. Unfortunately, these patients cannot overcome the diplopia with a compensatory face turn.

STRABISMUS SYNDROMES

Duane Retraction Syndrome

The Duane retraction syndrome (DRS) was originally described at the end of the 19th century (325,326,327,328,329). In 1905 Duane (330) described 54 cases, summarized all of the clinical findings, reviewed previous work, and offered theories on pathogenesis and treatment.

DRS more frequently occurs in the left eye than in the right and in women more than in men. Bilateral involvement is less frequent than unilateral occurrence. In several large series, the ratio of right eye to left eye involvement was 1:3, the prevalence of bilaterality was 20%, and there was a slight preponderance of women over men (331,332,333,334). Several investigators reported a frequent association of other ocular or systemic anomalies with DRS (329,335,336,337). The ocular anomalies include dysplasia of the iris stroma, pupillary anomalies, cataracts, heterochromia, Marcus Gunn jaw winking, coloboma, crocodile tears syndrome, and microphthalmos. The systemic anomalies include Goldenhar's syndrome; dystrophic defects, such as the Klippel-Feil syndrome, cervical spina bifida, cleft palate, facial anomalies, perceptive deafness, malformations of the external ear; and anomalies of the limbs, feet, and hands. These associated ocular and systemic findings strongly suggest that all patients with DRS should undergo a careful ocular and general physical examination.

Clinical Manifestations

The most characteristic clinical findings in DRS include an absence of abduction of an eye with slight limitation of adduction, retraction of the globe in attempted adduction, and upshooting and downshooting, or both in adduction. Huber (338), with the support of electromyography, provided a useful classification of DRS into three types:

Type I. Marked limitation or complete absence of abduction, normal or only slightly restrict adduction, narrowing of the palpebral fissure and retraction of the globe on adduction, and widening of the palpebral fissure on attempted abduction (Fig. 9.34). Electromyography shows absence of electrical activity in the lateral rectus muscle on abduction, but paradoxic electrical activity on adduction.

Type II. Limitation or absence of adduction with exotropia of the affected eye. Normal or slightly limited abduction. Retraction of the globe on attempted adduction (Fig. 9.35). Electromyography reveals electrical

activity of the lateral rectus muscle on both abduction and adduction.

Type III. Severe restriction of both abduction and adduction. Retraction of the globe and narrowing of the palpebral fissure on attempted adduction (Fig. 9.36). Electromyography demonstrates electrical activity of both horizontal rectus muscles on both adduction and abduction.

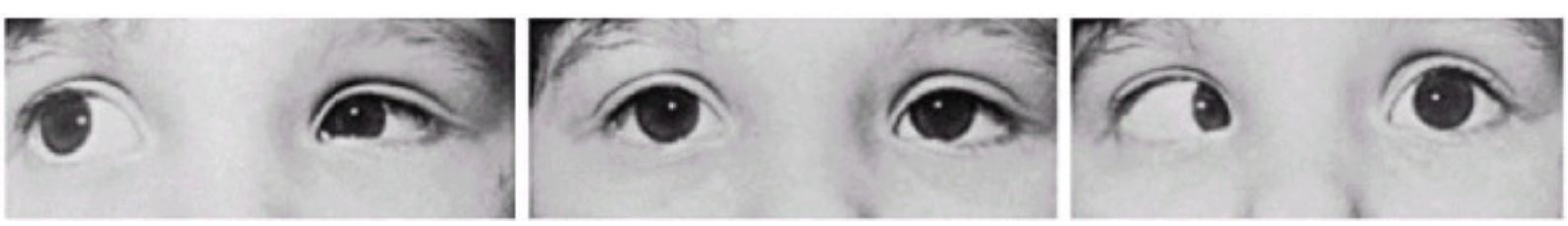

Figure 9.34 Type I DRS. Note the marked limitation of abduction of the left eye with narrowing of the palpebral fissure and retraction of the globe on adduction. (From Nelson LB, Catalano RA. *Atlas of ocular motility.* Philadelphia: WB Saunders, 1989, with permission.)

Type I is most common, followed in order of frequency by types II and III (334). Most patients with type I DRS have straight eyes in the primary position during infancy and childhood. Some children develop an increasing esodeviation in the primary position and adopt a compensatory head turn toward the side of the involved eye to maintain normal binocular vision.

Recently, a fourth variant of DRS has been described. In these patients, a large divergent strabismus occurs in upgaze secondary to coinnervation of the lateral and superior rectus (339,340). This vertical form of DRS may give the false appearance of inferior oblique overaction, or a Y pattern. In these cases, weakening of the inferior rectus will fail to treat the observed motility disturbance (337).

Pathogenesis

Although DRS has been well described clinically, the etiology remains unclear. Various theories have been formulated on the basis of data collected from surgical, electromyographic, and autopsy studies.

Structural Anomalies

Several investigators suggested that a posterior insertion of the medial rectus of the involved eye in DRS may cause

retraction of the globe on adduction (341). Others believed that a nonelastic lateral rectus muscle was the cause of retraction in adduction (342,343,344,345).

Figure 9.35 Type II DRS. Limitation of adduction of the left eye with narrowing of the palpebral fissure and retraction of the globe. Abduction of the left eye was normal. (From Nelson LB, Catalano RA. *Atlas of ocular motility*. Philadelphia: WB Saunders, 1989, with permission.)

Figure 9.36 Type III DRS. Severe restriction of both abduction and adduction of the left eye. (From Nelson LB, Catalano RA. *Atlas of ocular motility*. Philadelphia: WB Saunders, 1989, with permission.)

The upshooting and downshooting that frequently occur in adduction have been blamed on several structural anomalies (Fig. 9.37). Duane thought the cause was oblique muscle overaction, whereas others blamed the abnormal vertical eye movements on an overacting vertical rectus muscle (326,328). More recently, a "leash" phenomenon has been described to explain these motility patterns. It is suggested that the lateral rectus contracts during adduction and may slip vertically over the globe, causing a dynamic upshooting and downshooting of the eye (346,347,348). An intriguing theory proposed by several investigators to explain the high prevalence of ocular and systemic malformations associated with DRS suggests that a common teratogenic stimulus at 8 weeks of gestation may cause these findings (334,349). Further support for the teratogenic theory was provided by Arimoto, who found that 29 of 89 patients afflicted with the thalidomide syndrome also had DRS (350). Also, Mauro et al (333) found that 23 out of 266 patients with DRS had thalidomide embryopathy.

Innervational Anomalies

In 1957 Breinin (351), using electromyography, was the first to show paradoxic electrical activity of the lateral rectus in a patient with DRS. In this patient, Breinin recorded electrical activity from the lateral rectus, only when the eye was adducted. He suggested that the anomalous contraction of the medial and lateral rectus muscles is the cause of retraction in adduction.

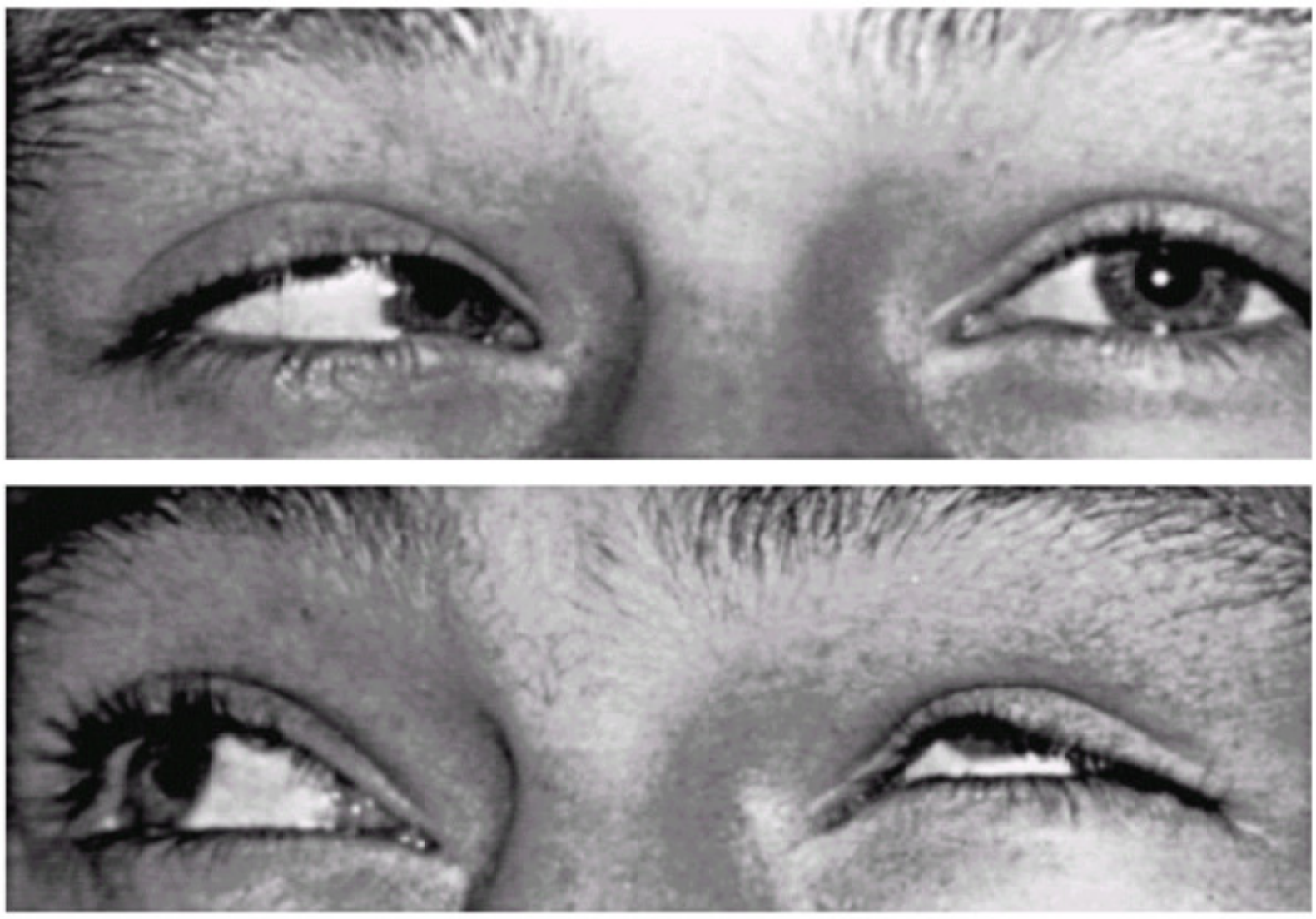

Figure 9.37 Type I DRS with significant upshooting and retraction of the globe on attempted adduction. (From Nelson LB, Catalano RA. *Atlas of ocular motility*. Philadelphia: WB Saunders, 1989, with permission.)

Breinin's electromyographic findings have been confirmed and expanded on by many other investigators (336,352,353,354). Abnormal synergistic innervation between the medial rectus and the vertical rectus or oblique muscles has also been demonstrated electromyographically, which may explain the upshooting and downshooting in adduction in DRS (352,355). Electromyographic studies have suggested that DRS is a neurogenic disorder involving either a supranuclear lesion or a cranial nerve anomaly in which branches of the oculomotor nerve innervate the lateral rectus (294).

Data from autopsy studies provide both direct and indirect evidence that DRS involves an abnormality of the sixth cranial nerve. In 1946 Matteucci (356) demonstrated absence of the ipsilateral abducens nerve and hypoplasia of its nucleus in an autopsy of a well-documented case of unilateral DRS. However, Matteucci did not discuss the innervation of the lateral rectus or trace the terminal branches of the oculomotor nerve. In an autopsy case of bilateral type III DRS, both abducens nuclei and nerves were absent, and both lateral rectus muscles were innervated by a branch from the inferior division of the oculomotor nerve (357). In a second patient with unilateral DRS, these same findings were limited to the involved side (358). MRI studies have shown an absence of the abducens nucleus in some, but not all, affected cases (359).

Considering the clinical evidence, anomalies of the vestibuloocular reflex, auditory-evoked responses, and opticokinetic nystagmus, and the frequent association of the gustolacrimal reflex crocodile tears with DRS, a primary brainstem abnormality seems likely in at least some cases of DRS (360,361,362).

Treatment

Before surgery is contemplated, coexisting significant refractive errors, anisometropia, and amblyopia must be treated. In two large series, the incidence of amblyopia in DRS patients was 10% and 14%, respectively (330,335). Tredici and von Noorden (363) noted a 3% incidence of amblyopia in their 72 patients and commented that this incidence is similar to that in the general population.

Indications for surgery for patients with DRS are a significant deviation in primary position, an anomalous head

position, a large upshoot or downshoot or retraction of the globe that is cosmetically intolerable.

In type I DRS, an esodeviation, usually less than 30 prism diopters, and a face turn in the direction of the involved eye, may develop. In most cases, an ipsilateral medial rectus recession can significantly improve the esodeviation and the face turn (346,364,365,366,367). Often the medial rectus of the involved eye is thickened, and there is positive forced duction to abduction because of the contracture of the muscle. Resection of the ipsilateral lateral rectus should be done with caution because it may increase retraction of the globe in adduction (368).

Some patients with DRS have markedly reduced adduction saccadic velocities caused by marked lateral rectus cofiring on adduction (369,370). There is a risk of severely compromising adduction and causing an exotropia postoperatively after large medial rectus recessions greater than 6 mm in such patients (364). An exotropia that occurs on attempted adduction, caused by cofiring of the lateral rectus, can also be produced in such cases. If there is more than 25 prism diopters of esotropia, a medial rectus recession greater than 6 mm will be necessary. If there is also a slow adduction saccadic velocity, limitation of adduction, and significant globe retraction, one should consider limiting the medial recession of the affected eye to 6 mm and adding a recession of the opposite medial rectus to correct fully the esotropia. However, there have been reports of poor outcomes when the contralateral medial rectus is recessed (371). Although some surgeons have recommended a transposition procedure in patients with type I DRS and severe limitation of abduction, others have obtained equally good results using a simplified approach of recessing the medial rectus of the affected eye (372,373).

Patients who have type 2 DRS with exotropia in primary position and a face turn away from the involved eye require a recession of the ipsilateral lateral rectus (346,367,363).

The upshooting or downshooting in DRS can be as cosmetically distracting as the abnormal head posture. Inferior oblique weakening alone has not been effective in eliminating upshooting (259,353). Recessing a very stiff, fibrotic lateral rectus may reduce the leash effect, if present. However, if there is no deviation in primary position, an ipsilateral medial rectus recession will be necessary to prevent a consecutive esotropia. Splitting of the lateral rectus into a Y configuration, or

the use of a posterior fixation suture on the lateral rectus, has been successful in reducing the leash effect without inducing strabismus in primary position (259,374,375). Recession of the vertical rectus muscle has also been shown to be helpful when the upshot is secondary to an innervational abnormality (376).

Patients who suffer from a cosmetically noticeable retraction of the globe in attempted adduction may benefit from recession of both horizontal recti to reduce the cocontraction that is present. This can be done in the absence of a deviation in primary gaze or adjusted to eliminate a deviation, if present.

MOBIUS' SYNDROME

Mobius' syndrome is a rare congenital disturbance consisting of varying involvement of facial and lateral gaze paresis. Mobius (377,378) first suggested that congenital bilateral abducens-facial paralysis might be an independent pathological entity, thus gaining eponymic distinction.

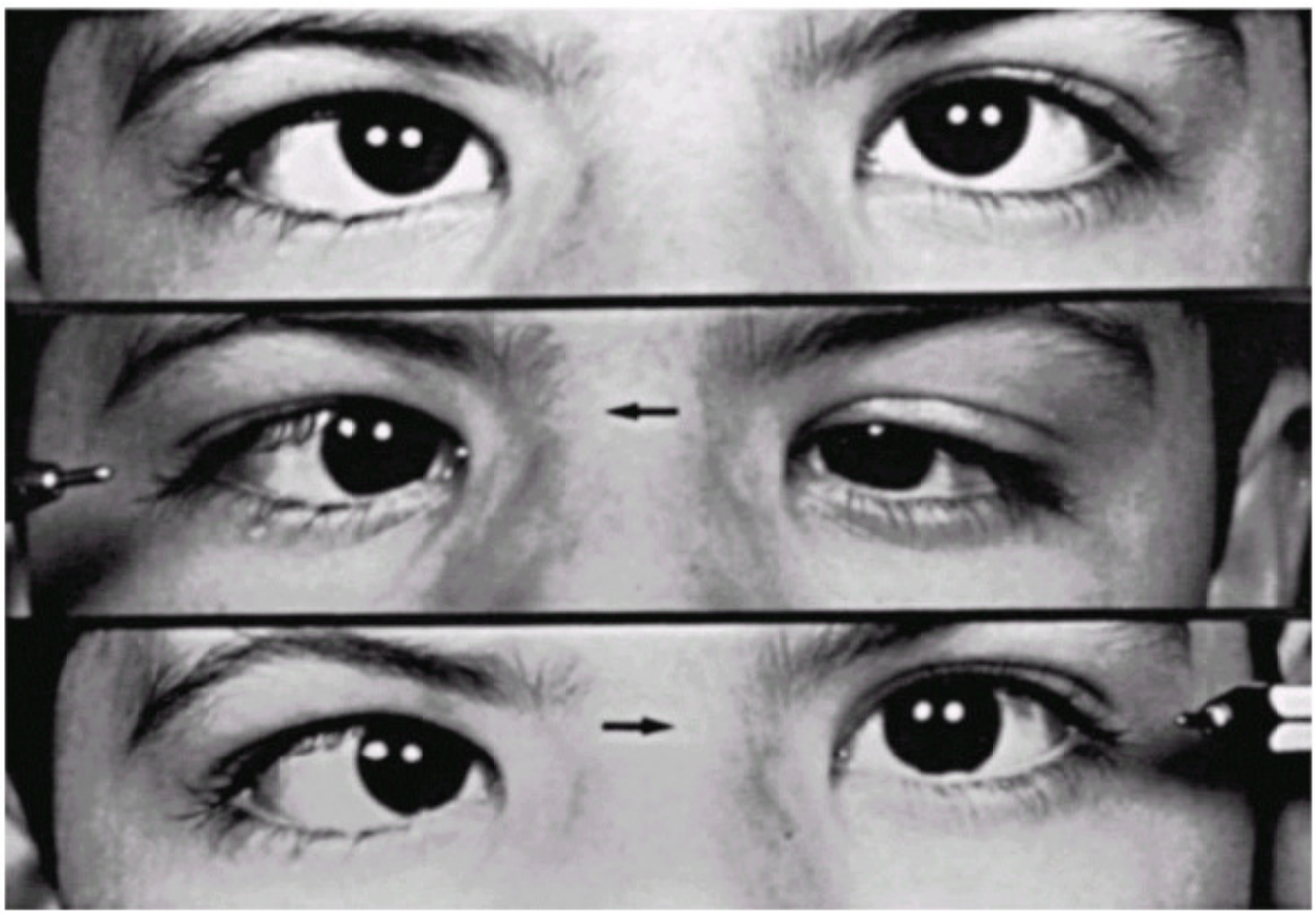

Figure 9.38 Mobius' syndrome. In the primary position there is esotropia of 45 prism diopters (top). There is inability to abduct the right eye even to the midline (center). Abduction of the left eye approaches the midline (bottom). (From Nelson LB, Brown GC, Arentsen JJ. *Recognizing patterns of ocular childhood diseases.* Thorofare, N**J:** Charles Slack, 1985, with permission.)

Clinical Manifestations

Mobius' syndrome is characterized by unilateral or bilateral inability to abduct the eyes (Fig. 9.38). Esotropia is the most common form of strabismus seen in Mobius' syndrome, but other deviations can exist as well (379,380). The unilateral or bilateral complete or incomplete facial palsy is usually observed during the first few weeks of life because of difficulty with sucking and feeding and incomplete closure of the eyelids during sleep. These patients typically have masklike faces with an inability to grin and wrinkle the forehead.

Mobius' syndrome is frequently associated with paresis of other muscles supplied by the cranial nerves (378,381). Often, there is partial atrophy of the tongue with inability to protrude the tongue beyond the lips (Fig. 9.39). Paralysis

of the soft palate and muscles of mastication may also occur. Various skeletal and muscle defects are common, including absence or hypoplasia of the pectoral muscles, syndactyly, club feet, and congenital limb amputations (377,382,383,384).

Figure 9.39 Mobius' syndrome with inability to protrude the tongue.

Pathogenesis

The etiology of Mobius' syndrome is presently unknown. Current evidence points to brainstem defects secondary to a vascular insult in utero that occurs during a vulnerable period in the fifth to sixth week of embryonic life (385,386,387,388,389).

Treatment

Most children with Mobius' syndrome who present with early onset esotropia have a preoperative deviation of 50 prism diopters or greater. Surgery for esotropia is commonly performed in patients of a young age, as is advocated for the primary type of congenital esotropia.

Usually, the forced duction test and the character of the muscles encountered at surgery in children with Mobius' syndrome are abnormal. The forced ductions are positive to both adduction and abduction, whereas vertical ductions are typically normal. The horizontal muscles are often thickened, taut, and fibrotic. Surgery for esotropia usually consists of a recession of the taut medial rectus muscles. Afterward, there is usually little horizontal movement because of the concomitant bilateral gaze palsy. In some cases, the addition of a lateral rectus resection or a transposition procedure may be useful (390).

BROWN'S SYNDROME

This ocular motility disorder, characterized by an inability to elevate the adducted eye actively or passively, was first described by Brown (391). It has since become recognized that there are a variety of causes, that the condition may be congenital or acquired, and that the defect can be permanent, transient, or intermittent.

Clinical Manifestations

Brown's syndrome is characterized by a deficiency of elevation in the adducting position (Fig. 9.40). Improved elevation is usually apparent in the midline, with normal or near-normal elevation in abduction. There is occasional widening of the palpebral fissure on attempted elevation in adduction. With lateral gaze in the opposite direction, the involved eye may depress in adduction, although no overdepression simulating overaction of the superior oblique muscle occurs on duction testing. Exodeviation V pattern often occurs as the eyes are moved upward in the midline (Fig. 9.41). Many patients are orthophoric in the primary position, although with time hypotropia may develop with a compensatory face turn toward the opposite eye. In some cases, there is discomfort on attempted elevation in adduction, the patient may feel or even hear a click under the same circumstances, and there may be a palpable mass or tenderness in the trochlear region. A positive forced duction test is the hallmark of Brown's syndrome.

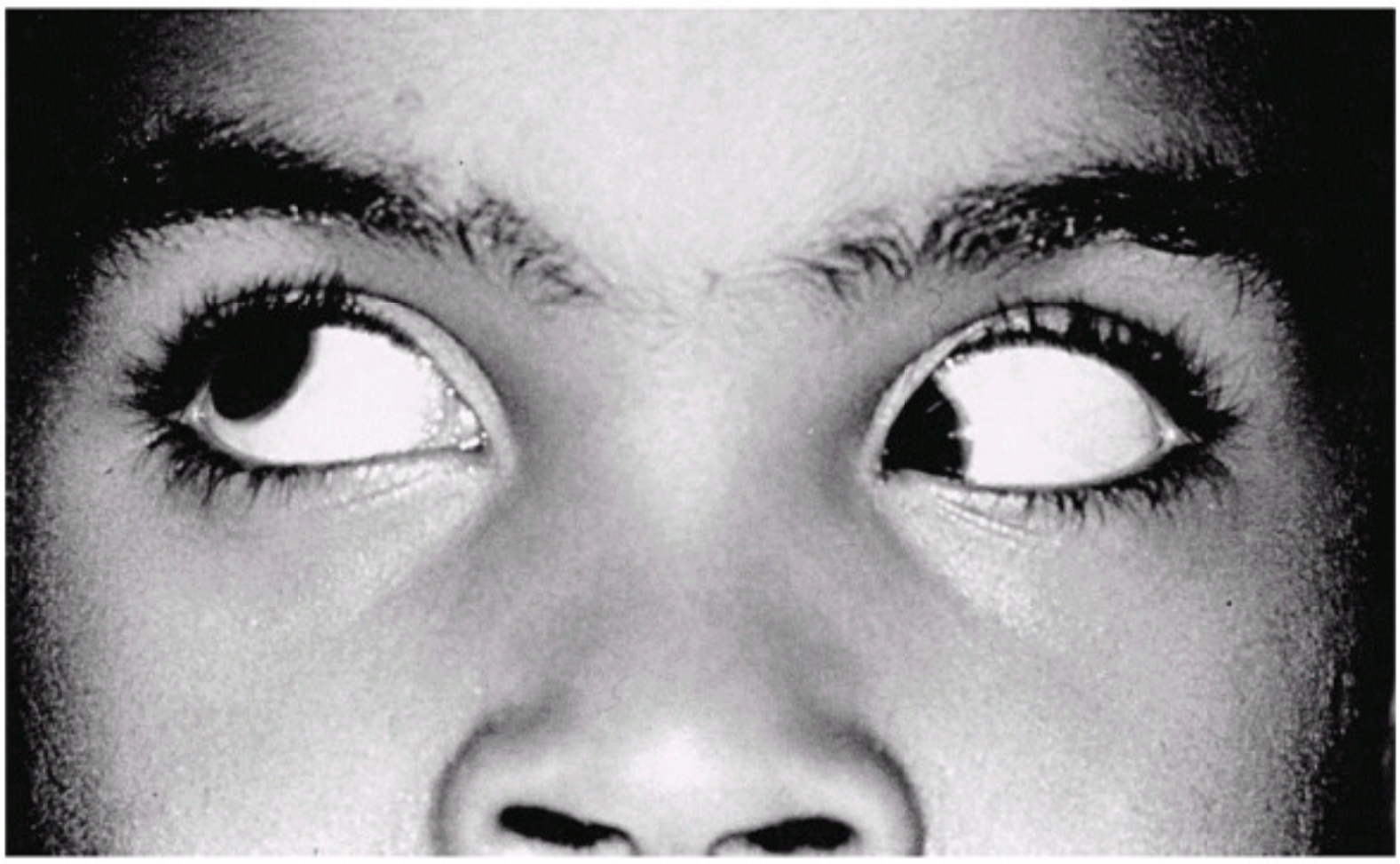

Figure 9.40 Brown's syndrome of the left eye. Note the inability of the left eye to elevate in the adducting position.

Pathogenesis

Brown (392) subsequently redefined the syndrome, recognizing that it was more complex than originally proposed. He initially believed that the simulated inferior oblique palsy was due to an innervational disturbance to this muscle, with secondary contracture of the anterior sheath of the superior oblique tendon. Metz (393) reported normal upward saccades in adduction, confirming the restrictive nature of the problem.

Brown (391) attributed the syndrome to congenital shortening of the sheath surrounding the reflected tendon of the superior oblique muscle. However, several investigators were unable to substantiate Brown's theory of a primary congenital anomaly of the anterior sheath of the superior oblique tendon (394,395). Crawford was the first to prove that the cause of the syndrome is a tight superior oblique tendon (395). By cutting the tendon or excising a portion of it, the restricted elevation of the involved eye was cured.

Acquired Brown's syndrome has been attributed to a variety of causes, including superior oblique surgery, scleral buckling bands, trauma, and following sinus surgery and inflammation in the trochlear region (396,397,398,399,400,401). An identical motility pattern, as seen in Brown's syndrome, can be acquired by patients with juvenile or adult rheumatoid arthritis (402,403,404,405,406,407). It appears that this form of Brown's syndrome represents a stenosing tenosynovitis of the trochlea and shares similar characteristics to inflammatory disorders that affect the tendons of the fingers (408).

Treatment

If patients with Brown's syndrome are orthophoric in primary position and without an anomalous head posture, surgery is not necessary. Such patients may experience diplopia when elevating the involved eye in adduction but

will learn to avoid this position of gaze. However, if the eye is hypotropic in primary position, or if a head turn is cosmetically significant, surgery is indicated to attempt to restore binocular function in the primary position.

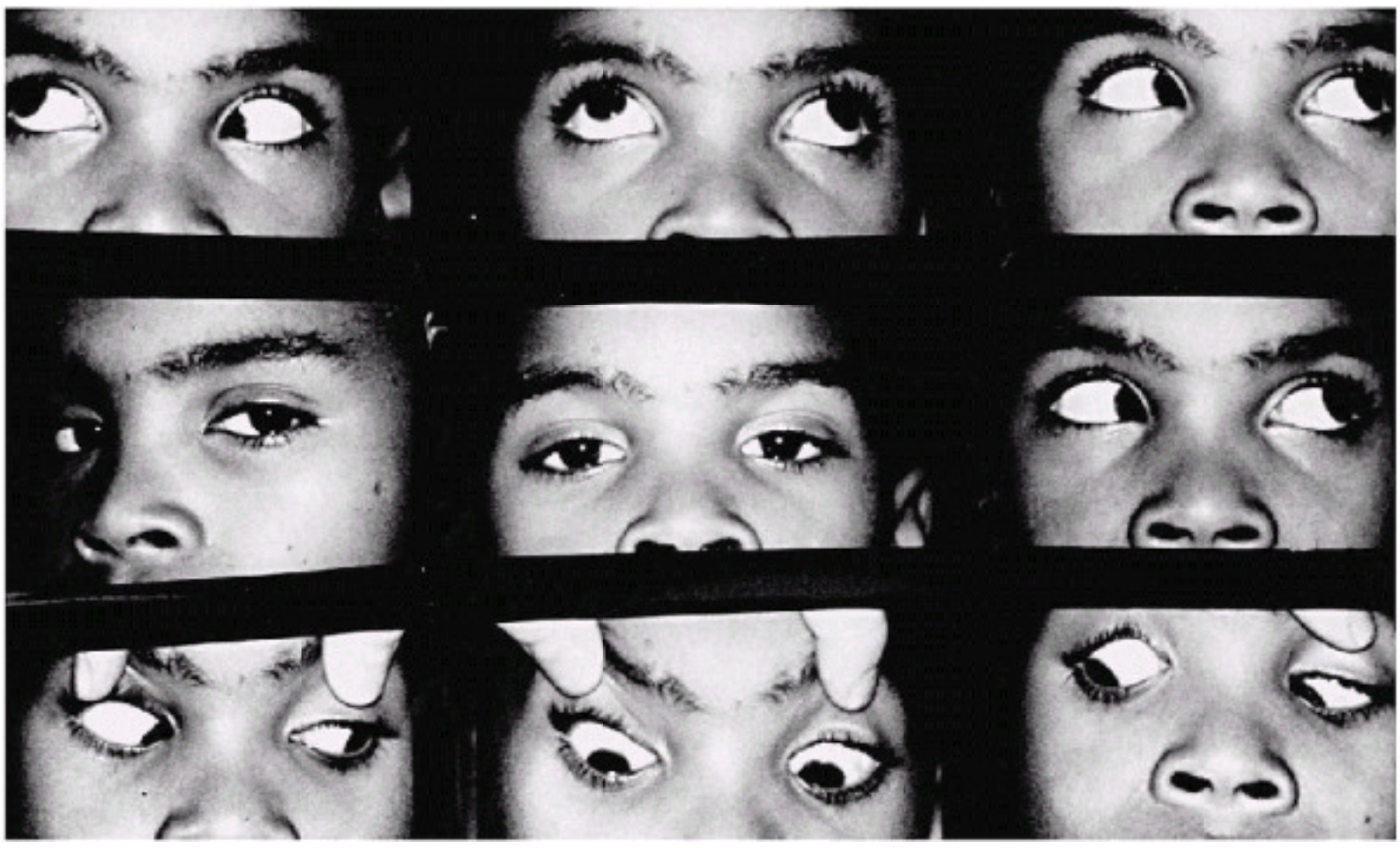

Figure 9.41 Brown's syndrome of the left eye. Note the ability of the eye to elevate as it abducts. Also notice the exotropia in upgaze leading to a V pattern.

Tenotomy or tenectomy of the superior oblique will eliminate the restriction to elevation in Brown's syndrome (391,409,410,411). However, these weakening procedures result in superior oblique palsy in 54% to 85% of all cases (408,409,412). In view of the high incidence of superior oblique palsy following surgery for Brown's syndrome, Parks and Eustis (413) advocated simultaneous superior oblique tenotomy and inferior oblique recession. Inferior oblique underaction was present in 75% of patients in the early postoperative period, but elevation in adduction improved over time. Recession of the superior oblique tendon can also be performed and has the advantage of allowing for a graded weakening effect to be obtained (414). Wright (232,415) advocates the use of superior oblique expander, sewn to the cut ends of the superior oblique tendon. This permits a graded amount of weakening to be performed as well as allowing retrieval of the cut ends of the tendon, if necessary. This procedure has been shown to be as effective as free tenotomy and less likely to cause a secondary superior oblique palsy.

DOUBLE ELEVATOR PALSY

Double elevator palsy suggests that both elevator muscles, superior rectus and inferior oblique, of one eye are weak, with resultant inability or reduced ability to elevate the eye and a hypotropia in the primary position (416,417). The term is generally used to describe diminished ocular elevation present in all fields of gaze.

Clinical Manifestations

Double elevator palsy is characterized by reduced elevation in all positions of gaze (Fig. 9.42). When the patient fixates with the nonparetic eye, the paretic eye will become hypotropic and the lid may become ptotic (418). Fixation with the paretic eye will cause a hypertropia of the nonparetic eye. Provided that the levator muscle is not involved, the ptosis will also disappear. Patients often present with a chin-up position to maintain binocular vision. The Bell's phenomenon is an important clinical sign in patients with double elevator palsy. It will be preserved when the condition is secondary to a supranuclear cause but absent in the presence of a restricted inferior rectus. Rarely, patients with double elevator palsy have reduced elevation in all positions of gaze but no hypotropia in the primary position. The absence of elevation in abduction helps to differentiate this disorder from Brown's syndrome.

Pathogenesis

Double elevator palsy may be due to innervational problems: supranuclear, nuclear, or infranuclear abnormality; mechanical and restrictive conditions in the orbit; or a combination of factors.

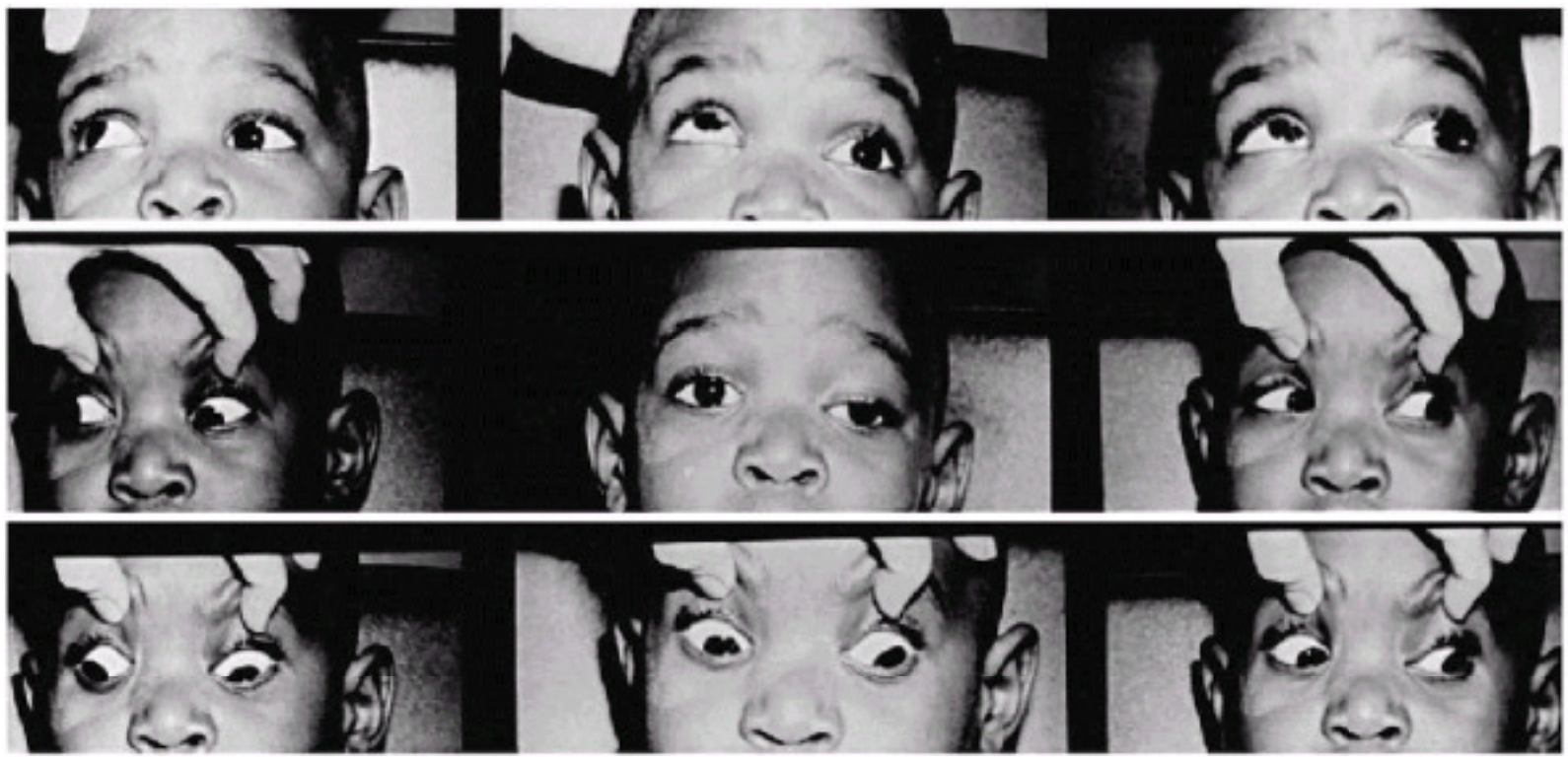

Figure 9.42 Double elevator palsy of the left eye. Note the apparent ptosis of the left upper eyelid in the primary position.

Both Rosner (419) and Watson (420) believed that double elevator palsy is due to a third nerve nucleus lesion on the same side. Jampel and Fells (421) proposed that a lesion in the midbrain tectum or pretectum near the oculomotor nucleus or in the nucleus is the likely cause of a monocular elevation paresis. This lesion involves the supranuclear fibers to the subnucleus of the oculomotor complex, which supplies the opposite superior rectus. These authors also believed that the superior rectus is the main elevator of the eye. Robinson's studies confirmed that the superior rectus is the major elevator in abduction (421). In adduction, it was still mechanically strong and could raise the eye 14 degrees by itself. Mather and Saunders (423) reported a case of bilateral absent superior rectus muscles, presenting clinically as a bilateral double elevator palsy.

Scott and Jackson (424) emphasized the importance of inferior rectus muscle restriction in patients with double elevator palsy. They found 73% of their patients to have restriction of the ipsilateral inferior rectus muscle, as determined by the forced duction test. They also noted an accentuated lower eyelid fold associated with inferior rectus restriction. This fold became more prominent with attempted upgaze. They postulated that this eyelid fold was caused by attachments of the capsulopalpebral head of the inferior rectus to the lower eyelid.

An acquired double elevator palsy has also been documented by a number of investigators (425,426,427,428,429). The frequent association with pupillary anomalies and weakness of convergence lends credence to the theory that this condition involves the pretectum of the brainstem. Most of these cases have been thought to result from small vascular lesions in this area (424,426).

Treatment

If a patient with double elevator palsy is orthophoric in primary position, surgery is not indicated. If there is a vertical deviation in primary position, a forced duction test is necessary. In patients with a positive forced duction test, indicating restriction to elevation, an inferior rectus recession is indicated. When the forced duction test is negative, a Knapp procedure transposing the medial and lateral recti to the corners of the insertion of the superior rectus should be performed (430). As much as 35 prism diopters of hypotropia can be corrected with the Knapp procedure. Some patients will require a later recession of the inferior rectus for undercorrections (431). However, only a modest increase in elevation is usually observed after this procedure. If the hypotropia is less than 30 prism diopters and the forced duction is negative, a graded resection of the superior rectus and recession of the inferior rectus can successfully correct the deviation.

If a patient has ptosis, the lowered-eyelid position may have resulted from the globe's hypotropic position pseudoptosis, intrinsic levator weakness true ptosis, or both hypotropic and levator weakness. Therefore, ptosis surgery should be avoided until the hypotropia is corrected. Once the eye alignment is improved, the ptosis can be reevaluated.

ISOLATED INFERIOR OBLIQUE PARESIS

Isolated paresis of the inferior oblique muscle is a rare entity (434). Although White and Brown (433), in a 1939 study of 1,955 patients with ocular muscle anomalies, described 20 with inferior oblique underaction, this group undoubtedly contained cases of Brown's syndrome that Brown himself described in 1950.

Clinical Manifestations

Patients with an inferior oblique paresis, depending on fixation preference, manifest either a hypotropia of the affected

eye or a hypertropia of the unaffected eye. The vertical deviation increases on gaze into the field of action of the involved inferior oblique but decreases in the opposite gaze. The Bielschowsky head-tilt is positive on tilting the head toward the normal side. With time, the superior oblique becomes contracted and shows moderate to marked overaction. Patients characteristically tilt the head toward the side of the paretic eye in an attempt to decrease the vertical deviation and maintain binocular vision.

Pathogenesis

The cause of isolated inferior oblique palsy is often unknown. Marlow (434) reported one case occurring after a sinus infection, another caused by a gumma of the orbit, and another associated with central nervous system (CNS) syphilis. Pollard (435) reported a series of 25 patients with inferior oblique palsy, including 2 with bilateral palsies. None of his patients had an abnormal neuroimaging study or was found to have myasthenia gravis; he therefore concluded that inferior oblique palsy is a benign entity.

Treatment

A forced duction is necessary to differentiate an isolated inferior oblique paresis from Brown's syndrome. In inferior oblique paresis, there should not be any

substantial restriction to elevation in adduction. Also, with inferior oblique palsy, superior oblique overaction will result in an A pattern. In Brown's syndrome, a V pattern will be noted.

Scott and Nankin (432) advocated tenotomy of the superior oblique to treat inferior oblique paresis. Olivier and von Noorden (436), however, reported a series of six patients with inferior oblique paresis treated by weakening the ipsilateral superior oblique with deterioration of binocularity.

Frey reported success in treating inferior oblique paresis with a contralateral superior rectus recession (437). When the hyperdeviation is greatest in the field of action of the inferior oblique, recessing the yoke muscle, which is the contralateral superior rectus, makes clinical sense. This procedure works well and decreases the risk for the development of an iatrogenically induced superior oblique palsy.

CONGENITAL FIBROSIS OF THE EXTRAOCULAR MUSCLES

This syndrome is characterized by replacement of normal muscle tissue by fibrous tissue in varying degrees (438,439,440). The various clinical presentations depend on the number of muscles affected, the degree of fibrosis, and whether the involvement is unilateral or bilateral (Fig. 9.43). Although the condition has been known since the 19th century, it was Brown who coined the term “general fibrosis syndrome” in 1950, after evaluation and treatment of three sporadic cases (441,442). In the current literature, this condition is referred to as congenital fibrosis of the extraocular muscles (CFEOM).

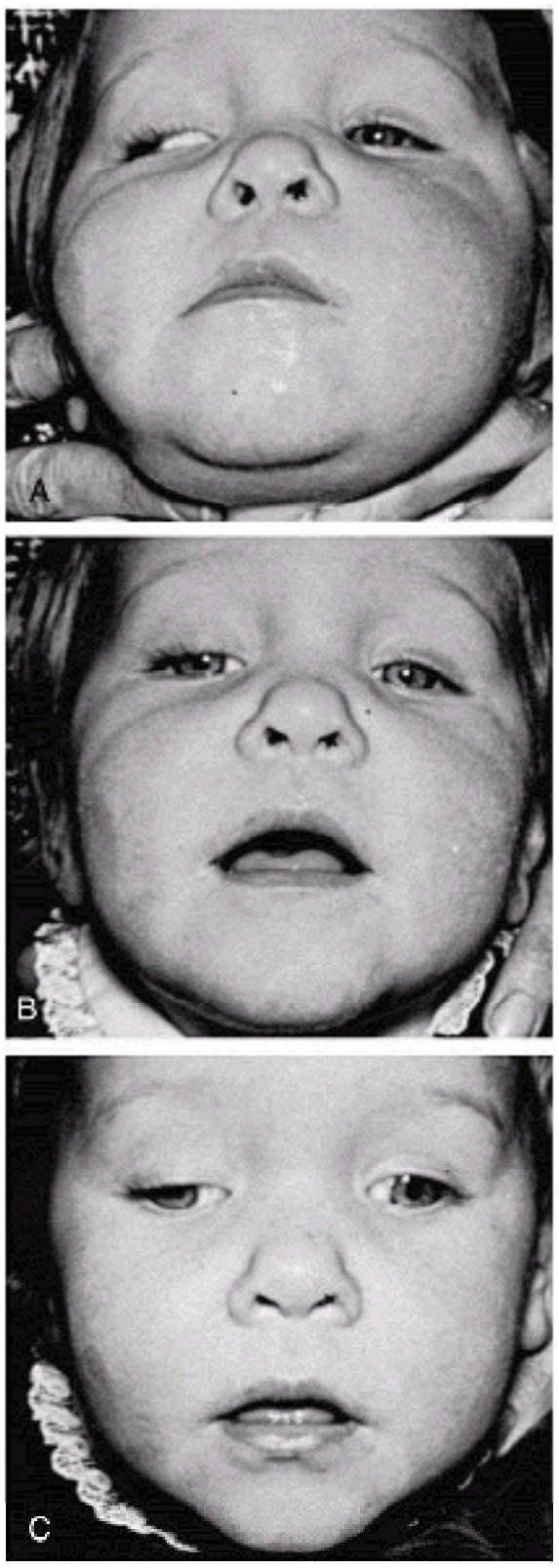

Figure 9.43 General fibrosis syndrome. **A:** The chin is elevated in an attempt to see, and a large exotropia of the right eye is present. Bilateral ptosis is evident. **B:** Convergence is exerted in an attempt to align the visual axis, but this cannot be maintained. **C:** Inability of the eyes to elevate to the primary position. (Courtesy of Donelson Menley, MD)

Clinical Manifestations

Laughlin (443) characterized the syndrome as encompassing the following: (a) fibrosis of the extraocular muscles; (b) fibrosis of Tenon's capsule; (c) adhesions between muscles, Tenon's capsule, and globe; (d) inelasticity and fragility of the conjunctiva; (e) absence of elevation or depression of the eyes; (f) little or no horizontal movement; (g) eyes fixed 20 degrees to 30 degrees below the horizontal;

(h) blepharoptosis; (i) chin elevation; and (j) the condition being present at birth.

Letson (444) added the following findings: (a) the disease is often autosomal dominant but may be sporadic; (b) there is often associated exotropia or esotropia; and (c) amblyopia is common, which may be partly due to the difficulty of wearing an optical correction when there are associated significant refractive errors. Currently, three forms of CFEOM have been described and their genetic loci have been mapped (445,446). In CFEOM1, affected individuals are born with bilateral ptosis and both eyes fixed in a downward position with absent upgaze and aberrant horizontal gaze. Individuals with CFEOM2 are born with bilateral ptosis and exotropia. Patients with CFEOM3 exhibit a more variable presentation, but vertical motility disturbances are generally more pronounced than horizontal abnormalities. CFEOM1 and CFEOM3 are inherited in an autosomal dominant fashion. CFEOM2 is autosomal recessive.

The condition may be unilateral or bilateral and is commonly asymmetrical. Because patients cannot typically elevate their eyes even to the midline, they adapt a compensating chin-up position to maintain binocular vision. Patients with isolated inferior rectus involvement may be the same as those patients who present with a double elevator palsy and a restricted inferior rectus on forced duction testing.

CFEOM may present as strabismus fixus, in which the eyes are in a markedly fixed position of esotropia or exotropia (447,448). The eyes are so firmly fixed that they cannot be actively or passively moved.

Pathogenesis

Historically, CFEOM was believed to result from primary extraocular muscle fibrosis (446,449,450). However, current neuropathological and genetic studies support the hypothesis that these disorders result from aberrant development of motor nuclei in the midbrain and pons (451, 452).

Treatment

The goal of surgical management in the general fibrosis syndrome is to center the eyes and improve the compensatory head posture. In patients with significant hypotropia, a large recession or disinsertion of the inferior rectus muscles is indicated. However, elevation of the hypotropic eye accentuates the ptosis. Bilateral frontalis suspension is required soon after the strabismus surgery. Because these patients often do not have a Bell's phenomenon, corneal drying may occur after ptosis surgery. Therefore, the lid should be elevated to the upper pupillary border only.

REFERENCES

1. Graham PA. Epidemiology of strabismus. *Br J Ophthalmol* 1974; 58:224-231.

2. Kordner LD, Nasey JN, Pratt-Johnson JA, et al. Detection of manifest strabismus in young children. Part 2. A retrospective study. *Am J Ophthalmol* 1974;77:211-214.

3. Olitsky SE, Sudesh S, Graziano A, et al. The negative psychosocial impact of strabismus in adults. *J AAPOS* 1999;3:209-211.

4. Uretmen O, Egrilmez S, Kose S, et al. Negative social bias against children with strabismus. *Acta Ophthalmol Scanc* 2003;2:138-142.

5. Nelson LB, Rubin SE, Wagner R, et al. Developmental aspects in the assessment of visual function in young children. *Pediatrics* 1984;73:375-381.

6. Nixon RB, Helveston EM, Miller K, et al. Incidence of strabismus in neonates. *Am J Ophthalmol* 1985;100:798-801.

7. Friedrich D, de Decker W. Prospective study of the development of strabismus in the first six months of life. In: Link-Schafer M, ed. *Orthoptic horizons.* Harrogate: UK LIPS, 1987:21-28.

8. Archer SM, Sondhi N, Helveston EM. Strabismus in infancy. *Ophthalmology* 1989;96:133-137.

9. Costenbader FD. Infantile esotropia. *Trans Am Ophthalmol Soc* 1961;59:397-429.

10. Ing MR. Early surgical alignment for congenital esotropia. *Trans Am Ophthalmol Soc* 1981;79:625-663.

11. Helveston EM, Ellis FD, Schott J, et al. Surgical treatment of congenital esotropia. *Am J Ophthalmol* 1983;96:218-228.

12. von Noorden GK. A reassessment of infantile esotropia (XLIV Edward Jackson Memorial Lecture). *Am J Ophthalmol* 1988;105:1-10.

13. von Noorden GK. Infantile esotropia: a continuing riddle. *Am Orthopt J* 1984;34:52-62.

14. Friedman Z, Neuman E, Hyams SW, et al. Ophthalmic screening of 38,000 children age 1 to 2½ years in child welfare clinics. *J Pediatr Ophthalmol Strabismus* 1980;17:261-267.

15. Mohney BG, Erie JC, Hodge DO, et al. Congenital esotropia in Olmsted County, Minnesota. *Ophthalmology* 1998;105:846-850.

16. Scott MH, Noble AG, Raymond WR, et al. Prevalence of primary monofixation syndrome in parents of children with congenital esotropia. *J Pediatr Ophthalmol Strabismus* 1994;31:298-301.

17. Chew E, Remaley NA, Tamboli A, et al. Risk factors for esotropia and exotropia. *Arch Ophthalmol* 1994;112:1349-1355.

18. Worth C. Squint, its causes and treatment. London: Bailliere, Tindall, and Cox, 1903.

19. Holton AC. Discussion of long-term results of concomitant convergent strabismus. *Trans Am Ophthalmol Soc U K* 1980;98:870.

20. Kennedy RJ, McCarthy JL. Surgical treatment of esotropia: analysis of case material and results in 315 consecutive cases. *Am J Ophthalmol* 1959;47:508-519.

21. Leahey BD. Criteria for early surgical correction of concomitant esotropia in infants and children. *Trans Am Ophthalmol Soc* 1960; 58:106-117.

22. Chavasse FB. *Worth's squint on the binocular reflexes and the treatment of strabismus*, 7th ed. Philadelphia: P. Blakiston's Son & Co, 1939.

23. Taylor DM. How early is early surgery in the management of strabismus? *Arch Ophthalmol* 1963;70:752-756.

24. Ing M, Costenbader FD, Parks MM, et al. Early surgery for congenital esotropia. *Am J Ophthalmol* 1966;62:1419-1427.

25. Parks MM. The monofixation syndrome. *Trans Am Ophthalmol Soc* 1969;67:609-657.

26. Ing MR. Early surgical alignment for congenital esotropia. *Trans Am Ophthalmol Soc* 1981;79:625-663.

27. Hubel DH. Exploration of the primary visual cortex, 1955-1978. *Nature* 1982;299:515-524.

28. Wiesel TN. Review article: postnatal development of the visual cortex and the influence of environment. *Nature* 1982;299: 583-591.

29. Tychsen L, Burkhalter A. Neuroanatomic abnormalities of primary visual cortex in macaque monkeys with infantile esotropia: preliminary results. *J Pediatr Ophthalmol Strabismus* 1995;32: 323-328.

30. Crawford JW, von Noorden GK, Meharg LS, et al. Binocular neurons and binocular function in monkeys and children. *Invest Ophthalmol Vis Sci* 1983;24:491-495.

31. Friendly DS. Management of infantile esotropia. In: Nelson LB, Wagner RS, eds. *Strabismus surgery*, *Int Ophthalmol Clin 25*. Boston: Little, Brown and Company, 1985.

32. Robb RM, Rodier DW. The variable clinical characteristics and course of early infantile esotropia. *J Pediatr Ophthalmol Strabismus* 1987;24:276-281.

33. Hiles DA, Watson A, Biglan AW. Characteristics of infantile esotropia following early bimedial rectus recession. *Arch Ophthalmol* 1980;98:697-703.

34. Birch EE, Stager DR. Monocular acuity and stereopsis in infantile esotropia. *Invest Ophthalmol Vis Sci* 1985;26:1624-1630.

35. Mayer DL, Fulton AB. Preferential looking grating acuities of infants at risk of amblyopia. *Trans Ophthalmol Soc UK* 1985;104: 903-911.

36. Thompson JT, Guyton DL. Ophthalmic prisms: measurement errors and how to minimize them. *Ophthalmology* 1983;90: 204-210.

37. Ing MR. Progressive increase in the angle of deviation in congenital esotropia. *Trans Am Ophthalmol Soc* 1994;92:117-125.

38. Ing MR. Surgical alignment in infants for congenital esotropia [Letter]. *Ophthalmology* 1996;103:701.

39. Shon MA, Hahm KH, Han SH, et al. Spontaneous resolution of infantile esotropia. *J AAPOS* 2001;5:44-47.

40. Parks MM, Wheeler MD. Concomitant esodeviations. In: Tasman W, Jaeger EA, eds. *Duane's clinical ophthalmology*. Philadelphia: Lippincott Williams & Wilkins, 2004.

41. Brown EUL. Net average yearly changes in refraction of atropinized eyes from birth to middle life. *Arch Ophthalmol* 1938;19: 719-734.

42. Raab EL. Etiologic factors in accommodative esodeviation. *Trans Am Ophthalmol Soc* 1982;80:657-694.

43. Burian HM. Hypermetropia and esotropia. *J Pediatr Ophthalmol* 1972;9:135-143.

44. Helveston EM. Dissociated vertical deviation, a clinical and laboratory study. *Trans Am Ophthalmol Soc* 1980;78:734-779.

45. Raab EL. Dissociated vertical deviation. In: Nelson LB, Wagner RS, eds. *Strabismus surgery*. *Int Ophthalmol Clin*. Boston: Little, Brown and Company, 1985.

46. Guyton DL. Dissociated vertical deviation: etiology, mechanism, and associated phenomena. *J AAPOS* 2000;4:131-144.

47. Neely DE, Helveston EM, Thuente DD, et al. Relationship of dissociated vertical deviation and the timing of initial surgery for congenital esotropia.

Ophthalmology 2001;108:487-490.

48. Vasquez R, Calhoun JH, Harley RD. Development of monofixation syndrome in congenital esotropia. *J Pediatr Ophthalmol Strabismus* 1981;18:42-44.

49. Nelson LB, Wagner RS, Simon JW, et al. Congenital esotropia. *Surv Ophthalmol* 1987;31:363-383.

50. Noel LP, Parks MM. Dissociated vertical deviation: associated findings and results of surgical treatment. *Can J Ophthalmol* 1982; 17:10-12.

51. Wilson ME, Parks MM. Primary inferior oblique overaction in congenital esotropia, accommodative esotropia, and intermittent exotropia. *Ophthalmology* 1989;96:950-955.

52. Eustis HS, Nussdorf JD. Inferior oblique overaction in infantile esotropia: fundus extorsion as a predictive sign. *J Pediatr Ophthalmol Strabismus* 1996;33:85-88.

53. Scott WE, Sutton VJ, Thalacker JA. Superior rectus recessions for dissociated vertical deviation. *Ophthalmology* 1982;89:317-322.

54. Evans DE, Biglan AW, Troost BT. Measurement of visual acuity in latent nystagmus. *Ophthalmology* 1981;88:134-138.

55. Sprunger DT, Wasserman BN, Stidham DB. The relationship between nystagmus and surgical outcome in congenital esotropia. *J AAPOS* 2000;4:21-24.

56. Trigler L, Siatkowski RM. Factors associated with horizontal reoperation in infantile esotropia. *J AAPOS* 2002;6:15-20.

57. Wright KW, Edelman PM, McVey JH, et al. High-grade stereo acuity after early surgery for congenital esotropia. *Arch Ophthalmol* 1994;112:913-919.

58. Morris RJ, Scott WE, Dickey CF. Fusion after surgical alignment of long-standing strabismus in adults. *Ophthalmology* 1993;100: 135-138.

59. Pratt-Johnson JA, Tillson G. Sensory results following treatment of infantile esotropia. *Can J Ophthalmol* 1984;18:175-177.

60. Parks MM. The monofixation syndrome. In: Tasman W, Jaeger EA, eds. *Duane's clinical ophthalmology*. Philadelphia: Lippincott Williams & Wilkins, 2004.

61. Arthur BW, Smith JT, Scott WE. Long-term stability of alignment in the monofixation syndrome. *J Pediatr Ophthalmol Strabismus* 1989;26:224-231.

62. Kushner BJ, Fisher M. Is alignment within 8 prism diopters of orthotropia a successful outcome for infantile esotropia surgery? *Arch Ophthalmol* 1996;114:176-180.

63. Rogers GL, Chazan S, Fellows R, et al. Strabismus surgery and its effect upon infant development in congenital esotropia. *Ophthalmology* 1982;89:479-483.

64. Tolchin JG, Lederman ME. Congenital infantile esotropia: psychiatric aspects. *J Pediatr Ophthalmol Strabismus* 1978;15: 160-163.

65. Fletcher MC, Silverman SJ. Strabismus. Part I: A summary of 1110 consecutive cases. *Am J Ophthalmol* 1966;61:86-94.

66. Lang J. The optimum time for surgical alignment in congenital esotropia. *J Pediatr Ophthalmol Strabismus* 1984;21:74-75.

67. Birch EE, Stager DR, Everett ME. Random dot stereoacuity following surgical correction of infantile esotropia. *J Pediatr Ophthalmol Strabismus* 1995;32:231-235.

68. Wright KW. Surgical alignment in infants for congenital esotropia. *Ophthalmology* 1996;103:700-701.

69. Birch E, Stager D, Wright K, et al. The natural history of infantile esotropia during the first six months of life. *J AAPOS* 1998;2: 325-328.

70. Pediatric Eye Disease Investigator Group. Spontaneous resolution of early-onset esotropia: experience of the Congenital Esotropia Observational Study. *Am J Ophthalmol* 2002;133: 109-118.

71. Ing MR. Outcome study of surgical alignment before six months of age for congenital esotropia. *Ophthalmology* 1995;102: 2041-2045.

72. Ing MR. The timing of surgical alignment for congenital infantile esotropia. *J Pediatr Ophthalmol Strabismus* 1999;36:61-68.

73. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2002;120:268-278.

74. Dickey CF, Metz HS, Stewart SA, et al. The diagnosis of amblyopia in cross-fixation. *J Pediatr Ophthalmol Strabismus* 1991;28:171-175.

75. Lam GC, Repka MX, Guyton DL. Timing of amblyopia therapy relative to strabismus surgery. *Ophthalmology* 1993;100:1751-1756.

76. Bedrossian EH, Krewson WE. Isoflurophate versus glasses in evaluating the accommodative element in esotropia. *Arch Ophthalmol* 1966;76:186-188.

77. von Noorden GK, Isaza A, Park ME. Surgical treatment of congenital esotropia. *Trans Am Acad Ophthalmol Otolaryngol* 1972;76: 1465-1478.

78. Nelson LB, Calhoun JH, Simon JW, et al. Surgical management of large-angle congenital esotropia. *Br J Ophthalmol* 1987;71: 380-383.

79. Tolun H, Dikici K, Ozkiris A. Long-term results of bimedial rectus recessions in infantile esotropia. *J Pediatr Ophthalmol Strabismus* 1999;36:201-205.

80. Vroman DT, Hutchinson AK, Saunders RA, et al. Two-muscle surgery for congenital esotropia: rate of reoperation in patients with small versus large angles of deviation. *J AAPOS* 2000;4: 267-270.

81. Bartley BG, Dyer JA, Ilstrup M. Characteristics of recession-resection and bimedial recession for childhood esotropia. *Arch Ophthalmol* 1985;103:190-195.

82. Fisher NF, Flom MC, Jampolsky A. Early surgery of congenital esotropia. *Am J Ophthalmol* 1968;65:439-443.

83. Lee DA, Dyer JA. Bilateral medial rectus muscle recession and lateral rectus muscle recession in the treatment of congenital esotropia. *Am J Ophthalmol* 1983;95:528-535.

84. Scott WE, Reese PD, Hirsch CR, et al. Surgery for large angle esotropia. Two vs. three and four horizontal muscles. *Arch Ophthalmol* 1986;104:374-377.

85. Forrest MP, Finnigan S, Finnigan S, et al. Three horizontal muscle squint surgery for large angle infantile esotropia. *Clin Experiment Ophthalmol* 2003;31:509-516.

86. Hess JB, Calhoun JH. A new rationale for the management of large angle esotropia. *J Pediatr Ophthalmol Strabismus* 1979;16:345-348.

87. Damanakis AG, Arvanitis PG, Ladas ID, et al. 8 mm bimedial rectus recession in infantile esotropia of 80-90 prism dioptres. *Br J Ophthalmol* 1994;78:842-844.

88. Weakley DR, Stager DR, Everett ME. Seven-millimeter bilateral medial rectus recessions in infantile esotropia. *J Pediatr Ophthalmol Strabismus* 1991;28:113-115.

89. Stager DR, Weakley DR, Everett M, et al. Delayed consecutive exotropia following 7-millimeter bilateral medial rectus recession for congenital esotropia. *J Pediatr Ophthalmol Strabismus* 1994;31:147-150.

90. Calhoun JH. Discussion on: how far can a medial rectus safely be recessed? and delayed consecutive exotropia following 7 millimeter bilateral medial rectus recession for congenital esotropia. *J Pediatr Ophthalmol Strabismus* 1994;31:151-152.

91. Magoon E. Chemodenervation of strabismic children. *Ophthalmology* 1989;96:931-934.

92. McNeer KW, Spencer RF, Tucker MG. Observations on bilateral simultaneous botulinum toxin injection in infantile esotropia. *J Pediatr Ophthalmol Strabismus* 1994;31:214-219.

93. Ing MR. Botulinum alignment for congenital esotropia. *Ophthalmology* 1993;100:318-322.

94. Jampolsky A. *Ocular deviations. Int Ophthalmol Clin*. Boston: Little, Brown and Company, 1964;4:642.

95. Cooper EL. The surgical management of secondary exotropia. *Trans Am Acad Ophthalmol Otolaryngol* 1961;65:595-608.

96. Freeley DA, Nelson LB, Calhoun JH. Recurrent esotropia following successful surgical correction of congenital esotropia. *J Pediatr Ophthalmol Strabismus* 1983;20:68-71.

97. Abrams MS, Olitsky SE, Reynolds JD. Accommodative esotropia following surgery for congenital esotropia. *Binocular Vision Eye Muscle Surg* 1996;11:195-198.

98. Birch EE, Fawcett SL, Stager DR. Risk factors for the development of accommodative esotropia following treatment for infantile esotropia. *J AAPOS* 2002;6:174-181.

99. Harcourt B, Mein J, Johnson F. Natural history and associations of dissociated vertical divergence. *Trans Ophthalmol Soc U K* 1980; 100:495-497.

100. Braverman DE, Scott WE. Surgical correction of dissociated vertical divergence. *J Pediatr Ophthalmol Strabismus* 1977;14: 337-342.

101. Sargent RA. Surgical correction of dissociated hyperdeviation. *Am Orthopt J* 1976;26:89-99.

102. Sprague JB, Moore S, Eggers H, et al. Dissociated vertical deviation: treatment with the Faden operation of Cuppers. *Arch Ophthalmol* 1980;98:465-468.

103. Parks MM. The weakening surgical procedures for eliminating overaction of the inferior oblique. *Am J Ophthalmol* 1972;73: 107-122.

104. Dyer JA. Tenotomy of the inferior oblique muscle at its scleral insertion. An easy and effective procedure. *Arch Ophthalmol* 1962; 68:176-181.

105. DelMonte MA, Parks MM. Denervation and extirpation of the inferior oblique. An improved weakening procedure for marked overaction. *Ophthalmology* 1983;90:1178-1185.

106. Davis G, McNeer KW, Spencer RF. Myectomy of the inferior oblique muscle. *Arch Ophthalmol* 1986;104:855-858.

107. Scott AB. Planning inferior oblique muscle surgery. In: Reinecke RD, ed. *Strabismus*. New York: Grune & Stratton, 1978:347.

108. Elliott RL, Nankin SJ. Anterior transposition of the inferior oblique. *J Pediatr Ophthalmol Strabismus* 1981;18:35-38.

109. Elliott RL, Parks MM. A comparison of inferior oblique muscle weakening by anterior transposition or denervation-extirpation. *Binocular Vision Eye Muscle Surg* 1992;7:205-224.

110. Mims JL, Wood RC. Bilateral anterior transposition of the inferior obliques. *Arch Ophthalmol* 1989;107:41-44.

111. Bacal DA, Nelson LB. Anterior transposition of the inferior oblique muscle for both dissociated vertical deviation and/or inferior oblique overaction: results of 94 procedures in 55 patients. *Binocular Vision Eye Muscle Surg* 1992;7:219-224.

112. Wright KW, Walonker F, Edelman P. 10-diopter fixation test for amblyopia. *Arch Ophthalmol* 1981;99:1242-1246.

113. von Noorden GK. The nystagmus compensation (blockage) syndrome. *Am J Ophthalmol* 1976;82:283-290.

114. von Noorden GK. The nystagmus blockage syndrome. *Trans Am Ophthalmol Soc* 1976;74:220-236.

115. Dell Osso LF, Ellenberger C, Abel LA, et al. The nystagmus blockage syndrome. Congenital nystagmus, manifest latent nystagmus or both? *Invest Ophthalmol Vis Sci* 1983;24:1580-1587.

116. Frank JW. Diagnostic signs in the nystagmus compensation syndrome. *J Pediatr Ophthalmol Strabismus* 1979;16:317-320.

117. Cuppers C. Probleme der operativen Therapie des okularen Nystagmus. *Klin Monatsbl Augenheilkd* 1971;195:145-147.

118. von Noorden GK, Wong SY. Surgical results in nystagmus blockage syndrome. *Ophthalmology* 1986;93:1028-1031.

119. Marg E, Freeman DN, Peltzman P, et al. Visual acuity development in human infants. Evoked potential measurement. *Invest Ophthalmol Vis Sci* 1976;15:150-153.

120. Haynes H, White B, Held R. Visual accommodation in human infants. *Science* 1965;148:528-530.

121. Pollard ZF. Accommodative esotropia during the first year of life. *Arch Ophthalmol* 1976;94:1912-1913.

122. Baker JD, Parks MM. Early onset accommodative esotropia. *Am J Ophthalmol* 1980;90:11-18.

123. Coats DK, Avilla CW, Paysse EA, et al. Early-onset refractive accommodative esotropia. *J AAPOS* 1998;2:275-278.

124. Parks MM. Abnormal accommodative convergence in squint. *Arch Ophthalmol* 1958;59:364-380.

125. Preslan MW, Beauchamp GR. Accommodative esotropia: review of current practices and controversies. *Ophthalmic Surg* 1987;18: 68-72.

126. Donders FC. *On the anomalies of accommodation and refraction of the eye*. London: New Syndenham Society, 1864.

127. Weakley DR, Birch E, Kip K. The role of anisometropia in the development of accommodative esotropia. *J AAPOS* 2001;5: 153-157.

128. Raab EL. Monitoring of controlled accommodative esotropia. *Trans Am Ophthalmol Soc* 2001;99:225-228.

129. Lambert SR, Lynn M, Sramek J, et al. Clinical features predictive of successfully weaning from spectacles those children with accommodative esotropia. *J AAPOS* 2003;7:7-13.

130. Havertape SA, Cruz OA, Miyazaki EA. Comparison of methods for determining the AC/A ratio in accommodative esotropia. *J Pediatr Ophthalmol Strabismus* 1999;36:178-183.

131. von Noorden GK, Morris J, Edelman P. Efficacy of bifocals in the treatment of accommodative esotropia. *Am J Ophthalmol* 1978;85:830-834.

132. Albert DG, Lederman ME. Abnormal distance—near esotropia. *Doc Ophthalmol* 1973;34:27-36.

133. Ludwig IH, Parks MM, Getson PR. Long-term results of bifocal therapy for accommodative esotropia. *J Pediatr Ophthalmol Strabismus* 1989;26:264-270.

134. Pratt-Johnson JA, Tillson G. The management of esotropia with high AC/A ratio (convergence excess). *J Pediatr Ophthalmol Strabismus* 1985;22:238-242.

135. Rosenbaum AL, Jampolsky A, Scott AB. Bimedial recession in high AC/A esotropia: a long-term follow-up. *Arch Ophthalmol* 1974;91:251-253.

136. O'Hara MA, Calhoun JH. Surgical correction of excess esotropia at near. *J Pediatr Ophthalmol Strabismus* 1990;27:120-123.

137. Millicent M, Peterseim W, Buckley EG. Medial rectus Faden operation for esotropia only at near fixation. *J AAPOS* 1997;1: 129-133.

138. Kushner BJ, Preslan MW, Morton GV. Treatment of partly accommodative esotropia with a high accommodative convergenceaccommodation ratio. *Arch Ophthalmol* 1987;105:815-818.

139. Kushner BJ. Fifteen-year outcome of surgery for the near angle in patients with accommodative esotropia and a high accommodative convergence to accommodation ratio. *Arch Ophthalmol* 2001;119:1150-1153.

140. Raab EL. Deterioration in accommodative esotropia. In: Reinecke RD, ed. *Strabismus II*. Orlando, FL: Grune & Stratton, 1984.

141. Wright KW, Bruce-Lyle L. Augmented surgery for esotropia associated with high hypermetropia. *J Pediatr Ophthalmol Strabismus* 1993;30:167-170.

142. Kushner BJ. Partly accommodative esotropia. Should you overcorrect and cut the plus? *Arch Ophthalmol* 1995;113:1530-1534.

143. Prism Adaptation Study Research Group: Efficacy of prism adaptation in the surgical management of acquired esotropia. *Arch Ophthalmol* 1990;108:1248-1256.

144. Costenbader FD, Mousel DK. Cyclic esotropia. *Arch Ophthalmol* 1964;71:180-181.

145. Parlato CJ, Nelson LB, Harley RD. Cyclic strabismus. *Ann Ophthalmol* 1983;15:1126-1129.

146. Burian HM. Round table discussion. In: Allen JH, ed. *Strabismus ophthalmic symposium II*. St. Louis: CV Mosby, 1958.

147. Helveston EM. Cyclic strabismus. *Am J Ophthalmol* 1973;23: 48-51.

148. Uemura Y, Tomita M, Tanaka Y. Consecutive cyclic esotropia. *J Pediatr Ophthalmol Strabismus* 1977;14:278-280.

149. Muchnick RS, Sanfilippo S, Dunlap EA. Cyclic esotropia developing after strabismus surgery. *Arch Ophthalmol* 1976;94:459-460.

150. Friendly DS, Manson RA, Albert DG. Cyclic strabismus. A case study. *Doc Ophthalmol* 1973;34:189-202.

151. Windsor CE, Berg EF. Circadian heterotropia. *Am J Ophthalmol* 1969;67:565-571.

152. Richter CP. Clock-mechanism esotropia in children: alternateday squint. *Johns Hopkins Med J* 1968;122:218-223.

153. Metz HS, Bigelow C. Change in the cycle of circadian strabismus. *Am J Ophthalmol* 1995;120:124-125.

154. Gadoth N, Dickerman Z, Lerman M, et al. Cyclic esotropia with minimal brain dysfunction. *J Pediatr Ophthalmol Strabismus* 1981; 18:14-17.

155. Caputo AR, Greenfield PS. Cyclic esotropia. *Ann Ophthalmol* 1978;10:775-778.

156. Chamberlain W. Cyclic esotropia. *Am J Ophthalmol* 1978;10: 775-778.

157. Goldman HD, Nelson LB. Acute acquired comitant esotropia. *Ann Ophthalmol* 1985;17:777-778.

158. Clark A, Nelson LB, Simon JW, et al. Acute acquired comitant esotropia. *Br J Ophthalmol* 1989;73:636-638.

159. Burian HM. Motility clinic: sudden onset of comitant convergent strabismus. *Am J Ophthalmol* 1945;28:407.

160. Swan KC. Esotropia following occlusion. *Arch Ophthalmol* 1947; 37:44.

161. Anderson WD, Lubow M. Astrocytoma of the corpus callosum presenting with acute comitant esotropia. *Am J Ophthalmol* 1970; 69:594-598.

162. Williams AS, Hoyt CS. Acute comitant esotropia in children with brain tumors. *Arch Ophthalmol* 1989;107:376-378.

163. Mohney BG, Huffaker RK. Common forms of childhood exotropia. *Ophthalmology* 2003;110:2093-2096.

164. Parks MM, Mitchell PR. Concomitant exodeviation. In: Tasman W, Jaeger EA, eds. *Duane's clinical ophthalmology*. Philadelphia: Lippincott Williams & Wilkins, 2004.

165. Biglan AW, Davis JS, Cheng KP, et al. Infantile exotropia. *J Pediatr Strabismus* 1996;33:79-84.

166. Hunter DG, Kelly JB, Buffenn AN, et al. Long-term outcome of uncomplicated infantile exotropia. *J AAPOS* 2001;5:352-356.

167. Costenbader FD. The physiology and management of divergent strabismus. In: Allen JH, ed. *Strabismus ophthalmic symposium II*. St. Louis: CV Mosby, 1958.

168. Hiles DA, Davies GT, Costenbader FD. Long-term observation on unoperated intermittent exotropia. *Arch Ophthalmol* 1968;80: 436-442.

169. Friendly DS. Surgical and non-surgical management of intermittent exotropia. *Ophthalmol Clin North Am* 1992;5:23-30.

170. Moore S. The prognostic value of lateral gaze measurements in intermittent exotropia. *Am Orthopt J* 1969;19:69-71.

171. Repka MX, Arnoldi KA. Lateral incomitance in exotropia: fact or artifact? *J Pediatr Ophthalmol Strabismus* 1991;28:125-128.

172. Bielschowsky A. Divergence excess. *Arch Ophthalmol* 1934;12: 157-166.

173. Duane A. A new classification of the motor anomalies of the eyes based upon physiological principles, together with their symptoms, diagnosis and treatment. *Ann Ophthalmol Otolaryngol* 1896;5:969.

174. Burian HM, Smity DR. Comparative measurement of exodeviations at twenty and one hundred feet. *Trans Am Ophthalmol Soc* 1971;69:188-199.

175. Kushner BJ. Exotropic deviations: a functional classification and approach to treatment. *Am Orthopt J* 1988;38:81-93.

176. Parks MM. Concomitant exodeviations. In: Tasman W, Jaeger EA, eds. *Duane's clinical ophthalmology*. JB Lippincott, 1990.

177. Dunlap EA. Overcorrections in exotropia. In: Manley DR, ed. *Symposium on horizontal ocular deviations*. St. Louis: CV Mosby, 1971.

178. Richard JM, Parks MM. Intermittent exotropia. Surgical results in different age groups. *Ophthalmology* 1983;90:1172-1177.

179. Pratt-Johnson JA, Barlow JM, Tillson G. Early surgery in intermittent exotropia. *Am J Ophthalmol* 1977;84:689-694.

180. Baker JD, Davies GT. Monofixational intermittent exotropia. *Arch Ophthalmol* 1979;97:93-95.

181. Abroms AD, Mohney BG, Rush DP, et al. Timely surgery in intermittent and constant exotropia for superior sensory outcome. *Am J Ophthalmol* 2001;131:111-116.

182. Coffey B, Wick B, Cotter S, et al. Treatment options in intermittent exotropia: a critical appraisal. *Optom Vis Sci* 1992;69: 386-404.

183. Duckman RH. Management of binocular anomalies: efficacy of vision therapy, exotropia. *Am J Optom Physiol Opt* 1987;64: 421-429.

184. Caltrider N, Jampolsky A. Overcorrecting minus lens therapy for treatment of intermittent exotropia. *Ophthalmology* 1983;90: 1160-1165.

185. Reynolds JD, Wackerhagen M, Olitsky SE. Overminus lens therapy for intermittent exotropia. *Am Orthopt J* 1994;44:86-91.

186. Knapp P. Divergent deviation. In: Allen JH, ed. *Strabismus symposium II*. St. Louis: CV Mosby, 1958.

187. Moore S. Orthoptic treatment for intermittent exotropia. *Am Orthopt J* 1963;13:14-20.

188. Kushner BJ. Selective surgery for intermittent exotropia based on distance/near differences. *Arch Ophthalmol* 1998;116:324-328.

189. Deutsch JA, Nelson LB, Sheppard RW, et al. Unilateral lateral rectus recession for the treatment of exotropia. *Ann Ophthalmol* 1992;24:111-113.

190. Nelson LB, Bacal DA, Burke MJ. An alternative approach to the surgical management of exotropia: the unilateral lateral rectus recession. *J Pediatr Ophthalmol Strabismus* 1992;29:357-360.

191. Dadeya S, Kamlesh. Long-term results of unilateral lateral rectus recession in intermittent exotropia. *J Pediatr Ophthalmol Strabismus* 2003;40:283-287.

192. Weakley DR, Stager DR. Unilateral lateral rectus recessions in exotropia. *Ophthalmic Surg* 1993;24:458-460.

193. Hardesty H. Management of intermittent exotropia. *Binocular Vision Eye Muscle Surg* 1990;5:145-152.

194. Beneish R, Flanders M. The role of stereopsis and early postoperative alignment in long-term surgical results of intermittent exotropia. *Can J Ophthalmol* 1994;29:119-124.

195. Stoller SH, Simon JW, Lininger LL. Bilateral lateral rectus recession for exotropia: a survival analysis. *J Pediatr Ophthalmol Strabismus* 1994;31:89-92.

196. Raab EL, Parks MM. Recession of the lateral recti: early and late postoperative alignments. *Arch Ophthalmol* 1969;82:203-208.

197. Ruttum MS. Initial versus subsequent postoperative motor alignment in intermittent exotropia. *J AAPOS* 1997;1:88-91.

198. Olitsky SE. Early and late postoperative alignment following unilateral lateral rectus recession for intermittent exotropia. *J Pediatr Ophthalmol Strabismus* 1998;35:146-148.

199. Cooper J, Duckman R. Convergence insufficiency: incidence, diagnosis, and treatment. *J Am Optom Assoc* 1978;49:673-680.

200. Daum KM. Convergence insufficiency. *Am J Optom Physiol Opt* 1984;61:16-22.

201. von Noorden GK. Resection of both medial rectus muscles in organic convergence insufficiency. *Am J Ophthalmol* 1976;81: 223-226.

202. Hermann JS. Surgical therapy for convergence insufficiency. *J Pediatr Ophthalmol Strabismus* 1981;18:28-31.

203. Choi DG, Rosenbaum AL. Medial rectus resections with adjustable suture for intermittent exotropia of the convergence insufficiency type. *J AAPOS* 2001;5:13-17.

204. Kraft SP, Levin AV, Enzenauer RW. Unilateral surgery for exotropia with convergence weakness. *J Pediatr Ophthalmol Strabismus* 1995;32:183-187.

205. Urretz-Zavalia A. Abduccion en la elevaccion. *Arch Oftalmol* 1948;22:124-134.

206. Urist JJ. Horizontal squint with secondary vertical deviations. *Arch Ophthalmol* 1951;46:245-247.

207. Albert DG. In: Parks MM, ed. *Annual review: strabismus. Arch Ophthalmol* 1957;58:136-153.

208. Urist JJ. Surgical treatment of esotropia with bilateral elevation in adduction. *Arch Ophthalmol* 1952;47:220-247.

209. Breinin GM. The physiopathology of the “A” and “V” patterns. *Trans Am Acad Ophthalmol Otolaryngol* 1964;68:363-374.

210. Scott AB. V pattern exotropia. Electromyographic study of an unusual case. *Invest Ophthalmol* 1973;12:232-233.

211. Brown HW. Vertical deviations. In *Symposium, strabismus. Trans Am Acad Ophthalmol Otolaryngol* 1953;57:157-162.

212. Melek NB, Mendoza T, Ciancia AO. Bilateral recession of superior rectus muscles: its influence on A and V pattern strabismus. *J AAPOS* 1998;2:333-335.

213. Kushner BJ. The role of ocular torsion on the etiology of A and V patterns. *J Pediatr Ophthalmol Strabismus* 1985;22:171-179.

214. Guyton DL, Weingarten PE. Sensory torsion as the cause of primary oblique muscle overaction/underaction and A and V pattern strabismus. *Binocular Vision Eye Muscle Surg* 1994;9: 209-236.

215. Miller MM, Guyton DL. Loss of fusion and the development of A or V patterns. *J Pediatr Ophthalmol Strabismus* 1994;31:220-224.

216. Knapp P. Vertically incomitant horizontal strabismus: the so-called A and V syndrome. *Trans Am Ophthalmol Soc* 1959;57: 666-698.

217. Knapp P. A and V pattern. In *Symposium on strabismus. Trans New Orleans Acad Ophthalmol* St. Louis: CV Mosby, 1972:242-254.

218. Metz HS, Schwartz L. The treatment of A and V patterns by monocular surgery. *Arch Ophthalmol* 1977;95:251-253.

219. Scott WE, Drummond GT, Keech RV. Vertical offsets of horizontal recti muscles in the management of A and V pattern strabismus. *Aust N Z J Ophthalmol* 1989;17:281-288.

220. Ribeiro GD, Brooks SE, Archer SM, et al. Vertical shift of the medial rectus muscles in the treatment of A-pattern esotropia: analysis of outcome. *J Pediatr Ophthalmol Strabismus* 1995;32: 167-171.

221. Goldstein JH. Monocular vertical displacement of the horizontal rectus muscles in the A and V patterns. *Am J Ophthalmol* 1967; 64:265-267.

222. Ohba M, Nakagawa T. Treatment for “A” and “V” exotropia by slanting muscle insertions. *Jpn J Ophthalmol* 2000;44:433-438.

223. Biedner B, Rothkoff L. Treatment for “A” or “V” pattern esotropia by slanting muscle insertion. *Br J Ophthalmol* 1995;79:807-808.

224. Stager DR, Parks MM. Inferior oblique weakening procedures. Effect on primary position horizontal alignment. *Arch Ophthalmol* 1973;90:15-16.

225. Fierson WM, Boger WP, Diorio PC, et al. The effect of bilateral superior oblique tenotomy on horizontal deviation in A-pattern strabismus. *J Pediatr Ophthalmol Strabismus* 1980;17:364-371.

226. Diamond GR, Parks MM. The effect of superior oblique weakening procedures on primary position horizontal alignment. *J Pediatr Ophthalmol Strabismus* 1981;18:35-38.

227. Shuey TF, Parks MM, Friendly DS. Results of combined surgery on the superior oblique and horizontal rectus muscles for A-pattern horizontal strabismus. *J Pediatr Ophthalmol Strabismus* 1992;29:199-201.

228. Rubin SE, Nelson LB, Harley RD. A complication of weakening the superior oblique in A-pattern esotropia. *Ophthalmic Surg* 1984;15:134-135.

229. Romano P, Roholt P. Measured graduated recession of the superior oblique muscle. *J Pediatr Ophthalmol Strabismus* 1983;20: 134-140.

230. Wright KW. Superior oblique silicone expander for Brown's syndrome and superior oblique overaction. *J Pediatr Ophthalmol Strabismus* 1991;28:101-107.

231. Bardorf CM, Baker JD. The efficacy of superior oblique split Z-tendon lengthening for superior oblique overaction. *J AAPOS* 2003;7:96-102.

232. Miller JE. Vertical recti transplantation in the A and V syndromes. *Arch Ophthalmol* 1960;64:175-179.

233. Richards BW, Jones FR, Younge BR. Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear and abducens cranial nerves. *Am J Ophthalmol* 1992;113:489-496.

234. Holmes JM, Mutyala S, Maus TL, et al. Pediatric third, fourth, and sixth nerve palsies: a population-based study. *Am J Ophthalmol* 1999;127:388-392.

235. Victor DI. The diagnosis of congenital unilateral third nerve palsy. *Brain* 1976;99:711-718.

236. Miller NR. Solitary oculomotor nerve palsy in childhood. *Am J Ophthalmol* 1977;83:106-111.

237. Harley RD. Paralytic strabismus in children. Etiologic incidence and management of the third, fourth, and sixth nerve palsies. *Ophthalmol* 1980;87:24-43.

238. Ing EB, Sullivan TJ, Clarke MP, et al. Oculomotor nerve palsies in children. *J Pediatr Ophthalmol Strabismus* 1992;29:331-336.

239. Kazarian EL, Flynn JT. Congenital third nerve palsy with amblyopia of the contralateral eye. *J Pediatr Ophthalmol Strabismus* 1978;15:366-367.

240. Keith CG. Congenital ocular palsy. *Br J Ophthalmol* 1972;56: 356-361.

241. Balkan R, Hoyt CS. Associated neurologic abnormalities in congenital third nerve palsies. *Am J Ophthalmol* 1984;97:315-319.

242. Gilles FH. Hypotensive brain stem necroses. *Arch Pathol* 1969; 88:32-41.

243. Lotufo DG, Smith J, Hopen GR, et al. The pupil in congenital third nerve misdirection syndrome. *J Clin Neuro-Ophthalmol* 1983;3:193-196.

244. Elston JS. Traumatic third nerve palsy. *Br J Ophthalmol* 1984;68:538-543.

245. Huang LT, Shih TY, Lui CC. Posterior cerebral artery aneurysm in a two-year-old girl. *J Formos Med Assoc* 1996;95:170-172.

246. Mehkri IA, Awner S, Olitsky SE, et al. Double vision in a child. *Surv Ophthalmol* 1999;44:45-51.

247. Schumacher-Feero LA, Yoo KW, Solari FM, et al. Third cranial nerve palsy in children. *Am J Ophthalmol* 1999;128:216-221.

248. Scott WE. Surgical considerations in paretic strabismus based on special diagnostic techniques. *Am Orthopt J* 1980;30:40.

249. Reinecke RD. Surgical management of third and sixth cranial nerve palsies. In: Nelson LB, Wagner RS, eds. *Strabismus surgery. Int Ophthalmol Clin.* Boston: Little, Brown and Company, 1985.

250. Sato M, Maeda M, Ohmura T, et al. Myectomy of lateral rectus muscle for third nerve palsy. *Jpn J Ophthalmol* 2000;44:555-558.

251. Peter LC. The use of the superior oblique as an internal rotator in third-nerve paralysis. *Am J Ophthalmol* 1934;17:297.

252. Costenbader FD. Round table discussion. In: Allen JH, ed. *Strabismus ophthalmic symposium II*. St. Louis: CV Mosby, 1958.

253. Harley RD. Complete tendon transposition for ocular muscle paralysis. *Ann Ophthalmol* 1971;3:459-463.

254. Metz HS, Yee D. Third nerve palsy: superior oblique transposition surgery. *Ann Ophthalmol* 1973;5:215-218.

255. Scott AB. Transposition of the superior oblique. *Am Orthopt J* 1977;27:11-14.

256. Saunders RA, Rogers GL. Superior oblique transposition for third nerve palsy. *Ophthalmology* 1982;89:310-316.

257. Neely JC. The treatment of traumatic diplopia. *Br J Ophthalmol* 1947;31:601.

258. Symonds C. Recurrent multiple cranial nerve palsies. *J Neurol Neurosurg Psychiatry* 1958;21:95-100.

259. Groves JS. Ocular manifestations of head injuries. *Trans Ophthalmol Soc UK* 1962;81:613.

260. Mansouri AM, Reinecke RD. Central trochlear palsy. *Surv Ophthalmol* 1986;30:279-297.

261. von Noorden G, Murray E, Wong SY. Superior oblique paralysis: a review of 270 cases. *Arch Ophthalmol* 1986;104:1771-1776.

262. Burian HM, Rowan PJ, Sullivan MS. Absence of spontaneous head tilt in superior oblique muscle palsy. *Am J Ophthalmol* 1975; 79:972-977.

263. Gobin MH. The diagnosis and treatment of IVth cranial nerve paralysis. *Ophthalmologica* 1976;173:292-295.

264. Parks MM. Isolated cyclovertical muscle palsy. *Arch Ophthalmol* 1958;60:1027-1035.

265. Wilson ME, Hoxie J. Facial asymmetry in superior oblique muscle palsy. *J Pediatr Ophthalmol Strabismus* 1993;30:315-318.

266. Goodman CR, Chabner E, Guyton DL. Should early strabismus surgery be performed for ocular torticollis to prevent facial asymmetry? *J Pediatr Ophthalmol Strabismus* 1995;32:162-166.

267. Canale ST, Griffen DW, Hubbard CN. Congenital muscular torticollis. A long-term follow-up. *J Bone Joint Surg* 1982;64:810-816.

268. Ferkel RD, Westin GW, Dawson EG, et al. Muscular torticollis. A modified surgical approach. *J Bone Joint Surg* 1983;65:894-900.

269. Ruedemann AD. Scoliosis and vertical muscle imbalance. *Arch Ophthalmol* 1956;56:389-414.

270. Guyton DL, von Noorden GK. Sensory adaptations in cyclodeviations: In: Reiecke RD, ed. *Strabismus. Proceedings of the Third Meeting of the International Strabismological Association*, May 10-12,1978, Kyoto, Japan. New York: Grune & Stratton, 1978: 399-403.

271. von Noorden GK. Clinical and theoretical aspects of cyclotropia. *J Pediatr Ophthalmol Strabismus* 1984;21:126-132.

272. Mittelman D, Folk E. The evaluation and treatment of superior oblique muscle palsy. *Trans Am Acad Ophthalmol Otolaryngol* 1976;81:893-898.

273. von Noorden GK. Clinical observations in cyclodeviations. *Ophthalmology* 1979;86:1451-1461.

274. Guyton DL. Clinical assessment of ocular torsion. *Am Orthopt J* 1983;33:7-15.

275. Bixenman WW, von Noorden GK. Apparent foveal displacement in normal subjects and in cyclotropia. *Ophthalmology* 1982;89: 58-62.

276. Hermann JS. Masked bilateral superior oblique paresis. *J Pediatr Ophthalmol Strabismus* 1981;18:43-48.

277. Kraft SP, Scott WE. Masked bilateral superior oblique palsy. Clinical features and diagnosis. *J Pediatr Ophthalmol Strabismus* 1986; 23:264-272.

278. Scott WE, Kraft SP. Classification and surgical treatment of superior oblique palsy. II. Bilateral palsies. *Trans New Orleans Acad Ophthalmol* 1986;265-291.

279. Jampolsky A. Vertical strabismus surgery. *Trans New Orleans Acad Ophthalmol* St. Louis: Mosby, 1971:366.

280. Mitchell PR, Parks MM. Surgery for bilateral superior oblique palsy. *Ophthalmology* 1982;89:484-488.

281. Kushner BJ. The diagnosis and treatment of bilateral masked superior oblique palsy. *Am J Ophthalmol* 1988;105:186-194.

282. Ellis FJ, Stein LA, Guyton DL. Masked bilateral superior oblique muscle paresis. A simple overcorrection phenomenon? *Ophthalmology* 1998;105:544-551.

283. Knapp P. Classification and treatment of superior oblique palsy. *Am Orthopt J* 1974;24:18-22.

284. Gonzalez C, Wong RF, Somers ME. Superior oblique palsy management: a survey of 300 strabismologists. *Binocular Vision Eye Muscle Surg* 1989;4:63-69.

285. Plager DA. Tendon laxity in superior oblique palsy. *Ophthalmology* 1992;99:1032-1038.

286. Plager DA. Traction testing in superior oblique palsy. *J Pediatr Ophthalmol Strabismus* 1990;27:136-140.

287. Reynolds JD, Biglan AW, Hiles DA. Congenital superior oblique palsy in infants. *Arch Ophthalmol* 1984;102:1503-1505.

288. Morris RJ, Scott WE, Keech RV. Superior oblique tuck surgery in the management of superior oblique palsies. *J Pediatr Ophthalmol Strabismus* 1992;29:337-346.

289. May MA, Beauchamp GR, Price RL. Recession and anterior transposition of the inferior oblique for treatment of superior oblique palsy. *Graefe's Arch Clin Exp Ophthalmol* 1998;226:407-409.

290. Bremer DL, Rogers DL, Quick LD. Primary-position hypotropia after anterior transposition of the inferior oblique. *Arch Ophthalmol* 1986;104:229-232.

291. Gonzalez G, Cinciripini G. Anterior transposition of the inferior oblique in the treatment of unilateral superior oblique palsy. *J Pediatr Ophthalmol* 1995;32:107-113.

292. Farvardin M, Nazarpoor S. Anterior transposition of the inferior oblique muscle for treatment of superior oblique palsy. *J Pediatr Ophthalmol Strabismus* 2002;39:100-104.

293. Muchnick RS, McCullough DH, Strominger MB. Comparison of anterior transposition and recession of the inferior oblique muscle in unilateral superior oblique paresis. *J AAPOS* 1998;2: 340-343.

294. Harada M, Ito Y. Surgical correction of cyclotropia. *Jpn J Ophthalmol* 1964;8:88-95.

295. Fells P. Management of paralytic strabismus. *Br J Ophthalmol* 1974;58:255-265.

296. Hoyt WF, Nachtigaller H. Anomalies of ocular motor nerves: neuroanatomic correlates of paradoxical innervation in Duane's syndrome and related congenital ocular motor disorders. *Am J Ophthalmol* 1965;60:443-448.

297. Ernest JT, Costenbader FD. Lateral rectus muscle palsy. *Am J Ophthalmol* 1968;65:721-726.

298. Rush JA, Younge BR. Paralysis of cranial nerves III, IV, and VI. Cause and prognosis in 1000 cases. *Arch Ophthalmol* 1981;99: 76-79.

299. Robertson DM, Hines DJ, Rucker DW. Acquired sixth nerve paresis in children. *Arch Ophthalmol* 1970;83:574-579.

300. Lee MS, Galetta SL, Volpe NJ, et al. Sixth nerve palsies in children. *Pediatr Neurol* 1999;20:49-52.

301. Knox DL, Clark DB, Schuster FF. Benign sixth nerve palsies in children. *Pediatrics* 1967; 40:560-564.

302. Barnett AM. Benign recurrent abducens palsy in children. *S Afr Med J* 1973;46:1662-1663.

303. Bixenman WW. Benign recurrent VI nerve palsy in childhood. *J Pediatr Ophthalmol Strabismus* 1981;18:29-34.

304. Reinecke RD, Thompson WE. Childhood recurrent idiopathic paralysis of the lateral rectus. *Ann Ophthalmol* 1981;13: 1037-1039.

305. Gradenigo G. A special syndrome of endocranial otitic complications (paralysis of the motor oculi externus of otitic organ). *Am Oto* 1904;13:637-638.

306. Holmes JM, Droste PJ, Beck RW. The natural history of acute traumatic sixth nerve palsy or paresis. *J AAPOS* 1998;2:265-268.

307. Scott AB, Kraft SP. Botulinum toxin injection in the management of lateral rectus paresis. *Ophthalmology* 1985;92:676-683.

308. Jampolsky A. Botulinum toxin injections. In: *Strabismus. Trans New Orleans Acad Ophthalmol*. New York: Raven Press, 1986.

309. Wagner RS, Frohman LP. Long-term results: botulinum for sixth nerve palsy. *J Pediatr Ophthalmol Strabismus* 1989;26:106-108.

310. Metz HS, Dickey CF. Treatment of unilateral acute sixth-nerve palsy with botulinum toxin. *Am J Ophthalmol* 1981;112: 381-384.

311. Lee J, Harris S, Cohen J, et al. Results of a prospective randomized trial of botulinum toxin therapy in acute unilateral sixth nerve palsy. *J Pediatr Ophthalmol* 1984;31:283-286.

312. Holmes JM, Beck RW, Kip KE, et al. Botulinum toxin treatment versus conservative management in acute traumatic sixth nerve palsy or paresis. *J AAPOS* 2000;4:145-149.

313. Holmes JM, Beck RW, Kip KE, et al. Predictors of nonrecovery in acute traumatic sixth nerve palsy and paresis. *Ophthalmology* 2001;108:1457-1460.

314. Hummelsheim E. Weitere Erfahrungen mit partieller Schnenuberpflanzung an den Augenmuskeln. *Arch Augenheilk* 1909;62: 71-75.

315. Brooks SE, Olitsky SE, deB Ribeiro G. Augmented Hummelsheim procedure for paralytic strabismus. *J Pediatr Ophthalmol Strabismus* 2000;37:189-195.

316. Jensen CD. Rectus muscle union: a new operation for paralysis of the rectus muscle. *Trans Pac Coast Oto-Ophthalmol Soc Annu Meet* 1964;45:359-387.

317. Selezinka W, Sandall GS, Henderson JW. Rectus muscle union in sixth nerve paralysis. Jensen rectus muscle union. *Arch Ophthalmol* 1974;92:382-386.

318. Scott WE, Werner DB, Lennarson L. Evaluation of Jensen procedures by saccades and diplopic fields. *Arch Ophthalmol* 1979;97: 1886-1889.

319. Foster RS. Vertical muscle transposition augmented with lateral fixation. *J AAPOS* 1997;1:20-30.

320. Bleik JH, Cherfan GM. Anterior segment ischemia after the Jensen procedure in a 10-year-old patient. *Am J Ophthalmol* 1995; 119:524-525.

321. Rosenbaum AL, Kushner BJ, Kirschen D. Vertical rectus muscle transposition and botulinum toxin (Oculinum) to medial rectus for abducens palsy. *Arch Ophthalmol* 1989;107:820-823.

322. McManaway JW, Buckley EG, Brodsky MC. Vertical rectus muscle transposition with intraoperative botulinum injection for treatment of chronic sixth nerve palsy. *Graefe's Arch Clin Exp Ophthalmol* 1990;228:401-406.

323. Flanders M, Qahtani F, Gans M, et al. Vertical rectus muscle transposition and botulinum toxin for complete sixth nerve palsy. *Can J Ophthalmol* 2001;36:18-25.

324. Holmes JM, Leske DA. Long-term outcomes after surgical management of chronic sixth nerve palsy. *J AAPOS* 2002;6:283-288.

325. Stilling J. Untersuchungen über die Entstehung der Kurzsichtigkeit. Wiesbaden, Germany: JF Bergmar, 1887:13.

326. Turk S. Bemerkurgen zu einem Falle von Retraction des Auges. *Zentralbl Prakt Augenheilk* 1989;23:14.

327. Bahr K. Vorstellung eines Fulles von eigenartiger Muskelanomalie eines Auges. *Ber Dtsch Ophthalmol Ges* 1896;25:334.

328. Sinclair WW. Abnormal associated movements of the eyelids. *Ophthalmol Rev* 1895;14:307-319.

329. Wolff J. Occurrence of retraction movement of the eyeball together with congenital defects in external ocular muscles. *Arch Ophthalmol* 1900;29:297.

330. Duane A. Congenital deficiency of abduction, associated with impairment of adduction, retraction movements, contraction of the palpebral fissure and oblique movements of the eye. *Arch Ophthalmol* 1905;34:133-159.

331. Pfaffenbach DD, Cross HH, Kearns TP. Congenital anomalies in Duane's retraction syndrome. *Arch Ophthalmol* 1972;88: 635-639.

332. Isenberg S, Urist MJ. Clinical observations in 101 consecutive patients with Duane's retraction syndrome. *Am J Ophthalmol* 1977;84:419-425.

333. Maruo T, Kusota N, Arimoto H, et al. Duane's syndrome. *Jpn J Ophthalmol* 1979;23:453.

334. Zhang F. Clinical features of 201 cases with Duane's retraction syndrome. *Chin Med J* 1997;110:789-791.

335. Velez G. Duane's retraction syndrome associated with Goldenhar's syndrome. *Am J Ophthalmol* 1970;70:945-946.

336. Cross HE, Pfaffenbach DD. Duane's retraction syndrome and associated congenital malformation. *Am J Ophthalmol* 1972;73: 442-450.

337. O'Malley ER, Helveston EM, Ellis FD. Duane's retraction syndrome—plus. *J Pediatr Ophthalmol Strabismus* 1982;19:161-165.

338. Huber A. Electrophysiology of the retraction syndrome. *Br J Ophthalmol* 1974;59:293-300.

339. Kushner BJ. Pseudo inferior oblique overaction associated with Y and V patterns. *Ophthalmology* 1991;98:1500-1555.

340. Weinacht S, Huber A, Gottlob I. Vertical Duane's retraction syndrome. *Am J Ophthalmol* 1996;122:447-449.

341. Apple C. Congenital abducens paralysis. *Am J Ophthalmol* 1939; 22:169.

342. Axenfeld TH, Schurenberg E. Angeborene Retractionsbewegungen. *Klin Monatsbl Augenheilkd* 1901;39:851.

343. Mayou MS. Presidential address and discussion of squint. *Trans Ophthalmol Soc U K* 1934;54:3.

344. Nawratzki I. A typical retraction syndrome: a case report. *J Pediatr Ophthalmol Strabismus* 1967;4:32.

345. Spaeth EB. Surgical aspects of defection abduction. *Arch Ophthalmol* 1953;49:49-52.

346. Wong GY, Scott A, Jampolsky A. Clinical and surgical findings in Duane's syndrome. *Invest Ophthalmol* 1970;9:983.

347. Jampolsky A. Surgical leashes and reverse leashes in strabismus surgical management. In *Symposium on strabismus. Trans New Orleans Acad Ophthalmol* St. Louis: CV Mosby, 1978:244-268.

348. Pressman SH, Scott WE. Surgical treatment of Duane's syndrome. *Ophthalmology* 1986;93:29-38.

349. Kruger KE. Beitag zur Atiologie des Stilling-Turk-Duane Syndromes. *Acta Ophthalmol* 1969;47:415-423.

350. Miller MT, Stromland K. Ocular motility in Thalidomide embryopathy. *J Pediatr Ophthalmol Strabismus* 1991;28:47-54.

351. Breinin GM. Electromyography: a tool in ocular and neurologic diagnosis. II. Muscle palsies. *Arch Ophthalmol* 1957;57:165-167.

352. Blodi FC, Van Allen MW, Yarbrough JC. Duane's syndrome: a brain stem lesion. An electromyographic study. *Arch Ophthalmol* 1964;72:171-177.

353. Strachan IM, Brown BH. Electromyography of extraocular muscles in Duane's syndrome. *Br J Ophthalmol* 1972;56:594.

354. Sato S. Electromyographic studies on Duane's retraction syndrome. Report 1. Qualitative changes of action currents of extraocular muscles in ocular movements. *Acta Soc Ophthalmol Jap* 1959;63:228.

355. Scott AB, Wong GY. Duane's syndrome: an electromyographic study. *Arch Ophthalmol* 1972;87:140-147.

356. Matteucci P. I dufetti congeniti di abduzione con particolare riguardo alla patogenesi. *Rass Ital Ottalmol* 1946;15:345.

357. Hotchkiss MG, Muller NR, Clark AW, et al. Bilateral Duane's retraction syndrome. A clinical-pathologic case report. *Arch Ophthalmol* 1980;98:870-874.

358. Miller NR, Kiel SM, Green WR, et al. Unilateral Duane's retraction syndrome type 1. *Arch Ophthalmol* 1982;100:1468-1472.

359. Ozkurt H, Basak M, Oral Y, et al. Magnetic resonance imaging in Duane's retraction syndrome. *J Pediatr Ophthalmol Strabismus* 2003;40:19-22.

360. Jay WM, Hoyt CS. Abnormal brain stem auditory-evoked potentials in Stilling-Turk-Duane retraction syndrome. *Am J Ophthalmol* 1980;89:814-818.

361. Ramsay J, Taylor D. Congenital crocodile tears: a key to the aetiology of Duane's syndrome. *Br J Ophthalmol* 1980;64:518-522.

362. Gourdeau A, Miller N, Zee D, et al. Central ocular motor abnormalities in Duane's retraction syndrome. *Arch Ophthalmol* 1981; 99:1809-1810.

363. Tredici TD, von Noorden GK. Are anisometropia and amblyopia common in Duane's syndrome? *J Pediatr Ophthalmol Strabismus* 1985;22:23-25.

364. Gobin MH. Surgical management of Duane's syndrome. *Br J Ophthalmol* 1974;58:301-306.

365. Feretis D, Papastratigakis B, Tsamparlakis J. Planning surgery in Duane's syndrome. *Ophthalmologica* 1981;183:148-153.

366. Nelson LB. Severe adduction deficiency following a large medial rectus recession in Duane's retraction syndrome. *Arch Ophthalmol* 1986;104:859-862.

367. Kraft SP. A surgical approach for Duane's syndrome. *J Pediatr Ophthalmol Strabismus* 1988;25:119-130.

368. Morad Y, Kraft SP, Mims JL. Unilateral recession and resection in Duane's syndrome. *J AAPOS* 2001;5:158-163.

369. Metz HS, Scott AB, Scott WE. Horizontal saccadic velocities in Duane's syndrome. *Am J Ophthalmol* 1975;80:901-906.

370. Raab EL. Clinical features of Duane's syndrome. *J Pediatr Ophthalmol Strabismus* 1986;23:64-68.

371. Greenberg MF, Pollard ZF. Poor results after recession of both medial rectus muscles in unilateral small-angle Duane's syndrome, type I. *J AAPOS* 2003;7:142-145.

372. Britt MT, Velez FG, Thacker N, et al. Partial rectus muscle-augmented transpositions in abduction deficiency. *J AAPOS* 2003; 7:325-332.

373. Barbe ME, Scott WE, Kutschke PJ. A simplified approach to the treatment of Duane's syndrome. *Br J Ophthalmol* 2004;88: 131-138.

374. Rogers GL, Bremer DL. Surgical treatment of the upshoot and downshoot in Duane's retraction syndrome. *Ophthalmology* 1984;91:1380-1383.

375. Rao VB, Helveston EM, Sahare P. Treatment of upshoot and downshoot in Duane's syndrome by recession and Y-splitting of the lateral rectus muscle. *J AAPOS* 2003;7:389-395.

376. Mohan K, Saroha V. Vertical rectus recession for the innervational upshoot and downshoot in Duane's retraction syndrome. *J Pediatr Ophthalmol Strabismus* 2002;39:94-99.

377. Möebius PJ. Ueber angeborenen doppelseitig Abducens-Facialis-Laemung. *Munchen Med Wochenschrift* 1888;35:91-94.

378. Möebius, PJ. Uber infantilen Kernschwund. *Munch Med Wochenschrift* 1892;39:17-21.

379. Miller MT, Stromland K. The mobius sequence: a relook. *J AAPOS* 1999;3:199-208.

380. Cronemberger MF, de Castro Moreira JB, Brunoni D, et al. Ocular and clinical manifestations of Mobius' syndrome. *J Pediatr Ophthalmol Strabismus* 2001;38:156-162.

381. Henderson JL. The congenital facial diplegia syndrome: clinical features, pathology and aetiology. A review of sixty-one cases. *Brain* 1939;62:381-403.

382. Rogers GL, Hatch GF, Gray I. Mobius syndrome and limb abnormalities. *J Pediatr Ophthalmol Strabismus* 1977;14:134-138.

383. Gadoth N, Biedner B, Torok G. Möbius syndrome and Poland anomaly: case report and review of the literature. *J Pediatr Ophthalmol Strabismus* 1978;16:374-376.

384. Winshnick MM, Nelson LB, Huppert L, et al. Moebius syndrome and limb abnormalities with dominant inheritance. *Ophthalmic Pediatr Genet* 1983;2:77.

385. D'Cruz OF, Swisher CN, Jaradeh S, et al. Mobius syndrome: evidence for a vascular etiology. *J Child Neurology* 1993;8:260-265.

386. Ghabrial R, Versace P, Kourt G, et al. Mobius' syndrome: features and etiology. *J Pediatr Ophthalmol Strabismus* 1998;35:304-311.

387. Lammens M, Moerman P, Fryns JP, et al. Neuropathological findings in Moebius syndrome. *Clin Genet* 1998;54:136-141.

388. Dooley JM, Stewart WA, Hayden JD, et al. Brainstem calcification in Mobius syndrome. *Pediatr Neurol* 2004;30:39-41.

389. Lipson AH, Gillerot Y, Tannenberg AE, et al. Two cases of maternal antenatal splenic rupture and hypotension associated with Moebius syndrome and cerebral palsy in offspring. Further evidence for a utero placental vascular aetiology for the Moebius syndrome and some cases of cerebral palsy. *Eur J Pediatr* 1996; 155:800-804.

390. Spierer A, Barak A. Strabismus surgery in children with Mobius syndrome. *J AAPOS* 2000;4:58-59.

391. Brown HW. Isolated inferior oblique paralysis: an analysis of 97 cases. *Trans Am Ophthalmol Soc* 1957;55:415-454.

392. Brown HW. True and simulated superior oblique tendon sheath syndromes. *Doc Ophthalmol* 1973;34:123-136.

393. Metz HS. Saccadic velocity measurements in Brown's syndrome. *Ann Ophthalmol* 1979;11:636-638.

394. Parks MM, Brown M. Superior oblique tendon sheath syndrome of Brown. *Am J Ophthalmol* 1975;79:82-86.

395. Crawford JS. Surgical treatment of true Brown's syndrome. *Am J Ophthalmol* 1976;81:289-295.

396. Helveston EM. Superior oblique tuck for superior oblique palsy. *Aust J Ophthalmol* 1983;11:215-220.

397. Jackson OB, Nankin SJ, Scott WE. Traumatic simulated Brown's syndrome: a case report. *J Pediatr Ophthalmol Strabismus* 1979; 16:160-162.

398. Baker RS, Conklin JD. Acquired Brown's syndrome from blunt orbital trauma. *J Pediatr Ophthalmol Strabismus* 1987;24:17-21.

399. Hermann JS. Acquired Brown's syndrome of inflammatory origin. *Arch Ophthalmol* 1978;96:1228-1232.

400. Wright KW, Silverstein D, Marrone AC, et al. Acquired inflammatory superior oblique tendon sheath syndrome. A clinicopathologic study. *Arch Ophthalmol* 1982;100:1752-1754.

401. Tychsen L, Tse DT, Ossoinig K, et al. Trochleitis with superior oblique myositis. *Ophthalmology* 1984;91:1075-1079.

402. Sandford-Smith JH. Intermittent superior oblique tendon sheath syndrome: a case report. *Br J Ophthalmol* 1969;53:412-417.

403. Killian PJ, McLain B, Lawless OJ. Brown's syndrome—an unusual manifestation of rheumatoid arthritis. *Arthritis Rheum* 1977; 20:1080-1084.

404. Beck M, Hickling P. Treatment of bilateral superior oblique tendon sheath syndrome complicating rheumatoid arthritis. *Br J Ophthalmol* 1980;64:358-361.

405. Wang FM, Weitenbaker C, Behrens MM, et al. Acquired Brown's syndrome in children with juvenile rheumatoid arthritis. *Ophthalmology* 1984;91:23-26.

406. Moore AT, Morin JD. Bilateral acquired inflammatory Brown's syndrome. *J Pediatr Ophthalmol Strabismus* 1985;22:26-30.

407. Roifman CM, Lavi S, Moore AT, et al. Tenosynovitis of the superior oblique muscle (Brown's syndrome) associated with juvenile rheumatoid arthritis. *J Pediatr* 1985;106:617-619.

408. Sandford-Smith JH. Superior oblique tendon sheath syndrome and its relationship to stenosing tenosynovitis. *Br J Ophthalmol* 1973;59:859-865.

409. Parks MM. Surgery for Brown's syndrome. Symposium on strabismus. *Trans Acad New Orleans Acad Ophthalmol* 1978;6: 157-177.

410. Crawford JS, Orton B, Labow-Darly L. Late results of superior oblique muscle tenotomy in true Brown's syndrome. *Am J Ophthalmol* 1980;89:824-829.

411. von Noorden GK, Olivier R. Superior oblique tenectomy in Brown's syndrome. *Ophthalmology* 1982;90:303-309.

412. Eustis HS, O'Reilly C, Crawford JS. Management of superior oblique palsy after surgery for true Brown's surgery. *J Pediatr Ophthalmol Strabismus* 1987;24:10-16.

413. Parks MM, Eustis HS. Simultaneous superior oblique tenotomy and inferior oblique recession in Brown's syndrome. *Ophthalmology* 1987;94:1043-1048.

414. Astle WF, Corncock E, Drummond GT. Recession of the superior oblique tendon for inferior oblique palsy and Brown's syndrome. *Can J Ophthalmol* 1993;28:207-212.

415. Wright KW. Results of the superior oblique tendon elongation procedure for severe Brown's syndrome. *Trans Am Ophthalmol Soc* 2000;98:41-48.

416. Wright KW, Min M, Park C. Comparison of superior oblique tendon expander to superior oblique tenotomy for the management of superior oblique overaction and Brown's syndrome. *J Pediatr Ophthalmol Strabismus* 1992;29:92-97.

417. Metz HS. Double elevator palsy. *Arch Ophthalmol* 1979;97: 901-903.

418. White JW. Paralysis of the superior rectus and the inferior oblique muscle of the same eye. *Arch Ophthalmol* 1942;27: 366.

419. Rosner S. Double elevator paralysis. *Am J Ophthalmol* 1963;55: 87-93.

420. Watson AG. A new operation for double elevator paresis. *Trans Can Ophthalmol Soc* 1962;25:182.

421. Jampel RS, Fells P. Monocular elevation paresis caused by a central nervous system lesion. *Arch Ophthalmol* 1968;80:45-57.

422. Robinson DA. A quantitative analysis of extraocular muscle cooperation and squint. *Invest Ophthalmol* 1975;14:801-825.

423. Mather TR, Saunders RA. Congenital absence of the superior rectus muscle: a case report. *J Pediatr Ophthalmol Strabismus* 1987;24:291-295.

424. Scott WE, Jackson OB. Double elevator palsy: the significance of inferior rectus restriction. *Am Orthopt J* 1977;27:5-10.

425. Spiller WG. The importance in clinical diagnosis of paralysis of associated movements of the eyeballs (Blicklachmung) especially of upwards and downwards associated movements. *J Nerv Ment Dis* 1905;32:417.

426. Malbran E, Norris AL. Unilateral paralysis of the elevators of supranuclear origin. *Br J Ophthalmol* 1955;39:73-84.

427. Lessell S. Supranuclear paralysis of monocular elevation. *Neurology* 1975;25:1134-1143.

428. Kirkham TH, Kline LB. Monocular elevation paresis, Argyll Robertson pupils and sarcoidosis. *Can J Ophthalmol* 1976;11: 330-335.

429. Bielschowsky A. Lectures on motor anomalies of the eyes. III. Paralyses of the conjugate movements of the eyes. *Arch Ophthalmol* 1935;13:569.

430. Knapp P. The surgical treatment of double elevator paralysis. *Trans Am Ophthalmol Soc* 1969;67:304-323.

431. Kocak-Altintas AG, Kocak-Midillioglu I, Dabil H, et al. Selective management of double elevator palsy by either inferior rectus recession and/or Knapp type transposition surgery. *Binocul Vis Strabismus Q* 2000;15:39-46.

432. Scott WE, Nankin SJ. Isolated inferior oblique paresis. *Arch Ophthalmol* 1977;95:1586-1593.

433. White JW, Brown HW. Occurrence of vertical anomalies. *Trans Am Acad Ophthalmol Otolaryngol* 1939;11:329-339.

434. Marlow SB. Isolated paralysis of the inferior oblique. *Arch Ophthalmol* 1923;52:12.

435. Pollard ZF. Diagnosis and treatment of inferior oblique palsy. *J Pediatr Ophthalmol Strabismus* 1993;30:15-18.

436. Olivier P, von Noorden GK. Results of superior oblique tenotomy in inferior oblique paresis. *Arch Ophthalmol* 1982;100: 581-584.

437. Frey T. Isolated paresis of the inferior oblique. *Ophthalmic Surg* 1982;13:936-938.

438. Apt L, Axelrod RN. Generalized fibrosis of the extraocular muscles. *Am J Ophthalmol* 1978;85:822-829.

439. Harley RD, Rodrigues MM, Crawford JS. Congenital fibrosis of the extraocular muscles. *Trans Am Ophthalmol Soc* 1978;76: 197-226.

440. Hiatt RL, Halle AA. General fibrosis syndrome. *Ann Ophthalmol* 1983;15:1103-1109.

441. Lawford JB. Congenital hereditary defect of ocular movements. *Trans Ophthalmol Soc U K* 1888;8:262.

442. Brown HW. Congenital structural anomalies. In: Allen JH, ed. *Strabismus ophthalmic symposium I*. St. Louis: CV Mosby, 1950.

443. Laughlin RC. Congenital fibrosis of the extraocular muscles; a report of size cases. *Am J Ophthalmol* 1956;41:432-438.

444. Letson RD. Surgical management of the ocular congenital fibrosis syndrome. *Am Orthopt J* 1980;30:97.

445. Engle EC. Applications of molecular genetics to the understanding of congenital ocular motility disorders. *Ann N Y Acad Sci* 2002;956:55-63.

446. Mackey DA, Chan WM, Chan C, et al. Congenital fibrosis of the vertically acting extraocular muscles maps to the FEOM3 locus. *Hum Genet* 2002;110:510-512.

447. Martinez L. A case of fixed strabismus. *Am J Ophthalmol* 1948; 31:80-81.

448. Villaseca A. Strabismus fixus. *Am J Ophthalmol* 1959;48: 751-762.

449. Helfand M. Congenital familial external ophthalmoplegia without ptosis. *Arch Ophthalmol* 1939;2:823.

450. Hansen E. Congenital general fibrosis of the extraocular muscles. *Acta Ophthalmol* 1968;46:469-476.

451. Engle EC, Goumnerov BC, McKeown CA, et al. Oculomotor nerve and muscle abnormalities in congenital fibrosis of the extraocular muscles. *Ann Neurol* 1997;41:314-325.

452. Engle EC. The molecular basis of the congenital fibrosis syndromes. *Strabismus* 2002;10:125-128.

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Surgical Management of Strabismus

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Strabismus surgery in the pediatric population is similar to adult surgery in most respects. The same surgical techniques, instruments, and sutures are utilized in all age groups. There are, however, differences that must be addressed. The size of the globes, palpebral fissures, tendons, and muscles are smaller, making the approach slightly different, depending on individual variations in anatomy. The presence of prominent epicanthal folds, a wide nasal bridge, and deep set orbits can make the surgical approach more challenging even for the experienced surgeon. Surgical complications, such as perforation of the globe and endophthalmitis, are more likely to occur when visualization and exposure are compromised (1,2). Other than reoperations following previous ocular surgery, recessions of the medial rectus muscles in very young children may be the most difficult type of strabismus surgery to perform, particularly when exposure of the surgical field is compromised.

Knowledge of the anatomy of the extraocular muscles and fascia is critical for surgical success. Average values for the anatomical insertions, tendon and muscle lengths, and the relative positions of the muscle insertions relative to the limbus (as depicted in the spiral of Tillaux) are important surgical reference points (Table 10.1). Experienced surgeons understand that distances are average values and are not surprised to measure the medial rectus muscle insertion at 3.5 mm from the limbus in a very young child (Fig. 10.1). For these reasons, some surgeons will vary the magnitude of their surgery, depending on the size of the globe.

TABLE 10.1 ANATOMICAL RELATIONSHIPS, ACTIONS, AND INNERVATIONS OF THE EXTRAOCULAR MUSCLES

	Distance from Insertion to Limbus (in mm)	Length of Muscle and Tendon (in mm)	Length of Tendon (in mm)	Action in Primary Position	Innervation
Medial Rectus	5.5	40.8	3.7	Adduction	Inferior CN III
Inferior Rectus	6.5	40	5.5	Depression extorsion adduction	Inferior CN III
Lateral Rectus	6.9	40.6	8.8	Abduction	CN VI
Superior Rectus	7.7	41.8	5.8	Elevation intorsion adduction	Upper CN III
Superior Oblique	14-18	32	26	Intorsion depression abduction	CN IV
Inferior Oblique	16-25	38	1-2	Extorsion elevation abduction	Inferior CN III

An important surgical principle in all strabismus surgery is avoidance of penetration of Tenon's capsule at the point approximately 10 mm from the limbus where the muscles pass through it. Compromising this barrier to orbital fat may result in excessive inflammation, scarring, and the surgical adherence syndrome, which may limit postoperative ocular motility (Fig. 10.2).

SURGICAL MANAGEMENT

Critical for success in strabismus surgery is the proper selection of instruments and sutures, perioperative sterile technique, and postoperative management.

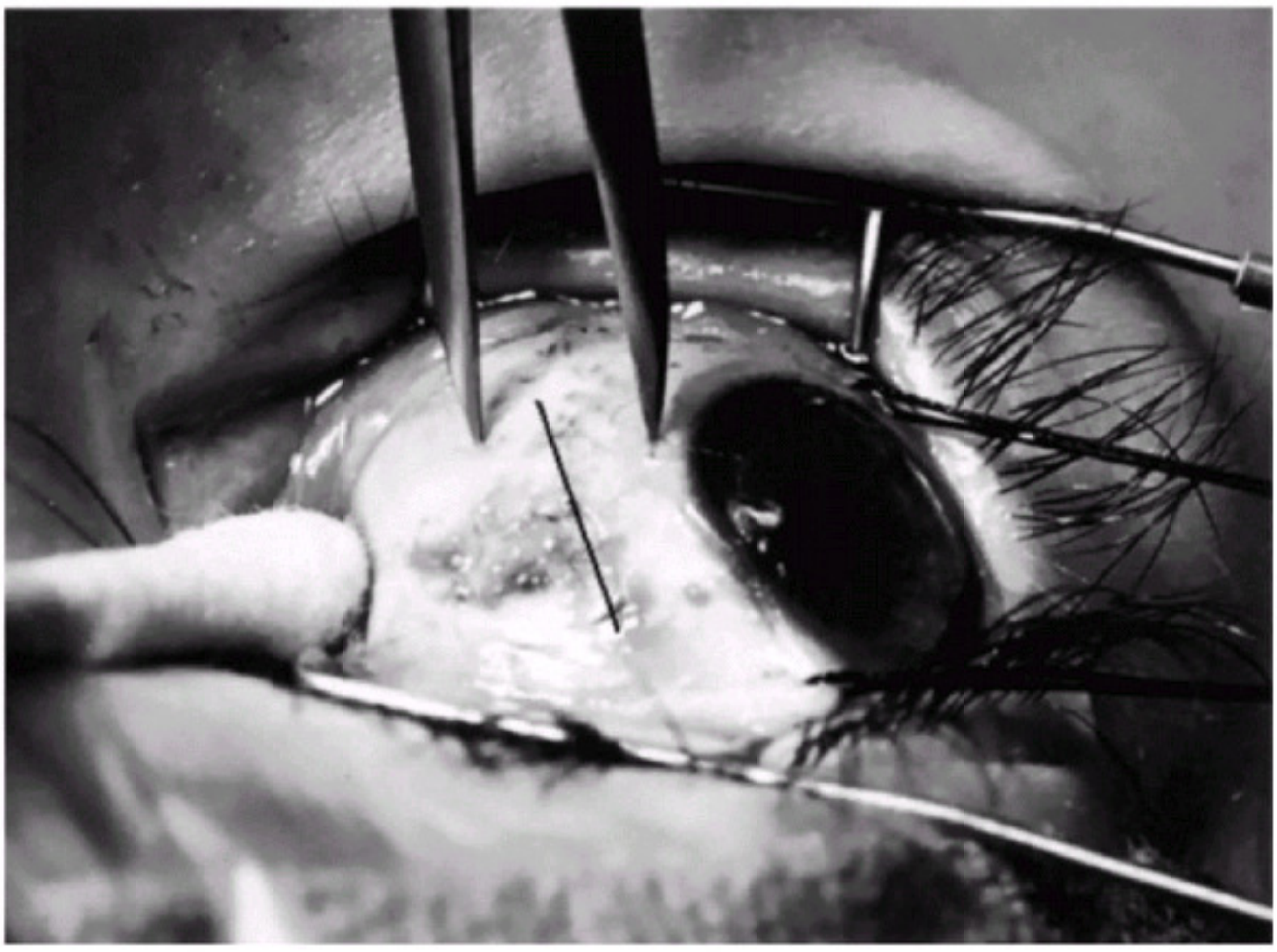

Figure 10.1 Line indicates anatomical insertion of the medial rectus muscle at 3.5 mm from the limbus. Caliper is measuring 5.5 mm from the limbus.

Part of the sterile surgical technique employed in most operating rooms includes a cleaning of the skin in the surgical field with povidone iodide. Some surgeons instill topical antimicrobials in the eye, 5% povidone iodide solution, or both, whereas others prefer to not apply any medications to the eye immediately before surgery. Two and one-half percent sterile phenylephrine drops instilled at the beginning of surgery may reduce bleeding by causing vasoconstriction and produce mydriasis. This will facilitate visualization of the retina with indirect ophthalmoscopy by the surgeon, if desired, upon completion of the procedure.

Individual surgeons develop preferences for surgical instruments, but a good basic instrument set is listed in Table 10.2. Some surgeons may prefer the Helveston Strabismus Surgery Instrument Set (Katena Products, Inc., Denville, NJ), depending on their training and technique. An excellent discussion of proper selection and handling of the surgical instruments during strabismus surgery is found in Dr. Marshall Parks's (3) *Atlas of Strabismus Surgery*.

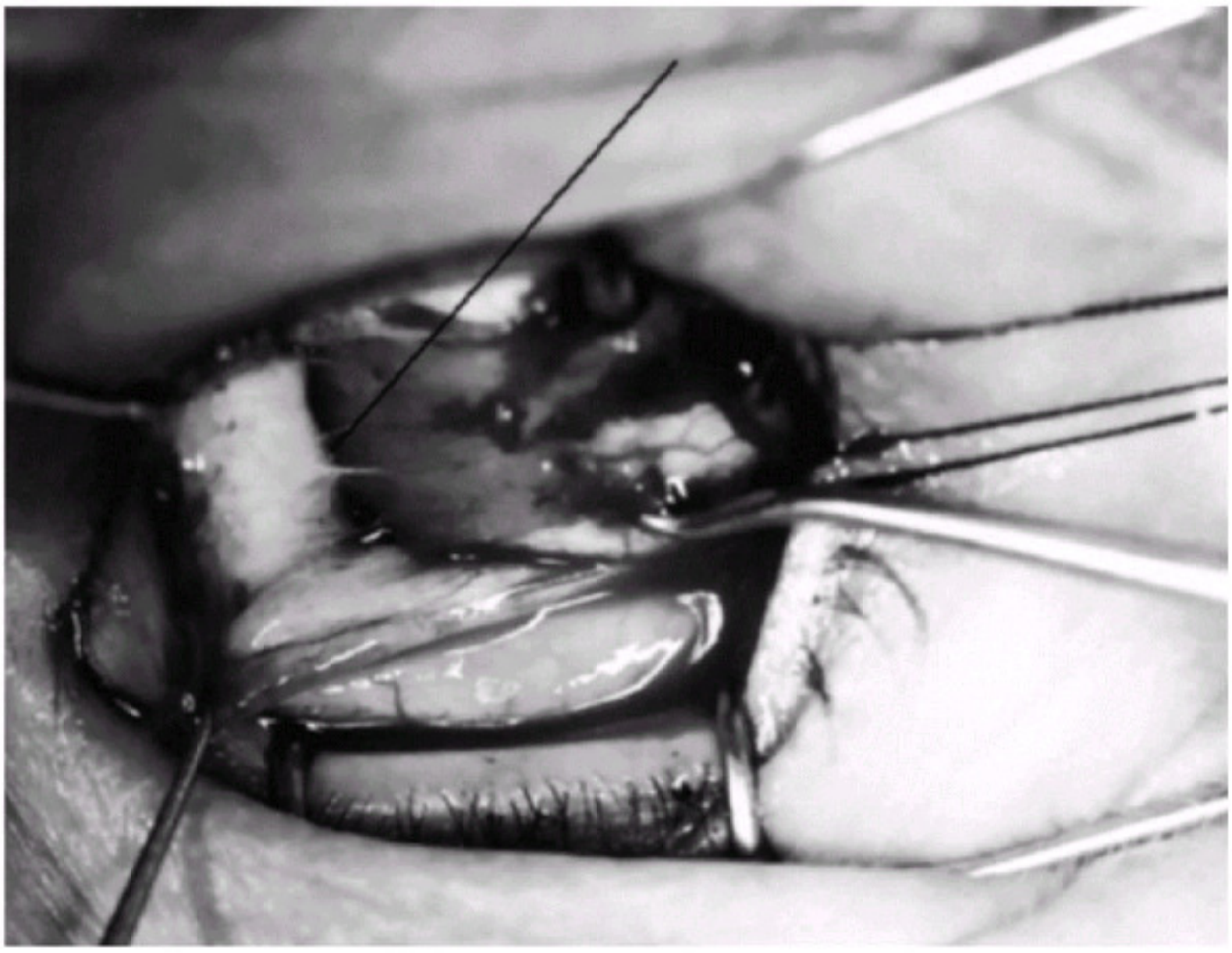

Figure 10.2 Area of penetration of the medial rectus muscle through Tenon's capsule is indicated by the black line.

TABLE 10.2 BASIC INSTRUMENTS REQUIRED FOR STRABISMUS SURGERY

Eye Specula	Lancaster eye speculum (Storz E-4056)[a] or Barraquer (Storz E4107)[b]
Forceps	Two Castroviejo suturing forceps 0.5 teeth (Storz E-1798),[c] two Stern-Castroviejo forceps with lock (Storz E-1798-S)[d]
Scissors	Wescott utility scissors with rounded tips (Storz E-3322),[e] Wescott stitch scissors with sharp, pointed tips (Storz E-3321)[f]
Muscle Hooks	Two Stevens tenotomy hooks (Storz E-600),[g] two Green strabismus hooks (Storz E-588), two Jameson muscle hooks (Storz E-586)[h]
Needle Holder	Barraquer curved-jaw needle holder with lock (Storz E-3843)[i]
Muscle Clamp	Hartman hemostatic mosquito forceps, straight (Storz E-3915)[j]
Caliper	Castroviejo caliper (Storz E-2404)[k]

[a-k] Storz Ophthalmic Instruments, a Division of Bausch and Lomb, 4935 Collection Center Drive, Chicago, IL 60693; other companies make the same instruments. Katena Products, Inc., has a complete Helveston set of strabismus instruments; 4 Stewart Court, Denville, NJ 07834.

In the immediate postoperative period many surgeons instill combination antibiotic/steroid ointment or drops and ask the parents to instill these in the eye three to four times daily during the week following surgery. Few surgeons routinely prescribe systemic antibiotics following strabismus surgery. Because the incidence of postoperative infection following strabismus surgery is so low, no data support a specific protocol regarding antibiotic use (4). Children's eyes are not routinely patched following surgery. Bilateral patching produces unnecessary anxiety in cases in which both eyes were operated on. Concerns about exposure to pathogens, upon leaving the surgical facility, might prompt the surgeon to send the child home with a sterile patch on the operated eye or eyes, in some cases.

Selection of sutures remains the choice of the surgeon, but spatula-type needles are essential for creation of the scleral tunnel for attachment of the operated muscle to the globe. Table 10.3 lists some preferred sutures. Preplacement of a double-armed suture (continuous suture with a needle at each end) is preferred to secure the muscle prior to disinsertion. A full-thickness “locking bite” is taken on opposite muscle margins (Fig. 10.3). Passage of the needle through the sclera at the proper depth is critical. If placed too deep, perforation into the choroids and retina might result. Too superficial placement may result in the suture pulling through the tunnel during tying. A slipped muscle might result, if this is not recognized. When the sclera is very thin, as in high myopia or when satisfactory positioning of the needle due to space limitations becomes problematic, reattachment at the original insertion can be performed. This “hang back,” or “hemi-hang back,” technique allows passage of the needle through the thicker sclera just

anterior to the original muscle insertion (Fig. 10.4). Surgical results comparing graded recessions in which the needle is passed through the sclera posterior to the insertion versus hanging backthe muscle to a measured point posterior to the insertion are equivalent (5).

TABLE 10.3 SOME PREFERRED SUTURES FOR STRABISMUS SURGERY

Traction Sutures	4-0 Black braided silk with P-3 cutting needle, 18 inches (Ethicon 641)[a]
Muscle Sutures	5-0 Polyglactin 910 synthetic absorbable suture with S-14 spatula needle, 8 inches (Coated Vicryl Violet Braided—Ethicon J591)[b] 6-0 Polyglactin 910 synthetic absorbable suture with S-14 or S-24 spatula needle, 8 inches (Coated Vicryl Violet Braided—Ethicon J590)[c]
Conjunctival Closure Sutures	6-0 Plain gut absorbable suture with G-1 cutting needle (Ethicon 770)[d]

[a-d] Ethicon, Inc., 405 Hoes Lane, PO Box 6800, Piscataway, NJ 08855.

The surgical decisions regarding which eye will be operated on and how much each muscle will be recessed, advanced, or resected are based on the preoperative evaluation. Intraoperative alteration of the surgical plan may need to be made in cases of reoperations, or when unexpected results, like an absent muscle, are encountered. The surgeon draws upon experience and knowledge of the aforementioned anatomical relationships in such cases. Adjustable suture surgery is generally reserved for adults, although some teenagers and, particularly, stoic children may tolerate this procedure. It is very difficult to predict compliance for the adjustment in most children.

The initial step in all strabismus surgery after placement of a lid retractor or speculum is fixation and proper positioning of the globe. A 4-0 silk traction suture passed through the conjunctiva and episclera near the limbus at two points 180 degrees apart provides excellent positioning of the globe. For horizontal muscle surgery the sutures are placed at the 6 and 12 o'clock positions.

Figure 10.3 Locking suture loops at superior and inferior margins of the medial rectus muscle.

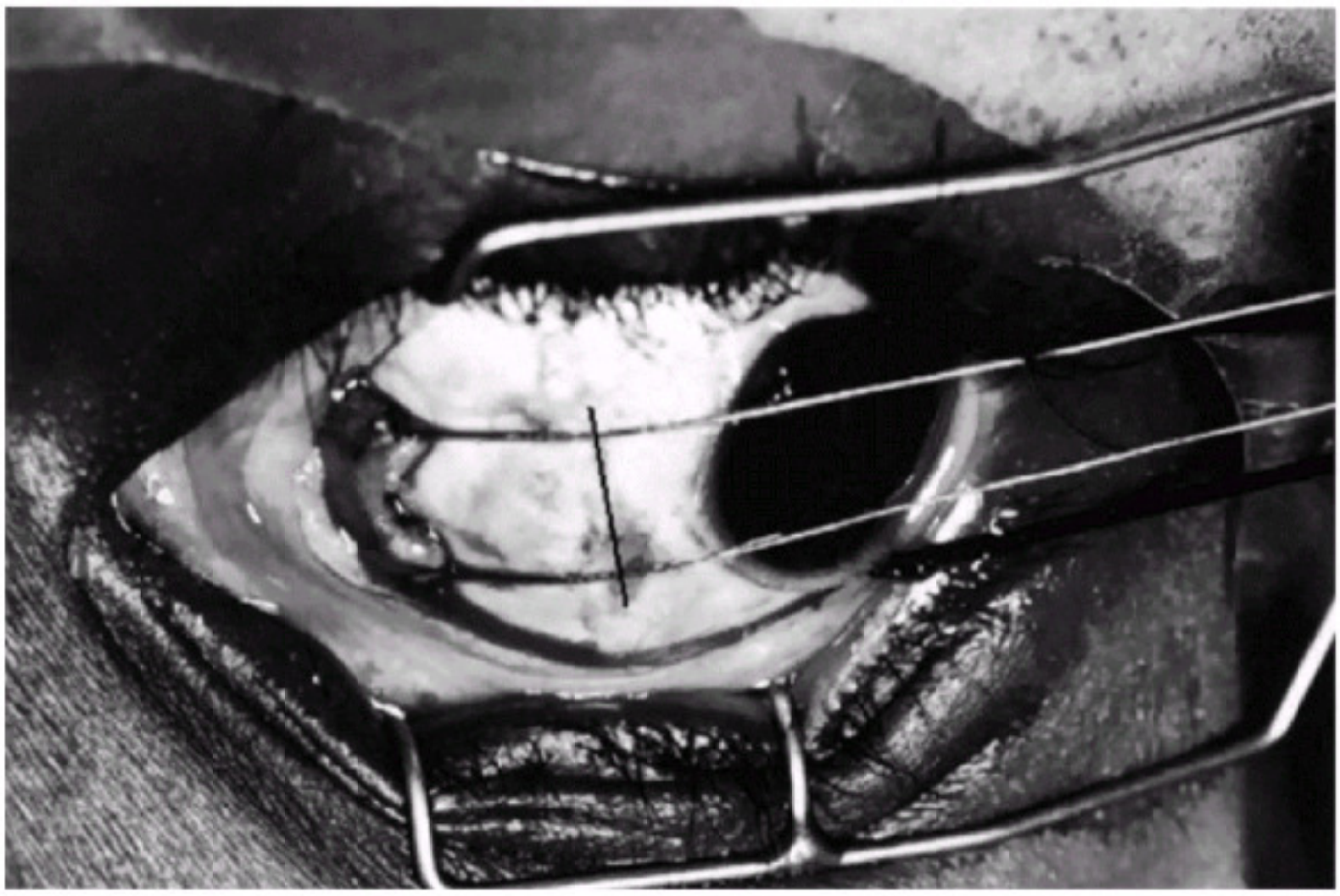

Figure 10.4 Black line indicates anatomical insertion. In “hang-back” technique, the needles are passed through the original insertion and the muscle recessed a measured distance from the limbus.

Many surgeons prefer the standard limbal incision, in which the conjunctiva is entered near the limbus and blunt dissection performed, avoiding the muscle and its insertion. This incision is required in most reoperations (6). A cul-de-sac or fornix incision is also useful, particularly for inferior oblique muscle surgery. This incision avoids the perilimbal conjunctiva and, in the initial healing period, results in a less visible scar. Surgery performed through a fornix incision provides less visualization of the operative field and requires an assistant well familiar with this technique (7). The standard limbal incision may be a better choice for the unassisted surgeon and when conjunctival recession is desired (Fig. 10.5). Occasionally, the surgeon will encounter excessive scar tissue, which precludes either of the above incisions and requires an incision directly over the muscle.

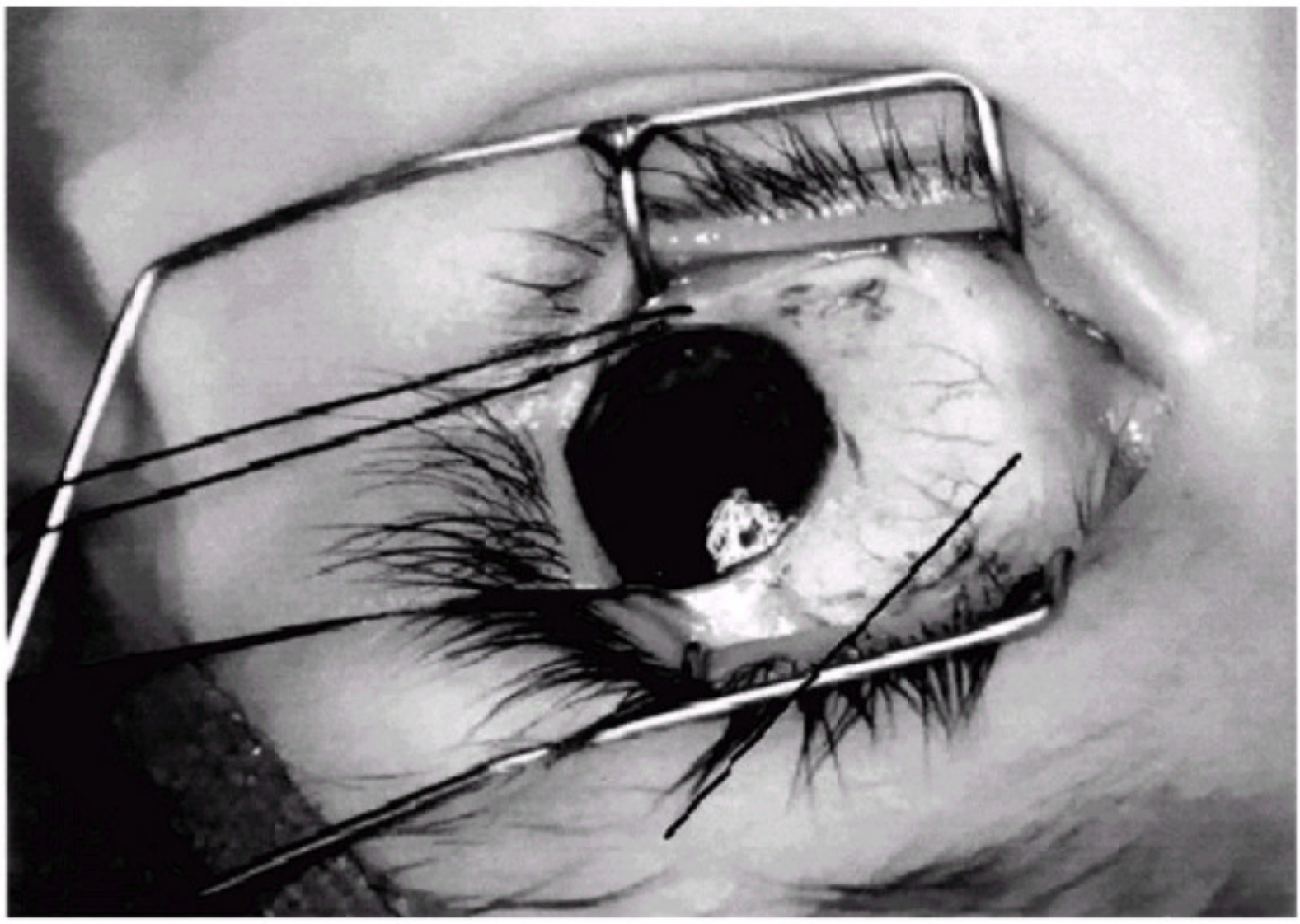

Figure 10.5 Line illustrates the recessed conjunctiva.

SURGICAL PROCEDURES

There are many excellent textbooks and atlases of strabismus surgery, which illustrate strabismus surgery procedures and different techniques (3,8,9,10,11).

Rectus Muscle Weakening

The most frequent strabismus surgical procedure performed is a recession of a rectus muscle. This involves removal and reattachment of a muscle on the globe so that its new insertion is closer to the muscle origin, usually posterior to the original insertion. Absorbable sutures are placed at a predetermined point in the sclera, or as mentioned earlier, allowed to hang back from a measured point where the sutures are passed and tied. Other weakening procedures include a marginal myotomy, in which a full-thickness incision is made through an edge of a muscle and extended about one third of the way across the width. This procedure may be used when a muscle has been maximally recessed and provides a minimal weakening effect. Injection of purified botulinum toxin A directly into an extraocular muscle (usually intraoperatively under anesthesia in children) also provides a temporary weakening effect of an extraocular muscle (12). This effect can be used to the surgeon's advantage when combined with strabismus surgery, as in extraocular muscle palsies (13). Some surgeons have reported good results in treating infantile esotropia with botulinum toxin injection alone (14).

A posterior fixation suture (Faden operation) attaches a rectus muscle to the sclera 10 to 18 mm posterior to the insertion, using a nonabsorbable suture. This procedure can weaken a muscle primarily in its field of action. It can be used in conjunction with a recession. Some possible uses for this procedure include the treatment of dissociated vertical deviation (DVD), nystagmus, high accommodative convergence to accommodation (AC:A) esotropia, and as a weakening procedure of a yoke muscle, in cases of paralytic or restrictive strabismus.

Rectus Muscle Strengthening

Rectus muscles are strengthened by shortening or resecting a portion of a muscle or, in cases of reoperations, by advancing a muscle closer to its original insertion. In a rectus muscle resection, a predetermined length of muscle is excised following preplacement of locked absorbable sutures. The residual muscle is usually advanced to the original insertion. Different techniques for suture placement in the muscle to be resected have been proposed. Some surgeons prefer to use a resection clamp to secure the muscle. A single double-armed suture can be used effectively in resections. The suture is “locked” on both margins posterior to the resection point prior to cutting the muscle. Whichever technique is utilized, care must be taken to avoid cutting the sutures. Direct visualization of the muscle and sutures is essential. Resections of the medial rectus muscles, particularly in restricted muscles, as found in reoperations, can be difficult. Often a second muscle hook can be utilized to better expose the muscle.

In cases of overcorrection in which a muscle has been recessed previously, the muscle can be advanced up to the original insertion. In these instances, knowledge of the average distances of the insertion site from the limbus is important for making intraoperative decisions as to muscle placement (Table 10.1). In resections and advancements care must be taken to avoid advancing the conjunctiva and, in medial rectus muscle surgery, the plica and semilunar fold too closely to the limbus. This results in a poor cosmetic appearance and can produce corneal dellen, if the tissue near the limbus is left elevated.

As stated, adjustable suture surgery may prove difficult in many children. Although techniques to postoperatively adjust a resected muscle have been proposed, this may be particularly difficult and might best be avoided.

Superior Oblique Tendon Surgery

Of all extraocular muscle surgeries, superior oblique muscle/tendon surgery is probably performed with the least frequency. This is due to many factors. Strabismus resulting from superor oblique muscle or trochlear nerve dysfunction is less common than other forms of strabismus. Superior oblique tendon surgery is less predictable because amounts of surgery in some procedures like “tucking” are based on intraoperative findings and prior surgical experience.

Folding or tucking strengthens the superior oblique tendon. Many approaches and techniques are available to perform this procedure, which is beneficial when there is underaction of the superior oblique muscle, as in recently acquired superior oblique muscle palsies. Posterior fibers of the tendon are responsible for vertical movement, whereas the anterior fibers are responsible for torsional eye movements. If correction of excyclotorsion is the primary objective, as in bilateral superior oblique muscle palsies, temporal advancement of the anterior half of the tendon can produce satisfactory results. This so-called Harada-Ito procedure can be performed as an adjustable procedure in older individuals (15). All procedures with tucking or strengthening the superior oblique tendon may produce Brown's syndrome. The superior oblique tendon can be advanced to a position proximal to the medial rectus muscle insertion in oculomotor nerve palsy.

Weakening of the superior oblique muscle is usually accomplished by performing a tenectomy or tenotomy. Superior oblique tendon expansion, utilizing a silicone retinal band or a nonabsorbable suture material, is an effective way to weaken the superior oblique tendon without producing the signs of a superior oblique palsy (16,17). This technique can be used effectively in Brown's syndrome and in A-pattern strabismus. Postoperative extrusion of the implant can occur occasionally.

Inferior Oblique Muscle Surgery

In contrast to surgery on the superior oblique tendon, surgery on the inferior oblique muscle is performed quite frequently. The high incidence of V-pattern strabismus with overacting inferior oblique muscles probably accounts for

this. Basic techniques to weaken the inferior oblique muscle include myotomy, myectomy, and recession. These procedures are best performed under direct visualization to avoid complications resulting from incomplete muscle surgery or adherence from prolapsed adipose tissue following disruption of Tenon's capsule.

The 14-mm recession popularized by Dr. Marshall Parks utilizes the inferior temporal vortex vein as a marker for suture placement for reattachment of the inferior oblique tendon to the sclera (18). The inferior oblique muscle, its vascular bundle, and the branch of the oculomotor nerve providing the innervation may be removed in the area where Tenon's capsule is penetrated for maximum weakening. This technique is called “denervation and extirpation.”

Presently, many surgeons prefer to weaken the inferior oblique muscle by advancing the tendon near the lateral margin of the inferior rectus muscle tendon. This procedure is useful in reducing overaction of the inferior oblique muscle and can also treat concurrent DVD (19). Advancing the inferior oblique tendon effectively converts the muscle to a depressor of the globe. The placement of the tendon behind or anterior to the insertion of the inferior rectus muscle can be used for grading the amount of effect desired. Lateral displacement of the inferior oblique tendon can result in unwanted depression of the globe in abduction. This limits elevation of the eye in abduction and mimics overaction of the inferior oblique muscle. This “antielevation syndrome” is best avoided by positioning the advanced inferior oblique tendon close to the lateral margin of the inferior rectus muscle (20).

Transposition

Transposition of portions of partial or complete rectus muscle tendons is done to improve ductions in the field of action of an absent or paretic muscle. Recently, augmentation of transposition procedures has been reported with excellent results. Foster (21) described total tendon transfer adjacent to the insertion of the paretic muscle. In addition, he advocates placing a posterior fixation suture on each transposed rectus muscle about 8 mm posterior to the insertion of the paretic

muscle, fixing the belly of each transposed muscle adjacent to the border of the paretic muscle. In an attempt to reduce the possibility of the development of anterior segment ischemia, a splitting of the rectus muscles can be performed and only one half of the tendon transposed for each muscle. This Hummelsheim procedure can be augmented by resecting 4 to 8 mm of the muscles to be transposed (22). Transpositions can be combined with recessions of the antagonist muscle or with botulinum chemodenervation.

COMPLICATIONS FOLLOWING STRABISMUS SURGERY

Although not usually the result of a surgical complication, unsatisfactory postoperative alignment may occur. There may be undercorrections or overcorrections resulting from many causes. An inability to accurately measure the true preoperative deviation may result in an untoward result. Strabismus surgery is not an exact science, however, and must be described as such to patients and families. In almost all circumstances, unsatisfactory postoperative alignment can be corrected with intervention by means of additional surgery, refractive error correction, or prisms. Reoperations are a major component of all strabismus surgeons' practice.

Slipped or even “lost” muscles can occur, during or following surgery, and may result from many factors. Successful management of these patients requires meticulous dissection with minimal manipulation of the globe and muscles (23,24). Orbital imaging as well as orbital endoscopy may prove useful in locating “lost” muscles (25).

More frequent complications following strabismus surgery include the development of conjunctival cysts and granulomas. Conjunctival inclusion cysts may result from entrapped conjunctival epithelial cells that form a translucent cyst, usually within weeks following strabismus surgery (Fig. 10.6). These often need to be excised surgically. Tenon's capsule left exposed at the conjunctival incision site may result in a granuloma formation. These may eventually form a pedunculated mass attached to the conjunctiva by a small central strand of tissue (Fig. 10.7). Topical application of steroids may reduce these granulomas, although some require surgical incision. Suture granulomas occur less frequently but present similarly. It is important to not leave sutures or Tenon's capsule exposed when the conjunctiva is closed, upon completion of strabismus surgery. “Wetting” the incision margin with balanced salt solution will cause any exposed Tenon's capsule to “fluff up” as solution is retained. This tissue can be easily distinguished from conjunctival tissue and excised or reposited.

In some patients polyglactin sutures may not dissolve rapidly and can remain for weeks following surgery. Surgical knots placed at the conjunctival margin may migrate to the surface and produce a foreign body sensation. These sutures may need to be surgically excised. Perhaps prolonged use of topical steroid medications may delay the dissolution of the suture material.

The advancement of conjunctival tissue or the plica semilunaris

toward the limbus may result in cosmetically unacceptable inflamed and thickened tissue postoperatively. Redundant tissue near the limbus may produce a corneal dellen or shallow depression near the limbus. These impede healing and produce discomfort. Frequent applications of artificial tears may relieve the symptoms in some patients.

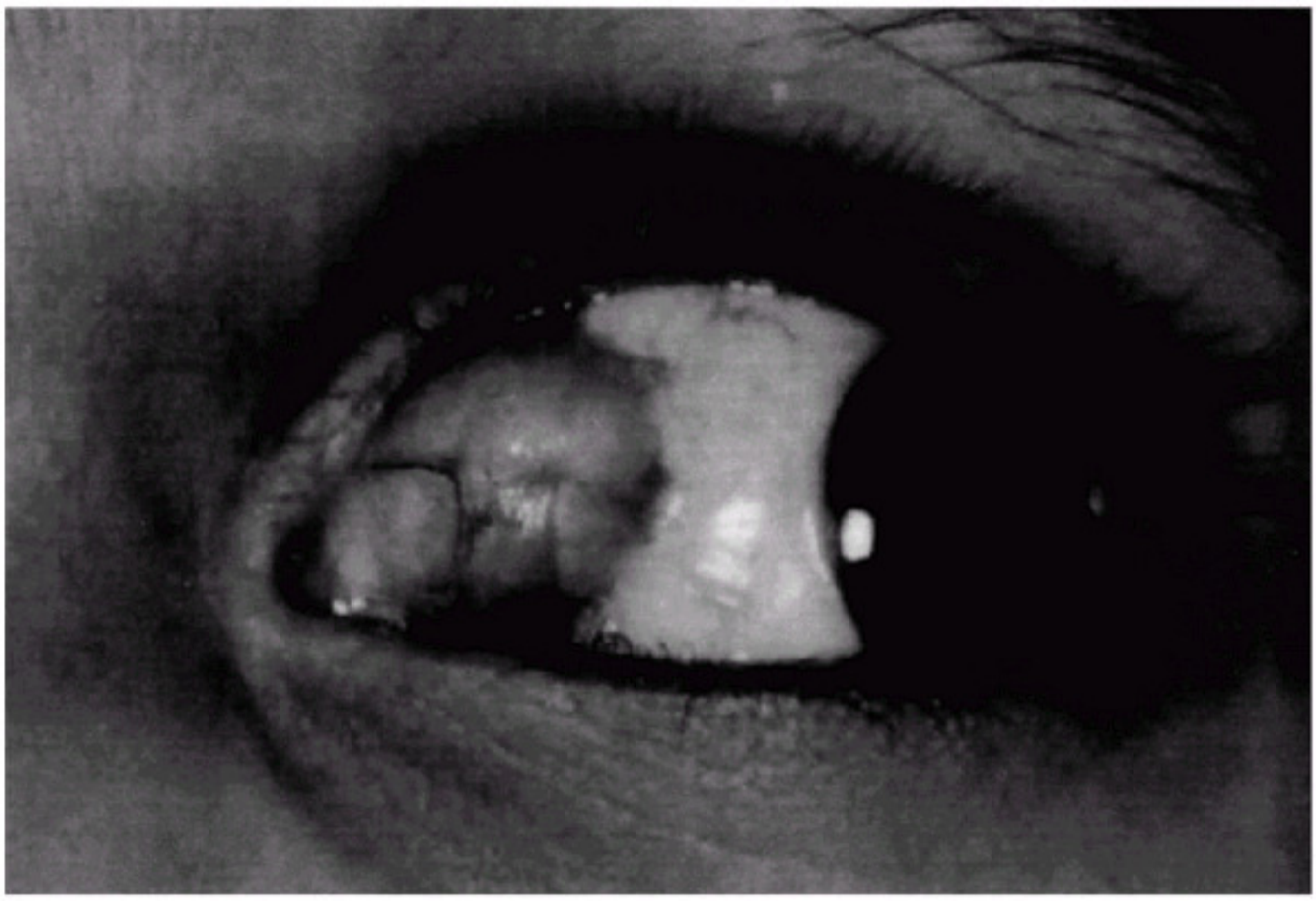

Figure 10.6 Conjunctival inclusion cyst following medial rectus muscle resection.

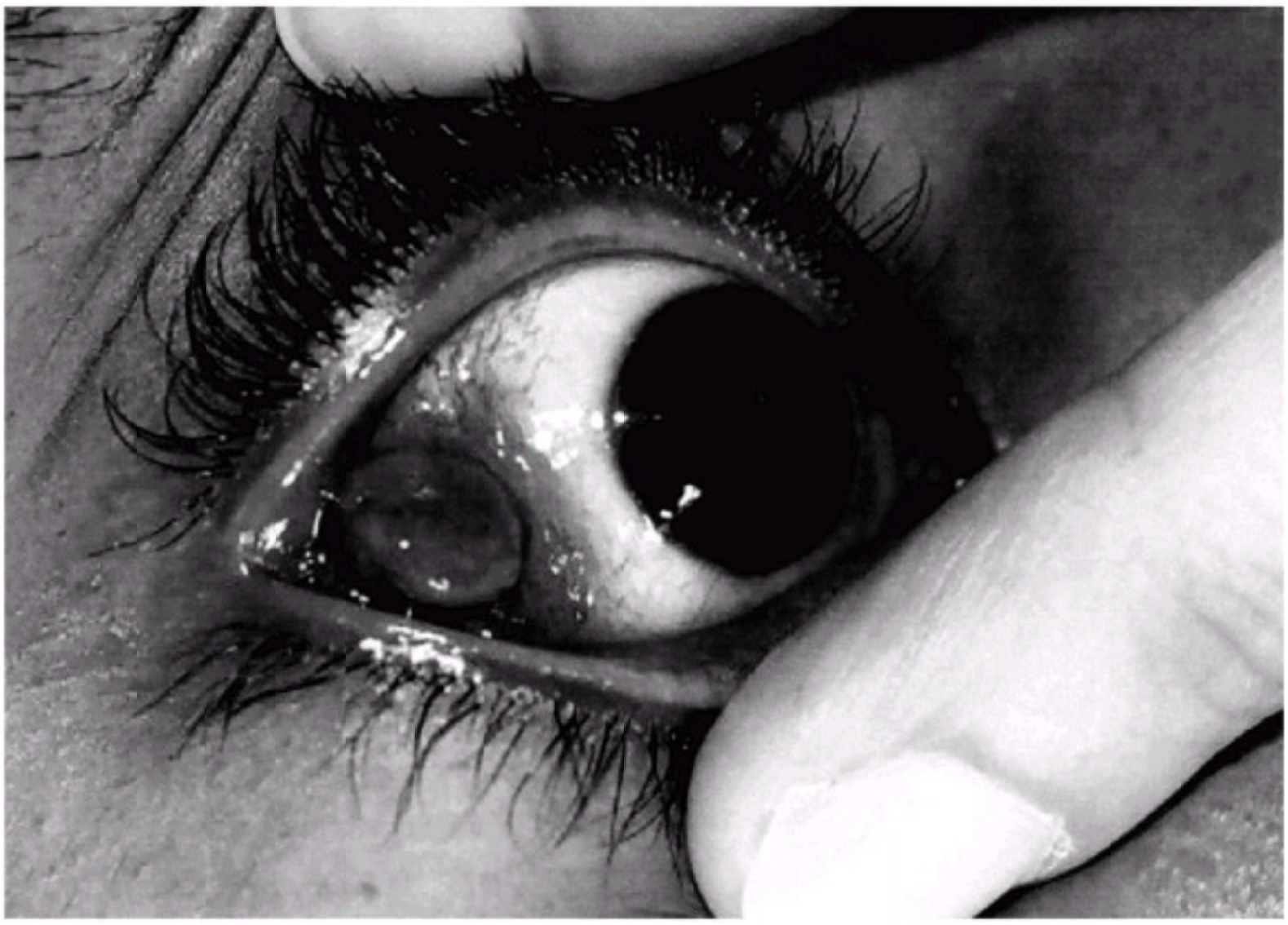

Figure 10.7 Granuloma following medial rectus muscle recession.

Perforation of the sclera during strabismus surgery probably occurs more frequently than is reported. In children, the formed vitreous makes traction and retinal detachment unlikely to occur. Some surgeons advocate instilling sterile drops of 2.5% phenylephrine at the beginning of surgery, in case indirect ophthalmoscopy is needed upon completion of the procedure. Many surgeons elect to follow patients with recognized perforations with frequent retinal exams. When perforation is recognized, the use of postoperative topical antibiotics is recommended.

Preseptal and, less likely, orbital cellulitis may occur a few days following strabismus surgery. Eyelid swelling, chemosis, and fever are signs of a postoperative infection. The preseptal type responds usually well to systemic antibiotics. Endophthalmitis following strabismus surgery is an extremely rare occurrence. It is unclear whether it always results from scleral perforation. It does seem to be more likely in young children. This may result from the excessive inflammatory response, as noted in pediatric cataract surgery versus adult surgery. Children present usually within 4 days following strabismus surgery, with lethargy and signs of excessive inflammation in the involved eye following bilateral strabismus surgery. By day 6, leukocoria may be found as a result of vitritis. A hypopion may also be seen. In spite of aggressive antibiotic and surgical therapy, most children will have significantly reduced vision following endophthalmitis (1).

When more than two extraocular muscles are operated on in one eye, the possibility of developing anterior segment ischemia exists. This condition most often occurs in older individuals with compromised circulation, as in thyroid ophthalmopathy. It presents with extreme pain within a week following strabismus surgery. There is associated iritis and, eventually, necrosis of the iris, cataract, and vision loss can occur. Topical and systemic corticosteroids may be useful in the management of this condition. It is more likely to follow vertical muscle surgery and rarely occurs in children (26).

TABLE 10.4 SURGERY FOR ESOTROPIA WITH MEDIAL RECTUS MUSCLE RECESSIONS IN BOTH EYES[a]

Esotropia (in prism diopters)	Recession (in mm)
15	3.0
20	3.5
25	4.0
30	4.5
35	5.0
40	5.5
50	6.0
60	6.5

[a] Measured from posterior edge of insertion to most anterior point of muscle tendon.

RECOMMENDATIONS FOR MILLIMETERS OF STRABISMUS SURGERY

There is individual surgeon variation in determining the muscles to be operated on in a particular case as well as the amount of a graded recession or resection. Some prefer to measure posterior from the original muscle insertion when performing a recession. Others measure from the limbus because there is individual anatomical variation in distances from the limbus to the insertion. This may be particularly obvious in infants and young children, where the insertions are closer and the globe smaller than in adults. Whatever measurement one uses, consistency is important so that surgical results will be reproducible. Experienced surgeons will establish their own “tables” for the amount they will recess or resect a muscle for a certain measured deviation.

TABLE 10.5 SURGERY FOR ESOTROPIA WITH LATERAL RECTUS MUSCLE RESECTIONS IN BOTH EYES[a]

Esotropia (in prism diopters)	Resection (in mm)
15	4.0
20	5.0
25	6.0
30	7.0
35	8.0
40	9.0
50	9.5

[a] Measurement of resected muscle.

TABLE 10.6 SURGERY FOR ESOTROPIA WITH MEDIAL RECTUS MUSCLE RECESSION AND LATERAL RECTUS MUSCLE RESECTION

Esotropia (in prism diopters)	Recession of MR	Resection of LR
15	3.0	4.0
20	3.5	5.0
25	4.0	6.0
30	4.5	7.0
35	5.0	8.0
40	5.5	9.0
50	6.0	9.0

MR, medial rectus; LR, lateral rectus.

For vertical rectus muscles, 1 mm of recession or resection will correct approximately 2 to 3 prism diopters of deviation. For horizontal deviations, no true linear relationship exists, and tables have been formulated to provide initial guidelines. Tables 10.4, 10.5, 10.6, 10.7, 10.8, 10.9 and 10.10 are useful for initial decision making.

TABLE 10.7 SURGERY FOR EXOTROPIA WITH LATERAL RECTUS MUSCLE RECESSIONS IN BOTH EYES[a]

Exotropia (in prism diopters)	Recession (in mm)
15	4.0
20	5.0
25	6.0
30	7.0
35	7.5
40	8.0
45	9.0
50	10.0

[a] Measured from posterior edge of insertion to most anterior point of muscle.

TABLE 10.8 SURGERY FOR EXOTROPIA WITH MEDIAL RECTUS MUSCLE RESECTIONS IN BOTH EYES[a]

Exotropia (in prism diopters)	Recession (in mm)
15	3.0
20	4.0
25	5.0
30	6.0
35	6.5

[a] Measurement of resected muscle.

TABLE 10.9 SURGERY FOR EXOTROPIA WITH LATERAL RECTUS MUSCLE RECESSION AND MEDIAL RECTUS MUSCLE RESECTION

Esotropia (in prism diopters)	Recession of MR	Resection of LR
15	4.0	3.0
20	5.0	4.0
25	6.0	5.0
30	7.0	5.5
35	7.5	6.0
40	8.0	6.0
50	9.0	7.0

LR, lateral rectus; MR, medial rectus.

TABLE 10.10 SUPERIOR RECTUS MUSCLE RECESSIONS FOR DISSOCIATED VERTICAL DEVIATIONS (DVD)

DVD (in prism diopters)	Recession (in mm)
<10	6.0
10	7.0
15	8.0
20	9.0
25	10.0

REFERENCES

1. Recchia FM, Baumal CR, Sivalingam A, et al. Endophthalmitis after pediatric strabismus surgery. *Arch Ophthalmol* 2000;118: 935-944.

2. Awad AH, Mullaney PB, Al-Hazmi AA, et al. Recognized globe perforation during strabismus surgery: incidence, risk factors, and sequelae. *J AAPOS* 2000;4:150-153.

3. Parks MM. *Atlas of strabismus surgery*. Philadelphia: Harper & Row, 1983.

4. Kivlin JD, Wilson ME Jr. Periocular infection after strabismus surgery. Periocular Infection Study Group. *J Pediatr Ophthalmol Strabismus* 1995;32:42-49.

5. Breckenridge AL, Dickman DM, Nelson LB, et al. Long-term results of hang-back medial rectus recession. *J Pediatr Ophthalmol Strabismus* 2003;40:81-84.

6. von Noorden GK. The limbal approach to surgery of the rectus muscles. *Arch Ophthalmol* 1968;80:94-97.

7. Parks MM. Fornix incision for horizontal rectus muscle surgery. *Am J Ophthalmol* 1968;65:907-915.

8. Calhoun JH, Nelson LB, Harley RD. *Atlas of pediatric ophthalmic surgery*. Philadelphia: WB Saunders, 1987.

9. Helveston EM. *Surgical management of strabismus*, 4th ed. St. Louis: Mosby, 1993.

10. Rosenbaum AL, Santiago AP. *Clinical strabismus management*. Philadelphia: WB Saunders, 1999.

11. Wright KW. *Color atlas of strabismus surgery strategies and techniques*. Irvine, CA: Wright, 2000.

12. Scott AB, Magoon EH, McNeer KW, et al. Botulinum treatment of strabismus in children. *Trans Am Ophthalmol Soc* 1989;87: 174-184.

13. Rosenbaum AL, Kushner BJ, Kirschen D. Vertical rectus muscle transposition and botulinum toxin to medial rectus for abducens palsy. *Arch Ophthalmol* 1989;107:820-831.

14. McNeer KW, Tucker MG, Spencer RF. Management of essential infantile esotropia with botulinum toxin A: review and recommendations. *J Pediatr Ophthalmol Strabismus* 2000;37:63-67.

15. Harada M, Ito Y. Surgical correction of cyclotropia. *Jpn J Ophthalmol* 1964;8:88-93.

16. Wright KW. Superior oblique silicone expander for Brown's syndrome and superior oblique overaction. *J Pediatr Ophthalmol Strabismus* 1991;28:101-107.

17. Suh DW, Guyton DL, Hunter DG. An adjustable superior oblique tendon spacer with use of nonabsorbable suture. *J AAPOS* 2001; 5:164-171.

18. Stager DR, Parks MM. Inferior oblique weakening procedures. Effect on primary position horizontal alignment. *Arch Ophthalmol* 1973;90:15-16.

19. Elliott RL, Nankin SJ. Anterior transposition of the inferior oblique. *J Pediatr Ophthalmol Strabismus* 1981;18:35.

20. Kushner BJ. Restriction of elevation in abduction after inferior oblique anteriorization. *J Am Assoc Pediatr Ophthalmol Strabismus* 1997;1:55.

21. Foster RS. Vertical muscle transposition augmented with lateral fixation. *J AAPOS* 1997;1:20-30.

22. Brooks SE, Olitsky SE, deB Ribeiro G. Augmented Hummelsheim procedure for paralytic strabismus. *J Pediatr Ophthalmol Strabismus* 2000;37:189-195.

23. Plager DA, Parks MM. Recognition and repair of the slipped rectus muscle. *J Pediatr Ophthalmol Strabismus* 1988;25:270-274.

24. Plager DA, Parks MM. Recognition and repair of the “lost” rectus muscle. *Ophthalmology* 1990;97:131-137.

25. Demer JL, Miller JM. Orbital imaging in strabismus surgery. In: Rosenbaum AL, Santiago AP, eds. *Clinical strabismus management*. Philadelphia: WB Saunders, 1999:84-98.

26. Caputo AR, Wagner RS. Anterior segment ischemia following strabismus surgery. In: Harley RD, ed. *Pediatric ophthalmology*, 2nd ed, vol 1. Philadelphia: WB Saunders, 1983:272-275.

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11

Conjunctival Diseases

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Although at first glance the conjunctiva is a seemingly minor contributor to ocular function, nothing could be further from the truth. This resilient “mucous membrane” ensures that our visual organs can be exposed to environmental stress and still function. This chapter reviews the anatomy, physiology, pathophysiology, and treatment of this versatile tissue.

EMBRYOLOGY, STRUCTURE, AND FUNCTION

Following neural fold closure, the superficial ectoderm of the early embryonic disc goes on to become skin, conjunctiva, corneal epithelium, cilia, glands, lacrimal glands, and the nasolacrimal system. By the third month of gestation, differentiation forms the rudimentary fused eyelids and adnexa. While the lids are fused, a bud of surface ectoderm originating from the lower lid forms the early caruncle that continues to evolve even after birth (1). During the sixth or seventh month of gestation, the eyelids are separated. Keratinization of the epithelium and meibomian gland development/secretion contribute to the separation of the eyelids.

The conjunctiva is a translucent vascular mucous membrane that is rich in immune components. Being firmly attached to the eyelid along the tarsus (palpebral) starting at the mucocutaneous junction and terminating 1 mm anterior of the corneal limbus (bulbar), the conjunctiva forms a sac with its contours, creating the fornices on the superior, inferior, and lateral boundaries. Medially the conjunctiva ends in the caruncle, which contains both skin and conjunctival elements. Tenon's capsule inserts into the bulbar conjunctiva and separates the conjunctiva from underlying tissues. Therefore, the bulbar and forniceal conjunctiva is only loosely attached to the posterior structures, including the levator and rectus muscle fascial tendon sheaths, allowing the motion of tissue upon eye and eyelid movement. The conjunctiva is also attached to the lower eyelid retractor muscles inferiorly and levator aponeurosis and Muller's muscle superiorly. These attachments, in addition to the connections with the canthal ligaments, trochlea, and lacrimal gland, maintain the “suspensory apparatus” (2).

On a cellular level the conjunctiva is made up of nonkeratinized, stratified columnar epithelium atop the highly vascular connective tissue, the substantia propria. The columnar cells transition to stratified squamous epithelium continuous with the corneal epithelium (3). Goblet cells populate the conjunctiva in an inferonasal preponderance and are found in greater numbers in children. Limbal stem cells and mucocutaneous junction cells go on to form the bulbar and palpebral epithelial cells. In disease states, absence or damage of the limbal stem cells, conjunctival epithelium may grow onto the cornea.

Mucin, aqueous, and outer lipid layers comprise the tear film. Conjunctival goblet cells produce the mucopolysaccharides that, along with vesicles from the palpebral epithelial cells, form the mucous layer of the tear film (4). The lacrimal and accessory lacrimal gland ducts open to the conjunctival surface and produce the aqueous layer with its multitude of immune factors. The outer lipid layer is produced by the meibomian glands and Zeis' glands. The lipid layer of the tear film is thicker in infants than in adults, with a longer tear breakup time (5). The proportion and interaction of these components create the stability of the tear film.

The conjunctiva protects the eye from pathogens by acting as a physical barrier and contributing immune components into the tear film. The immunological function occurs in all layers of the conjunctiva: the superficial epithelial goblet cells creating immune protective mucin, the deeper epithelial basal layer infused with Langerhans' cells, and the substantia propria containing mast cells, plasma cells, and neutrophils. The temporal lymphatic vessels transport lymph to the superficial parotid nodes while the nasal vessels drain into the submandibular nodes.

Bulbar innervation is derived from the ophthalmic division of the trigeminal nerve via the long ciliary nerves, branches of the nasociliary nerve. Superior palpebral and forniceal innervation is from the frontal and lacrimal branches of the ophthalmic division of the trigeminal nerve. Inferior palpebral and forniceal innervation is from the lacrimal branch of the ophthalmic division of the trigeminal

nerve laterally and from the infraorbital nerve in the maxillary division of the trigeminal nerve.

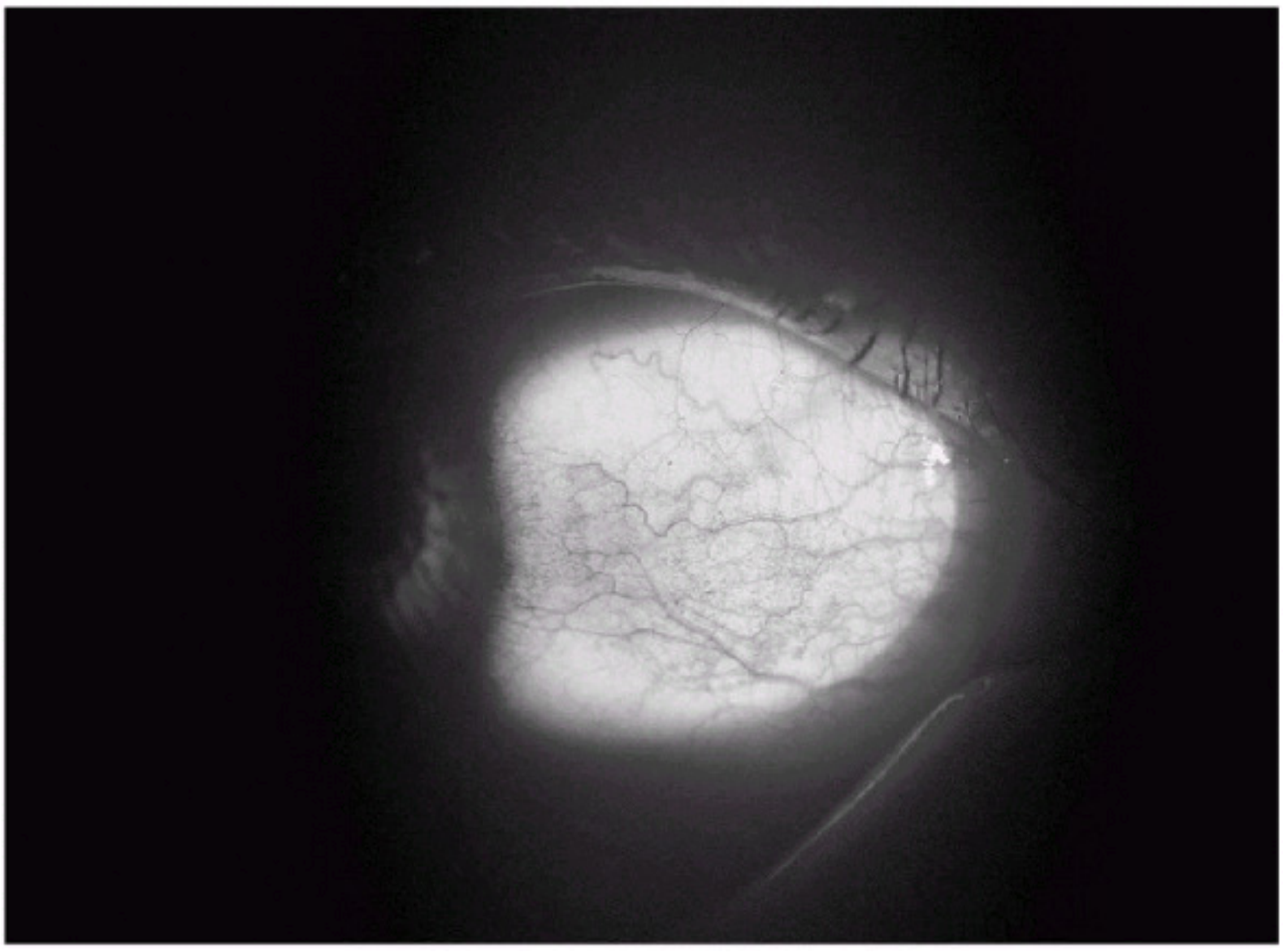

Figure 11.1 Kerato-conjunctivitis sicca Rose Bengal stain.

The bulbar conjunctiva thins with age and loses elasticity. Tenon's capsule also thins with age. The posterior conjunctival arteries are smaller and less tortuous in childhood. The combination of thinner, straighter blood vessels and a thicker Tenon's capsule create the whiter appearance of young conjunctiva.

Several histopathological or clinical stains are used on a routine basis to examine the conjunctiva. Scrapings are performed by cleaning the conjunctival sac with sterile saline before applying topical anesthesia. A flat spatula is scraped in the sac three times to obtain both bulbar and palpebral cells for slide plating. Impression cytology harvests superficial conjunctival cells by pressing cellulose acetate filter paper against the surface for a few seconds. The filter paper is then peeled away and processed onto a slide, which is fixed and stained. Fluorescein is employed routinely to diagnose and differentiate inflammatory states as well as grossly quantitate the tear meniscus and breakup time. Rose bengal stain has been shown to stain damaged cells as well as cells with deficient mucous coating (6). Lissamine green dye stains dead or damaged epithelial cells, producing less stinging sensation than rose bengal (see Color Plate I.A and Fig. 11.1).

PINGUECULA AND PTERYGIUM

Unlike adults, pinguecula and pterygium are rare in childhood. The same solar and arid risk factors produce basophilic degeneration of the conjunctival substantia propria. There is a marked decrease in elastin fibrils in these tissues (7). Invasion of the cornea associated with Bowman's layer destruction by a triangular area of bulbar conjunctiva (pterygium) can disrupt the tear film by creating an area of local drying on the cornea or dellen. Pterygia have increased numbers of mast cells (7). Pseudopterygia, which are usually not firmly adherent to the underlying tissue, can occur following corneal surgery or an inflammatory condition. Removal can be accomplished, as in adults, although recurrence is common. Because these are relatively uncommon in children, consideration should be given to masquerade diagnoses (Fig. 11.2).

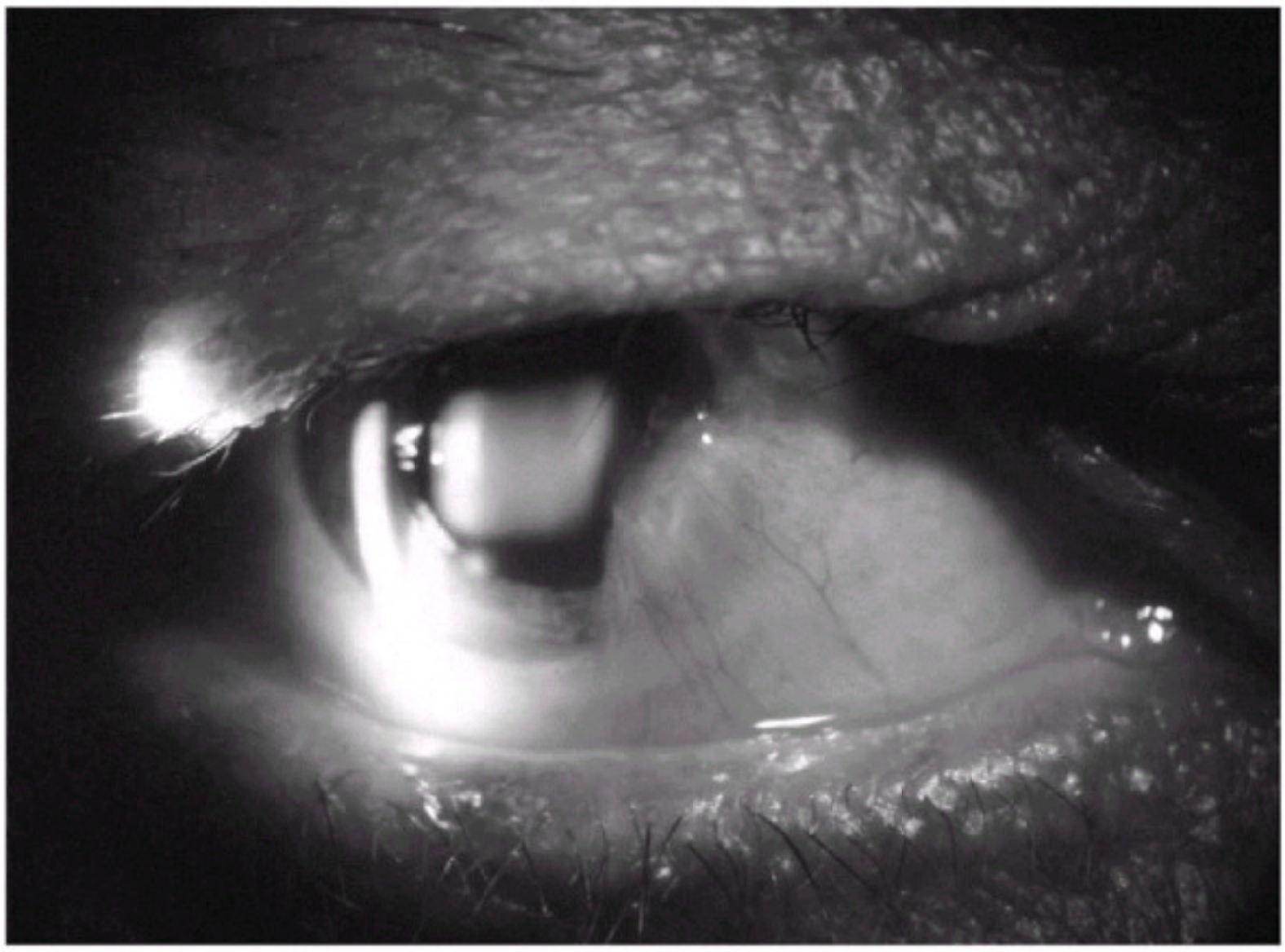

Figure 11.2 Pterygium.

PIGMENTED LESIONS

Nevi

Nevi are pigmented lesions classified like those of the skin: intraepithelial (junctional), subepithelial, compound (intraepithelial plus subepithelial), blue, and cellular blue (rarely seen in conjunctiva) (8). In adults, most conjunctival nevi are compound or subepithelial. Only in children are the pure intraepithelial (junctional) type observed (9).

Histologically, especially in young individuals, great cytologic pleomorphism can be present in conjunctival nevi. A junctional nevus may be indistinguishable from primary acquired melanosis with atypia, a condition of elderly individuals that has a tendency to evolve into melanoma. Large spindle or epithelioid-shaped melanocytes characteristic of Spitz nevi may mimic melanoma (10). Inclusions of conjunctival epithelium in the form of solid islands or cysts are usually observed (11). During puberty, several changes can occur in the conjunctival nevi: the melanocytes may proliferate or increase in pigmentation, and the epithelial cells within the inclusions may proliferate and secrete material, causing enlargement of the cysts. As the nevus becomes more prominent, it can cause irritation and inflammation. The inflammatory cell infiltrate can further increase the size, elevation, and vascularity of the nevus. These alterations tend to provoke concern that a malignant melanoma has arisen from the nevus, resulting in excision of a large number of benign conjunctival nevi (8).

Nevus pigmentation is variable, with some devoid of pigment or amelanotic, requiring differentiation from other epithelial lesions (see Color Plate I.B). Occasionally, an inflamed nevus may become vascular and be mistaken for an angiomatous tumor (11).

Melanosis

Melanosis describes excessive melanotic pigmentation in the absence of a mass causing elevation of the conjunctiva that is typical of a nevus. Melanosis can be at the level of the conjunctiva or deeper in the sclera, choroid, or periocular tissues.

Epithelial congenital melanosis is a stationary lesion present at birth or early childhood. It is characterized by melanocytes and excessive melanin mainly in the basal layers of the conjunctival epithelium. It is not a precursor of malignant melanoma (8). Technically, the subepithelial congenital melanosis is not a lesion of the conjunctiva, because the abnormal melanocytes are found in the sclera and episclera. It has two forms: (a) “ocular melanosis,” affecting ocular tissues only, and (b) “oculodermal melanosis,” or nevus of Ota, associated with ipsilateral melanosis of the lids or periocular facial skin. Most of the cases are unilateral and ipsilateral iris hyperpigmentation can be observed (12). It is more frequently seen in Asians and African descendants than in Caucasians (13,14) and may also be associated with melanosis of the orbital tissues and the meninges (9). Histologically, nevus of Ota is characterized by a congenital increase in the number, size, and pigmentation of the melanocytes of the uvea associated with increased numbers of pigmented melanocytes in the sclera, episclera, and dermis of the eyelids. Subepithelial congenital melanosis predisposes to the development of malignant melanoma (15,16). Children with oculodermal melanosis should be examined periodically because of a risk of pigmentary glaucoma and melanoma (17). Patients with ocular melanosis may also benefit from surveillance of the intraocular pressure (18) (see Color Plate I.C and Fig. 11.3).

Some syndromes and diseases may present with pigmented conjunctival lesions during their course, such as: (a) chronic forms of Gaucher's disease; (b) alkaptonuria, in which the pigmentation can be seen over the horizontal recti insertion; (c) Kartagener's syndrome, with characteristically marked conjunctival melanosis and hypertropia of the plica semilunaris; and (d) Peutz-Jegher's syndrome, in which freckles can be seen over the conjunctiva, lids, and lips.

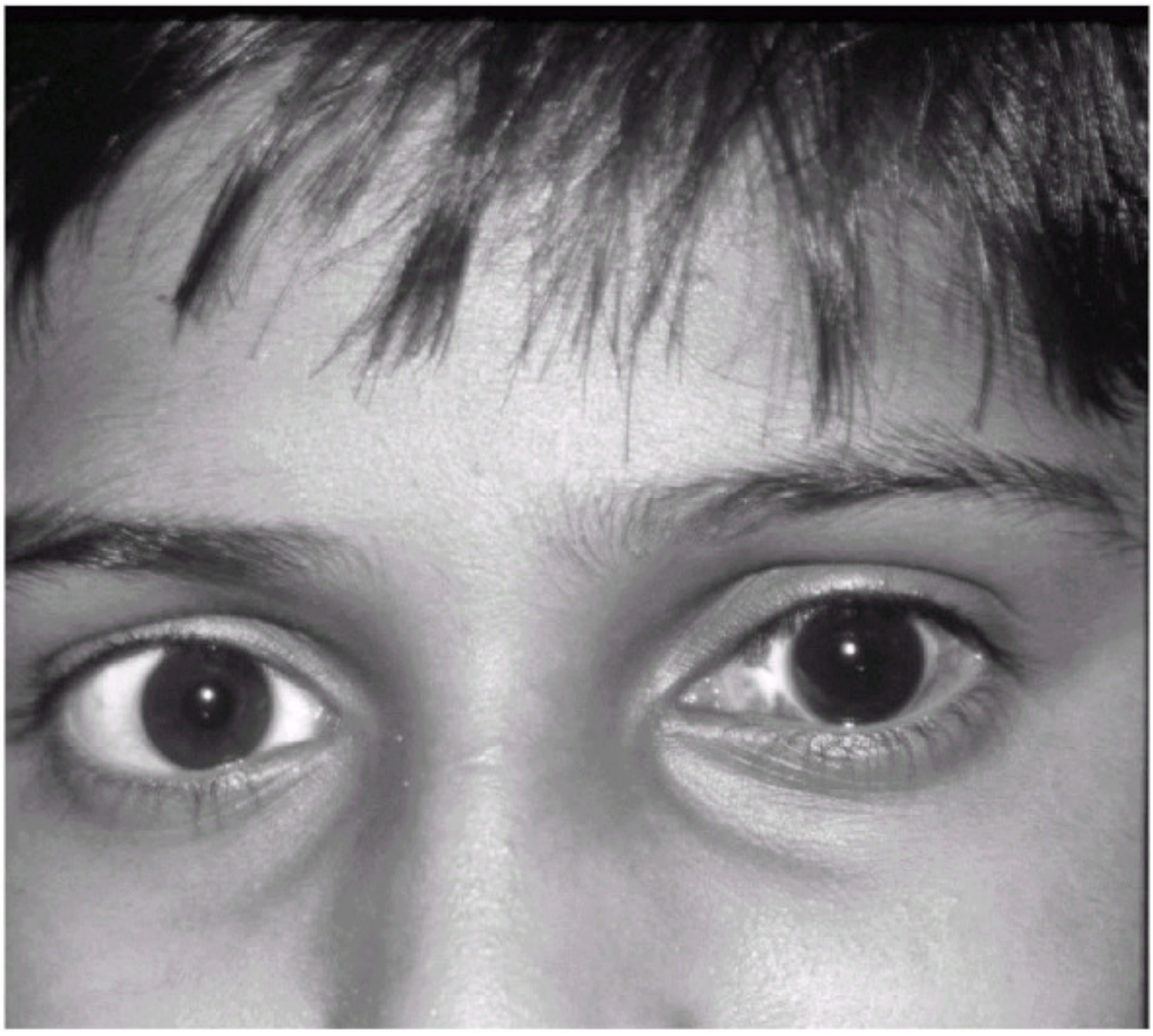

Figure 11.3 Ocular melanosis; congenital glaucoma.

Gaucher's Disease

Gaucher's disease, found most commonly among Ashkenazic Jews, is a hepatorenal syndrome caused by enzyme deficiency of glucocerebrosidase, and is characterized by pinguecula-like lesions, corneal epithelial deposits, vitreous deposits, paramacular ring, white retinal infiltrates, oculomotor apraxia, hepatosplenomegaly, pancytopenia secondary to hypersplenism, bone pain, and accumulation of glucocerebroside. The pinguecula-like lesions can often be differentiated by their tan coloring and histologically contain Gaucher's cells, enlarged lipid laden macrophages. These lesions usually appear during the teenage years. The gene locus has been found on Chromosome 1.

Alkaptonuria/Ochronosis

Alkaptonuria/ochronosis is a rare disorder of protein metabolism resulting in wasting of homogentisic acid in the urine. An enzyme deficiency of homogentisate-1,2-dioxygenase (ochronosis) results in the accumulation of homogentisic acid. The gene locus has been identified on chromosome 3q21-q23 and is inherited in an autosomal recessive fashion. This leads to pigment deposition in collagenous tissues. The manifestations are pigmented pinguecula, triangular scleral pigmentation near the horizontal rectus muscle insertions, episcleral pigment granules, oildroplet opacities in the limbal corneal epithelium and Bowman's layer, ochronotic arthropathy, ochronotic calculi in the genitourinary tract, and cardiovascular deposition, including calcification and stenosis in the aortic valve. Treatment is palliative.

Kartagener's Syndrome

Kartagener's syndrome was first described by Siewert in 1904 and later further characterized in the German literature by Kartagener in 1933. It is caused by mutations in the gene encoding the axonemal dynein intermediate chain. It is a rare syndrome associated with *situs inversus* (dextrocardia) and primary ciliary dyskinesia, leading to bronchiectasis and sinusitis. Conjunctival melanosis, hypertrophy of the semilunaris, myopia, and glaucoma have been described.

Peutz-Jegher's Syndrome

Peutz-Jegher's syndrome was initially described by Peutz, a Dutch internist, in 1921, as a familial syndrome. It is caused by mutations in the serine/threonine kinase STK11 gene chromosome locus 19p13.3. Peutz-Jegher's syndrome is characterized by periocular and perioral melanocytic epidermal lesions (freckle-like appearance) in association with gastrointestinal polyps, usually of the small intestine. The

macules present mainly on the lips and buccal mucosa but can appear on the palms, soles, and conjunctiva. The hyperpigmented macules precede the onset of gastrointestinal symptoms, including pain, bleeding, intussusception, and obstruction.

TUMORS AND INFILTRATES

Choristomas

Dermoids are the most common choristomas, lesions composed of tissue not normally found in the affected area. These solid, placoid tumors arise from the outer third of the sclera and often contain hair follicles, sebaceous glands, sweat glands, and fat lobules. Commonly occurring at the inferotemporal limbus, they appear as yellowish-white rounded elevations that are sometimes pigmented. Most dermoids do not cause any discomfort but may produce significant astigmatism with secondary amblyopia. Ocular irritation may result from poor lid closure, tear film anomaly, or trauma from the fine hair that may grow from the surface of these lesions. Dermolipomas are more posterior and are associated with a large amount of fatty tissue. Usually, they arise near the insertion of the lateral rectus and are firmly fixed to the underlying sclera. Rarely, they can form symblepharon-type adhesions, causing restriction of eye movement.

Dermoids and dermolipomas may be present with other systemic malformations, including Goldenhar's syndrome (facio-auricular vertebral syndrome), mandibulofacial dysostosis (Treacher-Collins' syndrome, Franceschetti's syndrome), and band-like cutaneous nevus and central nervous system dysfunction (Solomon's syndrome, linear sebaceous nevus of Jadassohn). Both tend to grow with the patient and do not usually undergo neoplastic transformation.

Treatment is generally conservative. However, removal is indicated when significant astigmatism, with or without amblyopia, irritation, or cosmetic deformity, occurs. Lamellar excision is usually required because the outer third of the sclera is often involved. When the cornea is more involved, the surgeon should anticipate lamellar or penetrating keratoplasty. Complications of the excision include: globe penetration, restriction to motility from scarring or injury of the associated rectus muscle, and increased astigmatism.

Other choristomas include: ectopic lacrimal gland, simple and composed choristoma, and osseous choristoma. Ectopic lacrimal gland is the second most common choristoma affecting the epibulbar surface. Osseous choristomas are stationary lesions that resemble conjunctival dermoids; histologically, however, they are composed of mature compact bone surrounded by other choristomatous elements (19,20).

Hamartomas

Hamartomas are lesions composed of tissue found normally in the affected area. Neurofibromas are solid nodular lesions affecting the bulbar or palpebral conjunctiva. They can be plexiform, solitary, or diffuse type and are almost always associated with neurofibromatosis type 1 or type 2.

Fibrous hamartomas are epibulbar lesions that contain abundant mature elastic fibers intermixed with fibrous tissue. They may be seen in patients with Proteus syndrome, a rare syndrome characterized by asymmetrical overgrowth that can affect any structure (bones, skin, viscera) and is generally progressive throughout childhood.

Another hamartomatous lesion that affects the conjunctiva is hemorrhagic lymphangiectasia. These lesions are irregularly dilated lymphatic channels of the bulbar conjunctiva that may sometimes be filled with blood. They may arise as a developmental anomaly or in association with trauma or inflammation (19,20).

Conjunctival Cysts

Conjunctival cysts are stable lesions that can be congenital or acquired. A common cause of acquired conjunctival inclusion cysts is the implantation of conjunctival epithelium islands after surgery or trauma. They may disappear spontaneously, but persistent cases often require surgical excision or diathermy (19).

Pyogenic Granuloma

Pyogenic granuloma is a vasoproliferative inflammatory response composed of granulation tissue. The term “pyogenic granuloma” is a misnomer. The lesion neither causes pus formation nor is a true granuloma. The pathogenesis is not well understood, but they can develop rapidly and are often associated with previous ocular and adnexal surgery, inflammation, foreign bodies, chemical burns, or phthisis bulbi. Spontaneus involution can occur or, if necessary, simple excisional biopsy with cautery of the base can be both diagnostic and curative (19) (Figs. 11.4 and 11.5).

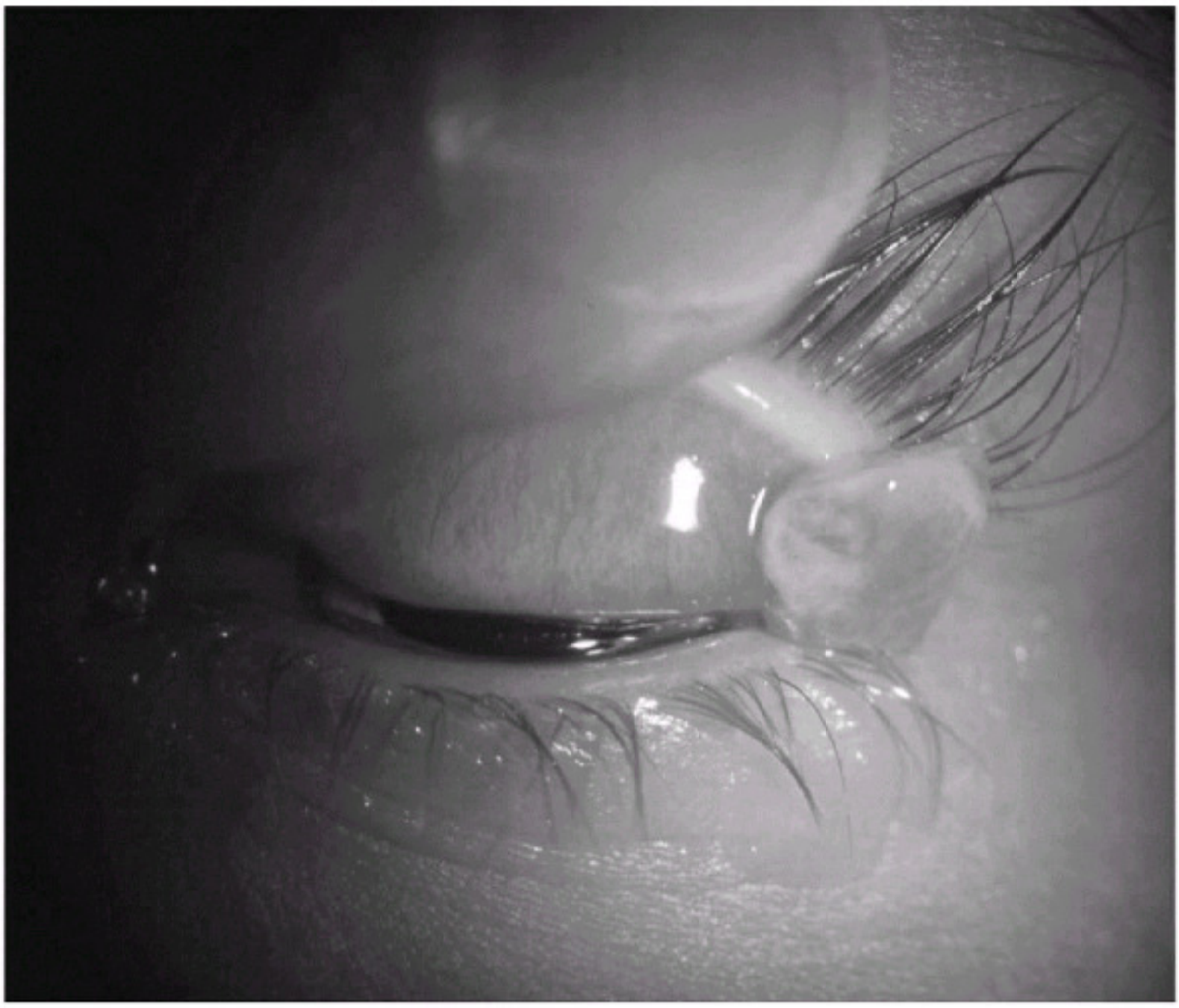

Figure 11.4 Pyogenic granuloma.

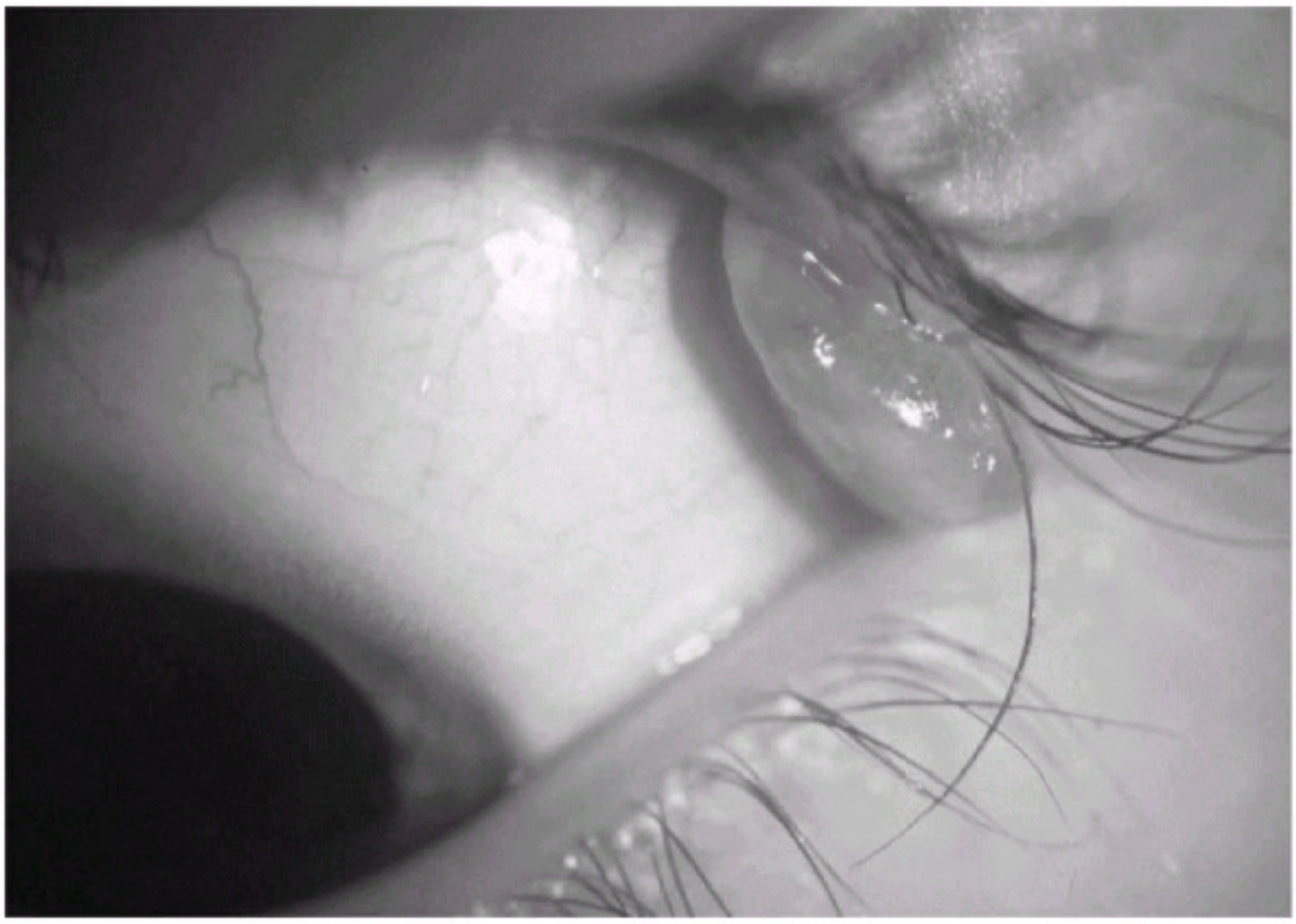

Figure 11.5 Pyogenic granuloma.

Xeroderma Pigmentosa Syndrome

This disease is a rare autosomal recessive disorder that manifests as an inability to repair deoxyribonucleic acid (DNA) damage induced by ultraviolet (UV) radiation. Clinically, this syndrome is characterized by the early development of pigmentary changes, atrophy, keratoses, and skin malignancies (carcinomas, melanomas, sarcomas, angiosarcomas, neuromas), predominantly on light-exposed skin. Some patients may present with recurrent conjunctivitis, dry eyes with areas of pigment deposition and keratin formation, as well as squamous cell carcinomas of the conjunctiva. The syndrome is sometimes associated with slowly progressive neurological abnormalities that include deafness, ataxia, mental retardation, and cerebellar atrophy (21). Most patients die of malignancy before age 20 (22). Treatment is avoidance of sunlight and UV exposure by use of sunblock and 100% UV-barrier spectacles with sidearms (20).

Benign Hereditary Epithelial Dyskeratosis

This is a rare disorder that affects primarily members of the Haliwa Indians (Halifax and Washington counties of North Carolina). It is an autosomal dominant disorder with high penetrance characterized by bilateral elevated plaques in the exposed areas of the conjunctiva. Benign hereditary epithelial dyskeratosis has a chronic course of ocular irritation/photophobia and may be associated with dyskeratosis of the oral mucosa. Histologically, the lesions show epithelial acanthosis, parakeratosis, and dyskeratosis, with the stroma usually containing chronic inflammatory cells. Atypia is absent, and there is no dysplastic potential. Treatment of choice is excision of the lesions, although the recurrence rate is high (19,20).

VASCULAR ABNORMALITIES

Hemangiomas are lesions composed predominantly of blood vessels and may occur as isolated lesions or in association with lid, orbital, or intracranial lesions. Clinically, they appear as red masses on the conjunctival surface and blanch on pressure. Spontaneous hemorrhage is not infrequent and may occur after trivial trauma. Surgical excision is difficult, and recurrences may occur.

Lymphangiomas are usually widespread, occasionally affecting an entire hemiface. Clinically, these lesions show clear fluid-filled cystic areas among the blood-filled hemangioma tissue. Surgical excision is difficult due to the diffuse nature of the lesions (20).

Several syndromes can have conjunctival vascular abnormalities among their features. The characteristic feature of Sturge-Weber syndrome is a cutaneous hemangioma, commonly in a trigeminal facial distribution, with the conjunctiva showing only a faint blush on the normal whiteness of the conjunctiva. Klippel-Trenaunay-Weber syndrome, a widespread vascular anomaly causing limb hypertrophy and vascular anomalies of skin, may also have conjunctival angiomas. Conjunctival vascular malformations may be seen associated with racemose angiomatous malformation of the retina in Wyburn-Mason syndrome. Louis-Bar syndrome is an autosomal recessive disorder that presents with a progressive ataxia and degeneration of central nervous system function (choreoathetosis, dysrhythmic speech, aberrant ocular movements and occasional seizures) and presence of extremely tortuous and telangiectatic conjunctival vessels without an associated lymphatic component in exposed areas of conjunctiva and skin. In Rendu-Osler-Weber syndrome, conjunctival telangiectases may be seen along with retinal vascular malformation (20).

CONJUNCTIVITIS OF THE NEWBORN

Neonatal conjunctivitis is inflammation of the conjunctiva that affects infants during the first month after birth. It is usually a hyperacute papillary conjunctivitis, because a follicular response is not seen before 6 to 8 weeks of life (23).

The period of time after birth until the onset of the conjunctivitis is variable, but it may be helpful in suggesting the cause by correlating it to the incubation time of the possible etiologic agents.

When the conjunctivitis affects the baby in the first few days after birth, the probable cause is the toxic effect of the prophylactic agent used at birth. It is

characterized by mild and transient conjunctival injection and tearing, which usually resolves in 24 to 48 hours.

Conjunctivitis due to *Neisseria gonorrhoeae* typically appears 2 to 5 days after birth. It is still common in developing countries but rare in the most industrialized countries. Clinically, it starts with a serosanguineous discharge that rapidly progresses to a thick purulent discharge associated with markedly edematous eyelids and chemosis. Conjunctival membranes may be seen. This bacteria has the propensity to produce a severe keratitis because of its ability to penetrate intact epithelial cells and replicate rapidly. A delay in diagnosis and treatment may lead to corneal ulceration and perforation.

Historically, the latent period for bacterial conjunctivitis,

other than *N. gonorrhoeae* has been 5 to 8 days after birth, but it can occur any time in the immediate postpartum period. Etiologic agents include: *Haemophilus sp., Streptococcus pneumoniae, Staphylococcus aureus* and, rarely, *Pseudomonas aeruginosa*. Although rare, this bacteria can rapidly progress from conjunctivitis to corneal ulceration and perforation. If *Pseudomonas* is not recognized as the etiologic agent, the conjunctival infection may lead to endophthalmitis and possible death.

Neonatal inclusion conjunctivitis caused by *Chlamydia trachomatis* serotype D-K represent the most common isolated pathogens in newborns with conjunctivitis in industrialized countries. The incubation period ranges from 5 to 14 days. Clinically, one sees a mild mucopurulent conjunctivitis associated with moderate lid swelling and mild chemosis typically beginning as unilateral but often becoming bilateral. Although generally considered benign and self-limited with spontaneous resolution in 8 to 12 months, if untreated it may result in the formation of a micropannus and scarring of the tarsal conjunctiva. Systemic spread of this ocular infection can cause disease involving the pharynx, lungs, and/or rectum, which can be fatal. The systemic potential of this disease dictates the need for systemic treatment.

Viral neonatal conjunctivitis caused by Herpes simplex virus (HSV) typically occurs within 6 to 14 days after birth. Although 80% of the babies affected with HSV have typical herpetic lesions on the skin, eyelids, or mouth, without these lesions the conjunctivitis is indistinguishable from other causes of neonatal conjunctivitis. Signs of corneal involvement include microdendrites or geographical ulcers. Herpetic keratoconjunctivitis is frequently associated with systemic infection, with mortality rates of disseminated disease around 50%.

A less frequent cause of neonatal conjunctivitis is *Candida albicans*. It presents as a pseudomembranous conjunctivitis, with the average time of onset of 5 days after exposure.

Congenital nasolacrimal duct obstruction is also frequently associated with conjunctivitis of the newborn typically caused by *Haemophilus sp*. and *S. pneumoniae*.

Clinically, these differentiation among the various etiologies can be difficult. However, because of the potentially serious complications of an improperly treated conjunctivitis, determination of the causative agent is mandatory at this age. Conjunctival smears and appropriate cultures should be done in all patients. Scrapings of the conjunctiva should be collected with a spatula and cultures obtained with a calcium-alginate swab, prewetted with sterile liquid culture media. Gram and Giemsa stains should be performed on the conjunctival scraping. Giemsa stain in chemical conjunctivitis shows neutrophils with occasional lymphocytes; in chlamydial infection, neutrophils, lymphocytes, plasma cells, and basophilic intracytoplasmic inclusions in epithelial cells; in viral conjunctivitis, lymphocytes, plasma cells, multinucleated giant cells and eosinophilic intranuclear inclusions; in fungal infections, neutrophils, and pseudohyphal budding yeast formation; and in bacterial infections, neutrophils, and bacteria. Certain bacteria can be identified on Gram stain. Gram-negative diplococci with polymorphonuclear leucocytes suggest gonococcal infection; Gram-negative coccobacilli correlate with *Haemophilus sp.*; Gram-positive cocci suggest *S. aureus* and *S. pneumoniae*. Recommended medias for culture include: reduced blood agar, thioglycolate, brain-heart infusion broth for aerobic bacteria; chocolate agar in CO_2 or Thayer-Martin for *N. gonorrhoeae;* Sabouraud's slant for fungus. McCoy cell culture has been the standard for diagnosing *C. trachomatis* in the past, but this technique is expensive and requires at least 2 to 3 days for results. Polymerase chain reaction (PCR) analysis and direct immunofluorescent monoclonal antibody stain (DFA) have comparable specificity with higher sensitivities and faster results than traditional culture testing. Viral cultures are expensive and take 2 to 4 days to grow. Viral antigens can be detected rapidly, using immunological tests, such as direct immunofluorescent testing, enzyme-linked immunosorbent assay (ELISA), and immunofiltration method.

Treatment is not required for chemical conjunctivitis caused by prophylactic agents, which typically resolves spontaneously in 24 to 48 hours. According to the World Health Organization (WHO) guidelines, all cases of conjunctivitis in the newborn should be treated for both *N. gonorrhoeae* and *C. trachomatis* because of the possibility of mixed infection.

The treatment of the *N. gonorrhoeae* conjunctivitis consists of intravenous Penicillin G 100,000 units/kg/day for 7 days. *N. gonorrhoeae* resistant to penicillin is found in many urban areas in the United States and worldwide. In this case, the conjunctivitis should be treated with a thirdgeneration cephalosporin. A single intramuscular dose of ceftriaxone 125 mg is highly effective and is the recommended treatment by WHO guidelines (24,25,26). Intravenous or intramuscular cefotaxime 25 mg/kg every 8 to 12 hours is also effective. In addition to antibiotics, hourly irrigation of the eyes of the infant with gonococcal conjunctivitis with saline is recommended to decrease the intracorneal sequelae. Most ophthalmologists will supplement with topical antibiotic therapy.

Nongonococcal, nonchlamydial bacterial conjunctivitis should be treated with broad-spectrum topical antibiotics. Gram-positive cocci are appropriately treated with tetracycline 1% or erythromycin 0.5% ointment every 4 hours for 7 days. Gram-negative bacilli may be treated with tobramycin 0.3% or ciprofloxacin 0.3% ointment every 4 hours for 7 days (27).

The WHO and American Academy of Pediatrics recommend erythromycin syrup, 50 mg/kg/day orally, in 4 divided doses for 14 days, as treatment for neonatal chlamydial conjunctivitis (28). Although there is no evidence that additional therapy with a topical agent provides further benefit, erythromycin 0.5% ointment 4 times a day is often added. If inclusion conjunctivitis recurs after therapy has been completed, erythromycin treatment should be reinstituted for 2 weeks. Oral erythromycin also treats chlamydial pneumonitis and eradicates nasopharyngeal colonization, which occurs in over 50% of infants with neonatal chlamydial conjunctivitis.

All suspected herpetic simplex infections should be treated with systemic acyclovir or vidarabine to reduce the chance of a systemic infection. An effective acyclovir dose is 30 mg/kg/day, intravenous, divided in 3 doses for 14

days, but higher doses may also be used (45-60 mg/kg/day). Infants with HSV keratoconjunctivitis should also receive a topical drug, trifluorothymidine 1% drops or vidarabine 3% ointment for 7 days, or until the cornea has reepithelialized.

Although rare, fungal infection may occur. Treatment should be with natamycin 5% drops or flucytosine 1% drops hourly for 10 to 14 days.

Neonatal conjunctivitis has been a major health problem in many parts of the world for centuries. At the end of the 19th century in Europe, for example, the prevalence of *Ophthalmia neonatorum* among live births in maternity hospitals exceeded 10%, producing corneal damage in 20% and blindness in approximately 3% of affected infants (29). For this reason, ocular prophylaxis is mandatory and widely accepted. Eye prophylaxis involves cleaning the eyes immediately after birth and applying drops or ointment within the first hour of birth. This prophylaxis should be directed primarily against gonococcal ophthalmia because this agent poses the greatest risk of eye injury. The three most frequently applied agents are erythromycin 0.5% ointment, 1% silver nitrate drops, and tetracycline 1% ointment (28). Prophylaxis with erythromycin has resulted in outbreaks of erythromycin-resistant staphylococcal conjunctivitis in neonates (30). Because the most dreaded pathogen of *O. neonatorum* is *N. gonorrhoeae,* the many reports of tetracycline resistance from such countries as the United Kingdom (31), the Netherlands (32), and the United States (33) are alarming. Tetracycline is thus no longer recommended as first-line therapy for gonococcal infections (34). *O. neonatorum* has occurred also after the use of silver nitrate (35,36). Isenberg et al, in 1994, showed that povidone-iodine 2.5% was more effective than silver nitrate or erythromycin against the conjunctival bacteria found in 100 healthy newborns and was less toxic than silver nitrate. It is also active against viruses, at least in vitro, including herpes simplex (37). In another report, Isenberg et al (38) showed that erythromycin and silver nitrate were not superior to povidone-iodine against any other bacteria encountered in the study. Because of the broad spectrum and exceedingly low cost of povidone-iodine, this agent may become the most widely used for ocular prophylaxis in the future.

ACUTE CONJUNCTIVITIS

Conjunctivitis refers to any inflammatory condition of the conjunctival lining of the eyelids and the exposed surface of the sclera. It is the most common cause of “red or pink eye” and is characterized by cellular infiltration, exudation, and vascular dilation. Chemosis is frequently present. The etiology can usually be determined by a careful history and an ocular examination. Cultures or other diagnostic tests are occasionally necessary to establish the diagnosis or to guide therapy.

As a response to this inflammation, five morphological conjunctival responses can occur: papillary, follicular, membranous/pseudomembranous, cicatrizing, or granulomatous.

Papillae are a nonspecific sign of conjunctival inflammation resulting from edema and polymorphonuclear cell infiltration into the conjunctiva. They are characterized by projections of hypertrophic epithelium that contain a central fibrovascular core whose blood vessels arborize on reaching the surface. True papillae can form only where the conjunctiva is attached to the underlying tissue by anchoring septae, such as over the tarsus or the bulbar limbus. Giant papillae that develop from breakdown of the fine, fibrous strands that make up the anchoring septae are found most commonly in the upper tarsal conjunctiva (Fig. 11.6).

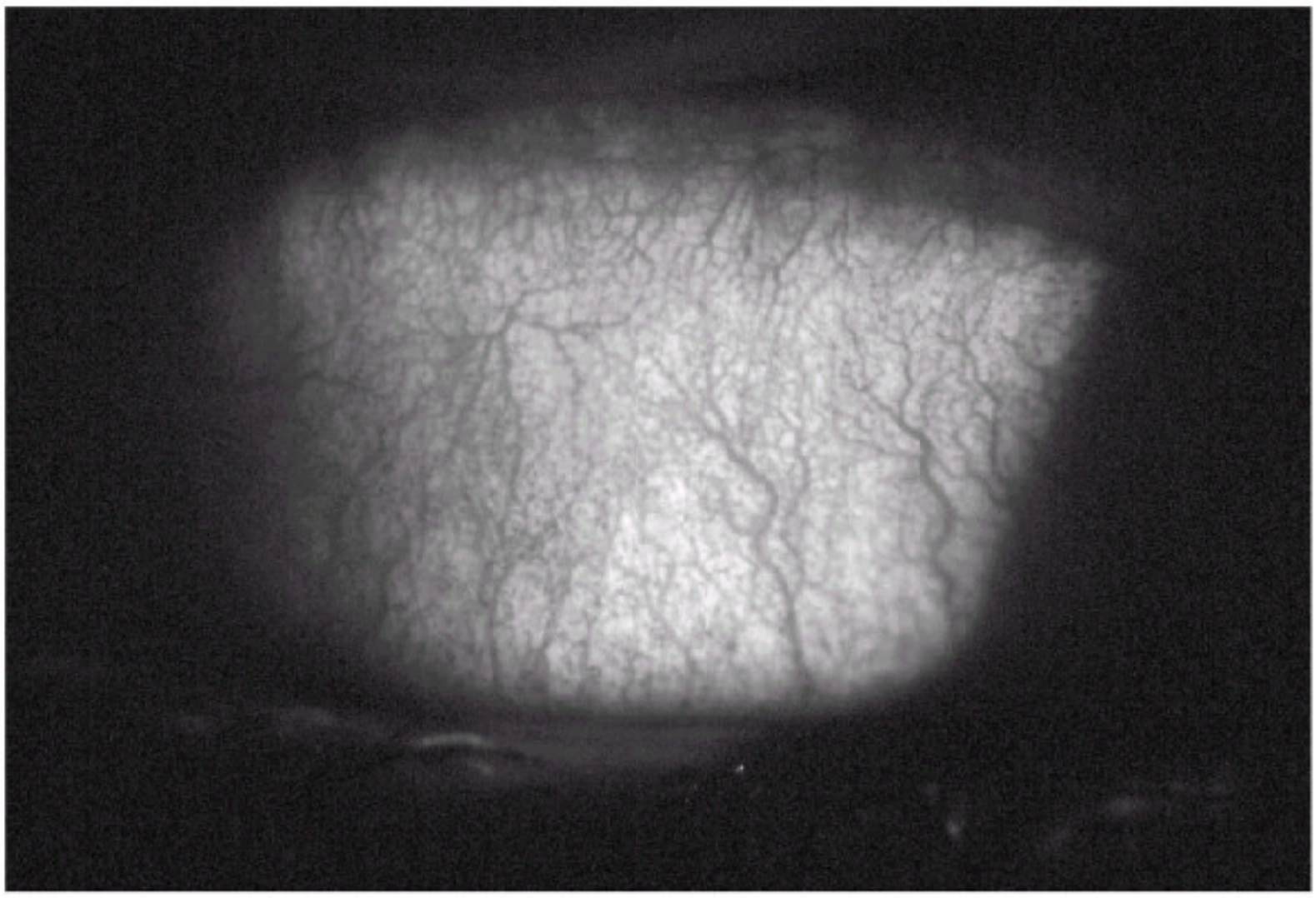

Figure 11.6 Papillae.

Follicles are discrete round elevations of the conjunctiva produced by a lymphocytic response. The central portion is avascular with blood vessels sweeping up over the convexity from the base. Follicles may be seen in normal conjunctiva, especially temporally in young patients.

Membranes are composed primarily of fibrin that coagulates on the epithelial surface. True membranes are adherent to the underlying epithelium and therefore cause bleeding when debrided. This characteristic differentiates them from nonbleeding pseudomembranes. True membranes represent more intense conjunctival inflammation and may lead to conjunctival scarring (Fig. 11.7).

Cicatricial changes occur only when there is destruction of the stromal tissue. An injury to the conjunctival epithelium

does not necessarily lead to scar formation. Cicatrization may cause shortening of the conjunctival fornix and subepithelial fibrosis. Subconjunctival scarring may cause complications, including symblepharon, cicatricial entropion, trichiasis; and in severe cases, obliteration of the conjunctival fornix, keratinization of the epithelium, and fusion of the eyelids (ankyloblepharon).

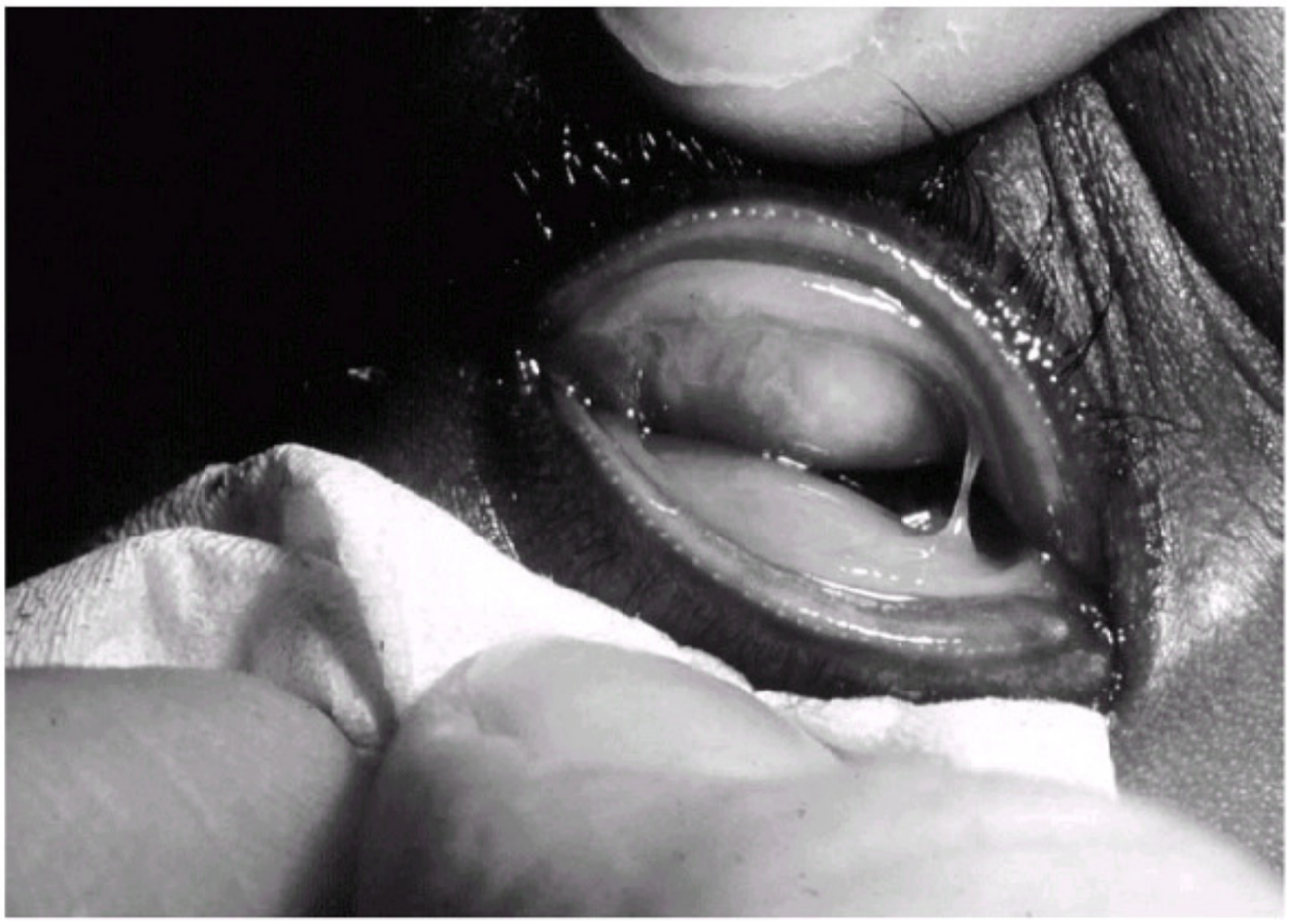

Figure 11.7 Membranous conjunctivitis in an infant.

Granulomas always affect the conjunctival stroma. They may be found in sarcoidosis, related to a retained foreign body or in Parinaud's oculoglandular syndrome.

Acute Papillary Conjunctivitis

Most cases of acute papillary conjunctivitis are bacterial in etiology.

N. gonorrhoeae and *Neisseria meningitidis* cause a hyperacute conjunctivitis, with a rapidly progressive course and purulent discharge. This starts usually as a unilateral disease but may rapidly affect the fellow eye. As noted earlier, these aggressive bacteria may also invade intact corneal epithelium and cause corneal ulceration that can lead to corneal perforation in untreated or poorly treated cases. *N. gonorrhoeae* occurs most often in sexually active patients but may be observed occasionally in young children who are the victims of sexual abuse. Rarely, *N. gonorrhoeae* may be transmitted innocently to toddlers who live in close contact with an infected adult (39). It has been suggested that unlike gonococcal infection at other locations, a nonsexual mode of transmission may exist in the eye (40). Although relatively rare, conjunctivitis by *N. meningitidis* has important implications because the conjunctiva is a potential portal of entry leading to meningococcemia and meningitis (41). Diagnosis with Gram stain and culture is mandatory because of the systemic implications. Gram stain will show gram-negative diplococci. Culture should be done in chocolate agar media with 4% to 8% CO_2 environment. These bacterial infections should be treated with topical and systemic antibiotics. When *N. gonorrhoeae* is isolated, parents of the child with conjunctivitis should be referred for evaluation and treatment. If *N. meningitidis* is identified, close contacts must be treated with a prophylactic oral antibiotic, such as rifampin.

Acute conjunctivitis, the most common ocular infection in childhood, usually affects children younger than 6 years with a peak incidence between 12 and 36 months. In children under age 2, nasolacrimal duct obstruction must be excluded to make a diagnosis of acute conjunctivitis. Pediatric acute conjunctivitis is diagnosed by clinical signs of purulent ocular discharge, matting of the lids, and/or hyperemia of the bulbar conjunctiva. The etiology of this infection has been documented as bacterial in most (up to 80%) pediatric cases (42,43). Acute conjunctivitis also has a rapid onset, less severe than the *Neisseria sp*. conjunctivitis. Bilateral disease is common with the second eye becoming affected within 1 week after the first symptoms appear. The most commom pathogens are *Haemophilus influenza, S. pneumoniae, S. aureus,* and anaerobic bacteria (44,45,46). Most of the cases are self-limited, and symptoms generally subside in about 14 days, even without treatment. Acute bacterial conjunctivitis is essentially a clinical diagnosis made by observation of signs and symptoms. However, clinical differentiation between bacterial and other causes of acute conjunctivitis can be difficult (44,47). Laboratory cultures are expensive, time-consuming and should usually be reserved for cases refractory to treatment, severe conjunctivitis, and cases suspected to be caused by *N. gonorrhoeae* and *N. meningitidis*. Treatment utilizing topical antibiotics with broad spectrum coverage and low toxicity is recommended. Treatment geared to the most rapid eradication of organisms should be used as first-line treatment, especially considering that bacterial conjunctivitis is usually first encountered by the primary care physician. Short courses of bacteriocidal broad spectrum antibiotics for bacterial conjunctivitis are unlikely to cause the formation of resistant organisms (Medical Letter, 2004). Moreover, shortening the course of a bacterial conjunctivitis decreases morbidity and allows prompt return to work for the parents and to school or daycare provisions for the child. By utilizing an antibiotic expected to work quickly, more worrisome diseases, like herpes, will be unmasked. Systemic antibiotics are rarely used for the treatment of uncomplicated acute conjunctivitis.

In 1982 Bodor (48) brought attention to a clinical syndrome characterized by the combination of conjunctivitis and otitis media: conjunctivitis-otitis media syndrome. This disease usually begins with a low grade fever and mild respiratory symptoms, including cough and mucopurulent nasal discharge. Simultaneous conjunctival and middle ear exudate cultures have shown concordance (49). *H. influenza* is the most commom pathogen, in up to 90% of cases, followed by *S. pneumoniae* (44,48,49,50,51). Treatment should first consist of systemic antibiotics, and topical therapy may be considered (51,52).

Acute Follicular Conjunctivitis

The most common causes of acute follicular conjunctivitis are viral infections. The early phase of chlamydial inclusion conjunctivitis and some topical medications may also present with the same clinical signs.

Adenovirus is by far the most common viral pathogen (44). Adenoviral eye infection can manifest itself in many forms ranging from conjunctivitis that is often self-limiting to keratitis, which can be prolonged. Disease severity similarly can be mild to severely disabling. The usual source of spread is via droplet,

person-to-person contact, contaminated ophthalmic instruments, or swimming water. The two most common forms of adenoviral infection are pharyngoconjunctival fever (PCF) and epidemic keratoconjunctivitis (EKC).

EKC is a highly contagious infection that is caused by adenovirus serotypes 8, 11, and 19. Clinical symptoms are typically seen 8 days after contact and include: rapid onset of watery discharge, injection of the conjunctiva, ocular discomfort associated with a foreign body sensation, and mild photophobia. Infection is often bilateral with involvement of the second eye 3 to 7 days after the first. In severe cases, petechial hemorrhages, pseudomembranes, and even true membranes may be present. Associated findings include lid edema and preauricular adenopathy. Conjunctivitis usually resolves in 10 to 14 days, but secondary corneal involvement may last weeks longer. Approximately 1 week

after onset, focal epithelial keratitis can coalesce into larger, coarse, epithelial infiltrates with irregular grey-white dots, eventually progressing to the subepithelial layers with increased photophobia and potentially decreased vision. The infiltrates, a delayed hypersensitivity reaction, gradually fade over weeks or months but can persist for years.

PCF is an acute follicular conjunctivitis associated with pharyngitis and fever. It is caused by adenovirus serotypes 3, 4, and 7 and affects children more than adults. Clinical symptoms are similar to those present in EKC. Membrane formation is unusual, and corneal involvement is limited to punctate keratitis. Subepithelial infiltrates are rare (see Color Plate I.D).

Treatment for EKC and PCF is palliative and may include compresses, lubrication, topical vasoconstrictors, and cycloplegic drops. Topical steroids are effective in relieving the signs and symptoms of the subepithelial infiltrates; however, the clinical result is probably the same, and weaning may be difficult. Most clinicians limit steroid use to patients who have marked visual changes or in those patients who are unable to perform normal activities. Clinical trials for the treatment of adenovirus conjunctivitis with cidofovir are underway (53,54). If effective, this would represent an advance in treating this pathogen, which produces significant ocular morbidity (55).

Many other viruses can cause an acute follicular conjunctivitis and include: Herpes simplex virus, Epstein-Barr virus, *Paramyxoviridae* (measles, mumps, Newcastle disease), *Picornaviridae* (enterovirus, Coxsackie virus), *Orthomyxoviridae* (influenza virus), *Togaviridae* (rubella, arbovirus), and *Poxviridae* (variola, vaccinia).

Acute conjunctivitis caused by HSV is frequently associated with periocular vesicular lesions. Primary HSV infection may include fever, upper respiratory symptoms, and a vesicular stomatitis or dermatitis. Within 2 weeks of onset, 50% of patients with primary HSV involving the lid margin will develop corneal epithelial manifestations ranging from fine punctate epithelial staining to dendritic ulcerations. The primary infection typically resolves without scarring. Treatment with vidarabine ointment 5 times a day to the conjunctival sac and eyelids should be used to speed resolution of the infection and prevent spread to the cornea. Neonates who develop primary HSV conjunctivitis should also receive intravenous treatment with vidaribine or acyclovir (56). Recurrent HSV ocular disease usually targets the cornea; however, recurrent conjunctivitis can occur in the absence of corneal disease (Figs. 11.8 and 11.9).

Figure 11.8 Herpes simplex virus of the eyelid, nasally infected, without affecting the cornea.

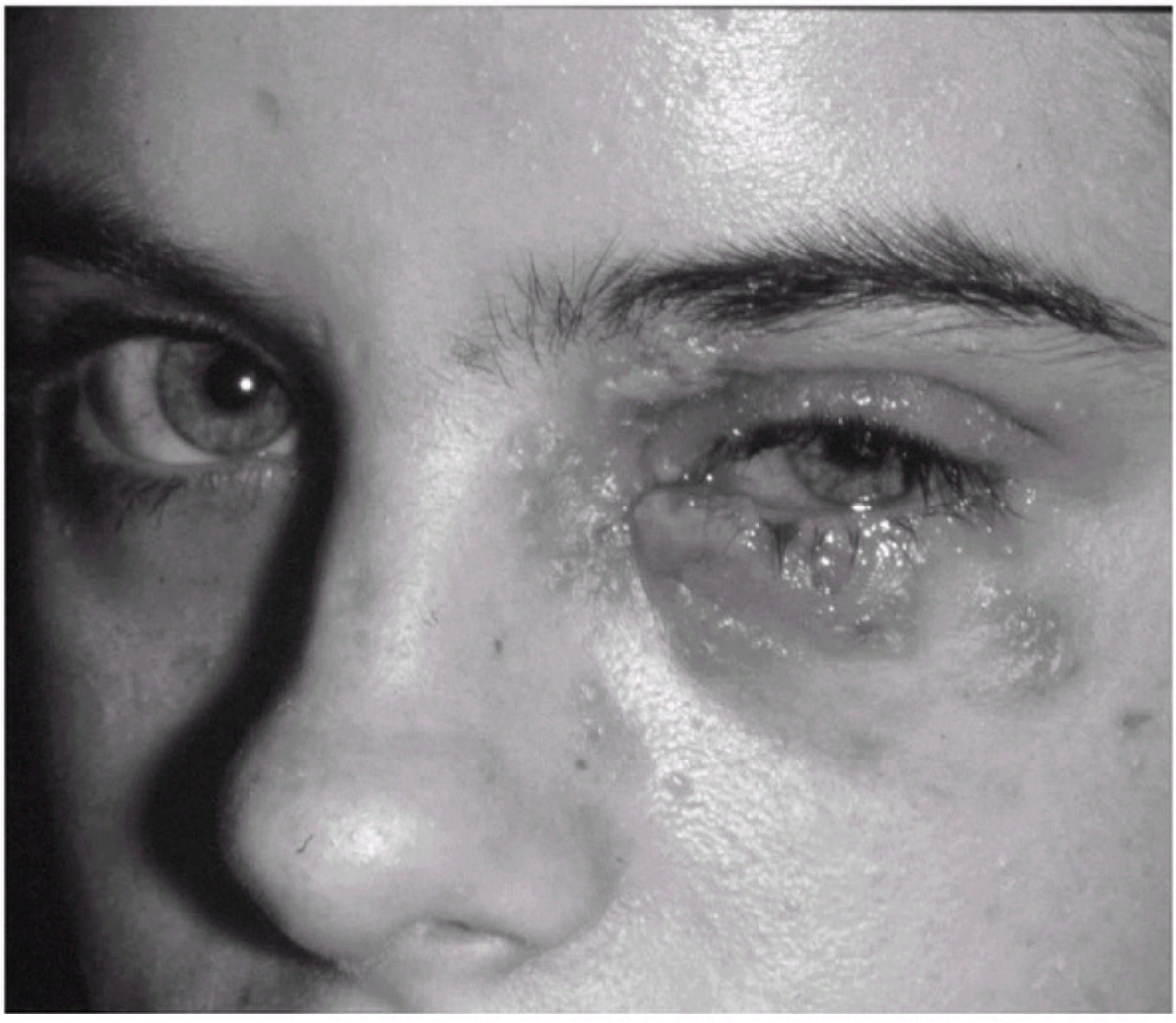

Figure 11.9 Herpes simplex virus involving upper and lower eyelid, sparing corneal involvement.

Inclusion conjunctivitis is caused by *C. trachomatis* serotypes D-K. It is a unilateral oculogenital disease that usually affects young, sexually active adults and is rarely transmitted through eye-to-eye contact. Incubation period ranges from 2 to 19 days, but an acute follicular conjunctivitis begins approximately 5 days after exposure. Fully developed follicles do not present until the second or third week of disease and become considerably larger and more opalescent than follicles seen in viral disease. Without treatment, the conjunctivitis can persist for months. Yellowishwhite subepithelial infiltrates may be seen in the peripheral cornea. Micropannus may develop at the superior limbus of the cornea, and a superficial punctate epithelial keratitis may be noted. Cultures or direct immunofluorescent antibody (DFA) stains are frequently needed to make a definitive diagnosis, and treatment should consist of systemic antibiotics (doxycycline 100 mg twice a day for 7 to 14 days, or one dose of azithromycin 1000 mg) (57,58,59).

CHRONIC CONJUNCTIVITIS

When the conjunctivitis has an indolent and prolonged course, it is classified as chronic disease. Onset is usually insidious and progression may also be slow. Symptoms are variable and include: foreign body sensation, conjunctival injection, minimal discharge, and loss of eyelashes (madarosis).

The most commonly isolated organism in chronic bacterial conjunctivitis is *S. aureus*. This bacteria causes a blepharoconjunctivitis with loss of eyelashes, trichiasis, and

hordeolum. The conjunctival inflammation may be the result of direct infection or release of toxins. The toxins produce the ulcerations surrounding the lash follicles on the eyelid margin and also produce a nonspecific conjunctivitis and superficial punctate keratitis. In severe cases, marginal corneal infiltrates and corneal ulcers may be seen. Symptoms are usually worse in the morning. Treatment includes mechanical cleansing of the eyelids, warm compresses, and topical antibiotics (60) (Figs. 11.10 and 11.11).

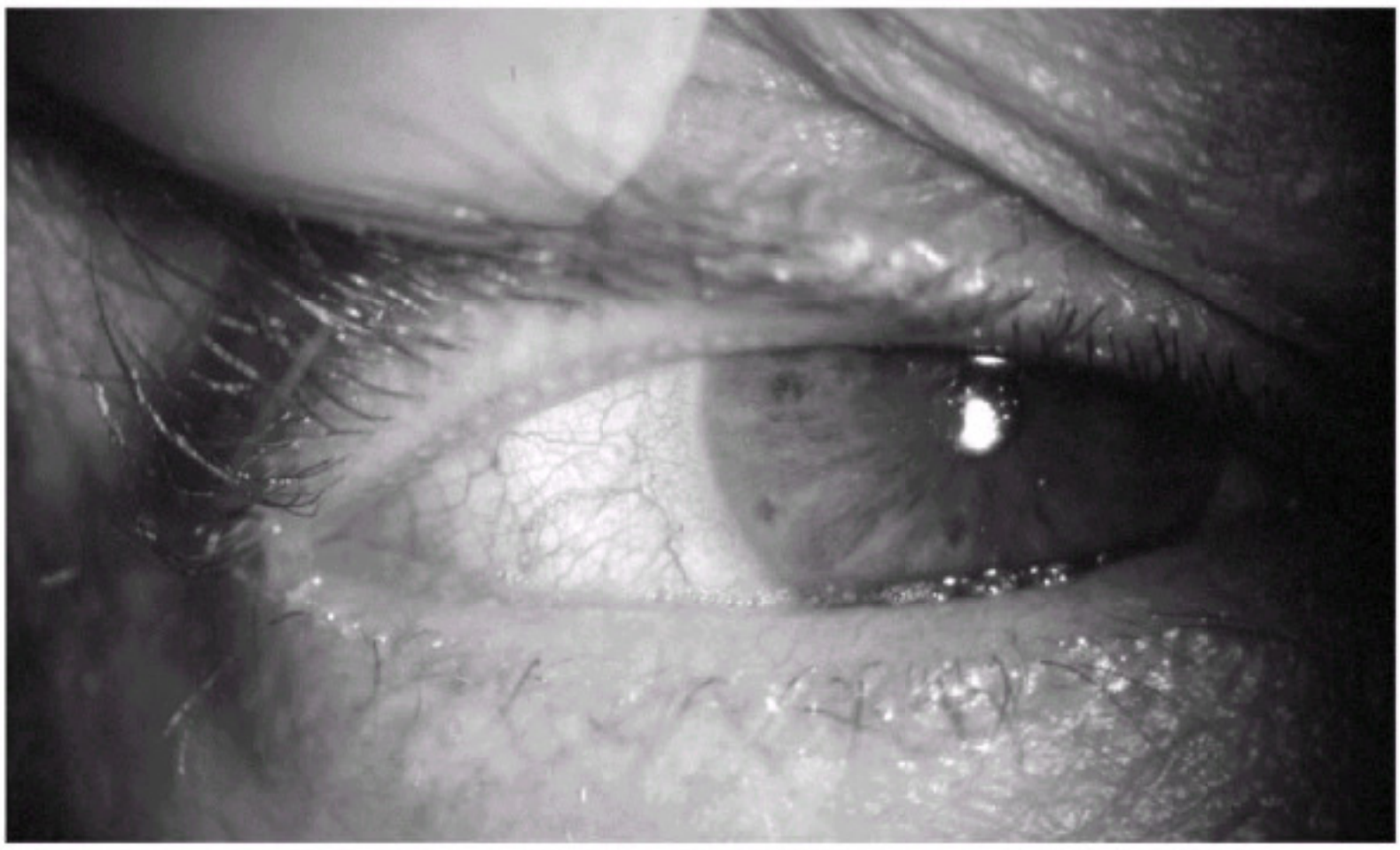

Figure 11.10 Conjunctival hyperemia associated with chronic meibomianitis; note “suds” in the tear film.

Moraxella lacunata causes “external angular conjunctivitis,” a chronic follicular conjunctivitis associated with an ulcerative canthal blepharitis (61). Other bacteria that cause chronic conjunctivitis include: *Staphylococcus epidermidis*, *Proteus sp.*, *Klebsiella pneumoniae*, *Serratia marcescens*, and *Escherichia coli*.

A chronic unilateral papillary conjunctivitis should arouse the suspicion of a masquerade syndrome caused by an underlying ocular surface malignancy, such as intraepithelial neoplasia, malignant melanoma, or sebaceous cell carcinoma. These conditions fortunately are uncommon in children (62).

Another important cause of unilateral chronic conjunctivitis is chronic canaliculitis caused by *Actinomyces israelii*, dacryocystitis, or congenital dacryostenosis.

Molluscum contagiosum is a poxvirus that produces a chronic follicular conjunctivitis. Small umbilicated lesions on the eyelids or the periocular skin are the hallmark of this condition. The simple excision of the lesions, including the central plug, will resolve the conjunctivitis (56) (Fig. 11.12).

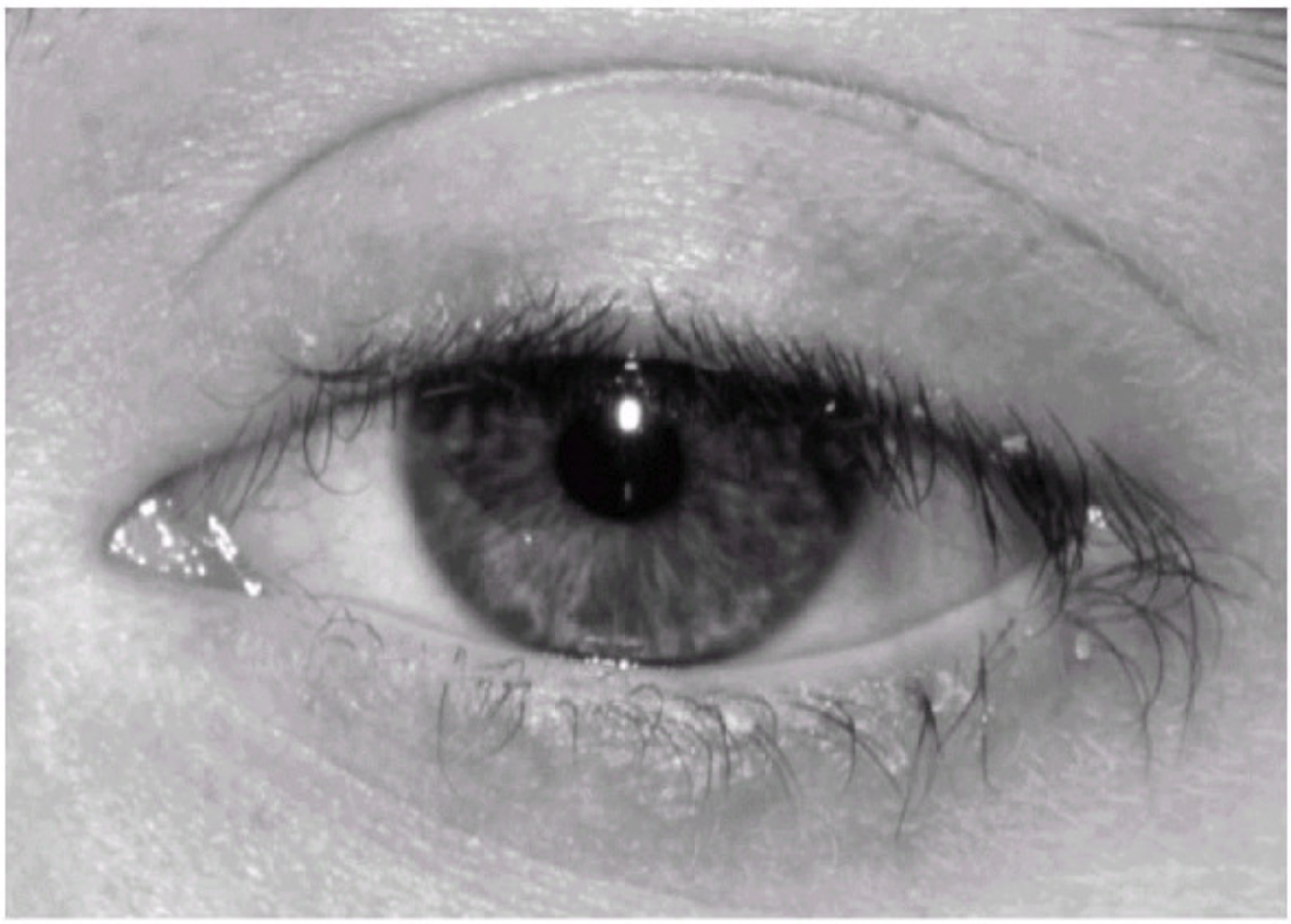

Figure 11.11 Seborrheic blepharitis in Down's syndrome.

Perhaps one of the most concerning chronic infections is trachoma: a bilateral chronic follicular conjunctivitis that is endemic in some developing countries and is the most common cause of preventable blindness. *C. trachomatis* serotypes A-C are transmitted between human beings by intimate social or sexual contact. The incubation period on average is 5 to 10 days. A subsequent self-limited mild mucopurulent conjunctivitis affects the individual and usually heals without any sequelae. Conjunctival scarring and other subsequent complications can result from a chronic, severe conjunctivitis caused by persistent or repeated chlamydial infection. Chronic inflammation is characterized by subepithelial follicles and papillary hypertrophy in the tarsal conjunctiva. Vascular infiltration of the superior portion of the cornea (pannus) is common but rarely progresses to involve the visual axis. These clinical signs of active disease are seen mainly in young children but may also occur in older children and some adults. Conjunctival follicles at the upper limbal margin of the cornea leave characteristic shallow depressions, known as Herbert's pits, after they resolve. Fibrosis and scarring of the upper subtarsal conjunctiva, caused by recurrent infections, is commonly known as Arlt's line. As the scarring progresses, distortion of the lid margin may be seen, causing entropion and trichiasis. Constant trauma to the cornea leads eventually to corneal keratinization, opacification, and blindness. Severe scarring is typically seen in older children, but blindness does not develop until age 40 or 50 (63). Trachoma is, in general, a clinical diagnosis. Laboratory exams, including examination of stained conjunctival scrapings for intracytoplasmic inclusions, tissue culture, immunofluorescence, ELISA, and nucleic-acid-amplification tests, such as PCR, can confirm the diagnosis (64).

Since the 1950s, topical tetracycline has been used widely in trachoma-control programs. The recommended treatment is topical tetracycline, twice a day for 6 weeks. Tetracycline ointment is irritating and difficult to use, particularly in infants, so compliance is poor. Oral antibiotic treatment is more effective than topical treatment because

it also eliminates extraocular sites of infection (65). Data from three randomized controlled trials suggest that 1 dose of 20 mg/kg azithromycin (maximum 1 g) is at least as effective in producing resolution of active trachoma as a prolonged course of directly observed topical tetracycline (66,67,68). The WHO promotes the use of the “SAFE” (*S*urgery for trichiasis, *A*ntibiotics to reduce the reservoir of infection, *F*acial cleanliness, and *E*nvironmental improvement to reduce transmission of *C. trachomatis*) strategy for trachoma control.

Figure 11.12 Molluscum contagiosum.

Allergy

The most common cause of chronic conjunctivitis is allergy, affecting more than 15% of the world population with a higher prevalence (around 30%) in industrialized countries (69). The eye and the eyelid are common sites of allergic and other hypersensitivity reactions. Patients frequently have a history of atopic diseases, such as eczema, asthma, or rhinitis. Peak age groups are late childhood and young adulthood (70). The ocular allergic response results from the exposure of the conjunctiva to an allergen. Two immune responses may occur. During a type I hypersensitivity ocular reaction (humoral), an environmental allergen binds to the sensitized IgE antibody on the mast cell. The binding of the allergen causes the mast cell (estimated 50 million per eye) to degranulate and release mediators, such as histamine, prostaglandins, and leukotrienes. These mediators, especially histamine, cause itching, vasodilatation, and increased vascular permeability. Type I hypersensitivity ocular reactions include seasonal allergic conjunctivitis and perennial allergic conjunctivitis. In the type IV hypersensitivity reaction (cell-mediated), the delayed allergic reaction is induced by T lymphocytes and macrophages. Contact lens-associated giant papillary conjunctivitis is an example of this category, because it involves both types I and IV responses. Atopic keratoconjunctivitis and vernal keratoconjunctivitis are also characterized by both type I and type IV hypersensitivity reactions (71).

Seasonal and perennial allergic conjunctivitis are the most common types of ocular allergy and are typically elicited by airborne allergens, such as pollen, grass, weeds, mold, dust mite, and animal dander (72). Perennial allergic conjunctivitis is distinguished from seasonal allergic conjunctivitis by the presence of symptoms throughout the year and is often considered less severe than the seasonal type. However, almost 80% of the patients with perennial conjunctivitis

experience seasonal exacerbations of their symptoms (73,74). Signs and symptoms include bilateral involvement, itching, tearing, mucoid discharge, conjunctival injection, mild eyelid edema, and chemosis. In some cases a fine conjunctival follicular reaction may also occur. However, corneal involvement is not commonly seen. Treatment should initially be aimed at avoiding or eliminating the causative agent, if possible. Lubricants and cold compress may be helpful in reducing conjunctival irritation in very mild cases but, generally, fail in children. Over-the-counter (OTC) topical antihistamine/vasoconstrictors and nonsteroidal antiinflammatory agents are generally ineffective for the persistent allergic response. Mast cell stabilizers are also used; however, their treatment lies primarily in the prevention of symptoms by inhibiting the initial release of inflammatory mediators. The delay in their onset limits their effectiveness. Therapy with combination antihistamine/mast cell stabilizer agents, preferably studied in humans, is the most appropriate choice. Human conjunctival mast cells represent a different population of mast cells as compared to lung mast cells and respond to medications differently (75,76). To date only olopatadine has been approved by the Food and Drug Administration (FDA) for treatment of all of the signs and symptoms of allergic conjunctivitis. Topical steroids can also be used for the most severe allergies, but their use remains limited and secondary due to their potential adverse effects (70,71).

Vernal keratoconjunctivitis (VKC) is a vision-threatening, chronic bilateral conjunctival inflammatory disorder that affects mostly young people with a male preponderance. The usual pattern is onset before age 10 and resolves during puberty. Individuals in warm, dry climates tend to be more affected. There is a significant history of other atopic manifestations, such as asthma and eczema (77). Symptoms include pain, itching, conjunctival injection, ptosis, and mucous discharge. Signs of this disease include large (more than 1 mm in diameter), flattened-top papillae on the superior tarsus, gelatinous confluent limbal papillae, conjunctival hyperemia with edema, and Horner-Trantas dots (clumps of eosinophils with dead epithelial cells on the superior limbus). These changes may lead to superficial corneal neovascularization. In severe cases, corneal ulcers can occur, in addition to epithelial keratitis. The punctate epithelial keratitis may coalesce to an epithelial erosion, leaving Bowman's membrane intact. If treatment is inadequate or no treatment is rendered, a fibrin and mucous plaque is deposited over the defect, delaying the epithelial healing and creating a shield ulcer.

Symptoms can be reduced with conservative measures, such as cold compresses and avoidance or elimination of environmental allergens. Although H1 receptor blockers are used for treatment, topical mast cell stabilizers, like lodoxamide, have been shown to treat VKC more effectively due to its effect on eosinophils (78). Because the complications of VKC can be very serious, topical steroids are almost invariably used at the onset of this disease and then tapered over several weeks while mast cell stabilizers are continued (see Color Plate I.E, Fig. 11.13).

Atopic keratoconjunctivitis is a bilateral chronic inflammation in individuals, with atopic dermatitis occurring more commonly in men between ages 20 and 50 (71). Up to 40% of the patients with atopic dermatitis have ocular involvement (79,80). The major symptom is itching, and patients often complain of mucous discharge in the morning, blurry vision, photophobia, and pain. At clinical examination, scaling dermatitis of the eyelids, lateral canthal ulceration, madarosis, punctate epithelial keratopathy, papillary reaction, and follicles in the conjunctiva (which are more prominent in the inferior fornix) may be seen. Complications can be severe and include: loss of vision related to the consequences of corneal epithelial defects, keratoconus, cataracts, corneal scarring, and superficial punctate keratitis; lichenified and woody eyelids may lead to cicatricial ectropion and lagophthalmos; and subepithelial fibrosis of the conjunctiva and, rarely, symblepharon

(77). The goal in treatment is to prevent visual complications and is similar to vernal conjunctivitis. Topical H1 receptor blockers and topical vasoconstrictors may bring only transient relief of the symptoms. Topical steroids for short periods can help to control symptoms and signs of atopic keratoconjunctivitis. Topical mast cell stabilizers also play a crucial role in the prevention of the disease. Oral antihistamines and nonsteroidal antiinflammatory drugs can help to relieve the systemic manifestations. Systemic antihistamines can cause decreased tear production as mucous membrane drying agents and should be used judiciously.

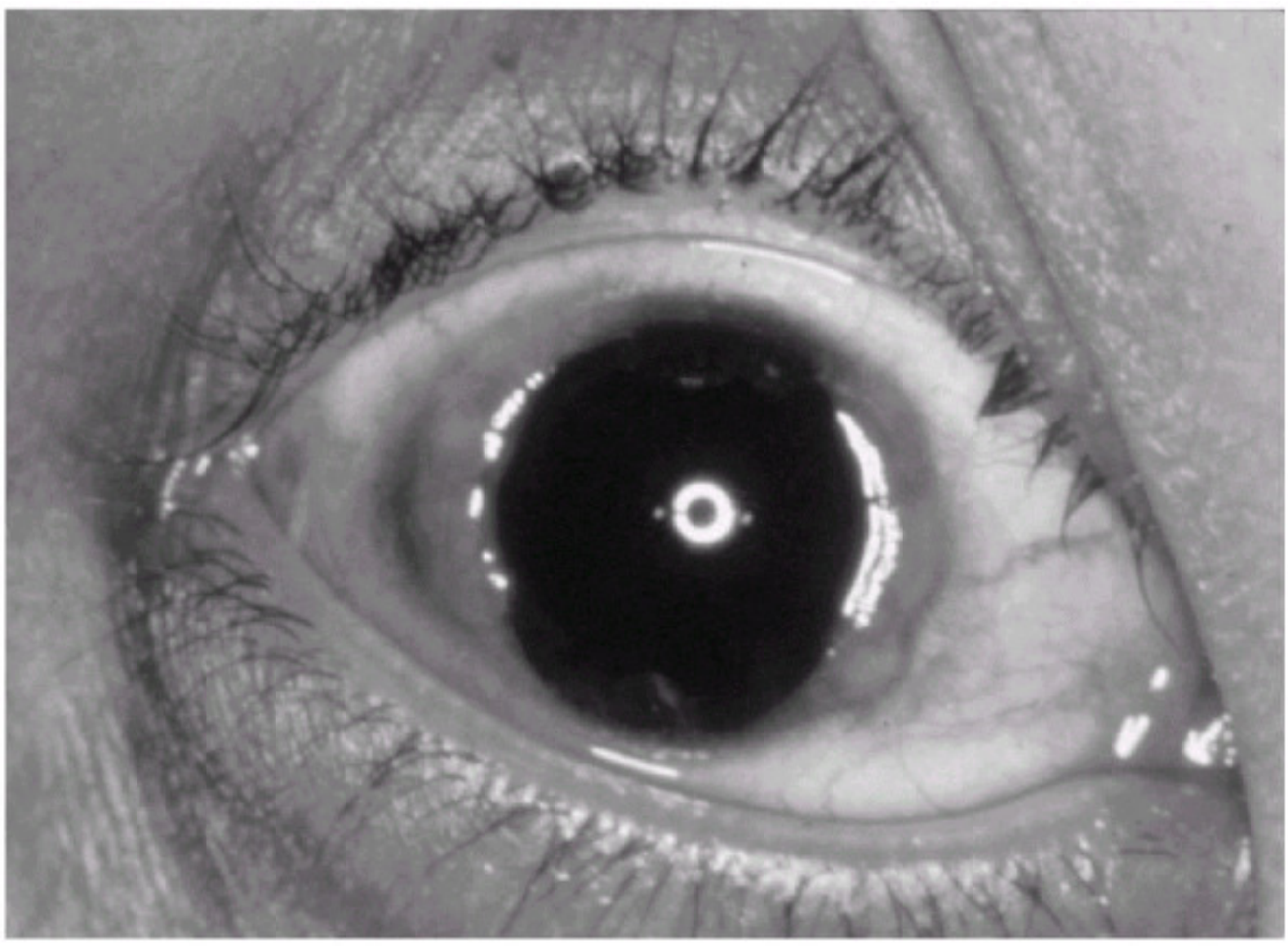

Figure 11.13 Limbal vernal conjunctivitis.

Giant papillary conjunctivitis (GPC) is a noninfectious inflammatory disorder that has been associated with soft contact lens wear, glaucoma filtering blebs, exposed sutures, ocular prosthetics, and extruded scleral buckles (81). GPC may occur with rigid contact lenses but less commonly than with soft (hydrophilic) contact lenses. Symptoms of giant papillary conjunctivitis are low grade at onset. Persistent contact lens wear and/or continued exposure to the inciting material leads to progression of the conjunctivitis with worsening symptoms of itching, blurred vision, mucus production, and lens intolerance. Giant papillae (greater than 0.3 mm) are seen on the superior conjunctival tarsus and, in early cases, are associated with conjunctival injection. The giant papillae appear to manifest increased amounts of mucus-secreting goblet cells with the overlying conjunctiva often thickened and irregular. Corneal involvement in GPC is rare, although pannus formation may occur with persistent soft contact lens wear, despite ocular signs and symptoms. Discontinuation of contact lens or prosthesis use, removal of suture or scleral buckle, helps to reduce, if not eliminate, the clinical manifestations of GPC. However, because many patients do not want to stop wearing

contact lenses or prostheses, therapy is directed toward improving lens and prosthesis hygiene by using disposable lenses and finding more compatible lens and prosthesis designs and materials for patients (71). Topical agents, such as histamine antagonists and receptor-blocking agents, have shown limited benefit. Topical steroids help to reduce tarsal hyperemia and inflammation. Mast cell stabilizers have been shown to promote resolution of early giant papillary conjunctivitis when combined with meticulous lens hygiene. Advanced giant papillary conjunctivitis does not respond to mast cell stabilizers, and, in this case, contact lens and prosthesis use should be discontinued for at least several weeks followed by gradual reintroduction of the contact lens with adjuvant mast cell stabilizer treatment (81) (Figs. 11.14 and 11.15).

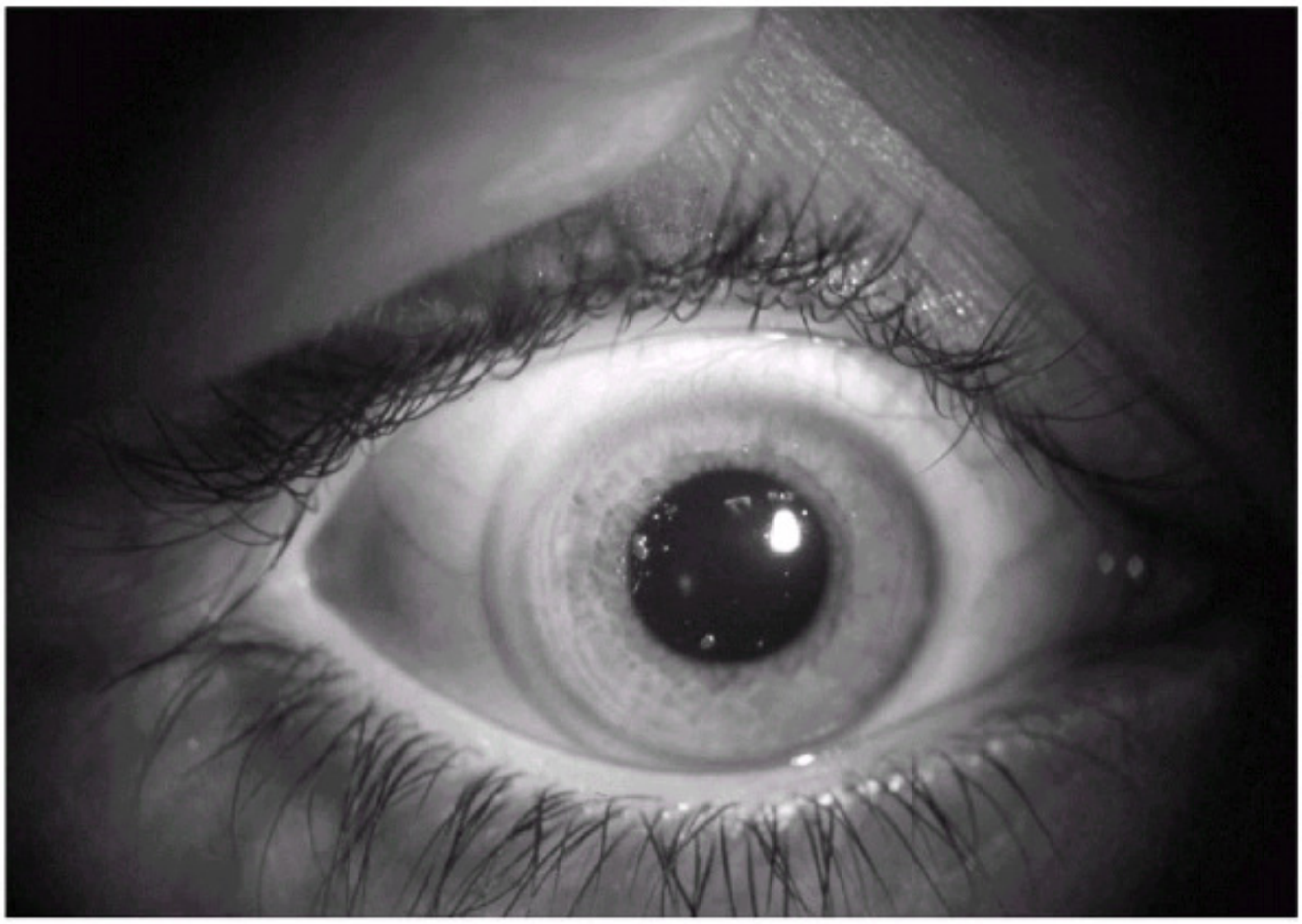

Figure 11.14 Soft contact lens with deposits.

Figure 11.15 Giant papillary conjunctivitis.

ALLERGIC AND TOXIC CONTACT REACTIONS TO DRUGS

Allergic reactions to topical ophthalmic medications are not uncommon; however, about 90% of conjunctival drug reactions are toxic (the result of direct chemical irritation) not allergic. In general, allergic reactions are characterized by chronicity (sensitization time is needed for reaction to develop), and a toxic reaction may occur with the first exposure to the agent. Allergies are caused predominantly by active pharmaceutical agents and seldom by preservatives or other additives. Drug-induced ocular allergies are most

often the result of type-IV hypersensitivity. They result from contact of inciting drugs with the affected tissues. The drug acts as a hapten (incomplete antigen) and becomes immunogenic only after it binds to tissue proteins. The immunological responses result in conjunctival hyperemia with a papillary reaction and eczema of the skin of the eyelids. Initial sensitization requires at least 5 days and can take months or years of exposure to the hapten. When prior sensitization has occurred, reexposure to the hapten may result in inflammation within 12 to 72 (usually 24-48) hours (82).

The earliest sign of allergic and toxic contact reactions is hyperemia; rose bengal dye may reveal punctate staining of the inferonasal bulbar conjunctiva, where topical medications gravitate on their way to the lacrimal outflow system; and eczema of the skin of the eyelids. If the drug is continued, the symptoms and signs worsen. A papillary conjunctivitis with pronounced vasodilation, chemosis, and watery discharge may be seen, although follicles may also be present. In severe cases, keratitis can develop with epithelial defects and, rarely, corneal infiltrates. Corneal involvement is more common in toxic than allergic reactions. Eczema of the skin of the eyelids in the absence of any conjunctival sign indicates that something other than a topical ocular medication is causative, namely, something that has come into contact only with the eyelids (a topical ointment, skin and hair care products, cosmetics, nail polisher, etc.). Misapplication of eye medication should also be considered.

The most common drugs that cause allergy and toxic reactions include atropine, neomycin, aminoglycoside antibiotics, hyoscine (scopolamine), penicillin, apraclonidine, brimonidine, dorzolamide, and older antiviral agents (idoxuridine and, less often, vidarabine) (83). Preservatives and other additives are uncommon causes of allergic contact reactions, except for thimerosal. However, especially with repeated use, preservatives may be quite toxic to the corneal and conjunctival epithelium. Recognition of toxicity is the key to the treatment, which usually involves stopping the causative agent (84).

ERYTHEMA MULTIFORME AND ITS VARIANTS

Erythema multiforme is an acute mucocutaneous hypersensitivity reaction characterized by a symmetrically distributed skin eruption, with or without mucous membrane lesions. It may present within a wide spectrum of severity. The minor form affects primarily the skin and one mucosal surface at most. The major form is known as Stevens-Johnson syndrome. About 20% of cases occur in children and adolescents. It is characterized by involvement of skin and *two* or more mucosal surfaces with possible internal organ involvement leading to systemic symptoms. There is controversy as to whether toxic epidermal necrolysis is a severe manifestation of erythema multiforme or a distinct entity. The frequent presence of overlapping clinical features in a given patient often makes definitive classification difficult.

Drugs and infections are the most common precipitating factors, but other factors, such as mechanical or physical factors (radiotherapy and sunlight), can also trigger the disease (85). This syndrome presents with a prodrome of fever and influenza-like symptoms, followed by the rapid onset of cutaneous blistering within 1 to 3 weeks after exposure and hours after the reexposure to the inciting agent (86). The initial ocular findings in erythema multiforme is a bilateral nonspecific conjunctivitis with hyperemia and chemosis then progressing to a pseudomembranous conjunctivitis with secondary bacterial conjunctivitis complicating the initial ocular involvement. Anterior uveitis may also occur. The conjunctivitis resolves in 2 to 4 weeks. Pseudomembranous conjunctival erosions may result in scarring and symblepharon formation. These lead to entropion formation, trichiasis, and tear film instability. Persistent corneal defects with scarring and neovascularization can result from the chronic irritation due to eyelid changes. Affected patients can also have severely dry eyes due to cicatrization or stenosis of the lacrimal ducts and destruction of the conjunctival goblet cells responsible for the mucus secretion of the tear film.

Treatment of this ocular disease includes frequent conjunctival irrigation and instillation of prophylactic antibiotic drops and preservative-free artificial tears. Use of topical steroids is controversial because they do not decrease the symblepharon formation and may contribute to secondary infection. Lysis of symblepharon should be performed daily, and a symblepharon ring may also be used. If corneal involvement is severe and there is risk of perforation, a conjunctival flap or penetrating keratoplasty should be performed. Chronic ocular involvement in Stevens-Johnson syndrome is a challenge to most ophthalmologists. Trichiasis and entropion can be corrected surgically with frequent recurrence. Epithelial corneal defects can be treated with a soft contact lens, conjunctival graft, keratoprosthesis, or keratolimbal allograft with limited results. Frequent use of artificial tears, and sometimes tarsorrhaphy, are used to treat keratoconjunctivitis sicca that develops after the acute inflammation (87). The prognosis depends upon the severity of the initial event. Usually, children have the best prognosis (88). Patients should avoid contact with the precipitating agent to decrease the risk of recurrence.

LIGNEOUS CONJUNCTIVITIS

Ligneous conjunctivitis is a rare but devastating form of chronic conjunctivitis characterized by recurrent development of firm fibrin-rich, woody-like pseudomembranous lesions, mainly on the tarsal conjunctiva. It presents in childhood and may affect other mucous membranes of the gastrointestinal, respiratory, and female genital tract. It is more common in women and may be unilateral or bilateral. The initial lesion (raised, friable, and highly vascularized) can be easily removed with forceps. Eventually, this progresses to a white avascular mass that appears above the neovascular membrane. In late stages this lesion replaces the normal conjunctival mucosa as a thickened, vascularized firm mass with a wood-like consistency. Corneal

involvement, occurring in about one third of cases, may lead to blindness as a result of scarring, vascularization, keratomalacia, and corneal perforation. The central features of ligneous conjunctivitis are impaired wound healing, chronic and overwhelming local inflammation, and excessive depositions of fibrin and other plasma proteins, due to an impaired extracellular (plasmin-mediated) fibrinolysis (89).

In predisposed subjects, ligneous conjunctivitis results from an exaggerated inflammatory response to tissue injury and may be triggered by local injuries, local and systemic infections, and surgical procedures to the eyes. The diagnosis is based mainly on the clinical picture. The typical histological findings are an acellular, eosinophilic, periodic acid-Schiff-positive, hyaline material with areas of granulation tissue, and areas of cellular infiltration (90,91).

Spontaneous resolution of ligneous conjunctivitis has been reported, but these cases are rare (90,92). Local treatment options available for ligneous conjunctivitis are mostly disappointing. Many local drugs have been tried: Topical hyaluronidase (1.5 mg/mL) alone, or in combination with alpha-chymotrypsin (0.2 mg/mL), has been reported to be helpful in some studies but not in others (91,93,94). Limited success was also reported using topical antibiotics, steroids, sodium cromoglycate, and silver nitrate (95).

Some studies have shown that long-term topical treatment with corticosteroids combined with cyclosporine A significantly decreased the frequency and the severity of recurrences after surgical excisions of the pseudomembranes. Systemic side effects of cyclosporine A were not described (96,97). The most promising approach seems to be the initial application of a topical fibrinolytic agent, followed by surgical removal of the pseudomembranes with subsequent intense and long-term topical application of heparin in combination with topical corticosteroids and alpha-chymotrypsin (98). Heparin appears to reduce the otherwise high risk of local recurrence after surgery alone; however, the number of excisions of pseudomembranes and other mechanical manipulations should be kept to a minimum.

SUMMARY

The conjunctiva is a mucous membrane that serves multiple functions for the eye. It provides a smooth surface for appositional motion, immune protection, aids in lubrication, and is resilient to physical trauma. This amazing tissue allows the eye to be an external organ surviving in a hostile environment. Without the conjunctiva, the ability of the eye to function as our organ of sight would not be possible.

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REFERENCES

1. Torczynski E. Normal development of the eye and the orbit before birth. In: Isenberg SJ, ed. *The eye in infancy*. Chicago: Mosby International, 1988:25-26.

2. Kikkawa DO. Ophthalmic facial anatomy and physiology. In: Kaufman P, Alm A, eds. *Adler's physiology of the eye*. Philadelphia: WB Saunders, 2002:23-25.

3. Lawton A. Structure and function of the eyelids and conjunctiva. In: Kaufman H, Barron B, McDonald M, eds. *The Cornea*. Boston: Butterworth-Heinemann, 1998.

4. Greiner JV, Kenyon KR, Henriquez AS, et al. Mucus secretory vesicles in conjunctival epithelial cells of wearers of contact lenses. *Arch Ophthalmol* 1980;98(10):1843-1846.

5. Isenberg SJ, Del Signore M, Chen A, et al. The lipid layer and stability of the preocular tear film in newborns and infants. *Ophthalmology* 2003;110(7):1408-1411.

6. Tseng SC, Zhang SH. Interaction between rose bengal and different protein components. *Cornea* 1995;14(4):427-435.

7. Yanoff M, Fine BS. *Ocular pathology*, 5th ed. Philadelphia: Mosby, 2002:761.

8. Mclean IW. Melanocytic neoplasms of the conjunctiva. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *The Cornea*. St. Louis: Mosby-Year Book, 1997:715-722.

9. Folberg R, Jakobiec FA, Bernardino VB, et al. Benign conjunctival melanocytic lesions: clinicopathologic features. *Ophthalmology* 1989;96(4):436-461.

10. Kantelip B, Boccard R, Nores JM, et al. A case of conjunctival Spitz nevus: review of literature and comparison with cutaneous locations. *Ann Ophthalmol* 1989;21(5):176-179.

11. Jakobiec FA, Folberg R, Iwamoto T. Clinicopathologic characteristics of premalignant and malignant melanocytic lesions of the conjunctiva. *Ophthalmology* 1989;96(2):147-166.

12. Ticho BH, Tso MO, Kishi S. Diffuse iris nevus in oculodermal melanocytosis: a light and electron microscopic study. *J Pediatr Ophthalmol Strabismus* 1989;26(5):244-250.

13. Gonder JR, Shields JA, Albert DM, et al. Uveal malignant melanoma associated with ocular and oculodermal melanocytosis. *Ophthalmology* 1982;89(8):953-960.

14. Dutton JJ, Anderson RL, Schelper RL, et al. Orbital malignant melanoma and oculodermal melanocytosis: report of two cases and review of the literature. *Ophthalmology* 1984;91(5):497-507.

15. Yamamoto T. Malignant melanoma of the choroid in the nevus of Ota. *Ophthalmologica* 1969;159:1-10.

16. Singh M, Kaur B, Annwar NM. Malignant melanoma of the choroid is a naevus of Ota. *Br J Ophthalmol* 1988;72:131-134.

17. Roldan M, Llanes F, Negrete O, et al. Malignant melanoma of the choroid associated with melanosis oculi in a child. *Am J Ophthalmol* 1987;104(6):662-663.

18. Goncalves V, Sandler T, O'Donnell FE Jr. Open angle glaucoma in melanosis oculi: response to laser trabeculoplasty. *Ann Ophthalmol* 1985;17(1):33-36.

19. Warner M, Jakobiec F. Subepithelial neoplasms of the conjunctiva. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea-cornea and external disease: clinical diagnosis and management*. St Louis: Mosby, 1997:723-743.

20. Taylor D. Conjunctiva and subconjunctival tissue. In: Taylor D, ed. *Paediatric ophthalmology*. Oxford, England: Blackwell Science, 1997:237-251.

21. Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases. *Arch Dermatol* 1987;123(2):241-250.

22. Rook A. Xeroderma pigmentosa. In: Rook A, Wilkinson D, Ebling F, eds. *Textbook of dermatology*. Oxford, England: Blackwell Scientific, 1979.

23. Fransen L, Klauss V. Neonatal ophthalmia in the developing world. Epidemiology, etiology, management and control. *Int Ophthalmol* 1988;11(3):189-196.

24. Haase DA, Nash RA, Nsanze H, et al. Single-dose ceftriaxone therapy of gonococcal ophthalmia neonatorum. *Sex Transm Dis* 1986;13(1):53-55.

25. Hoosen AA, Kharsany AB, Ison CA. Single low-dose ceftriaxone for the treatment of gonococcal ophthalmia—implications for the national programme for the syndromic management of sexually transmitted diseases. *S Afr Med J* 2002;92(3):238-240.

26. Laga M, Naamara W, Brunham RC, et al. Single-dose therapy of gonococcal ophthalmia neonatorum with ceftriaxone. *N Engl J Med* 1986;315(22):1382-1385.

27. [No authors listed]. Ophthalmia neonatorum. *Afr Health* 1995;17(5):30.

28. AAP, AAOP, Red Book: 2003 Report of the Committee on Infectious Diseases, 26th ed. Elk Grove Village, IL, 2003.

29. Klauss V, Schwartz E. Other conditions of the outer eye. In: Johnson GJ, Weale RA, Minassian DC, et al, eds. *The epidemiology of eye disease*. London: Chapman & Hall, 1998.

30. Hedberg K, Ristinen TL, Soler JT, et al. Outbreak of erythromycin-resistant staphylococcal conjunctivitis in a newborn nursery. *Pediatr Infect Dis J* 1990;9(4):268-273.

31. Ison CA, Terry P, Bendayna K, et al. Tetracycline-resistant gonococci in UK. *Lancet* 1988;1(8586):651-652.

32. van Klingeren B, Dessens-Kroon M, Verheuvel M. Increased tetracycline resistance in gonococci in The Netherlands. *Lancet* 1989;2(8674):1278.

33. Knapp JS, Zenilman JM, Biddle JW, et al. Frequency and distribution in the United States of strains of Neisseria gonorrhoeae with plasmid-mediated, high-level resistance to tetracycline. *J Infect Dis* 1987;155(4):819-822.

34. Schwarcz SK, Zenilman JM, Schnell D, et al. National surveillance of antimicrobial resistance in Neisseria gonorrhoeae. The Gonococcal Isolate Surveillance Project. *JAMA* 1990;264(11):1413-1417.

35. Hammerschlag MR, Cummings C, Roblin PM, et al. Efficacy of neonatal ocular prophylaxis for the prevention of chlamydial and gonococcal conjunctivitis. *N Engl J Med* 1989;320(12):769-772.

36. Zanoni D, Isenberg SJ, Apt L. A comparison of silver nitrate with erythromycin for prophylaxis against ophthalmia neonatorum. *Clin Pediatr (Phila)* 1992;31(5):295-298.

37. Isenberg SJ, Apt L, Del Signore M, et al. Povidone-iodine for ophthalmia neonatorum prophylaxis. *Am J Ophthalmol* 1994;118(6):701-706.

38. Isenberg SJ, Apt L, Wood M. A controlled trial of povidone-iodine as prophylaxis against ophthalmia neonatorum. *N Engl J Med* 1995;332(9):562-566.

39. Wald ER. Conjunctivitis in infants and children. *Pediatr Infect Dis J* 1997;16[2 Suppl]:S17-S20.

40. Lewis LS, Glauser TA, Joffe MD. Gonococcal conjunctivitis in prepubertal children. *Am J Dis Child* 1990;144(5):546-548.

41. Irani F, Ruddell T. Meningococcal conjunctivitis. *Aust N Z J Ophthalmol* 1997;25(2):167-168.

42. Bodor FF. Diagnosis and management of acute conjunctivitis. *Semin Infect Dis* 1998;9:27-30.

43. Weiss A. Acute conjunctivitis in childhood. *Curr Probl Pediatr* 1994;24(1):4-11.

44. Gigliotti F, Williams WT, Hayden FG, et al. Etiology of acute conjunctivitis in children. *J Pediatr* 1981;98(4):531-536.

45. Brook I. Anaerobic and aerobic bacterial flora of acute conjunctivitis in children. *Arch Ophthalmol* 1980;98(5):833-835.

46. Brook I. Ocular infections due to anaerobic bacteria. *Int Ophthalmol* 2001;24(5):269-277.

47. Leibowitz HW, Pratt MV, Flagstad IJ, et al. Human conjunctivitis. I. Diagnostic evaluation. *Arch Ophthalmol* 1976;94(10):1747-1749.

48. Bodor FF. Conjunctivitis-otitis syndrome. *Pediatrics* 1982;69(6):695-698.

49. Bodor FF, Marchant CD, Shurin PA, et al. Bacterial etiology of conjunctivitis-otitis media syndrome. *Pediatrics* 1985;76(1):26-28.

50. Bodor F. [Purulent conjunctivitis-otitis media syndrome]. *Lijec Vjesn* 1987;109(6):220-223.

51. Bodor FF. Systemic antibiotics for treatment of the conjunctivitis-otitis media syndrome. *Pediatr Infect Dis J* 1989;8(5):287-290.

52. Gigliotti F, Hendley JO, Morgan J, et al. Efficacy of topical antibiotic therapy in acute conjunctivitis in children. *J Pediatr* 1984;104(4):623-626.

53. Hillenkamp J, Reinhard T, Ross RS, et al. The effects of cidofovir 1% with and without cyclosporin 1% as a topical treatment of acute adenoviral keratoconjunctivitis: a controlled clinical pilot study. *Ophthalmology* 2002;109(5):845-850.

54. Hillenkamp J, Reinhard T, Ross RS, et al. Topical treatment of acute adenoviral keratoconjunctivitis with 0.2% cidofovir and 1% cyclosporine: a controlled clinical pilot study. *Arch Ophthalmol* 2001;119(10):1487-1491.

55. Ritterband DC, Friedberg DN. Virus infections of the eye. *Rev Med Virol* 1998;8(4):187-201.

56. Stamler JF. Viral conjunctivitis. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea—cornea and external disease: clinical diagnosis and management*. St. Louis: Mosby, 1997:773-777.

57. Katusic D, Petricek I, Mandic Z, et al. Azithromycin vs. doxycycline in the treatment of inclusion conjunctivitis. *Am J Ophthalmol* 2003;135(4):447-451.

58. Chandler JW. Chlamydial infections. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea-cornea and external disease: clinical diagnosis and management*. St. Louis: Mosby, 1997:779-788.

59. Basualdo JA, Huarte L, Bautista E, et al. [Follicular conjunctivitis due to Chlamydia trachomatis]. *Medicina (B Aires)* 2001;61(4):397-400.

60. Soukiasian SH, Baum J. Bacterial conjunctivitis. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea-cornea and external disease: clinical diagnosis and management*. St. Louis: Mosby, 1997:759-772.

61. Taylor D. External eye diseases. In: Taylor D, ed. *Paediatric ophthalmology*. London: Blackwell Science, 1997:185-198.

62. Lindquist TD. Conjunctivitis: an overview and classification. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea-cornea and external disease: clinical diagnosis and management*. St. Louis: Mosby, 1997:745-758.

63. Bowman RJ, Jatta B, Cham B, et al. Natural history of trachomatous scarring in the Gambia: results of a 12-year longitudinal follow-up. *Ophthalmology* 2001;108(12):2219-2224.

64. Mabey DC, Solomon AW, Foster A. Trachoma. *Lancet* 2003;362(9379):223-229.

65. Schachter J, West SK, Mabey D, et al. Azithromycin in control of trachoma. *Lancet* 1999;354(9179):630-635.

66. Bailey RL, Arullendran P, Whittle HC, et al. Randomised controlled trial of single-dose azithromycin in treatment of trachoma. *Lancet* 1993;342(8869):453-456.

67. Dawson CR, Schachter J, Sallam S, et al. A comparison of oral azithromycin with topical oxytetracycline/polymyxin for the treatment of trachoma in children. *Clin Infect Dis* 1997;24(3):363-368.

68. Tabbara KF, Abu-el-Asrar A, al-Omar O, et al. Single-dose azithromycin in the treatment of trachoma. A randomized, controlled study. *Ophthalmology* 1996;103(5):842-846.

69. Bielory L. Update on ocular allergy treatment. *Expert Opin Pharmacother* 2002;3(5):541-553.

70. Teoh DL, Reynolds S. Diagnosis and management of pediatric conjunctivitis. *Pediatr Emerg Care* 2003;19(1):48-55.

71. Trocme SD, Sra KK. Spectrum of ocular allergy. *Curr Opin Allergy Clin Immunol* 2002;2(5):423-427.

72. Abelson MB, Schaefer K. Conjunctivitis of allergic origin: immunologic mechanisms and current approaches to therapy. *Surv Ophthalmol* 1993;[38 Suppl]:115-132.

73. Dart JK, Buckley RJ, Monnickendan M, et al. Perennial allergic conjunctivitis: definition, clinical characteristics and prevalence. A comparison with seasonal allergic conjunctivitis. *Trans Ophthalmol Soc U K* 1986;105(Pt 5):513-520.

74. Friedlaender MH. Conjunctivitis of allergic origin: clinical presentation and differential diagnosis. *Surv Ophthalmol* 1993;[38 Suppl]:105-114.

75. Irani AM, Schwartz LB. Mast cell heterogeneity. *Clin Exp Allergy* 1989;19(2):143-155.

76. Irani AM, Butrus SI, Tabbara KF, et al. Human conjunctival mast cells: distribution of MCT and MCTC in vernal conjunctivitis and giant papillary conjunctivitis. *J Allergy Clin Immunol* 1990;86(1):34-40.

77. Barney NP. Vernal and atopic keratoconjunctivitis. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea-cornea and external disease: clinical diagnosis and management*. St. Louis: Mosby, 1997:811-817.

78. Verin P, Allewaert R, Joyaux JC, et al. Comparison of lodoxamide 0.1% ophthalmic solution and levocabastine 0.05% ophthalmic suspension in vernal keratoconjunctivitis. *Eur J Ophthalmol* 2001;11(2):120-125.

79. Garrity JA, Liesegang TJ. Ocular complications of atopic dermatitis. *Can J Ophthalmol* 1984;19(1):21-24.

80. Rich LF, Hanifin JM. Ocular complications of atopic dermatitis and other eczemas. *Int Ophthalmol Clin* 1985;25(1):61-76.

81. Dunn SP, Heidemann DG. Giant papillary conjunctivitis. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea-cornea and external disease: clinical diagnosis and management*. St. Louis: Mosby, 1997:819-825.

82. Wilson FI. Toxic and allergic reactions to topical ophthalmic medications. In: Arrffa R, ed. *Grayson's diseases of the cornea*. St. Louis: Mosby, 1997:669-683.

83. Wilson FM II. Allergy to topical medications. *Int Ophthalmol Clin* 2003;43(1):73-81.

84. Chang S. Toxic conjunctivitis. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea-cornea and external disease: clinical diagnosis and management*. St. Louis: Mosby, 1997:847-856.

85. Pruksachatkunakorn C, Schachner L. Erythema Multiforme. In: Farmer E, ed. *Reactive and inflammatory dermatoses*. E-medicine, 2003.

86. Metry DW, Jung P, Levy ML. Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. *Pediatrics* 2003;112(6 Pt 1):1430-1436.

87. Palmon FE, Webster GF, Holland EJ. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea-cornea and external disease: clinical diagnosis and management*. St. Louis: Mosby, 1997:835-846.

88. Giannetti A, Malmusi M, Girolomoni G. Vesiculobullous drug eruptions in children. *Clin Dermatol* 1993;11(4):551-555.

89. Schuster V, Seregard S. Ligneous conjunctivitis. *Surv Ophthalmol* 2003;48(4):369-388.

90. Hidayat AA, Riddle PJ. Ligneous conjunctivitis. A clinicopathologic study of 17 cases. *Ophthalmology* 1987;94(8):949-959.

91. Kanai A, Polack FM. Histologic and electron microscope studies of ligneous conjunctivitis. *Am J Ophthalmol* 1971;72(5):909-916.

92. McGrand JC, Rees DM, Harry J. Ligneous conjunctivitis. *Br J Ophthalmol* 1969;53(6):373-381.

93. Francois J, Victoria-Troncoso V. Treatment of ligneous conjunctivitis. *Am J Ophthalmol* 1968;65(5):674-678.

94. Eagle RC Jr, Brooks JS, Katowitz JA, et al. Fibrin as a major constituent of ligneous conjunctivitis. *Am J Ophthalmol* 1986;101(4):493-494.

95. Holland R, Schwartz G. Ligneous conjunctivitis. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea-cornea and external disease: clinical diagnosis and management*. St. Louis: Mosby, 1997:863-868.

96. Holland EJ, Chan CC, Kuwabara T, et al. Immunohistologic findings and results of treatment with cyclosporine in ligneous conjunctivitis. *Am J Ophthalmol* 1989;107(2):160-166.

97. Rubin BI, Holland EJ, de Smet MD, et al. Response of reactivated ligneous conjunctivitis to topical cyclosporine. *Am J Ophthalmol* 1991;112(1):95-96.

98. De Cock R, Ficker LA, Dart JG, et al. Topical heparin in the treatment of ligneous conjunctivitis. *Ophthalmology* 1995;102(11):1654-1659.

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12

Diseases of the Cornea

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Diseases affecting the cornea and anterior segment in children differ little from diseases in adults, with the exception of congenital and developmental abnormalities. Specific corneal diseases first appear in infancy and childhood, so that careful screening and examination during the initial period of disease would have elucidated the nature of disorders recognized later in adulthood.

This chapter delineates the common diseases of the earlier years of life that primarily affect the cornea but may also involve surrounding structures, such as the eyelids, conjunctiva, sclera, iris, lens, and anterior chamber.

EMBRYOLOGY AND DEVELOPMENTAL ABNORMALITIES

The anterior segment of the eye—the cornea, anterior chamber angle, iris, and lens—contains several anatomical and physiological systems packed into a small space, so that its embryology and malformations are sometimes difficult to understand. The use of multiple names for each malformation further complicates the picture. For example, the term *mesodermal dysgenesis* of the iris, also called *Rieger's anomaly*, includes both posterior embryotoxon and Axenfeld's anomaly and sometimes coexists with Peters' anomaly. We can reduce the confusion by reviewing the development of the anterior segment, observing how each abnormality might derive from arrested or aberrant growth, and classifying the abnormalities on a simple anatomical basis.

Congenital anomalies of the anterior segment result from abnormal induction, differentiation, and maturation of the tissues. All cells of one individual begin with the same gene pool in their deoxyribonucleic acid (DNA) unless there is a chromosomal abnormality, but each differentiates to manifest a morphology controlled by only a portion of those genes—the genotype. Both internal and environmental influences regulate which genes will express themselves. During differentiation, different tissues are maximally susceptible to injury at different times, so that any agent that interferes during this sensitive period may produce an abnormality. Thus, similar malformations may result from abnormal genes, excessive or inadequate metabolites, viral or other infectious agents, exogenous toxins, hypoxia, or mechanical insults. Similarly, the same agents affecting the developing fetus at different times produce different abnormalities, depending on which tissues are the most vulnerable at that particular moment. In some instances, such as congenital rubella, we know both the cause of the abnormalities and the approximate time of their development. In most instances, however, these factors are unknown, and we must fall back on more simple anatomical descriptions of the abnormalities, to which we often give eponyms, refining chronology and etiology as more information becomes available.

Developmental Variations in Limbal Anatomy

The limbus is a junctional zone where corneal epithelium and its basement membrane meet stem cells and conjunctival epithelium and basement membrane. Corneal stroma juxtaposes sclera. Descemet's membrane ends at Schwalbe's ring and the trabecular meshwork. Corneal endothelium becomes continuous with the trabecular endothelium.

These transitional zones form a number of circular structures at the limbus that can be seen on slit-lamp examination (Fig. 12.1), and variations in these structures are common in congenital malformations of the anterior segment (1,2).

Epithelium

Corneal and conjunctival epithelia are continuous over the limbus. Corneal epithelium, a five- to eight-layered stratified squamous epithelium, attaches to a smooth basement membrane that is supported by the acellular, fibrillar feltwork of Bowman's layer. The conjunctival epithelium, a stratified cuboidal layer that contains goblet cells, lies on an undulating basement membrane, supported by irregular vascular connective tissue. At the limbus the conjunctival epithelium forms a series of radially arranged extensions into the subepithelial connective tissue, each extension

flanked by vascular connective tissue pegs that protrude into the epithelium. Pigmentation of the basal layers makes these epithelial extensions, the limbal palisades of Vogt, visible between the white connective tissue spaces (Figs. 12.1 and 12.2). Sometimes the pigmented areas are erroneously called the “limbal palisades.” If the connective tissue projections are not prominent, the pigmented limbal epithelium appears as a continuous dark brown circle at the corneal margin. In whites the structural limbal palisades can be seen on careful slit-lamp examination, but the absence of pigment flanking them makes them less prominent.

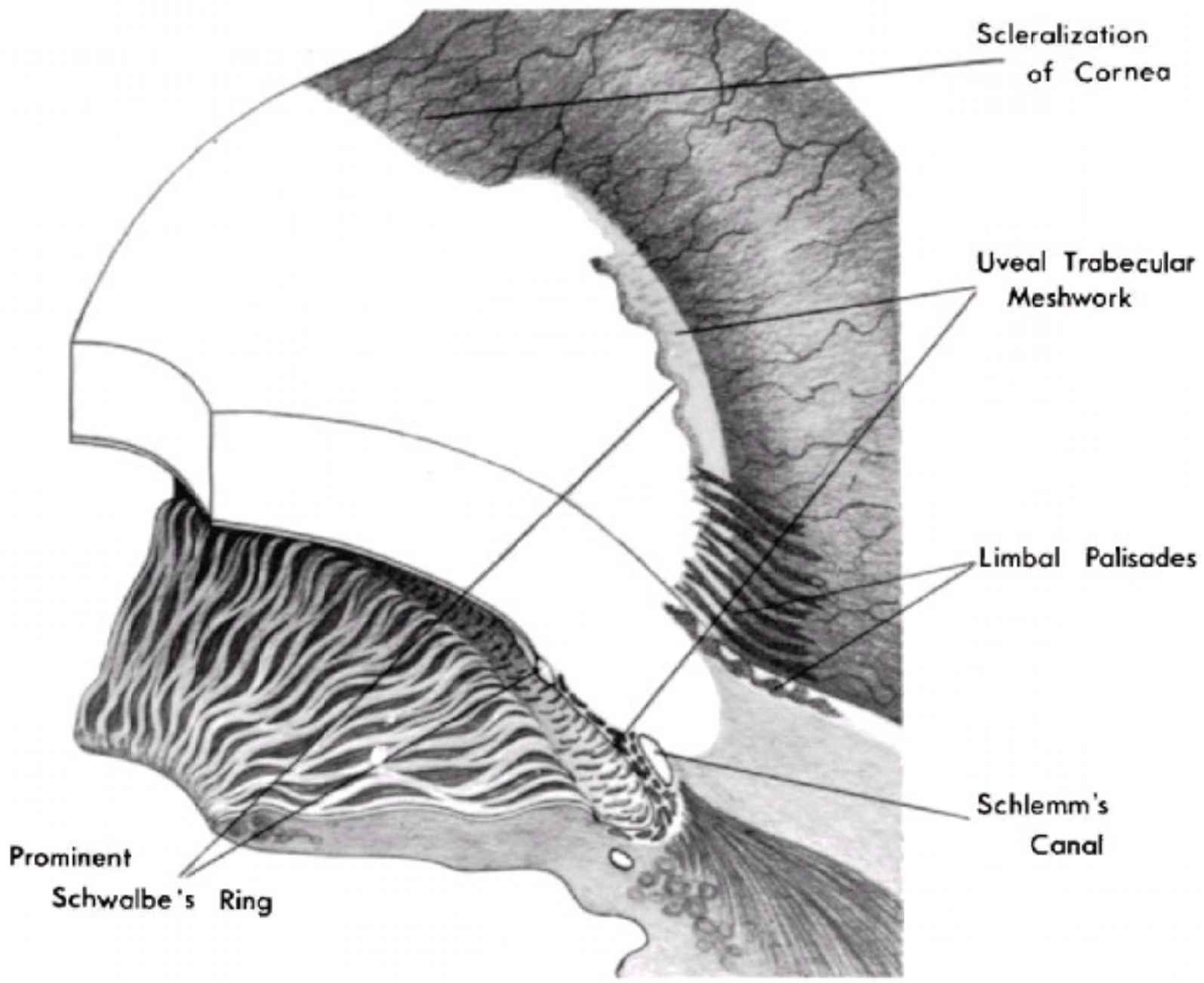

Figure 12.1 Developmental variations in limbal anatomy. This diagrammatic representation of limbal structures illustrates the appearance of each structure on the anterior surface and demonstrates its location in cross section.

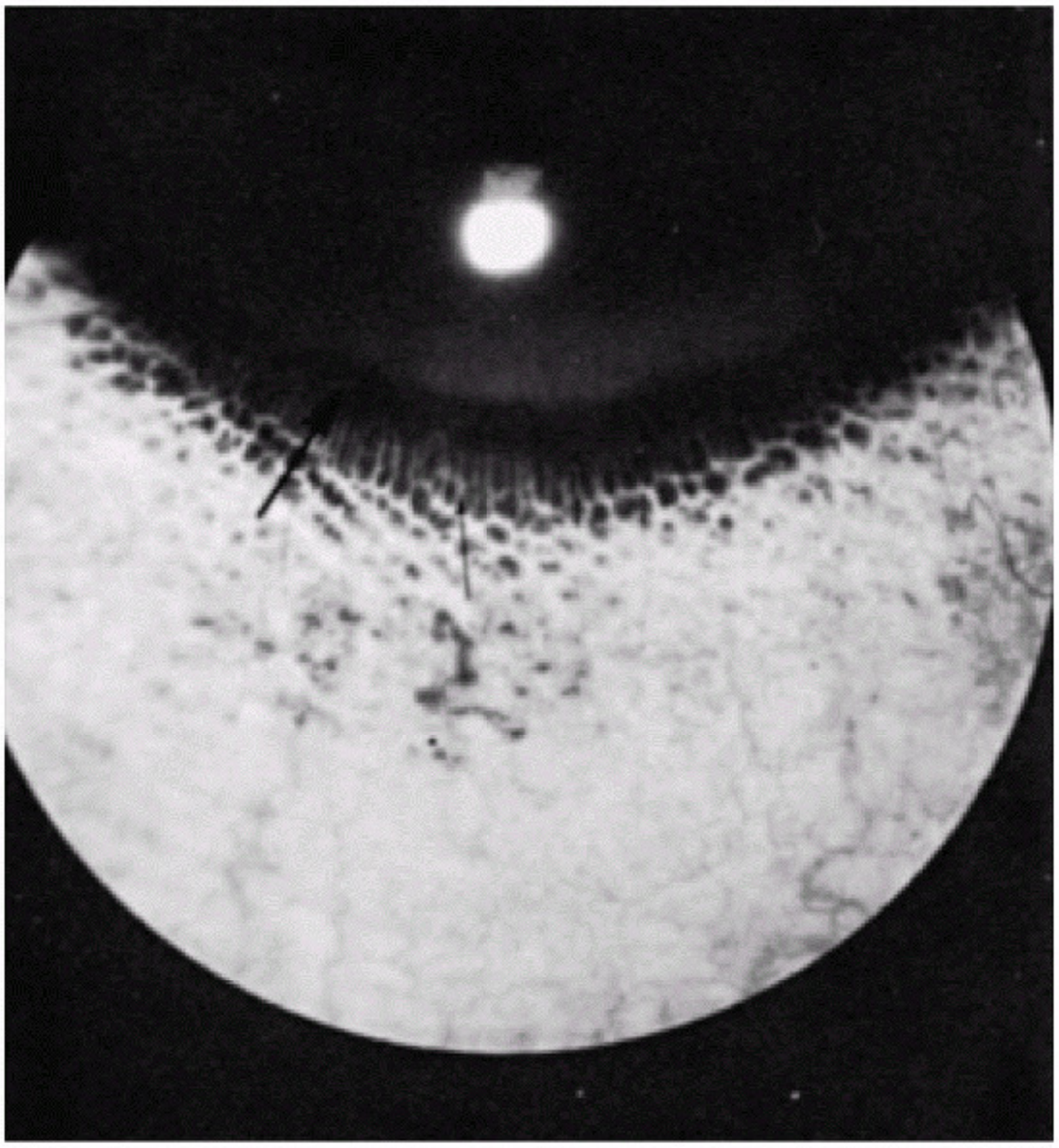

Figure 12.2 Limbal palisades of Vogt. This circle of white, finger-like projections (*small arrow*) that breaks up the limbal pigment ring (*large arrow*) results from subepithelial connective tissue papillae pushing up near the surface, interrupting the pigmentation of the basal conjunctival epithelium.

Corneoscleral Junction

The components of both corneal stroma and sclera are the same: collagen fibrils, proteoglycans (acid mucopolysaccharides), water, and fibrocytes. The tissues appear different because the corneal collagen fibers have a uniform diameter and arrangement, and the proteoglycans are dehydrated, whereas scleral fibrils vary in size, are randomly oriented, and remain hydrated. At the limbus the cornea inserts into the sclera as a wedge, like a watch crystal into its casing. Normally, the superficial rim of sclera extends 0.5 mm centrally over the wedge of cornea superiorly and inferiorly as a white, vascularized crescent (Figs. 12.1 and 12.3), so that the vertical corneal diameter is about 1 mm less than the horizontal diameter when measured on the anterior surface. Thus, deeper limbal structures, such as a prominent Schwalbe's ring or uveal trabecular meshwork, are usually visible only medially and laterally. When this scleral tissue extends farther centrally, or when it is present for 360 degrees, the abnormality is called *scleralization* or *scleral overriding*.

Trabecular Meshwork

A thin, translucent, gray band of uveal trabecular meshwork may extend up to and past Schwalbe's line to form a gray arc on the posterior cornea, one sometimes accentuated by a pigmented epithelial ring and a prominent Schwalbe's ring (Figs. 12.1, 12.4, and 12.5).

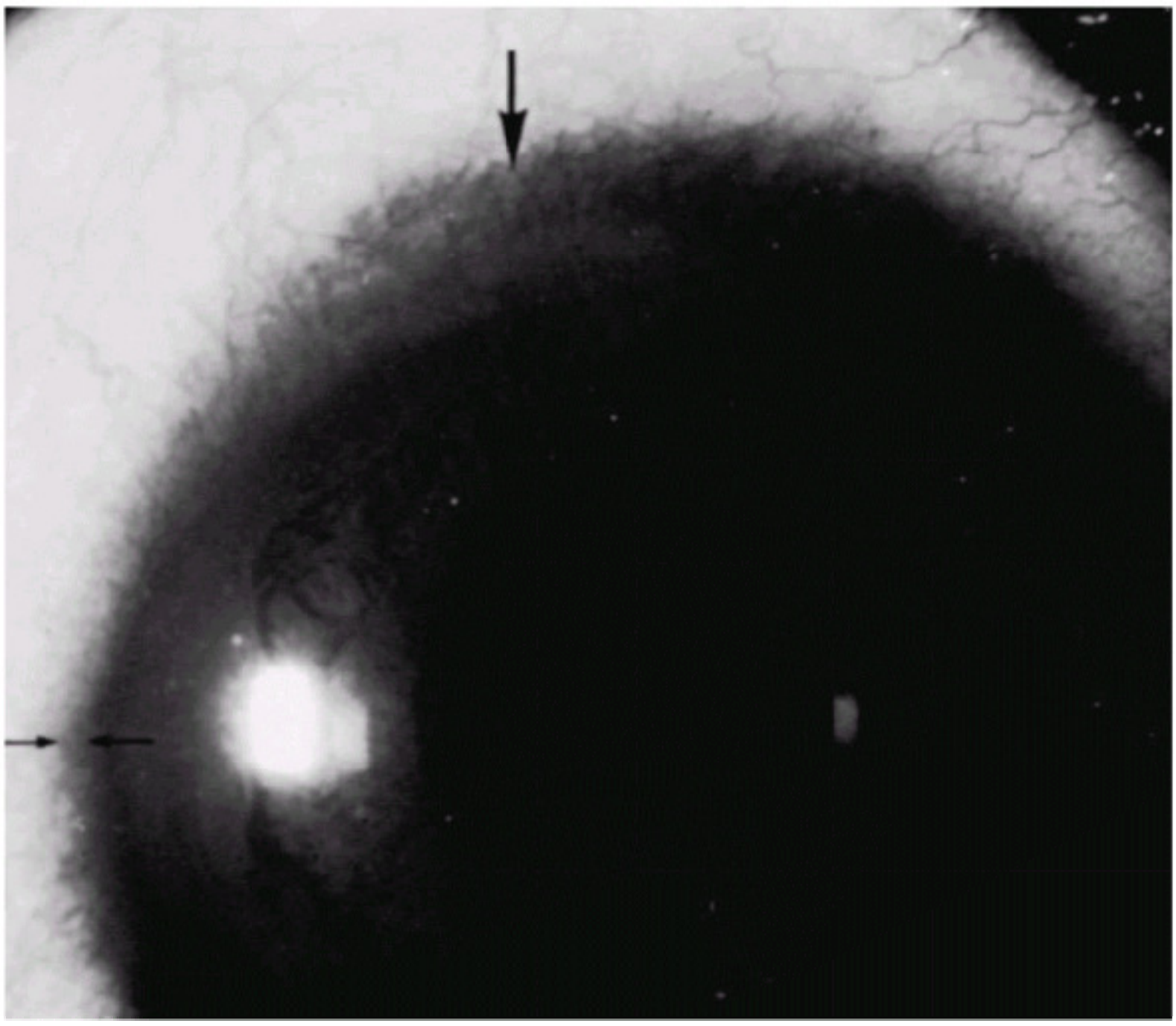

Figure 12.3 Scleralization of the cornea. At 12 o'clock position the sclera and its vessels extend superficially into the cornea, hiding underlying iris and angle details (*area between two large arrows*). Compare the normal extent of sclera over the limbus at 9 o'clock position (*area between two small arrows*).

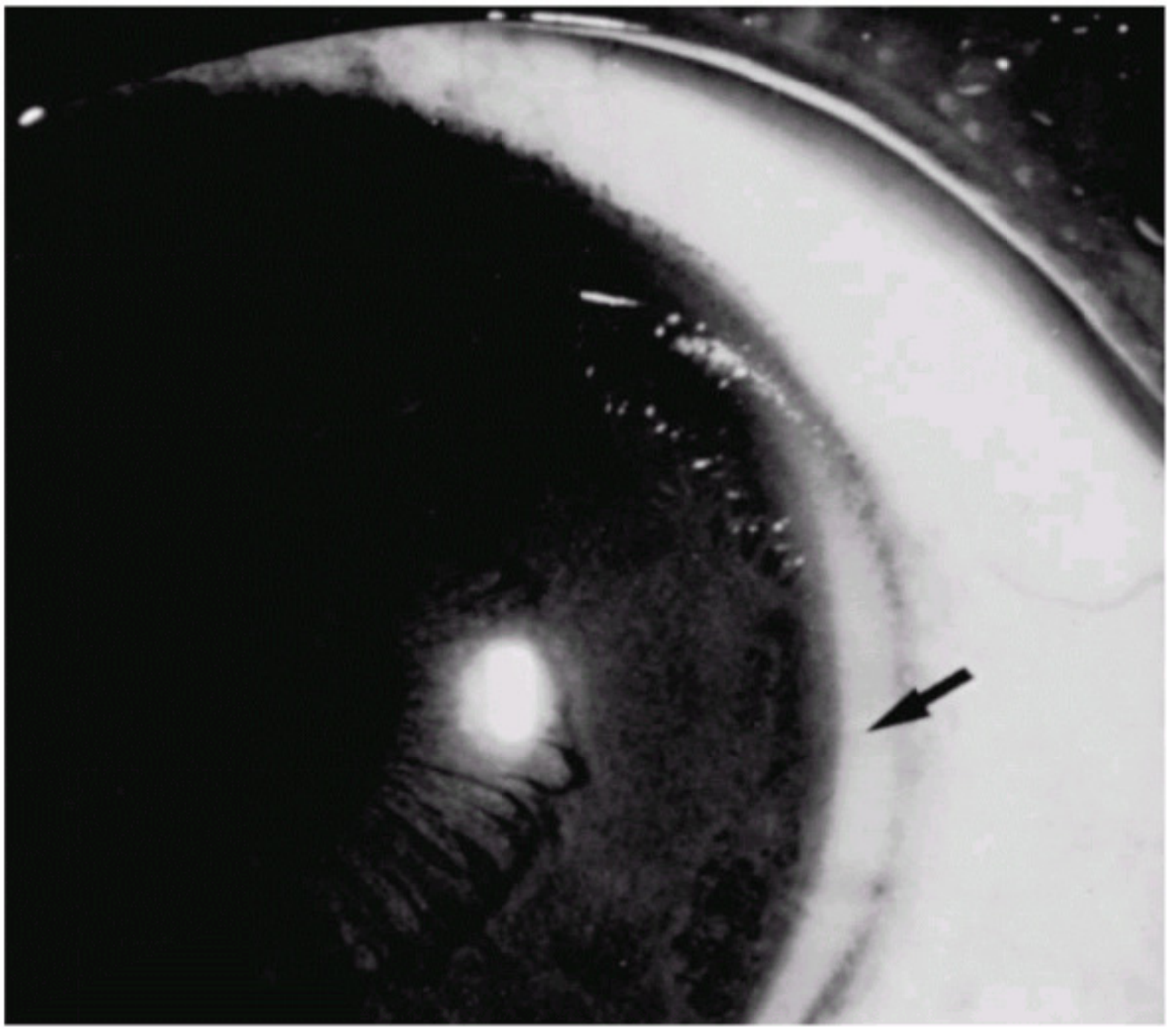

Figure 12.4 Prominent uveal trabecular meshwork. The limbus of the eye is demarcated by a pigment ring. Sclera extends up to but not beyond the ring. The light tissue lying central to the pigment ring (*arrow*) is the uveal trabecular meshwork.

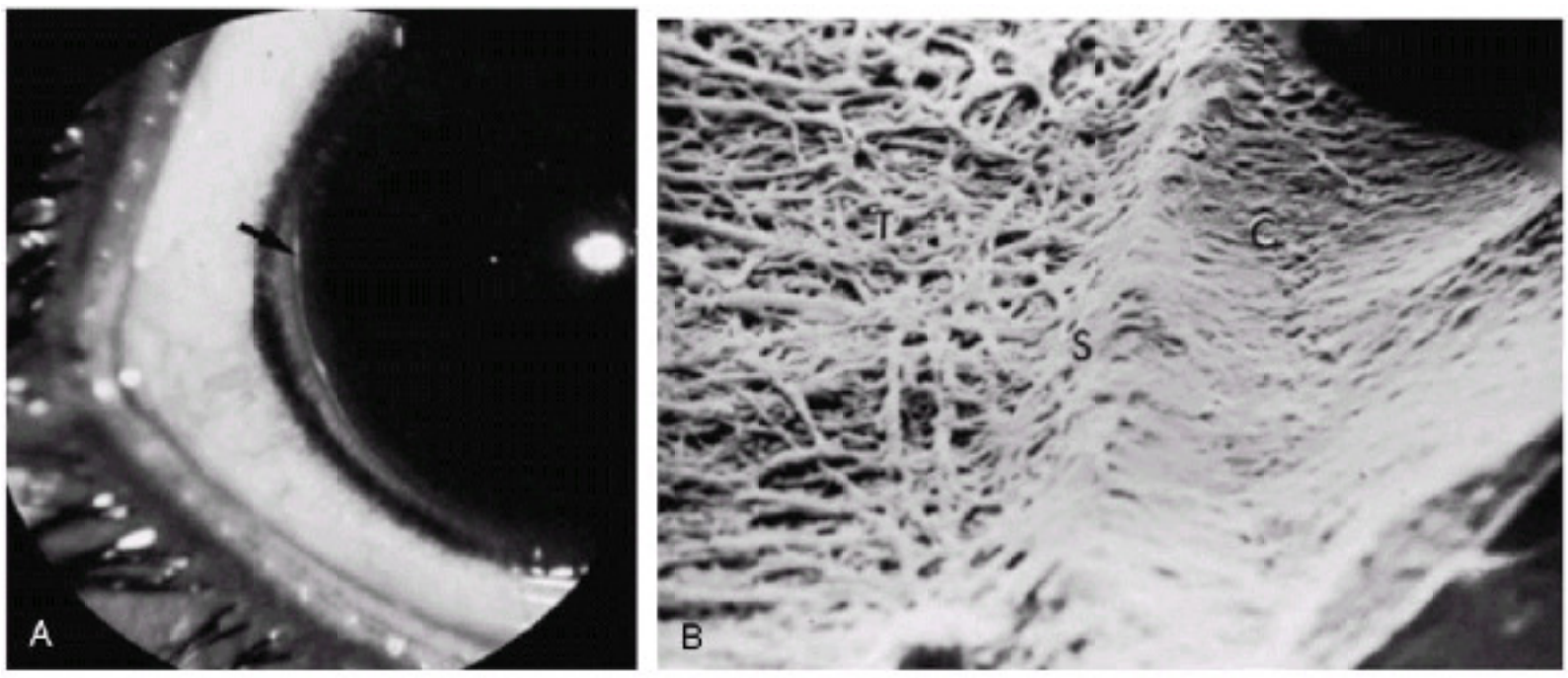

Figure 12.5 A: Prominent Schwalbe's ring (posterior embryotoxon). The limbal pigment ring and prominent uveal trabecular meshwork are present. The distinct white ring demarcating the uveal meshwork centrally is the enlarged, displaced Schwalbe's ring (*arrow*), which may be seen in about 10% of normal eyes. B: Scanning electron micrograph of normal Schwalbe's ring (*S*), cornea (*C*), and uveal trabecular meshwork (*T*) about at this junction. C: Scanning electron micrograph of prominent Schwalbe's ring (posterior embryotoxon). Endothelium covers both cornea (*C*) and elevated Schwalbe's ring (*S*). (Scanning electron micrographs, courtesy of Morton Smith, MD.)

Schwalbe's Ring

The corneal endothelium and Descemet's membrane meet the uveal trabecular meshwork at a junction designated as the anterior border ring of Schwalbe, or Schwalbe's line. This ring, part of the uveal meshwork, has a structure similar to a trabeculum, that is, a collagen-proteoglycan core surrounded by thin leaves of the terminal portion of Descemet's membrane and covered on its inner surface by endothelium. With a gonioscope the clinician sees it as a change from the refractile corneal endothelium to the reticulated translucent trabecular meshwork.

Schwalbe's ring may be thickened and positioned centrally, making it visible biomicroscopically as an irregular, refractile, white line lying concentric to the limbus and gonioscopically as a ridge protruding into the anterior chamber. It may be broken or continuous and frequently has pigment spots on its inner surface that represent previous attachment of iris strands. This centrally located prominent Schwalbe's ring is commonly called a *posterior embryotoxon* (Greek, *embryon* [“embryo”] plus *toxon* [“bow”]). It appears in 8% to 15% of normal eyes but is seen this frequently only by those who specifically look for it.

Congenital Anomalies of the Cornea

The clinician confronted with a child who has a developmental anomaly of the anterior ocular segment often has difficulty classifying and naming the disorder. This is an activity of more than academic value, because precise diagnosis is necessary before the ophthalmologist can predict the natural history of the disorder, look for specific associated ocular or systemic abnormalities, provide genetic counseling, and begin appropriate medical or surgical therapy. It is easiest to describe these abnormalities in terms of their anatomical components. Once clinicians have made a thorough description of the anatomical abnormalities, they can more precisely label the disorder.

This anatomical approach makes sense embryologically, because it is the neural crest-derived mesenchymal tissue that differentiates into the cornea (except the epithelium), the angle structures, and the iris stroma, and because this mesenchymal tissue may have an inductive effect on the optic cup that determines the size and shape of the pupil and ciliary ring. This approach also makes sense clinically, because many of the abnormalities so easily described in isolation occur in combination with other anomalies. For example, Rieger's anomaly (prominent Schwalbe's ring, iris strands to Schwalbe's ring, and hypoplasia of the anterior iris stroma) is accompanied by megalocornea in about 25 % of cases, scleralization of cornea in about 80% of cases, juvenile glaucoma without buphthalmos in about 25% of cases (3), and one form of Peters' anomaly in occasional cases.

Abnormalities of Corneal Size and Shape

Megalocornea

The newborn cornea measures about 10 mm in horizontal diameter and reaches the average adult measurement of 11.75 mmby age 2. Megalocornea is present, if the horizontal diameter of a newborn cornea is 12 mm or more and if an adult cornea is 13 mm or more (Fig. 12.6).

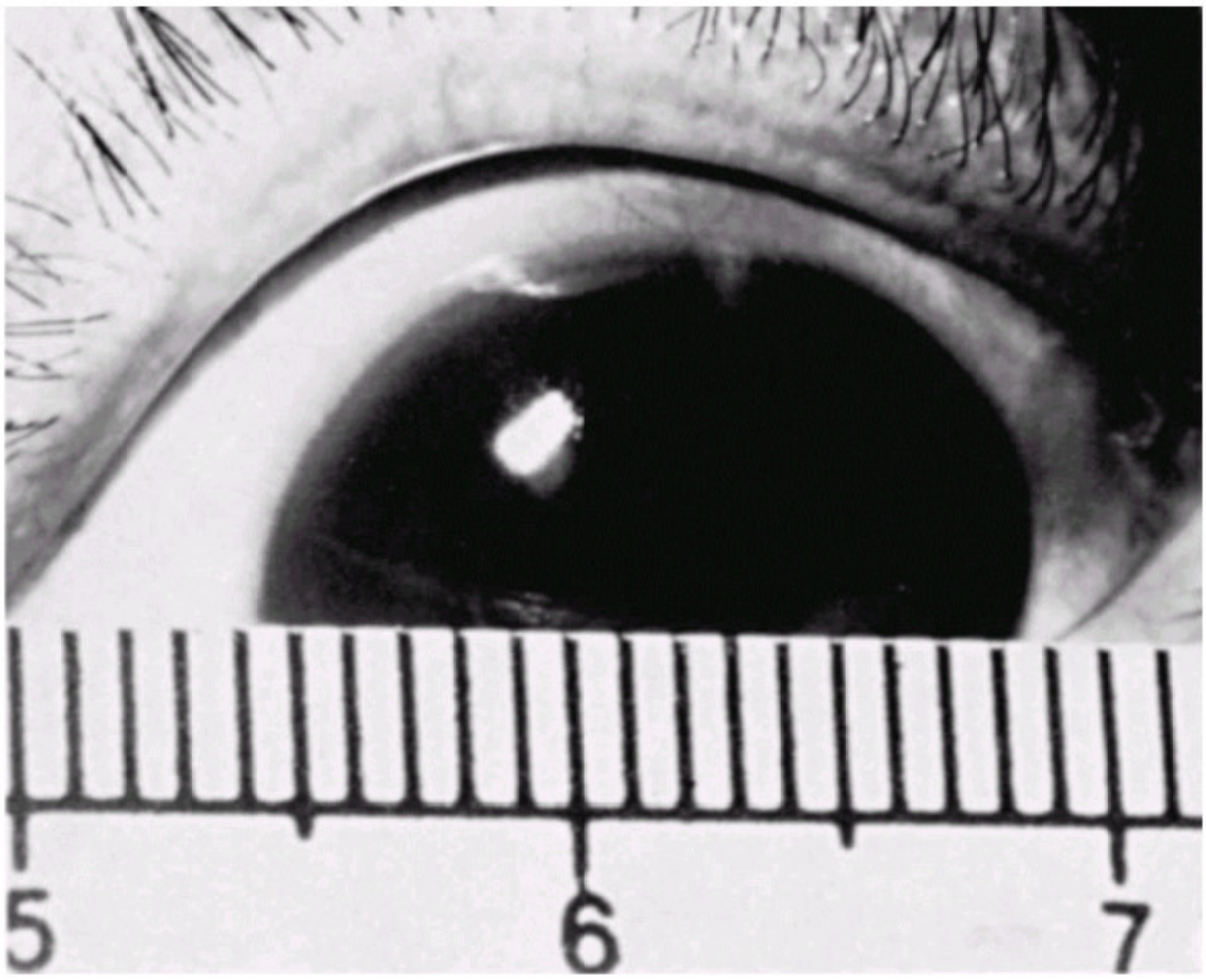

Figure 12.6 Anterior megalophthalmos. This cornea measures 15 mm in diameter and has normal thickness and clarity. The disorder is accompanied by transillumination defects in the iris and is associated with lens subluxation and cataract development in the fourth decade.

An enlarged cornea occurs in three patterns: (a) megalocornea unassociated with other ocular abnormalities, usually inherited as an autosomal dominant trait (4); (b) X-linked megalocornea or anterior megalophthalmos, an X-linked recessive trait that consists of megalocornea, iris and angle abnormalities, and lens subluxation with early cataract formation; and (c) buphthalmos in infantile glaucoma (5). In keratoglobus the protuberant thin cornea appears enlarged clinically but usually has a normal diameter. There seems to be no entity of “megaloglobus” in which the entire globe is congenitally enlarged with a normal intraocular pressure.

Simple Megalocornea

If bilateral clear corneas of normal thickness measure 13 mm or more in diameter without associated ocular abnormalities, the nonprogressive disorder of simple megalocornea exists, and once the diagnosis is clearly made, no other follow-up is necessary (6,7,8).

X-Linked Megalocornea (Anterior Megalophthalmos)

X-linked megalocornea, a recessive disorder that is the most common type of megalocornea, manifests as bilateral, symmetrically enlarged corneas that remain stable throughout life and sometimes contain a stromal mosaic pattern (9,10,11). The deep anterior chamber occurs because the normal-sized lens, which is too small for the enlarged ciliary ring, subluxates. The iridocorneal angle is open but contains excess mesenchymal tissue, whereas the iris manifests a hypoplastic anterior stroma and transillumination defects. The pupil is often ectopic.

The two associations that threaten vision are the frequently

elevated intraocular pressure, which requires lifelong annual examinations for early detection; and cataracts, which often appear in the fourth decade and may require the use of vitrectomy-type instruments during extraction, because the lenses are dislocated.

TABLE 12.1 DIFFERENTIAL DIAGNOSIS OF ENLARGED CORNER

	Simple Megalocornea	Anterior Megalophthalmos	Primary Infantile Glaucoma with Buphthalmos
Inheritance	Autosomal dominant (?)	X-linked recessive (male preponderance)	Sporadic
Time of Appearance	Congenital	Congenital	First year of life
Bilaterality	Bilateral	Bilateral	Unilateral or bilateral
	Symmetrical	Symmetrical	Asymmetrical
Natural History	Nonprogressive	Nonprogressive	Progressive
Symptoms	None	None	Photophobia, epiphora
Corneal Clarity	Clear	Clear or mosaic dystrophy	Diffuse edema, tears in Descemet's membrane
Intraocular Pressure	Normal	Elevated in some adults	Elevated
Corneal Diameter	13-18 mm	13-18 mm	13-18 mm
Corneal Thickness	Normal	Normal	Thick
Keratometry	Normal	Normal; ? astigmatism	Flat
Gonioscopy	Normal	Excessive mesenchymal tissue	Excessive mesenchymal tissue
Globe Diameter (A-scan)	23-26 mm	23-26 mm	27-30 mm
Anterior Chamber Depth (A-scan)	Presumably normal (3 mm)	Approximately 5 mm	Approximately 4 mm
Major Ocular Complications	None	Lens dislocation, cataract <40 yr, secondary glaucoma	Optic disc damage, late corneal edema
Associated Systemic Disorders	None	Occasionally Marfan's and other skeletal abnormalities	None consistent

yr, year.

The clinician may have difficulty distinguishing among isolated megalocornea, anterior megalophthalmos, and infantile glaucoma in a young child with an enlarged cornea. Table 12.1 presents the distinctive features of these three disorders.

Keratoglobus

Keratoglobus is a distinct, rare entity different from keratoconus, megalocornea, and corneal enlargement secondary to congenital glaucoma. In this condition, the cornea exhibits generalized thinning and anterior bulging. The thinning is greatest in the midperiphery of the cornea. Keratoglobus may occur as an autosomal recessive disorder that is part of the Ehlers-Danlos syndrome type VIA, in which it is accompanied by hyperextensible joints, blue sclerae, and neurosensory hearing loss. It has also been reported as an acquired condition, associated with various disorders, including vernal keratoconjunctivitis and thyroid ophthalmopathy. In keratoglobus the cornea is one-third normal thickness, usually has a normal diameter, and arcs highly over the iris, creating a very deep anterior chamber. Acute spontaneous breaks in Descemet's membrane may produce focal stromal edema (acute hydrops) and heal spontaneously in weeks to months. Minor blunt trauma to the eye or to the head frequently ruptures the cornea and sclera, so the ophthalmologist must counsel the parents of these children to provide a safe environment and protective spectacles or eyeguards. Amblyopia is often severe because of the high myopia, a problem diminished by carefully fitted spectacles or contact lenses. In patients with severe thinning and anterior bulging of the cornea, surgical treatment may be contemplated. Given the diffuse corneal thinning to the limbus, surgical repair is problematic at best. Perhaps the best approach is a large limbus-to-limbus onlay lamellar keratoplasty or epikeratoplasty to both reinforce the corneal integrity and provide a more normal curvature. If the central cornea is scarred, typically from a previous episode of hydrops, a subsequent central visual penetrating keratoplasty can be performed (12,13,14,15).

Microcornea

A cornea 7 to 10 mm in diameter occurs in a variety of clinical settings, making classification difficult (Fig. 12.7). Both autosomal dominant and autosomal recessive patterns of inheritance occur, but microcornea may appear sporadically.

Microcornea may be an isolated abnormality in an otherwise normal eye (16,17,18). It may be associated with nanophthalmos (also called simple microphthalmos), a small, anatomically normal globe (19,20,21,22); or part of microphthalmos (also called complex microphthalmos), a small globe with multiple anomalies (23). A-scan ultrasonography can help distinguish isolated microcornea from microphthalmos (17).

Management of eyes with microphthalmos varies according to the associated abnormalities. In each case a careful, early refraction may help prevent amblyopia. Lifelong

examinations will detect intraocular pressure elevation, which occurs more commonly in eyes with microcornea. Associated cataracts should be removed, using special care in eyes manifesting other anomalies (24).

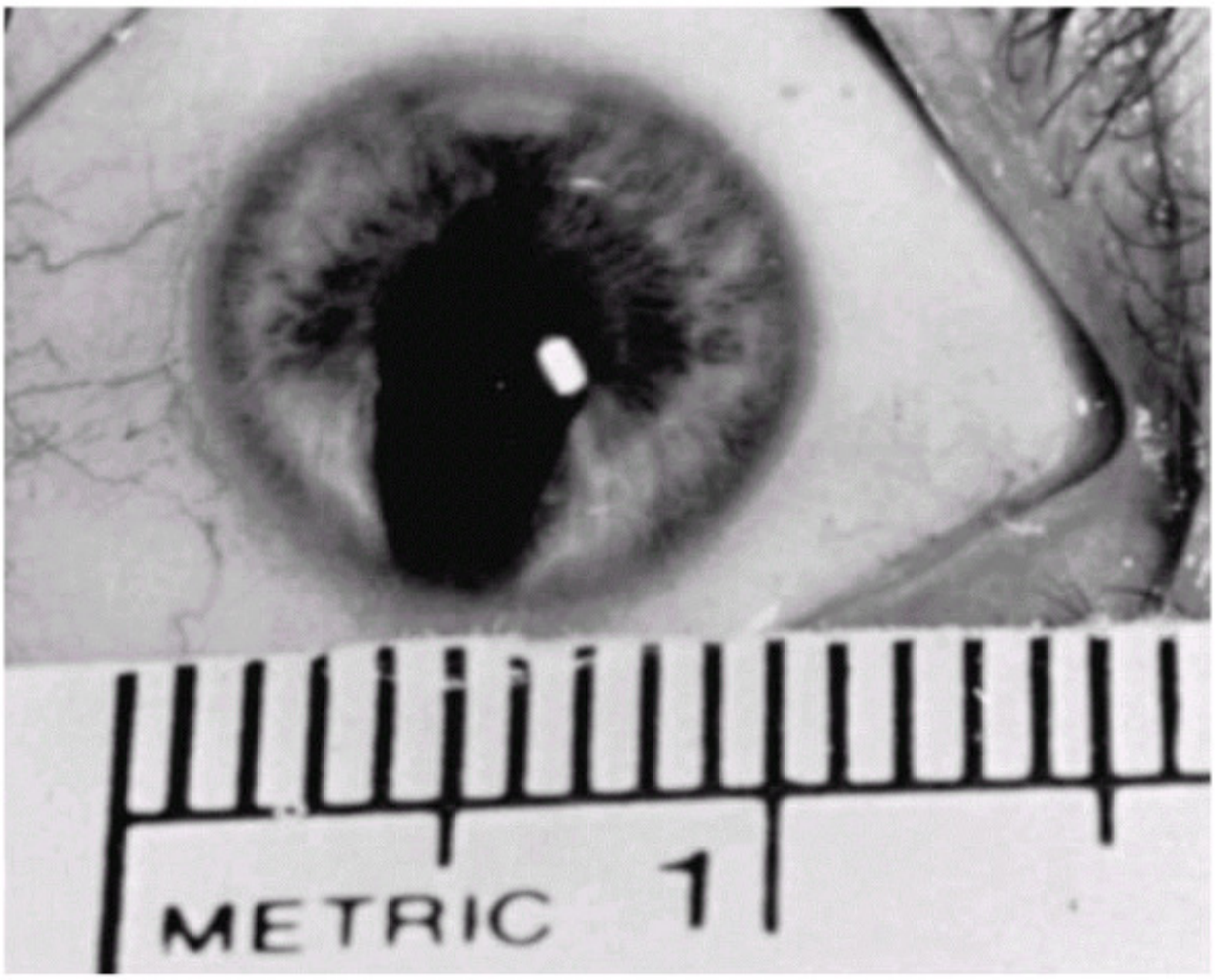

Figure 12.7 Microcornea, measuring 9 mm in diameter and accompanied by atypical iris coloboma and congenital cataracts. The disorder was inherited as an autosomal dominant trait in this family.

Anterior Chamber Cleavage Syndrome

Many abnormalities of the cornea, angle, and iris can be classified in anatomical stepladder fashion, which builds from simple to more complex combinations (25). This approach simplifies our understanding of these anomalies, because the clinician or pathologist needs only to describe the anatomical findings, rather than worry about the proper eponyms or obscure Latin phrases (26). Unusual anomalies that do not fit into preestablished categories (27) can be inserted into this tabular classification on the basis of their anatomical components. Figure 12.8 represents this classification and includes commonly used eponyms.

We prefer the term coined by Reese and Ellsworth (28), “anterior chamber cleavage syndrome,” because it is easy to remember and has a graphic quality that

brings to mind the contact between the cornea, iris, and lens. When accompanied by an accurate anatomical description, the term is quite useful. Others may prefer descriptive designations, such as “mesodermal dysgenesis of the iris and cornea,” (3) although this term is outdated, because it is now thought that the iris and cornea arise from neural crest ectoderm (29).

These malformations conveniently fall into three groups: (a) peripheral (prominent Schwalbe's ring, iris strands to Schwalbe's ring, and hypoplasia of the anterior iris stroma); (b) central (central posterior corneal defect, central iridocorneal adhesions, corneolenticular approximation); and (c) combinations of the peripheral and central components.

Peripheral Anterior Chamber Cleavage Abnormalities

Prominent Schwalbe's Ring with Attached Iris Strands (Axenfeld's Anomaly)

Iris strands that span the angle to insert on the prominent Schwalbe's ring (Fig. 12.9) display variable morphology: fine threadlike filaments with a terminal knob, broad conical bands, or a confluent, fenestrated, lattice-like membrane. In some cases the pupil is distorted. About 50% of patients with this abnormality develop glaucoma, usually of a juvenile type, which often goes unrecognized. Therefore, the prudent clinician who spots a prominent Schwalbe's ring on slit-lamp examination will perform a quick gonioscopy, searching for the iris strands of Axenfeld's anomaly. If the anomaly is present, the patient should have lifelong measurements of intraocular pressure. Axenfeld's syndrome is defined as Axenfeld's anomaly plus glaucoma. In some cases of both Axenfeld's anomaly and syndrome, skeletal anomalies are present (25).

Prominent Schwalbe's Ring with Attached Iris Strands and Hypoplastic Anterior Iris Stroma (Rieger's Anomaly)

Rieger's anomaly (Figs. 12.10, 12.11, 12.12, 12.13 and 12.14), which is autosomal dominant in 70% of cases (3), with a 95% penetrance and extreme variation in expressivity, lacks the superficial iris stroma, so that instead of crypts, furrows, and a collarette, the iris manifests a stringy appearance because the delicate radial fibrils of the posterior stroma show through. Abnormally shaped pupils occur commonly: slit-shaped, pearshaped, round, ectopic, part of an atypical coloboma, or very large pupils, as in a partial aniridia. In rare cases the iris atrophy progresses.

Open-angle glaucoma is found in about 60% of these patients, appearing usually between ages 5 and 30 years, but may occur at any time throughout life, requiring annual intraocular pressure measurements in all affected individuals. Rieger's syndrome occurs when systemic anomalies are also present. Commonly associated systemic abnormalities include maxillary hypoplasia; telecanthus with a broad, flat nasal root; dental abnormalities, such as microdontia or anodontia; and umbilical hernia. Less commonly, visceral defects, such as congenital heart anomalies, middle ear deafness, mental retardation, and cerebellar hypoplasia, occur. Skeletal anomalies include malformation of the limbs and spine and Marfan's syndrome.

Chromosomal analysis has mapped the genetic abnormality in Rieger's syndrome to the long arm of chromosome 4, specifically 4q25 or 4q27 (30). Rieger's anomaly, on the other hand, has been shown not to map to the same area as Rieger's syndrome (31).

Iris Strands in Angle and Hypoplasia of Anterior Iris Stroma (Iridogoniodysgenesis)

This abnormality, inherited in an autosomal dominant pattern, resembles Rieger's anomaly without the prominent Schwalbe's ring (32). Affected individuals very commonly have juvenile glaucoma.

Prominent Schwalbe's Ring and Hypoplasia of the Anterior Iris Stroma

This uncommon abnormality illustrates the usefulness of the anatomical stepladder approach, since no eponym has been given to it. Affected individuals are at risk of developing juvenile glaucoma.

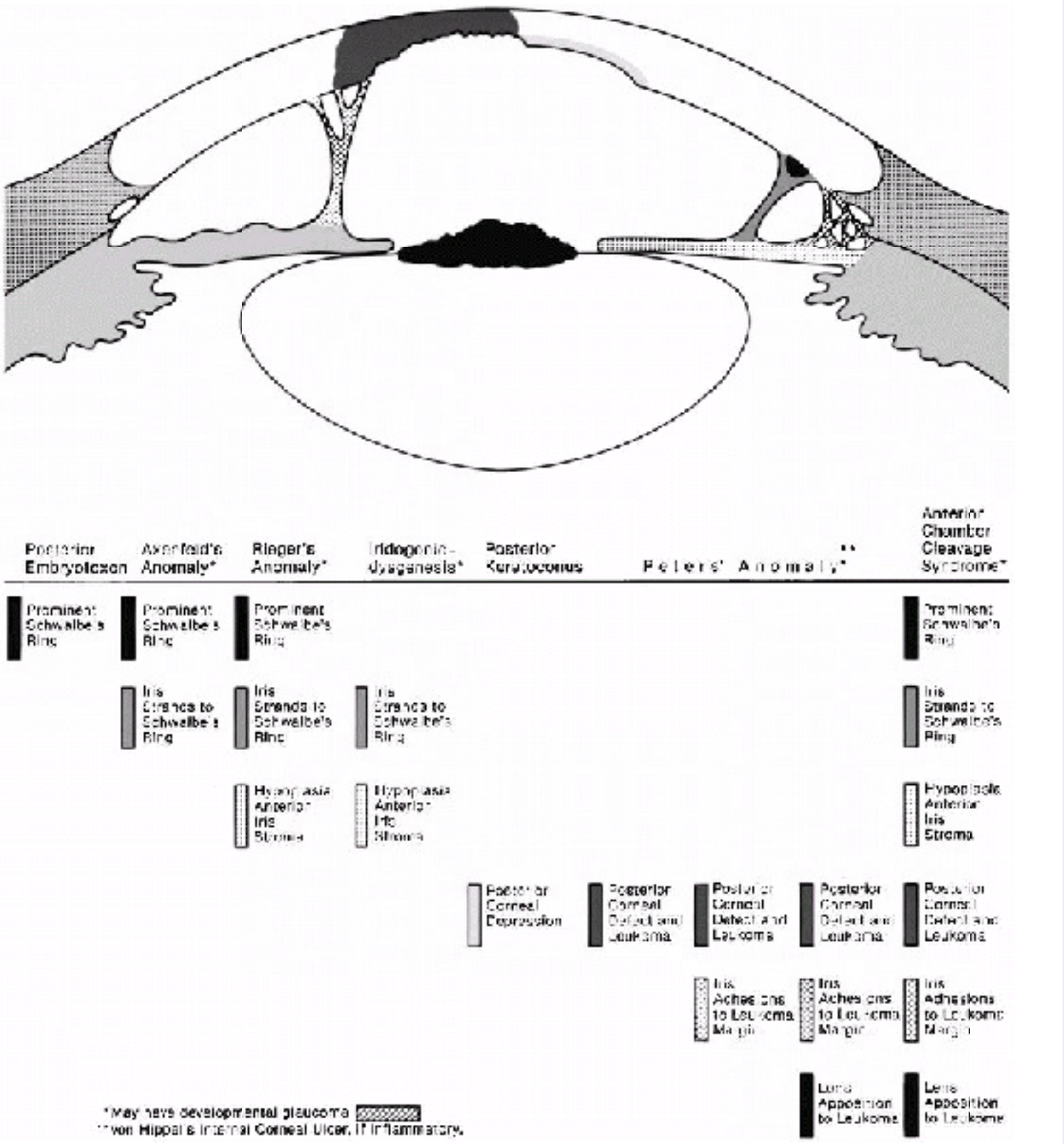

Figure 12.8 Composite illustration of the anatomical findings in the anterior chamber cleavage syndrome. The stepladder table demonstrates the spectrum of anatomical combinations and the terms by which they are commonly known. The colored markers in the table indicate the corresponding anatomical component in the illustration. (From Waring GO, Rodrigues M, Laibson PR, et al. Anterior chamber cleavage syndrome: a stepladder classification. *Surv Ophthalmol* 1975;20:5, with permission.)

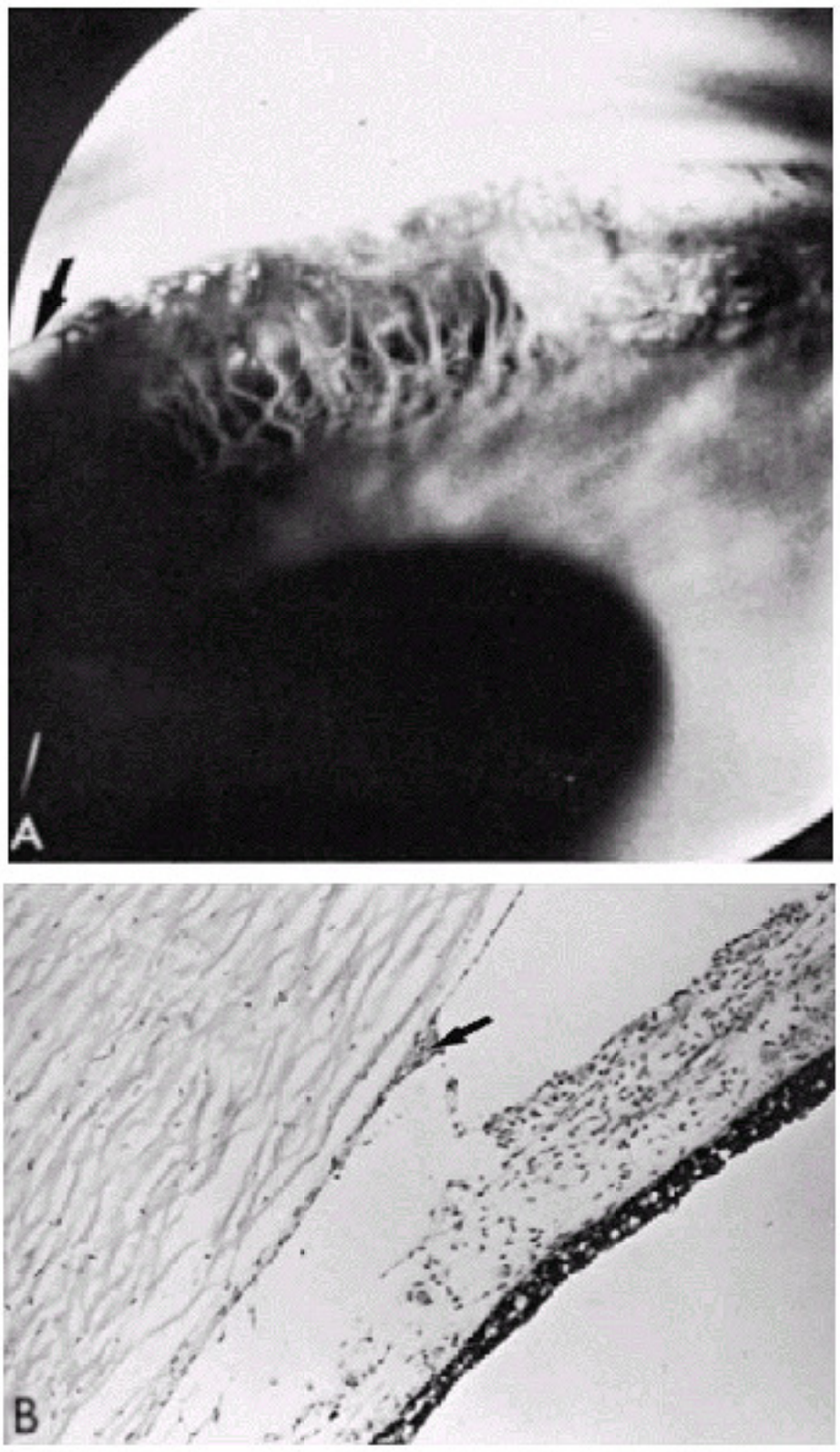

Figure 12.9 Axenfeld's anomaly. **A:** Gonioscopic view shows the angle recess filled with dense iris processes (persistent mesenchymal tissue) that extend to a prominent Schwalbe's ring (*arrow*). This configuration may exist alone or as a part of a variety of iridocorneal dysgeneses (Courtesy of Robinson D. Harley, MD). **B:** Histological section showing the prominent centrally displaced Schwalbe's ring (*arrow*) with iris processes extending to it and across the angle recess (×64). (Courtesy of Merlyn Rodrigues, MD.)

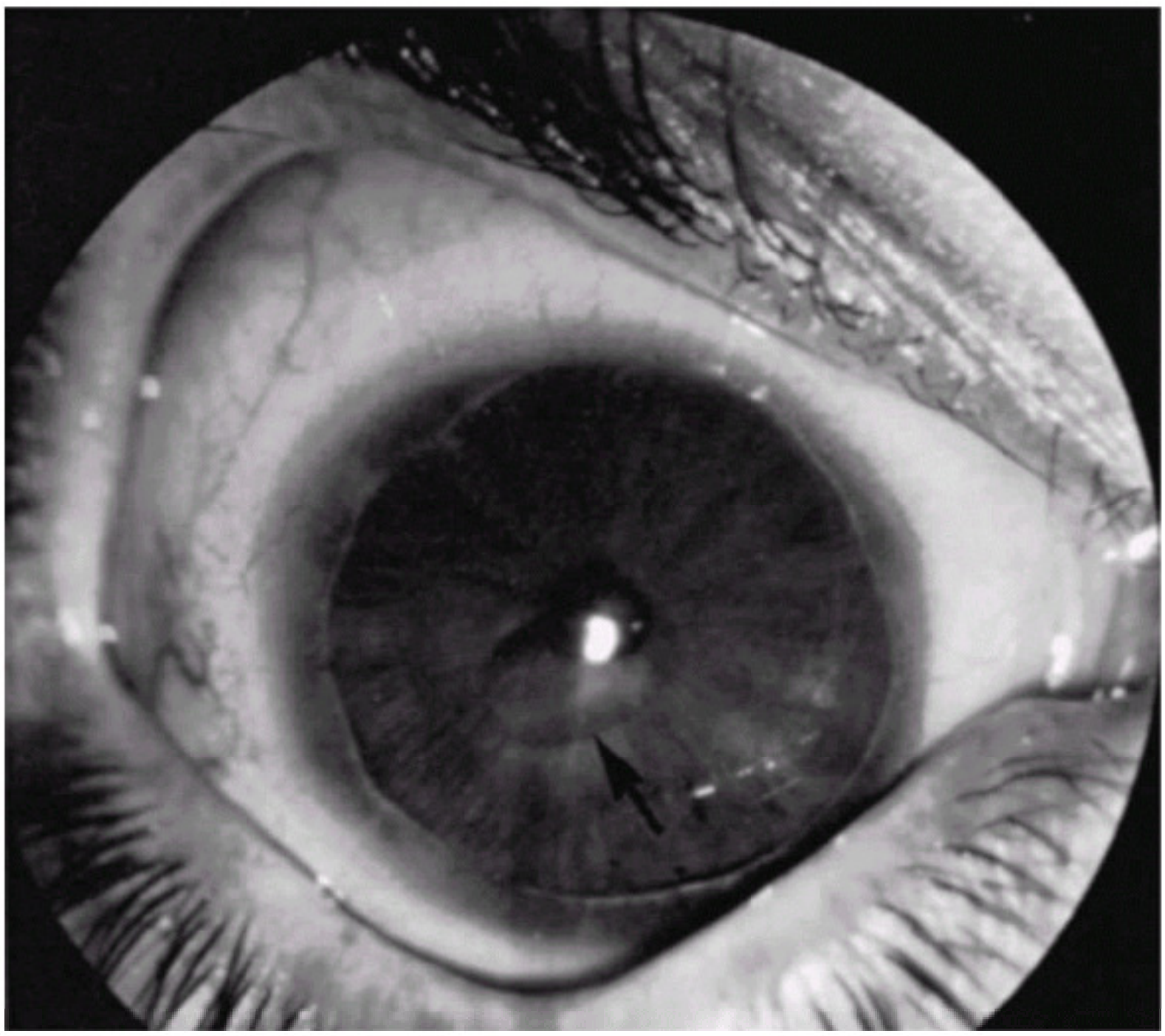

Figure 12.10 Rieger's anomaly with central posterior corneal defect. This right eye of a 23-year-old dwarf demonstrates a prominent Schwalbe's ring with the iris process extending to it, an atrophic anterior iris stroma, and a central posterior corneal defect (posterior keratoconus) (*arrow*). Intraocular pressure was normal. The left eye appeared similar.

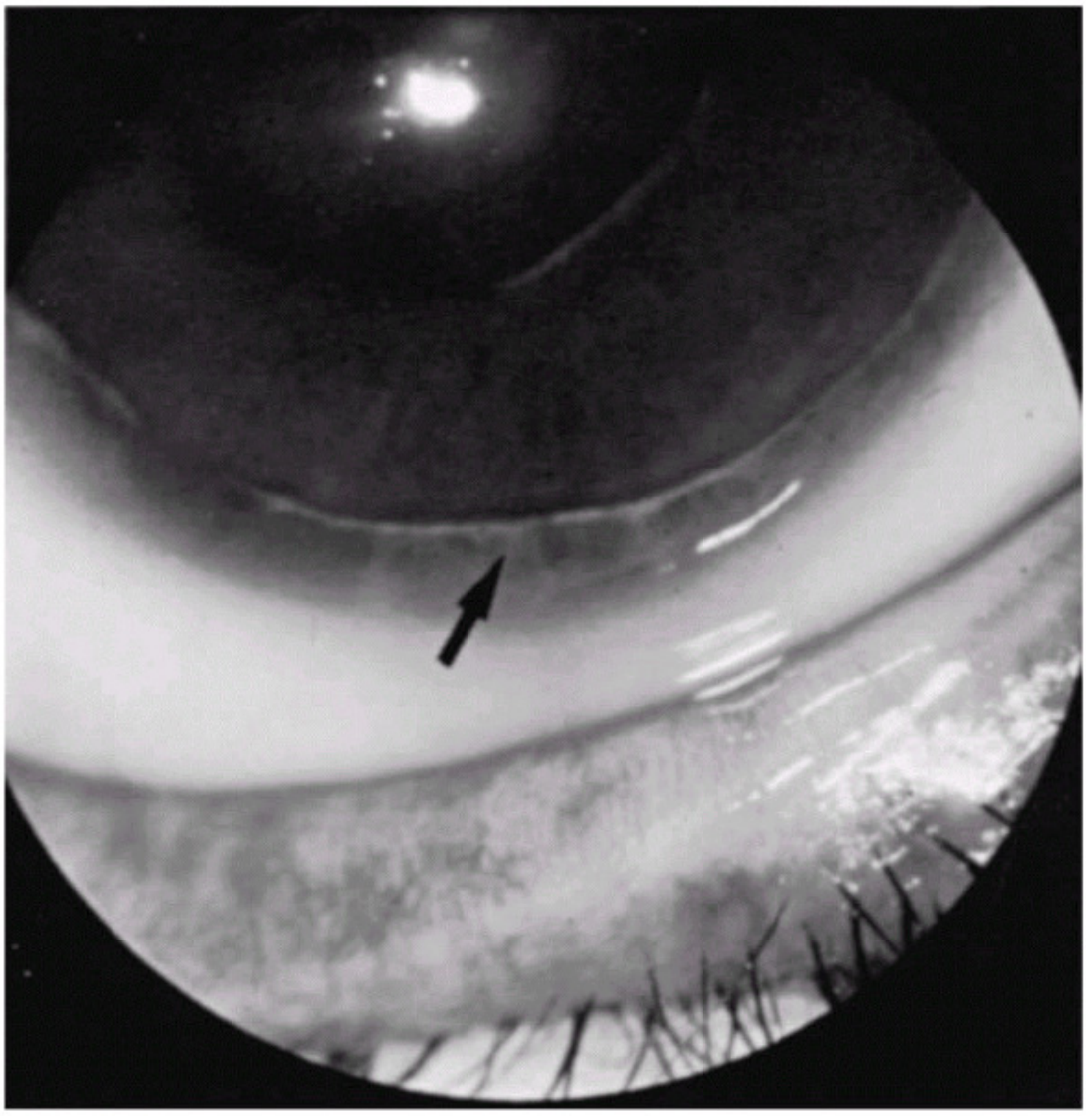

Figure 12.11 Rieger's anomaly. Closeup of 6 o'clock limbus of eye. Iris processes (*arrow*) extend to the irregular prominent Schwalbe's ring.

Infantile Glaucoma

If this classification is extended, infantile glaucoma (with or without buphthalmos) can be added, on the basis that it represents a mesenchymal goniodysgenesis. In fact, some authors think that the megalocornea seen in infantile glaucoma is a result of a primary keratodysgenesis, rather than a result of stretching from increased intraocular pressure (33).

The management of infantile and juvenile glaucoma is discussed in Chapter 14.

Central Anterior Chamber Cleavage Abnormalities

General Features

The basic abnormality in this group is a focal attenuation or absence of the corneal endothelium and Descemet's

membrane, usually associated with an overlying corneal opacity. In contrast with the peripheral abnormalities, the central disorders have two separate etiologies, primary dysgenesis and secondary to inflammation, but the clinical and histopathological distinction between the two is difficult. Presumably, if the cornea is avascular and there are no signs of inflammation, one can assume that the disorder is a primary dysgenesis; however, if the cornea is opaque and vascularized, intrauterine inflammation may have been present. Therefore, these entities are discussed on the basis of their anatomical findings alone, rather than their pathogenesis. Although an autosomal recessive pattern has been described (3), sporadic cases appear most frequently. Glaucoma is present in about half the cases, usually appearing as a nonbuphthalmic infantile form.

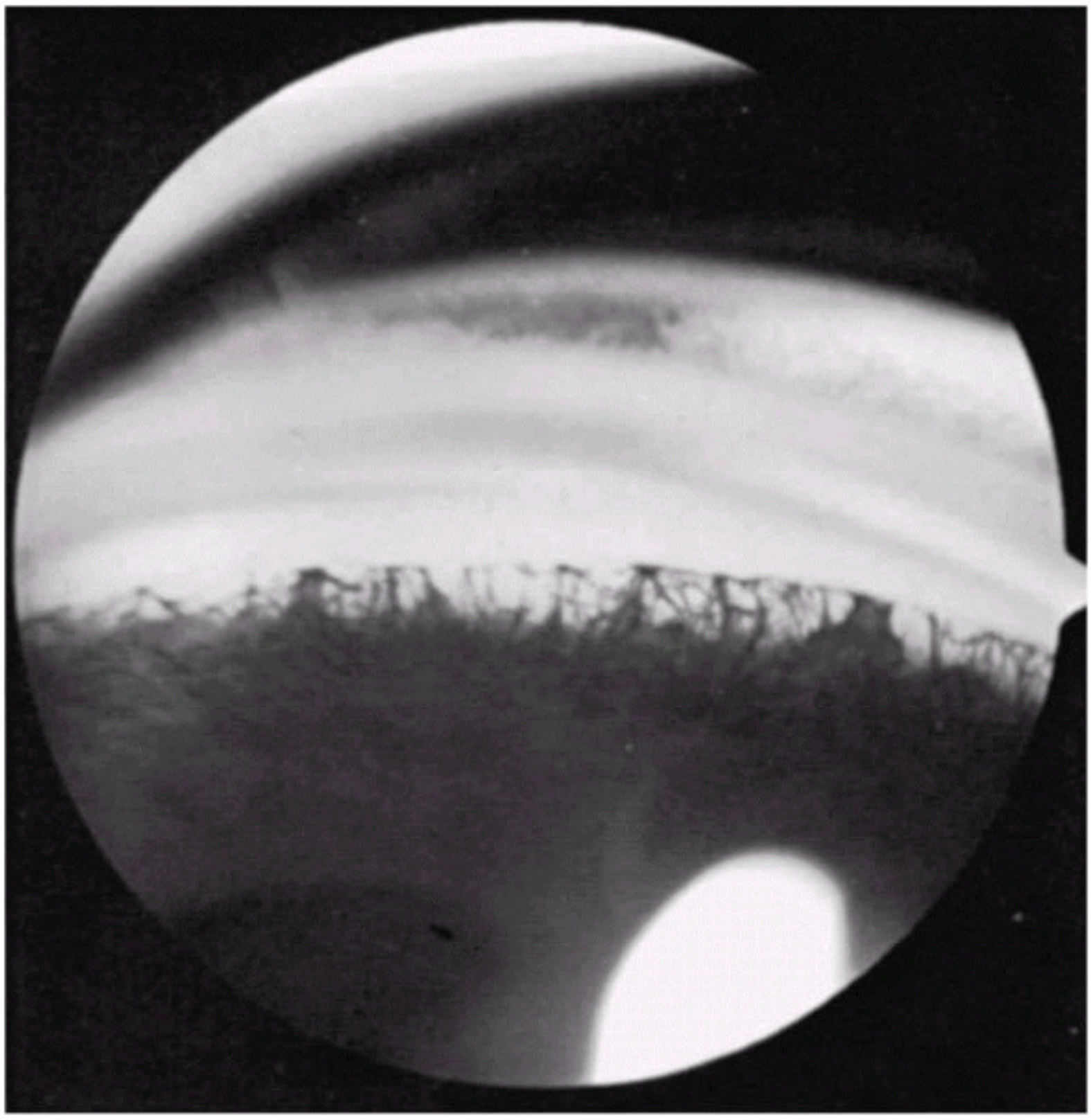

Figure 12.12 Angle in Rieger's anomaly. Gonioscopic appearance of eye in Figure 12.11, showing iris processes extending to the prominent Schwalbe's ring.

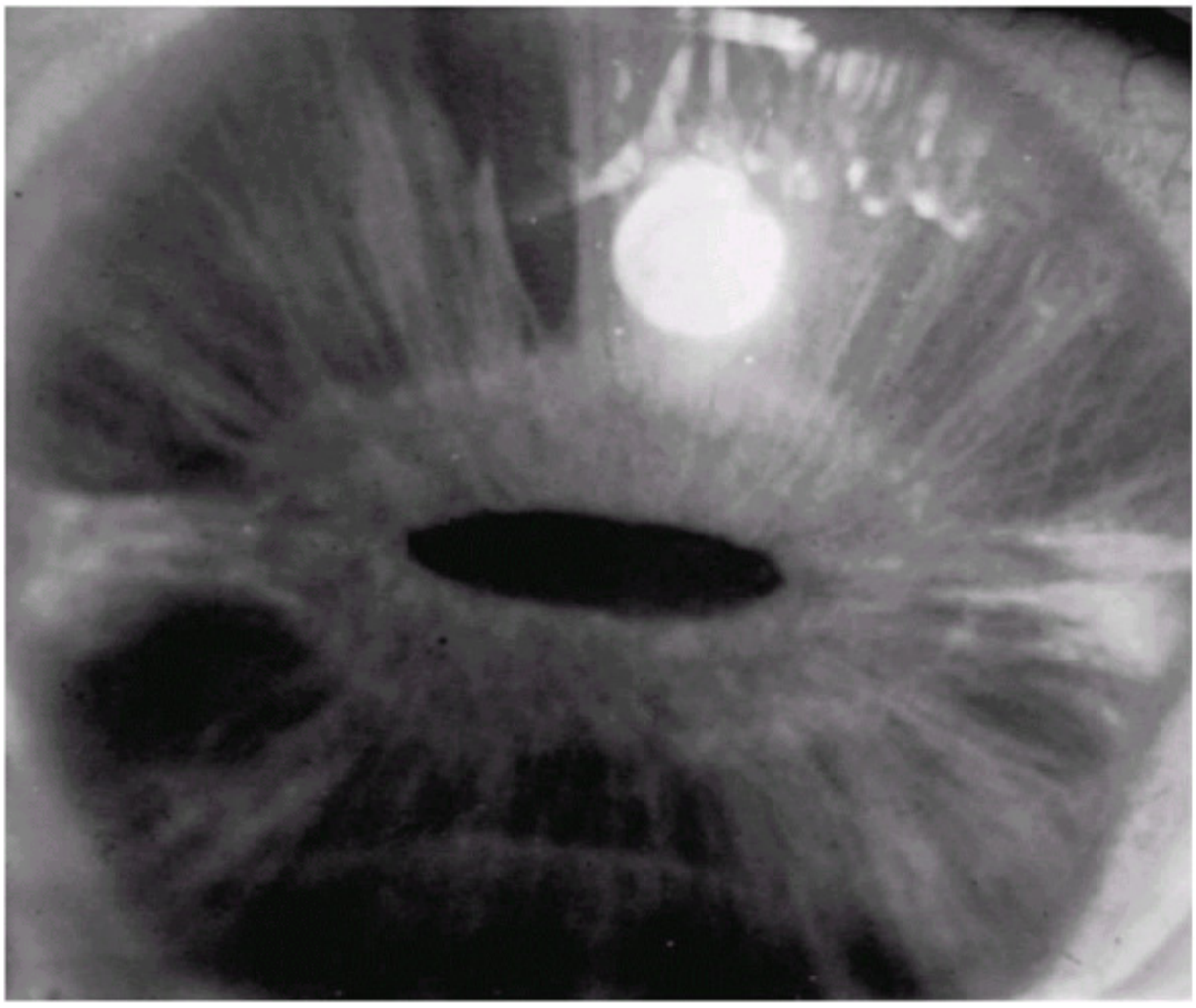

Figure 12.13 Rieger's anomaly. The right eye shows marked hypoplasia of the anterior iris stroma. The deep stroma is thin and fibrillary, revealing the underlying iris epithelium and pupillary sphincter. The pupil is slit-shaped and central. The prominent Schwalbe's ring is poorly illustrated. (Courtesy of George Spaeth, MD.)

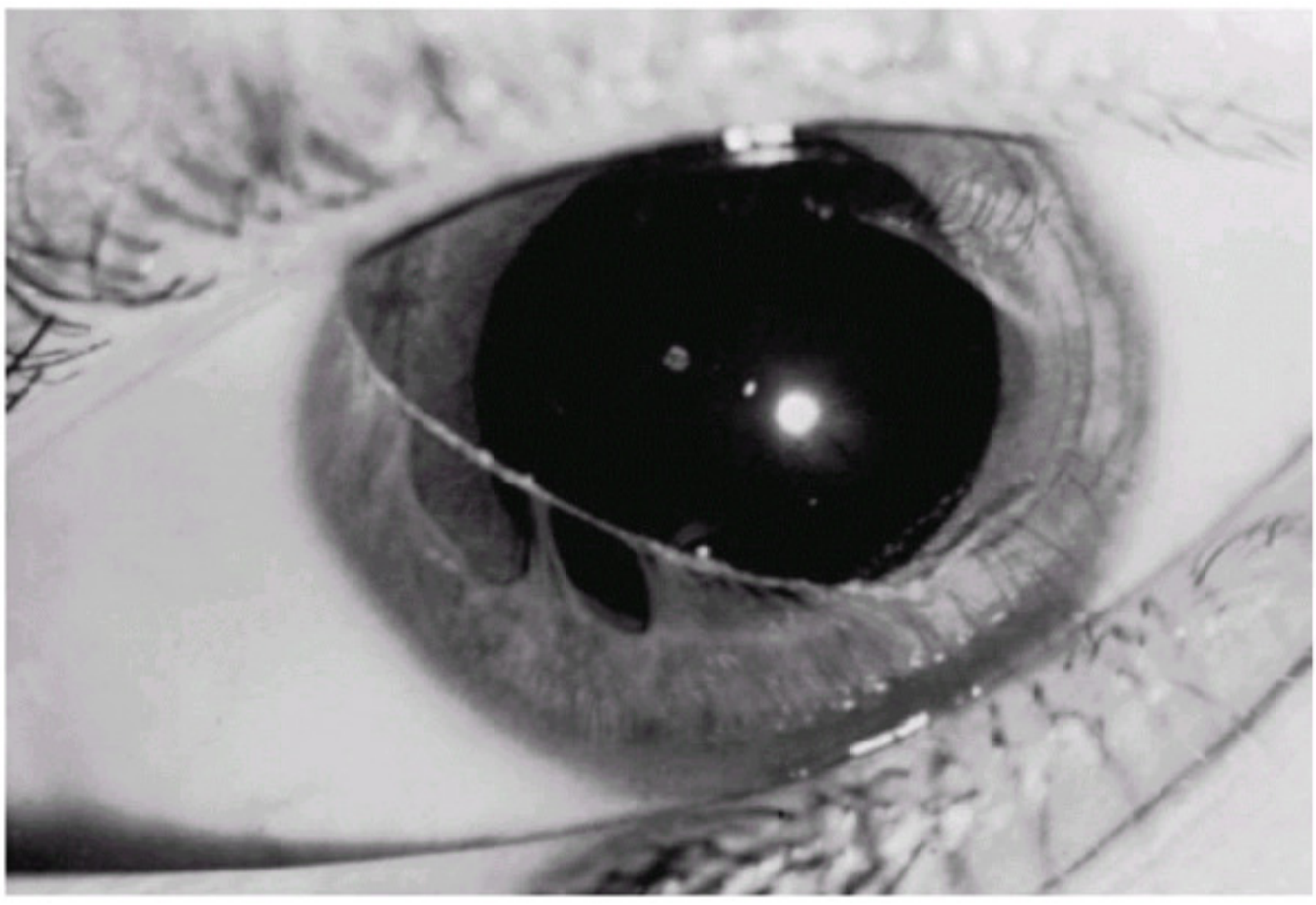

Figure 12.14 Rieger's anomaly. This 10-year-old white girl has a centrally displaced prominent Schwalbe's ring with iris processes extending to it from the angle recess and the collarette. Anterior iris stroma is absent at 11 o'clock position. The configuration is accentuated by the dilated pupil. Intraocular pressure was normal. No other ocular anomalies existed. (Courtesy of Harold Koller, MD.)

Postnatally, the corneal opacity may clear somewhat, particularly if it is avascular, central, and consists mostly of edema. On the other hand, the opacity may progressively vascularize, particularly if the cornea is ectatic and the anterior segment derangement is severe.

Posterior Corneal Depression (Central Posterior Keratoconus)

This focal, discrete, posterior corneal indentation has a faint overlying stromal haze and is usually central, unilateral, and nonprogressive (Fig. 12.15) (34,35). In some instances a ring of pigment clumps surrounds the depression, indicating previous iris contact (36). The anterior corneal curvature is not dramatically irregular, and the disorder is unrelated to the more common form of acquired progressive keratoconus. Visual acuity is only moderately reduced, presumably because of the irregular astigmatism resulting in mild amblyopia. Some authors described a total posterior keratoconus, which may be a variant of the more common

progressive degenerative type. Histopathologically, abnormalities include an irregularly thickened epithelial basement membrane, focal disruption of Bowman's layer, stromal irregularity, and a multilaminar Descemet's membrane that contains wide-spacing material and focal excrescences (37). Scanning electron microscopy was recently used to evaluate a cornea with posterior keratoconus, revealing no excrescences of Descemet's membrane or endothelial tags (38). Given these findings, Al-Hazzaa et al. suggest there may be a subset of posterior keratoconus patients who do not fall into the category of anterior chamber cleavage abnormalities.

Figure 12.15 Posterior keratoconus. Slit-lamp view of the eye in Figure 12.11, showing the depression in the posterior corneal surface (*arrow*). The cornea overlying it is clear, and no iris processes extend to its margin.

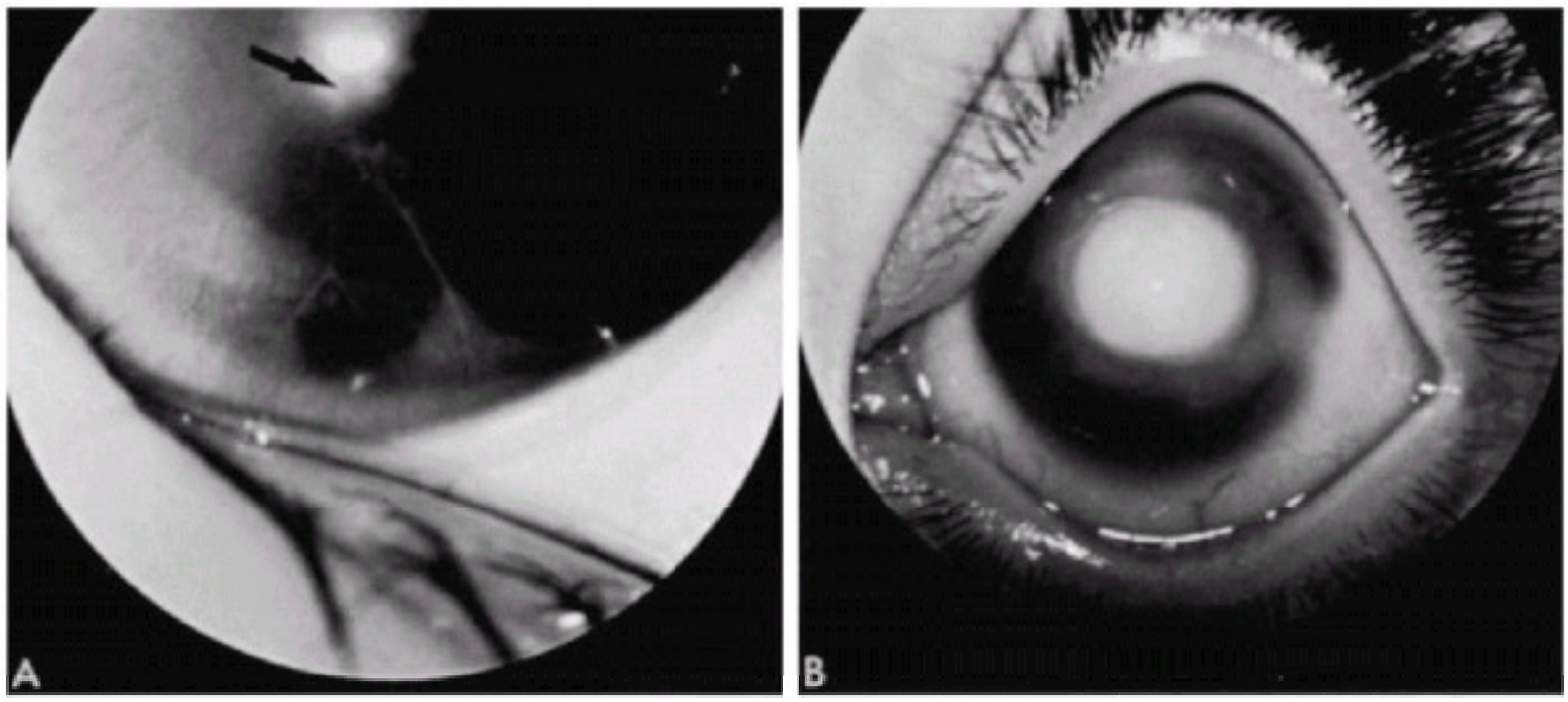

Figure 12.16 A: Peters' anomaly. A mild form showing attenuated iris adhesions to the border of a small corneal opacity (*arrow*). This was present bilaterally in this 9-month-old white girl. **B:** Peters' anomaly. This 10-month-old white girl had bilateral congenital central corneal opacities. During penetrating keratoplasty, iris adhesions were found extending from the pupillary margin to the borders of the opacity. An anterior polar cataract was present. (Courtesy of Harold Koller, MD.)

The anterior corneal curvature in eyes with posterior keratoconus has generally been described as essentially normal. One problem is that most methods used to evaluate corneal curvature, including the keratometer and keratoscope, do not examine the central few millimeters of cornea well at all. With the recent advent of computerized corneal videokeratography, central as well as midperipheral anterior corneal curvature can be effectively analyzed. Computerized corneal videokeratography was performed on an eye with posterior keratoconus, revealing a central steepened “cone” associated with the area of posterior corneal thinning (39).

Posterior Corneal Defect with Overlying Leukoma

This is the simplest form of Peters' anomaly, in which the iris and lens are normal but a defect in the posterior cornea has produced an overlying opacity. If the opacity is dense enough, it may obscure the more normal anterior segment anatomy.

Posterior Corneal Defect with Stromal Opacity and Adherent Iris Strands (Peters' Anomaly)

The size and density of the corneal opacity and the depth of the posterior defect vary widely, from a small, central, focal, ground-glass opacity (Fig. 12.16A); to a dense, round leukoma (Fig. 12.16B); to total corneal vascularization and scarring with an elevated mass (see Fig. 12.18A). The lens is clear and in normal position. The configurations of the iris strands that extend from the collarette to the margin of the posterior defect are as diversified as the opacity and include fine filaments (Fig. 12.16A), broad bands, and fenestrated sheets.

The histopathological findings are equally varied but usually include thickening or fragmentation of Bowman's layer, disorganization of stromal architecture, central absence of Descemet's membrane and endothelium (both of

which are present peripherally), and central iridocorneal adhesions (Figs. 12.17 and 12.18C, D).

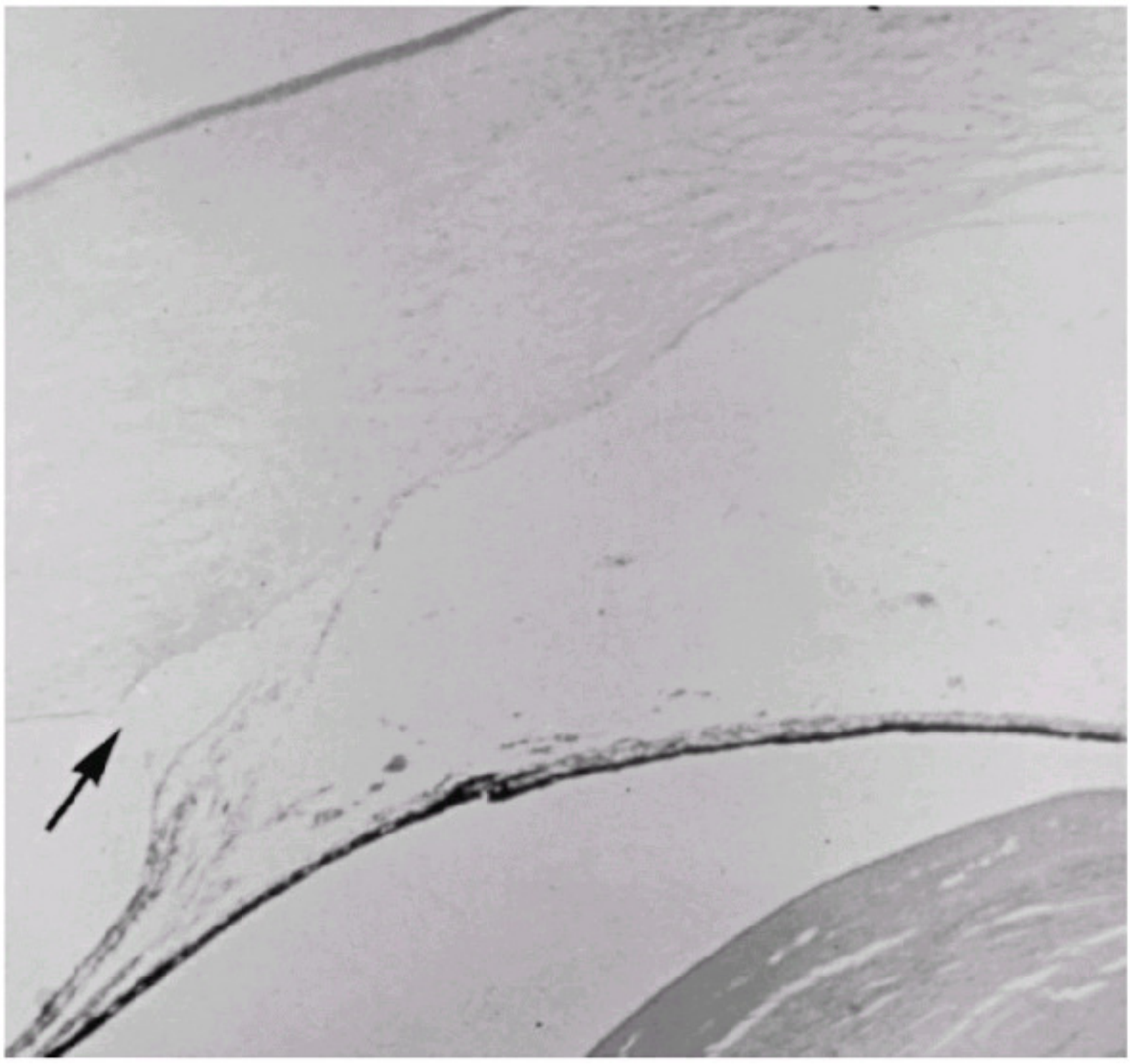

Figure 12.17 Peters' anomaly. Histological section demonstrates iris adhesions that extend from the collarette to the margin of a central posterior corneal defect. The overlying cornea is edematous. Descemet's membrane ends abruptly at the margin of the central defect (*arrow*) (×6). (Courtesy of Robert D'Amico, MD.)

Posterior Corneal Defect with Stromal Opacity, Adherent Iris Strands, and Corneolenticular Contact or Cataract (Peters' Anomaly)

In this variant of Peters' anomaly, a variety of lens abnormalities occur (40), including adhesion of lens cortex to the corneal stroma at the site of the posterior defect (Fig. 12.19) (41), approximation to the back of the cornea with an intact lens capsule, displacement into the anterior chamber or into the pupil, or a central cataract with maintenance of a normal position (42). Patients with this type of anomaly frequently have systemic abnormalities and microphthalmos with vitreoretinal disorganization (43).

Peters' anomaly has been found in combination with numerous chromosomal abnormalities. It has been associated with a ring chromosome 21, a deletion of chromosome 2, a trisomy of chromosome 9, a deletion of the long arm of chromosome 11, a deletion of the short arm of chromosome 4, a deletion of the long arm of chromosome 18, a translocation of chromosomes 2 and 15, and a partial trisomy of chromosome 5 (44).

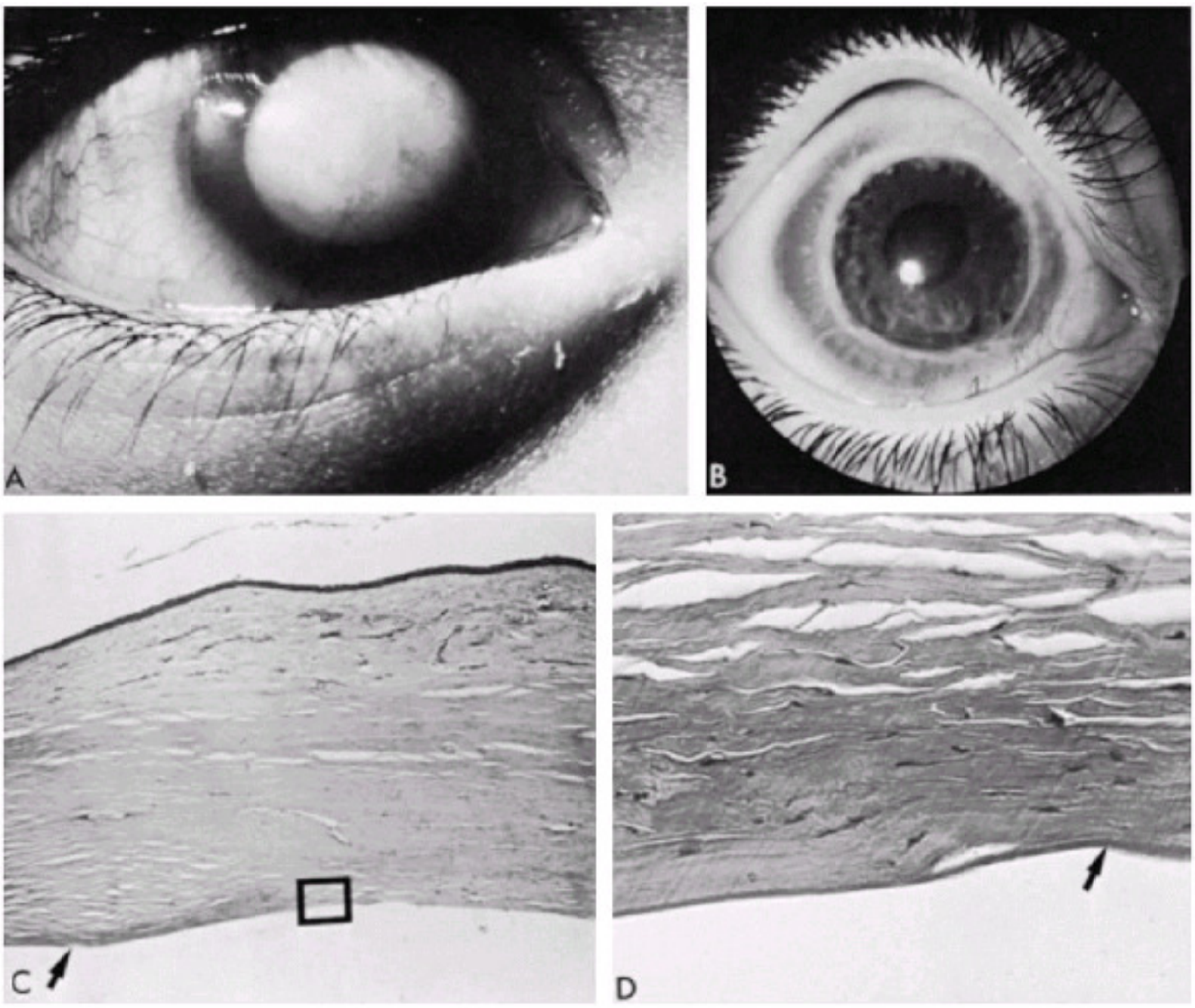

Figure 12.18 Anterior chamber cleavage syndrome. **A:** This 7-month-old boy had bilateral megalocornea (13 mm in diameter), (**A-D**) a central posterior corneal defect with corneal leukoma in the right eye (Peters' anomaly), and (**E, F**) Rieger's anomaly of the left eye (Courtesy of Turgut Hamdi, MD). B: Keratoplasty for central posterior corneal defect. A penetrating keratoplasty was performed in the right eye at age 22 months, and the graft remained clear for 5 months until graft rejection occurred. No iris processes extended to the corneal leukoma. An anterior polar cataract was discovered postoperatively. **C:** Central posterior corneal defect with scarring. Histopathologically, the corneal button shows superficial fibrovascular invasion and deep stromal edema. In this area, Bowman's layer and Descemet's membrane are absent. The margin of the button (*left side*) shows more normal cornea with edematous stroma. Descemet's membrane is present in this area (*arrow*) (Periodic acid-Schiff (PAS) × 25). **D:** Central posterior corneal defect. The area of C in the box shows the transition (*arrow*) from intact Descemet's membrane peripherally to its replacement by fibrous tissue centrally. Only fragments of endothelium were seen (PAS × 250). *(Figure continues.)*

Corneal Staphyloma and Keloid

In this most severe form of posterior corneal defect, the ectatic, thin, scarred, vascularized cornea is lined by uveal tissue and may protrude between the eyelids (Fig. 12.20) (45,46). The ectasia may be present at birth but usually becomes worse in the first week of life. Intraocular pressure is usually elevated, and the lens is incorporated into the scarred ectatic cornea. In rare instances, the cornea develops a hypertrophic keloid scar (47).

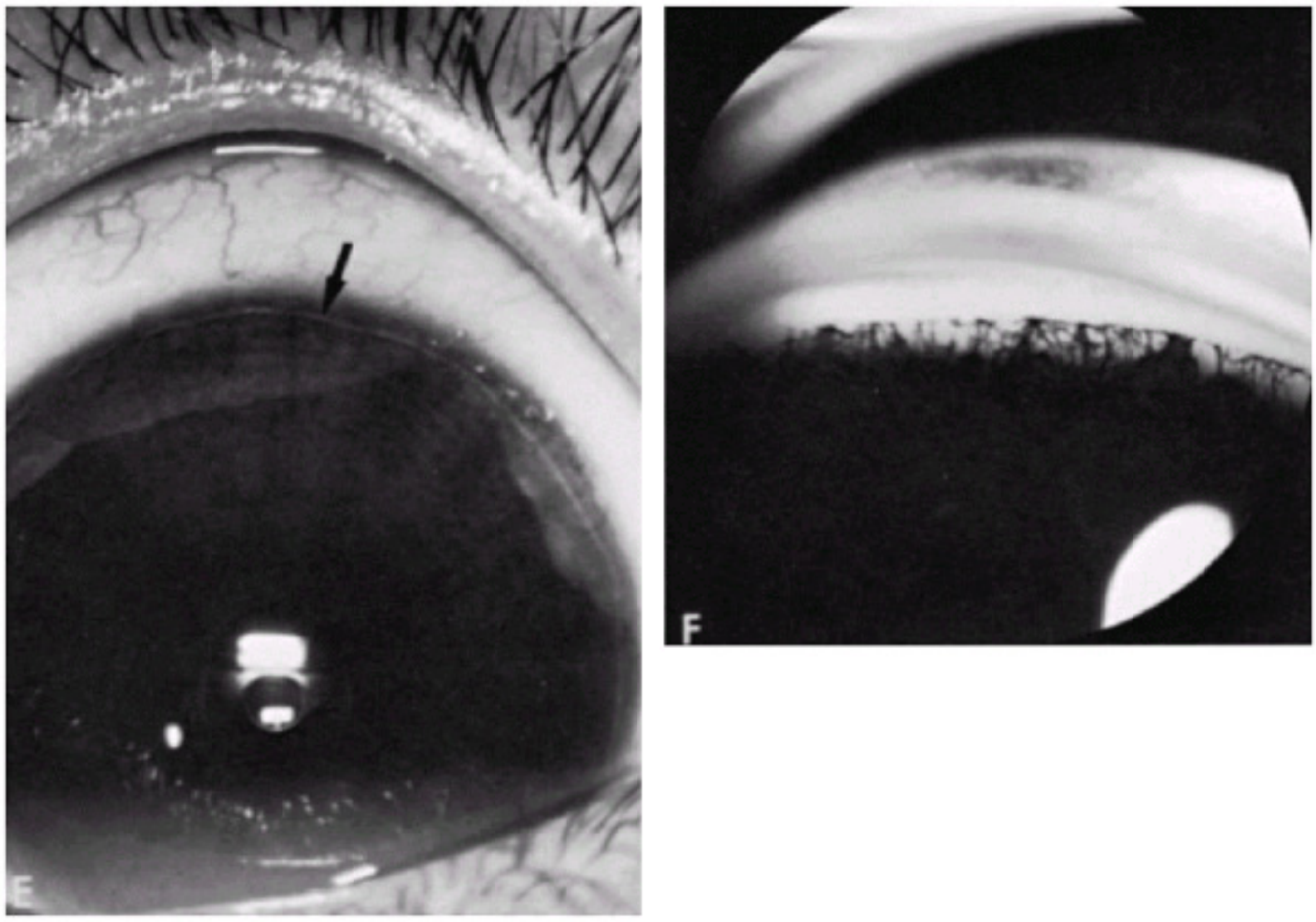

Figure 12.18 *Continued.* **E:** Megalocornea and Rieger's anomaly. The left eye of this patient exhibited a 13-mm diameter cornea, a prominent Schwalbe's ring (*arrow*) with iris processes extending to it, and a hypoplastic iris stroma. **F:** Iris processes in Rieger's anomaly. The angle filled with delicate iris processes and mesenchymal tissue extending up to the prominent Schwalbe's ring.

Pathogenesis of Posterior Corneal Defects

There are four pathogenic theories (3,40,48,49): (a) intrauterine keratitis, leaving a posterior defect commonly called the *internal corneal ulcer of von Hippel*; (b) incomplete central migration of the neural crest mesenchymal waves that form the corneal endothelium and stroma; (c) improper separation of the lens vesicle from the surface ectoderm, which may produce the central defect by blocking the ingrowth of the neural crest mesenchymal tissue and may result in a persistent keratolenticular adhesion without an intact lens capsule; and (d) secondary anterior displacement of the lens by a vitreoretinal mass-like persistent hyperplastic primary vitreous or pupillary block from a persistent pupillary membrane. Because none of these four theories adequately explains all the clinical or histopathological findings, and because there is experimental evidence supporting each one, these congenital anomalies must be regarded as a heterogeneous group with a similar clinical appearance.

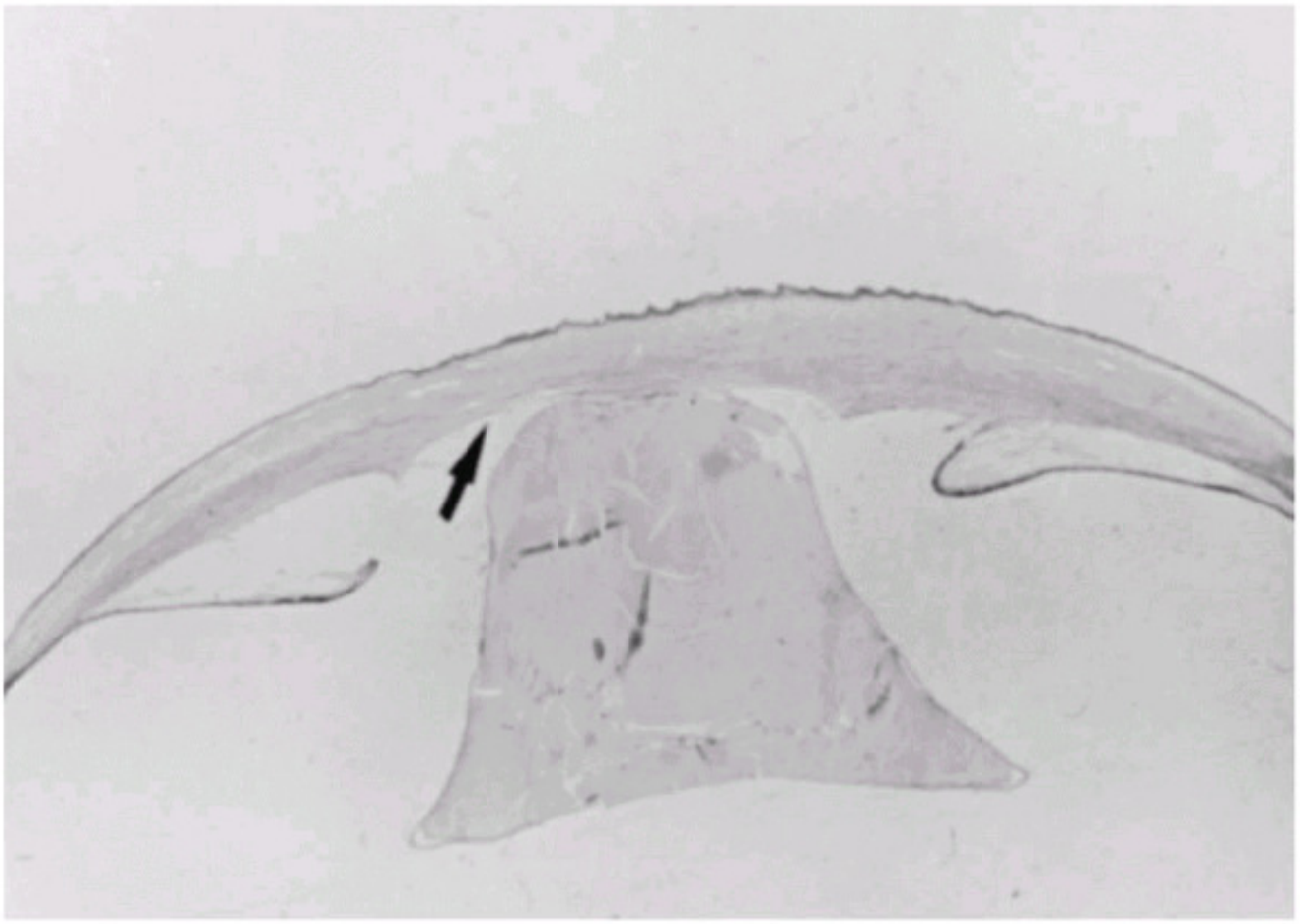

Figure 12.19 Congenital lens-corneal adhesion (Peters' anomaly). The eye of this newborn demonstrates irregular and thickened corneal epithelium and stroma, central absence of Bowman's and Descemet's membranes, a central posterior corneal defect (*arrow*) with a lens-corneal adhesion, a conical cataractous lens, and malformation of the anterior chamber angles with adhesion of the iris to the cornea. (PAS × 3) (Courtesy of Charles G. Steinmetz, MD.)

Peripheral and Central Combinations (Anterior Chamber Cleavage Syndrome)

Central and peripheral anterior chamber cleavage abnormalities may coexist in one eye (Fig. 12.10), in two eyes of one individual (Fig. 12.18), or in separate individuals in the same family (3,25,50). About 10% of cases of Rieger's anomaly have a central or paracentral corneal opacity with iris strands adherent to it. These combinations are seen more often clinically than pathologically; thus, Townsend et al (43) found only one combined case in 32 instances of congenital corneal leukomas examined histopathologically.

The descriptive anatomical classification is especially helpful in the central-peripheral combinations, because it allows one to see the exact components in each case, instead of resorting to a combination of eponyms.

Neonatal Corneal Opacities

Differential Diagnosis

The ophthalmologist often feels stumped when confronted by a child with a neonatal corneal opacity. These feelings

provide an apt acronym for the causes of neonatal corneal opacities: *STUMPED* (Table 12.2).

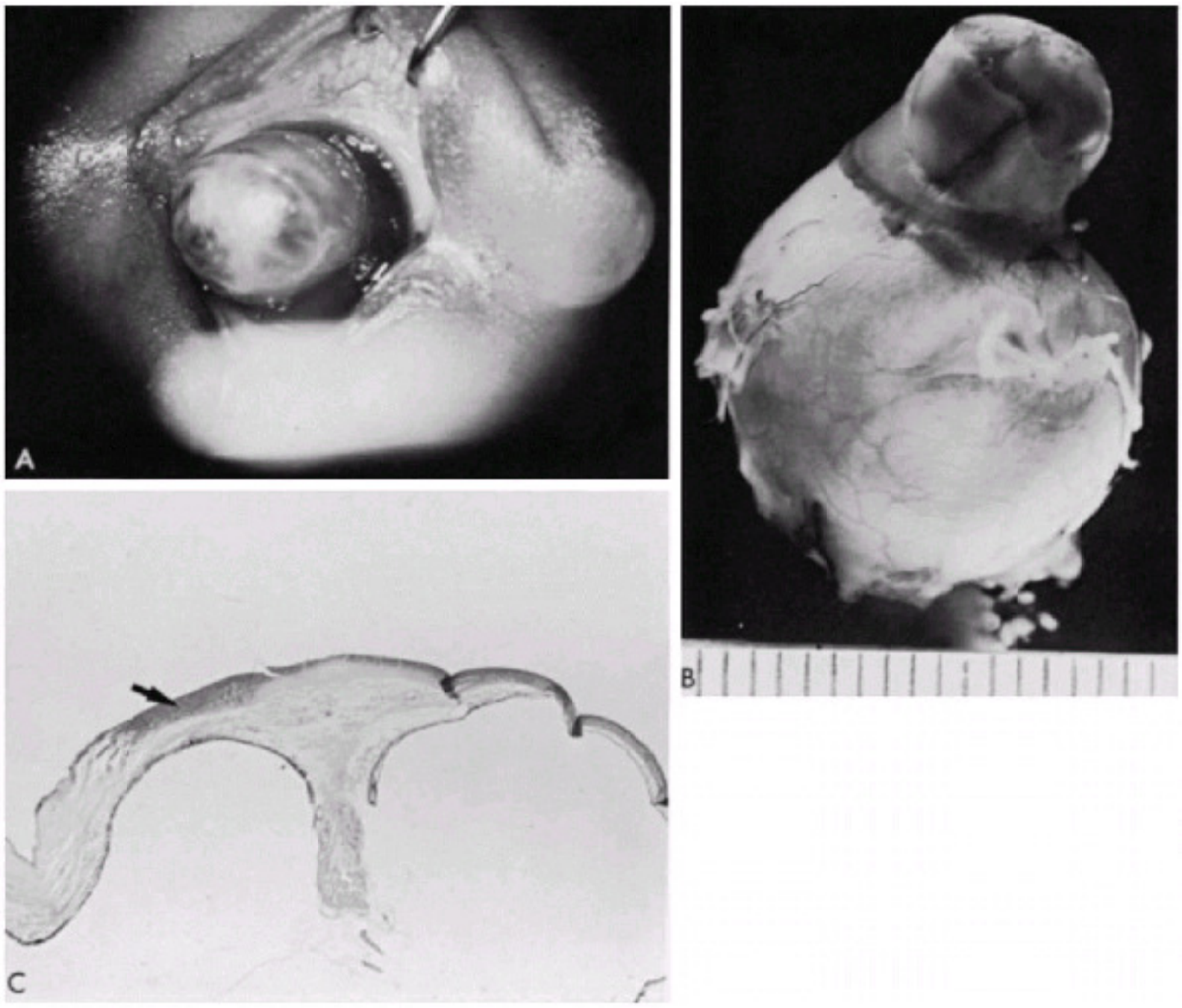

Figure 12.20 Congenital corneal staphyloma. **A:** This 5-day-old infant was born with a flat opaque right cornea. By age 2 days, the cornea had become blue and ectatic, as shown here. The left eye was normal, except for persistent pupillary membrane (Courtesy of Joseph H. Calhoun, MD). **B:** Gross appearance of the globe. The ectatic area is limited to the cornea (Courtesy of Merlyn Rodrigues, MD). C: Histological section of globe. Areas of the cornea are thin and ectatic. A superficial corneal abscess from exposure is present (*arrow*). Bowman's and Descemet's membranes are absent. A rudimentary lens is adherent to the central posterior cornea, blending with stromal tissue. Uveal tissue is firmly adherent to the posterior cornea, sweeping down along the lens rudiment (Hematoxylin-eosin × 3). (Courtesy of Merlyn Rodrigues, MD.)

Sclerocornea (Stumped)

Clinicians often use the term “sclerocornea” as a nonspecific description for any congenitally opaque, vascularized cornea. Too broad a use of the term, however, obscures valuable distinctions. Clinically, sclerocornea denotes a congenital peripheral white vascularized opacity that blends with the sclera, obliterates the corneoscleral limbus and scleral sulcus, and leaves the central cornea somewhat clearer than the periphery (51,52). Sclerocornea is not a discrete diagnostic entity. Howard and Abrahams (53) emphasized this when they reported a variety of associated ocular abnormalities: flattened cornea (cornea plana) in about 77%, shallow anterior chamber in about 39%, iris abnormalities in about 60%, and microphthalmos in about 8%.

We classify sclerocornea into four groups but realize that the distinction among them is imprecise (54):

1. Isolated sclerocornea (Fig. 12.21A). Patients in this group have no other ocular abnormalities and show either exaggerated scleral extension across the superior and inferior corneoscleral limbus (scleralization, scleral overriding) or more extensive peripheral corneal opacification.
2. Sclerocornea plana. Bilateral flat corneas with keratometry readings of less than 38 diopters occur as a sporadic or autosomal dominant anomaly in association with a shallow anterior chamber, iris abnormalities, and corneal diameters of 10 to 11 mm, on the small side of normal (55).
3. Anterior chamber cleavage anomalies. A scleralized peripheral cornea is present in 80% of eyes with Rieger's syndrome (3,56) and is common in Peters' anomaly.
4. Total sclerocornea (Fig. 12.21B). When the cornea is

opaque enough to prohibit visualization of the iris and lens, a precise clinical diagnosis is difficult.

TABLE 12.2 *STUMPED:* DIFFERENTIAL DIAGNOSIS OF NEONATAL CORNEAL OPA

Diagnosis	Laterality	Opacity	Ocular Pressure	Other Ocular Abnormalities	Natural Histo
S-Sclerocornea	Unilateral or bilateral	Vascularized, blends with sclera, clearer centrally	Normal or elevated	Cornea plana	Nonprogre
T-Tears in endothelium and Descemet's membrane					
Birth trauma	Unilateral	Diffuse edema	Normal, possibly elevated	Possible hyphema, periorbital ecchymoses	Spontane improvem 1 month
Infantile glaucoma	Bilateral	Diffuse edema	Elevated	Megalocornea, photophobia and tearing, abnormal angle	Progressiv unless tre
U-Ulcers					
Herpes simplex keratitis	Unilateral	Diffuse with dendritic or geographical epithelial defect	Normal or elevated	None	Often progressiv
Congenital rubella	Bilateral	Disciform or diffuse edema, no frank ulceration	Normal or elevated	Microphthalmos, cataract, pigment epithelial mottling	Stable, ma clear
Neurotrophic or exposure	Unilateral or bilateral	Central ulcer	Normal	Lid anomalies, congenital sensory neuropathy	Progressiv unless tre
M-Metabolic (rarely present at birth) (all mucopolysaccharidoses except II, III; mucolipidosis Type IV)*	Bilateral	Diffuse haze, denser peripherally	Normal	Few	Progressiv
P-Posterior corneal defect (Peters' anomaly)	Unilateral or bilateral	Central, diffuse haze or vascularized leukoma	Normal or elevated	Anterior chamber cleavage syndrome	Stable; sometime early clea or vasculariz
E-Endothelial dystrophy					

Congenital hereditary endothelial dystrophy	Bilateral	Diffuse corneal edema, marked corneal thickening	Normal	None	Stable
Posterior polymorphous dystrophy	Bilateral	Diffuse haze, normal to moderate corneal thickening	Normal or elevated	Occasional peripheral anterior synechiae	Slowly progressiv
Congenital hereditary stromal dystrophy	Bilateral	Flaky, feathery stromal opacities; normal corneal thickness	Normal	None	Stable
D-Dermoid	Unilateral or bilateral	White vascularized mass, hair, lipid arc	Normal	None	Stable

* Mucopolysaccharidosis II (Hunter's syndrome); mucopolysaccharidosis III (Sanfilippo's syndrome)

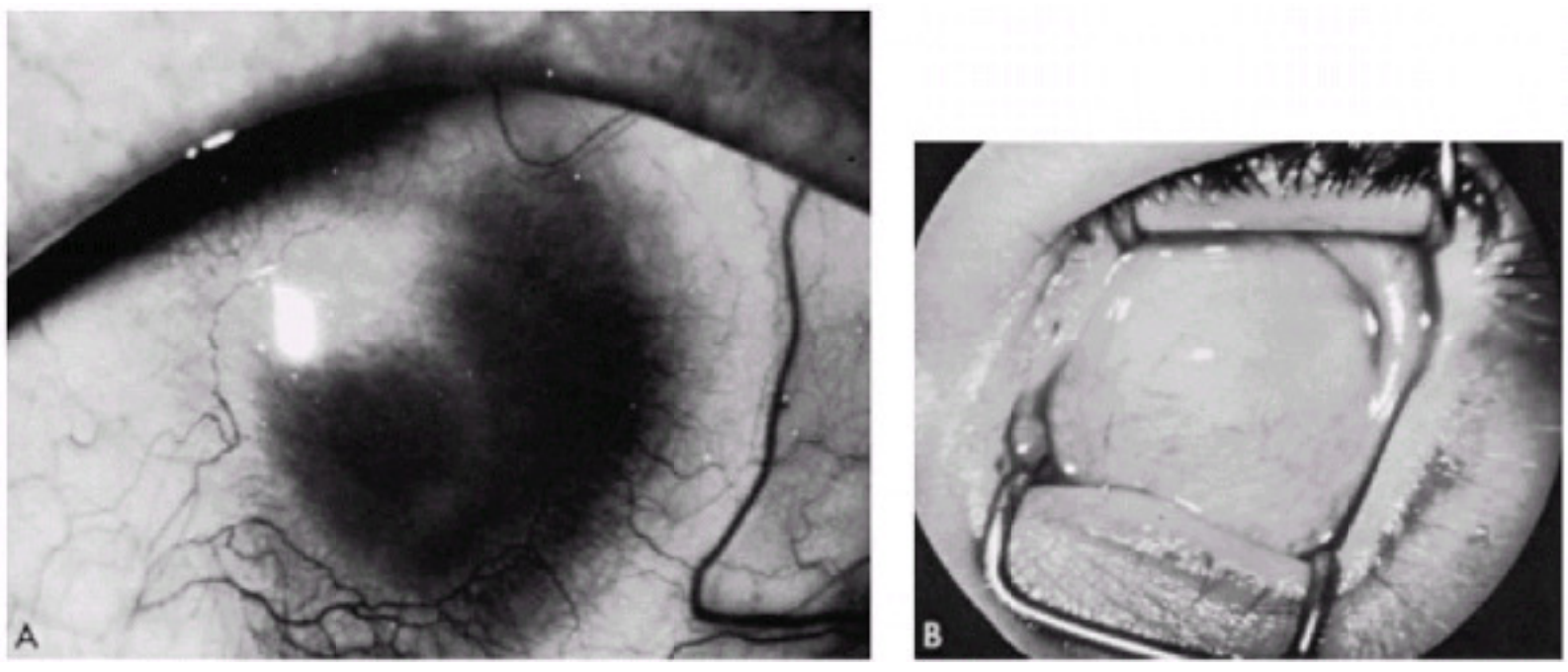

Figure 12.21 Sclerocornea. **A:** Scleral tissue extends in a geographical pattern toward the central cornea. Some clear cornea remains centrally. **B:** Total replacement of the cornea by sclera. Penetrating keratoplasty was unsuccessful. The iris and lens were grossly malformed. (Courtesy of Joseph Calhoun, MD.)

No systemic abnormalities consistently accompany sclerocornea, but a variety has been reported (Table 12.3) (52,56,57,58,59,60,61,62,63).

Histopathologically, sclerocornea shows an irregular epithelium with variably thick basement membrane, a fragmented or absent Bowman's layer, and disorganized spindles of vascularized stromal collagenous tissue that contain collagen fibrils 60 to 150 nm in diameter (64). The random structure of these large fibrils and their attendant blood vessels scatter light and gives the cornea its white clinical appearance. Descemet's membrane is abnormal, either being present as a thin irregular layer with collagenous tissue behind it (65) or showing focal dehiscences that may

contain fibrous tissue (63). The endothelium is usually damaged, precluding detailed description (53).

TABLE 12.3 SYSTEMIC ABNORMALITIES REPORTED WITH SCLEROCORNEA

Study	Abnormalities
	Skeletal
Goldstein & Cogan (64) (1962); Bloch (68) (1965)	Polydactyly, skull malformations, abnormally shaped external ears, spina bifida, high-arched palate, mandibular hypoplasia
	Central Nervous System
Goldstein & Cogan (64) (1962); March & Chalkley (74) (1974)	Cerebellar dysfunction, defective hearing
	Chromosomal
Rodrigues et al. (75) (1974); Ginsberg et al. (71) (1968); Cernea et al. (69) (1966)	17p,10q unbalanced translocation, trisomy 18
	Syndromes
Harben et al. (72) (1977)	Smith-Lemli-Opitz (microcephaly, mental and growth retardation, abnormal genitalia, hand and foot anomalies)
Lapri (73) (1949)	Biemond (hexadactyly of hands and feet, lacunae of cranial bones); Lohmann
Desvignes et al. (70) (1967)	Lobstein (fragile bones, blue sclerae, decreased hearing)
Mietens & Weber (136) (1966); Waring & Rodrigues (66) (1980)	Mietens (abnormal radii, flat nose, elbow flexion contractures, growth, and, sometimes, mental retardation)
Perry et al. (137) (1978)	Melnick-Needles (exophthalmos, hypertelorism, micrognathia, and multiple bone deformities)
Schanzlin et al. (138) (1980)	Hallermann-Streiff (dyscephaly with a bird-like face, dental anomalies, proportionate dwarfism, hypotrichosis, atrophy of the skin, bilateral microphthalmos, and congenital cataract)
Kolbert & Seelenfreund (139) (1970); Ying et al. (140) (1982); Moriarty & Kerr-Muir (131) (1992)	Various chromosomal abnormalities (trisomy 13; chromosome 9 deletion, chromosome 6 deletion)

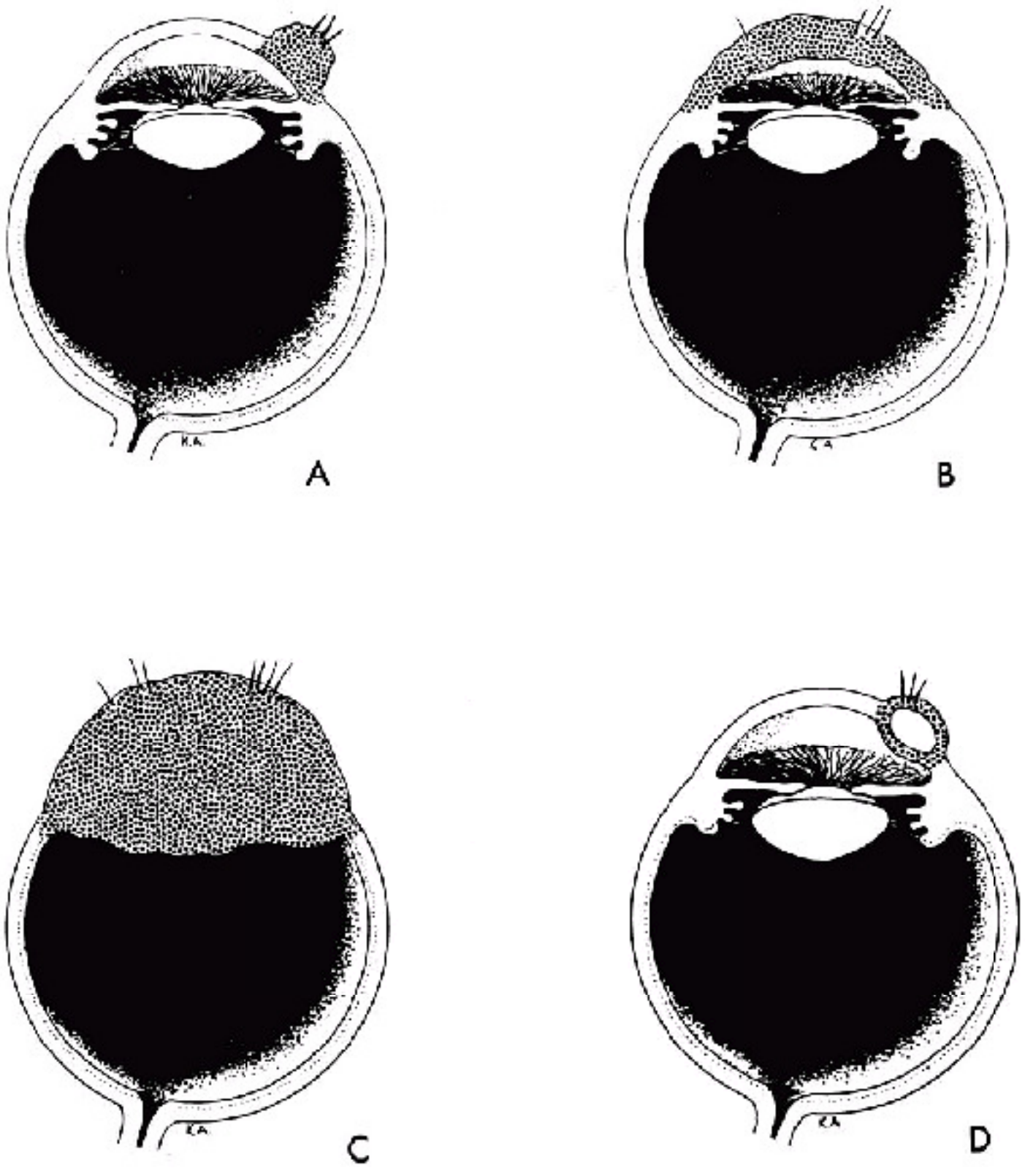

Figure 12.22 Corneal dermoids. **A:** Limbal dermoid tumor. **B:** Dermoid tumor replacing the entire cornea. **C:** Dermoid tumor replacing the entire anterior segment. **D:** Dermoid cyst of cornea (After Ida Mann).

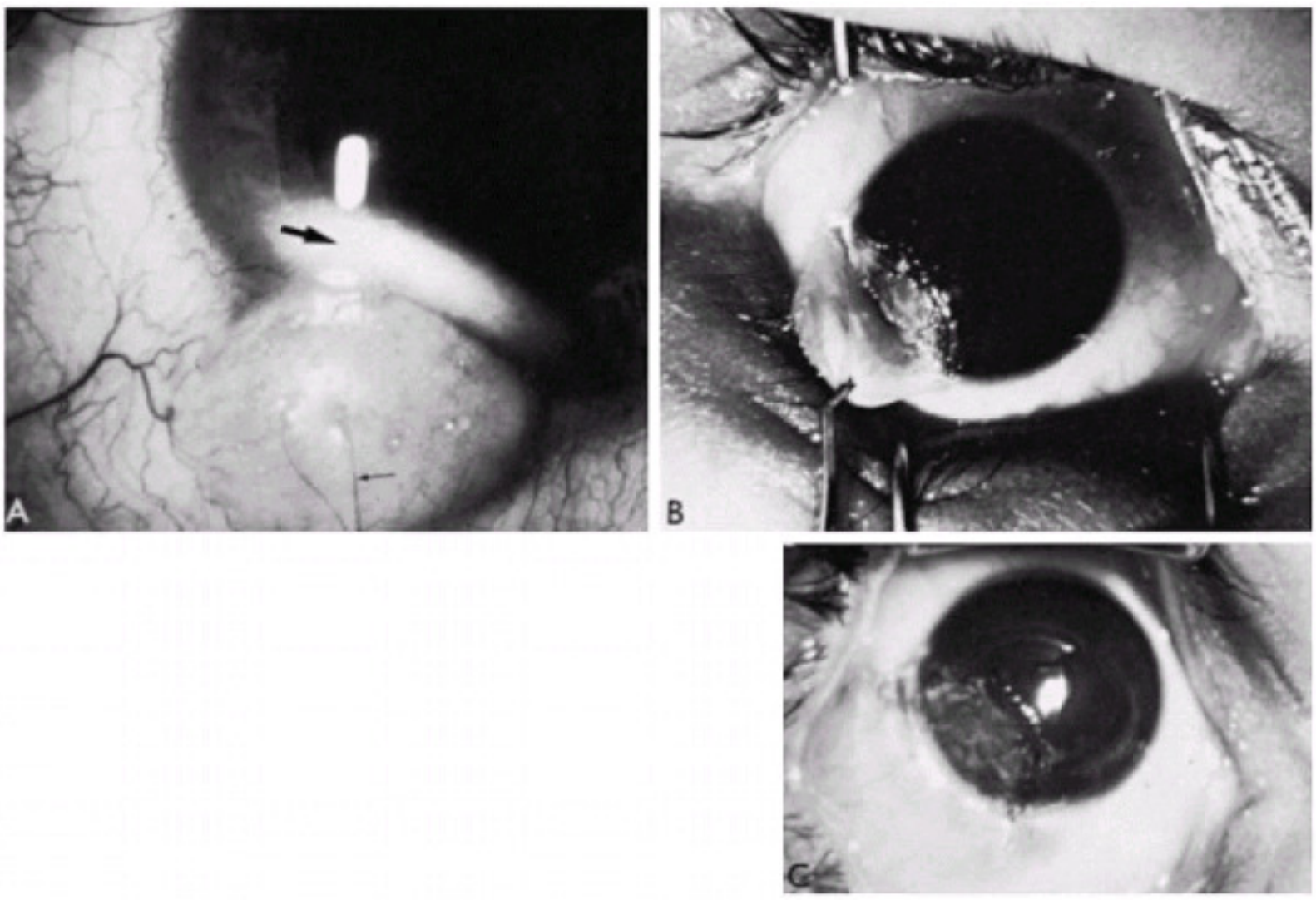

Figure 12.23 Limbal dermoid tumor. **A:** Vascularized limbal nodule with hair protruding from its surface (*small arrow*). A white lipid line in superficial corneal stroma extends parallel to the dermoid (*large arrow*). **B:** Tumor removed by superficial keratectomy. **C:** A significant corneal scar remains.

Tears in Endothelium in Descemet's Membrane (Stumped)

Birth trauma is discussed later in this chapter. Infantile glaucoma is discussed in Chapter 14.

Ulcers (Stumped)

We have observed one patient with a congenital sensory neuropathy of unknown type who was born with bilateral, shallow, central corneal ulcers. Corneal melting persisted, and in spite of therapy with tarsorrhaphies, soft contact lenses, and keratoplasties, both eyes were finally enucleated.

Viral infections of the cornea are discussed later in this chapter.

Metabolic (Stumped)

Because the fetus has access to maternal enzymes, systemic metabolic disorders, such as the mucopolysaccharidoses, mucolipidosis, and tyrosinosis that later develop corneal opacities, are rarely present at birth. A consistent exception to this is mucolipidosis type IV (ganglioside neuraminidase deficiency). These metabolic disorders are discussed in more detail in Chapter 23.

Posterior Corneal Defect, Peters' Anomaly (Stumped)

These central corneal opacities are discussed earlier in this chapter.

Endothelial Dystrophies (Stumped)

These dystrophies are discussed later in this chapter.

Dermoid (Stumped)

A corneal dermoid tumor (Fig. 12.22) is a solid, congenital, rounded mass consisting of keratinized epithelium overlying fibrofatty tissue that contains hair follicles, sebaceous glands, and sweat glands (66,67). It is usually a single unilateral pink-white-gray mass, 1 to 5 mm in diameter, that straddles the limbus inferotemporally (Figs. 12.23, 12.24 and 12.25). The clinical picture is highly variable, however. The masses may be multiple, bilateral, confined to the cornea alone, minutely small, or large enough to obscure the entire cornea (Figs. 12.26, 12.27 and 12.28). The dermoid extends into the corneal stroma and sclera but seldom occupies the full thickness and only rarely grows into the angle. Hair is not always present on the surface.

Dermoids may enlarge slowly, especially at puberty or after trauma or irritation. A limbal dermoid often leaves visual acuity unaffected, but if it grows over the visual axis or produces significant corneal astigmatism, amblyopia will likely result. Dermoids contain considerable fatty tissue, and a white arcuate haze of lipoid material commonly extends into the corneal stroma in front of the tumor. This lipid may encroach on the visual axis and blur vision.

Approximately one third of patients with limbal dermoids have associated developmental anomalies. Among the most frequent is the constellation of epibulbar dermoids, preauricular appendages, and vertebral anomalies (Goldenhar's syndrome [oculoauriculovertebral dysplasia]) (Figs. 12.22 and 12.25) (68,69,70).

In Goldenhar's syndrome the epibulbar dermoid straddles the limbus in the inferotemporal quadrant. It is bilateral in about 25% of cases. A subconjunctival lipodermoid or dermolipoma (lipoma covered by keratinized or nonkeratinized epithelium with hair on the surface) is found in the superotemporal quadrant in about 50% of cases. This lipodermoid may blend with the epibulbar dermoid. A coloboma of the upper eyelid is present at the junction of the middle and inner third in about 25% of cases. Other associated ocular anomalies include Duane's syndrome, lacrimal duct stenosis, and iris and choroidal colobomas.

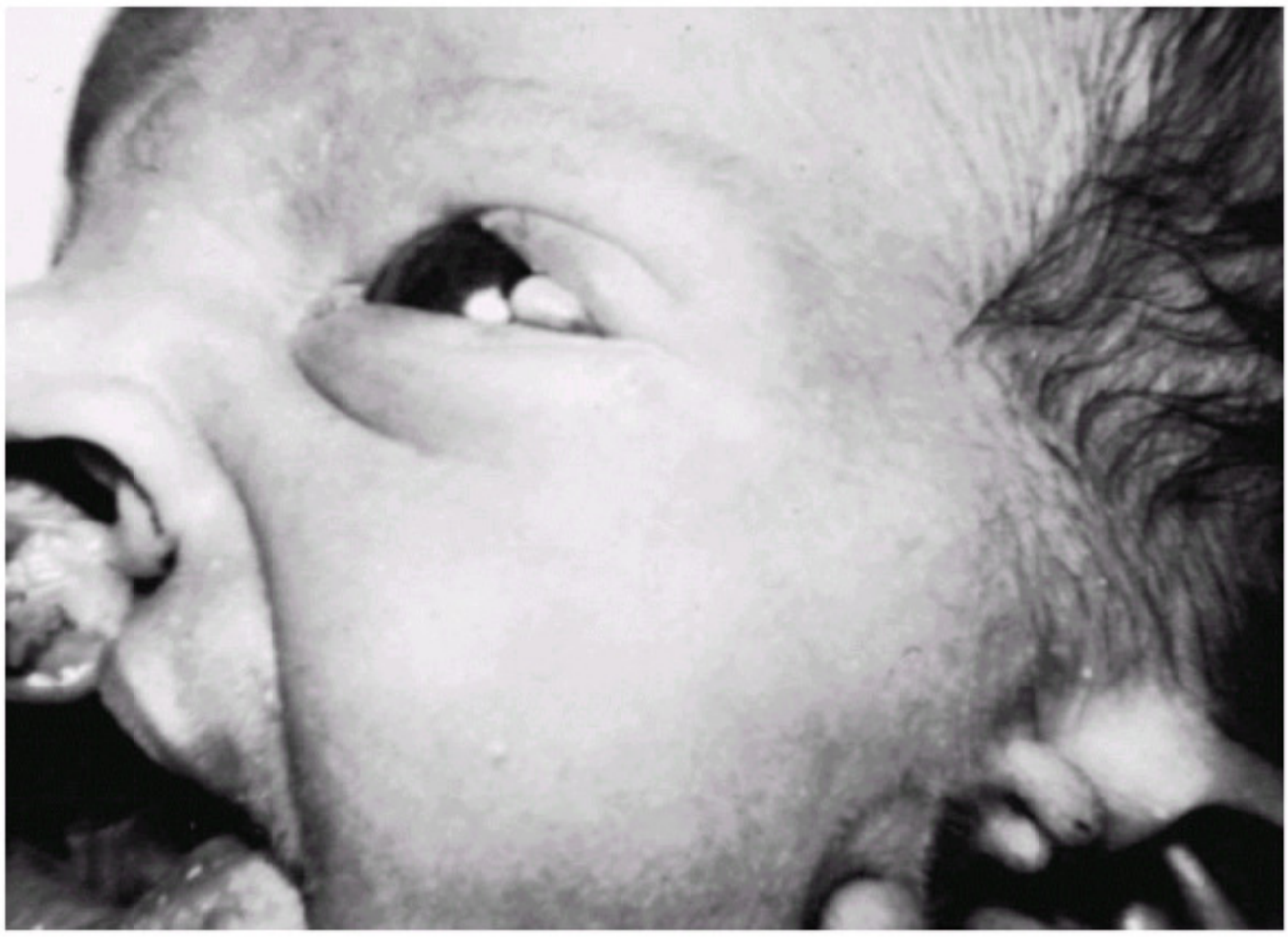

Figure 12.24 Goldenhar's syndrome. The limbal dermoid and preauricular skin tags are present, in addition to a cleft lip. (Courtesy of Robison D. Harley, MD.)

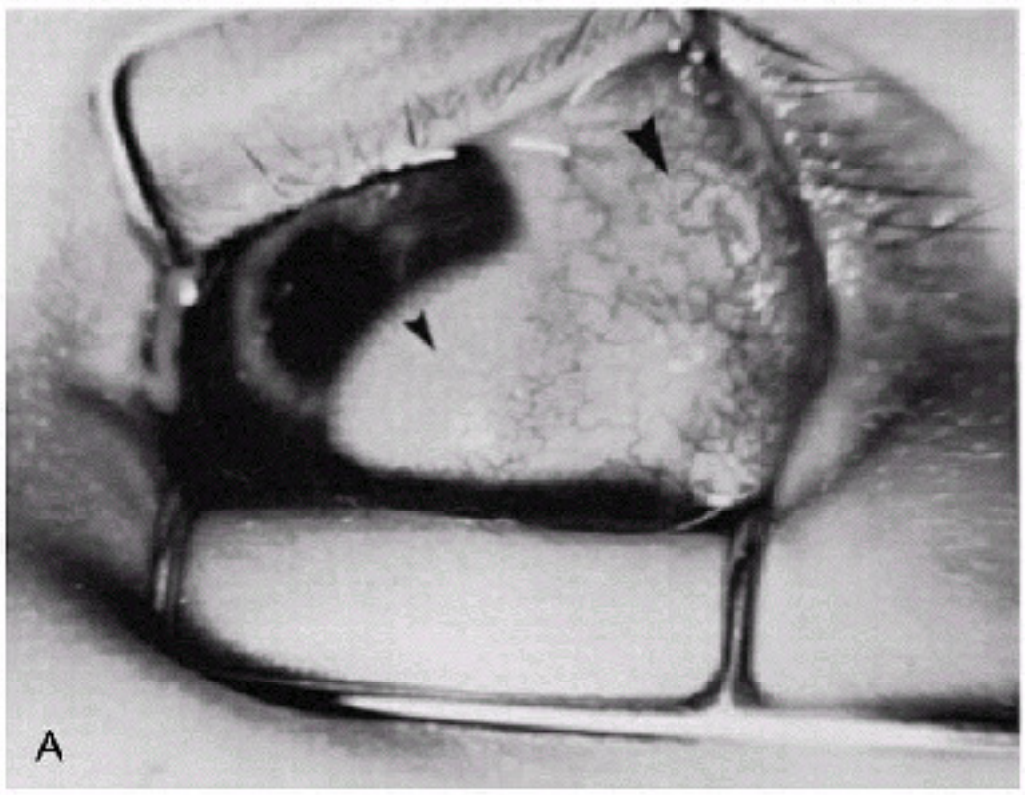

Figure 12.25 Goldenhar's syndrome. **A:** A lipodermoid of the conjunctiva (*large arrow*) and an epibulbar dermoid of the limbus (*small arrow*) are present concurrently in about half the cases. **B:** A coloboma of the upper lid at the junction of the middle and inner thirds is present in about one fourth of cases (*large arrow*). The limbal dermoid tumor has been excised (*small arrows*). (Courtesy of Jules Baum, MD.)

Auricular anomalies—usually on the same side as the dermoid—include preauricular appendages, posteriorly placed ears, preauricular sinuses, and stenosis of the external auditory meatus. Vertebral anomalies occur in about two thirds of patients, including fused cervical vertebrae, hemivertebrae, spina bifida, and occipitalization of the atlas. Lumbosacral abnormalities also occur. Facial malformations include micrognathia, macrostomia, dental abnormalities, and facial asymmetry. The diagnosis of Goldenhar's syndrome should lead to complete examination for associated systemic abnormalities, especially cardiovascular, renal, genitourinary, and gastrointestinal defects. Goldenhar's syndrome occurs sporadically.

Limbal dermoids should be excised if they are producing visual disturbance, are irritated, or are cosmetically embarrassing (Fig. 12.23). Small asymptomatic tumors may be observed. Surgical intervention should be tempered by

three facts: (a) The attempt to remove all of the dermoid may lead to corneal perforation, (b) the scar remaining after excision is sometimes as unsightly as the original tumor, and (c) astigmatism may not improve significantly postoperatively. Performing a lamellar keratoplasty may help minimize the dangers of ocular perforation and subsequent scar formation. It is worthwhile to perform gonioscopy on patients before or at the time of surgery to discover possible angle involvement. A high frequency ultrasound biomicroscopy (UBM) evaluation may be very helpful in determining the depth and extent of the dermoid preoperatively (71,72). A donor cornea should be available at surgery, in case the anterior chamber is entered. Dermoids rarely recur.

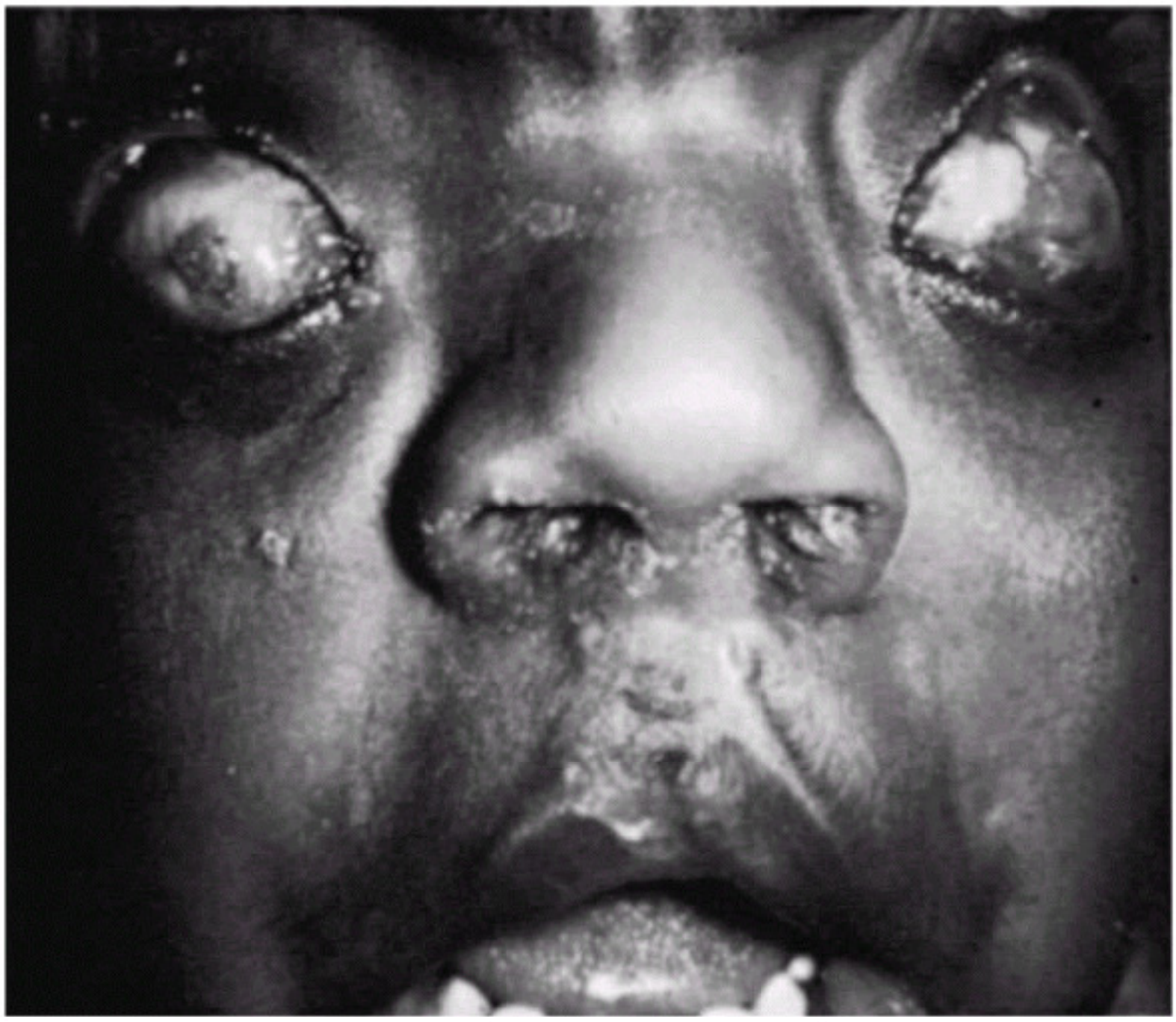

Figure 12.26 Bilateral dermoid tumors replacing the entire cornea. This 3-year-old boy was born with masses of vascularized tissue containing surface hair protruding grotesquely between his lids. He has had repair of cleft lip and palate. (Courtesy of Robison D. Harley, MD.)

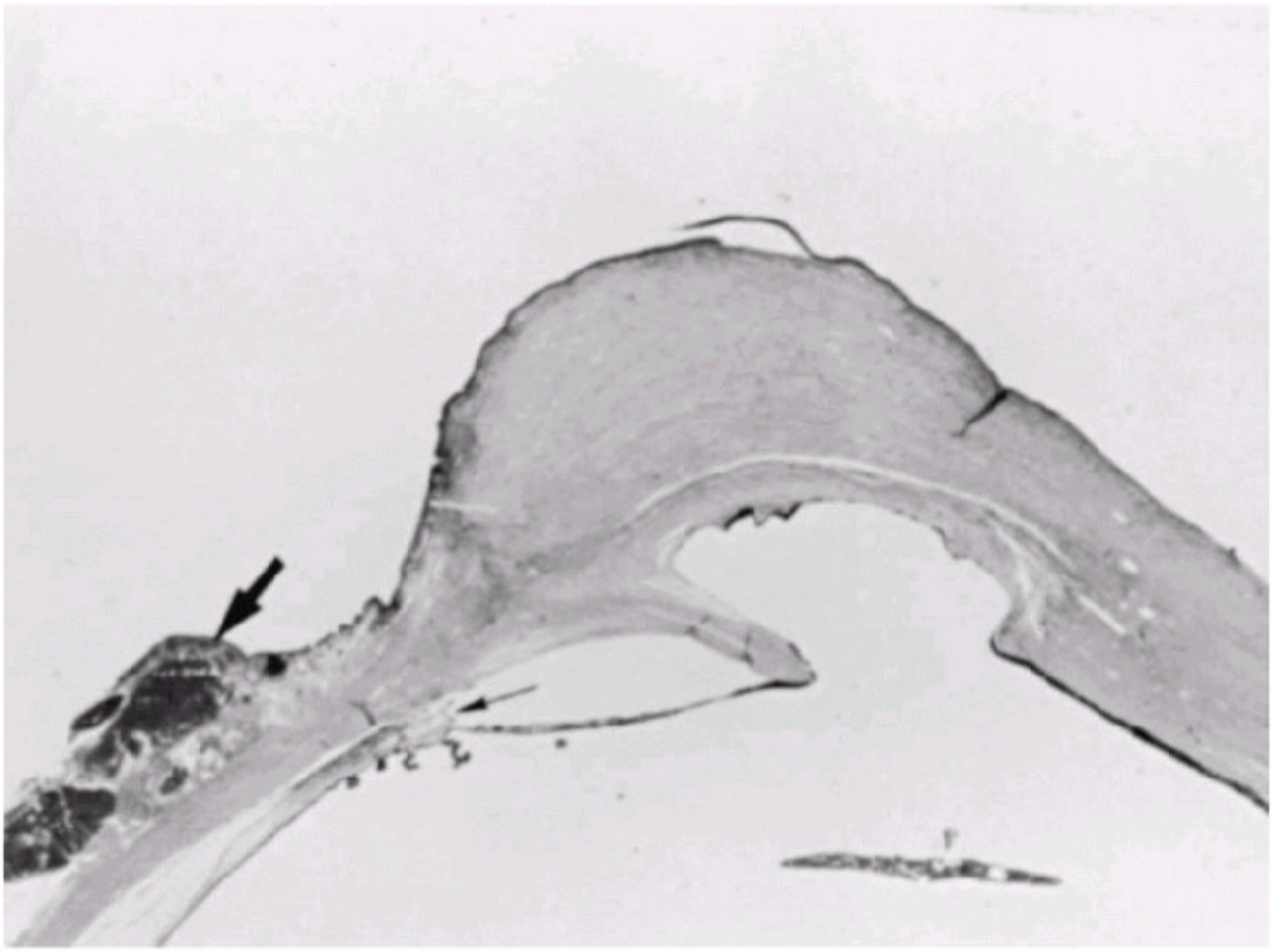

Figure 12.27 Corneal dermoid, posterior corneal defect, and Axenfeld's anomaly. In the right eye, cornea is replaced by a mass of vascularized connective tissue. Ectopic lacrimal gland is present at the limbus (*large arrow*). In this area the angle is deep and contains a prominent Schwalbe's ring with iris processes adherent to it (*small arrow*). A central posterior corneal defect is present. On one side, the iris stretches from the angle to the edge of the defect. Descemet's membrane is present in this area. On the opposite side, iris lines the corneal defect and posterior cornea; Descemet's membrane is absent in these areas (Hematoxylin-eosin × 3).

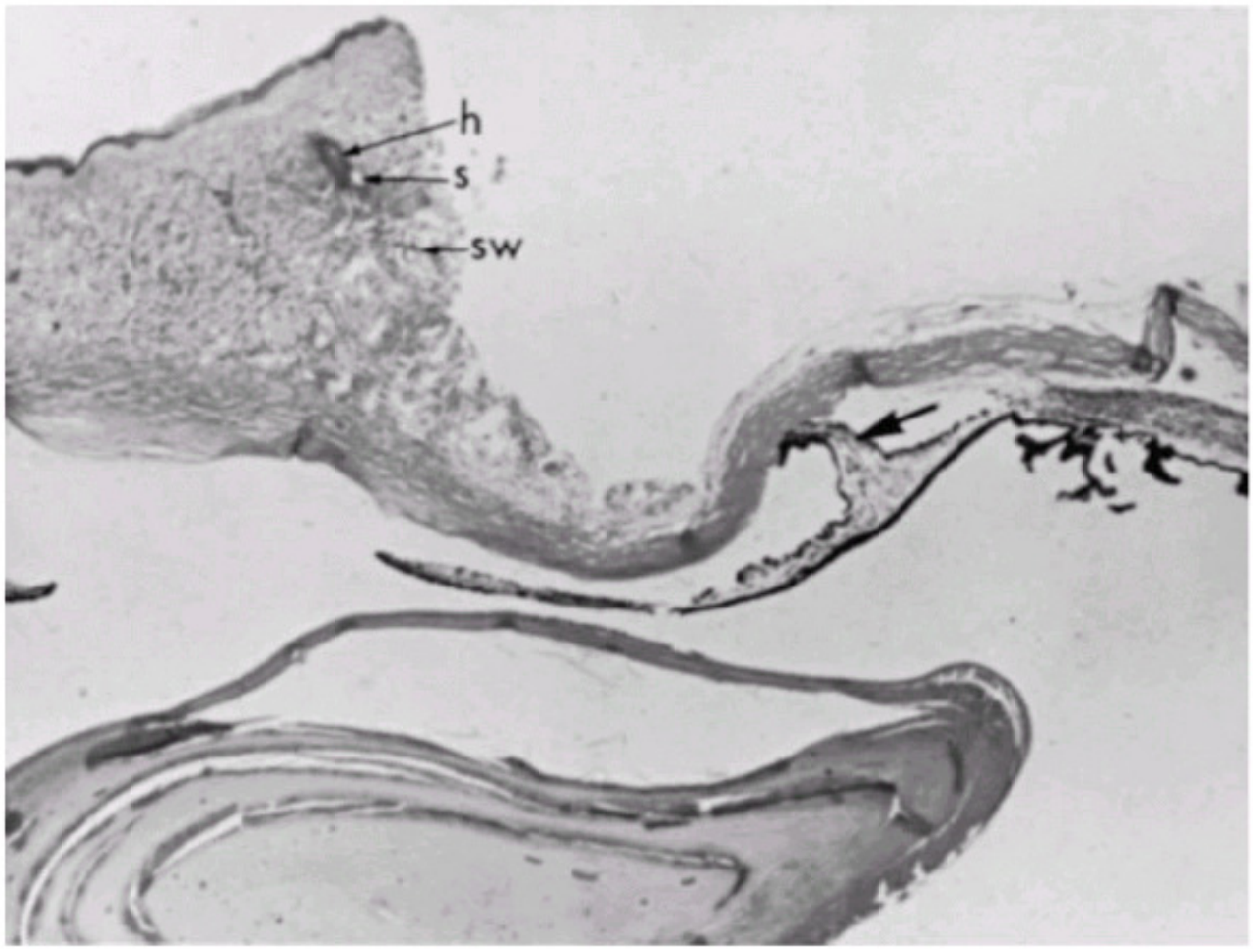

Figure 12.28 Corneal dermoid, central posterior corneal defect, and iris-corneal adhesion. The left eye of the patient shown in Figure 12.27. Anterior cornea is replaced by vascularized connective tissue containing hair follicle (*h*), sebaceous gland (*s*), and sweat gland (*sw*). A biopsy has been taken for diagnostic purposes, leaving a defect. Descemet's membrane is present peripherally but absent centrally. An iris adhesion (*arrow*) is present centrally. Angle structures are disorganized (Hematoxylin × 4).

Management of Neonatal Corneal Opacities

Team Approach

The ophthalmologist who takes care of an infant with opaque corneas must decide whether or not keratoplasty is indicated. This complex undertaking is often best managed by subspecialty consultants who form a team to provide optimal management. The team may consist of (a) the coordinating ophthalmologist, who usually practices near the family and is aware of its social and medical circumstances; (b) a social service person, who can look after the details of transportation, economic difficulties, proper delivery of medications at home, and maintenance of appointments; (c) the corneal surgeon, who is experienced in infant keratoplasty and anterior segment reconstruction; (d) the glaucoma consultant, who is experienced in medical and surgical management of infantile and developmental glaucomas; (e) a pediatric ophthalmologist, who is facile in the treatment of amblyopia and strabismus; (f) a contact lens specialist, who has a large inventory of both hard and soft contact lenses, especially those in powers from+20.00 diopters to + 30.00 diopters to correct infant aphakia; and (g) motivated parents who understand all of the necessary tasks and are willing and able to perform them before, and for many years after, a corneal transplant in a child. Although the assembly of such an entourage may seem excessive, the complexity and nuances of rehabilitating these eyes over the years of infancy and childhood often require such expertise and dedication.

Preoperative Examination

The preoperative pediatric ophthalmologic examination (73,74) is reviewed briefly here. Examination under anesthesia is often not necessary to evaluate the eyes of infants with corneal opacities, because a hungry child held on the parent's lap and sucking on a bottle will hold still and seldom cry after the instillation of topical anesthetic and the insertion of an infant eyelid speculum or a Koeppe lens. A portable slit lamp provides diagnostic accuracy and the ability to observe structural details, which can be recorded in a color-coded sketch that serves as a basis for planning the surgical approach. Measurement of intraocular pressure through edematous or scarred corneas in infants is inaccurate with Schiotz and Goldmann applanation tonometers. A handheld applanation tonometer may be used, if the cornea has a regular surface. Most helpful, however, is an electronic Tono-Pen XL (Medtronics, Inc., Minneapolis, MN) or a pneumotonometer (75).
High-frequency UBM can be extremely helpful in evaluating the anterior segment architecture in the presence of an opacified cornea (76,77,78,79,80). A high-resolution B-scan ultrasonogram provides rapid information about the architectural integrity of the vitreous and retina, information usually unobtainable by ophthalmoscopy because of the opaque cornea, small pupil, or cataractous lens. Careful A-scan and B-scan ultrasonographic examination can also help define anterior segment anatomy. A ruler or caliper allows the ophthalmologist to record corneal diameter, to document whether or not the cornea is enlarging as a result of elevated intraocular pressure, and to measure the diameter of the corneal opacity as a basis for selecting the size of the donor button.

Indications for Keratoplasty in Infants

A child with dense bilateral corneal opacities should receive a penetrating keratoplasty along with other indicated ocular surgery within the first 3 months of life. This surgery, followed by prompt optical correction with contact lenses or spectacles, gives the best chance for prevention of severe amblyopia. For the child with

a unilateral neonatal corneal opacity and a contralateral normal eye, the ophthalmologist must weight surgical and social morbidity against the probability of prolonged graft clarity, effective treatment of the amblyopia, and cosmetic improvement. The chance of developing vision better than 20/200, even when keratoplasty is performed in the first month of life, is low. The poor prognosis for prolonged graft clarity also tempers the decision to operate, especially in eyes that are not disfiguring and have only mild corneal opacities. On the other hand, the amblyopia in these eyes, if left untreated, will render them visually useless, so that even if a small percentage retain clear grafts with some improved vision, the effort and risk may be justified, particularly when one considers that trauma may damage the normal eye later in life. For grotesque eyes in which the cornea is ectatic or exhibits a fibrous mass, reconstructive surgery may improve appearance, as well as produce some vision. The team approach and modern microsurgical techniques are improving the prognosis for these grafts—a prognosis that heretofore has been extremely poor (73,81,82,83,84,85,86,87).

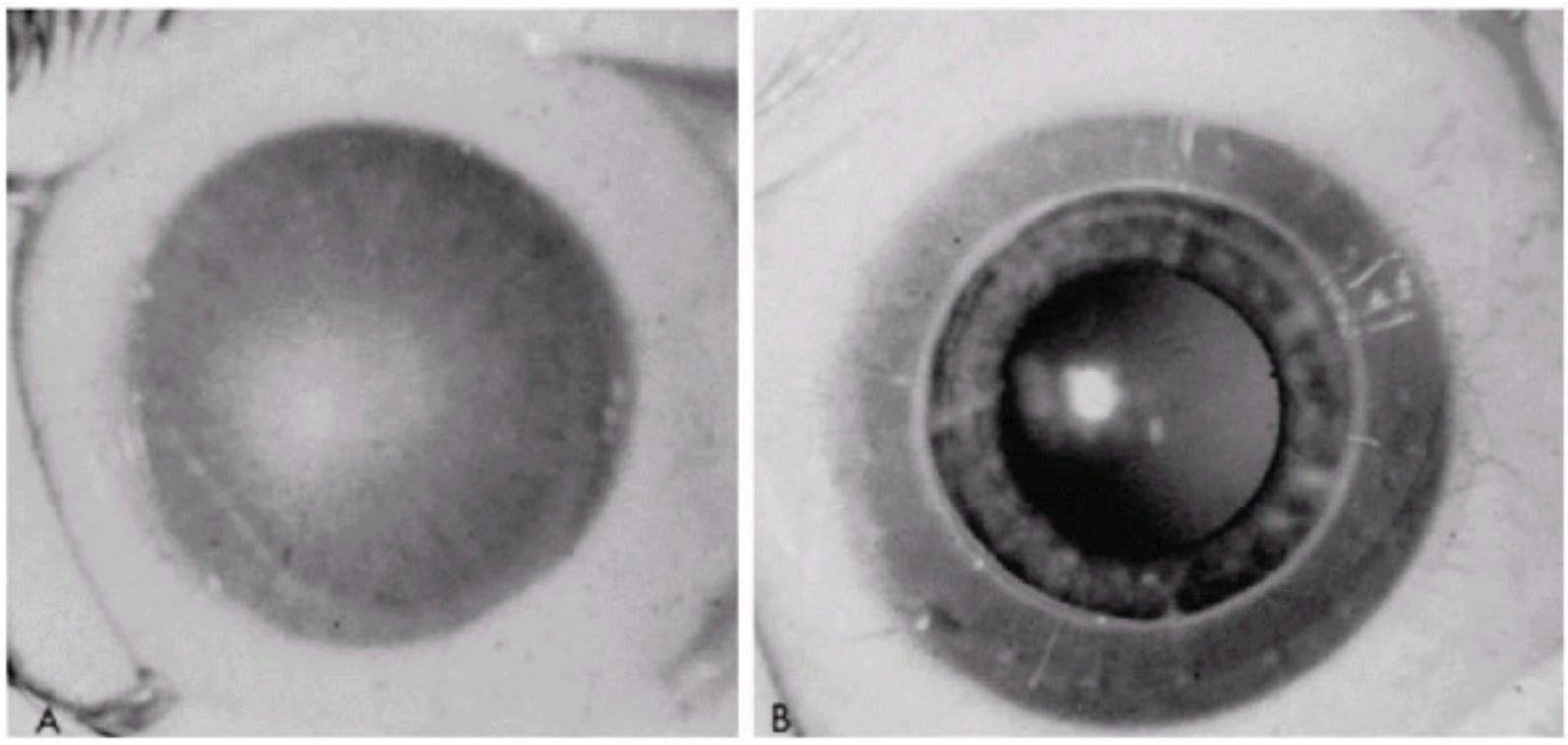

Figure 12.29 Congenital posterior polymorphous dystrophy with successful keratoplasty. **A:** White man, whose mother and maternal grandfather exhibited classic posterior polymorphous dystrophy, was born with bilateral, diffusely hazy corneas of normal thickness. Careful slit-lamp examination showed coarse gray geographical lesions at the level of Descemet's membrane through the ground-glass stromal haze. **B:** Penetrating keratoplasty was performed in both eyes, which remain clear and compact at 1 year postoperatively.

Neonatal corneal opacities fall into three groups with different prognoses for successful penetrating keratoplasty: (a) avascular corneas with either diffuse corneal edema or a central corneal opacity and clear periphery, with or without iris adhesions that have about a 50% chance for clarity at 2 years (Fig. 12.29); (b) eyes with dense vascularized corneas, often with keratoirideal and corneolenticular adhesions that have about a 10% chance of success; and (c) eyes with both anterior segment and vitreoretinal disorganization demonstrated by ultrasonography that, in desperation, can be approached with combined keratoplasty,

anterior segment reconstruction, open-sky vitrectomy, possible temporary keratoprosthesis, and pars plana vitrectomy and retinal reattachment procedures. These last eyes have an extremely guarded prognosis.

Surgical Techniques and Postoperative Care

High intraocular pressure must be controlled surgically. Goniotomy cannot be readily performed in infants with opaque corneas. Trabeculotomy *ab externo* may work, if the surgeon can see the anterior chamber, iris, and lens. Trabeculectomies frequently fail, and cyclocryotherapy is a destructive procedure usually saved until other surgical techniques have failed. An alloplastic tube shunt may be performed prior to the corneal transplant, if there is adequate visualization. Alternatively, a goniotomy or tube shunt may be performed at the same time or a few weeks after the corneal transplant procedure.

The techniques for neonatal keratoplasty differ little in their broad outline from those used for adults. In general, surgeons search for younger donor tissue for these patients. However, donor tissue less than age 2 years (when combined with 0.5-mm oversized grafts) was associated with abnormally steep corneal transplant curvatures and extremely high postoperative myopia (88). The infant sclera and cornea are much floppier than the adult structures, and therefore a single or double scleral ring, perhaps with an attached blepharostat, secured with 8 to 16 sutures prevents collapse of the globe. If multiple anterior segment abnormalities are present, fine intraocular scissors, delicate iris sweeps, and mechanical vitrectomy instruments allow more elegant reconstruction. The surgeon can use viscoelastic agents to dissect iris from cornea hydrostatically, to maintain the anterior chamber, and to prevent rubbing of the donor endothelium on the iris and lens. We prefer interrupted 10-0 nylon sutures with the knots buried in the host, because healing is often irregular in these corneas, requiring early individual suture removal.

Postoperatively, these infants should be examined weekly. The corneas heal rapidly, and sutures often loosen 2 to 6 weeks after surgery. Because these infants cannot communicate any of the symptoms of ocular inflammation, and because most parents are incapable of detecting the minimal red eye or slight graft haze that occurs with immunological graft rejection, the physician must examine the cornea weekly until all sutures are removed for this phenomenon, promptly instituting treatment in the hospital, if it occurs. Social service support is often imperative during these trying times. Examinations under anesthesia are required, if adequate evaluation in the office is not possible. The sutures are removed early compared with adults. Half of the sutures are removed between 2 to 6 weeks and the other half 2 to 6 weeks later.

Management of postoperative elevations of intraocular pressure may require repeated goniotomies, filtering procedures, tube shunts and cyclocryotherapies, with the addition of the appropriate doses of carbonic anhydrase inhibitors and topical antiglaucoma medications.

Nonhealing epithelial defects may require lateral tarsorrhaphies, therapeutic soft contact lenses, and vigorous use of artificial tear drops, gels, and ointments.

Prompt contact lens fitting is the cornerstone for prevention of amblyopia. Extended-wear soft contact lenses are most effective, but infants tend to rub them out of their eyes, and an extensive inventory and backup system—including a supply of replacement lenses for parents to keep—will avoid delays in reordering lenses from the manufacturer. This optical correction may also require multiple examinations under anesthesia for refractions, keratometry, and contact lens refitting (89).

INFECTION

Corneal infections that occur in newborns and infants can cause corneal changes ranging from mild punctate keratitis to severe corneal ulceration and permanent opacity. A review (90) of 29 cases of microbial keratitis in infants and children found that 10 cases had preceding trauma. In eight cases there was a severe systemic illness and in seven cases contact lens use. Also, seven other cases had exposure keratopathy, and in six cases there was preceding trauma. It is essential to diagnose a corneal ulcer early and determine its etiology before it spreads and involves the deeper corneal stroma, causing permanent blurred vision from corneal scarring. Scrapings of the ulcer are necessary as soon as possible to try to identify the organism responsible for the disease. Gram and Giemsa stains are taken for the cornea scrapings, whereas blood, chocolate agar, and broth tubes are used for the cultures. If bacteria are found in cultures, antibiotic sensitivity plates should be set up.

An antibiotic should be selected that has the greatest likelihood of controlling the corneal infection as quickly as possible. For that reason, bactericidal rather than bacteriostatic drugs are preferred. Gram-negative organisms, such as *Pseudomonas,* can rapidly destroy corneal stroma and lead to descemetocele formation and corneal perforation within 24 to 48 hours of onset of infection. Another bacterium that may cause severe, rapid corneal melting and perforation is *Neisseria gonorrhoeae* (gonococcus). This organism typically causes an acute purulent conjunctivitis. This is a true ocular emergency and must be treated immediately to prevent severe ocular sequelae, such as corneal perforation.

The examination of an infant or young child is difficult because of the child's pain, fright, and inability to cooperate. When it is necessary to examine such a patient with a slit lamp, sedation or general anesthesia may be needed so that the eye may be adequately seen. A portable or handheld slit lamp may aid examination but does not provide as accurate details. Heavy sedation or general anesthesia allows for corneal scraping or surface debridement, if necessary, and subconjunctival or sub-Tenon's injections, when indicated at the conclusion of the examination. This type of examination should be repeated as needed to follow the progress of the disease. If the socioeconomic situation in the family is not conducive to regular, continuous administration of medication by a parent or guardian, hospitalization is required. When bacterial or viral corneal infections require medication hourly or every 2 hours, or when the home situation is not conducive to regular administration of medication, hospitalization is strongly recommended.

Inflammation and infection of the conjunctiva may extend to the cornea, resulting in a punctate keratitis, corneal ulceration, stromal infiltrate, or combinations of these changes. Once the stroma is affected, a benign conjunctivitis becomes a serious problem. If adequate examination and treatment are performed early in the disease, corneal involvement may be prevented and subsequent loss of vision avoided. If the child is not examined with appropriate thoroughness early in the disease, using general anesthesia, if necessary, the diagnosis can be missed or delayed, and serious permanent corneal damage can occur.

The appropriate diagnosis of corneal disease in infants and children is usually made only by slit-lamp examination. Small changes in the cornea that do not show up with a penlight can readily be seen after a diagnostic dye, such as fluorescein or rose bengal, is placed in the tear film. Application of drops is difficult for parents, because the child may be struggling and crying, and the drops will be washed out of the lower cul-de-sac with the child's tears. Even if the drops remain in place, they may be diluted with tears. For these reasons, ointments may be preferred in uncooperative infants and children. Once the child is old enough to be annoyed by the blurred vision from ointments, drops should be used instead. Parents must be taught by the ophthalmologist or office staff how to use topical medications properly. Occasionally, we have seen parents who, when asked to demonstrate drug application, place ointment on their fingertip and apply it to the child's closed lids. By demonstrating the technique of pulling the lower lid down, applying the ointment or drop to the lower cul-de-sac, and holding the lid open for 10 seconds, accurate drug application is achieved. If daily atropine is required in the infant for long-term cycloplegia, digital pressure should be applied over the punctum and canaliculus of the lower lid to prevent systemic adsorption and side effects.

Bacterial Ulceration

Bacteria that cause corneal ulceration in children are similar to those organisms that cause infection in adults (91). The workup and treatment are also similar in children as in adults (92). *Staphylococcus, Streptococcus pneumoniae,* and *Pseudomonas* are the more common bacteria that cause corneal infections in children. The most common bacterial infection is due to *Staphylococcus aureus,* a gram-positive organism that usually causes a punctate keratitis adjacent to the corneal limbus in the lower and upper portions of the cornea (Fig. 12.30). There is almost always a concomitant conjunctival inflammation and frequently an associated blepharitis with this corneal infection. The meibomian glands may be infected and serve as a reservoir for continued bacterial release and keratitis (see Color Plate IIA). Chronic staphylococcal blepharitis and keratoconjunctivitis in children may be a severe and recurrent problem that requires continued treatment until the source of the infection is eradicated. In children the primary treatment is bacitracin or erythromycin ointment in conjunction with lid hygiene, consisting of warm compresses and lid massage. A first-generation cephalosporin agent or a fluoroquinolone in eye-drop form has broad-spectrum effectiveness but is only variably useful against *Streptococcus* and anaerobic species. With more severe staphylococcal infection, and particularly for recurrent disease that does not respond to this treatment, systemic antibiotics, such as tetracycline or doxycycline and erythromycin, and topical corticosteroids are frequently necessary (93). Tetracycline and doxycycline can cause discoloration of the permanent teeth in children, so they should be avoided until these are developed. These systemic antibiotics are often started at one half the appropriate dose for the patient's age and weight for several weeks. The dose is then decreased in half and continued for months. Topical application of weak corticosteroids, prednisolone 1/8%, loteprednol 0.2% to 0.5%, or fluorometholone, is often used in chronic staphylococcal keratitis, because the superficial punctate keratitis, limbal infiltrates, and limbal neovascularization respond well to low doses of topical corticosteroids. Hot compresses for 5 to 10 minutes 1 to 2 times a day also helps decrease eyelid inflammation. Staphylococcal desensitization may rarely be needed, if it is found that the child has a marked hypersensitivity to the *Staphylococcus* exotoxin.

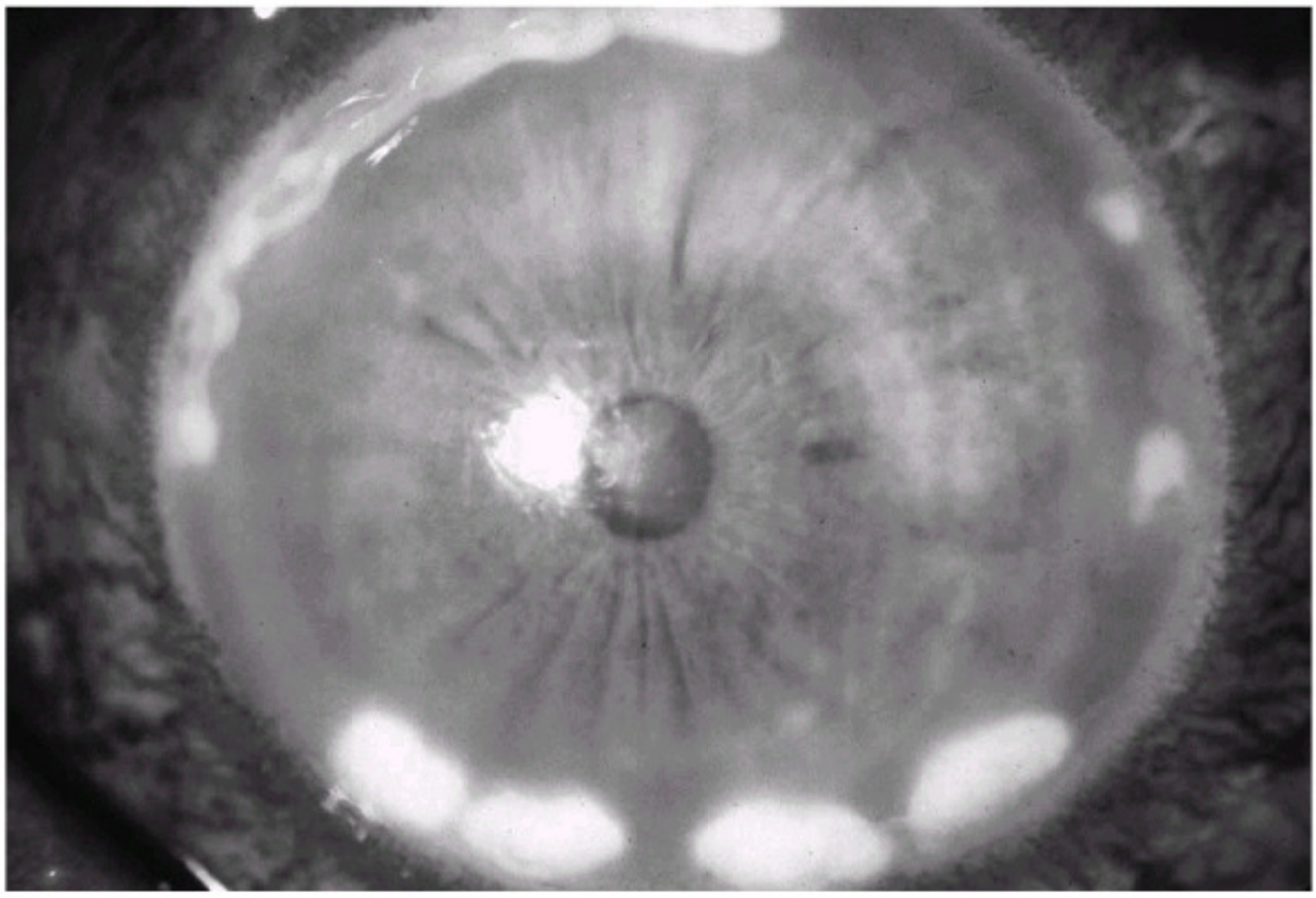

Figure 12.30 Peripheral corneal infiltrates from staphylococcal keratitis.

Other bacteria that mainly cause conjunctivitis, but may cause corneal ulceration, are *Haemophilus influenzae* and *Moraxella* spp. Both are gram-negative organisms, the first a coccobacillus and the second a rod form of bacteria. The incidence of *H. influenzae* ocular infections is lower since the widespread use of vaccination for this bacteria.

Marginal corneal ulcers can be caused by each of these organisms, but *S. aureus* is the most common bacterium causing limbal ulcers. *Moraxella* may produce an angular blepharitis by involving the skin at the lateral canthus, resulting in a serous or mucous discharge accompanied by irritation and pain.

Contact lens use, an important risk factor for bacterial keratitis is adults, is increasingly common in children. A recent study highlights the dangers of orthokeratology, the sequential fitting of rigid gas permeable contact lenses to flatten the cornea to treat myopia, in children. The authors report a series of corneal ulcers in six children, ages 9 to 14, using orthokeratology lenses. Five of the six ulcers were culture-positive for *Pseudomonas aeruginosa*, and all patients suffered a loss of best-corrected visual acuity (94).

Fungal Keratitis

Fungal keratitis generally occurs in adults but can also occur in children (91,95). It is usually associated with trauma from materials, such as wood, vegetables, or plant matter. Fungal infections are also encountered in the compromised host.

Infants rarely develop fungal keratitis, but young children and teenagers may, if they are injured by vegetable material, wood, sticks, dirt, or other outdoor foreign bodies. Other risk factors include previous systemic illness and previous ocular surgery (95). Fungal keratitis may at first be difficult to distinguish from bacterial keratitis. There is loss of epithelium and a surface ulcer with white stromal infiltrate. Fungal keratitis is characterized by a slowly advancing stromal ulcer unresponsive to antibiotics. There may be satellite lesions around the edge of the central ulceration or an immune ring around the infected area. Recognition of this depends on a suspicion, based on the history and course of the ulcer, that fungal keratitis may be present.

It is essential to make the correct diagnosis early. This requires a careful slit-lamp evaluation, under anesthesia, if necessary, and corneal scrapings for cell type, organisms, and fungal cultures. These cultures must be held for 3 weeks and examined daily. As in adults, fungal keratitis is often difficult to treat. Pimaricin (natamycin) is commercially available and effective against *Candida* and most filamentous fungi (*Fusarium* and *Aspergillus*). Amphotericin, another polyene that is topically applied, is available and a number of oral antifungal agents are used. Oral agents should be used with only culture-proved and sensitivitytested fungal keratitis. Clotrimazole, miconazole, ketoconazole, fluconazole, itraconazole, and voriconazole are oral agents that can be used usually in conjunction with a pediatric infectious disease specialist.

Viral Infections

Corneal infection due to herpes simplex virus (HSV) causes more morbidity and loss of vision than any other corneal infection seen in children. The newborn infant usually has maternal antibodies to HSV for the first 6 months of life, affording protection from infection with this virus. After the maternal antibodies are lost, the infant may acquire HSV infection of the skin or eye, or systemically (Fig. 12.31). Infection with HSV is probably acquired by close contact (kissing, handling) with someone who has an active lesion either around the lids or fingers (paronychia) or elsewhere on the skin's surface. Inapparent infection with HSV is usually the rule in children. They are exposed to the infection and acquire the disease but do not develop obvious HSV lesions.

Unfortunately, HSV ocular infection is not readily diagnosed early in the disease course. The pediatrician, emergency room physician, or general practitioner usually sees the child first, and treatment is started for what appears to be an obvious red eye. This treatment frequently consists of an antibiotic or antibiotic-steroid combination. Slit-lamp examination is not performed, although sometimes fluorescein dye is placed on the conjunctival or corneal surface, and the eye is looked at with a penlight. Small epithelial corneal or conjunctival dendritic ulcers can be seen only with a slit lamp. If there are dendritic epithelial lesions forming on the cornea or conjunctiva (see Color Plate IIB), the use of a local corticosteroid medication exacerbates the infection and can cause wider spread of viral keratitis in the epithelium and deeper involvement of the corneal stroma, even though the eye appears less inflamed. It is only then that an ophthalmologist is typically consulted.

Figure 12.31 Primary herpes simplex keratitis involving the skin around the eye and lip in a 4-month-old child.

The ophthalmologist sees an uncooperative infant or child who has been medicated for several days to weeks and has a very uncomfortable eye. Some form of sedation or anesthesia may be necessary to see enough of the cornea to make the proper diagnosis. If the ophthalmologist does not see the child's eye under magnification (with a slit lamp), the diagnosis may be missed. With a history of poor response to previous medication (usually antibiotics or an antibiotic-steroid combination), the index of suspicion for HSV infection should be high. To obtain a satisfactory examination, examination under anesthesia, application of fluorescein dye or rose bengal (see Color Plate IID), examination with a slit lamp or operating microscope, and removal of the dendritic or small geographical lesion at this time by mechanical debridement, may be necessary.

Until recently, the current choice of an antiviral agent was vidarabine (Vira-A) in ointment form. It was the only available ophthalmic antiviral drug in ointment form in the United States, although acyclovir ophthalmic ointment is used overseas. Unfortunately, Vira-A ointment is no longer commercially available in the United States. It may be formulated for use by a compounding pharmacy. Trifluorothymidine

(Viroptic) drops, every 2 hours, is the most effective antiviral agent against dendritic keratitis in the United States, but it is not overwhelmingly better, and an ointment is preferable in children as a first choice for an antiviral drug. Our first choice for infants and children is Vira-A ointment every 4 hours or 4 to 5 times a day. Our second choice is Viroptic drops 8 to 9 times a day. Topical acyclovir ointment 5 times a day would be preferable, if available. In addition to the antiviral drug, a cycloplegic, such as atropine sulfate 1% or scopolamine 1/4%, may be used if symptoms such as photophobia or ocular pain are present.

Primary HSV infection in children is not the most serious form of this disease. Recurrent viral infection is common after the initial bout with herpes simplex virus, and these recurrences are responsible for most of the corneal scarring and visual loss. About 25% of patients with primary ocular herpes develop a recurrent dendritic herpetic infection within 2 years of the initial lesion. Almost 50% of those who have more than one attack of herpetic keratitis have a third or more recurrences within 2 years. Recurrent HSV keratitis may occur after upper respiratory tract infections, fever, minor trauma (e.g., exposure to sunlight at the beach), or other triggering events.

When an infant or child who has had HSV keratitis develops any redness or irritation of the previously involved eye, whether or not this is preceded by an initiating event, the parent must suspect recurrent HSV infection and seek ophthalmic care immediately. Reevaluation with careful slit-lamp examination is necessary to determine whether the recurrent red eye is due to conjunctivitis or an actual recurrent dendritic or geographic ulcer of the corneal epithelium, with evidence of active viral replication in the epithelium, or whether this is secondary stromal inflammation or iritis. Parents of children who have HSV infection might benefit from having an antiviral drug available to start using immediately, even before seeing the ophthalmologist, if they see recurrent inflammation. Management of these recurrent herpetic infections, if they are dendritic or geographical lesions limited to the epithelium, consists of antiviral drugs, preferably Vira-A ointment or Viroptic drops, as for the primary lesion. For children who resist medication, mechanical debridement may be considered, followed by antiviral drug use. An oral antiviral

drug, such as acyclovir, can be used in children or infants, if they are unable to use topical medication. The dosage should be checked with a pediatrician, and kidney disease must be ruled out. Oral antiviral drugs are effective for primary and recurrent dendritic and geographical keratitis. If recurrent infection due to herpes simplex virus is not properly diagnosed, significant corneal scarring, thinning, vascularization, and even perforation can occur. Deeper stromal diseases with corneal vascularization and disciform keratitis may require use of topical corticosteroids, even though these antiinflammatory agents are contraindicated in superficial herpetic disease (Figs. 12.32 and 12.33).

Ophthalmologists should use the smallest amount of steroid necessary to control the stromal inflammation and should perform frequent examinations. Children should be seen at least twice a week for the first few weeks of this therapy, and the steroid tapered as soon as a response is achieved. In conjunction with steroid treatment, either Viroptic drops every 2 hours or Vira-A 4 times a day should be used. There have been reports of superinfection with bacteria when steroids and antiviral drugs are used long term for corneal epithelial infections known to be caused by herpes, emphasizing the need for frequent follow-up visits.

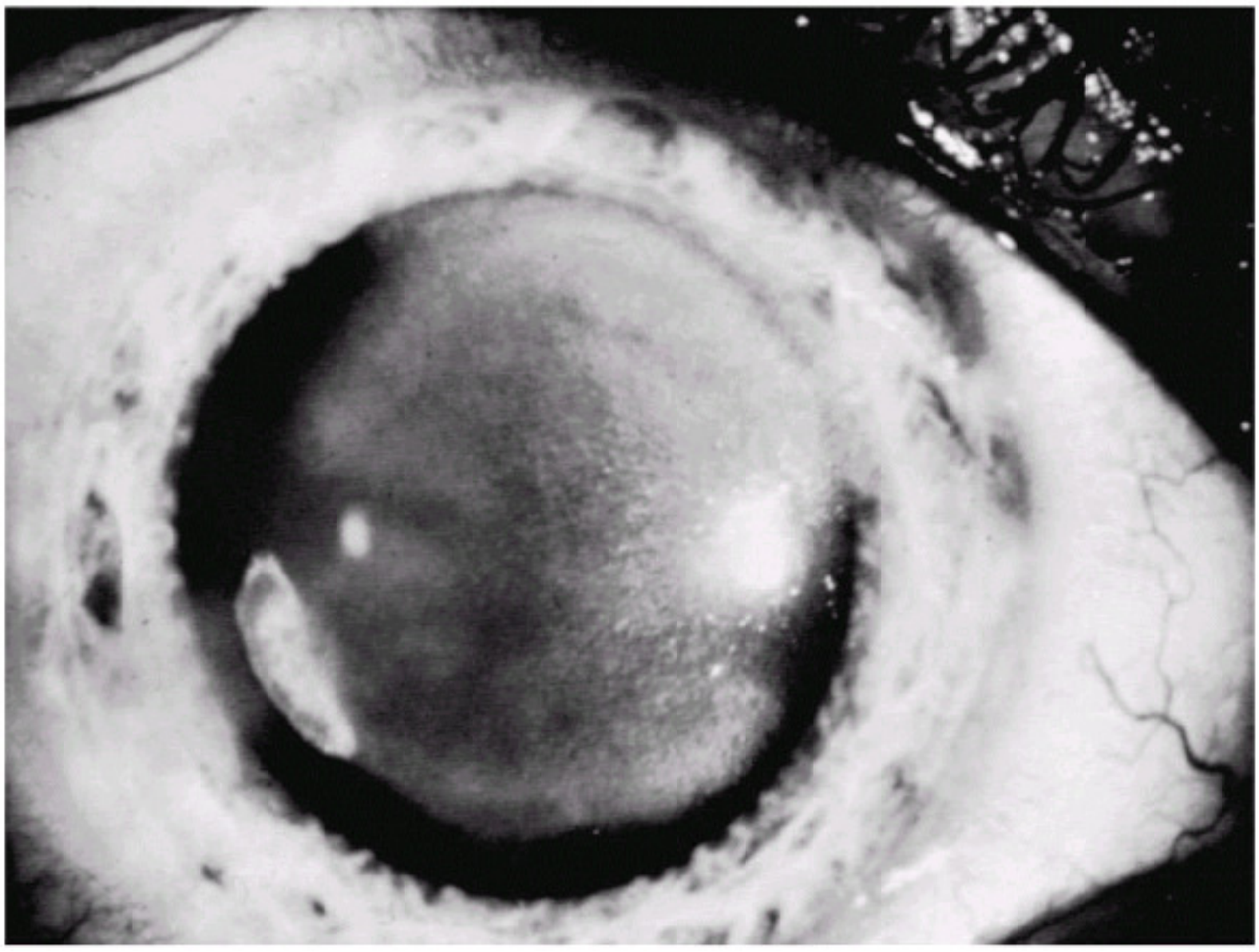

Figure 12.32 Disciform keratitis secondary to herpes simplex virus infection and recurrent disease.

Toxicity from extended use of an antiviral drug is a further problem, so these medications should be tapered and discontinued within 2 to 3 weeks of their initiation. With severe ocular toxic reactions to the antiviral drug and repeated corneal ulceration, hospitalization may be necessary to ensure effective drug delivery.

Oral or intravenous acyclovir is indicated for disseminated neonatal herpes simplex with encephalitis and may be lifesaving in these situations. It can be used in infants and children who are immunocompromised and develop HSV keratitis but should be administered by a pediatrician familiar with its use. Prophylactic oral acyclovir is often

used in children when treating with topical steroids for stromal keratitis and in preventing recurrent dendritic disease (96).

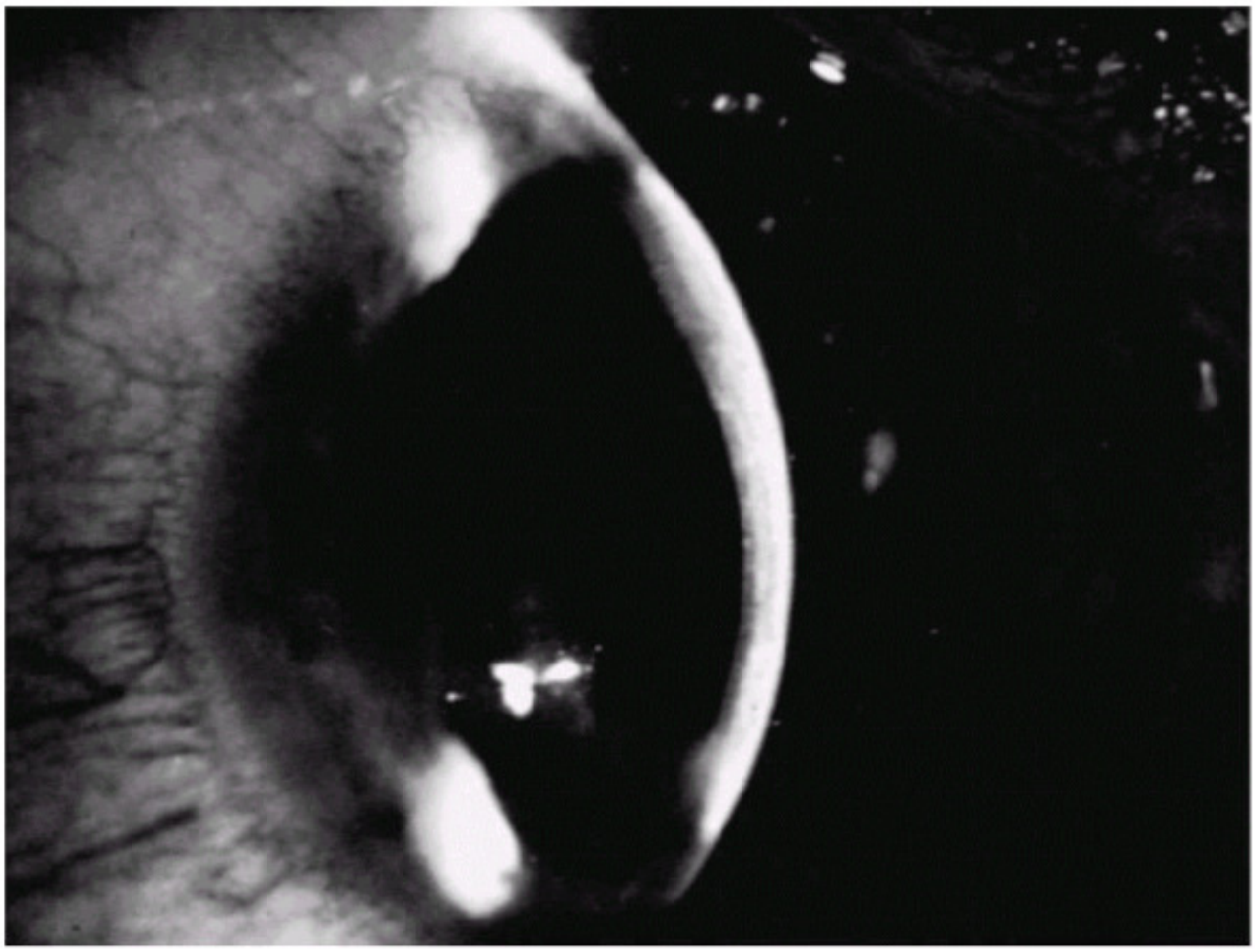

Figure 12.33 Slit-lamp view of disciform keratitis in patient.

Adenoviral Infections

Childhood adenovirus infections are marked by follicular conjunctivitis with systemic flu-like symptoms and preauricular adenopathy. The adult forms of adenovirus infection are also manifested by marked follicular conjunctivitis, but systemic symptoms are not nearly as common. As in adults, it is extremely contagious, and precautions need to be taken to avoid spreading the infection in the doctor's office and at home and school.

Pseudomembrane formation on the conjunctiva may be seen accompanying adenovirus infection in children. Despite follicular conjunctivitis and pseudomembrane formation, the cornea usually remains clear except for an initial fine, superficial punctate keratitis. Subepithelial changes commonly seen in adults are less often noted in children, which makes the diagnosis more difficult in children.

Numerous adenovirus types, including types 2, 3, 4, 5, 7, 8, 11, and 13, have been isolated in children. The corneal changes seen in adults with adenovirus types 8, 13, and 19 (Fig. 12.34) are not usually seen, or are much milder, in infants and children. In one large epidemic of adenovirus type 8, the youngest person involved was 8 years old, and only 3 of 102 persons examined who had the disease were under age 15. In a study of the infantile form of adenovirus type 8, no instance of subepithelial stromal keratitis was noted, although follicular changes and pseudomembranes were prominent in 12 cases. If corneal infiltrates do appear in children, they are usually transient, leaving no permanent corneal scar. In some adults the corneal infiltrates may last for many months or even years, and, rarely, permanent corneal scars remain.

The treatment of adenovirus in children is different from that in adults. Bacterial superinfection of the cornea is very uncommon, and therefore topical therapy with antibiotics once a day is unnecessary. Warm compresses are helpful, if there is much caking or debris from the marked follicular conjunctivitis and clear fluid discharge. Topical corticosteroids, which are often used in severe adenovirus infections in adults, are not indicated in children unless they are very symptomatic from marked follicular conjunctivitis and pseudomembrane formation. In these cases 0.125% prednisolone, 0.1% fluorometholone, or 0.2% loteprednol, 4 to 5 times a day for a few days, is indicated. The disease in children is self-limited, and no permanent ocular disorder results.

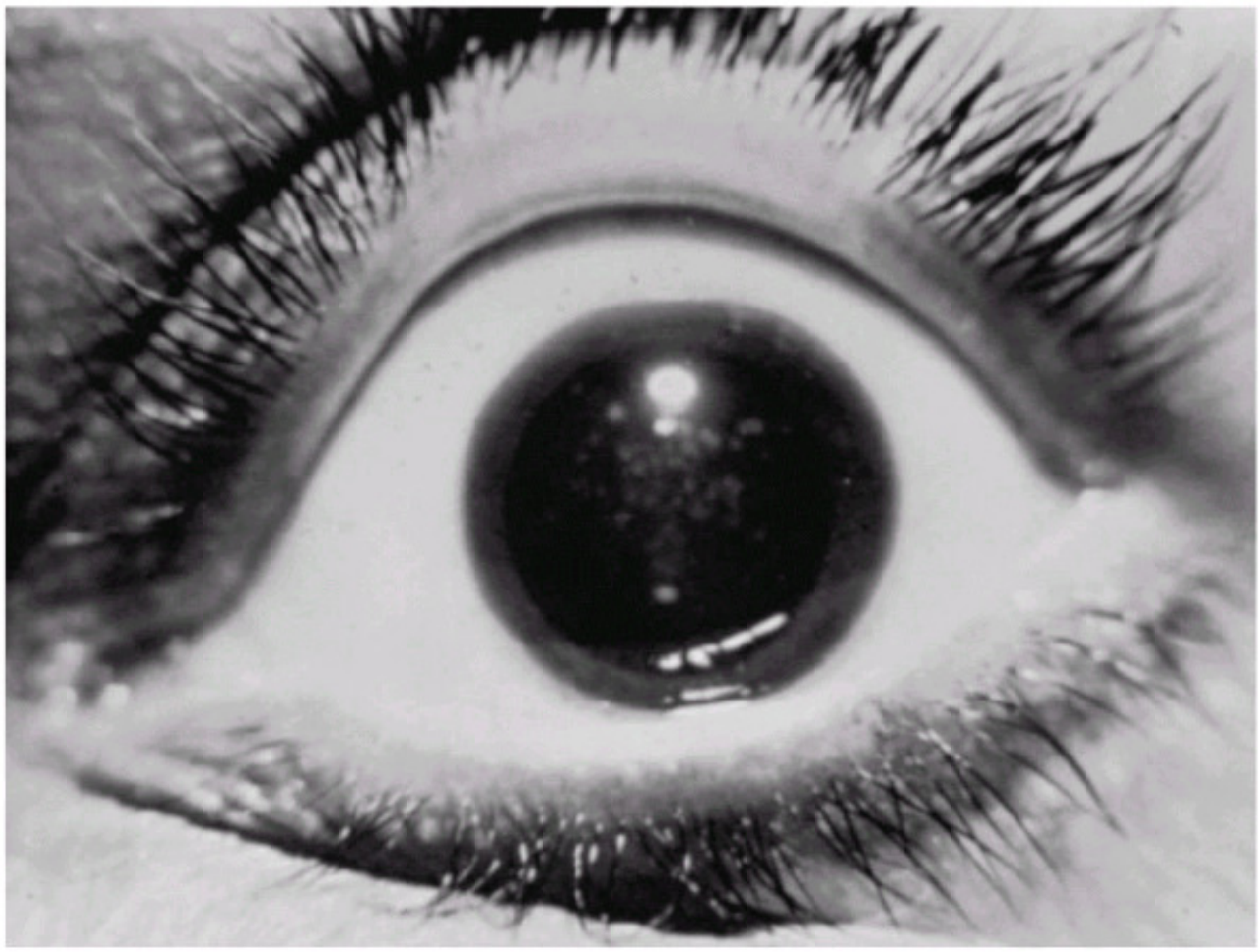

Figure 12.34 Subepithelial corneal infiltrates centrally in a patient with adenovirus type 8 infection 3 months after the onset of disease.

Varicella Zoster Keratitis

Chickenpox in children and shingles in adults are caused by the same virus, varicella zoster. This virus is responsible for varicella in children, which is highly contagious, and for herpes zoster (shingles) in adults, which is much less infectious. Shingles in adults is usually a reactivation of latent virus from childhood chickenpox. There are cases of herpes zoster keratoconjunctivitis in children, although this disease is overshadowed by the marked prevalence of chickenpox (varicella) in young people.

Various forms of corneal involvement may occur in children with chickenpox. The mildest form is an epithelial keratitis that is self-limited and requires no treatment. The corneal involvement consists of a fine punctate keratitis with some microcystic corneal edema. It is unusual to find more than this. There may be a limbal vesicle with stromal infiltrate and vascularization (see Color Plate IIID). This is unusual but has been seen in children. Disciform keratitis or stromal edema may also occur with severe ocular involvement caused by chickenpox. This finding is less common and resembles the disciform keratitis in herpes simplex keratitis.

Unilateral clear facial and forehead blisters or similar lesions of the brow may be seen in children without systemic skin involvement. These lesions may be herpes zoster, although they may be a localized varicella infection. When the nasociliary branch of the ophthalmic nerve is involved, there is a greater likelihood that ocular involvement will occur after herpes zoster infection (Hutchinson's sign). About half the patients with nasociliary nerve disease develop ocular involvement. With inflammation of the nasociliary branch of this nerve, vesicles may appear on the side of the nose on the same side on which the skin vesicles appeared on the brow or forehead.

Corneal involvement in children with herpes zoster may be seen as a punctate keratitis alone or accompanied by stromal keratitis with vascularization and keratouveitis. Episcleritis or scleritis is also common. There may be phlyctenular limbal and corneal involvement. Varicella zoster infections and ocular sequelae in children are much less common since the widespread use of the chickenpox virus vaccine. However, herpes zoster virus (HZV) sclerokeratitis with anterior uveitis has been reported in a 9-year-old 3 years after vaccination (97).

Oral acyclovir has been used for herpes zoster infections in adults, 800 mg, 5 times a day for 7 days, if the disease is first detected within 72 hours of disease onset. Valacyclovir (Valtrex) 1 gm tid is a prodrug that may have better antiviral

action due to better absorption. Famciclovir (Famvir) 500 mg tid is also effective against herpes zoster ophthalmicus in adults.

Oral acyclovir is indicated for children age 2 and older with chickenpox. Intravenous acyclovir is also indicated in the treatment of herpes zoster infections in immunocompromised children and adults. Consultation with a pediatrician or infectious disease specialist may be indicated in these situations. Famciclovir and valacyclovir have not been fully tested in children.

Treatment of herpes zoster keratitis is the same for children and adults. For the milder forms of herpes zoster ocular involvement, such as punctate keratitis, mild stromal edema, and minimal anterior chamber reaction, cycloplegia is all that is necessary, along with an antibiotic to prevent secondary bacterial infection. With more severe punctate keratitis, stromal edema, and anterior chamber involvement, the addition of topical corticosteroids is necessary, but this is rare in infants and children. The question of the use of systemic steroids in children who have herpes zoster has not been completely resolved. Because of the concern that the varicella virus may be spread systemically, the use of systemic steroids in children with herpes zoster ocular involvement should be approached with caution; they should be employed only under the joint care of a pediatrician specially trained in infectious diseases and an ophthalmologist. Local corticosteroid drops are usually sufficient to quiet the moderate or severe corneal, scleral, and anterior chamber inflammation of herpes zoster and varicella in children. Systemic acyclovir and the other, newer oral antiviral drugs are currently used for immunocompromised infants and children with herpes zoster ophthalmicus by pediatric infectious

disease specialists.

Other viruses that may cause epithelial keratitis are rubeola, mumps, and molluscum contagiosum. In molluscum contagiosum the molluscum lesions on the eyelid margins can cause a superficial punctate keratitis but rarely corneal ulcers. Surgical removal is recommended for these eyelid lesions. Epithelial keratitis is the most likely corneal manifestation in mumps, but cases of disciform keratitis have been reported, and local topical steroid therapy is usually all that is required. In most cases there is no residual scarring.

Vaccinia

The increase in terrorism worldwide over the past several years has revived the use of smallpox (vaccinia) vaccine. History of a recent smallpox vaccination or close contact with a recently vaccinated person is usually the way vaccinia blepharitis, conjunctivitis, and keratitis are contracted (Fig. 12.35). Vaccinia may be shed from the vaccination site for approximately 3 weeks. The incubation period from exposure to development of symptoms is 5 to 19 days. It has been estimated that 1 in 40,000 vaccinations leads to ocular vaccinia. It is generally treated similarly to herpes simplex infections with topical trifluorothymidine drops or vidarabine ointment. Vaccinia immune globulin (currently available only through the Centers for Disease Control [CDC] and Prevention in the United States) may also be used in more severe infections.

Figure 12.35 Vaccinial involvement of the outer canthus with lid swelling.

Chlamydial Keratitis

Trachoma is endemic in many parts of the world and is the second leading cause of blindness worldwide. In the Far and Middle East there are areas where 90% of the population have trachoma. In endemic areas, it may be possible to control the disease by placing children in an isolated environment (e.g., boarding school), but reinfection is common during visits to the family and local community.

In childhood trachoma, there may be epithelial punctate keratitis in the upper half of the cornea, in addition to superior limbal follicles. With further extension of corneal changes, subepithelial infiltrates at the limbus and pannus may develop as the disease progresses (Fig. 12.36). These limbal inflammatory infiltrates eventually scar and are referred to as Herbert's pits.

Control of this disease is essential, because it is by far the most common worldwide cause of corneal scarring and

blindness. Estimates of disease prevalence in child and adult populations are in the range of up to one quarter of a billion people. In a study in Tanzania, children with sustainably clean faces had reduced odds of having severe trachoma. The authors felt that improved face-washing and a reduced fly count on the face plus antibiotic treatment would reduce the risk for blinding trachoma in adulthood (98). In addition to improved hygiene, treatment includes systemic antibiotics (e.g., azithromycin or erythromycin) and topical antibiotics (e.g., erythromycin) for several weeks.

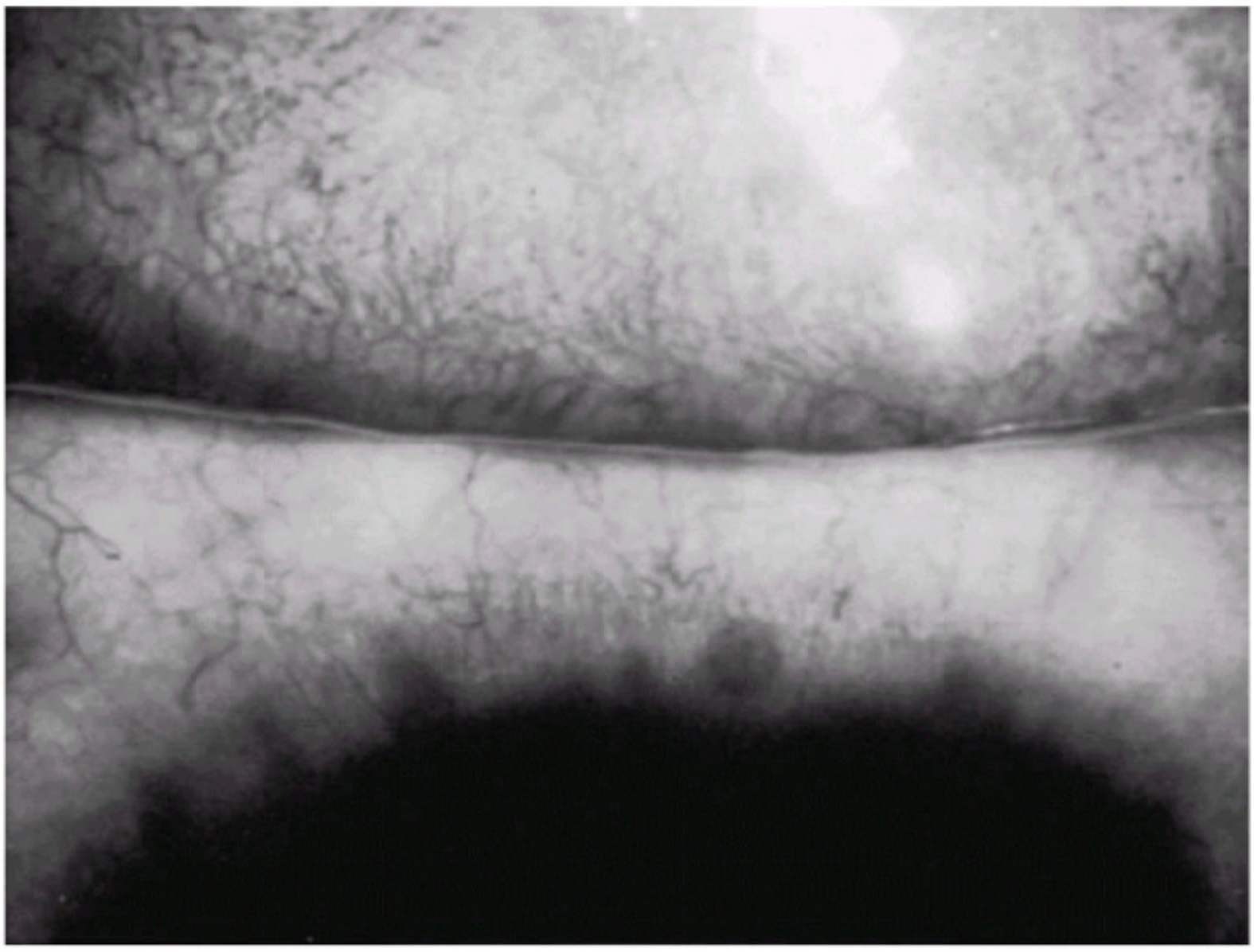

Figure 12.36 Superior limbal scarring and Herbert's pits in trachoma.

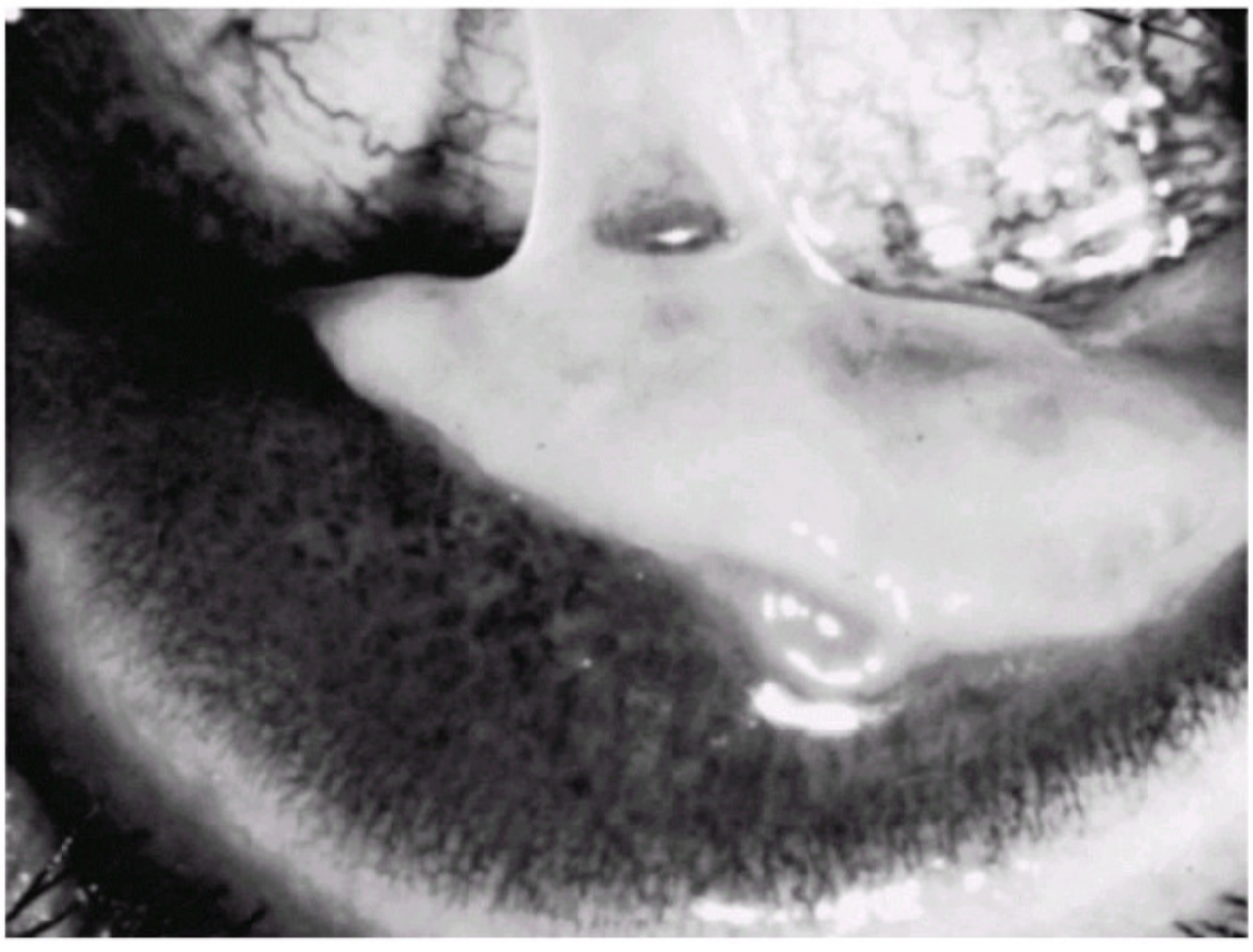

Figure 12.37 Purulent conjunctivitis and lid erythema in inclusion conjunctivitis.

Inclusion conjunctivitis (inclusion blennorrhea) of the newborn is seen throughout the United States (see Color Plate IIE). The organism responsible is the trachoma-inclusion conjunctivitis (TRIC) agent. This disease should not be confused with gonorrheal ophthalmia, which appears within 2 days of birth. Inclusion conjunctivitis is noted usually after birth, between days 4 and 15. Inclusion conjunctivitis is acquired during passage through the birth canal of infected mothers. Corneal involvement, when keratitis does occur, is limited to the epithelium. There are few, if any, long-lasting corneal changes. The main form of disease is a mucopurulent papillary and follicular conjunctivitis (Fig. 12.37). Treatment for early stages of this disease includes systemic antibiotics (e.g., azithromycin, doxycycline, or erythromycin) for 1 week to the patient and parents and topical antibiotics (e.g., erythromycin) for several weeks. The tetracycline family of medications is contraindicated in children, pregnant women, and nursing mothers. Additional information is covered in Chapter 11.

IMMUNOLOGICAL MANIFESTATIONS OF CORNEAL DISEASE

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis is a disease of childhood and teenagers that affects men more often than women. Vernal conjunctivitis or spring catarrh is generally more prevalent in the spring but may be symptomatic all year. It usually begins in the upper palpebral conjunctiva with papillary hypertrophy. Although children with vernal conjunctivitis usually have a history of allergy, there is no definite known cause for this disease. Itching, tearing, and light sensitivity are the most common symptoms. There is usually a mucoid, ropy discharge. The disease may last for many years with remission and exacerbations (Figs. 12.38 and 12.39).

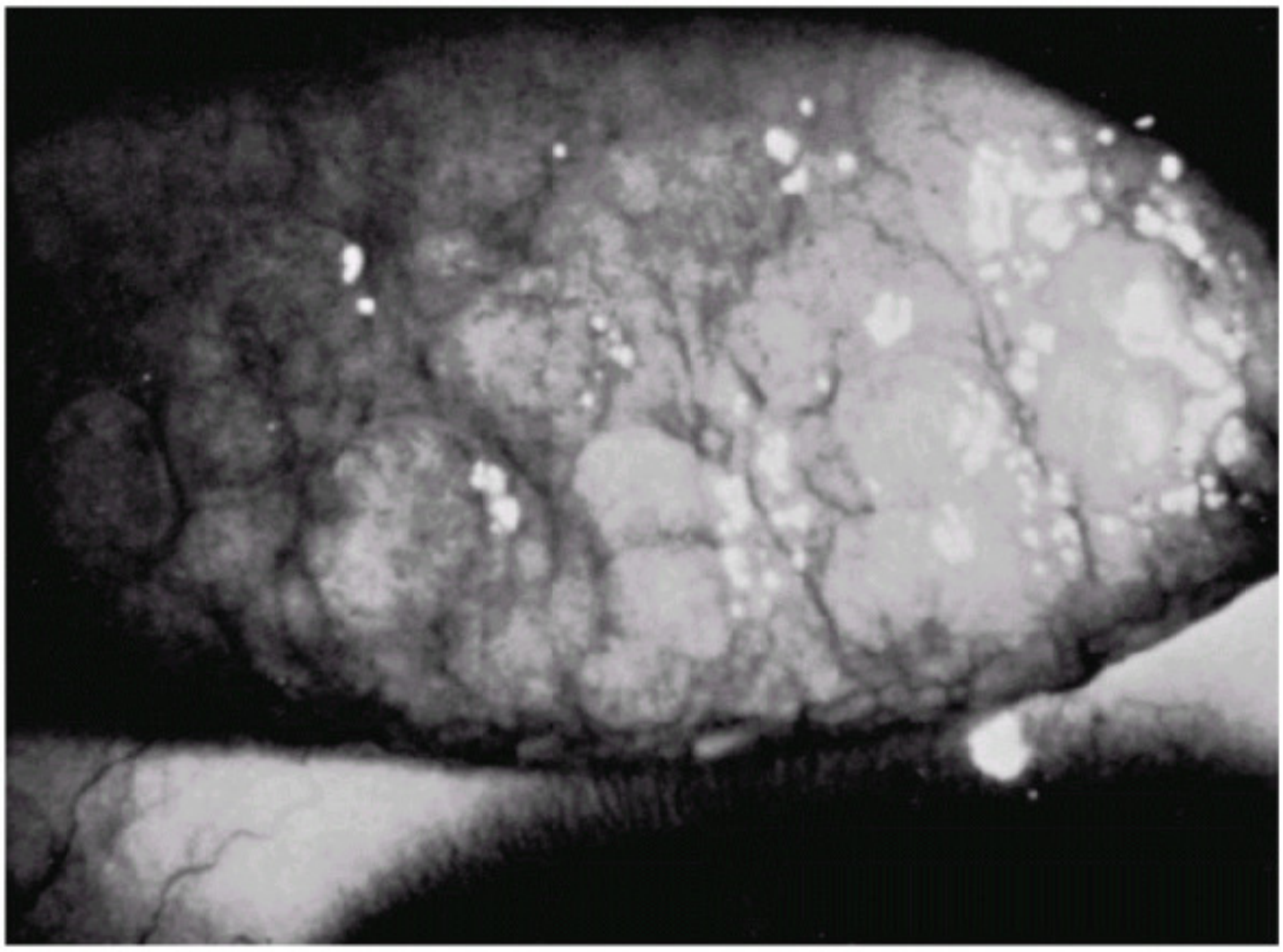

Figure 12.38 Large papillary cobblestone excrescences in vernal conjunctivitis involving the upper lid.

Limbal vernal keratoconjunctivitis is another manifestation of vernal conjunctivitis. Fine lymphoid follicles, which may appear yellow to light brown, occur around the limbus (see Color Plate IIF). The follicles do not stain with fluorescein and do not become ulcerated. When these limbal changes take the form of white or yellow-white hard dots, they are known as “Trantas' dots.”

Epithelial punctate keratitis is noted in both the main form of vernal conjunctivitis, in which the upper tarsal conjunctiva is involved, and the limbal form. Superficial punctate

epithelial staining is noted, usually in the upper half of the cornea, but staining may occur all over the cornea in severe disease. This may be accompanied by filamentary keratitis. Subepithelial stromal changes are not common. The classic corneal change in vernal conjunctivitis, the shield or plaque ulcer, is seen much more often with upper tarsal conjunctival involvement than with the limbal form (see Color Plate IIG). This is usually an irregularly oval plaque, with elevated hypertrophic epithelial cells and fibrin, which stains bright green with fluorescein. This is not usually an ulcer but an elevated plaque-like change on the surface of the cornea. Although this lesion is most often due to the upper tarsal conjunctival form of vernal conjunctivitis, the shield ulcer probably is not caused by the papillary changes in the conjunctiva. If such patients can wear soft contact lenses for any length of time, the shield ulcer persists beneath the soft lens even though the papillary changes are not rubbing the cornea. Treatment of the shield ulcer is the same as for the papillary hypertrophy in this disease: topical corticosteroids, usually in ointment form. Often, scraping the hard, crusty debris from the shield ulcer down to smooth (although hazy) cornea can greatly accelerate reepithelialization. Children who have vernal conjunctivitis shield ulcers are extremely light-sensitive and tear profusely. In these patients the drop form of corticosteroids is usually less effective. Topical antibiotic drops or ointment are used, especially after corneal scraping.

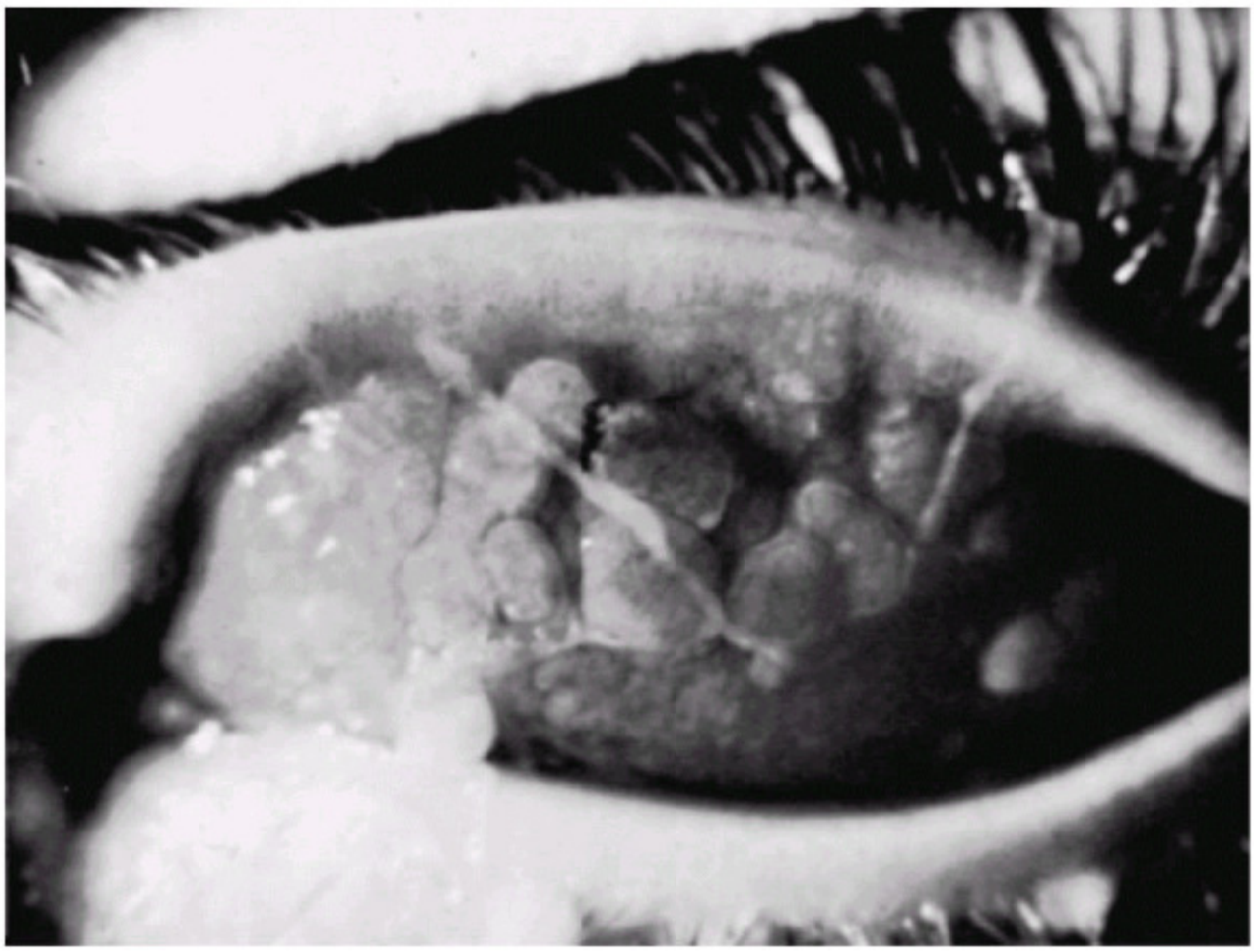

Figure 12.39 Individual giant follicles in vernal conjunctivitis with excessive mucus.

Mast cell stabilizing drugs, such as cromolyn sodium (Crolom), lodoxamide (Alomide), and pemirolast (Alamast) reduce the production of histamine, which is responsible for the severe itching in vernal conjunctivitis. In clinical drug studies, the use of cromolyn sodium for vernal keratoconjunctivitis in children proved effective and reduced or eliminated the need for topical corticosteroids (99,100). There have been no serious side effects from the use of cromolyn sodium drops 4 times a day, except for occasional irritation, which may be due to the preservative in the drug preparation. These mast cell stabilizers are generally used 4 times a day. Newer topical allergy medications with mast cell stabilizing properties are also often effective, including azelastine (Optivar), epinstine (Elestat), ketotifen (Zaditor), nedocromil (Alocril), and olopatadine (Patanol). These antihistamine/mast cell stabilizers are generally used 2 times a day. Patients who are very symptomatic and require corticosteroids are not helped initially by a mast cell stabilizer alone. Patients must use steroids along with the mast cell stabilizer, and as the mast cell stabilizer effect builds up, steroids can be slowly tapered and discontinued. If they tolerate the medication satisfactorily, patients may be kept on the mast cell stabilizer for months or years without ocular side effects.

When both vernal conjunctivitis and the shield ulcer are present, a mast cell stabilizer alone does not show benefit as quickly as do corticosteroids and this agent in combination. The minimum dose of steroids should be used to control the disease, because steroids have potential side effects. In one study, 6% of patients with vernal developed corneal damage, cataract, or glaucoma (101).

Recently, topical cyclosporin A 0.05% (Restasis) has been shown to be safe and at least somewhat effective in relieving the signs and symptoms of severe atopic keratoconjunctivitis (an allergic ocular condition similar to vernal) in patients refractory to topical steroid treatment. The drops were initially used 6 times a day for 2 weeks and then decreased to 4 times a day (102). Topical cyclosporin A was also found to be effective in the management of vernal shield ulcers in four patients at a concentration of 1% to 2% (103).

Phlyctenular Keratoconjunctivitis

This form of keratoconjunctivitis was thought to be due to only a hypersensitivity reaction to tuberculin protein, but a specific cause is not known.

The phlyctenular changes consist of an elevated, pinkish lymphoid follicle, which invades the cornea at the limbus, leaving a vascularized track behind (see Color Plate IIH). Eventually, the phlyctenular appearance is that of a flat or slightly raised gray, vascularized, wedge-shaped area in the cornea with a leash of vessels to the limbus.

A small corneal ulcer may occur at the head of the lesion. Phlyctenules may appear around the corneal limbus, but usually only one lesion advances farther into the central cornea. These lesions may cause visual loss when they affect the pupillary area but are usually treated and become quiescent before reaching the pupil.

Staphylococcal infection can also cause phlyctenular conjunctivitis. In these patients, treatment of staphylococcal infection of the eyelid margin, and, particularly, the meibomian gland, quickly quiets the corneal changes, preventing corneal damage. Patients with tuberculosis-associated phlyctenules have more severe lesions and more recurrences (104).

Phlyctenular conjunctivitis may be treated with topical corticosteroids, at first usually 1% prednisolone or 0.5% loteprednol 3 or 4 times a day and then tapering to 0.125 % prednisolone, 0.1% fluorometholone, or 0.2% loteprednol once a day or every other day, over a period of a month or more, once the disease is controlled. The corticosteroids may be discontinued when the eye quiets but may have to be restarted, if there is a flare-up of the phlyctenular conjunctivitis. If staphylococcal infection of the meibomian glands is present, a concomitant eyelid hygiene and antibiotic is generally used, either bacitracin or erythromycin ointment once or twice a day. The response to steroids is dramatic, and corticosteroids remain the cornerstone of acute occular treatment for this disease (105).

Erythema Multiforme (Stevens-Johnson Disease and Drug Reaction)

Erythema multiforme is a severe systemic reaction that usually occurs after use of certain systemic medications, such as sulfonamides, salicylates, phenytoin

sodium, and barbiturates, among others (106). Topical sulfonamides after only a few applications have rarely caused this severe problem. Hypersensitivity to the drug administered may be responsible for the acute eruption. There are vesicular and bullous skin eruptions involving mucous membranes of the mouth and nose, as well as conjunctival eruption. Mucopurulent and pseudomembranous conjunctivitis may be

seen along with ulcerations of the eyelid. There is corneal involvement secondary to the eyelid reaction. After healing of the eyelid margins, epidermalization occurs on the palpebral surface of the eyelid (Fig. 12.40). With continued irritation from the rough conjunctival surface, the cornea develops superficial punctate keratitis and pannus formation, usually inferiorly or superiorly. In severe cases, cicatrization and symblepharon develop. Epidermalization may involve the corneal epithelium as well as the conjunctival epithelium, so that the end result is a totally scarred conjunctiva and cornea, with firm adhesion of the eyelid margin to the cornea itself (Fig. 12.41). Corneal transplantation is the only hope of maintaining vision in these patients, but the prognosis is poor. Treatment of the acute disease is difficult. Only systemic and local corticosteroids offer any hope of aborting the later, more severe consequences. When symblepharon and epidermalization occur, scleral or soft contact lenses can be applied to protect the cornea. Surgical reformation of the inferior cul-de-sac may be necessary when symblepharon develops (107). Amniotic membrane grafting may be beneficial. In older children with severe corneal scarring from erythema multiforme, there is loss of limbal stem cells. Limbal transplantation, either from the opposite healthy eye (usually not feasible because both eyes are usually affected) or from a close relative, is necessary before corneal transplantation has a chance of working (108).

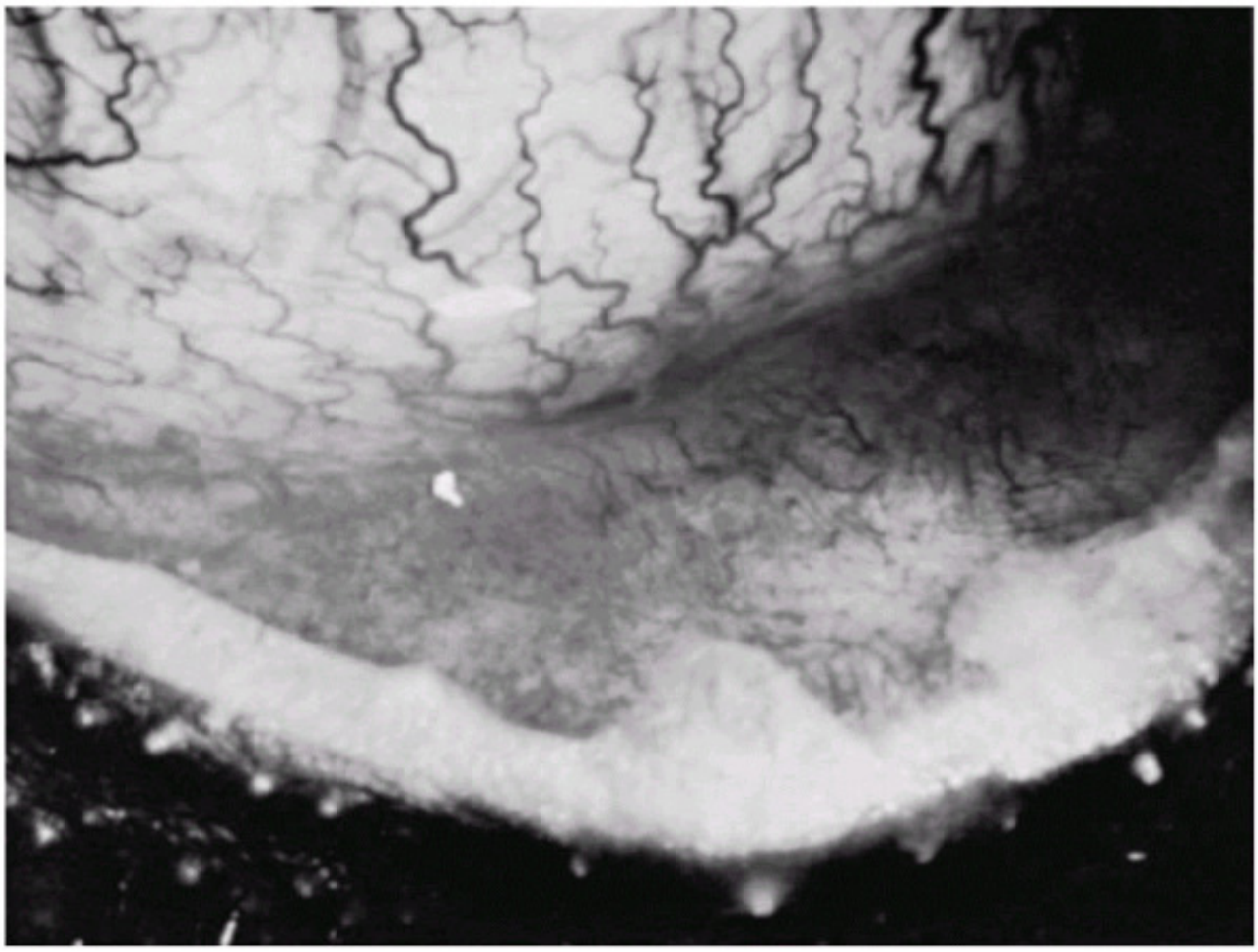

Figure 12.40 Epidermalization of the palpebral conjunctiva of the lower lid in Stevens-Johnson disease. This is a keratinization of the normal, smooth, glistening palpebral conjunctiva.

Figure 12.41 Lid changes in Stevens-Johnson disease with total scarring and symblepharon involving the lid and cornea.

Children who have had bone marrow transplants for aplastic anemia or leukemia may develop graft-versus-host disease and reject their conjunctiva along with other mucous membranes and their skin. They can develop an erythema multiforme-like picture and are treated as severe burn cases.

Epidermolysis Bullosa

The cornea is involved in the severest form of this disease. There is corneal clouding in the region of Bowman's membrane and epithelium. Bullae similar to those found in the skin result in corneal ulceration, and perforation of the cornea can occur.

CORNEAL DYSTROPHIES AND DEGENERATIONS

Corneal dystrophies are unusual and dramatic when seen against a background of clear corneal tissue. Some degree of corneal opacification or clouding is present in these patients. Dystrophies are bilateral, are hereditary in nature, occur more centrally than peripherally, are nonvascularized, and do not usually manifest inflammatory signs or symptoms. On the other hand, corneal degenerations may be unilateral or bilateral, involve the peripheral as well as the central cornea, and often follow inflammation of the cornea. They are not hereditary and may occur after other ocular or systemic disease.

Over the past several years, many advances have been made in our understanding of the genetics of corneal dystrophies. New classification systems are being developed to incorporate this new information, which will hopefully help in comprehending the pathogenesis of these disorders and in developing new treatment approaches (109).

The corneal dystrophies are not limited to children, and, although they occasionally begin in childhood, most are first seen in the adolescent or later years. They become progressively worse during middle adult life. The corneal dystrophies first seen in childhood are emphasized in this section.

Anterior Corneal Dystrophies

The anterior corneal dystrophies include those that involve the epithelium, basement membrane, and Bowman's membrane with *very* superficial stromal changes, but they do not involve primarily the stroma.

Hereditary Juvenile Epithelial Dystrophy of Meesmann

Meesmann dystrophy is a rare, dominantly inherited epithelial dystrophy seen in early childhood, usually by ages 3 or 4 years. Visual acuity is not usually seriously affected. The corneal lesions appear as hundreds of tiny cystic changes in the deep epithelium and are noted best during slit-lamp examination by retroillumination. They are concentrated in the interpalpebral zone. On histopathology, the vesicles contain a PAS positive substance known as “peculiar substance.” The disease is not progressive; however, if vision is reduced to less than 20/60, epithelial debridement, superficial keratectomy, or excimer laser phototherapeutic keratectomy (PTK) may be performed to replace the abnormal superficial cornea. Unfortunately, when host epithelium grows back, the cystic changes will, eventually, once again appear. Corneal sensitivity is reduced in Meesmann dystrophy. Grossly, the cornea may appear slightly hazy, but only on slit-lamp examination is the disease readily evident.

Corneal Dystrophies of Bowman's Membrane

Corneal epithelial scarring and irregularity accompanied by opacities and scarring in the region of Bowman's membrane, as well as recurrent epithelial erosions, characterize a group of dystrophic corneal changes with various eponyms. These changes were (and still are) called Reis-Bücklers corneal dystrophy, superficial variant of granular dystrophy, and Thiel-Behnke corneal dystrophy (110). In many cases these corneal changes begin in the first decade of life and are all dominantly inherited.

Kuchle et al (111) offered a classification that simplified these dystrophies, based on clinical appearance, as well as light and electron microscopy. They divided these anterior dystrophies into two classifications: CDB-I and CDB-II—corneal dystrophy of Bowman's. Type I is synonymous with Reis-Bücklers original dystrophy (see Color Plate IIIA) and has been called the “superficial variant of granular dystrophy.” Recurrent corneal erosion may begin in childhood and may be marked by early and possibly severe visual loss. CDB-II has been known as the honeycomb dystrophy and was described by Thiel and Behnke. Symptoms are similar, but vision is reduced later in life than with CDB-I. Transmission electron microscopy differentiates these two dystrophies. In CDB-I ultrastructural deposits of rod-like bodies are present, similar to those seen in granular stromal dystrophy. In CDB-II curly fibers are evident, rather than the rod-like granules.

Treatment has been directed early at correcting the multiple corneal erosions that lead to scarring superficially. As these erosions persist, more scarring occurs, and irregular surface leads to further visual loss. Now, instead of performing a lamellar keratoplasty or peeling technique, or even a penetrating corneal transplantation, excimer laser PTK is used. Eventually, a corneal transplant is needed in adulthood, because deeper scars are formed over numerous years of recurrent erosion.

Epithelial Basement Membrane Dystrophy and Dystrophic Recurrent Erosion

Recurrent corneal erosion is usually a result of superficial corneal trauma. There are cases in older children and teenagers that stem from a corneal hereditary dystrophy. Reports have been published of recurrent erosions in families covering several generations. Epithelial basement membrane dystrophy is the main familial dystrophy in which recurrent erosions are common, but there is generally little, if any, permanent scarring or visual loss.

Management of recurrent erosions in children is similar to that in adults. Antibiotic and lubricating ointments, patching, occasionally soft contact lenses, and debridement are the main choices for therapy in children. Rarely, a diamond burr polishing of Bowman's membrane procedure or an excimer laser PTK is required in eyes unresponsive to more conservative treatment.

Stromal Corneal Dystrophies

Of the three common corneal dystrophies (granular, lattice, and macular), only macular corneal dystrophy is seen in early childhood.

Granular Dystrophy

Granular dystrophy may be seen later in the first decade, but visual acuity is not decreased. There is relatively good vision in the first few decades of life because the lesions are discrete and sharply outlined, leaving clear cornea around them (see Color Plate IIIB). This dystrophy, which does not usually cause significant epithelial irregularity and does not impair normal corneal sensitivity in the first and second decades of life, is dominant in its mode of inheritance. It does not lead to corneal vascularization or corneal erosion. Histopathological findings have revealed that the abnormal tissue represents a hyalin degeneration in the stroma. Corneal transplants are rarely performed in children or teenagers with this dystrophy.

Very superficial granular dystrophy has been described that may be evident in the second decade of life. It is treated by excimer laser PTK, if there are severe visual symptoms in the teenage years.

Lattice Dystrophy

Lattice dystrophy is also dominant in inheritance and appears at its earliest toward the end of the first decade. The corneal epithelium is typically spared early on, and therefore vision is good until the third or fourth decade. There is progressive opacification in a linear pattern in the superficial stroma, usually in the central region of the cornea (Fig. 12.42). Corneal sensitivity is decreased when more pathological changes develop, but this does not occur in adolescence. The lesions appear as irregular, thick, opacified linear changes that cannot be followed to the limbus and therefore can be differentiated from blood vessels and corneal nerves by careful slit-lamp examination. The stroma around these pathological changes remains clear until later in life, when recurrent erosions and opacifications reduce vision to less than 20/200. Histopathologically, the abnormalities

are amyloid material in the stroma. Amyloid is not seen in granular and macular corneal dystrophies. In eyes with very superficial opacities, excimer laser PTK may significantly improve vision and recurrent erosion symptoms. A penetrating corneal transplant is indicated, if vision deteriorates and the disease involves most of the corneal stroma. This is rarely necessary in children.

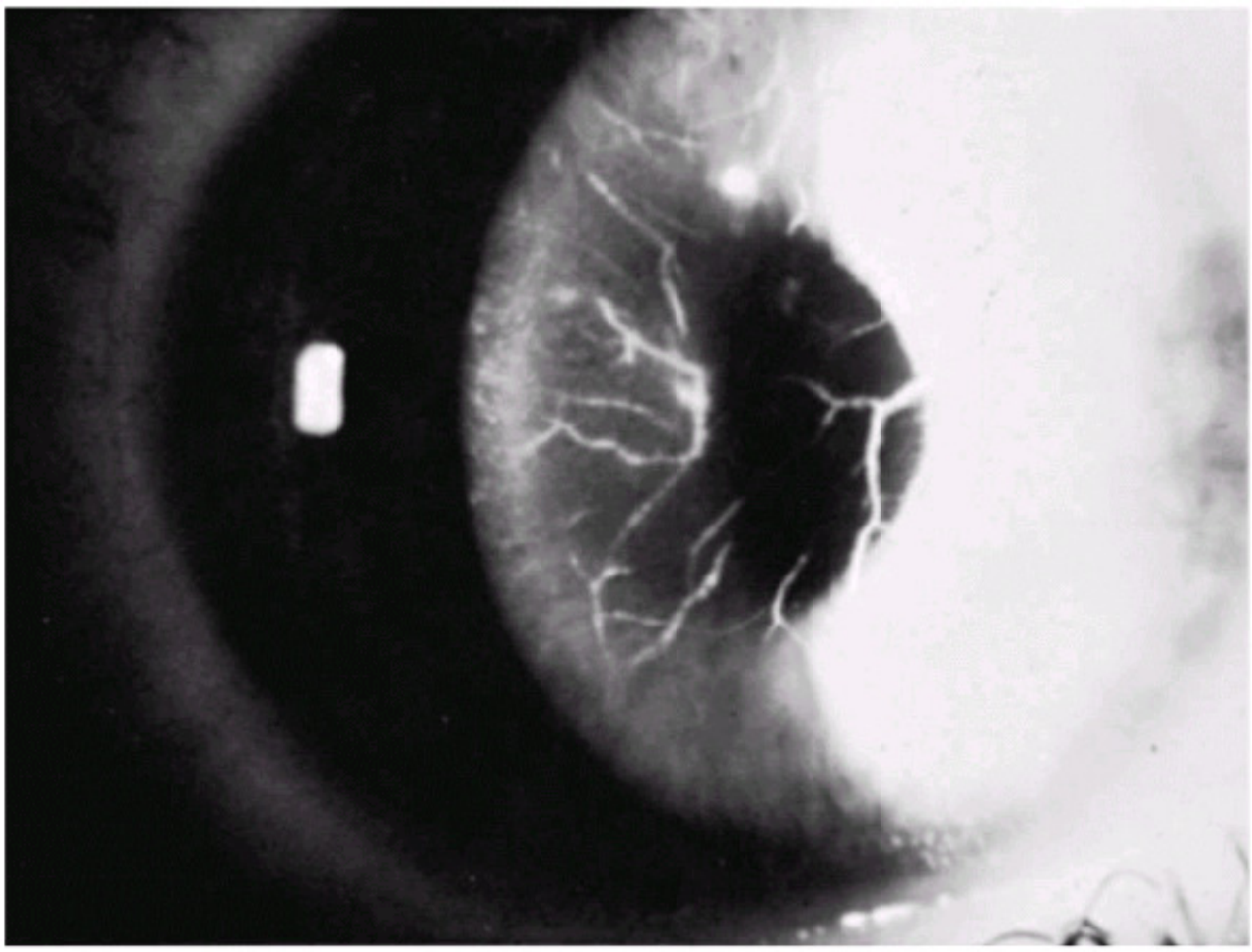

Figure 12.42 Lattice dystrophic changes in the corneal stroma, found in a 19-year-old with a family history of lattice dystrophy.

Macular Corneal Dystrophy

Inherited as an autosomal recessive trait, macular dystrophy is usually seen early during the first decade and leads to more corneal opacity than that caused by granular and lattice dystrophies. The lesions are not as clearly circumscribed as in granular and lattice dystrophies. In macular dystrophy the cornea appears hazy, with poorly defined margins to the opacities, which blend into normal-appearing cornea. The lesions vary in size and shape in the stroma. The dense opacities are located anteriorly in the central cornea and posteriorly in the peripheral cornea. Beginning in the second or third decade, the central corneal thickness is typically reduced, often in the range of 400 microns. Histopathologically, the corneal opacifications are deposits of acid mucopolysaccharide (glycosaminoglycan) throughout the stroma, even involving the endothelium. This dystrophy is much less common than the two dominant corneal dystrophies, lattice and granular.

Patients generally notice decreased vision and recurrent erosion symptoms. If the central opacities are very superficial, they may be amenable to treatment with excimer laser PTK. Penetrating corneal transplantation is seldom necessary early in life. Recurrent stromal changes similar to those in the original dystrophy often occur after excimer laser PTK and corneal transplantation for the stromal corneal dystrophies, especially granular and lattice. Macular dystrophy may rarely be operated on in childhood, and one may expect to see recurrent disease in the teenage years, if transplantation is carried out early in life (112,113).

Although the corneal transplant may later partially opacify because of recurrent disease, this does not mean that the operation should be avoided, because the reason for the transplant in the first place is very poor vision. It is usually many years before the transplant is clouded enough to warrant a repeat transplant operation for recurrent macular dystrophy in the graft. Recurrent macular dystrophy in the corneal transplanted tissue is less common than with granular and lattice dystrophies.

Crystalline Dystrophy of Schnyder

Schnyder's dystrophy is an autosomal dominant disorder that may be seen in childhood and, rarely, early in infancy or at birth. The corneal changes are bilateral, although often asymmetrical, and consist of many fine, small cholesterol crystals in the superficial central stroma. Corneal sensitivity is normal. There is slow progression of the dystrophy with no vascularization. Full thickness opacity and dense arcus lipoides develop later in life. Vision remains good throughout early life, despite the crystalline changes in the cornea. Corneal transplantation, when necessary, is usually done at midlife or later because vision is typically satisfactory, despite the opacities in the central cornea. Patients diagnosed with Schnyder's crystalline dystrophy should undergo a lipid workup because it is associated with hypercholesterolemia, with and without hypertriglyceridemia.

Deep Corneal Dystrophies

Dystrophies involving the endothelium are not common in early life. Alterations in Descemet's membrane may be seen at birth, but these are changes from congenital glaucoma or birth injuries, or developmental changes, rather than corneal dystrophies or degenerations.

Congenital Hereditary Endothelial Dystrophy

Full-thickness bilateral clouded corneas seen at birth or soon after may represent congenital hereditary endothelial dystrophy (CHED). It may be dominantly inherited in some families and autosomal recessive in others. Symptoms depend on the age of onset and severity and include nystagmus, pain, tearing, and photophobia. The corneal appearance at birth may be mistaken for congenital glaucoma, but the intraocular pressure is normal, and the eye is not enlarged. Full-thickness corneal and epithelial edema are present, although the anterior chamber and iris are normal. An interesting finding in this disease is the thickening

of collagen fibrils seen histologically. This is not present in any other corneal dystrophy. The endothelium is very attenuated or absent, leading to marked corneal swelling from stromal edema.

Corneal sensitivity is normal. Electron microscopic findings have been reported, but the cause of this dystrophy is unknown. Penetrating corneal transplantation in this disease is successful in 60% to 70% of patients (see Color Plate IIIC) (114).

Posterior Polymorphous Dystrophy

Posterior polymorphous dystrophy is usually autosomal dominant but may be sporadic. There may be circular or

linear vesicles on the posterior surface of the cornea. The changes may be present in the first few years of life and occasionally at birth. There may be peripheral anterior synechiae and iridocorneal adhesions; glaucoma is found in approximately 15%. The disease is usually slowly progressive. Various degrees of corneal abnormality may be present in different members of the same family. The mildest form shows only single or multiple vesicles, sometimes in lines with normal overlying stroma. The severe form shows multiple vesicular changes on the back of the cornea, enough to cause stromal edema and scarring, but seldom requiring corneal transplantation. This disease, unlike endothelial dystrophy and Fuchs' dystrophy, is seen in young people, but either is much slower in its progression or does not progress at all. Very few patients require corneal transplantation.

Corneal Degeneration

Keratoconus

The most common corneal degeneration in early adolescent years is keratoconus, a bilateral, noninflammatory condition that affects both sexes but is slightly more common in women. It often manifests itself at puberty. Keratoconus may be difficult to recognize in the early and middle adolescent years. It can be very difficult to differentiate from high astigmatism. Progression occurs in the mid- to late teens and into the 20s and occasionally later. Unilateral keratoconus may also be seen, but bilateral cases are far more frequent. About 10% of patients have other family members with keratoconus. Abnormal computerized corneal topography with inferior steepening has been seen in relatively asymptomatic family members. There is some evidence that keratoconus may develop from long-term contact lens use, but this is controversial. Constant eye rubbing may also be a factor.

In childhood the earliest changes are characterized by distorted images at the keratometer or with the Placido disc. With retinoscopy, there is an uneven motion or slit in the reflex. This has been described as a scissors motion (Fig. 12.43). One of the earliest ways to diagnose keratoconus is with computerized corneal topography.

With the direct ophthalmoscope, there is a dense, irregular, dark reflex in the center of the reflected red reflex. In the early stages, slit-lamp examination reveals central or paracentral thinning, but this may be hard to detect. There may be deep corneal stromal striae, and with the slit lamp a Fleischer's ring can be found at the upper or lower border of the early cone. Acute hydrops or edema of the cornea following breaks in Descemet's membrane is not usually seen in the first decade but may occur in the middle or late teens (Fig. 12.44). Hydrops is seen only in the more advanced cases of keratoconus and is most common with keratoconus in Down's syndrome (see Color Plate IIID). Keratoconus may be seen with other conditions, such as floppy eyelid syndrome, Leber's congenital amaurosis, retinitis pigmentosa, Down's syndrome, and Ehlers-Danlos syndromes. Keratoconus can be associated with atopic disease, and many children with keratoconus have some history of allergy. They often rub their eyes excessively.

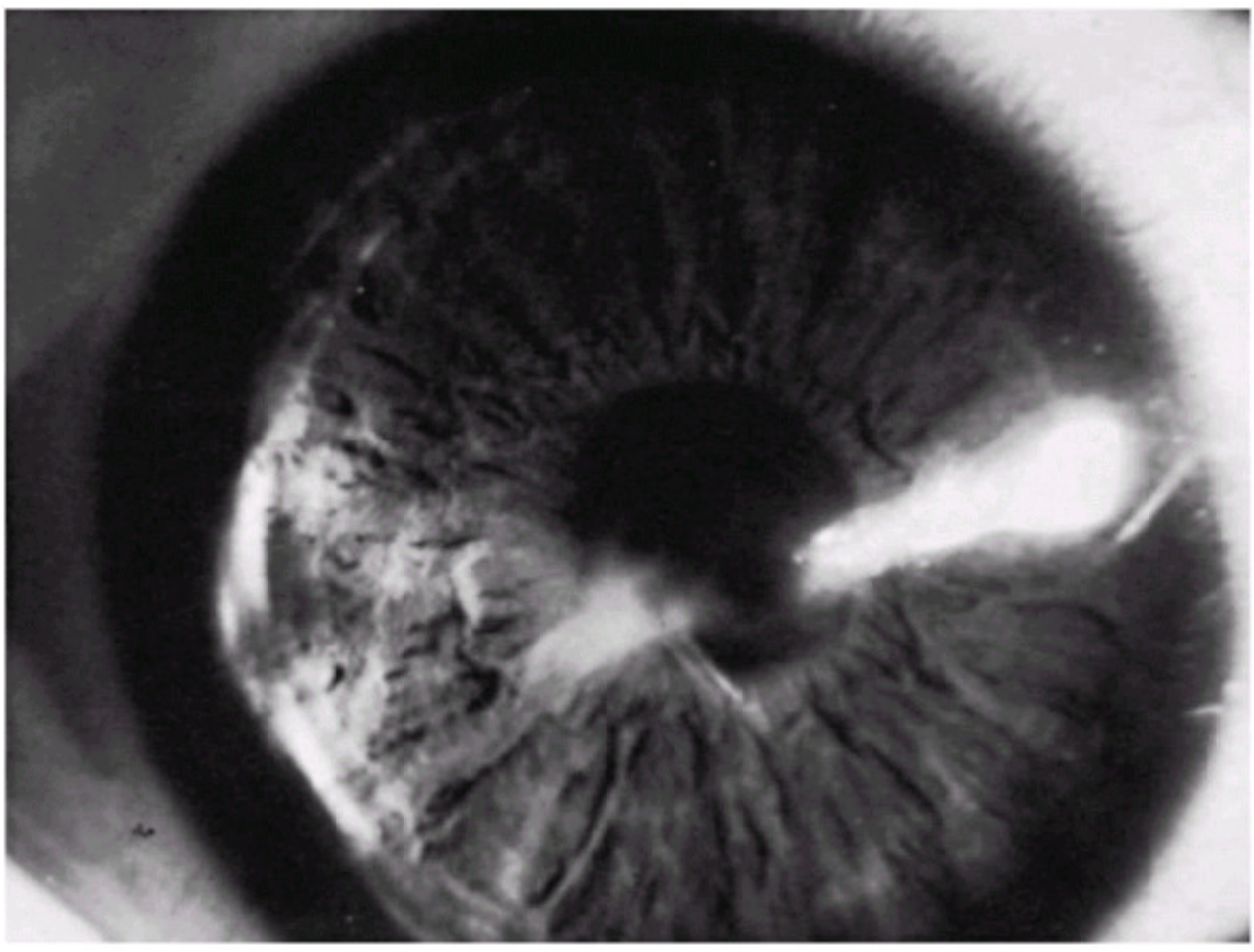

Figure 12.43 Keratoconus with abnormal light reflex of the surface of the cornea owing to the central cone.

There is no successful treatment to prevent progression of keratoconus. Contact lenses are the main form of therapy for the mild and moderate forms. Corneal transplantation offers the opportunity to restore vision in more severe cases. Corneal transplantation is over 95% successful in appropriate patients but is rarely

necessary in childhood. Deep anterior lamellar keratoplasty avoids the problem of endothelial graft rejection and may be successful in some eyes. Intracorneal ring segments may also be of use in some eyes with relatively mild keratoconus (115).

Calcific Corneal Degeneration

Calcific degeneration of the cornea in children is usually secondary to systemic or other corneal diseases. In young children, injuries with alkaline materials, such as cement,

lye, lime, and ammonia, are not uncommon, and this severe chemical trauma may quickly lead to secondary calcific changes in the cornea, sometimes within 2 or 3 weeks of the original injury.

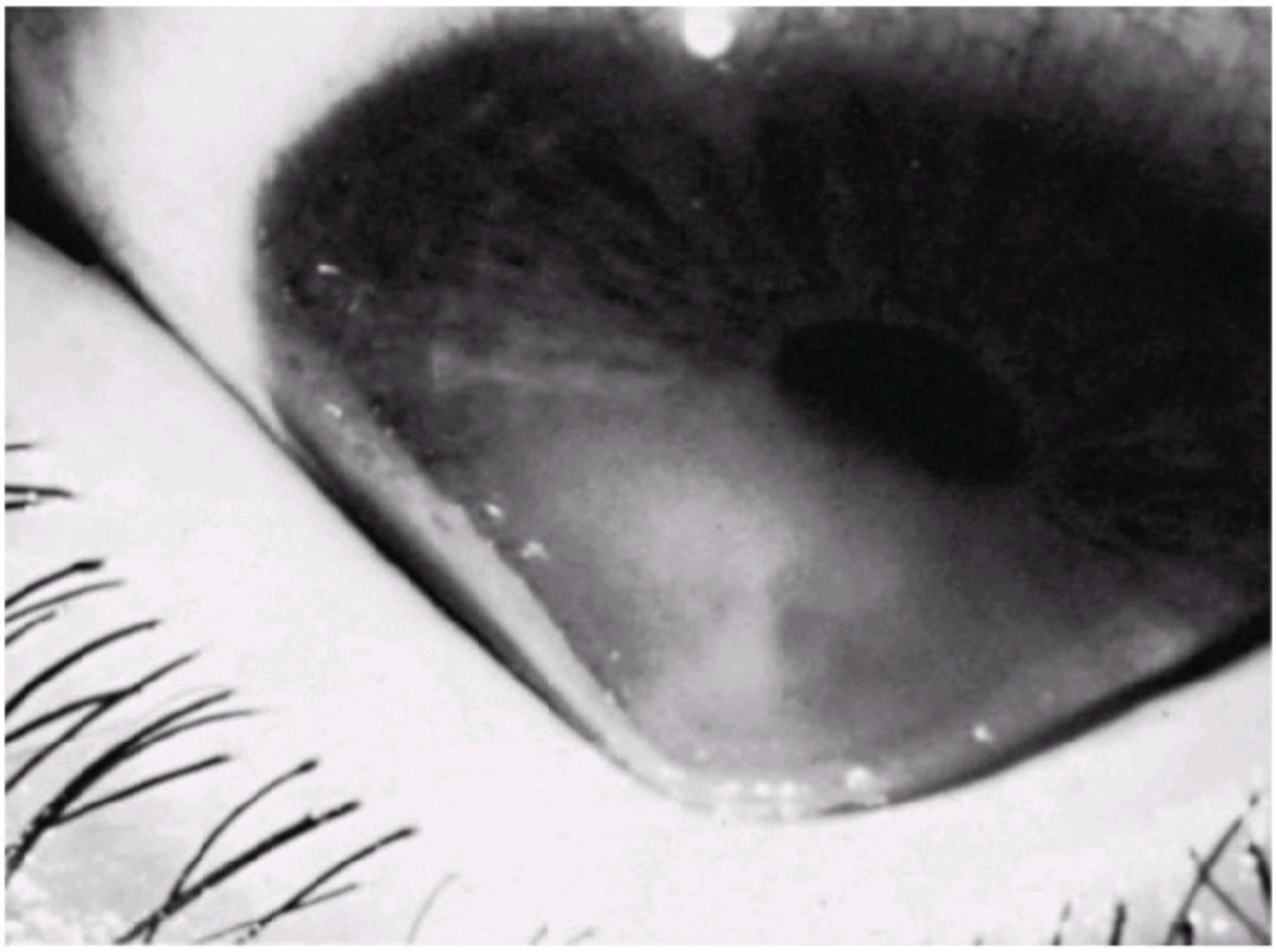

Figure 12.44 Acute hydrops in keratoconus. The lower lid is pushed away from the cornea owing to the cone formed by the edematous stroma.

Systemic disease associated with hypercalcemia may result in calcium deposits in the cornea. Hyperparathyroidism, vitamin D toxicity, milk-alkali syndrome, renal rickets, and hypophosphatasia, which result in elevations of blood calcium levels, may also induce calcific degeneration in the cornea.

Calcium in the cornea appears either as a paralimbal, slight gray opacification in the region of the basement membrane or Bowman's membrane nasally and temporally, or in a band-shaped distribution across the central cornea. There are small holes in the degenerative area, which are characteristic of calcific degeneration. This corneal degeneration may also result from inflammatory disease of the anterior segment, such as chronic uveitis (as with juvenile rheumatoid arthritis) and trauma.

Debridement with chelating agents, such as ethylenediaminetetraacetic acid (EDTA), enhances removal of the calcium after the epithelium is removed. This is usually better and less expensive than excimer laser PTK.

CORNEAL MANIFESTATIONS OF SYSTEMIC DISEASE

The corneal changes seen in systemic disease of infancy and childhood may or may not affect vision in the young patient. Many of these diseases are rare in children and may have been described in only one or two cases, in either the English or foreign literature. Only the more common systemic conditions seen in infancy and childhood, rather than the adult forms, are discussed in this section.

Diseases of Abnormal Carbohydrate Metabolism

The mucopolysaccharidoses are a group of diseases with definite systemic physical characteristics. They are described in detail in Chapter 23. They are all autosomal recessive, except Hunter's syndrome, which is X-linked recessive.

Hurler's disease, mucopolysaccharidosis (MPS) I-H is important because the disease may be confused with congenital glaucoma and congenital hereditary corneal dystrophy, and possibly interstitial keratitis. The cornea is hazy, with edema and thickened stroma (see Color Plate IIIE). The disease has many systemic characteristics, and demonstration of mucopolysaccharides in the urine helps in making the diagnosis. The cornea may be clear at first but becomes diffusely clouded in time, without signs of inflammation or vascularization.

In Hunter's disease, MPS II, clouding of the cornea is absent until late in the disease. Pigmentary degeneration of the retina may be responsible for visual loss. Sanfilippo's syndrome, MPS III, does not show corneal changes, whereas Morquio's syndrome, MPS IV, does show corneal clouding.

Scheie's syndrome, MPS I-S, is present in affected children by age 7 or 8. The cornea undergoes progressive clouding and becomes thicker. In Maroteaux-Lamy syndrome, MPS VI, corneal opacities are seen early.

It is evident that with clouded corneas early in life, both urinalysis and testing of the intraocular pressure are essential to rule out a mucopolysaccharidosis or congenital glaucoma as soon as the disorder is recognized.

Diseases of Abnormal Protein Metabolism

Cystinosis is a disease of altered amino acid metabolism, allowing cystine to accumulate in the body. Infantile, adolescent, and adult forms are found. The infantile form (Fanconi's syndrome) is the most severe and is typically fatal early in life without renal transplantation. The adolescent and adult forms are less severe. Growth and development in the infantile form are usually normal until the sixth month of life, when growth fails to continue and muscular weakness develops. Deposits of soluble cystine crystals are found in the conjunctiva, cornea, sclera, and choroid. The cornea is clouded and has very tiny glistening punctate dots, which are the crystals reflecting light from the cornea. They are noted throughout the full thickness of cornea; however, there is a concentration of crystal toward the corneal periphery. The disease is transmitted as an autosomal recessive trait (116). Long-term oral cysteamine can improve renal function but does not seem to improve the corneal opacities. Topical cysteamine has been demonstrated to improve the corneal crystals. Rarely, corneal transplantation may be required to treat severe corneal opacity. Other diseases of the cornea that involve crystals, that is, gout and the dysproteinemias, are not seen in childhood.

Inborn errors of metabolism with corneal changes are rarely seen. In phenylpyruvic oligophrenia, corneal opacities are present, in addition to cataracts. In porphyria, another inborn error of metabolism, the cornea may show ulceration and vascularization as well as keratomalacia. The full-blown picture appears later in life.

Diseases of Abnormal Lipid Metabolism

Corneal changes accompanying abnormal lipid metabolism are not usually seen in infancy and childhood. Arcus juvenilis has previously been described under Embryology and Developmental Abnormalities.

In Fabry's disease, an X-linked, recessively transmitted disorder, abnormal lipid storage, and corneal changes are noted. In the epithelium of the cornea, fine brown pinpoint opacities involving the central and peripheral cornea may be found. The changes radiate from the central cornea to the periphery in a fanlike fashion and is termed *cornea verticillata.* The first manifestations of this disease may be the corneal opacities. Although these opacities appear in early childhood and are asymptomatic, they are significant in that systemic changes will later occur and may herald the full-blown disease and early death. There are other ocular signs as well, including focal vascular dilatations of the conjunctival and retinal vessels. Interestingly, the corneal changes are also present in most female carriers of the gene.

Corneal Changes in Avitaminosis

In severe malnutrition, corneal changes from vitamin A deficiency may be seen. Keratomalacia with thickening of the corneal epithelium, epidermalization, and keratinization can occur. In the late stages, Bowman's membrane is replaced by pannus, and the cornea may appear hazy and thickened. Bitot's spot, a foamy surface conjunctival change, nasal or temporal to the limbus, is also seen in vitamin A deficiency (see Color Plate IIIF).

In riboflavin deficiency, a superficial punctate keratitis may be evident, which causes photophobia. Vascularization of the cornea is seen in the later stages.

Hereditary Benign Intraepithelial Dyskeratosis

Intraepithelial dyskeratosis is a rare disease characterized by plaque-like elevations on the conjunctiva and cornea, as well as on the oral mucous membrane, occurring in the first decade of life. This disease is present only in the descendants of an inbred triracial group of people of black, white, and American Indian origin, who trace their roots to northeastern North Carolina. The bulbar conjunctiva is involved nasally and temporally, and later corneal changes also occur. There is a dyskeratotic hyperplastic epithelial change on the conjunctiva extending into the cornea, causing blurred vision. The thick, opaque, unilateral and bilateral involvement may cause stromal changes, leading to deep stromal vascularization. Corneal involvement varies and may become apparent in early infancy or even from birth. The plaque-like changes persist throughout life, sometimes worsening and causing severe visual loss (117).

The disease is transmitted as an autosomal dominant trait with a high degree of penetrance. The use of topical corticosteroids is not effective. Except for artificial tears, which may make the patient more comfortable, no topical medication helps. Surgical excision of the corneal lesions later in life, after childhood, usually results in regrowth of similar tissue in the bed of the resection. Surgical excision should be reserved for the most severe cases associated with marked corneal involvement. This is not usually necessary in infancy or childhood (117).

Other hereditary disorders have been associated with hereditary, benign intraepithelial dyskeratosis, including retinitis pigmentosa, Axenfeld's anomaly, and various systemic abnormalities.

Interstitial Keratitis of the Cornea Secondary to Congenital Syphilis

Before the age of penicillin, the most common cause of interstitial keratitis in children was congenital syphilis. The corneal manifestations of this disease acquired in utero occurred in the first decade of life. Corneal changes are uncommon at birth or in early infancy.

Congenital syphilis is first seen in the cornea as a rapid progression of corneal edema diffusely involving the cornea. After this, vascularization of the deep cornea occurs adjacent to Descemet's membrane. The cornea may take on a salmon-pink color because of the marked vascularization, which lasts for several weeks. Later, gradual clearing of these corneal vessels occurs over a period of weeks to many months. These empty deep blood vessels (ghost vessels) remain in the deep cornea. The lines of clearing in the deep cornea are called Fuchs' lines and are characteristic of congenital syphilis.

Treatment in this early stage of corneal involvement consists of topical corticosteroids and systemic therapy for the congenital syphilis. Dilatation of the pupil and antibiotics to prevent secondary infection are also used. During later years, if vision is significantly involved because of the corneal scarring, a penetrating corneal transplant may be made. It is important to examine the lens for opacities and the retina for degenerative changes, which may also cause visual loss.

The ophthalmologist should be aware of the corneal changes in this disease, as well as the Hutchinson's triad (corneal changes, abnormal dentition, and a flat bridge of the nose), all due to congenital syphilis.

Tubercular Interstitial Keratitis

Interstitial keratitis due to tuberculosis was more prevalent in the past when tuberculosis was a common disease. Tuberculosis in children is not rare, although corneal changes from tuberculosis are extremely rare. These corneal changes include nodular corneal lesions with dense residual scarring and opacities, which remain after healing occurs. In children with undiagnosed corneal lesions and midstromal vessels, a tuberculin test and chest x-ray should be obtained if the cause of the corneal disease is unknown. Usually, such corneal disease is due to herpes simplex virus keratitis, rather than tuberculosis.

Viral Interstitial Keratitis

Interstitial keratitis due to herpes simplex virus is much more common than either of the two previously mentioned diseases. In addition to herpes simplex virus, other viral infections, particularly mumps, measles, and vaccinia, may cause these stromal changes. Herpes zoster and varicella keratitis can also cause

interstitial keratitis. Ocular Lyme borreliosis is the latest infection causing interstitial keratitis in children and young adults (118,119).

Wilson's Disease

Wilson's disease (hepatolenticular degeneration) is a disorder of abnormal protein metabolism. There are hepatic and extrapyramidal changes that, if not corrected early in life, lead to permanent brain damage. Decrease in the ceruloplasmin is associated with an increase in the serum copper that is not bound to protein. In addition, there is an increase of copper in the urine as well as copper deposition in various tissues, such as liver and cornea.

The corneal changes are diagnostic of this disease. An orange-brown ring in the periphery of the cornea, called the Kayser-Fleischer ring, is the characteristic feature (see

P.250

Color Plate IIIG). The ring is deposited in the deep stroma in and around Descemet's membrane (see Color Plate IIIH). There is a clear zone separating Descemet's membrane from the limbus. It is essential that all children manifesting undiagnosed progressive mental or hepatic disease be examined with the slit lamp. Gonioscopy may be required to see the earliest changes.

Refsum's Syndrome

Retinitis pigmentosa is part of this autosomal recessive disease along with other findings, such as chronic polyneuritis. The corneal changes may consist of epithelial thickening and degeneration, with pannus formation in the region of Bowman's membrane. Hypertrophy of corneal nerves is present in this disease, but the corneal changes are not the cause of the marked visual loss.

Keratoconjunctivitis Sicca

This is an unusual finding in children, although dry eyes should not be overlooked in a differential diagnosis of irritative phenomena in older children. Punctate keratitis, and very rarely filamentary keratitis, may be seen in older children with decreased production of tears. In addition, there is an excess of mucus in the precorneal tear film and an increase in viscosity of the tear film itself. Keratoconjunctivitis sicca may be found accompanying Still's disease or rheumatoid arthritis in children and in lupus erythematosus, among other connective tissue diseases.

Treatment of keratoconjunctivitis sicca in children is similar to that in adults. The use of artificial tear drops, as frequently as necessary to make the patient comfortable, is recommended. If the patient requires artificial tear drops every 2 hours or more frequently, a solid bar of Lacrisert tears is recommended. This consists of a hydroxypropyl cellulose small pellet, which is inserted inside the lower lid on awakening. The insert gradually melts as the day progresses, reducing the necessity for frequent applications of artificial tears. Because it is sometimes difficult for children to apply artificial tear drops during school hours, the use of the Lacrisert is recommended, at least for a short trial for the unusual child with keratoconjunctivitis sicca. This is also effective in eliminating filamentary keratitis, when this disorder accompanies dry eyes in children (Fig. 12.45). Topical cyclosporin A 0.05% was recently FDA-approved for the treatment of dry-eye disease, using a twicea-day regimen. It may be effective in certain children with severe dry eyes.

In more severe keratitis sicca cases, punctal closure is indicated. This can be done on a temporary basis with punctal plugs or permanently with cautery. Rarely, a small lateral tarsorrhaphy may be required to decrease ocular surface evaporation.

Familial Dysautonomia (Riley-Day Syndrome)

In early infancy this disease may manifest as failure to thrive. The ocular changes result from an absence of tearing and corneal anesthesia. Symptoms may be mild with punctate keratitis or more severe with corneal ulceration resembling neuroparalytic keratitis and keratomalacia. Depending on the severity of the ocular surface disease, treatments range from artificial tears, autologous serum drops, cyclosporin A drops, punctal occlusion to lateral tarsorrhaphy. The prognosis for life is poor, and the ocular problem becomes less important as systemic changes occur.

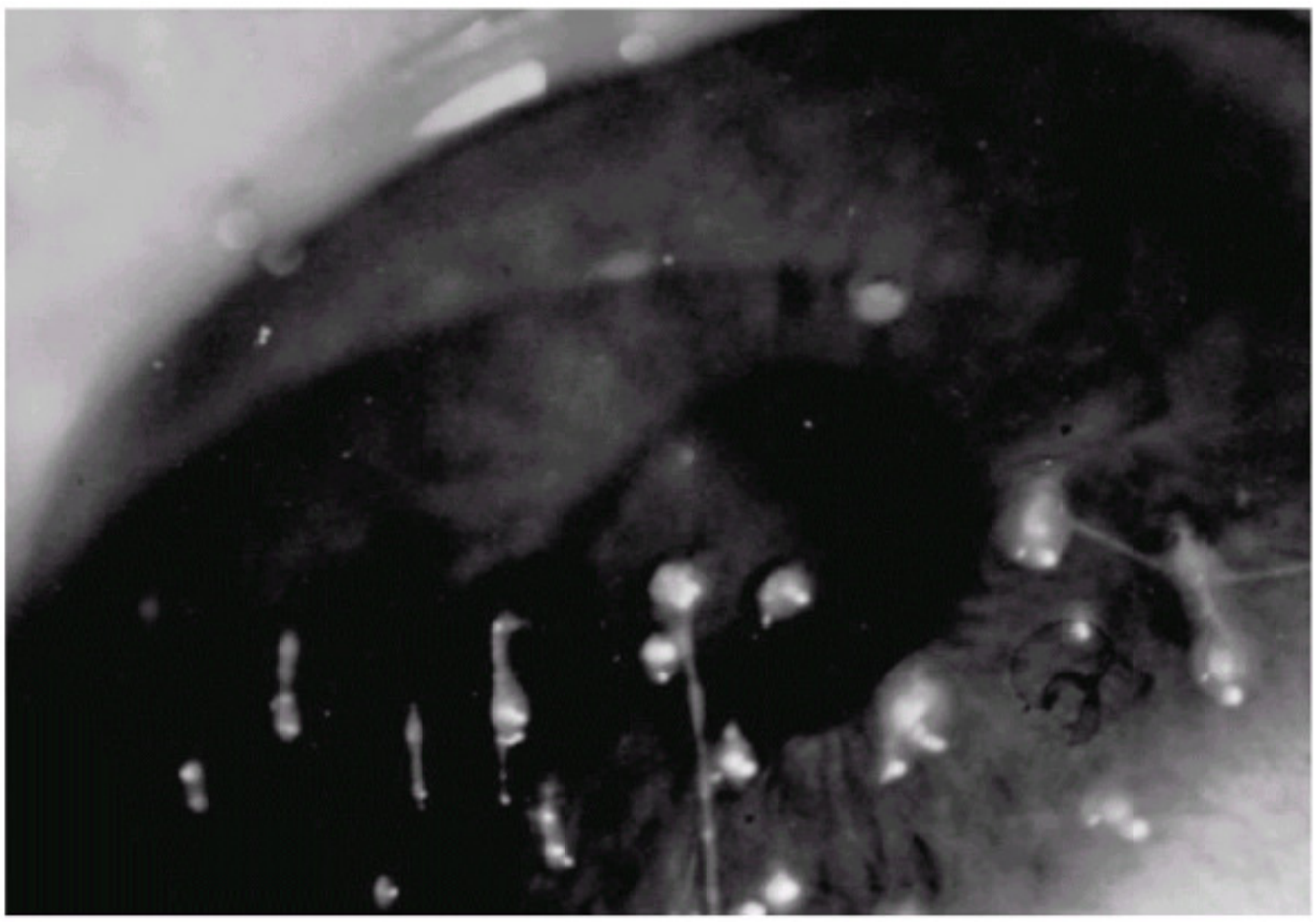

Figure 12.45 Filamentary keratitis in childhood keratoconjunctivitis sicca.

CORNEAL INJURIES

Unfortunately, corneal injuries in children may lead to significant or total visual loss as well as psychological problems due to severe corneal scarring and disfigurement (120,121). Ocular injuries in adults resulting from accidents may be prevented by the use of safety lenses. In children these accidents are especially tragic, because they are often preventable by keeping harmful chemicals and sharppointed toys and instruments out of reach. Amblyopia is another concern in children under ages 6 to 8 years. This potentially permanent decrease in vision needs to be kept in mind when treating children after trauma.

Corneal lacerations with sharp instruments, such as pencils, darts, and scissors, usually strike the lens also, and the additional problem arises of how to handle the secondary cataract and iris in the corneal wound. The lens material may resorb in children, leaving a thin secondary membrane. If the laceration is paracentral, the visual axis may be clear after injury, allowing a satisfactory image to form on the retina. If the scar is centrally located (Fig. 12.46) and the corneal periphery is clear, a rotating autokeratoplasty after the initial trauma may be helpful in rotating the central scar out of the pupillary axis. During initial laceration repair, it is best to attempt removal of anterior synechiae to the back of the cornea. This may be done through the wound itself by passage of a synechiolysis spatula through the wound to sweep iris or lens remnants from the back of the cornea. It is important to do this to prevent vascularization or retrocorneal membrane formation (Fig. 12.47). Cataract removal at the time of ruptured globe repair is recommended only if the lens capsule is grossly ruptured and lens material is fluffing up into the anterior chamber or out of the wound. Cataract removal at the time

of corneal laceration repair is often quite difficult due to poor visualization. Cataract removal at the time of subsequent anterior segment reconstruction or corneal transplantation is generally successful, and an intraocular lens can often be placed. Intraocular lenses for infant traumatic aphakia are controversial. Epikeratophakia for contact lens-intolerant children with aphakia has been helpful (122), but the commercial manufacturer has stopped making these lenses, and they are rarely used.

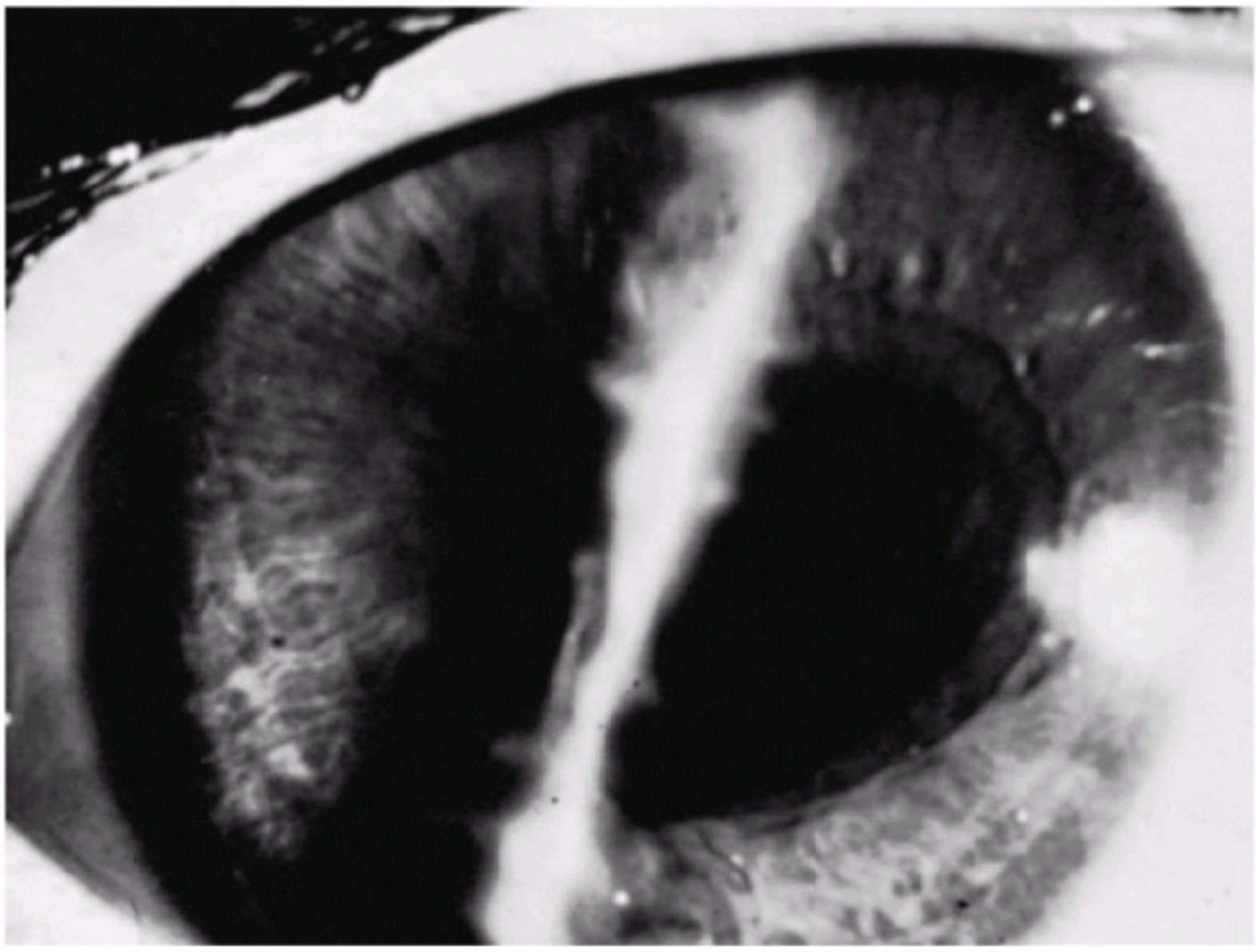

Figure 12.46 Central linear healed laceration that involved the cornea and did not strike the lens, thus leaving a clear pupillary opening.

Chemical injuries may be serious in children, particularly alkali burns of the cornea and sclera. The common household cleaner, ammonia, is exceedingly dangerous and easily accessible to children, because it is usually stored in a cabinet beneath the sink or on a low shelf. Within seconds of splashing ammonia on the eye, the pH in the anterior chamber may climb to 12.0, causing denaturation of stromal protein and inflicting permanent damage to the iris and lens. The iris may balloon forward and touch the back of the cornea. Lens opacities develop rapidly in these accidents, and the healing stage is exceedingly long, frequently years after injury. Calcific degeneration may occur following alkali burns in small children. This complication must be sought by slit-lamp examination, so that proper therapy can be instituted. Alkali burns in children are treated similarly to those in adults, but therapy is difficult with children, who are invariably uncooperative. Collagenase inhibitors have been used in the past to prevent stromal melting, but the results are equivocal. Amniotic membrane transplantation may be beneficial, in some cases. EDTA is used to remove secondary calcific degeneration. In addition to ammonia, products such as lye, cement, grout, and lime may be found around the house. Acids cause corneal burns but are not usually as severe as alkali chemical injuries of the cornea. All chemicals should be kept out of the reach of children, including turpentine, shellac, paints, and other fluids that may be ingested or splashed into the eye.

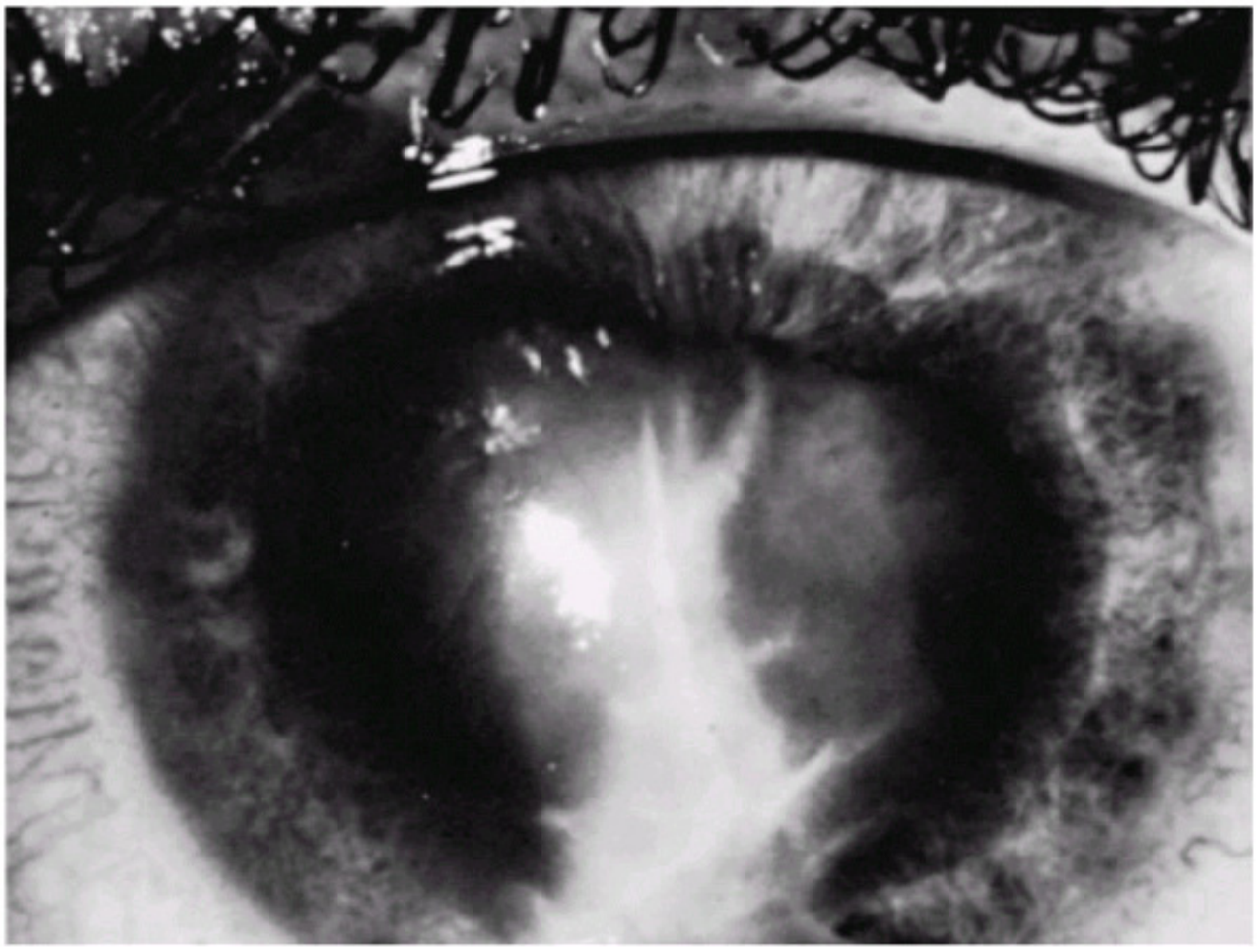

Figure 12.47 Central corneal laceration with lens opacification and anterior synechia.

Blast injuries of the cornea, secondary to air guns, such as B-B guns or pellet guns fired at close range, do great injury to a child's eye. Pellets have considerable range and may cause perforation of the cornea even at 45 m (50 yards). At present, tear gas pen guns are readily available to children and have caused injury to the eyes. Most states have no law prohibiting the sale or use of such guns. Injuries are caused by the blast when the gun is shot within 30 to 60 cm (1 to 2 feet) of the face. The blast comes from the gunpowder used to propel the gas. Particles of gas that are more than 2 years old may act as missiles and cause corneal perforation. In addition, the plastic housing may be split, and the plastic itself can also act as a missile at very close range. It is important to recognize that, in addition to corneal lacerations, contusions of the cornea with deep folds in Descemet's membrane and anterior chamber hemorrhage may occur from these injuries (Figs. 12.48 and 12.49). Recession of the angle, macular edema, and retinal hemorrhages have also been found. More recently, airbagassociated ocular injuries (123,124) and paintball ocular injuries (125) have been reported in children. Injuries to children's eyes are handled in the same way as adult ocular

injuries. It is important to examine the child's eyes thoroughly. If this is impossible, general anesthesia should be used for careful microscopic examination at the earliest time after injury.

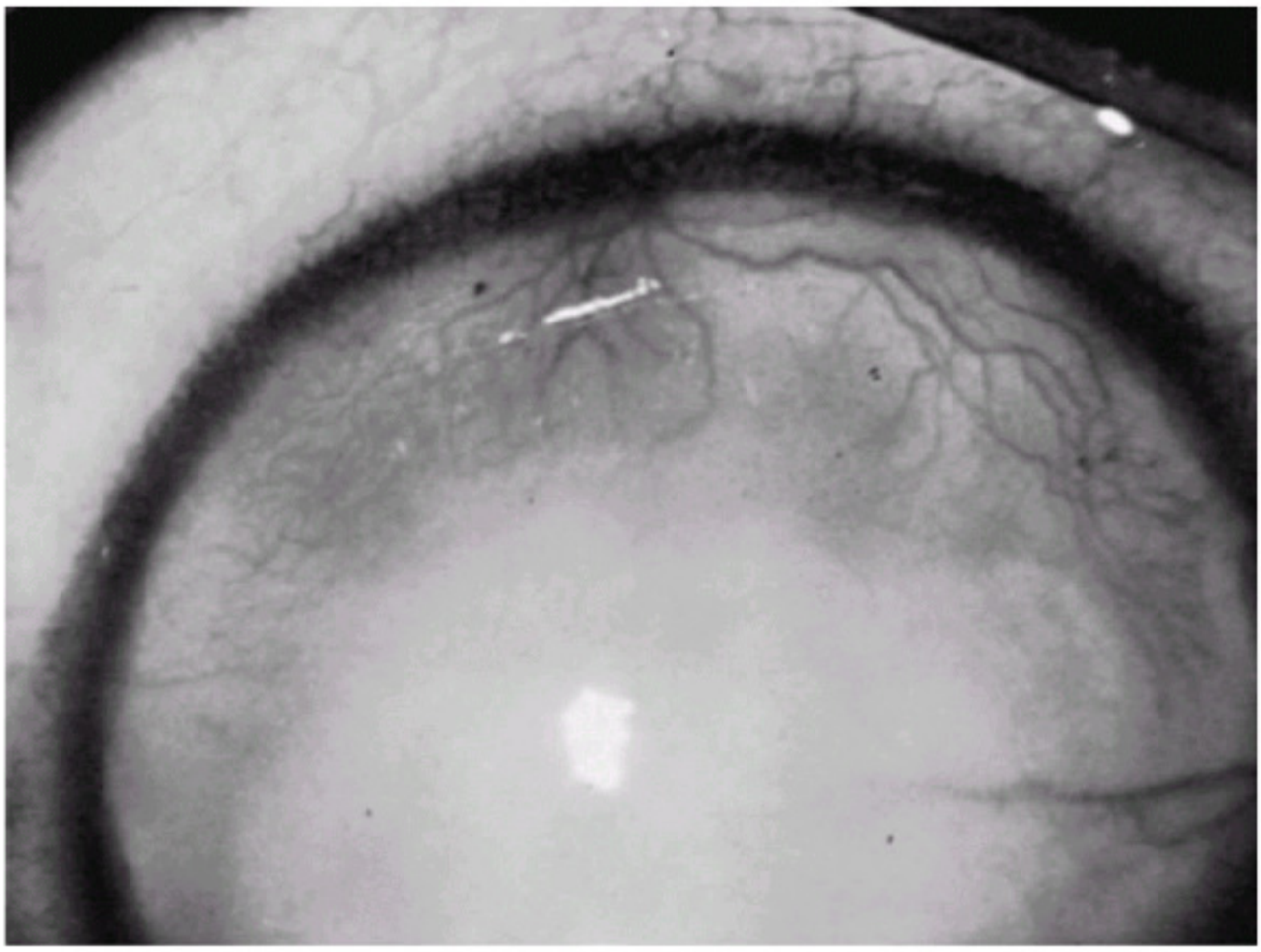

Figure 12.48 Total organized hyphema with vascularization of the cornea after corneal injury.

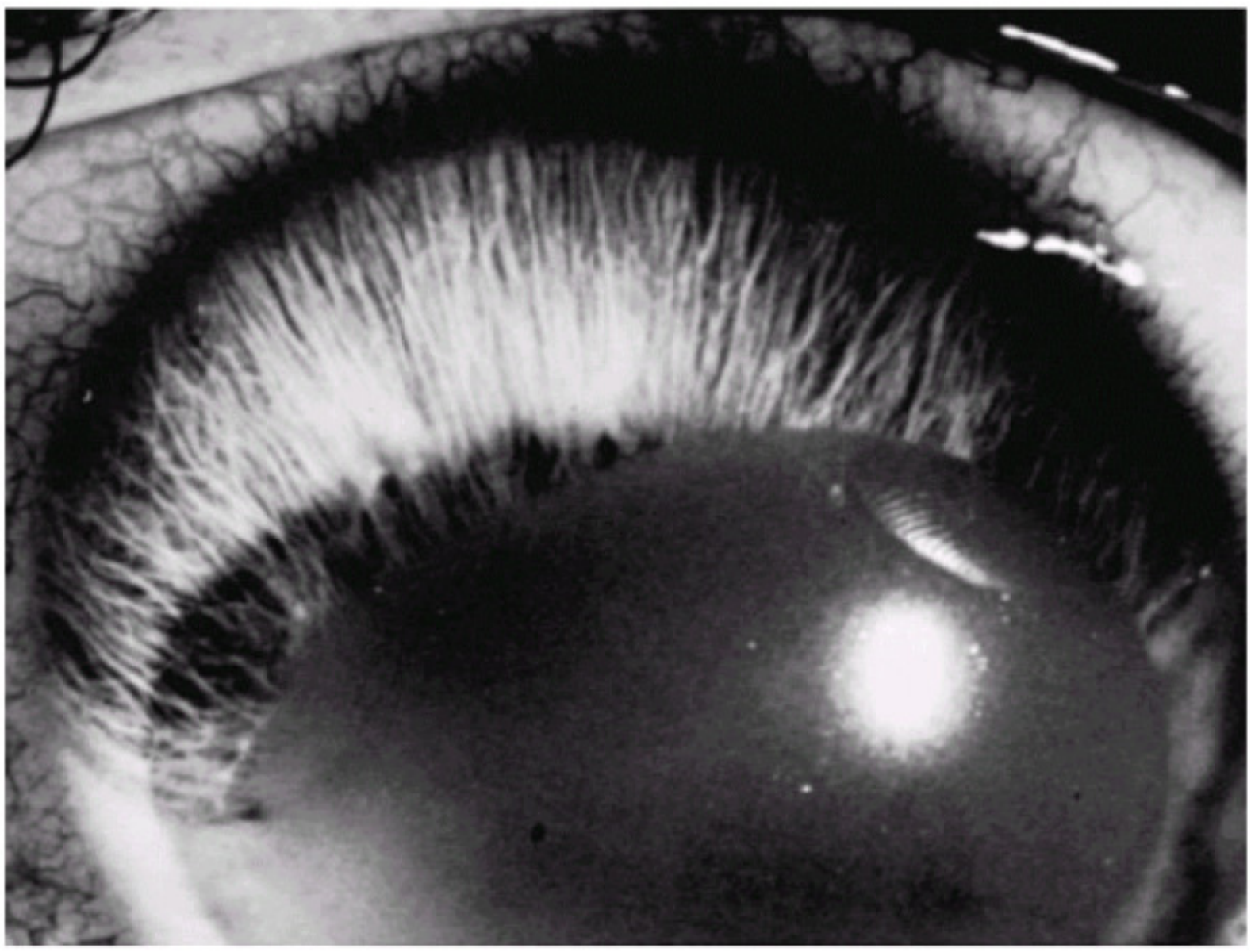

Figure 12.49 Blood staining of the cornea following total hyphema with resolution of the peripheral blood staining of the cornea.

Trauma at birth is usually caused by forceps application in which one of the blades may be placed across the cornea. This results in excessive pressure to the cornea and breaks in Descemet's membrane. These breaks lead to corneal edema at birth, which clears in the first months of life. Unlike congenital glaucoma with diffuse corneal stromal edema, the edema with birth trauma is localized to the area of the break in Descemet's membrane. The breaks in the cornea, which are usually vertical or slightly off the vertical, persist and appear as ridges of folded Descemet's membrane attached at both ends to the cornea in later life (Figs. 12.50 and 12.51). Large astigmatic refractive errors may result. These must be recognized and optically treated with spectacles or contact lenses. Amblyopia from anisometropia or from corneal edema is frequent and must be vigorously treated. Corneal transplantation in infancy and childhood is not usually necessary for this condition. There is generally some visual loss, which is sometimes severe. Corneal edema from endothelial decompensation may occur later in life. Penetrating keratoplasty has been successful in restoring some vision to these eyes.

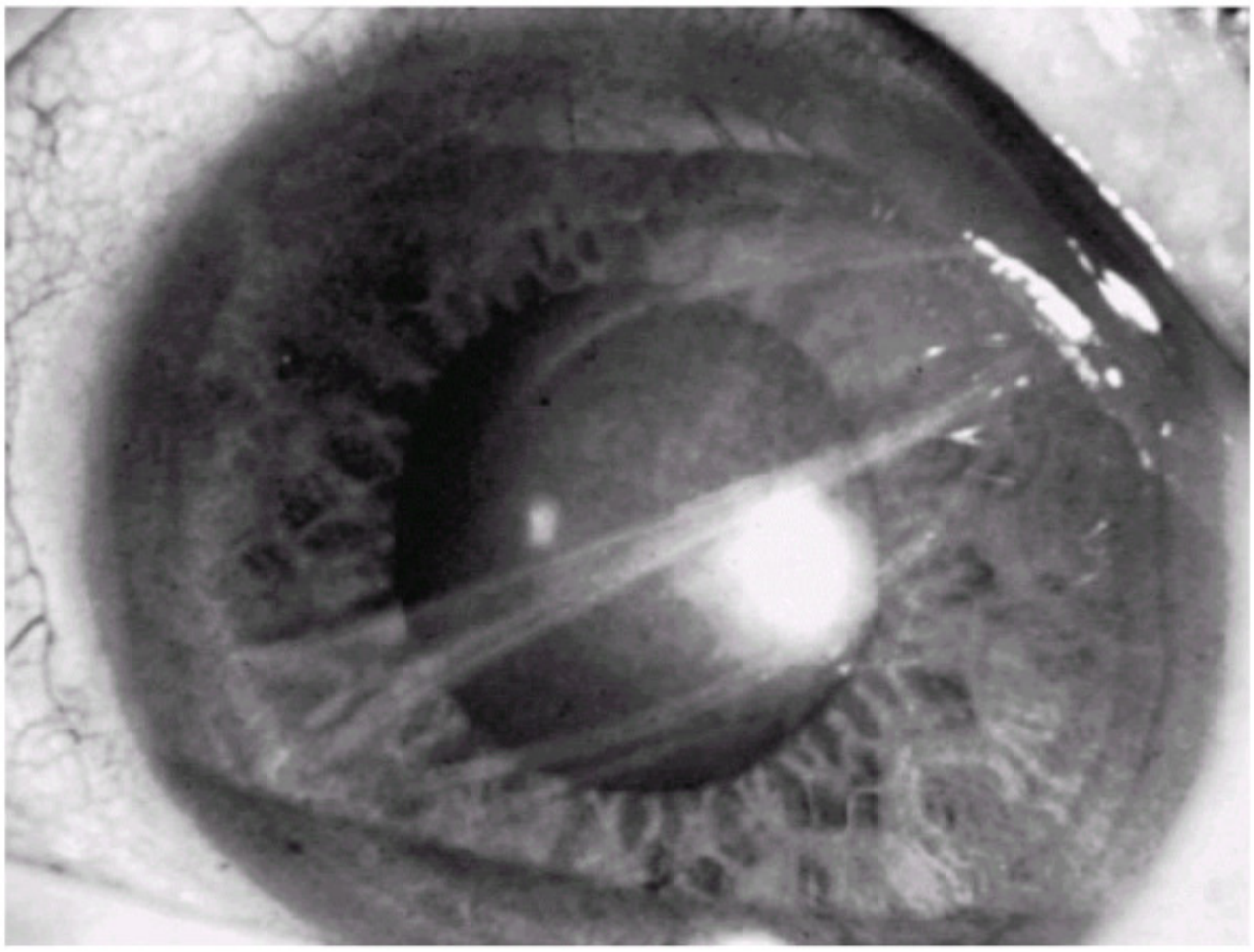

Figure 12.50 Linear folded tubes of Descemet's membrane on the back of the cornea after birth trauma. The patient's vision was 20/30, despite these corneal changes.

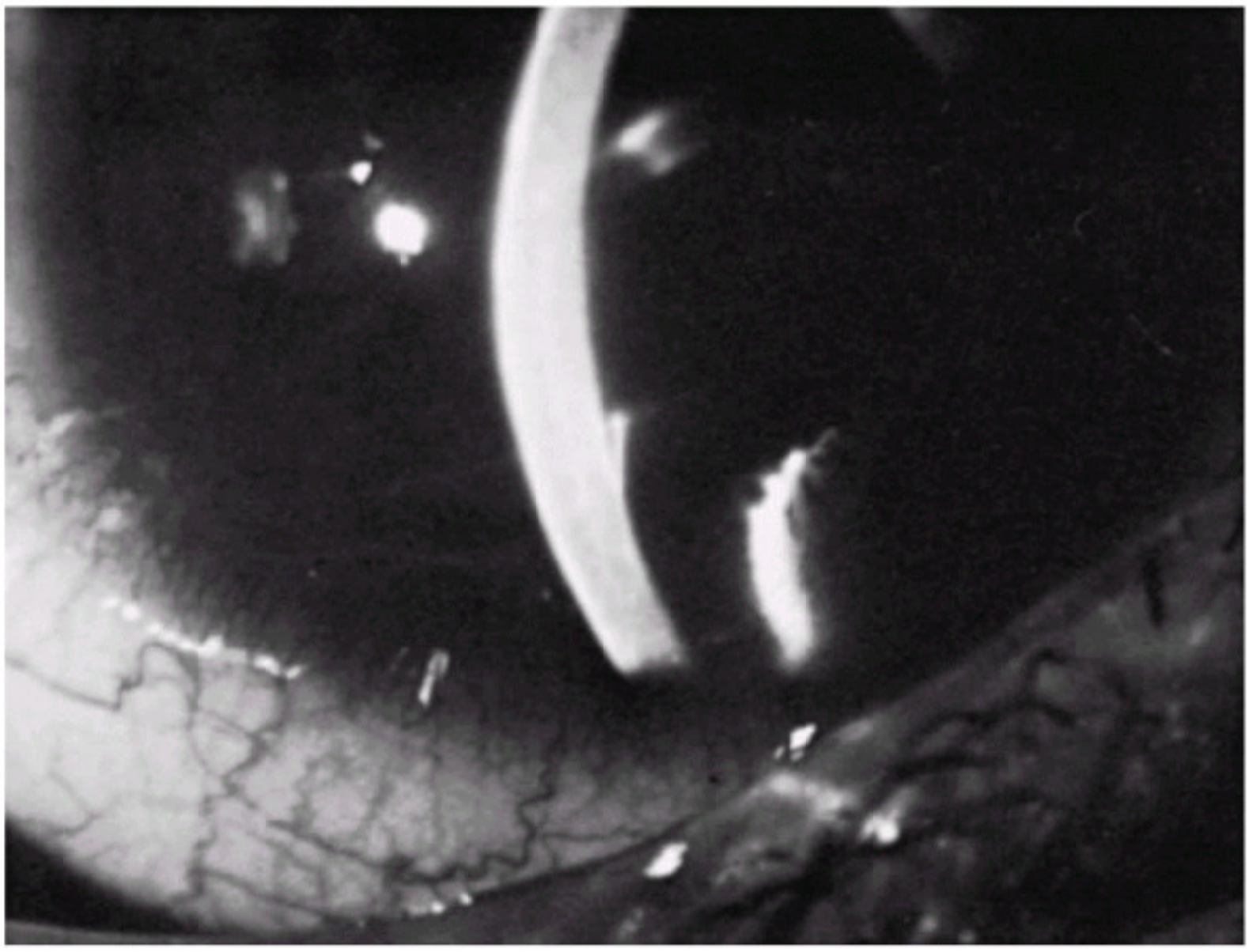

Figure 12.51 Slit-lamp view of folded tubes of Descemet's membrane attached to the cornea inferiorly and in the anterior chamber centrally.

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REFERENCES

1. Allen L, Burian HM, Braley AE. A new concept of the development of the anterior chamber angle. *Arch Ophthalmol* 1955;53:783.

2. Burian HM, Braley AE, Allen L. External and gonioscopic visibility of the ring of Schwalbe and the trabecular zone. *Trans Am Ophthalmol Soc* 1955;52:389.

3. Alkemade PP*H. Dysgenesis mesodermalis of the iris and the cornea: a study of Rieger's syndrome and Peters' anomaly*. Assen. Netherlands: Royal Van Gorcum, 1969.

4. Topouzis F, Karadimas P, Gatzonis SD, et al. Autosomal-dominant megalocornea associated with ocular hypertension. *J Pediatr Ophthalmol Strabismus* 2000;37:173-175.

5. Meire FM. Megalocornea. *Doc Ophthalmol* 1994;87:1.

6. Rogers GL, Polomeno RC. Autosomal-dominant inheritance of megalocornea associated with Down's syndrome. *Am J Ophthalmol* 1974;78:526.

7. Wood WJ, Green WR, Marr WG. Megalocornea: a clinico pathologic clinical case report. *Md State Med J* 1974;23:57.

8. Ho CL, Walton DS. Primary megalocornea: clinical features for differentiation from infantile glaucoma. *J Pediatr Ophthalmol Strabismus* 2004;41:11-17.

9. Malbran E, Dodds R. Megalocornea and its relation to congenital glaucoma. *Am J Ophthalmol* 1960;49:908.

10. Meire FM, Delleman JM. Biometry in X-linked megalocornea: pathognomonic findings. *Br J Ophthalmol* 1994;78:781.

11. Vail DT. Adult hereditary anterior megalophthalmus sine glaucoma: a definite disease entity. *Arch Ophthalmol* 1931;6:38.

12. Biglan AW, Brown SI, Johnson BL. Keratoglobus and blue sclera. *Am J Ophthalmol* 1977;83:225.

13. Cameron JA. Keratoglobus. *Cornea* 1993;12:124-130.

14. Judisch GF, Waziri M, Krachmer JH. Ocular Ehlers-Danlos syndrome with normal lysyl hydroxylase activity. *Arch Ophthalmol* 1976;94:1489.

15. McKusick VA. *Mendelian inheritance in man*, 5th ed. Baltimore: The Johns Hopkins University Press, 1978.

16. Batra DV, Paul SD. Microcornea with myopia. *Br J Ophthalmol* 1967;51:57.

17. Tane S, Sakuma Y, Ito S. The studies on the ultrasonic diagnosis in ophthalmology. Report 13. Ultrasonic biometry in microphthalmos and buphthalmos. *Acta Soc Ophthalmol Jpn* 1977;81:1112.

18. Waardenburg PJ. Gross remnants of the pupillary membrane, anterior polar cataract and microcornea in a mother and her children. *Ophthalmologica* 1949;118:828.

19. Cross HE, Yoder F. Familial nanophthalmos. *Am J Ophthalmol* 1976;81:300.

20. Vignolo EM, Steindl K, Forte R, et al. Autosomal dominant simple microphthalmos. *J Med Genet* 1994;31:721.

21. Weiss AH, Kousseff BG, Ross EA, et al. Simple microphthalmos. *Arch Ophthalmol* 1989;107:1625.

22. Reddy MA, Francis PJ, Berry V, et al. A clinical and molecular genetic study of a rare dominantly inherited syndrome (MRCS) comprising of microcornea, rod-cone dystrophy, cataract, and posterior staphyloma. *Br J Ophthalmol* 2003;87:197-202.

23. Elder MJ. Aetiology of severe visual impairment and blindness in microphthalmos. *Br J Ophthalmol* 1994;78:332.

24. Hallerman HP, Breinert HP, Trauzettel H. Prognostische Aspekte zur Kataraktextraktion bei Mikrokornea and Mikro phthalmie. *Klin Monatsbl Augenheilk* 1974;165:225.

25. Waring GO, Rodrigues MM, Laibson PR. Anterior chamber cleavage syndrome: a stepladder classification. *Surv Ophthalmol* 1975;20:3.

26. Falls HF. A gene producing various defects of the anterior segment of the eye. *Am J Ophthalmol* 1949;32:41.

27. Jerndal T, Hansson HA, Anders B. *Goniodygenesis*. Copenhagen: Bogtrykkeriet Forum, 1978.

28. Reese AB, Ellsworth RM. The anterior chamber cleavage syndrome. *Arch Ophthalmol* 1966;75:307.

29. Bahn CF, Falls HE, Varley GA, et al. Classification of corneal endothelial disorders based on neural crest origin. *Ophthalmology* 1984;91:558.

30. Vaux C, Sheffield L, Keith CG, et al. Evidence that Rieger syndrome maps to 4q25 or 4q27. *J Med Genet* 1992;29:256.

31. Legius E, de Die-Smulders CEM, Verbraak F, et al. Genetic heterogeneity in Rieger eye malformation. *J Med Genet* 1994;31:340.

32. Henkind P, Friedman AH. Iridogoniodysgenesis. *Am J Ophthalmol* 1971;72:949.

33. Barkan O. Pathogenesis of congenital glaucoma. *Am J Ophthalmol* 1955;40:1.

34. Jacobs HB. Posterior conical cornea. *Br J Ophthalmol* 1957;41:31.

35. Jerndal T, Hansson HA, Anders B. *Goniodysgenesis.* Copenhagen: Bogtrykkeriet Forum, 1978.

36. Donaldson DD. *Atlas of external diseases of the eye*, 1st ed., Vol I. *Congenital anomalies and systemic diseases*. St. Louis: Mosby, 1966.

37. Krachmer JH, Rodrigues MM. Posterior keratoconus. *Arch Ophthalmol* 1978;96:1867.

38. Al-Hazzaa SAF, Specht CS, McLean IW, et al. Posterior keratoconus: case report with scanning electron microscopy. *Cornea* 1995;14:316.

39. Mannis MJ, Lightman J, Plotnik RD. Corneal topography of posterior keratoconus. *Cornea* 1992;11:351.

40. Townsend WM, Font RL, Zimmerman LE. Congenital corneal leukomas. II. Histopathologic findings in 19 eyes with central defect in Descemet's membrane. *Am J Ophthalmol* 1974;77:192.

41. Waring GO, Parks MM. Successful lens removal in congenital corneolenticular adhesion (Peters' anomaly). *Am J Ophthalmol* 1977;83:526.

42. Hamburg A. Incomplete separation of the lens and related malformations. *Am J Ophthalmol* 1967;64:729.

43. Townsend WM, Font RL, Zimmerman LE. Congenital corneal leukomas. III. Histopathologic findings in 13 eyes with paracentral defect in Descemet's membrane. *Am J Ophthalmol* 974;77:400.

44. Dichtl A, Jonas JB, Naumann GOH. Atypical Peters' anomaly associated with partial trisomy 5p. *Am J Ophthalmol* 1995;120:541.

45. Leff SR, Shields JA, Augsburger JJ, et al. Congenital corneal staphyloma: clinical, radiological, and pathological correlation. *Br J Ophthalmol* 1986;70:427.

46. Mullaney PB, Risco JM, Heinz GW. Congenital corneal staphyloma. *Arch Ophthalmol* 1995;113:1206.

47. O'Grady RB, Kirk HQ. Corneal keloids. *Am J Ophthalmol* 1972;73:206.

48. Townsend WM, Font RL, Zimmerman LE. Congenital corneal leukomas. I. Central defect in Descemet's membrane. *Am J Ophthalmol* 1974;77:80.

49. Waring GO, Laibson PR. Anterior chamber cleavage syndrome: diagnosis and management. *Contact Intraocul Lens Med J* 1979;5:171.

50. Donaldson DD. *Atlas of external diseases of the eye*, 2nd ed. Vol III. *Cornea and sclera*. St. Louis: Mosby, 1980.

51. Duke-Elder S. *System of ophthalmology*, Vol III. *Embryology*. St. Louis: Mosby, 1963.

52. Goldstein JE, Cogan DG. Sclerocornea and associated congenital anomalies. *Arch Ophthalmol* 1962;67:761.

53. Howard RO, Abrahams IW. Sclerocornea. *Am J Ophthalmol* 1971;71:1254.

54. Waring GO, Rodrigues MM. Ultrastructure and successful keratoplasty of sclerocornea in Mietens' syndrome. *Am J Ophthalmol* 1980;90:469.

55. Larsen V, Eriksen A. Cornea plana. *Acta Ophthalmol* 1949;27:275.

56. Bloch N. Les différents types de sclérocornee, leurs modes d'hérédité et les malformations congénitales concomitantes. *J Genet Hum* 1965;14:133.

57. Cernea P, Remuea M, Scripcaru G, et al. Lésions oculaires dans la trisomie 17. *Arch Ophthalmol* 1966;26:345.

58. Desvignes P, Pouliquen Y, Legras M, et al. Aspect iconographique d'une cornea plana clans une maladie de Lobstein. *Arch Ophthalmol* 1967;27:585.

59. Ginsberg J, Perrin EV, Sueoka WT. Ocular manifestations of trisomy 18. *Am J Ophthalmol* 1968;66:59.

60. Harben RL, Katz JI, Frias JL, et al. Sclerocornea associated with the Smith-Lemli-Optiz syndrome. *Am J Ophthalmol* 1977;84:72.

61. Lapri G. Un casa di malformazioni oculari ed extraoculari congenite (sindrome di Lohmann). *Arch Oftalmol* 1949;53:203.

62. March WF, Chalkley THF. Sclerocornea associated with Dandy-Walker cyst. *Am J Ophthalmol* 1974;78:54.

63. Rodrigues MM, Calhoun J, Weinreb F. Sclerocornea with an unbalanced translocation (17p,10q). *Am J Ophthalmol* 1974;78:49.

64. Kanai A, Wood TC, Polack FM, et al. The fine structure of sclerocornea. *Invest Ophthalmol* 1971;10:687.

65. Wood TO, Kaufman HE. Penetrating keratoplasty in an infant with sclerocornea. *Am J Ophthalmol* 1970;70:609.

66. Dailey EG, Lubowitz RM. Dermoids of the limbus and cornea. *Am J Ophthalmol* 1962;53:661.

67. Shields JA, Laibson PR, Augsburger JJ, et al. Central corneal dermoid: a clinicopathologic correlation and review of the literature. *Can J Ophthalmol* 1986;21:23.

68. Baum JL, Feingold M. Ocular aspects of Goldenhar's syndrome. *Am J Ophthalmol* 1973;75:250.

69. Mansour AM, Wang F, Henkind P, et al. Ocular findings in the facioauriculovertebral sequence (Goldenhar-Gorlin syndrome). *Am J Ophthalmol* 1985;100:555.

70. Sugar HS. The oculoauriculovertebral dysplasia of Goldenhar. *Am J Ophthalmol* 1966;62:678.

71. Hoops JP, Ludwig K, Boergen KP, et al. Preoperative evaluation of limbal dermoids using high-resolution biomicroscopy. *Graefes Arch Clin Exp Ophthalmol* 2001;239:459-461.

72. Lanzl IM, Augsburger JJ, Hertle RW, et al. The role of ultrasound biomicroscopy in surgical planning for limbal dermoids. *Cornea* 1998;17:604-606.

73. Waring GO, Laibson PR. Keratoplasty in infants and children. *Trans Am Acad Ophthalmol Otolaryngol* 1977;83:283.

74. Waring GO, Laibson PR. Keratoplasty in young children. In: Kwitko ML, ed. *Surgery of the infant eye*. New York: Appleton-Century-Crofts, 1979a:197-215.

75. Bordon AF, Katsumi O, Hirose T. Tonometry in pediatric patients: a comparative study among Tono-pen, Perkins, and Schiotz tonometers. *J Pediatr Ophthalmol* 1995;32:373.

76. Milner MS, Liebmann JM, Tello C, et al. High resolution ultrasound biomicroscopy of the anterior segment in patients with dense corneal scars. *Ophthalmic Surg* 1994;25:284.

77. Mondino BJ, Kowalski RP. Phlyctenulae and catarrhal infiltrates. *Arch Ophthalmol* 1982;100:1968.

78. Pavlin CJ. Practical application of ultrasound biomicroscopy. *Can J Ophthalmol* 1995;30:225.

79. Kim T, Cohen EJ, Schnall BM, et al. Ultrasound biomicroscopy and histopathology of sclerocornea. *Cornea* 1998;17:443-445.

80. Casanova FH, Adan CB, Allemann N, et al. Findings in the anterior segment on ultrasound biomicroscopy in Maroteaux-Lamy syndrome. *Cornea* 2001;20:333-338.

81. Dana MR, Schaumberg DA, Moyes AL, et al. Outcome of penetrating keratoplasty after ocular trauma in children. *Arch Ophthalmol* 1995;113:1503.

82. Dana M-R, Moyes AL, Gomes JAP, et al. The indications for and outcome in pediatric keratoplasty: a multicenter study. *Ophthalmology* 1995;102:1129-1138.

83. Dana M-R, Schaumberg DA, Moyes AL, et al., for the multicenter pediatric keratoplasty study: Corneal transplantation in children with Peters' anomaly and mesenchymal dysgenesis. *Ophthalmology* 1997;104:1580-1586.

84. Comer RM, Daya SM, O'Keefe M. Penetrating keratoplasty in infants. *J AAPOS* 2001;5:285-290.

85. Cameron JA. Good visual result following early penetrating keratoplasty for Peters' anomaly. *J Pediatr Ophthalmol Strabismus* 1993;30:109.

86. Vail A, Gore SM, Bradley BA, et al., and Corneal Transplant Follow-up Study Collaborators: Corneal graft survival and visual outcome: a multicenter study. *Ophthalmology* 1994;101:120.

87. Vail A, Gore SM, Bradley BA, et al., and Corneal Transplant Follow-up Study Collaborators: Clinical and surgical factors influencing corneal graft survival, visual acuity, and astigmatism. *Ophthalmology* 1996;103:41.

88. Gloor P, Keech RV, Krachmer JH. Factors associated with high postoperative myopia after penetrating keratoplasties in infants. *Ophthalmology* 1992;99:775.

89. Enoch JM. Fitting parameters which need to be considered when designing soft contact lenses for the neonate. *Contact Intraocul Lens Med J* 1979;5:31.

90. Clinch TE, Palmon FE, Robinson MJ, et al. Microbial keratitis in children. *Am J Ophthalmol* 1994;117:65.

91. Kunimoto DY, Sharma S, Reddy MK, et al. Microbial keratitis in children. *Ophthalmology* 1998;105:252-257.

92. Stretton S, Gopinathan U, Willcox MD. Corneal ulceration in pediatric patients: a brief overview of progress in topical treatment. *Paediatr Drugs* 2002;4:95-110.

93. Meisler DM, Raizman MB, Traboulsi EI. Oral erythromycin treatment for childhood blepharokeratitis. *J AAPOS* 2000;4:379-380.

94. Young AL, Leung AT, Cheng LL, et al. Orthokeratology lens-related corneal ulcers in children: a case series. *Ophthalmology* 2004;111:590-595.

95. Panda A, Sharma N, Das G, et al. Mycotic keratitis in children: epidemiologic and microbiologic evaluation. *Cornea* 1997;16:295-299.

96. Schwartz GS, Holland EJ. Oral acyclovir for the management of herpes simplex virus keratitis in children. *Ophthalmology* 2000;107:278-282.

97. Naseri A, Good WV, Cunningham ET Jr. Herpes zoster virus sclerokeratitis and anterior uveitis in a child following varicella vaccination. *Am J Ophthalmol* 2003;135:415-417.

98. West SK, Munoz B, Lynch M, et al. Risk factors for constant, severe trachoma among preschool children in Kongwa, Tanzania. *Am J Epidemiol* 1996;143:73.

99. Foster CS. The cromolyn sodium collaborative study group: evaluation of topical cromolyn sodium in the treatment of vernal keratoconjunctivitis. *Ophthalmology* 1988;95:194.

100. Tabbara KF, Arafat NT. Cromolyn effects on vernal keratoconjunctivitis in children. *Arch Ophthalmol* 1977;95:2184.

101. Bonini S, Coassin M, Aronni S, et al. Vernal keratoconjunctivitis. *Eye* 2004;18:345-351.

102. Akpek EK, Dart JK, Watson S, et al. A randomized trial of topical cyclosporin 0.05% in topical steroid-resistant atopic keratoconjunctivitis. *Ophthalmology* 2004;111:476-482.

103. Cetinkaya A, Akova YA, Dursun D, et al. Topical cyclosporine in the management of shield ulcers. *Cornea* 2004;23:194-200.

104. Rohatgi J, Dhaliwal U. Phlyctenular eye disease: a reappraisal. *Jpn J Ophthalmol* 2000;44:146-150.

105. Mondino BJ, Kowalski RP. Phlyctenulae and catarrhal infiltrates. *Arch Ophthalmol* 1982;100:1968.

106. Forman R, Koren G, Shear NH. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of 10 years' experience. *Drug Saf* 2002;25:965-972.

107. Genvert GI, Cohen EJ, Donnenfeld ED, et al. Erythema multiforme following use of topical sulfacetamide. *Am J Ophthalmol* 1985;99:456.

108. Tsubota K, Toda I, Saito H, et al. Reconstruction of the corneal epithelium by limbal allograft transplantation for severe ocular surface disorders. *Ophthalmology* 1995;102:1486.

109. Gupta SK, Hodge WG. A new clinical perspective of corneal dystrophies through molecular genetics. *Curr Opin Ophthalmol* 1999;10:234-241.

110. Thiel JH, Behnke H. Fine bisher unbekannte: subepitheliale hereditare Hovnhant dystrophies. *Kim Monatsbl Augenheilkd* 1967;150:86.

111. Kuchle M, Green WR, Volcker HE, et al. Reevaluation of corneal dystrophies of Bowman's layer and the anterior stroma (Reis-Bucklers' and Thiel-Behnke types): a light and electron microscope study of eight corneas and a review of the literature. *Cornea* 1995;14:333.

112. Dinh R, Rapuano CJ, Cohen EJ, et al. Recurrence of corneal dystrophy after excimer laser phototherapeutic keratectomy. *Ophthalmology* 1999;106:1490-1497.

113. Marcon A, Cohen EJ, Rapuano CJ, et al. Recurrence of corneal stromal dystrophies after penetrating keratoplasty. *Cornea* 2003;22:19-21.

114. Schaumberg DA, Moyes AL, Gomes JA, et al. Corneal transplantation in young children with congenital hereditary endothelial dystrophy. Multicenter Pediatric Keratoplasty Study. *Am J Ophthalmol* 1999;127:373-378.

115. Boxer Wachler BS, Christie JP, Chandra NS, et al. Intacs for keratoconus. *Ophthalmology* 2003;110:1031-1040.

116. Tsilou ET, Rubin BI, Reed GF, et al. Age-related prevalence of anterior segment complications in patients with infantile nephropathic cystinosis. *Cornea* 2002;21:173-176.

117. Reed JW, Cashwell LF, Klintworth GK. Corneal manifestations of hereditary benign intraepithelial dyskeratosis. *Arch Ophthalmol* 1979;97:297.

118. Huppertz HI, Munchmeier D, Lieb W. Ocular manifestations in children and adolescents with Lyme arthritis. *Br J Ophthalmol* 1999;83:1149-1152.

119. Winward KE, Lawton-Smith J, Culbertson WW, et al. Ocular Lyme borreliosis. *Am J Ophthalmol* 1989;108:651.

120. Tomazzoli L, Renzi G, Mansoldo C. Eye injuries in childhood: a retrospective investigation of 88 cases from 1988 to 2000. *Eur J Ophthalmol* 2003;13:710-713.

121. Serrano JC, Chalela P, Arias JD. Epidemiology of childhood ocular trauma in a northeastern Colombian region. *Arch Ophthalmol* 2003;121:1439-1445.

122. Morgan KS, McDonald B, Hiles DA, et al. The nationwide study of epikeratophakia for aphakia in children. *Am J Ophthalmol* 1987;103:366.

123. Motley WW III, Kaufman AH, West CE. Pediatric airbag-associated ocular trauma and endothelial cell loss. *J AAPOS* 2003;7:380-383.

124. Lueder GT. Air bag-associated ocular trauma in children. *Ophthalmology* 2000;107:1472-1475.

125. Listman DA. Paintball injuries in children: more than meets the eye. *Pediatrics* 2004;113:e15-e18.

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13

Pediatric Cataracts and Lens Anomalies

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Abnormalities of the crystalline lens, which constitute a significant source of visual impairment in children, include changes in opacification (cataract), shape (lenticonus), size (microspherophakia), location (ectopia lentis), and development (persistent fetal vasculature) (Table 13.1). Recent epidemiological studies have shown the prevalence of congenital cataract from 1.2 per 10,000 births (measured by using hospital discharge data for birth defects in newborns) to up to 6 per 10,000 infants (measured by reviewing medical records of children with known ocular diagnosis) (1). They can be the presenting sign of diseases that affect primarily the central nervous system, genital urinary tract, skeletal system, and skin. Pediatric lens abnormalities provide a special challenge to the clinician because early detection and prompt treatment are necessary to obtain good visual outcomes. Unfortunately, even though treatment modalities are improving, many children still suffer permanent visual loss.

TABLE 13.1 TYPES OF LENS ANOMALIES

Opacity (Cataract)

- Zonular
- Polar
- Total
- Membranous
- Pulverulent
- Speckled

Shape

- Coloboma
- Spherophakia
- Lenticonus
- Lentiglobus

Size

- Microspherophakia
- Disciform

Location

- Subluxed

Subluxed

Development

Persistent fetal vasculature (PFV)

ANATOMY AND EMBRYOLOGY

The crystalline lens consists of five major structures: embryonic nucleus, fetal nucleus, cortex, lens epithelium, and lens capsule. The lens forms from a layer of surface ectodermal cells overlying the optic vesicle (Fig. 13.1). Beginning about the 28th day of gestation, the ectodermal layer thickens to form the lens plate (2). Within days the lens placode invaginates to form a lens cup (3), which separates to form the lens vesicle by the end of week 5. The inner lining of

the vesicle consists of a layer of epithelial cells covered by a basal lamina, which eventually thickens to become a lens capsule. By week 7 the posterior cells (primary lens fibers) elongate anteriorly to fill the vesicle lumen (embryonic nucleus) (Fig. 13.2). The epithelial cells on the anterior surface of the lens vesicle then migrate laterally to the equatorial region. Beginning at weeks 12 to 14 these equatorial lens fibers grow anteriorly and posteriorly around the embryonic nucleus, forming the anterior and posterior “Y” sutures. The anterior lens suture has an upright “Y” configuration, whereas the posterior suture has an inverted “Y” configuration. The sum of these fibers forms the fetal nucleus. At birth, the fetal nucleus and embryonic nucleus make up most of the lens volume. The cortex, the outermost layer, is produced continually throughout life by the anterior lens epithelium. Because the size of the lens capsule remains relatively constant, the lens density increases. Thus, infants and young children have a relatively soft lens, which can easily be removed by simple aspiration. Older adults, on the other hand, have dense, hard lenses, especially in the nuclear area, which often requires intact removal (extracapsular or intracapsular surgery) or fragmentation before aspiration (phacoemulsification).

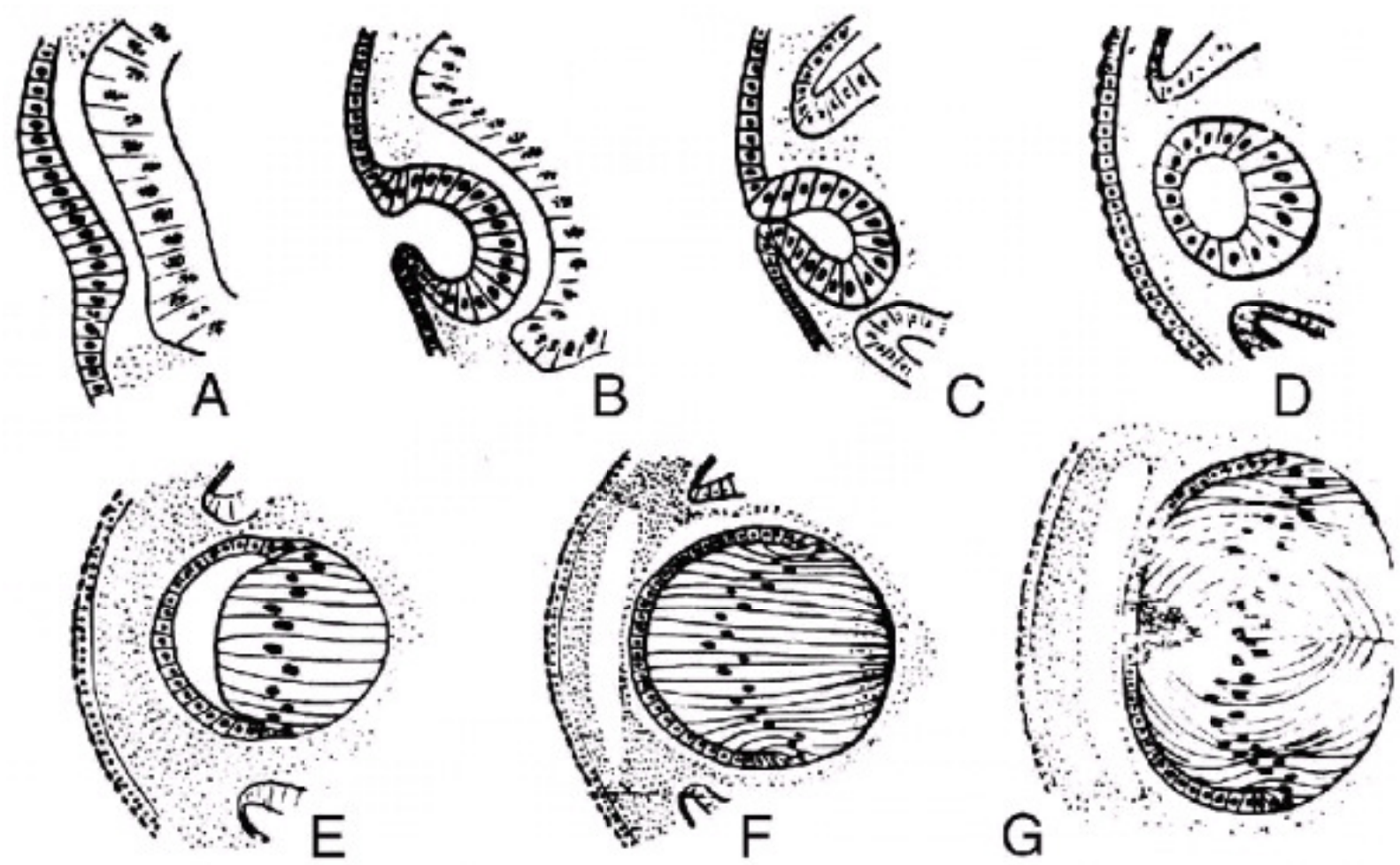

Figure 13.1 Lens embryology. A: Ectodermal layer thickens to form lens plate. B: Lens placode invaginates to form a lens cup. C: Lens vesicle forms by the fifth week. D: Lens vesicle. E: Posterior cells elongate anteriorly to fill vessel lumens (primary lens fibers). F: Epithelial cells on the anterior surface of the lens vesicle migrate laterally. G: Equatorial fibers grow anteriorly and posteriorly along the embryonic nucleus.

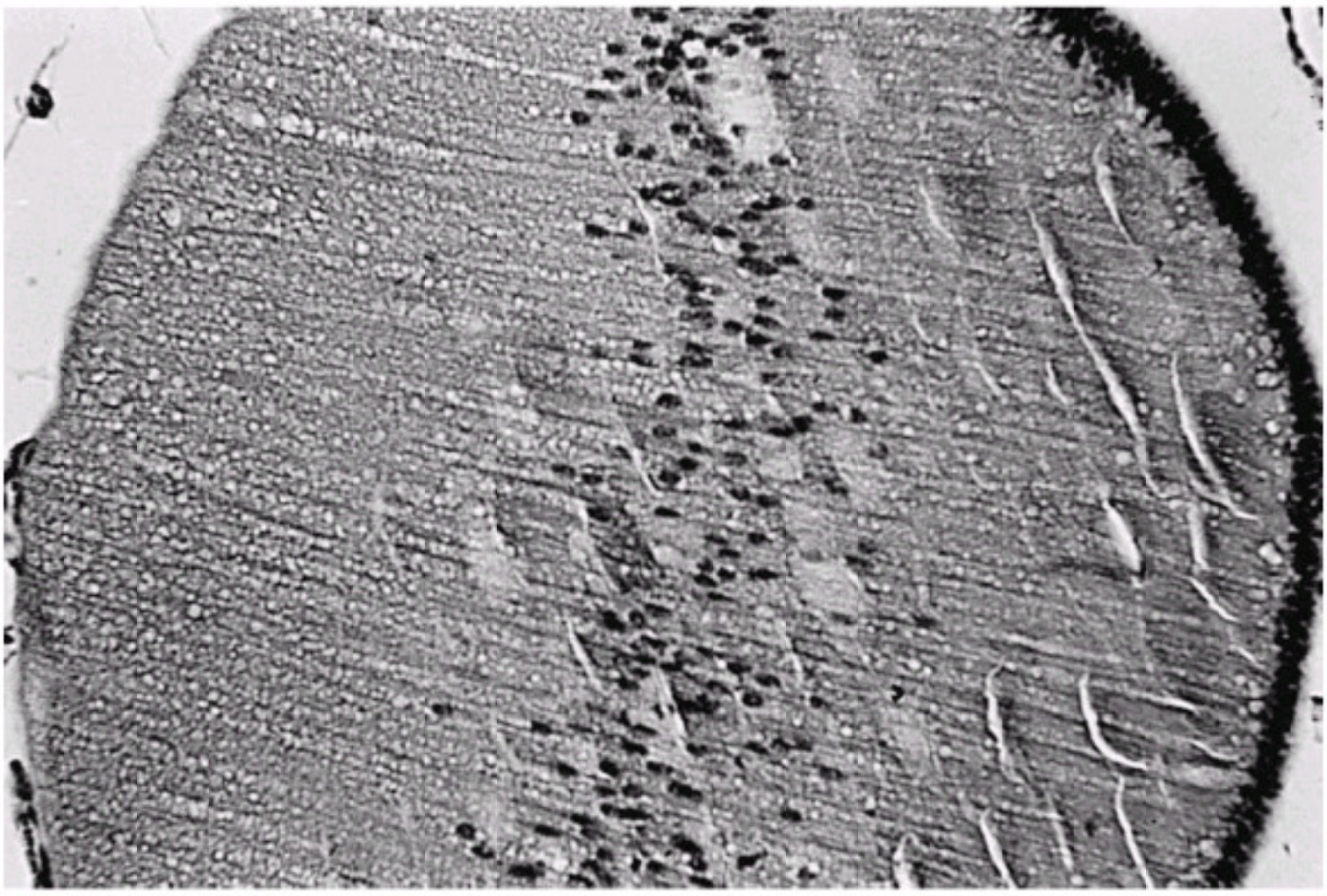

Figure 13.2 Micrograph showing the posterior lens cells elongating anteriorly to fill the lens lumens (primary lens fibers).

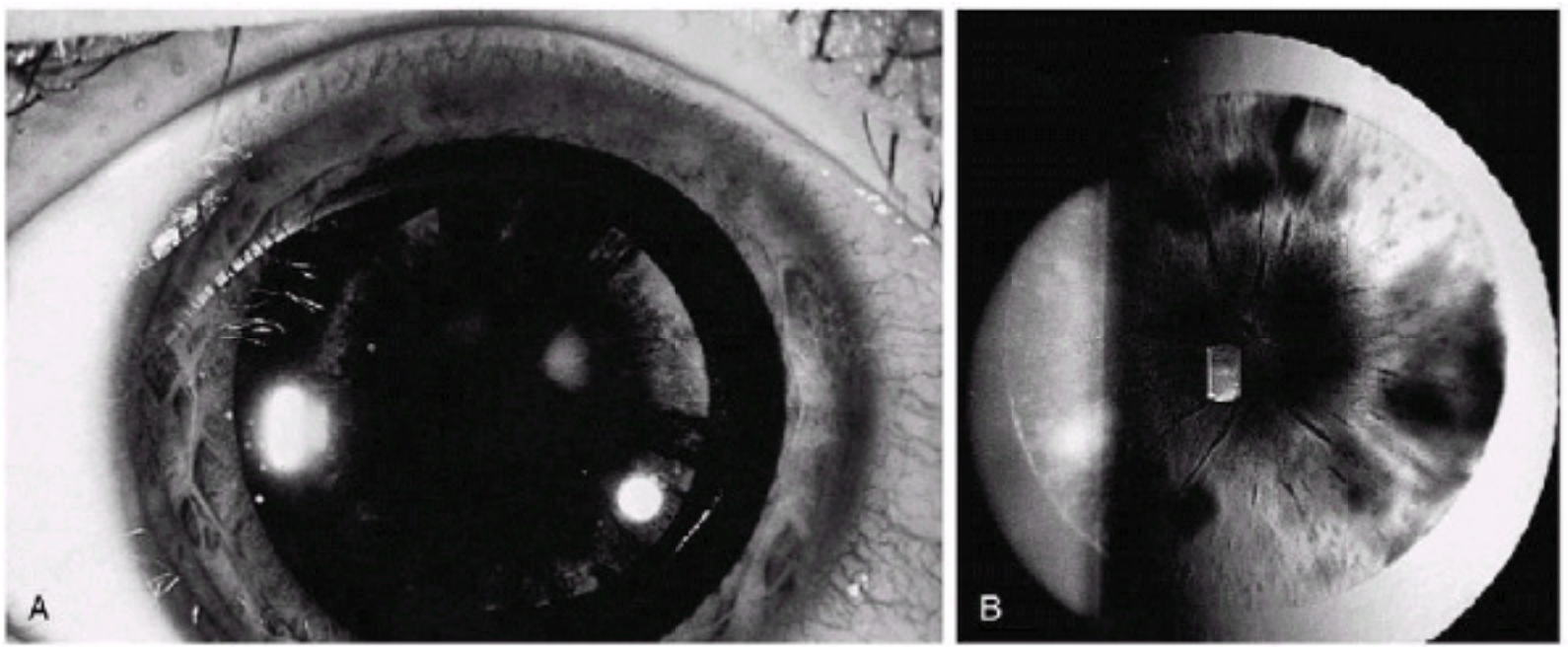

Figure 13.3 A: Slit-lamp examination of a galactosemia lamellar cataract. **B:** Retroillumination of lamellar cataract. Note clear cortex surrounding opacity. (Courtesy of Sandra Brown, MD.)

Because of the layered development of the lens, the timing of insults can be judged by the location of lens opacities or defects. Fetal nuclear opacities result from insults in utero and are usually stable. Lamellar cataracts, which are opacities in the inner cortical material, are frequently seen in metabolic diseases, such as neonatal hypoglycemia and galactosemia. In these conditions the embryonic and fetal nucleus develops before the metabolic insult occurs and remains clear. Thus, it is often possible to estimate the time of lamellar cataract formation from the cataract's relative depth, or location, within the lens.

LENS OPACITIES (CATARACTS)

The most common lens abnormality in children is an opacity, or cataract. Congenital cataracts are responsible for nearly 10% of all visual loss in children worldwide (1). It has been estimated that 1 in 250 newborns has some form of cataract (4). The etiology of the vast majority of cataracts is unknown; fortunately, however, cataracts caused by specific entities are usually easily identified (Tables 13.2, 13.3, and 13.4).

The visual significance of a cataract depends on the age of onset, location, and, most important, its morphology. The morphological appearance of pediatric cataracts provides important clues to the etiology and visual prognosis (Table 13.5) (5,6,7). Care must be exercised, however, because there is a great deal of variability in the morphology of cataracts even within the same family pedigree (1,8,9). The morphological characteristics can be divided into four major categories,

which include zonular, polar, total, and membranous (1,4,10).

Zonular Cataract

Zonular cataract occupies a particular zone of the lens, sparing the remaining lens material. The most common is a lamellar cataract, which is an opacification of lens material lying between the clear nucleus and cortex (Figs. 13.3A,B and 13.4). Lamellar cataracts are usually secondary to an

intrauterine insult and are often bilateral. They can be asymmetrical in their appearance. Lamellar cataracts can be progressive and may eventually require surgery in late infancy and early childhood. Metabolic diseases, such as neonatal hypoglycemia and galactosemia, can cause bilateral lamellar cataracts (4).

TABLE 13.2 HEREDITARY FACTORS IN PEDIATRIC CATARACTS

Autosomal Dominant (1,169,170,171,172,173)

Locus	Gene	Protein	Cataract Phenotype	Reference
1q21-q25	GJA8/GJA27	Connexin 50	Coppock (zonular pulverulent)	(26)
				(174)
1p36			Volkman (pulverulent) or posterior polar	(24)
				(175)
2q33-q35	CRYGD/CRYGC	? D and C Crystallin	Polymorphic	(176)
			Punctate	(177)
	CRYGE	? E Crystallin	Nuclear lamellar	(178)
			Coppock-like	(25)
3q21-q22		Beaded filament structural protein-2		(179)
10q24-q25	PITX3	Pitx3	Total	(180)
11q22-q22.3	CRYAB	a B Crystallin	Posterior polar	(181)
12q12-q14.1			Nuclear	(182)
12q14	MIP	MIP/AQP0		(183)
13q11-q13	CX46	Connexin 46	Polymorphic	(184)
			Pulverulent	(28)
13cen	GJA3	? D Crystallin 28/Connexin 4629	Zonular pulverulent	(27)

13cen	GJA3	? D Crystallin 28/Connexin 4629	Zonular pulverulent	(27)
14q24			Anterior polar	(32)
15q21-q22			Central pouch-like sutural	(185)
16q22.1			Marner	(186)
			Nuclear lamellar	(187)
			Posterior polar	(188)
16p13.3				(34)
17q11.1-q12	CRYBA1	BA1, Crystallin	Zonular sutural	(189)
17q23.1-q23.2			Zonular pulverulent	(30)
17q24			Cerulean	(190)
17p13			Anterior polar	(191)
19			Breadcrumb-like	(192)
20p12-q12			Posterior polar	(171)
21q22.3	CRYAA	a A1 Crystallin	Zonular/Central nuclear	(193)
22q11.2	CRY BB2	ß B2 Crystallin 30	Cerulean	(194)
			Coppock-like	(31)
Autosomal recessive (195,196)				
9q13-q22			Pulverulent	(29)
X-Linked (197)				
X			Posterior lenticonus	(198)
Xp22.2-p22.3			Cataract with microcornea	(37)
Nance-Horan syndrome				(36)
			Nuclear	(35)
Xp22				(199)
Mitochondrial				

Mitochondrial				
			Zonular (Pearson's syndrome)	(200)

See also: Online *Mendelian Inheritance in Man* (201)

TABLE 13.3 HEREDITARY FACTORS IN PEDIATRIC CATARACTS

Chromosomal Disorders				
Trisomy			Turner's syndrome	(246)
21 (Down's syndrome)	(216)		Translocation	
13-15	(244)		3:4	(33)
18 (Edward's syndrome)	(245)		2:14	(32)
10q			2:16	(34)
20p			Deletion/cri-du-chat syndrome	(247)

TABLE 13.4 POSSIBLE ETIOLOGIES OF CATARACTS IN INFANCY AND CHILDHOOD

I. Intrauterine Infection

A. Viruses

1. Rubella (49)

2. Rubeola

3. Chickenpox/herpes zoster (46)

4. Poliomyelitis

5. Herpes simplex (206)

6. Cytomegalovirus (208)

B. Protozoa

1. Toxoplasmosis (208)

II. Prematurity (211)

III. Metabolic Disorders

A. Galactosemia

1. Galactose-1-phosphate uridyltransferase deficiency (213)

2. Galactokinase deficiency (214)

B. Hypoparathyroidism (44)

C. Pseudohypoparathyroidism (216)

D. Diabetes mellitus (216)

E. Refsum's syndrome (219)

F. Oculocerebrorenal (Lowe's) syndrome (220)

G. Hypoglycemia (223)

H. Mannosidosis (225)

I. Hereditary familial congenital hemorrhagic nephritis (Alport's syndrome) (228)

J. Wilson's disease

K. Multiple sulfatase deficiency

L. Fabry's syndrome

L. Fabry's syndrome

IV. Ocular Anomalies

A. Microphthalmia (232)

B. Mesodermal dysgenesis

C. Coloboma

D. Aniridia

E. Persistent pupillary membrane

F. Posterior lenticonus (65)

G. Persistent fetal vasculature (235)

V. Renal Disease

A. Lowe's syndrome (237)

B. Alport's syndrome

C. Hallermann-Streiff-Francois syndrome (16)

VI. Trauma

A. Laser (61,100,240)

B. Radiation

C. Accidental

D. Lightning (243)

VII. Musculoskeletal

A. Chondrodysplasia punctata

B. Myotonic dystrophy (202)

C. Albright osteodystrophy

D. Congenital stippled epiphysis (Conradi's syndrome) (203,204)

E. Potter's syndrome (205)

F. Chondrodystrophic myotonia (207)

G. Smith-Lemli-Opitz syndrome (209)

H. Rhizomelic chondrodysplasia punctata

I. Spondylo-ocular syndrome (210)

VIII. Central Nervous System

A. Marinesco-Sjogren syndrome (49)

B. Laurence-Moon-Bardet-Biedl syndrome (212)

C. Sjogren-Larsson syndrome

D. Peroxisomal Disorders

1. Zellweger's (cerebrohepatorenal) syndrome (215)

E. Cerebral giantism (Sotos' syndrome) (217)

F. Batten disease (ceroid-lipofuscinosis) (218)

IX. Dermatologic

A. Cockayne's syndrome (221,222)

B. Poikiloderma atrophicans (Rothmund-Thomson syndrome) (224)

C. Incontinentia pigmenti (226)

D. Congenital ichthyosis (227)

E. Atopic dermatitis (229)

F. Ectodermal dysplasia (230)

G. Progeria (231)

X. Craniofacial

A. Hallermann-Streiff François syndrome

B. Rubenstein-Taybi syndrome (233)

C. Smith-Lemli-Opitz syndrome

D. Cerebro-oculo-facial-skeletal syndrome (234)

E. Pierre Robin syndrome

F. Oxycephaly

G. Crouzon's syndrome

G. Crouzon's syndrome

H. Apert's syndrome

I. Congenital cataracts facial dysmorphism neuropathy (236)

XI. Autoimmune/Inflammatory

A. Uveitis

B. Bechet's disease (238)

Nuclear Cataract

A nuclear cataract is an opacification of the embryonic and/or fetal nucleus (Fig. 13.5). These cataracts are often bilateral and can be dense. They are commonly associated with microphthalmos and microcornea (11). Bilateral cases may also be associated with autosomal dominant inheritance (4).

Sutural Cataract

Sutural cataracts are opacities involving the Y sutures of the lens (Fig. 13.6). They can be unilateral or bilateral and are inherited as either an X-linked or autosomal recessive trait.

They are usually visually insignificant unless there is also involvement of the nucleus or surrounding cortex.

TABLE 13.5 CONGENITAL CATARACTS: CATARACT APPEARANCE

Cataract Morphology	Diagnosis	Other Possible Findings
Spoke-like	Fabry's syndrome	+ Urine sediment
Vacuoles	Mannosidosis	Hepatosplenomegaly
	Diabetes	Blood glucose level increased
Multicolor flecks	Hypoparathyroidism	Serum calcium
	Myotonic dystrophy	Absent facial features; tonic “grip”
Green “sunflower”	Wilson's disease	Kaiser-Fleischer corneal ring
Thin disciform	Lowe's syndrome	Hypotonia
Lamellar	Galactosemia	RBC enzymes
	Hypoglycemia	Blood glucose level decreased

RBC, red blood cell.

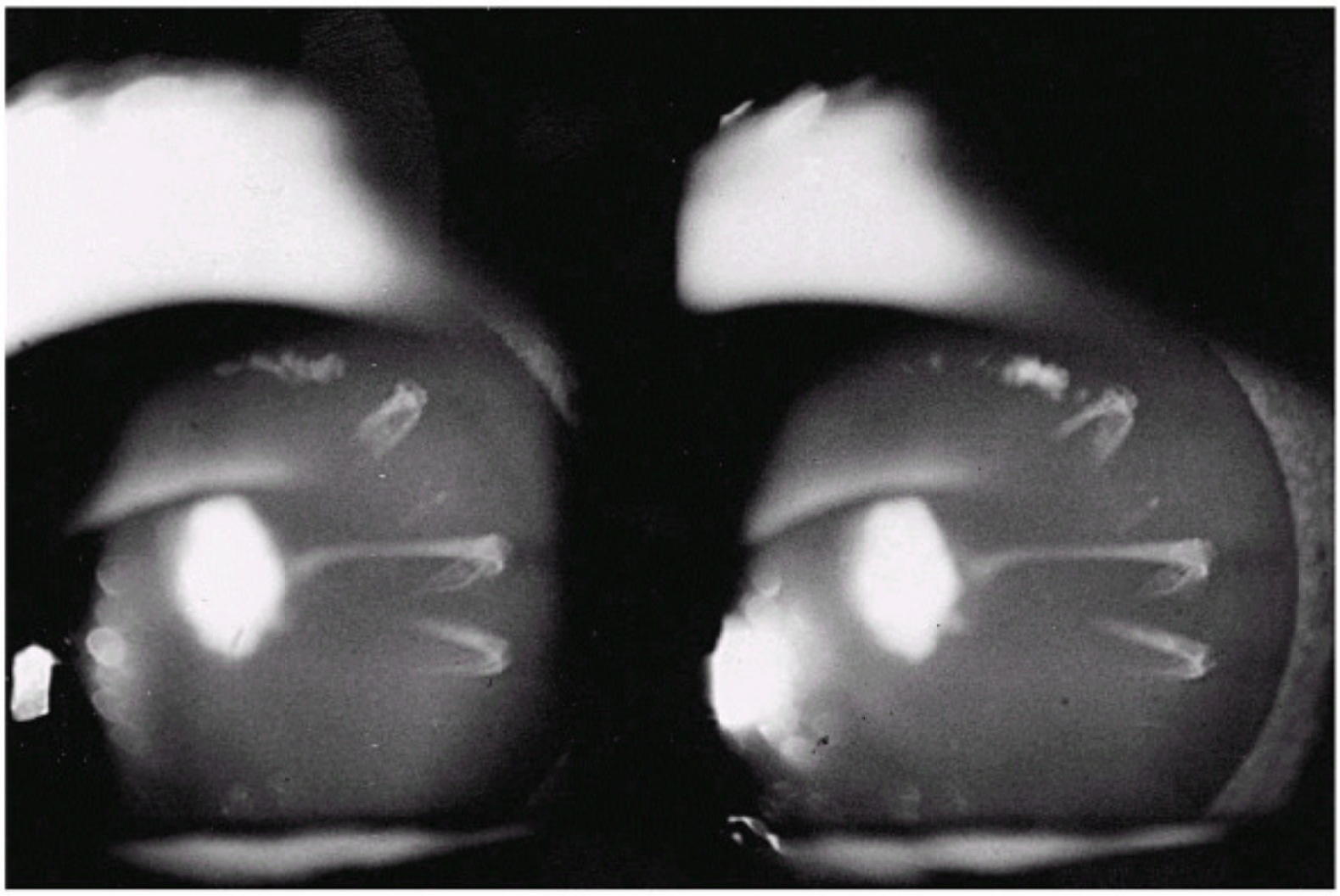

Figure 13.4 Zonular cataract involving selected sutural fibers.

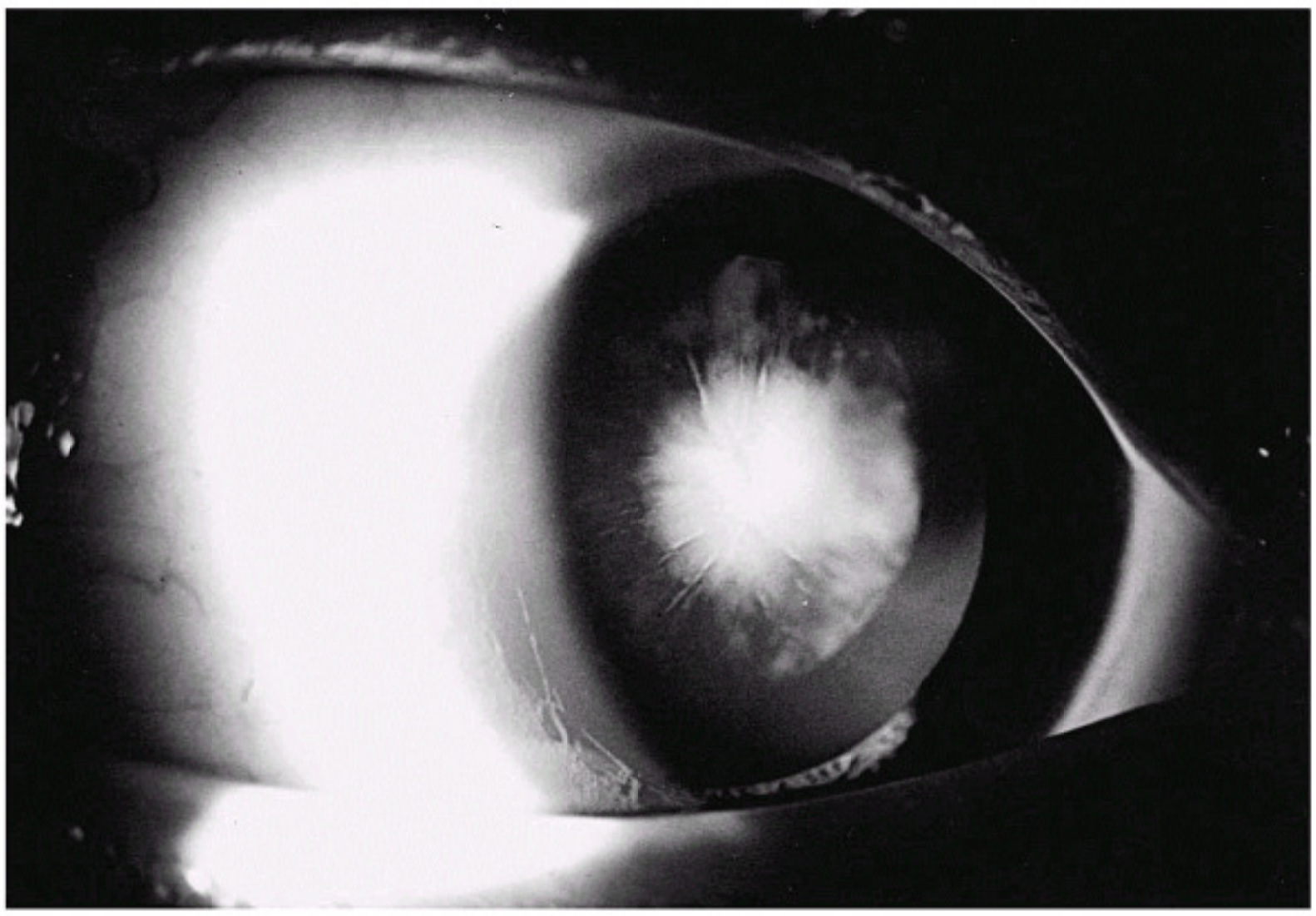

Figure 13.5 Nuclear cataract with opacification of embryonic and fetal nucleus.

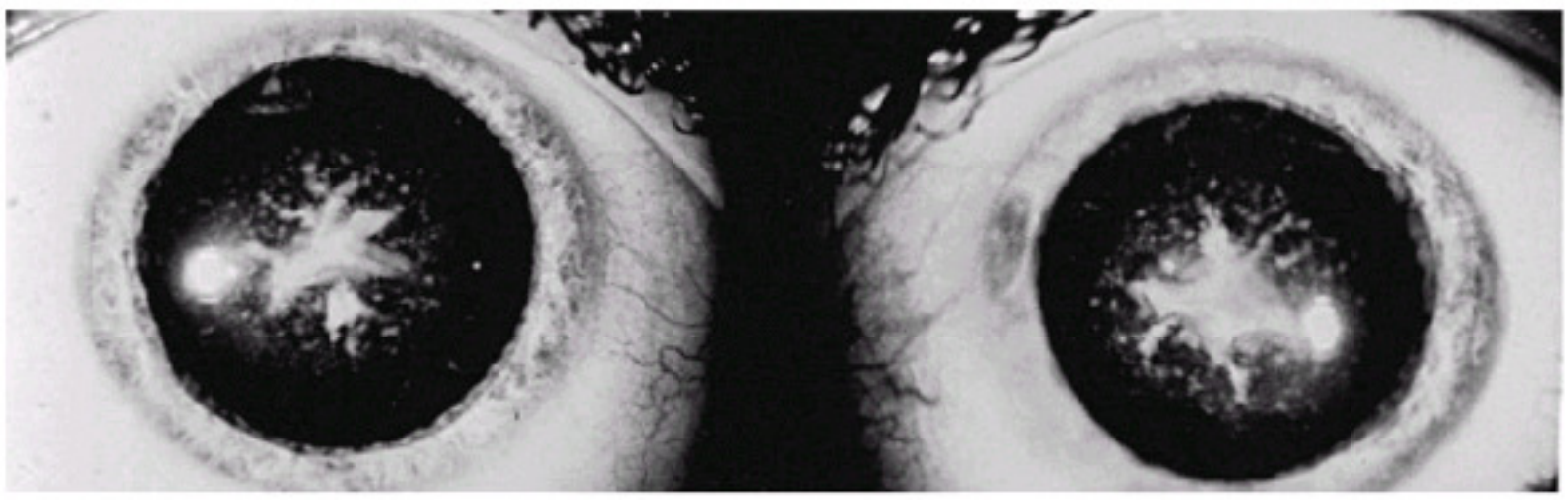

Figure 13.6 Sutural cataract involving the anterior fibers bilaterally. These can be dense and asymmetrical.

Subcapsular Cataract

Subcapsular cataracts occur immediately beneath either the anterior or posterior capsule, sparing the remainder of the lens. They usually indicate an acquired lens opacity that develops sometime after birth. Anterior subcapsular cataracts are the most common and are often associated with trauma or Alport's syndrome (nephritis and deafness). Anterior subcapsular cataracts are not usually visually significant. Posterior subcapsular cataracts are most often idiopathic but can occur after chronic steroid use, trauma, and Down's syndrome (4). Posterior subcapsular cataracts are often visually significant, and relatively small opacities located in the visual axis can have a profound effect on visual acuity (Fig. 13.7). The effect on visual function can often be best appreciated by streak retinoscopy or retroillumination.

Polar Cataract

Polar cataracts are opacities involving the subcapsular cortex or capsule in the polar regions of the lens. Anterior

polar cataracts are usually small (less than 3 mm), white, and located in the center of the anterior capsule (Fig. 13.8). They are felt to arise from abnormal separation of the lens vesicle during embryonic lens development. They can be inherited as an autosomal dominant trait. Although most are visually insignificant, a small percentage can progress, and visual loss can occur from strabismus, anisometropia, or amblyopia (12,13). Posterior polar cataracts, like their anterior counterpart, are usually a small, dense, white, central posterior lens opacity. They are commonly seen in children with aniridia (1,14). Because of the central location in the posterior part of the lens, as with posterior subcapsular cataracts, a small opacity can result in significant visual dysfunction.

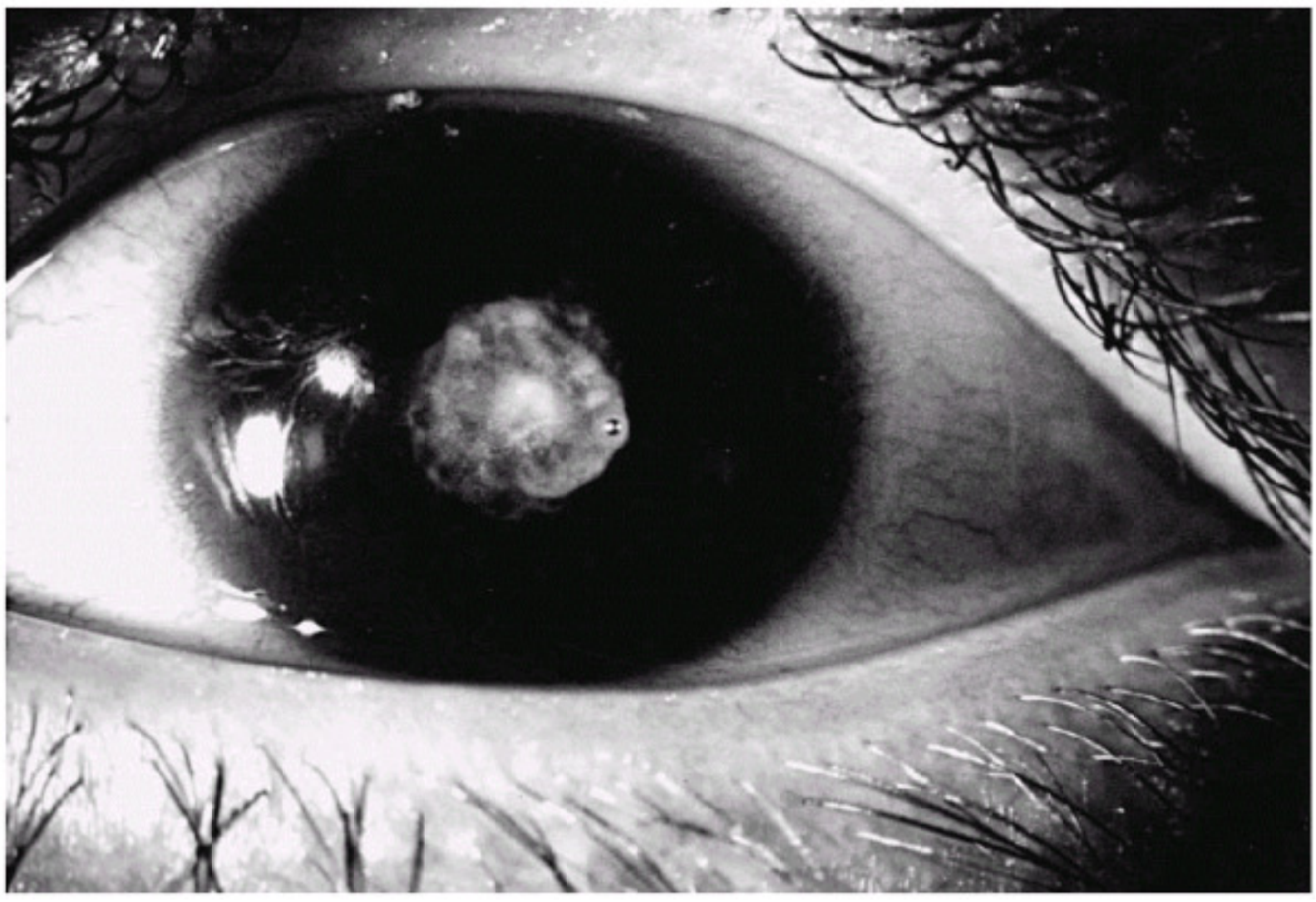

Figure 13.7 Posterior subcapsular cataract.

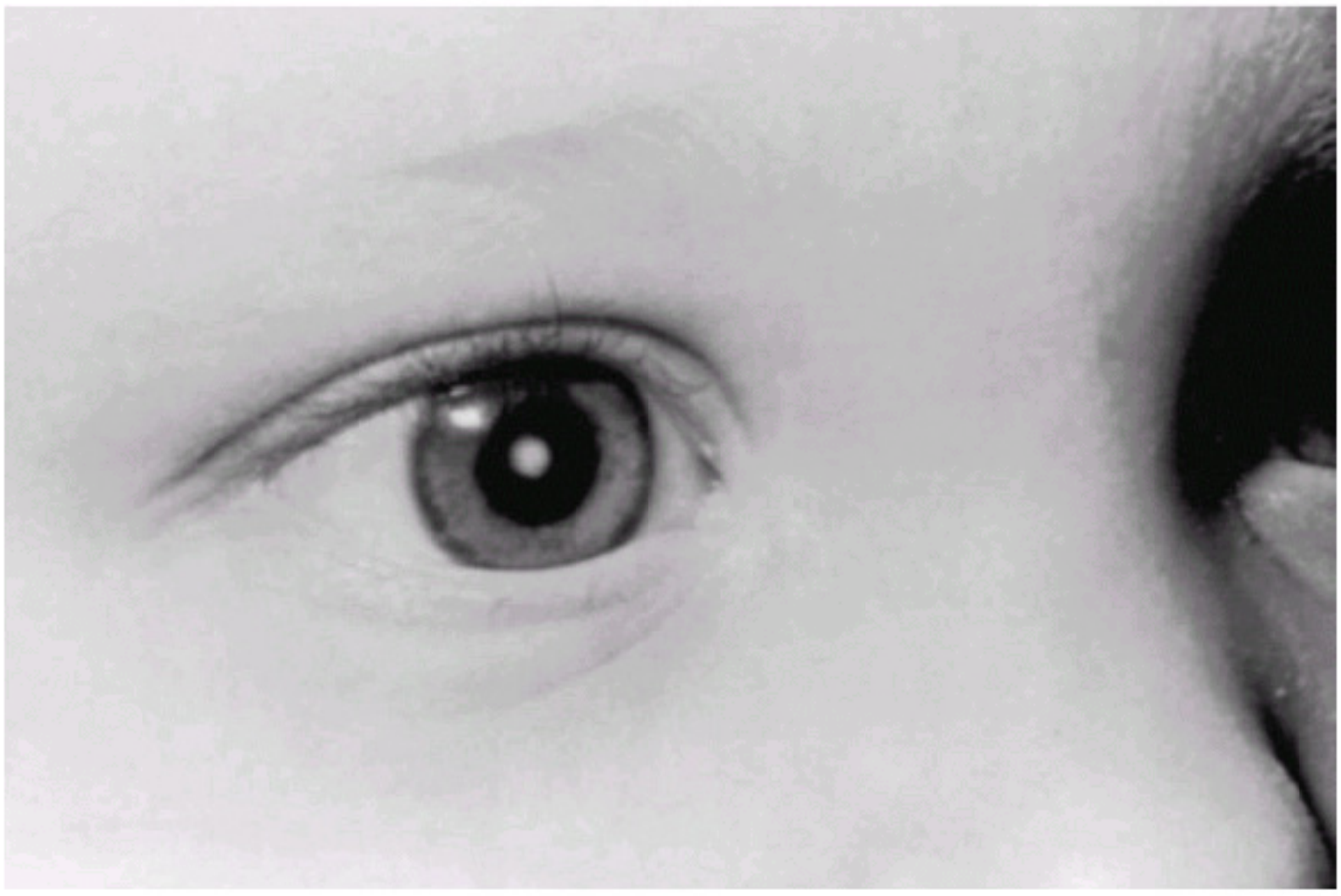

Figure 13.8 Anterior polar cataract. Note small, very dense opacity in the optical axis.

Total Cataract

Total cataracts are a complete opacity of the entire lens (Fig. 13.9). They can be caused by a variety of conditions, and their presence is not diagnostic of any one disorder. In most situations visual function is completely blocked, and immediate removal is indicated. Total cataracts may occur as a result of significant posterior segment disease, such as retinal detachment or tumor, and B-scan ultrasound is often helpful in diagnosing these conditions before intervention. Total cataracts can result as a natural progression from any of the partial cataracts listed earlier. Trauma should be suspected when cataract is present unilaterally in an otherwise previously normal child.

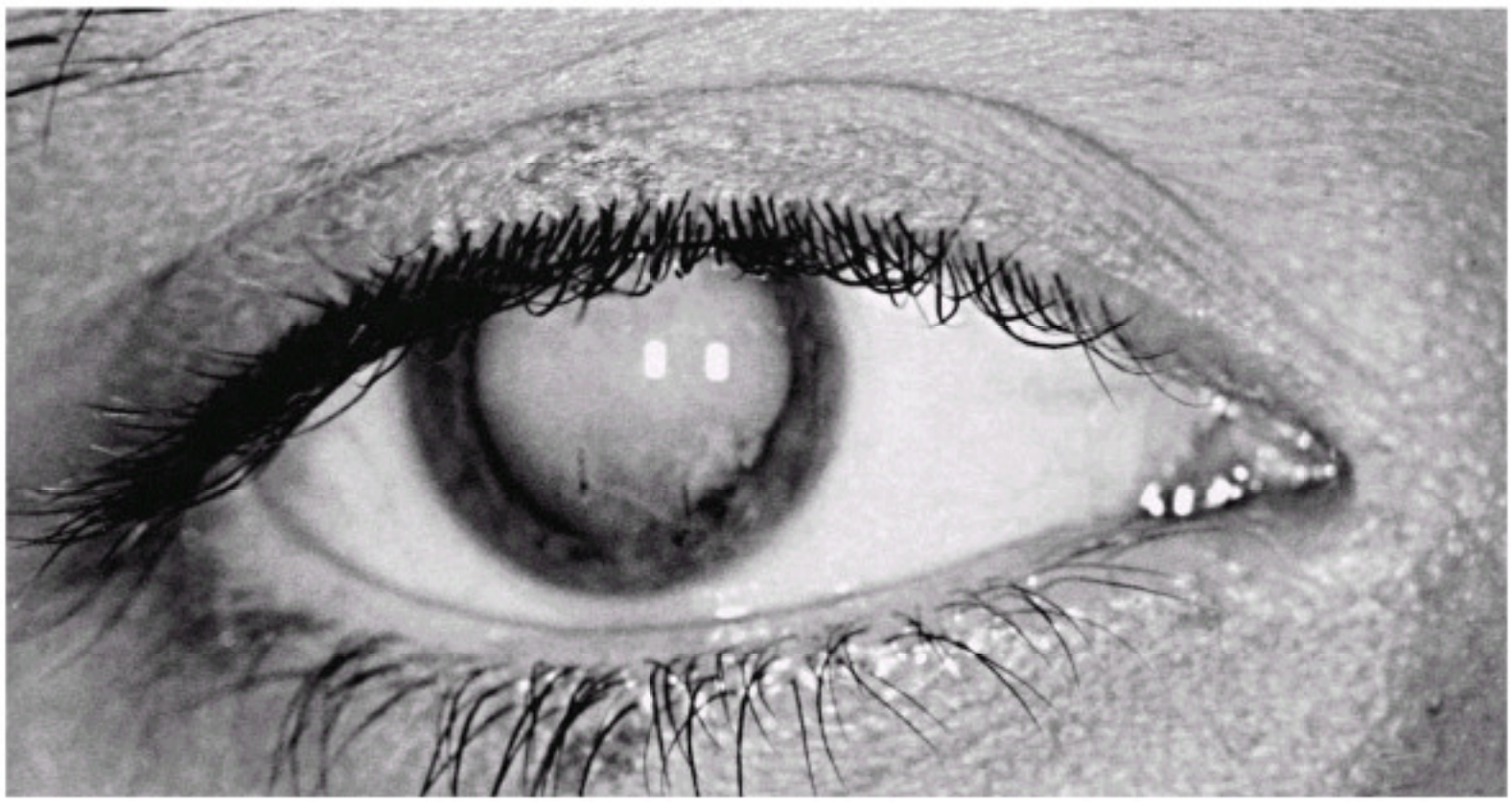

Figure 13.9 Total dense cataract secondary to trauma.

Membranous Cataract

A membranous cataract is a thin, fibrotic lens caused by reabsorption of lens protein and subsequent thinning in the anterior-posterior direction of the lens. The anterior and posterior capsules fuse to form a dense white membrane. It is often associated with a posterior capsular defect. It is commonly the end-stage result

of trauma. Membranous cataracts are commonly seen in congenital rubella, Hallermann-Streiff-Francois syndrome, and are associated with Lowe's syndrome (15,16).

Mittendorf's Dot

Mittendorf's dot is a small white opacity on the exterior surface of the posterior capsule, just nasal to the central visual axis. A small remnant of the hyaloid artery may extend from the optic nerve to the opacity. This may represent a very mild form of the persistent hyperplastic primary vitreous spectrum. Normally, this is an incidental finding and does not significantly interfere with vision.

Oil Droplet Cataract

Oil droplet cataract presents as a faint irregularity in the central aspect of the posterior lens cortex. On direct observation, it is very difficult to see but becomes readily apparent on retroillumination. These lens opacities have been classically described in patients with galactosemia. Initially, only the lens cortex is dysfunctional, but, if dietary restriction of galactose occurs, the lens changes are reversible. Prolonged ingestion of galactose eventually results in a total cataract.

"Christmas Tree" Cataract

This lens abnormality consists of small slit-like crystalline flecks scattered diffusely throughout the lens. On examination with the slit lamp, these lens abnormalities appear to be various colors of red, blue, and green, hence the name "Christmas tree" cataract. This particular lens abnormality has been shown to be present in patients (even asymptomatic) with myotonic dystrophy and hypoparathyroidism.

Cerulean (Blue-Dot) Cataracts

Cerulean cataracts are bilateral, small, bluish-white opacities that lie in the cortex peripheral to the nucleus. The opacities are felt to be degenerated cortical fibers. Patients are usually asymptomatic with little or no visual symptoms. They have been seen in Down's syndrome and in normal individuals during puberty (4).

Posterior Lenticonus/Lentiglobus

Posterior lenticonus/lentiglobus lens anomalies are due to a thinning of the posterior capsule that results in a bulging

posteriorly of the lens material (Fig. 13.10) (11). This change in lens architecture results in myopia and irregular astigmatism. The distorted posterior lens cortex often becomes opacified, progressing to a posterior subcapsular cataract. Occasionally, the posterior lens capsule spontaneously ruptures, resulting in total lens opacification. The visual prognosis after surgery is generally good, regardless of the time of intervention (17,18). Posterior lentiglobus implies a much larger area of abnormality, and this defect can often be eccentric (19). Over 90% of lenticonus is unilateral.

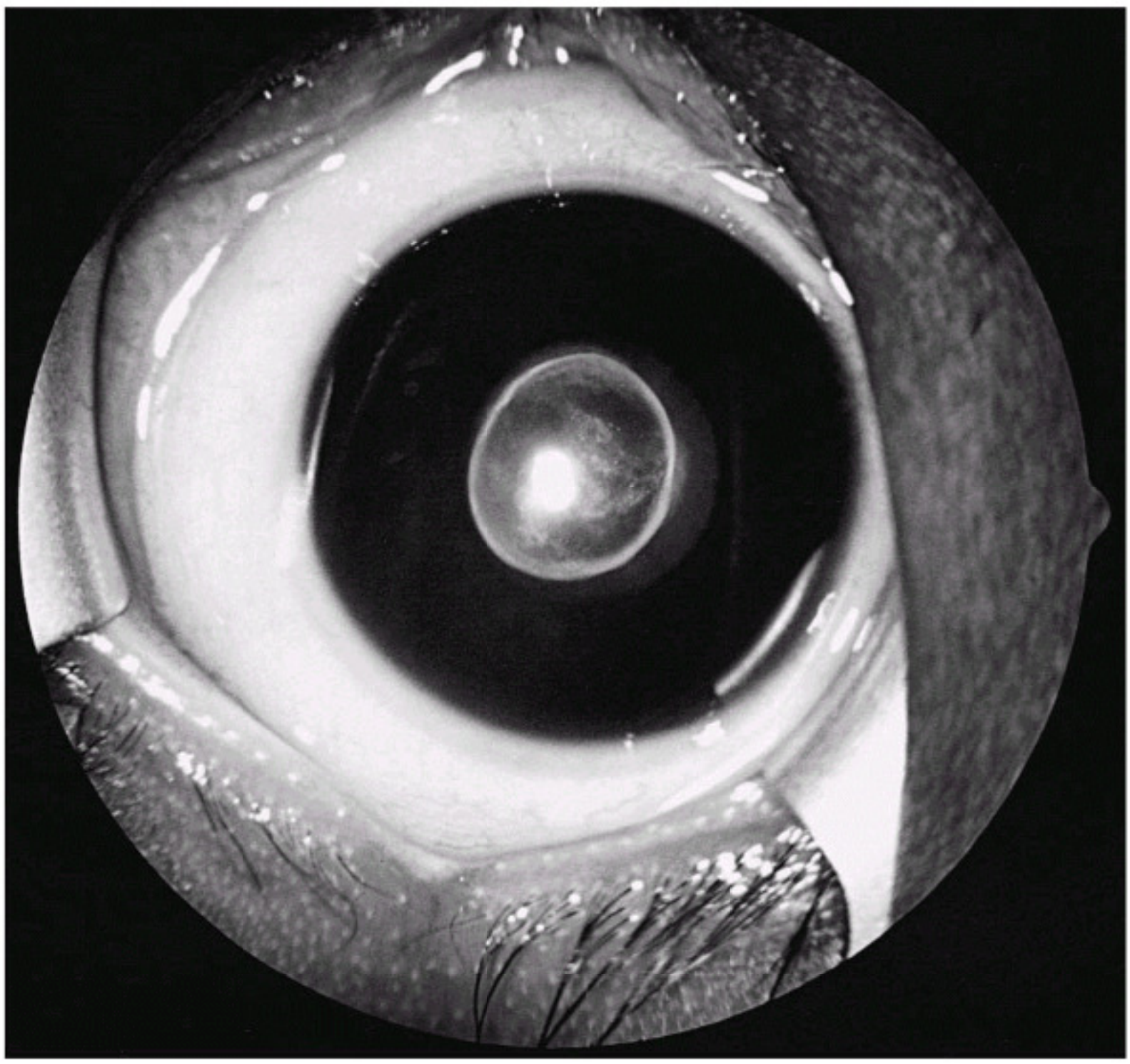

Figure 13.10 Posterior lenticonus with thinning and opacification of the posterior capsule. The whitish area bulges posteriorly. Note the very regular circular appearance of the opacity.

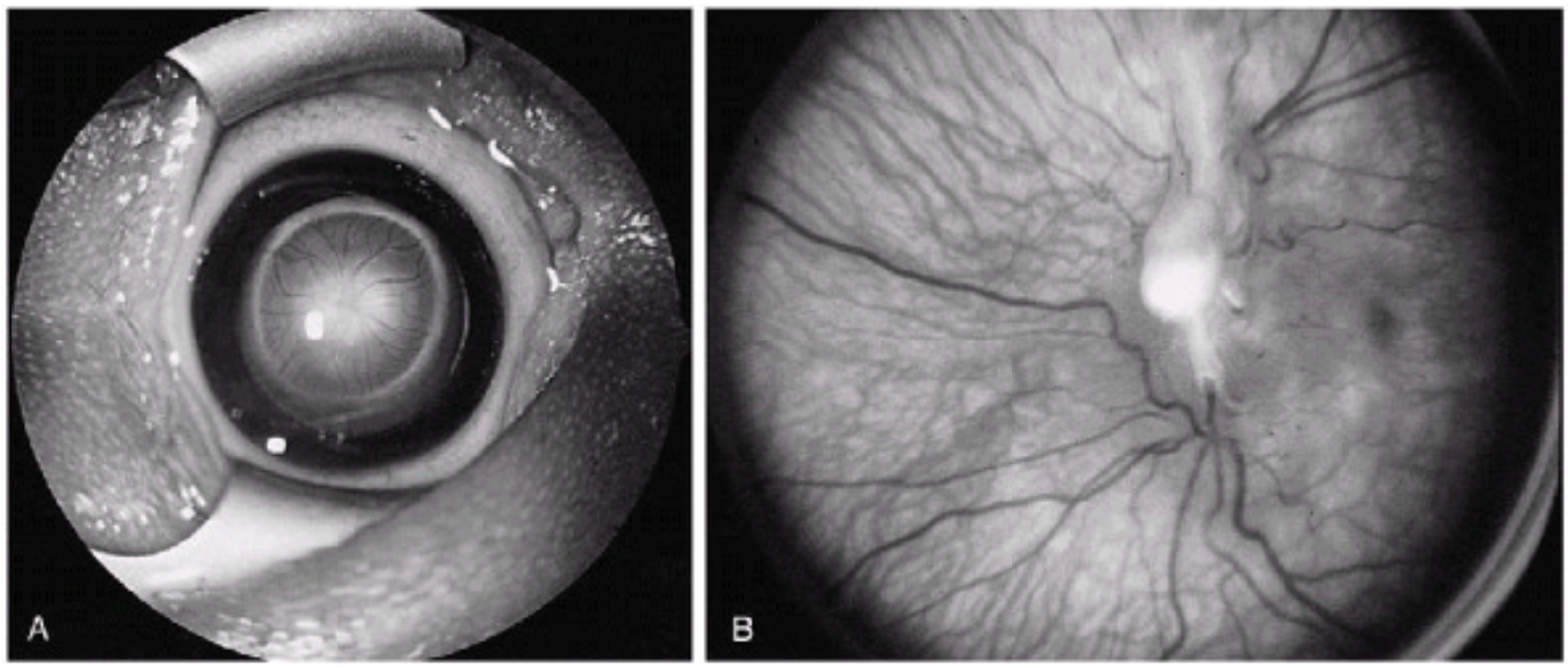

Figure 13.11 A: Persistent hyperplastic primary vitreous with opacified membrane on the posterior capsule. Note radial vascular structures present in the membrane. B: Fundus photograph of optic nerve showing persistent hyaloid remnant. Note marked structural abnormality of both optic nerve and surrounding vessels.

Persistent Fetal Vasculature

Persistent fetal vasculature (PFV), also known as persistent hyperplastic primary vitreous (PHPV), is an ocular condition caused by a failure of the primitive hyaloid vascular system to regress. This results in a retrolenticular fibrovascular membrane and can be accompanied by a fibrovascular stalk, which extends from the posterior lens to the optic disc (Fig. 13.11A,B). A white vascular membrane covers the posterior lens and can even extend to involve the ciliary processes. Initially, the lens is clear but often opacifies with time. The lens may be pushed forward by the retrolenticular membrane, and glaucoma may develop (20,21). The majority of eyes are microphthalmic (22). If fibrovascular proliferation extends to the optic nerve and adjacent retina, a tractional retinal detachment of the macula may occur. Visual prognosis in such situations is very poor. The treatment involves removing the lens and the fibrovascular membrane. This is often difficult because the membrane is tough and is not easily cut with standard vitreous cutters. Care must be used when removing the peripheral lens tissue, because the ciliary processes are often rotated inward and are susceptible to injury. With current microsurgical techniques, the visual outcome in these eyes has improved (18).

ETIOLOGY

Most bilateral cataracts are due to inherited and/or systemic diseases, whereas unilateral cataracts are almost always caused by some local ocular phenomenon or developmental abnormality that involves other structures of the eye as well. However, after a thorough evaluation, 60% of unilateral and 40% of bilateral cataracts have no discernible cause.

Hereditary Cataracts

A significant portion of bilateral cataracts is hereditary. The most common pattern is *autosomal dominant* with variable expressivity and a high degree of penetrance. Almost any morphological pattern can be inherited, and there is considerable variability among and between families (Fig. 13.12A,B; Table 13.5) (9). The most extensively studied autosomal dominant cataract is the pulverulent cataract. The name is derived from the Latin word *pulvis* for “powdery.” This type of cataract was first reported in an extensive study of the Coppock family (23). Pulverulent cataracts are bilateral and symmetrical. The gene for pulverulent cataract has been linked to eight different loci, indicating the likelihood of more than one cause (Table 13.2) (24,25,26,27,28,29,30,31).

As more genetic studies are performed, it is becoming apparent that hereditary cataracts, even of similar morphology, can be caused by many different gene defects. Recent work in molecular genetics have found many gene loci linked to autosomal dominant cataracts. In many cases, specific genes and proteins have been identified, which may, ultimately, help to understand the specific etiologies of different hereditary cataracts (Table 13.2). Trisomy conditions of chromosomes 13, 18, 21, 10q and 20p, and chromosome translocations, including 3:4, 2:14, and 2:16 (32,33,34), have all been associated with cataracts. Isolated congenital cataract transmitted as a recessive disease is rare and is usually seen only in populations with a high percentage of consanguineous marriages.

X-linked congenital cataracts can be divided into three categories: (a) a dense cataract in affected men, with the female carrier manifesting a sutural cataract; (b) congenital cataract with microphthalmia or microcornea; and (c) the syndrome of congenital cataract and dental anomalies (Nance-Horan syndrome), which is characterized by men who have a dense congenital central cataract, microcornea, nystagmus, as well as ear, hand, and dental anomalies. Recently, this abnormality has been mapped to the short arm of the X chromosome (35,36,37).

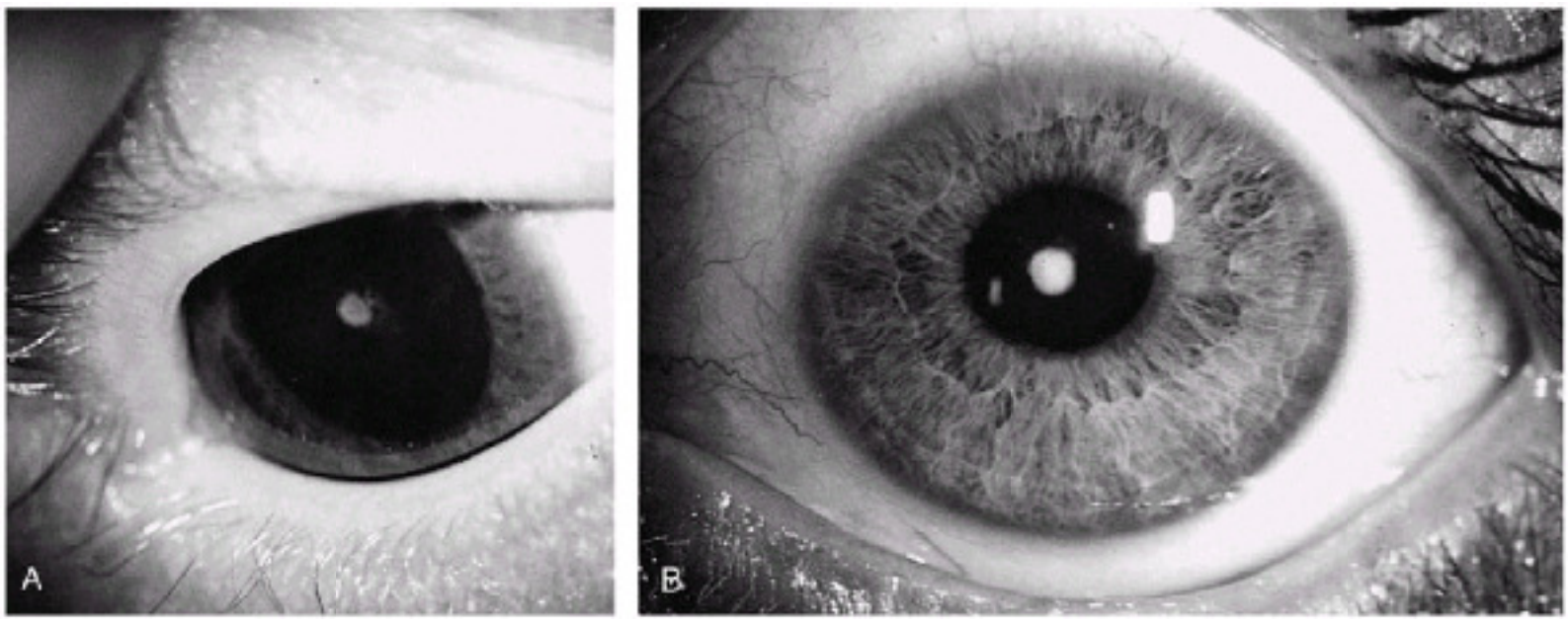

Figure 13.12 Hereditary cataracts. **A:** Six-week-old infant with small anterior polar cataract. **B:** Mother with similar anterior polar cataract.

Metabolic Causes

A variety of metabolic disturbances can result in lens opacities (Table 13.4). Usually, there is no particular morphology to the appearance of the cataracts, and, although most are permanent injuries, some can be reversed if they are recognized and treated.

Galactosemia

Galactosemia is the most common metabolic disturbance causing cataracts in infancy. It is autosomal recessive, bilateral, and may be the presenting sign of the disorder. Galactosemia, which results in cataract formation, is caused by a defect in galactokinase, uridine diphosphate galactoseepimerase, or galactose-1-phosphate uridyltransferase. The result is that galactose is converted to galactitol in the crystalline lens, resulting in an influx of water into the lens by osmosis. The hydration of the lens then disrupts the normal packing of the lens fibers, resulting in a loss of transparency. Initially, the lens changes have the appearance of an “oil droplet” in the cortical material of the lens. These changes are initially reversible with the elimination of galactose from the diet (38). Untreated, a total dense cataract rapidly develops. Children with transferase or epimerase defects often have multiple systemic abnormalities and present as infants who fail to thrive with hepatomegaly in the initial neonatal period. In addition to the cataracts, subsequent mental retardation and death can be prevented with diet control. Unfortunately, dietary restriction of galactose does not completely eliminate the formation of cataracts in later childhood or other systemic abnormalities that often occur in this syndrome. In contrast, galactokinase deficiency may have no systemic abnormalities. It has been localized to chromosome 17 (39). Evaluation for galactosemia includes urine testing for reducing substance 2 hours after a milk feeding, red blood cell (RBC) galactokinase activity, and RBC galactose-l-phosphate uridyltransferase.

Fabry's Syndrome

Fabry's syndrome is a rare, X-linked recessive metabolic disorder caused by a defect of a-galactosidase A. Abnormal storage of glycosphingolipids occurs in the eyes, kidneys, nervous system, and cardiac muscle. Affected men develop renal failure and die of cardiovascular disease in their third or fourth decade. The symptoms usually do not begin until the teenage years with the onset of punctate reddish-purple skin lesions, burning and severe pain of the hands and feet, and generalized malaise. Ocular findings consist of two very characteristic lens abnormalities. The first is a spoke-like posterior subcapsular cataract that is pathognomonic for the condition and is seen in 40% of patients. The second is an anterior subcapsular, usually inferior, wedge-shaped opacity. This is seen in approximately 35% of patients. About 15% of the female carriers have lens changes. Other ocular findings include vascular lesions of the conjunctiva, whorl-like opacities of the cornea, and vascular lesions of the retina (40,41). There is no known treatment for this disorder.

Mannosidosis

Mannosidosis is an autosomal recessive disorder that results in defective degradation of lipoproteins. Patients have cyclomotor retardation and coarse facies. Cataracts are common and present early within the first year of life. They appear as punctate lenticular opacities and, when present, are diagnostic. Diagnosis is confirmed by assay for a-mannosidase.

Wilson's Disease

Wilson's disease (hepatolenticular degeneration) is transmitted as an autosomal recessive trait and is characterized by liver disease and cerebellar dysfunction. It is caused by defective copper metabolism, which results in incorporation of copper into ceruloplasmin. Serum copper is increased, and copper deposits are found in the liver, brainstem, and eye. As the lens accumulates copper, a very unique “sunflower” cataract with a yellowish starlike anterior subcapsular discoloration forms. This may resolve with the use of penicillamine.

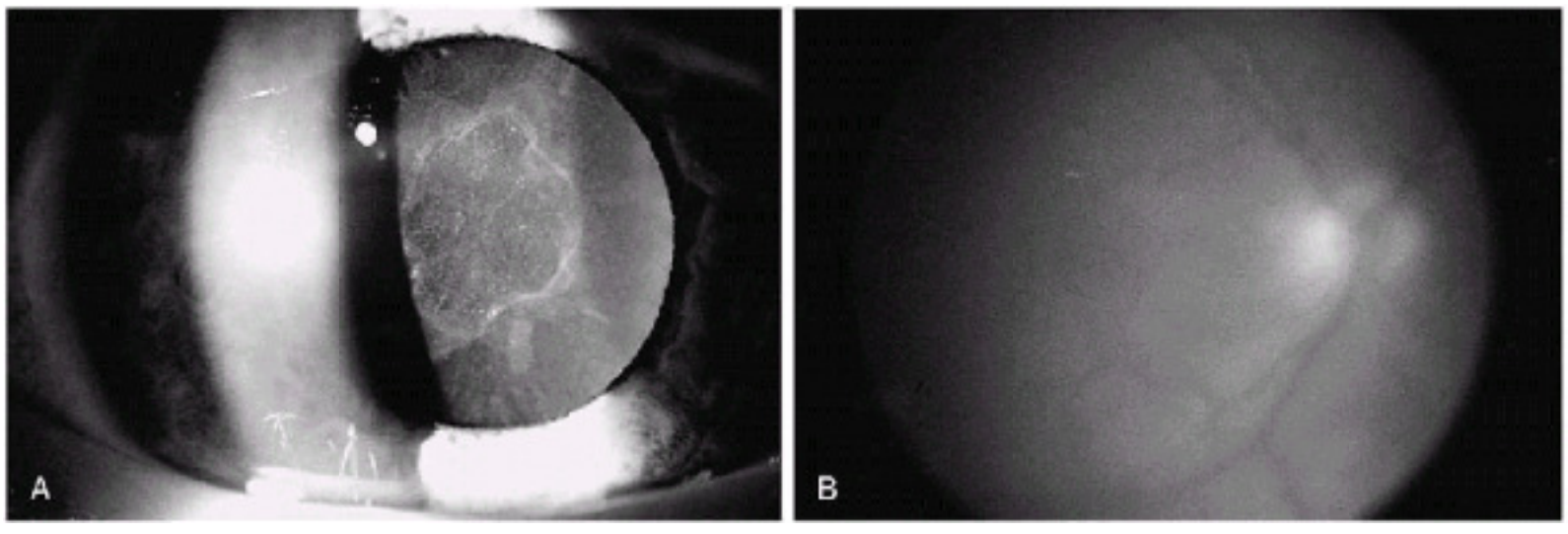

Figure 13.13 Diabetic cataract. A: Slit-lamp examination of cataract in 12-year-old patient with diabetes. B: Fundus photograph through lens opacity illustrating marked image degradation.

Hyperglycemia or Hypoglycemia

Hyperglycemia and hypoglycemia are rare causes of cataracts in children. Neonatal hypoglycemia is common in low birth weight infants. Cataracts are usually bilateral and of the lamellar type (4). Hyperglycemic cataracts (diabetes mellitus) occur usually in older children but have been seen as early as age 1 year (42). These are usually diffuse, cortical, or subcapsular cataracts, and visual function may be decreased out of proportion to the slit-lamp appearance of the lens (Fig. 13.13A). Retroillumination or streak retinoscopy help confirm the poor optical qualities of the lens (Fig. 13.13B). The lens changes may be reversible, if blood glucose level can be brought under control and the onset is recent.

Disorders of Cholesterol Synthesis

Because the lens membrane contains the highest cholesterol content of any known membrane, inherited defects in enzymes of cholesterol metabolism are associated with cataracts. Mevalonic aciduria, cerebrotendinous xanthomatosis, and Smith-Lemli-Opitz syndrome all involve mutations in enzymes of cholesterol metabolism (43). The cause of cataract formation in these entities is either a disruption of cholesterol synthesis or, more likely, a direct toxicity of the abnormal by-products.

Hypoparathyroidism and Pseudohypoparathyroidism

Hypoparathyroidism and pseudohypoparathyroidism have been associated with cataracts in childhood. The cataracts are related to hypocalcemia, consist of diffuse multicolor flecks (“Christmas tree” cataract), and are usually not visually significant (44).

Intrauterine Infection

Infantile cataracts can occur from a variety of intrauterine infections, including rubella, toxoplasmosis, varicella (45), and herpes simplex (46,47). Of these, rubella cataracts are by far the most common. Until the recent development of a rubella vaccine, they constituted approximately 15% of all cataracts. The congenital rubella syndrome consists of heart defects, deafness, and mental retardation. Ocular findings include retinopathy, microphthalmos, optic atrophy, corneal haze, and glaucoma. The cataracts are usually bilateral, dense central opacities, and are due to the invasion of the lens by the rubella virus (48,49). Elevated IgM antibodies against rubella, or serial IgG showing increasing IgG titer, is indicative of an intrauterine infection (4).

Although rare, infantile cataracts can also occur after bacterial or fungal infections and may occur late after the infection has been treated (50).

Multisystem Disorders Associated with Hereditary Cataracts

Cataracts are a common finding in a whole host of multisystem disorders (Table 13.3). The incidence of cataracts varies widely in this group, but there is a subset for which cataracts are found in a high percentage of involved patients. Given that cataracts are a common entity in such a diverse group of disorders attests to the susceptibility of the lens to injury.

Lowe's Syndrome

Lowe's syndrome (oculocerebrorenal) is an X-linked recessive disorder in which cataracts occur in almost 100% of patients. These are usually flattened, disc-like opacities (membranous) and may have a posterior lenticonus configuration (51). Other ocular abnormalities include glaucoma due to an abnormal “embryonic type” angle, miosis resulting from segmental hypoplasia of the pupillary dilator muscles, and corneal opacities. Systemic abnormalities include mental retardation and renal aminoaciduria. Female carriers of Lowe's syndrome may be recognized by characteristic spoke-like opacities in the posterior cortex or diffuse punctate or flake-like opacities (52,53). Because the gene for Lowe's syndrome has been linked, suspected carriers can now be confirmed by molecular genetic studies.

Alport's Syndrome

Alport's syndrome is an X-linked or autosomal dominant disorder consisting of interstitial nephritis, hearing defects, and ocular abnormalities. The lens abnormality, anterior lenticonus, is felt to be pathognomonic for this syndrome. Other lens opacities can occur, but the cataracts are only rarely visually significant. Additional ocular abnormalities include a macular pigment epitheliopathy. Urine testing reveals red blood cells and elevated protein.

Conradi's Syndrome

Conradi's syndrome (chondrodysplasia punctata) is characterized by asymmetrical limb shortness, skin abnormalities, and sparse, coarse hair. Seventeen percent of the patients have infantile cataracts (54,55). In this group there is no cyclomotor retardation, and there is a good prognosis if the patient survives the neonatal period. A recessive form (rhizomelia) has also been described in which cataracts occur in up to 70% of the patients (56). This group has cyclomotor retardation, and the patients usually die within the first year.

Myotonic Dystrophy

Myotonic dystrophy is an autosomal dominant muscular dystrophy whose manifestation is progressive muscle wasting. This occurs usually in the second and third decades of life. In addition, there is mental deterioration, cardiac abnormalities, and hypogonadism. Ocular features include ptosis, microphthalmos, extraocular muscle paresis, hypotony, retinal pigmentary degeneration, and cataracts. Typical lens changes occur in all patients in the second decade of life as multicolored crystalline iridescent flecks in the cortex (“Christmas tree” cataract) or small, white spheric opacities (snowball-like) in the cortex. The lens opacity is so characteristic as to constitute a method of identifying presymptomatic gene carriers. Recently, however, specific molecular tests for this disorder have been developed (57).

Neurofibromatosis Type 2

Neurofibromatosis Type 2 (NF-2) is an autosomal dominant disorder characterized by the development of vestibular schwannomas and central nervous system tumors. Cataracts are found in over 60% of patients and can be the initial mode of presentation. The most common type is a posterior subcapsular or cortical cataract (58).

Zellweger's Syndrome

Zellweger's syndrome (cerebrohepatorenal) consists of abnormal development of the head, face, ears, hands, and feet. Patients are mildly retarded and have liver, renal, and ocular abnormalities. Zonular cataracts are a consistent finding in most cases. Asymptomatic carriers have been found to have curvilinear lens opacities. Ultrastructurally, the lens fibers are abnormal with a high density of mitochondria and inclusion bodies. Other ocular abnormalities include corneal opacities, retinal dystrophies with an abnormal electroretinogram (ERG), and optic atrophy. This disorder results from an abnormality in peroxisomal function, and laboratory evaluation reveals elevated long-chain fatty acids and reduced plasmalogen levels (59,60).

Cockayne's Syndrome

Cockayne's syndrome is an autosomal recessive, primary dermatologic abnormality, with onset in early childhood.

The most striking feature of the disorder is premature aging and cachectic dwarfism. Other features include microcephaly, sensory neural deafness, and photodermatitis. Ocular abnormalities include cataracts and retinal degeneration. Because of the skin abnormalities, the patient's lids are abnormal, and they are at risk for exposure keratitis and blepharitis.

Rothmund-Thomson Syndrome

Rothmund-Thomson syndrome is an autosomal recessive condition consisting of atrophic skin with patches of depigmentation and hyperpigmentation. Patients have sparse hair, short stature, defective dentition, and hypogonadism. Telangiectasias appear during the first year of life. Cataracts occur in the majority of patients and often have a sudden onset between ages 3 and 6 years. Keratoconus can also occur in these patients.

Bloch-Sulzberger Syndrome

Bloch-Sulzberger syndrome *(incontinentia pigmenti)* is an X-linked dominantly inherited abnormality that consists of generalized ectodermal dysplasia, dental abnormalities, alopecia, and ocular anomalies. The skin has a swirl-like cutaneous pigmentation on the trunk and extremities. The lens abnormality is reminiscent of that seen with persistent hyperplastic primary vitreous. Often there is also an associated retinal dysplasia. The condition is seen in women only.

Smith-Lemli-Opitz Syndrome

Smith-Lemli-Opitz syndrome is an autosomal recessive cranial facial abnormality whose general features include a broad nasal tip with inverted nares, low-set ears, micrognathia, syndactyly, developmental delay, and growth retardation. Ocular abnormalities include cataracts, corneal endothelial microvesicles, optic atrophy, prominent epicanthal folds, and choroidal hemangiomas. The abnormality is caused by a deficiency of 7-dehydrocholesterol reductase, leading to low cholesterol tissue levels, which appears to be the major cause of cataracts in these patients. Other inhibitors of this pathway may result in cataracts, including mevalonic aciduria and cerebrotendinous xanthomatosis.

Toxic and Traumatic Cataracts

Direct *trauma* to the eye is the most common cause of acquired cataracts in children (Fig. 13.14). This should be strongly suspected in an otherwise healthy child who suddenly develops a dense lens opacity. Although most cataracts are caused by significant ocular damage, occasionally mild, nonpenetrating injuries can result in lens capsule disruption leading to the development of an intumescent lens. In the very young child, nonaccidental trauma should be considered. In those cases with no obvious history of trauma, B-scan ultrasonography and computed tomography (CT) scan should be considered to rule out a retained intraocular foreign body, retinal detachment, or tumor.

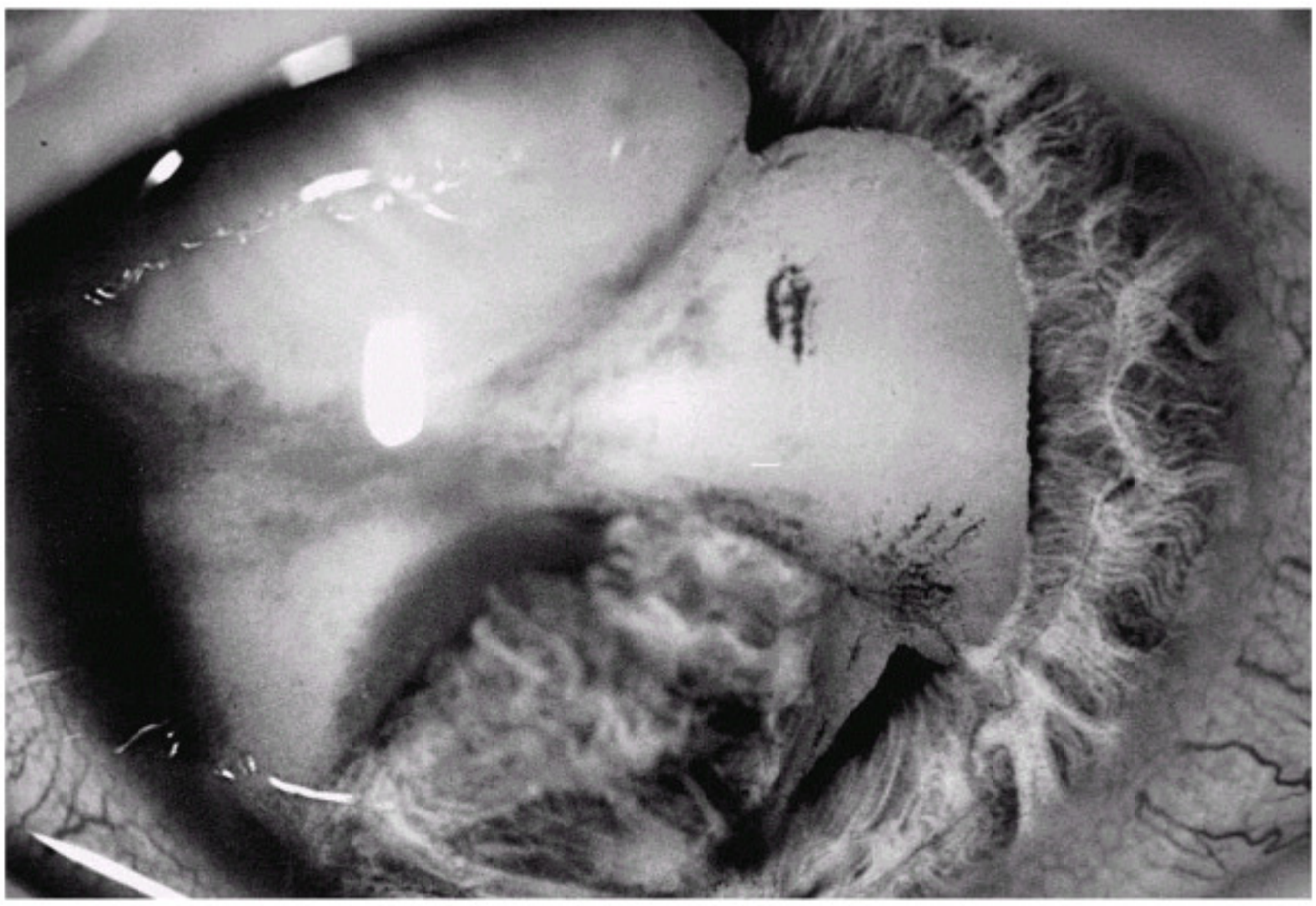

Figure 13.14 Traumatic cataract in 3-year-old after injury with pencil. Note marked associated iris and anterior segment injury.

Traumatic injury to the lens after *laser photocoagulation* in premature patients with retinopathy of prematurity has been observed. Laser photocoagulation is rapidly replacing cryotherapy as the treatment of choice for this disorder. Laser-induced cataracts have been seen after treatment with both argon and diode laser (1,61).

The lens can be sensitive to the systemic and topical administration of *medication,* particularly corticosteroids. This appears to be dose- and duration-dependent, once an accumulative dose of 1 g of prednisone has been reached (62). The type of cataract initially occurs in the posterior subcapsular region but can progress to involve the entire lens.

The development of cataracts after *exposure to radiation* is dose- and duration-dependent and can be seen with as little as 1 to 2 Gy, but the incidence increases to as high as 50% with 15 Gy (63). Cataracts do not usually develop until 1 to 2 years after completion of radiation therapy (1).

WORKUP

Unilateral Versus Bilateral Cataracts

A thorough ophthalmic examination is necessary in all patients with cataracts. This is especially important in patients with *unilateral cataracts,* because these are usually due to an abnormality of the eye (Tables 13.6 and 13.7). In these

cases, emphasis on detecting other anterior segment abnormalities, such as microcornea, iris hypoplasia, and glaucoma, is important. If possible, a thorough retinal and optic nerve evaluation should be performed. If unable, B-scan ultrasonography is helpful in detecting any preexisting posterior segment abnormalities, such as retinal detachment, intraocular tumor, or hyaloid stalk. Axial length measurements should also be obtained and may reveal microphthalmia, an indicator of congenital rather than acquired lens opacity (64). Finally, evaluation of ocular alignment should be included and may give the clinician insight as to the onset of the cataract(s). In unilateral cataracts, the presence of either an afferent pupillary defect or a jerk nystagmus with a fast phase in the direction of the normal eye (manifest latent nystagmus) is a poor prognostic sign for good vision postoperatively.

TABLE 13.6 UNILATERAL CATARACTS: ETIOLOGY

- Idiopathic
- Persistent fetal vasculature (PFV)
- Trauma
- Posterior lenticonus
- Anterior polar
- Anterior cleavage syndrome (Peter's anomaly)
- Rubella

TABLE 13.7 CONGENITAL CATARACTS: ASSOCIATED OCULAR ABNORMALITIES

Anterior Segment	Posterior Segment
Aniridia	Choroideremia
Glaucoma	Retinitis pigmentosa
Microcornea	Persistent fetal vasculature (PFV)
Corneal dystrophy	Stickler's syndrome
Microphthalmos	Wagner vitreoretinal degeneration
Iris atrophy	Norrie's disease
Anterior cleavage syndromes Peter's anomaly Rieger's syndrome	Favre vitreoretinal degeneration

In *bilateral cataracts,* more emphasis is placed on the morphology of the lens (Table 13.2) and on the associated systemic signs (Table 13.4). Most bilateral cataracts are idiopathic, hereditary, or secondary to some systemic derangement. In most situations the systemic abnormality is obvious, especially when the cataracts are noted during the first year of life. Because many cataracts are hereditary in nature, a thorough family history, including examination of “asymptomatic” parents, is important (Fig. 13.12A,B). As with unilateral cataracts, a thorough ophthalmic evaluation is helpful.

TABLE 13.8 CONGENITAL CATARACTS: DIAGNOSTIC EVALUATION

Condition	Laboratory Test
Galactosemia	Urine reducing substance
	RBC galactokinase activity, RBC galactose-1-phosphate uridyltransferase
Lowe's syndrome	Urine amino acids
Alport's syndrome	Urine microscopy, urine protein
Rubella	Antibody titers
Syphilis	VDRL test
Smith-Lemli-Opitz syndrome	Cholesterol pathway enzymes
Mevalonic aciduria	
Cerebrotendinous xanthomatosis	
Hypoparathyroidism	Serum calcium, phosphorus, alkaline phosphatase
Wilson's disease	Serum ceruloplasmin
Hyperglycemia/hypoglycemia	Blood glucose
Fabry's disease	Urine “Maltese cross” (polarized light)

RBC, red blood cell; VDRL, Venereal Disease Research Laboratories.

Visual Significance

The ophthalmic examination can be helpful in determining the visual impact of a lens opacity. In general, the more posterior, central, and sizable the opacity is, the more it degrades the retinal image. Assessing the red reflex with the direct ophthalmoscope before dilation and after dilation can give the clinician a feeling for the amount of obstruction that a cataract is producing in the physiological state and whether the patient may be able to “look around” the opacity, if dilated. Often the visible opacity is surrounded by an even larger area of optical irregularity, only appreciated by attempted retinoscopy indicating that the “functional cataract” is much larger than the “visible cataract.” If a retinoscopic reflex is adequate to refract, or, if the disc can be seen with a direct ophthalmoscope, 20/60 vision or better is attainable through the cataract.

Some have recommended removal of all small central cataracts (3 mm or greater). Other authors have countered that some children with large central opacities have normal visual acuity. Therefore, each patient should be evaluated on an individual basis using all diagnostic tools. Also, an attempt should be made to identify the onset of the cataract to help predict the visual impact. Reviewing old photographs may be helpful. Smaller axial length, esotropia, and nystagmus have been associated with congenital opacities. The type of cataract may also be predictive of onset (nuclear-congenital, lamellar, and posterior lentiglobus-acquired). Last, in those patients in whom a good streak retinoscopy can be performed, efforts should be made to

ensure that a significant anisometropia is not present, which may be contributing to the visual loss.

TABLE 13.9 CONGENITAL CATARACTS: LABORATORY EVALUATION

	Result	Possible Diagnosis
Urine	+ Reducing substance	Galactokinase deficiency
	Aminoaciduria	Lowe's syndrome
	Hematuria, proteinuria	Alport's syndrome
	“Maltese cross” figures	Fabry's disease
Blood	Erythrocyte enzymes	Galactokinase deficiency
	Glucose	Hyperglycemia/hypoglycemia
	TORCH titers, VDRL test	Rubella, toxoplasmosis, CMV, herpes, syphilis
	Calcium, phosphorus	Hypoparathyroidism or pseudohypoparathyroidism

CMV, cytomegalovirus; VDRL, Venereal Disease Research Laboratories.

Laboratory Evaluation

Given the long list of possible causes of infantile cataracts (Table 13.4), an extensive evaluation would seem to be indicated (Table 13.8). Fortunately, in almost all of these disorders there is some other systemic or historical piece of information to guide the clinician to the proper diagnosis. Rarely do any of these systemic abnormalities appear to the ophthalmologist unsuspected and undiagnosed, because cataract is infrequently the presenting sign of most systemic diseases. Therefore, evaluation should be directed by the presence of the other associated systemic signs rather than the eye findings.

The workup, in part, should be directed to whether the cataract(s) is unilateral or bilateral. Since unilateral cataracts are often due to local ocular abnormalities, laboratory investigation is not usually indicated. Occasionally, intrauterine infections can give rise to a unilateral cataract, and, if suspected, a TORCH (toxoplasmosis, rubella, cytomegalic virus, herpes simplex) titer can be obtained. In patients with bilateral cataract, a complete evaluation would involve those studies shown in Table 13.9. However, in an otherwise normal child, a TORCH titer, RBC transferase, and galactokinase levels (required in many states as a part of newborn metabolic screening) are the only findings likely to be helpful. Any patient with a positive workup should be referred to his or her pediatrician, or possibly a geneticist, for a more thorough evaluation. An infant with a positive family history for autosomal dominant cataracts, who is otherwise normal, does not need an extensive laboratory workup.

NATURAL COURSE OF CATARACTS

Nearly all types of congenital or infantile cataracts progress in size and density over months or years. Neonates and infants with visually insignificant cataracts should be observed closely during the first several years of life for progression that could lead to amblyopia. Certain types of cataracts do not usually progress. These are the Mittendorf's dot, small opacities of the Y sutures, and dots or snowflakes in the cortex. Some types always progress, and these include posterior lenticonus, zonular or lamellar cataracts, and opacities associated with PFV.

Anterior polar cataracts were once thought not to progress, but, in fact, some do to a visually significant degree. The opacity may develop in the anterior cortex, not visible to external examination, behind the easily seen white opacity on the anterior lens capsule (12,13). Therefore, these infants should be seen more frequently during the first year of life to look for progression not apparent to the parents.

Posterior lenticonus is a unique type of unilateral cataract that has especially good visual prognosis (65). It may present at any age in childhood. One can assume that the lens was relatively normal at birth with the development of normal vision, but that for some unknown reason there is a weakness of the posterior capsule. This weakness leads to a protrusion of the lens posteriorly into the vitreous. In the early stages this may appear as an oil droplet on the posterior surface by the red reflex test. Usually, the lens material within and surrounding the lenticonus gradually becomes opacified. The entire lens may be opaque, and the posterior protrusion may be seen only at surgery, when the opaque cortex has been removed. Removal of the lens usually restores the eye to reasonably normal vision.

MANAGEMENT

The greatest concern in children with cataracts is irreversible visual loss secondary to lack of a formed focused image (visual deprivation). This is compounded in unilateral cataracts because, even after surgical removal, there still exists anisometropia, aniseikonia, and intraocular competition that is often very difficult to treat. Patients with dense monocular or bilateral cataracts develop irreversible amblyopia, if the cataract is not removed by age 2 months (66). The presence of strabismus, or even more important, nystagmus, is a poor prognostic sign, and once nystagmus is present it rarely resolves after cataract removal (64). Visual function

in these individuals is usually no better than 20/60 to 20/80 postoperatively. When present in unilateral cataract patients, nystagmus often takes the form of a jerk nystagmus with a fast phase in the direction of the better-seeing eye (manifest latent nystagmus). This type of nystagmus is also seen in other ocular conditions in which vision is markedly decreased in one eye at a young age.

In patients who do not have total dense cataracts, it is sometimes difficult to tell whether the lens opacity is visually significant. The most important factors are the location of the opacity, size, and density. As a general rule, the larger, denser, posterior, and centrally located the cataract, the greater the resultant visual impairment. In general, a lens opacity of less than 3 mm is probably not visually significant (67).

Medical

In patients who have small opacities or in whom the red reflex is not considered significantly impaired, a trial of patching should be considered before any surgical intervention. In those patients with small central opacities (3 mm or less), dilation can also be instituted. Ideally, phenylephrine hydrochloride (Neo-Synephrine) 2.5% can be used 2 or 3 times daily. In some patients with heavily pigmented irises, Neo-Synephrine will not provide adequate dilation. A weak cycloplegic agent, such as tropicamide (Mydriacyl) 0.5% or cyclopentolate 0.5%, can be used. If visual acuity after patching and/or dilation improves to the 20/60 or better level, then cataract extraction is probably not indicated. In individuals who require chronic cycloplegic agents to maintain dilation and in whom visual acuity has improved significantly, surgical optical iridectomy can be considered. This should also be considered in high-risk patients or in those who have associated ocular abnormalities, such as corneal opacities. A classic example is Peter anomaly in which the patient has a central cataract and corneal opacity but has a clear peripheral lens and cornea. An optical iridectomy may be a better solution than a corneal transplant and cataract extraction with its resultant poor prognosis.

Surgical

If the lens opacity is deemed to be visually significant, then prompt removal is indicated. The timing of removal is critical and should be as soon as possible after its detection. In dense unilateral or bilateral cataracts present at birth, the critical period appears to be within the first 2 months of life. The first 6 weeks of life have been termed as the “precortical stage” of development, whereas from 6 weeks to 8 months is considered the “cortical stage.” Therefore, good vision, and even stereoacuity, can be obtained in dense unilateral cataracts operated on by age 6 weeks (6,67,68). The same is true for bilateral cataracts with a slightly larger window of ages 8 to 10 weeks (69). Numerous studies have shown that a clear focused image is necessary for good visual development, and this must occur within the first 2 months of life (70,71). Failure to remove the cataracts early, however, does not always mean poor visual outcomes. In patients whose congenital cataracts are not dense and total, approximately 40% of unilateral cataract and 70% of bilateral cataract patients have been reported to achieve visual function of 20/60 or better (4,18,64). Late removal of unilateral cataracts of unknown duration can result in good visual function, if not associated with other significant ocular abnormalities, such as microphthalmos (64).

The possibility of the development of amblyopia in children also has to be taken into account in the decision for surgery. When the cataracts are of unequal density in a child, the child may function well with the sight afforded by the eye with the less dense cataract. However, the eye with the denser cataract will very likely develop amblyopia; and even if this cataract is removed later, the visual result may be poor. If the estimated visual loss from the density is such that patching would be unreasonable, cataract surgery on the denser cataract should be performed.

All reports emphasize the importance of early surgery, early optical correction, and aggressive patching of the phakic or sound eye. Parental cooperation is an essential part of the management program. Surgery is only the first step in a long and tedious program to obtain useful vision in the afflicted eyes. The ophthalmologist must ensure that optical correction remains appropriate and must provide support for the families during the years of patching required for a successful visual outcome.

Surgical Approach

Historical Perspective

Most patients with congenital cataracts require surgical removal of the cataract at some time during infancy or childhood. Before 1960, most congenital cataracts were removed by an extracapsular technique (72). In this procedure, an incision involving several clock hours was made at the limbus, the capsule was cut with a cystitome and the lens removed either manually by pressure applied through the cornea or by irrigation. The posterior capsule was left intact. In nearly all cases the posterior capsule became optically imperfect and required discission. The complication rate was fairly high with this procedure.

In 1960, Scheie introduced a discission and aspiration technique. Immature cataracts were “ripened” by making an anterior capsular discission and disrupting the cortex. In several days the cataract would soften or become almost totally opaque, transforming the lens material into a less viscous state. Several days later the remaining cortical material was aspirated. The posterior capsule was usually left intact, and a secondary posterior capsule discission was often required.

In the mid-1960s there were various minor modifications to this technique to maintain the depth of the anterior chamber throughout the procedure. This was accomplished by placing a separate infusion line. At about the same time, operating microscopes became popular. This allowed clear cortex to be seen and removed by aspiration. With better visualization, the need for a preliminary discission to ripen or soften the lens cataract was avoided.

In 1972 Machemer et al developed a new instrument,

the vitreous infusion suction cutter (VISC), which revolutionized the treatment for cataracts. The ability to aspirate, cut, and maintain anterior chamber depth allowed a one-stage complete removal of the lens. It also introduced the possibility of removing the posterior capsule at the time of the initial procedure, thereby preventing the secondary membrane formation that was a prominent feature of other surgical approaches.

Current Surgical Technique

Vitrectomy cutting instruments, irrigation/aspiration, phacoemulsification, or some combination of these techniques can remove pediatric cataracts. Although commonly used in adults, phacoemulsification is not necessary in children because the lens material in children is soft, and the posterior capsule is thin. The phaco instrument also requires a significantly larger opening than the other instruments and may damage corneal endothelium. The most common techniques use a vitrectomy instrument and either one or two ports. The one-port technique requires that infusion accompany the instrument. This necessitates a larger opening and sometimes hinders removal of superior peripheral cortical lens material. A two-port technique uses a separate site for infusion (Fig. 13.15A). The two openings are small, and the vitrectomy instrument and infusion can be

switched to allow easier access to peripheral lens material. With either technique the irrigation/aspiration instrument can be substituted for the vitrectomy instrument to allow safe removal of the far peripheral lens material (Fig. 13.15B, C). This is especially important if intraocular lens implantation is anticipated. Most surgeons advocate an anterior limbal approach as opposed to a pars plana approach. Because most young children have no pars plana, entrance sites must be made through the peripheral retina. There does not appear to be any increased benefit from the posterior approach, and the risk of retinal injury is higher. The anterior approach is also preferred, if intraocular lens implantation is to be performed.

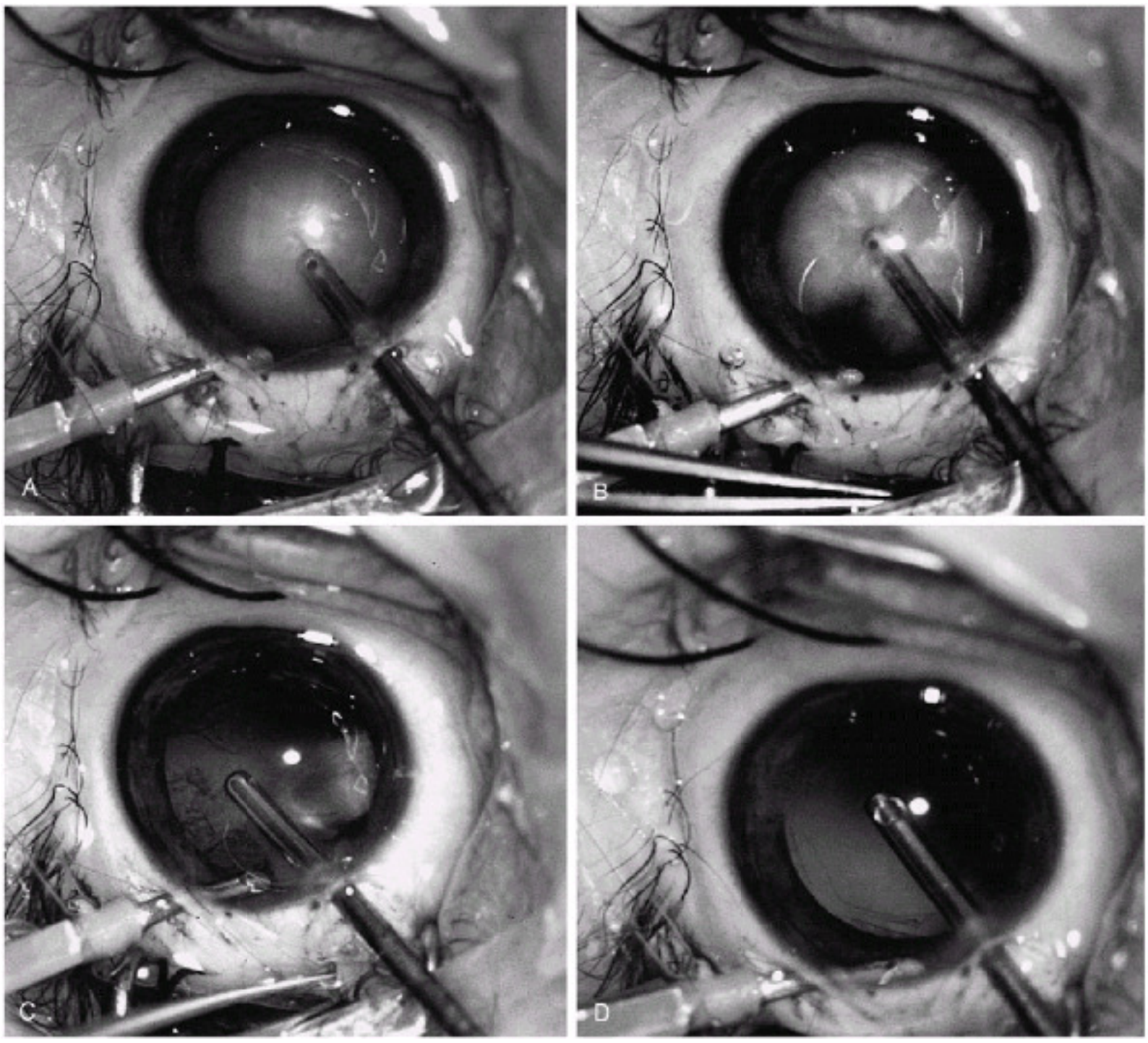

Figure 13.15 Surgical removal of congenital cataract. **A:** Surgeon's view of two-port technique. Infusion (*right*) is with a 23-gauge cannula. An irrigation aspiration instrument (*left*) is used to remove the soft nucleus and cortex. **B:** Cortical material is gently aspirated using irrigation aspiration apparatus. **C:** Complete removal of all lens cortex is essential in preventing secondary pupillary membrane and iris capsular adhesions. **D:** Posterior capsulotomy and limited anterior vitrectomy are performed with a vitrector instrument. A large capsular opening is necessary. A small residual remnant should be left for future intraocular lens placement.

The posterior capsule tends to opacify rather quickly in children and should be removed along with the anterior vitreous surface, if at all possible (Fig. 13.15D). Peripheral lens fibers in children use the capsule and anterior vitreous as scaffolding and quickly grow across and reopacify the opening. This process can result in marked delay in visual rehabilitation and necessitate subsequent surgery. This is not as crucial in older children who can cooperate for a yttrium-aluminum-garnet (YAG) capsulotomy. However, even after YAG capsulotomy, there is a significant rate of reopacification of the visual axis, and multiple treatments may be required (73). The best approach, when in doubt, is to remove a significant portion of the posterior capsule. Posterior capsule removal can be performed from an anterior approach after cortex removal or during pars plana lensectomy. Anterior vitrectomy may also be performed, at this time, to decrease the risk of secondary membrane formation or vitreous opacification. Care, however, should be exercised in leaving a small portion of the posterior capsule to act as a support mechanism anticipating the possibility of a secondary intraocular lens implant in the future.

Most patients with bilateral cataracts have an operation on each eye separately, waiting at least a week between procedures to assess the likelihood of any postoperative complications before proceeding with surgery on the second eye (74). It has been recently shown, however, that bilateral simultaneous cataract extractions can be safely performed (75,76,77,78). This reduces the theoretical risks from a second anesthesia induction and provides prompt visual rehabilitation to both eyes. The major risk with this approach is the development of bilateral endophthalmitis. To reduce this possibility, separate instrumentation and infusion fluids should be used for each eye (79).

Primary Intraocular Lens Implantation

Intraocular lenses (IOLs) are becoming increasingly popular as a way to treat unilateral and bilateral aphakia in children (Fig. 13.16) (80,81,82,83,84). However, children present some unique challenges to the surgeon, and the standard technique used for adults must be modified somewhat for these younger patients. Anterior capsular openings in adults can usually be accomplished easily with continuous curvilinear capsulorhexis. This is much more difficult to perform in children, because the capsular material is thicker and tends to tear radially. A second option to create a capsular opening is by burning a circular opening using a diathermy capsulotomy needle (85). A third alternative, which is preferred by the authors, is to open the anterior capsule with the vitrector instrument. This allows a controlled capsular opening and appears just as stable as the continuous curvilinear capsulorhexis (83). In cases where the anterior or posterior capsule are difficult to visualize, some have used tryptan blue or ICG dye to stain the capsule (86,87). Additionally, the tryptan blue has been used to stain epithelial cells to ensure a more complete clean up and minimize cell proliferation postoperatively (88).

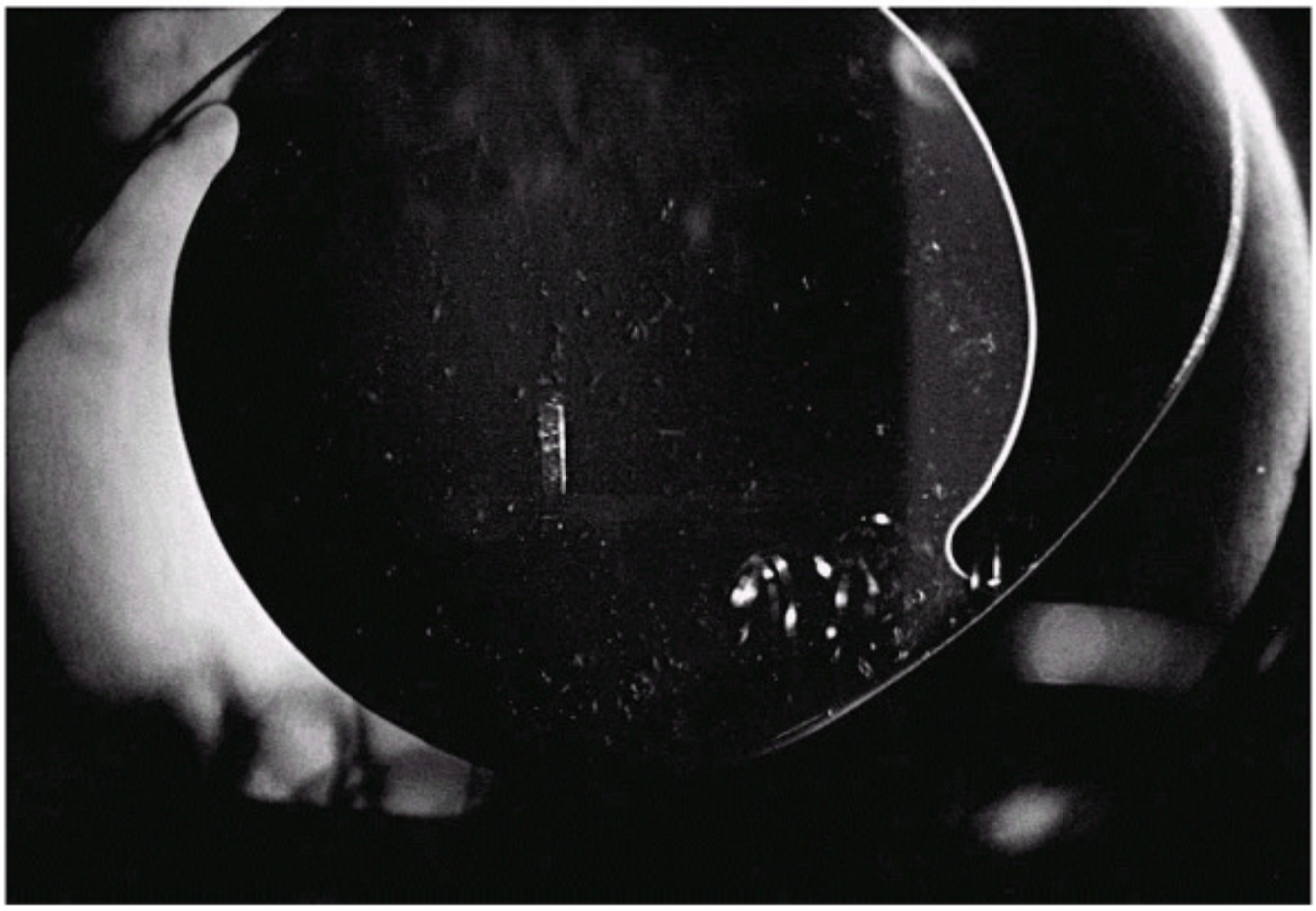

Figure 13.16 Slit-lamp photograph of intraocular lens in a patient with aniridia.

The choice of lenses is somewhat controversial. The best intraocular lens for children is one that is small enough for the infantile eye, while maintaining support as the child grows, one that is biocompatible and noninflammatory, and one that does not encourage lens epithelial cell proliferation. Most people currently favor either the one-piece polymethyl methacrylate (PMMA) lens or the newer single piece acrylic foldable lens, which has shown a good safety record (89,90,91). Recent studies have shown a decreased incidence of IOL cell deposits and synechiae and a similar rate of posterior capsular opacification in the acrylic lens versus the PMMA lens in the pediatric population (92). There was some concern about the long-term stability of three-piece lenses (80), and the older foldable silicone lenses were associated with a high rate of lens deposits. Lenses with smaller overall diameters and larger optics are also preferred to facilitate “in the bag” implantation and minimize any optical effects of lens decentration. The use of a heparin-surface-modified IOL in cases of children with chronic uveitis may help to decrease postoperative lens deposits (93,94,95).

Posterior capsular opacification (PCO) occurs in nearly 100% of infantile eyes after cataract extraction, if the posterior capsule is left intact. Therefore, different surgical methods and IOL designs have been evaluated to reduce the incidence of PCO. Primary removal of the posterior capsule is advocated by most (in children younger than about age 7) either before IOL implantation or after the lens is in place. This can be accomplished by anterior segment approach or pars plana approach, using the vitrector as described previously (80). However, others have shown different techniques for preventing PCO. Radiofrequency

diathermy on both the anterior and posterior capsules has also been described to prevent PCO with anterior vitrectomy (96). Tassignon et al have described and tested in vivo a “bag-in-the-lens” technique, in which both anterior and posterior curvilinear capsulorhexis are created and then inserted into the flange of the IOL, thus preventing lens epithelial growth (97). Last, many authors have found lower rates of PCO formation with prolapsing the IOL optic through the posterior capsulotomy (optic capture) without anterior vitrectomy (98,99,100). Alternatively, some prefer leaving the posterior capsule intact and performing secondary discission (especially in cooperative older patients) by YAG capsulotomy that can be performed weeks to months later. Because of the rapid opacification and thickness of children's posterior capsules after surgery, YAG capsulotomy should be entertained sooner than one would normally perform this in adults. A second intraocular procedure may be required to remove an opacified posterior capsule (101).

Secondary Intraocular Lens Implantation

Secondary IOLs can be used safely in children (102,103). In most situations, the lens is placed in the sulcus supported by the capsular remnant. The authors have found this to be an excellent scaffold for the placement of a secondary intraocular lens, even in the absence of a 360-degree ring. The presence of significant posterior iris pigment epithelial adhesion to the capsular remnants in most patients requires delicate manipulation to gain access to the sulcus without damage to the iris. This can usually be achieved with an iris spatula, Sinskey hook, or a sharp cutting instrument, such as an MVR blade. Wilson et al have advocated in-the-bag secondary IOL placement in which the anterior and posterior leaflets are reopened using a “vitrectorhexis” technique, and the IOL is implanted in the bag (104). This offers the theoretical advantage of decreased inflammation and better centration. Suturing intraocular lenses into the sulcus can be performed in those patients who lack adequate support, such as in some cases of infantile cataracts, trauma, or ectopia lentis. The long-term safety of this approach in children is not known. However, several authors have shown it to be a reasonable approach when no support exists (102,105,106,107). Complications of suture-fixated IOLs in adults include persistent uveitis, continued pigment dispersion, glaucoma, hyphema, IOL decentration, cystoid macular edema, lens haptic erosion, and retinal detachment (102). Pupillary distortion, transient pupillary membrane, papillary capture, and anterior uveitis were reported as the most common complications in children. There has also been a report of a child with endophthalmitis and retinal detachment (106). Few advocate anterior IOL placement due to anatomical considerations (small eyes) and concern of increased inflammation and glaucoma.

Intraoperative Complications

Fortunately, with the development of modern vitrectomy and cataract instrumentation, the incidence of intraoperative complications has decreased significantly (Table 13.10). One of the most problematic is *poor pupillary dilation.* Many patients with congenital cataracts have underdeveloped iris dilator muscles and, even with vigorous topical mydriatics, fail to dilate sufficiently enough to perform safe lens removal. Iris hooks, iris sphincterectomies, or sector iridectomies can be used to enhance visualization. Care must be exercised when using the vitrector in the anterior segment, especially in the cutting mode. Because of the large size of the port, the iris can easily be damaged by inadvertently cutting it. Iris can also be incarcerated in the port if the vitrector is used for peripheral cortical cleanup. Damage to the iris can result in intraoperative bleeding and postoperative hyphema. The size of the limbal opening should be large enough to allow insertion of

instrumentation without excessive force. Too small of an opening can result in opacification of the cornea at the entrance site as the instrument is inserted, which can persist postoperatively. Too large an opening results in the need for large amounts of infusion to maintain the anterior chamber. Excessive infusion flow and/or pressure can also result in corneal opacification. This is especially true in those cases in which the cornea is already developmentally compromised, such as in Peter's anomaly or in congenital glaucoma. If corneal cloudiness does occur, reducing the infusion pressure to the lowest possible level can be helpful. In addition, a bright light source, such as a “light pipe” placed at the limbus, can facilitate visualization.

TABLE 13.10 COMPLICATIONS OF CATARACT SURGERY

Intraoperative

- Small pupil
- Hemorrhage
- Iris damage
- Retinal hemorrhage
- Retinal detachment
- Corneal edema

Postoperative (IOL)

- Posterior capsule opacification
- Secondary membrane
- Glaucoma
- Lens reproliferation
- Inflammation
- Cystoid macular edema
- Pupillary abnormalities
- Retained cortical material
- Vitreous to wound
- Wound leak
- Endophthalmitis
- Iris to wound
- Corneal edema
- IOL decentration
- Refractive surprises

	Refractive surprises
	Wound-induced astigmatism
	Iris synechiae
	Iris color change/heterochromia

IOL, intraocular lenses.

Postoperative Complications

The most common postoperative complications are shown in Table 13.10. The incidence of problems postoperatively is higher in children than adults and is undoubtedly due to the technical aspects of operating on a small eye, increased postoperative inflammatory response, coexisting abnormalities of the anterior segment, difficulty with postoperative examination, and problems administering postoperative medications. This increased complication rate seems to be even greater in children younger than 6 months (108). The risks of glaucoma and retinal detachment increase with time and may not be seen until many years after surgery (109).

Persistent postoperative inflammation can occur from a variety of causes. The most common is incomplete removal of the lens cortex. This may be due to poor pupillary dilation, corneal edema, or posterior capsule rupture. Although all retained lens material will, in time, absorb by the action of circulating macrophages, this creates a phacolytic uveitis that may cause persistent inflammation of the postoperative eye. Also, in cases of a sulcus placed lens or an anterior chamber IOL, the increased contact with the uvea theoretically may increase inflammation. Inflammation can usually be controlled with cycloplegic agents and topical steroids. Patients with juvenile rheumatoid arthritis-associated uveitis may minimize complications related to postoperative inflammation through the use of systemic immunosuppressive agents as well as intensive topical corticosteroids (110).

Postoperative infection leading to endophthalmitis is a rare complication after congenital cataract surgery, with a prevalence of 7 in 10,000 procedures (111). It is most frequently caused by *staphylococcus* and *streptococcus* organisms. Good et al showed an increased incidence in patients with nasolacrimal duct obstruction, periorbital eczema, and upper respiratory infections (74). Most children have a poor visual outcome following endophthalmitis.

Glaucoma is a common finding in postoperative cataract patients and can occur years after the original surgery. Incidence has been noted to range from 3% to 41% (112,113). In the immediate postoperative period, pupillary block and/or angle-closure glaucoma can occur. The intense inflammatory response that occurs in some patients' eyes often results in a fibrinous pupillary membrane that can occlude the pupillary axis and is particularly problematic in patients who have had an IOL implant. Alternatively, the intact anterior hyaloid face can prolapse into the anterior chamber, and the iris can develop synechiae. Postoperative mydriasis, intensive topical corticosteroids, and a peripheral iridectomy are helpful in reducing the incidence of this type of glaucoma (1).

The most common type of glaucoma to develop after infantile cataract surgery is open-angle glaucoma seen especially in children who undergo surgery before age 9 months (113). This often occurs years later. Simon et al (114) reported a mean interval of 7 years from the time of cataract surgery until glaucoma was diagnosed. Therefore, continued surveillance is necessary to detect this problem. In the first years of life, an asymmetrical change in refraction may herald the onset of glaucoma. Normally, both eyes of an aphakic child have similar refractions and, if one eye suddenly becomes less hyperopic, glaucoma should be suspected. Between ages 2 and 4 years, the only sign of glaucoma may be a change in the appearance of the optic nerve. Starting at about age 4, most children begin to allow applanation tension measurements. Treatment of aphakic glaucoma in children is extremely difficult and usually requires surgical intervention (Chapter 14). Interestingly, Asrani et al have found a decreased incidence of aphakic glaucoma in those children with primary IOL placement, although their mean follow-up was only 3.9±2.7 years (115).

Retinal detachments after congenital cataract surgery can appear anytime postoperatively, even many years later (mean interval from surgery to detachment ranged from 23-34 years in three large series) (1). This interval, plus the recent advances in instrumentation for cataract extraction, makes it difficult to ascertain the true incidence of retinal detachment in patients who have had congenital cataracts removed with the newer techniques. Factors that seem to increase the risk of detachment include high myopia and multiple operations. Despite newer techniques, visual results after retinal reattachment surgeries in the pediatric population, in general, are poor.

Secondary membranes may form across the visual axis, necessitating YAG capsulotomy or surgical removal. These can be particularly common in microphthalmic eyes and in eyes with excessive intraoperative iris manipulation. Also, they have been associated with an intact posterior capsule and a younger age at surgery (108,116). Using topical corticosteroids and cycloplegic agents postoperatively can lower the incidence of secondary membrane formation.

Cystoid macular edema, another postoperative complication, is rare in children presumably because of healthy vasculature. Rao et al (117) recently reported a small series with no angiographic CME after cataract extraction with IOL implantation, posterior capsulotomy, and anterior vitrectomy. Corneal edema is rare in pediatric eyes, which were otherwise uncompromised. In fact, Votruba (118) found endothelial cell counts after pediatric cataract surgery to be similar to those of normal children.

Visual Rehabilitation

The optical correction of pediatric aphakia can be achieved with glasses, contact lenses, epikeratophakia, or intraocular lenses. Each of these methods has associated problems that make them less than ideal, and there is no uniform consensus on their use.

Aphakic Spectacles

Aphakic spectacles are the safest method available (Fig. 13.17). They are more commonly used in bilateral aphakia but can be used in unilateral situations as well. In addition to safety, their other major advantage is that they can easily be updated to match the rapidly changing refractions in young children. Disadvantages include lens thickness and weight, as well as optical distortions, such as ring scotomas. In newborns, lens powers of + 24 to + 26 diopters are often required, and these can only be accomplished with very thick bubble-shaped lenses. In older children the thinner, high-density aphakic spectacles can be used. In children

younger than age 2, the lens power should be selected to allow relatively clear focusing at near because it is very difficult for a child this age to learn how to use a bifocal. A flat-top bifocal can be introduced somewhere between ages 18 months and 2 years. Later, this can be changed to a progressive bifocal segment. Unilateral aphakia can also be managed with aphakic spectacles, especially in those situations in which binocular function is not anticipated. Because of the marked aniseikonia from the aphakic lens, patching of the normal eye is usually necessary when the child is wearing the aphakic spectacles (119).

Figure 13.17 A 1-year-old aphakic child happily wearing spectacles after bilateral cataract surgery.

Contact Lenses

Contact lenses are the most common method used to treat both bilateral and unilateral aphakia in the United States. Unlike spectacles, the optical quality is good, and some contact lenses can be worn 24 hours a day. The power of the lenses can be changed as the eye grows, thereby ensuring the optimal focused image on the retina. The major disadvantage is that pediatric aphakic contact lenses are relatively thick, and they are easily lost or rubbed out of the eye. It is not uncommon for parents to report losing a lens once a month. This can become an extremely expensive and time-consuming endeavor. They are also associated with potential corneal complications, including infection and ulcers (120,121,122).

Fitting pediatric contact lenses is a challenge and requires patience and skill for the clinician and caregiver. Despite the initial resistance of caregivers to contact lens maintenance and administration, most adjust quite well (123). In very young children silicone lenses are used because of their high oxygen permeability, enabling extended wear (most recommend 1 week). Fitting these lenses is often done by a trial-and-error method, and a reasonable selection must be available to accomplish a good fit. In children younger than 6 months, lens powers to 36 diopters are often necessary. These children should be fitted so that they are slightly myopic, facilitating near vision until they get old enough to use bifocals. In situations where silicone lenses are not tolerated, frequently lost, or high astigmatism exists, gas permeable lenses can also be used. However, these do require removal on a daily basis.

Epikeratophakia

This procedure was first performed in the United States in 1980 to address some of the problems of spectacles and contact lenses. The procedure involves removing a central half-thickness of the cornea and then suturing prelathed corneal donor tissue whose power has been predetermined in a fashion similar to a corneal transplant (124,125,126). Initial results were good with a high success rate. A major disadvantage of the procedure was persistent haziness, especially at the interface between the host and the graft that could take up to a year to clear. In addition, late myopia and astigmatism occurred in many eyes. At the present time the epikeratophakic donor material is no longer commercially available. There are a few centers, however, that continue to manufacture their own grafts.

Intraocular Lenses

Intraocular lenses (IOLs) have become increasingly popular as a way to rehabilitate unilateral aphakia and bilateral aphakia in children. Intraocular lenses avoid many of the problems of spectacles and contact lenses. An initial concern was the long-term safety of these lenses in the pediatric population, but as more experience is gained, this appears to be less of a problem. Buckley et al suggested that pseudophakic infants (younger than 6 months) had actually better visual acuity and less strabismus than aphakic infants being corrected with contact lens (127). Other authors found little difference in visual acuity but did report better stereopsis in pseudophakic children (128,129). There has been discrepancy as to rates of complications between the two groups (127,130).

As the age of implantation in children decreases, the selection of the appropriate intraocular lens power becomes more important. As can be seen in Table 13.11, a significant change in intraocular lens power necessary to achieve emmetropia occurs during the first 5 years of life. Younger children will undergo a larger change in axial length and refraction (131,132). If the patient is made emmetropic

at the time of implantation, a significant myopic shift can be expected into the teenage years (133,134,135,136,137,138,139,140). A review of 77 patients who received IOL implantation at our institution showed a myopic shift of approximately one-half diopter per 6 months that persisted to age 10. To compensate for this

change and minimize the necessity of lens exchange, *undercorrection at the time of implantation* has been recommended (Table 13.12) (134,135,136,137,138,139,141). The ultimate goal is to make the patient's *adul*ı refraction slightly *myopic.* The undercorrection is initially made up of some hyperopic spectacles because a bifocal is often needed for near-work anyway. As the child grows, the hyperopic refraction decreases. To the contrary, Superstein et al found a mean myopic shift of 1.5 diopters for pseudophakic patients (note median age at surgery was 7) and advocates IOL powers for an emmetropic goal immediately postoperatively (142). Immediate postoperative emmetropia can also be achieved with a piggy back lens placed during the initial surgery, which can be removed at a later date when the child becomes more myopic (143). Concern has been raised that creating unilateral hyperopic anisometropia might contribute to persistent amblyopia. A comparison between similar patients corrected with contact lenses does not support this claim.

TABLE 13.11 INTRAOCULAR LENSES POWER TO ACHIEVE EMMETROPIA

Birth	34.4
0-1 yr	28.7
1-2 yr	26.4
2-3 yr	23.0
3-4 yr	22.1
4-5 yr	20.9
5-6 yr	19.5

TABLE 13.12 OPTICAL CORRECTION OF APHAKIA WITH INTRAOCULAR LENS (141)

Age	Target Postoperative Refraction (diopters)
<2 yr	+4.00
2-4 yr	+3.00
4-6 yr	+2.00
6-8 yr	+1.00
>8 yr	Emmetropia

Note: Limit anisometropia to <3.00 diopters and adjust for fellow eye refraction.

Regardless of the refractive goal, it has been shown that the predictive value of regression and theoretical IOL formulas in pediatric IOL implantation were quite good. Andreo et al found that all four formulas (SRK-II, SRK-T, Holladay, and Hoffer Q) tested predicted mean refractive outcome within 1.4 diopters (144). Tromans also found refractive outcomes (predicted vs. actual) to be quite good except for axial lengths less than 20 and children younger than 36 months (145).

TABLE 13.13 VISUAL OUTCOMES WITH UNILATERAL INFANTILE CATARACTS CORRECTED WITH CONTACT LENSES

Author	Year	No. of Patients	Best Corrected Visual Acuity (%)		
			>20/40	20/50-20/100	<20/200
Birch & Stager (69)	1988	19	11	42	47
Drummond et al (153)	1989	13	24	38	38
Birch et al (152)	1993	14	50	36	14
Neumann et al (154)	1993	14	14	14	72
Lorenz et al (248)	1994	17	8	34	58

Last, one author has advocated the use of a multifocal IOL to decrease in dependency for near correction and improve stereopsis in children (146).

Visual Prognosis

In general, cataracts in children have a poorer visual prognosis than cataracts in adults. It is now recognized, however, that early surgery, accurate optical correction, and vigorous treatment of any amblyopia can result in excellent vision in many cases. Any anomaly of the eye reduces the likelihood of a good visual outcome.

Unilateral cataract patients, as a group, do not generally do well with over 50% achieving visual acuity of only 20/200 (Tables 13.13 and 13.14), in spite of early surgery, proper optical correction, and vigorous patching of the sound eye (1,147,148). However, recent reports have given optimism for an aggressive approach to this clinical problem. Early treatment of congenital unilateral cataract is thought to minimize unequal competition. Several authors have reported that surgery undertaken within the first 2 to 8 weeks of life will result in better visual outcomes. This speaks to the relative plasticity of the visual system (68,149). Beller et al (1981) described eight neonates with monocular congenital cataracts, all of whom achieved good or excellent Snellen acuities, seven of the eight, 20/40 or better. All had surgery under age 41 days, were kept binocularly patched until time for contact lens fitting, and began with 4 days of total occlusion of the sound eye after the contact lens was fitted (150). Others have described good visual results, but none have had the high rate of success noted in this report. Birch et al (1986) reported that of 16 children who had early surgery, early contact lens fitting, and good compliance with patching regimens, only 1 achieved a Snellen acuity of 20/25, with most between 20/50 and 20/100 (151). In another study using the same techniques, 50% of the children obtained visual acuities of 20/40 or better (152). Other authors have not been as successful, reporting visual acuities of 20/40 or better in only 14% to 24% of patients (153,154). Suggested occlusion

therapy regimens have also varied from almost full-time occlusion to a mere 1 hour per day to preserve best visual acuity without sacrificing the stereoacuity. Jeffrey et al, as well as Brown et al, found that a reduced patching protocol showed better sensory outcomes with less strabismus without reducing visual acuity (155,156). Factors contributing to poor vision and stereopsis include age at surgery, age at onset of cataract, type of cataract, optical correction difficulties, amblyopia, treatment compliance, and associated ocular anomalies (157). Nystagmus and microphthalmos are also poor prognostic signs (158).

TABLE 13.14 VISUAL OUTCOMES WITH UNILATERAL INFANTILE CATARACTS CORRECTED WITH INTRAOCULAR LENSES

Author	Year	No. of Patients	Best Corrected Visual Acuity (%)		
			>20/40	20/50-20/100	<20/200
Burke et al (249)	1989	4	0	25	75
Dahan & Salmenson (250)	1990	13	8	23	69
Cheng et al (251)	1991b	10	10	0	90
Markham et al (252)	1992	7	0	86	14

Bilateral cataract patients do generally better than unilateral cataract patients, but there is still a significant percentage of those who have persistent visual loss even after treatment (Table 13.15) (75).

Although the presence of preoperative nystagmus and strabismus are usually thought of as poor prognostic signs, Rabiah et al found that 46% of patients with bilateral cataract and nystagmus obtained greater than 20/60 visual acuity (159). Prompt removal and rapid optical rehabilitation are essential to maximize vision potential in this group. As with unilateral cataracts, associated ocular anomalies and late aphakic glaucoma contribute to the decreased visual outcome (1,148).

DISLOCATED LENSES IN CHILDREN

When the lens is not in its normal anatomical position, it is said to be dislocated, subluxed, subluxated, luxed, luxated, or ectopic. Subluxed, subluxated, or ectopic

lenses are displaced but remain attached to the ciliary body. Luxed or luxated lenses are completely detached from the ciliary body and are either loose in the posterior chamber or can present in the anterior chamber. Subluxation of the lens may be mild and recognizable only by a slight displacement of the lens and iridodonesis to severe the free ends of the lens barely seen at the papillary margin. A dislocated lens is most often associated with multisystem disease or an inborn error of metabolism. It can occur with trauma, although this is not common and usually requires a significant force to the eye. The incidence of dislocated lenses is not known.

TABLE 13.15 VISUAL OUTCOME WITH BILATERAL INFANTILE CATARACTS

				Best Corrected Visual Acuity (%)		
Lens Status	**Author**	**Year**	**No. of Patients**	**>20/40**	**20/50-20/100**	**<20/200**
Aphakia	Gelbart et al (253)	1982	24	33	42	25
Aphakia	Neumann et al (154)	1993	14	78	22	0
Aphakia	Bradford et al (254)	1994	23	43	43	14
Aphakia	Lorenz et al (248)	1994	11	32	46	22
Bilateral primary IOL	Peterseim et al (75)	2000	23	88	7.5	7.5
Bilateral secondary IOL	Peterseim et al (75)	2000	7	100	0	0

IOL, intraocular lenses.

Presentation

Children with dislocated lenses present usually to the ophthalmologist with the complaint of poor vision. If the lens zonules have loosened uniformly, the lens will assume a spheric shape (spherophakia), and the thickened lens will induce myopia. If the zonular abnormality is localized to one area, astigmatism results. As the lens shifts off-center, a distorted, irregular myopic astigmatic refractive error occurs. This often cannot be fully optically corrected. In rare circumstances the lens can completely dislocate into the anterior chamber, producing a sudden painful glaucoma. A lens in the anterior chamber, in the absence of trauma, is suspicious of homocystinuria.

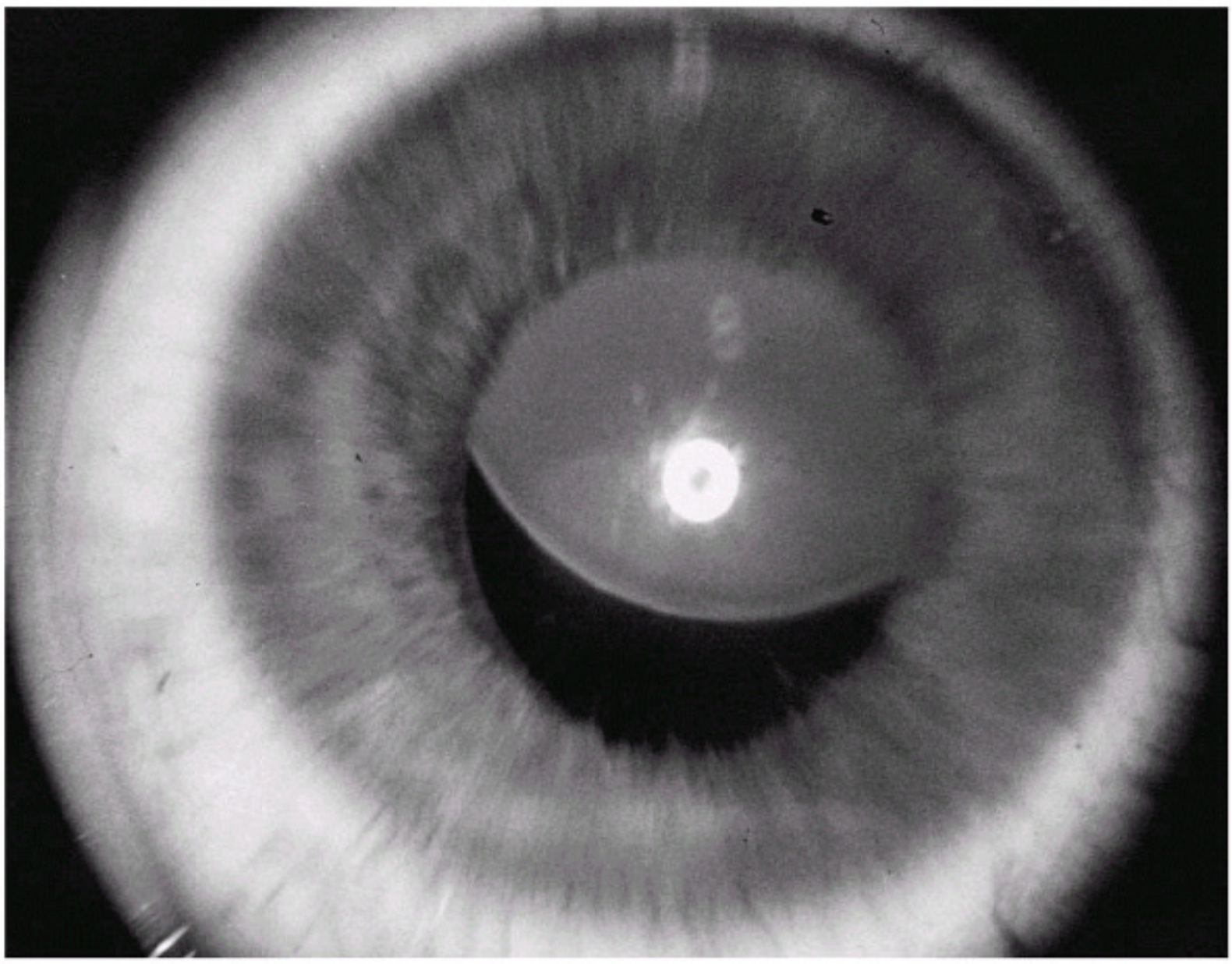

Figure 13.18 Slit-lamp photograph of superiorly dislocated lens. The lens edge is in the pupillary aperture, resulting in severe myopic astigmatism.

Diagnosis

In older children, the diagnosis of a dislocated lens can be made with a slit lamp (Fig. 13.18). In younger children, external examination with a penlight may show iridodonesis. After dilation, the edge of the lens can often be seen either directly or on retroillumination. Streak retinoscopy also reveals the marked myopic astigmatism that is present in these situations.

Etiology

Dislocated lenses occur as a result of trauma, ocular abnormalities, or as part of a systemic disease (Table 13.16). *Blunt trauma* to the head, orbit, or eye can result in dislocation of the lens. This is seen most commonly when the eye is hit directly with a high-energy projectile, such as a BB, golf ball, or baseball. It is often accompanied by iris trauma, sphincter tears, anterior chamber angle recession, vitreous hemorrhage, and choroidal rupture. Occasionally, the lens can be completely dislocated into the vitreous. Lens dislocation after minor trauma should raise the suspicion of an underlying systemic condition or previous ocular infection (e.g., syphilis).

TABLE 13.16 SUBLUXED LENSES: ASSOCIATED CONDITIONS

Systemic Condition	Ocular Condition
Marfan's syndrome	Ectopia lentis et pupillae
Metabolic disorders	Aniridia
Homocystinuria	Iris coloboma
Sulfite oxidase deficiency	Trauma
Hyperlysinemia (?)	Hereditary ectopia lentis autosomal dominant)
Weill-Marchesani syndrome	
Ehlers-Danlos syndrome	Glaucoma (congenital)

Ocular abnormalities that can have an associated lens displacement are listed in Table 13.16. All of these conditions have significant abnormalities with either the anterior chamber angle or iris. In aniridia the lens dislocation is manifested initially by the flattening of the equator for a portion of the lens' circumference. As this progresses, the lens shifts away from the direction of the weak zonules. It rarely progresses to the point that the patient functions optically as an aphakic.

Infantile glaucoma can progress to the point that the ciliary body ring can become large. This may result in the stretching of the zonules to the extent that the lens dislocates to some degree. The additional myopia that is induced by this subluxation may further increase the refractive error created by the elongated eye. Lens subluxation should be suspected in glaucoma patients who experience a sudden 3 or 4 diopter-myopic shift, especially when intraocular pressure is under good control. The lens rarely dislocates out of the pupil.

Iris coloboma is a defect in the closure of the embryonic fissure. This often results in a defect in the iris, usually inferonasally (Fig. 13.19). It can also be associated with retinal and optic nerve colobomas. Depending on the extent of the abnormality, the zonular structure adjacent to the area of iris defect can also be affected. This most often results in a simple flattening of the lens at that location without any dislocation (Fig. 13.20). In significant colobomatous defects, lens dislocation superotemporally can occur. Unlike in other disorders, these lenses do not usually get progressively worse.

Ectopia lentis et pupillae, or ectopia of the lens and ectopia of the pupil, is a rare autosomal recessive condition. It is manifested by bilateral displacement of the pupil, usually temporally, with lens dislocation in the other direction (Fig. 13.21). Patients have microspherophakia, miosis, and poor pupillary dilation with mydriatics (160). There is an increased transillumination of the iris periphery indicating a defect in the posterior pigmented layer of the iris. This is felt to be a defect in neuroectodermal tissue development because the pigmented layer of the iris, zonules, and iris dilator are all involved. Some family members may have only subluxation without the pupillary displacement. The condition appears to be nonprogressive.

Figure 13.19 Note inferior iris coloboma, right eye. This is often associated with lens, retina, and optic nerve defects.

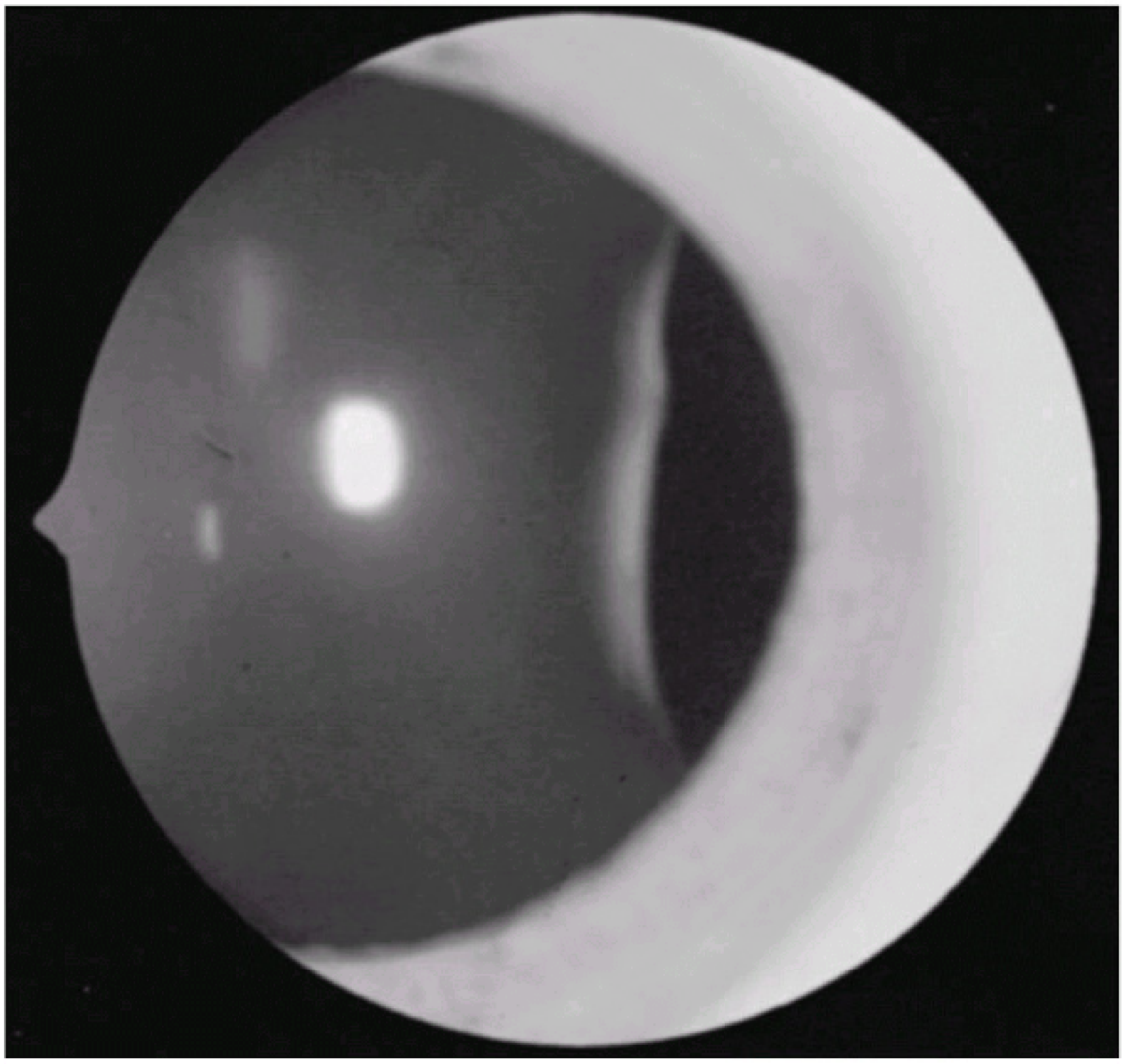

Figure 13.20 Coloboma lentis: actually not a coloboma but a localized zonular defect causing flattening of the lens equator.

Hereditary Lens Subluxation

The tendency toward subluxation of the lenses can be inherited as either an autosomal dominant or recessive trait. The dominant condition usually has full penetrance and similar expressivity. The lenses are mostly displaced upward. The subluxation is bilateral, symmetrical, and congenital. There is a rare dominant form in which the subluxation occurs late in life between ages 30 and 60. These lenses are usually dislocated inferiorly. This may be due to a progressive deterioration of the zonular support (161). An autosomal recessive form of lens subluxation has been described. It is similar to the dominant form in its appearance. This particular inheritance pattern has not been well documented.

Marfan's Syndrome

Marfan's syndrome is by far the most common systemic disease associated with dislocated lenses. It consists of abnormalities of the cardiovascular, musculoskeletal, and ocular systems. Marfan's syndrome is inherited in an autosomal dominant fashion; however, in about 15% of patients there is no family history.

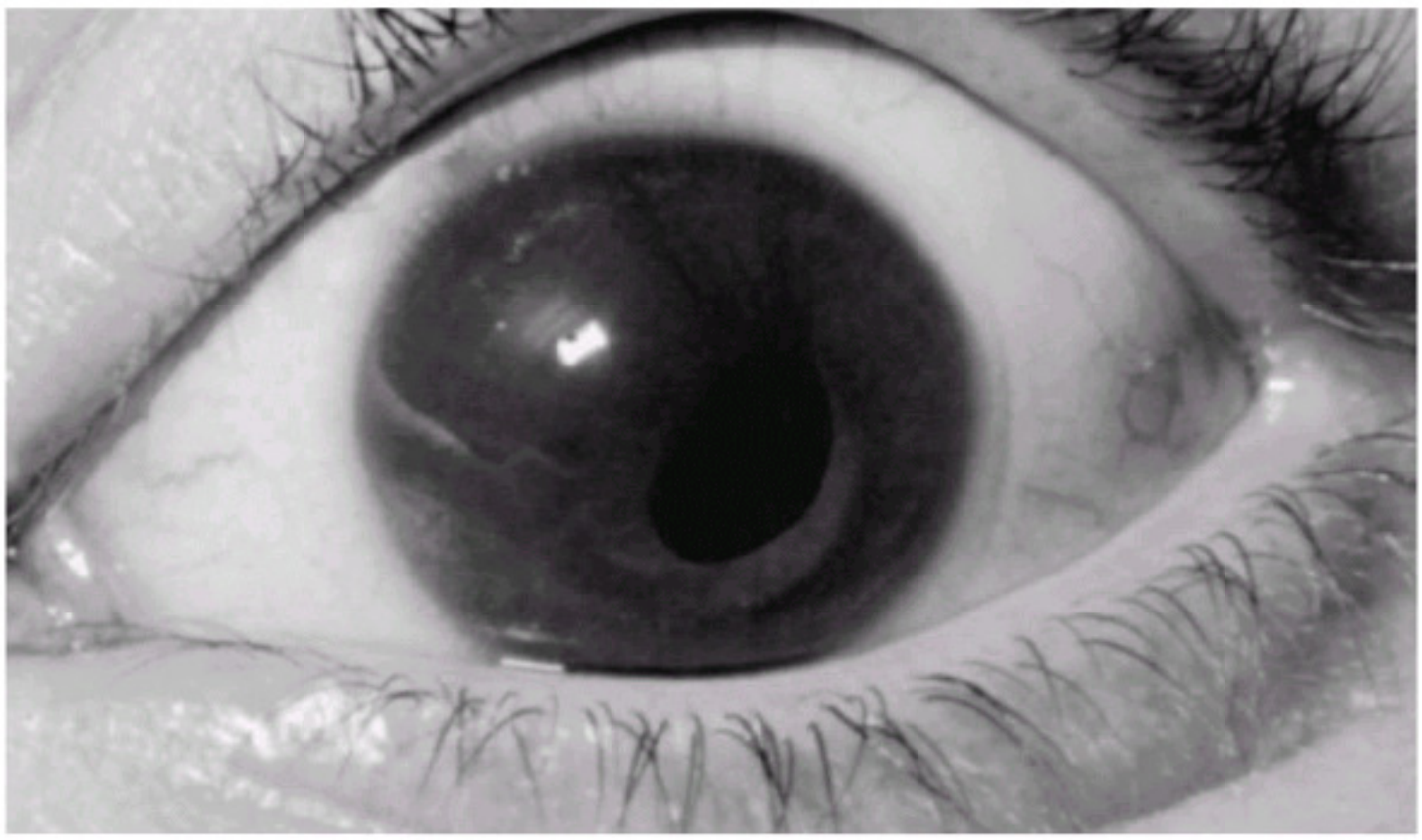

Figure 13.21 *Ectopia lentis et pupillae*. Note the temporal dislocation of the pupil. The lens is dislocated in the opposite direction, out of the pupil in this case.

Cardiovascular abnormalities are the source of significant mortality in this syndrome. This is commonly manifested as an enlargement of the aortic root, which leads to dilation of the descending aorta. This is best detected by echocardiography. The patient subsequently develops aortic insufficiency and aneurysms. The life expectancy of patients with Marfan's syndrome is about half that of the normal population. Therefore, it is important that all patients in whom this diagnosis is suspected be examined systemically.

Musculoskeletal system abnormalities are common in nearly all patients with Marfan's syndrome. The most characteristic is dolichostenomelia (long limbs compared with the length of the trunk). This is often associated with arachnodactyly with elongated fingers and toes. In addition, the face, chin, and nose may be longer than normal, and the chest often has a sunken sternum (*pectus excavatum*) or bulges outward (*pectus carinatum*). Kyphoscoliosis may be prominent, giving the patient a somewhat bent figure. Joint laxity is a useful clinical sign and is suggested if, when the patient flexes the thumb into the fist, the tip of the thumb protrudes beyond the fifth finger or if, when grasping the opposite wrist, the thumb and fingers overlap (Fig. 13.22A, B). An inherited weakness of other organs is also common, as is inguinal hernia. Weak facial muscles and loss of subcutaneous fat give the patient's face a characteristic thin appearance. In some there is a hypoplastic molar or cheek bone augmenting this appearance.

Ocular findings occur frequently with over 80% of patients manifesting some form of anterior segment abnormality. Lens dislocation is common, and about 75% of the time the lens is dislocated in an upward direction. Typically, the zonules that are visible are intact or unbroken in contradistinction to the broken zonules seen in homocystinuria. There may be areas visible through the pupil when the zonules are few or absent. Examination of the iris may reveal transillumination defects, which are more marked near the iris base. The iris characteristically has a homogeneous appearance with few to no crypts and furrows (162). The pupil is small and/or dilates poorly. A hypoplastic dilator muscle is seen histologically. The axial length is increased, and patients are usually myopic. Retinal detachments often occur spontaneously in the second through the third decades.

Homocystinuria

Homocystinuria (homocystine in the urine) is a rare autosomal recessive condition caused by an abnormality in the enzyme cystathionine beta-synthase. It occurs in approximately 1 in every 100,000 newborns. The deficiency of cystathionine beta-synthase limits the conversion of homocystine to cystathionine with the accumulation of homocystine in the plasma and its excretion in the urine. Normally, no detectable homocystine is found in either plasma or urine. As a result of the abnormally high plasma homocystine levels, an elevated plasma level of methionine occurs. The renal reabsorption of methionine is so efficient

in contrast to homocystine that even with elevated plasma levels, the urine may be normal.

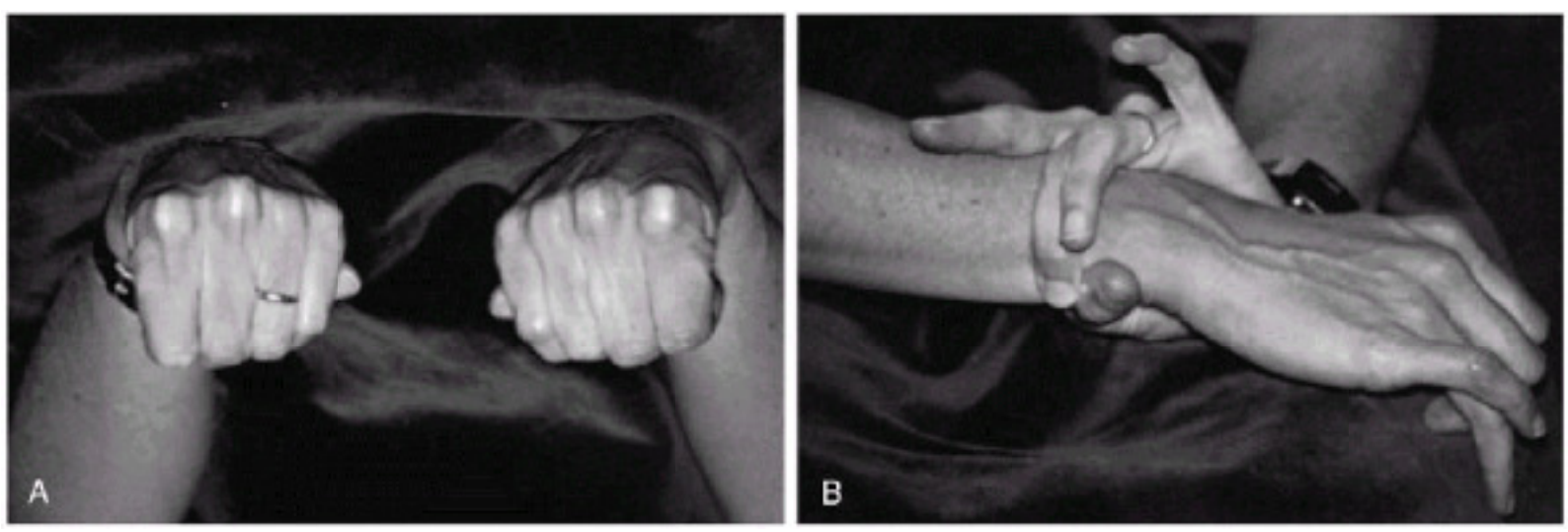

Figure 13.22 A: A positive thumb sign in a patient with Marfan's syndrome. Note the thumbs protruding beyond the clenched fist. **B:** Note the overlapping thumb and middle finger. This is a function of the small, thin wrist, and long fingers. This and the thumb sign are strongly suggestive but not diagnostic of Marfan's syndrome.

The clinical manifestations of homocystinuria vary markedly from severely affected to nearly normal and affect the eye, skeletal system, central nervous system, and vascular system (Table 13.17). The clinical characteristics develop after birth and are progressive.

Ocular findings consist mainly of dislocated lenses. This occurs usually between ages 3 and 10 years and is generally downward in location. The lens may dislocate into the anterior chamber, a finding suggestive of homocystinuria (Fig. 13.23). The zonules are typically broken, and a curled portion of the zonule may be visible at the lens equator (163). Because of the zonular abnormality, accommodation is poor. The dislocation is usually symmetrical. Myopia, retinal detachment, and secondary glaucoma can also occur.

The *skeletal abnormality* most commonly found is osteoporosis. It is seen mainly in the spine and long bones. Most patients are tall and thin with dolichostenomelia. This appearance may resemble that of Marfan's syndrome. Central nervous system abnormalities occur in approximately 50% of the individuals. Mental retardation is the most common finding and may present as developmental delay in the first year or two of life. A seizure disorder is common, occurring in approximately 50% of patients.

TABLE 13.17 CLINICAL MANIFESTATIONS OF HOMOCYSTINURIA

	Very Frequent	Less Frequent
Ocular	Dislocated lens	Glaucoma
	Broken zonules	Cataract
		Optical atrophy
		Retinal detachment
		CRA occlusion
Skeletal	Osteoporosis	Pectus carinatum or excavatum
	Dolichostenomelia	
	Biconcave vertebrae	
	Scoliosis	
CNS	Retardation	Seizures
Vascular	Thromboemboli	
	Malar flush	
	Livedo reticularis	

CNS, central nervous system; CRA, central retinal artery.

Vascular complications are secondary to thromboembolic disease, which affects large or medium-sized arteries and veins, and can occur in any part of the body. Anesthesia holds a higher risk for patients with homocystinuria because of this thromboembolic phenomenon. Hypertension, cardiac murmurs, and cardiomegaly are seen frequently.

The diagnosis of homocystinuria can be made using either the urinary sodium nitroprusside test that detects disulfides, including homocystine, in the urine. More sophisticated quantitative tests of amino acids in the plasma are needed to determine the exact etiology.

The medical management of homocystinuria is directed

toward normalizing the biochemical abnormality. A diet low in methionine is provided. Large doses of pyridoxine (vitamin B_6), a cofactor of cystathionine beta-synthase, stabilize the biochemical abnormalities in about 40% of patients.

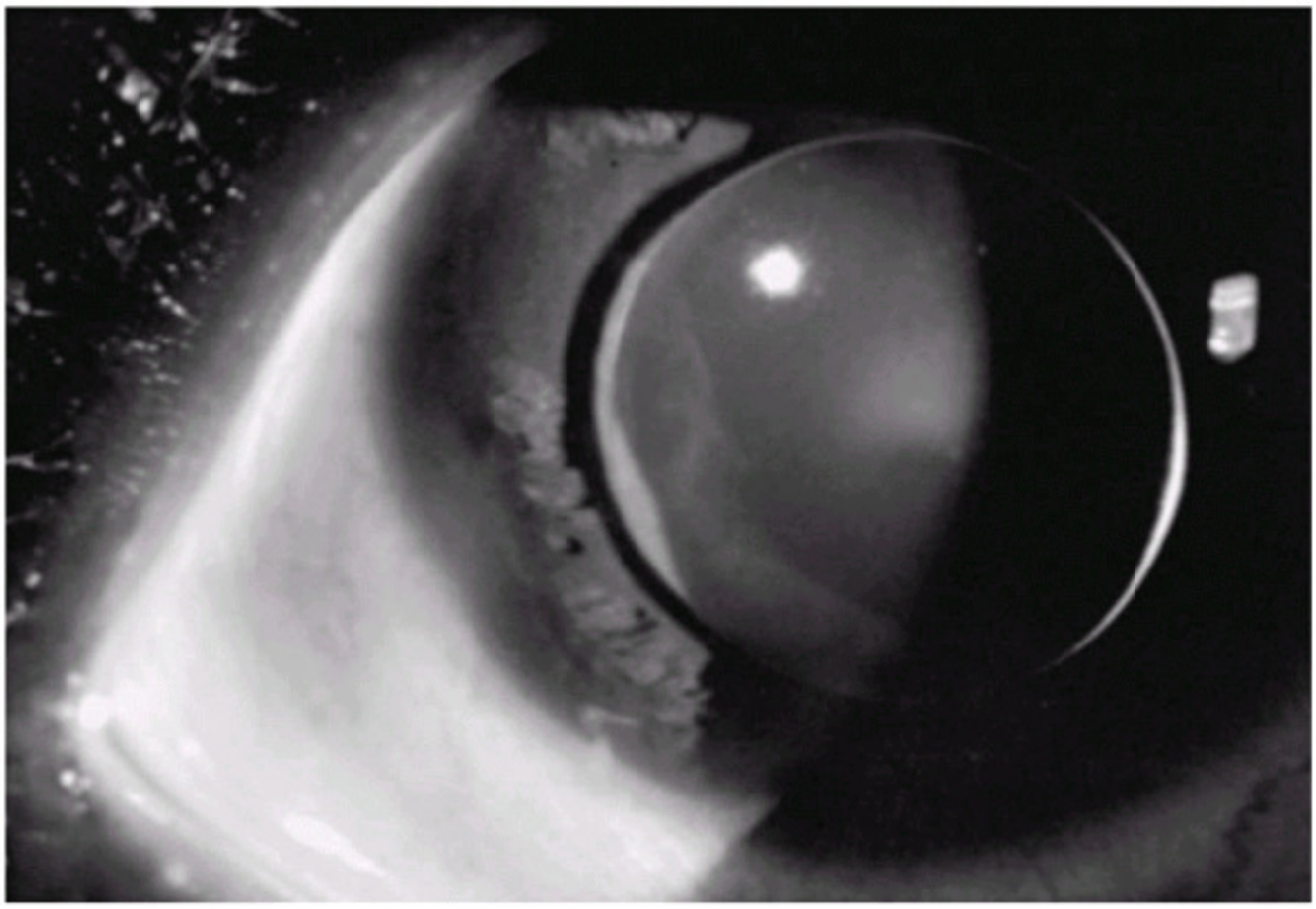

Figure 13.23 Lens dislocated into the anterior chamber, suggestive of homocystinuria.

Weill-Marchesani (Spherophakia Brachymorphia) Syndrome

Weill-Marchesani syndrome is a rare cause of dislocated lenses that can be thought of as clinically opposite to Marfan's syndrome. It is characterized by short stature and short limbs (brachymorphia). The dislocated lens is typically not eccentrically displaced but appears smaller and more nearly round (spherophakia). This results in significant myopia. With time the lens dislocates anteriorly and pupillary block glaucoma occurs in over 80% of cases (164). Because of this, prophylactic laser peripheral iridectomy is recommended in patients with this syndrome. Both sexes are equally affected, and it is inherited as both an autosomal dominant and recessive trait (165).

Sulfite Oxidase Deficiency

Sulfite oxidase deficiency is a very rare hereditary disorder of sulfur metabolism that is manifested by severe neurological disorders and ectopia lentis (166). The enzyme deficiency interferes with the conversion of sulfite to sulfate, with the resulting increased urinary secretion of sulfite. The diagnosis can be confirmed by the absence of sulfite oxidase activity in skin fibroblasts. Neurological abnormalities include infantile hemiplegia, choreoathetosis, and seizures. Irreversible brain damage and death occur usually by age 5.

Hyperlysinemia

Hyperlysinemia is a result of a deficiency of lysine alphaketoglutarate reductase and has been found in mentally retarded patients, some of whom have dislocated lenses. The same biochemical abnormality and enzyme deficiency has been found in normal individuals identified through newborn screening. Therefore, the association between hyperlysinemia and dislocated lenses is not clearly documented (167).

Treatment of Dislocated Lenses

Optical correction of the refractive error caused by dislocated lenses is often difficult. Depending on the extent of dislocation, the patient may see better with a myopic astigmatic correction or aphakic correction. In patients with very mild subluxation, the lens tends to increase in its anteroposterior diameter, and the patient may be myopic only. This lenticular myopia is usually easily treated with glasses, and the patient's visual function is good. A more moderate amount of dislocation presents two problems. First, the patient is now looking through the peripheral part of the lens, which is optically less pure, and the edge of the lens starts to become a factor (Fig. 13.18). Refractions through the peripheral part of the lens usually have a significant amount of astigmatism and determining the amount and axis of the astigmatism is often difficult, because the retinoscopic reflections can be of poor quality. The patient also experiences some visual blurring even with the “best corrected” refraction in place. The further off-center the lens moves, the larger the refractive error becomes. Eventually, the lens is so decentered that the edge is now in the pupillary aperture. At this point, a decision must be made as to whether or not the patient should try to use the lens or resort to “looking around the lens” to see. Often the aphakic correction is superior to the irregular myopic astigmatism from the edge of the lens. Refractions predilation and postdilation are often helpful in deciding which is the best choice. Occasionally, better vision is obtained with the aphakic correction, but the undilated pupil obstructs the view. Chronic dilation can be used under these circumstances. Pupilloplasty or laser applications to the iris stroma can increase the size of the pupil. If satisfactory visual function cannot be obtained with the lens in place, surgical removal should be considered.

The *surgical removal* of subluxed lenses in children has traditionally been discouraged because of concerns about poor surgical results and unacceptable complication rates (162). Recent reports, however, have shown that with the use of vitrectomy instruments these lenses can be removed safely with good visual results (168). The indications for lens removal are similar to those for cataract surgery in childhood. If the visual acuity is poor enough to prevent the child from functioning at the level necessary for normal activity and education, then removal should be entertained. In most instances, this requires bilateral removal to

prevent anisometropic amblyopia from developing. This is especially important in young children.

Subluxed lenses can be removed from either the anterior segment through a limbal incision or through the pars plana. Either approach is effective, and the selection depends on the comfort of the surgeon and familiarity with the technique. When the lenses are removed by the limbal approach, a two-port technique provides the greatest versatility. Using an infusion cannula also allows a smaller opening to be used. Attempts should be made to remove the lens in its entirety, leaving only that material that could not be safely removed because of potential injury to the iris or ciliary body. A limited anterior vitrectomy can also be performed at the same time. This technique significantly diminishes related complications of vitreous loss, secondary membrane formation, pupillary block, and retinal detachment (168). These same good results can be obtained through a pars plana approach.

Postoperative visual rehabilitation can be performed using either contact lenses or glasses. The use of intraocular lenses in this group of patients has not been well described. These lenses would have to be sutured into the sulcus, thereby increasing the risks of long-term complications, including retinal detachment. Patients with homocystinuria present a special risk due to the potential thromboembolic phenomenon that can occur with general anesthesia. Removing the lenses of both eyes at the same time may be advisable because the risk of anesthetic complications is much higher

than the risk of potential intraocular complications, such as endophthalmitis. Postoperative visual acuities are good in these patients with over 90% achieving visual acuity of 20/40 or better (168).

REFERENCES

1. Lambert SR, Drack AV. Infantile cataracts. *Surv Ophthalmol* 1996;40:427-458.

2. Zwaan J. Fine structure of the developing lens. *Int Ophthalmol Clin* 1975;15:39-52.

3. Ozanics V, Jakobiec FA. Prenatal development of the eye and its adnexa. In: Tasman W, ed. *Biomedical foundations of ophthalmology*. Philadelphia: JB Lippincott Co, 1993:1-86.

4. Wright KW, Kohn T, Matsumoto E. Lens abnormalities. In: Wright KWE, ed. *Pediatric Ophthalmology*. St. Louis: Mosby, 1995:367-389.

5. Jain IS, Pillai P, Gangwar DN, et al. Congenital cataract: etiology and morphology. *J Pediatr Ophthalmol Strabismus* 1983;20:238.

6. Parks MM. Visual results in aphakic children. *Am J Ophthalmol* 1982;94:441-449.

7. Parks MM, Johnson DA, Reed GW. Long-term visual results and complications in children with aphakia. *Ophthalmology* 1993;100:826-841.

8. Gibbs ML, Jacobs M, Wilkie AO, et al. Posterior lenticonus: clinical patterns and genetics. *J Pediatr Ophthalmol Strabismus* 1993;30:171-175.

9. Salmon JF, Wallis CE, Murray ADN. Variable expressivity of autosomal dominant microcornea with cataract. *Arch Ophthalmol* 1988;106:505-510.

10. Merin S, Crawford JS. The etiology of congenital cataracts. *Can J Ophthalmol* 1971;6:178.

11. Johnson DA, Parks MM. Cataracts in childhood: prognosis and complications. *Semin Ophthalmol* 1991;6:201-211.

12. Jaafar MS, Robb RM. Congenital anterior polar cataract: a review of 63 cases. *Ophthalmology* 1984;91:249-254.

13. Nelson LB, Calhoun JH, Simon JW. Progression of congenital anterior polar cataracts in childhood. *Arch Ophthalmol* 1985;103:1842.

14. Nelson LB, Spaeth GL, Nowinski TS. Aniridia. *Surv Ophthalmol* 1984;28:621-642.

15. Smith GT, Shun-Shin GA, Bron AJ. Spontaneous reabsorption of a rubella cataract. *Br J Ophthalmol* 1990;74:564-565.

16. Soriano JM, Funk J. Bilateral spontaneous reabsorption of a rubella cataract: a case of Hallerman-Streiff syndrome. *Win Mbl Augenheilkd* 1991;199:195-198.

17. Khalil M, Saheb N. Posterior lenticonus. *Ophthalmology* 1984;91:1429.

18. Wright KW, Christensen LE, Noguchi BA. Results of late surgery for presumed congenital cataracts. *Am J Ophthalmol* 1992;114:409-415.

19. Cheng KP, Hiles DA, Biglan AW, et al. Management of posterior lenticonus. *J Pediatr Ophthalmol Strabismus* 1991;28:143-149.

20. Karr DJ, Scott WE. Visual acuity results following treatment of persistent hyperplastic primary vitreous. *Arch Ophthalmol* 1986;104:662-667.

21. Pollard ZE. Results of treatment of persistent hyperplastic primary vitreous. *Ophthalmic Surg* 1991;22:48-52.

22. Haddad R, Font RL, Reeser E. Persistent hyperplastic primary vitreous: a clinicopathologic study of 62 cases and review of the literature. *Surv Ophthalmol* 1978;23:123-134.

23. Nettleship E, Ogilvie FM. A peculiar form of hereditary congenital cataract. *Trans Am Ophthalmol Soc U K* 1906;26:191-206.

24. Eiberg H, Lund AM, Warburg M, et al. Assignment of congenital cataract Volkmann type (CCV) to chromosome 1p36. *Hum Genet* 1995;96:33-38.

25. Lubsen NH, Renwick JH, Tsui LC, et al. A locus for human hereditary cataracts is closely linked to the gamma-crystalline gene family. *Proc Natl Acad Sci U S A* 1987;84:489-492.

26. Renwick JH, Lawler SD. Probable linkage between a congenital cataract locus and the Duffy blood group locus. *Ann Hum Genet* 1963;27:67.

27. Mackay D, Ionides A, Berry V, et al. A new locus for dominant “zonular pulverulent” cataract, on chromosome 13. *Am J Hum Genet* 1997;60:1474-1478.

28. Mackay D, Ionides A, Kibar Z, et al. Connexin 46 mutations in autosomal dominant congenital cataract. *Am J Hum Genet* 1999;64:1357-1364.

29. Heon E, Paterson AD, Fraser M, et al. A progressive autosomal recessive cataract locus maps to chromosome 9q13-q22. *Am J Hum Genet* 2001;68:772-777.

30. Bateman JB, Geyer DD, Flodman P, et al. A new beta A1-crystallin splice junction mutation in autosomal dominant cataract. *Invest Ophthalmol Vis Sci* 2000;41:3278-3285.

31. Gill D, Klose R, Munier FL, et al. Genetic heterogeneity of the Coppock-like cataract: a mutation in CRYBB2 on chromosome 22q11.2. *Invest Ophthalmol Vis Sci* 2000;41:159-165.

32. Moross T, Vaithilingam SS, Styles S, et al. Autosomal dominant anterior polar cataracts associated with a familial 2;14 translocation. *J Med Genet* 1984;21:52-53.

33. Reese PD, Tuck-Muller CM, Maumenee IH. Autosomal dominant congenital cataract associated with chromosomal translocation (t(3:4) (p26.2:p150). *Arch Ophthalmol* 1987;105:1382.

34. Yokoyama Y, Uchida M, Matsumoto S, et al. Autosomal dominant congenital cataract and microphthalmia associated with a familial t(2;16) translocation. *Hum Genet* 1992;90:177-178.

35. Lewis AL, Nussbaum RL, Stambolian D. Mapping X-linked ophthalmic diseases. IV. Provisional assignment of the locus for X-linked congenital cataracts and microcornea (the Nance-Horan syndrome) to Xp22.2-p22.3. *Ophthalmology* 1992;97:110-120.

36. Stambolian D, Lewis RA, Buetow K. Nance-Horan syndrome: localization within the region Xp21.1-Xp22.3 by linkage analysis. *Am J Hum Genet* 1990;47:13-19.

37. Zhu D, Alcorn DM, Antonarakis SE, et al. Assignment of Nance-Horan syndrome to the distal short arm of the X chromosome. *Hum Genet* 1990;86:54-58.

38. Burke JP, O'Keefe M, Bowell R, et al. Ophthalmic finding in classical galactosemia: a screened population. *J Pediatr Ophthalmol Strabismus* 1989;26:165-168.

39. Stambolian D, Ai Y, Sidjanin D. Cloning of the galactokinase cDNA and identification of mutations in two families with cataracts. *Nat Genet* 1995;10:307-312.

40. Franceschetti AT. Fabry disease: ocular manifestations. *Birth Defects* 1976;12:195-208.

41. Sher NA, Letson RD, Desnick RJ. The ocular manifestations in Fabry's disease. *Arch Ophthalmol* 1979;97:671-676.

42. Ehrlich RM, Kirsh S, Deneman D. Cataracts in children with diabetes mellitus. *Diabetes Care* 1987;10:798-799.

43. Cenedella RJ. Cholesterol and cataracts. *Surv Ophthalmol* 1996;40:320-327.

44. Gass JDI. The syndrome of keratoconjunctivitis, superficial moniliasis, idiopathic hypoparathyroidism and Addison's disease. *Am J Ophthalmol* 1962;54:660.

45. Robb RM. Cataracts acquired following varicella infection. *Arch Ophthalmol* 1972;87:352.

46. Cotlier E. Congenital varicella cataract. *Am J Ophthalmol* 1978;86:627-629.

47. Lambert SR, Fernandes A, Drews-Botsch C, et al. Multifocal versus monofocal correction of neonatal monocular aphakia. *J Pediatr Ophthalmol Strabismus* 1994;30:195-201.

48. Scheie HG, Schaffer DB, Plotkin SA. Congenital rubella cataracts: surgical results and virus recovery from intraocular tissue. *Arch Ophthalmol*

1967;77:440-444.

49. Zimmerman LE. Histopathologic basis for ocular manifestations of congenital rubella syndrome. *Am J Ophthalmol* 1968;65:837-862.

50. Clinch TE, Duker JS, Eagle RC Jr, et al. Infantile endogenous candida endophthalmitis presenting as a cataract. *Surv Ophthalmol* 1989;34:107-112.

51. Tripathi RC, Cibis GW, Harris DJ. Lowe's syndrome. *Birth Defects* 1982;18:629-644.

52. Brown N, Gardner RJM. Lowe syndrome: identification of the carrier state. *Birth Defects* 1976;12:579-591.

53. Johnston SS, Nevin NC. Ocular manifestations in patients and female relatives of families with oculocerebrorenal syndrome of Lowe. *Birth Defects* 1976;12:569-577.

54. Happle R. X-linked dominant chondrodysplasia punctata: review of the literature and report of a case. *Hum Genet* 1979;53:65.

55. Spranger J, Opitz JM, Bidder U. Heterogeneity of chondrodysplasia punctata. *Humangenetik* 1971;11:190.

56. Jones KL. *Smith's recognizable patterns of human malformation*. Philadelphia: WB Saunders Co, 1976:340.

57. Reardon W, MacMillan JC, Myring J. Cataract and myotonic dystrophy: the role for molecular diagnosis. *Br J Ophthalmol* 1993;77:7579-7583.

58. Ragge N, Baser MB, Klein J. Ocular abnormalities in neurofibromatosis 2. *Am J Ophthalmol* 1995;120:634-641.

59. Folz SJ, Trobe JD. The peroxisome and the eye. *Surv Ophthalmol* 1991;35:353-368.

60. Hittner HM, Kretzer FL, Mehta RS. Zellweger syndrome. *Arch Ophthalmol* 1981;99:1977-1982.

61. Christiansen SP, Bradford JD. Cataract in infants treated with argon laser photocoagulation for threshold retinopathy of prematurity. *Am J Ophthalmol* 1995;119:175-180.

62. Dunn JP, Jabs DA, Wingard J, et al. Bone marrow transplantation and cataract development. *Arch Ophthalmol* 1993;11:1367-1373.

63. Henk JM, Whitelocke RA, Warrington AP, et al. Radiation dose to the lens and cataract formation. *Int J Radiat Oncol Biol Phys* 1993;25:815-820.

64. Kushner BJ. Visual results after surgery for monocular juvenile cataracts of undetermined onset. *Am J Ophthalmol* 1986;102:468-472.

65. Crouch ERJ, Parks MM. Management of posterior lenticonus complicated by unilateral cataract. *Am J Ophthalmol* 1978;85:503.

66. Rogers GL, Tishler CL, Tsou BH. Visual acuities in infants with congenital cataracts operated on prior to 6 months of age. *Arch Ophthalmol* 1981;99:999.

67. Wright K, Matsumoto E, Edelmann P. Binocular fusion and stereopsis associated with early surgery for monocular congenital cataracts. *Arch Ophthalmol* 1992;110:1607-1609.

68. Birch EE, Stager DR. The critical period for surgical treatment of dense congenital unilateral cataract. *Invest Ophthalmol Vis Sci* 1996;37:1532-1538.

69. Birch EE, Stager DR. Prevalence of good visual acuity following surgery for congenital unilateral cataract. *Arch Ophthalmol* 1988;106:40-42.

70. von Noorden GK, Crawford MLJ. The effects of total unilateral occlusion vs. lid suture on the visual system of infant monkeys. *Invest Ophthalmol Vis Sci* 1981;21:142.

71. Wiesel TN, Hubel DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J Neurophysiol* 1963;26:1003-1017.

72. Cordes FC. Linear extraction in congenital cataract surgery. *Am J Ophthalmol* 1961;52:355.

73. Hutcheson K, Drack AV, Ellish NJ, et al. Anterior hyaloid face opacification after pediatric Nd:YAG laser capsulotomy. *J AAPOS* 1999;3:303-307.

74. Good WV, Hing S, Irvine AR, et al. Postoperative endophthalmitis in children following cataract surgery. *J Pediatr Ophthalmol Strabismus* 1990;27:283-285.

75. Peterseim MW, Wilson ME. Bilateral intraocular lens implantation in the pediatric population. *Ophthalmology* 2000;107(7):1261-1266.

76. Zwaan J. Simultaneous surgery for bilateral pediatric cataracts. *Ophthalmic Surg Lasers* 1996;27:15-20.

77. O'Keefe M, Mulvihill A, Yeoh PL. Visual outcome and complications of bilateral intraocular lens implantation in children. *J Cataract Refract Surg* 2000;26:1758-1764.

78. Totan Y, Bayramlar H, Cekic O, et al. Bilateral cataract surgery in adult and pediatric patients in a single session. *J Cataract Refract Surg* 2000;26:1008-1011.

79. Guo S, Nelson LB, Calhoun J, et al. Simultaneous surgery for bilateral congenital cataracts. *J Pediatr Ophthalmol Strabismus* 1990;27:23-25.

80. Buckley EG, Klombers LA, Seaber JH, et al. Management of the posterior capsule during pediatric intraocular lens implantation. *Am J Ophthalmol* 1993;115:722-728.

81. Gimbel HV, Ferensowicz M, Raanan M, et al. Implantation in children. *J Pediatr Ophthalmol Strabismus* 1993;30:69-79.

82. Gupta AK, Grover AK, Gurha N. Traumatic cataract surgery with intraocular lens implantation in children. *J Pediatr Ophthalmol Strabismus* 1992;29:73-77.

83. Wilson ME, Bluestein EC, Wang XH. Current trends in the use of intraocular lenses in children. *J Cataract Refract Surg* 1994;20:579-583.

84. Wilson ME. Intraocular lens implantation: has it become the standard of care for children? *Ophthalmology* 1996;103:1719-1720.

85. Wilson M, Saunders RA, Roberts EL, et al. Mechanized anterior capsulotomy as an alternative to manual capsulorhexis in children undergoing intraocular lens implantation. *J Pediatr Ophthalmol Strabismus* 1996;33(4):237-240.

86. Saini JS, Jain AK, Sukhija J, et al. Anterior and posterior capsulorhexis in pediatric cataract surgery with and without tryptan blue dye. *J Cataract Refract Surg* 2003;29:1733-1737.

87. Guo S, Caputo A, Wagner R, et al. Enhanced visualization of capsulorhexis with indocyanine green staining in pediatric white cataracts. *J Pediatr Ophthalmol Strabismus* 2003;40:268-271.

88. Kiel AW, Butler T, Gregson R. A novel use for tryptan blue to minimize epithelial cell proliferation in pediatric cataract surgery. *J Pediatr Ophthalmol Strabismus* 2003;40:96-97.

89. Trivedi RH, Wilson ME. Single-piece acrylic intraocular lens implantation in children. *J Cataract Refract Surg* 2003;29:1738-1743.

90. Mullner-Eidenbock A, Amon M, Moser E, et al. Morphological and functional results of Acrysof intraocular lens implantation in children: prospective randomized study of age-related surgical management. *J Cataract Refract Surg* 2003;29:285-293.

91. Kuchle M, Lausen B, Gusek-Schneider GC. Results and complications of hydrophobic acrylic vs PMMA posterior chamber lenses in children under 17 years of age. *Graefes Arch Clin Exp Ophthalmol* 2003;241:637-641.

92. Wilson ME, Elliott L, Johnson B, et al. AcrySof acrylic intraocular lens implantation in children: clinical indications of bioavailability. *J AAPOS* 2001;5:377-380.

93. BenEzra D, Cohen E. Cataract surgery in children with chronic uveitis. *Ophthalmology* 2000;107:1255-1260.

94. Basti S, Aasuri MK, Reddy MK, et al. Heparin-surface-modified intraocular lenses in pediatric cataract surgery: prospective randomized study. *J Cataract Refract Surg* 1999;25:782-787.

95. Lundvall A, Zetterstrom C. Cataract extraction and intraocular lens implantation in children with uveitis. *Br J Ophthalmol* 2000;84:791-793.

96. Comer RM, Abdulla N, O'Keefe M. Radiofrequency daithermy capsulorhexis of the anterior and posterior capsules in pediatric cataract surgery: preliminary results. *J Cataract Refract Surg* 1997;23:641-644.

97. Tassingnon MJ, De Groot V, Vrensen GF. Bag-in-the-lens implantation of intraocular lenses. *J Cataract Refract Surg* 2002;28:1182-1188.

98. Gimbel HV. Posterior continuous curvilinear capsulorhexis and optic capture of the intraocular lens to prevent secondary opacification in pediatric cataract surgery. *J Cataract Refract Surg* 1997;23:652-656.

99. Argento C, Badoza D, Ugrin C. Optic capture of the AcrySof intraocular lens in pediatric cataract surgery. *J Cataract Refract Surg* 2001;27:1638-1642.

100. Capone A, Drack AV. Transient lens changes after diode laser retinal photoablation for retinopathy of prematurity. *Am J Ophthalmol* 1994;118:533-535.

101. Mitra S, Ganesh A. Pars plana capsulovitrectomy for posterior capsular opacification in children. *Ophthalmic Surg Lasers Imaging* 2003;34:327-331.

102. DeVaro JM, Buckley EG, Awner S, et al. Secondary posterior chamber intraocular lens implantation in pediatric patients. *Am J Ophthalmol* 1997;123:24-30.

103. Biglan AW, Cheng KP, Davis JS, et al. Results following secondary intraocular lens implantation in children. *Trans Am Acad Ophthalmol Otolaryngol* 1996;94:353-373.

104. Wilson ME, Englert JA, Greenwald MJ. In-the-bag secondary intraocular lens implantation in children. *J AAPOS* 1999;3:350-355.

105. Buckley E. Scleral fixated (sutured) posterior chamber intraocular lens implantation in children. *J AAPOS* 1999;3:289-294.

106. Ozmen AT, Dogru M, Erturk H, et al. Transsclerally fixated intraocular lenses in children. *Ophthalmic Surg Lasers* 2002;33:394-399.

107. Mittelviefhaus H, Mittelviefhaus K, Gerling J. Transscleral suture fixation of posterior chamber intraocular lenses in children under 3 years. *Graefes Arch Clin Exp Ophthalmol* 2000;238:143-148.

108. Plager DA, Yang S, Neely D, et al. Complications in the first year following cataract surgery with and without IOL in infants and older children. *J AAPOS* 2002;6:9-14.

109. Toyofuku H, Hirose T, Schepens CL. Retinal detachment following congenital cataract surgery. *Arch Ophthalmol* 1980;98:669-675.

110. Lam L, Lowder CY, Baerveldt G, et al. Surgical management of cataracts in children with juvenile rheumatoid arthritis-associated uveitis. *Am J Ophthalmol* 2003;135:772-778.

111. Wheeler DT, Stager DR, Weakley DRJ. Endophthalmitis following pediatric intraocular surgery for congenital cataracts and congenital glaucoma. *J Pediatr Ophthalmol Strabismus* 1992;29:139-141.

112. Magnusson G, Abrahamsson M, Sjostrand J. Glaucoma following congenital cataract surgery: an 18-year longitudinal follow-up. *Acta Ophthalmol Scand* 2000;78:65-70.

113. Rabiah PK. Frequency and predictors of glaucoma after pediatric cataract surgery. *Am J Ophthalmol* 2004;137:30-37.

114. Simon JW, Mehta N, Simmons ST. Glaucoma after pediatric lensectomy/vitrectomy. *Ophthalmology* 1991;98:670-674.

115. Asrani S, Freedman S, Hasselblad V, et al. Does primary intraocular lens implantation prevent “aphakic” glaucoma in children? *J AAPOS* 2000;4:33-39.

116. Hosal BM, Biglan AW. Risk factors for secondary membrane formation after removal of pediatric cataract. *J Cataract Refract Surg* 2002;28:1898.

117. Rao SK, Ravishankar K, Sitalakshmi G, et al. Cystoid macular edema after pediatric intraocular lens implantation: fluorescein angiography results and literature review. *J Cataract Refract Surg* 2001;27:432-436.

118. Votruba M, Lumb RJ, Markham RH. Corneal endothelial cell count in children after surgery for congenital cataracts. *Invest Ophthalmol* 1995;36[Suppl].

119. Katsumi O, Miyanaga Y, Hirose T, et al. Binocular function in unilateral aphakia: correlation with aniseikonia and stereoacuity. *Ophthalmology* 1988;95:1088-1093.

120. Lambert SR, Amaya I, Taylor D. Detection and treatment of infantile cataracts. *Int Ophthalmol Clin* 1989;29:51-56.

121. Lorenz B, Wo J. Visual results in congenital cataract with the use of contact lenses. *Graefes Arch Clin Exp Ophthalmol* 1991;229:123-132.

122. Aasuri MK, Venkata N, Preetam P, et al. Management of pediatric aphakia with Silsoft contact lenses. *CLAO J* 1999;25:209-212.

123. Ma J, Morad Y, Mau E, et al. Contact lenses for the treatment of pediatric cataracts. *Ophthalmology* 2003;110:299-305.

124. Arffa RC, Marvelli TL, Morgan KS. Long-term follow-up of refractive and keratometic results of pediatric epikeratophakia. *Arch Ophthalmol* 1986;104:668-670.

125. Kelly CG, Keates RH, Lembach RG. Epikeratophakia for pediatric aphakia. *Arch Ophthalmol* 1986;104:680.

126. Morgan KS, Arffa RC, Marvelli TL. Five year follow-up of epikeratophakia in children. *Ophthalmology* 1986;93:423.

127. Buckley E, Drack AV, Fawcett SL. A comparison of grating visual acuity, strabismus, and reoperation outcomes among children with aphakia and pseudophakia after unilateral cataract surgery during the first six months of life. *J AAPOS* 2001;5:70-75.

128. Greenwald MJ, Glaser SR. Visual outcomes after surgery for unilateral cataract in children more than two years old: posterior chamber intraocular lens implantation versus contact lens correction of aphakia. *J AAPOS* 1998;2:168-176.

129. Ainsworth JR, Cohen S, Levin AV, et al. Pediatric cataract management with variations in surgical technique and aphakic optical correction. *Ophthalmology* 1997;104:1096-1101.

130. Hutchinson AK, Wilson ME, Saunders RA. Outcomes and ocular growth rates after intraocular lens implantation in the first 2 years of life. *J Cataract Refract Surg* 1998;24:846-852.

131. Dahan E, Drusedau MU. Choice of lens and diopteric power in pediatric pseudophakia. *J Cataract Refract Surg* 1997;23:618-623.

132. Flitcroft DI, Knight-Nanan D, Bowell R, et al. Intraocular lenses in children: changes in axial length, corneal curvature, and refraction. *Br J Ophthalmol* 1999;83:265-269.

133. Enyedi L, Buckley EG. Refractive changes in pediatric patients with pseudophakia. *Invest Ophthalmol* 1996;37[Suppl]:588.

134. Crouch E, Crouch ERJ. Prospective analysis of pediatric pseudophakia: myopic shift and postoperative outcomes. *J AAPOS* 2002;6:277-282.

135. Enyedi LB, Peterseim MW, Freedman SF, et al. Refractive changes after pediatric intraocular lens implantation. *Am J Ophthalmol* 1998;126:772-781.

136. Hutchinson AK, Drews-Botsch C, Lambert SR. Myopic shift after intraocular lens implantation during childhood. *Ophthalmology* 1997;104:1752-1757.

137. Plager D, Kipfer H, Sprunger DT, et al. Refractive change in pediatric pseudophakia: 6-year follow-up. *J Cataract Refract Surg* 2002;28:810-815.

138. McClatchey S, Parks M. Theoretic refractive changes after lens implantation in childhood. *Ophthalmology* 1997;105:1571-1574.

139. McClatchey S. Intraocular lens calculator for childhood cataracts. *J Cataract Refract Surg* 1998;24:1125-1129.

140. Spierer A, Desatnik H, Blumenthal M. Refractive status in children after long-term follow up of cataract surgery with intraocular lens implantation. *J Pediatr Ophthalmol Strabismus* 1999;36:25-29.

141. Awner S, Buckley EG, DeVaro JM, et al. Unilateral pseudophakia in children under 4 years. *J Pediatr Ophthalmol Strabismus* 1996;33:230-236.

142. Superstein R, Archer S, Del Monte MA. Minimal myopic shift in pseudophakic versus aphakic pediatric cataract patients. *J AAPOS* 2002;6:271-276.

143. Wilson ME, Peterseim MW, Englert JA, et al. Pseudophakia and polypseudophakia in the first year of life. *J AAPOS* 2001;5:238-245.

144. Andreo LK, Wilson ME, Saunders RA. Predictive value of regression and theoretical IOL formulas in pediatric intraocular lens implantation. *J Pediatr Ophthalmol Strabismus* 1997;34:240-243.

145. Tromans C, Haigh PM, Biswas S, et al. Accuracy of intraocular lens power calculation in pediatric cataract surgery. *Br J Ophthalmol* 2001;85:939-941.

146. Jacobi PC, Dietlien TS, Konen W. Multifocal pediatric lens implantation in pediatric cataract surgery. *Ophthalmology* 2001;108:1375-1380.

147. Frey T, Friendly D, Wyatt D. Re-evaluation of monocular cataracts in children. *Am J Ophthalmol* 1973;76:381.

148. Seaber JH, Buckley EG. Functional outcome of monocular and binocular congenital cataract. Part 1: Visual acuity. *Am Orthop J* 1997;47:29.

149. Watts P, Abdolell M, Levin AV. Complications in infants undergoing surgery for congenital cataract in the first 12 weeks of life: is early surgery better? *J AAPOS* 2003;7:81-85.

150. Beller R, Hoyt CS, Marg E, et al. Good visual function after neonatal surgery for congenital monocular cataracts. *Am J Ophthalmol* 1981;91:559.

151. Birch EE, Stager DR, Wright WW. Grating acuity development after early surgery for congenital unilateral cataract. *Arch Ophthalmol* 1986;104:1783-1787.

152. Birch EE, Swanson WH, Stager DR, et al. Outcome after very early treatment of dense congenital unilateral cataract. *Invest Ophthalmol Vis Sci* 1993;34:3687-3698.

153. Drummond GT, Scott WE, Keech RV. Management of monocular congenital cataracts. *Arch Ophthalmol* 1989;107:45-51.

154. Neumann D, Weissman BA, Isenberg SJ. The effectiveness of daily wear contact lenses for the correction of infantile aphakia. *Arch Ophthalmol* 1993;111:927-930.

155. Jeffrey BG, Birch EE, Stager DR Jr, et al. Early binocular visual experience may improve binocular sensory outcomes in children after surgery for congenital unilateral cataract. *J AAPOS* 2001;5:209-216.

156. Brown SM, Archer S, Del Monte MA. Stereopsis and binocular vision after surgery for unilateral infantile cataract. *J AAPOS* 1999;3:109-113.

157. Zubcov AA, Stahl E, Rossillion B, et al. Stereopsis after primary in-the-bag posterior chamber implantation in children. *J AAPOS* 1999;3:227-233.

158. Alexandrakis G, Scott IU, Flynn HW Jr, et al. Visual acuity outcomes with and without surgery in patients with persistent fetal vasculature. *Ophthalmology* 2000;107:1068-1072.

159. Rabiah PK, Smith SD, Awad AH, et al. Results of surgery for bilateral cataract associated with sensory nystagmus in children. *Am J Ophthalmol* 2002;134:586-591.

160. Luebbers JA, Goldberg MF, Herbst R, et al. Iris transillumination and variable expression in ectopia lentis et pupillae. *Am J Ophthalmol* 1977;83:647-656.

161. Nelson LB, Maumenee IH. Ectopia lentis. *Surv Ophthalmol* 1982;27:143-160.

162. Maumenee IH. The eye in the Marfan syndrome. *Trans Am Ophthalmol Soc* 1981;69:685.

163. McKusick VA. *Heritable disorders of connective tissue*. St. Louis: Mosby, 1972.

164. Jensen AD, Cross HE, Paton D. Ocular complications in the Weill-Marchesani syndrome. *Am J Ophthalmol* 1974;77:261-269.

165. Young ID, Fielder AR, Casey TA. Weill-Marchesani syndrome in mother and son. *Clin Genet* 1986;30:475.

166. Shih VE, Abroms IF, Johnson JL. Sulfite oxidase deficiency: biochemical and clinical investigations of a hereditary metabolic disorder in sulfur metabolism. *N Engl J Med* 1977;297:1022-1028.

167. Dancis J, Hutzler J, Ampola MG, et al. The prognosis of hyperlysinemia: an interim report. *Am J Hum Genet* 1983;35:438.

168. Plager DA, Parks MM, Helveston EM. Surgical treatment of subluxated lenses in children. *Ophthalmology* 1992;99:1018-1023.

169. Parrow RD. Hereditary cataract in two families. *Acta Pediatr* 1955;44:460.

170. Francis P, Berry V, Bhattacharya S, et al. Congenital progressive polymorphic cataract caused by a mutation in the major intrinsic protein of the lens, MIP (AQP0). *Br J Ophthalmol* 2000;84:1376-1379.

171. Yamada K, Tomita H, Yoshiura K, et al. An autosomal dominant posterior polar cataract locus maps to human chromosome 20p12-q12. *Eur J Hum Genet* 2000;8:535-539.

172. Amaya L, Taylor D, Russell-Eggitt I, et al. The morphology and natural history of childhood cataracts. *Surv Ophthalmol* 2003;48:125-144.

173. Fallaha N, Lambert SR. Pediatric cataracts. *Ophthalmol Clin North Am* 2001;14:479-492.

174. Donahue R, Bias WB, Renwick JH, et al. Probable assignment of the Duffy blood group locus to chromosome 1 in man. *Proc Natl Acad Sci U S A* 1968;61:949-955.

175. Ionides A, Berry V, Mackay DS, et al. A locus for autosomal dominant posterior polar cataract on chromosome 1p. *Hum Mol Genet* 1997;6:47-51.

176. Rogaev EI, Rogaeva EA, Korovaitseva GI, et al. Linkage of polymorphic congenital cataract to the gamma-crystallin gene locus on human chromosome 2q33-35. *Hum Mol Genet* 1996;5:699-703.

177. Stephan DA, Gillanders E, Vanderveen D, et al. Progressive juvenile-onset punctate cataracts caused by mutation of the gamma D-crystallin gene. *Proc Natl Acad Sci U S A* 1999;96:1008-1012.

178. Heon E, Liu S, Billingsley G, et al. Gene localization for aculeiform cataract, on chromosome 2q33-35. *Am J Hum Genet* 1998;63:921-926.

179. Conley YP, Erturk D, Keverline A, et al. A juvenile-onset, progressive cataract locus on chromosome 3q21-q22 is associated with a missense mutation in the beaded filament structural protein-2. *Am J Hum Genet* 2000;66:1426-1431.

180. Semina EV, Ferrell RE, Mintz-Hittner HA, et al. A novel homeobox gene PITX3 is mutated in families with autosomal dominant cataracts and ASMD. *Nat Genet* 1998;19:167-170.

181. Berry V, Francis P, Reddy MA, et al. Alpha-B crystallin gene (CRYAB) mutation causes dominant congenital posterior polar cataract in humans. *Am J Hum Genet* 2001;69:1141-1145.

182. Francis P, Berry V, Bhattacharya S, et al. Congenital progressive polymorphic cataract caused by a mutation in the major intrinsic protein of the lens. *Br J Opthalmol* 1998;84:1376-1379.

183. Berry V, Francis P, Kaushal S, et al. Missense mutations in the MIP gene, encoding the major intrinsic protein of the lend, underlie autosomal dominant “polymorphic” and lamellar cataracts on 12q. *Nat Genet* 2000;25:15-17.

184. Watts P, Rees M, Clarke A, et al. Linkage analysis in an autosomal dominant “zonular nuclear pulverulent” congenital cataract, mapped to chromosome 13q11-13. *Eye* 2000;14:172-175.

185. Vanita, Singh JR, Sarhadi VK, et al. A novel form of central pouchlike cataract, with sutural opacities, maps to chromosome 15q21-22. *Am J Hum Genet* 2001;68:509-514.

186. Marner E. A family with eight generations of hereditary cataracts. *Acta Ophthalmol* 1949;27:537.

187. Eiberg H, Marner E, Rosenberg T, et al. Marner's cataract (CAM) assigned to chromosome 16: linkage to haptoglobin. *Clin Genet* 1988;34:272-275.

188. Maumenee IH. Classification of hereditary cataracts in children by linkage analysis. *Trans Am Acad Ophthalmol Otolaryngol* 1979;86:1554-1558.

189. Padma T, Ayyagari R, Murty JS, et al. Autosomal dominant zonular cataract with sutural opacities localized to chromosome 17q11-12. *Am J Hum Genet* 1995;57:840-845.

190. Armitage MM, Kivlin JD, Farrell RE. A progressive early onset cataract gene maps to human chromosome 17q24. *Nat Genet* 1995;9:37-40.

191. Berry V, Ionides AC, Moore AT, et al. A locus for autosomal dominant anterior polar cataract on chromosome 17p. *Hum Mol Genet* 1996;5:415-419.

192. Chang-Godinich A, Ades S, Schenkein D, et al. Lens changes in hereditary hyperferritinemia-cataract syndrome. *Am J Ophthalmol* 2001;132:786-788.

193. Quax-Jeuken Y, Quax W, Van Rens G, et al. Assignment of the human alpha-A-crystallin gene (CRYA1) to chromosome 21. *Cytogenet Cell Genet* 1985;40:727-728.

194. Kramer P, Yount J, Mitchell T, et al. A second gene for cerulean cataracts maps to the beta-crystallin region on chromosome 22. *Genomics* 1996;35:39-42.

195. Saebo J. An investigation into the mode of heredity of congenital and juvenile cataracts. *Br J Ophthalmol* 1949;33:601.

196. Forsius H, Arentz-Grastvedt B, Eriksson AW. Juvenile cataract with autosomal recessive inheritance. *Acta Ophthalmol* 1992;70:26-32.

197. Krill AE, Woodbury G, Bowman JE. X-chromosomal-linked sutural cataracts. *Am J Ophthalmol* 1969;68:867.

198. Russell-Eggitt IM. Non-syndromic posterior lenticonus a cause of childhood cataract: evidence for X-linked inheritance. *Eye* 2000;14:861-863.

199. Francis PJ, Berry V, Hardcastle AJ, et al. A locus for isolated cataract on human Xp. *J Med Genet* 2002;39:105-109.

200. Cursiefen C, Kuchle M, Scheurlen W, et al. Bilateral zonular cataract associated with the mitochondrial cytopathy of Pearson syndrome. *Am J Ophthalmol* 1998;125:260-261.

201. OMIM, OMliM. *www.ncbi.nlm.nih.gov*. 2004.

202. Simon KA. Diabetes and lens changes in myotonic dystrophy. *Arch Ophthalmol* 1962;67:312.

203. Armaly MF. Ocular involvement in chondrodystrophia calcificans congenital punctata. *Arch Ophthalmol* 1957;57:491.

204. Levine RE, Snyder AA, Surgarman GI. Ocular involvement in chondrodysplasia punctata. *Am J Ophthalmol* 1974;77:851-858.

205. Brownstein S, Kirkham TH, Kalousek DK. Bilateral renal agenesis with multiple congenital ocular anomalies. *Am J Ophthalmol* 1976;82:770.

206. Nahmias AJ, Visintine AM, Caldwell DR. Eye infections with herpes simplex viruses in neonates. *Surv Ophthalmol* 1976;21:100.

207. Keating PD, Hepler RS. Blepharophimosis and acquired somatofacial dysmorphism associated with congenital cataracts. *Arch Ophthalmol* 1969;82:1.

208. Stago S, Reynolds DW, Amos CS. Auditory and visual defects resulting from symptomatic and subclinical congenital cytomegaloviral and toxoplasma infections. *Pediatrics* 1977;59:669.

209. Cotlier E, Rice P. Cataracts in the Smith-Lemli-Opitz syndrome. *Am J Ophthalmol* 1971;72:955-959.

210. Rudolph G, Kalpadakis P, Bettecken T, et al. Spondylo-ocular syndrome: a new entity with crystalline lens malformation, cataract, retinal detachment, osteoporosis, and platyspondyly. *Am J Ophthalmol* 2003;135:681-687.

211. Liebman SD. Postnatal development of lamellar cataracts in premature infants. *Arch Ophthalmol* 1955;54:257.

212. Green JS, Parfrey PS, Harnett JD, et al. The cardinal manifestations of Bardet-Biedl syndrome, a form of Laurence-Moon-Biedl syndrome. *N Engl J Med* 1989;321:1002-1009.

213. Cordes FC. Galactosemia cataract: a review. *Am J Ophthalmol* 1960;50:1151.

214. Stambolian D. Galactose and cataract. *Surv Ophthalmol* 1988;32:333.

215. Moser HW. Peroxisomal diseases. *Adv Pediatr* 1989;36:1.

216. Duke-Elder S. *System of ophthalmology*. St. Louis: Mosby, 1969:a: 166-172; b:175-182; c: 1135-1141.

217. Yeh H, Price RL, Lonsdale D. Cerebral gigantism (Sotos' syndrome) and cataracts. *J Pediatr Ophthalmol Strabismus* 1978;15:231.

218. Bateman JB, Phillipart M. Ocular features of the Hagberg-Santavuori syndrome. *Am J Ophthalmol* 1986;102:262-271.

219. Toussaint D, Davis P. An ocular pathologic study of Refsum's syndrome. *Am J Ophthalmol* 1971;72:342.

220. Wilson WA, Richards W, Donnell GN. Oculo-cerebral-renal syndrome of Lowe. *Arch Ophthalmol* 1963;70:5.

221. Pearce WG. Ocular and genetic features of Cockayne's syndrome. *Can J Ophthalmol* 1972;7:435.

222. Ferreira RC, Roeder ER, Bateman JB. Cataract in early onset and classic Cockayne syndrome. *Ophthalmic Genet* 1997;18:193-197.

223. Merin S, Crawford JS. Hypoglycemia and infantile cataracts. *Arch Ophthalmol* 1971;86:495.

224. Wahl JW, Ellis PP. Rothmund-Thomson syndrome. *Am J Ophthalmol* 1965;60:722-726.

225. Letson RD, Desnick RJ. Punctate lenticular opacities in type II mannosidosis. *Am J Ophthalmol* 1978;85:218-224.

226. Scott JG, Friedmann AI, Chitters M. Ocular changes in the Bloch-Sulzberger syndrome (incontinentia pigmenti). *Br J Ophthalmol* 1955;30:276-292.

227. Jay B, Black RK, Wells RS. Ocular manifestations in ichthyosis. *Br J Ophthalmol* 1968;52:217-226.

228. Nielson CE. Lenticonus anterior and Alport's syndrome. *Acta Ophthalmol* 1978;56:518.

229. Cowan A, Klauder JV. Frequency of occurrence of cataract in atopic dermatitis. *Arch Ophthalmol* 1950;43:759-768.

230. Marshall D. Ectodermal dysplasia. *Am J Ophthalmol* 1958;45:143-156.

231. Jones KL. *Smith's recognizable patterns of human malformation*, 4th ed. Philadelphia: WB Saunders Co, 1988.

232. Zeiter HJ. Congenital microphthalmos. *Am J Ophthalmol* 1963;55:910.

233. Roy FH, Summitt RL, Hiatt RL. Ocular manifestations of the Rubinstein-Taybi syndrome. *Arch Ophthalmol* 1968;79:272.

234. Insler MS. Cerebro-oculo-facio-skeletal syndrome. *Ann Ophthalmol* 1987;19:54-55.

235. Reese AB. Persistent hyperplastic primary vitreous. *Am J Ophthalmol* 1955;40:317.

236. Tournev I, Kalaydjieva L, Youl B, et al. Congenital cataracts facial dysmorphism neuropathy syndrome: a novel complex genetic disease in Balkan Gypsies: clinical and electrophysiological observations. *Ann Neurol* 1999;45:742-750.

237. Tripathi RC, Cibis GW, Tripathi BJ. Pathogenesis of cataracts in patients with Lowe's syndrome. *Ophthalmology* 1986;93:1046-1051.

238. Tugal-Tutkun I, Urgancioglu M. Childhood-onset uveitis in Behcet disease: a descriptive study of 36 cases. *Am J Ophthalmol* 2003;136:1114-1119.

239. Mondkar SV, Biswas J, Ganesh SK. Analysis of 87 cases with Vogt-Koyanagi-Harada disease. *Jpn J Ophthalmol* 2000;44:296-301.

240. Repka MX, Summers CG, Palmer EA, et al. The incidence of ophthalmic interventions in children with birth weights less than 1251 grams. Results through 5 1/2 years. Cryotherapy for retinopathy of prematurity cooperative group. *Ophthalmology* 1998;105:1621-1627.

241. Frisk P, Hagberg H, Mandahl A, et al. Cataracts after autologous bone marrow transplantation in children. *Acta Paediatr* 2000;89:814-819.

242. Holmstrom G, Borgstrom B, Calissendorff B. Cataract in children after bone marrow transplantation: relation to conditioning regimen. *Acta Ophthalmol Scand* 2002;80:211-215.

243. Dinakaran S, Desai SP, Elsom DM. Ophthalmic manifestations of lightning strikes. *Surv Ophthalmol* 2002;47:292.

244. Apple DJ, Holden JD, Stallworth B. Ocular pathology of Patau's syndrome with an unbalanced D/D translocation. *Am J Ophthalmol* 1970;70:383.

245. Mullaney J. Ocular pathology in trisomy 18 (Edward's syndrome). *Am J Ophthalmol* 1973;76:246.

246. Lessell S, Forbes AP. Eye signs in Turner's syndrome. *Arch Ophthalmol* 1966;76:211.

247. Farrell JW, Morgan KS, Black S. Lensectomy in an infant with cri du chat syndrome and cataracts. *J Pediatr Ophthalmol Strabismus* 1988;25:131-134.

248. Lorenz B, Wö J, Friedl N, et al. Monocular and binocular functional results in cases of contact lens corrected infant aphakia. In: Cotlier E, Taylor D, eds. *Congenital cataracts*. Boca Raton, FL: RG Landes/CRC Press, 1994:151-162.

249. Burke JP, Willshaw HE, Young JDH. Intraocular lens implants for uniocular cataracts in childhood. *Br J Ophthalmol* 1989;73:860-864.

250. Dahan E, Salmenson BD. Pseudophakia in children: precautions, technique, and feasibility. *J Cataract Refract Surg* 1990;16:75-82.

251. Cheng KP, Hiles DA, Biglan AW, et al. Visual results after early surgical treatment of unilateral congenital cataracts. *Ophthalmology* 1991;98:903-910.

252. Markham RHC, Bloom PA, Chandna A, et al. Results of intraocular lens implantation in paediatric aphakia. *Eye* 1992;6:493-498.

253. Gelbart SS, Hoyt CS, Jastrebski G, et al. Long-term results in bilateral congenital cataracts. *Am J Ophthalmol* 1982;93:615-621.

254. Bradford GM, Keech RV, Scott WE. Factors affecting visual outcome after surgery for bilateral congenital cataracts. *Am J Ophthalmol* 1994;117:58-64.

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14

Glaucoma in Infants and Children

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Childhood glaucomas constitute a rare, heterogeneous and vision-threatening group of disorders. Pediatricians and eye care providers are often the first health care professionals to encounter children with glaucoma; familiarity with the clinical features of this disease, and with the children most at risk for developing glaucoma, may increase correct diagnosis and timely treatment for affected children. In adults, glaucoma is often occult; however, in children, strong suggestive signs of glaucoma are more often present. Although there is considerable common ground, children with glaucoma often require examination techniques and treatment strategies that differ markedly from those most appropriate for their adult counterparts. Genetic, pharmacological, and technological advances in the diagnosis and treatment of glaucoma, raise the hope that this disease will, some day, no longer cause visual impairment in either adults or children.

The group of childhood glaucomas can be considered by subdividing them into those of primary and secondary origin. Hence, a primary glaucoma is one caused by an intrinsic disease of the aqueous outflow mechanism and is often of genetic origin, whereas a secondary glaucoma is one caused by another ocular disease, injury, drug, or systemic disease (Table 14.1). Both primary and secondary pediatric glaucoma may be associated with significant systemic conditions. It is therefore important for the ophthalmologist to accurately interpret eye signs as clues for the diagnosis and classification of both the glaucoma and associated systemic disease.

SIGNS AND SYMPTOMS OF GLAUCOMA IN CHILDREN

The signs and symptoms of glaucoma vary greatly among children, according to the age of the child and the suddenness and severity of the intraocular pressure (IOP) elevation. During the first year of life, glaucoma is commonly suspected because of signs and symptoms related to secondary corneal changes. Older children are seen more often with loss of vision from chronic glaucoma or with symptoms of pain and vomiting related to acute glaucoma. Elevation of IOP is required to confirm the diagnosis of childhood glaucoma, although its presence (past or present) may be strongly suspected on the basis of classical symptoms and other signs of the disease (see later). Although somewhat lower in young infants than in school-age children and adults, the range of normal IOP in childhood approximates the normal adult range; rarely are normal measurements above 22 mm Hg or below 10 mm Hg. Accurate IOP measurements are essential not only to the diagnosis, but also to the management of children with glaucoma (see Examination).

Infants and young children with glaucoma most often present for ophthalmological evaluation because the pediatrician or parents have noted something unusual about the appearance of the child's eyes or behavior. Corneal opacification and/or enlargement (a response to elevated IOP) are the signs most commonly heralding glaucoma in the infant; both may progress over the first 2 years of life, if IOP remains elevated (Figs. 14.1, 14.2 and 14.3). At other times, the child's glaucoma may manifest itself as one or more of the “classic triad” of findings: epiphora, photophobia, and blepharospasm (Fig. 14.4) (1). Photophobia and epiphora result from corneal edema (often with associated breaks in Descemet's membrane called *Haab's striae*). The baby may be noted to withdraw from light or to bury his or her head against parent or bedding to prevent exposure to light; eye rubbing may also be noted. Even indoors, the infant may show an apparent reluctance to face upward and may mistakenly be considered shy (Fig. 14.5).

These corneal signs and symptoms of glaucoma in early life may be of sudden onset, with dramatic opacification of the cornea and onset of photophobia occurring over a

few hours. Such an acute onset of signs is probably related to initial or additional breaks in Descemet's membrane (Fig. 14.6). The occurrence of breaks appears to be confined to the first 2 years of life, when rapid expansion of the cornea may occur secondary to glaucoma. Breaks are permanent and remain as important evidence of early glaucoma; although some are subtle, at other times significant associated corneal scarring may result (Fig. 14.7). The defects appear as wavy parallel lines on the inner side of the cornea and are usually curvilinear and horizontal. They represent the separated edges of Descemet's membrane. Breaks with more vertical orientation may be seen secondary to the acute bending of the cornea, rarely occurring with delivery using forceps (Fig. 14.8) (2).

TABLE 14.1 PRIMARY AND SECONDARY CHILDHOOD GLAUCOMAS

I. Primary Glaucomas

A. Congenital open-angle glaucoma (PCG)

1. Newborn congenital glaucoma (iridotrabeculodysgenesis)
2. Infantile glaucoma (trabeculodysgenesis)
3. Late recognized

B. Autosomal dominant juvenile glaucoma

C. Primary angle-closure glaucoma

D. Associated with systemic abnormalities

1. Sturge-Weber syndrome
2. Neurofibromatosis type 1 (NF-1)
3. Stickler syndrome
4. Oculocerebrorenal (Lowe's) syndrome
5. Rieger syndrome (Axenfeld-Rieger syndrome)
6. SHORT syndrome
7. Hepatocerebrorenal syndrome
8. Marfan syndrome
9. Rubinstein-Taybi syndrome
10. Infantile glaucoma with mental retardation and paralysis
11. Oculodentodigital dysplasia
12. Open-angle glaucoma associated with microcornea and absence of frontal sinuses
13. Mucopolysaccharidosis
14. Trisomy 13
15. Caudal regression syndrome
16. Trisomy 21 (Down syndrome)
17. *Cutis marmorata telangiectasia congenita*

18. Warburg syndrome

19. Kniest syndrome (skeletal dysplasia)

20. Michel syndrome

21. Nonprogressive hemiatrophy

22. PHACE syndrome

23. Sotos syndrome

24. Linear scleroderma

25. GAPO syndrome

26. Roberts pseudothalidomide syndrome

27. Wolf-Hirschhorn (4p) syndrome

28. Rabinow syndrome

29. Nail-patella syndrome

30. Proteus syndrome

31. Fetal hydantoin syndrome

32. Cranio-cerebello-cardiac (3C) syndrome

33. Brachmann-deLange syndrome

E. Associated with ocular abnormalities

1. Primary

2. Aniridia

a. Congenital glaucoma

b. Acquired glaucoma

3. Congenital ocular melanosis

4. Sclerocornea

5. Congenital iris ectropion syndrome

6. Peters syndrome

7. Iridotrabecular dysgenesis (iris hypoplasia)

7. Iridotrabecular dysgenesis (iris hypoplasia)

8. Posterior polymorphous dystrophy

9. Idiopathic or familial elevated episcleral venous pressure

10. Anterior corneal staphyloma

11. Congenital microcornea with myopia

12. Congenital hereditary endothelial dystrophy

13. Iridocorneal endothelial syndrome (ICE)

II. Secondary Glaucomas

A. Traumatic glaucoma

1. Acute glaucoma

a. Angle concussion

b. Hyphema

c. Ghost cell glaucoma

2. Late-onset glaucoma with angle recession

3. Arteriovenous fistula

B. Secondary to intraocular neoplasm

1. Retinoblastoma

2. Juvenile xanthogranuloma

3. Leukemia

4. Melanoma

5. Melanocytoma

6. Iris rhabdomyosarcoma

7. Aggressive nevi of the iris

C. Secondary to uveitis

1. Open-angle glaucoma

2. Angle-blockage glaucoma

a. Synechial angle closure

a. Synechial angle closure

b. Iris bombe with pupillary block

c. Trabecular endothelialization

D. Lens-induced glaucoma

1. Subluxation-dislocation and pupillary block

a. Marfan syndrome

b. Homocystinuria

c. Weill-Marchesani syndrome

2. Spherophakia and pupillary block

3. Phacolytic glaucoma

E. Following surgery for congenital cataract

1. Lens tissue trabecular obstruction

2. Pupillary block

3. Chronic open-angle glaucoma associated with angle abnormalities

F. Steroid-induced glaucoma

G. Secondary to rubeosis

1. Retinoblastoma

2. Coats disease

3. Medulloepithelioma

4. Familial exudative vitreoretinopathy

5. Chronic retinal detachment

H. Secondary angle-closure glaucoma

1. Retinopathy of prematurity

2. Microphthalmos

3. Nanophthalmos

4. Retinoblastoma

5. Persistent hyperplastic primary vitreous

6. Congenital pupillary iris-lens membrane

7. Topiramate

8. Central retinal vein occlusion

9. Ciliary body cysts

I. Malignant glaucoma

J. Glaucoma associated with increased venous pressure

1. Cavernous or dural-venous fistula

2. Orbital disease

K. Secondary to maternal rubella

L. Secondary to intraocular infection

1. Acute recurrent toxoplasmosis

2. Acute herpetic iritis

3. Endogenous endophthalmitis

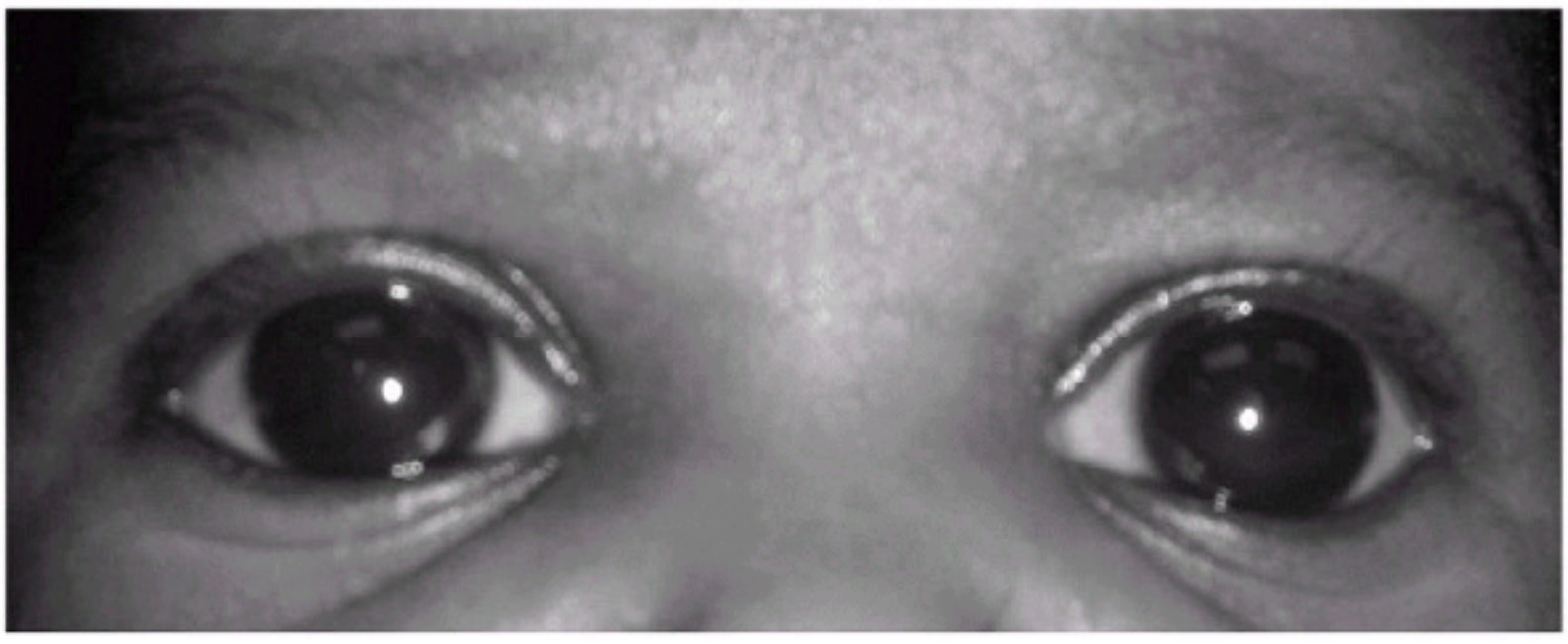

Figure 14.1 Corneal enlargement bilaterally, with corneal haze. This infant was 5 months old at diagnosis and responded well to angle surgery.

Figure 14.2 Corneal opacification and enlargement of the left eye, secondary to congenital glaucoma.

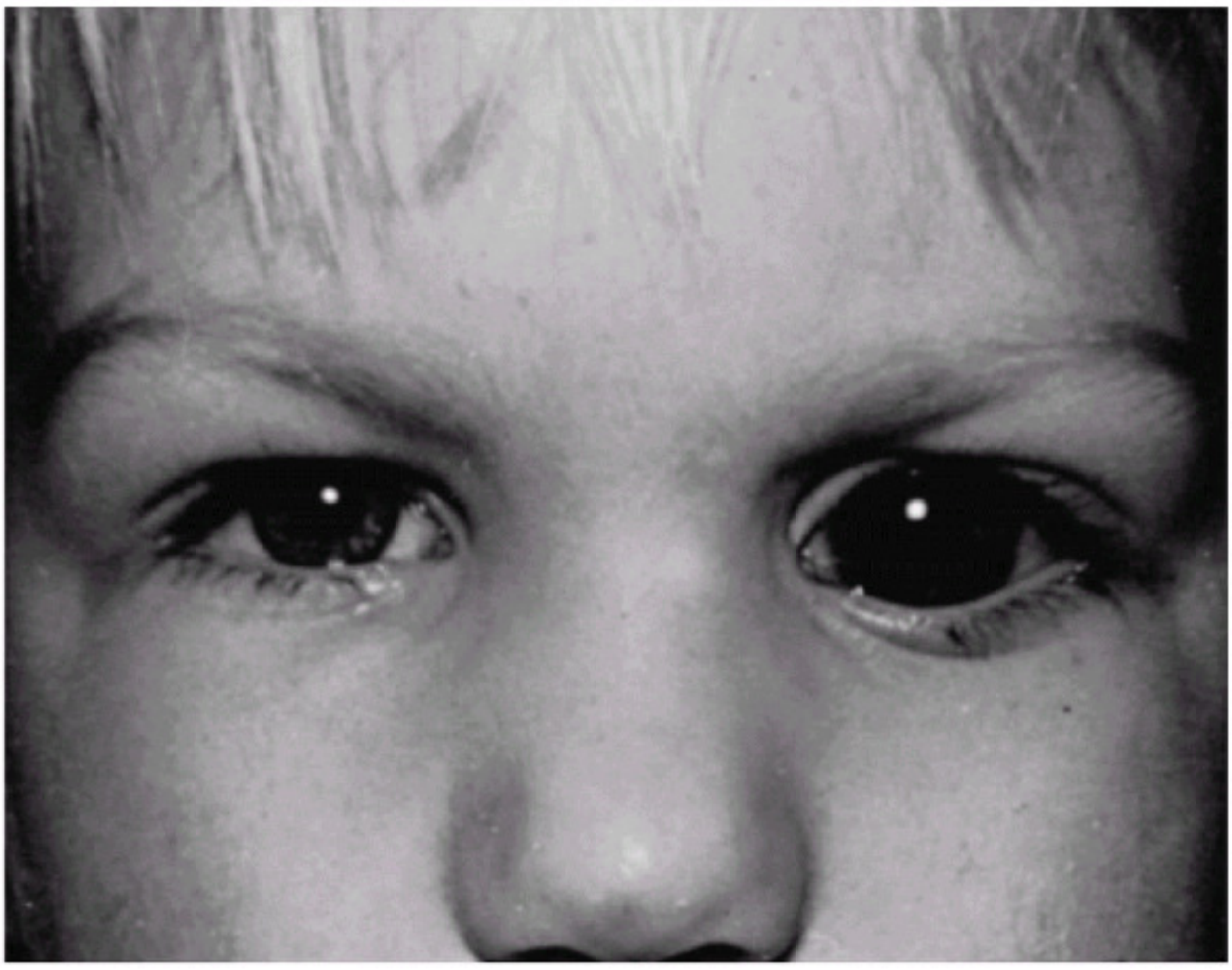

Figure 14.3 Corneal enlargement of the left eye that developed slowly over a period of 2 years. The child was first evaluated after failing a vision test. Generalized corneal haziness was present.

Figure 14.4 Tearing of the right eye caused by glaucoma. Note the increased corneal diameter of the right eye.

If glaucoma in infancy and early childhood is not treated, progressive enlargement of the cornea may occur throughout the first 2 years of life. The corneal diameter may, in extreme cases, enlarge to 17 to 18 mm; in these cases, concordant enlargement of the ciliary ring often results in iridodonesis and lens subluxation (Fig. 14.9). Stretched, buphthalmic eyes are easily traumatized, even to the point of rupture.

Additional nonspecific signs of glaucoma in early life include the presence of a deep anterior chamber and optic nerve cupping. The extent of optic nerve cupping does not

always correlate closely with the anterior segment signs of glaucoma. In the absence of optic atrophy, the optic cup may decrease greatly in size, with IOP reduction, and will enlarge again, if control of IOP is lost. By contrast, the optic atrophy that may result from chronic or severe IOP elevation is irreversible (Fig. 14.10).

Figure 14.5 Hiding of the face caused by intense photophobia secondary to congenital glaucoma.

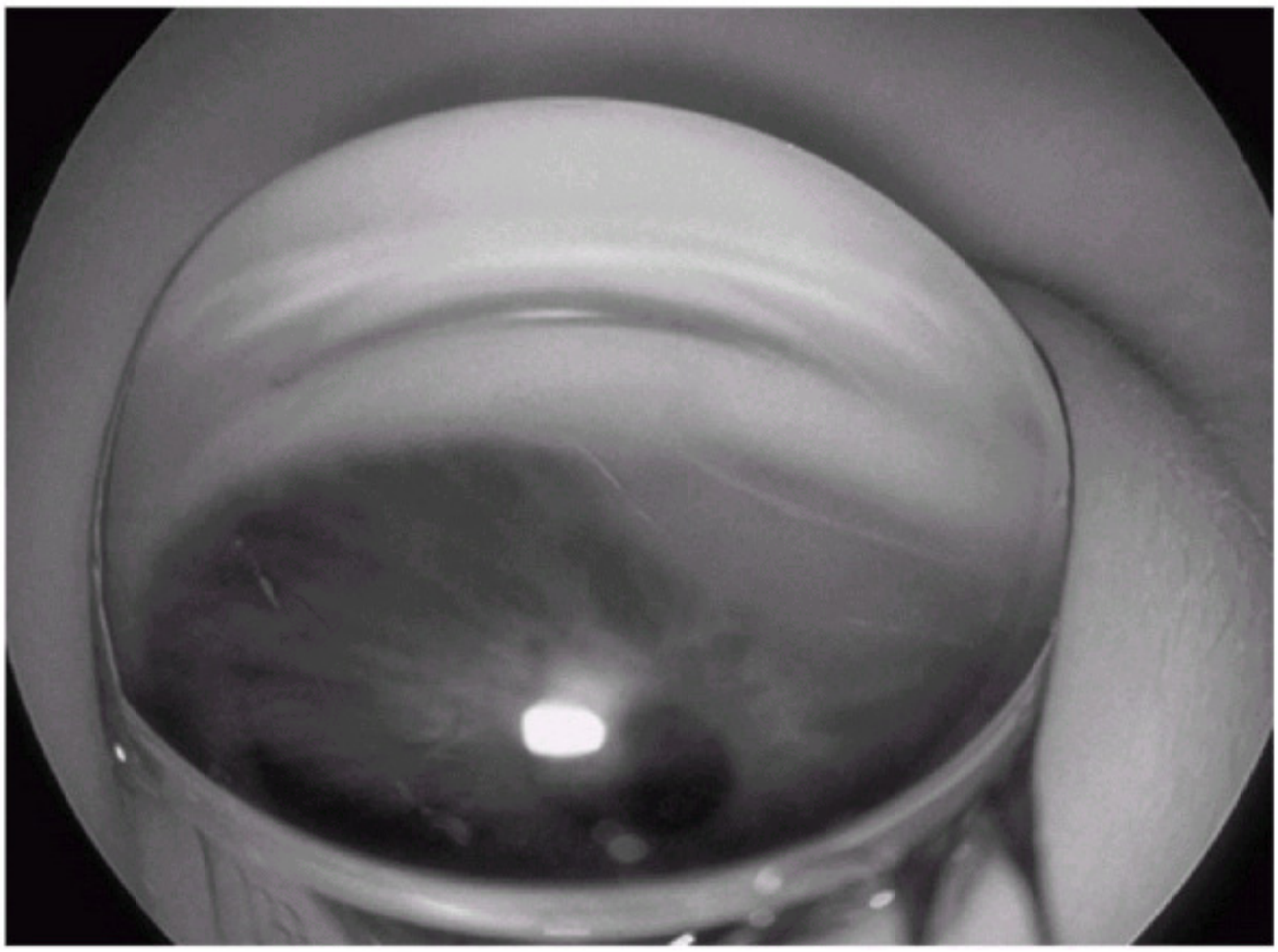

Figure 14.6 An acute break in Descemet's membrane seen through a Koeppe lens, in an infant with newly diagnosed congenital glaucoma. Note the curvilinear shape to the break as well as the associated, localized corneal edema.

In older children, the anterior segment signs of glaucoma play a less important role in the recognition of this disorder. Of greater significance is the evaluation of the eyes because of decreased vision (usually from induced myopia) or circumstances in which secondary glaucoma might be suspected, such as chronic iridocyclitis, blunt trauma to the anterior segment, neoplasm, or after eye surgery. The presence or absence of disc cupping, in older as well as in young children, is by itself an unreliable diagnostic sign but remains very important in the follow-up management of children with glaucoma. Older children infrequently

present with acute glaucoma inducing nauseating eye pain, headaches, and even colored halos around lights. This sudden-onset glaucoma may be the result of traumatic hyphema or of angle-closure glaucoma from lens dislocation or cicatricial retinopathy of prematurity. Less frequently, acute glaucoma develops secondary to other processes (Table 14.1).

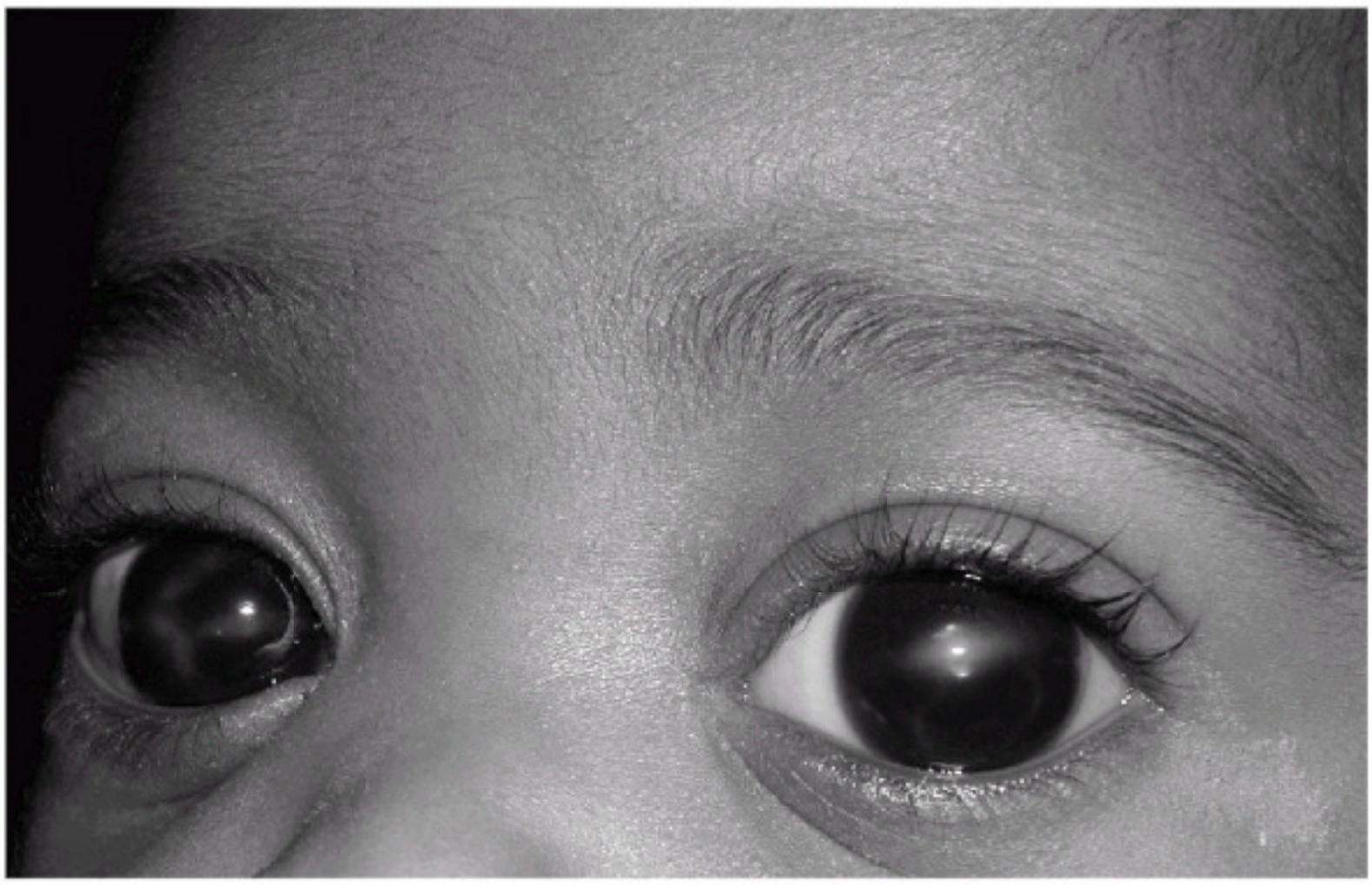

Figure 14.7 Corneal scarring in a striking pattern, correlating with the presence of Haab's striae. The associated corneal edema has cleared, and the pressure is normalized after goniotomy surgery, but the visually significant corneal opacities remain in both eyes.

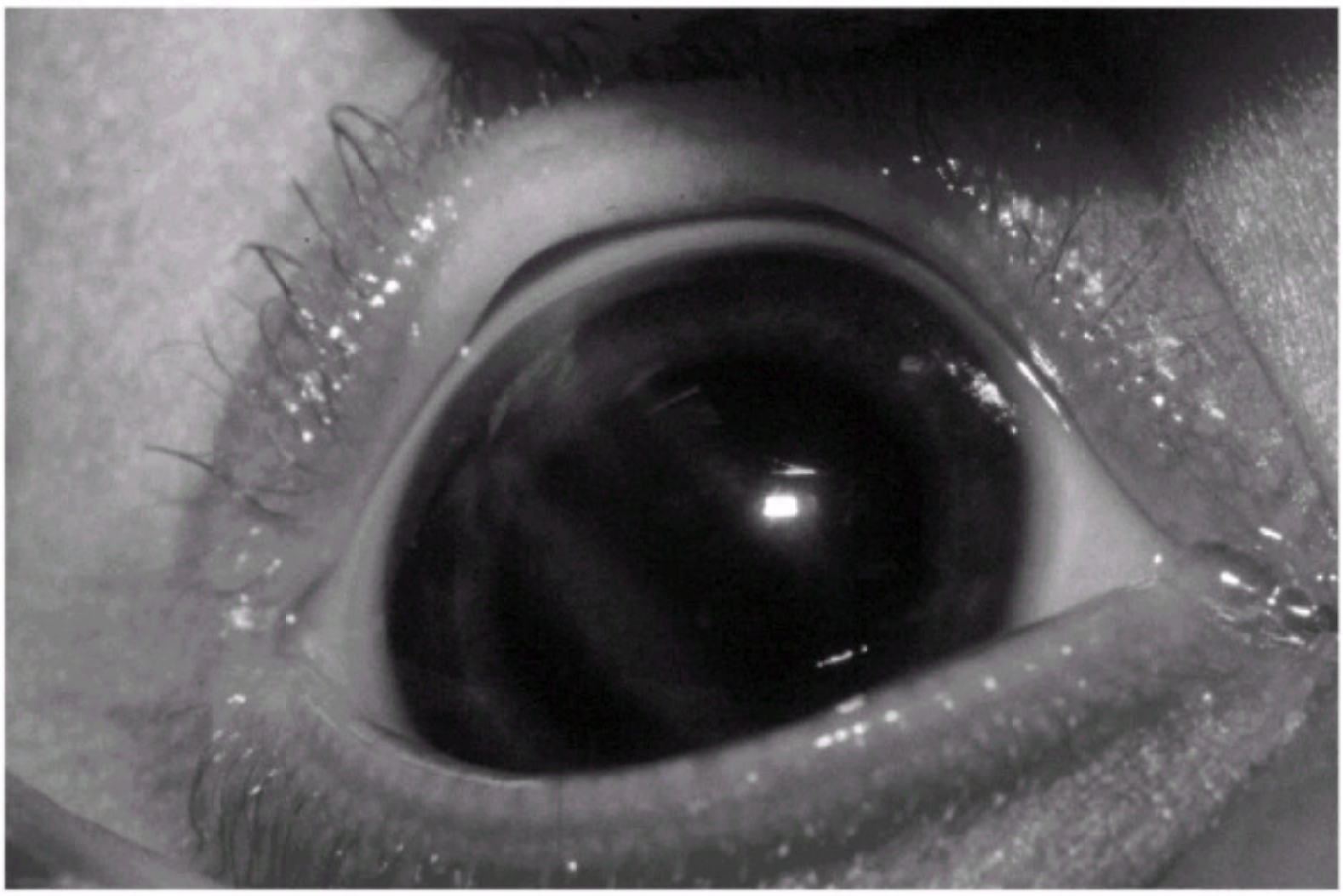

Figure 14.8 Forceps injury to the right cornea at birth resulted in two parallel linear breaks in Descemet's membrane running in an oblique direction across the visual axis; this eye showed high astigmatism and best corrected vision of 20/80, despite aggressive patching.

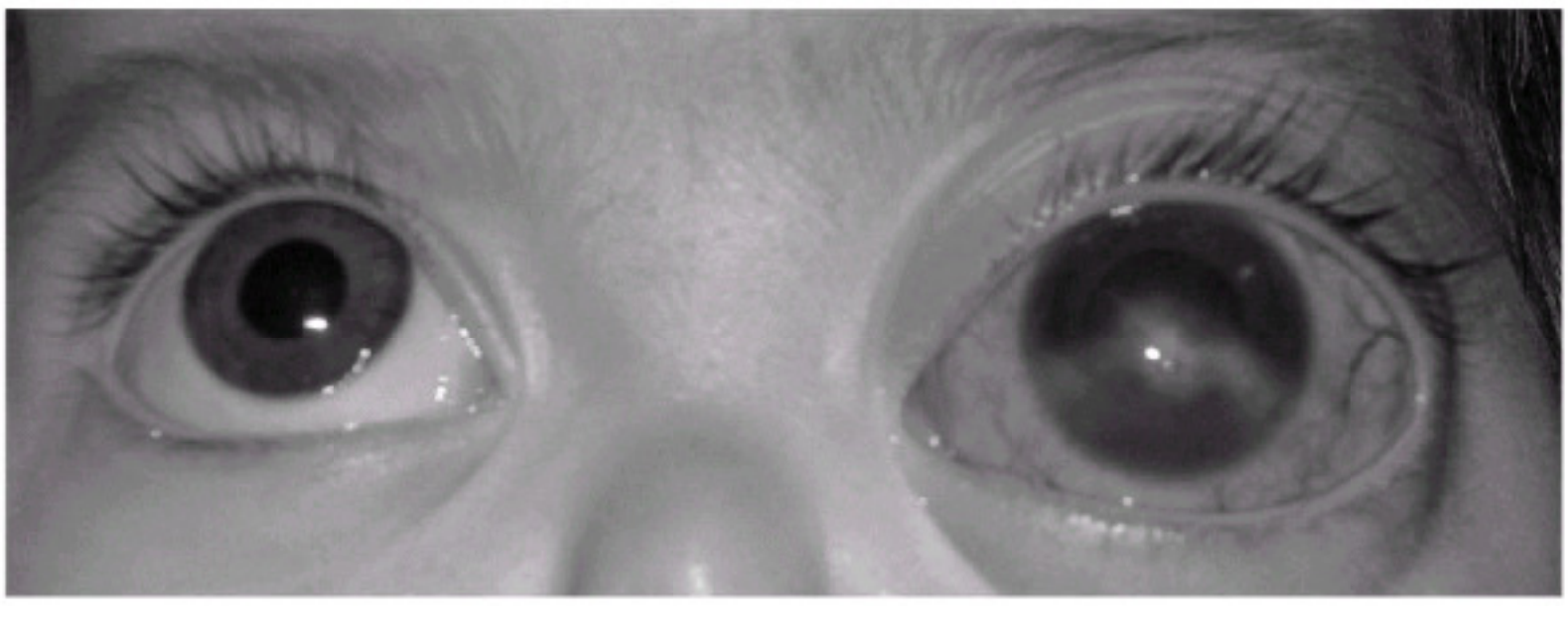

Figure 14.9 Hugely enlarged, buphthalmic left eye, in a 6-month-old infant with Pierre Robin syndrome and uncontrolled, congenital glaucoma in that eye. Corneal scarring has resulted from exposure, corneal diameter is 17 mm on the left, and spontaneous posterior lens dislocation has occurred. The eye is blind.

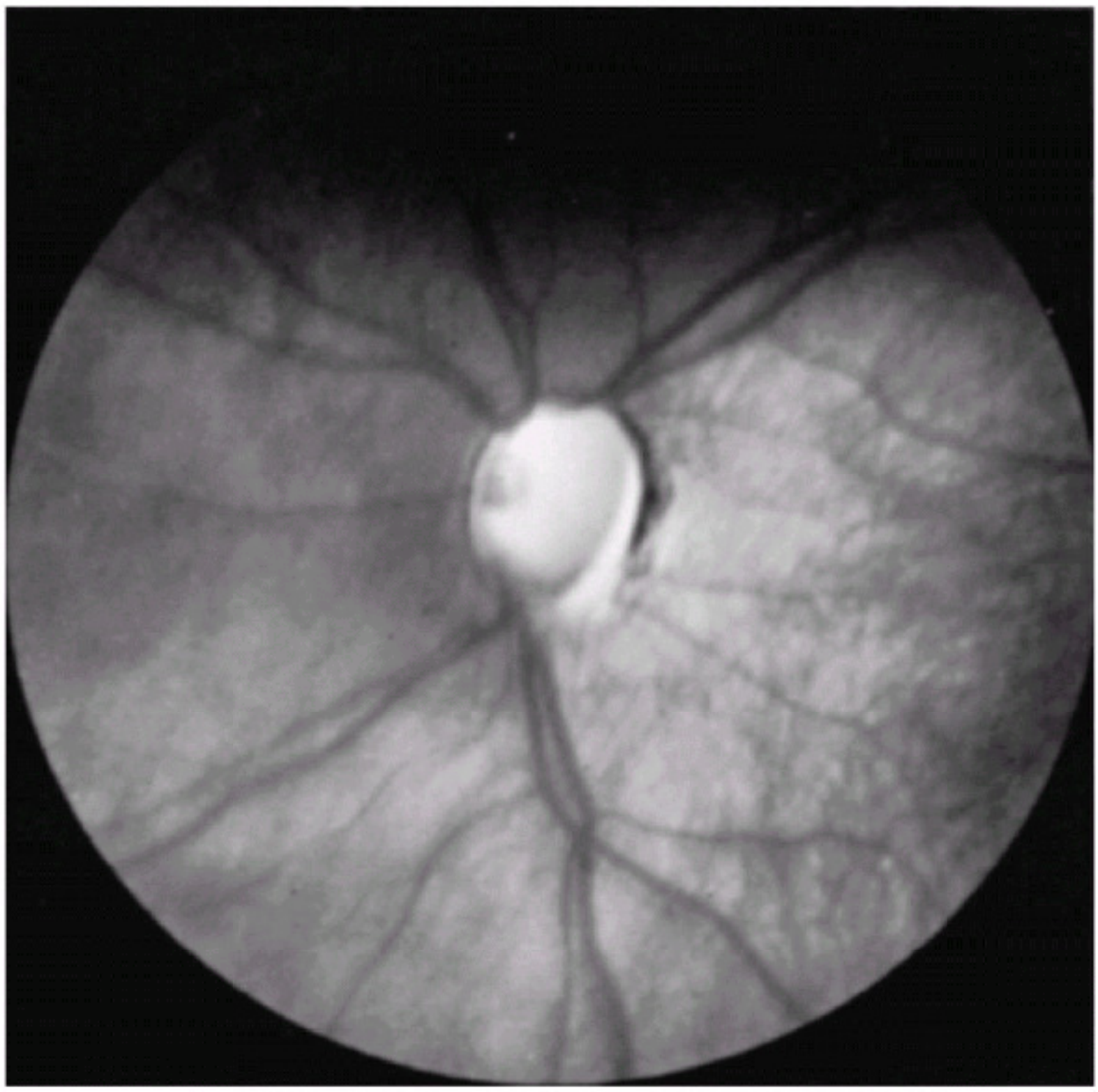

Figure 14.10 Advanced cupping and atrophy caused by congenital glaucoma in an 11-year-old boy.

Loss of vision from childhood glaucoma occurs secondary to pathological changes in the eye, such as corneal opacification and optic nerve damage. Poor vision may also occur secondary to the development of unilateral or bilateral refractive errors, which, in turn, produce amblyopia, often with associated strabismus.

OCULAR EXAMINATION

The examination of a child with suspected glaucoma includes the components of the complete pediatric eye examination. However, the glaucoma portion of this examination should address several specific objectives: (a) confirming or excluding the diagnosis of glaucoma, (b) determining the etiology of the glaucoma (if present), and (c) obtaining additional information (including any prior glaucoma treatment) needed to plan for correct management. If one can confidently exclude the diagnosis of glaucoma, or if an older child with glaucoma is to undergo a trial of medical therapy, examination under anesthesia may *not* be indicated. If indicated, the exam under anesthesia allows more detailed gonioscopy and optic nerve head examination, followed by any indicated surgical treatment.

Vision testing techniques vary greatly with the patient's age. In infants, good fixation and following and the absence of nystagmus are important indicators of good visual function. In children over age 3, visual acuity and, eventually, visual field testing can also be assessed.

The *external examination* is important to detect evidence of associated abnormalities, inflammation, or lacrimal duct obstruction.

Tonometry should be performed in both office and operating room settings. Careful measurements of IOP in the office, uninfluenced by general anesthesia, are important for diagnosis of glaucoma in either eye and for following the results of treatment. A handheld applanation tonometer is a useful instrument for determining these eye pressure measurements in infants and young children who are difficult to position precisely for more than a moment. Among various instruments used to measure IOP in children, the Perkins applanation tonometer and the Tono-Pen (a handheld Mackay-Marg-type tonometer) rank highly in terms of accuracy and ease of use in these patients (3,4). In older children the standard slit lamp-mounted Goldmann applanation instrument is often successful.

Intraocular pressure measurements are variably lowered by sedatives, narcotics, and inhalation anesthetic agents (5,6,7), while endotracheal intubation and ketamine variably raise IOP (1,8). With the possible exception of chloral hydrate conscious sedation (9), IOP measurements influenced by such drugs are generally less reliable, but high preoperative IOP measurements remain generally in an abnormal range, even under the effect of these agents. Asymmetrical IOP measurements performed under general anesthesia are a more reliable indicator of an abnormality than the interpretation of borderline abnormal IOP measurements. Normal IOP rises from infancy to reach normal adult levels by middle childhood (10). The normal range of intraocular pressure in childhood can be considered from 10 to 22 mm Hg (1). Newborns with glaucoma may demonstrate a transient postnatal interval of normal IOP, after which the IOP will again rise.

Careful inspection of the anterior segment provides vital information about a childhood glaucoma patient. The cornea is inspected for changes secondary to elevated IOP. The normal horizontal corneal diameter at birth ranges from 9.5 to 10.5 mm (mean 10 mm), enlarging to approximately 11.5 by the end of the

second year. Under age 1 year, diameters of 12 to 12.5 mm are suggestive of glaucoma, and a measurement of 13 mm or more at any time in childhood strongly suggests abnormality, as does asymmetry in corneal diameter between eyes in a child (1,11,12,13).

The depth and clarity of the anterior chamber are assessed. The pupil and irides are examined for evidence of primary anomalies or abnormalities secondary to other eye diseases (e.g., aniridia, Axenfeld-Rieger syndrome, ectropion uvea, etc.).

Gonioscopy provides the most important anatomical information about the mechanism of the glaucoma present. Koeppe gonioscopy is a useful technique for this purpose, in both the office and operating room (Figs. 14.11 and 14.12). The iris and angle structures should be inspected carefully and the results recorded.

The most characteristic feature of the child's anterior chamber angle is the trabecular meshwork, which has the appearance of a smooth, homogeneous membrane, extending from peripheral iris to Schwalbe's line, during the first year of life. It becomes coarser and more pigmented with the passing years. In addition, the peripheral iris in the young child tends to be thinner and flatter (14).

Figure 14.11 Operating room gonioscopy, using Koeppe lenses, and a portable slit lamp, provides vital diagnostic information and preparation for glaucoma surgery.

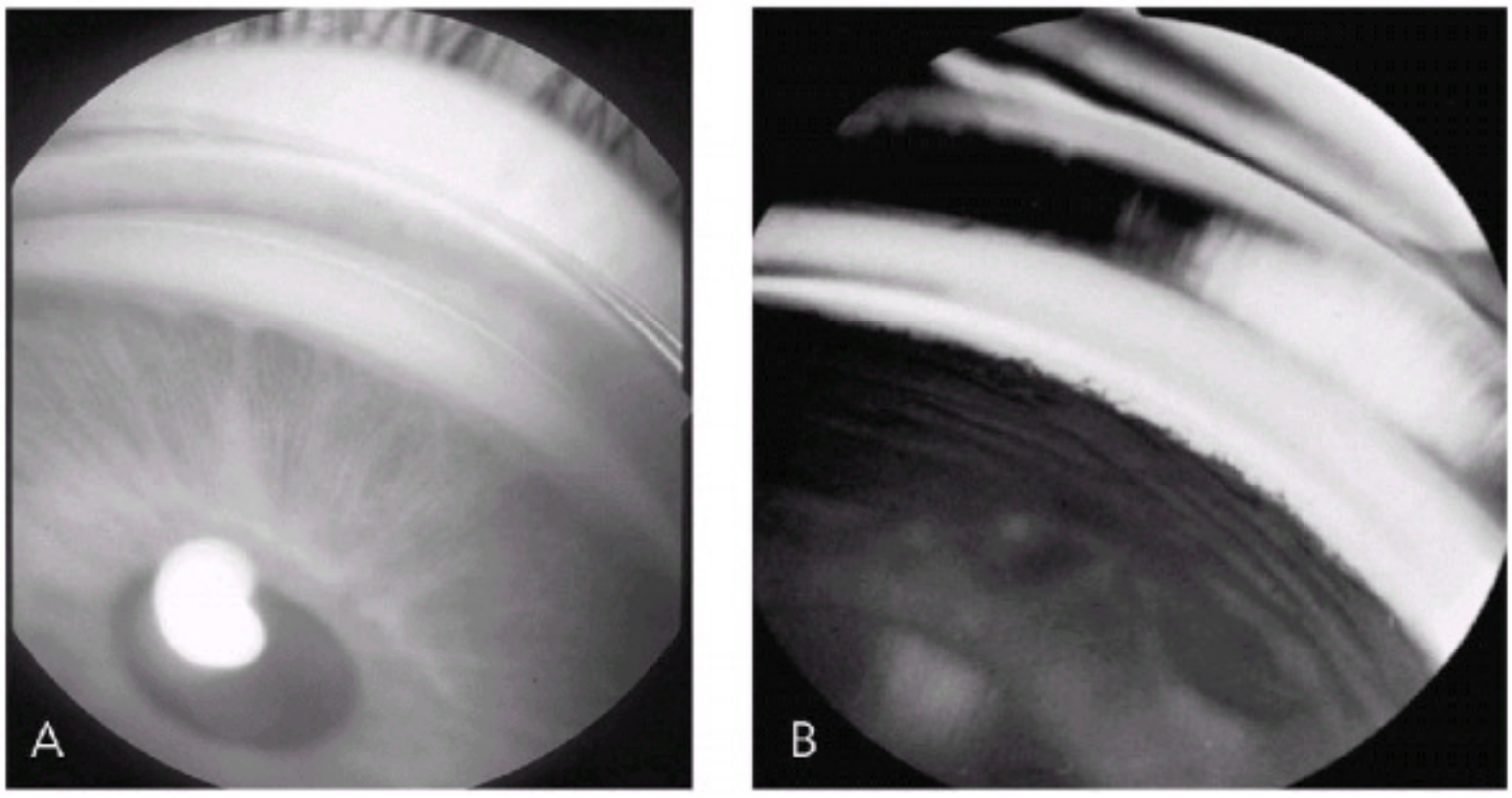

Figure 14.12 Goniophotographs of eyes with congenital glaucoma. A: Appearance often seen in lightly pigmented races, showing scalloped border of ciliary body band, no visible scleral spur, and uniform membrane-line appearance of trabecular meshwork band. B: Anterior insertion of the iris with prominent uveal processes inserted onto the trabecular meshwork. This type is more commonly seen in heavily pigmented eyes.

The iris in infantile glaucoma often shows a more anterior insertion than that of the normal infant, with altered translucency of the angle face producing an indistinct ciliary body band, trabecular mesh, and scleral spur. This translucent tissue has been historically referred to as “Barkan's membrane” (15). The angle may show other characteristics suggestive of the etiology of glaucoma. For example, in glaucoma after cataract surgery, a closed angle suggests pupillary block and the need for peripheral iridectomy/synechialysis, whereas an open angle suggests trabecular meshwork dysfunction and a different treatment strategy. An abnormally prominent Schwalbe's line and iris adhesions to the angle structures may alternatively suggest Axenfeld-Rieger syndrome (also known as iridocorneal dysgenesis). Juvenile open-angle glaucoma patients demonstrate usually a normal-appearing open angle, often with a prominent, lacy uveal meshwork.

Taken together with other findings of anterior examination (mentioned previously), the adequacy of the angle view and its findings are important guides to the appropriate surgical intervention that may be needed.

Funduscopy concentrates usually on a careful assessment of the appearance of the optic disc. Large size of the optic nerve cup and asymmetry of cupping between fellow eyes is suggestive, but not definite, evidence of glaucoma. Illustratively, the cup/disc ratio exceeded 0.3 in 68% of 126 eyes with primary infantile glaucoma examined by Shaffer and Hetherington (16) but in only 2.6% of 936 normal newborn eyes examined by Richardson (17). Marked optic cup asymmetry was noted in only 0.6% of normal eyes in the latter series, contrasted with 89% noted for infants with monocular glaucoma. Indirect ophthalmoscopy using a 28-or 20-diopter condensing lens in the office often underestimates the optic nerve cupping, which more accurately can be assessed with a 14-diopter lens or with direct ophthalmoscopy through a Koeppe lens in the operating room (Fig. 14.13). In infants and young children, initial findings can be usefully compared with changes seen after control of glaucoma (or failure of control) as a measure of success of treatment. Drawings (and when possible, photographs) of the optic nerves are valuable for later comparison. Choroidal abnormalities may also be observed, that is, in childhood glaucoma associated with a facial nevus flammeus.

Determination of refractive errors can be helpful, especially when they are asymmetrical in the setting of probable unilateral glaucoma; in this case, relative myopia of the affected eye supports the diagnosis of glaucoma. *Visual field* testing (using Goldmann kinetic or automated techniques) can be useful in older children (beginning at age 6 or 7), allowing assessment of the extent of initial field loss, as well as stability of the remaining visual field over time. Axial length measurement with *ultrasound* (during examination under anesthesia) can be an adjunct to serial corneal diameter measurements in following infants and young children under treatment for glaucoma (13). Ultrasound pachymetry (to measure the central corneal thickness) has recently proven relevant to evaluation of IOP in cases of adult open-angle glaucoma, especially when the cornea is much thinner or thicker than average (hence, causing an underestimation or overestimation, respectively, of the true IOP by Goldmann applanation) (18,19). The importance of central corneal thickness in the evaluation and management of children with glaucoma remains to be determined at the present time. Ocular coherence tomography of the nerve fiber layer (20) is now routinely used as an adjunct to optic nerve evaluation in the diagnosis and management

of adults with glaucoma; these and other techniques may someday also prove valuable in the care of children with glaucoma.

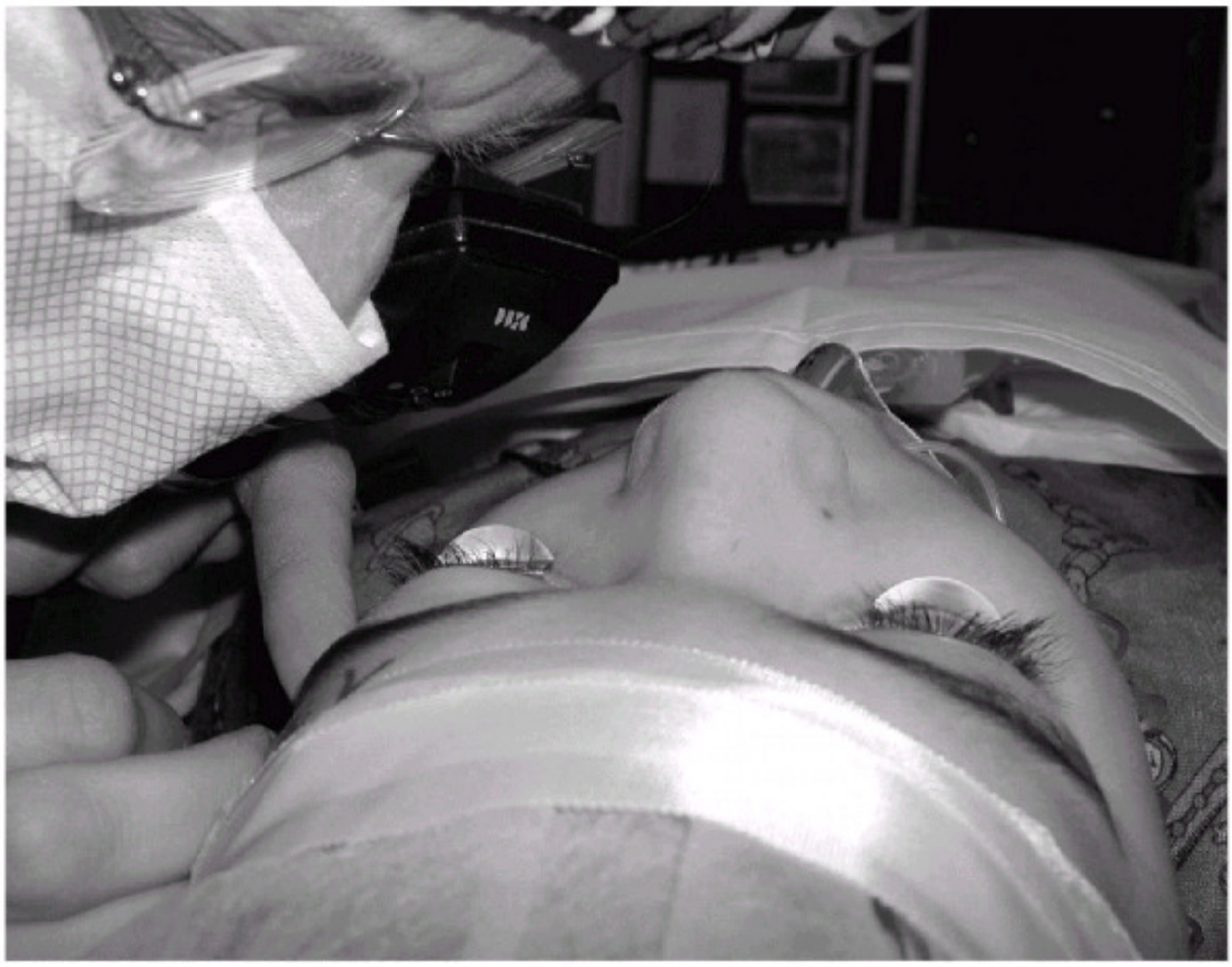

Figure 14.13 The appearance of the optic nerve can be well seen through a Koeppe lens. This helps neutralize the changes in size due to refractive error and facilitates the exam through a fairly small pupil. Drawings of the cupping are helpful, as are photographs that allow future comparisons to be made.

DIFFERENTIAL DIAGNOSIS

Many conditions of the eye may produce ocular changes that suggest glaucoma, including corneal disease or anterior chamber inflammation, which may cause photophobia and tearing. Storage diseases associated with corneal clouding or hereditary corneal dystrophies with opacification of the cornea could stimulate concern for glaucoma in a child. Corneal enlargement can also be a primary disorder without associated glaucoma. Tearing is most often secondary to temporary congenital nasolacrimal duct obstruction. It is important to *always rule out* glaucoma when any of these signs or symptoms is present, even when initial evidence suggests a more common nonglaucomatous cause. Glaucoma may also complicate inflammation or trauma to the anterior segment, may be found with storage diseases and with primary enlargement of the cornea, and is seen, certainly, coincidentally with lacrimal duct obstruction (21).

In summary, the signs of glaucoma are shared by other eye diseases and indicate the careful anterior segment examination and tonometry necessary to rule out this abnormality. The identification of some other cause of such signs does not, in itself, eliminate the risk of glaucoma.

Table 14.1 reveals that a wide variety of conditions is associated with primary and secondary glaucoma in children.

PRIMARY CHILDHOOD GLAUCOMA

Primary Congenital Open-Angle Glaucoma

Primary congenital open-angle glaucoma (PCOAG) is the most common primary pediatric glaucoma, with an estimated incidence of approximately 1 in 10,000 live births and with no predilection for race or gender. Most cases (65% to 80%) are bilateral (1). More than 80% of all cases have onset of the disease within the first year of life, with about 25% diagnosed as newborns and more than 60% presenting by age 6 months (1,22). Evidence suggests that this glaucoma is always present early in life and is of variable severity. When it is mild, recognition may be delayed, allowing time for chronic visual changes to occur secondary to the elevations in intraocular pressure. Typically, the corneal abnormalities consisting of progressive edema associated with breaks in Descemet's membrane occur during the first year of life. Recognition of glaucoma depends on the sensitivity of caretakers to the significance of these signs and symptoms (23).

Although the majority of primary infantile glaucoma cases are sporadic (no known family history), about 10% are familial, transmitted usually as an autosomal recessive trait, with penetrance varying from 40% to 100% (24,25). More recently, several investigators have localized primary infantile glaucoma-related genes. Two loci, GLC3A, linked to the 2p21 region; and GLC3B, linked to 1p36 region, have been identified, and the presence of at least a third locus in the human genome, responsible for congenital glaucoma, is suspected. Mutations in the CYP1B1 (cytochrome P4501B1) gene have been identified in those cases of congenital glaucoma linked to GLC3A (26,27).

The significant inherited defect is confined to the filtration tissues, rendering them less permeable to the passage of aqueous humor. The gonioscopic abnormality features typically decreased transparency of the tissues over the scleral spur and ciliary body band, so that these normal angle landmarks are difficult to define. The width of the trabecular meshwork and ciliary body may also be diminished, giving the impression of an anterior insertion of the iris (see earlier text on gonioscopy).

Surgical intervention is the definitive treatment for primary congenital glaucoma, with angle surgery (usually goniotomy or trabeculotomy) successful in the majority of cases, especially those with presentation between ages 3 and 12 months; surgical success drops for those with presentation at birth or after ages 1 to 2 years

(see later text). In cases refractory to angle surgery, filtration surgery (28,29,30,31), glaucoma implant surgery (31,32,33,34,35,36), and cycloablation (37) have been used with variable success, depending upon the reported series (see Treatment in later text). Visual prognosis is dependent not only upon the timely diagnosis and IOP reduction, but also upon the secondary corneal, refractive, and optic nerve changes produced by the initially elevated IOP (1).

Juvenile Open-Angle Glaucoma (JOAG)

In contrast to primary congenital or infantile glaucoma, juvenile open-angle glaucoma (JOAG), a rare disease, is an autosomal dominant early-onset form of primary open-angle glaucoma. JOAG is characterized by acquired and marked bilateral IOP elevation, with usual onset between ages 4 and 35 years, often with a strong family history. Ocular damage, usually in the form of optic nerve cupping and visual field loss, is usually asymptomatic, unless myopia brings the child to eye examination for decreased distance vision. Absent are the corneal stigmata present usually in infant-onset glaucoma. Gonioscopy reveals normal-appearing angle structures. Treatment is difficult, often beginning with medication and proceeding to filtration or tube implant surgery, although angle surgery may be helpful in some cases (see later text).

JOAG was first linked to chromosome 1q21-31 by Sheffield et al (38) in 1993. Four years later, mutations were reported in the responsible gene, the trabecular meshwork glucocorticoid response gene (TIGR, now renamed myocilin) (39).

Primary Pediatric Glaucoma Associated with Systemic Diseases

Primary glaucoma in children may be seen in association with certain systemic diseases in which ocular abnormalities are included in the syndrome complex (Table 14.1).

Sturge-Weber Syndrome

Glaucoma is present commonly with Sturge-Weber syndrome in association with a facial nevus flammeus of the ipsilateral upper eyelid and abnormal vasculature of the leptomeninges. Intracranial involvement may be complicated by epilepsy, paralysis, and visual field defects. The glaucoma may be congenital or acquired and is most often unilateral. The onset of glaucoma seems bimodal, with some cases presenting in early infancy, while others occur later in childhood. Inspection of the conjunctiva often shows an abnormal number and tortuosity of blood vessels with elevation of venous pressure. A striking episcleral vascular abnormality is present behind the limbus circumferentially. Gonioscopy reveals minor angle anatomical changes, usually without vascular abnormalities of the angle; blood can often be identified in Schlemm's canal. The iris of the involved eye is often more pigmented than that of the fellow eye. Funduscopy reveals, generally, evidence of a choroidal hemangioma and disc changes secondary to glaucoma. The etiology of glaucoma in Sturge-Weber syndrome is most often considered to be increased episcleral venous pressure secondary to the ipsilateral choroidal hemangioma, although congenitally abnormal angle structures may contribute to infant-onset disease (40).

Congenital or infancy-onset glaucoma in Sturge-Weber syndrome requires usually surgical intervention. Although goniosurgery is typically less effective than in cases of primary congenital glaucoma, IOP reduction has been reported with both trabeculotomy and with combined trabeculotomy-trabeculectomy for these cases (41,42). Medication is the first-line treatment for glaucoma presenting after infancy, with aqueous suppressants being the mainstay of therapy. Although guarded trabeculectomy has been performed in these cases, success has also been reported with glaucoma implant surgery (43,44) as well as with careful cycloablation (45). In these eyes with choroidal hemangioma, rapid choroidal expansion and hemorrhage may complicate any intraocular surgery that decompresses the eye, either during or after the procedure.

Neurofibromatosis

Neurofibromatosis type 1 (NF-1) is a common systemic disease transmitted by autosomal dominant inheritance. Expression of this disease is variable, as are the tissues affected. Skin involvement with café-au-lait spots is common but may not appear until the end of the first year of life. Lisch nodules appear on the iris in the majority of affected individuals but do not often appear until puberty. Childhood glaucoma associated with this disease is congenital, rare, usually unilateral, and most often associated with a lid plexiform neuroma (46). Enlargement of the involved eye may be striking, suggesting other causes of accelerated growth, in addition to glaucoma. The iris possesses an ectropion uvea by the end of the first year of life, and the choroid often appears more densely pigmented than the contralateral structure. The angle shows a circumferential covering by an anterior extension of iris stromal tissue.

Several possible mechanisms of glaucoma in NF-1 have been proposed, including direct effects on the normal angle development, secondary changes to the angle tissue, as well as angle closure by thickened ciliary body and choroid or directly by fibrovascular tissue (47). NF-1 has been linked to the neurofibromin gene, located on 17q11.2 (OMIM reference no. 162200) (48). The treatment of glaucoma associated with NF-1 is difficult, with angle surgery unlikely to be successful in glaucoma control. If medical therapy is unsuccessful, reasonable surgical options in the older child include filtration surgery, glaucoma implant surgery, or cycloablation.

Lowe (Oculocerebrorenal) Syndrome

A rare X-linked recessive disease, Lowe syndrome is associated with a high incidence of bilateral glaucoma and cataracts. Affected children usually have associated mental retardation, renal rickets, aminoaciduria, hypotonia, acidemia, and irritability. Additional ophthalmic features of Lowe syndrome include microphthalmia, strabismus, nystagmus, miosis (rendering cataract removal difficult), and iris atrophy. Lowe syndrome has been linked to the locus Xq26.1 (48,49) (OMIM reference no. 309000). Gonioscopy does not show a characteristic angle anomaly; rather, the angle closely resembles that seen in patients with primary congenital open-angle glaucoma.

Treatment of this glaucoma is difficult. Medical control rarely proves adequate. Goniotomy surgery may be disappointing and is more frequently complicated by serious hemorrhage than when tried in primary congenital open-angle glaucoma. Judicious use of glaucoma drainage implant devices and cyclodestructive surgery may also be needed in cases refractory to medications (50,51).

Axenfeld-Rieger Syndrome

Axenfeld-Rieger syndrome represents a type of the anterior chamber cleavage disorder often associated with systemic abnormalities. The collective term *Axenfeld-Rieger* (A-R) syndrome includes all clinical variations within this spectrum of developmental anomalies (52). Regardless of ocular manifestations, all patients with A-R syndrome share the same general features: (a) a bilateral, developmental disorder of the eyes; (b) a frequent family history of the disorder, with an autosomal dominant mode of inheritance; (c) no sex predilection; (d) frequent systemic developmental defects; and (e) a high incidence of associated glaucoma. The iris may show hypoplasia of the anterior stromal leaf, iridotrabecular and iridocorneal processes, and posterior embryotoxon. Other deformities may occur in the iris, such as corectopia. Glaucoma is a common complication, occurring in more than 50% of cases, often in middle or late childhood. Dental anomalies in the form of oligodontia and anodontia, dysplasias of the skull and skeleton, and umbilical abnormalities are common.

Three chromosomal loci have recently been demonstrated to link to Axenfeld-Rieger syndrome and related phenotypes. These loci are on chromosomes 4q25, 6p25, and 13q14. The genes at chromosomes 4q25 and 6p25 have been identified as PITX2 and FKHL7, respectively (53). Mutations in these genes can cause a wide variety of

phenotypes that share features with Axenfeld-Rieger syndrome.

Primary Pediatric Glaucoma Associated with Ocular Anomalies

Primary pediatric glaucomas may also be associated with other ocular anomalies. In some of these well-recognized disorders, systemic abnormalities may also occur (Table 14.1).

Aniridia

Aniridia is a bilateral developmental disorder, characterized by the congenital absence of a normal iris; the iris is invariably partially absent, with a rudimentary stump of variable width. Glaucoma occurs in at least 50% of patients with aniridia. Aniridia is associated with multiple ocular defects, which variably manifest from birth to later childhood or after. Some forms of aniridia also have associated systemic abnormalities.

Aniridia is inherited in an autosomal dominant fashion with almost complete penetrance in about two thirds of cases, with the remaining cases being sporadic. This disorder has been associated with mutations in the PAX6 gene, located on chromosome 11p13 (locus symbol AN2), telomeric to the Wilms tumor predisposition gene (WT1) (48) (OMIM reference no. 106210).

It has been reported that approximately 68% of patients with a deletion of chromosome 11 and aniridia will develop Wilms tumor before age 3 years (54).

The congenital ocular anomalies associated with aniridia include a small cornea, hypoplastic iris leaf, cataracts, macular hypoplasia, and filtration angle abnormalities. Progressive dystrophic ocular abnormalities occur in aniridia, causing corneal opacification, increased lens opacification, and glaucoma secondary to increased filtration angle abnormalities. On gonioscopy, progressive trabecular blockage by movement of the residual iris tissue in front of the trabeculum can usually be seen in most aniridia patients with glaucoma (55).

In aniridic infants with a family history of aniridic glaucoma, careful monitoring of the angle by serial gonioscopy is indicated, with consideration of prophylactic goniosurgery to prevent blockage of the trabecular meshwork, if progressive abnormalities of the angle occur (56).

If significant glaucoma is present, medical therapy is appropriate. No form of surgical treatment has been proved to be best for aniridia glaucoma. Goniotomy may be helpful in infantile cases. Trabeculectomy may be successful but is particularly challenging due to the propensity of these eyes to develop postoperative flat anterior chambers. Glaucoma implant surgery and very careful cycloablation may be needed for particularly refractory cases (57,58,59).

Anterior Chamber Cleavage Syndrome (Iridocorneal Dysgenesis)

Malformations of the ocular anterior segment occur, often involving the cornea, angle, iris, and lens, and usually show evidence of incomplete formation of the anterior chamber cavity. Although there are variable phenotypes, several of these conditions may actually be allelic with the A-R syndrome. The term *Axenfeld's anomaly*, in which the filtration angle is partially obscured from view attachments between the iris and a prominent Schwalbe's ring, is better considered as part of the A-R syndrome (see earlier text).

Peters Anomaly

This variation of the so-called anterior chamber cleavage syndrome consists of a posterior defect in Descemet's membrane associated with a leukoma in that area with attachment of the iris to much of the periphery of the corneal abnormality. The lens may also be involved, with cataract and/or attachment between the lens and the posterior corneal defect. The angle may also be defective, the low incidence of glaucoma in about 50% of cases.

Peters anomaly presents at birth and is usually bilateral and sporadic. Although it typically occurs in the absence of additional abnormalities, associations with a wide range of systemic and other ocular anomalies have been reported (60). Because of the varied genetic and nongenetic patterns and the spectrum of ocular and systemic abnormalities, some consider Peters anomaly to be a morphological finding rather than a distinct entity (61). Peters anomaly can be caused by mutation in the PAX6 gene, the PITX2 gene, the CYP1B1 gene, or the FOXC1 gene (48) (OMIM reference nos. 607108, 601542, 601771, 601090, respectively).

Management of the glaucoma associated with Peters anomaly is often complicated by the presence of corneal opacity, cataract, and shallow or absent anterior chamber. In these cases, where angle surgery is not feasible, medical therapy is the first-line treatment, followed by surgical treatment with glaucoma implant surgery and/or cycloablation. Repeated surgeries are often needed, often with an adverse effect on an existing corneal transplant. Phthisis and retinal detachment may result from a variety of mechanisms in these small, complex eyes.

Corneal transplant should be avoided in favor of optical iridectomy in cases where corneal opacification is only partial and a visual axis can be obtained without it (Fig. 14.14) (62,63,64).

Familial Hypoplasia of the Iris

Individuals with this rare cause of childhood glaucoma may have congenital hypoplasia of the iris but lack the anterior chamber abnormalities of the A-R syndrome. This autosomal dominant disorder (also termed *iridogoniodysgenesis anomaly, type I*), characterized by iris hypoplasia, goniodysgenesis, and juvenile glaucoma, has been mapped to gene locus 6p26 and appears due to mutations in the gene FKHL7. A similar condition has been identified, which includes nonocular features; this has been dubbed iridogoniodysgenesis type 2, maps to 4q25, results from mutations in the gene PITX2, and may be allelic to A-R syndrome (OMIM reference nos. 6011631 and 137600, respectively) (48). Treatment by goniotomy is sometimes successful in these cases.

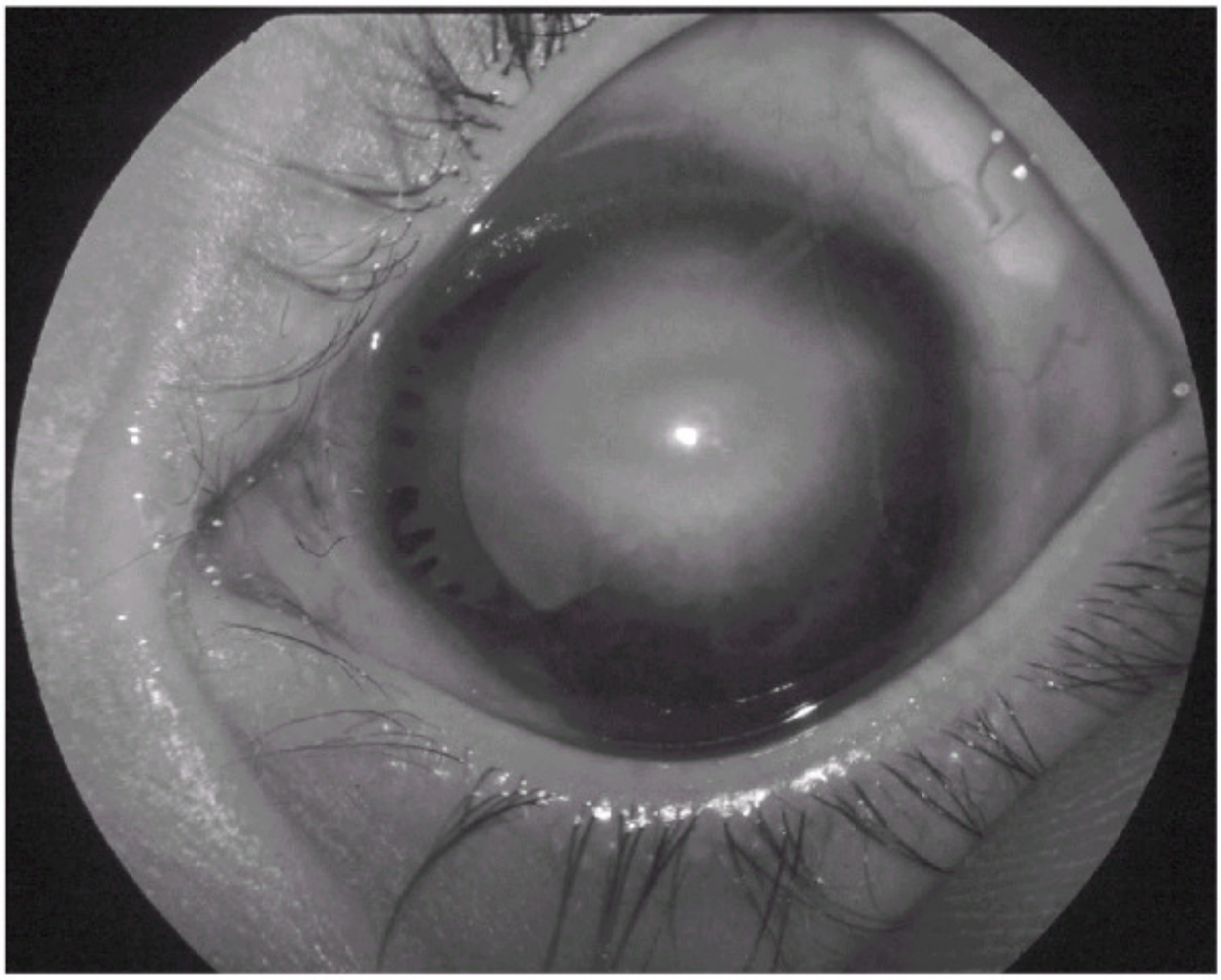

Figure 14.14 Left eye of an infant afflicted with severe bilateral Peters' anomaly. After lowering of IOP by Ahmed glaucoma implant, an optical iridectomy has been performed, creating an imperfect visual axis in this phakic eye, without resorting to penetrating keratoplasty (which has already failed in the fellow eye).

Posterior Polymorphous Dystrophy

This spectrum of disorders is an autosomal dominant condition that is characteristically responsible for bilateral defects of the cornea at the level of Descemet's membrane and usually has little effect on vision. However, a more severe expression of this disease exists that is evident in children from birth or early life. It is characterized by corneal opacification secondary to edema of the stroma and epithelium and opacification at the level of Descemet's membrane. These abnormalities may be associated with the acute onset of light sensitivity during the first year of life, with or without complicating glaucoma. The latter abnormality can be of variable severity in any quadrant of the involved eye and is seen as an irregular, diffuse, white opacification of Descemet's membrane. In some affected individuals, corneal changes are associated with peripheral iridocorneal adhesions, iris atrophy, and corectopia. Glaucoma occurs in about 15% of patients with posterior polymorphous dystrophy, in both the presence and apparent absence of iridocorneal adhesions. The disorder has been mapped to locus 20p11.2-q11.2 (OMIM reference no. 122000) (48).

SECONDARY CHILDHOOD GLAUCOMA

Pediatric glaucoma may occur secondary to a wide variety of ophthalmic conditions (Table 14.1). Secondary glaucoma is a complication of another eye disease rather than a primary disorder of the aqueous humor filtration mechanism.

Trauma

The most important glaucoma in children, following injury, is that caused by an acute or secondary hemorrhage into the anterior chamber (hyphema). This may occur rarely acutely in association with blunt injury but is seen more commonly secondarily, 1 to 3 days after the injury, in association with a secondary hemorrhage or with very large initial hyphemas. Children with significant trauma to the eye should be examined promptly for evidence of serious injury. The finding of a gross hyphema increases the likelihood of secondary hemorrhage. Such patients are placed at rest and treated with topical steroids and cycloplegics, with avoidance of acetylsalicylic acid. Serial examination, including IOP measurement, is important, especially in children with sickle cell hemoglobinopathies, where moderate IOP rise may result in significant optic nerve damage (65). There are conflicting reports regarding the use of various agents to lessen the occurrence of rebleeding, including oral steroids and antifibrinolytic agents (most notably aminocaproic acid) (66). The occurrence of glaucoma secondary to recurrent hemorrhage can be both painful and damaging. Medical glaucoma treatment and anterior chamber irrigation for persistent glaucoma may be required. IOP normalizes usually after resolution of acute hyphema; however, such eyes need long-term follow-up for the development of angle recession glaucoma, which may be delayed many years in onset.

Neoplasm

The most common cause of glaucoma secondary to neoplasia is retinoblastoma. Its occurrence is usually not associated with the presence of tumor cells in the anterior chamber but, rather, is secondary to rubeosis iridis and/or angle closure. Such eyes usually show advanced posterior segment tumor growth and require enucleation. Medulloepithelioma, a neoplasm of the ciliary epithelium, can also induce secondary neovascular glaucoma.

Juvenile xanthogranuloma is a rare condition associated with histiocytic infiltration of the iris. Glaucoma may occur secondary to the accumulation of histiocytes in

the angle structures or secondary to spontaneous hyphema formation. Treatment is usually medical. Acetazolamide may be necessary for better control of the intraocular pressure, and systemic and topical steroids should be used to treat the histiocyte accumulation. Difficult cases may require surgical intervention in the form of glaucoma implant and/or cycloablation.

Inflammation

Acute or chronic glaucoma in children may occur secondary to inflammation. When acute, the blockage of aqueous humor outflow is usually secondary to iris bombe formation and angle closure.

Chronic glaucoma secondary to inflammation is more common than the acute form and may be asymptomatic. It is most often seen with chronic anterior uveitis, which may be associated with signs of juvenile rheumatoid arthritis or chronic cyclitis. The possible adverse effect of steroid medication on the glaucoma must also be considered. Treatment of acute glaucoma associated with iris bombe is usually surgical to produce an iridotomy or iridectomy.

Synechialysis may be necessary to open the angle, even after pupillary block is relieved. Both goniotomy and medical treatment of chronic open-angle glaucoma secondary to iritis are helpful for treatment of this condition; tube implant surgery has also been reported to be quite successful in refractory cases (67,68).

Lens-Induced Glaucoma

Children with ectopia lentis (from a variety of causes, e.g., homocystinuria, Weill-Marchesani, Marfan syndrome) may develop acute glaucoma secondary to forward shifting of the lens into the papillary aperture, with resultant pupillary block and angle closure. This glaucoma is acute, painful, and often associated with vomiting and high IOP. Nonsurgical treatment of this acute glaucoma includes: placing the patient supine, manual displacement of the lens posteriorly in the eye, using a muscle hook (often with a bandage contact lens placed), medication with aqueous suppressants, mydriatics, analgesics, and post-episode use of miotics. Iridectomy performed at a later time will prevent the acute glaucoma but may not prevent displacement of the lens into the pupil and the anterior chamber (69). Surgical lensectomy, for repeated cases, is more safely accomplished after IOP has been normalized.

Aphakic Glaucoma

Glaucoma is quite common after removal of congenital developmental cataracts (reported incidence from 3% to 41%) and is usually of the open-angle type, although cases of angle closure glaucoma have also been reported (associated usually with forward movement of the vitreous face and/or iris bombe from pupil seclusion). Children with cataract removal at an early age, those associated with microphthalmia, and those with persistent hyperplastic primary vitreous, are at higher risk for glaucoma after lens removal. The onset of open-angle glaucoma after cataract removal is often delayed by many years and may be asymptomatic in onset (70,71). The angle, while open, demonstrates typical abnormalities not present before cataract removal (72). Peripheral iridectomy (with or without vitrectomy) can be curative in angle-closure cases. Medical therapy is the first-line treatment for cases of open-angle glaucoma in aphakia. Angle surgery is not usually successful in these cases, which can do well with glaucoma implant surgery, and cycloablation in selected refractory cases (73). Primary or secondary intraocular lens implantation does not have an obvious impact, either causative or protective, with regard to associated glaucoma. The mechanism of aphakic glaucoma is not known, although several disparate theories each have their proponents.

Miscellaneous Causes

Secondary glaucoma in children may occur after use of steroid eye drops and as a complication of retinopathy or prematurity. It may also occur secondary to prenatal infection with rubella virus and be manifest as a congenital glaucoma or may occur later in childhood. Other rarer causes have also been noted (Table 14.1).

In summary, the causes of secondary childhood glaucoma are extensive, and this possibility must be considered frequently in pediatric ophthalmology. Determining the mechanism of glaucoma in each given case helps the physician to outline the optimal treatment strategy for that particular child.

TREATMENT

As with adult glaucoma, the success of pediatric glaucoma treatment depends on early diagnosis and adequate IOP control. The specific therapy is determined by the type of glaucoma present. Both medical treatment and surgery are often used.

Medical Management

Although surgical management is still the first-line treatment for many children with glaucoma, medical therapy plays an ever-important role in the management of many childhood glaucomas. Hence, angle surgery is indicated for most cases of primary congenital glaucoma (and all angle-closure glaucomas), whereas medical therapy is the initial first-line treatment for juvenile and aphakic open-angle glaucoma, as well as most causes of secondary open-angle glaucoma (see previous text). In the past decade, tremendous advances in pharmacological therapy of glaucoma have increased the options for medical treatment of childhood glaucoma, although all currently FDA-approved hypotensive drugs achieved that approval without safety of efficacy testing in the pediatric population. Clinical experience has proven the worth of some drugs, while highlighting the significant dangers of others when used in infants and young children. Besides inadequate IOP reduction, multiple factors conspire against the success of long-term medical therapy of children with glaucoma: the difficulties with long-term compliance, adequate ascertainment of drug-induced side effects, and potential adverse systemic effects of protracted therapy, among others.

The glaucoma drugs can be divided into five main categories. The following brief descriptions and comments regarding their use in children will hopefully guide the clinician who uses medications to treat children with glaucoma.

Carbonic Anhydrase Inhibitors

Oral carbonic anhydrase inhibitors, primarily acetazolamide (Diamox), have effectively reduced elevated IOP in infants and children with primary infantile (and other types) glaucoma for decades and often reduce IOP in these patients about 20% to 35%. Acetazolamide should be given orally with food or milk tid, at a dose range of 10 to 20 mg/kg per day. Notable side effects include diarrhea, diminished energy levels, and loss of appetite and weight. Metabolic acidosis may develop in infants, often manifest in infants as tachypnea, and is treatable with oral sodium

citrate and citric acid oral solution (Bicitra, 1 meq/kg per day).

Two topical carbonic anhydrase inhibitors are now available—dorzolamide (Trusopt) and brinzolamide (Azopt). These two drugs offer a viable alternative to acetazolamide, with little or no occurrence of systemic side effects. The addition of dorzolamide to oral acetazolamide has been reported, in selected cases, to reduce IOP further than when either drug is used alone. Both dorzolamide and brinzolamide should be dosed at bid (or tid for maximal effect) and produce similar IOP reduction, with slightly less ocular stinging reported from brinzolamide (author's personal experience).

The carbonic anhydrase inhibitors are very useful drugs for treating pediatric glaucoma patients and may be appropriate first- and second-line agents, respectively, in cases where ß-blocker use is contraindicated or inadequately effective (Table 14.2; see also later text).

TABLE 14.2 TOPICAL GLAUCOMA MEDICATIONS IN PEDIATRIC GLAUCOMA

Medication (*Class*)	Indications	Contraindications/Side Effects
ß-*Blockers* Nonselective Selective (?safer with asthma)	1st-line for many; 2nd-line for some older children	Systemic effects: bronchospasm, bradycardia; avoid in premature or tiny infants, any history of reactive airways; start with 0.25% in higher risk children
Carbonic Anhydrase Inhibitors Topical (dorzolamide, brinzolamide)	1st- or 2nd-line in young children; add as well to other classes	Systemically safe; may wish to avoid or use as later option in children with compromised corneas, especially with corneal transplant
Miotics Echothiophate iodide Pilocarpine	Echothiophate rarely used in aphakia; pilocarpine after angle surgery and some JOAG	Systemic effects (echothiophate): diarrhea (sometimes); interaction with succinyl choline for general anesthesia; possible proinflammatory effect; (both) headache; (both) myopic shift
Adrenergic Agonists Epinephrine compounds a-2-agonists Apraclonidine (0.5%) Brimonidine	Not very useful During/after angle surgery; short-term in infants and after corneal transplant Only in older children!!! 2nd- or 3rd-line in JOAG, aphakia; older children with other glaucoma types	Systemic effects: hypertension, tachycardia Systemically safe; effect may wear off; rarely local allergy or red eye Do not use in infants and small children less than 40 pounds (may cause bradycardia, hypotension, hypothermia, hypotonia, apnea, especially if used with ß-blocker)
Prostaglandins and Similar Latanoprost; travoprost; bimatoprost; unoprostone	1st-, 2nd-, or 3rd-line in JOAG; usually 2nd- or 3rd-line after ß-blockers and topical CAIs in others	Systemically; grows long, thick, eyelashes; redness not uncommon (especially with bimatoprost); use caution with all in uveitic glaucoma

CAI, carbonic anhydrase inhibitors; JOAG, juvenile open-angle glaucoma.

Miotics

Miotic drugs (cholinergic stimulators) have largely been supplanted by newer medications, in the treatment of both adults and children with glaucoma. Pilocarpine retains its usefulness to induce and maintain miosis before and after goniotomy or trabeculotomy for congenital glaucoma. Stronger miotics, such as echothiophate iodide (Phospholine Iodide), have also been useful in selected cases of aphakic glaucoma.

Beta-Adrenergic Antagonists (Beta Blockers)

Topical ß-blockers are effective aqueous suppressants that play an important role in the treatment of children with glaucoma. Most published studies have examined the effects of timolol, the first topical ß-blocker to become available (in 1978). Although ß-blockers are well tolerated from

an ocular point of view, systemic side effects—most notably bradycardia and respiratory distress due to apnea or asthma exacerbation—have been reported in a minority of children treated with timolol (74). Topical ß-blockers should be used (or not at all) with extreme caution in neonates. When used in small children, timolol treatment should always begin with 0.25% drops, excluding those children with a history of asthma or bradycardia; punctal occlusion should be performed when possible (75). Based on experience in adults, betaxolol, as a relatively ß-1-selective agent, may be less prone to precipitating acute asthma attacks (which may present as coughing) than the nonselective ß-blockers. Beta blockers are usually additive to carbonic anhydrase inhibitors in treating children with glaucoma. Topical beta blockers have an important role in treating children with glaucoma and are appropriate first-line drugs for many (Table 14.2).

Adrenergic Agonists

Epinephrine compounds, with significant systemic and ocular side effects, coupled with limited effectiveness, have little place in the current treatment of adults and children with glaucoma. Two a-2-agonists (apraclonidine and brimonidine) are currently approved for treating adults with glaucoma. Although the authors are aware of no published data to guide the use of apraclonidine (Iopidine 0.5%) in children with glaucoma, this drug can be useful in the setting of angle surgery to minimize intraoperative hyphema (see later text) and may have a role in the short-term treatment of infants and small children who cannot tolerate ß-blockers or who have had recent corneal transplantation (and in whom one therefore wishes to avoid topical carbonic anhydrase inhibitors) (personal unpublished data).

Brimonidine (currently available as Alphagan P 0.15% and brimonidine 0.2%) can be useful in reducing IOP in older children but must be used with extreme caution in younger children. Topical brimonidine use has produced life-threatening systemic side effects in infants (bradycardia, hypotension, hypothermia, hypotonia, and apnea), and severe somnolence in toddlers (76). Even older children placed on brimonidine should be warned of its propensity to cause fatigue. Brimonidine is rarely an appropriate first-line drug for children but may be a useful adjunctive therapy in those older children needing additional IOP reduction (Table 14.2).

Prostaglandins

The newest class of drugs for glaucoma treatment is the prostaglandin-like drugs, which lower IOP primarily by enhancing the outflow of aqueous humor through the nontrabecular uveoscleral pathway. Published data in children are scarce, but these drugs can prove useful in some selected cases. Reported studies using latanoprost (Xalatan) find it most effective for cases of juvenile open-angle glaucoma. Selected cases of juvenile onset glaucoma secondary to Sturge-Weber syndrome have also responded well to latanoprost therapy. Although no serious systemic side effects have been reported in children, exuberant lengthening and darkening of eyelashes occur frequently, with increased iris pigmentation and aphakic cystoid macular edema not yet reported (77). To our knowledge, no published series using the other drugs in this group (bimatoprost, unoprostone, travoprost) have yet been reported. Except, perhaps, for selected cases of juvenile open-angle glaucoma with special risk for ß-blocker use, prostaglandin-like agents do not yet seem appropriate as first-line treatment for children. They may play an important adjunctive role in cases where IOP control is inadequate, despite use of other medications already discussed previously (Table 14.2).

Surgical Management

Glaucoma surgery is indicated as primary treatment for primary congenital glaucoma, angle-closure glaucoma, and other cases of childhood glaucoma where medical therapy has failed to adequately control IOP. Although the appropriate intervention (angle surgery) is widely agreed upon in the case of primary congenital glaucoma, the optimal surgical algorithm is, in numerous circumstances, open to disagreement, even among experts in the care of these children. Among the reasons for this diversity of opinion, in the optimal surgical algorithm for pediatric glaucoma, undoubtedly relates to the challenges inherent in the surgical management of these children and in the often suboptimal outcomes of such surgery.

Surgical interventions used for pediatric glaucoma can be broadly divided into these categories: angle surgery (goniotomy or trabeculotomy), filtering surgery (trabeculectomy ± antifibrotic agents), glaucoma implant (seton) surgery, cycloablation (cryotherapy or using laser), and others (such as peripheral iridectomy, combined trabeculotomy/trabeculectomy). Finally, enucleation may be the appropriate procedure for blind, disfigured, and painful eyes. Although most surgical procedures used in children with glaucoma are similar to those regularly applied to adult glaucoma patients, angle surgery (goniotomy and trabeculotomy) is used almost exclusively in children and deserves special mention.

Goniotomy

Goniotomy, a procedure that involves incising the uveal trabecular meshwork under direct visualization, is the surgical procedure of choice in most cases of primary congenital glaucoma. Trabeculotomy *ab externo* (see later text), an alternative and equally effective procedure, is especially useful when corneal clouding prevents an optimal view of the angle structures by gonioscopy. The discovery of the benefit of goniotomy by Barkan (78) represents the most significant advance that has occurred in the surgical management of this condition, and approximately 80% of children may be cured by this procedure (Figs. 14.15 and 14.16). Goniotomy also deserves special consideration as a prophylactic procedure in congenital aniridia (79).

Various modifications have been used for performing this simple but elegant procedure. Common to all of them are fixation of the globe, magnification and light source (loupes or microscope), operating goniotomy lens, and a

sharp instrument for incision (goniotomy knife or disposable needle). The ability to view the angle intended for surgery is critical to the goniotomy surgery; topical hypertonic saline drops and removal of a segment of corneal epithelium may assist in cases of mild corneal edema. (Trabeculotomy is necessary if corneal opacity prevents an angle view by gonioscopy prior to the surgery.) Corneal clearing is promoted by preoperative treatment with aqueous suppressant drugs for several days and with iopidine 0.5% and Pilocarpine 2% upon entry to the operating room.

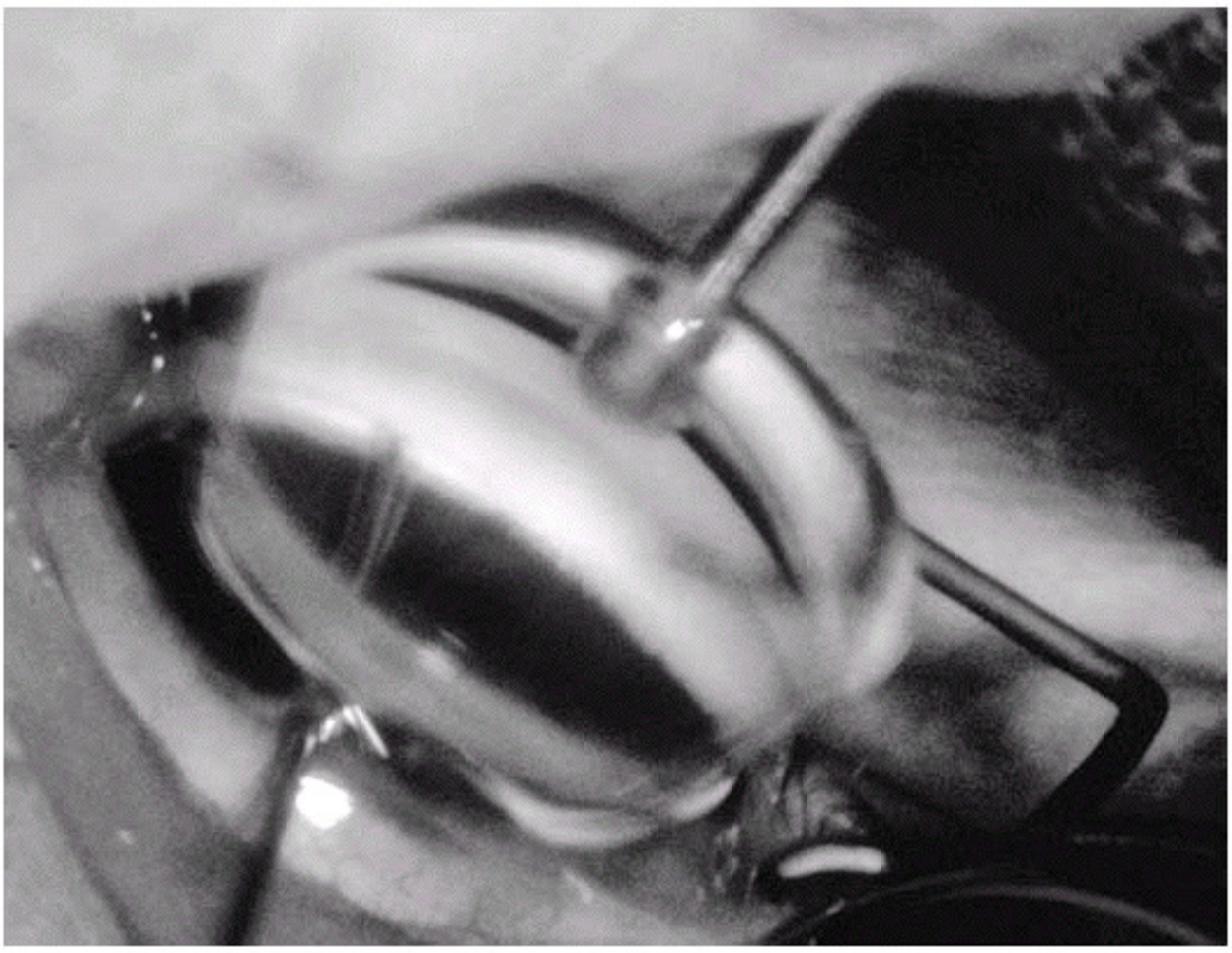

Figure 14.15 Goniotomy. Actual surgical photograph of goniotomy surgery. Fixation of the eye is obtained by the assistant grasping the tenon's insertion near the limbus at the 6 o'clock and 12 o'clock positions. A Barkan goniotomy lens is shown (modified by addition of a handle), cushioned on healon, and held in place by the surgeon. The cleft is being made with a 23-gauge needle, beginning to the left side of the angle.

One technique involves use of a modified Barkan goniotomy lens (with a handle) placed onto the cornea on a cushion of healon. The surgeon sits opposite the angle to be operated (e.g., on the temporal side for nasal goniotomy), using the microscope tilted about 45 degrees from the vertical. The assistant fixates the eye with locking forceps placed on the Tenon's insertion near the limbus at 6 o'clock and 12 o'clock positions for a nasal or temporal goniotomy, and the head is slightly turned away from the surgeon. A 25-gauge disposable needle on a syringe filled with Miochol or viscoelastic is used to enter the peripheral, clear cornea opposite the intended angle surgery, and the needle is carefully guided over the iris to engage the trabecular meshwork in its anterior one-third. The needle is first carefully passed in one direction, and then the other, with slight rotation of the eye by the assistant to maximize the incised angle tissue. A cleft should be seen in the wake of the incision, and often the peripheral iris will move slightly posteriorly in the case of congenital glaucoma. The needle is then carefully withdrawn after injection of a small amount of viscoelastic near the entry point, and the entry is closed with a single suture of 10-0 Vicryl. Approximately 4 to 5 clock hours of angle can be opened in this way. Bleeding, although common, is minimized by refilling the eye to a normal pressure prior to suture closure. Subconjunctival antibiotic may be used. Postoperatively, antibiotic, steroid, and miotics (except in uveitic glaucoma) are used for various time periods by different surgeons.

Figure 14.16 The patient in Figure 14.4, now age 6 years. The intraocular pressure was normalized after one goniotomy. The cornea remained enlarged, and refractive error was OD -4.00 sph and OS +1.50 sph. Glasses and occlusion were started, and corrected visual acuity in the right eye is now 20/80.

The results of goniotomy surgery are best—reportedly from 70% up to more than 90%—in patients with primary congenital open-angle glaucoma who possess a less severe angle anomaly and who are recognized between ages 3 and 12 months. Newborn patients who are found to have glaucoma because of enlarged and cloudy corneas often possess a more severe angle defect and do significantly less well with goniotomy surgery. Patients found to have primary congenital open-angle glaucoma in later childhood also do less well with goniotomy, possibly as a result of damage to the filtration mechanism caused by the chronic elevation of IOP.

Trabeculotomy *ab externo*

In this procedure, Schlemm's canal is identified by radial incision in the bed of a partial-thickness scleral flap, cannulated, and opened from the outside inward, tearing through the poorly functioning trabecular meshwork in that area (80,81) (Fig. 14.17). Standard trabeculotomy uses a stiff, curved metal trabeculotome to tear through the inner wall of Schlemm's canal, opening a comparable portion of the angle to goniotomy. A modification suture trabeculotomy, involves the threading of a flexible 6-0 Prolene suture into Schlemm's canal for 180 degrees or 360 degrees; when the suture is then pulled taut, the angle is opened up to 360 degrees. Although both procedures produce excellent success in uncomplicated cases of primary congenital open-angle glaucoma, neither has been compared against the other nor against goniotomy in a randomized, prospective fashion. Advantages to trabeculotomy include its similarity to trabeculectomy, for surgeons comfortable with the prior procedure, and ability to perform the surgery in the absence of an angle view. Disadvantages include the need to incise conjunctiva and sclera, and the possibility of being unable to locate or cannulate Schlemm's canal.

Combined Trabeculotomy-Trabeculectomy

Some surgeons advocate the combined use of trabeculotomy and trabeculectomy in cases resistant to goniotomy or

in selected populations where birth presentation, severely opaque corneas, and poor prior success with primary trabeculotomy have been reported. These surgeons report excellent success with this technique in selected cases (82,83).

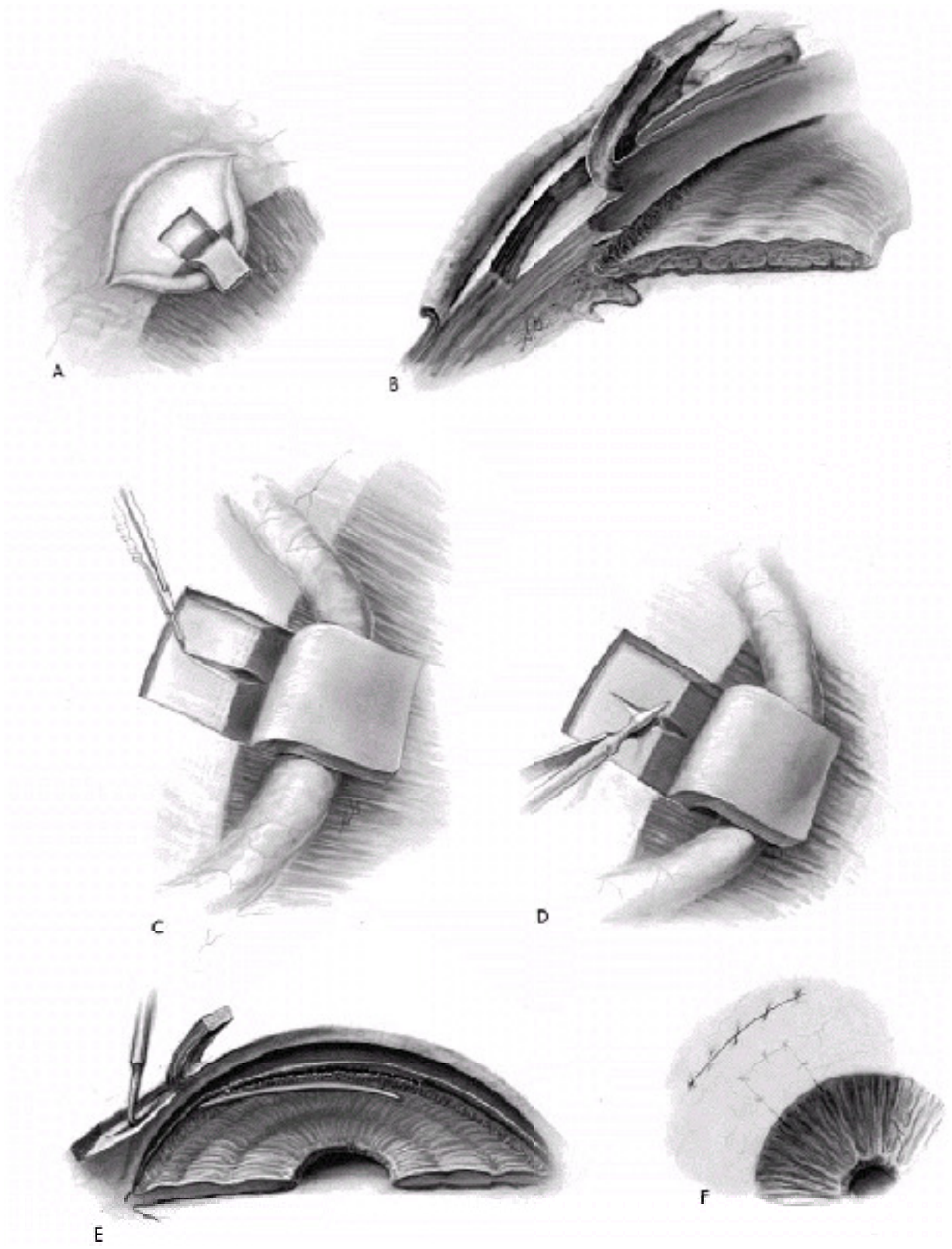

Figure 14.17 Trabeculotomy. **A:** A limbus-based conjunctival flap is made 4 to 5 mm from the cornea. (Many surgeons prefer a fornix-based flap.) A 3 × 3-mm wide limbus-based scleral flap is made extending one half to two thirds the thickness of the sclera. **B:** Cut-away view of the scleral flap showing the posterior extension of the cornea into the sclera. The location of the canal of Schlemm is indicated. **C:** Using high magnification, a scratch-down incision is made just over the junction of the blue cornea and white sclera. Aqueous (sometimes admixed with blood) may be seen to escape when the canal has been cut. The location of the canal is shown in dotted lines. **D:** Vannas scissors may be introduced into both cut ends of the canal, to make it easier to enter the canal. **E:** A trabeculotomy probe is placed into one side and rotated into the anterior chamber, thus rupturing through the inside wall of the canal, the trabecular meshwork, and the pretrabecular tissue. The probe is then passed in a similar manner in the other cut end of the canal. (An alternative is to pass a blunted 6-0 Prolene suture into one cut end of Schlemm's canal. At times it can be threaded the circumference of the eye, and then pulled to open 360 degrees of angle.) **F:** The scleral flap is closed with interrupted 10-0 Ethilon (or Vicryl) sutures, and the conjunctiva is closed with 8-0 or 9-0 Vicryl.

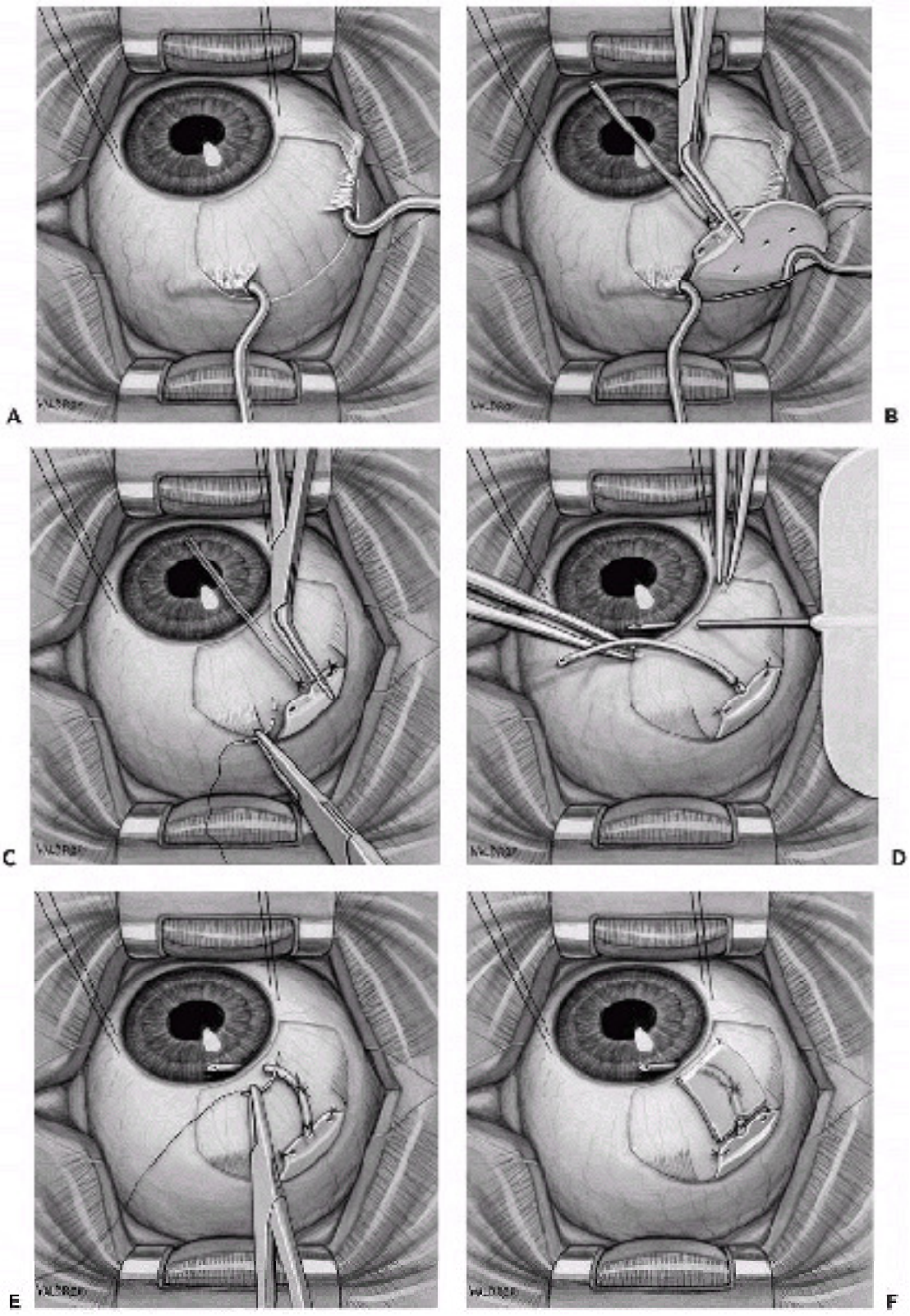

Figure 14.18 Technique of glaucoma drainage implant surgery in children. **A:** Surgeon's view of the right eye. A traction suture of 7-0 Vicryl has been placed through the limbal tissue/peripheral cornea at the 2 o'clock and 8 o'clock positions. A conjunctival peritomy has been made from 9 o'clock to 12 o'clock positions, with a radial wing on each end. A muscle hook has been placed under the superior and lateral rectus muscles to expose the superotemporal quadrant. **B:** A Baerveldt glaucoma implant (size 250 mm2) is being placed into the superotemporal quadrant against the sclera. The tubing of the implant has been completely ligated 1 mm from the anterior edge of the reservoir, using a 6-0 Vicryl suture. A muscle hook retracts the conjunctiva and tenon's capsule, as the superior wing of the reservoir enters the space just behind the superior rectus insertion. **C:** Final position of the Baerveldt reservoir, being secured into place with 8-0 nylon suture through the anterior positioning holes of the plate, 6 to 8 mm from the limbus. **D:** The eye is stabilized with forceps at the limbus, while a 23-gauge needle enters the anterior chamber parallel to the iris and almost parallel to the superior limbus. The tube of the Baerveldt implant has been trimmed to its desired length with a bevel up. **E:** The Baerveldt tube has been placed into the anterior chamber through the 23-gauge needle tract and is secured in place with a figure-of-eight suture of 9-0 nylon. The 9-0 nylon needle is then used to create several “venting slits” in the tubing anterior to its ligature. **F:** A patch graft of donor sclera is fashioned to cover the Baerveldt tubing at its entry site into the eye. Care is taken not to cover the 6-0 Vicryl suture around the tubing. The scleral patch graft is secured with 8-0 Vicryl suture. (Illustration by Tom Waldrup.)

Trabeculectomy (Filtering Surgery)

The trabeculectomy procedure seeks to bypass the resistance of the angle tissues by excising them under a partial thickness scleral flap, creating a so-called

filtering bleb of aqueous fluid that seeps out through the overlying tenon's capsule and conjunctival layers. This procedure is reserved usually when angle surgery fails or is unlikely to succeed, as is the case in many secondary glaucomas. As might be expected from the exuberant healing response in young children, simple trabeculectomy has a very low success rate in infants and children in most published series. More recently, the use of the antifibrotic agents 5-fluorouracil and mitomycin-C has improved the success of trabeculectomy in adults and in young patients but at an increased risk of later bleb leak and infection. Variable doses of mitomycin, ranging from 0.2 to 0.5 mg/mL, have been applied to the sclera for variable time periods, with little evidence supporting a single dosing strategy. Most pediatric glaucoma surgeons have long used a limbus-based conjunctival incision for trabeculectomy; several now advocate fornix-based incisions (personal communication). Even with the use of mitomycin, infants younger than ages 1 to 2 years and aphakic children do not fare well with trabeculectomy (28,29,84). Children with successful filtering blebs must be diligently observed for any signs of bleb leak or infection, because the risk of this occurrence may be cumulative over time. Fibrosis and loss of IOP control can likewise occur years after successful filtration surgery in children. In infants, aphakic eyes, and children at especially high risk for inadequate infection precautions, alternative surgical strategies may be warranted (see later text).

Drainage Implant (Seton) Surgery

Drainage implant surgery involves the placement of a flexible tube into the eye to conduct aqueous humor posteriorly to a plate sewn against the sclera, which becomes encapsulated to form a posterior reservoir, out of which aqueous then percolates into surrounding tissues (Fig. 14.18). Although the Molteno valve implant has been used in children for nearly 2 decades, experience is now also available for the Baerveldt and the Ahmed glaucoma implants (Fig. 14.19). Reported success and complication rates vary widely (33,34,35,36,85). Although common problems with the use of drainage implant in children include tube malposition and encapsulation of the reservoir (the latter with elevation of IOP), numerous other complications have been reported, as with this procedure in adult patients. The incidence of endophthalmitis, although nonzero, does seem lower with this procedure than with mitomycin-augmented trabeculectomy in children. However, the final IOP achieved after drainage implant surgery is not as low as after successful filtering surgery, and at least 50% of cases require continued adjunctive medication. In one reported series, drainage implant surgery appeared more successful at IOP control than did trabeculectomy for children below age 2 years (86).

Cycloablation

By contrast to all of the procedures described previously, cyclodestructive procedures reduce the rate of aqueous production by injuring the ciliary processes; results are often unpredictable, and complications frequent. Once medical and other surgical means have been exhausted or have proven inadequate to the task, cyclodestruction nonetheless constitutes a valid means of attempting control of otherwise vision-threatening glaucoma in children.

Cyclocryotherapy, freezing the ciliary processes from an external approach, has been used as therapy for difficult childhood glaucomas for many years and is applied with a similar technique to that used in adults. Success of this procedure is modest at best, with repeat sessions frequently needed, and with an appreciable incidence of devastating complications, such as phthisis and severe visual loss reported in up to 15%. In children, cryotherapy should be applied to a maximum of 180 degrees of the circumference of the eye at one session, using six or seven freezes (45-60

seconds each at -80°C) with the anterior edge of a 2.5-mm diameter cryoprobe placed 1 to 1.5 mm from the limbus (in a nonbuphthalmic eye) (58,87).

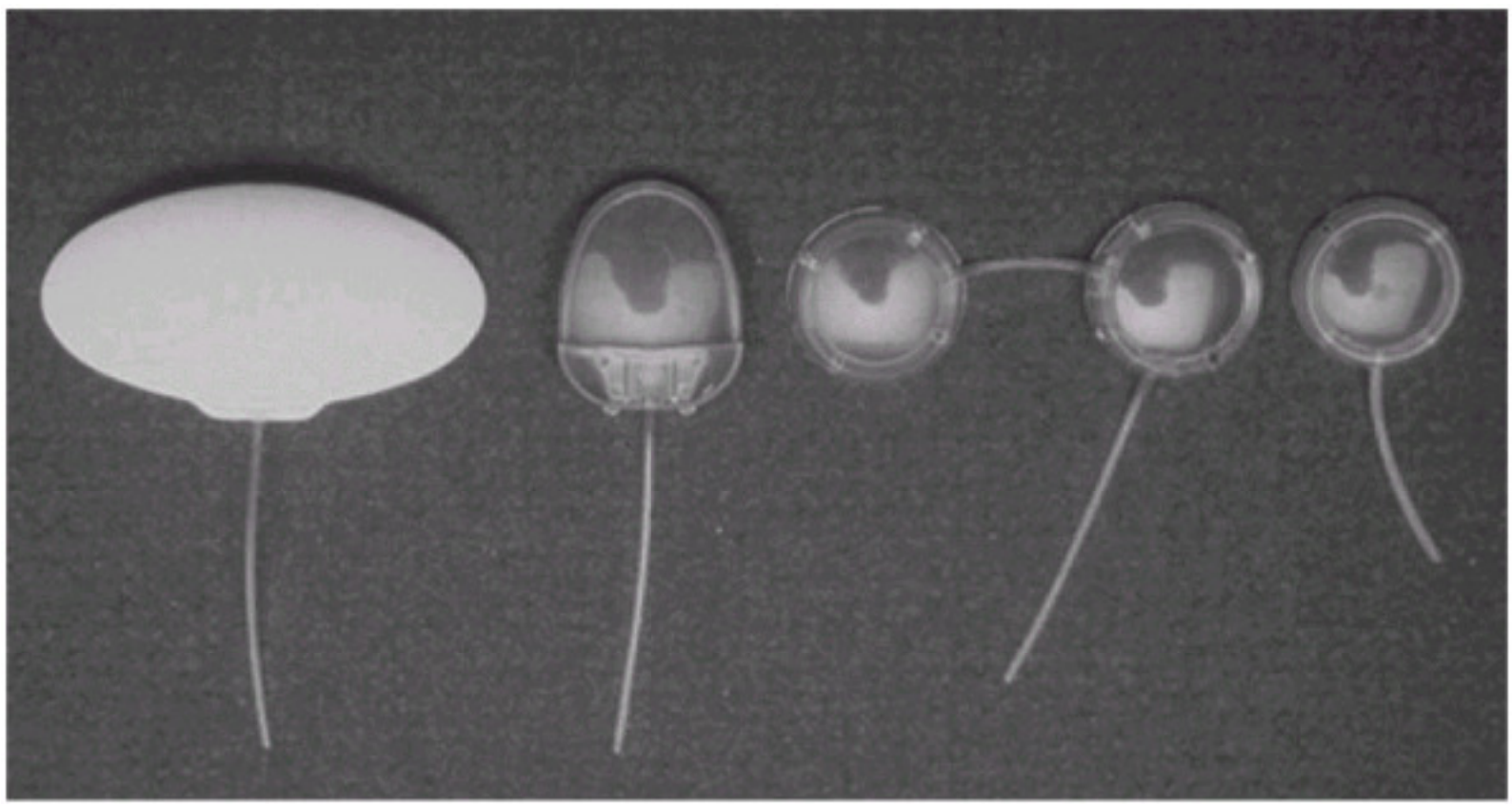

Figure 14.19 Glaucoma drainage implants commonly used for treatment of refractory pediatric glaucoma. Shown from right to left are: the Baerveldt 250 mm^2, the Ahmed (adult S-2) implant, and the single- and double-plate Molteno implants, respectively.

Transscleral laser to the ciliary processes has been performed in children using both the Nd:YAG sapphire probe as well as the diode laser G-probe. *Laser cyclophotocoagulation (transscleral and endoscopic)* has met with modest success (reported at approximately 50%, with retreatments in most cases), seems to produce less severe pain and inflammation than cyclocryotherapy, and may have a lower incidence of phthisis and severe complications seen with cyclocryotherapy. Limitations include loss of effect over time and inaccurate placement of the laser energy from an external approach in eyes, which often have unusual anterior segment anatomy (88,89,90).

Endoscopic cyclophotocoagulation has recently been applied in children with refractory glaucoma, using the diode laser and a microendoscopic system with a 20-gauge probe (Microprobe Endo Optiks, Little Silver, NJ). Although this procedure allows direct application of laser energy to the intended target of the ciliary processes and may produce less inflammation than either cyclocryotherapy or transscleral cycloablation, this procedure has only modest reported success, with retreatment often needed. Hence, cumulative success of all procedures at last follow-up was 43% in a reported series of 36 eyes, after a mean cumulative arc of treatment of 260 degrees, with mean follow-up time of 19 months. Retinal detachment, hypotony, and visual loss were reported in this series, which included both aphakic and phakic eyes (37).

Long-Term Follow-Up of Children with Glaucoma

All children with glaucoma require lifetime follow-up. The older child (young adult) may suffer asymptomatic loss of IOP control in months or even decades after initial successful surgery; progressive changes, such as cataract or corneal decompensation, may occur many years after initial presentation of glaucoma. Children with functioning filtering surgery or drainage implants must be followed for complications specific to these surgeries. The target pressure must be reassessed if progressive optic nerve or visual field changes occur, despite previously acceptable levels of IOP control. In addition, young children with glaucoma often face vision-threatening difficulties, such as corneal scarring, anisometropia, and resultant amblyopia even after IOP control has been achieved. Children with glaucoma that is controlled without medications should be followed at least every 6 months; and young children, or those whose IOP has been controlled for less than 2 years, should be evaluated at least every 3 or 4 months. Despite tremendous advances in the treatment of childhood glaucomas, many children still suffer permanent visual loss from these serious diseases.

REFERENCES

1. DeLuise VP, Anderson DR. Primary infantile glaucoma (congenital glaucoma). *Surv Ophthalmol* 1983;28:1-18.

2. Chandler PA, Granta WM. *Glaucoma*. Philadelphia: Lea & Febiger, 1980.

3. Van Buskirk EM, Plamer EA. Office assessment of young children for glaucoma. *Ann Ophthalmol* 1979;11:1749.

4. Minckler DS, Baerveldt G, Heuer DK, et al. Clinical evaluation of the Oculab tono-pen. *Am J Ophthalmol* 1987;104:168-173.

5. Watcha MF, Chu FC, Stevens JL, et al. Effects of halothane on intraocular pressure in anesthetized children. *Anesth Analg* 1990;71:181-184.

6. Murphy DF. Anesthesia and intraocular pressure. *Anesth Analg* 1985;64:520-530.

7. Dominguez A, Banos MS, Alvare MG, et al. Intraocular pressure measurement in infants under general anesthesia. *Am J Ophthalmol* 1974;78:110-116.

8. Ausinsch B, Rayburn RL, Munson ES, et al. Ketamine and intraocular pressure in children. *Anesth Analg* 1976;55:773-775.

9. Jaafar MS, Ghulamqadir AK. Effect of oral chloral hydrate sedation on the intraocular pressure measurement. *J Pediatr Ophthalmol Strabismus* 1993;30:372-376.

10. Pensiero S, DaPozza S, Perissutti P, et al. Normal intraocular pressure in children. *J Pediatr Ophthalmol Strabismus* 1992;29:79-84.

11. Sampaolesi R, Caruso R. Ocular echometry in the diagnosis of congenital glaucoma. *Arch Ophthalmol* 1982;100(4):574-577.

12. Becker B, Shaffer RN. *Diagnosis and therapy of the glaucomas*. St. Louis: Mosby, 1965.

13. Kiskis AA, Markowitz SN, Morin JD. Corneal diameter and axial length in congenital glaucoma. *Can J Ophthalmol* 1985;20:93.

14. Walton DS. Primary congenital open-angle glaucoma. In: Chandler PA, Grant WM, eds. *Glaucoma*. Philadelphia: Lea & Febiger, 1979:329.

15. Barkan O. Pathogenesis of congenital glaucoma: gonioscopic and anatomic observation of the angle of the anterior chamber in the normal eye and in congenital glaucoma. *Am J Ophthalmol* 1955;40:1-11.

16. Shaffer RN, Heatherington J. Glaucomatous disc in infants. A suggested hypothesis for disc cupping. *Trans Am Acad Ophthalmol Otolaryngol* 1969;73:929-935.

17. Richardson KT. Optic cup symmetry in normal newborn infants. *Invest Ophthalmol* 1968;7:137-147.

18. Argus AA. Ocular hypertension and central corneal thickness. *Ophthalmology* 1995;102:1810-1812.

19. Herndon LW, Choudhri SA, Cox T, et al. Central corneal thickness in normal, glaucomatous, and ocular hypertensive eyes. *Arch Ophthalmol* 1997;115:1137-1141.

20. Guedes V, Schuman JS, Hertzmark E, et al. Optical coherence tomography measurement of macular and nerve fiber layer thickness in normal and glaucomatous human eyes. *Ophthalmology* 2003;110:177-189.

21. Shaffer RN, Weiss DI. *Congenital and pediatric glaucomas*. St. Louis: Mosby, 1970.

22. Chandler PA, Grant WM. *Lectures in glaucoma*. Philadelphia: Lea & Febiger, 1965.

23. Walton DS. Primary congenital open angle glaucoma. A study of the anterior segment abnormalities. *Trans Am Ophthalmol Soc* 1979;77:746-768.

24. Phelps DD, Podos SM. Glaucoma. In: Goldberg MD, ed. *Genetic and metabolic eye disease*. Boston: Little, Brown and Company, 1974:252-253.

25. Waardenburg PJ, Franceschetti P, Klein D. *Genetics and ophthalmology*, vol 1. Springfield, IL: Charles C Thomas Publisher, 1961.

26. Sarfarazi M, Akarsu AN, Hossain A, et al. Assignment of a locus (GLC3A) for primary congenital glaucoma (buphthalmos) to 2p21 and evidence for genetic heterogeneity. *Genomics* 1995;30(2):171-177.

27. Sarfarazi M. Recent advances in molecular genetics of glaucomas. *Hum Mol Genet* 1997;6(10):1667-1677.

28. Freedman SF, McCormick K, Cox T. Mitomycin C-augmented trabeculectomy with postoperative wound modulation in pediatric glaucoma. *J AAPOS* 1999;3:117-124.

29. Beck AD, Wilson WR, Lynch MG, et al. Trabeculectomy with adjunctive mitomycin C in pediatric glaucoma. *Am J Ophthalmol* 1998;126:648-657.

30. Mandal AK, Prasad K, Naduvilath TJ. Surgical results and complications of mitomycin C-augmented trabeculectomy in refractory developmental glaucoma. *Ophthalmic Surg Lasers* 1999;30(6):473-480.

31. Sidoti PA, Belmonte SJ, Liebmann JM, et al. Trabeculectomy with mitomycin C in the treatment of pediatric glaucomas. *Ophthalmology* 2000;107:422-429.

32. Molteno AC, Ancker E, Van Biljon G. Surgical technique for advanced juvenile glaucoma. *Arch Ophthalmol* 1984;102(1):51-57.

33. Englert JA, Freedman SF, Cox TA. The Ahmed valve in refractory pediatric glaucoma. *Am J Ophthalmol* 1999;127:34-42.

34. Fellenbaum PS, Sidoti PA, Heuer DK, et al. Experience with the Baerveldt implant in young patients with complicated glaucomas. *J Glaucoma* 1995;4:91-97.

35. Coleman AL, Smyth RJ, Wilson MR, et al. Initial clinical experience with the Ahmed glaucoma valve implant in pediatric patients. *Arch Ophthalmol* 1997;115:186-191.

36. Morad Y, Craig ED, Kim YM, et al. The Ahmed drainage implant in the treatment of pediatric glaucoma. *Am J Ophthalmol* 2003;135:821-829.

37. Neely DE, Plager DA. Endocyclophotocoagulation for management of difficult pediatric glaucomas. *J AAPOS* 2001;5(4):221-229.

38. Sheffield VC, Stone EM, Alward WL, et al. Genetic linkage of familial open angle glaucoma to chromosome 1q21-1q31. *Nature Genet* 1993;4:47-50.

39. Stone DL, Fingert JH, Alward WL, et al. Identification of a gene that causes primary open angle glaucoma. *Science* 1997;275:668-670.

40. Phelps CD. The pathogenesis of glaucoma in Sturge-Weber syndrome. *Ophthalmology* 1978;85(3):276-286.

41. Mandal AK. Primary combined trabeculotomy-trabeculectomy for early-onset glaucoma in Sturge-Weber syndrome. *Ophthalmology* 1999;106(8):1621-1627.

42. Olsen KE, Huang AS, Wright MM. The efficacy of goniotomy/trabeculotomy in early-onset glaucoma associated with the Sturge-Weber syndrome. *J AAPOS* 1998;2(6):365-368.

43. Budenz DL, Sakamoto D, Eliezer R, et al. Two-staged Baerveldt glaucoma implant for childhood glaucoma associated with Sturge-Weber syndrome. *Ophthalmology* 2000;107(11):2105-2110.

44. Hamush NG, Coleman AL, Wilson MR. Ahmed glaucoma valve implant for management of glaucoma in Sturge-Weber syndrome. *Am J Ophthalmol* 1999;128(6):758-760.

45. van Emelen C, Goethals M, Dralands L, et al. Treatment of glaucoma in children with Sturge-Weber syndrome. *J Pediatr Ophthalmol Strabismus* 2000;37(1):29-34.

46. Payne MS, Nadell JM, Lacassie Y, et al. Congenital glaucoma and neurofibromatosis in a monozygotic twin: case report and review of the literature. *J Child Neurol* 2003;18:504-508.

47. Grant WM, Walton DS. Distinctive gonioscopic findings in glaucoma due to neurofibromatosis. *Arch Ophthalmol* 1968;79(2):127-134.

48. Online Mendelian Inheritance in Man, OMIM (TM). ed. M.-N.I.F.G. Medicine. World Wide Web URL: http://www.ncbi.nlm.-nih.gov/omim/: Johns Hopkins University, Baltimore, MD; and National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD, 2000.

49. Mueller OT, Hartsfield JK Jr, Gallardo LA, et al. Lowe oculocerebrorenal syndrome in a female with a balanced X;20 translocation: mapping of the X chromosome breakpoint. *Am J Hum Genet* 1991;49(4):804-810.

50. Walton DS. Diagnosis and treatment of glaucoma in childhood. In: Epstein DL, ed. *Chandler and Grant's glaucoma*. Philadelphia: Lea & Febiger, 1986.

51. Donahue SP, Keech RV, Munden P, et al. Baerveldt implant surgery in the treatment of advanced childhood glaucoma. *J AAPOS* 1997;1:41-45.

52. Shields MB, Buckley EG, Klintworth GK, et al. Axenfeld-Rieger syndrome. A spectrum of developmental disorders. *Surv Ophthalmol* 1985;29:387.

53. Alward WL. Axenfeld-Rieger syndrome in the age of molecular genetics. *Am J Ophthalmol* 2000;130(1):107-115.

54. Turleau C, DeGrouchy J, Tournade M-F, et al. Del 11p/aniridia complex. Report of three patients and review of 37 observations from the literature. *Clin Genet* 1984;26:356.

55. Grant WM, Walton DS. Progressive changes in the angle in congenital aniridia, with development of glaucoma. *Am J Ophthalmol* 1974;78(5):842-847.

56. Chen TC, Walton DS. Goniosurgery for prevention of aniridic glaucoma. *Arch Ophthalmol* 1999;117:1144-1148.

57. Adachi M, Dickens CJ, Hetherington J Jr, et al. Clinical experience of trabeculotomy for the surgical treatment of aniridic glaucoma. *Ophthalmology* 1997;104(12):2121-2125.

58. Wagle NS, Freedman SF, Buckley EG, et al. Long-term outcome of cyclocryotherapy for refractory pediatric glaucoma. *Ophthalmology* 1998;105(10):1921-1926; discussion 1926-1927.

59. Wiggins RE Jr, Tomey KF. The results of glaucoma surgery in aniridia. *Arch Ophthalmol* 1992;110(4):503-505.

60. Traboulsi EI, Maumenee IH. Peters' anomaly and associated congenital malformations. *Arch Ophthalmol* 1992;110(12):1739-1742.

61. Kivlin JD, Fineman RM, Crandall AA, et al. Peters' anomaly as a consequence of genetic and nongenetic syndromes. *Arch Ophthalmol* 1986;104:61.

62. Yang LL, Lambert SR. Peters' anomaly. A synopsis of surgical management and visual outcome. *Ophthalmol Clin North Am* 2001;14(3):467-477.

63. Zaidman GW, Rabinowitz Y, Forstot SL. Optical iridectomy for corneal opacities in Peters' anomaly. *J Cataract Refract Surg* 1998;24(5):719-722.

64. Gollamudi SR, Traboulsi EI, Chamon W, et al. Visual outcome after surgery for Peters' anomaly. *Ophthalmic Genet* 1994;15(1):31-35.

65. Goldberg MF. The diagnosis and treatment of secondary glaucoma after hyphema in sickle cell patients. *Am J Ophthalmol* 1979;87:43.

66. Farber MD, Fiscella R, Goldberg MF. Aminocaproic acid versus prednisone for the treatment of traumatic hyphema. A randomized clinical trial. *Ophthalmology* 1991;98:279.

67. Da Mata A, Burk SE, Netland PA, et al. Management of uveitic glaucoma with Ahmed glaucoma valve implantation. *Ophthalmology* 1999;106(11):2168-2172.

68. Freedman SF, Rodriguez-Rosa RE, Rojas MC, et al. Goniotomy for glaucoma secondary to chronic childhood uveitis. *Am J Ophthalmol* 2002;133(5):617-621.

69. Harrison DA, Mullaney PB, Mesfer SA, et al. Management of ophthalmic complications of homocystinuria. *Ophthalmology* 1998;105(10):1886-1890.

70. Egbert JE, Wright MM, Dahlhauser KF, et al. A prospective study of ocular hypertension and glaucoma after pediatric cataract surgery. *Ophthalmology* 1995;102(7):1098-1101.

71. Parks MM, Johnson DA, Reed GW. Long-term visual results and complications in children with aphakia. A function of cataract type. *Ophthalmology* 1993;100(6):826-840; discussion 840-841.

72. Walton DS. Pediatric aphakic glaucoma: a study of 65 patients. *Trans Am Ophthalmol Soc* 1995;93:403-413; discussion 413-420.

73. Plager DA, Neely DE. Intermediate-term results of endoscopic diode laser cyclophotocoagulation for pediatric glaucoma. *J AAPOS* 1999;3(3):131-137.

74. Passo MS, Palmer EA, Van Buskirk EM. Plasma timolol in glaucoma patients. *Ophthalmology* 1984;91:1361-1363.

75. Zimmerman TJ, Kooner KS, Morgan KS. Safety and efficacy of timolol in pediatric glaucoma. *Surv Ophthalmol* 1983;28:262-264.

76. Enyedi LB, Freedman SF. Safety and efficacy of brimonidine in children with glaucoma. *J AAPOS* 2001;5(5):281-284.

77. Enyedi LB, Freedman SF. Latanoprost for the treatment of pediatric glaucoma. *Surv Ophthalmol* 2002;47[Suppl 1]:S129-S132.

78. Barkan O. Operation for congenital glaucoma. *Am J Ophthalmol* 1942;25:552.

79. Chen TC, Walton DS. Goniosurgery for prevention of aniridic glaucoma. *Trans Am Ophthalmol Soc* 1998;96:155-165; discussion 165-169.

80. Burian HM. A case of Marfan's syndrome with bilateral glaucoma with a description of a new type of operation for developmental glaucoma. *Am J Ophthalmol* 1960;50:1187-1192.

81. Smith R. A new technique for opening the canal of Schlemm. *Br J Ophthalmol* 1960;44:370-373.

82. Mandal AK, Gothwal VK, Bagga H, et al. Outcome of surgery on infants younger than 1 month with congenital glaucoma. *Am J Ophthalmol* 2003;110:1909-1915.

83. Mandal AK, Bhatia PG, Gothwal VK, et al. Safety and efficacy of simultaneous bilateral primary combined trabeculotomy-trabeculectomy for developmental glaucoma. *Indian J Ophthalmol* 2002;50(1):13-19.

84. Susanna RJ, Oltrogge EW, Carani JCE, et al. Mitomycin as adjunct chemotherapy with trabeculectomy in congenital and developmental glaucomas. *J Glaucoma* 1995;4(3):151-157.

85. Molteno ACB. Children with advanced glaucoma treated by draining implants. *S Afr Arch Ophthalmol* 1973;1:55-61.

86. Beck AD, Freedman S, Kammer J, et al. Aqueous shunt devices compared with trabeculectomy with mitomycin-C for children in the first two years of life. *Am J Ophthalmol* 2003;136:994-1000.

87. Al Faran MF, Tomey KF, Al Mutlag FA. Cyclocryotherapy in selected cases of congenital glaucoma. *Ophthalmol Surg* 1990;21:794-798.

88. Kirwan JF, Shah P, Khaw PT. Diode laser cyclophotocoagulation: role in the management of refractory pediatric glaucomas. *Ophthalmology* 2002;109(2):316-323.

89. Bock CJ, Freedman FF, Buckley EG, et al. Transscleral diode laser cyclophotocoagulation for refractory pediatric glaucomas. *J Pediatr Ophthalmol Strabismus* 1997;34:235-239.

90. Phelan MJ, Higginbotham EJ. Contact transscleral Nd:YAG laser cyclophotocoagulation for the treatment of refractory pediatric glaucoma. *Ophthalmic Surg Lasers* 1995;26:401-403.

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Uveitis in Children

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Although the improvement in the management of glaucoma and cataract has helped mitigate a portion of devastating visual loss associated with uveitis in children, the significant surgical advances that have characterized the field of ophthalmology since the 1980s have not been mirrored in similar striking medical, therapeutic, or diagnostic breakthroughs. Endogenous uveitis is the most common inflammatory disease involving the uveal tract in children. Exogenous inflammatory processes may be metastatic, but for the most part they follow penetrating injury to the globe and are considered elsewhere in this text. Because early diagnosis and prompt treatment significantly improve prognosis, ocular inflammatory disease in a child provides an enormous therapeutic challenge to the clinician, especially in a preverbal child. Because early diagnosis is the exception, a young child's first presentation with this disease is frequently accompanied by significant secondary complications. This chapter discusses the therapeutic dilemmas and appropriate responses to the problems associated with ocular inflammatory disease in children.

CLASSIFICATION

There is no universal agreement about the most efficient way to classify uveitis. Classification can be based on time (acute, subacute, chronic), cell type (granulomatous, nongranulomatous), frequency (recurrent, isolated), activity (active, inactive), or location (anterior, intermediate, posterior). Theorists argue the merits of one classification over the other, but we believe that focusing on the affected anatomic structure is the most effective way to handle the diagnosis and management of young patients with uveal inflammatory disease (Table 15.1).

Discussion in this chapter therefore centers on the three segments of the uveal tract: anterior, intermediate, and posterior. Historically, anterior segment inflammatory disease has been called iritis, iridocyclitis, and even on occasion cyclitis. Intermediate segment disease has been referred to as chronic cyclitis, pars planitis, or peripheral uveitis. Retinitis, retinochoroiditis, chorioretinitis, and choroiditis have been the terms used to describe posterior uveal inflammation. In some entities in which all segments may be involved, the term “panuveitis” is appropriate.

FREQUENCY

The frequency of uveitis is relatively low in children aged less than 16 years. Although an element of bias in the viewpoints of reporting institutions makes it difficult to determine the exact frequency, an approximate incidence of 8% can be extrapolated from the world literature (Table 15.2). It is even more difficult to ascertain which of the uveitis syndromes predominates in the general pediatric population because of regional differences in nomenclature (e.g., chronic uveitis vs. peripheral uveitis vs. pars planitis) and the various clinical interests in university teaching centers. Table 15.3 lists statistics from seven reports. The total number of patients with inflammation affecting the anterior and peripheral portions of the uveal tract in childhood approximates that of patients with uveitis in the posterior portion of the uvea.

ANTERIOR UVEITIS

General Comments

A clear understanding of what causes anterior uveitis in children presents the ophthalmologist with the greatest opportunity for preventing the serious complications associated with this disease. The ophthalmologist's primary concern should be anticipating and identifying those patients who are prone to the development of relatively asymptomatic disease.

Symptoms

Some children with anterior uveitis present with the characteristic red eye, associated light sensitivity, decreased vision,

and pain. A significant percentage of children with anterior uveitis, however, fail to present with these classic symptoms. The “white iritis” described by Knox et al, although frequently associated with pauciarticular juvenile rheumatoid arthritis (JRA) (Fig. 15.1), is also seen in other patients with uveitis. More often, patients with anterior uveitis present first to the ophthalmologist during a routine screening examination or because strabismus develops from markedly decreased vision (Fig. 15.2).

TABLE 15.1 ANATOMICAL DIVISIONS FOR PEDIATRIC UVEITIS

Anterior

- Juvenile rheumatoid arthritis
- Juvenile spondyloarthropathies
- Fuchs heterochoromic iridocyclitis
- Sarcoidosis
- Herpetic iridocyolitis
- Syphilis
- Acute interstitial nephritis

Intermediate

- Pars planitis
- Peripheral uveitis
- Chronic cyclitis

Posterior

- Toxoplasmosis
- Toxocariasis
- Sarcoidosis
- Syphilis
- Acute retinal necrosis
- Cytomegalovirus
- Rubella retinitis
- Subacute sclerosing panencephalitis

Panuveitis

- Sympathetic ophtalmia
- Vogt-Koyanagi-Harada syndrome
- Behcet's syndrome
- Ocular Lyme borreliosis

Ocular Lyme borreliosis

TABLE 15.2 INCIDENCE OF UVEITIS IN CHILDREN

Authors	Total in Series	No. of Children	Age Group (y)	Percentage of Total
Blegvad (1941)	816	20	<16	2.2
Guyton and Woods (1941)	562	7	<10	1.3
Marchesan (1949)	451	59	10-19	3.8
Davis (1953)	400	21	<16	3.0
Kimura et al. (1954)	810	47	=16	5.8
Bennett (1955)	332	7	<15	2.1
Perkins (1951)	1718	40	<11	2.1
		169	11-20	
Kimura and Hogan (1964)	1900	202	=16	10.6
Jütte (1950-1965)	8000	287	<14	3.6
Witmer and Korner (1966)	434	37	=16	19.4
Schlaegel (1967)	1385	134	=16	9.68

Modified from Schlaegel TF Jr. *Essentials of uveitis.* Boston: Little, Brown & Co., 1969:68, with permission.

Signs

All the signs commonly associated with adult uveitis may be found in children. External examination may show ciliary flush. Unless there is associated elevated intraocular pressure, the only corneal manifestation of the disorder is keratic precipitates (Fig. 15.3). These deposits naturally vary in size. Frequently, in cases of anterior uveitis in children, the deposits are small to medium in size rather than the larger precipitates noted in patients with granulomatous uveitis. Corneal edema may be present when the intraocular pressure is elevated.

Flare and cells are present in the anterior chamber. The condition of the iris is directly related to the severity and chronicity of the intraocular inflammatory response. The pupil is characteristically small during the active phase of the inflammation and may be bound to the lens with posterior synechiae. The angle is generally open, but it may show peripheral anterior synechiae formation even early in the course of the disease. Acute episodes of anterior uveitis seldom directly affect the lens, but with chronic disease characteristic cataract formation is found, beginning first in the posterior subcapsular area (posterior subcapsular cataract, or cataracta complicata) (Fig. 15.4). When inflammation is limited to the anterior segment, occasional white blood cells may be found in the anterior vitreous space. Intraocular pressure is usually low because of the significant reduction in aqueous production during the inflammatory episode. Hypopyon occurs uncommonly in children, and when it does, it is more frequently associated with severe disease of unknown cause rather than with Behçet's syndrome. Hyphema may also occur with uveitis in children and is associated most often with herpes simplex virus (HSV), herpes zoster virus (HZV), and gonococcus.

TABLE 15.3 NUMBER OF CASES OF UVEITIS DIAGNOSED IN CHILDREN REPORTED IN PUBLISHED SERIES

Author	Anterior	Posterior	Peripheral	Total
Kimura et al. (1954)	14	29	4	47
Kimura and Hogan (1966)	59	78	41	178
Perkins (1966)	74	53	23	150
Witmer and Korner (1966)	18	25	31	74
Kazden et al. (1967)	24	59	21	1.04
Makley et al. (1969)	7	45	13	65
Jütte et al. (1969)	96	114	62	272
Total	292	403	195	890

Cause

Table 15.4 lists the causative agents associated with anterior uveitis in children aged less than 16 years. In approximately one third of the patients, no specific cause or associated disorder was identified. Fifty percent of the patients with anterior uveitis in whom associated disease was present exhibited JRA. A number of causes listed in Table 15.4 require only an accurate and complete ophthalmologic examination. Herpes simplex virus and HZV are in this diagnostic category. Corneal epithelial changes in the case of HSV and the appearance of skin vesicles in the distribution of the trigeminal nerve help delineate the exact cause of the herpes zoster keratouveitis. Further, although the list is extensive, the evaluation undertaken in pursuit of identifying a cause of uveitis is neither expensive nor painful to the patient.

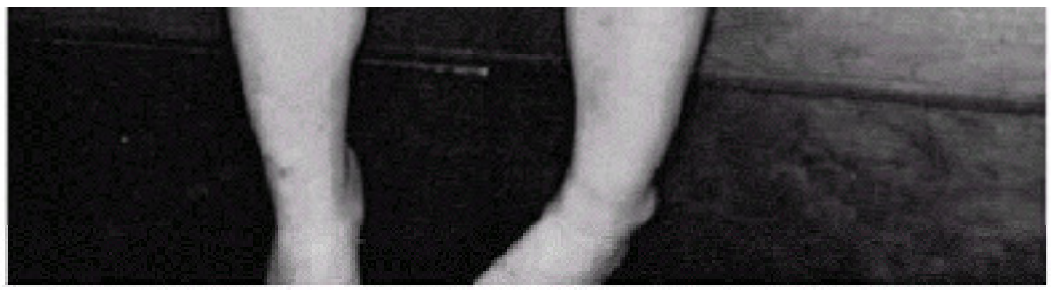

Figure 15.1 A 21/2-year-old child with pauciarticular juvenile rheumatoid arthritis (JRA) who was antinuclear antibody (ANA) positive.

The most important tool for obtaining the “road map” for an evaluation is the patient's complete history. A history of previous viral injections (chickenpox, mumps, measles), joint pain, trauma, or gastrointestinal disturbances should help the practitioner make an early specific diagnosis. A history of trauma, for example, in a patient with mild anterior uveitis or in a patient with a first episode of anterior uveitis makes further evaluation unnecessary. Uveitis after the childhood exanthems (which respond quickly to local steroids and mild cycloplegics) can be managed in the same fashion. On the other hand, an otherwise healthy patient without an obvious disease beyond the ocular manifestation requires a more extensive evaluation.

What follows is a brief description of disease states and specific causes associated with anterior uveitis. Immediately after this section, additional material pertaining to the causative evaluation will be discussed.

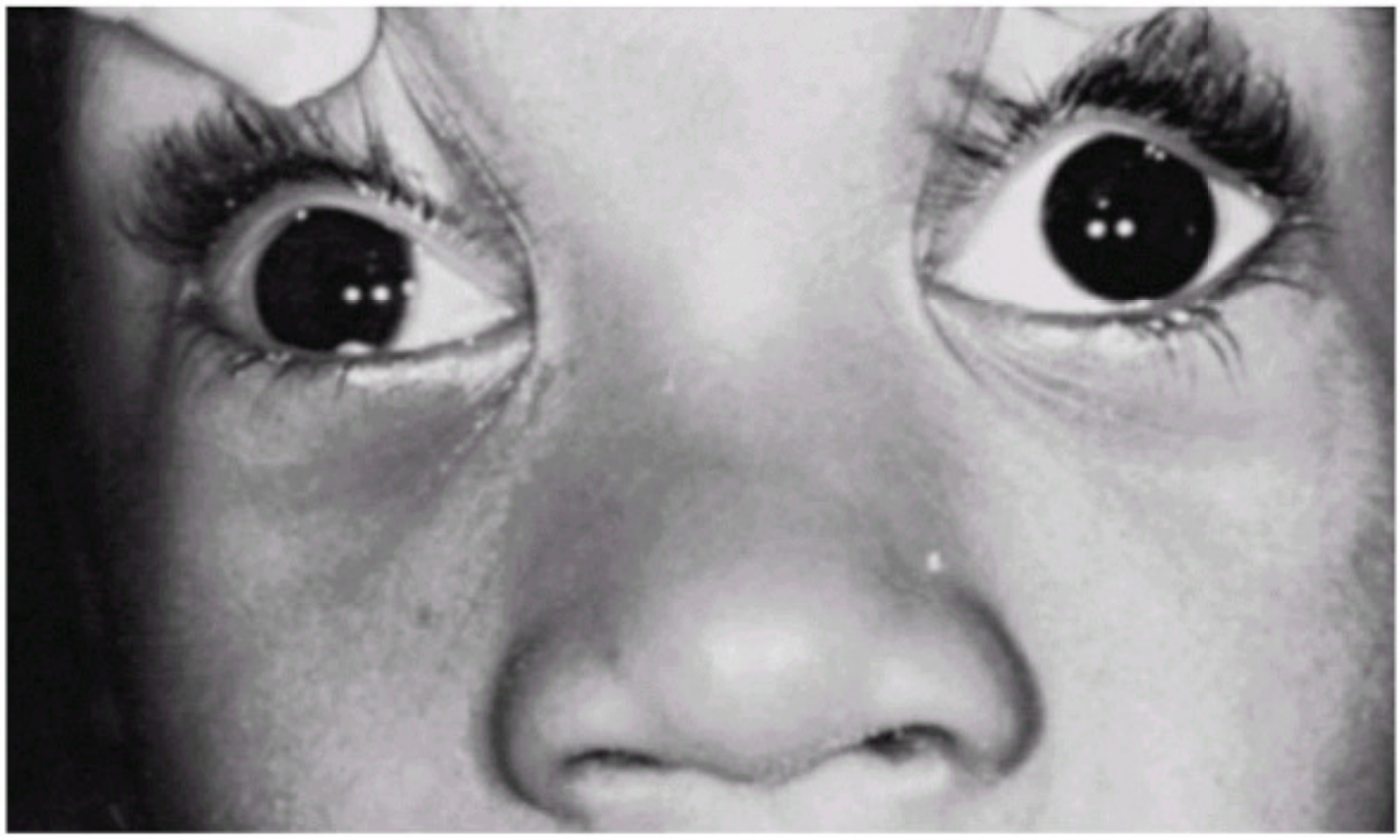

Figure 15.2 Mild injection in a young boy with advanced anterior uveitis, decreased vision, and right exotropia at first ophthalmologic evaluation.

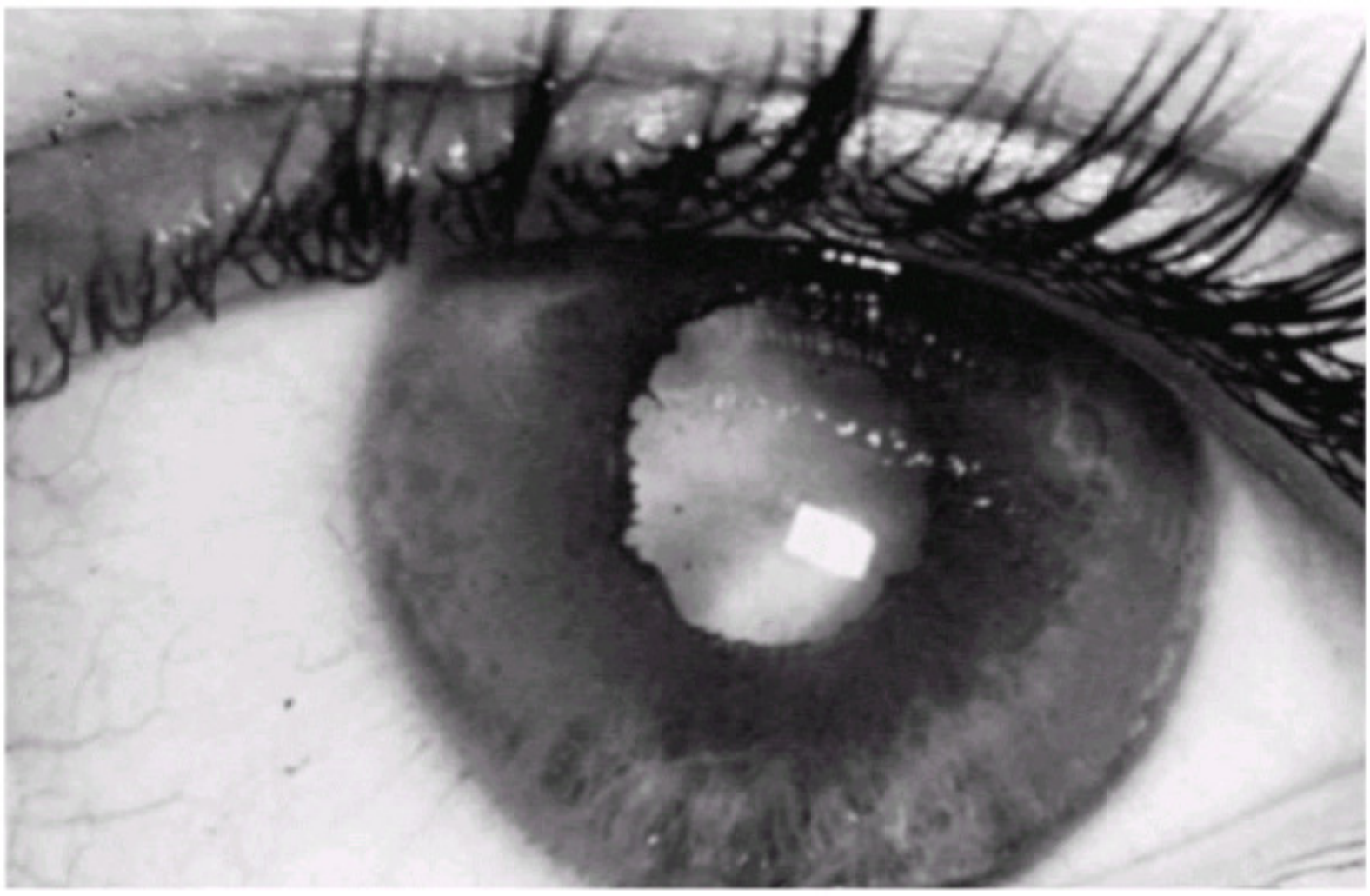

Figure 15.3 Cataract, posterior synechia formation, and keratic precipitates in a patient with chronic anterior and posterior uveitis.

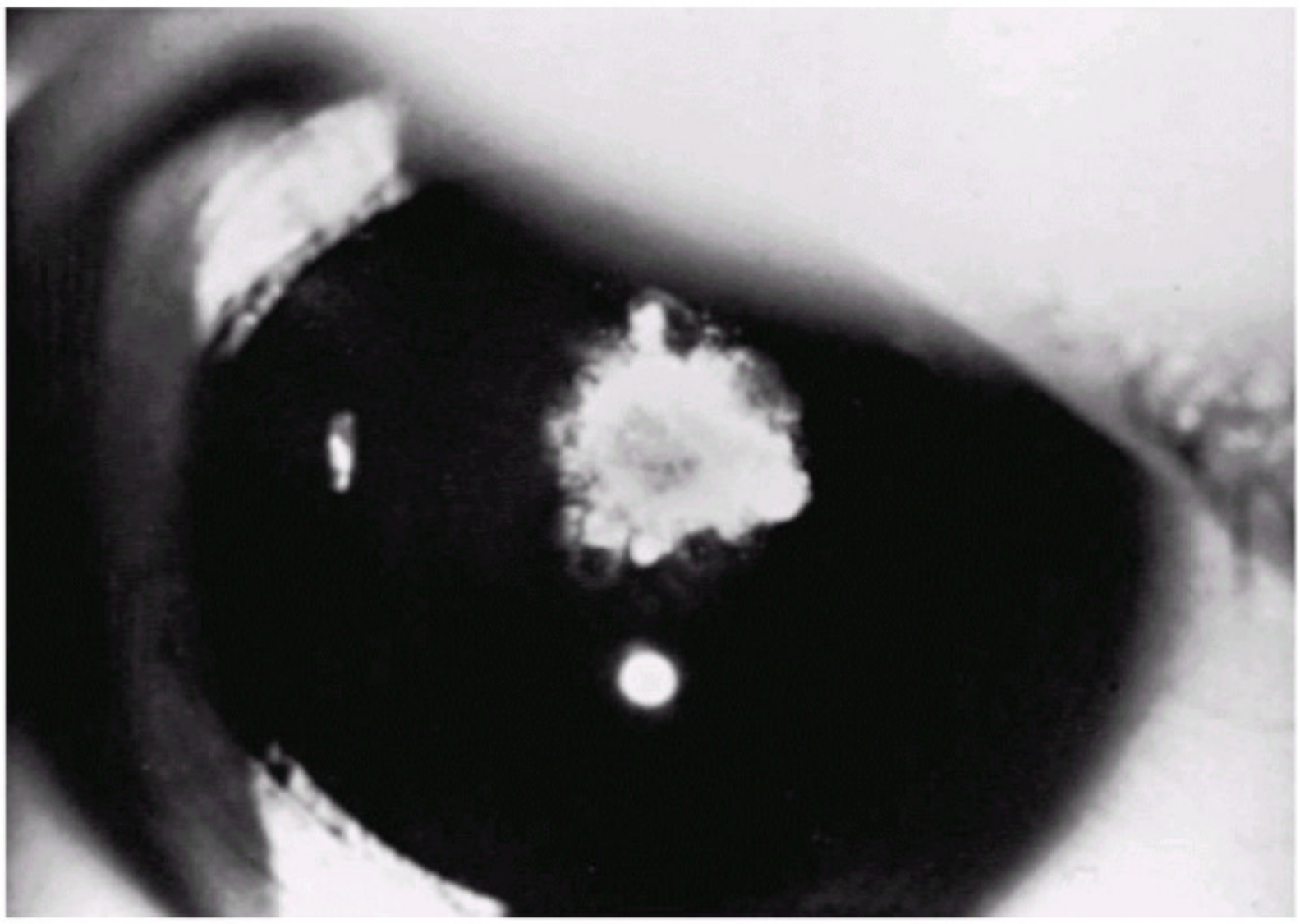

Figure 15.4 Posterior subcapsular cataract formation as seen on slit lamp examination.

TABLE 15.4 CAUSE OF ANTERIOR UVEITIS IN CHILDREN

Juvenile rheumatoid arthritis	46
Fuchs heterochromic iridocyclitis	9
Sarcoid	9
Syphilis	4
Ankylosing spondylitis	3
Tuberculosis	4
Trauma	3
Ulcerative colitis	1
Reiter syndrome	1
Sympathetic ophthalmia	2
Keratouveitis	
Herpes simplex	8
Herpes zoster	2
Undetermined	138
Total	230

SYSTEMIC DISORDERS AND ANTERIOR UVEITIS

Juvenile Rheumatoid Arthritis

Juvenile arthritis is divided into JRA and the human leukocyte antigen (HLA)-B27-related juvenile spondyloarthropathies. JRA is the leading cause of uveitis in children and is attributed to 5.5% to 76.7% of childhood uveitis cases. JRA is diagnosed in children aged less than 16 years with at least 3 months duration of arthritis. Before a diagnosis of JRA can be made, other causes of arthropathy must be excluded. Other cases may include trauma, sickle cell disease, bone tumors, rheumatic fever, or vasculitis. Approximately 70% of all cases of juvenile arthritis are classified as JRA. The peak incidence is between the second and fourth year of life. Girls are affected more often than boys at a 3:2 ratio. JRA may be divided into systemic disease, polyarticular-onset JRA, and pauciarticular JRA (Table 15.5). Polyarticular JRA is further divided into rheumatoid factor (RF) negative and RF positive disease. Pauciarticular JRA is either early onset or late onset.

Systemic Onset (Still's Disease)

Systemic-onset JRA (Still's disease) is characterized by fever, hepatosplenomegaly, arthralgias, maculopapular rash, and lymphadenopathy. Patients are antinuclear antibody (ANA) negative and RF negative. Twenty percent of patients with JRA have systemic onset. Between 1% and 6% of patients with JRA with uveitis have systemic onset. Because of the infrequency of uveitis in this group, ophthalmology screening is advised yearly for patients with systemic JRA.

Polyarticular Onset

Polyarticular-onset JRA is characterized by low-grade fever, anemia, and malaise with involvement of five or more joints within the first 3 months of disease. Girls are affected more often than boys. Patients are classified with RF positive or RF negative disease. Patients with RF positive disease seldom develop uveitis. Twenty-five percent of those with RF negative disease are ANA positive. Seventy-five percent of those patients who are RF positive are ANA positive as well. Polyarticular JRA accounts for 20% of patients with JRA. Between 7% and 15% of patients with JRA with uveitis have polyarticular onset. Screening is recommended every 6 months in this population.

Pauciarticular Onset

Pauciarticular-onset JRA is the most frequent form of JRA encountered, accounting for 60% of cases. This group is characterized by the involvement of fewer than five joints in the first 3 months of disease. The knees are the most common joints involved. There are few extra-articular manifestations; the predominant one is chronic iridocyclitis. Pauciarticular-onset JRA accounts for between 78% and 91% of all uveitis cases in patients with JRA. Patients are further subdivided on the basis of early or late onset of disease.

TABLE 15.5 SUBGROUPS OF JUVENILE RHEUMATOID ARTHRITIS

Subgroup		Girls:Boys Ratio	Age at Onset	Joints Affected	Serology, Genetic	Extra-articular Manifestations
1.	Systemic onset (Still's disease)	8:10	Any age	Any joints	ANA negative RF negative	High fever, rash, organomegaly, polyserositis, leukocytosis, growth retardation
2.	Rheumatoid factor Negative polyarticular	8:1	Any age	Any joints	ANA 25% RF negative	Low-grade fever, mild anemia, malaise, growth retardation
3.	Rheumatoid factor Positive polyarticular	6:1	Late childhood	Any joints	ANA 75% RF 100%	Low-grade fever, anemia, malaise, rheumatoid nodules
4.	Pauciarticular Early onset	8:1	Late childhood	Few large joints (hips and sacroiliac joints spared)	ANA 50% RF negative	Few constitutional complaints, chronic iridocyclitis in 50%
5.	Pauciarticular Late onset	1:10	Late childhood	Few large joints (hips and sacroiliac involvement common)	ANA negative RF negative HLA-B27 75%	Few constitutional complaints, acute iridocyclitis in 5% to 10% during childhood

ANA, Antinuclear antibody; RF, rheumatoid factor; HLA, human leukocyte antigen.

Modified from Schaller JG. The seronegative spondyloarthropathies of childhood. *Clin Orthop* 1979;143: 786, with permission.

The majority of early-onset disease occurs in girls; knees and hips are the joints most often involved. The sacroiliac joints are spared. Fifty percent of patients are ANA positive, and all patients are RF negative. Chronic iridocyclitis is seen in 50% of patients. Ophthalmologic screening is recommended every 3 months in this group for a period of 5 years if no ocular inflammatory signs are found.

Boys are affected more often than girls in late-onset pauciarticular JRA. Knees, hips, and sacroiliac joints are affected. Patients are both ANA and RF negative. Approximately 75% of boys with late-onset pauciarticular JRA are HLA-B27 positive. Acute recurring iridocyclitis is seen in 5% to 10% of patients.

The mainstay of treatment for anterior uveitis associated with JRA remains topical steroids and cycloplegics. The goal of treatment is to control inflammation and prevent potentially devastating, vision-threatening complications. Anterior uveitis in the pediatric population is often of an insidious onset because patients are either asymptomatic or nonverbal until late in the disease course. It is for this reason that inflammation must be treated aggressively on diagnosis. Periocular and systemic steroids may be necessary in cases refractory to topical treatment. Immunosuppressants sometimes may be required. In cases of uncontrolled inflammation, surgical therapy sometimes becomes necessary and is discussed later.

Juvenile Spondyloarthropathies

Juvenile spondyloarthropathies have a high association with the HLA-B27 haplotype. Most patients are RF negative. The spondyloarthropathies are further divided into juvenile ankylosing spondylitis, juvenile psoriatic arthritis, juvenile bowel-associated arthritis, and juvenile Reiter's syndrome. Boys are most often affected, with age of onset usually between 8 and 10 years.

Juvenile Ankylosing Spondylitis

Ankylosing spondylitis affects boys more often than girls. Disease is characterized by lower extremity symptoms. In contrast, adult disease often presents with lower back symptoms. Ninety-four percent of patients are HLA-B27 positive. Between 0.7% and 12.7% of uveitis cases in children are attributable to spondylitis. Ocular symptoms include a recurrent nongranulomatous anterior uveitis. Disease is bilateral in 80% of cases but rarely occurs in both eyes simultaneously. Cases of severe anterior uveitis may present with hypopyon formation.

Juvenile Psoriatic Arthritis

Juvenile psoriatic arthritis is seen more often in girls than in boys. Patients present with psoriatic skin changes, nail pitting, and joint disease. Joint disease often involves the distal hands and feet and may be either pauciarticular or polyarticular. A chronic nongranulomatous anterior uveitis is seen. One case series reported that 2.4% of childhood uveitis is associated with psoriatic arthritis.

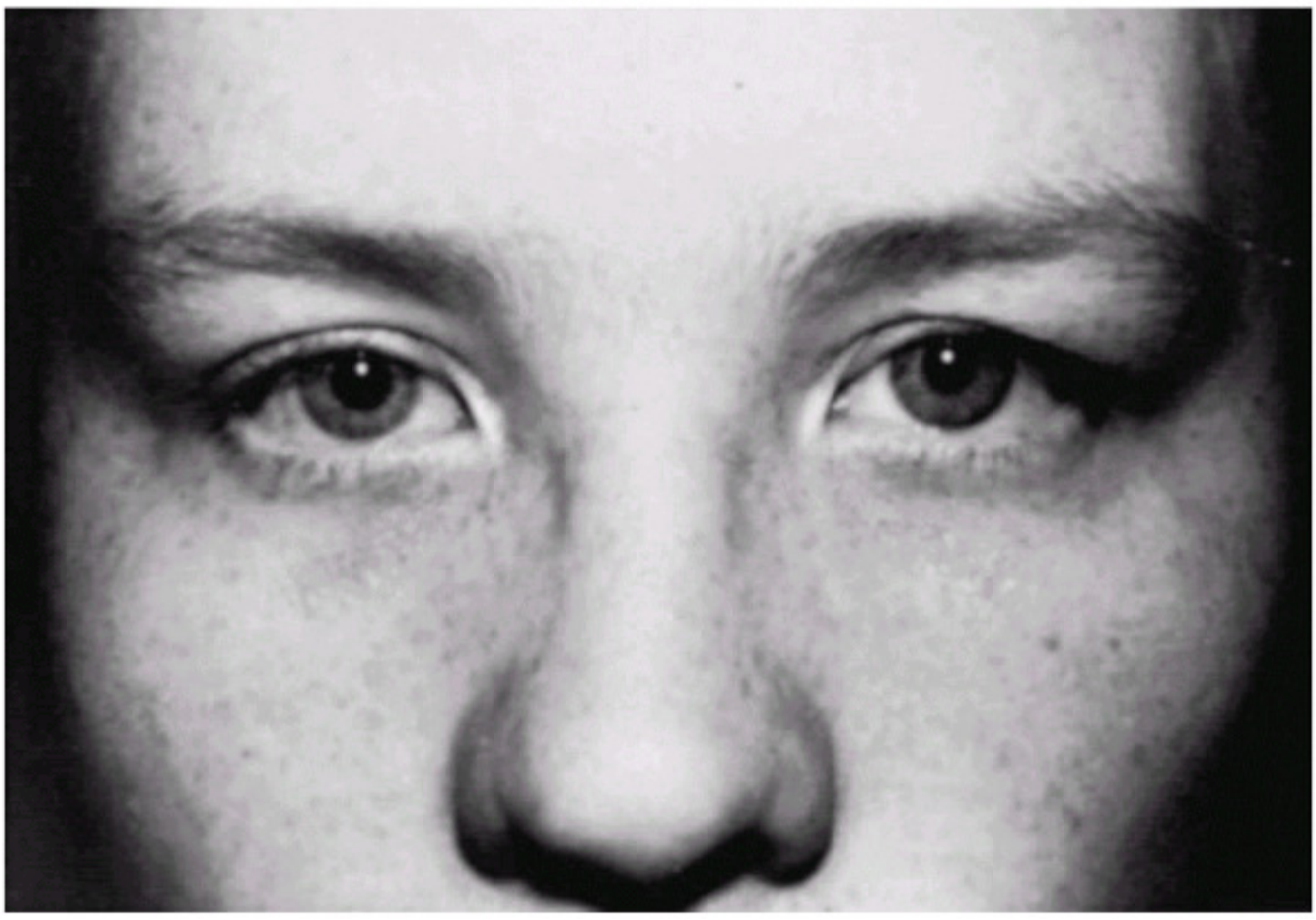

Figure 15.5 Fuchs heterochromic iridocyclitis of the right eye. Lightening of the iris occurs as a result of low-grade chronic anterior uveitis.

Juvenile Reiter's Syndrome

Reiter's syndrome is described with the classic triad of urethritis, arthritis, and conjunctivitis. This entity is rarely seen in children, with boys affected more often than girls. A nongranulomatous anterior uveitis develops in 3% to 12% of patients. Reiter's syndrome in children often follows an episode of *Salmonella* or *Shigella enterocolitis.*

Fuchs Heterochromic Iridocyclitis

Fuchs heterochromic iridocyclitis, although rare, is one of the more commonly misdiagnosed entities in ophthalmology. Care in the evaluation of the iris by using natural lighting conditions, the presence of the characteristic lattice-like keratic precipitates, and the very mild anterior chamber reaction accompanying this disorder all permit the clinician to make this diagnosis with a routine ophthalmologic examination (Figs. 15.5 and 15.6). Cataracts and open-angle glaucoma are the major complications. Treatment with topical corticosteroids is usually ineffective. Mydriatics are often not required because posterior synechiae are

uncommon.

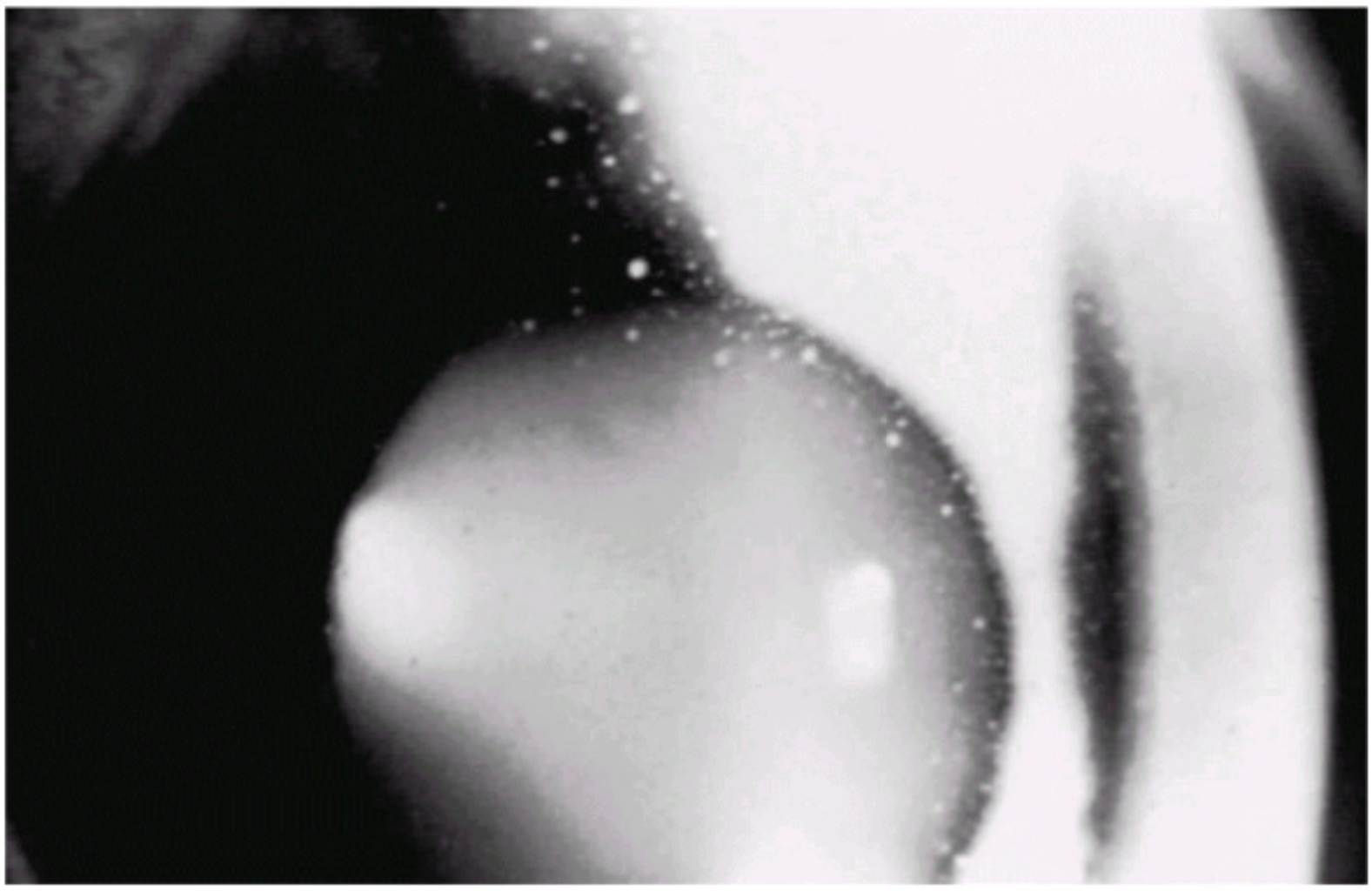

Figure 15.6 Fine, lattice-like endothelial deposits in a patient with Fuchs heterochromic iridocyclitis.

Sarcoidosis

Sarcoidosis is a noncaseating granulomatous multisystem disease that is rarely seen in children. Childhood sarcoid arthritis (CSA) is the most common form of sarcoidosis seen in children less than 5 years of age. Childhood sarcoid is characterized with the classic triad of arthritis, skin rash, and uveitis. Two thirds of patients with CSA are girls. The second group of affected patients is aged between 8 and 15 years. Findings include lymphadenopathy, pulmonary involvement, hepatosplenomegaly, and ocular involvement. In contrast with CSA, arthritis is rare in this group. The most common ocular finding in both groups is anterior uveitis, which affects 21% to 48% of patients who are older at onset and 81% of patients with CSA. Uveitis in the setting of sarcoid is responsible for 0.8% to 3.9% of childhood uveitis cases. Uveitis most often takes the form of chronic granulomatous inflammation with mutton fat keratic precipitates. Patients seldom complain of pain or photosensitivity. Less commonly, acute nongranulomatous inflammation is associated with pain, redness, and photosensitivity. Additional anterior segment findings include band keratopathy and conjunctival granuloma. Posterior segment involvement may include vitreitis or retinal phlebitis and will be discussed later in this chapter.

Evaluation for sarcoid includes serum lysozyme level, chest x-ray, and gallium scan. Age-matched controls must be used in assessment if angiotensin-converting enzyme (ACE) levels in children are obtained, because this age group often has higher than normal ACE levels. Chest radiography often shows pulmonary involvement in elderly patients. Gallium scanning highlights lung and lacrimal gland involvement. Definitive diagnosis is made with biopsy. Conjunctiva, skin, or lymph node may be used for biopsy. Histopathology shows noncaseating granulomatous disease.

It is important to distinguish sarcoid-associated uveitis from JRA because both entities present with rash, arthralgias, and uveitis. Posterior uveitis, polyarticular arthritis, erythema nodosum, and granulomatous uveitis are all features more consistent with sarcoid disease than JRA. Treatment of anterior uveitis consists of topical corticosteroids and cycloplegics. Severe cases may require periocular injection or systemic steroid therapy.

Herpetic Iridocyclitis

Iridocyclitis in children may result from infection with either HSV or HZV.

Herpes Simplex Virus

Uveitis associated with HSV accounts for 2% to 3.4% of childhood uveitis cases. Uveitis may be acute or chronic and often occurs in association with disciform keratitis. On rare occasions, HSV uveitis may be seen in the absence of corneal disease. Newborns with severe systemic HSV infection may develop posterior uveitis in the form of necrotizing retinochoroiditis. Treatment is with topical corticosteroids and cycloplegics. Posterior involvement warrants

systemic antiviral treatment and is described later. If there is corneal epithelial involvement topical antivirals may be added.

Herpes Zoster Virus

Herpes zoster infection is responsible for 0.8% of childhood uveitis cases. Ophthalmic findings include uveitis, conjunctivitis, dendritic keratitis, keratic precipitates, elevated intraocular pressure, hypopyon, or hyphema. Inflammation is thought to occur secondary to virus-mediated vasculitis, which ultimately leads to vascular occlusions and ischemia. Treatment involves topical corticosteroids and cycloplegics. In contrast with HSV infection, topical antivirals are ineffective.

Syphilis

Although rare, syphilis must be considered in cases of childhood anterior uveitis. Syphilis accounts for between 0.4% and 3.4% of uveitis cases in the childhood population. Disease may be acquired or congenital. Salt and pepper fundus along with bilateral disease are indicators of congenital infection. Acquired syphilis is typically a unilateral disease. Symptoms include decreased vision, photophobia, and pain. Stromal ghost vessels may be seen on examination. Persistent

inflammation despite corticosteroid therapy should alert the clinician to the possibility of syphilis. Testing with PTA-ABS is used to confirm syphilis infection. Penicillin is used for treatment of all types and stages of syphilis. Patients allergic to penicillin may be treated with doxycycline or tetracycline.

Lens-Induced Uveitis

Rupture of the lens capsule liberates lens material into the eye cavities. This results in one of two different types of uveitis that subside when the lens substance is removed. The uveitis is often associated with glaucoma. The phacotoxic reaction usually occurs in the presence of a hypermature cataract. The lens material acts as a chemical irritant, probably acting directly on the iris and ciliary body. Macrophages enter to engulf the liberated material. No polymorphonuclear cells are seen.

Endophthalmitis phacoanaphylactica results from an underlying sensitivity to lens protein that is probably amplified by bacteria or their toxins. Typically, a break in the lens capsule occurs in one eye as a result of surgery or injury. After inflammation has subsided in the first eye, the second eye develops a severe anterior granulomatous uveitis after surgery or trauma. Polymorphonuclear cells and macrophages are found in the aqueous iris and lens. Treatment involves removal of the lens in addition to the general therapy for uveitis discussed in the *Treatment* section.

Kawasaki Disease

Mild uveitis is associated in greater than two thirds of the patients with Kawasaki disease. This is an acute exanthematous disease in childhood that is characterized by weeklong fever, congestion of the conjunctiva and mucous membranes in approximately 96% of patients, and peripheral extremity changes. Approximately 85% of patients are aged less than 5 years, and the cause of this worldwide disease is unknown. Occasionally, systemic vasculitis can lead to coronary arteritis, and sudden death from coronary disease occurs in 1% to 2% of patients. Synechiae have not been reported, and topical steroids with short-acting cycloplegics are the only treatment necessary (Puglise et al, 1982).

Acute Tubulointerstitial Nephritis

Acute interstitial nephritis is an uncommon renal disorder as a result of an immune reaction to antibiotics, nonsteroidal anti-inflammatory drugs, or infection. This diagnosis, which carries with it an excellent prognosis, is associated with an increased erythrocyte sedimentation rate, elevated serum creatinine values, proteinuria, glucosuria, microhematuria, leukocyturia, increased levels of urinary Beta 2 microglobulin, and excretion of casts. Bilateral anterior uveitis associated with this disorder may indeed precede, follow, or occur concomitantly with the acute phase of the disease. Treatment involves the use of topical and occasionally systemic corticosteroids, which generally relieves the inflammation promptly.

Orbital Pseudotumor

Orbital pseudotumor is primarily a disorder of adults, although it occasionally occurs in the first or second decade of life. It is an idiopathic inflammatory condition involving the anterior, posterior, or both segments of the eye and is associated with other signs of swelling of the lids: ptosis, pain, and diplopia. Unlike the adult form of the disease, uveitis may be associated with pediatric orbital pseudotumor. Patients with uveitis have an increased incidence of recurrence of orbital pseudotumor, as well as bilateral involvement. Orbital pseudotumor should be considered in those pediatric patients with a persistent or recurrent uveitis and previous negative diagnostic workup. Diagnostic workup should include ultrasonography, computed tomography (CT), or magnetic resonance imaging. Treatment consists of systemic corticosteroids.

Associated Systemic Disorders

Both juvenile diabetes and multiple sclerosis have been implicated as associated systemic disorders. Although the anterior uveitis segment is the primary uveal inflammatory focus in type 1 diabetes, both the anterior and peripheral uveal segments have been identified in multiple sclerosis. However, recurrent anterior uveitis has been implicated as a manifestation of the poststreptococcal syndrome.

Anterior uveitis has been associated with tonsillitis, upper respiratory infection, and rheumatic fever. Both traditional uveitis anti-inflammatory mediation and tonsillectomy have been used in its management.

On rare occasions, contact lens wear seems to be associated with anterior uveitis. If discontinuing contact lens wear results in prompt improvement in the inflammation, upon clearing, contact lens wear can once again be attempted. If a recurrence of inflammation is then seen, contact lens wear should be discontinued.

Chronic Inflammatory Bowel Disease

A relatively rare association between chronic inflammatory bowel disease and anterior uveitis bears additional mention. The disease is relatively mild and is also asymptomatic in approximately 20% of those with Crohn's disease. Asymptomatic disease in chronic ulcerative colitis occurred rarely (2.79%). As is the case in uveitis associated with JRA, no relationship was observed between the activity of bowel disease and the presence of ocular inflammation.

Evaluation

Although it was once traditional to present a flowchart and table suggesting a causative evaluation in a patient with uveitis, Table 15.6 is offered with some hesitation. The “shotgun” approach to a causative evaluation should be abandoned in favor of evaluation on the basis of history and cost-effectiveness. Table 15.6 is relevant only for the patient with severe disease in whom no localizing clue to cause can be elicited.

Routine blood studies should include a complete blood count to rule out the presence of leukemia as well as the fluorescent treponemal antibody absorption test for syphilis, which is most specific in cases of syphilitic ophthalmologic involvement. A number of different studies can be performed in an attempt to diagnose sarcoid uveitis. These include ACE, serum lysozyme elevation and serum protein electrophoresis, ANA, and HLA B27 studies. The ACE is of great value in the presence of active disease in adults, but results in children may be spurious. Serum lysozyme elevation and serum protein electrophoresis with an increased a2-globulin fraction are highly suggestive of sarcoid. Because of its association with JRA, ANA is a most important serologic examination. Finally, although the presence of HLA-B27 is an important marker in patients with uveitis, it is not helpful for management and therefore is not obtained routinely except in a research setting. Until a clearer picture regarding the ocular manifestations of Lyme disease is available, immunologic testing for this spirochete with enzyme-linked immunosorbent assay (ELISA) or indirect fluorescent antibody (IFA) is indicated in patients with idiopathic chronic uveitis.

TABLE 15.6 DIAGNOSTIC EVALUATION OF ANTERIOR UVEITIS IN CHILDREN

History

Ocular examination

Pediatric evaluation

Complete blood count

Serologic

- ANA
- Serum lysozyme
- Serum protein electrophoresis
- FTA-ABS test
- HLA typing
- ELISA, IFA for Lyme disease

Skin tests

- Tuberculin
- Kveim

Radiographic

- Chest
- Sacroiliac joint
- Gastrointestinal series

Aqueous tap

Fluorescein angiography

Lumbar puncture

ANA, Antinuclear antibody; FTA-ABS, fluorescent treponemal antibody absorption; HLA, human leukocyte antigen; ELISA, enzyme-linked immunosorbent assay; IFA, indirect fluorescent antibody.

Skin testing with the Kveim test has been used in some centers in which fresh antigen is available. A positive diagnosis of sarcoid may be obtained by a biopsy of the skin test site 4 to 6 weeks after deposition of the antigen and identification of the characteristic granuloma. Blind conjunctival biopsy has proved generally ineffective in attempts to diagnose sarcoid. When a significant conjunctival nodule is present, the yield is high. Biopsy of the lacrimal gland and surrounding conjunctiva has also proved helpful in establishing a diagnosis of sarcoid. The tuberculin skin test (intermediate-strength purified protein derivative), which is used to diagnose the rare case of tuberculous-induced uveitis, identifies patients in whom antituberculous therapy is indicated when systemic corticosteroids are used.

Radiographic studies include chest x-rays (to rule out sarcoid and tuberculosis), sacroiliac joint study (to exclude rheumatoid spondylitis), and a gastrointestinal series in patients in whom ulcerative colitis or regional enteritis is suspected. Additional studies using fluorescein angiography, vitreous and aqueous aspiration,

and lumbar puncture are only occasionally helpful.

Treatment

Over the past 45 years, corticosteroids have been the cornerstone of therapy for anterior uveitis. Although the concentration of the drug and its vehicle have been modified and refined, these nonspecific anti-inflammatory agents remain the most effective therapy for virtually all patients with childhood uveitis. Of currently available local corticosteroids, prednisolone acetate 1% is the ideal solution because of its ability to penetrate the intact corneal epithelium. When this agent is used as frequently as every 30 minutes, most children do not need periocular and systemic corticosteroids.

Treatment requirements of the identified causative entities vary widely. Some, such as traumatic anterior uveitis and Fuchs heterochromic iridocyclitis, require minimal amounts of local corticosteroids to control inflammation. On the other hand, acute fibrinous uveitis in patients with spondylitis may require maximal application of corticosteroids.

With the onset of chronic anterior segment inflammation, careful monitoring is required to regulate drug dosage. Generally, the presence of flare without significant anterior chamber cells does not warrant treatment. We prefer to use chronic steroid therapy to maintain the anterior segment with slightly less than a 1 + response present (scale-trace to 4+). Periocular corticosteroids have been widely used for two decades, but their use in children aged less than 14 years is somewhat limited because general anesthesia is usually needed for delivery. Systemic corticosteroids are seldom required to treat anterior segment inflammatory disease. In addition, the potential side effect of early closure of the epiphyseal plate, and its resultant stunting of growth in the adolescent patient, increases the risk of using corticosteroids. The occasional use of systemic corticosteroids, however, has proved important in selected patients. In very young patients, the maximal dosage is 4 mg/kg (prednisone) administered on an alternate-day, singledosage schedule. We use no more than 80 mg of oral prednisone every other day to treat anterior segment inflammation.

The use of methotrexate with increasing frequency in the treatment of joint manifestations of JRA has served to highlight the importance of the use of immunosuppressive agents as an adjunct to local and systemic corticosteroid therapy in uveitis. The use of methotrexate, usually in collaboration with the rheumatologist, can facilitate substantial moderation of corticosteroid therapy, both locally and systemically when chronic disease is present.

Cycloplegic-mydriatic agents are important in the treatment of childhood uveitis because of the significant tendency to form synechiae. In the early phases of inflammation, atropine 1% must be used as often as four times daily. Some ophthalmologists are concerned that long-term use of mydriatic agents may result in a chronically dilated pupil. However, it has been our experience that the complications associated with the pupil have not been related to dilatation but to relative miosis and the formation of posterior synechiae. As soon as the inflammation has diminished, homatropine 5% two times daily is substituted for atropine. In chronic anterior uveitis with minimal anterior chamber reaction, the pupil is dilated once daily. The parent is instructed to administer homatropine 5% or tropicamide 1.0%, 1 hour before the child's sleeping hour, inspect the pupil carefully for change in size and regularity, and report any change in the pupil to the ophthalmologist the next morning. Refraction and prescription of bifocals for reading and near vision are important in these patients because of the potential long-term use of these cycloplegic agents.

Specific therapy for anterior uveitis in children is limited to the use of specific antiviral agents (trifluridine in HSV) and antibacterial agents in infectious uveitis (e.g., penicillin in syphilis). Nonsteroidal anti-inflammatory agents such as indomethacin (Indocin, Merck & Co., Inc., Whitehouse Station, NJ), phenylbutazone, ibuprofen, and aspirin are only occasionally effective in anterior segment inflammatory disease. Whenever high-dosage corticosteroids have failed, nonsteroidal anti-inflammatory agents have also failed.

Course and Complications

With early diagnosis and prompt treatment, inflammation generally subsides within 2 to 6 weeks. The poor response reported in childhood anterior uveitis is directly related to the delay in diagnosis. It is this delay that makes the following complications more common in children than those associated with adult-onset uveitis.

Band Keratopathy

This is the most consistent and benign of all complications associated with chronic anterior chamber inflammation in children (Fig. 15.7). Although hypercalcemia and phthisis bulbi also cause band keratopathy, most band formation is secondary to uveitis. Unless the band results in a cosmetic defect or reduces acuity, treatment is not indicated. When treatment is required, the band is easily removed. After deepithelialization of the cornea, Gelfoam (Pharmacia & Upjohn, Kalamazoo, MI), moistened with a 0.1 mol/L edetate disodium (sodium versenate) solution, is placed over the affected cornea; 5- to 10-minute applications produce chelation of the band. If vision is present in the other eye, patching the affected eye after instilling a local antibiotic or sulfa medication for 24 hours aids in the reepithelialization process. When there is little or no vision in the untreated eye, no patch is used. This procedure may be repeated as often as necessary and is almost uniformly successful.

Glaucoma

The mechanism for the production of glaucoma is as varied in childhood uveitis as it is in the adult form of the disorder. Unfortunately, the prognosis for children with inflammatory glaucoma is far worse than for adults. Medical management, when successful, usually requires the use of long-term carbonic anhydrase inhibitors, because beta-blocking agents (timolol, betaxolol) and epinephrine derivatives are rarely successful. Medical therapy controls elevated intraocular pressure in 50% of patients who develop glaucoma.

The variety of surgical procedures suggested by glaucoma

specialists is adequate testimony to the procedures' lack of success. Filtering procedures have always been fraught with difficulty in all patients with inflammatory disease, but in younger patients the success rate is less than 50%. Trabeculectomy, peripheral iridectomy with thermal sclerostomy (Preziosa, 1929; Scheie, 1958), and, more recently, trabeculodialysis, as advocated by Kanski (1990), have all failed to appreciably improve the prognosis of this complication (Fig. 15.8). Most recently, the use of immunosuppressive agents such as 5-fluorouracil and mitomycin has permitted filtration to occur with a greater frequency after surgery in patients with uveitis. The long-term outlook, however, cannot be assessed at the time of this publication.

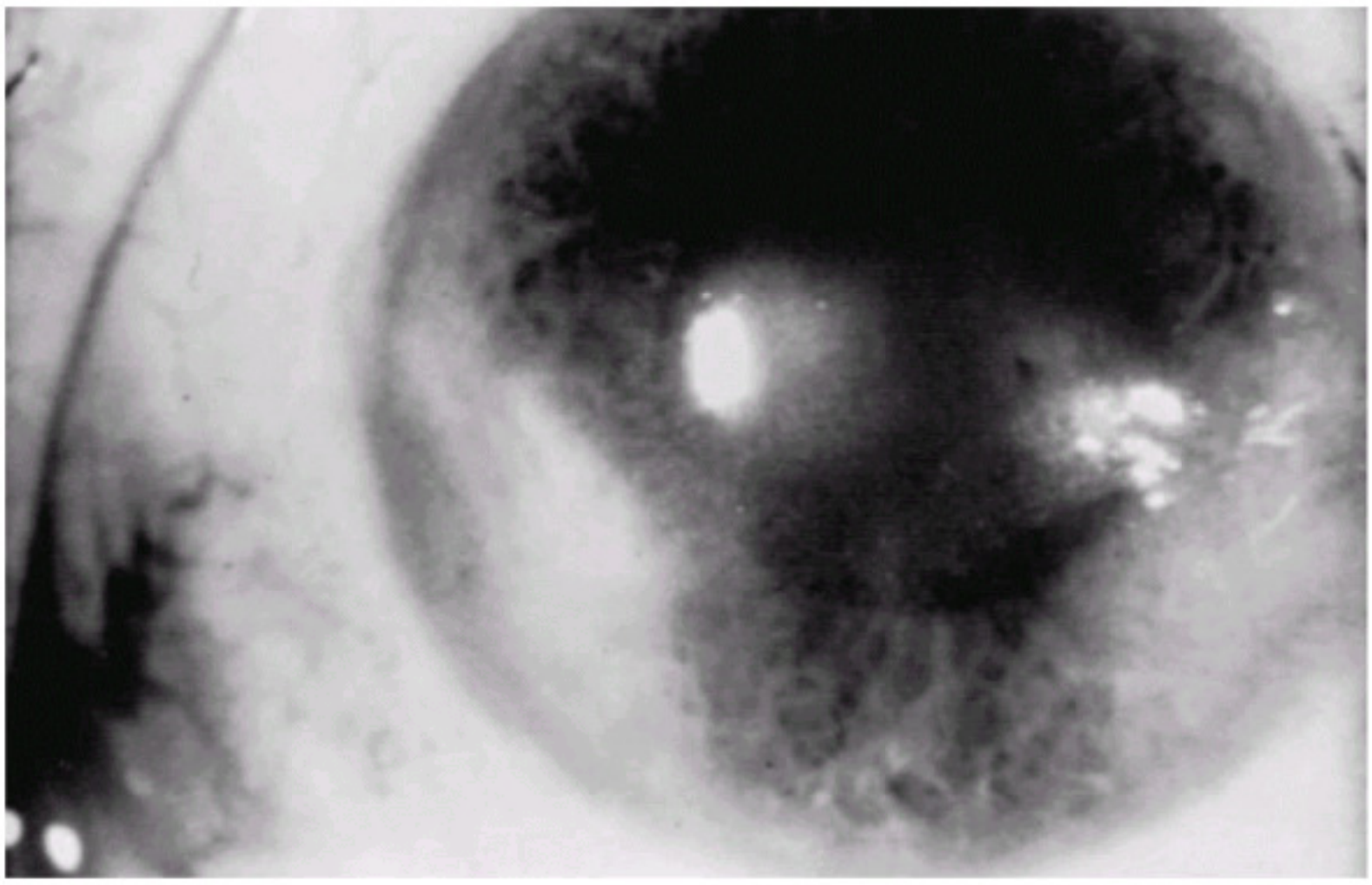

Figure 15.7 Early band keratopathy associated with posterior synechiae formation in a young patient with chronic uveitis and JRA.

Cataract

The management of cataract in children with uveitis (Fig. 15.9) with lensectomy-vitrectomy has markedly improved the outlook for these patients (Fig. 15.10). Although the prognosis remains guarded in the management of cataract associated with inflammation, improved techniques now offer significant hope for the young patient who presents with advanced cataract formation. Lensectomy-vitrectomy in these patients theoretically removes a portion of the antigenic stimulation responsible for chronic uveitis. Elimination of the posterior capsule also prevents the later development of secondary and pupillary membranes, thereby reducing the incidence of hypotony from ciliary body shutdown.

For these reasons, we prefer the lensectomy-vitrectomy procedure to simple extracapsular lens extraction. A period of 6 months of relative inflammatory inactivity before surgery is desirable. Periocular corticosteroids are administered at the time of surgery, and most of these eyes do not show marked additional inflammation. Orally administered postoperative corticosteroids are given only when indicated on a case-by-case basis. When extensive band keratopathy suggests that aphakic contact lens fitting will prove difficult, the cornea should be chelated at the time of cataract surgery.

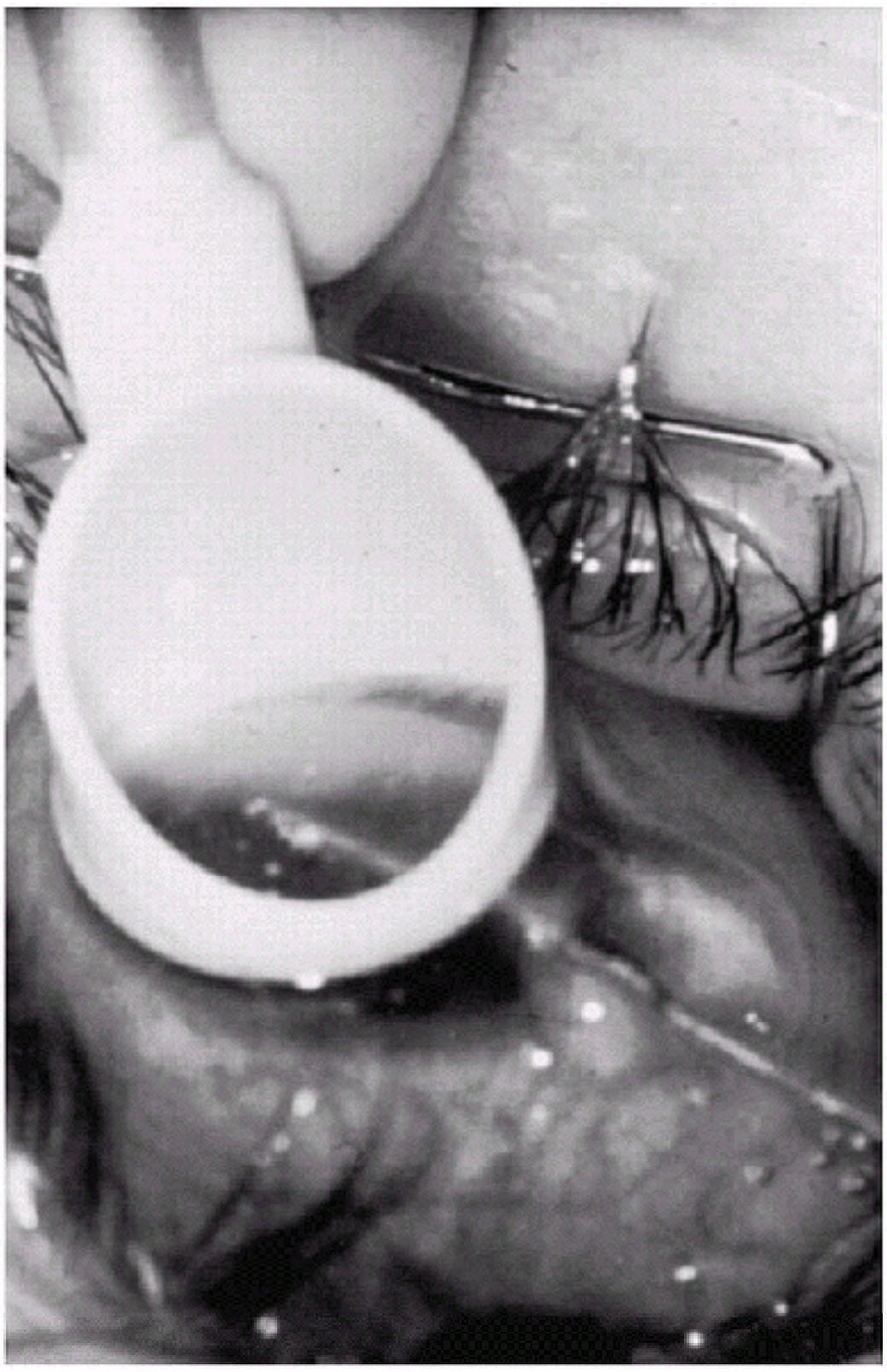

Figure 15.8 Intraoperative photograph during trabeculodialysis performed in a patient with intractable secondary glaucoma associated with JRA. (Courtesy of Jack Kanski, MD.)

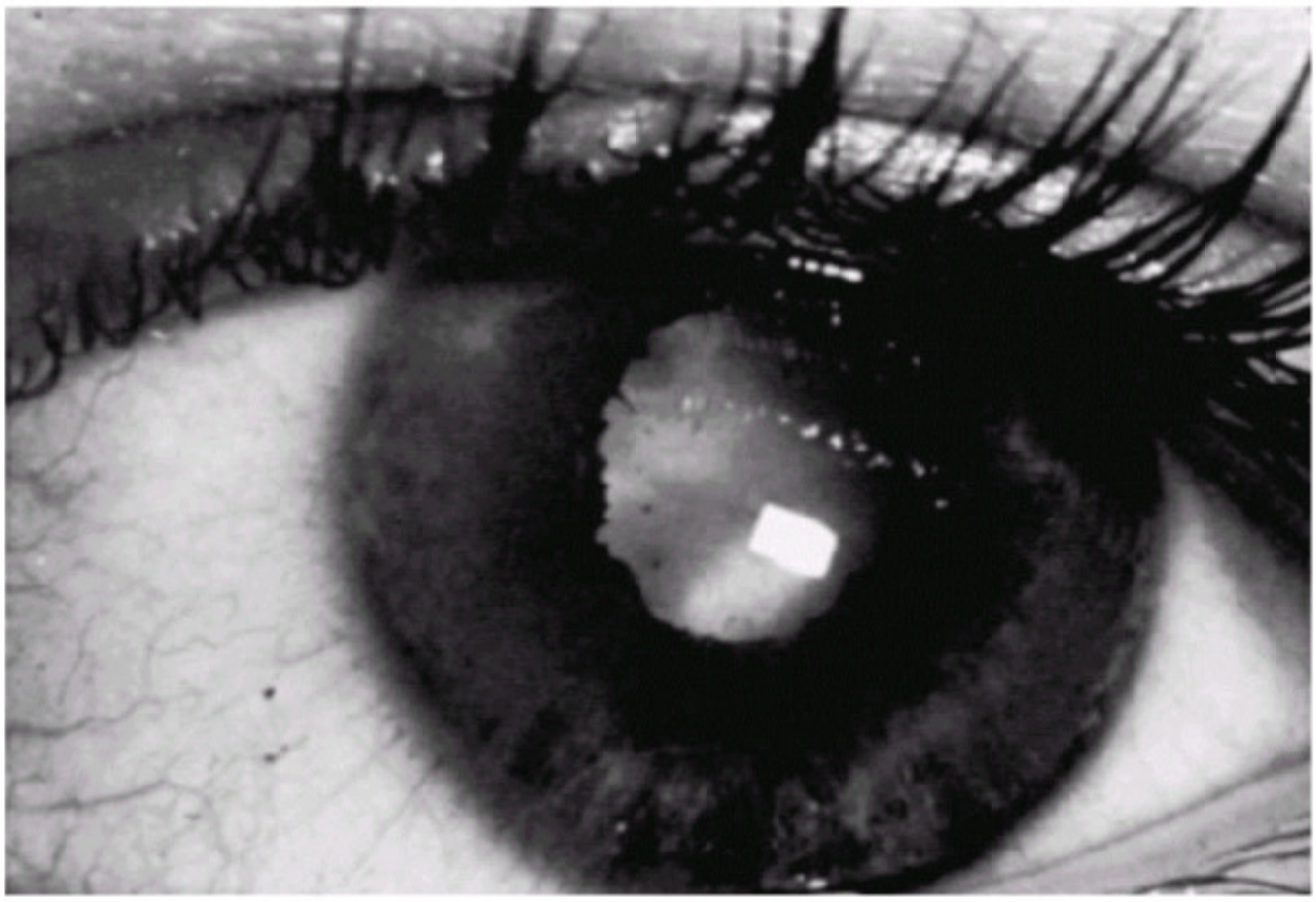

Figure 15.9 Advanced cataract formation in a child with chronic anterior uveitis.

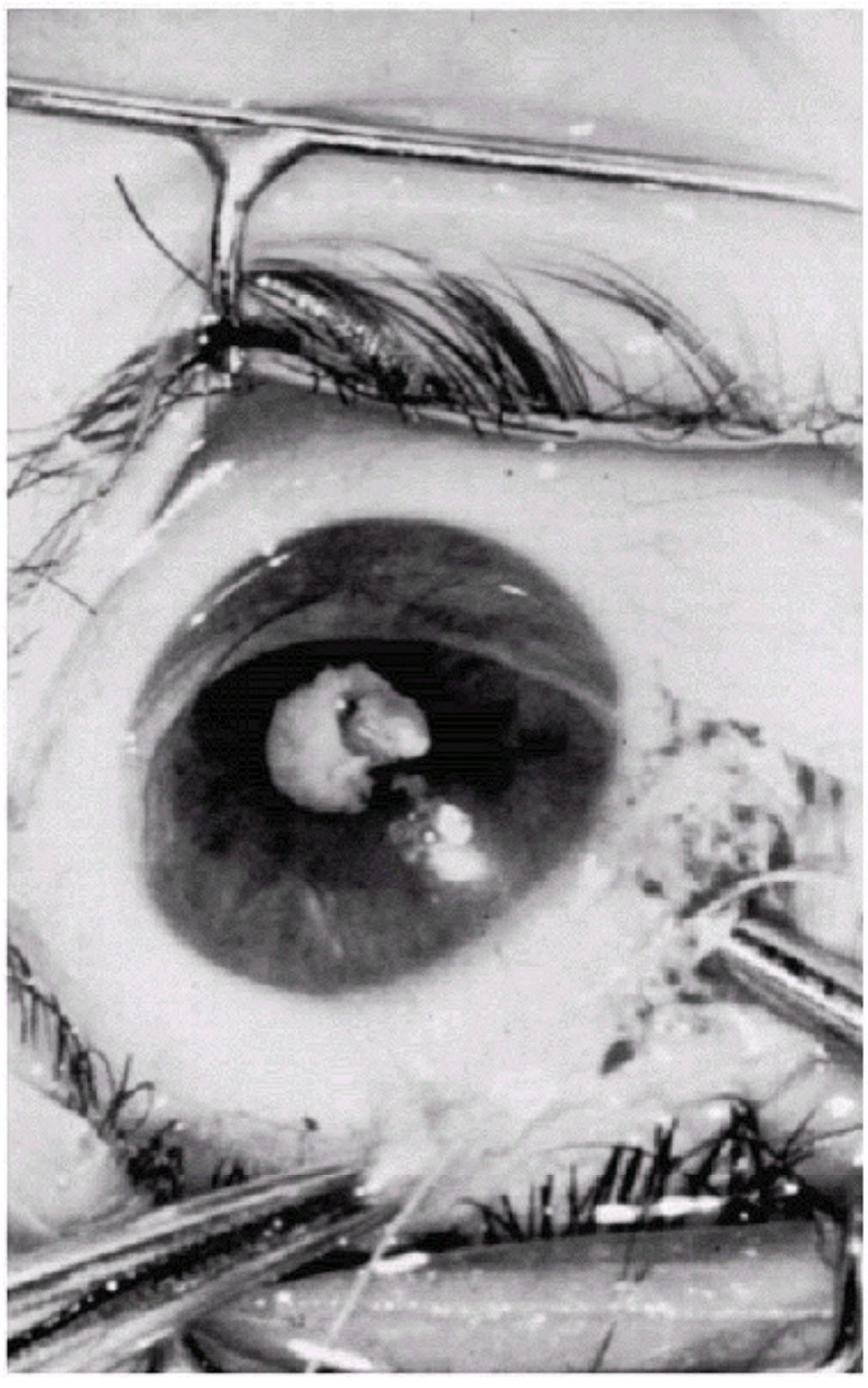

Figure 15.10 Lensectomy-vitrectomy performed through the pars plana.

There is increasing evidence that intraocular lens (IOL) implantation may be well tolerated in patients with JRAassociated uveitis. Certainly, the use of IOL in patients with mild and quiescent anterior uveitis has long been advocated. Recent reports have concluded that with adequate preoperative and postoperative control of inflammation, children with cataracts and JRA tolerate IOL implantation with little additional risk of complication.

Phthisis Bulbi

Phthisis bulbi represents the end stage of severe anterior uveitis in children. On occasion, however, these eyes respond well to a lensectomy-vitrectomy procedure even in the presence of a clear lens. The success of this operation may depend on the removal of the cyclitic membrane, with restoration of aqueous formation, and elimination of hypotony.

INTERMEDIATE UVEITIS

Intermediate uveitis in children provides little problem in diagnosis. However, experience suggests that there is a great disparity between the ability to diagnose this entity and the manner in which to treat it. Emphasis is therefore placed on the treatment of this disorder. The introduction of the term “intermediate” by the International Committee on Uveitis Nomenclature is an effort to set aside three entities (pars planitis, peripheral uveitis, and chronic cyclitis) that have had regional prominence. Certain subtle nuances exist between the diagnosis of these three entities, but careful reading of the literature suggests that they represent nearly identical clinical states.

Symptoms

In its classic form, intermediate uveitis is largely asymptomatic until the disease is well advanced and vision is markedly reduced. Because the eyes are characteristically white, there are few clues to bring the condition to the parents' attention. Routine school or pediatric vision screening, the presence of strabismus associated with reduced acuity, or pain (in the more advanced forms) alert the parent to this disorder. Less characteristic, but relatively common in children nevertheless, are the classic symptoms of acute anterior uveitis with increased lacrimation, redness, and pain. When a patient appears with this symptom complex, the more subtle underlying intermediate component of what appears to be primarily an anterior uveal inflammation becomes more apparent as the anterior portion of the inflammation initially responds but then slips into a chronic phase. This expression of the disease is probably far more common in children than in adults, because children are unable to detect the early signs of minimal blurring of vision and the presence of vitreous floaters.

Signs

Except in eyes with associated acute anterior uveitis, the signs of this syndrome are relatively subtle. Early in the course of the disease, the presence of anterior vitreous cells is the only sign seen on routine examination (Fig. 15.11). Initially, these cells are fine and separate, but as the disorder progresses, they aggregate and may acquire a fibrillar state in the anterior one third of the vitreous. The anterior segment may be quiet, although a trace flare and occasional cells are frequently seen. A few peripheral anterior synechiae may form, and occasional cellular deposits may be present in the trabecular meshwork. Characteristically in children, there is usually posterior subcapsular cataract formation at the time of presentation. Scleral depression early in the course of the illness reveals debris in the pars plana, which may progress circumferentially. Another ophthalmoscopic sign of the disease is peripheral retinal vasculitis with sheathing of both the venules and the arterioles. Peripapillary edema may be present at any time in its course (Fig. 15.12). When vision is reduced below a level of 20/30, ophthalmoscopically visible cystoid macular edema is usually seen (Figs. 15.13 and 15.14). Later in the course of the illness, these cystoid changes may become loculated and associated with hemorrhage. An inconsistent finding in this disorder is peripheral retinal neovascularization and vitreous hemorrhage.

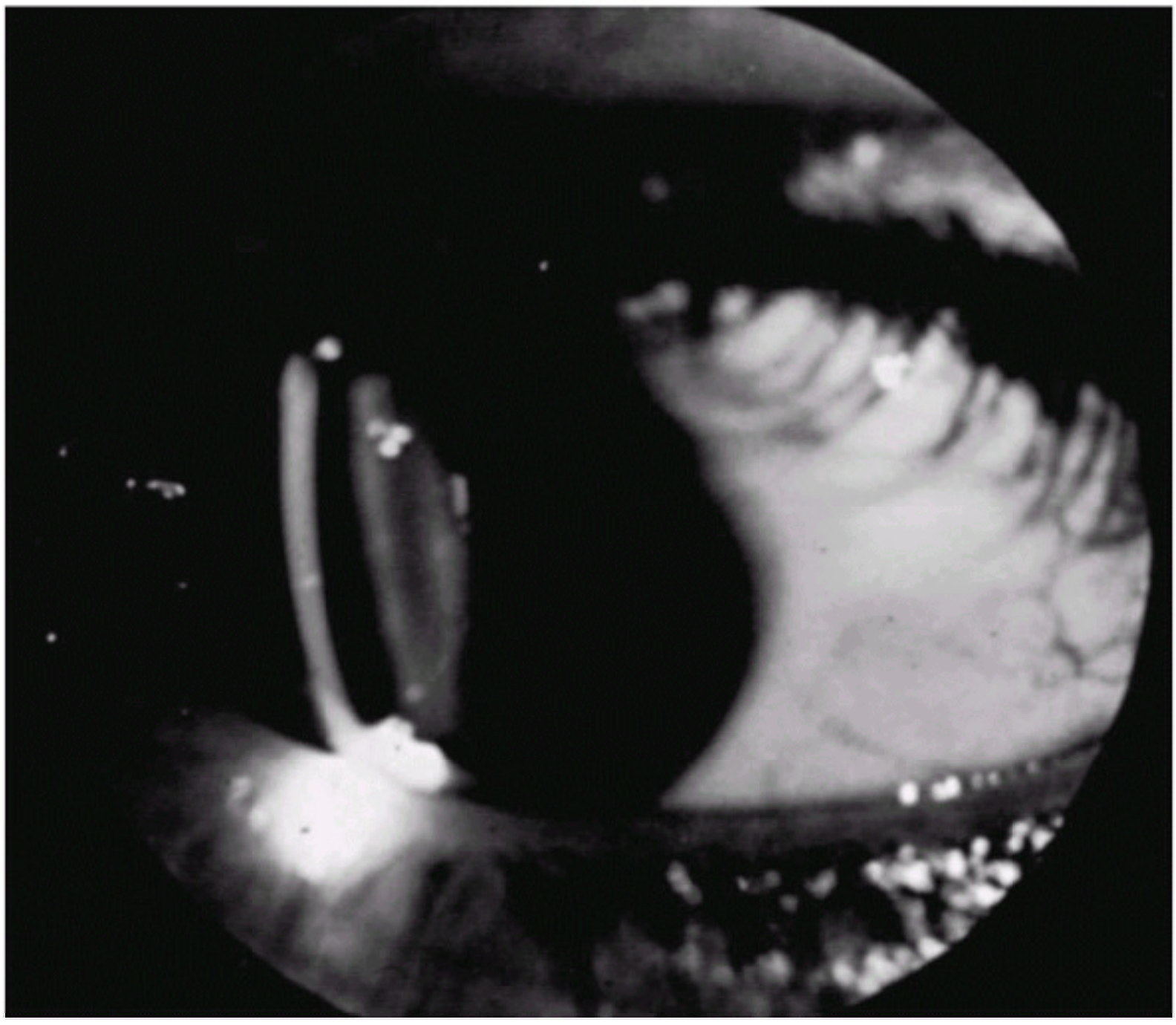

Figure 15.11 Fibrillar pattern and anterior vitreous cellular deposits in the retrolental space in a young patient with chronic intermediate uveitis.

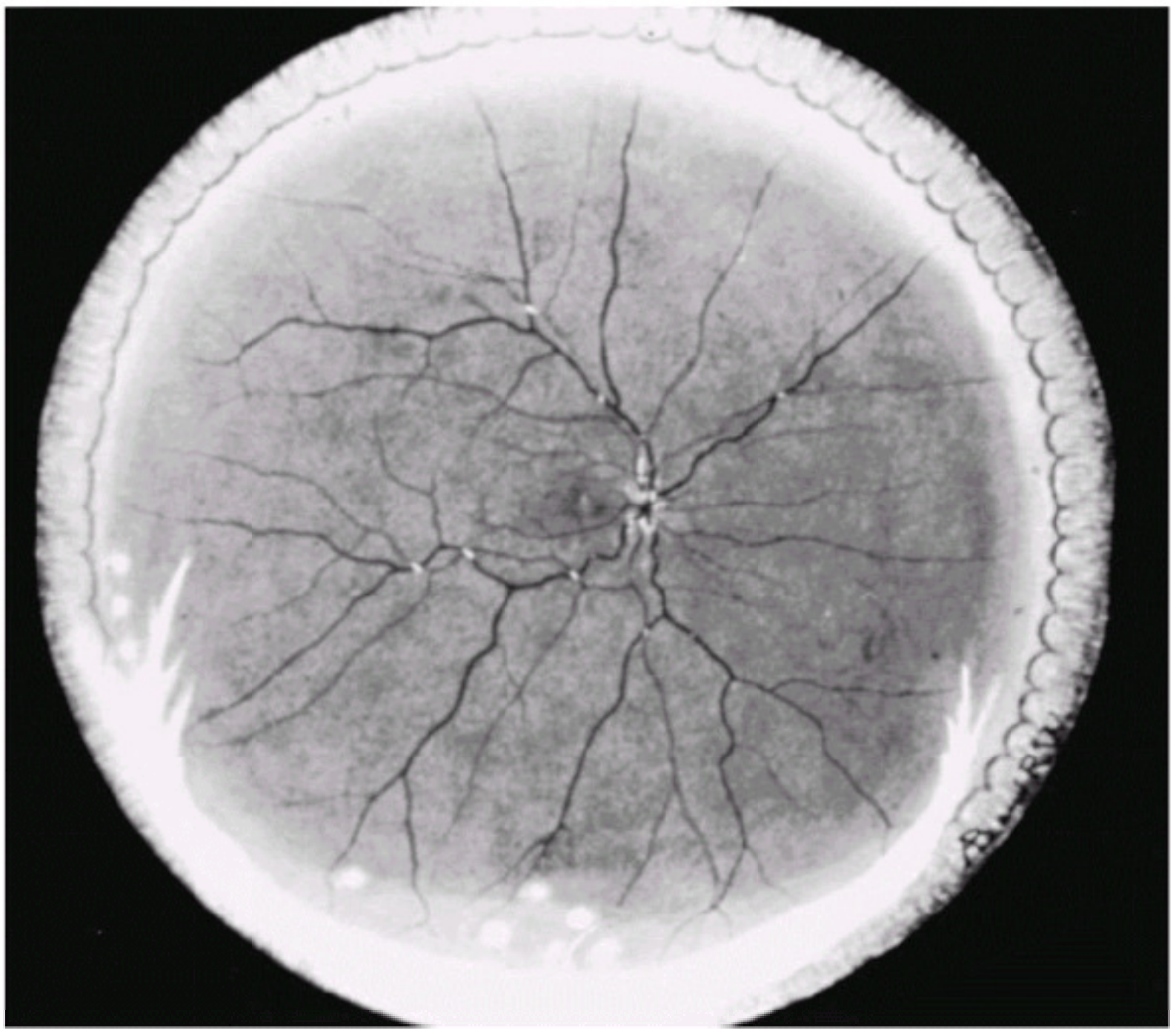

Figure 15.12 Artist's rendering of chronic intermediate uveitis with exudate present inferiorly at the vitreous base, peripheral retinal vasculitis, cystoid macular edema, and peripapillary edema.

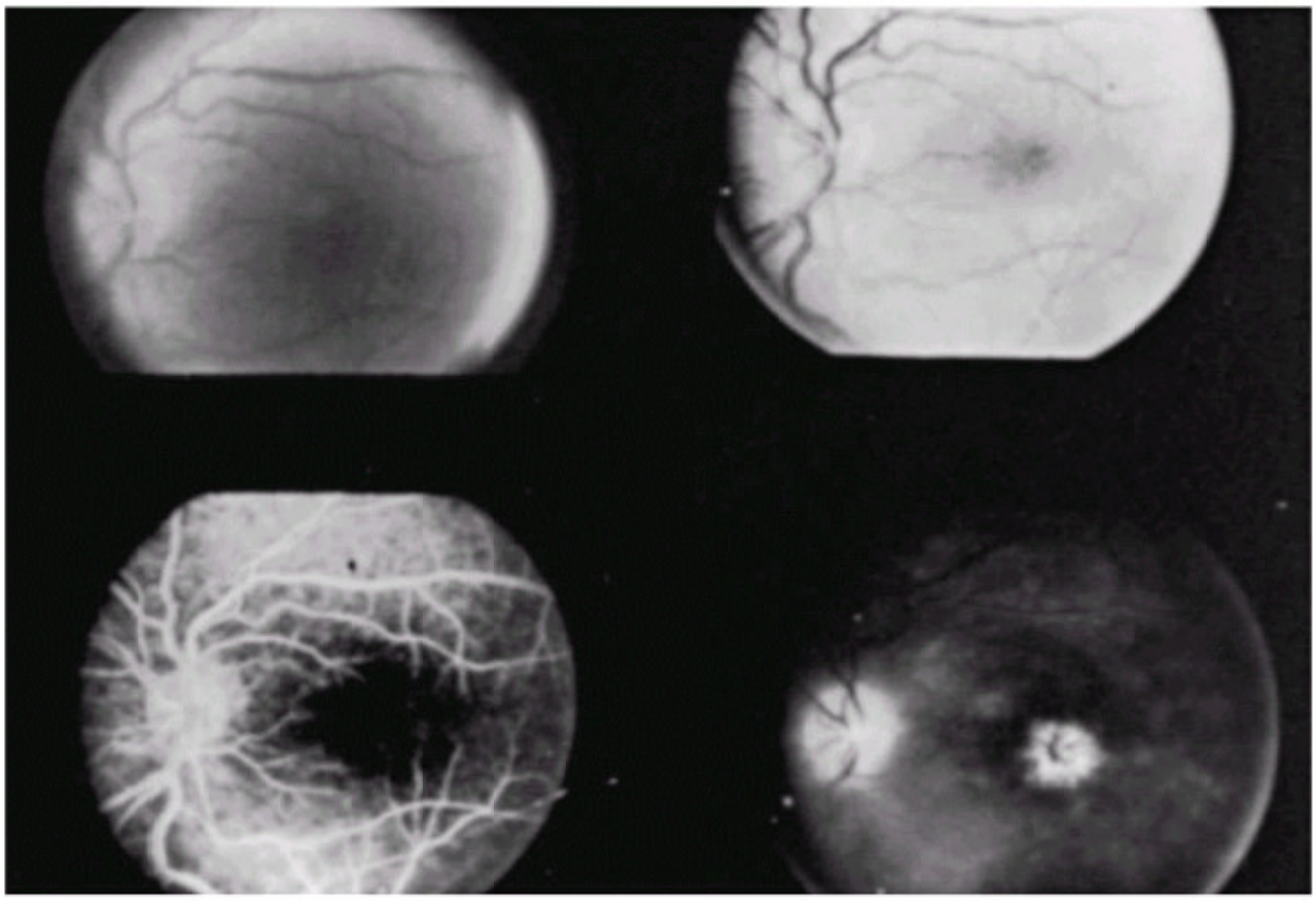

Figure 15.13 Cystoid macular edema in a patient with chronic intermediate uveitis.

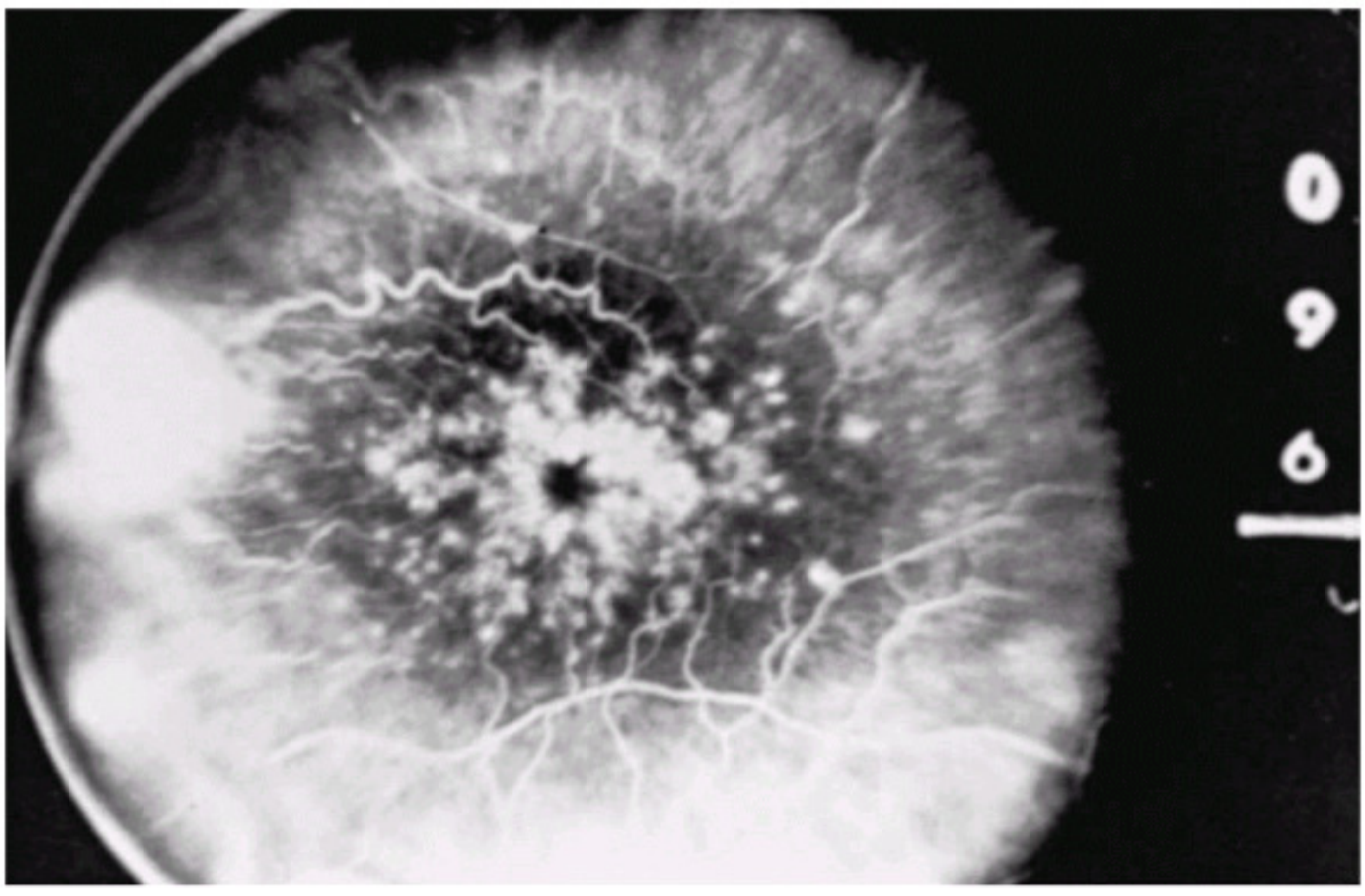

Figure 15.14 Fluorescein angiographic study in a patient with cystoid macular edema and chronic anterior segment inflammation.

Cause

In most patients with intermediate uveitis, the cause is obscure. Although retinal vasculitis frequently accompanies tuberculous uveitis, it has been especially prominent on the European continent. Retinal vasculitis has rarely been associated with tuberculosis in the United States, but nevertheless a tuberculin skin test

should be given to these patients routinely because of possible treatment with systemic corticosteroids. Because many of the changes described may be seen in patients with sarcoid uveitis, sarcoid evaluation is also required, including chest x-ray and serum lysozyme studies. Finally, rare case reports implicate toxocariasis. For this reason, an ELISA study for *Toxocara* is indicated. Most patients remain without a specific diagnosis. Even if an associated systemic disease is found, the treatment remains the same.

As a result of one of the authors' (CLG) experiences in managing 60 young patients with intermediate uveitis, a treatment algorithm has been devised (Fig. 15.15). Local corticosteroids are used only if the patient's vision is 20/40 or better and significant anterior chamber reaction is present. Patients with minimal anterior chamber reaction and vision of 20/40 or better receive no treatment. If vision is less than 20/40 and subretinal exudation, optic nerve papillitis, or disturbing floaters are found, periocular steroids are given weekly (up to six doses) until improvement occurs. In children aged less than 14 years, general anesthesia

is usually required. However, children between 11 and 14 years old may become cooperative enough to permit periocular injection in the office without general anesthesia (Fig 15.16). If improvement does not continue and the signs triggering the intervention are not eliminated, injection should continue weekly for six more weeks.

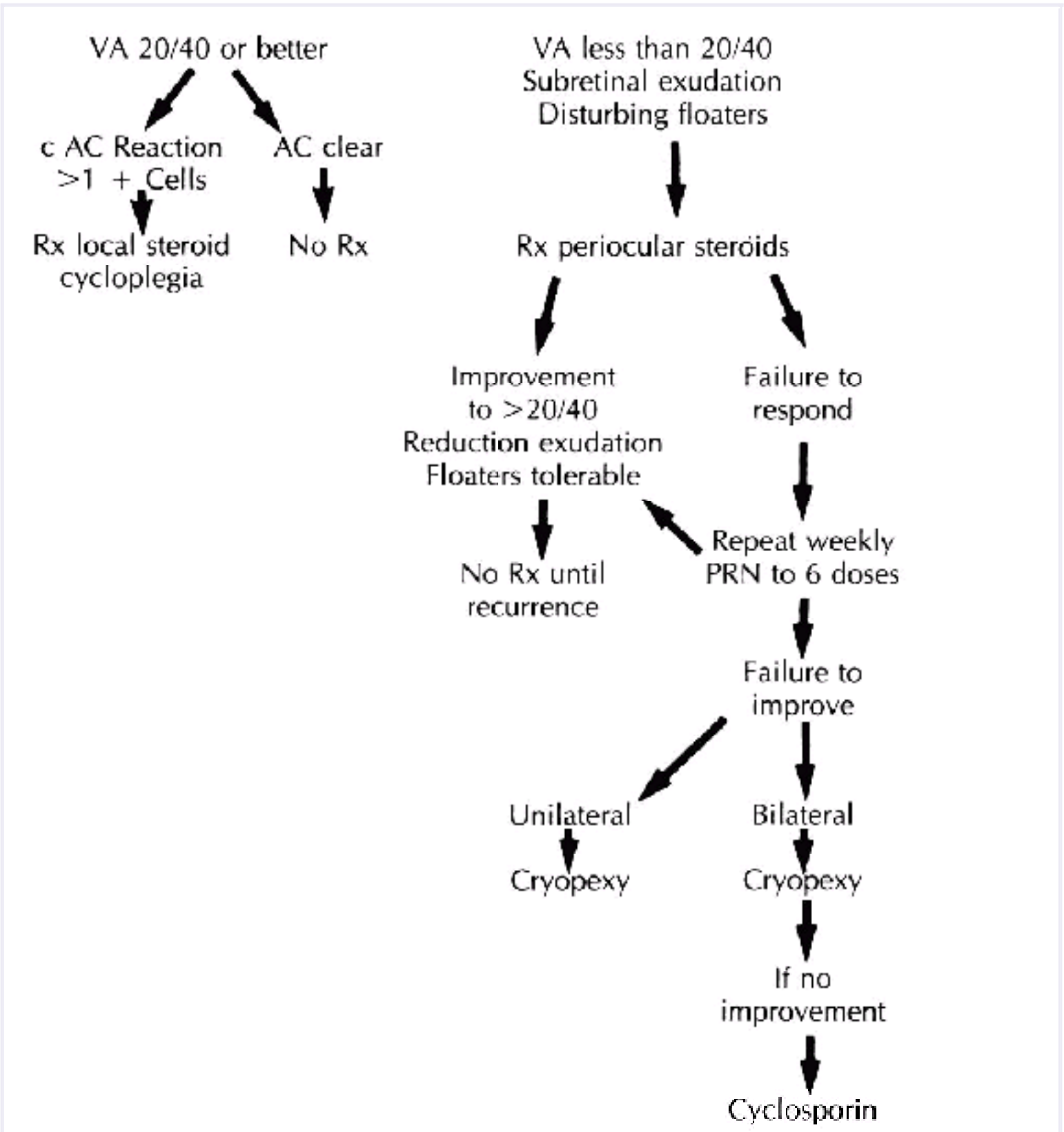

Figure 15.15 Treatment algorithm for intermediate uveitis. (From Giles CL. Pediatric intermediate uveitis. *J Pediatr Ophthalmol Strabismus* 1989;26:138, with permission.)

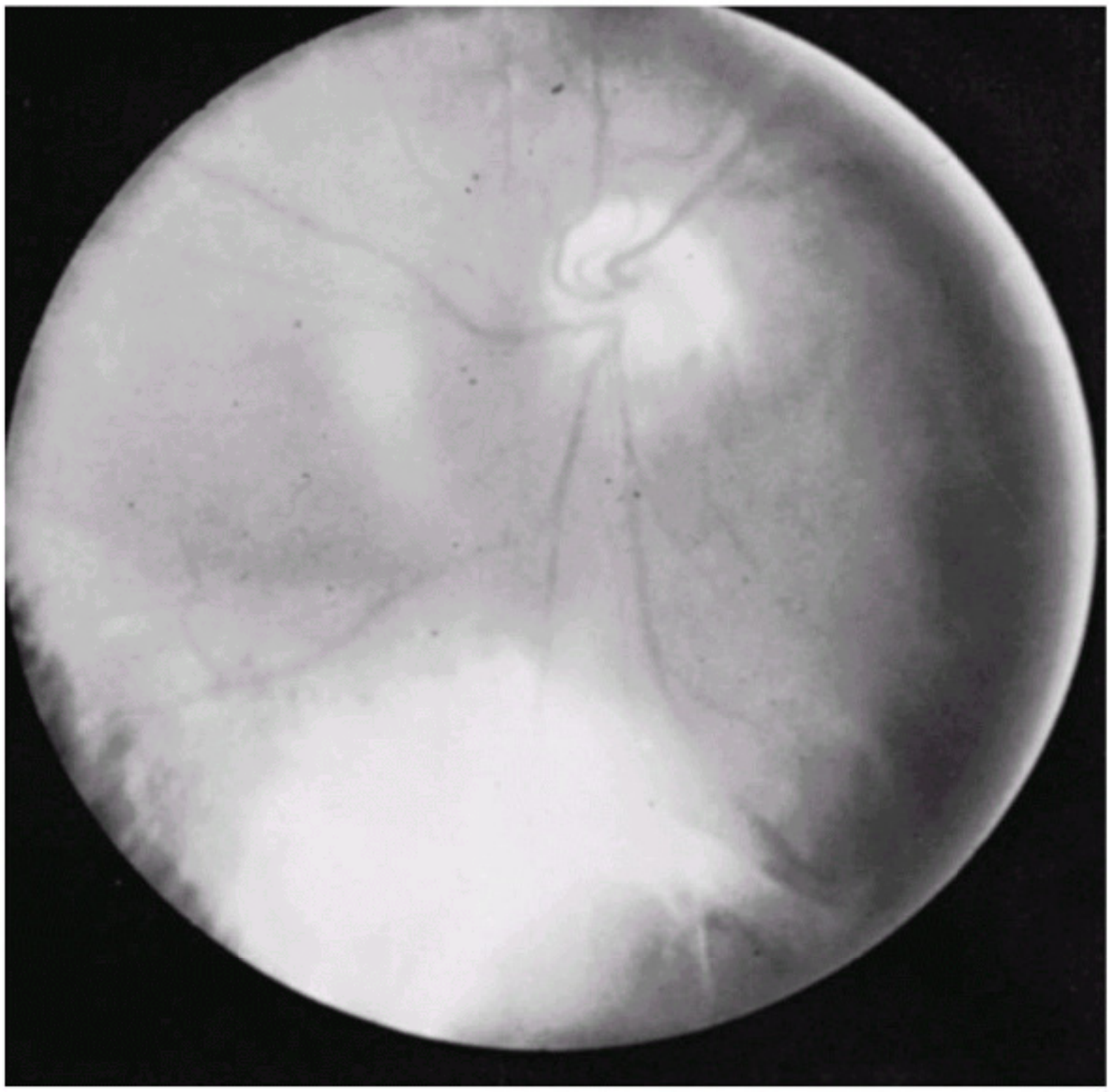

Figure 15.16 Retinal detachment after perforation of the globe during periocular corticosteroid therapy.

The use of systemic corticosteroids in combination with methotrexate and cyclosporine can be considered if the periocular injections fail to result in improvement in vision to 20/40.

Course and Complications

When intervention is early and treatment is vigorous, most patients obtain normal or near normal vision. Again, difficulties in the management of this disorder are attributable to the late presentation of patients in the pediatric age group. Cystoid macular edema, if present for long periods, becomes irreversible. Cataract formation seen early in the course of the illness does little to reduce acuity, but with progression it may reduce vision to the point at which cataract extraction is required. The presence of peripheral retinal neovascularization is especially threatening because recurrent vitreous hemorrhages may require ablation of the vessels and a vitrectomy. Retinal detachment may also occur and provides a great clinical challenge because of the associated inflammatory changes. Secondary glaucoma is rarely a problem in patients with intermediate uveitis, although it may complicate the postoperative management of the cataract extraction.

Differential Diagnosis

Few complications arise to confuse the clinician in the differential diagnosis of this disorder. A rare patient with a peripheral lesion of toxoplasmosis may cause clinical confusion only if careful scleral depression is not carried out. “Mutton fat” keratic precipitates should also alert the clinician to the possibility of toxoplasmosis. Retinitis pigmentosa often presents with cells in the anterior one third of the vitreous (Fig. 15.17). The ophthalmoscopic changes in retinitis pigmentosa coupled with the electro-oculographic and electroretinographic findings should enable the ophthalmologist to differentiate retinitis pigmentosa from intermediate uveitis.

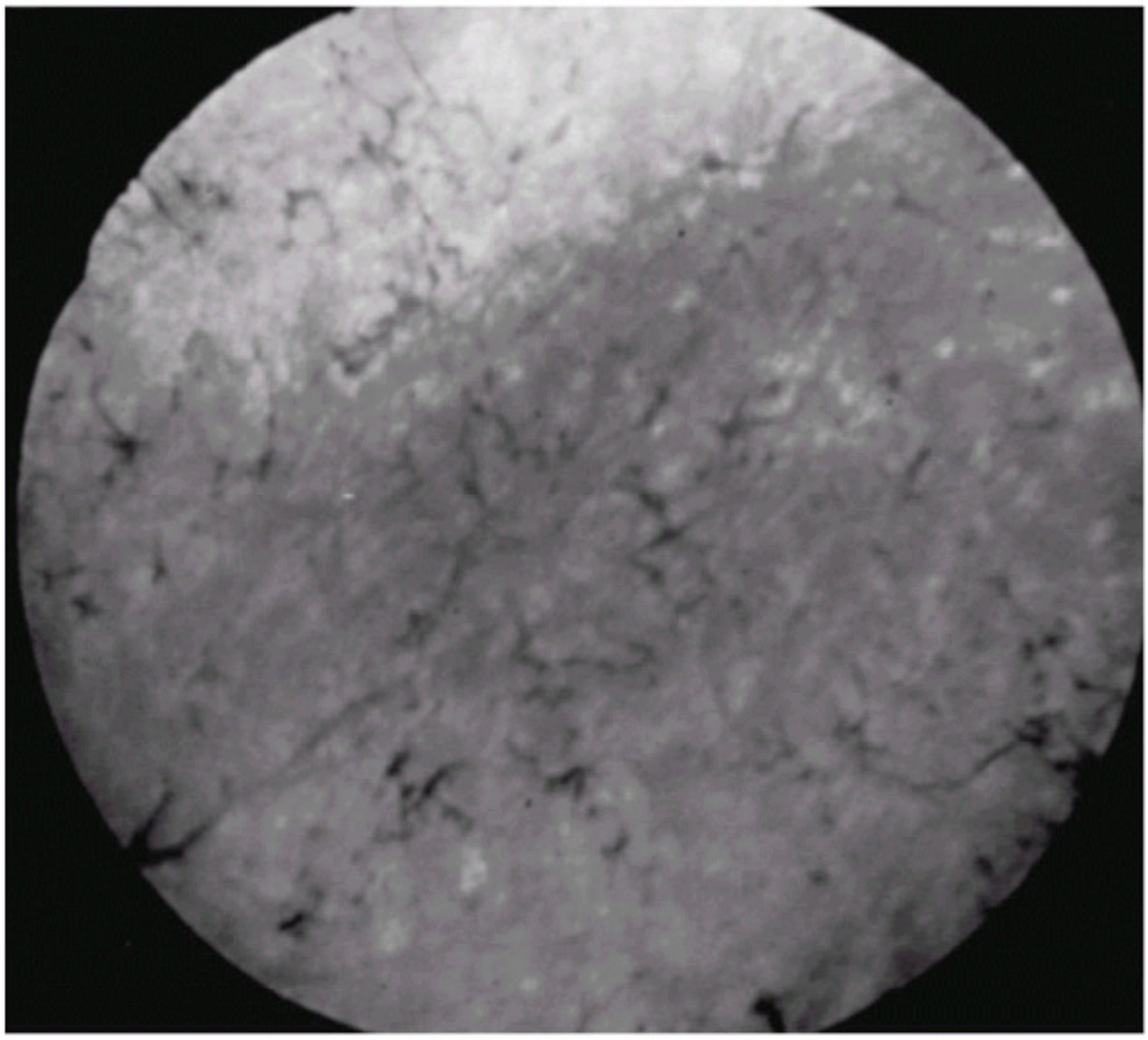

Figure 15.17 Retinitis pigmentosa in a patient demonstrating characteristic bone-corpuscle retinal pigmentation.

POSTERIOR UVEITIS

Of the anatomic divisions of uveitis, posterior inflammation carries the greatest potential for visual loss. Children seldom relate symptoms until visual loss is profound. Vitreous floaters are an uncommon complaint until the age of 12 years. Delay in presentation often leads to loss of vision. Toxoplasmosis, *Toxocara canis,* cytomegalovirus (CMV), and sarcoidosis are the leading causes of posterior uveitis in children (Table 15.7).

Toxoplasmosis

Toxoplasmosis accounts for approximately 50% of the posterior uveitis cases in the pediatric population. Infection is caused by the intracellular protozoan *Toxoplasma gondii,* for which cats are the definitive host. Infection is incidental with humans being an intermediate host after ingestion of the encysted (bradyzoite) organism in undercooked meat. After ingestion, the bradyzoite migrates to cardiac, muscular, and neural (including the retina) tissue. Rupture of the cyst leads to an actively proliferating form of the organism (tachyzoite) causing reactivation of disease. Virtually all disease seen in humans is a result of congenital infection.

Transplacental transmission by infected mothers accounts for up to 40% of cases. Infection during the first trimester of pregnancy may result in hydrocephalus, intracerebral calcifications, hepatosplenomegaly, seizures, and pneumonia. Second or third trimester infection is associated with mild generalized disease during the first few months of life.

TABLE 15.7 CAUSE OF POSTERIOR UVEITIS AND PANUVEITIS IN CHILDREN

Posterior Uveitis
Toxoplasmosis (70%)
Nematodiasis (10%-15%)
Cytomegalovirus
Sarcoid
Tuberculosis
Syphilis
Rubella
Subacute sclerosing panencephalitis
Herpes simplex
AIDS
Panuveitis
Sympathetic ophthalmia
Vogt-Koyanagi-Harada syndrome
Behçet's syndrome
Ocular Lyme borreliosis

AIDS, Acquired immune deficiency syndrome.

Congenital disease may present with bilateral macular scars. Acquired disease is suspected in the setting of retinitis in the absence of scarring. Active disease adjacent to an old scar most often represents reactivation (Fig 15.18). Active disease presents as a localized area of retinochoroiditis with overlying vitreitis (Fig. 15.19). Severe vitreous inflammation may present with a classic “headlight in the fog” presentation. Inflammation may spill over into the anterior chamber in severe cases. Toxoplasmosis usually prefers the anterior layers of the retina for multiplication. A deep retinal form of toxoplasmosis also exists in which disease does not cause vitreitis early (Fig. 15.20). As the infection extends into the anterior retina and breaks through the posterior hyaloid membrane, vitreitis develops. The diagnosis of toxoplasmosis is a clinical and serologic one. Tests include IFA tests, ELISA, Sabin-Feldman dye study, Lunde-Jacobs hemagglutination test, and complement fixation studies.

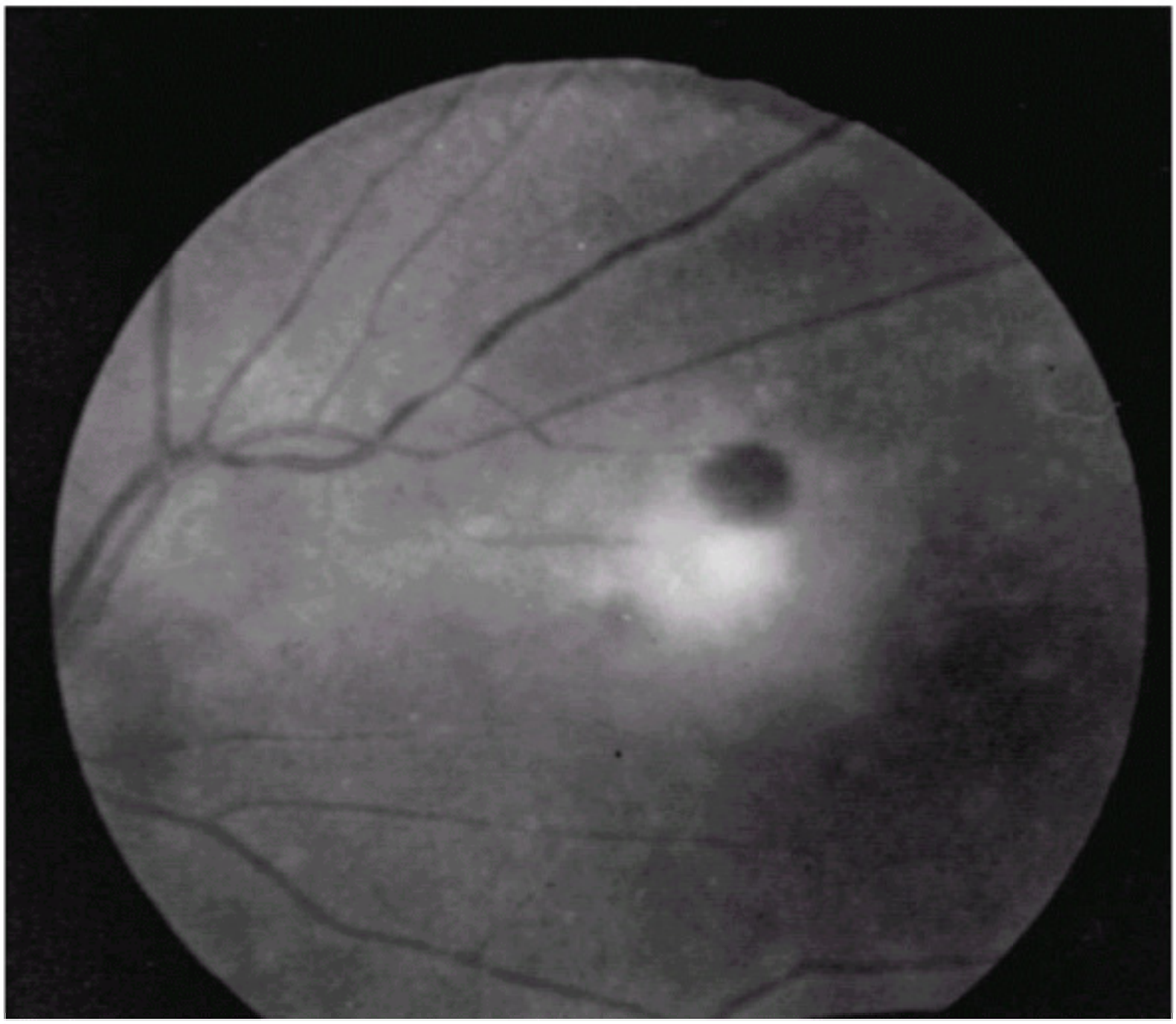

Figure 15.18 Active inflammatory focus adjacent to healed, deeply pigmented chorioretinal scar in a teenage patient with 1:16 indirect fluorescent antibody (IFA) titer for toxoplasmosis.

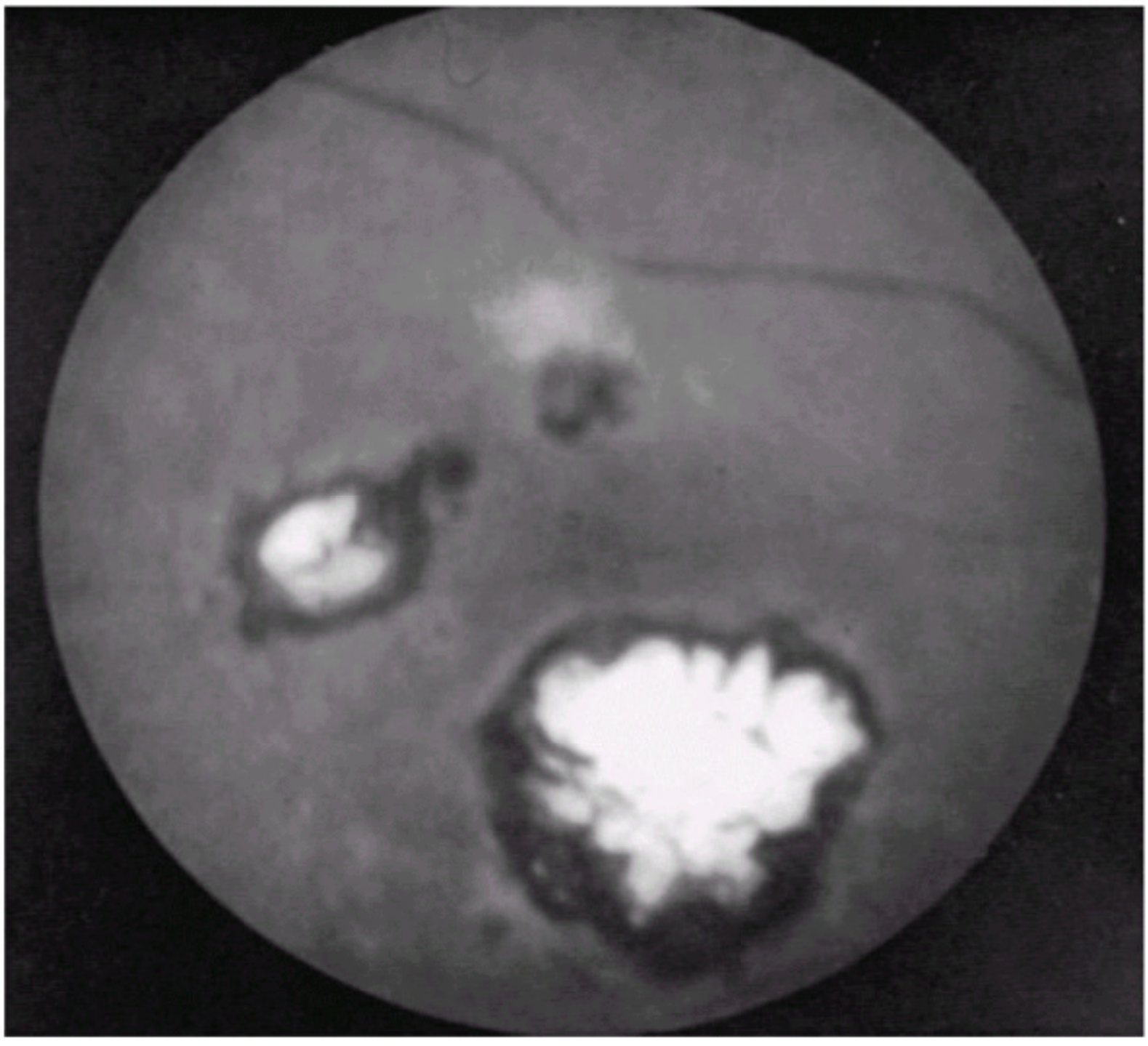

Figure 15.19 Example of presumed toxoplasmic chorioretinitis.

Toxoplasmosis is a self-limited disease in immunocompetent individuals. Infection generally resolves in 1 to 2

months. Healing is dependent on the patient's immune system. Treatment is indicated in cases causing severe loss of vision, threatening the macula or optic nerve. Small peripheral lesions should be observed without treatment. Standard treatment consists of pyrimethamine (Daraprim; GlaxoSmithKline, Research Triangle Park, NC), sulfonamides, and clindamycin. Pyrimethamine is given orally at a loading dose of 150 mg followed by 25 to 50 mg daily for 6 weeks. Concomitant use of folic acid, 3-mg doses twice per week, generally prevent the leukopenia and thrombocytopenia associated with pyrimethamine use. Leukocyte and platelet count must be monitored on a weekly basis during pyrimethamine use. Sulfa or sulfadiazine is loaded with a 2-g dose followed by a 1-g dose four times per day for 6 weeks. Clindamycin should be used at a dosage of 300 mg three times daily or in infants at a dosage of 25 mg/kg per day. Alternative regimens may include treatment with DS Bactrim or doxycycline. Corticosteroids are used with caution and only with concomitant antibiotic use. An oral dose of 100 to 150 mg of prednisone once every other day may help quell inflammatory lesions. Periocular injection of corticosteroid should be avoided.

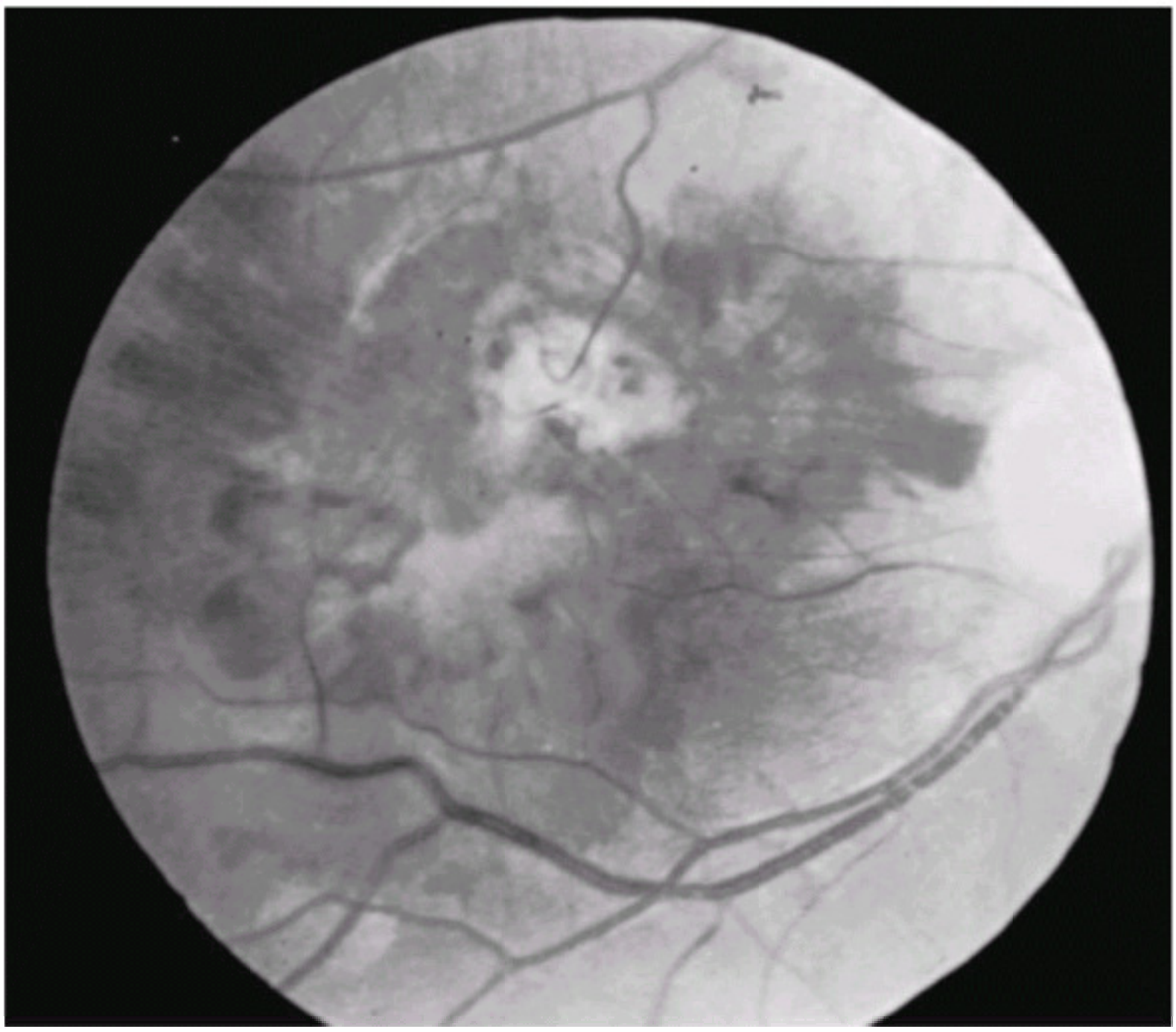

Figure 15.20 Deep retinal form of presumed ocular toxoplasmosis. (Courtesy of David Knox, MD.)

Toxocariasis

Ocular toxocariasis is a disease of children caused by ingestion of soil containing eggs of the canine roundworm *Toxocara canis.* The eggs are ingested and hatched in the intestine. From here they travel systemically to the liver, lungs, brain, skin, and eye. The human is an incidental host for *Toxocara.* It does not develop beyond the larvae stage in humans. Systemic infection is termed “visceral larvae migrans.” Associated symptoms include cough, fever, seizures, and malaise (Table 15.8). Visceral larvae migrans is most common in patients from age 6 months to 3 years, with boys being affected more often than girls.

Ocular involvement is usually unilateral and takes one of three different forms: endophthalmitis, posterior pole granuloma, and peripheral granuloma (Fig. 15.21).

Endophthalmitis

Patients aged 2 to 9 years are affected. Moderate to severe vitreitis causes a significant loss of vision. There may be spillover of inflammation into the anterior chamber leading to anterior chamber inflammation, keratic precipitates, hypopyon, or posterior synechiae formation. Retinal detachment may also be seen.

TABLE 15.8 OCULAR PRESENTATIONS IN OCULAR TOXOCARIASIS

1. Chronic endophthalmitis with retinal detachment
2. Posterior pole granuloma
3. Peripheral granuloma
4. Vitreous abscess
5. Pars planitis
6. Papillitis
7. Keratitis
8. Anterior uveitis
9. Hypopyon
10. Motile larva in vitreous cavity

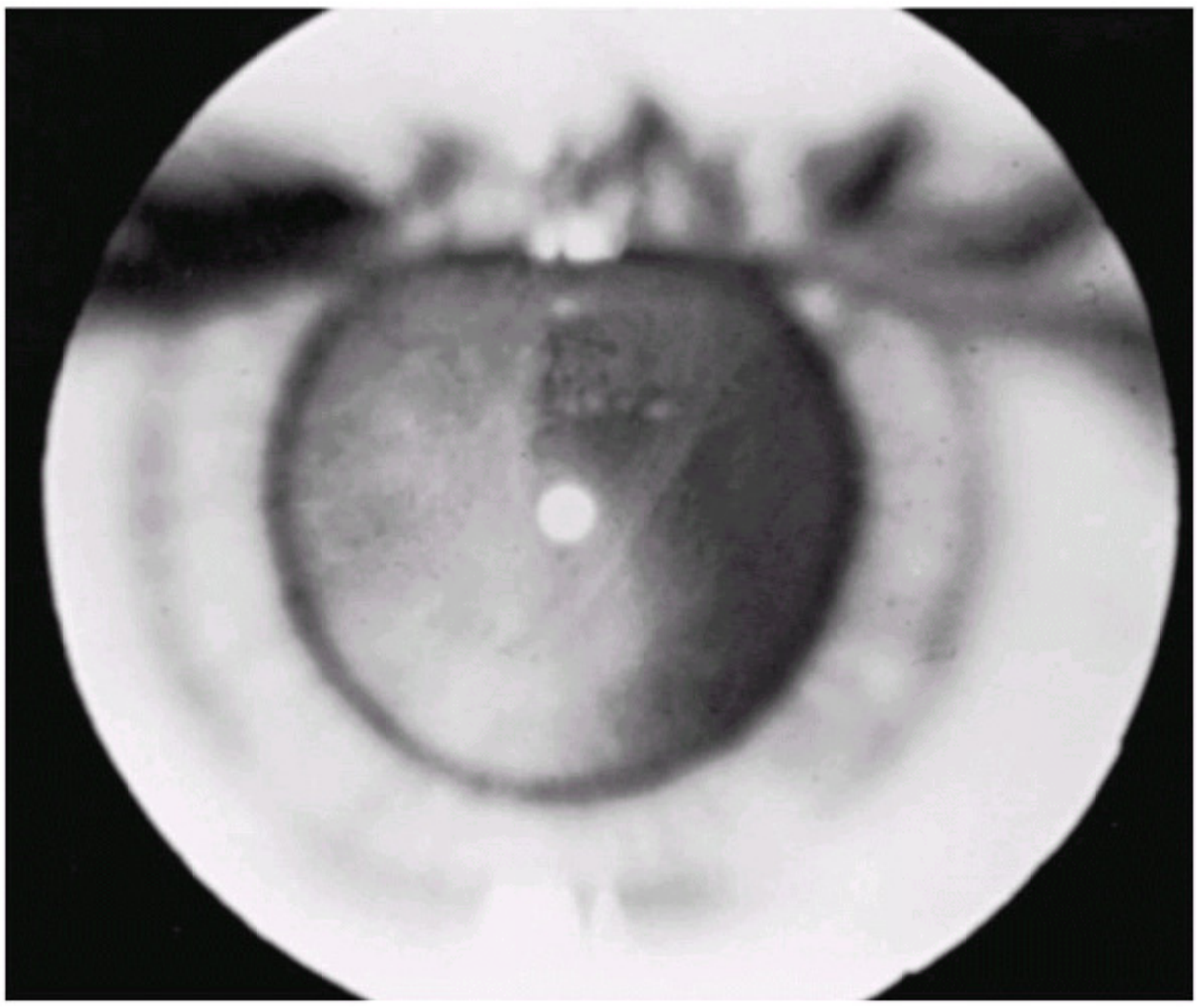

Figure 15.21 Pupillary view of retinal detachment in a patient with presumed toxocariasis and endophthalmitis.

Posterior Pole Granuloma

Posterior pole granuloma is the most common form of ophthalmic toxocariasis infection seen in children. Children aged 6 to 14 years are commonly affected. Externally the eye appears quiet with an elevated whitish mass noted in the posterior pole on dilated funduscopic examination. The mass is associated with an overlying vitreitis and may have associated traction bands extending to the macula or optic disc. Presenting complaints include a decrease in vision or strabismus.

Peripheral Granuloma

This form of ophthalmic toxocariasis presents at an older age than posterior pole granuloma. The eye is again quiet externally with presenting complaints including a decrease in vision and strabismus. A peripheral elevated white lesion is seen. Traction bands extending to the macula and optic nerve are associated with peripheral granuloma (Figs. 15.22 and 15.23). The disease is unilateral.

Diagnosis is made by clinical examination, history, and ELISA test for *Toxocara.* An ELISA test may be run on aqueous or vitreous fluid, which may sometimes yield a positive titer with negative serum testing. Humans are incidental hosts, and as such, testing of stool specimens for ova and parasites is not helpful.

Oral and periocular steroids are used in the treatment of *Toxocara* endophthalmitis. Steroids are useful in curbing inflammation caused by infection. Antihelminthic agents such as thiabendazole or diethylcarbazine have not proven beneficial and may worsen inflammation after treatment.

If antihelminthic treatment is considered, it should not be administered without concurrent steroid therapy. Laser treatment has been used in cases in which a live nematode has been visible on examination. As in the case of antihelminthic agents, laser therapy and resultant worm death may actually worsen the inflammation in the eye.

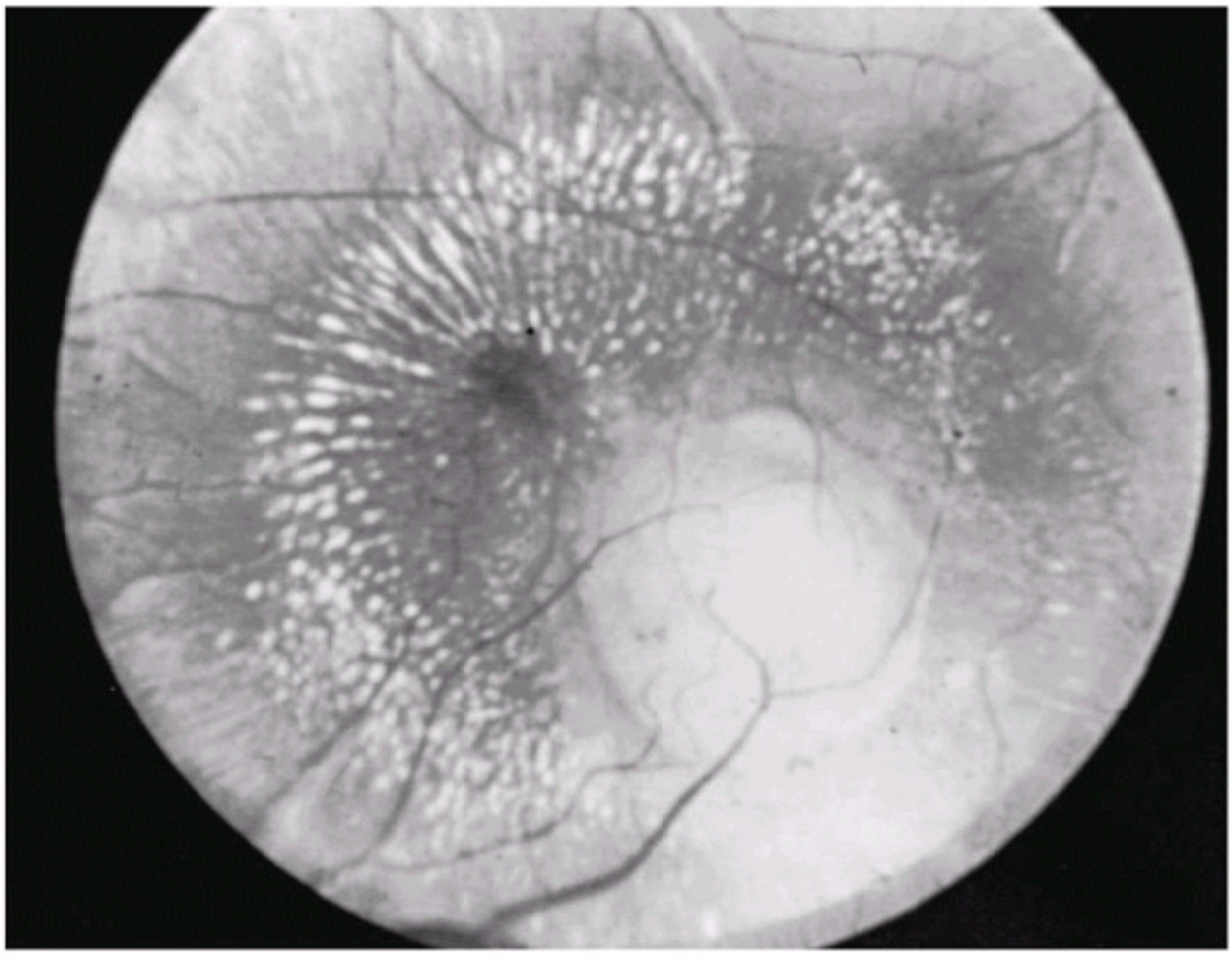

Figure 15.22 Posterior pole granuloma representing probable toxocariasis. (Courtesy of Malcolm Mazow, MD)

Sarcoidosis

Sarcoid eye disease may present with posterior or anterior uveitis as described before. Sarcoidosis is responsible for between 0.8% and 3.9% of uveitis cases in children. A diagnosis or orbital sarcoidosis has been proven with biopsy of the orbit or other site, no history of trauma, which may result in granulomatous reaction, and systemic positive findings such as a chest x-ray or an elevated ACE level. Patients present with reduced vision, photosensitivity, pain, swelling, and proptosis. Examination of the posterior pole often reveals focal exudative lesions described as candle wax drippings (taches de bougie) (Fig. 15-.24). Systemic and periocular steroids have been used in treatment of sarcoid-associated posterior uveitis.

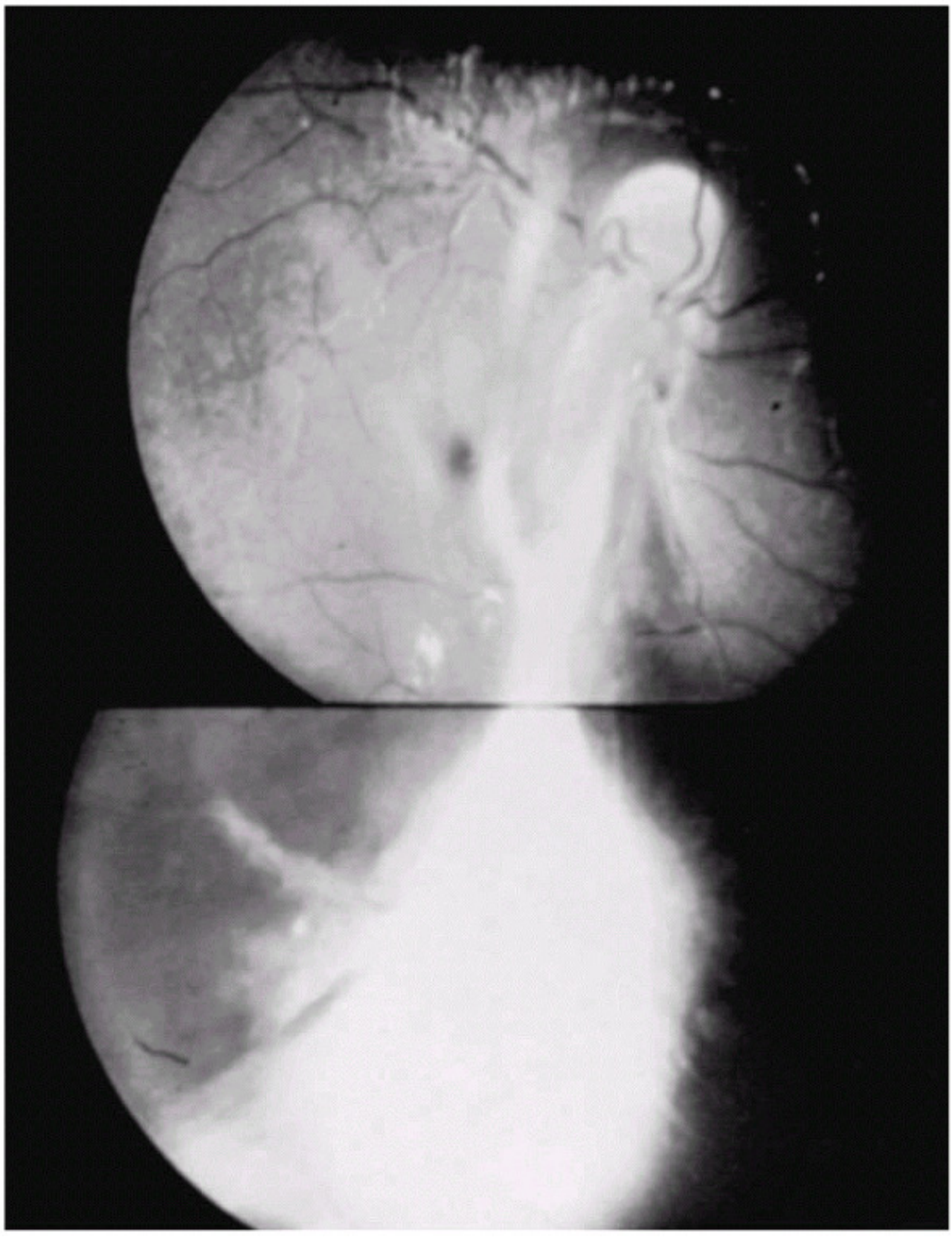

Figure 15.23 Presumed nematode disease with peripheral granuloma. (Courtesy of Jerry Shields, MD.)

Syphilis

Syphilis may be either acquired or congenital. Serologic testing at the time of marriage and the beginning of pregnancy, as well as widespread availability and use of antibiotics, has drastically reduced the incidence of congenital syphilis in the United States. Children with congenital syphilis present with fever, rash, pneumonia, and hepatosplenomegaly. Active choroiditis may be seen in the peripheral retina. Funduscopic examination reveals “salt-and-pepper” or bone spicule chorioretinitis. Patients also present with Hutchinson's triad: deafness, Hutchinson's teeth, and interstitial keratitis. Often the only evidence of choroiditis is peripheral pigment change noted on examination later in life. Anterior inflammation may rarely be seen. Patients are usually responsive to cycloplegics and topical steroids.

Acquired syphilis presents with either anterior or posterior inflammation. Posterior manifestations include vitreitis, vasculitis, chorioretinitis, papillitis, or optic atrophy. Acquired syphilis does not respond well to steroids. Treatment consists of a 10-day course of intravenous penicillin.

Acute retinal necrosis is a form of viral retinitis thought to be caused by HSV or HZV. There is no sex or race predilection. Patients are most often otherwise healthy. Acute retinal necrosis has recently been described in immunocompromised patients as well. Patients present with pain, photosensitivity, redness, and decreased vision. Inflammation is often anterior but may be found in all locations,

with patients often presenting with panuveitis. Dilated funduscopic examination classically reveals areas of peripheral retinal whitening, necrosis, and vasculitis associated with hemorrhage. Macular edema is often present. Active retinitis lasts 4 to 6 weeks and may be followed by tractional or rhegmatogenous retinal detachment. Up to 75% of cases develop retinal detachment. Elevated HSV or HZV titers are nonspecific and may not be elevated in patients with isolated ocular disease. Diagnostic vitrectomy and retinal biopsy have been described. The diagnosis remains largely a clinical one. Treatment is with intravenous acyclovir followed by an oral course. Intravenous acyclovir is dosed at 1500 mg intramuscularly twice per day for 1 to 3 weeks followed by a 4- to 6-week oral course. Corticosteroids may be used to control inflammation but only after institution of antiviral therapy.

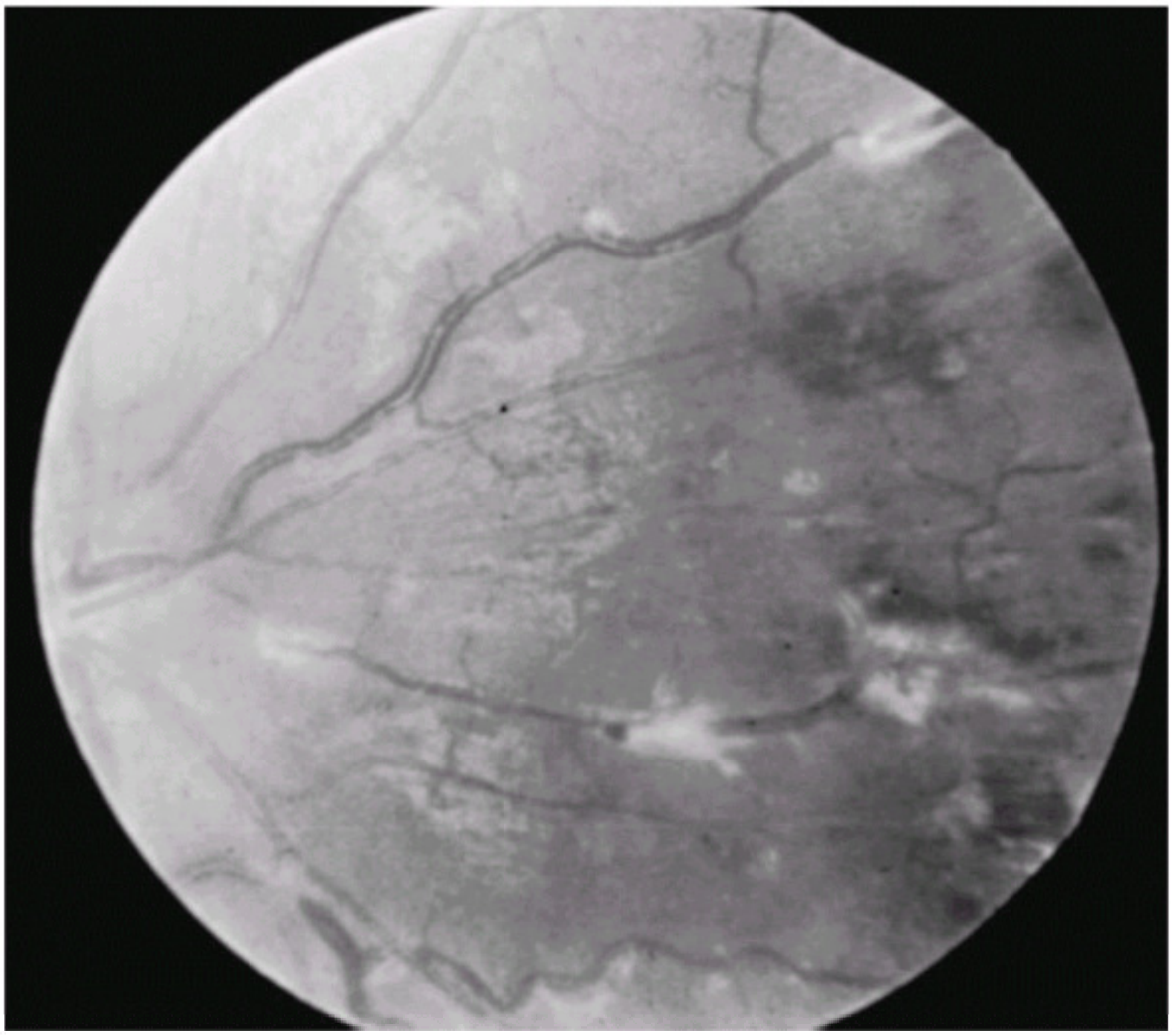

Figure 15.24 Classic picture of sarcoid uveitis.

Cytomegalovirus

CMV retinitis is seen in immunocompromised populations. CMV retinitis is the leading cause of visual loss in adult patients with acquired immunodeficiency virus. The pediatric population with acquired immunodeficiency virus is predominantly composed of newborn infants of affected mothers and hemophiliacs who have received an infected blood transfusion. Funduscopic examination is significant for patchy areas of retinal ischemia, edema, and hemorrhage. Vasculitis and macular edema may be seen (Figs. 15.25 and 15.26). Patients may develop retinal detachment as a result of frequent retinal tears. Vitreitis is often less than would be expected because of a reduced immune response. Treatment is with systemic antiviral therapy or local intravitreal ganciclovir implant. The incidence of CMV retinitis has decreased with the advent of highly active antiretroviral therapy.

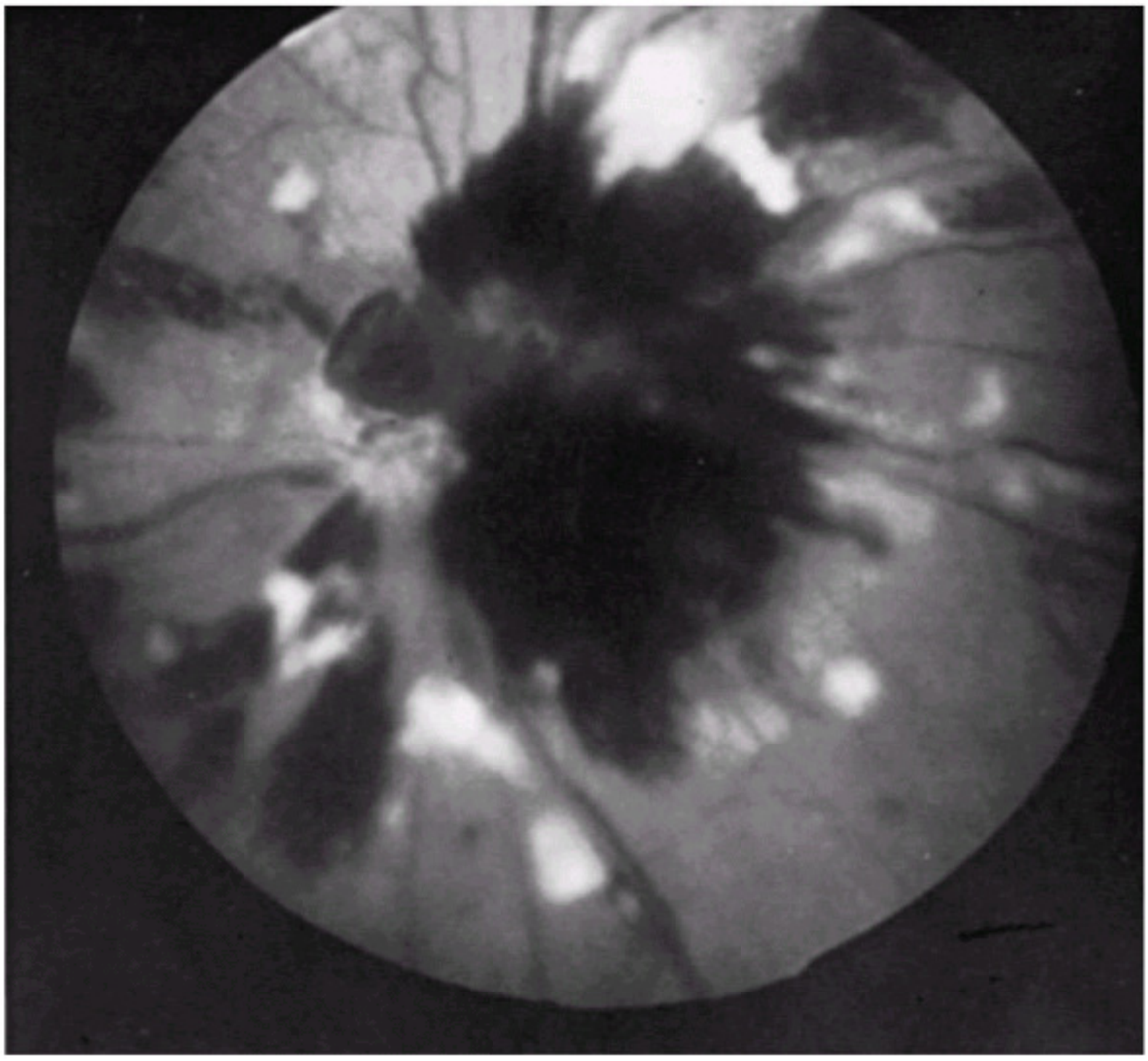

Figure 15.25 Immunocompromised patient with cytomegaloviral uveitis after renal transplantation.

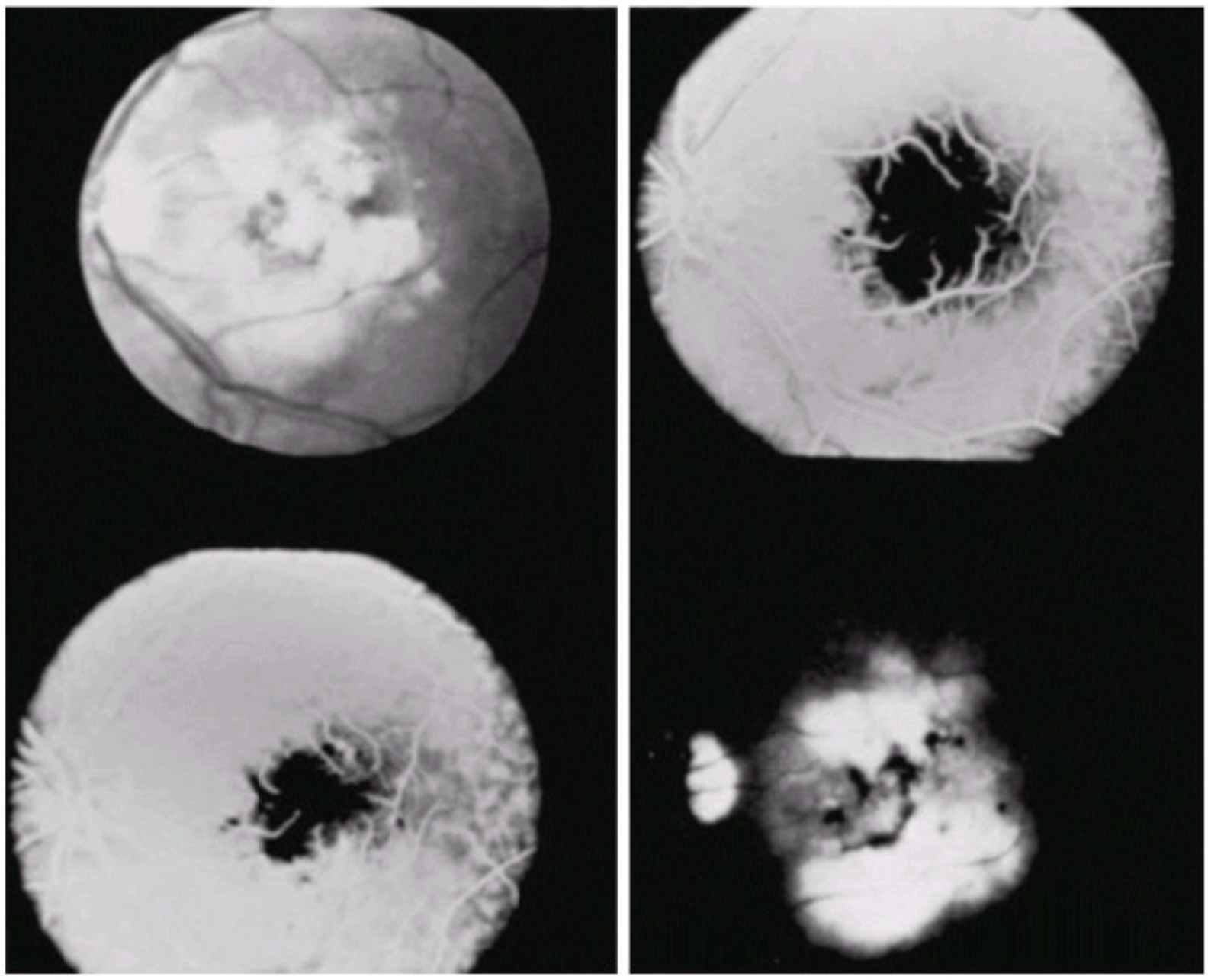

Figure 15.26 Fundus photograph and fluorescein angiography in a patient with cytomegaloviral infection.

Other Viral Entities

Rubella retinitis is present in 25% to 50% of infants with maternal rubella syndrome. Unilateral or bilateral pigment deposits are usually limited to the posterior pole (Fig. 15.27). They may appear as fine, powdery, or granular to more discrete shapes. The retinopathy is benign and nonprogressive and does not interfere with vision except in cases with neovascularization involving the macula.

Subacute sclerosing panencephalitis presents with a posterior uveitis without vitreitis (Fig. 15.28). The myxovirus rubeola is thought to be the causative agent in subacute sclerosing panencephalitis. The disease affects school-aged children and is accompanied by changes in behavior and intellectual deterioration. Disorder may progress with myoclonic seizures followed by spastic paralysis and profound dementia. Cortical blindness, nystagmus, papilledema, and optic atrophy have been observed. Most patients die within 1 to 2 years of onset.

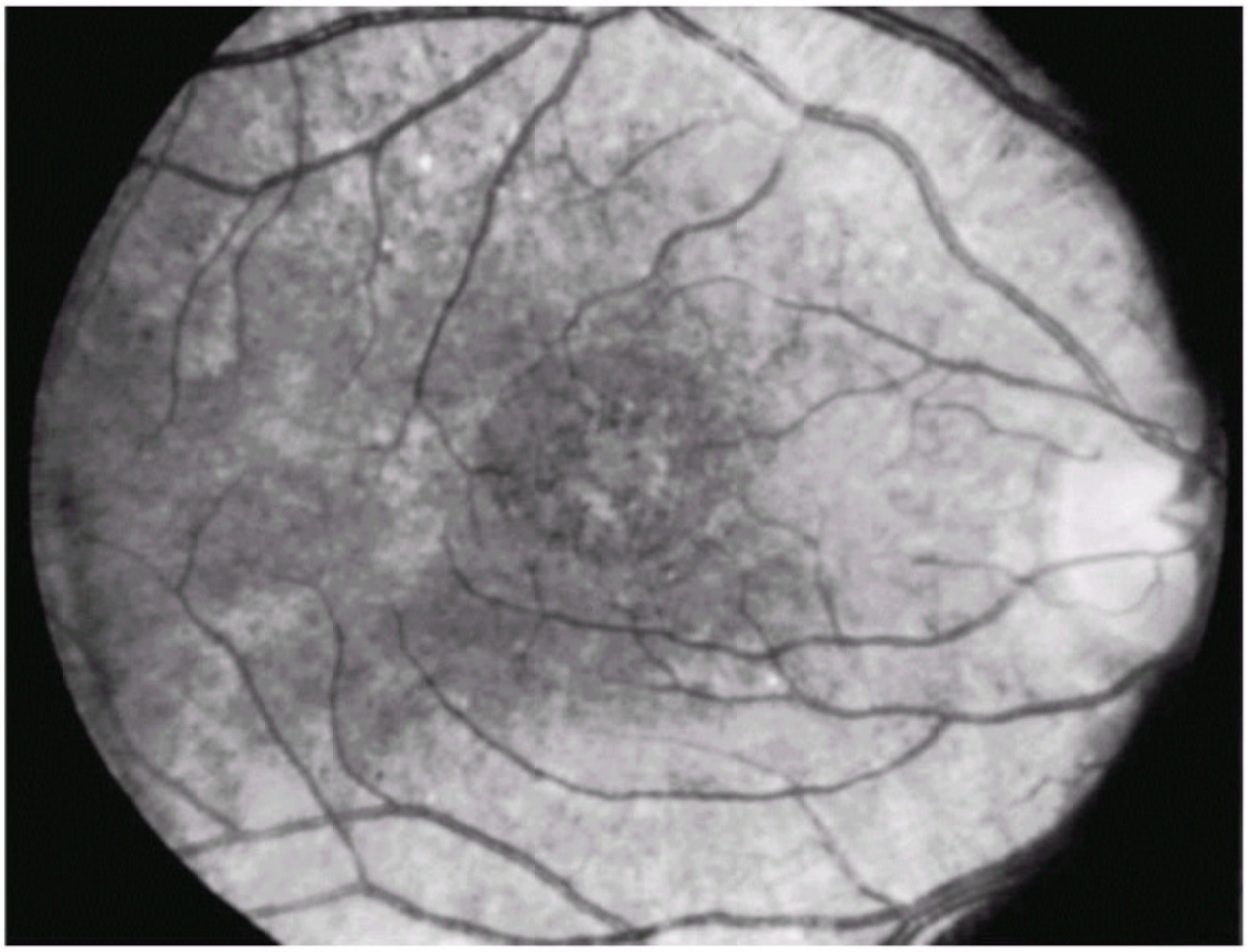

Figure 15.27 Macular changes in a patient with congenital rubella retinitis.

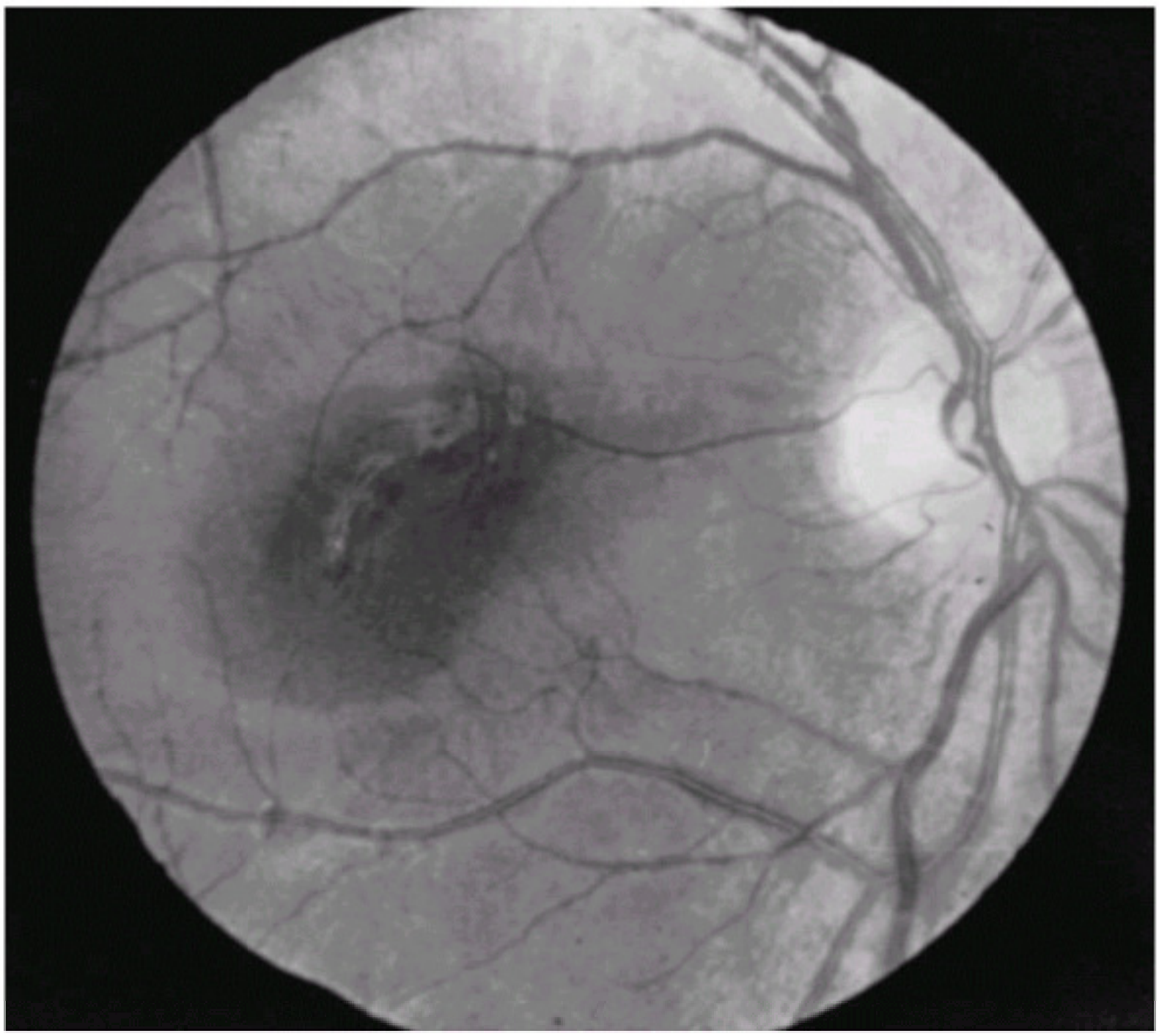

Figure 15.28 Retinal findings in a child with posterior uveitis and subacute sclerosing panencephalitis.

Panuveitis

Sympathetic Ophthalmia

Sympathetic ophthalmia is bilateral granulomatous panuveitis seen after penetrating ocular trauma or surgery. The condition affects all ages and has no sex predilection. The incidence of sympathetic ophthalmia ranges from 0.19% to 0.7% in cases of trauma and from 0.007% to 0.015% in surgical cases. A majority of cases are seen after ocular trauma. Trauma often involves injury to the iris and ciliary body with incarceration of uveal tissue. Sympathetic ophthalmia is seen in the undamaged eye 2 weeks to decades after the original injury. Ninety percent of cases occur within 1 year of injury. Patients may present with pain, redness, photophobia, or decreased vision. Examination is significant for anterior chamber cell and flare, mutton-fat keratic precipitates, vitreitis, and yellow-white Dalen-Fuchs nodules throughout the fundus (Fig. 15.29). Inflammation is bilateral with the injured, or excited, eye often developing signs first and the other sympathizing eye developing signs later.

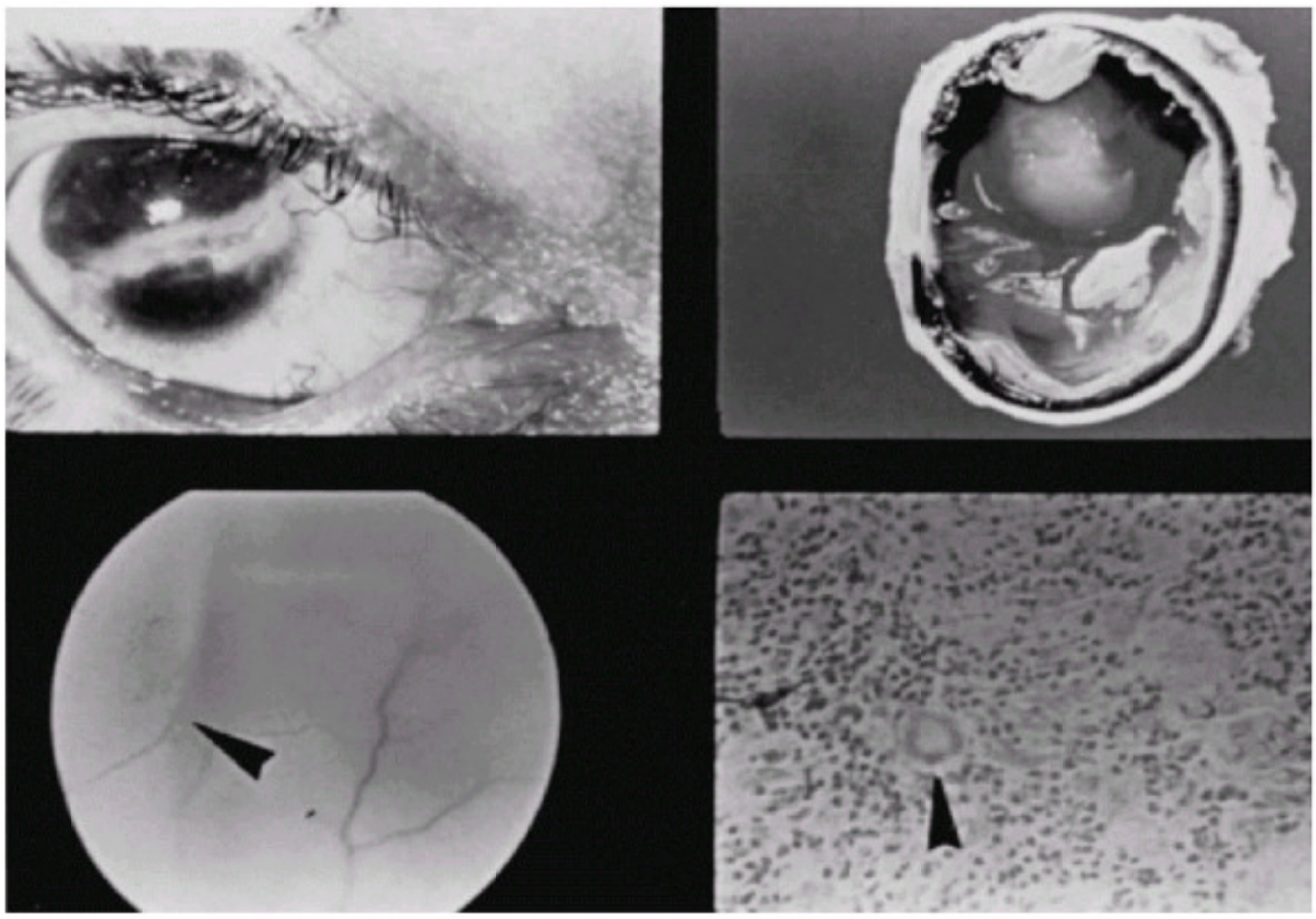

Figure 15.29 Clinical representation of Dalen-Fuchs nodules in the posterior pole of a patient with sympathetic ophthalmia. *Clockwise from upper left:* External photograph, sectioned globe, clinical retinal photograph, and microscopic section.

Removal of the exciting, or previously damaged, eye may alleviate inflammation in the “sympathetic eye.” A blind eye is frequently removed in cases of sympathetic ophthalmia; however, evidence to support removal of an eye with vision is scant. Pharmacologic treatment consists of systemic, local, and periocular steroids. Immunosuppressant agents are used when steroids fail to control the inflammation.

Vogt-Koyanagi-Harada Syndrome

Vogt-Koyanagi-Harada syndrome is a bilateral panuveitis associated with dermatologic and neurologic manifestations. Disease is typically seen in darkly pigmented races. The disease course is divided into three stages. Stage one is the prodromal stage characterized by flu-like symptoms. Patients with stage one disease also present with headaches, tinnitus, and meningismus. Stage two disease is the ophthalmic stage. Patients develop a granulomatous panuveitis. Optic disc hyperemia and exudative serous retinal detachments are seen. The convalescent stage is stage three. Dermatologic manifestations such as vitiligo and alopecia are seen. The fundus undergoes pigmentary changes and is classically described as a “sunset glow” fundus. Raised yellow-white lesions are seen in the fundus, similar to the Dalen-Fuchs nodules of sympathetic ophthalmia. Fluorescein angiography is significant for speckled, multifocal areas of hyperfluorescence in early frames with late leakage.

The precise disease etiology is unknown. Autoimmune mechanism has been suggested by which reaction to retinal antigens or uveal melanocytes is responsible for disease. Complications are frequent and include glaucoma, cataracts, and neovascularization. Glaucoma occurs in up to 40% of patients.

Treatment consists of systemic steroids. Topical corticosteroids may be added to help control anterior uveitis. Cases unresponsive to steroids may require addition of cyclosporine.

Behçet's Syndrome

Behçet's syndrome is a systemic vasculitis of unknown cause. There is a greater incidence among patients of Mediterranean descent, from the Middle East, or from Japan. Behçet's syndrome is responsible for between 0.4% and 0.7% of uveitis cases among children. The disease is classified by four major criteria. Patients with complete disease fulfill all four criteria. Those with incomplete disease have only three criteria or present with uveitis in conjunction with one other major criterion. The four major criteria are recurrent uveitis, recurrent oral aphthous ulcers, skin lesions, and genital ulceration.

Ocular manifestations are seen in up to 79% of patients. Anterior uveitis *with* hypopyon is classically described in association *with* Behçet's syndrome and is seen in approximately one third of patients. Funduscopic examination reveals an occlusive vasculitis, retinal hemorrhage, exudates, and vitreitis. Recurrent disease often results in neovascularization or retinal detachment. The diagnosis of Behçet's syndrome is a clinical one. Treatment consists of topical corticosteroids and mydriatic agents for anterior uveitis. Systemic steroids are used initially with patients often requiring immunosuppressants and addition of cyclosporine. Prolonged therapy is required to control frequent recurrences.

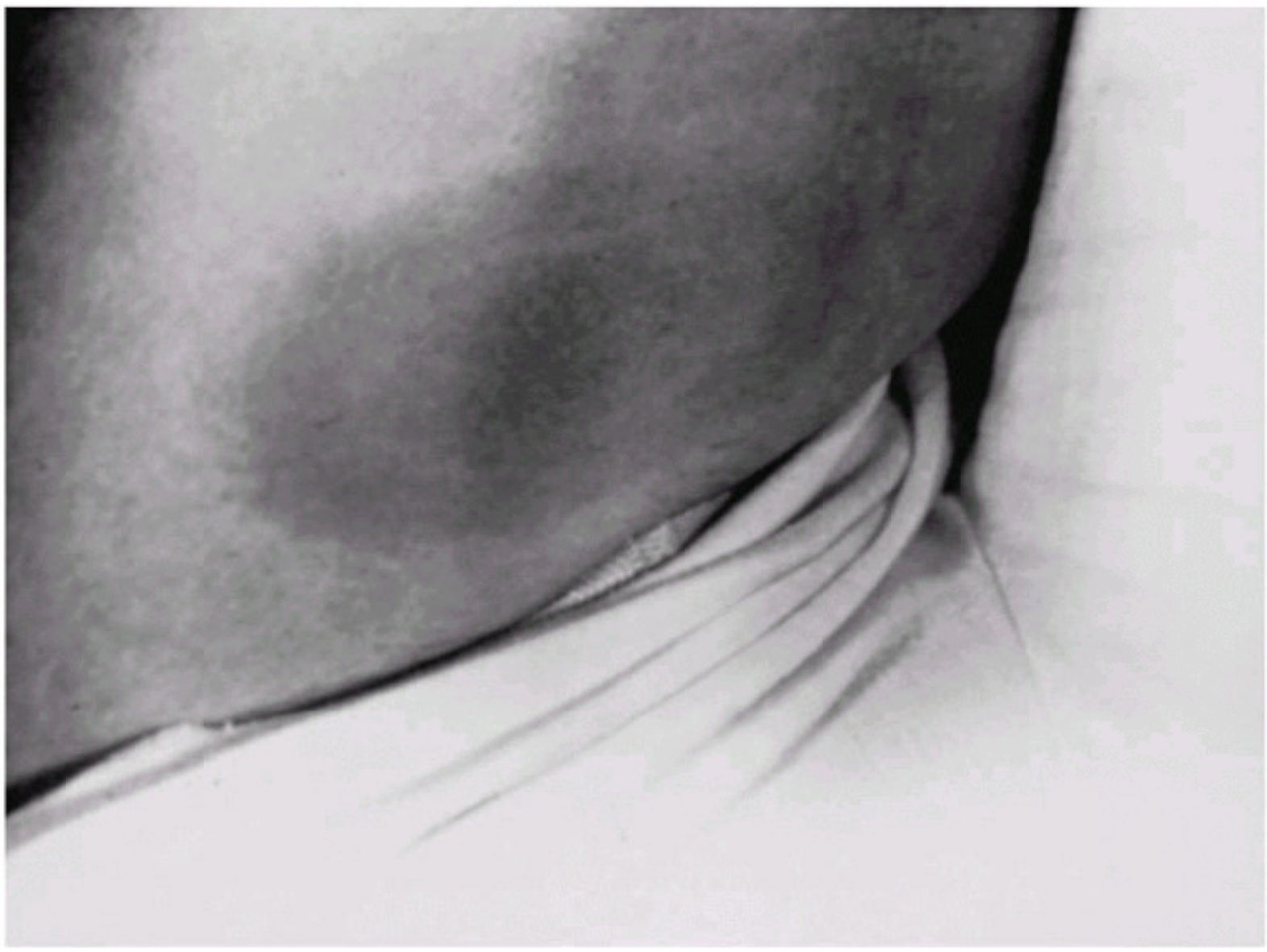

Figure 15.30 Characteristic erythematous, spreading macular skin lesion (bull's-eye lesion) in Lyme disease.

TABLE 15.9 DIAGNOSTIC CRITERIA FOR LYME DISEASE

Area	Criteria
Endemic	Erythema migrans with exposure no more than 30 d before onset Involvement of one organ system and a positive antibody test
Nonendemic	Erythema migrans with positive antibody test Erythema migrans with involvement of two organ systems

Ocular Lyme Borreliosis

Lyme disease is caused by the spirochete *Borrelia burgdorferi* and is transmitted by the tick *Ixodes dammini*. Lyme disease is divided into three clinical stages. Stage 1 disease follows infection by the tick and is heralded by a characteristic erythematous, spreading rash (erythema chronicum migrans), flu-like symptoms, and conjunctivitis (Fig. 15.30). Stage 2 disease is characterized by cardiac and neurologic disease. Third, sixth, and seventh cranial nerve palsies are seen in stage 2 disease. Neurologic findings also include meningitis and radiculoneuropathy. Cardiac signs include acute myocarditis and symptoms associated with rheumatic fever. Ophthalmic findings of stage 2 disease in addition to cranial nerve palsies include dermatitis. Stage 3 disease presents with arthritis and chronic neurologic symptoms. Patients may also present with migratory pain in the muscles, joints, and tendons. Chronic fatigue syndrome and focal central nervous system disease have been described as part of stage 3 Lyme disease. Ophthalmologic findings include granulomatous inflammation, vitreitis, diffuse choroiditis, and panophthalmitis. Ischemic optic neuropathy, retrobulbar neuritis, optic papillitis, and pseudotumor cerebri have also been described.

Diagnosis is by history, clinical examination, and laboratory testing (Table 15-9). Antibody titers to *Borrelia burgdorferi* may be measured with IFA assay and ELISA test. Titers may be low or absent in stage 1 disease but 95% sensitive in stage 2 or 3 disease. Syphilis serology should also be performed given the potential similarities between Lyme disease and syphilis. Treatment consists of oral antibiotics for early-stage disease. Tetracycline, doxycycline, penicillin, erythromycin, and ceftriaxone have all been reported to be effective. Intravenous antibiotics are used in later stages. Topical steroids and mydriatics are used for anterior segment inflammation. Treatment course may be prolonged up to several months in some patients.

SURGICAL TREATMENT OF PEDIATRIC UVEITIS

Some patients prove unresponsive to aggressive pharmacotherapy and may require surgical intervention. Each patient

should be individually evaluated to determine when the benefits of surgical intervention outweigh the potential risks. Intervention may be considered for diagnostic or therapeutic reasons.

Diagnostic surgery is considered in cases with severe inflammation, resistant to attempts at therapy, without known cause, or with suspicion of malignancy. An anterior chamber paracentesis may be considered to provide aqueous for cell study or culture. Retinal or chorioretinal biopsy provides tissue for diagnosis of a localized chorioretinal inflammatory process. Diagnostic vitrectomy provides vitreous humor for cell study and culture. Vitreous sample should be obtained “dry” before the infusion fluid is turned on for maximum yield. The aim of diagnostic intervention is to provide a precise cause to improve treatment in cases of sight-threatening uveitis.

Therapeutic surgery may address either uveitis directly or complications as a result of persistent inflammation. Please also note the surgical management of bond keratopathy, glaucoma, and cataract in the section detailing complications of anterior uveitis.

Pars Plana Vitrectomy

Pars plana vitrectomy is used for removal of chronic vitreitis, removal of vitreous opacification, repair of tractional retinal detachment, treatment of impending retinal detachment, and peeling of epiretinal membranes. Up to 10% of patients with pediatric uveitis may require pars plana vitrectomy. Vitrectomy may also be used in the removal of cyclitic membranes encountered in patients with chronic uveitis. As with glaucoma surgery and cataract extraction, pars plana vitrectomy ideally is performed in an eye that has been quiet for at least 3 months. Postoperative inflammation must be treated aggressively to increase changes of successful surgery.

Laser and Cryotherapy

Between 3% and 8% of pediatric eyes with uveitis require laser photocoagulation or cryotherapy. Laser or peripheral cryotherapy is used to treat retinal or disc neovascularization. Laser and cryotherapy are usually followed by a brisk inflammatory response. Cryotherapy and laser therapy have also been used in the treatment of chronic, unremitting pars planitis cases. Therapy is thought to work by the destruction of peripheral tissues responsible for inflammatory response.

TABLE 15.10 MASQUERADE SYNDROMES: POSTERIOR SEGMENT

	Age	Signs of Inflammation	Diagnostic Studies
Retinitis pigmentosa	Any	Cell in vitreous	ERG, EOG, visual fields
Lymphoma[a]	15+	Retinal hemorrhages, exudates, vitreous cells	Node biopsy, bone marrow, complete physical examination
Retinoblastoma[a]	<5	Vitreous cells, retinal exudates	Ultrasonography, aqueous tap
Malignant melanoma	15+	Vitreous cells	^{32}P test, fluorescein ultrasonography
Multiple sclerosis	15+	Periphlebitis	Neurologic examination

[a] Also may mimic diffuse uveitis.

ERG, Electroretinogram; EOG, electro-oculogram.

Modified from Section 3: *Intraocular inflammation, uveitis and ocular tumors. Home study manual.* San Francisco: American Academy of Ophthalmology, with permission.

MASQUERADE SYNDROMES

Masquerade syndromes must be kept in mind when evaluating a child with uveitis. Although not primarily inflammatory in nature, masquerade syndromes may present with anterior or posterior inflammation. Recognition and diagnosis are vital to the health and well-being of the patient. Disease entities include retinoblastoma, leukemia, and juvenile xanthogranuloma (JXG) (Tables 15.10 and 15.11).

Retinoblastoma

Retinoblastoma is the most common malignant ocular tumor in the pediatric population. The incidence is approximately 1 in 15,000. The most common presenting signs are leukocoria and strabismus. Examination may reveal anterior or posterior inflammation, hypopyon, hyphema, vitreous hemorrhage, and glaucoma. Retinoblastoma should be ruled out in any patient aged less than five years presenting with intraocular inflammation.

Retinoblastoma must be considered in the differential diagnosis of a patient with *Toxocara* infection. Retinoblastoma and *Toxocara* both may present with leukocoria. In distinction to retinoblastoma, *Toxocara* rarely demonstrates calcifications on imaging. Patients with retinoblastoma are generally younger than patients with *Toxocara.* A positive titer for *Toxocara* cannot rule out retinoblastoma, because a significant portion of the general pediatric population possesses increased positive *Toxocara* titers. A negative result is an indicator against parasitic infection.

patterns. Endophytic tumors appear as yellow-white masses that break through the internal limiting membrane. Endophytic tumors may be associated with vitreous seeding. Vitreous seeds may be so extensive as to resemble hypopyon or endophthalmitis. Exophytic tumors appear as yellow-white masses in the subretinal space often with overlying tortuous vasculature. Exophytic retinoblastoma is often associated with accumulation of subretinal fluid. In advanced cases, the tumor may resemble an exudative retinal detachment and mimic the presentation of Coats' disease. CT scan, ultrasound, bone marrow aspirate, and lumbar puncture may aid diagnosis. Retinoblastoma classically demonstrates intraocular calcifications on CT scan. Enucleation is most commonly used with a cure rate of greater than 95%. Eye-sparing treatments include external beam radiation, scleral plaque brachytherapy, cryotherapy, and photocoagulation and have been met with variable success. Children must be followed closely because they are at an increased risk of developing secondary nonocular tumors later in life.

TABLE 15.11 MASQUERADE SYNDROMES: ANTERIOR SEGMENT

	Age (y)	Signs of Inflammation	Diagnostic Studies
Retinoblastoma	<15	Flare/cells, pseudohypopyon	Aqueous tap for lactic dehydrogenase levels and cytology
Leukemia	<15	Flare/cells, heterochromia	Bone marrow, peripheral blood smear, aqueous cytology
Intraocular foreign body	Any	Flare/cells	X-ray, ultrasonography
Malignant melanoma	Any	Flare/cells	^{32}P test, fluorescein, ultrasonography
Juvenile xanthogranuloma	<15	Flare/cells, hyphema	Examination of skin, iris biopsy
Peripheral retinal detachment	Any	Flare/cells	Careful ophthalmoscopy

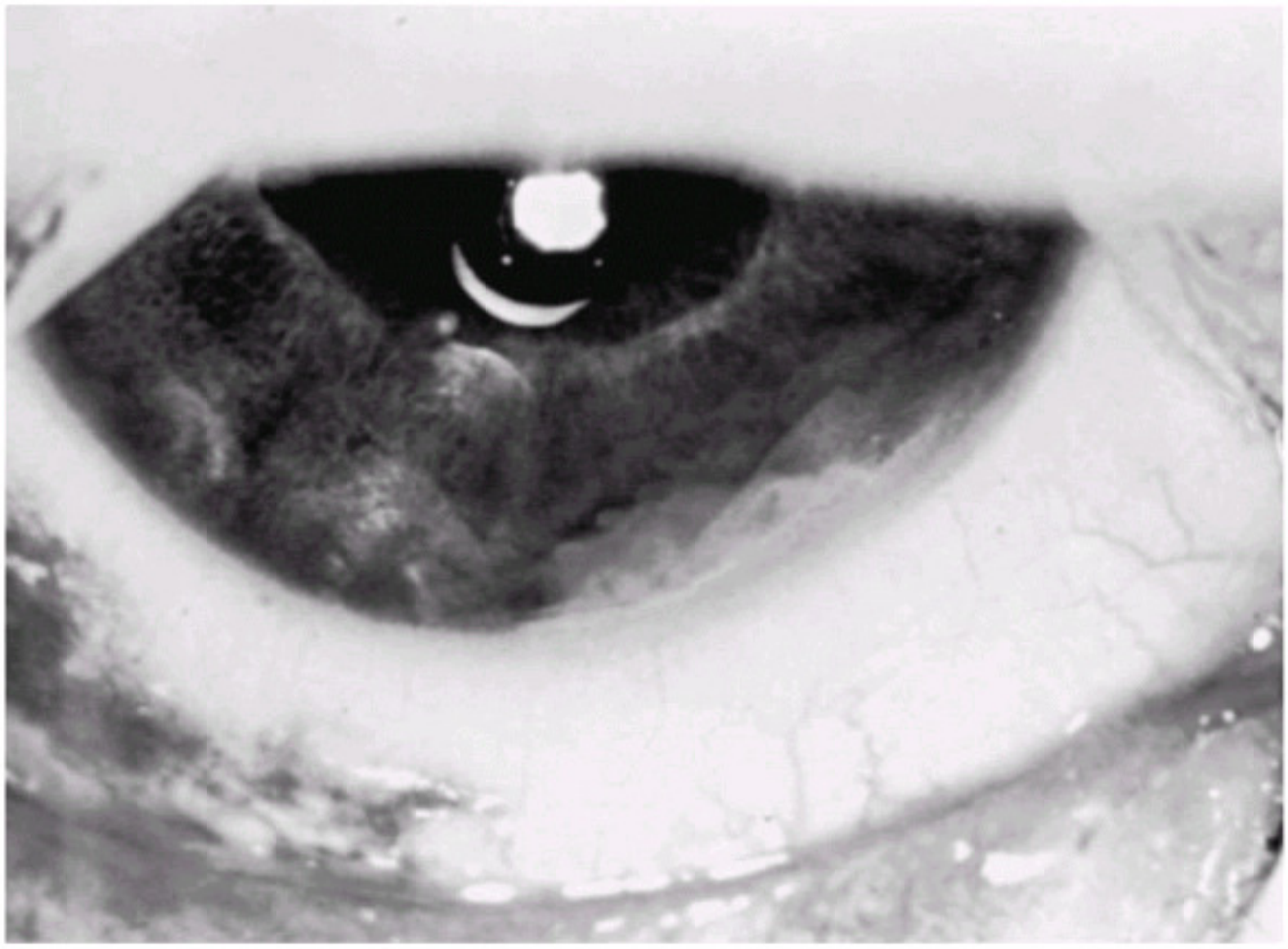

Figure 15.31 Iris tumor with minimal hyphema in a child with juvenile xanthogranuloma (JXG).

Leukemia

Patients with acute lymphoblastic, acute myelogenous, and acute monocytic leukemias may present with ocular findings. Most commonly, retinal hemorrhages are seen on funduscopic examination. Leukemic infiltrates in the anterior segment may also lead to heterochromia iridis, spontaneous hyphema, anterior uveitis, and hypopyon. Optic nerve involvement is considered a medical emergency with potential permanent visual loss. Urgent evaluation for radiation therapy is indicated.

Juvenile Xanthogranuloma

JXG is a non-neoplastic histocytic proliferation seen in children less than 2 years of age. Yellow-brown masses are

found either localized or distributed throughout the iris (Fig. 15.31). Patients often present with spontaneous hyphema. Anterior chamber cell and flare are present. Disease is unilateral. Examination of the skin may reveal orangetan papules (Fig. 15.32). The diagnosis of JXG should be considered in cases of uveitis or heterochromia. JXG is self-limited and will usually regress by the age of 5 years. Treatment of acute events requires topical corticosteroids and pressure-lowering agents. Rarely, surgical intervention may be required for uncontrolled glaucoma.

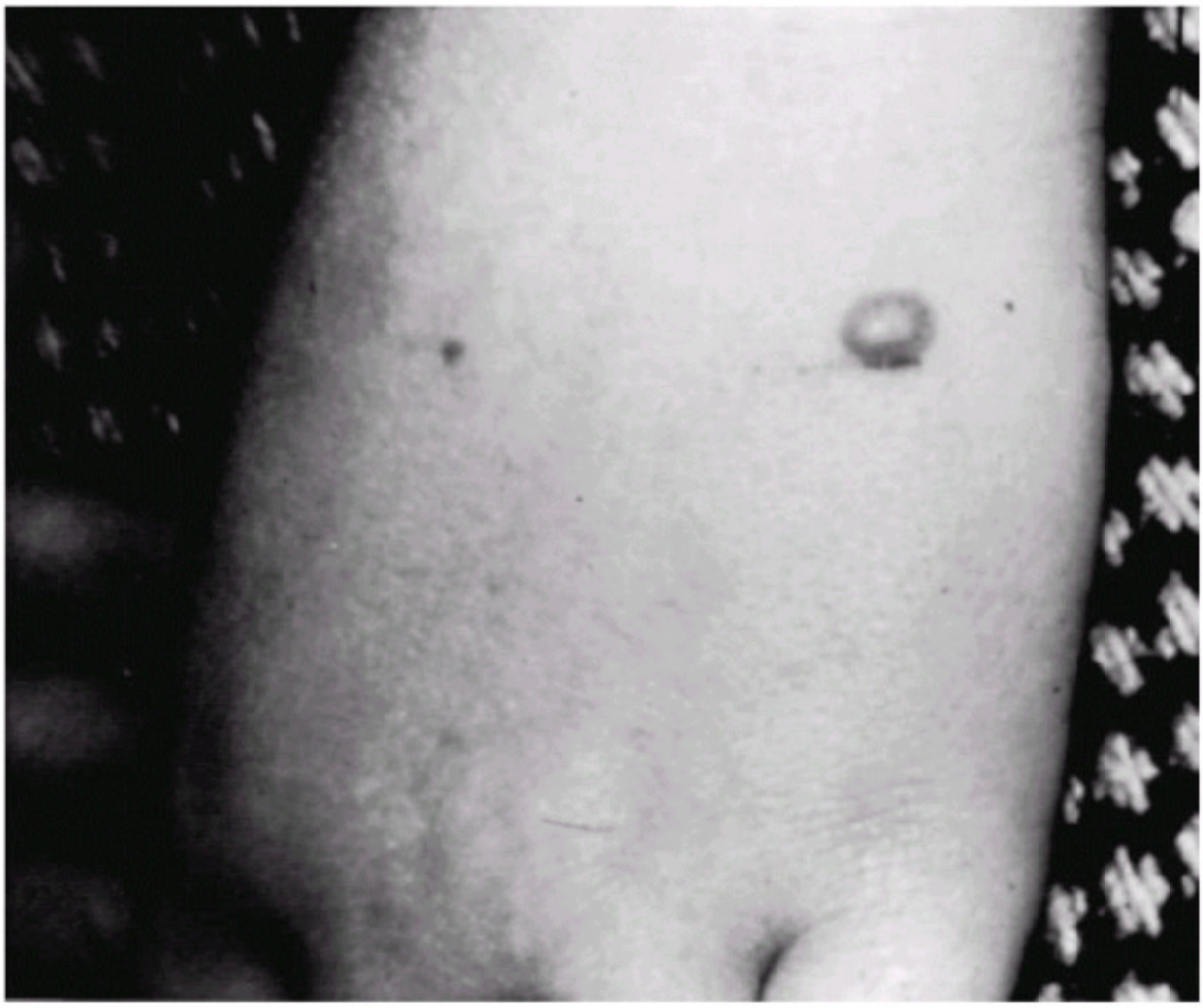

Figure 15.32 Characteristic xanthomata of the skin in a patient with JXG.

CONCLUSION

Uveitis is a complicated and potentially vision-threatening condition in the pediatric population. The lack of symptoms and communication difficulties unique to children make this a challenging disease to treat. Proper recognition of pediatric uveitis is essential in establishing cause, guiding medical evaluation, and administering the appropriate pharmacologic or surgical intervention.

SUGGESTED READINGS

Aaberg TM, Cesarz TJ, Flickinger RR. Treatment of peripheral uveoretinitis by cryotherapy. *Am J Ophthalmol* 1973;75:685.

Benjamin A, Tufail A, Holland GN. Uveitis as the only clinical manifestation of post-streptococcal syndrome. *Am J Ophthalmol* 1997; 123(2):258-260.

Bloom JN, Graviss ER, Byrne BJ. Orbital pseudotumor in the differential diagnosis of pediatric uveitis. *J Pediatr Ophthalmol Strabismus* 1992;29:59.

Burns JC, Joffe L, Sargent RA, et al. Anterior uveitis associated with Kawasaki syndrome. *Pediatr Infect Dis* 1985;4:258.

Chylack LT Jr, Bienfang DC, Bellows R, et al. Ocular manifestations of juvenile rheumatoid arthritis. *Am J Ophthalmol* 1975;79: 1026-1033.

Cleasby GA. Nevoxanthoendothelioma (juvenile xanthogranuloma) of the iris: diagnosis by biopsy and treatment with x-rays. *Trans Am Acad Ophthalmol Otolaryngol* 1961;65:609.

Davis JL, Mittal KK, Freidlin V, et al. HLA associations and ancestry in Vogt-Koyanagi-Harada disease and sympathetic ophthalmia. *Ophthalmology* 1990;97:1137.

Dobbie JG. Cryotherapy in the management of Toxoplasma retinochoroiditis. *Trans Am Acad Ophthalmol Otolaryngol* 1968;72:364.

Felberg NT, Shields JA, Federman JL. Antibody to Toxocara canis in the aqueous humor. *Arch Ophthalmol* 1981;99:1563-1564.

Forster DJ, Rao NA. Uveitis in children. In: Wright KM, editor. *Pediatric ophthalmology and strabismus.* New York: Mosby-Year Book, 1995 409-428.

Forster DJ, Rao NA, Hill RA, et al. Incidence and management of glaucoma in Vogt-Koyanagi-Harada syndrome. *Ophthalmology* 1993; 100:613-618.

Freeman WR, Thomas EL, Rao NA, et al. Demonstration of herpes group virus in acute retinal necrosis syndrome. *Am J Ophthalmol* 1986;102:701-709.

Friedmann CT, Knox DL. Variations in active toxoplasmic retinochoroiditis. *Arch Ophthalmol* 1969;81:481.

Giles CL. Uveitis in childhood—part I anterior. *Ann Ophthalmol* 1989; 21:13-19

Giles CL. Uveitis in childhood—part II intermediate. *Ann Ophthalmol* 1989;21:20-22

Giles CL. Uveitis in childhood—part III posterior. *Ann Ophthalmol* 1989;21:23-28.

Giles CL. Pediatric intermediate uveitis. *J Pediatr Ophthalmol Strabismus* 1989;26:136.

Giles CL, O'Connor GR. Toxoplasmosis and toxocariasis. In: Yanuzzi LA, Gitter KA, Schatz H, eds. *The macula.* New York: Williams & Wilkins, 1979:339-349.

Gordon D, Browne BH. Macular oedema associated uveitis and cataract following presentation of Type 1 diabetes mellitus in severe ketoacidosis. *Diabet Med* 2000;17(4):326-328.

Hofley P, Roarty J, McGinty, et al. Asymptomatic uveitis in children with chronic inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 1993;17:397-400.

Hogan MJ, Kimura SJ, Spencer WH. Visceral larva migrans and peripheral retinitis. *JAMA* 1965;194:1345.

Holland GN, Stieam ER. Special considerations in the evaluation of uveitis in children. *Am J Ophthalmol* 2003;135(6):867-875.

Jütte A, Lempke L, Opitz J. Chronische zyklitis im kindesalter. *Ophthalmologica* 1969;157:169.

Kadayifcilar S, Eldeam B, Tumer B. Uveitis in childhood. *J Pediatr Ophthalmol Strabismus* 2003;40:335-340.

Kanski JS. Juvenile arthritis and uveitis. *Surv Ophthalmol* 1990;34:253.

Kanski JS, Shun-Shin GA. Systemic uveitis syndromes in childhood: an analysis of 340 cases. *Ophthalmology* 1984;91:1247.

Key SN III, Kimura SJ. Iridocyclitis associated with juvenile rheumatoid arthritis. *Am J Ophthalmol* 1975;80:425-429.

Khan JA, Hoover DL, Giangiacomo J, et al. Orbital and childhood sarcoidosis. *J Pediatr Ophthalmol Strabismus* 1986;23(4):190-194.

Kilmartin DJ, Forrester JV, Dick AD. Cyclosporin A therapy in refractory noninfectious childhood uveitis. *Br J Ophthalmol* 1998;82(7): 737-742.

Kincaid MC, Green WR. Ocular and orbital involvement in leukemia. *Surv Ophthalmol* 1983;27:211-232.

Knox DO, VanMetre TE, Brown WH. The relationship between nongranulomatous uveitis and arthritis. *J Allergy* 1965;36:158.

Lam LA, Lowder CY, Baervelt G, et al. Surgical management of cataract in children with juvenile rheumatoid arthritis. *Am J Ophthalmol* 2003;125:772-778.

Leopold IH. Is the dog really man's best friend? *Am J Ophthalmol* 1965: 59:717.

Lubin JR, Albert DM, Weinstein M. Sixty-five years of sympathetic ophthalmia: a clinicopathologic review of 105 cases (1913-1978). *Ophthalmology* 1980;87:109-121.

Lundvall A, Zetter Strom C. Cataract extraction and intraocular lens implantation in children with uveitis. *Br J Ophthalmol* 2000;84(7): 791-793.

Mishima S, Masuda K, Izawa Y, et al. Behcet's disease in Japan: ophthalmologic aspects. *Trans Am Ophthalmol Soc* 1979;77:225-279.

Murphree AL, Villalance JG, Deegan WF III, et al. Chemotherapy plus local treatment in the management of intraocular retinoblastoma. *Arch Ophthalmol* 1996;114:1348-1356.

Narayama KM, Bora A, Biswas J. Patterns of uveitis in children presenting at a tertiary care center in south India. *Indian J Ophthalmol* 2003; 51(2):129-132.

Nozik RA. Results of treatment of ocular toxoplasmosis with injectable corticosteroids. *Trans Am Acad Ophthalmol Otolaryngol* 1977;83: 811.

Nussenblatt RB, Palestine AG, Chan CC. Cyclosporin A therapy in the treatment of intraocular inflammatory disease resistant to systemic corticosteroids and cytotoxic agents. *Am J Ophthalmol* 1983;96: 275.

O'Connor GR, Frenkel JK. Dangers of steroid treatment in toxoplasmosis: periocular injections and systemic therapy. *Arch Ophthalmol* 1976;94:213.

Ortiz SM, Kamerling JM, Fischer D, et al. Scleritis, uveitis and glaucoma in a patient with rheumatic fever. *Am J Ophthalmol* 1995:120(4): 538-539.

Ovchinsky A, Schulman S, Rosenfeld RM. Adenotonsillectomy as a treatment option for poststreptococcal uveitis. *Laryngoscope* 2002; 112(4):658-660.

Patel H, Goldstein D. Pediatric uveitis. *Pediatr Clin N Am* 2003;50: 125-136.

Perkins ES. Pattern of uveitis in children. *Br J Ophthalmol* 1966;59: 169.

Preziosi L. Results of the electrocautery puncture in the treatment of glaucoma. 13th Concilium opthalmological, September 1929, Amsterdam.

Puglise JV, Rao NA, Weiss RA, et al. Ocular features of Kawasaki's disease. *Arch Ophthalmol* 1982;100:1101.

Reynard M, Riffenburgh RS, Maes EF. Effect of corticosteroid treatment and enucleation on the visual prognosis of sympathetic ophthalmia. *Am J Ophthalmol* 1983;96:290.

Rosenbaum JT. Bilateral anterior uveitis and interstitial nephritis. *Am J Ophthalmol* 1988;105:534.

Rosenberg AM, Oen KG. The relationship between ocular and articular disease activity in children with juvenile rheumatoid arthritis and associated uveitis. *Arthritis Rheum* 1986;29:797-800.

Rosenthal AR. Ocular manifestation of leukemia. A review. *Ophthalmology* 1983;90:899-905.

Schaller JC. The seronegative spondyloarthropathies of childhood. *Clin Orthop* 1979;143:76.

Scheie H. Retraction of scleral wound edges as a fistulizing procedure for glaucoma. Am J Ophthalmol 1958:45;220-228.

Schlaegel TF Jr. *Essentials of uveitis.* Boston: Little, Brown & Co., 1969: 68.

Shields JA. Ocular toxocariasis. A review. *Surv Ophthalmol* 1984;28: 361-381.

Spalter HE, Campbell CJ, Noyori KS, et al. Prophylactic photocoagulation of recurrent toxoplasmic retinochoroiditis: a preliminary report. *Arch Ophthalmol* 1966;75:21.

Steere AC. Lyme disease. *N Engl J Med* 1989;321:586-596.

Stoffel PB, Sauvain MJ, von Vigier RO, et al. Non-infectious causes of uveitis in 70 Swiss children. *Acta Paediatr* 2000;89:955-958.

Takemura T, Okada M, Hino S, et al. Course and outcome of tubulointerstitial nephritis and uveitis syndrome. *Am J Kidney Dis* 1999; 34(6):1016-1021.

Tessler HH. Diagnosis and treatment of ocular toxoplasmosis. In: Smith RE, ed. *Focal points 1985: clinical modules for ophthalmologists, Vol. 3, module 2.* San Francisco: American Academy of Ophthalmology, 1985:1-12.

Tungal-Tukun I, Havrlikova K, Power WJ, et al. Changing patterns in uveitis of childhood. *Ophthalmology* 1996;103:375-383.

Valimaki J, Airaksinen JA, Tuulonen A. Molteno implantation for secondary glaucoma in juvenile rheumatoid arthritis-associated uveitis. *Am J Ophthalmol* 2003;125:772-778.

Vohra S, Eddy A, Levin AV, et al. Tubulointerstitial nephritis and uveitis in children and adolescents. Four new cases and review of the literature. *Pediatr Nephrol* 1999;13(5):426-432.

Weiss AH, Wallace CA, Sherry DD. Methotrexate for resistant chronic uveitis in children with JRA (comment). *J Pediatr* 1998;133(2): 179-180.

Winter FC. Sympathetic uveitis: a clinical and pathologic study of the visual result. *Am J Ophthalmol* 1955;39:340-347.

Winward KE, Smith JL, Culbertson WW, et al. Ocular Lyme borreliosis. *Am J Ophthalmol* 1989;108:651-657.

Witmer R, Korner G. Uveitis in children. *Ophthalmologica* 1966;152: 277.

Wolf MD, Lichter PR, Ragsdale CG. Prognostic factors in the uveitis of juvenile rheumatoid arthritis. *Ophthalmology* 1987;94:1242.

Yanoff M, Schaffer DB, Scheie HG. Rubella ocular syndrome: correlation of clinical, viral, and pathologic studies. *J Am Acad Ophthalmol* 1968;72:896.

Zscheile FP. Recurrent toxoplasmic retinitis with weakly positive methylene blue dye test. *Arch Ophthalmol* 1964;71:645.

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16

Diseases of the Retina and Vitreous

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X-LINKED RECESSIVE RETINOSCHISIS

X-linked recessive retinoschisis is an inherited ocular disorder that occurs in males (1). It is characterized by degeneration of the vitreous and splitting of the retina at the level of the nerve fiber layer (2). The most common finding involves the macula and consists of a petaloid configuration (3). Usually there are numerous folds that radiate in a spoke-wheel configuration (Fig. 16.1). This may give the clinical appearance of cystoid macular edema, but the macula does not stain with fluorescein. When seen in a young boy, this sign should alert the observer to the possibility of the peripheral changes seen in X-linked retinoschisis. Peripheral retinoschisis, seen 50% of the time, is more common in the inferotemporal quadrant. The schisis is always bilateral but may be asymmetric. The anterior limit of the retinoschisis seldom extends to the ora serrata, and the posterior limit may extend to the optic disc. Nerve fiber layer breaks are common and appear as large round or oval holes (Fig. 16.2). In some eyes the nerve fiber layer breaks are so large that only remnants of the nerve fiber layer remain. Often, bridging retinal blood vessels are present, and there is hemorrhage into the vitreous. When vitreous hemorrhaging occurs, some patients develop dragging of the retina. Most recently, ocular coherence tomography (OCT) has demonstrated a characteristic finding of a wide hyporeflective space between the thin reflective outer layer and thicker, more reflective inner retinal layers (Fig. 16.3) (4).

Vitreous veils and strands may also be present. The electroretinogram (ERG) often shows a subnormal b-wave in conjunction with a normal a-wave (5). Color vision abnormalities parallel the degree of foveal involvement. The results of electrooculogram (EOG) and dark adaptation tests are usually normal. Most commonly, patients are first seen because of decreased vision. The visual acuity on presentation is usually between 20/70 and 20/100. This often (but not always) deteriorates up until age 20 years, reaching the 20/200 range. Other presenting symptoms are vitreous hemorrhage, retinal detachment, and strabismus.

The natural history of retinoschisis is that of a stationary or slowly progressive disease. The most important complications are vitreous hemorrhage and retinal detachment. It is important to realize that progression of X-linked retinoschisis may be followed by spontaneous partial regression, and that fluctuations in the appearance of the fundus are common during the first few years of life.

Differential diagnoses include retinal detachment, persistent hyperplastic primary vitreous (PHPV), Goldmann-Favre disease, retinitis pigmentosa (RP), Norrie disease, Stickler's syndrome, and (because of occasional dragged

retinas) retinopathy of prematurity (ROP) and familial exudative vitreoretinopathy (FEVR).

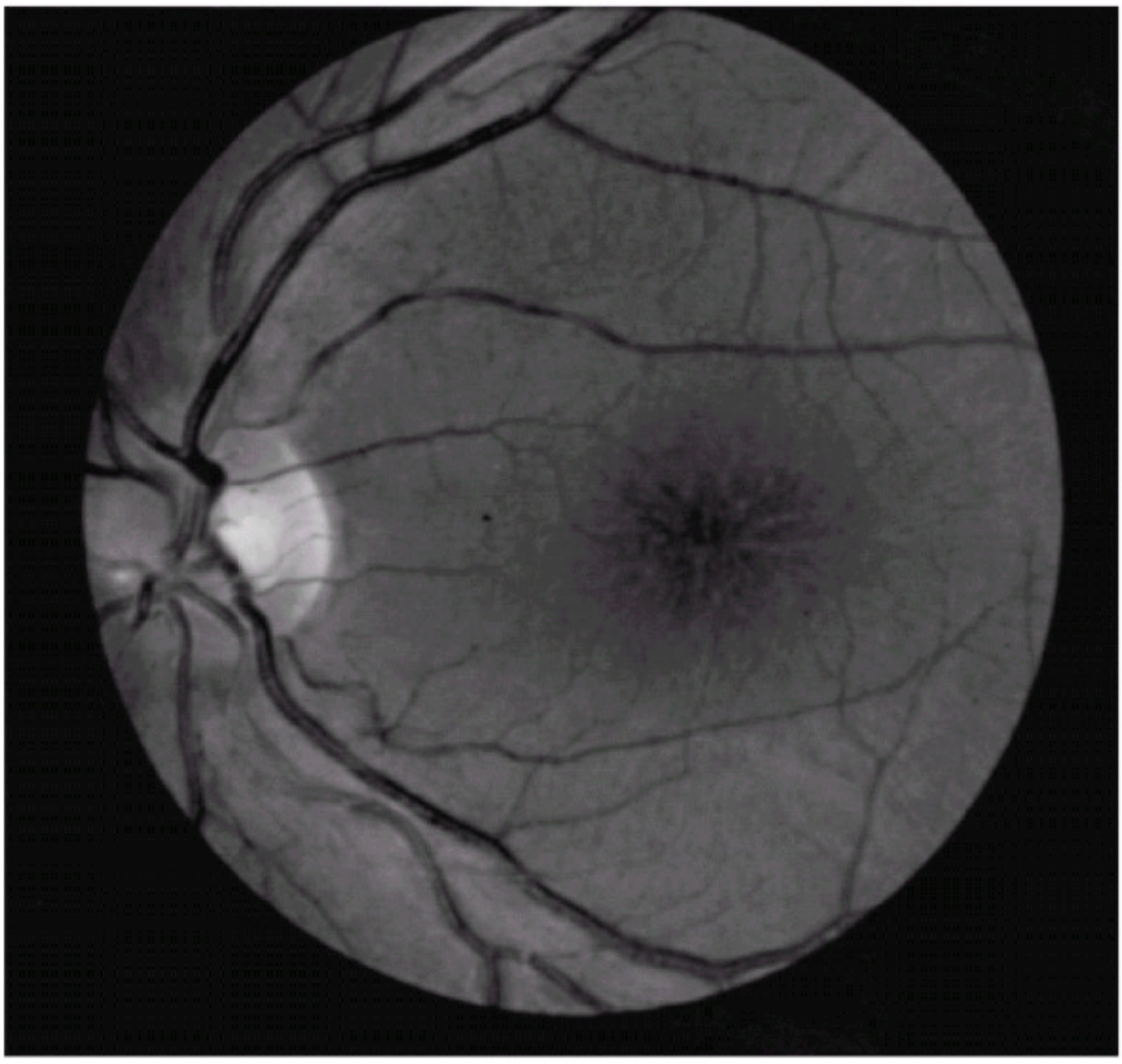

Figure 16.1 Foveoschisis with typical retinal cysts in a petaloid configuration and radial striae in X-linked retinoschisis.

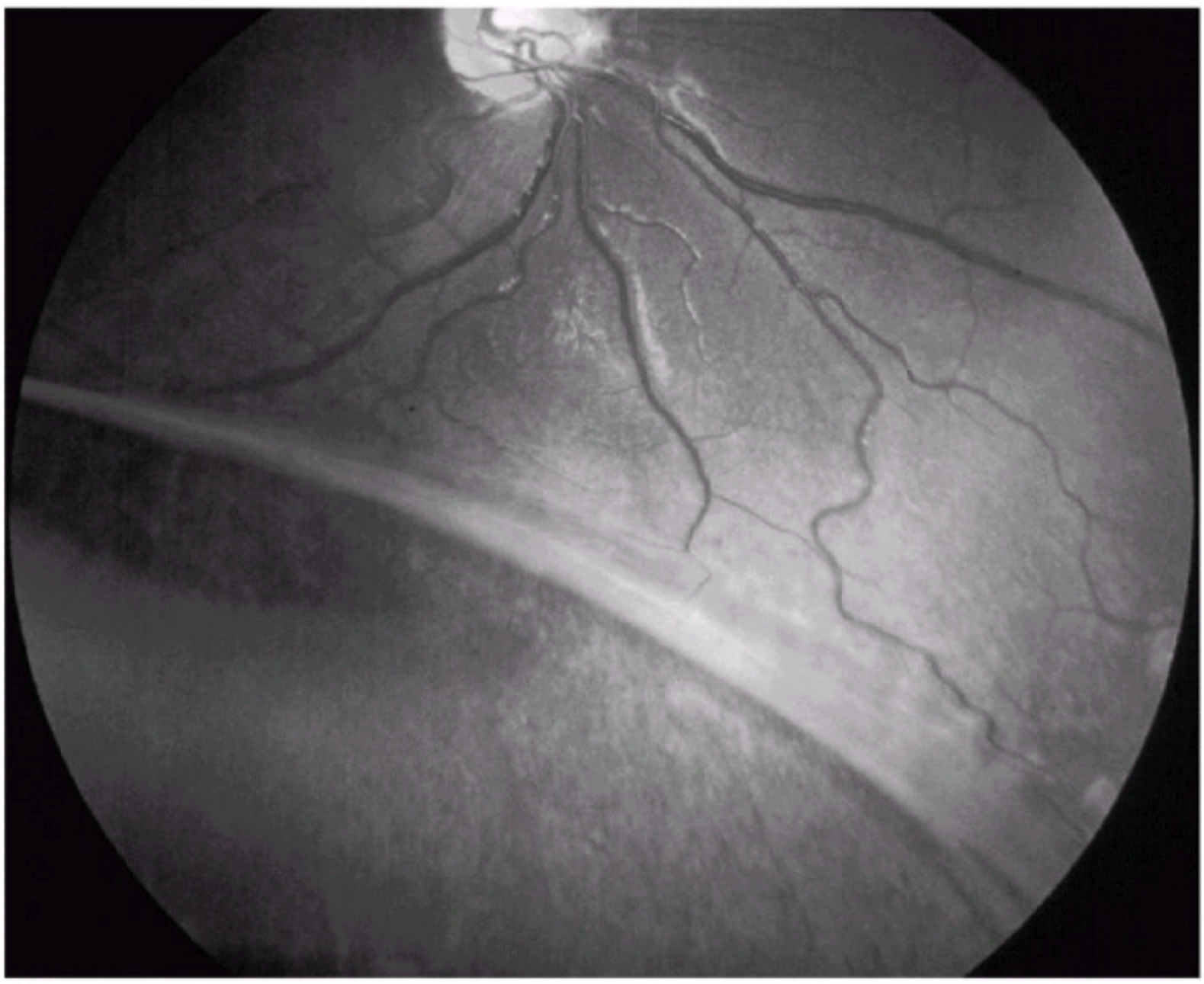

Figure 16.2 Peripheral nerve fiber layer dehiscence in X-linked retinoschisis.

Retinal detachment in a child may be differentiated from X-linked retinoschisis because the latter is always bilateral. In addition, retinal detachment, unlike X-linked retinoschisis, usually extends to the ora serrata.

In some cases of PHPV, extensive hyaloid remnants that are adherent to the disc and inferior retina may contract and cause an inferior retinal detachment, with or without visible retinal breaks. This condition is generally unilateral and associated with microphthalmos, and is neither familial nor hereditary.

Goldmann-Favre vitreoretinal degeneration is transmitted as an autosomal recessive trait. Although peripheral retinoschisis is often present, the disease is also characterized by night blindness and fundus changes resembling those of RP (6).

Stickler's syndrome is transmitted as an autosomal dominant trait. Elevation of the retina is attributable to rhegmatogenous retinal detachment rather than retinoschisis. Additional ophthalmologic and systemic features help to distinguish this entity from X-linked retinoschisis.

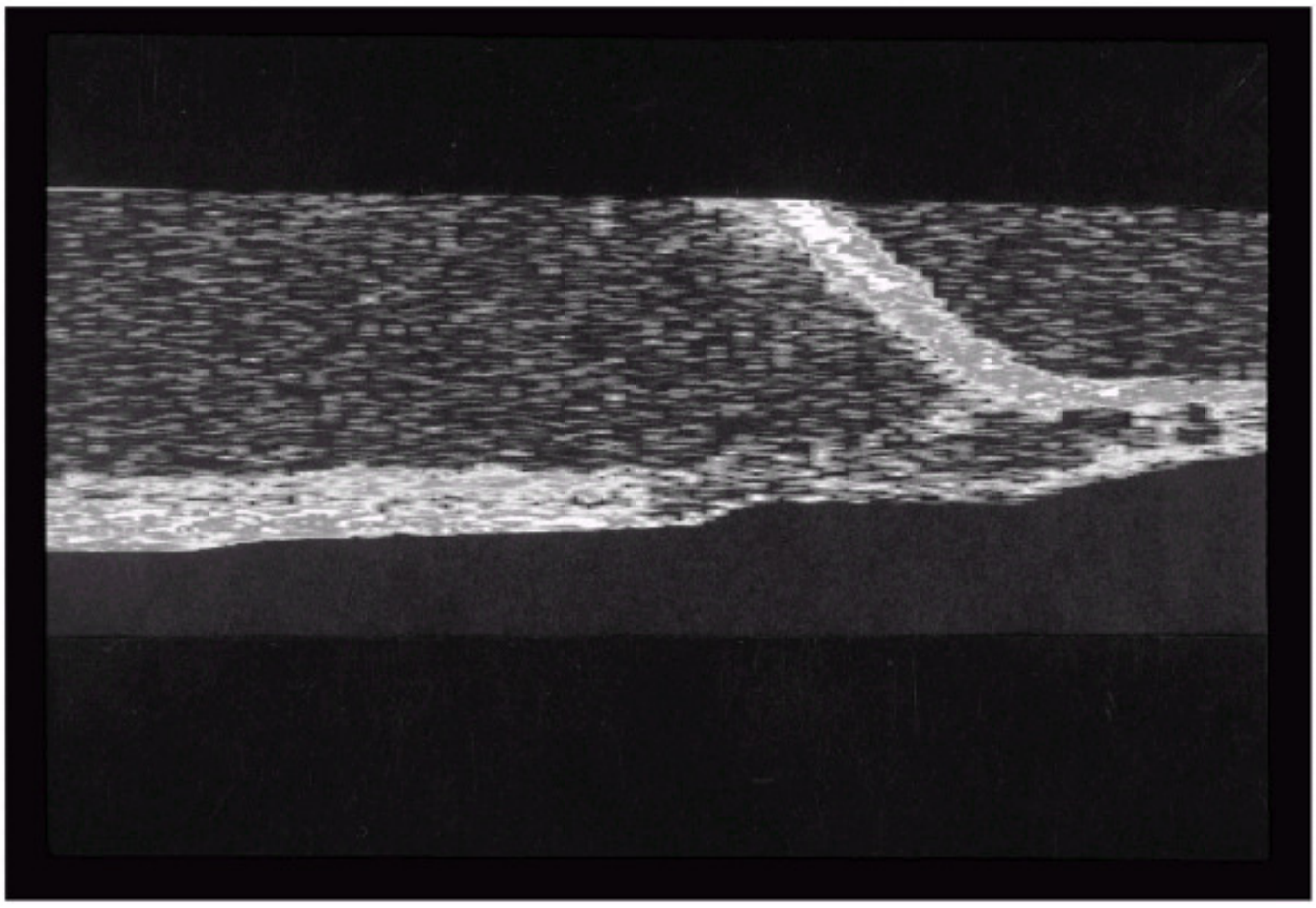

Figure 16.3 Ocular coherence tomography (OCT) of X-linked retinoschisis showing schisis of nerve fiber layer.

Although dragging of the retina may occur in ROP and FEVR, the additional fundus features of these two entities are distinct and rarely confused with X-linked retinoschisis. In addition, ROP and FEVR can usually be identified because of a history of prematurity in the case of ROP and autosomal dominant inheritance with respect to FEVR.

As long as X-linked retinoschisis is not accompanied by rhegmatogenous retinal detachment, no treatment is indicated. Recurrent vitreous hemorrhages are usually best treated conservatively, but vitrectomy occasionally becomes necessary because of the presence of organized vitreous membranes leading to retinal detachment.

X-linked retinoschisis has a prevalence ranging from 1: 5,000 to 1:25,000 (7). Female carriers of X-linked retinoschisis generally do not show any ocular abnormalities, although peripheral retinal alterations similar to those found in affected males have been reported (8). The X-linked retinoschisis gene (XLRS1) is located on the distal short arm of the X chromosome (Xp22) (9). DNA analysis can reveal evidence of the carrier state and is of use when performing genetic counseling (10).

HEREDITARY VITREORETINOPATHY WITH SYSTEMIC FINDINGS

Stickler's Syndrome

Stickler and associates (11) described an autosomal dominant, progressive arthro-ophthalmopathy associated with high myopia, optically empty vitreous, and retinal detachment. Opitz (12) designated Stickler's syndrome as the most common disorder associated with high myopia and retinal detachment. Systemic findings include midfacial flattening (Fig. 16.4), cleft palate, micrognathia, glossoptosis,

hearing loss, and skeletal dysplasia. The ocular findings include an optically empty vitreous with bands. Myopia is common. Lattice degeneration is present and often radial and perivascular (Fig. 16.5). There is a high incidence of retinal breaks, which may be multiple or giant retinal tears. Cataracts and glaucoma are often present.

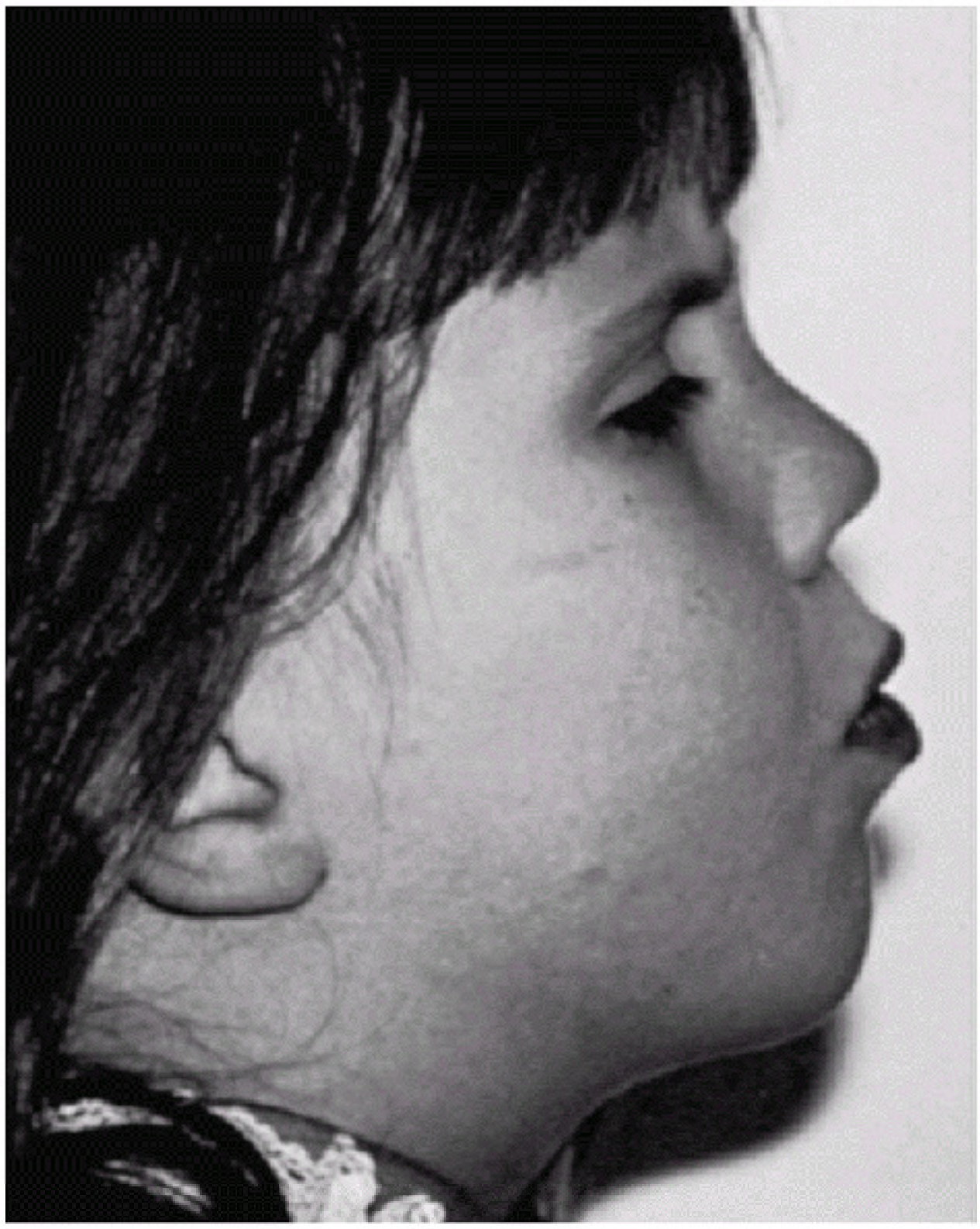

Figure 16.4 Flattened facies in a young patient with Stickler's syndrome.

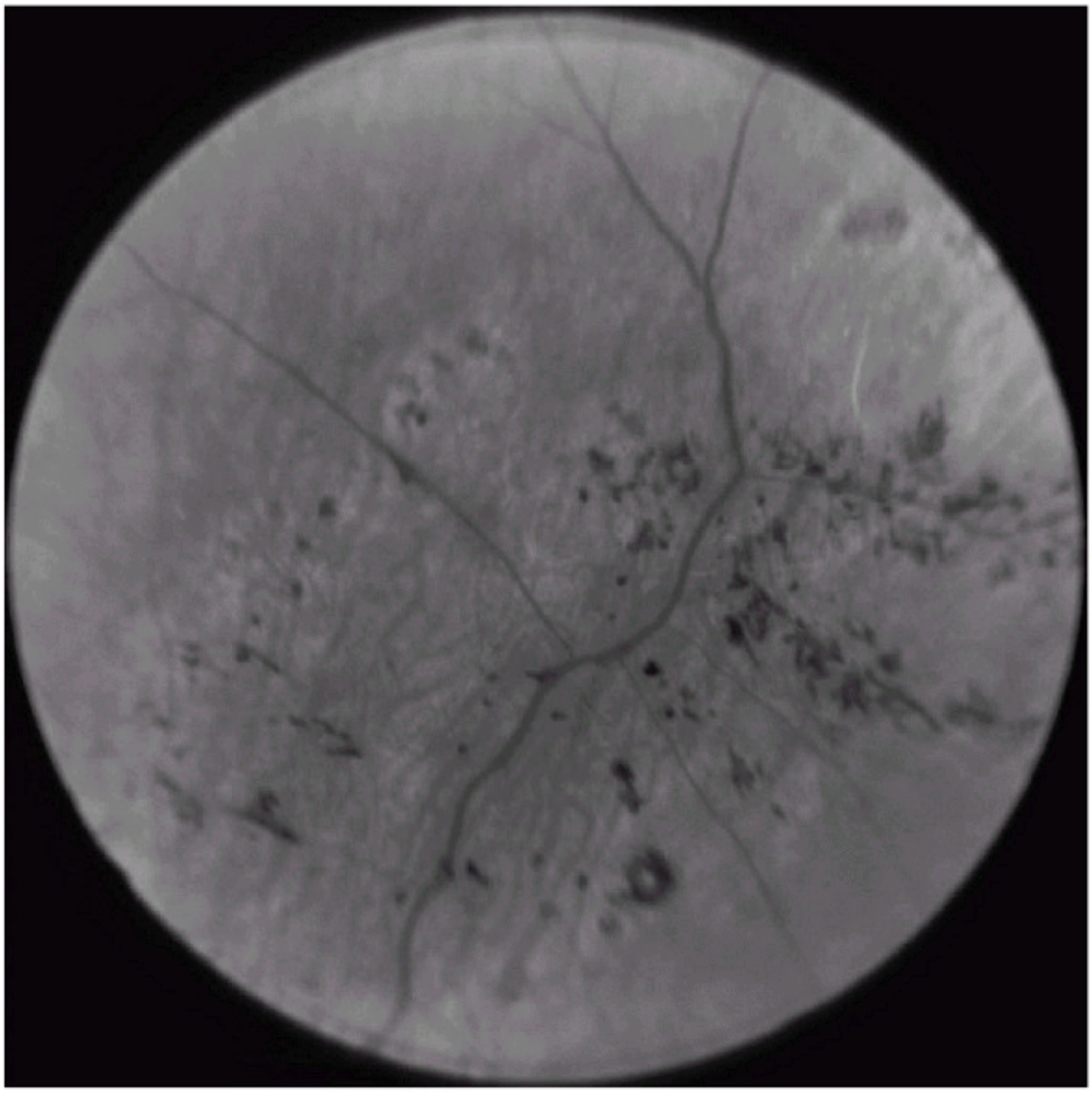

Figure 16.5 Radially oriented lattice degeneration in a patient with Stickler's syndrome.

Treatment of retinal detachment in Stickler's syndrome is difficult because of posterior retinal breaks and a high incidence of proliferative vitreoretinopathy. Prophylactic laser treatment to areas of lattice degeneration and retinal breaks may reduce the risk of detachment.

Stickler's syndrome has been linked to mutations in the type II procollagen (*COL2A1*) gene. A polymerase chain reaction assay is available to assist in genetic counseling (13).

HEREDITARY VITREORETINOPATHIES WITHOUT SYSTEMIC FINDINGS

Wagner's Syndrome and Jansen's Syndrome

The two conditions described are Wagner's syndrome (Wagner's hereditary vitreoretinal degeneration) (14) and Jansen's syndrome (15). Both conditions are very similar to Stickler's syndrome without any systemic abnormalities. These patients have myopia, an optically empty vitreous cavity, preretinal avascular membranes, perivascular pigmentation, retinal degeneration, and progressive chorioretinal atrophy. They also develop lenticular changes between the ages of 20 and 40 years. Both conditions are autosomal dominant, and Wagner's syndrome has been localized to chromosome 5q13-q14 (16). Patients with Wagner's syndrome infrequently develop retinal detachment compared with a much higher incidence of retinal detachments in patients with Stickler's syndrome or Jansen's syndrome.

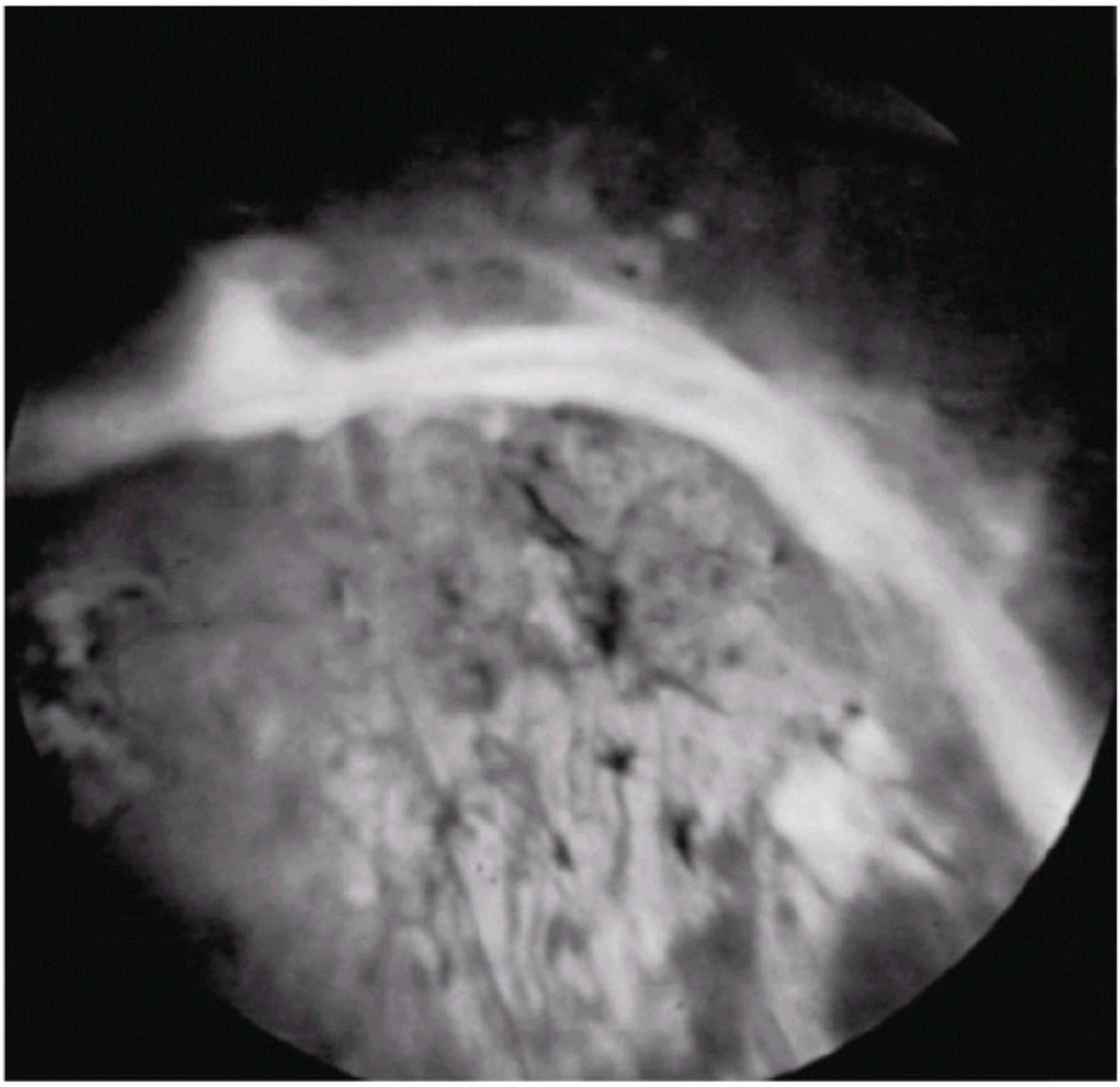

Figure 16.6 Preretinal membranes and retinal pigmentary changes in a 34-year-old woman with Goldmann-Favre disease.

Goldmann-Favre Disease

Goldmann-Favre disease (17) is inherited in an autosomal recessive manner. It is characterized by night blindness with absent or diminished ERG response, foveal and peripheral retinoschisis, pigment changes resembling RP, and progressive decreased visual function (Fig. 16.6) (6). As in Stickler's syndrome, the vitreous is liquefied with vitreous strands and veils (Fig. 16.7). Retinal detachments and cataract formation are common in this condition. Retinal detachments have a guarded prognosis for successful repair; therefore,

asymptomatic breaks should be treated prophylactically before detachment. The enhanced S cone syndrome is a variant of Goldmann-Favre disease with night blindness and foveal cystic changes without the vitreous abnormalities.

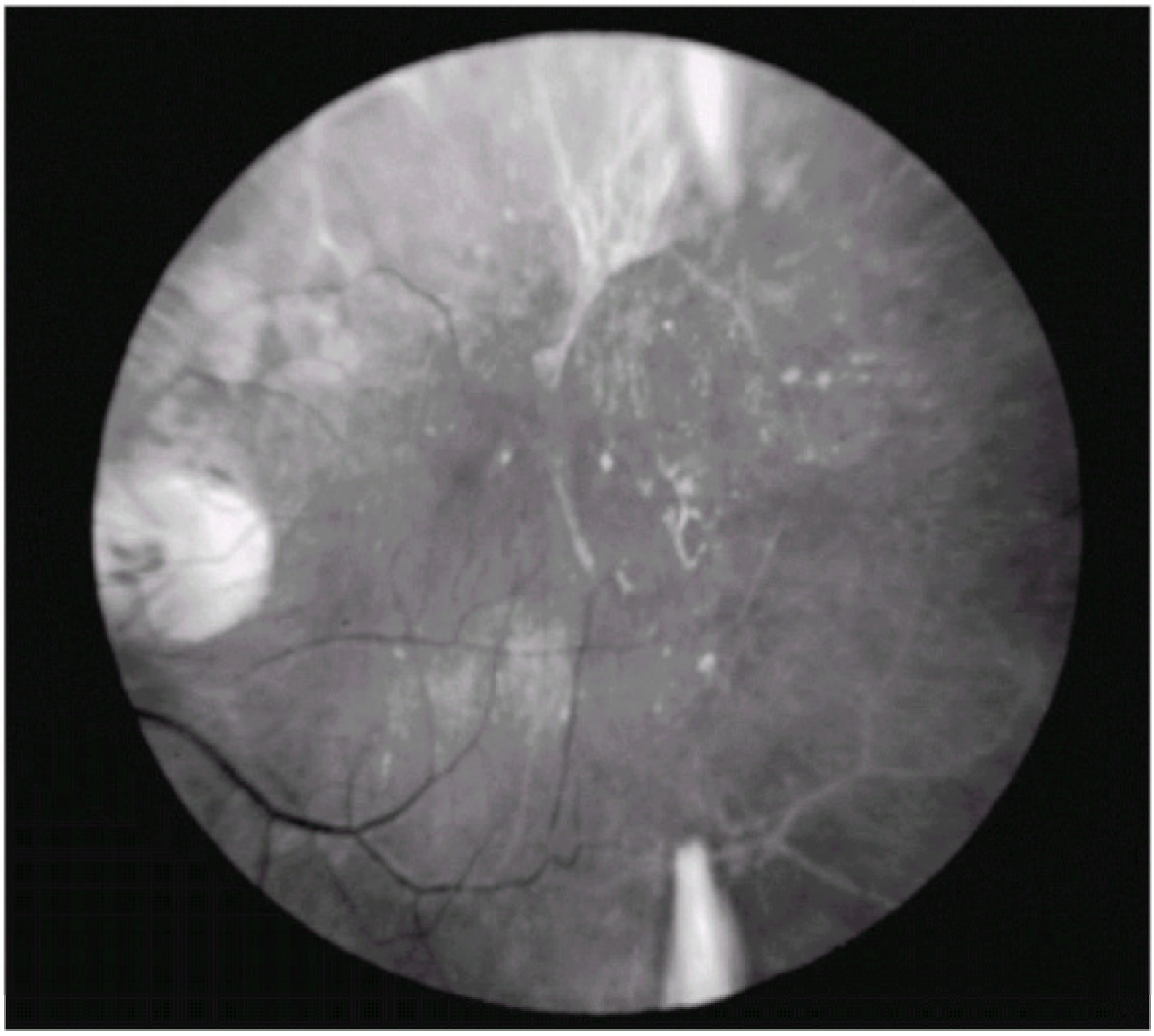

Figure 16.7 Vitreous strands, disc pallor, narrowing of retinal vessels, and foveoschisis in a patient with Goldmann-Favre disease.

STARGARDT'S DISEASE (FUNDUS FLAVIMACULATUS)

Stargardt's disease is most often an autosomal recessive condition that usually appears between 8 and 14 years of age. It is bilateral, slowly progressive, and sometimes associated with macular degeneration (18). Characteristically the foveal reflex is absent or grayish in color. Pigmentary spots sometimes develop in the macular area and may accumulate irregularly. Yellowish-white pisciform flecks may be visible in the deep retina or retinal pigment epithelium (RPE) (Fig. 16.8). They are typically seen in the posterior pole but can extend out to the equator. Eventually, in some cases, a circular area of depigmentation and chorioretinal atrophy of the macula follow (Figs. 16.9 and 16.10). In the early stages of the disease, the loss of central vision may be out of proportion to the appearance of the fundus. Fluorescein angiography may reveal abnormalities, particularly a dark fundus (the so-called silent choroid) (19) before any fundus abnormalities become apparent. Fluorescein angiography of the flecks may reveal hypofluorescence, presumably because of blockage. Later, some areas may hyperfluoresce because of damage to the RPE. Sometimes, the entire choroid may show blockage on fluorescein angiography.

The evolution is slow, symmetric, and progressive, and the disease is usually well established by age 30 years, with vision in the 20/200 range. Late in life, large areas of chorioretinal atrophy may develop (20).

The disease was first described by Stargardt in 1909 (21). Fundus flavimaculatus was described independently as a separate entity. Today, however, Stargardt's disease and fundus flavimaculatus are thought to have a common cause and to represent different parts on the spectrum of a single disease (22). Stargardt's disease is caused by a mutation of the ABCR gene located on the short arm of chromosome 1 (23). Other sites have been identified in patients with the autosomal dominant form. The mechanism of photoreceptor death has been postulated (24) with histopathology revealing the accumulation of lipofuscin within the RPE (25). Stargardt's disease refers to predominantly macular involvement, and fundus flavimaculatus refers to more peripheral involvement. In fundus flavimaculatus, the vision is near normal unless macular involvement develops.

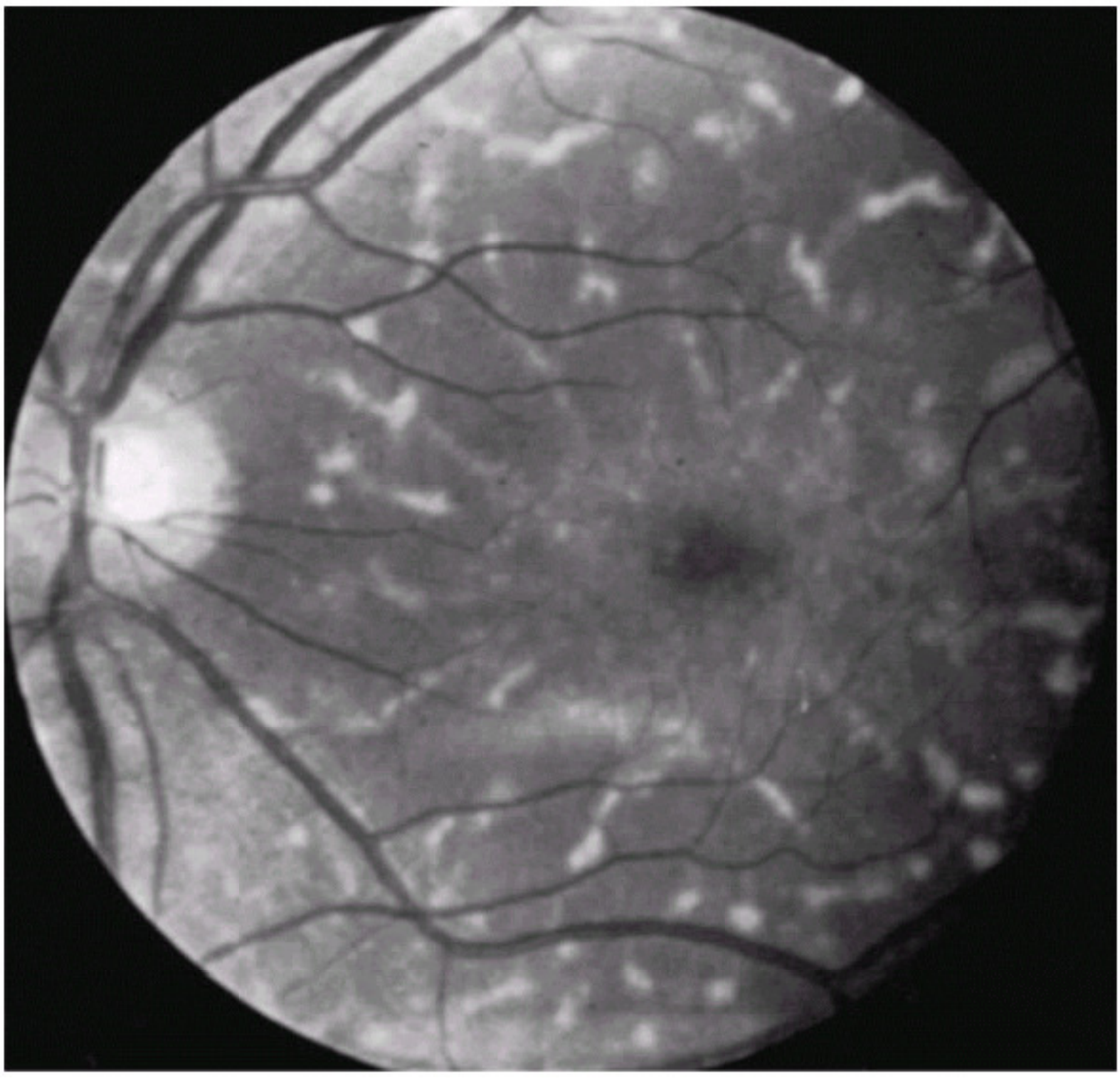

Figure 16.8 Typical pisciform lesion of fundus flavimaculatus. The dark fundus and pisciform lesions are the result of excessive amounts of lipofuscin in the pigment epithelium.

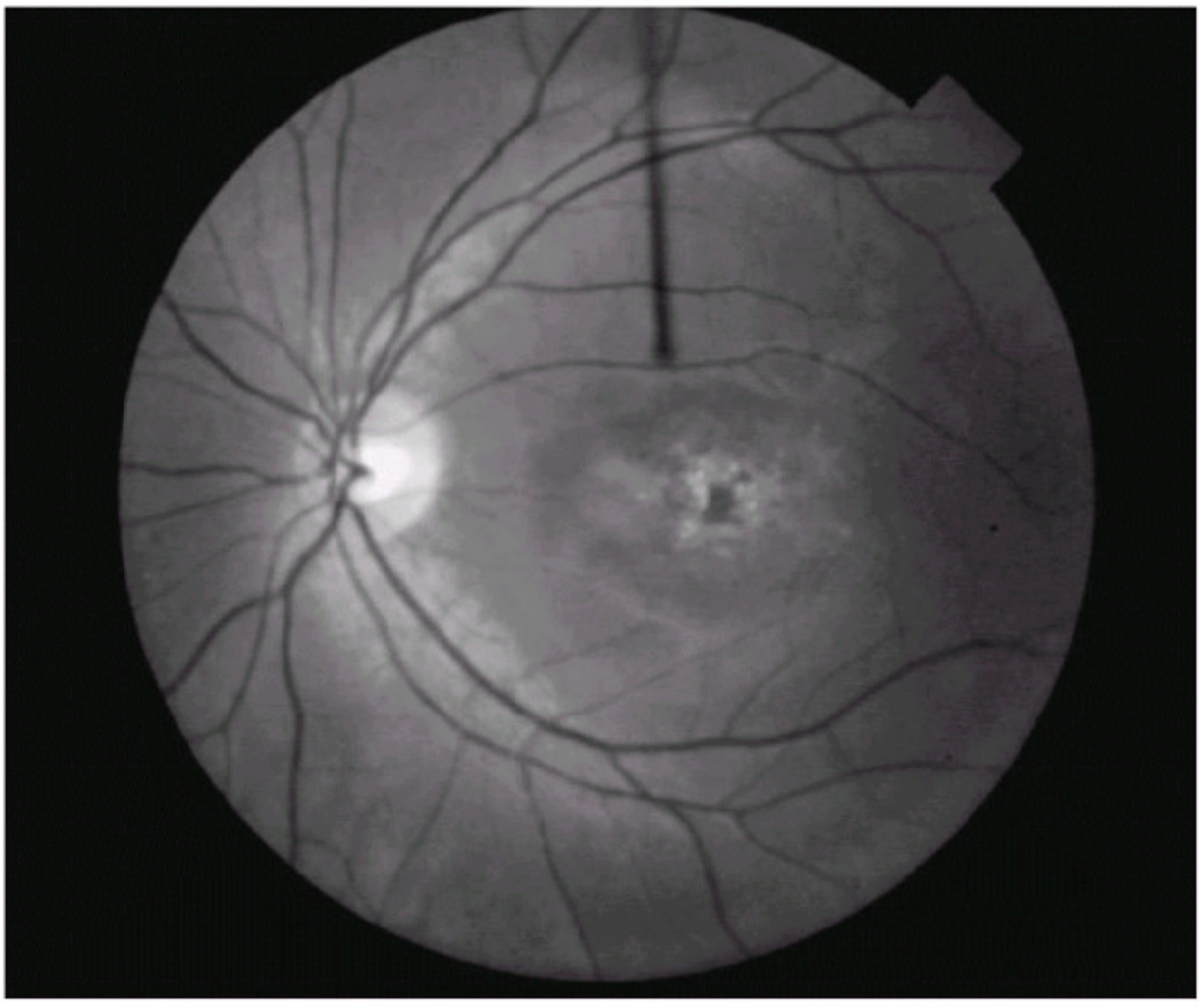

Figure 16.9 Typical retinal pigment epithelium (RPE) atrophy in a bull's-eye pattern in a patient with Stargardt's disease.

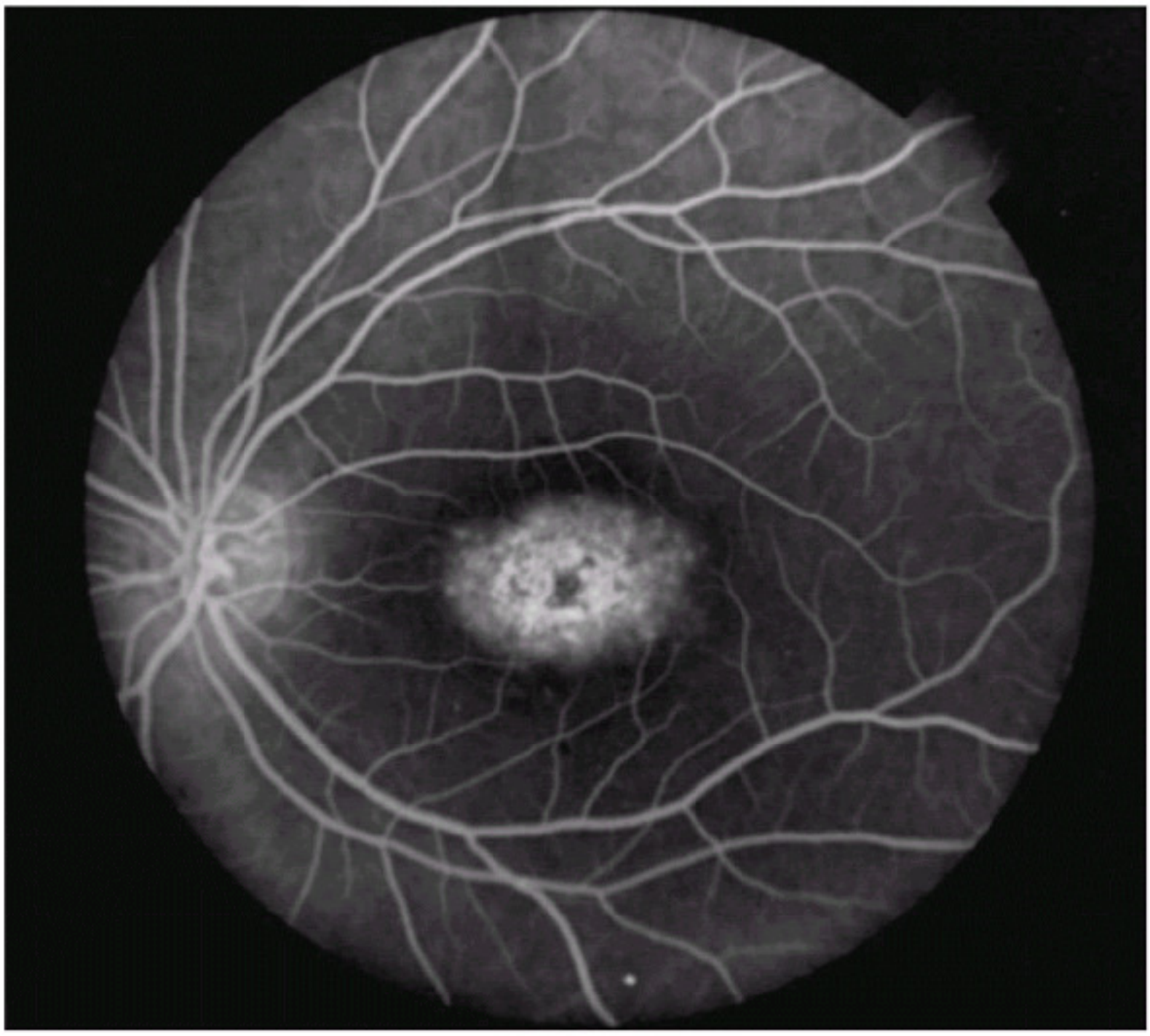

Figure 16.10 Corresponding fluorescein angiography with central hyperfluorescence.

BEST'S VITELLIFORM DEGENERATION

In 1905, Best reported eight members of one family with an interesting macular dystrophy, now called Best's vitelliform degeneration (26). The transmission in this disease is autosomal dominant, but there may be variable expressivity. Vitelliform macular degeneration has a distinctive appearance characterized by a sharply defined discoid formation in, or immediately adjacent to, the macula (Fig. 16.11; see Color Plate IVA). The disc is usually yellow-orange or pinkish yellow and varies in size from 0.5 to 4 disc diameters. The abnormality is subretinal and resembles the yolk of a poached egg (27). It is usually diagnosed between 5 and 15 years of age and is bilateral, although unilateral cases have been reported. Multiple vitelliform lesions in the same eye have also been described. The condition is very slowly progressive. The vision is usually normal or mildly reduced at this stage. Gradually the homogeneous contents of the vitelliform disc may “scramble,” giving an irregular yellow lesion, eventually leaving abnormal pigmentation and chorioretinal atrophy (Fig. 16.12). The appearance at that point is often indistinguishable from that associated with other types of macular degeneration. Vision loss develops from these atrophic changes or, in some cases, a choroidal neovascular membrane. These macular changes can also be assessed with the OCT (28).

Braley (29) concluded that the vitelline dystrophy of the macula is present at birth and that if no change is visible postnatally, the clinical signs will not develop later. We identified the fundus changes in one infant within 2 weeks of birth.

ERG results are normal, as are the peripheral visual fields. Central scotomata cannot be elicited in eyes with normal visual acuity but are present late in the disease. Dark adaptation is normal. The EOG, however, is always abnormal in patients with vitelliform macular degeneration, even in those who do not express the disease clinically (5). Thus, EOG testing is helpful diagnostically and in genetic counseling, because unaffected carriers have a 50% chance of passing the condition to their offspring. Carriers who have a normal ophthalmologic examination will have a subnormal EOG (30).

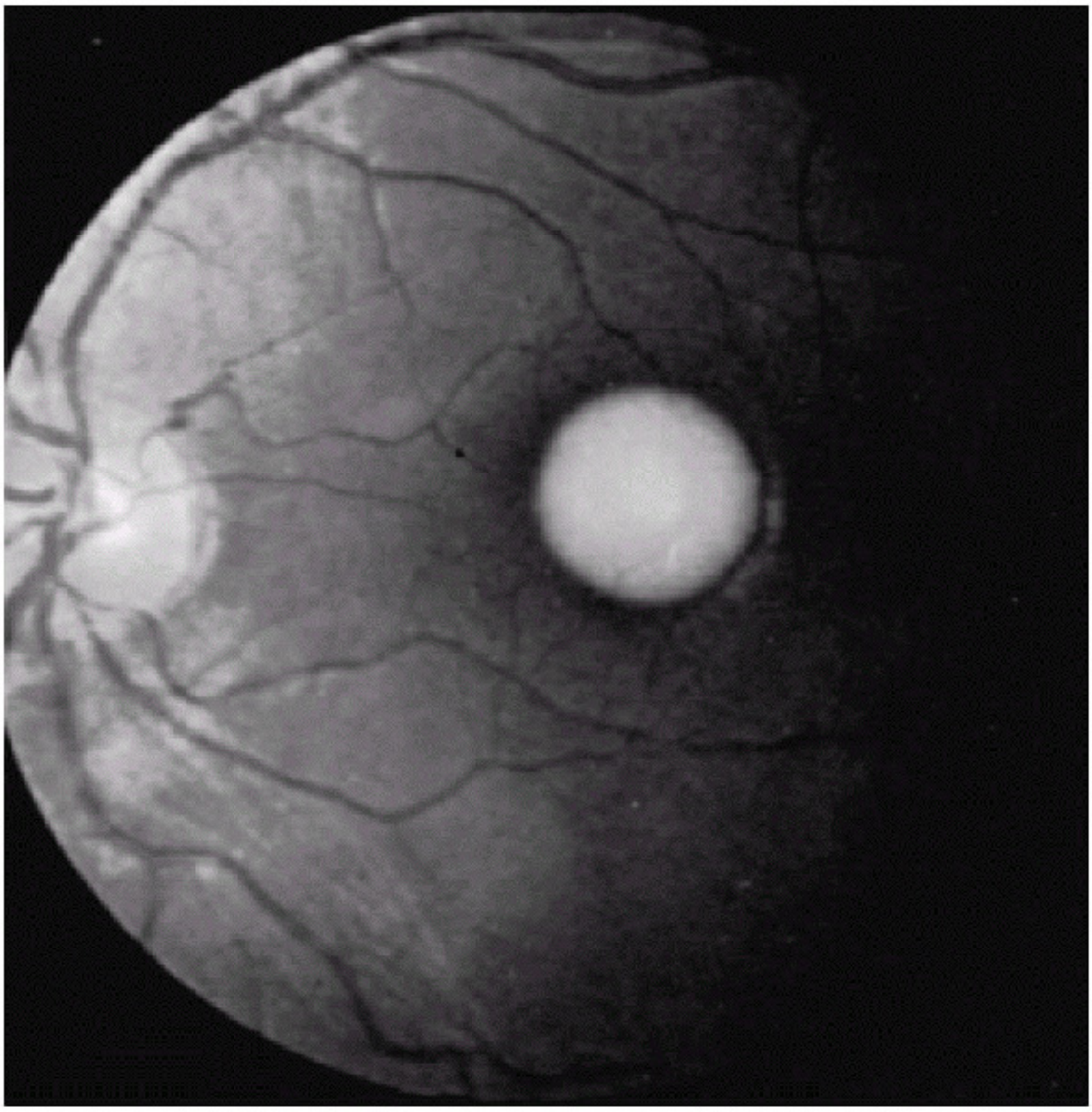

Figure 16.11 Fried-egg appearance of a typical vitelliform macular degeneration.

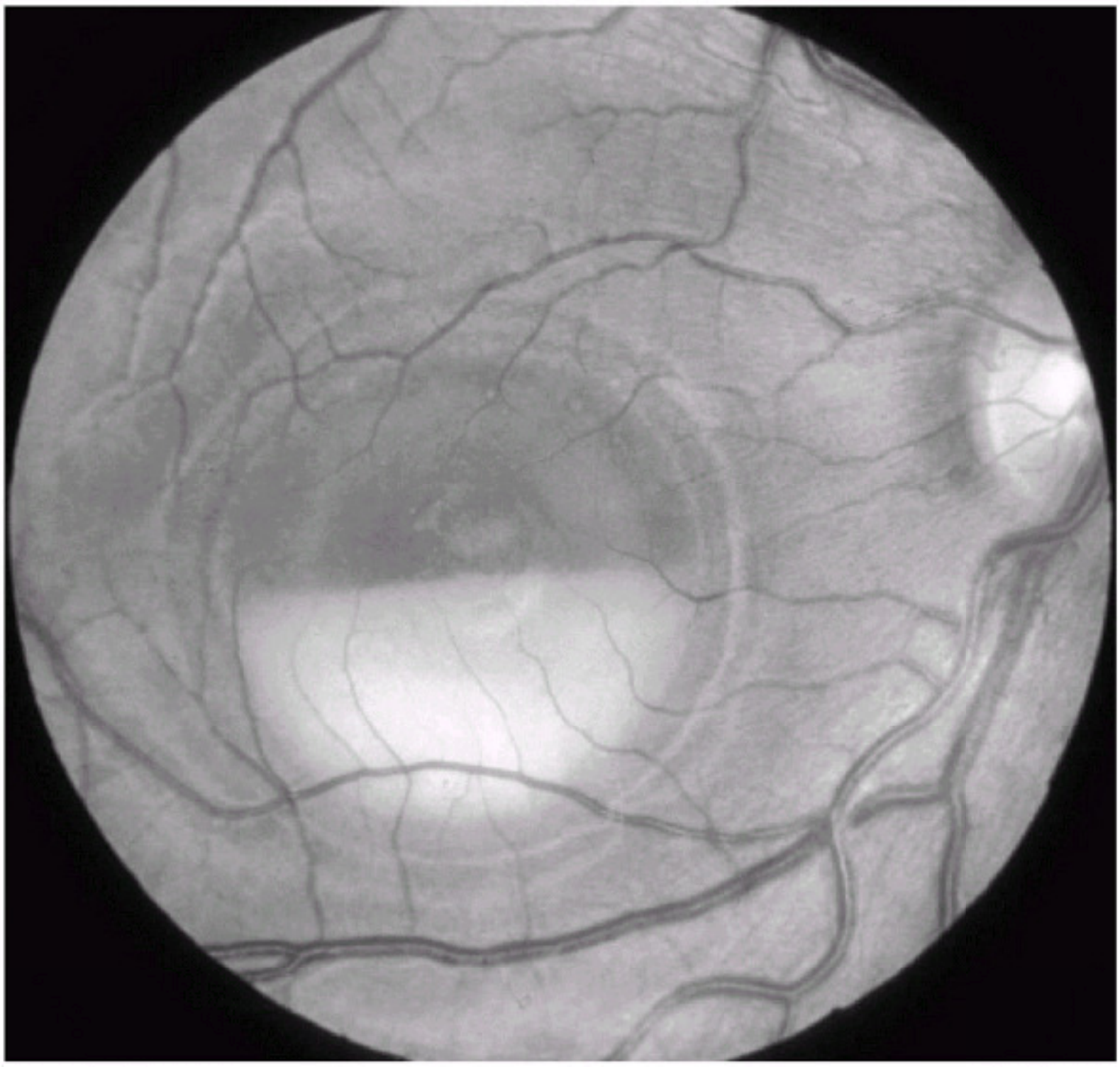

Figure 16.12 Pseudohypopyon stage of Best's disease resulting from a fluid level within a cystic space.

The pathogenesis of vitelliform degeneration is uncertain. In the past, Francois (31) postulated that an unknown abnormal substance was responsible, and he localized the lesion to the pigment epithelium, Bruch's membrane, or the potential space between the pigment epithelium and Bruch's membrane. Other studies have provided additional information and indicate that the lesion is caused by excess lipofuscin-like material, just as in Stargardt's disease (32). The gene causing Best's disease has been localized to 11q13 with an identified encoded protein called bestrophin, which has an unknown function (33).

STATIONARY FORMS OF CONGENITAL NIGHT BLINDNESS

The stationary forms of congenital night blindness are congenital stationary night blindness, Oguchi's disease, and fundus albipunctatus. These diseases should be considered in the differential diagnosis of early-onset night blindness that is not progressive. All of the former differ from the progressive disorders, such as RP, Goldmann-Favre disease, and gyrate atrophy.

Congenital Stationary Night Blindness

Congenital stationary night blindness exhibits three modes of inheritance: (a) X-linked (most common), (b) autosomal dominant, and (c) autosomal recessive (34). Molecular genetic testing has found numerous mutations in genes

encoding proteins of photoreceptors or the RPE (35). Color vision and visual fields characteristically are normal. Visual acuity is normal or mildly reduced. The fundi are entirely normal (36). Histopathologically the retina is normal. Dark adaptation reveals a reduced retinal sensitivity, and ERG shows a decreased scotopic response with a normal photopic response. The defect is caused from a failure of communication between the proximal end of the photoreceptor and the bipolar cell. No Purkinje shift in relative luminosity curves is seen. Initially the disease can be confused with early-onset RP, but the lack of progression with the former serves to distinguish these two entities.

Oguchi's Disease

Oguchi's disease, another stationary form of congenital night blindness, is usually diagnosed by a combination of two readily observable phenomena (37). First is the unusual color of the fundus, which has been described as various shades of gray-white to yellow. The abnormal color may be limited to a small section of the mid-periphery or extend throughout the entire fundus in a discontinuous or homogeneous pattern. The second unique characteristic of Oguchi's disease is the Mizuo phenomenon (38), which is a change in the color of the fundus in the dark-adapted state (see Color Plate IVB). When light is prevented from entering the eye, the color of the fundus changes from the light shade, seen initially, to a reddish, more normal appearance. The time needed to elicit this change varies among patients. Dark adaptation testing reveals a prolonged dark adaptation time and normal retinal sensitivities. ERG testing reveals a decreased scotopic response, which may revert to normal during prolonged dark adaptation. The genetic defect has been localized to the arrestin gene, which is responsible for

terminating the signaling that triggers cellular response in the rod phototransduction cascade (39). These patients have a good prognosis, with near-normal vision that remains stable (40,41).

Fundus Albipunctatus

Fundus albipunctatus is another stationary form of night blindness first described in 1910 (42). Patients present with nyctalopia and have essentially normal visual acuity, color vision, and visual fields. This presentation is identical to that of congenital stationary night blindness and Oguchi's disease, but fundus albipunctatus is easily differentiated by the presence of multiple white dots scattered throughout the fundus (43) (Fig. 16.13), most likely at the level of the RPE (44,45). Patients with fundus albipunctatus have normal-appearing vessels and discs. These patients have a good prognosis, because the vision usually remains normal; however, macular degeneration may develop (5).

This condition is ophthalmoscopically similar to retinitis punctata albescens. However, retinitis punctata albescens is a form of night blindness with progressive retinal degeneration. The discrete uniform white dots in this condition involve the mid-peripheral retina and spare the macula. The autosomal dominant form is associated with a mutation in the human peripherin/RDS gene (46), and the autosomal recessive form is associated with a mutation in the retinaldehyde binding protein gene (RLBP1) (47).

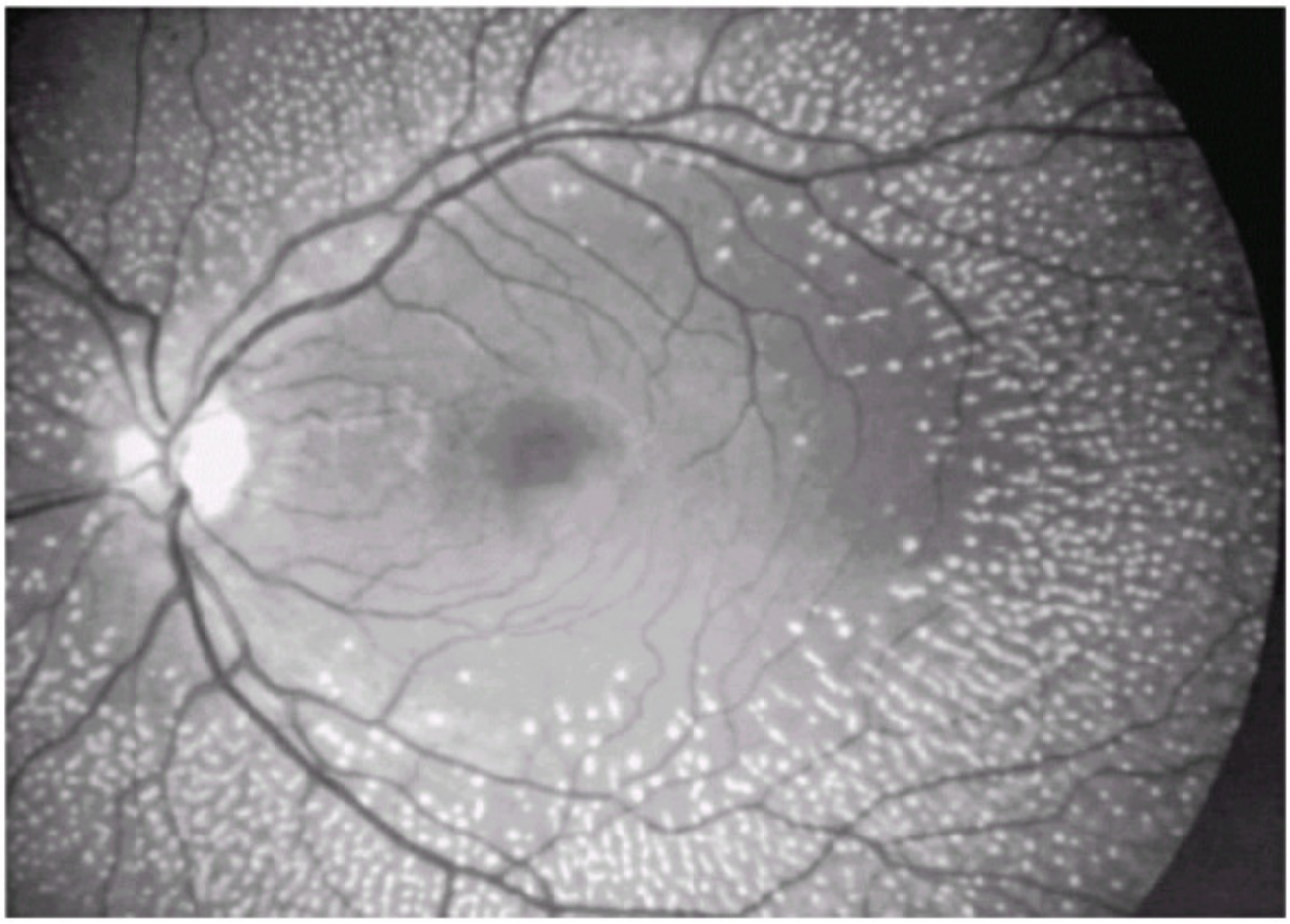

Figure 16.13 Patient with fundus albipunctatus with punctate white spots at the level of the RPE throughout the posterior pole, sparing the macula. Note that the disc and retinal vessels are normal.

CONGENITAL DEVELOPMENTAL ABNORMALITIES

Aplasia and Hypoplasia of the Macula

Aplasia of the macula is a rare disorder often associated with gross ocular deformities such as microphthalmos, aniridia, coloboma of the optic nerve, monocular myopia, albinism, and medullated nerve fibers. *Hypoplasia of the macula,* another rare entity, has been suggested as a possible cause of certain forms of amblyopia. In this condition the central retina does not differentiate completely and is usually arrested at a stage equivalent to 6 to 8 months of intrauterine development. Clinically, this is detected by the lack of the normal perifoveal capillary network, lack of a foveal reflex, absence of the macula lutea pigment, and decreased pigmentation in the foveal pigment epithelium. Visual loss is variable. The cause is uncertain.

Persistent Hyperplastic Primary Vitreous

The most constant feature in PHPV, also known as persistent fetal vasculature (48), is a dense, white vitreous band that usually extends from the disc to the fundus periphery or to the lens (see Color Plate IVC). It may occur in any meridian but is most common nasally. Limited retinal detachments or other evidence of vitreoretinal traction, such as traction folds, macular pigmentary degeneration, or pigmented demarcation lines, are often associated findings. Prominent uveal processes (Fig. 16.14) and relative microphthalmos are also characteristic of hyperplastic vitreous.

As in other anomalous vascular systems, PHPV can vary in degree. The spectrum includes Bergmeister's papilla, vitreoretinal

veils around the disc and macula, vitreous stalks and hyaloid remnants, and retinal folds. Each is related to the other and to congenital abnormalities of the anterior primary vitreous.

Figure 16.14 Elongated ciliary processes and white pupil, characteristic of persistent hyperplastic primary vitreous (PHPV).

The prognosis in PHPV is variable depending largely on the severity of the microphthalmia and retinal detachment, if present. Removal of the vitreous opacification and cataract may yield significant visual improvement in selected cases. Aggressive amblyopia therapy is usually necessary (49).

Myelinated Nerve Fibers

Myelinated nerve fibers occur because of extension of myelination anterior to the lamina cribrosa where it does not belong. The cause is unknown. Myelinated nerve fibers appear during the first year of life, rarely affect visual acuity, and occur predominantly among males; although bilateral cases occur, unilaterality is the rule. The medullated fibers have a feather-like appearance and are usually adjacent to the disc. Sometimes the myelination process is located away from the optic nerve, but unless the macula is affected, vision is preserved (see Color Plate IVD). If it is inherited, the mode of transmission is usually autosomal dominant.

Coats' Disease

Coats' disease is a nonhereditary abnormality of the retinal vasculature, first described by Coats in 1908 (50). Peripheral retinal telangiectasia, sometimes with a “light bulb” appearance, and secondary exudation are the characteristic findings (Fig. 16.15). In advanced cases, serous detachment of the sensory retina may occur. Discrete dilated vessels and telangiectasia are noted early on fluorescein angiography with marked late leakage. In addition, extensive capillary dropout in areas of peripheral retinal telangiectasia is common. In certain cases, telangiectasia and microaneurysms can occur in the posterior pole and may be associated with exudation posterior to the equator. Macular exudate may also develop in eyes in which the retinal vascular leakage is limited to the periphery. Although the vitreous is usually clear in mild cases, retinal neovascularization and vitreous hemorrhage may occur in advanced cases. Optic nerve involvement in Coats' disease is rare. In the end stages of Coats' disease, neovascular glaucoma and phthisis bulbi may develop.

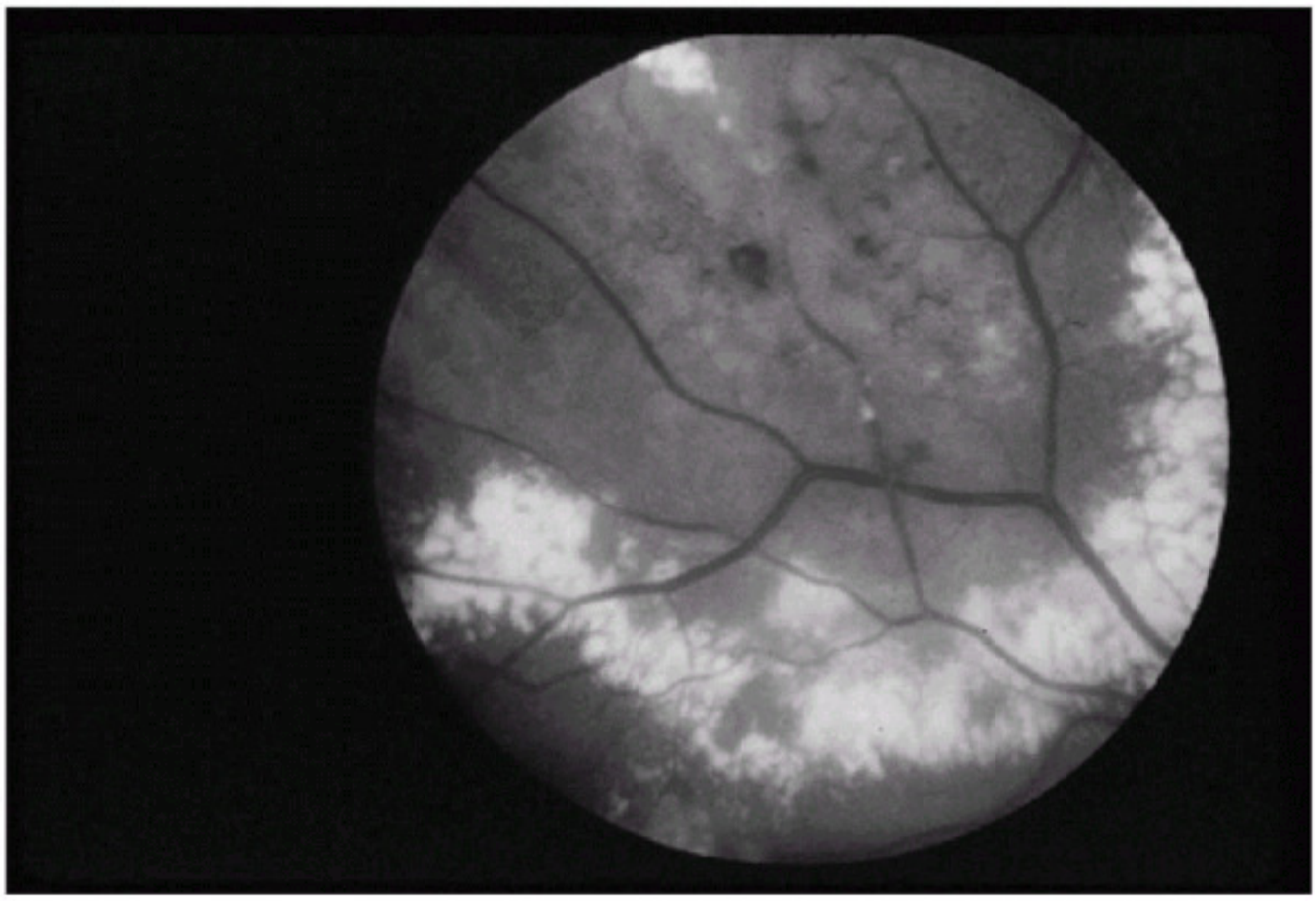

Figure 16.15 Light bulb lesions with exudation in Coats' disease.

Coats' disease is much more common in males than in females but does affect both sexes. It is unilateral in 90% of cases and tends to occur in childhood. A similar, although usually less severe, condition occurs in adulthood. It is uncertain whether this represents the same underlying disease as the classic form of Coats' disease.

Treatment is directed at elimination of the abnormal vessels. Cryotherapy is an effective means of eliminating the vessels and can be used from the equator to the ora serrata. Indirect laser photocoagulation may be possible if there is no subretinal fluid and the exudate is not too marked. In patients with vascular abnormalities posterior to the equator, photocoagulation is preferable. Usually, two to three treatment sessions are necessary at 4- to 6-week intervals to eliminate the abnormal vasculature.

Patients with marked Coats' disease may develop serous detachment of the sensory retina. In these individuals, scleral buckling with drainage of subretinal fluid followed by cryotherapy to the anomalous vessels can lead to reattachment of the retina.

With elimination of the anomalous vessels, subretinal exudate begins to clear. This is a slow process that may take as long as 1 year until all the exudation has absorbed. With macular involvement, a subretinal organized nodule may remain permanently in the fovea. The prognosis for recovery of macular function is poor if foveal exudation is present.

Even in patients who have been successfully treated, recurrences have been noted up to 5 years later. It is therefore recommended that patients be followed at 6-month intervals, so further treatment can be given if necessary before the process becomes too extensive.

The differential diagnosis of Coats' disease includes angiomatosis

of the retina, retinoblastoma, FEVR, ROP, PHPV, nematode infestation, and astrocytoma of the retina.

PRIMARY AND SECONDARY RETINAL DEGENERATION

Retinitis Pigmentosa

Although given the name “retinitis pigmentosa” by Donders in 1855, this condition probably is more accurately called “retinal pigmentary dystrophy.” It is often hereditary and is characterized by progressive deterioration of the visual cells, pigment epithelium, and choroid. Typical clinical findings are thinning of the retinal vessels, waxy pallor of the optic disc, and appearance of “bone-corpuscle” pigment, initially at the equator. The pigmentary changes typically become visible during the first decade of life and may begin as fine dots that gradually assume the spidery bone-corpuscle appearance (Fig. 16.16). As the disease progresses, the equatorial girdle widens and a ring scotoma is produced in the visual field.

The ring scotoma is the characteristic field defect. The defect usually begins inferotemporally and enlarges to form the ring scotoma. In more advanced stages, the scotoma may progress so only inferotemporal field and central vision are preserved.

Almost all patients with RP have night blindness, and this is reflected initially by abnormalities in dark adaptation. The adaptation curve initially shows an increased rod threshold with a normal cone response. As the disease progresses, the rods and the cones become involved, the curve being monophasic.

Of equal importance in the diagnosis is the ERG. In primary pigmentary degeneration of the retina, the ERG response is subnormal or absent, a change that appears before the subjective visual deterioration or ophthalmoscopically visible changes.

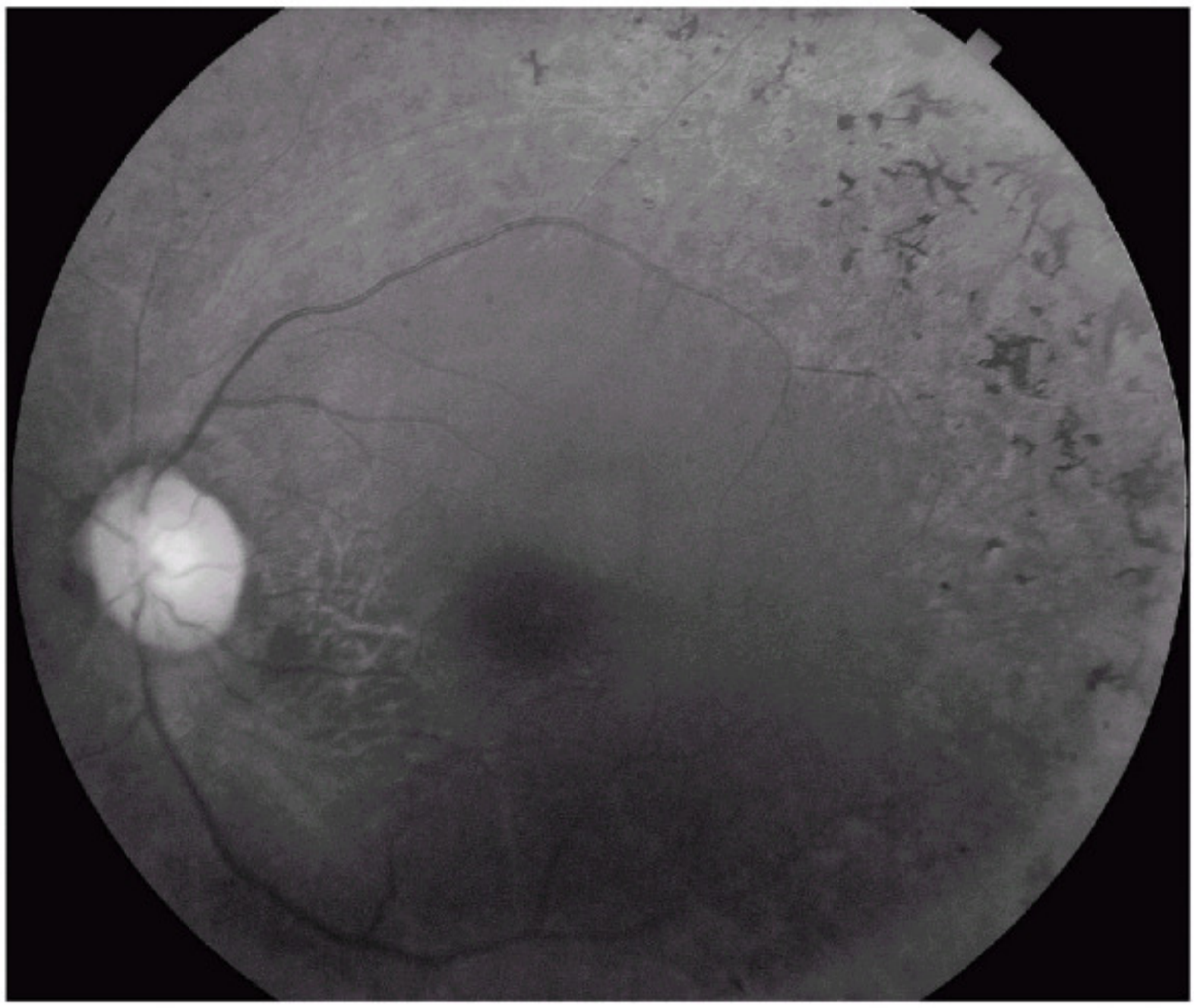

Figure 16.16 Attenuation of retinal vessels, waxy pallor of the optic disc, and peripheral “bone-corpuscle” pigmentation in a patient with retinitis pigmentosa (RP).

Histologic study reveals a general disappearance of the neuroepithelial elements, a proliferation of glial cells, changes in the pigment epithelium, and an obliterative sclerosis of the retinal vessels (51). First to be affected are the rods, as opposed to the ganglion cells and nerve fiber layer, which may remain unaffected even when the eye is blind. The migration of pigment into the retina, aided by macrophages, follows the degeneration.

Previously, classification of the photoreceptor degeneration depended largely on the clinical manifestations and the modes of inheritance: autosomal recessive, autosomal dominant, and X-linked (52). Recent advances in genetic analysis have shown that one gene may be responsible for several different clinical entities (phenotypes) and that several different genes may be responsible for one phenotype. Mutations affecting multiple loci of the rhodopsin and peripherin genes are among the many described (53). Although the advent of genetic analysis is dramatically altering the classification and genetic counseling of RP, some general statements concerning inheritance are still worth noting. The most common form is autosomal recessive, followed by autosomal dominant and X-linked recessive. The autosomal dominant type is the most benign form, and X-linked is the most severe form (54). Of greater importance, however, is that the severity and rate of progression are similar within a family; this can be helpful in individual patient counseling.

Other significant ocular findings include posterior subcapsular cataract, vitreous opacities, glaucoma, myopia, and keratoconus. Macular changes occur as cystoid macular edema and retinal pigment epithelial atrophy.

Numerous systemic associations with RP have been described (Table 16.1). Well-established extraocular manifestations include deafness, diencephalic and endocrine anomalies, oligophrenia, ophthalmoplegia, and lipidoses.

Perhaps the best known condition in the differential diagnosis of RP is the Laurence-Moon-Biedl-Bardet syndrome, which is characterized by mental retardation, hypogenitalism, retinal changes, and a recessive inheritance pattern (55). It occurs predominantly among males, and the retinal changes may simulate typical RP or be characterized by macular degeneration (56). It is now differentiated into Laurence-Moon and Biedl-Bardet syndromes (57) on the basis of whether polydactyly and obesity are present (Biedl-Bardet) or absent (Laurence-Moon).

Other disorders associated with an atypical RP pattern are Refsum syndrome and Bassen Kornzweig disease. In Refsum syndrome, phytanic acid accumulates in swollen RPE because of a deficiency of the enzyme ot-hydroxylase. The sensory retina is affected (58), and there are changes in the RPE (59). Systemic findings include cerebellar ataxia, polyneuritis, and anosmia (60).

In Bassen-Kornzweig disease, an absence of serum 3-lipoprotein (61) leads to malabsorption and subsequent vitamin A deficiency (62). Systemic findings include steatorrhea, acanthocytosis, ataxic neuropathy, and growth retardation (63).

In addition to these two syndromes, any vitamin A or zinc deficiency can cause symptoms of nyctalopia. It is important

to recognize Refsum syndrome and Bassen Kornzweig disease, because treatment is often possible. The differential diagnosis also includes syphilis, rubella, trauma, and drug-induced retinopathies.

TABLE 16.1 RETINITIS PIGMENTOSA AND ASSOCIATED SYSTEMIC DISORDERS

1. Lipidoses
    a. Gaucher disease
    b. Neuronal ceroid lipofuscinosis

        A constant finding in the juvenile form (Batten-Mayou disease, Spielmeyer-Vogt disease), but a variable finding in the late infantile form (Jansky-Bielschowsky disease), in which ocular signs may vary between the infantile and juvenile forms

2. Late form of Pelizaeus-Merzbacher disease (a form of sudanophilic cerebral sclerosis)
3. Progressive familial myoclonic epilepsy
4. Spinopontocerebellar degeneration
    a. Marie ataxia
    b. Friedreich ataxia
    c. Unclassified spastic paraplegias
    d. Charcot-Marie-Tooth disease
    e. Progressive pallidal degeneration with retinitis pigmentosa
    f. Hereditary muscular atrophy, ataxia, and diabetes mellitus
5. Specific syndromes with progressive external ophthalmoplegia and retinitis pigmentosa
    a. Progressive external ophthalmoplegia (progressive nuclear ophthalmoplegia ocular myopathy)
    b. Retinitis pigmentosa, external ophthalmoplegia, and heart block
    c. Retinitis pigmentosa, ophthalmoplegia, and spastic quadriplegia
    d. Abetalipoproteinemia (Bassen-Kornzweig syndrome, acanthocytosis)
    e. Refsum syndrome
6. Generalized muscular dystrophy
7. Myotonic dystrophy (Steinert disease)
8. Syndromes in which a hearing loss is a prominent finding
    a. Hallgren syndrome

a. Hallgren syndrome

b. Refsum syndrome

c. Usher syndrome

d. Retinitis pigmentosa with deafness of varying severity

e. Cockayne disease (Cockayne-Neill disease, Neill-Dingwall syndrome)

f. Alstrom syndrome (retinitis pigmentosa, deafness, obesity, and diabetes)

9. Syndromes with renal disease as a prominent feature

a. Familial juvenile nephrophthisis (Fanconi nephrophthisis)

b. Hereditary nephritis, retinitis pigmentosa, and chromosomal abnormalities

c. Cystinuria

d. Cystinosis (Fanconi syndrome I)

e. Oxalosis

10. Syndromes in which bone disease is a prominent feature

a. Paget disease

b. Osteogenesis imperfecta (Lobstein syndrome)

c. Marfan syndrome

d. Osteopetrosis “familiaris” (marble bone, osteosclerosis fragilis generalisata, Albers-Schonberg disease)

11. Syndromes with skin disease

a. Werner disease

b. Psoriasis

12. Laurence-Moon-Biedl-Bardet syndrome

13. Dresbach syndrome (elliptocytosis, ovalocytosis)

14. Klinefelter syndrome

15. Mucopolysaccharidoses: retinal degeneration has now been reported in types I, II, III, and V

16. Hooft disease (hypolipidemia syndrome)

From Krill AE. Retinitis pigmentosa: a review. *Sight Sav Rev* 1972;42: 26, with permission.

From Krill AE. Retinitis pigmentosa: a review. *Sight Sav Rev* 1972;42: 26, with permission.

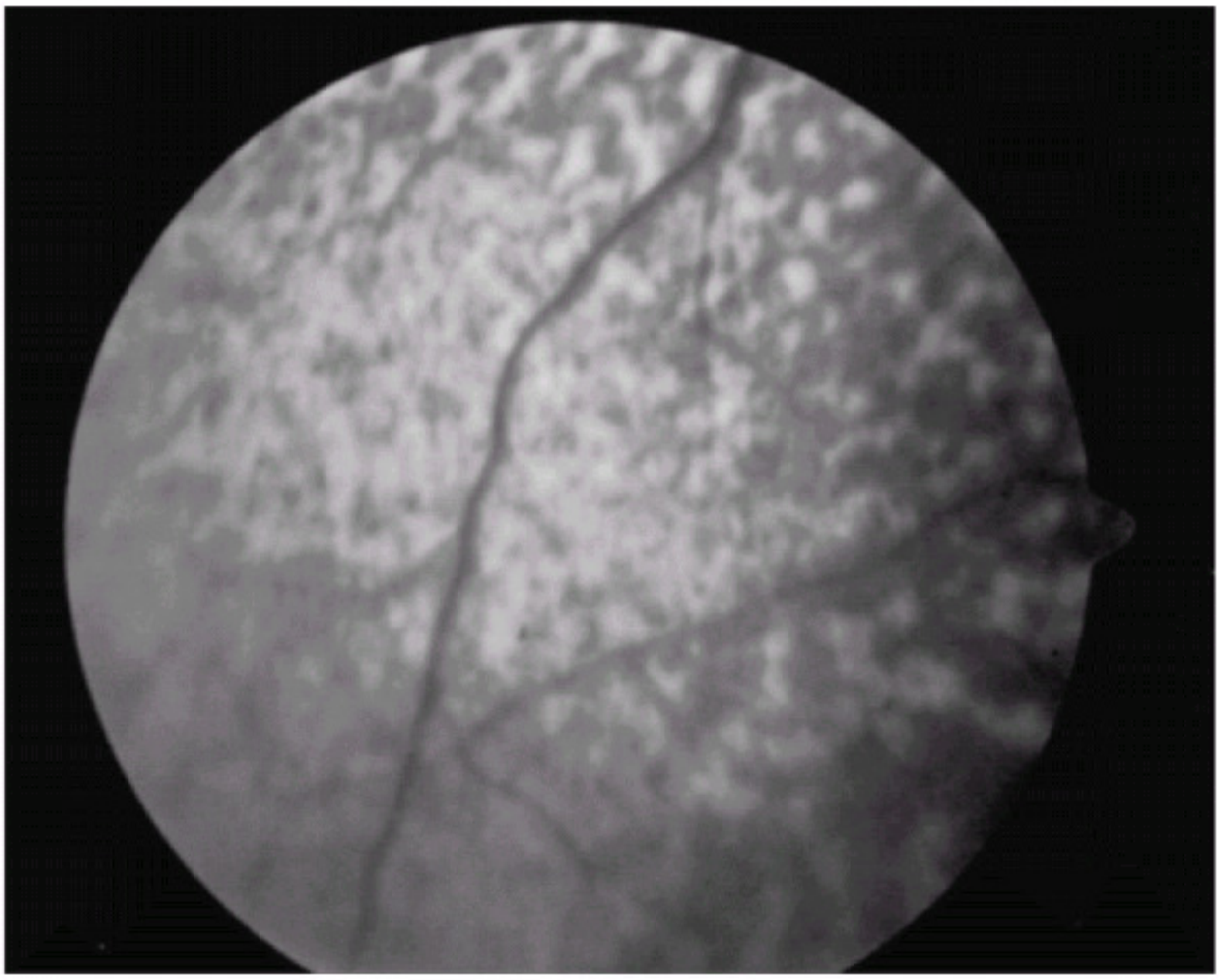

Figure 16.17 Marbleized pattern, with white subretinal deposits in patient with Leber's congenital amaurosis.

Leber's Congenital Amaurosis

Leber's congenital amaurosis is an autosomal recessive congenital retinal dystrophy that has a broad spectrum of fundal presentations, ocular findings, and systemic associations. Mutations have been found on four known genes for this condition. Clinically, patients present with decreased vision during the first year of life. The ophthalmoscopic appearance is variable, ranging from normal to an RP-like picture (64). Other findings in the fundus are macular colobomas, salt-and-pepper changes, a marbleized pattern (Fig. 16.17), and a nummular pigmentary pattern (Fig. 16.18) (65). Other ocular signs include eye rubbing "oculodigital

sign," high hyperopia, pendular nystagmus, poorly reactive pupils, cataracts, keratoconus, and strabismus.

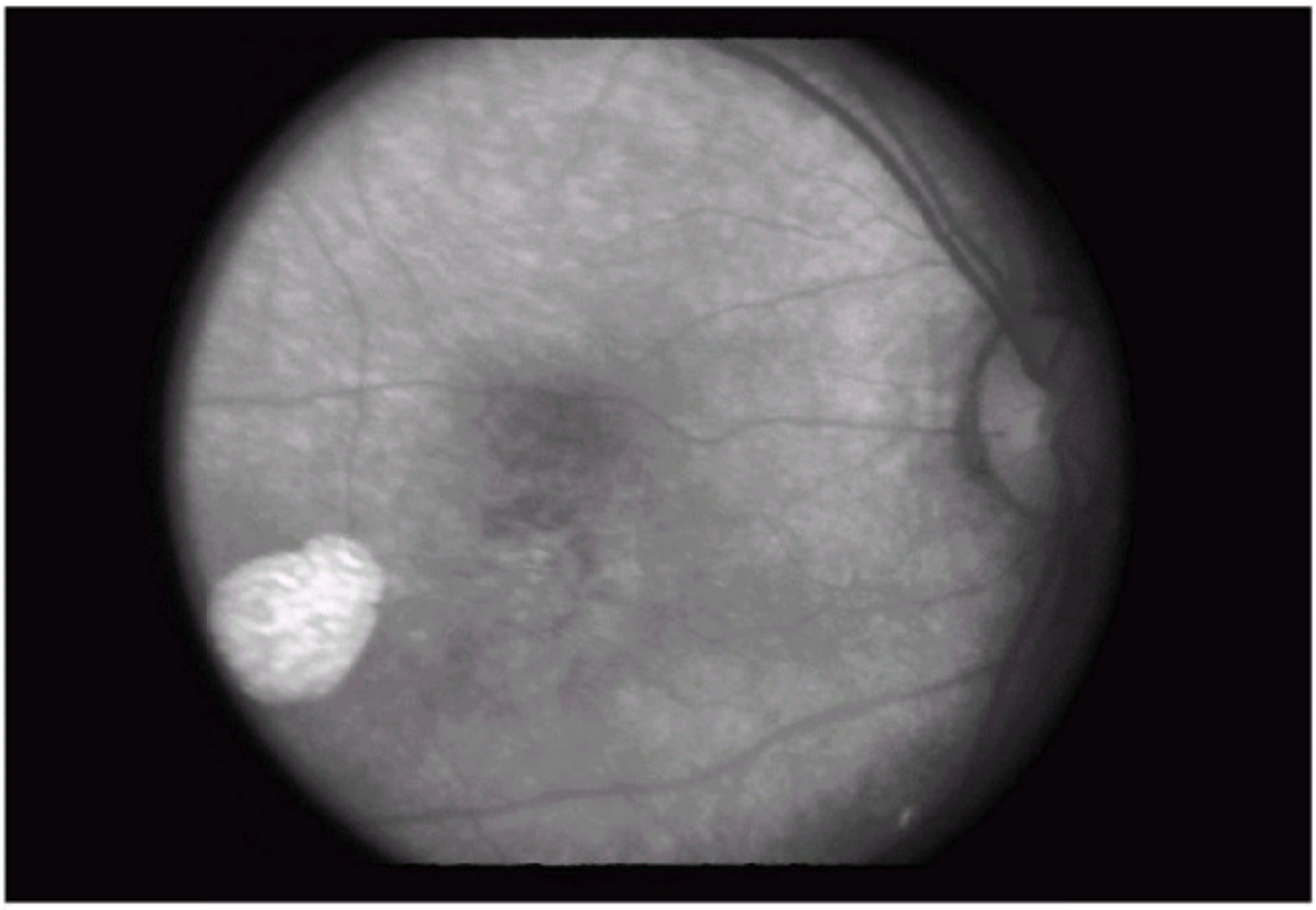

Figure 16.18 Nummular pigmentary pattern; well-defined round-to-oval pigmented lesions in a patient with Leber's congenital amaurosis.

The ERG is essential to a correct diagnosis because of the varied clinical presentation (66). The photopic and scotopic ERG response is extinguished in Leber's congenital amaurosis.

Leber's congenital amaurosis has been associated with many systemic abnormalities and neurologic disorders (65). Systemic associations include polycystic kidney disease, osteopetrosis, cleft palate, and skeletal anomalies. Neurologic associations include mental retardation, seizures, and hydrocephalus.

There is much controversy concerning these associations as well as over the classification of Leber's congenital amaurosis. It is important to realize that this is not a single disease state but a constellation of eye findings associated with several diseases.

Treatable metabolic disorders confused with Leber's congenital amaurosis include abetalipoproteinemia (Bassen-Kornzweig syndrome), infantile phytanic acid storage disease (Refsum disease), and infantile Batten disease (ceroid lipofuscinosis) (67).

Bietti's Crystalline Dystrophy

This retinal degeneration was first described by Bietti in 1937 (68) characterized by crystalline deposits in all retinal layers with associated choriocapillaris and RPE loss (see Color Plate IVE). Some cases also have limbal corneal crystals. This condition is inherited in an autosomal recessive pattern, and the genetic defect has been mapped to 4q35 (69).

Patients complain of progressive decrease in night vision, which correlates with a decrease in the ERG. The fluorescein angiogram typically demonstrates focal areas of choriocapillaris atrophy in the posterior pole.

Cone Dystrophy

Cone degeneration is characterized by loss of central vision, photophobia, abnormalities of color vision, and an abnormal photopic ERG (70). Most patients present in the first or second decade of life. There is usually no family history, because most patients have an autosomal recessive inheritance pattern, although autosomal dominant pedigrees have been described. An acquired nystagmus is occasionally a presenting sign. Ophthalmoscopically, the patient may be normal, exhibit the classic “bull's-eye” lesion, have diffuse pigmentary changes, or have regions of chorioretinal atrophy involving the macula (Fig. 16.19). Optic atrophy has also been described. The diagnosis is confirmed, however, by the presence of an abnormally low ERG response to a 25-Hz flickering light, an abnormal photopic ERG, and a normal scotopic ERG. Color vision testing shows severe abnormalities early in the course of the disease. The prognosis is usually poor, most patients progressing to a vision of 20/200 or worse.

Another rare cone disorder is achromatopsia or rod monochromatism (71). This disorder presents in the first year of life with a pendular nystagmus, photopia, and decreased vision. The fundus appears normal on examination. The inheritance is typically autosomal recessive, and the diagnosis is confirmed by the presence of an abnormal response to a flicker stimulus, an abnormal photopic ERG, and a normal scotopic ERG. Vision usually is in the 20/200 to 20/400 range and remains unchanged throughout life.

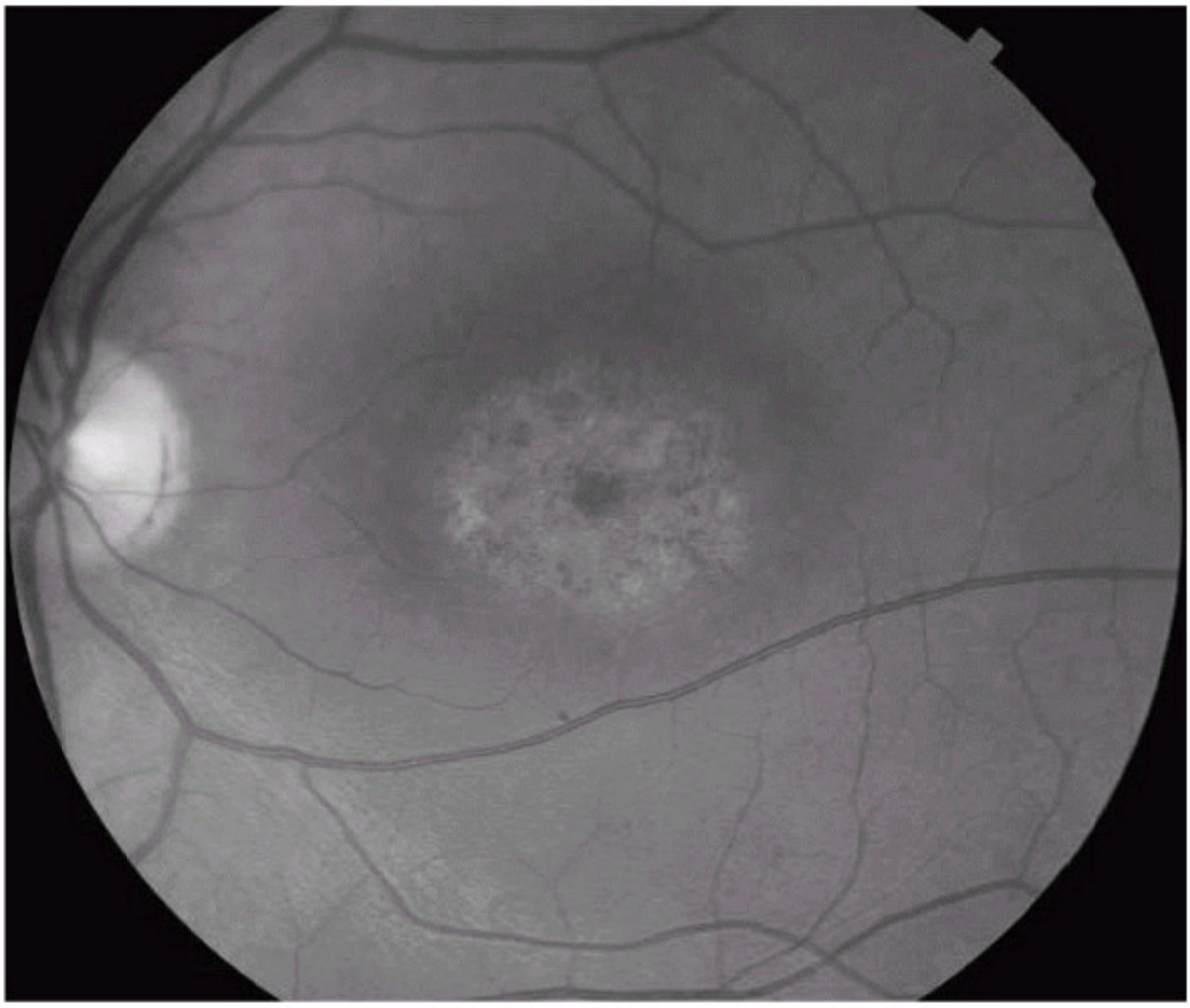

Figure 16.19 Cone dystrophy with pigmentary changes and areas of chorioretinal atrophy involving the macula.

Choroideremia

Choroideremia is a progressive retinal degeneration that can be confused with RP first described by Mauthner in 1871 (72). Patients present with progressive nyctalopia and visual field loss secondary to a progressive degeneration of the RPE, retina, and choroid. The choroideremia gene has been cloned from chromosome Xq13-q22 (73), and laboratory testing has been developed to diagnose choroideremia in patients (74).

The condition is inherited as an X-linked trait, and affected males show loss of the RPE and choriocapillaris (Fig. 16.20) (75). This loss begins in the mid-periphery and progresses both anteriorly and posteriorly. An island of normal macula is retained until late in the disease. The patient therefore can have good central vision with poor peripheral fields. The disease is seen in the first two decades, and loss of central vision appears by the fifth decade (76). Female carriers usually display mild abnormalities involving the RPE. This disorder should be differentiated from RP and gyrate atrophy, which can usually be identified by a careful examination of the fundus. The X-linked pattern of inheritance and examination of the female carriers, who often demonstrate irregular pigment clumping, also provide useful clues.

Gyrate Atrophy

Gyrate atrophy is an autosomal recessive disorder with a typical onset in the late teens to mid-40s (77). The disease gene for gyrate atrophy, ornithine-d-aminotransferase has been linked to chromosome 10q26 and has been cloned (78). It can also present as early as 10 years of age with symptoms of nyctalopia and loss of visual field. The initial

changes are first seen in the mid-periphery as “scalloped,” well-circumscribed atrophic areas in the RPE and choriocapillaris. The fundi are more pigmented than in choroideremia. High myopia and cataracts are associated ocular findings. The disease generally progresses slowly, with patients maintaining central vision into the fourth decade. As new areas of atrophy appear and the older areas coalesce, the peripheral vision worsens.

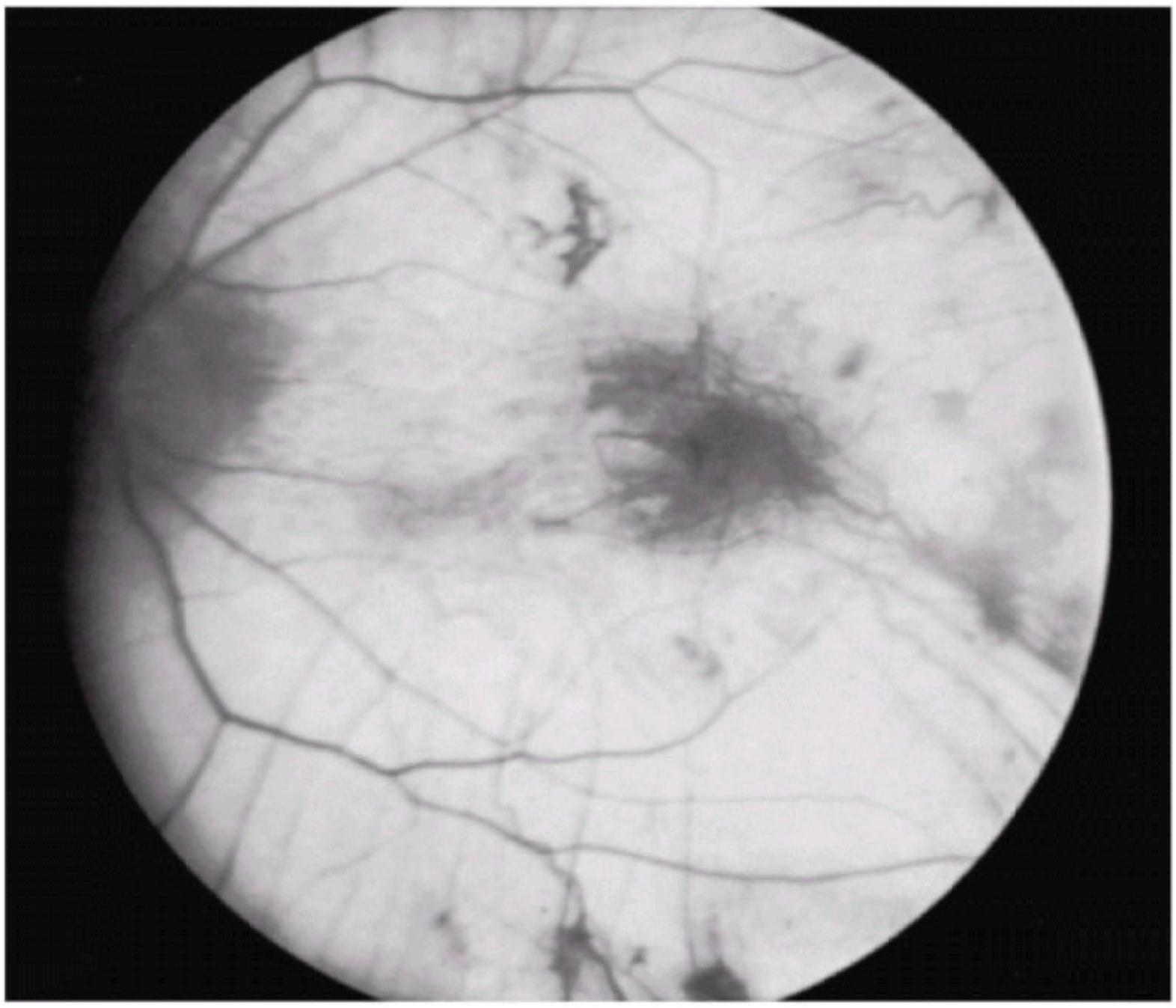

Figure 16.20 Extensive atrophy of the choroid and RPE in a patient with choroideremia, with preservation of some of the RPE centrally.

The disorder is believed to be the result of a deficiency of the mitochondrial enzyme ornithine aminotransferase. This deficiency leads to elevated levels of ornithine, which is believed to be toxic to the RPE (79). The elevated levels of ornithine can be detected in the blood and help in establishing the diagnosis. The diagnosis can also be confirmed by determining enzyme levels in cultures of skin fibroblasts. Levels are reduced or absent in affected individuals and reduced in carriers. Treatment with pyridoxine and restriction of arginine in the diet can reduce serum ornithine levels by 27% or more, but whether this slows or halts progression of the disease is unproved (80).

Albinism

The term “albinism” refers to decreased pigmentation. True albinism is often divided into oculocutaneous and ocular varieties, depending on whether the skin is involved or not. Sometimes this is difficult to assess. It is probably more accurate to classify the conditions in terms of a physiologic approach. In ocular albinism (X-linked disease), only the eyes are affected and there is a decrease in the number of melanosomes, but each melanosome is often fully pigmented—a so-called macromelanosome (81). Female carriers may show partial iris transillumination defects or fundus hypopigmentation. In oculocutaneous albinism (autosomal recessive disease), both the skin and the eyes are involved, and there is a decreased amount of melanin deposited in each melanosome (82). Oculocutaneous albinism is further subdivided on the basis of tyrosinase test results. Tyrosinase-negative albinos lack any pigment in the eyes, skin, or hair.

The eye findings are similar in all true cases of albinism, regardless of type. Patients present with decreased vision and pendular nystagmus secondary to foveal hypoplasia. OCT has been used to demonstrate a widespread thickening of the retina throughout the fovea (83). These patients are sometimes photophobic, display iris transillumination defects, and have decreased pigmentation in the RPE and choroid (Fig. 16.21; see Color Plate IVF) (84). Abnormal retinogeniculostriate projections have been found in true albinos, in whom many of the temporal nerve fibers decussate rather than project to the ipsilateral geniculate body.

Two important forms of albinism for the clinician to be aware of are the Hermansky-Pudlak and the Chediak-Higashi syndromes. In the former, petechiae and ecchymoses are present because of a platelet defect; these patients are susceptible to bleeding. In the latter, patients are susceptible to recurrent infections because of a leukocyte defect (85).

Retinopathy of Prematurity

ROP is a peripheral proliferative retinal vascular disorder affecting primarily markedly premature infants and leading, in severe cases, to complex retinal detachment and profoundly abnormal vision. Fortunately, with the timely application of treatment this devastating result can often be avoided.

Retinopathy of prematurity was first described by Terry in 1942. In the 1950s, Campbell and, later, Patz implicated high levels of inspired oxygen in the development of ROP. Although hyperoxia shortly after birth is a definite risk factor for ROP, even with modern oxygen monitoring techniques and avoidance of high oxygen levels, ROP continues to develop. The most important risk factor for the development

of ROP is low birth weight. Infants with a birth weight of 1250 g have a 47% risk of developing ROP, whereas infants weighing only 750 g have a 90% risk. The

signs of ROP usually are first apparent 32 to 34 weeks after conception, regardless of the gestational age at birth.

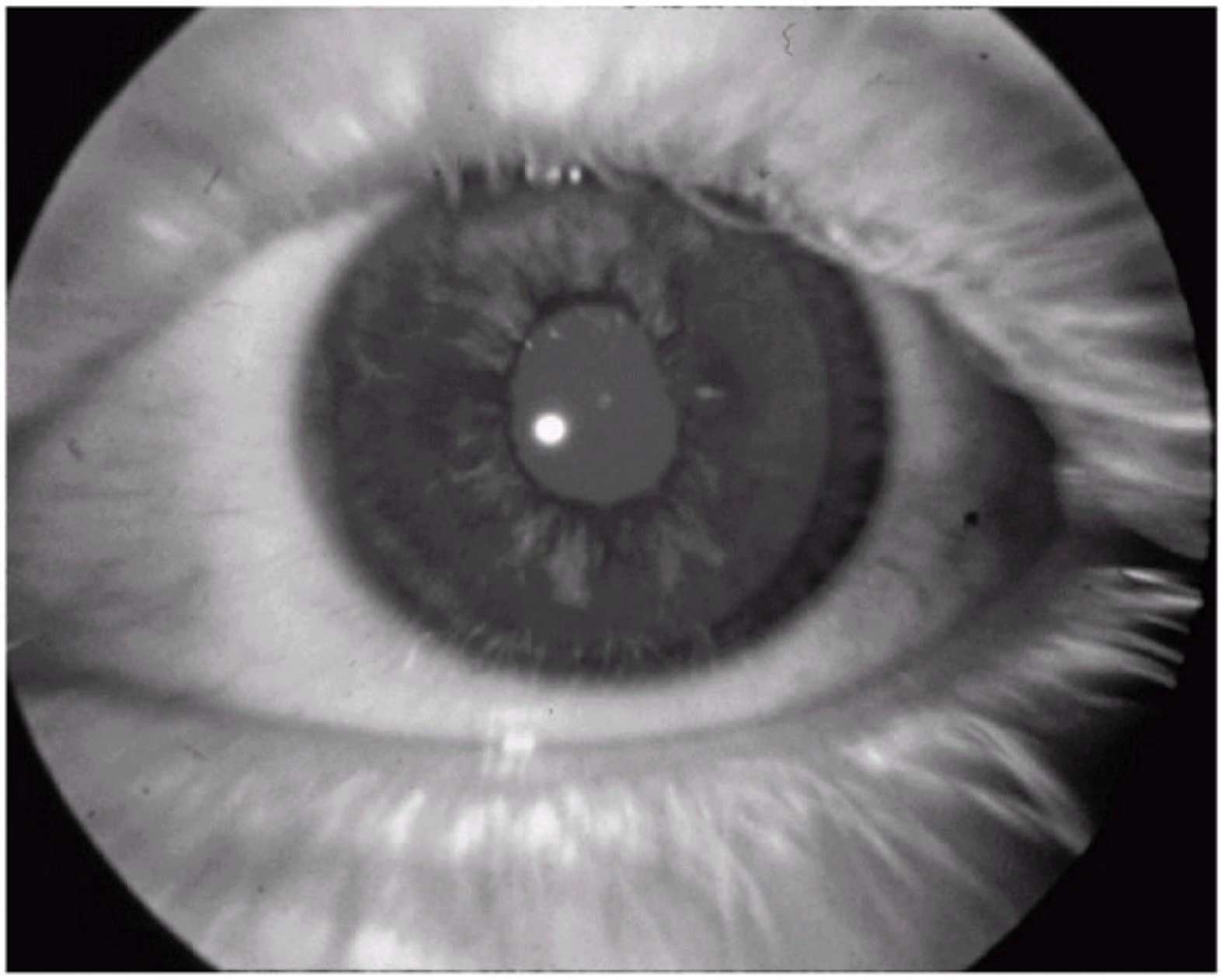

Figure 16.21 Iris transillumination defects secondary to ocular albinism.

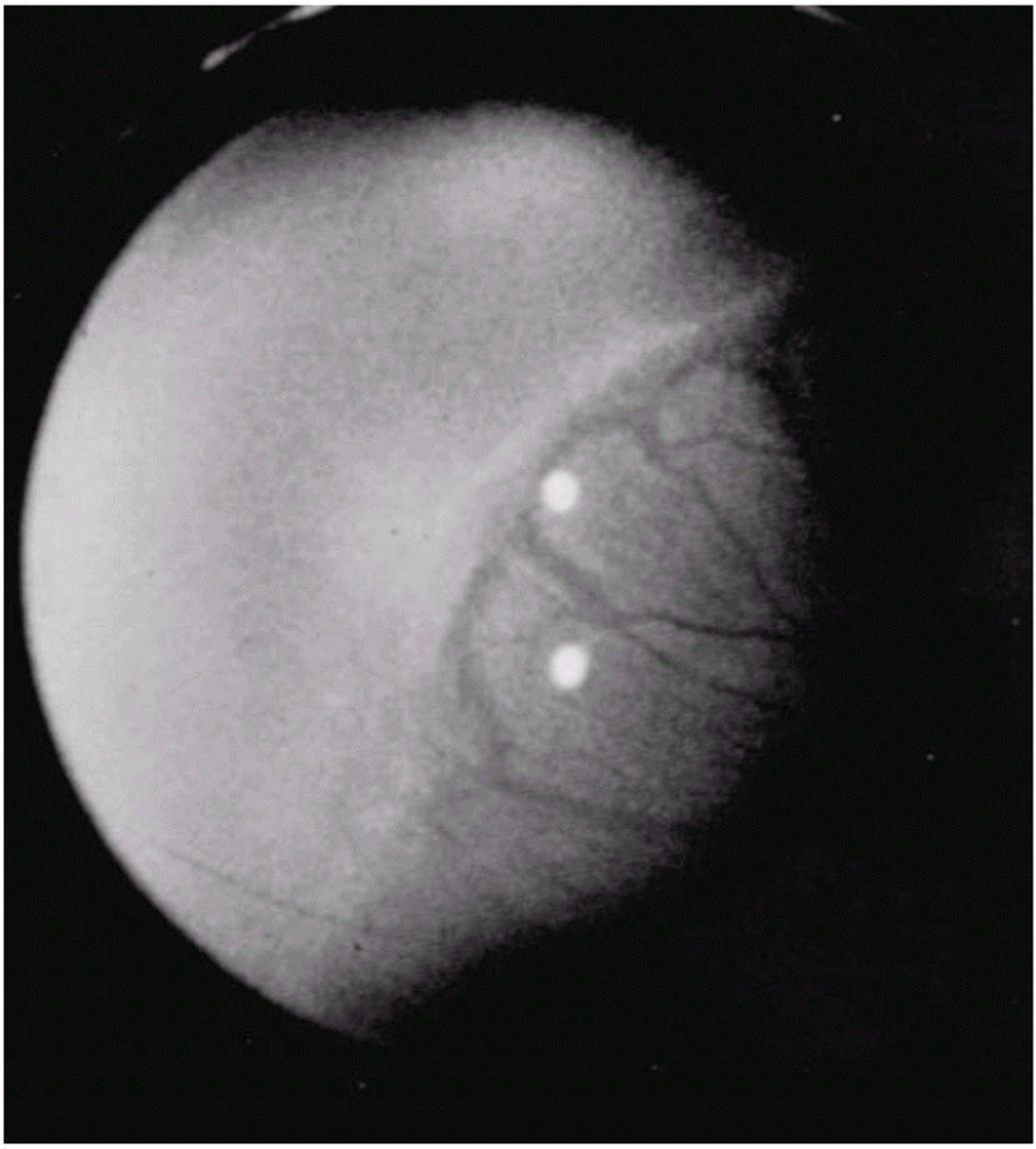

Figure 16.22 Peripheral mesenchymal shunt in a newborn infant with active retinopathy of prematurity (ROP). The retina peripheral to the shunt is avascular.

The International Classification of Retinopathy of Prematurity describes the various features of ROP and is widely accepted (86,87). Funduscopic variables include the anteroposterior location (“zone”), circumferential extent (“clock hours” or “sectors”), severity (“stage”) of disease, and presence or absence of “plus disease” (Figs. 16.22, 16.23, 16.24 and 16.25). Plus disease is an extremely important prognostic variable and is defined as dilation and tortuosity of vessels in the posterior pole. The features of the International Classification are defined in Table 16.2.

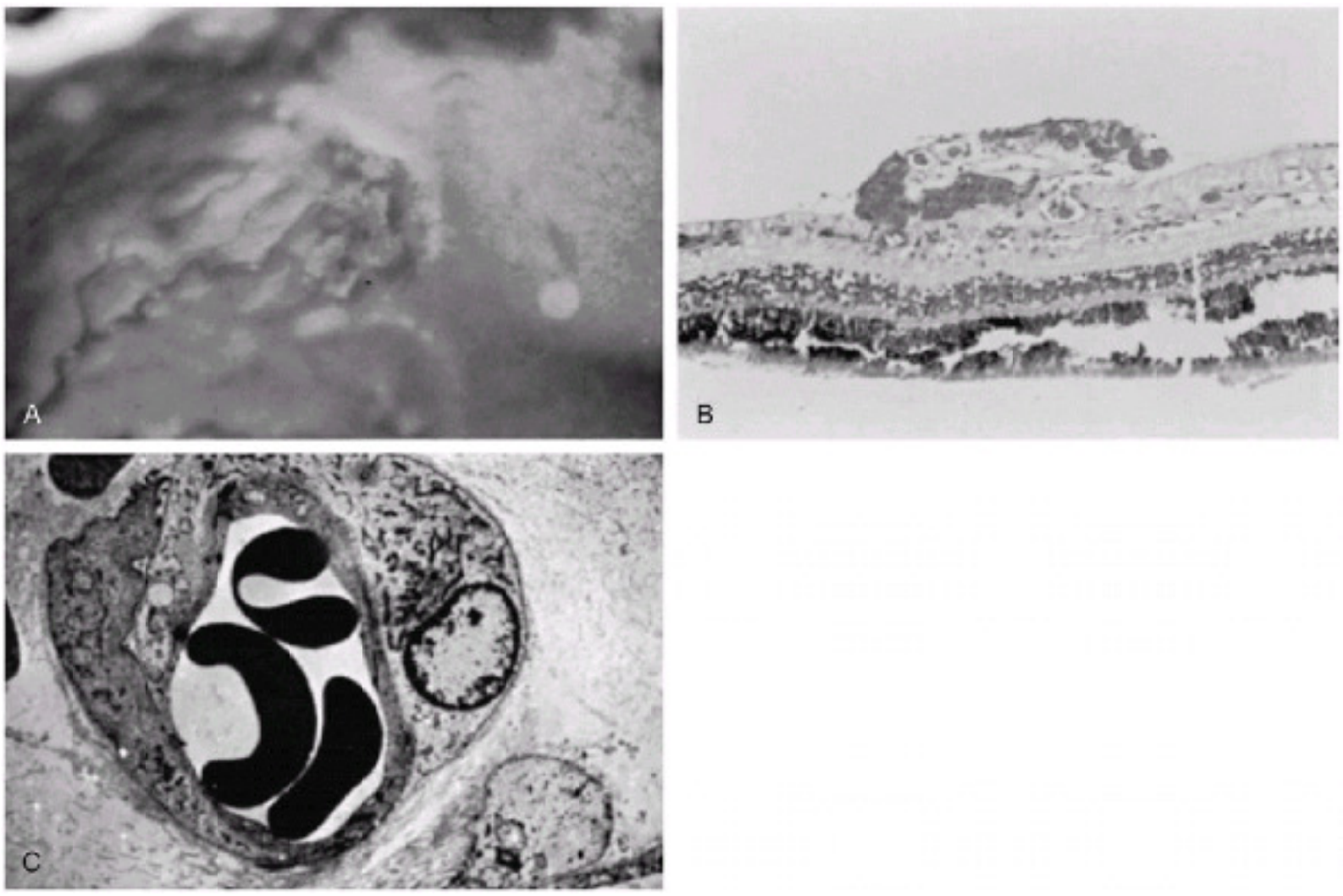

Figure 16.23 Stage 2 ROP ridge.

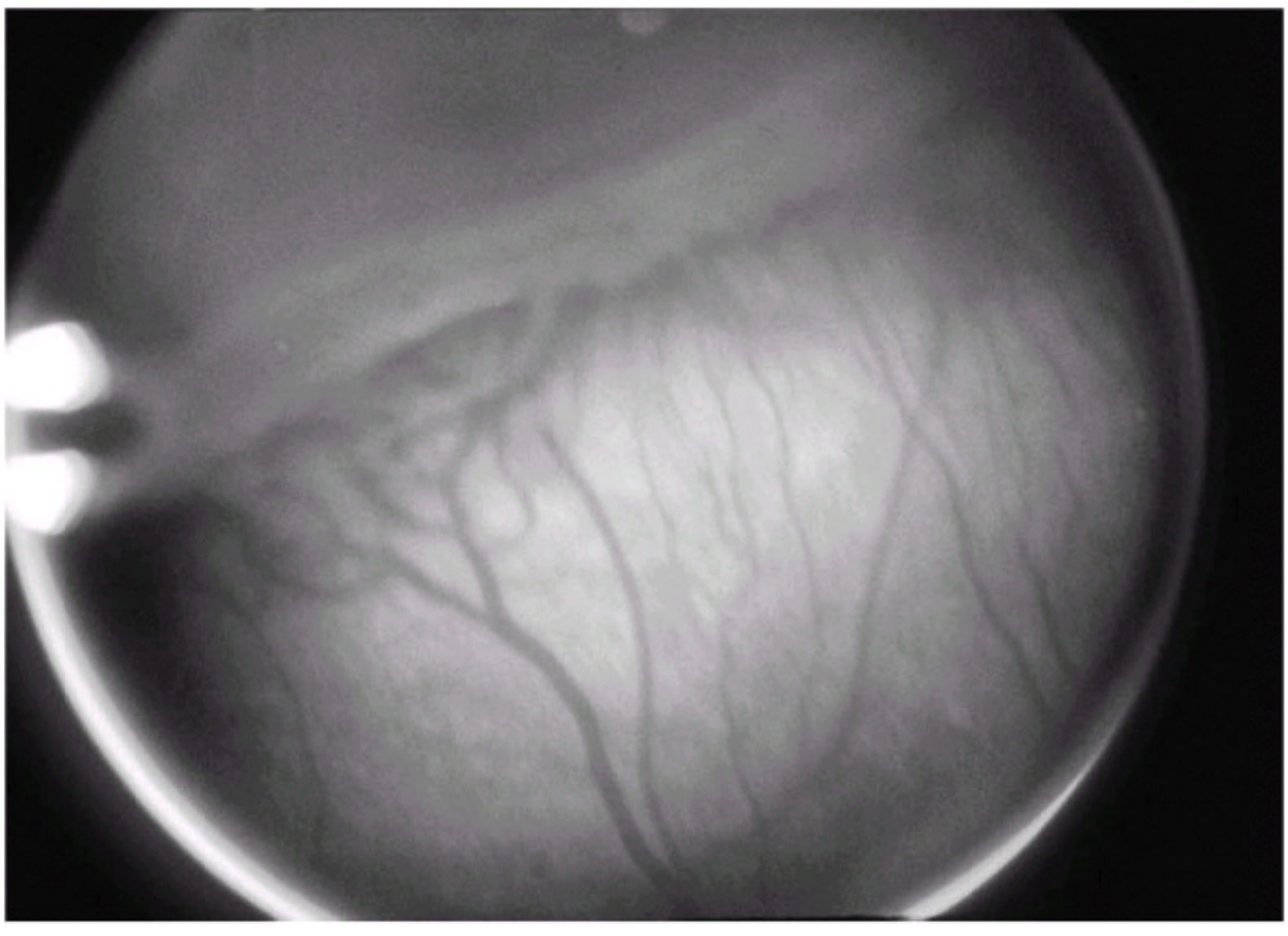

Figure 16.24 Stage 3 ROP ridge with extraretinal fibrovascular proliferation.

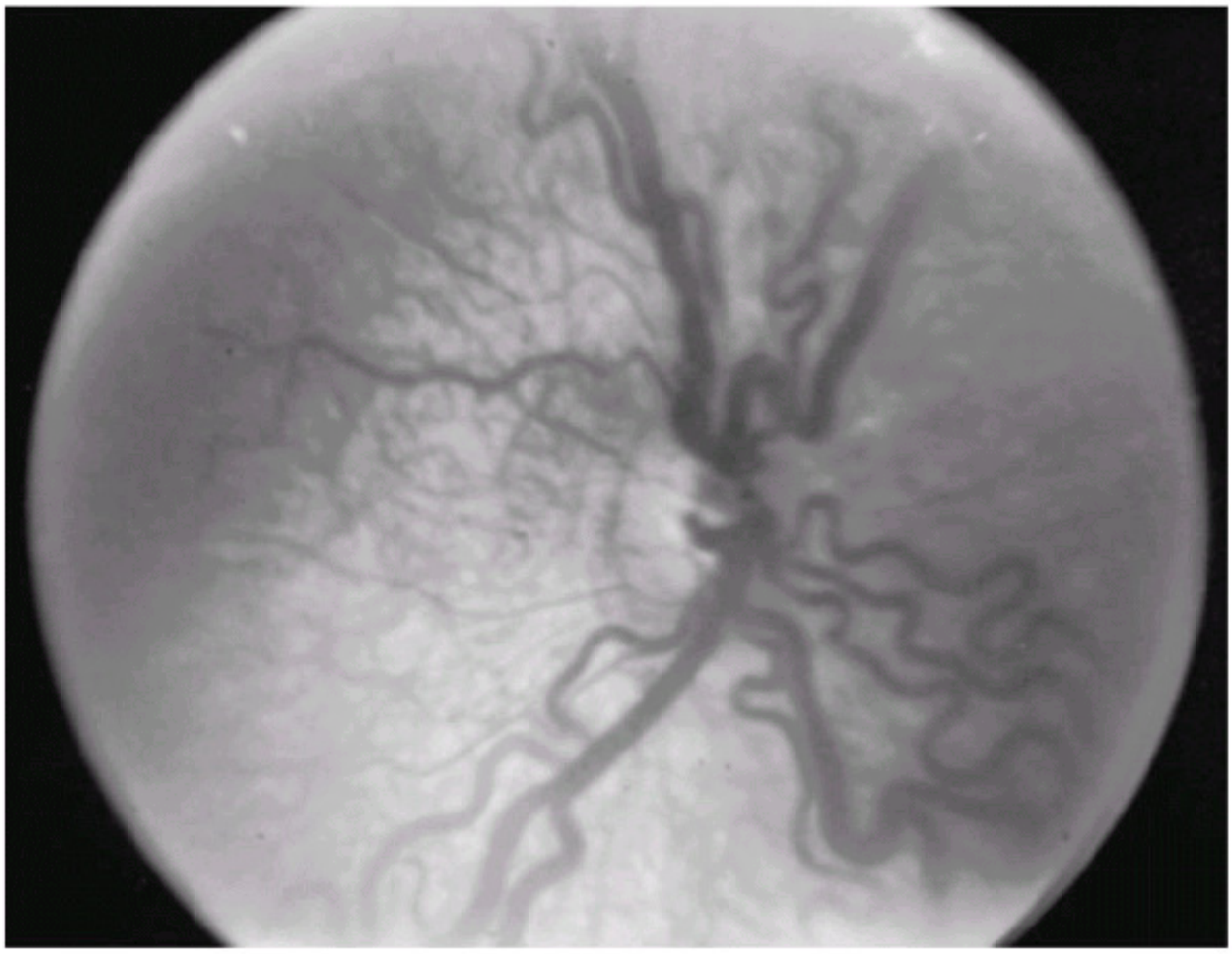

Figure 16.25 Tortuous and dilated retinal vasculature in plus disease.

Although the fundamental reason for failure of normal peripheral retinal vascularization to develop in the extrauterine environment of the premature infant is unknown, the clinical progression through the stages of ROP is well documented and shares many features with other retinal vascular disorders such as diabetes and venous occlusions. Initially, shunting of blood through dilated vascular channels occurs at the border of vascularized and nonvascularized retina. Peripheral retinal nonperfusion presumably alters the balance of growth and inhibitory factors within the eye, leading to development of neovascularization. Progressive traction leads to the end-stage sequelae of ROP, including retinal detachment, retinal fold, and vitreous hemorrhage.

The most severe expression of the acute phase of ROP usually occurs by 40 to 42 weeks postconceptional age. Regression is the most common outcome of ROP. In general, the more severe the acute changes, the more advanced the fundus changes during regression. The first sign of regression is usually growth of normal-appearing retinal vessels across the ridge into the anterior, avascular retina. Regression may take several months and in some cases, the retinal vessels fail to advance fully to the ora serrata. Associated with the International Classification is a list of common long-term sequelae of ROP (Table 16.3).

TABLE 16.2 STAGES OF RETINOPATHY OF PREMATURITY

Stage No.		Characteristic
1		Demarcation line
2		Ridge
3		Ridge with extraretinal fibrovascular proliferation
4		Subtotal retinal detachment
	A	Extrafoveal
	B	Retinal detachment including fovea
5		Total retinal detachment
	Funnel	
		Anterior
			Open
			Narrow
		Posterior
			Open
			Narrow

One of the most common findings associated with regressed ROP is myopia. In our experience, myopia occurs in more than 80% of children with regressed ROP, and is usually more than 6 diopters. It occurs early and falls into the congenital group of myopias. The condition may be noted within the first 2 months of life and may progress during the first 6 years. Although the cause is obscure, there appears to be a significant relationship between the degree of myopia and the severity of ROP. The myopia is most likely caused by forward displacement of the lens iris diaphragm rather than by increased axial length.

Retinal pigmentation alterations are common in regressed ROP and may be found in the posterior pole and the fundus periphery. Pigment clumping similar to that seen in hyperplasia of the pigment epithelium may occur,

as well as discrete patches characterized by loss of the pigment epithelium and outer sensory retinal layers.

TABLE 16.3 LONG-TERM SEQUELAE OF RETINOPATHY OF PREMATURITY

Peripheral Changes

Vascular

1. Failure to vascularize peripheral retina
2. Abnormal, nondichotomous branching of retinal vessels
3. Vascular arcades with circumferential interconnection
4. Telangiectatic vessels

Retinal

1. Pigmentary changes
2. Vitreoretinal interface changes
3. Thin retina
4. Peripheral folds
5. Vitreous membranes with or without attachment to retina
6. Lattice-like degeneration
7. Retinal breaks
8. Traction/rhegmatogenous retinal detachment

Posterior Changes

Vascular

1. Vascular tortuosity
2. Straightening of blood vessels in temporal arcade
3. Decrease in angle of insertion of major temporal arcade

Retinal

1. Pigmentary changes
2. Distortion and ectopia of macula
3. Stretching and folding of retina in macular region leading to periphery
4. Vitreoretinal interface changes
5. Vitreous membrane

5. Vitreous membrane

6. Dragging of retina over disc

7. Traction/rhegmatogenous retinal detachment

In mild regressed ROP, peripheral vitreous membranes develop anterior to the equator, especially on the temporal side. These may be present when there are no alterations in the posterior pole. However, the converse is not true. If posterior pole changes (e.g., dragging of the retina) are detected, peripheral changes will almost invariably be present.

Equatorial retinal folds usually occur between the equator and the ora serrata and may be the sole retinal finding consistent with regressed ROP. They are found at the location of the vascular demarcation line that was present during the active phase of ROP and are often associated with areas of retinal pigmentation. The retinal vessels cross the folds and travel anteriorly toward the ora serrata (Fig. 16.26).

Dragging of the retina is a hallmark of regressed ROP. In 80% of the cases, dragging or displacement is to the temporal side (Fig. 16.27). The macular displacement causes pseudoheterotopia.

Lattice-like degeneration occurs in 15% of patients with regressed ROP. This is considerably higher than the 6% to 7% incidence reported in the general population.

Retinal breaks associated with ROP tend to be primarily on the temporal side. Usually they are round or oval in shape and equatorial in location. They may occur in association with lattice degeneration. Marked equatorial folds indicative of severe vitreous traction are common just anterior to the breaks. Operculated tears have also been noted, as well as breaks close to the optic nerve and giant retinal tears. Retinal breaks and detachment secondary to ROP may occur many years after regression, even in adulthood. Thus, ROP is truly a lifelong disease and requires periodic fundus examination.

Treatment for ROP consists primarily of ablative therapy to the peripheral retina once funduscopic evidence of early proliferative changes develops. After several investigators reported positively on the use of cryotherapy for ROP, the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study (a multicenter, randomized trial) was performed to determine whether treatment was efficacious (88). Eligible patients included those with at least 5 contiguous or 8 cumulative clock hours of extraretinal fibrovascular proliferation in stage 3 ROP, zone I or II disease, and the presence of plus disease. Cryotherapy was then used to treat the entire anterior avascular retina back to the ridge. Treatment did not involve the ridge itself or the pars plana. An unfavorable result was defined as a macular fold, retinal detachment, or retrolental tissue.

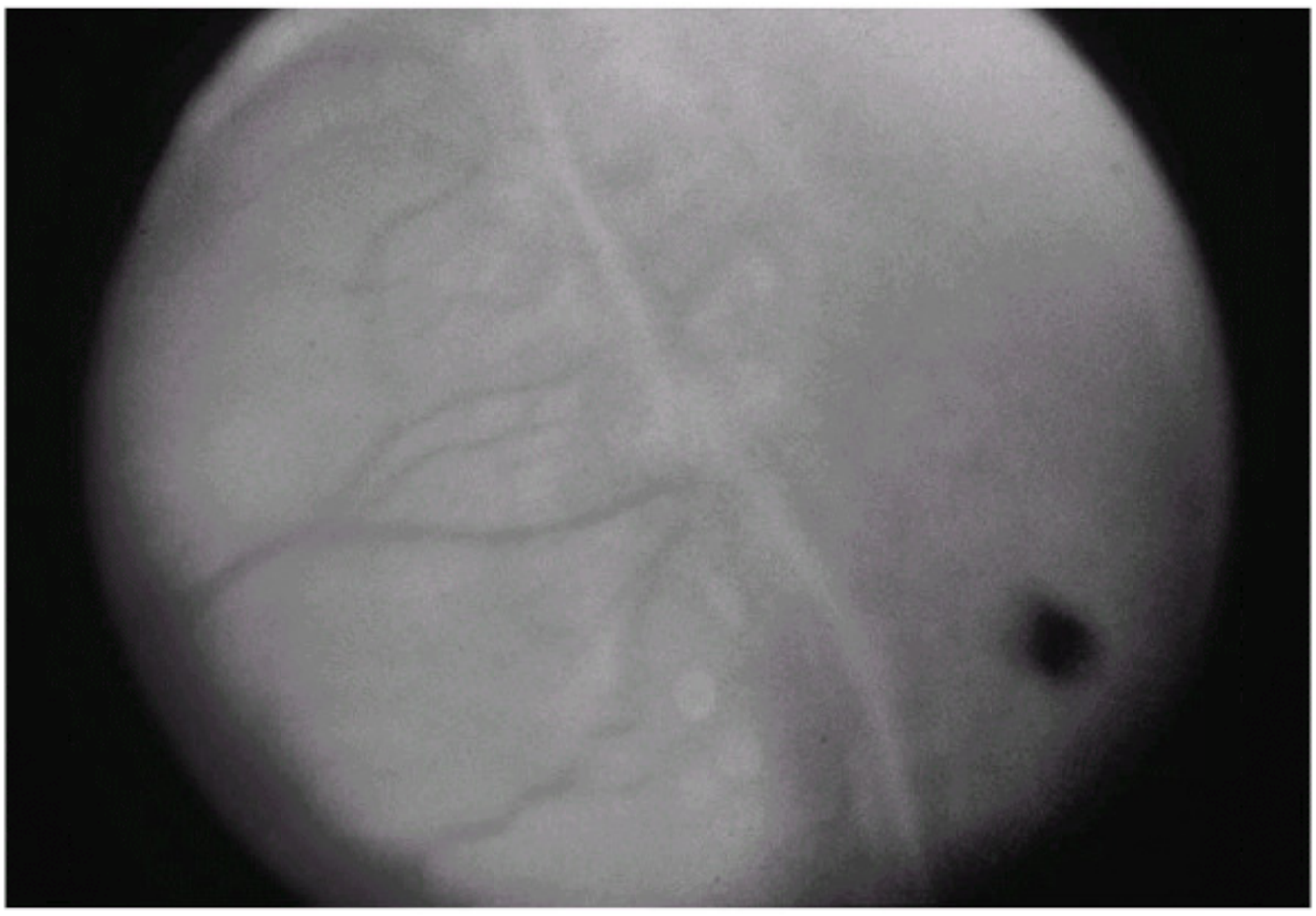

Figure 16.26 Regressing ROP showing retinal vessels growing past the vascular demarcation line toward the ora serrata.

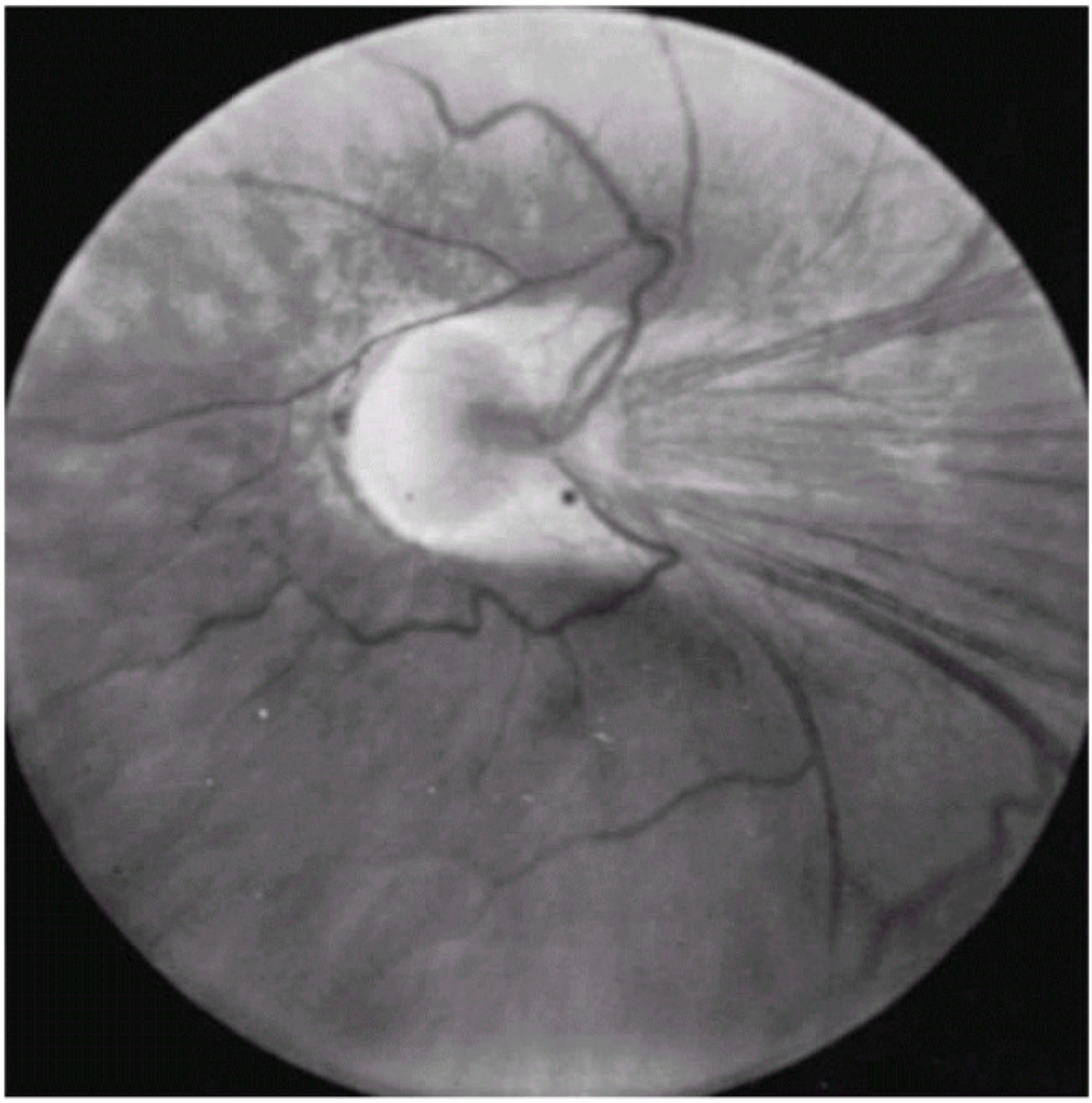

Figure 16.27 Dragging of the retina in a patient with cicatricial ROP.

The CRYO-ROP study revealed that an unfavorable outcome was significantly less common in eyes undergoing cryotherapy (22%) than in untreated eyes (43%) at 3 months follow-up (88). The benefit persisted after years of follow-up. Early anatomic results have been correlated with long-term visual results.

Indirect laser photocoagulation has produced comparable results in several reports and has gained favor, especially for treatment of zone I ROP. Although a few reports of cataract after laser therapy have appeared, the advantages of laser therapy, including ease of application, less physical stress to small infants, and less postoperative swelling, have led to its widespread use. In general, treatment is applied if CRYO-ROP threshold disease is reached; however, early treatment for posterior ROP may help to further reduce the unfavorable outcome rate.

In cases with an unfavorable outcome, surgical intervention may be considered. Cases with a macular fold or retrolental tissue are not good candidates for surgery. Scleral buckling is often successful, however, for stage 4 retinal detachments and shallow, “open funnel” stage 5 detachments. Vitrectomy, with or without removal of the lens, is often used for the more extensive detachments, sometimes with good anatomic result. Unfortunately, long-term follow-up reveals that useful vision frequently fails to develop even in eyes with a successful anatomic result. Therefore, prevention with prompt treatment for those eyes at risk of developing severe anatomic changes is critical.

Most recently, the Early Treatment for Retinopathy of Prematurity Randomized Trial (ETROP) demonstrated a reduction

of unfavorable outcomes in treatment of high-risk pre-threshold ROP compared with conventional treatment. The study compared functional and structural outcomes. Functional outcome was measured using visual acuity data obtained by the Teller acuity grating system at a 9-month follow-up (89).

The ETROP defined two groups of high-risk pre-threshold ROP. This classification was designed to identify infants with pre-threshold ROP who were at highest risks for unfavorable outcomes while minimizing treatment of eyes that were likely to spontaneously regress. Type 1 ROP was defined as (a) zone 1, any stage ROP with plus disease; (b) zone 1, stage 3 ROP with or without plus disease; and (c) zone 2, stage 2 or 3 ROP with plus disease. Plus disease required at least two quadrants (=6 clock hours) of dilation and tortuosity of the posterior retinal blood vessels. Type 2 ROP was defined as (a) zone 1, stage 1 or 2 ROP without plus disease, and (b) zone 2, stage 3 ROP without plus disease (89).

The ETROP treated all type 1 ROP with peripheral retinal ablation and observed type 2 ROP for regression of ROP or progression to type 1 ROP. The results showed a statistical significant reduction in both functional and structural outcomes with ablation of the avascular retina in high-risk pre-threshold ROP compared with conventional treatment. Unfavorable visual acuity outcomes were reduced from 19.5% to 14.5%, and unfavorable structural outcomes were reduced from 15.6% to 9.1%. Using these new criteria as the indication for treatment will result in many more infants being treated. The study recommendations are best interpreted as guidelines rather than identifying a rigid set of indications. Clinical judgment will continue to assist in determining the ideal time for intervention (89).

Familial Exudative Vitreoretinopathy

Criswick and Schepens (90) described a hereditary disease of the vitreous and retina that they termed “familial exudative vitreoretinopathy.” The striking feature on ophthalmoscopic examination is peripheral retinal exudation, which is subretinal and intraretinal and, unlike peripheral uveitis, occurs posterior to the ora serrata, most commonly on the temporal side. Occasionally, however, exudation is not present. Peripheral retinal nonperfusion, often with retinal neovascularization, is present. Unlike in ROP, no discrete ridge is present in FEVR. Typically, neovascularization appears as isolated tufts at a brush border between vascular and avascular retina. FEVR may be diagnosed shortly after birth but may not produce symptoms until early adulthood. Although evidence of the condition is invariably present bilaterally, marked asymmetry may be noted. In advanced cases, the vitreous cavity features organized membranes in all quadrants, both peripherally and centrally, that appear to be intimately bound to the retina. Localized retinal detachment, often forming a broad fold, usually extends temporally from the disc (Fig. 16.28). The ocular changes are slowly progressive and tend to run a downhill course, with increasing proliferation of blood vessels, increasing exudation, membrane formation, and retinal detachment.

Familial exudative vitreoretinopathy usually has an autosomal dominant mode of inheritance with incomplete penetrance. A family history is often not present, however. The condition may occur subclinically in relatives of symptomatic patients. In a review of three separate families with FEVR, 85% of those with the disorder were asymptomatic. In asymptomatic persons with the condition, the retina often has an avascular peripheral zone (Fig. 16.29). In some

pedigrees an X-linked inheritance pattern is suspected, and in some cases there is no family involvement and a new mutation is suspected as the source for the disease. Recently, the frizzled 4 (FZD4) gene mutation has been found in both autosomal and sporadic cases of FEVR (91). The mutant allele of FZD4 encodes a truncated protein that is retained in the endoplasmic reticulum and is linked to FEVR (92).

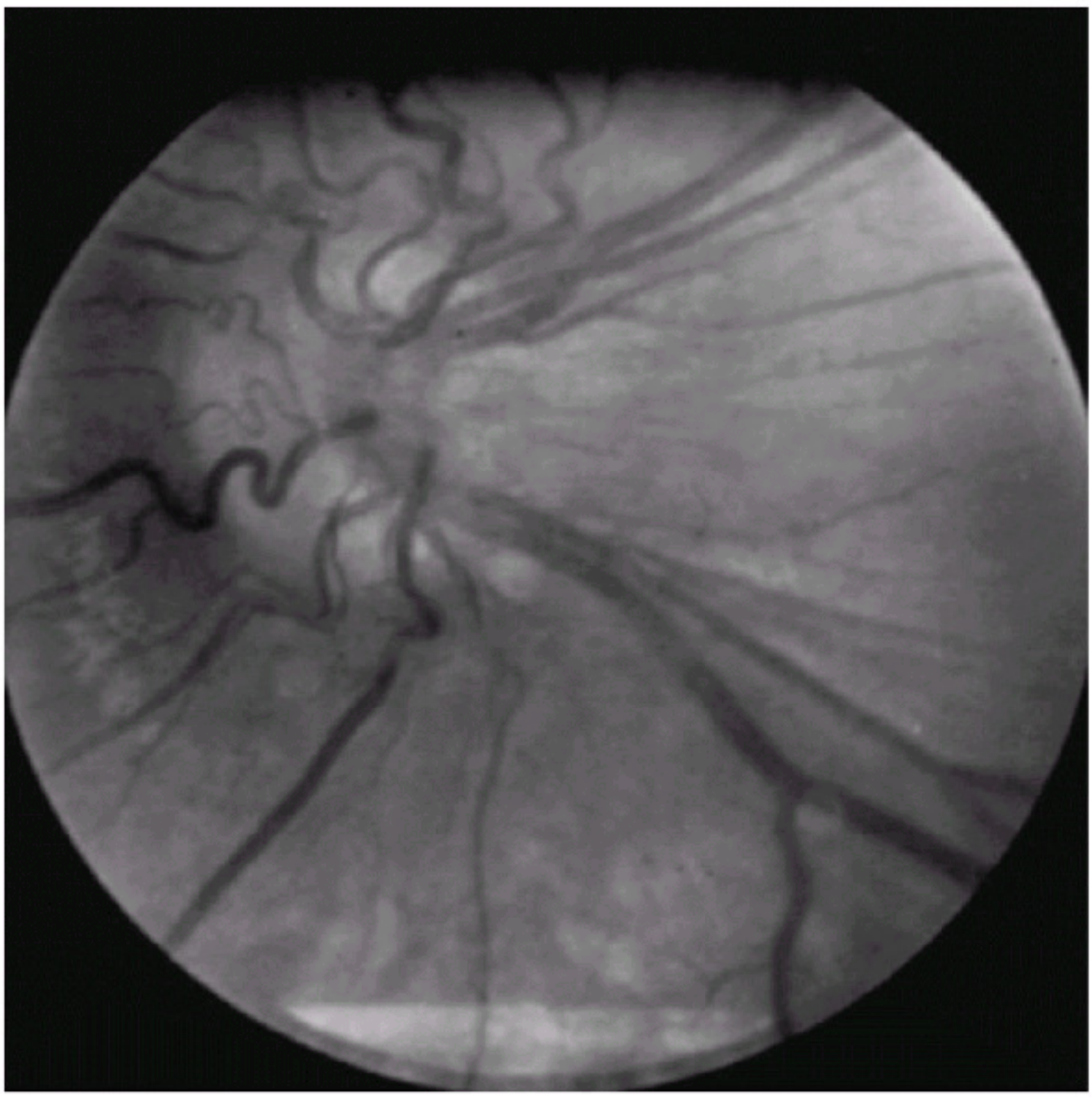

Figure 16.28 Dragging of the retina in a 6-year-old girl with familial exudative vitreoretinopathy (FEVR). This condition may simulate ROP (see Fig. 16.27).

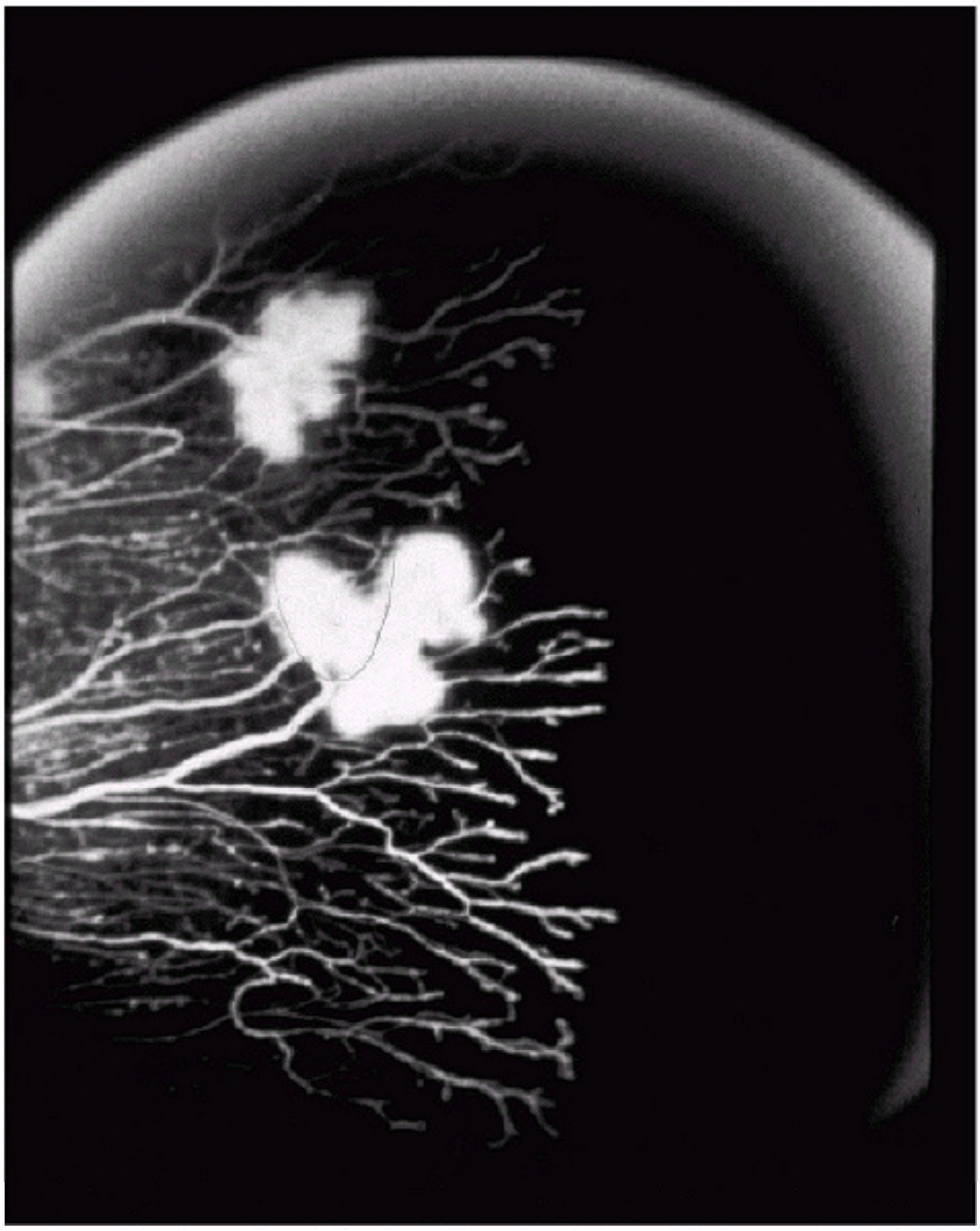

Figure 16.29 Avascular zone and retinal periphery of an asymptomatic man with FEVR.

The role of treatment with laser or cryotherapy during the proliferative phase of the disease has not been proven in a clinical trial. Some studies have shown a benefit of performing vitrectomy surgery for retinal detachments or vitreous hemorrhage (93,94).

The features of FEVR resemble those seen in ROP. It differs from ROP in that it is hereditary and there is no history of prematurity or oxygen therapy. The disorder may also resemble ROP, Norrie's disease, incontinentia pigmenti, Coats' disease, PHPV, retinoblastoma, nematode endophthalmitis, and peripheral uveitis.

Norrie's Disease

Norrie's disease is a bilateral X-linked recessive syndrome associated with degeneration of the ocular structures with auditory and mental impairment. The condition was first described by Norrie in 1935; Norrie's disease only affects males, and females are silent carriers. The penetrance is complete, which prevents unaffected males from passing this genetic defect to their offspring. The Norrie's disease gene has been localized to Xp11.3 and encodes a protein called norrin with unknown function (95). The gene for Norrie's disease has also been associated with the FEVR gene (96). Most cases demonstrate bilateral blindness observed at birth secondary to retinal detachments, PHPV, vitreous hemorrhage, iris atrophy, or corneal opacities. Eventually, these eyes progress to phthisis bulbi.

The systemic findings include mental retardation (60%) and hearing impairment (30%). The mental retardation is variable in progression. Sensorineural hearing loss appears in the second to fifth decade of life. The life span is normal duration. Treatment of the retinal detachment has not been successful in long-term retinal attachment rates or functional success. Prenatal testing has been used to exclude Norrie's disease in the male fetus of a high-risk carrier (97).

Incontinentia Pigmenti

Incontinentia pigmenti (Bloch-Sulzberger syndrome) is inherited as an X-linked dominant trait at gene locus Xq28. The NEMO gene, an NF ?B pathway gene deletion, accounts for 90% of new mutations (98). It is lethal in males. Peripheral retinal nonperfusion and neovascularization are the typical fundus features, similar to FEVR and ROP. The diagnosis is generally made by the associated findings, which include (a) skin vesicles in infancy on the trunk and extremities with later form areas of skin depigmentation (Figs. 16.30 and 16.31); (b) central nervous system defects such as cortical blindness, developmental delay, mental retardation, and spastic paralysis; (c) alopecia; and (d) incomplete dentition or pegged teeth (Fig. 16.32).

Other ophthalmologic features are strabismus, cataract, microphthalmia, optic nerve atrophy, iris hypoplasia, nystagmus, corneal opacities, retinal folds, and

macular ischemia (99,100,101).

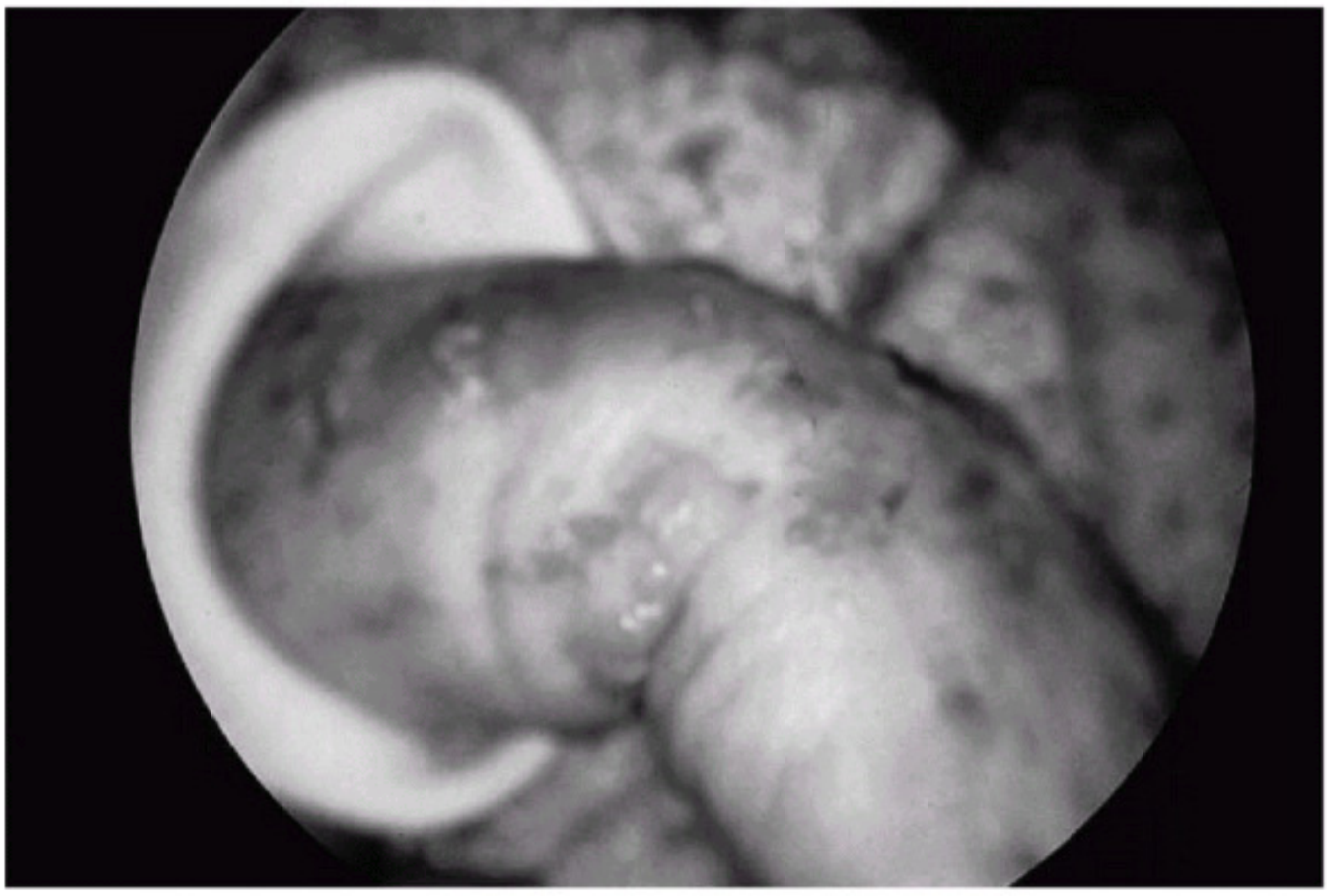

Figure 16.30 Incontinentia pigmenti skin vesicles on the arm of an infant.

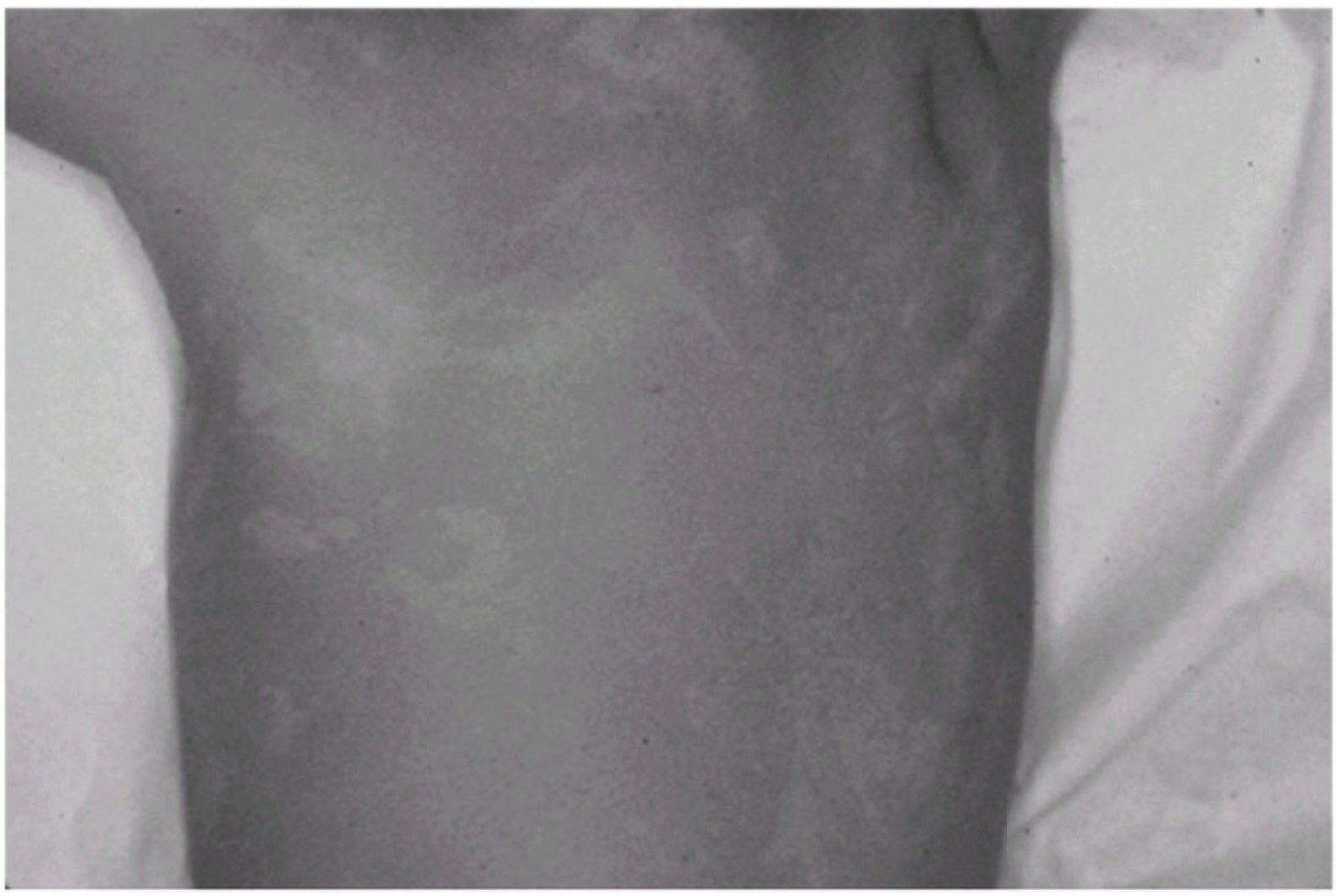

Figure 16.31 “Whorls” of skin depigmentation of the trunk of an incontinentia pigmenti patient.

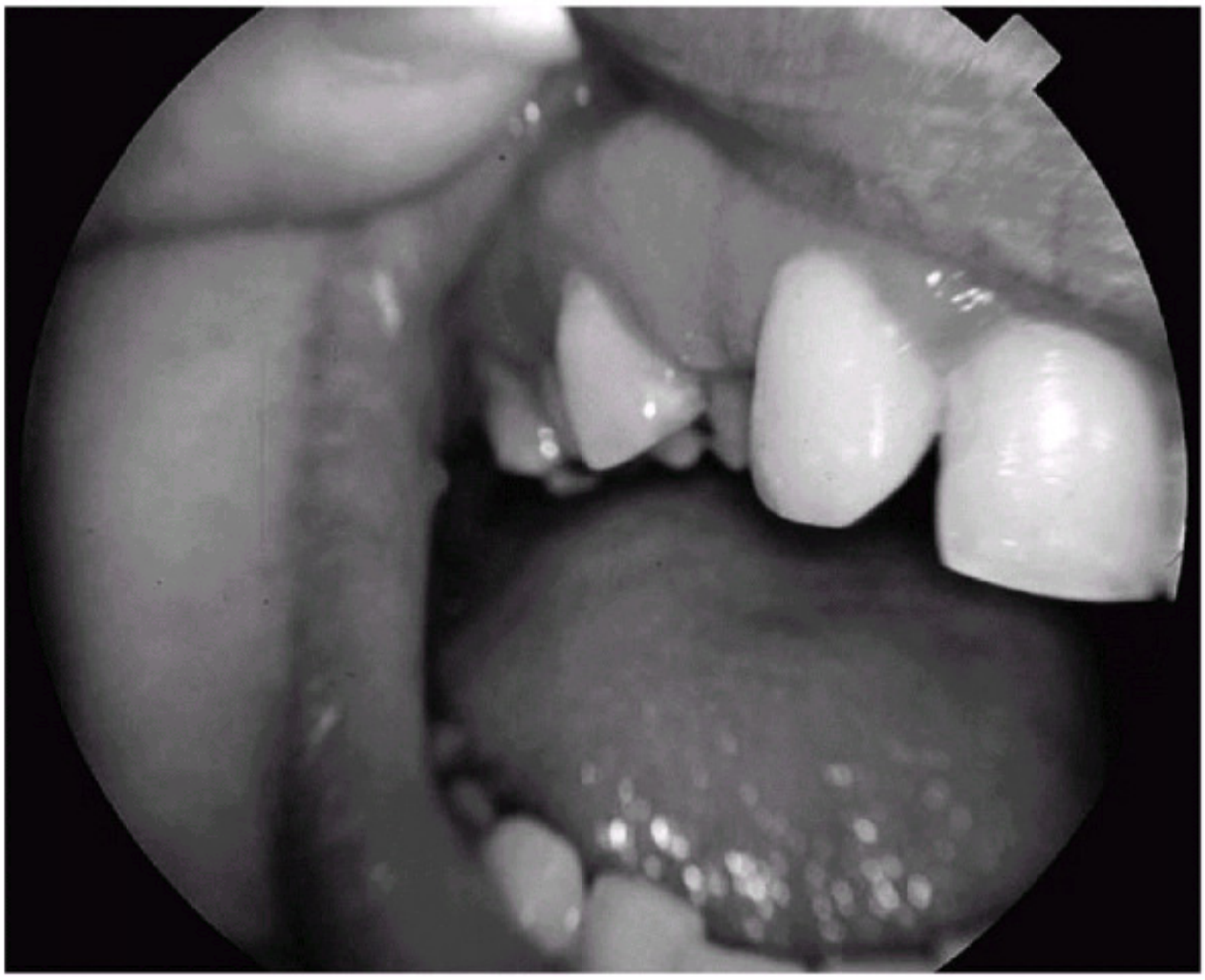

Figure 16.32 Peg-shaped tooth in a patient with incontinentia pigmenti.

The differential diagnosis of incontinentia pigmenti includes ROP, Norrie's disease, FEVR, Coats' disease, and PHPV. The management includes laser or cryotherapy for neovascularization and vitrectomy for retinal detachment (102,103).

Retinal Detachment

Primary rhegmatogenous retinal detachment is rare in children. Risk factors for retinal detachment include congenital or developmental structural ocular abnormalities, trauma, previous ophthalmic surgery, and preceding uveitis (104).

Traumatic retinal detachment occurs more often in males than in females. Blunt trauma and penetrating injuries can both cause detachment. However, in the case of blunt trauma there may be a latent period of months or even years between the injury and the diagnosis of detachment (105). This is understandable for two reasons: first, children are often reluctant to report an injury or symptom, and second, many traumatic detachments start inferiorly and do not cause a subjective awareness until the macula is threatened.

Because traumatic retinal detachments may initially be asymptomatic, one or more demarcation lines are often present. When found, these confirm a duration of at least several months. A multiplicity of demarcation lines indicates successive increases in the size of the detachment and is evidence that chorioretinal adhesions cannot be counted on to wall off a detachment. The detachments are seldom bullous but tend to be smooth and flat. Fixed star folds are rare, although they may occur, and intraretinal cysts may be present if the detachment is old. These disappear spontaneously in a few days if the retina reattaches after surgery.

Retinal detachment often results from a retinal dialysis, which tends to occur primarily in the inferotemporal and superonasal quadrants (Fig. 16.33). Sometimes the retina tears along both the anterior and posterior borders of the vitreous base; the base itself is avulsed and may hang like a pigmented loop in the vitreous cavity with its underlying strip of attached retina. Superonasal avulsion of the vitreous base is pathognomonic of traumatic retinal detachment.

Another form of traumatic peripheral retinal damage is extensive detachment of the ora serrata, with retinal breaks in the nonpigmented epithelium of the pars plana ciliaris along the anterior border of the vitreous base. Pars plana breaks appear as small or large dialyses and cannot usually be seen without scleral depression. Although the epithelium of the pars plana ciliaris is thin and may appear more translucent than the posterior retina, the difference in thickness may not be striking enough to permit identification of the ora serrata. The position of the ora, however, may be made more obvious by a variable amount of pigment that has been dragged from the underlying pigment epithelium. Another clue to the position of the ora is the presence of cystoid degeneration, which differentiates the extreme periphery of the retina from the epithelium of the pars plana. Traumatic retinal detachments with dialyses have a favorable surgical prognosis.

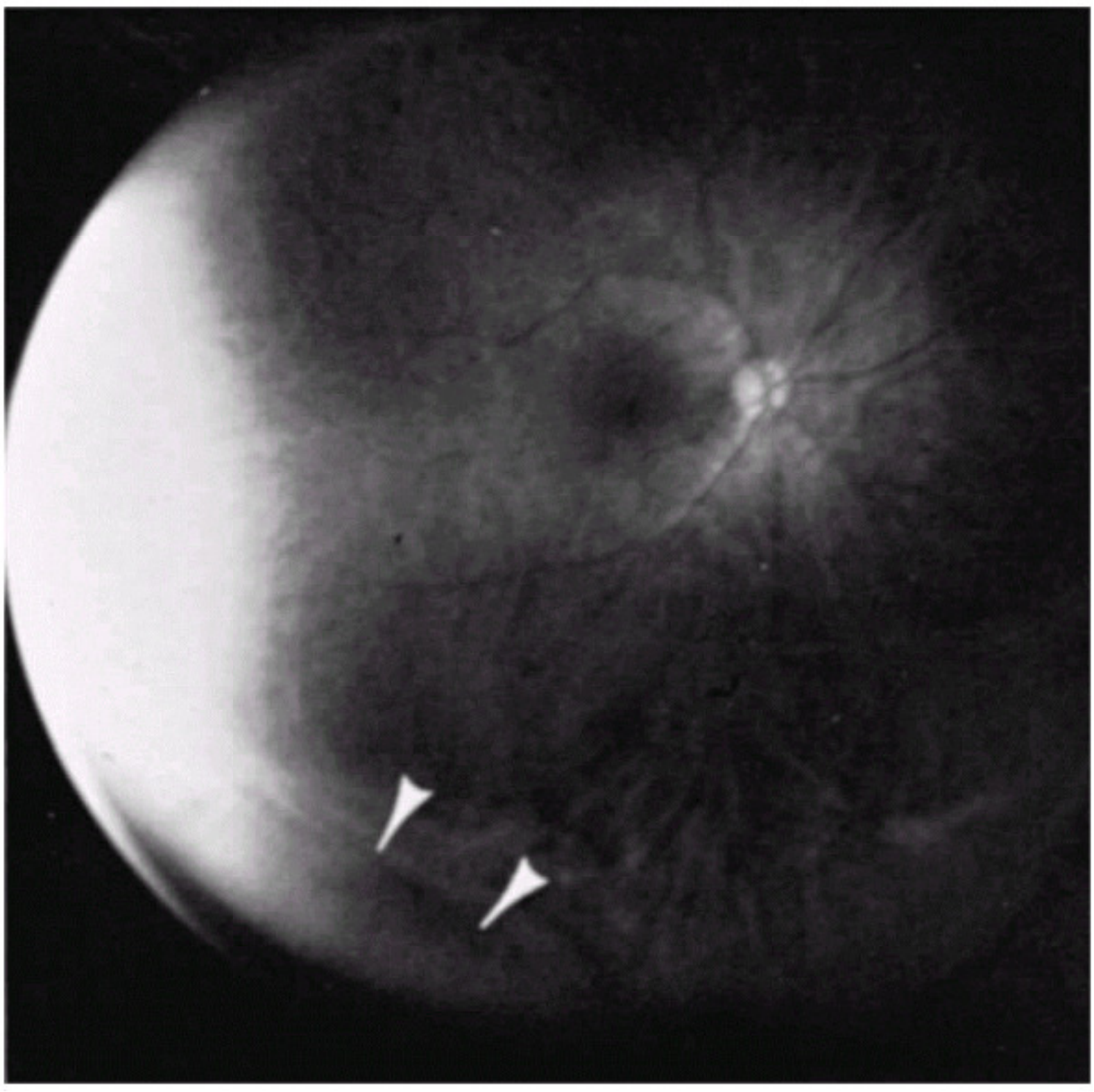

Figure 16.33 Inferior temporal retinal dialysis (*arrows*) in a young patient who had a retinal detachment in the fellow eye from dialysis.

REFERENCES

1. Ewing CC, Ives EJ. Juvenile hereditary retinoschisis. *Trans Ophthalmol Soc U K* 1970;89:29-39.

2. Yanoff M, Kertesz Rahn E, Zimmerman LE. Histopathology of juvenile retinoschisis. *Arch Ophthalmol* 1968;79(1):49-53.

3. Harris GS, Yeung J. Maculopathy of sex-linked juvenile retinoschisis. *Can J Ophthalmol* 1976;11(1):1-10.

4. Ozdemir H, Karacorlu S, Karacorlu M. Optical coherence tomography findings in familial foveal retinoschisis. *Am J Ophthalmol* 2004;137(1):179-181.

5. Krill AE, Deutman AF. The various categories of juvenile macular degeneration. *Trans Am Ophthalmol Soc* 1972;70:220-245.

6. Fishman GA, Jampol LM, Goldberg MF. Diagnostic features of the Favre-Goldmann syndrome. *Br J Ophthalmol* 1976;60(5): 345-353.

7. Mooy CM, Van Den Born LI, Baarsma S, et al. Hereditary X-linked juvenile retinoschisis: a review of the role of Muller cells. *Arch Ophthalmol* 2002;120(7):979-984.

8. Kaplan J, Pelet A, Hentati H, et al. Contribution to carrier detection and genetic counseling in X linked retinoschisis. *J Med Genet* 1991;28(6):383-388.

9. Sauer CG, Gehrig A, Warneke-Wittstock R, et al. Positional cloning of the gene associated with X-linked juvenile retinoschisis. *Nat Genet*

1997;17(2):164-170.

10. Bergen AA, ten Brink JB, van Schooneveld MJ. Efficient DNA carrier detection in X linked juvenile retinoschisis. *Br J Ophthalmol* 1995;79(7):683-686.

11. Stickler GB, Belau PG, Farrell FJ, et al. Hereditary progressive arthro-ophthalmopathy. *Mayo Clin Proc* 1965;40:433-455.

12. Opitz JM. Ocular anomalies in malformation syndromes. *Trans Am Acad Ophthalmol Otolaryngol* 1972;76(5):1193-1202.

13. Ahmad NN, McDonald-McGinn DM, Dixon P, et al. PCR assay confirms diagnosis in syndrome with variably expressed phenotype: mutation detection in Stickler syndrome. *J Med Genet* 1996; 33(8):678-681.

14. Wagner H. Ein Bisher unbekanntes Erbleiden des Auges (degeneratio hyaloideo-retinalis hereditaria) beobachtet im Kanton Zurich. *Klin Monatsbl Augenheilkd* 1938;100:840.

15. Maumenee IH. Vitreoretinal degeneration as a sign of generalized connective tissue diseases. *Am J Ophthalmol* 1979;88(3 Pt 1):432-449.

16. Zech JC, Morle L, Vincent P, et al. Wagner vitreoretinal degeneration with genetic linkage refinement on chromosome 5q13-q14. *Graefes Arch Clin Exp Ophthalmol* 1999;237(5):387-393.

17. Favre M. [Two cases of hyaloid-retinal degeneration.] *Ophthalmologica* 1958;135(5-6):604-609.

18. Franceschetti A. A special form of tapetoretinal degeneration: fundus flavimaculatus. *Trans Am Acad Ophthalmol Otolaryngol* 1965;69(6):1048-1053.

19. Fish G, Grey R, Sehmi KS, et al. The dark choroid in posterior retinal dystrophies. *Br J Ophthalmol* 1981;65(5):359-363.

20. Fishman GA, Farber M, Patel BS, et al. Visual acuity loss in patients with Stargardt's macular dystrophy. *Ophthalmology* 1987; 94(7):809-814.

21. Stargardt K. Ueber familiare, progressive degeneration in der Makulagegend des Auges. *Albrecht von Graefes Arch Klin Exp Ophthal* 1909;71:534-549.

22. Noble KG, Carr RE. Stargardt's disease and fundus flavimaculatus. *Arch Ophthalmol* 1979;97(7):1281-1285.

23. Allikmets R, Singh N, Sun H, et al. A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. *Nat Genet* 1997;15(3):236-246.

24. Glazer LC, Dryja TP. Understanding the etiology of Stargardt's disease. *Ophthalmol Clin North Am* 2002;15(1):93-100, viii.

25. Eagle RC Jr, Lucier AC, Bernardino VB Jr, et al. Retinal pigment epithelial abnormalities in fundus flavimaculatus: a light and electron microscopic study. *Ophthalmology* 1980;87(12): 1189-1200.

26. Best F. Uber eine hereditare Macullaffektoin: Beitrage zur Vererbungslere. *Z Augenheilkd* 1905;13:199.

27. Cavender JC. Best's macular dystrophy. *Arch Ophthalmol* 1982; 100(7):1067.

28. Pierro L, Tremolada G, Introini U, et al. Optical coherence tomography findings in adult-onset foveomacular vitelliform dystrophy. *Am J Ophthalmol* 2002;134(5):675-680.

29. Braley AE. Dystrophy of the macula. *Am J Ophthalmol* 1966; 61(1):1-24.

30. Deutman AF. Electro-oculography in families with vitelliform dystrophy of the fovea. Detection of the carrier state. *Arch Ophthalmol* 1969;81(3):305-316.

31. Francois J. Vitelliform degeneration of the macula. *Bull N Y Acad Med* 1968;44(1):18-27.

32. Weingeist TA, Kobrin JL, Watzke RC. Histopathology of Best's macular dystrophy. *Arch Ophthalmol* 1982;100(7):1108-1114.

33. Bakall B, Marknell T, Ingvast S, et al. The mutation spectrum of the bestrophin protein—functional implications. *Hum Genet* 1999;104(5):383-389.

34. Krill AE. *Hereditary retinal and choroidal diseases.* Vol. 2. Hagerstown, MD: Harper & Row, 1977:1299-1338.

35. Dryja TP. Molecular genetics of Oguchi disease, fundus albipunctatus, and other forms of stationary night blindness: LVII Edward Jackson Memorial Lecture. *Am J Ophthalmol* 2000;130(5): 547-563.

36. Carr RE. Congenital stationary nightblindness. *Trans Am Ophthalmol Soc* 1974;72:448-487.

37. Carr RE, Gouras P. Oguchi's disease. *Arch Ophthalmol* 1965;73: 646-656.

38. Mizuo A. On new discovery in dark adaptation in Oguchi's disease. *Acta Soc Ophthalmol Jpn* 1913;17:1148.

39. Nakazawa M, Wada Y, Fuchs S, et al. Oguchi disease: phenotypic characteristics of patients with the frequent 1147delA mutation in the arrestin gene. *Retina* 1997;17(1):17-22.

40. Wilder H. Oguchi's disease. *Am J Ophthalmol* 1953;36(5): 718-719.

41. Oguchi C. Über die eigenartige Hemeralopie mit diftuser weissgraulicher Verfarbung des Augenhintergrundes. *Albrecht von Graefes Arch Ophthalmol* 1912(81):109.

42. Lauber H. Die sogenannte retinitis punctata albescens. *Klin Monatsbl Augenheilkd* 1910;48:133.

43. Carr RE, Margolis S, Siegel IM. Fluorescein angiography and vitamin A and oxalate levels in fundus albipunctatus. *Am J Ophthalmol* 1976;82(4):549-558.

44. Gelber PJ, Shah A. Fluorescein study of albipunctate dystrophy. Report of a case. *Arch Ophthalmol* 1969;81(2):164-169.

45. Levy NS, Toskes PP. Fundus albipunctatus and vitamin A deficiency. *Am J Ophthalmol* 1974;78(6):926-929.

46. Kajiwara K, Sandberg MA, Berson EL, et al. A null mutation in the human peripherin/RDS gene in a family with autosomal dominant retinitis punctata albescens. *Nat Genet* 1993;3(3): 208-212.

47. Burstedt MS, Sandgren O, Holmgren G, et al. Bothnia dystrophy caused by mutations in the cellular retinaldehyde-binding protein gene (RLBP1) on chromosome 15q26. *Invest Ophthalmol Vis Sci* 1999;40(5):995-1000.

48. Goldberg MF. Persistent fetal vasculature (PFV): an integrated interpretation of signs and symptoms associated with persistent hyperplastic primary vitreous (PHPV). LIV Edward Jackson Memorial Lecture. *Am J Ophthalmol* 1997;124(5):587-626.

49. Gulati N, Eagle RC Jr, Tasman W. Unoperated eyes with persistent fetal vasculature. *Trans Am Ophthalmol Soc* 2003;101:59-64; discussion 64-65.

50. Coats G. Forms of retinal disease with massive exudation. *R Lond Ophthalmol Hosp Rep* 1908;17:440-525.

51. Kolb H, Gouras P. Electron microscopic observations of human retinitis pigmentosa, dominantly inherited. *Invest Ophthalmol* 1974;13(7):487-498.

52. Ammann F, Klein D, Franceschetti A. Genetic and epidemiological investigations on pigmentary degeneration of the retina and allied disorders in Switzerland. *J Neurol Sci* 1965;2(2):183-196.

53. Bird AC. Retinal photoreceptor dystrophies LI. Edward Jackson Memorial Lecture. *Am J Ophthalmol* 1995;119(5):543-562.

54. Bird AC. X-linked retinitis pigmentosa. *Br J Ophthalmol* 1975; 59(4):177-199.

55. Blumel J, Kniker WT. Laurence-Moon-Bardet-Biedl syndrome: review of the literature and a report of five cases including a family group with three affected males. *Tex Rep Biol Med* 1959; 17:391-410.

56. Ackerman J, Brody PE, Kanarek I, et al. Macular wrinkling and atypical retinitis pigmentosa in Laurence-Moon-Biedl-Bardet syndrome. *Ann Ophthalmol* 1980;12:632.

57. Campo RV, Aaberg TM. Ocular and systemic manifestations of the Bardet-Biedl syndrome. *Am J Ophthalmol* 1982;94(6): 750-756.

58. Refsum S. Heredopathia atactica polyneuritiformis phytanic acid storage disease (Refsum's disease) with particular reference to ophthalmological disturbances. *Metab Ophthalmol* 1977;1:73.

59. Weleber RG, Tongue AC, Kennaway NG, et al. Ophthalmic manifestations of infantile phytanic acid storage disease. *Arch Ophthalmol* 1984;102(9):1317-1321.

60. Refsum S. Heredopathia atactica polyneuritiformis: a familial syndrome not hitherto described, a contribution to the clinical study of the hereditary diseases of the nervous system. *Acta Psychiatr Neurol* 1946;38(Suppl):1.

61. Cogan DG, Rodrigues M, Chu FC, et al. Ocular abnormalities in abetalipoproteinemia. A clinicopathologic correlation. *Ophthalmology* 1984;91(8):991-998.

62. Bishara S, Merin S, Cooper M, et al. Combined vitamin A and E therapy prevents retinal electrophysiological deterioration in abetalipoproteinaemia. *Br J Ophthalmol* 1982;66(12):767-770.

63. Bassen FA, Kornzweig AL. Malformation of the erythrocytes in a case of atypical retinitis pigmentosa. *Blooc* 1950;5:381.

64. Francois J. Leber's congenital tapetoretinal degeneration. *Int Ophthalmol Clin* 1968;8(4):929-947.

65. Schroeder R, Mets MB, Maumenee IH. Leber's congenital amaurosis. Retrospective review of 43 cases and a new fundus finding in two cases. *Arch Ophthalmol* 1987;105(3):356-359.

66. Franceschetti A, Dieterle P. [Diagnostic and prognostic importance of the electroretinogram in tapetoretinal degeneration with reduction of the visual field and hemeralopia.] *Confin Neurol* 1954;14(2-3):184-186.

67. Batten FE. Cerebral degeneration with symmetrical changes in the maculae in two members of a family. *Trans Ophthalmol Soc U K* 1903;23:386.

68. Bietti G. Uber familiärs Vorkommen von “Retinitis punctata albescens” (verbunden mit “Dystrophia marginalis cristallinea corneae”). Glitzern des Glask ärpers und anderen degeneration Augenveränderungen. *Klin Monatsbl Augenheilkd* 1937;99: 737-756.

69. Jiao X, Munier FL, Iwata F, et al. Genetic linkage of Bietti crystallin corneoretinal dystrophy to chromosome 4q35. *Am J Hum Genet* 2000;67(5):1309-1313.

70. Berson EL, Gouras P, Gunkel RD. Progressive cone-rod degeneration. *Arch Ophthalmol* 1968;80(1):68-76.

71. Franceschetti A, Francois J, Bobel J. *Choroidal heredodegenerations.* Springfield, IL: Charles C Thomas, 1974.

72. Mauthner L. Ein Fall von Choroideremia. *Berd Naturw Med Ver Innsbruch* 1871;2:191.

73. van Bokhoven H, van den Hurk JA, Bogerd L, et al. Cloning and characterization of the human choroideremia gene. *Hum Mol Genet* 1994;3(7):1041-1046.

74. MacDonald IM, Mah DY, Ho YK, et al. A practical diagnostic test for choroideremia. *Ophthalmology* 1998;105(9):1637-1640.

75. Kurstjens JH. Choroideremia and gyrate atrophy of the choroid and retina. *Doc Ophthalmol* 1965;19:1.

76. Rubin ML, Fishman RS, McKay RA. Choroideremia. Study of a family and literature review. *Arch Ophthalmol* 1966;76(4): 563-574.

77. McCulloch C, Marliss EB. Gyrate atrophy of the choroid and retina: clinical, ophthalmologic, and biochemical considerations. *Trans Am Ophthalmol Soc* 1975;73:153-171.

78. Mitchell GA, Looney JE, Brody LC, et al. Human ornithine-deltaaminotransferase. cDNA cloning and analysis of the structural gene. *J Biol Chem* 1988;263(28):14288-14295.

79. Takki K. Gyrate atrophy of the choroid and retina associated with hyperornithinemia. *Br J Ophthalmol* 1974;58(1):3-23.

80. Kaiser-Kupfer MI, de Monasterio F, Valle D, et al. Visual results of a long-term trial of a low-arginine diet in gyrate atrophy of choroid and retina. *Ophthalmology* 1981;88(4):307-310.

81. Garner A, Jay BS. Macromelanosomes in X-linked ocular albinism. *Histopathology* 1980;4(3):243-254.

82. Fulton AB, Albert DM, Craft JL. Human albinism. Light and electron microscopy study. *Arch Ophthalmol* 1978;96(2):305-310.

83. Meyer CH, Lapolice DJ, Freedman SF. Foveal hypoplasia in oculocutaneous albinism demonstrated by optical coherence tomography. *Am J Ophthalmol* 2002;133(3):409-410.

84. O'Donnell FEJ, Green WR. The eye of albinism. In: Duane TD, ed. *Clinical Ophthalmology.* New York: Harper & Row; 1979, 1-24.

85. Spencer WH, Hogan MJ. Ocular manifestations of Chediak-Higashi syndrome: report of a case with histopathologic examination of ocular tissues. *Am J Ophthalmol* 1960;50:1197.

86. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. *Arch Ophthalmol* 1984;102(8):1130-1134.

87. An international classification of retinopathy of prematurity. II. The classification of retinal detachment. The International Committee for the Classification of the Late Stages of Retinopathy of Prematurity. *Arch Ophthalmol* 1987;105(7):906-912.

88. Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Arch*

Ophthalmol 1988;106(4):471-479.

89. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol* 2003;121(12): 1684-1694.

90. Criswick VG, Schepens CL. Familial exudative vitreoretinopathy. *Am J Ophthalmol* 1969;68(4):578-594.

91. Kondo H, Hayashi H, Oshima K, et al. Frizzled 4 gene (FZD4) mutations in patients with familial exudative vitreoretinopathy with variable expressivity. *Br J Ophthalmol* 2003;87(10):1291-1295.

92. Kaykas A, Yang-Snyder J, Heroux M, et al. Mutant frizzled 4 associated with vitreoretinopathy traps wild-type frizzled in the endoplasmic reticulum by oligomerization. *Nat Cell Biol* 2004; 6(1):52-58. Epub 2003 Dec 14.

93. Pendergast SD, Trese MT. Familial exudative vitreoretinopathy. Results of surgical management. *Ophthalmology* 1998;105(6): 1015-1023.

94. Ikeda T, Fujikado T, Tano Y, et al. Vitrectomy for rhegmatogenous or tractional retinal detachment with familial exudative vitreoretinopathy. *Ophthalmology* 1999;106(6):1081-1085.

95. Berger W, Meindl A, van de Pol T, et al. Isolation of a candidate gene for Norrie disease b positional cloning. *Nat Genet* 1992(1): 199-203.

96. Chen Z, Battinelli EM, Hendriks RW. Norrie disease gene: characterization of deletions and possible function. *Genomics* 1993;16: 533-535.

97. Redmond RM, Graham CA, Kelly ED, et al. Prenatal exclusion of Norrie's disease. *Br J Ophthalmol* 1992;76(8):491-493.

98. Aradhya S, Woffendin H, Jakins T, et al. A recurrent deletion in the ubiquitously expressed NEMO (IKK-gamma) gene accounts for the vast majority of incontinentia pigmenti mutations. *Hum Mol Genet* 2001;10(19):2171-2179.

99. Goldberg MF. The blinding mechanisms of incontinentia pigmenti. *Trans Am Ophthalmol Soc* 1994;92:167-176; discussion 176-179.

100. Holmstrom G, Thoren K. Ocular manifestations of incontinentia pigmenti. *Acta Ophthalmol Scand* 2000;78(3):348-353.

101. Goldberg MF. Macular vasculopathy and its evolution in incontinentia pigmenti. *Ophthalmic Genet* 1998;19(3):141-148.

102. Nguyen JK, Brady-Mccreery KM. Laser photocoagulation in preproliferative retinopathy of incontinentia pigmenti. *J AAPOS* 2001;5(4):258-259.

103. Wald KJ, Mehta MC, Katsumi O, et al. Retinal detachments in incontinentia pigmenti. *Arch Ophthalmol* 1993;111(5):614-617.

104. Weinberg DV, Lyon AT, Greenwald MJ, et al. Rhegmatogenous retinal detachments in children: risk factors and surgical outcomes. *Ophthalmology* 2003;110(9):1708-1713.

105. Cox MS, Schepens CL, Freeman HM. Retinal detachment due to ocular contusion. *Arch Ophthalmol* 1966;76(5):678-685.

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17

Congenital Abnormalities of the Optic Disc

Gary C. Brown

Melissa M. Brown

VASCULAR ANOMALIES OF THE OPTIC DISC

Prepapillary Vascular Loops

First described by Liebrich in 1871 (1), prepapillary vascular loops were originally thought to be remnants of an incompletely regressed hyaloid system. Most evidence now suggests that they occur as a separate entity (2,3,4). Despite the fact that some of these anomalies appear dark and venous, approximately 95% of prepapillary loops are arterial (3).

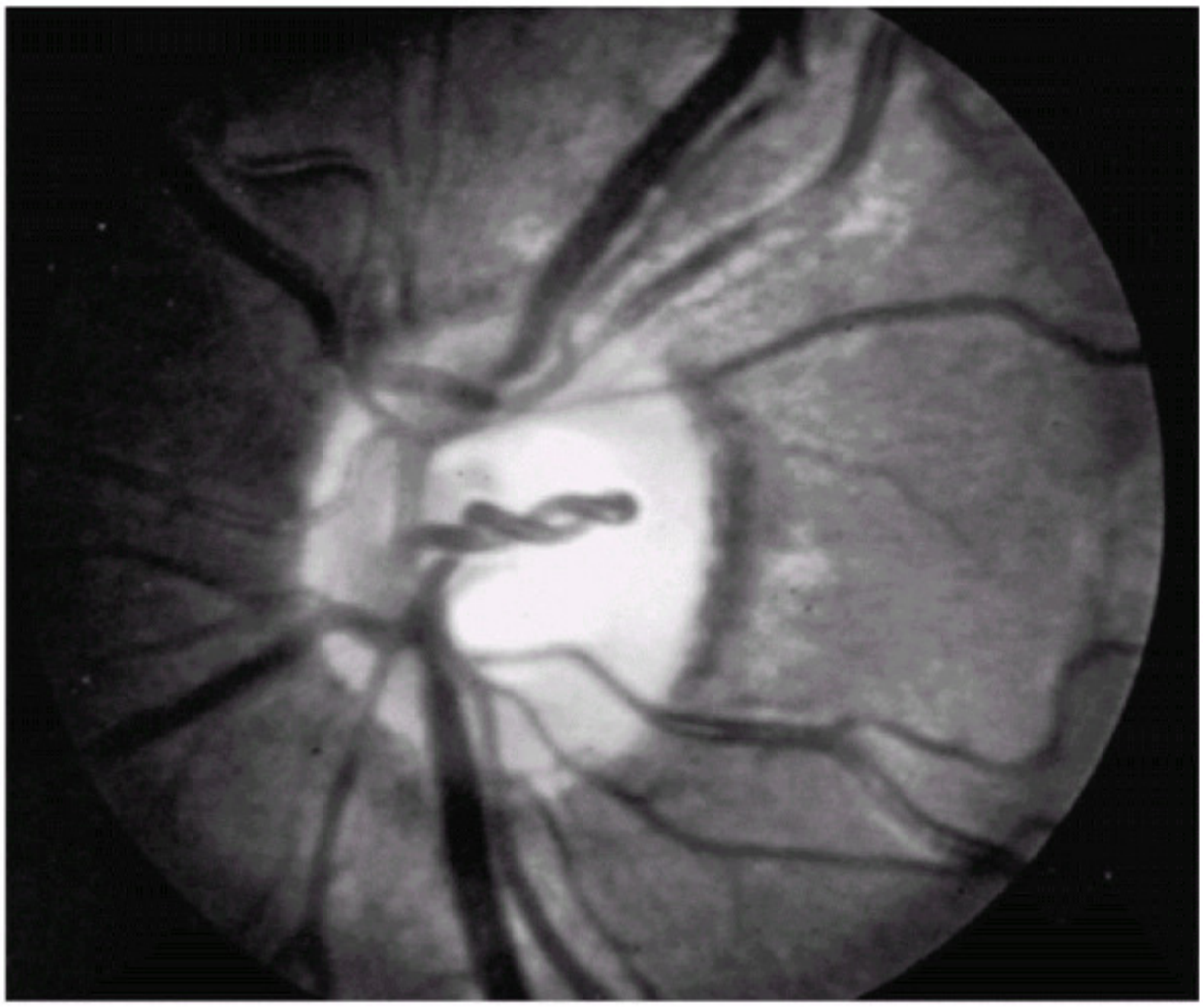

Figure 17.1 Congenital prepapillary arterial loop with a corkscrew configuration.

Clinically, the vessels appear as loops that extend from the optic disc into the vitreous cavity and then back to the disc (Fig. 17.1). In contrast with a single hyaloid artery, each prepapillary loop has at least one ascending and one descending branch. Loops can assume a spiral or corkscrew shape, have a figure-of-eight appearance, or manifest with a simple hairpin turn configuration (3). Spontaneous movement, coincident with the heartbeat, is seen in approximately half of the cases, whereas approximately 30% are encased by a white, glial-appearing sheath (Fig. 17.2).

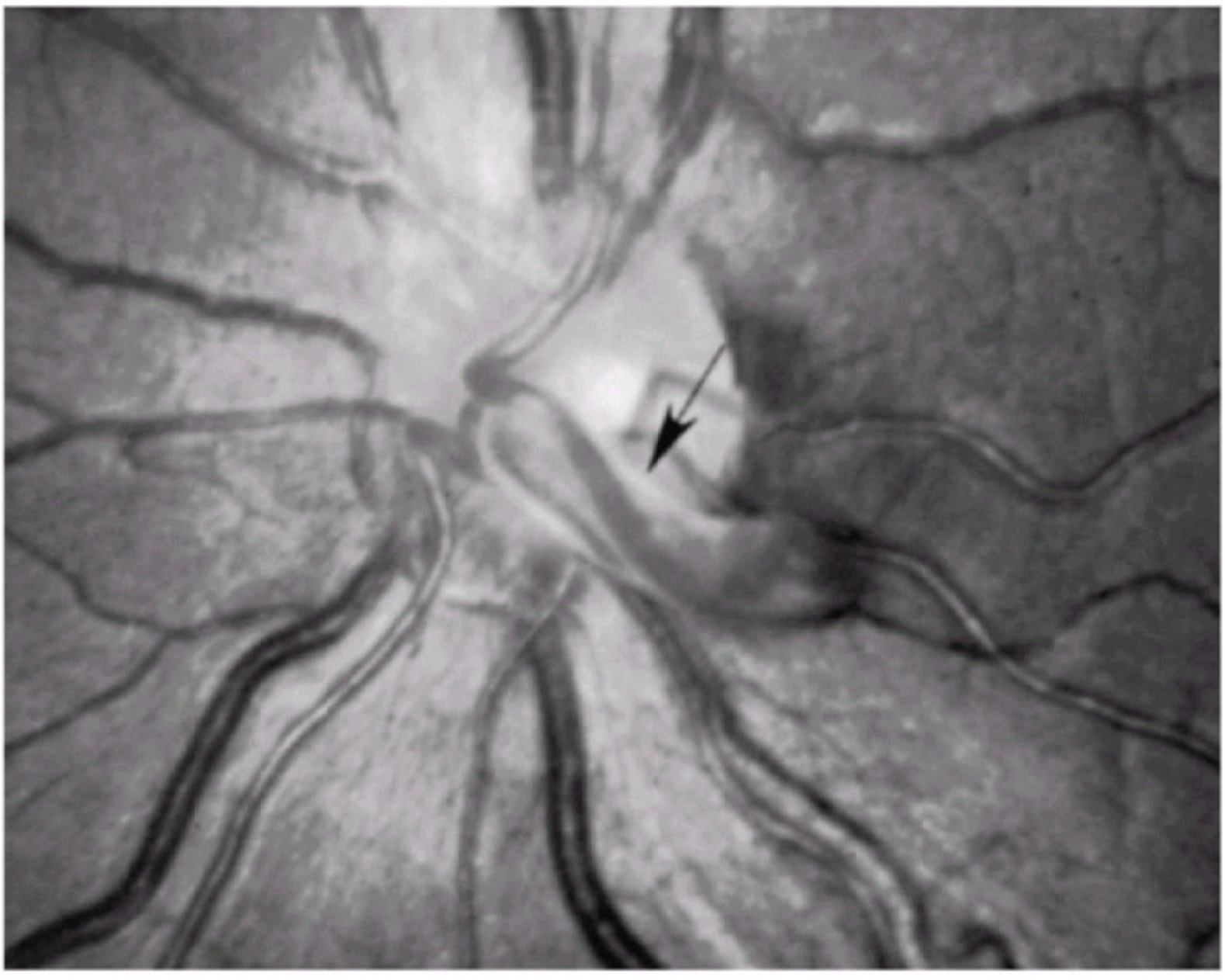

Figure 17.2 Fibroglial sheath (*arrow*) surrounding a prepapillary arterial loop extending into Cloquet's canal.

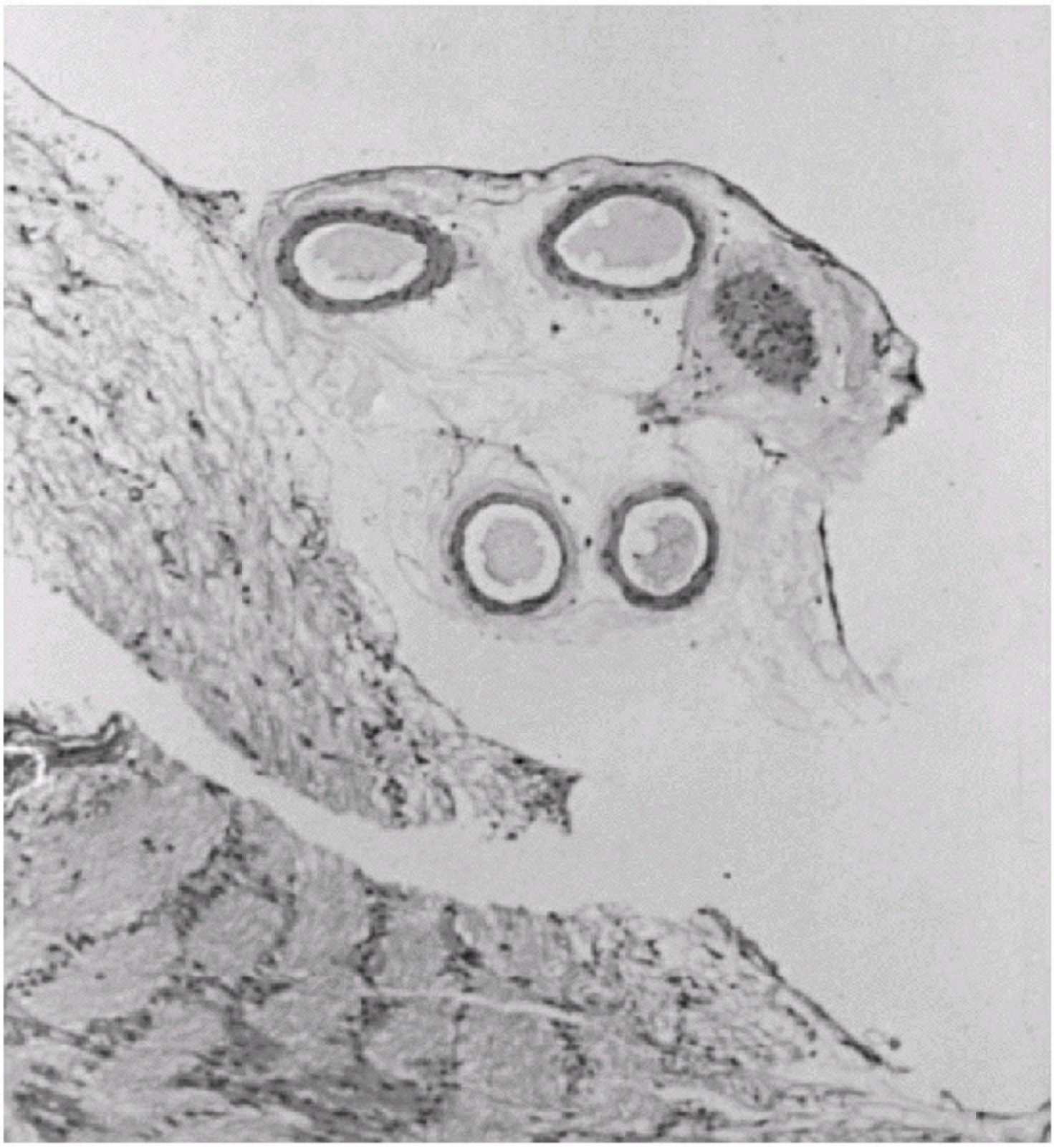

Figure 17.3 Histopathology of prepapillary arterial loop. The vessel is located with amorphous connective tissue beneath the internal limiting membrane of Elschnig.

Arterial prepapillary loops average approximately 1.5 mm in height and project in the vitreous cavity into Cloquet's canal (3). In contrast with a persistent hyaloid artery, arterial prepapillary loops achieve only a maximum height of approximately 5 mm and do not extend anteriorly to the posterior capsule of the lens.

Bilaterality is present in 9% to 17% of cases (2), and cilioretinal arteries have been noted in up to 75% of affected eyes. Systemic associations have not been routinely noted.

Histopathologically, a prepapillary arterial loop has been shown to contain intima, but not an internal elastic lamina (Fig. 17.3) (5). The vessel reported was demonstrated to lie beneath a loose connective tissue sheath continuous with the internal limiting membrane of the retina.

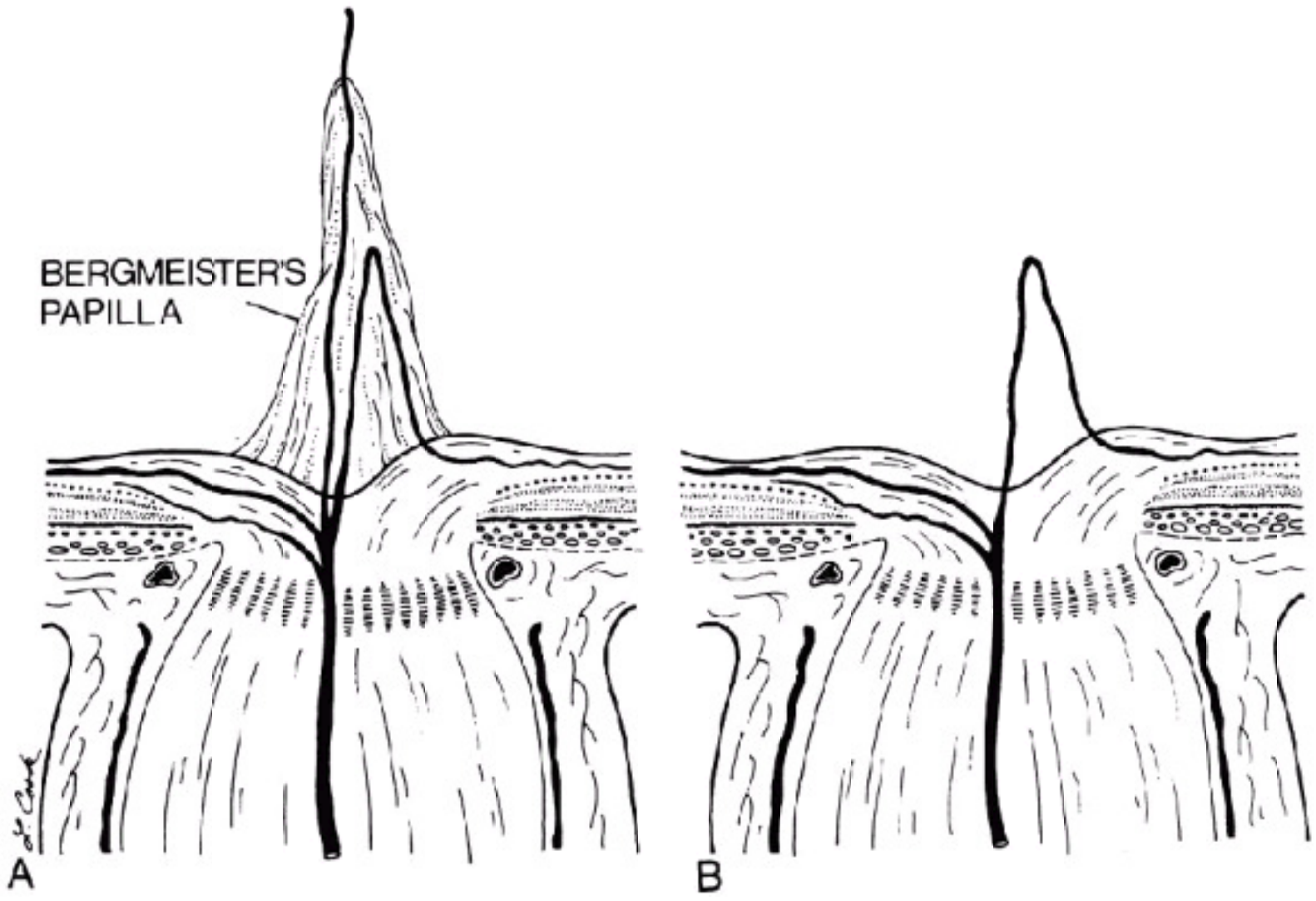

Figure 17.4 A: Prepapillary arterial loop growing into Bergmeister's papilla during gestation. Hyaloid artery (*left*). B: Bergmeister's papilla and the hyaloid artery have regressed by birth, leaving the loop within the confines of Cloquet's canal. (From Brown GC, Tasman WS. *Congenital anomalies of the optic disc*. New York: Grune & Stratton, 1983:50, with permission.)

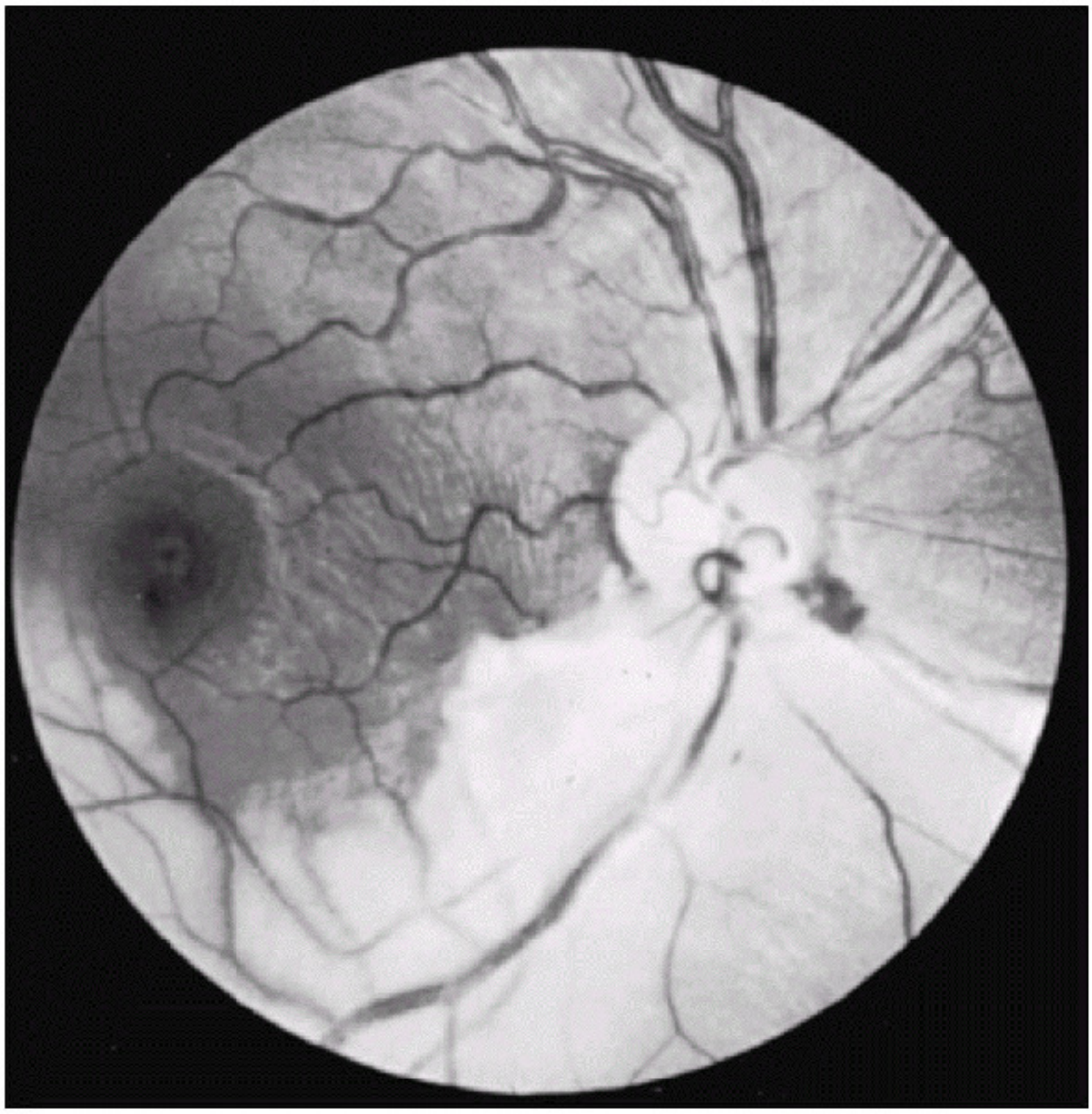

Figure 17.5 Inferior branch retinal artery obstruction in the right eye of an 18-year-old youth with a prepapillary arterial loop. (From Brown GC, Magargal LE, Augsburger JJ, et al. Preretinal arterial loops and retinal arterial occlusion. *Am J Ophthalmol* 1978;87: 646-651. Reprinted with permission of Ophthalmic Publishing Company.)

Mann (4) has suggested that prepapillary arterial loops arise at approximately the 100-mm stage (3.5 to 4 months) of gestation. At this time, mesenchymal cells, the precursors of retinal capillary endothelial cells and retinal vessels, inadvertently grow anteriorly into the supporting tissue of Bergmeister's papilla overlying the optic nerve head. They then proceed back down onto the disc and on their course into the developing retina (Fig. 17.4). Bergmeister's papilla

subsequently regresses, leaving the vascular abnormality within Cloquet's canal.

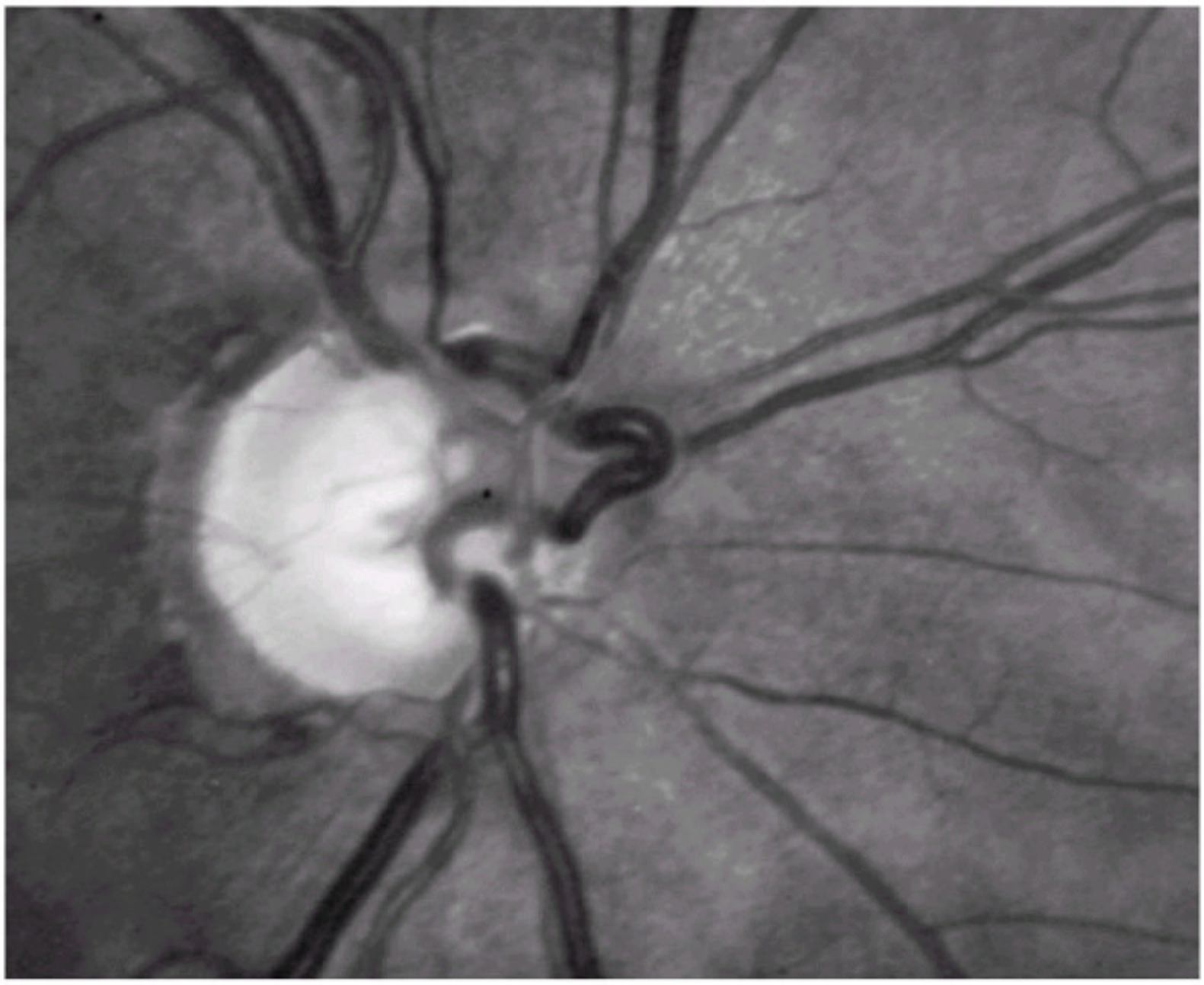

Figure 17.6 Congenital prepapillary venous loop in the right eye. (From Brown GC, Tasman WS. *Congenital anomalies of the optic disc*. New York: Grune & Stratton, 1983:53, with permission.)

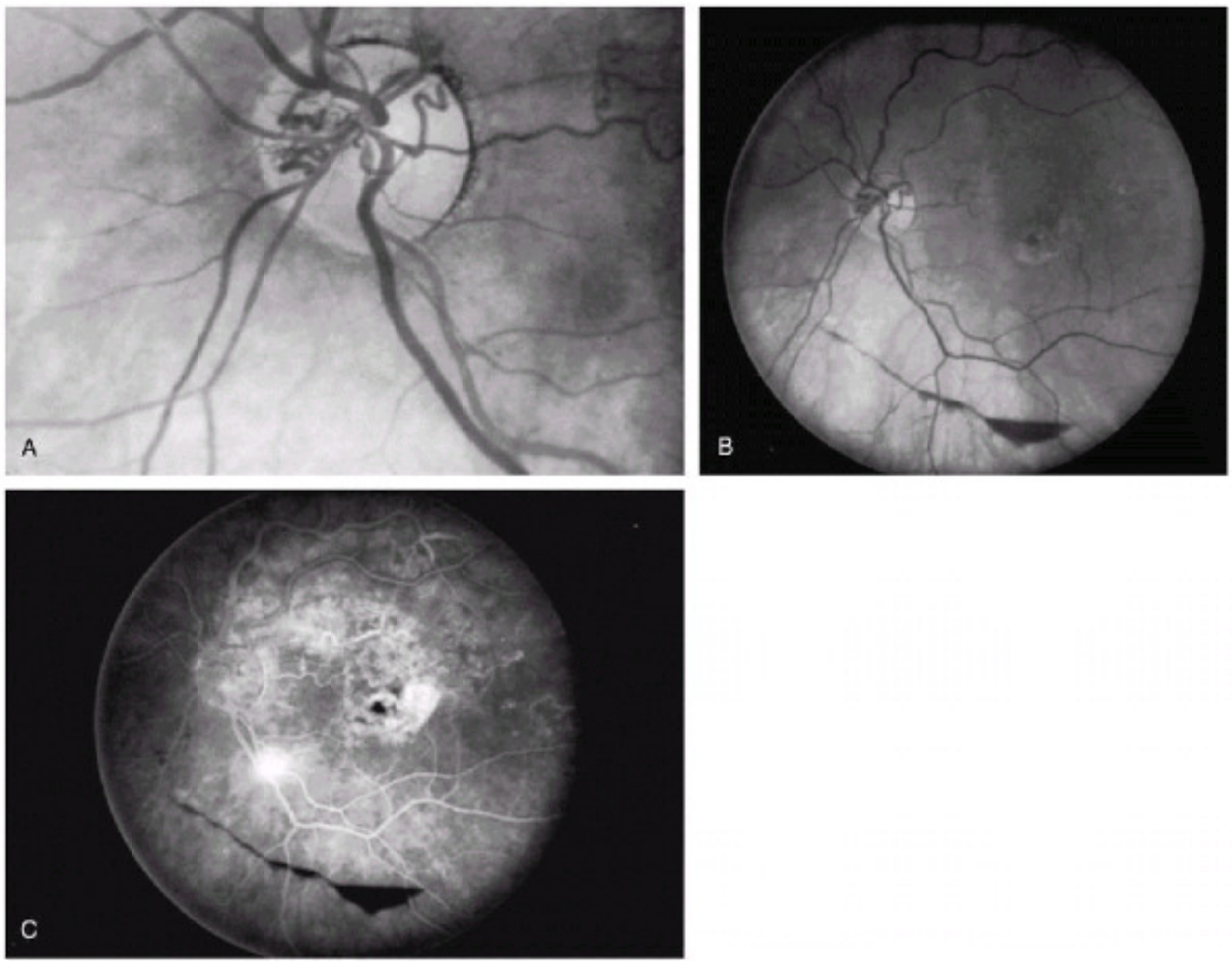

Figure 17.7 A: Multiple acquired prepapillary venous loops. B: Larger field in same eye as (A) discloses retinal vascular abnormalities in the superior macula, retinal pigment epithelial changes in the central macula, and preretinal blood inferiorly. C: Fluorescein angiogram corresponding to (B) reveals evidence of a previous superotemporal retinal branch vein obstruction. (From Brown GC, Tasman WS. *Congenital anomalies of the optic disc.* New York: Grune & Stratton, 1983:54-55, with permission.)

The major complication associated with prepapillary arterial loops is retinal artery obstruction in the distribution of the area supplied by the loop (Fig. 17.5) (2). Reported in approximately 10% of cases of prepapillary loops described in the literature, the obstruction has been hypothesized to occur secondary to turbulent flow, which predisposes to endothelial damage and thrombus formation. Vitreous hemorrhage and hyphema also have been noted (3).

Congenital prepapillary venous loops are usually single vessels that extend 0.5 mm or less into the vitreous cavity (Fig. 17.6). Acquired prepapillary venous loops are more common and often multiple, seen in adults, and found in conjunction with retinal venous obstruction or diseases associated with retinal venous obstruction, such as glaucoma, meningioma, or increased intracranial pressure (Fig. 17.7).

Persistent Hyaloid Artery

A persistent hyaloid artery presents clinically as a single vessel that travels from the optic disc—through Cloquet's

canal—anteriorly to the posterior capsule of the lens (Fig. 17.8) (2). The point of attachment to the posterior capsule, most often located inferonasal to the visual axis, is known as Mittendorf's dot.

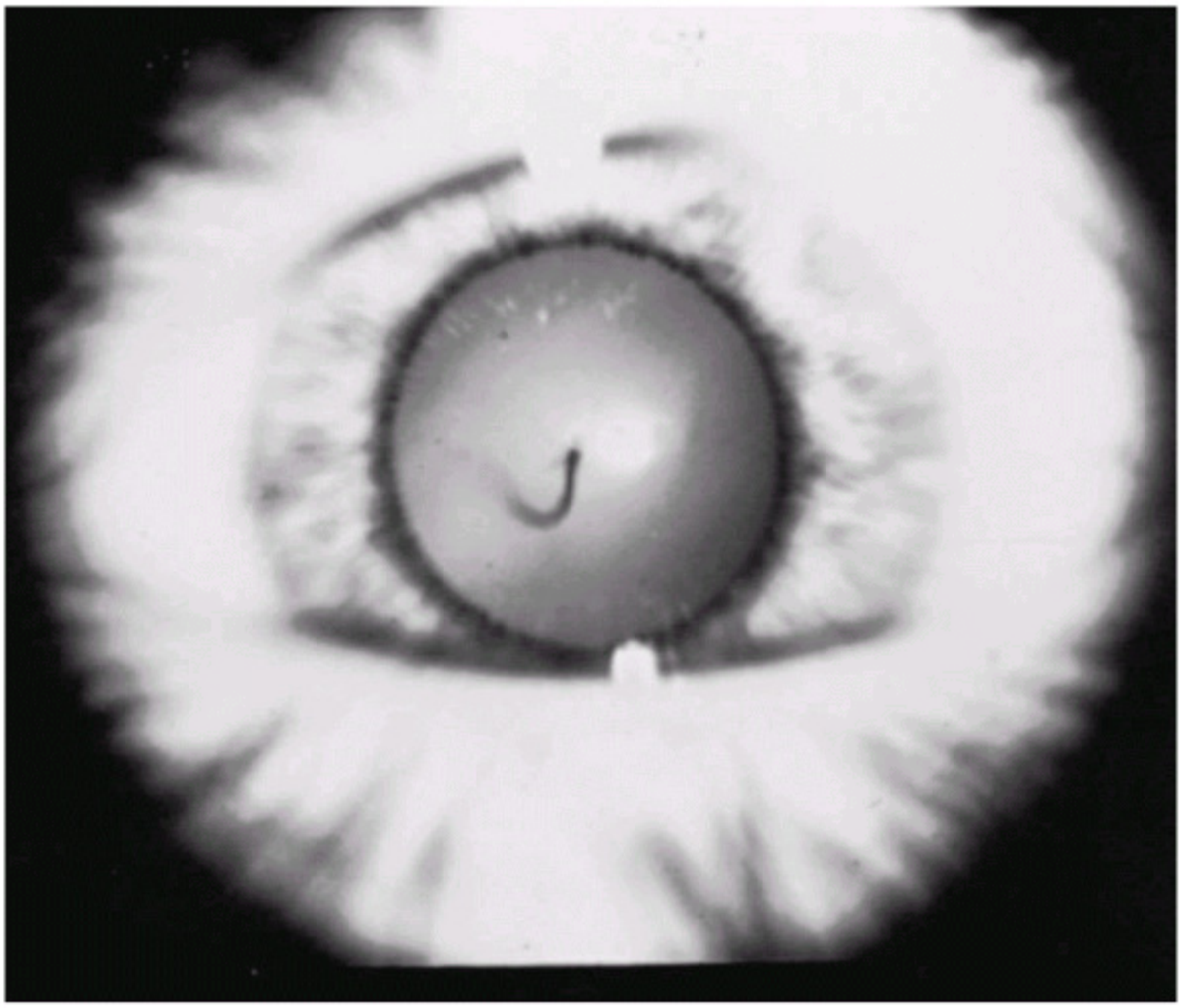

Figure 17.8 Single loop of a persistent hyaloid artery extending anteriorly in the vitreous cavity to insert on the posterior capsule of the lens.

Hyaloid artery remnants are seen in the eyes of premature infants in up to 95% of cases, but they are observed in only 3% of full-term infants (6). The incidence in children and adults is lower, but exact figures are lacking. Most commonly, a persistent hyaloid artery in a child is bloodless, but in rare instances it can contain blood and be associated with vitreous hemorrhage (7). Ocular associations reported with persistent hyaloid artery include persistent hyperplastic primary vitreous, coloboma of the optic disc, optic nerve hypoplasia, and posterior vitreous cysts (2).

Persistent Bergmeister's Papilla

Although not a vascular abnormality in the strictest sense, Bergmeister's papilla develops around the posterior aspect of the fetal hyaloid artery. It is therefore included in this section.

Between the first and second months of gestation, a group of neuroectodermal cells within the optic cup at the superior end of the embryonic fissure differentiates into a structure known as the primitive epithelial papilla (8). This primitive epithelial papilla becomes the optic nerve head when axons traveling from the retinal ganglion cells to the lateral geniculate nuclei pass through it.

At the end of the fourth month of gestation, neuroectodermal glial cells on the surface of the optic disc multiply and form a sheath around the hyaloid artery that extends anteriorly for approximately one third the length of the vessel (Fig. 17.9). The sheath is maximally developed at approximately 5.5 months of gestation, after which atrophy occurs. The amount of regression determines, in part, the degree of physiologic cupping of the optic disc.

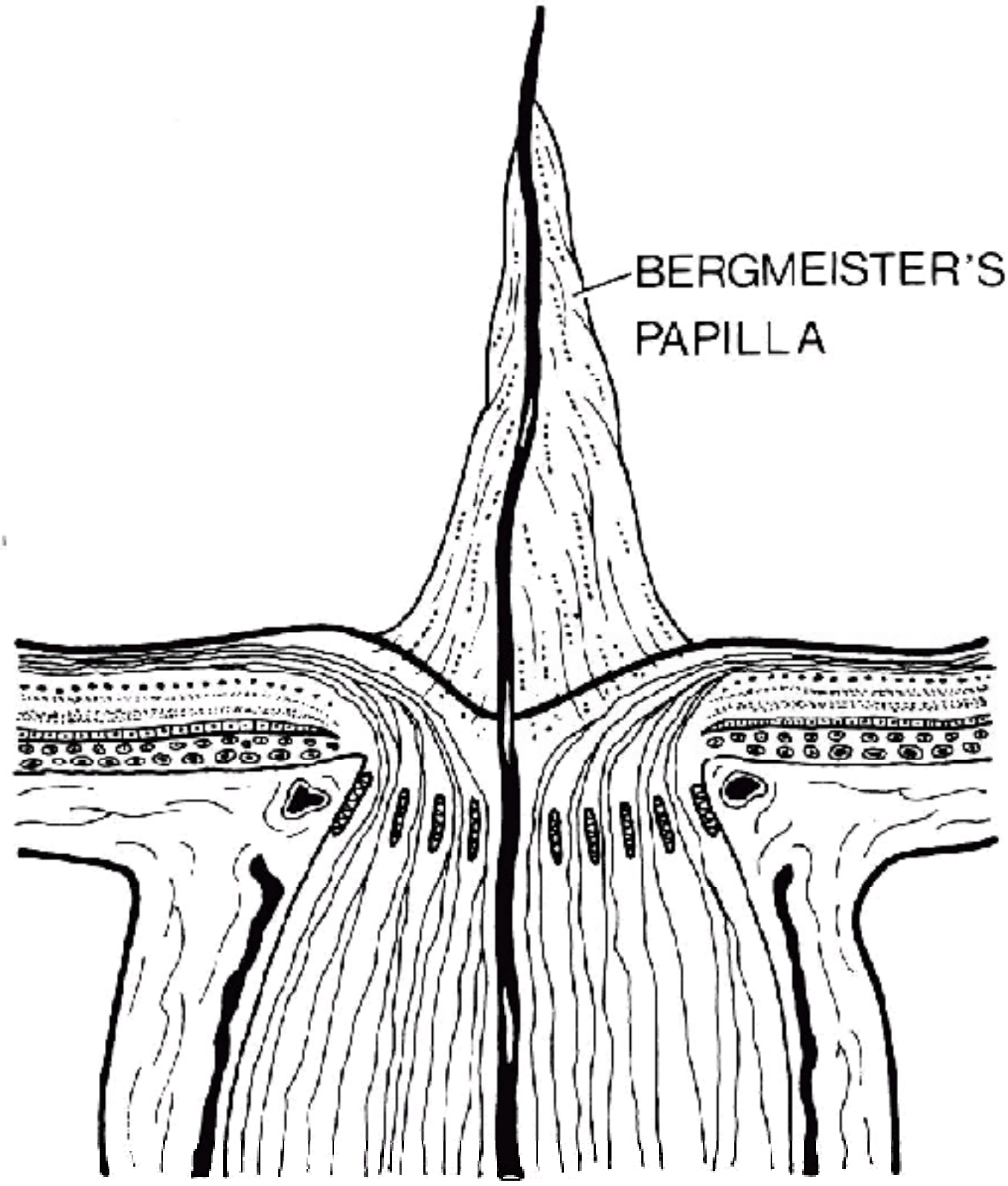

Figure 17.9 Bergmeister's papilla at its maximum height during the fifth month of gestation. It usually regresses by birth.

Incomplete regression of Bergmeister's papilla causes a persistent Bergmeister's papilla, also known as an *epipapillary veil*. Clinically, the entity appears as a tuft of glial tissue that is most commonly located on the nasal aspect of the nerve head (Fig. 17.10). Absence of physiologic cupping can also be seen in affected eyes. The visual acuity is unaffected

by the abnormality, and systemic associations are generally lacking.

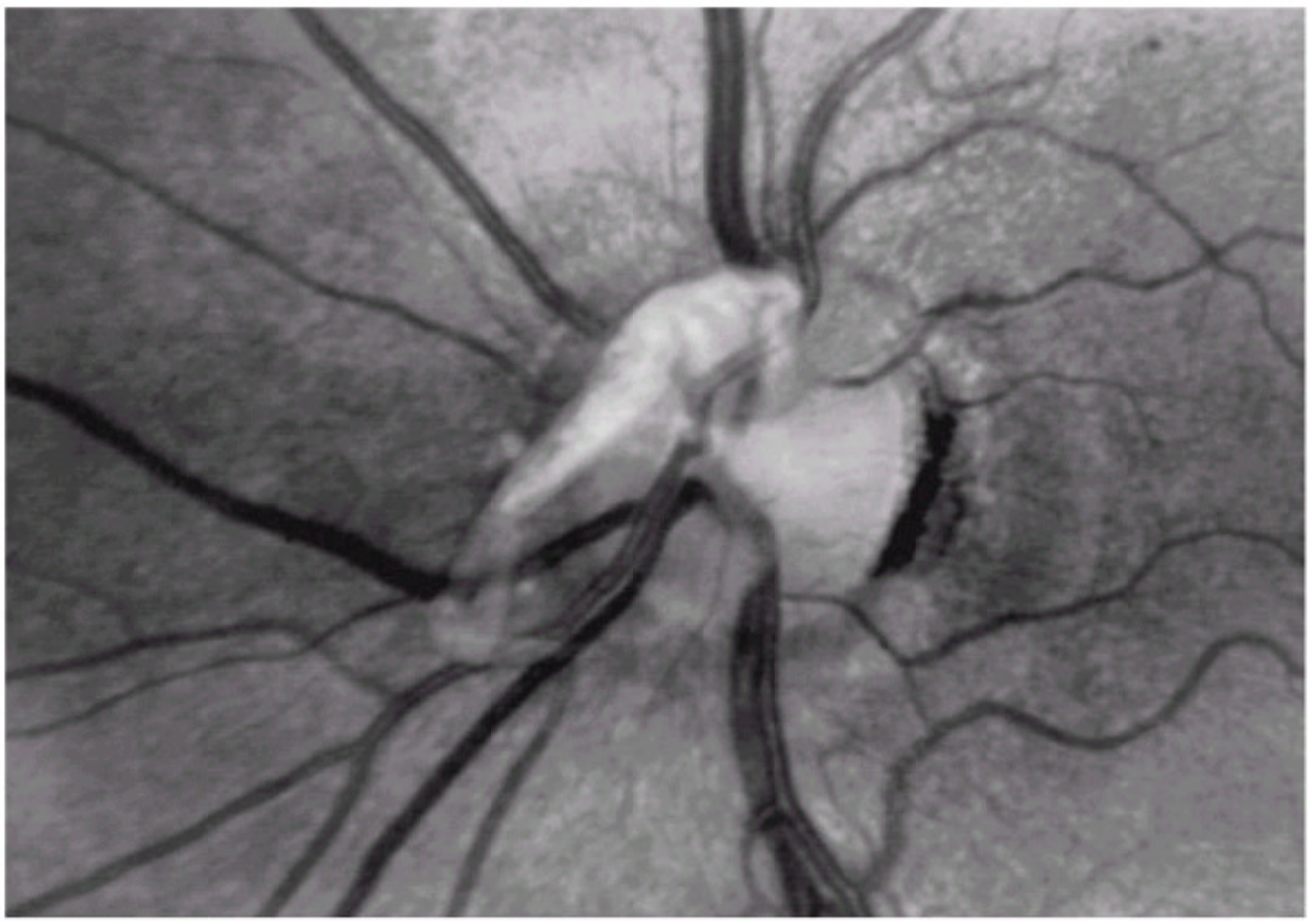

Figure 17.10 Persistent Bergmeister's papilla in the nasal aspect of the disc, left eye. (From Brown GC, Tasman WS. *Congenital anomalies of the optic disc*. New York: Grune & Stratton, 1983:68, with permission.)

Enlarged Vessels

Causes of enlarged vessels on the optic disc in children include arteriovenous malformations, retinal capillary hemangiomas (von Hippel tumors), and retinoblastoma. Because the latter two conditions are most appropriately classified as tumors, they will not be addressed in this section. Choroidal melanoma also has been noted to cause enlarged vessels on the optic disc (9), but the tumor is generally not seen in children.

Arteriovenous malformations in the retina can be mild, moderate, or severe, and thus have been correspondingly classified by Archer and associates (10) as grades I, II, and III abnormalities. A grade I arteriovenous communication, the mildest variant, has also been called a *congenital retinal macrovessel* (11). A congenital macrovessel is a single enlarged retinal vessel, usually a vein, that traverses both sides of the horizontal raphe (Fig. 17.11). Some of these vessels are associated with readily apparent arteriovenous communications, whereas others are not. Cysts in the central fovea have been seen in association with congenital retinal macrovessels, but they appear to affect the visual acuity only minimally.

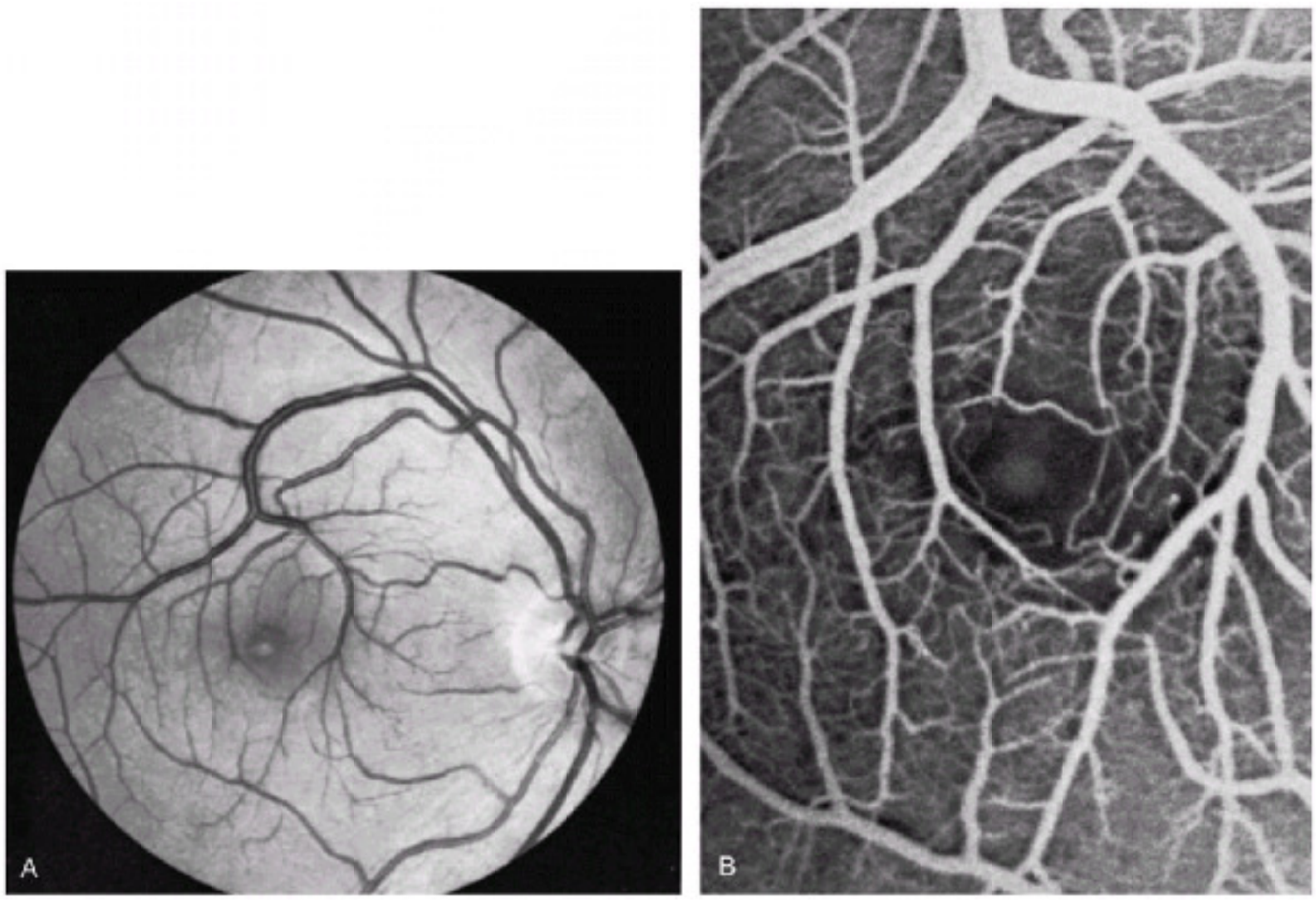

Figure 17.11 A: Congenital retinal macrovessel. Enlarged vein drains the retina, both superior and inferior to the horizontal raphe. Visual acuity in the eye was 20/20, despite the presence of a yellow foveolar cyst. B: Enlarged fluorescein angiogram of the central macula seen in (A). Area of central hyperfluorescence in the foveal avascular zone corresponds to the cyst. Vessel forming the superior border of the foveal avascular zone is an arteriovenous communication.

Grade II and III arteriovenous communications have also been called racemose angiomas or racemose hemangiomas. The grade II variant is moderate and usually associated with normal vision (Fig. 17.12), whereas in grade III the vision can be severely reduced because of replacement of optic nerve tissue by enlarged vascular elements (Fig. 17.13) (12,13). Both grade II and III arteriovenous communications can be associated with arteriovenous communications in the face, scalp, mandible, and central nervous system. The eponym Wyburn-Mason syndrome has been applied to retinal arteriovenous communications associated with similar systemic abnormalities (14). Rundles and Falls (15) found that among 34 cases of congenital retinal arteriovenous malformations reported through 1951, 18 (53%) had associated central nervous system and/or dermatologic involvement.

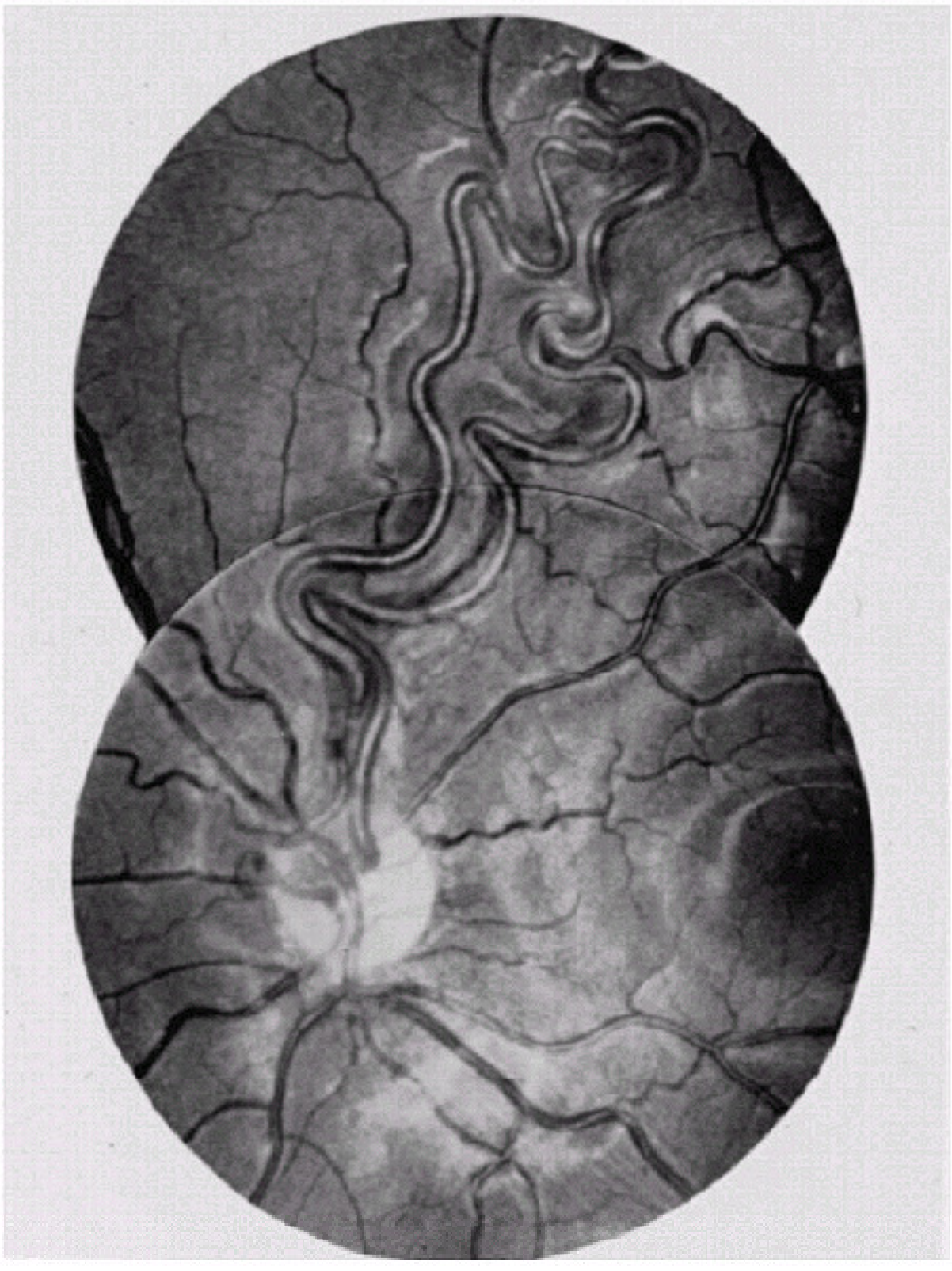

Figure 17.12 Grade II arteriovenous communication in a 12-year-old boy. Visual acuity in the eye was 20/20. (From Brown GC, Tasman WS. *Congenital anomalies of the optic disc*. New York: Grune & Stratton, 1983:75, with permission.)

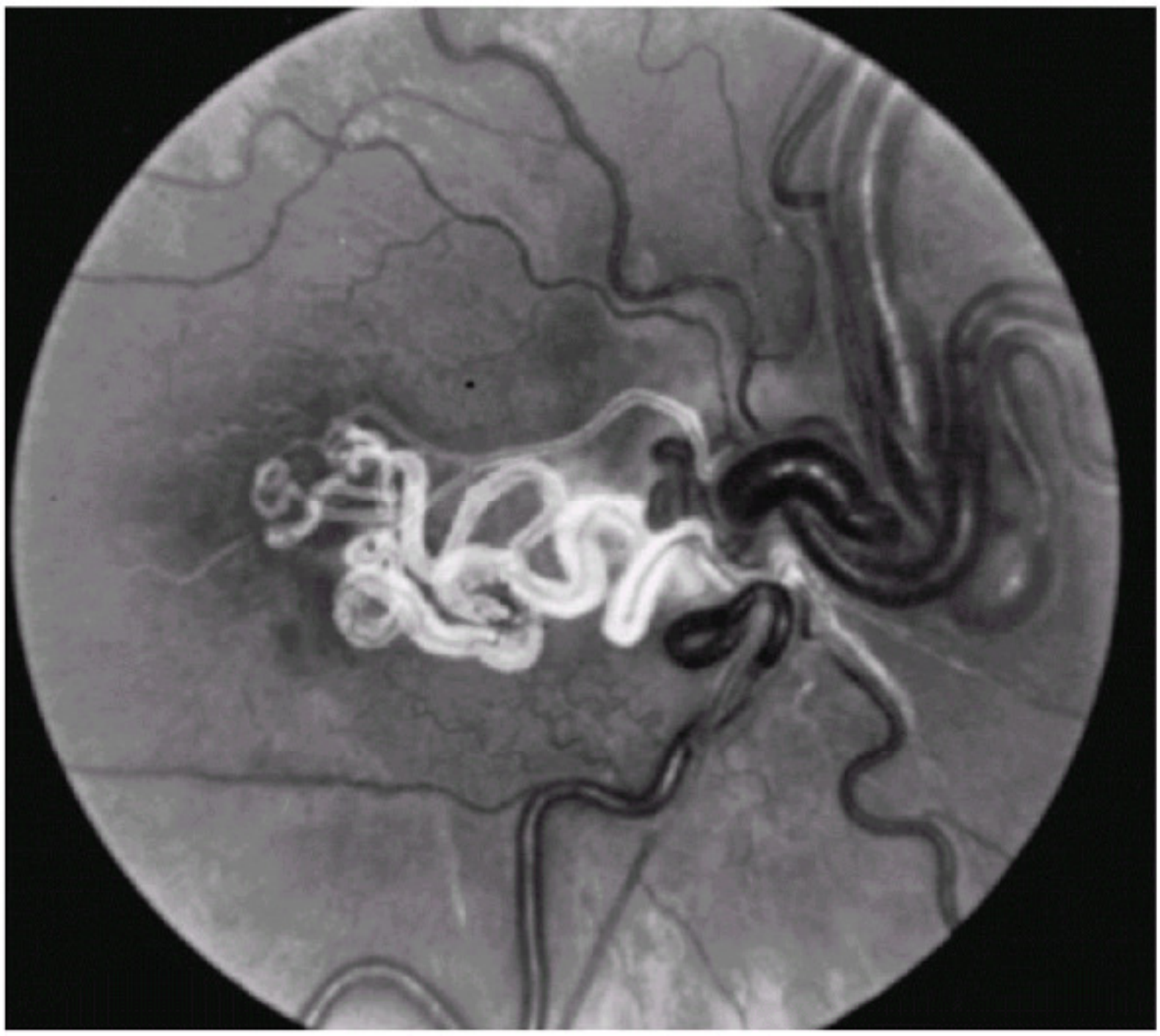

Figure 17.13 Grade III arteriovenous communication. Visual acuity in the eye was no light perception, presumably because of the replacement of the normal optic nerve tissue by vessel. (Courtesy of Dr. Jerry Shields.)

COLOBOMATOUS AND OTHER EXCAVATED DEFECTS

Congenital Pit of the Optic Disc

Found in approximately 1 per 11,000 patients (16), a congenital pit of the optic nerve head appears as a localized depression that can be yellow-white, gray, or black in color (Figs. 17.14 and 17.15). The defects generally range in size from 0.25 to 0.40 disc diameters. More than 50% are located on the temporal aspect of optic disc.

Peripapillary retinal pigment epithelial disturbances are present in 95% of eyes with optic pits that are not centrally located (Fig. 17.16) (17). Peripapillary choroidal neovascularization has been seen rarely in these cases (18). In unilateral cases, the nerve head with the pit is larger than the normal contralateral nerve head in 85% of patients. Most pits are single, but approximately 5% of affected eyes have more than one defect on the disc. Cilioretinal arteries are frequently associated.

Approximately 40% of eyes with a congenital optic pit have an associated or previous serous detachment of the sensory retina (Fig. 17.17) (17,19,20). Retinal detachment is more commonly seen with larger, temporally located pits and usually involves the macula. A splitting of the retinal layers, or macular retinoschisis, has also been described in eyes with congenital optic pits and retinal detachment (21). Centrally located pits generally are not associated with detachment. The subretinal fluid rarely extends beyond the posterior pole and in most cases can be seen extending to the optic disc in the vicinity of the pit. Cystic changes within the detached retina are found in two thirds of cases, and a macular hole develops in approximately 25%. In contrast with most lamellar macular holes, in which absence of the inner retinal layers is observed, the macular holes seen in conjunction with optic pits tend to involve the outer retina, giving the appearance that the internal limiting membrane is intact.

The age of onset of the retinal detachment is variable, with the mean age being approximately 30 years (17). Nevertheless, it has been seen in children within the first decade of life.

Uncertainty exists as to the origin of the subretinal fluid seen in conjunction with congenital optic pits. Although evidence in the collie dog model suggests that it originates from the vitreous cavity (19), other possible sources in the human include cerebrospinal fluid from the subarachnoid space, leakage from choroidal vessels, and leakage from small vessels located at the base of the pit (17).

Evidence indicates that, in many instances, the presence of an associated retinal detachment of the posterior pole is visually disabling. Although the fluid can wax and wane spontaneously, one group found that among 20 such untreated eyes followed for at least 1 year the visual acuity was 20/100 or worse in 55% (20). When the vision is decreased because of serous macular retinal detachment, laser treatment has been advocated in the peripapillary region to induce reattachment of the retina to the underlying retinal pigment epithelium and subsequent reabsorption of the subretinal fluid (Fig. 17.18). The treatment does not have

to be sufficiently heavy to involve the nerve fiber layer. With cases of severe visual loss that do not respond to laser therapy after 1 to 2 months, the possibility of repeat laser treatment in conjunction with pars plana vitrectomy and an air-gas/fluid exchange can be considered (22,23). Unless a macular hole develops within the detached macular retina, the retina can remain detached for months without negating the possibility of good visual return with therapy.

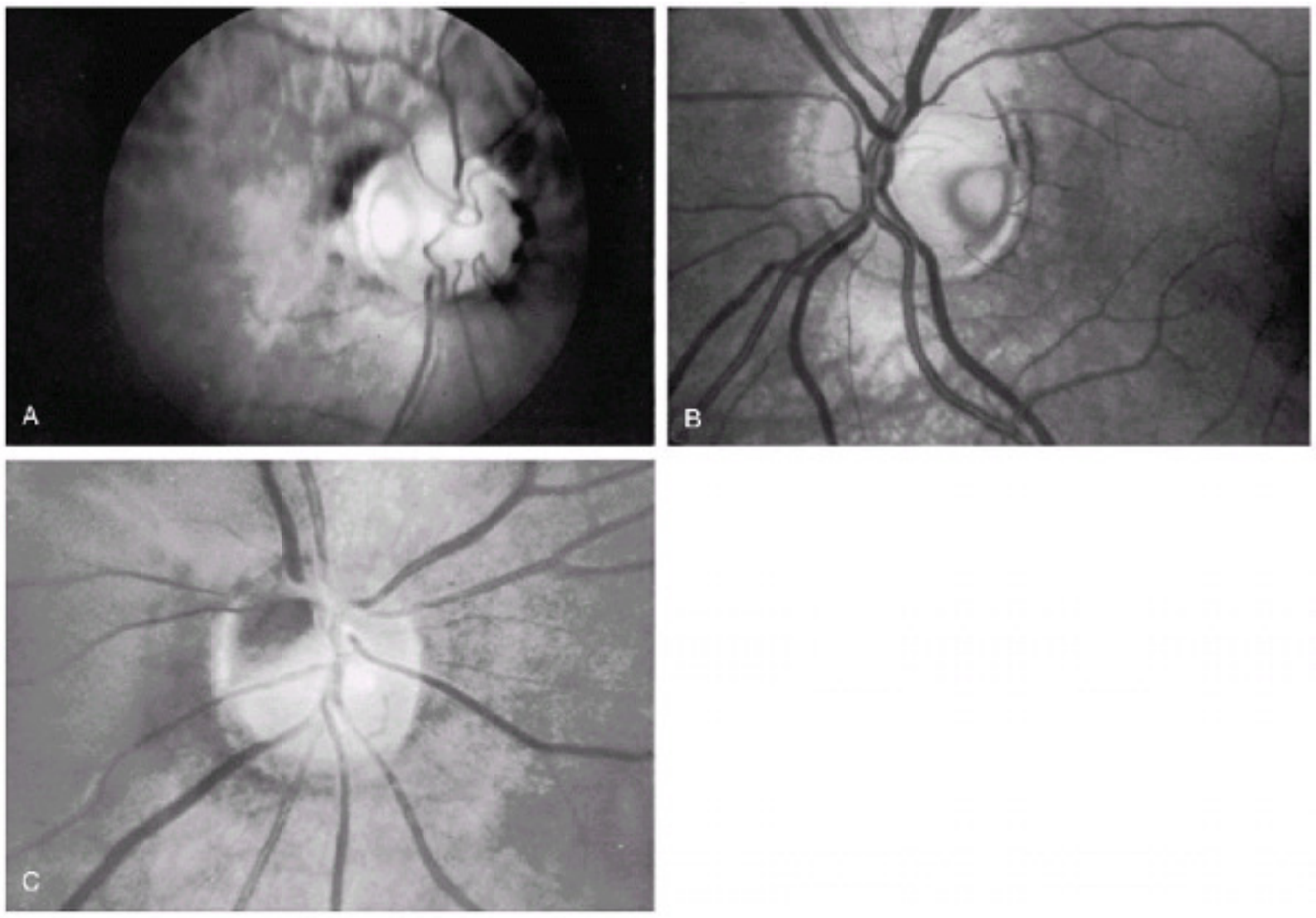

Figure 17.14 Yellow-white (A), gray (B), and black (C) congenital pit of the optic nerve head.

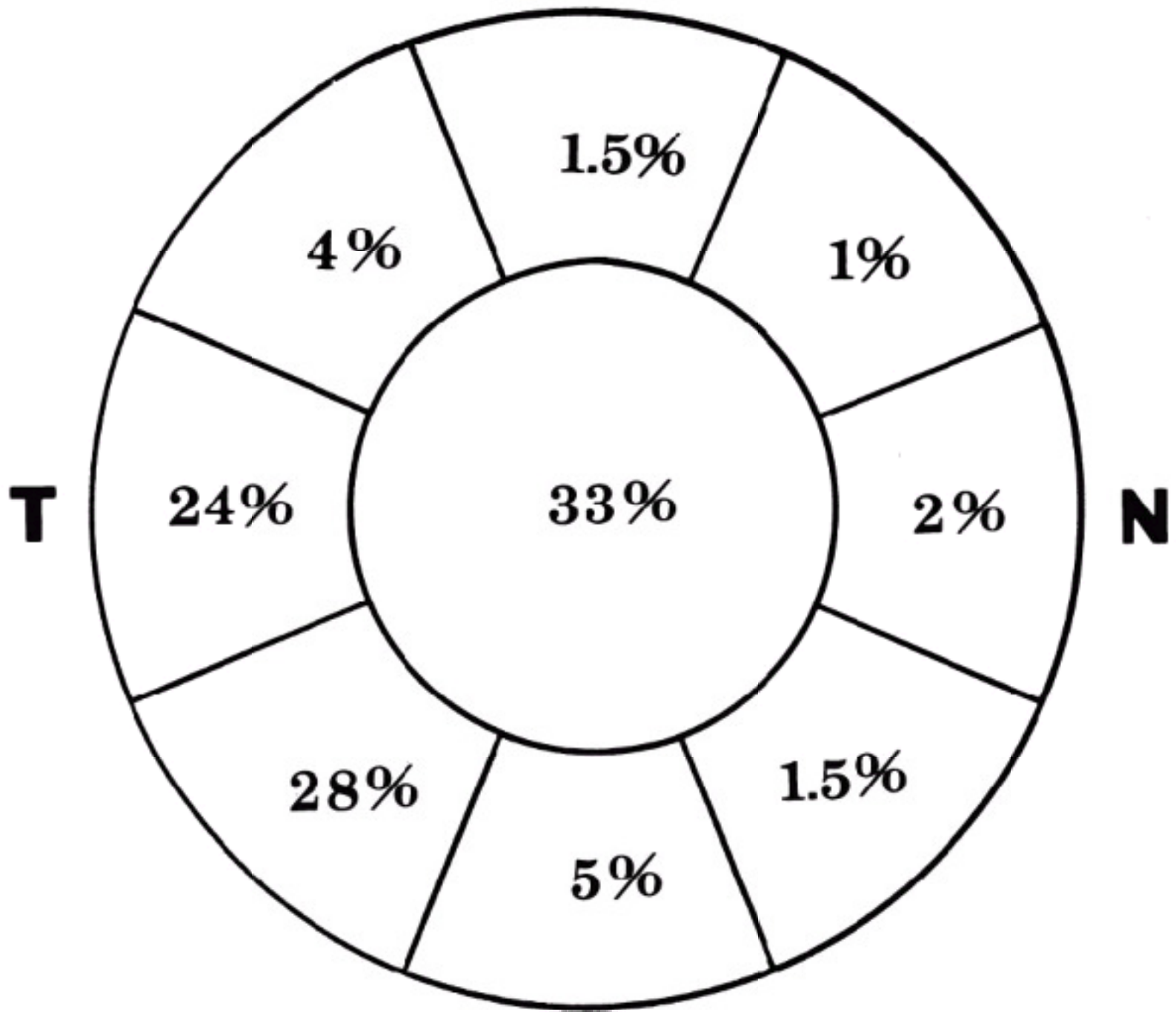

Figure 17.15 Location of the optic nerve head of congenital pits. T, temporal; N, nasal. (From Brown GC, Tasman WS. *Congenital anomalies of the optic disc*. New York: Grune & Stratton, 1983: 100, with permission.)

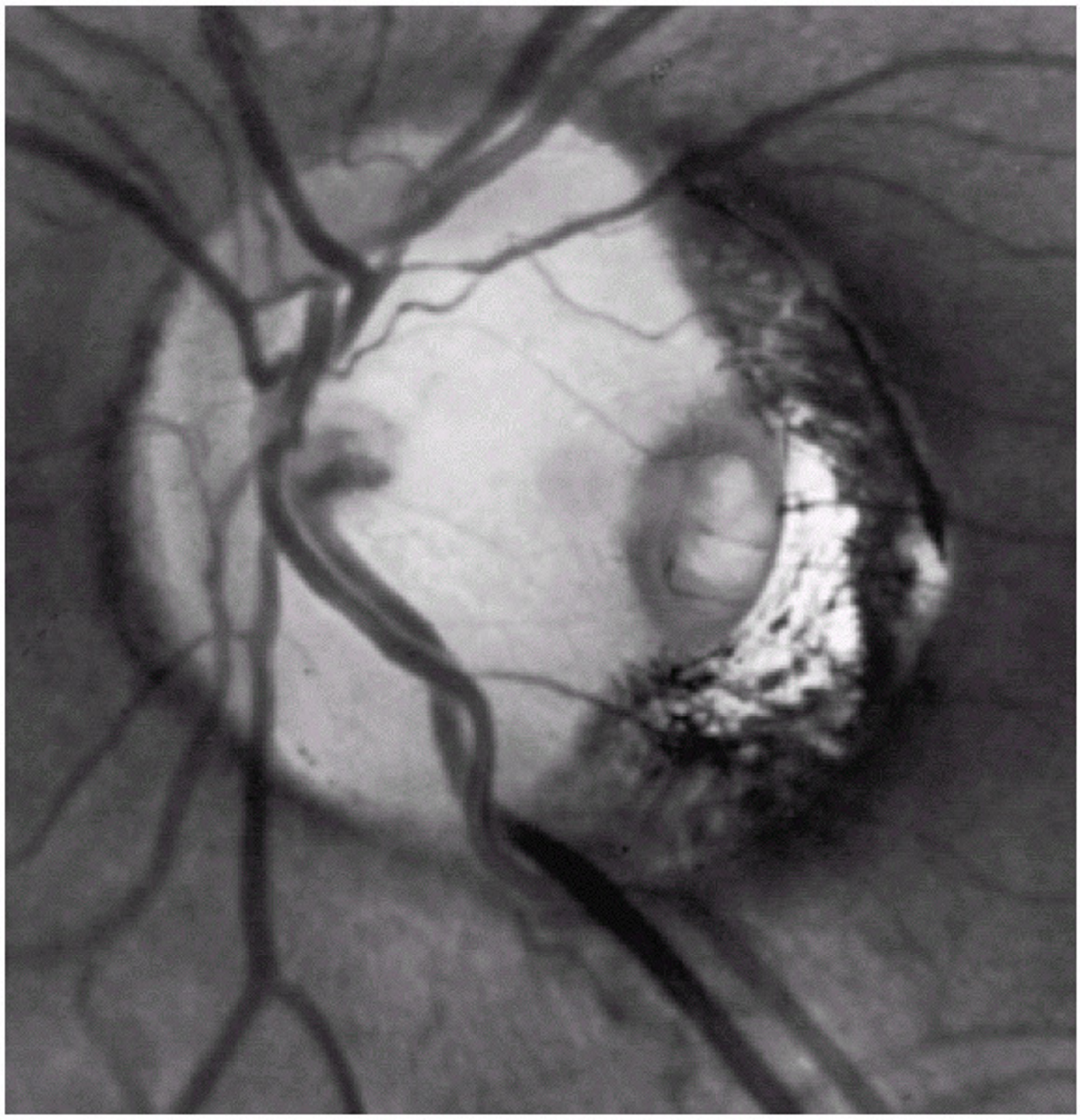

Figure 17.16 Prominent peripapillary retinal pigment epithelial changes adjacent to a temporal optic pit in the left eye.

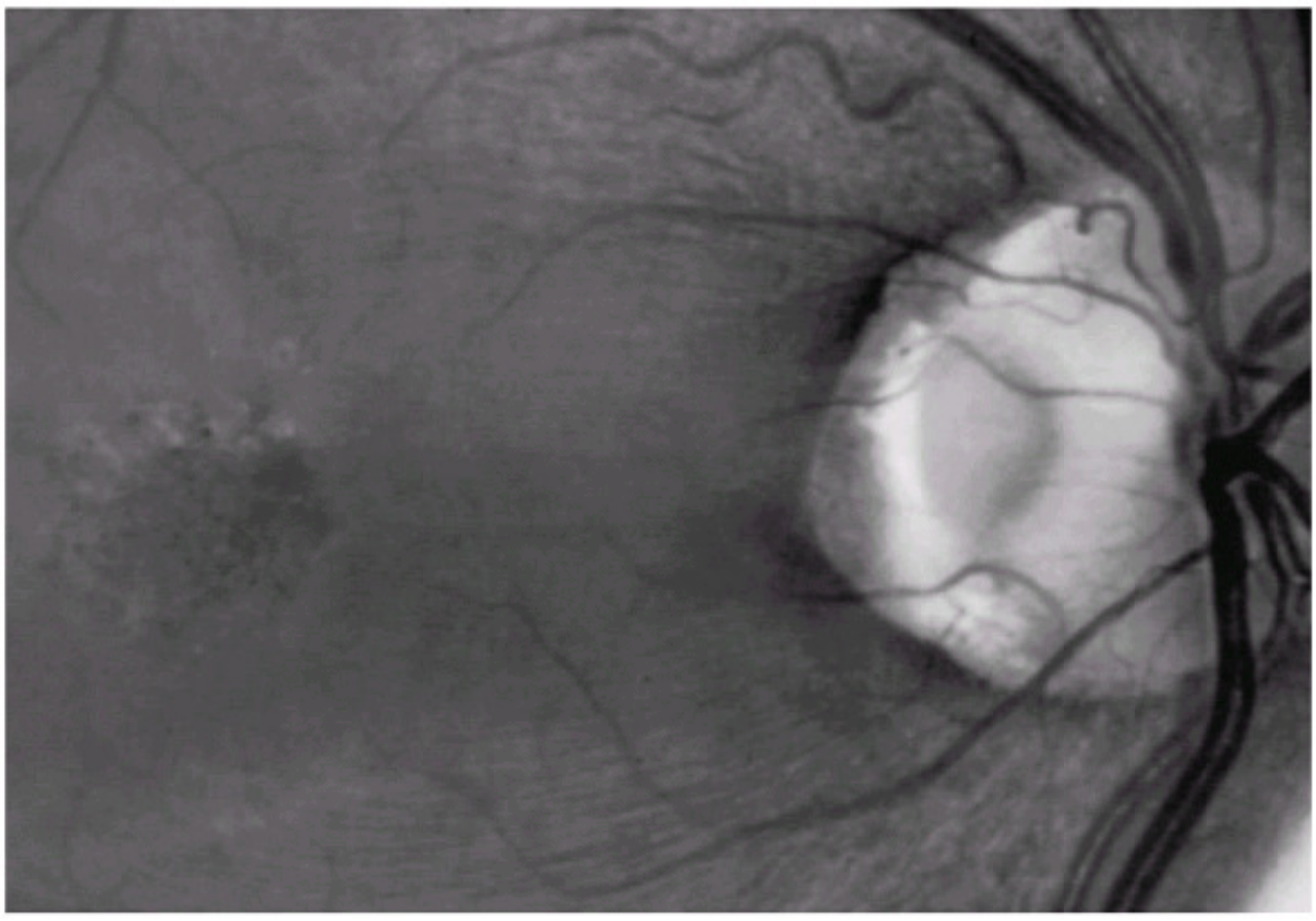

Figure 17.17 Right eye of a patient with a temporal congenital optic pit and serous detachment of the sensory retina in the macular region. A lamellar macular hole is present with the internal limiting membrane remaining intact over it. (From Brown GC, Tasman WS. *Congenital anomalies of the optic disc*. New York: Grune & Stratton, 1983:107, with permission.)

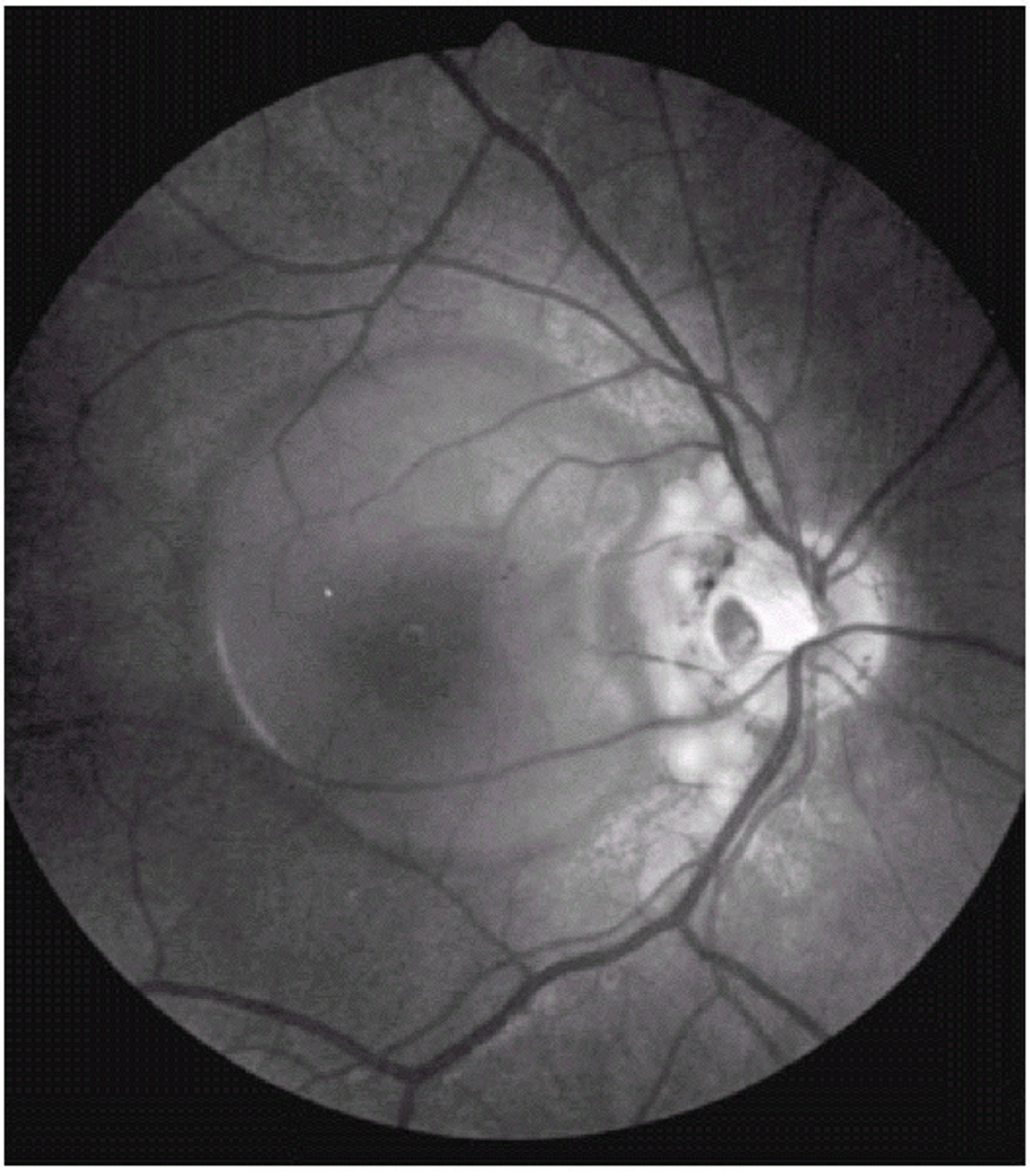

Figure 17.18 Peripapillary laser treatment with 200-µm spotsized burns in the right eye of a 15-year-old girl with a congenital optic pit and serous retinal detachment. Subretinal fluid reabsorbed after the treatment, and visual acuity improved (from 20/60 to 20/25).

Fluorescein angiography typically reveals early hypofluorescence of the pit, with progression to late hyperfluorescence. Associated visual field defects, excluding the enlarged blind spots from larger discs and central scotomas from macular retinal detachments, mimic those found with glaucoma and are seen in 55% to 60% of eyes (20). Included among these are arcuate scotomas, altitudinal defects, paracentral scotomas, generalized and peripheral localized constrictions, sector defects extending from the disc, and nasal or temporal steps.

In general, systemic abnormalities have not been linked with congenital optic pits. Nevertheless, one instance of the association of a basal encephalocele with agenesis of the corpus callosum has been reported (24). A hereditary pattern is not usually present, although autosomal dominant inheritance has been noted (25). The defect is thought to arise, in most cases, from abnormal differentiation of the primitive epithelial papilla (26).

Optic Nerve Coloboma

Occurring in approximately 1 per 12,000 patients (20), an optic nerve coloboma has several identifying features (Fig. 17.19). Included among these are (a) enlargement of the papillary area, (b) partial or total excavation of the disc, more so inferiorly, (c) a glistening white surface, and (d) retinal blood vessels entering and exiting the nerve head from the border of the defect. Depths are variable and may range up to 50 diopters (27).

The abnormality can be unilateral or bilateral. Visual acuity is variable and has been noted to range from normal to no light perception (28). Concomitant retinochoroidal and/or iris colobomatous defects may also be present (Fig. 17.20).

The anomaly is believed to occur secondary to incomplete closure of the embryonic fissure during the second month of gestation (28).

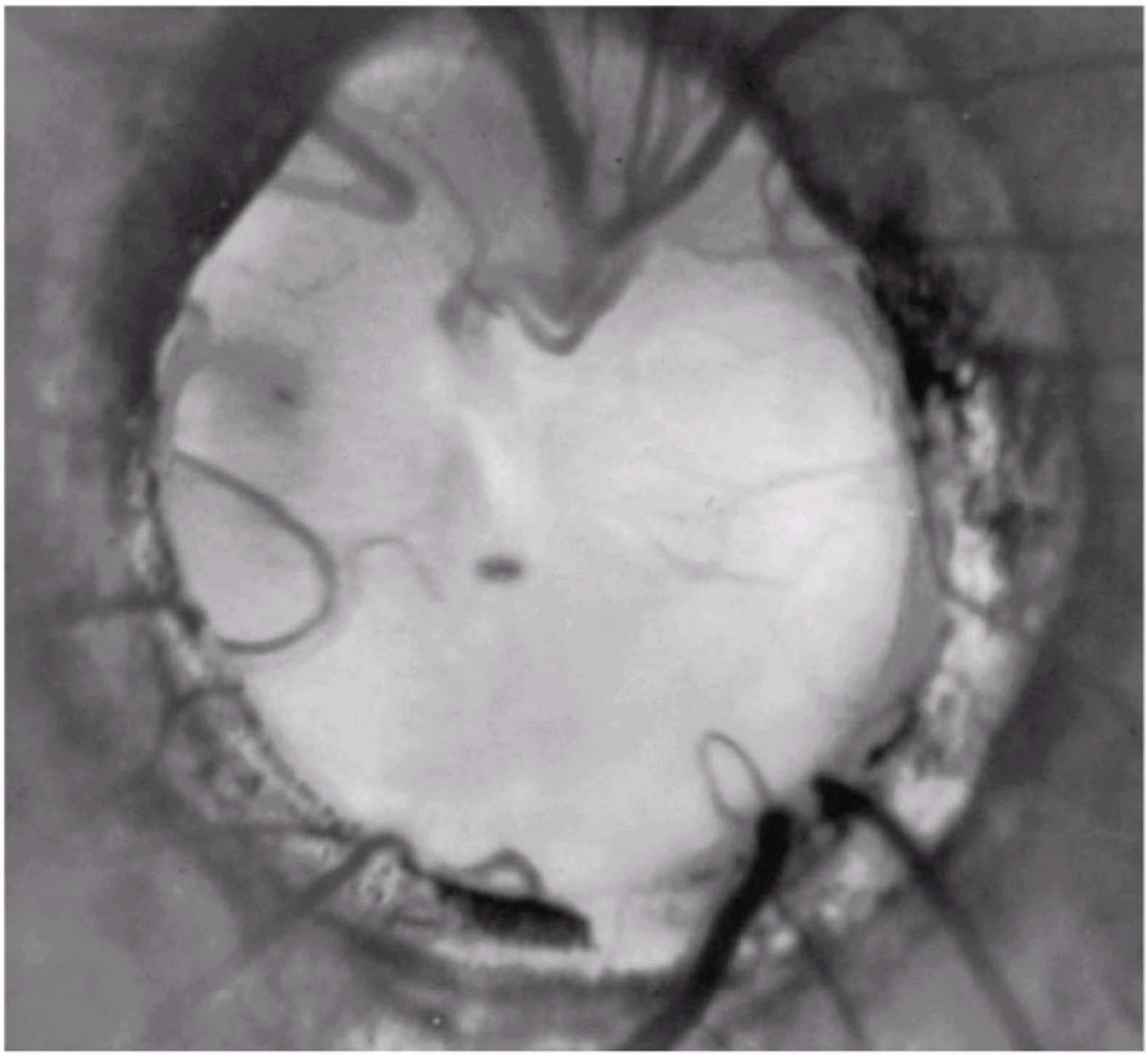

Figure 17.19 Coloboma of the optic disc.

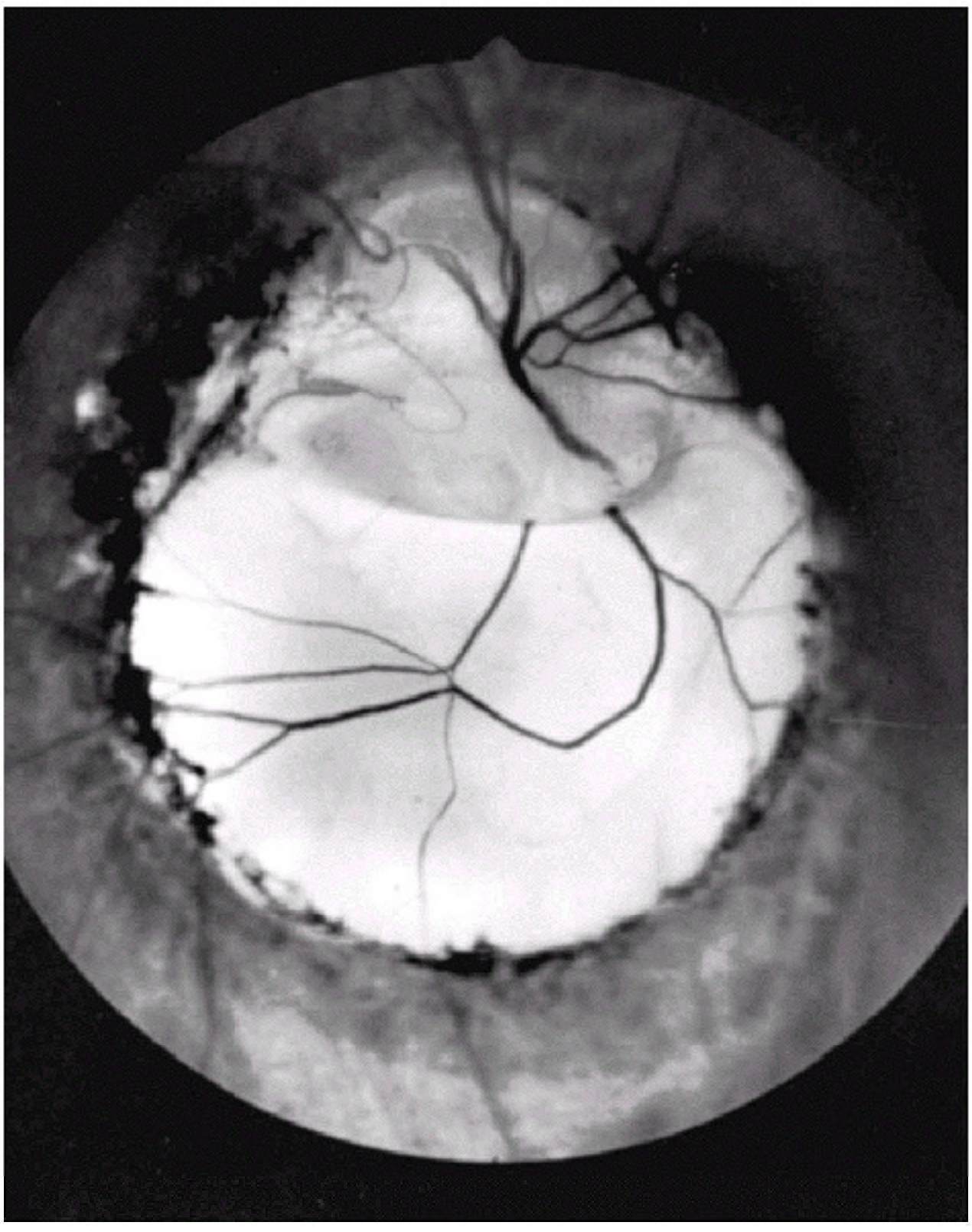

Figure 17.20 Retinochoroidal coloboma extending superiorly to involve the optic nerve head.

Non-rhegmatogenous retinal detachment can be seen in association with optic nerve colobomas (28). The detachment most often occurs in the second or third decade of life and usually extends outward from the optic disc (25). Peripapillary laser therapy in association with pars plana vitrectomy and air-gas/fluid exchange has been used successfully in our institution to flatten the retina (22). The source of the subretinal fluid is uncertain.

Numerous systemic abnormalities have been reported in conjunction with colobomatous defects in the eye (20). Included among these are diseases of the cardiovascular, central nervous, dermatologic, gastrointestinal, genitourinary, nasopharyngeal, and musculoskeletal systems. Of particular note is the CHARGE syndrome (*c*oloboma, heart disease, *a*tresia choanae, *r*etarded growth, *g*enital hypoplasia, *e*ar anomalies, and/or deafness) (29).

Morning Glory Disc Anomaly

In 1970 Kindler (30) reported on 10 patients with a unilateral, congenital optic nerve head anomaly that resembled the morning glory flower. Among the features of the morning glory optic disc are (a) enlargement and excavation, (b) a central core of white tissue, (c) a peripapillary annulus of variably pigmented subretinal tissue, and (d) retinal vessels that enter and exit from the borders of the defect (Fig. 17.21). The retinal vessels are frequently sheathed and straightened.

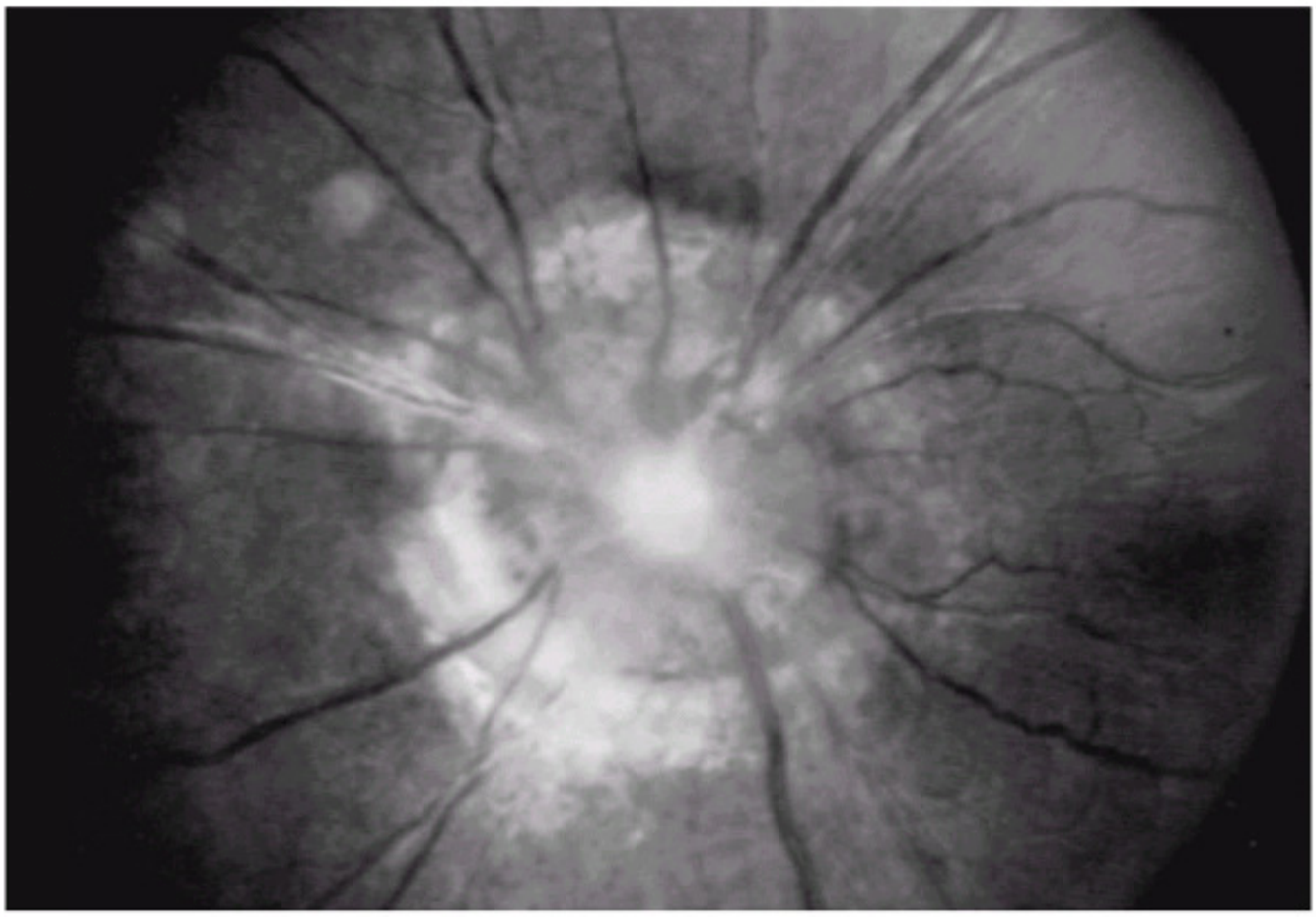

Figure 17.21 Morning glory optic disc anomaly. The enlarged disc is excavated centrally and has a central tuft of glial tissue, a surrounding annulus of subretinal peripapillary tissue, and straightened sheathed arteries.

In approximately 30% of eyes, a non-rhegmatogenous retinal detachment develops (Fig. 17.22) (30,31). It can involve the posterior pole or extend to the periphery. As is the case with optic nerve head coloboma, the origin of the subretinal fluid is uncertain. Peripapillary laser therapy in conjunction with vitrectomy and air-gas/fluid exchange can be of benefit for flattening the retina in some cases (22).

The visual acuity in eyes with the morning glory optic disc anomaly and no retinal detachment can range from near normal to hand motion recognition (20).

Strabismus

may be associated. In unilateral cases, the possibility of concomitant strabismic amblyopia should be considered, particularly because the visual loss in affected eyes in bilateral cases does not seem to be as severe as the visual loss in unilateral affected eyes (32).

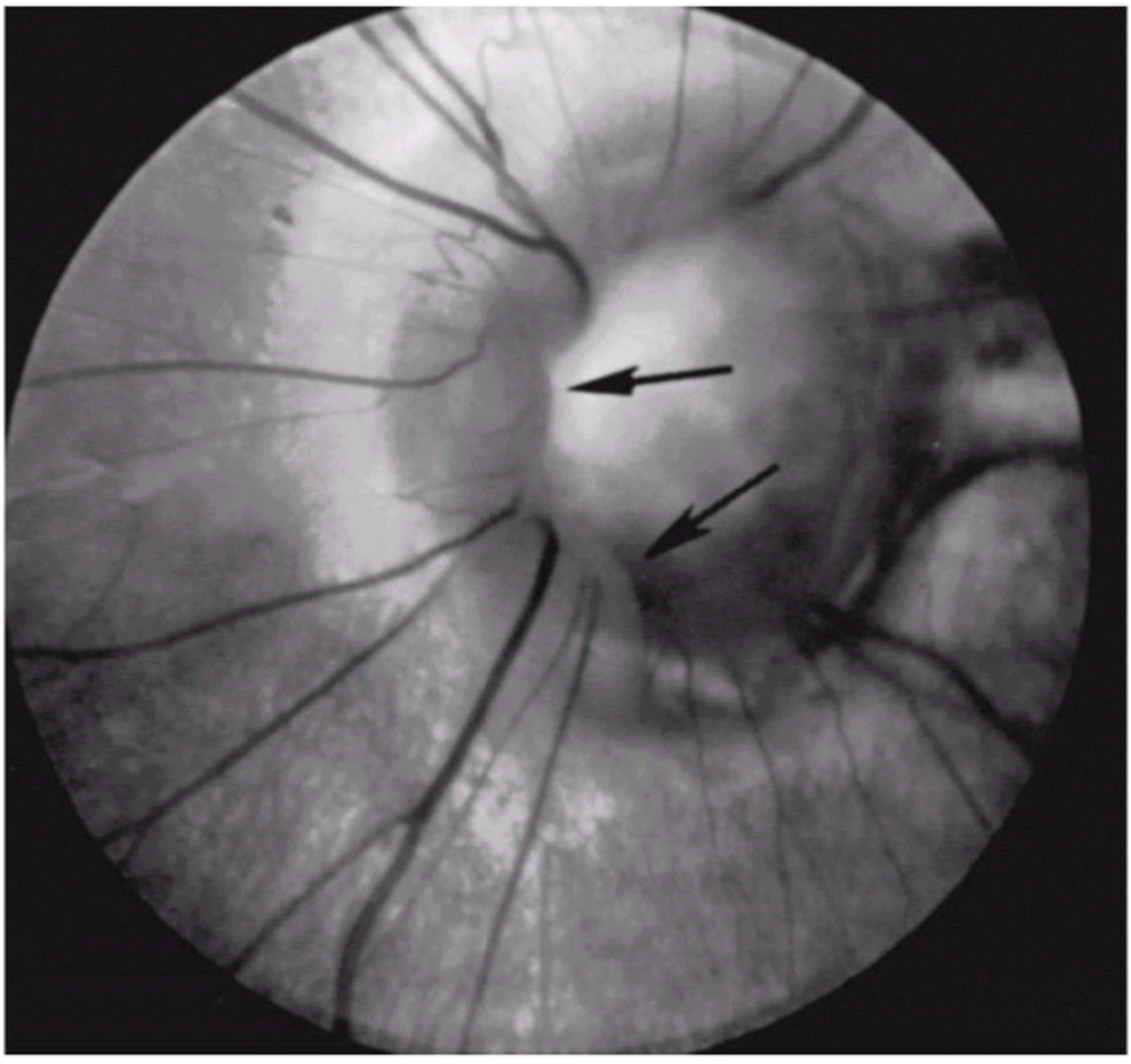

Figure 17.22 Nasal retinal detachment (*arrows*) in an eye with the morning glory optic disc anomaly. (From Brown GC, Tasman WS. *Congenital anomalies of the optic disc*. New York: Grune & Stratton, 1983:162, with permission.)

Basal encephalocele has been noted in conjunction with the morning glory disc anomaly (33). Other congenital optic disc abnormalities that have been reported with basal encephalocele include optic pit, coloboma, and megalopapilla (20).

Peripapillary Staphyloma

A rare congenital anomaly, the peripapillary staphyloma is an excavated defect surrounding a relatively normal-appearing optic disc (Fig. 17.23). Atrophic changes of the choroid and retinal pigment epithelium are usually seen within the walls of the defect. Although the depth of the optic disc often ranges from 8 to 20 diopters (20), the macula is usually within 1 to 2 diopters of emmetropia. The visual acuity can be normal in mild cases, but severe visual loss is generally seen with more pronounced defects (20). Contractions of the walls of larger staphylomas have been reported (34).

Tilted Disc Syndrome

Present in approximately 1% to 2% of the population, the tilted disc syndrome has the features shown in Table 17.1 (Figs. 17.24 and 17.25) (35,36). It has a number of alternative nomenclatures (20), including the nasal fundus ectasia syndrome, Fuchs coloboma, inverse myopia, inversion of the optic disc, and dysversion of the optic disc. The entity may actually be a form of colobomatous defect (20).

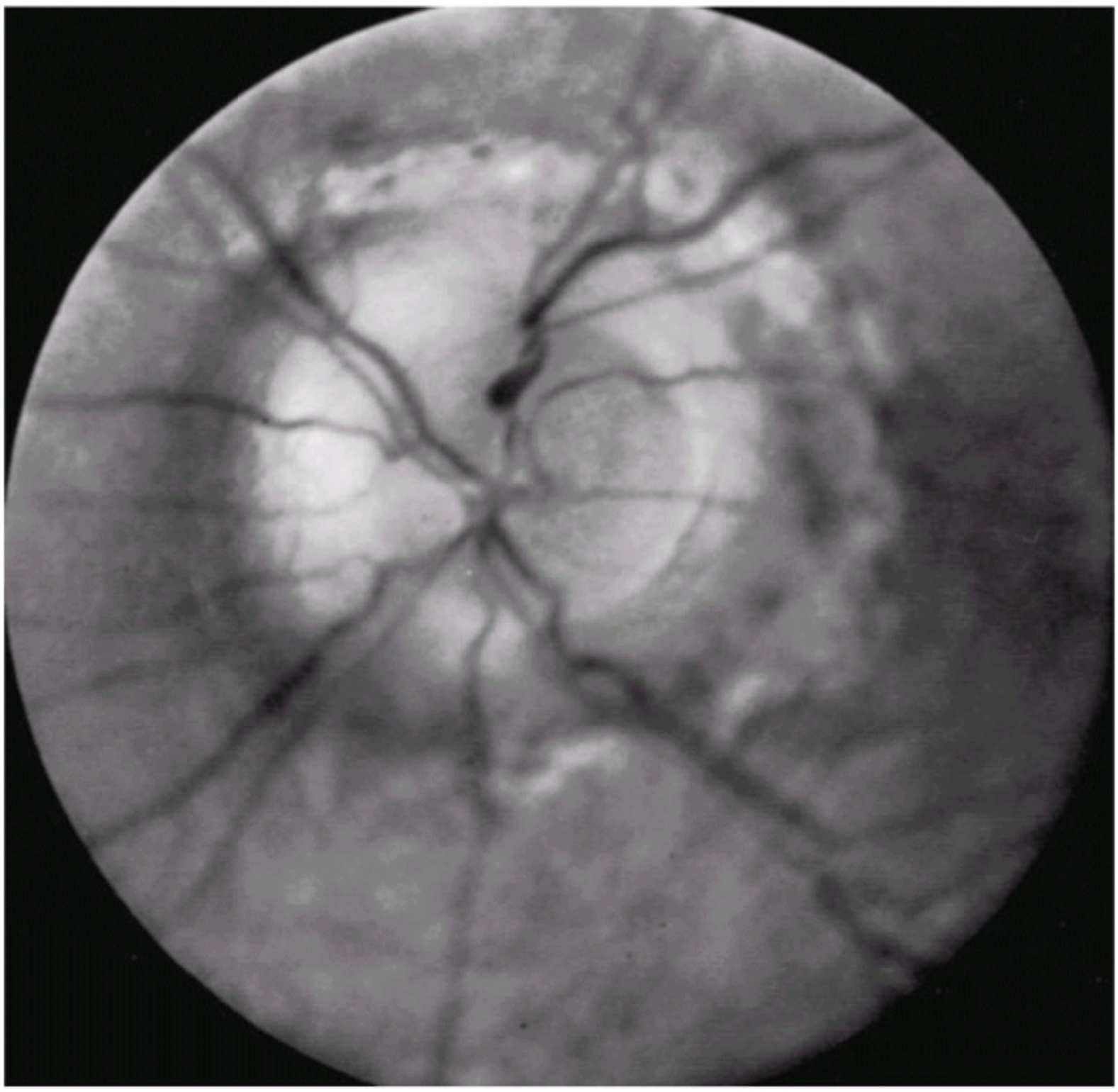

Figure 17.23 Relatively normal-appearing optic disc recessed within the confines of a peripapillary staphyloma.

TABLE 17.1 TILTED DISC SYNDROME

	No. of Cases (%)
Inferonasal disc tilting	65
Inferonasal or inferior crescent	88
Situs inversus of the retinal vessels	80
Myopia (>1 diopter)	85-90
Astigmatism (>1 diopter)	71
Hypopigmented, inferior fundus ectasia	72-90

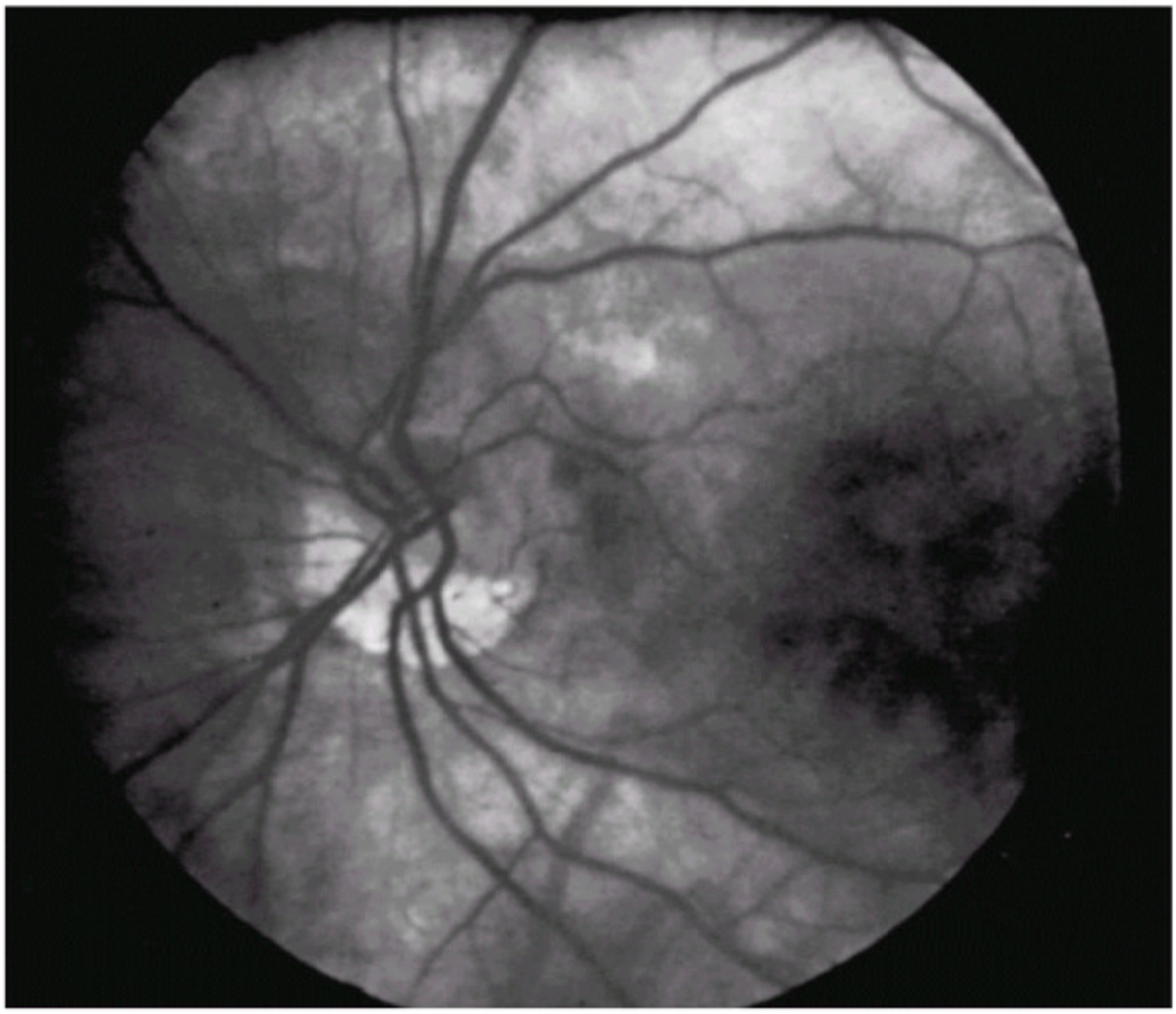

Figure 17.24 Tilted disc syndrome. The optic nerve is tilted inferiorly, an inferonasal conus is present, and situs inversus can be seen.

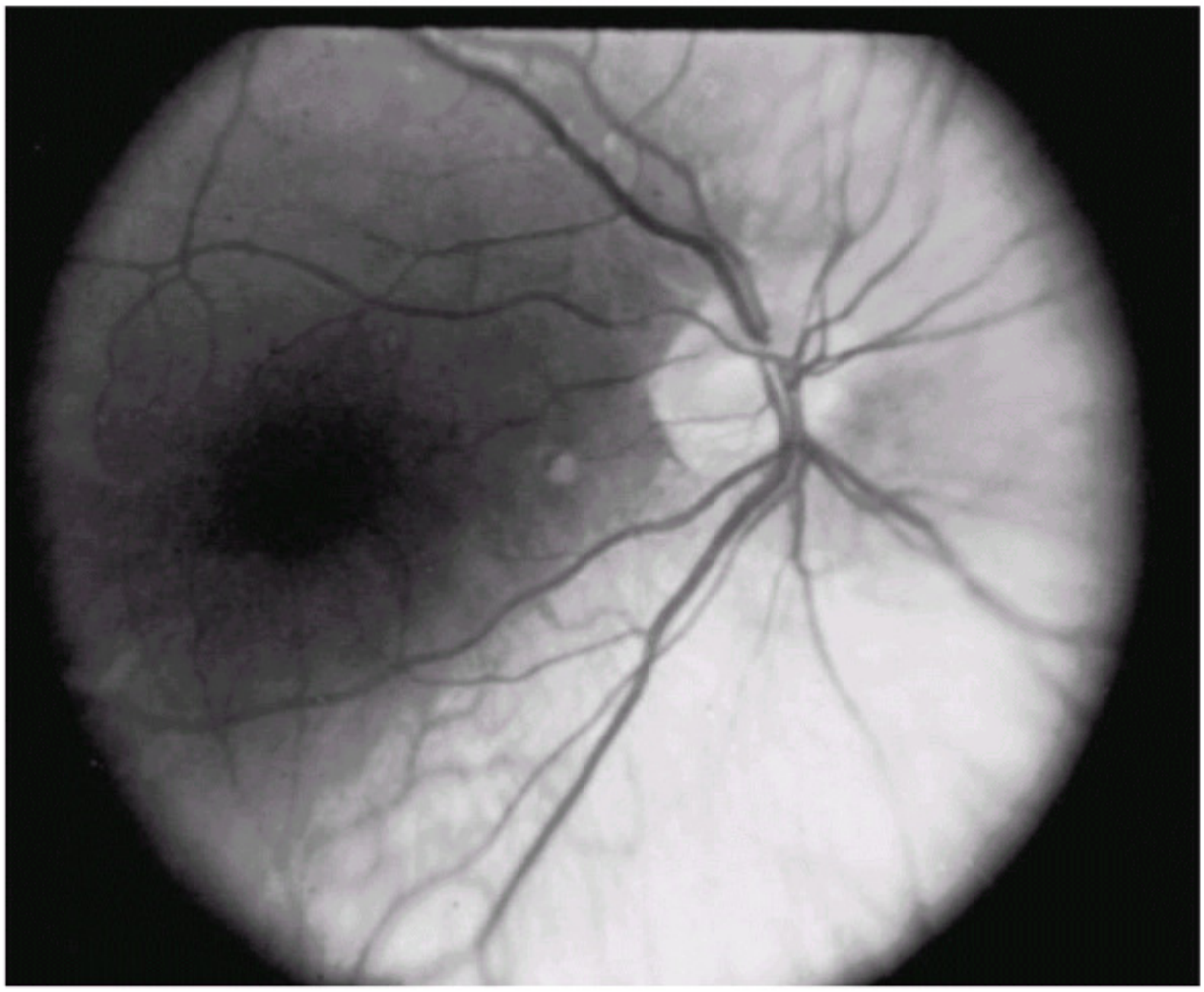

Figure 17.25 Tilted disc syndrome in another eye shows lightening of the inferior ectatic fundus and blurring of the superior disc margin.

The margins of the optic nerve head are often elevated superiorly because of the tilting effect, at times mimicking the appearance of papilledema. Bilaterality is seen in 75% of cases, and most eyes with hypopigmented, inferior fundus ectasia have associated superotemporal visual field defects. Bilateral disc swelling, decreased vision, and field defects in persons with the tilted disc syndrome have led to the misdiagnosis of a pituitary tumor in the past. Unlike the field abnormalities associated with perichiasmal lesions, which respect the vertical midline, those seen in the tilted disc syndrome are often relative and cross the vertical midline (35,36).

In 75% of eyes with the tilted disc syndrome, the visual acuity is reduced to the 20/25 to 20/50 range. Despite decreased visual acuity, these patients generally do not experience visual loss. It is uncertain why the vision is decreased, but the possibility that obliquely oriented macular cones account for the loss has been proposed (36).

SIZE ABNORMALITIES

Optic Nerve Hypoplasia

Variants of this entity range from almost imperceptible hypoplasia to severe involvement of the optic disc. The typical funduscopic appearance is that of a small disc in which the retinal vessels enter and exit centrally (Fig. 17.26), in contrast with their usual more nasal location on the normal optic nerve head. The retinal vessels are generally normal in caliber. A “double ring” sign may be present, the outer ring of which has been shown histopathologically to correlate with the junction of the sclera and lamina cribrosa and corresponds to the size of the normal disc (37). The inner ring is formed by the border of the central optic nerve head tissue with the retina and retinal pigment epithelium, which extend abnormally posteriorly over the surface of the disc.

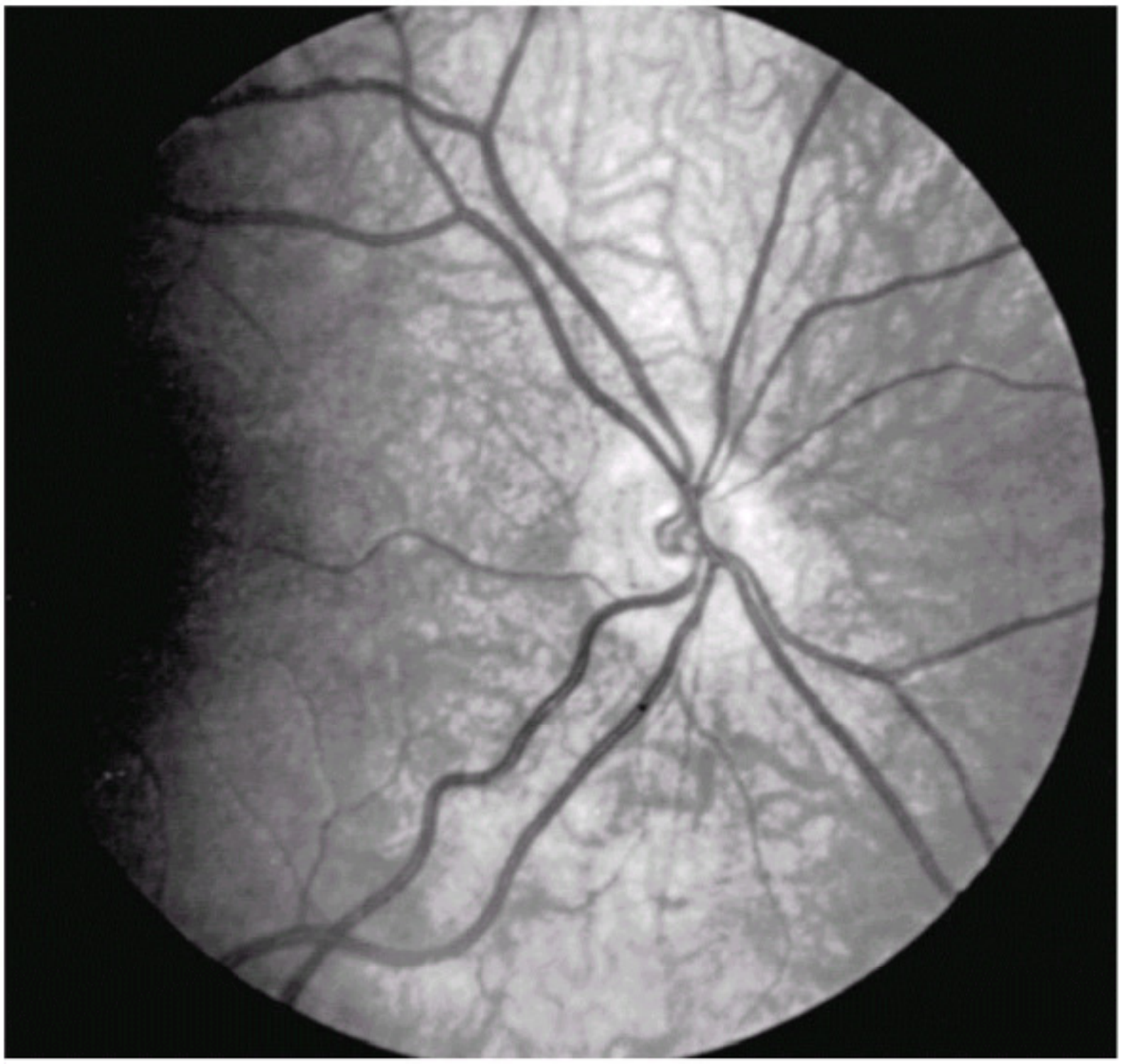

Figure 17.26 Hypoplastic optic disc. The retinal vessels are normal in size and enter and exit relatively centrally on the disc.

Optic nerve hypoplasia is believed to occur secondary to failure of development of the ganglion cell layer of the retina (38), although retrograde degeneration caused by congenital lesions of the cerebral hemispheres has also been reported (39). An autosomal dominant hereditary pattern has been rarely noted (40). Pharmacologic insults that have been associated prenatally in mothers of children with optic nerve hypoplasia include the use of phenytoin (41), quinine (42), lysergic acid diethylamide, meperidine, diuretics, and corticosteroids (43). As is the case with pharmacologic agents, the role of maternal infections during pregnancy in causing optic nerve hypoplasia in the child is uncertain. The entity has been seen in conjunction with congenital cytomegalovirus, as well as maternal syphilis and rubella (43,44). Diabetes mellitus in the mother has also been associated in a number of cases (43,45).

Unilateral and bilateral cases seem to occur with almost equal frequency. The visual acuity is variable and can range from normal to no light perception. Visual field abnormalities can be seen, including altitudinal defects, localized and generalized constriction, centrocecal scotomas, bitemporal hemianopsias, and binasal hemianopsias (20). Concomitant nystagmus and strabismus may be present, particularly in more severe cases.

Optic nerve hypoplasia has been associated with a number of systemic abnormalities. Approximately 13% of affected patients have pituitary dysfunction, including anterior pituitary defects with growth hormone insufficiency, posterior pituitary dysfunction (diabetes insipidus), and panhypopituitarism (46). This can occur in unilateral or bilateral cases. Partial or complete absence of the septum pellucidum has been seen in approximately one fourth of patients. Agenesis of the septum pellucidum in conjunction with optic nerve hypoplasia is known as DeMosier's syndrome (47).

Optic Nerve Aplasia

With optic nerve hypoplasia, the retinal blood vessels and optic disc are present. In contrast, with true optic nerve aplasia, both the disc and retinal vessels are absent (Fig. 17.27), as are the retinal ganglion cells (48). Fortunately, the entity is usually unilateral. Some early reported cases of optic nerve aplasia were probably variants of optic nerve hypoplasia.

The visual acuity with optic nerve aplasia is no light perception. Fluorescein angiography discloses only a choroidal flush, whereas electroretinography is subnormal, but a-waves and b-waves can be present (48). Concurrent microphthalmos and retinochoroidal coloboma have been reported (48).

Optic nerve aplasia can occur as an isolated finding, but it has been associated with cyclopia, partial agenesis of the central nervous system, and a Hallermann-Streiff-like syndrome (48). Causative associations are lacking.

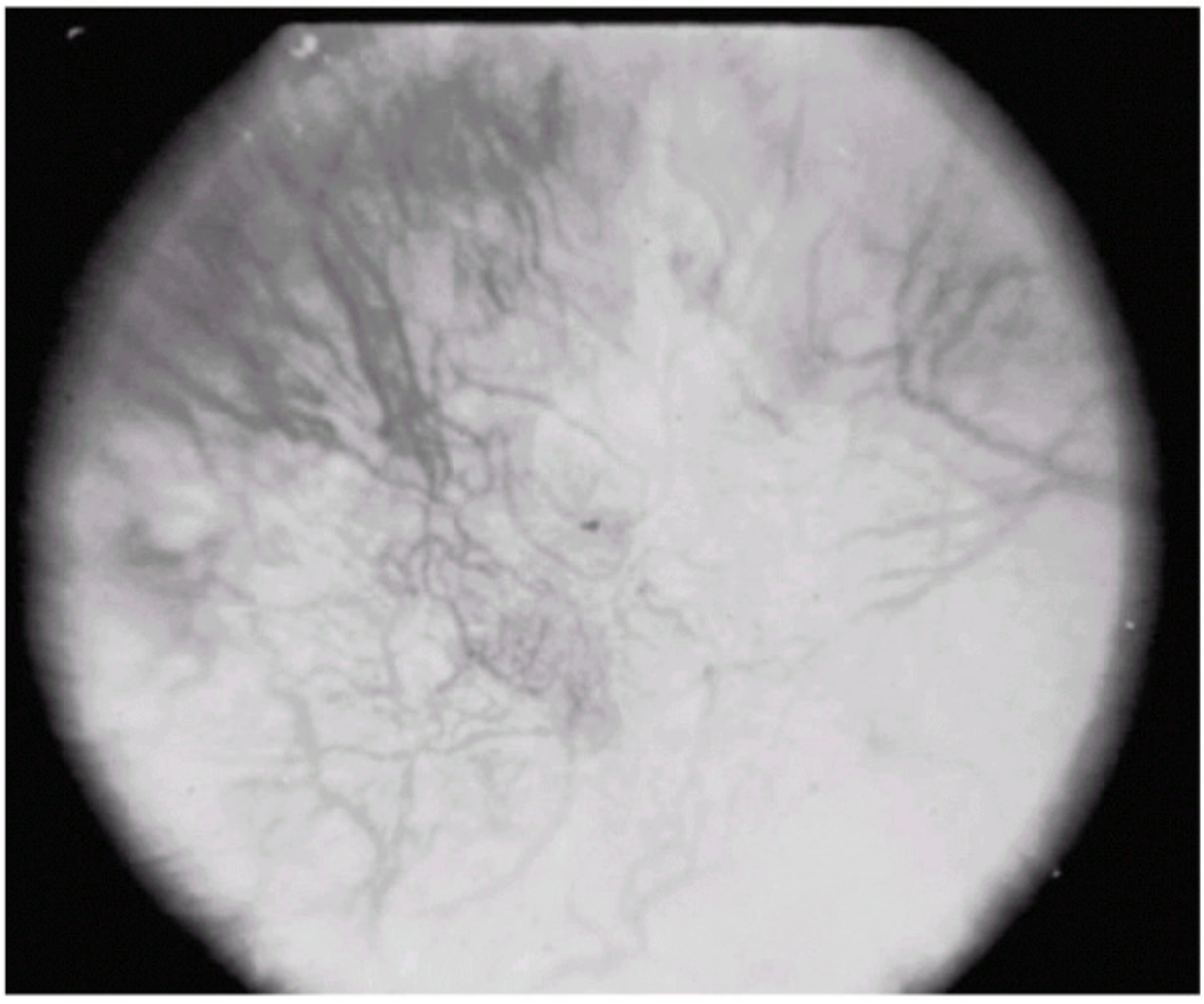

Figure 17.27. Optic nerve aplasia. The nerve head and retinal vessels are absent. (Courtesy of Leonard Nelson, MD, Wills Eye Hospital.)

Megalopapilla

Abnormalities that have been associated with an enlarged optic disc include coloboma of the optic disc, congenital optic pit, morning glory disc anomaly, high myopia, and megalopapilla. Clinically, megalopapilla manifests as an enlarged but otherwise usually normal-appearing optic disc (Fig. 17.28). A mild peripapillary, retinal pigment epithelial disturbance is frequently observed, but other intraocular abnormalities have not been consistently associated.

First described by Franceschetti and Bock in 1950 (49), megalopapilla is generally not associated with decreased visual acuity, although mild to moderate visual loss has been noted (50). By strict definition, the entity includes optic discs with averaged horizontal and vertical diameters that measure approximately 2.1 mm or greater. The embryologic derivation is uncertain, but it is thought to arise from abnormal development of the primitive epithelial papilla (51).

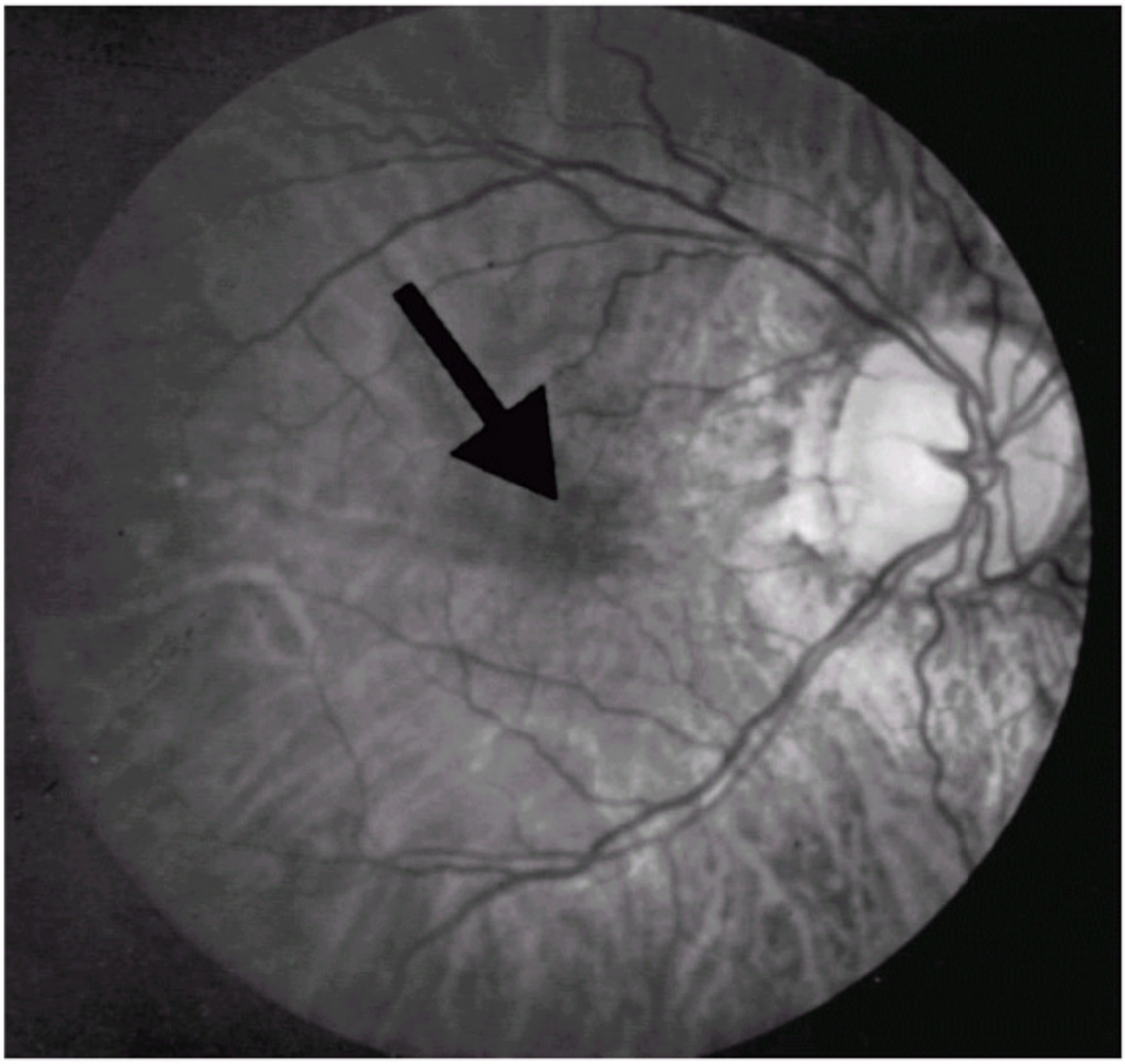

Figure 17.28 Megalopapilla. Central fovea (*arrow*). Note that the distance between the arrow and the disc margin is only approximately 1 disc diameter. The retinal vessels are normal in caliber but appear small because of the enlarged size of the disc.

An enlarged blind spot is present on visual field examination, but partial superotemporal quadrantanopsia has also been noted (52). Systemic abnormalities that have been described in conjunction with megalopapilla include basal encephalocele, cleft palate, and mandibulofacial dysostosis (49,50,51,52,53).

REFERENCES

1. Liebrich R. Demonstration of diseases of the eye. Persistent hyaloid artery and vein. *Trans Pathol Soc Lond* 1871;22:221-224.

2. Brown G, Tasman W. *Congenital anomalies of the optic disc*. New York: Grune & Stratton, 1983a:31-93; 1983b:95-215.

3. Degenhart W, Brown GC, Augsburger JJ, et al. Prepapillary vascular loops: a clinical and fluorescein angiographic study. *Ophthalmology* 1981;88:1126-1131.

4. Mann I. *Developmental abnormalities of the eye*, 2nd ed. Philadelphia: JB Lippincott Co., 1957:133-136.

5. Shakin EP, Shields JA, Augsburger JJ, et al. Clinicopathologic correlation of a prepapillary vascular loop. *Retina* 1988;8:55-58.

6. Jones HE. Hyaloid remnants in the eyes of premature babies. *Br J Ophthalmol* 1963;47:37-44.

7. Delaney WW. Prepapillary hemorrhage and persistent hyaloid artery. *Am J Ophthalmol* 1980;90:419-421.

8. Mann IC. *Development of the human eye*, 3rd ed. New York: Grune & Stratton, 1969:27-28, 228-231.

9. Shields JA, Joffe L, Guibor P. Choroidal melanoma clinically simulating a retinal angioma. *Am J Ophthalmol* 1978;85:67-81.

10. Archer DB, Deutman A, Ernest JT, et al. Arteriovenous communications in the retina. *Am J Ophthalmol* 1973;75:224-241.

11. Brown GC, Donnoso LA, Magargal LE, et al. Congenital retinal macrovessels. *Arch Ophthalmol* 1982;100:1430-1436.

12. Augsburger JJ, Goldberg. RE, Shields JA, et al. Changing appearance of retinal arterial malformation. *Albrecht von Graefes Arch Klin Exp Ophthalmol* 1980;215:65-70.

13. Cameron ME, Greer CH. Congenital arteriovenous aneurysm of the retina. *Br J Ophthalmol* 1968;52:768-772.

14. Wyburn-Mason R. Arteriovenous aneurysm of midbrain and retina, optic nerve, chiasm and brain. *Brain* 1943;66:165-203.

15. Rundles WZ, Falls HF. Congenital arteriovenous (racemose) aneurysm of the retina. *Arch Ophthalmol* 1951;46:408-418.

16. Kranenburg EW. Crater-like holes in the optic disc and central serous retinopathy. *Arch Ophthalmol* 1960;64:912-928.

17. Brown GC, Shields JA, Goldberg RE. Congenital pits of the optic nerve head. II. Clinical studies in humans. *Ophthalmology* 1980; 87:51-65.

18. Borodic GE, Gragoudas ES, Edward WO, et al. Peripapillary subretinal neovascularization and serous macular detachment. Association with congenital optic nerve pits. *Arch Ophthalmol* 1984; 102(2):229-231.

19. Brown GC, Shields JA, Patty BE, et al. Congenital pit of the optic nerve head. I. Experimental studies in collie dogs. *Arch Ophthalmol* 1979;97:1341-1344.

20. Brown G, Tasman W. *Congenital abnormalities of the optic disc*. New York: Grune and Stratton, 1983b, 92-215.

21. Lincoff H, Lopez R, Kreissig I, et al. Retinoschisis associated with optic pits. *Arch Ophthalmol* 1988;106:61-67.

22. Brown GC, Brown MM. Treatment of retinal detachment associated with congenital excavated defects of the optic disc. *Ophthalmic Surg* 1995;26:11-15.

23. Cox MS, Witherspoon CD, Morris RE, et al. Evolving techniques in the treatment of macular detachment caused by optic nerve pits. *Ophthalmology* 1988;95:889-896.

24. Van Nouhuys JM, Bruyn GW. Nasopharyngeal transsphenoidal encephalocele, craterlike hold in the optic disc and agenesis of the corpus callosum; pneumoencephalographic visualisation in a case. *Psychiatr Neurol Neurochir* 1964;67:243-258.

25. Babel PJ, Farpour E. L'origene genetique des fossettes colobomateuses des nerf optique. *J Genet Hum* 1967;16:187-198.

26. Vossias A. Beitrag zur lehre von den angeborenen conis. *Klin Monatsbal Augenheilkd* 1885;23:137-157.

27. Lyle DJ. Coloboma of the optic nerve. *Am J Ophthalmol* 1932;15: 347-349.

28. Savell J, Cook JR. Optic nerve colobomas of autosomal-dominant heredity. *Arch Ophthalmol* 1976;94:395-400.

29. Pagan RA, Graham JM, Zonana J, et al. Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr* 1981;99:223-227.

30. Kindler P. Morning glory syndrome: unusual congenital optic disc anomaly. *Am J Ophthalmol* 1970;69:376-384.

31. Steinkuller PG. The morning glory disc anomaly: case report and literature review. *J Pediatr Ophthalmol* 1980;17:81-87.

32. Beyer WB, Quencer RM, Osher RH. Morning glory syndrome: a functional analysis including fluorescein angiography, ultrasonography, and computerized tomography. *Ophthalmology* 1982; 100:1361-1367.

33. Pollock JA, Newton TH, Hoyt WF. Transsphenoidal and transethmoidal encephaloceles. *Radiology* 1968;90:442-453.

34. Wise JB, MacLean JL, Gass JDM. Contractile peripapillary staphyloma. *Arch Ophthalmol* 1966;75:626-630.

35. Riise D. Visual field defects in optic disc malformation with ectasia of the fundus. *Acta Ophthalmol* 1966;44:906-918.

36. Riise D. The nasal fundus ectasia. *Acta Ophthalmol* 1975; 126(Suppl):5-108.

37. Mosier MA, Lieberman MF, Green WR, et al. Hypoplasia of the optic nerve. *Arch Ophthalmol* 1978;96:1437-1442.

38. Jerome B, Forster HW. Congenital hypoplasia (partial aplasia) of the optic nerve. *Arch Ophthalmol* 1948;34:669-672.

39. Ellenberger C, Runyan TE. Holoprosencephaly with hypoplasia of the optic nerves, dwarfism and agenesis of the septum pellucidum. *Am J Ophthalmol* 1970;70:960-967.

40. Hackenbruch Y, Meerhoff E, Besio R, et al. Familial bilateral optic nerve hypoplasia. *Am J Ophthalmol* 1975;79:314-320.

41. Hoyt CS, Billson FA. Maternal anticonvulsants and optic nerve hypoplasia. *Br J Ophthalmol* 1978;62:3-6.

42. McKinna AJ. Quinine induced hypoplasia of the optic nerve. *Can J Ophthalmol* 1966;1:261-266.

43. Hotchkiss ML, Green WR. Optic nerve aplasia and hypoplasia. *J Pediatr Ophthalmol* 1979;16:225-240.

44. Hittner HM, Desmond MM, Montgomery JR. Optic nerve manifestations of human congenital cytomegalovirus. *Am J Ophthalmol* 1976;81:661-665.

45. Petersen RA, Walter DS. Optic nerve hypoplasia with good visual acuity and visual field defects. *Arch Ophthalmol* 1977;95:254-258.

46. Acers TE. Optic nerve hypoplasia: septo-optic pituitary dysplasia syndrome. *Trans Am Ophthalmol Soc* 1981;79.425-457.

47. DeMosier G. Agenesie du septum lucidum avec malformation du tractus optique: la dysplasie septo-optique. *Schweiz Arch Neurol Neurochir Psychiatr* 1956;77:267-292.

48. Little LE, Whitmore PU, Wells TU. Aplasia of the optic nerve. *J Pediatr Ophthalmol* 1976;13:84-88.

49. Franceschetti A, Bock RH. Megalopapilla: a new congenital anomaly. *Am J Ophthalmol* 1950;33:227-235.

50. Strieff B. Uber megalopapillae. *Klin Monatsbl Augenheilkd* 1961; 139:824-827.

51. Badtke G. Ober die grossenanomalien der papilla nervi optici, unter besonderer: berucksichtigung der schwarzen megalopapille. *Klin Monatsbl Augenheilkd* 1959;135:502-510.

52. Merin S, Harwood-Nash DC, Crawford JS. Axial tomography of optic nerve defects. *Am J Ophthalmol* 1971;72:1122-1129.

53. Malbran JL, Roveda JM. Megalopapilla. *Arch Oftalmol B Aires* 1951; 26:331-335.

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18

Disorders of the Lacrimal Apparatus in Infancy and Childhood

Deborah K. VanderVeen

This chapter reviews the anatomy and physiology of the lacrimal apparatus, and the identification and management of lacrimal disorders in infants and children. The lacrimal apparatus includes both structures involved in the production of tears and those that allow drainage of tears away from the eye and into the nose.

ANATOMY

The main tear-producing structures are the lacrimal gland and the accessory glands of Krause and Wolfring. Tears are composed of three components: an inner mucinous layer, a middle aqueous layer, and an oily outer layer. Mucin is produced by goblet cells of the conjunctiva, the aqueous layer is produced by the lacrimal glands, and the oily layer is produced by the meibomian glands.

The main lacrimal gland is located in the superolateral quadrant of the anterior orbit, within the lacrimal gland fossa. It is separated into the orbital and palpebral lobes by the lateral horn of the levator aponeurosis. The ducts from the orbital lobe run through the palpebral lobe and empty into the superior cul-de-sac approximately 5 mm above the lateral tarsal border. The palpebral lobe of the lacrimal gland is a tan, globular structure and can often be seen in the lateral portion of the superior fornix, when the eye looks down and in. It is important to remember the location of the lacrimal gland when operating in this area (e.g., during dermolipoma excision or for ptosis surgery), because damage to the palpebral portion of the gland can seriously reduce secretion from the entire gland.

The main lacrimal gland is responsible for reflex tearing. Stimulation of the fifth cranial nerve receptors provides the stimulus for tear production, for example, from irritation of the surface of the eye or within the nose. The lacrimal gland is supplied by both sympathetic and parasympathetic nerves, although secretory function is under parasympathetic control. Parasympathetic fibers enter the lacrimal gland through the lacrimal nerve after traveling along the facial nerve and then the zygomatic nerve.

The accessory glands of Krause and Wolfring are found in the subconjunctival tissue, mainly in the upper eyelid between the superior tarsal border and the fornix, and to a limited degree in the inferior fornix. They are responsible for the basal or constant level of lacrimal secretion that is necessary for lubrication of the surface of the globe.

Evaporation plays a minor role in the elimination of tears, and most tear drainage occurs through a series of structures that carry tears away from the eye and into the nose. The superior and inferior puncta are openings found on the lid margins approximately 5 to 6 mm from the medial canthus. They are situated on relatively avascular slight elevations called papillae. The puncta are normally in a slightly inverted position against the globe and the tear lake. The lower punctum is slightly lateral to the upper, so a line drawn between them makes an angle of approximately 15 degrees with the long axis of the body. Each punctum is the opening to the canalicular system. The ampullae are slight dilatations of the canaliculi just distal to the puncta, are approximately 2 mm long in adults, and lie perpendicular to the lid margin. This short vertical segment is followed by an 8- to 10-mm horizontal segment that gently curves toward the medial canthus and lies just below the lid margin surface. In 90% of patients, the canaliculi

join to form a single common canaliculus that enters the lateral wall of the tear sac. The puncta and canalicular system are surrounded by elastic tissue, so each can be dilated to approximately three times its normal diameter of 0.5 to 1 mm.

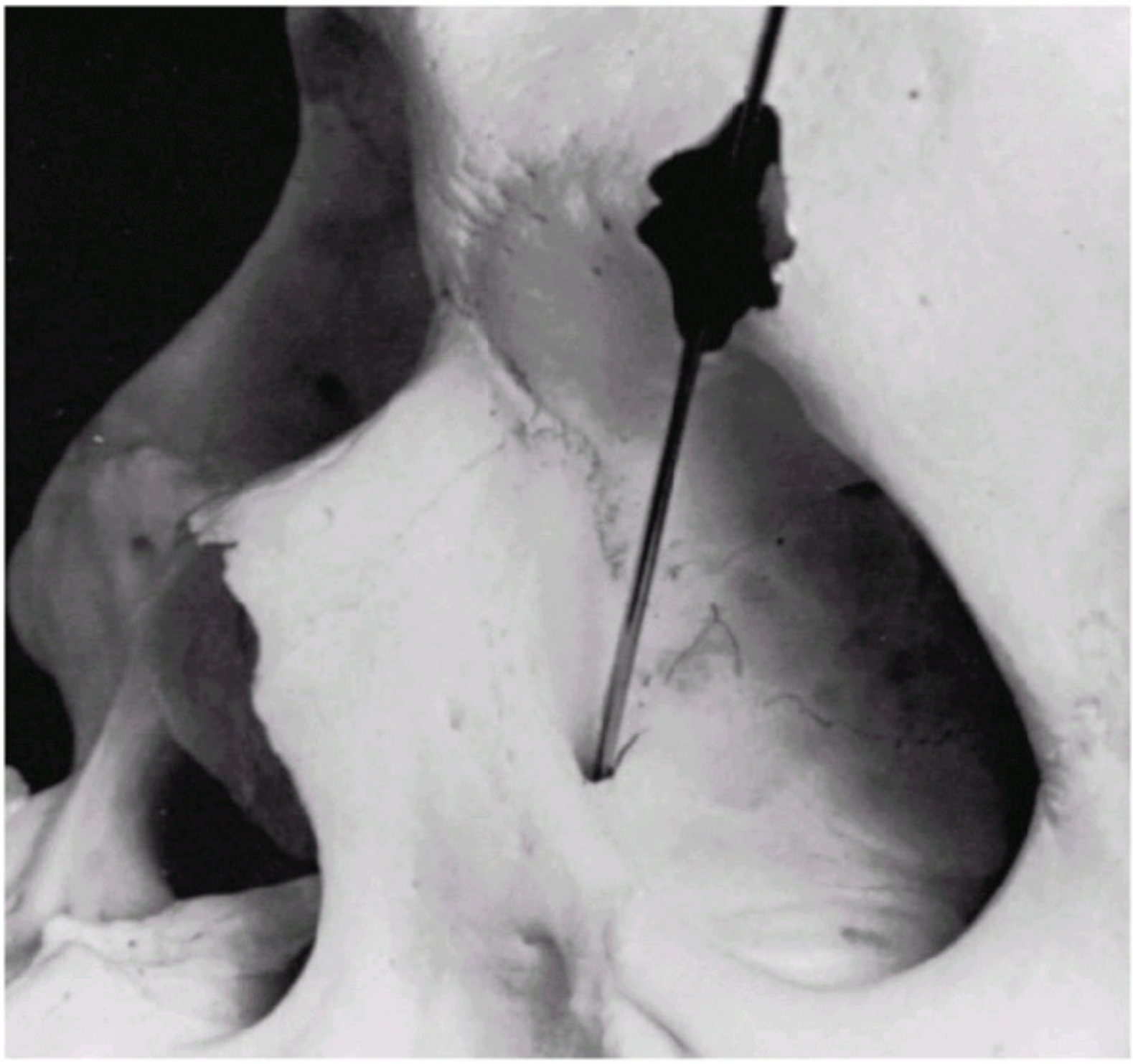

Figure 18.1 Bowman probe is in the bony nasolacrimal duct that begins at the inferior portion of the shallow lacrimal sac fossa.

The lacrimal sac lies within the lacrimal fossa, which is formed by the frontal process of the maxilla and the lacrimal bone (Fig. 18.1). The valve of Rosenmuller is a small fold of mucosa that normally prevents tear reflux from the sac back into the canaliculi. The adult lacrimal sac is approximately 12 to 15 mm in height and lies between the anterior and posterior crus of the medial canthal tendon. Most of the sac is situated below the medial canthal tendon, and for this reason dacryocystoceles or lacrimal sac abscesses typically present just inferior to the medial canthal tendon. The nasolacrimal duct is inferior to the lacrimal sac and measures approximately 12 mm in length. The nasolacrimal duct opens into the nose through an ostium that is usually partially covered by a mucosal fold called the valve of Hasner. The ostium is usually found under the anterior portion of the inferior turbinate (Fig. 18.2).

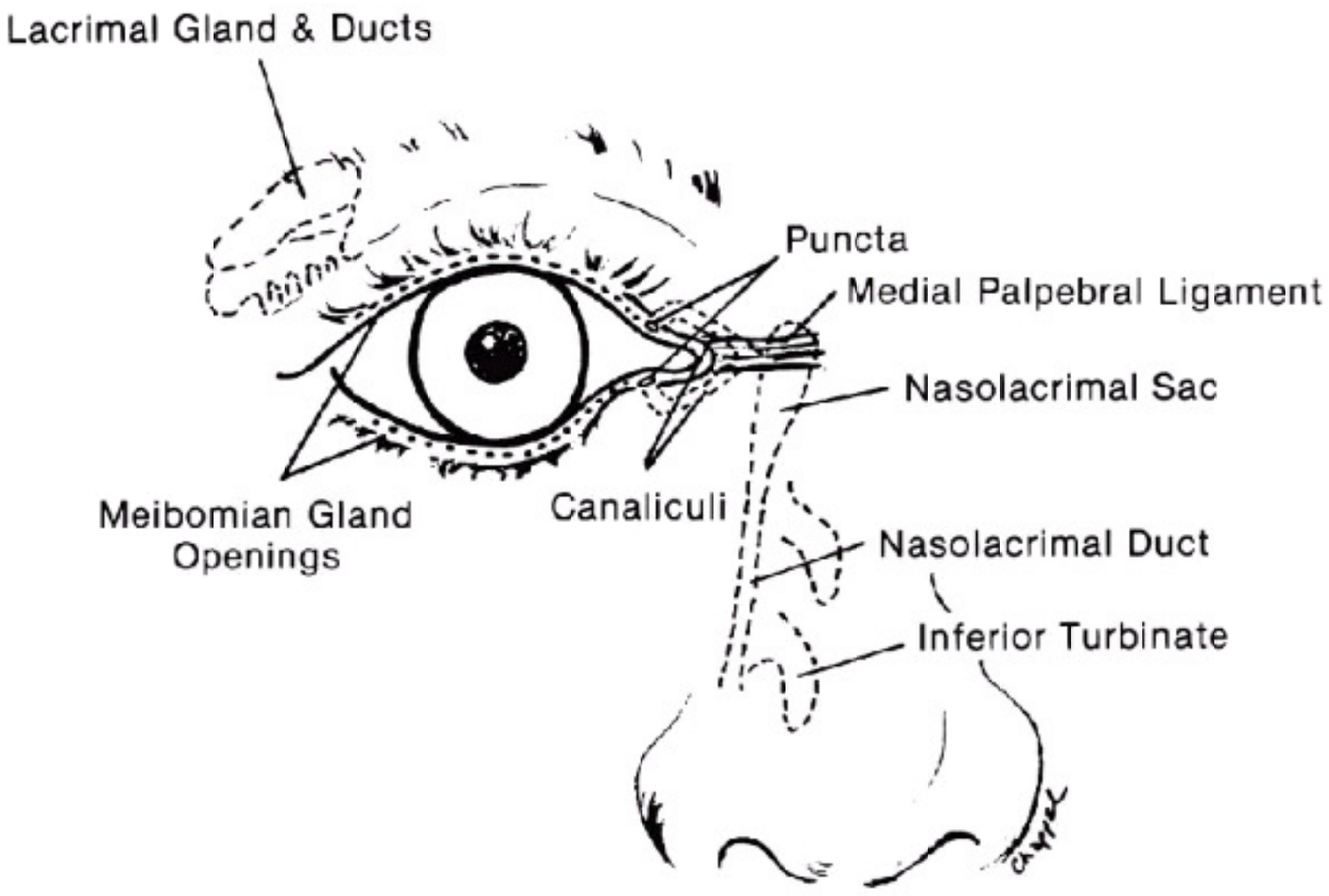

Figure 18.2 Lacrimal system showing the location of the lacrimal gland and the drainage system.

The lining of the canalicular system, lacrimal sac, and duct is pseudostratified columnar epithelium, similar to that found in the upper respiratory system. Mucus-producing goblet cells are present, and irritation or chronic lowgrade infection stimulates the production of the mucus or mucopurulent secretions that are often seen in nasolacrimal duct obstruction.

Most of the tear lake is actively pumped away from the eye by the actions of the orbicularis muscle. Jones (1) proposed that during eye closure the superficial and deep heads of the pretarsal orbicularis muscle compress the ampullae and shorten the horizontal canaliculus. At the same time the deep heads of the preseptal orbicularis, which are attached to the lacrimal sac fascia, contract, which expands the sac and creates negative pressure. This draws the tears from the canalicular system into the sac. When the eye opens, the orbicularis muscles relax and the resilience of the lacrimal sac fascia collapses the tear sac, forcing tears through the duct and into the nose. As the lids open and the puncta move laterally, the tears of the tear lake once again fill the ampullae and canaliculi. An alternative theory (Rosengren-Doane) suggests that the contraction of the orbicularis creates a positive pressure in the tear sac, which forces the tears into the nose, and as the eye opens the negative pressure created from reexpansion of the sac draws tears into the canaliculi when the puncta separate.

EMBRYOLOGY

The tear drainage system begins as a solid cord of ectoderm between the lateral and medial maxillary processes, and grows laterally and downward beginning at approximately the 10-mm stage of development. The cord separates from

the overlying ectoderm by the 15-mm stage, and the lateral portion grows toward the lids to form the canaliculi and toward the nose to form the duct. Cavitation of the system begins in the third month by degeneration and shedding of the central cells, and the process is mostly complete by the seventh month. The duct is the last portion of the system to canalize. Obstruction of the distal end of the duct (valve of Hasner) is often present at birth, but patency occurs spontaneously within the first few months of life in the majority of cases.

CONGENITAL ANOMALIES OF LACRIMAL SECRETORY APPARATUS

Absence of the lacrimal gland is a rare condition that may present as chronic irritation of the conjunctiva and cornea from dryness, and is treated as such. Computed tomography shows no discernible lacrimal gland (2). Alacrima may also occur in association with conditions of other developmental anomalies, such as anophthalmos or cryptophthalmos, or may be inherited as an autosomal dominant or recessive trait.

Absence of reflex tearing may be reported by parents as no tears in one eye or both eyes when the infant is crying. Usually such children do show normal basal tearing, but examination of the ocular surface should be performed to ensure that adequate lubrication exists. There should be no sign of ocular irritation with absent reflex tearing because the basal secretion from accessory lacrimal glands provides a sufficient tear film. No investigation or treatment is necessary.

“Crocodile tears,” or paradoxic gustolacrimal reflex, is unilateral tearing with mastication. This is rarely seen as a congenital defect, usually associated with an ipsilateral Duane syndrome or lateral rectus palsy. It is more commonly seen as an acquired condition, after a paralysis of the facial nerve, from trauma or surgery.

Prolapse of the palpebral lobe of the lacrimal gland may occur, and the palpebral lobe can often be identified under the conjunctiva in the lateral aspect of the superior fornix. This should be recognized as normal tissue and left undisturbed, because surgical excision would transect the ducts from the orbital portion and could produce a dry eye. Aberrant lacrimal tissue may be located elsewhere on the surface of the eye, under the conjunctiva. It may appear similar to a dermoid, except that it is not usually in the lower outer quadrant typical of dermoids (Fig. 18.3). Aberrant lacrimal tissue appears as a slightly raised, well-vascularized, multicystic mass, and histopathologically it is often described as a choristomatous malformation containing a lacrimal gland, among other elements. Usually there are no symptoms, but excision may be performed for diagnosis or cosmesis. Aberrant lacrimal gland tissue may also occur within the sclera or in the eye.

Lacrimal secretory ducts may be absent or become obstructed, leading to distention and cystic development, dacryops, of the lacrimal gland. Rarely, a portion of the tears from the lacrimal gland may exit in the lid above the tarsus from a fistula. The opening is typically surrounded by several hairs, and excision with closure in layers should correct the condition.

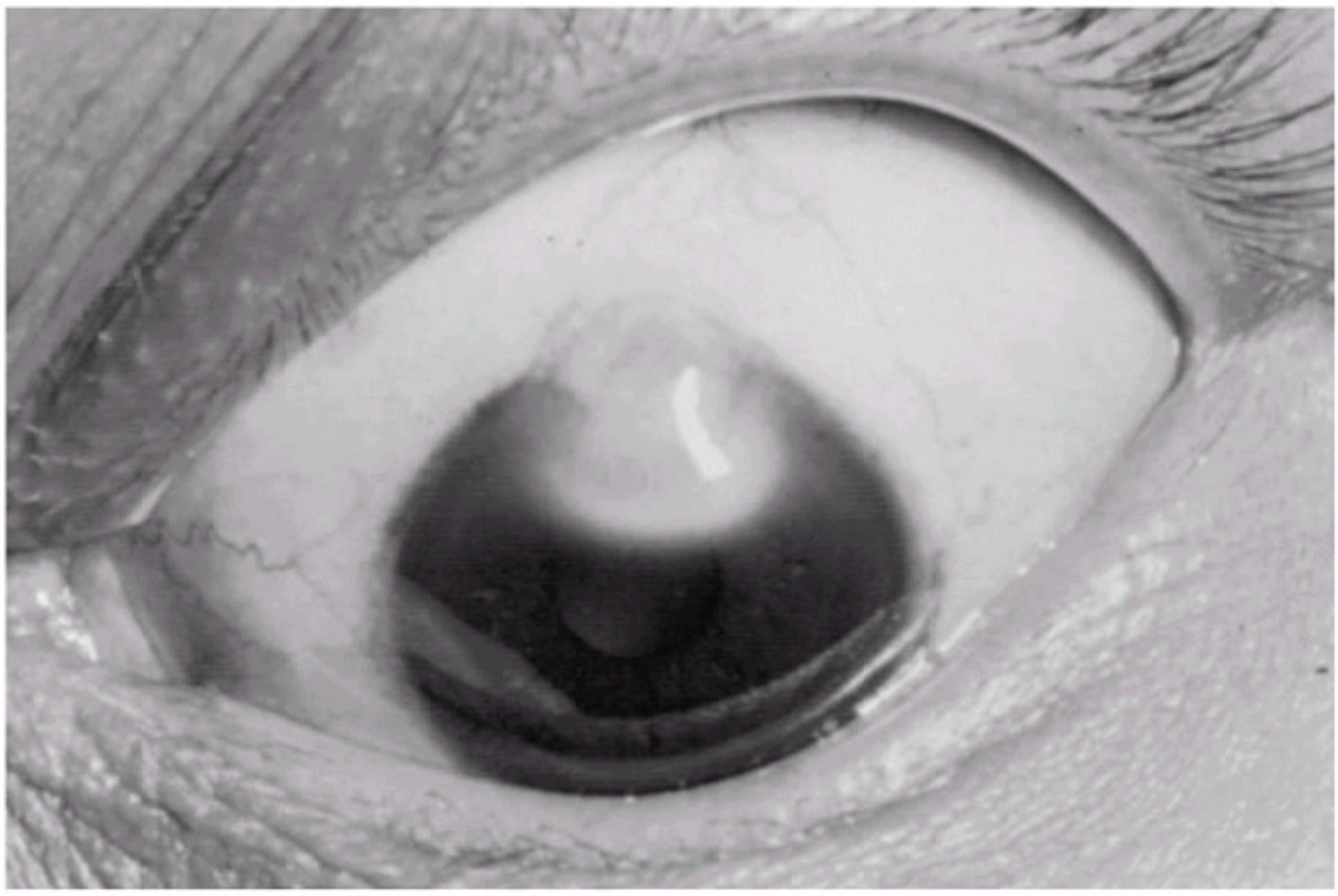

Figure 18.3 Choristoma at the limbus containing aberrant lacrimal gland.

ANOMALIES OF THE LACRIMAL DRAINAGE SYSTEM

Anomalies of the puncta and canaliculi include complete absence, stenosis, and duplication. The epithelium covering the opening into the lacrimal drainage system may fail to absorb or atrophy, and patients with this condition usually present with tearing but no discharge. The site to the imperforate punctum can be located by identifying the papilla, which is slightly pale, relatively avascular, and slightly raised. A sharp pin can sometimes perforate the membrane, after which a punctal dilator may be used to enlarge the opening, and a patent canaliculus may be found. If only the upper punctum is patent, a pigtail probe may be carefully passed through the upper canaliculus into the lower canaliculus and the location of the lower punctum determined by palpation. An incision may then be made directly onto the tip of the pigtail probe. This should be followed by placement of a silicone tube, which should be left in place for several months to maintain patency. Puncta may also be anomalous in position and number.

In addition to atresia of the lacrimal punctum, there may be atresia of the adjoining canaliculus. After attempts to perforate the suspected punctal membrane, a short 2-mm vertical incision can be made through the lid margin, several millimeters nasal to the papilla or nasal border of the tarsus. Searching for the severed ends of the canaliculus may allow probing in each direction to determine patency of the proximal system and to open the distal canaliculus at the punctum. Silicone intubation can then be performed with repair of the canaliculus in the standard fashion.

Dacryocystocele (amniotocele, or mucocele) is not uncommon at birth. This appears as a bluish, cystic, nontender, firm mass just inferior to the medial palpebral tendon along the side of the nose (Fig. 18.4). Occasionally this is confused with a hemangioma and must be also differentiated from a medial encephalocele. The typical appearance

and location, however, usually lend to easy diagnosis. The formation of a dacryocystocele requires both distal and proximal obstruction of the lacrimal drainage system. Mucous glands lining the lacrimal sac secrete mucus, and without a patent distal or proximal system, the lacrimal sac distends until the pressure within the distended sac ends further production.

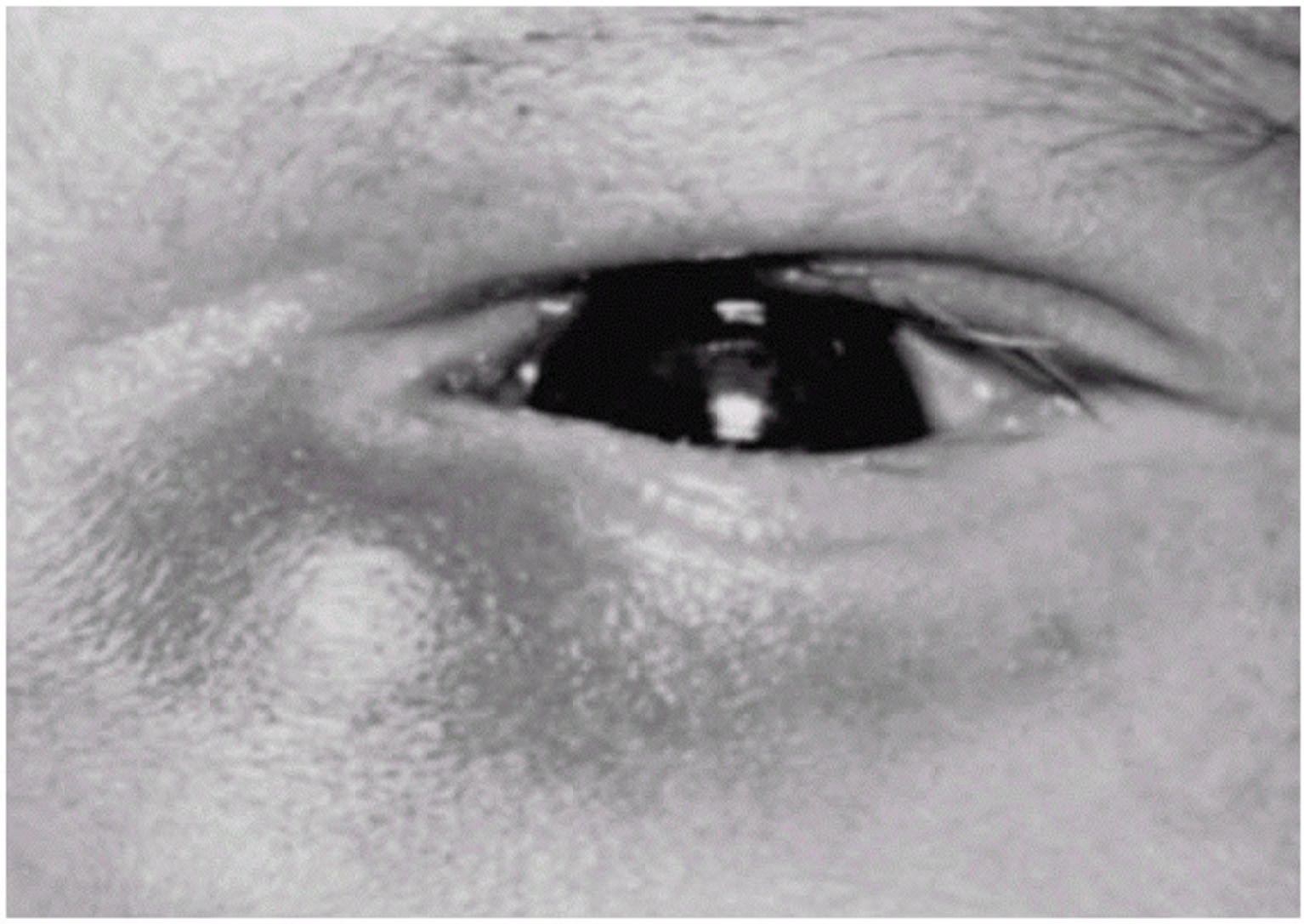

Figure 18.4 Dacryocystocele. Note the characteristic location.

On presentation, gentle pressure over the lacrimal sac should be tried, because this may allow decompression with drainage of the lacrimal sac contents into the nose, curing the problem. Often the obstruction will only be relieved proximally; consequently, the contents empty onto the eye. This maneuver, along with warm compresses and lid hygiene, may be repeated over the course of several days. If conservative management does not relieve the obstruction after several days or a week, the lacrimal system should be probed, which will allow the lacrimal sac contents to empty into the nose (3).

It is imperative to realize that untreated dacryocystoceles may gradually become inflamed and infected (Fig. 18.5). First, erythema of the overlying skin is seen, and this soon spreads to adjacent skin, creating a cellulitis, and the lacrimal sac takes on all the characteristics of an abscess. A healthy baby can quickly become a sick toxic one and should be treated with intravenous antibiotics under the guidance of a pediatrician. Probing should be delayed until an infection is under control. If there has been inflammation or infection, there is greater risk of causing a tear of the sac or creating a false passage, which will likely cause or reignite a cellulitis. Also, the dacryocele may resolve once the infection has been treated (4).

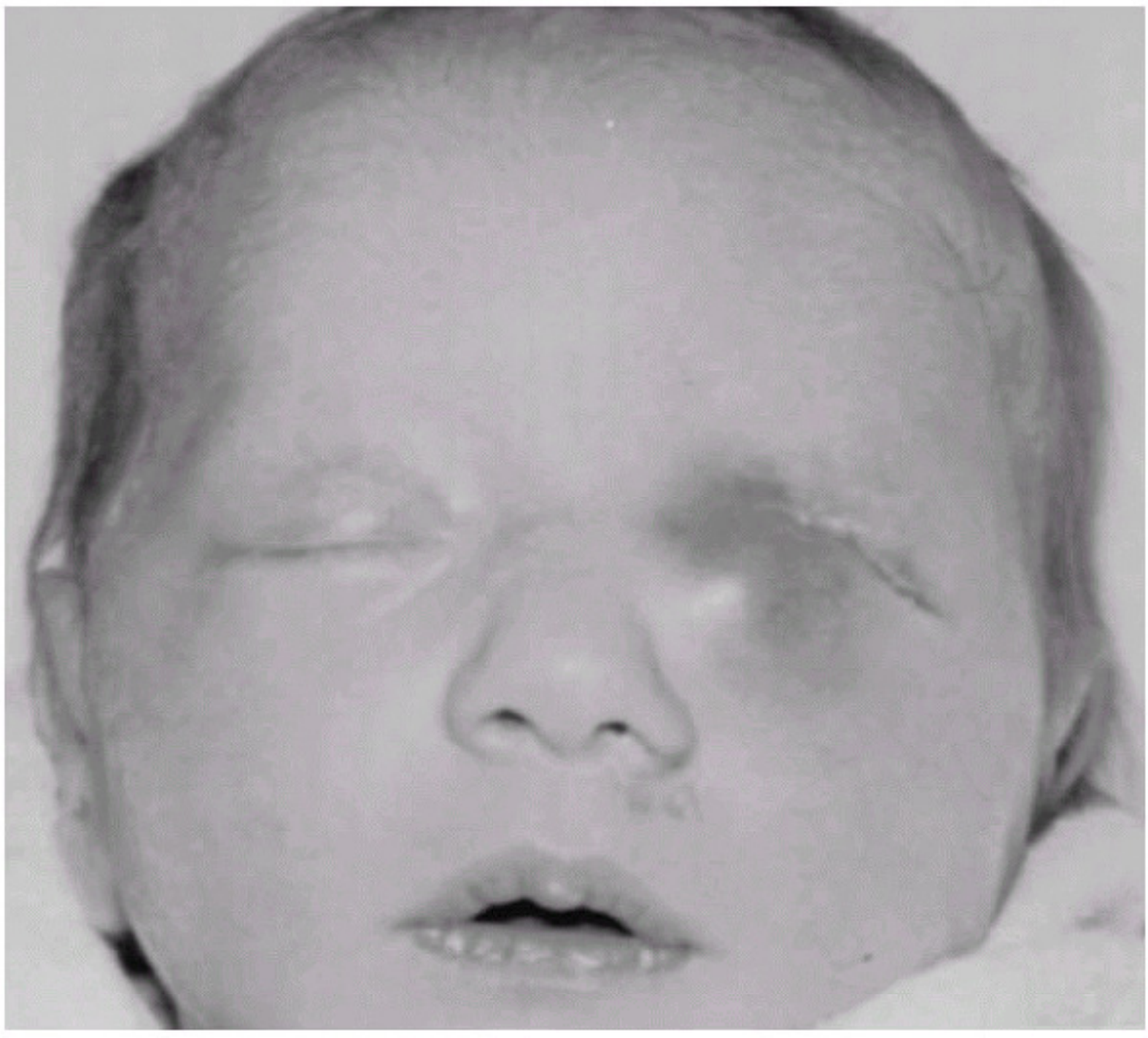

Figure 18.5 Same patient as in Figure 18.4. The mucocele is red, inflamed, tense, and larger than it was several days previously at birth.

It is not uncommon for dacryocystoceles to extend into the nasal cavity as an intranasal cyst (5,6). Identification of the cyst can be made by computed tomography or nasal endoscopy. Some infants will present with respiratory difficulty resulting from blockage of the nasal cavity by the cyst, especially if cysts are present bilaterally. Standard probing is often successful, but some infants require endoscopic removal of the redundant mucosa of the nasal cyst. Silicone intubation is not required.

A rare condition that may mimic dacryocystocele is a lacrimal sac diverticulum. This presents as a mass below the medial palpebral ligament and may be uninfected or infected. When the lacrimal system is drained, however, a palpable or visible mass remains. Treatment consists of surgical excision of the diverticulum, suturing closed the wall of the lacrimal sac where the diverticulum originated.

Lacrimal fistulae may allow tears to drain onto the surface of the skin in the medial canthal region, or below the medial canthal ligament, in the region where dacryocystoceles present. Pressure over the lacrimal sac may produce tears or mucopurulent discharge. If there is distal obstruction, tears or discharge will spontaneously exit the fistula, and probing should be performed. In some cases the fistula will then close spontaneously, and tears will drain into the nose in the normal manner. If the fistula persists, it may be excised to its exit from the lacrimal sac or the canaliculus. If normal drainage is not established before excision, the fistula is likely to recur. Occasionally a small depression or dimple can be found in this region, which may represent the cutaneous site of a lacrimal fistula that closed spontaneously, either in utero or after birth.

EVALUATION AND MANAGEMENT OF THE TEARING CHILD

In the evaluation of the tearing child, other causes of tearing such as corneal disease, congenital glaucoma, or infection must be ruled out. Distinction may be made between tearing alone, tearing with discharge, or intermittent tearing and discharge. Office evaluation includes inspection of the lid margins for the presence and apparent patency of puncta, as well as an anterior segment examination to look for other causes of tearing. Inspection of the medial canthal region for associated defects, such as medial encephalocele, dacryocele, or fistulae, is important. Digital pressure over the lacrimal sac should be performed to look for reflux. Dye disappearance testing may be performed, and delayed or asymmetric drainage after 5 minutes may provide evidence of partial obstruction. The Jones dye tests are difficult to perform accurately in pediatric patients in the office, because insertion of a cotton applicator into the nose will be resisted by the patient, and irrigation of the lacrimal sac generally cannot be safely performed in young patients.

CONGENITAL NASOLACRIMAL DUCT OBSTRUCTION

Congenital nasolacrimal duct obstruction is easily the most common abnormality of the lacrimal system in children. The management of this condition is also the most controversial.

Usually within the first several weeks of life, the affected infant is noticed by the parents to have excessive mucus or mucopurulent discharge on the lashes and

conjunctiva in the medial canthal region. The discharge is most evident after the infant awakens in the morning or from a nap. Sometimes the parents must use a moistened cloth to loosen the dried mucus on the lashes so that the infant can open his eyes. The family may note that the eye always looks wet (Fig. 18.6). Usually the conjunctiva remains white and uninflamed through these episodes, differentiating the condition from conjunctivitis. Epiphora is less commonly reported, but the family may notice overflow tears on the cheek, especially when the infant is taken outside during cold or windy weather.

Conservative management consists of waiting for spontaneous resolution, with regular lid hygiene and occasionally antibiotics or “massage.” The antibiotic drops or ointments reduce the infectious component of the discharge. Parents should be instructed that antibiotics will not cure the obstruction but may minimize the amount of the discharge or change the character of the discharge from mucopurulent to mucoid until either spontaneous resolution occurs or probing is performed. Lacrimal sac massage has been advocated to hasten resolution, and although “massage” is a misnomer, it is the commonly used term and no other word satisfactorily describes the proper technique. The technique was first described by Creiger in 1923 and is thus called the Creiger maneuver. It consists of applying pressure over the lacrimal sac with the finger sliding down the nose toward the mouth. This represents an attempt to trap fluid in the lacrimal sac, with the downward motion breaking the obstruction in the lacrimal duct with hydrostatic pressure. Its effectiveness has been shown to increase the rate of nonsurgical resolution (7).

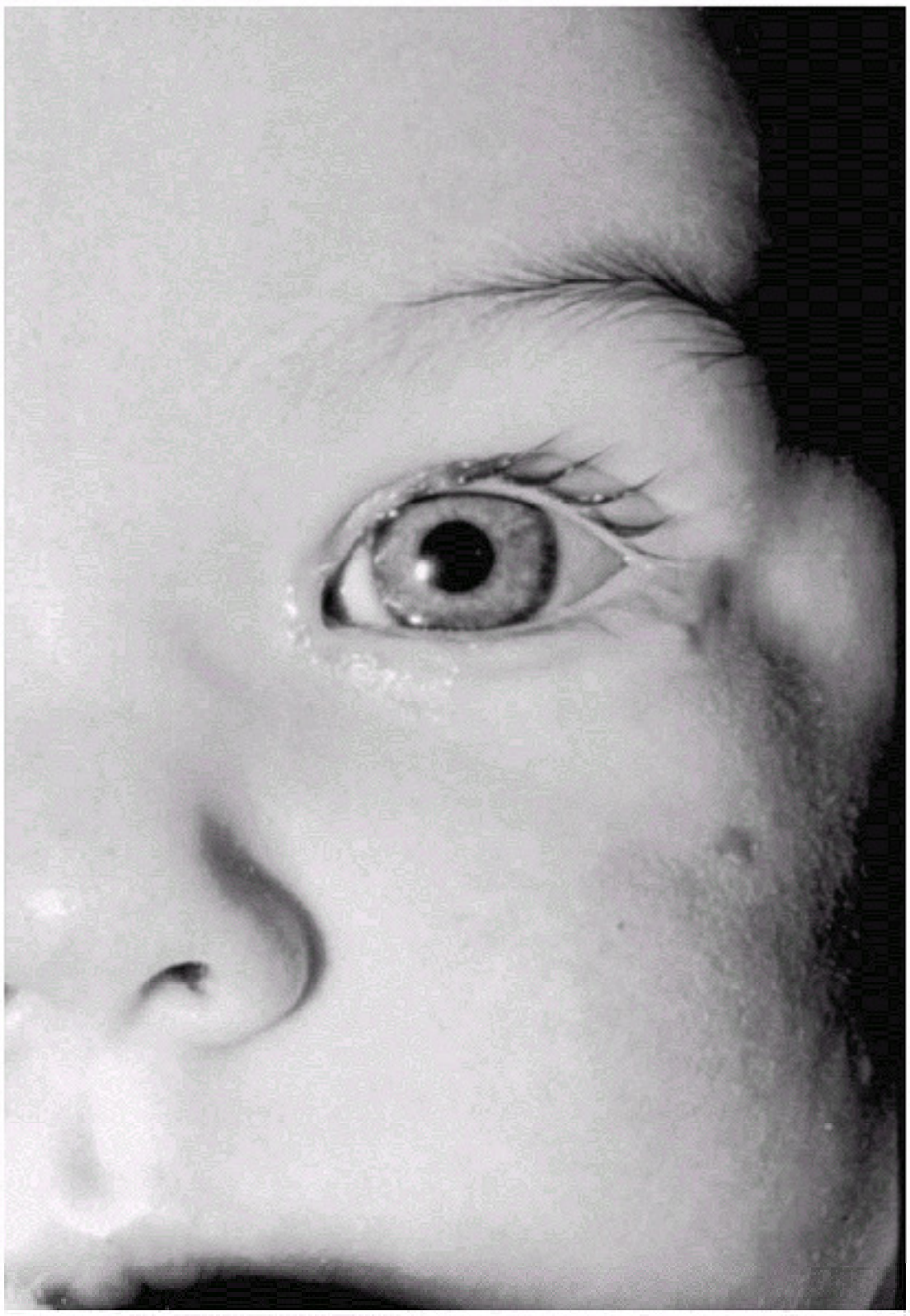

Figure 18.6 Infant with a blocked nasolacrimal duct. Note the large tear meniscus and wet-looking eye, which reflects the light from the camera flash. Note also the noninflamed white conjunctiva.

Several studies have documented the high rate of spontaneous resolution with conservative management (8,9,10,11,12,13). The largest prospective study of the natural history of congenital nasolacrimal duct obstruction was performed by MacEwen and Young in 1991. This study included a cohort of 4792 infants, and 20% showed evidence of defective lacrimal drainage at some time during their first year of life. By 1 year of age, more than 96% had resolved spontaneously. In this cohort, antibiotics were used only in a few patients who developed superimposed conjunctivitis, and dacryocystitis did not occur. No surgery was performed in the first year. For this reason, any decision to probe before 1 year of age should take into consideration this high rate of spontaneous resolution.

There is little controversy over the fact that probing, with or without irrigation, relieves most obstructions. When probing, it is useful to remember that the upper system begins with a short vertical segment for each canaliculus, followed by an 8-mm horizontal segment that gently curves toward the medial canthus. Probing through the upper canaliculus is preferred, because the angles from the punctum to the valve of Hasner are less acute than from the lower canaliculus. Probing is a delicate maneuver, and care should be taken to avoid a false passage. An appropriate diameter of probe (e.g., Bowman number 0 or 1 probe) should be used, and a slight curve of the probe aids in gentle passage. Lateral stretching of the lid allows smooth passage through the canalicular system into the lacrimal sac, where a hard stop should be felt. Rotation of the probe downward and posteriorly then should allow passage into the nasal cavity. The probe should pass under the inferior turbinate and then pass freely backward along the floor of the nose. Often a “pop” is felt when the distal obstruction is overcome on entry into the nose. Irrigation is performed by some surgeons at the conclusion to confirm patency of the system. Only a small amount of saline should be irrigated to avoid laryngospasm. Some surgeons irrigate saline with fluorescein, which is then retrieved from the nasal cavity to confirm patency, and some inject air and observe

for the movement of a soap bubble placed over the nostril.

Experienced pediatric ophthalmologists disagree on when probing should be performed and in what setting. Those who choose to probe early, in the office, consider that infants and their families should not have to endure

the months of chronic discharge in the affected eye or the inconvenience and annoyance of frequent instillation of topical antibiotics if this is required. The infant is restrained in some manner to restrict movement, and topical anesthesia is instilled. The probe is passed through the upper canaliculus, with care not to create a false passage. Confirmation of entry into the nose may be made using a larger probe and establishing metal on metal contact, but irrigation is not performed to avoid aspiration. Simple office probing has been shown to be safe, cost-effective, and predictably successful in the majority of cases. Use of this technique should be limited to ophthalmologists experienced in probings and to infants who are young enough to safely immobilize, usually before 6 to 8 months of age (14).

Those who choose to probe later, if resolution does not occur by 1 year of age, perform the procedure with general anesthesia. This avoids early probing for the majority of patients who would have shown spontaneous resolution and allows for controlled passage of the probe under anesthesia. Irrigation may be performed under anesthesia, but without excessive amounts of fluid to avoid laryngospasm. It is also easier to confirm passage into the nose with metal on metal contact. In addition, infracture of the turbinate may be performed if free irrigation is not obtained.

In deciding to probe early, some have suggested that lid or orbital cellulitis may be more likely in infants who have a chronic and untreated blocked nasolacrimal duct. In several prospective studies, however, this has not been seen (7,9,10,11). Delayed probing has been suggested to be less successful than early probing (15,16,17), but other studies show that probings performed before or after 1 year of age show comparable success rates (12,18,19). Several investigators have suggested that waiting allows selection of only patients with more complicated obstructions that are less likely to resolve spontaneously or with a simple probing. Patients with a simple obstruction at the valve of Hasner have been shown to have high success rates with probing regardless of the age at which it is performed (20).

In view of these arguments, a logical approach would involve a period of conservative management, with simple lid hygiene, the Creiger maneuver, and topical antibiotics as needed. Before 6 to 8 months of age, when the infant becomes too old to restrain, the ophthalmologist may decide to perform a careful probing in the office. This decision will be based on various factors, including the experience of probing in the office, the availability of anesthesia and hospital facilities should later probing be required, the feelings of the family, and whether the symptoms and discharge are being minimized with conservative management. If one waits, probing with general mask anesthesia is usually performed at 12 to 15 months of age. Early probing may be a logical choice for infants who have significant inflammation and discharge with associated irritation of the skin and conjunctiva despite medical management, either in the office or under anesthesia, or for those infants who are undergoing anesthesia for other procedures.

If symptoms persist despite an initial probe, the ophthalmologist must decide which procedure to undertake next. Often a second probing is performed, usually with larger probes, and often with an infracture of the inferior turbinate. If the inferior turbinate is so closely apposed to the lateral wall of the nose that the two mucosal surfaces touch each other, the drainage of tears will be blocked. Because the turbinate is composed of cartilage, no true fracturing occurs, but the turbinate may be pushed medially with a larger probe or other instrument, or grasped with a clamp and rotated medially.

If the nasolacrimal system remains blocked, most ophthalmologists proceed to the placement of silicone tubing or balloon dacryoplasty. Both show similar success rates. Crawford tubes (21,22) may be placed, passing in bicanalicular fashion, with retrieval of each olive tip using the Crawford hook (Fig. 18.7). The two ends are tied together (Fig. 18.8), with care not to close the loop too tightly (which would cause erosion of the puncta), and left in place for several months. An alternate method of inserting silicone tubing is with the Ritleng probe (23). This system has the advantage of tubing that often spontaneously exits the nose, allowing easy retrieval of each end of the tubing, and both monocanalicular and bicanalicular tubes are available. If bicanalicular tubing is passed, the ends may be secured in the standard fashion. If a monocanalicular tube is passed, a small flange that is nonirritating is seated in the punctum. Tubing that is tied with a luminal suture or a simple square knot in the silicone can usually be easily extracted from above, through the canaliculi, during an office visit. If a stent has been tied to the silicone to keep the tubing in the nose, it must be removed from below with the patient under anesthesia.

Balloon catheter dilatation has been recommended for cases that are resistant to simple probing or in older infants as a primary procedure under the assumption that the success rate of simple probing decreases with increasing age (24,25). The balloon catheter is relatively expensive, but it may be useful in dilatation of the lacrimal sac in addition to the distal nasolacrimal duct.

When these procedures fail, dacryocystorhinostomy (DCR) may be required. Endoscopic DCR has had a high

success rate even in children (26) and avoids an external scar. This involves identification of the site for a nasal ostium using a 20-gauge light pipe and nasal endoscopy to create a new ostium or enlarge the existing ostium, followed by placement of silicone tubing. Endoscopic DCR is less successful for revisions. External DCR remains the gold standard and involves creating an incision nasal to the medial canthus to expose the lacrimal sac and directly making a connection from the lacrimal sac into the nose. Conjunctival DCR may be needed if the puncta and canaliculi are congenitally absent. Jones' technique uses placement of a Pyrex tube in the medial canthal area, which extends through the lacrimal fossa into the nose through a DCR-type incision. Once the passageway becomes epithelialized, a polyethylene tube can be exchanged for the glass tube. Practically speaking, however, the care and preservation of this system in a young child are difficult.

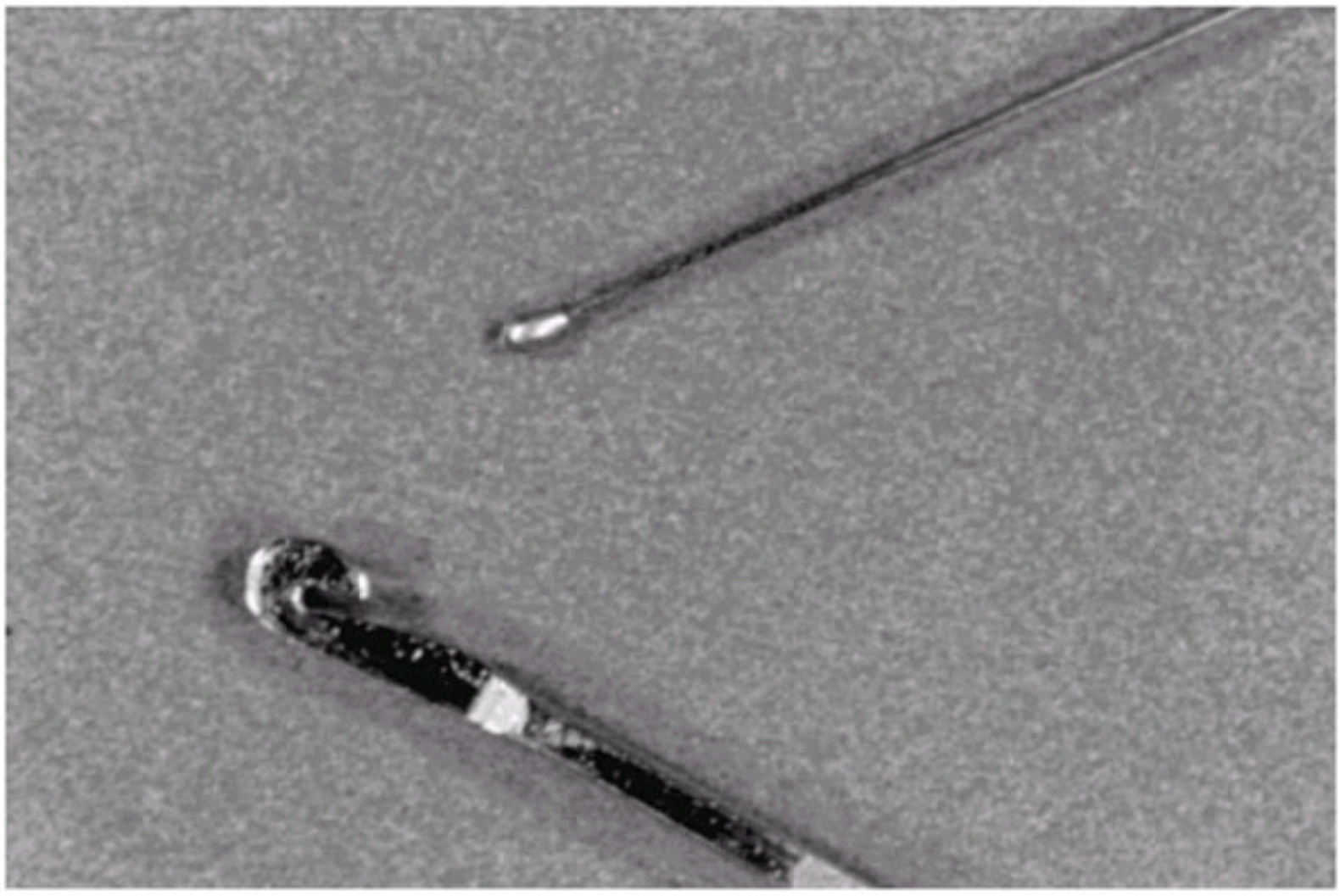

Figure 18.7 Portion of the Crawford silicone tube nasal intubation system. One of the two flexible rods with its bulbous tip is shown. To each of these rods is attached one end of the silicone tube. The end of the retrieving hook engages the rod under the inferior turbinate and withdraws it from the nose.

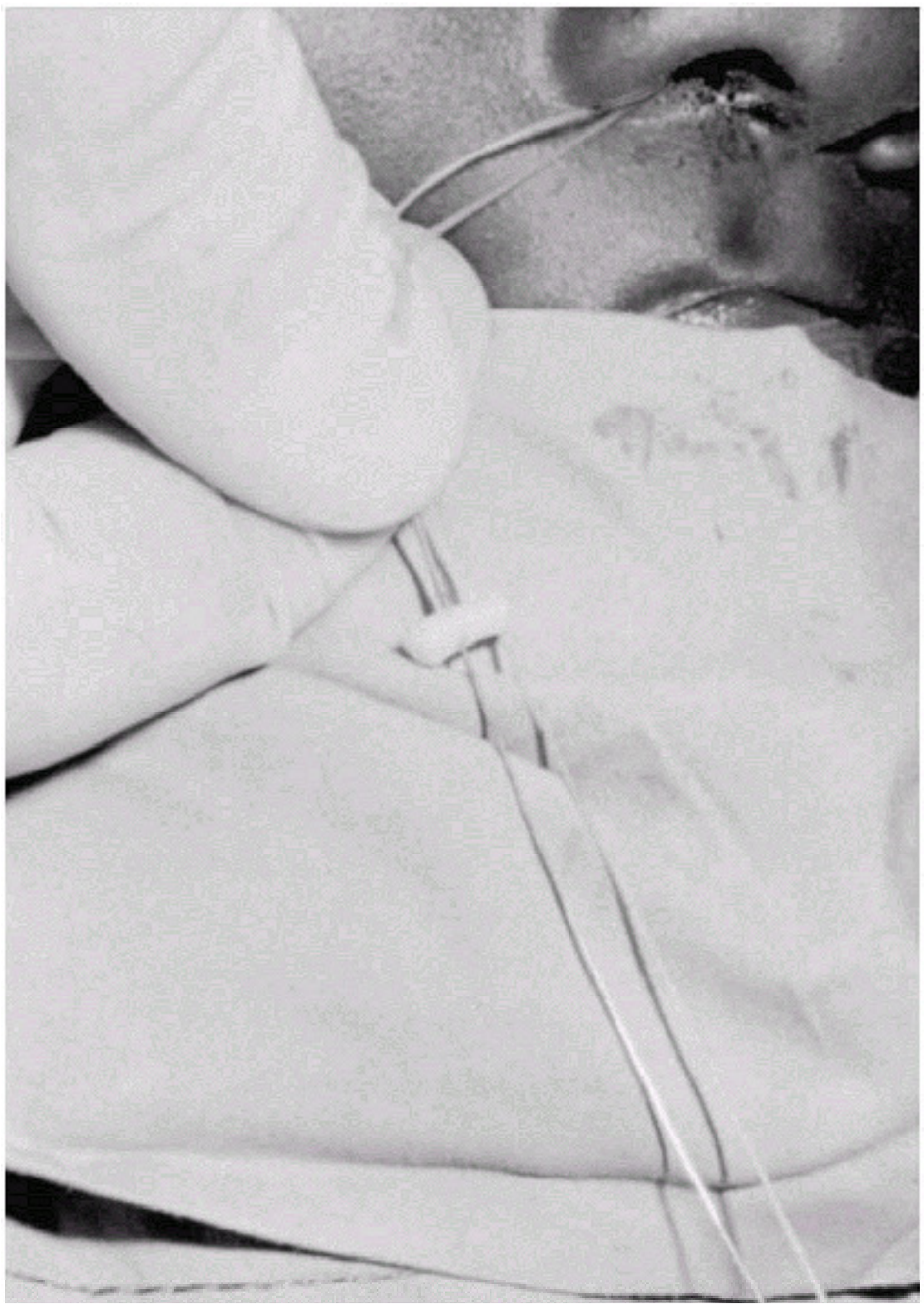

Figure 18.8 The rods, having been passed through the nasolacrimal duct and pulled out of the nose, are in this case pushed through a piece of silicone sponge over which the ends of the tubing will be tied. Alternatively, the ends may be tied with a square knot and secured to the lateral wall of the nose with an absorbable anchoring suture.

REFERENCES

1. Jones LT. An anatomical approach to problems of the eyelids and lacrimal apparatus. *Arch Ophthalmol* 1961;66:111-124.

2. Keith CG, Boldt DW. Congenital absence of the lacrimal gland. *Am J Ophthalmol* 1986;102:800-801.

3. Mansour AM, Cheng KP, Mumm JV, et al. Congenital dacryocele. A collaborative review. *Ophthalmology* 1991;98:1744-1751.

4. Schnall BM, Christian CJ. Conservative treatment of congenital dacryocele. *J Pediatr Ophthalmol Strabismus* 1995;5:219-222.

5. Grin TR, Mertz JS, Stass-Isern M. Congenital nasolacrimal duct cysts in dacryocystoceles. *Ophthalmology* 1991;98:1238-1242.

6. Paysse EA, Coats DK, Bernstein JM, et al. Management and complications of congenital dacryocele with concurrent intranasal mucocele. *J AAPOS* 2000;4(1):46-53.

7. Kushner BJ. Congenital nasolacrimal system obstruction. *Arch Ophthalmol* 1982;100:597-600.

8. Petersen RA, Robb RM. The natural course of congenital obstruction of the nasolacrimal duct. *J Pediatr Ophthalmol Strabismus* 1978;15:246-250.

9. Baker JD. Treatment of congenital nasolacrimal system obstruction. *J Pediatr Ophthalmol Strabismus* 1985;22:34-36.

10. Nelson LB, Calhoun JH, Menduke H. Medical management of congenital nasolacrimal duct obstruction. *Pediatrics* 1985;76: 172-175.

11. Paul TO. Medical management of congenital nasolacrimal duct obstruction. *J Pediatr Ophthalmol Strabismus* 1985;22:68-70.

12. Nucci P, Capoferri C, Alfarano R, et al. Conservative management of congenital nasolacrimal duct obstruction. *J Pediatr Ophthalmol Strabismus* 1989;26:39-43.

13. MacEwen CJ, Young JKH. Epiphora during the first year of life. *Eye* 1991;5:596-600.

14. Stager D, Baker JD, Frey T, et al. Office probing of congenital nasolacrimal duct obstruction. *Ophthalmic Surg Lasers* 1992;23: 482-484.

15. Katowitz JA, Welsh MC. Timing of initial probing and irrigation in congenital nasolacrimal duct obstruction. *Ophthalmology* 1987; 94:698-705.

16. Mannor GE, Rose GE, Frimpong-Ansah K, et al. Factors affecting the success of nasolacrimal duct probing for congenital nasolacrimal duct obstruction. *Am J Ophthalmol* 1999;127(5):616-617.

17. Honavar SG, Prakash VE, Rao GN. Outcome of probing for congenital nasolacrimal duct obstruction in older children. *Am J Ophthalmol* 2000;130(1):42-48.

18. El-Mansoury J, Calhoun JH, Nelson LB, et al. Results of late probing for congenital nasolacrimal duct obstruction. *Ophthalmology* 1986;93:1052-1054.

19. Robb RM. Success rates of nasolacrimal duct probing at time intervals after 1 year of age. *Ophthalmology* 1998;105:1307-1310.

20. Kushner BJ. The management of nasolacrimal duct obstruction in children between 18 months and 4 years old. *J AAPOS* 1998; 2:57-60.

21. Crawford JS. Intubation of the lacrimal system. *Ophthalmol Plastic Reconstr Surg* 1989;5:261-265.

22. Kraft SP, Crawford JS. Silicone tube intubation in disorders of the lacrimal system in children. *Am J Ophthalmol* 1982;94:290-299.

23. Pe MRL, Langford JD, Linberg JV, et al. Ritleng intubation system for treatment of congenital nasolacrimal duct obstruction. *Arch Ophthalmol* 1998;116:387-391.

24. Becker BB, Berry FD, Koller H. Balloon catheter dilatation for treatment of congenital nasolacrimal duct obstruction. *Am J Ophthalmol* 1996;121:304-309.

25. Leuder GT. Balloon catheter dilation for treatment of older children with nasolacrimal duct obstruction. *Arch Ophthalmol* 2002; 120(12):1685-1688.

26. VanderVeen DK, Jones DT, Tan H, et al. Endoscopic dacryocystorhinostomy in children. *J AAPOS* 2001;5(3)143-147.

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19

Pediatric Eyelid Disorders

Forrest J. Ellis

EYELID DEVELOPMENT

Eyelid development is intimately associated with the development of the eye (1). During the fourth week of gestation, the optical vesicle forms as a projection from the side of the forebrain. The optical vesicle invaginates, forming the optic cup. The overlying ectoderm forms the lens placode, which separates and migrates internally to form the lens of the eye. The ectodermal surface overlying the optic cup develops into the cornea. Further development during week six results in small folds of the surface ectoderm with its underlying mesenchyme. These two folds become the upper and lower eyelids. These folds grow toward each other and ultimately result in fusion of the upper and lower eyelids between weeks eight and ten of gestation. The eyelids remain fused until approximately the sixth month of gestation, at which time separation of the eyelids occurs. In addition to primary eyelid developmental abnormalities, eyelid and ocular development may be affected by abnormalities or defects in facial development. Abnormalities in orbital development can also cause secondary abnormalities in eyelid development.

ANATOMY OF THE EYELIDS

Upper Eyelid

The upper eyelid margin forms a curved arch from the medial canthus to the lateral canthus and overlies the superior 1 to 2 mm of the cornea. The peak of this curve is approximately 1 mm nasal to the center of the cornea. The upper eyelid crease is formed by the attachment of strands of the external levator aponeurosis to the skin (2). An absent upper eyelid crease can be seen in conditions of abnormal levator development such as congenital ptosis. However, the normal Asian eyelid has a low set and less developed eyelid crease. In addition, dehiscence of the levator aponeurosis can result in an abnormally elevated eyelid crease.

The upper eyelid tarsus is approximately 10 mm in its vertical height in the adult and proportionately shorter in children. It is formed of dense fibrous tissue. Medially and laterally the tarsus is attached firmly to the orbital rims by the canthal tendons. The medial canthal tendon attaches to the anterior and posterior lacrimal crests and the fascia of the lacrimal sac. The lateral canthal tendon attaches to the lateral border of the tarsus and to the Whitnall tubercle inside the lateral orbital rim. The lateral canthus is normally even with or just slightly above the medial canthal tendon in the horizontal plane. Externally an extra fold of skin can be seen in the medial canthal area overlying and potentially obscuring the medial canthal tendon. This extra fold of skin is referred to an epicanthal fold.

The anatomy of the upper eyelid overlying the tarsal plate consists of eyelid skin covering the orbicularis oculi muscle. This pretarsal orbicularis is adherent to the underlying tarsal plate. Conjunctiva is also firmly adhered to the tarsus posteriorly. Superior to the tarsus, the skin covers the preseptal orbicularis muscle. Beneath the preseptal muscle is the orbital septum, which defines the anterior boundary of the orbit and overlies orbital fat. The orbital septum is important in eyelid anatomy. In Caucasian upper eyelids, the orbital septum and levator aponeurosis fuse at approximately the superior tarsal boarder 10 mm above the lid margin. However, in Asian eyelids, the septum inserts much lower into the levator aponeurosis, resulting in inferior displacement of orbital fat and a lower eyelid crease (3). Posterior to the levator aponeurosis is the underlying Müller muscle.

Lower Eyelid

The lower eyelid margin usually crosses the inferior corneoscleral limbus. Lower eyelid anatomy has similar features

to upper eyelid anatomy (4). However, the lower eyelid tarsus is only 5 mm in its greatest vertical height. Arising from the area of inferior rectus muscle is the capsulopalpebral fascia. In a similar, but less well-developed fashion to the levator aponeurosis, this fascia inserts into the lower eyelid tarsus where it retracts and stabilizes the lower eyelid. The orbital septum of the lower lid inserts directly onto the tarsus.

Levator Palpebrae Superioris and Müller Muscle

The levator muscle has its origin at the lesser wing of the sphenoid. It runs posterior to anterior in the superior aspect of the orbit. Just inside the superior orbital rim, the levator muscle crosses and fuses with the Whitnall ligament. This attachment provides support to the levator muscle and aponeurosis. At this point, the levator muscle turns in an inferior direction while becoming more fibrous. The levator aponeurosis spreads out horizontally to form a fan-shaped structure with attachments medially and laterally, the medial and lateral horns, which insert in the periosteum. The levator aponeurosis inserts broadly across the anterior surface of the upper eyelid tarsus. Small strands of the levator aponeurosis also project anteriorly, inserting into the eyelid skin and forming the eyelid crease.

The Müller muscle complex arises from the posterior aspect of the levator muscle, lies along the posterior surface of the levator aponeurosis, and inserts into the superior border of the tarsus.

Eyelid Innervation

Cranial nerve VII (the facial nerve), which divides into six branches, innervates the facial musculature. The temporal branch of the facial nerve provides innervation to the orbicularis oculi, frontalis, pars ciliaris, and corrugator muscles. However, the superior division of cranial nerve III innervates the levator palpebrae superioris muscle. The Müller muscle is innervated by the sympathetic nervous system. Interruption of ocular sympathetic supply causes ptosis, miosis, and anhydrosis. This triad of signs is known as Horner syndrome (5).

Vascular Supply to the Eyelids

The vascular supply to the eyelids is rich with many collaterals. The supraorbital, supratrochlear, lacrimal, and dorsal nasal branches of the ophthalmic artery supply the eyelids, forehead, and orbit. An anastomosis between the dorsal nasal and lacrimal arteries in the upper eyelid forms the marginal arcade, which lies 2 mm above the lid margin between the tarsus and orbicularis oculi muscles. A peripheral arcade is located at the superior border of the tarsus between the levator aponeurosis and Müller muscle. The lower lid has a similar anatomic configuration of the arterial arcades. A rich venous drainage network exists throughout the eyelids. Because of the rich vascular supply, ischemic necrosis of the eyelids is rare.

EYELID DISORDERS

Anophthalmos and Microphthalmos

True anophthalmos is an extremely rare condition and results from an absence of the development of the optic vesicle (Fig. 19.1). Most cases of clinical anophthalmos likely represent severe microphthalmos when careful histology is obtained from serial orbital sections. Microphthalmos represents a range of ocular developmental abnormalities from near complete absence of identifiable ocular structures to a small normally formed eye, a condition referred to as nanophthalmos. Because eyelid and orbital development are dependent on the underlying ocular development, microphthalmos often is associated with abnormal or reduced orbital bony size. Eyelid deformities that result include shortened horizontal palpebral fissure lengths. The mainstay of treatment involves serial prosthetic conformers to enlarge the cul-de-sacs. In more severe cases, the orbital volume can be expanded using dermis fat grafts, orbital implants, and orbital expanders (6). Soft tissue growth will parallel bone growth. Using these various techniques, an acceptable cosmetic appearance is often achieved.

Cryptophthalmos

Cryptophthalmos is an extremely rare condition in which there is complete failure of development of the lid folds. One of the most distinct features of cryptophthalmos is failure of the brow to develop normally, resulting in fusion of the hairline and brow. This is distinct from an abnormal separation of the eyelid folds. Without development of the normal eyelid folds, the underlying cornea and conjunctiva do not normally form. The anterior segment of the globe is severely malformed, and the posterior segment of the

globe is sometimes disorganized. If attempts are made to separate the eyelids, then the globe will often require corneal transplantation to close the anterior segment defect and mucous membrane grafting to form conjunctival culde-sacs. Preoperative evaluation with an electroretinogram, visual evoked potentials, imaging studies, and ultrasound may provide preoperative insight into the structure and function of the underlying globe. While reconstructive surgery may allow for an improved cosmetic result, rarely is useful vision achieved. When associated cutaneous syndactyly, malformations of the larynx and genitourinary tract, craniofacial dysmorphism, orofacial clefting, mental retardation, and musculoskeletal anomalies occur, Fraser syndrome should be considered (7).

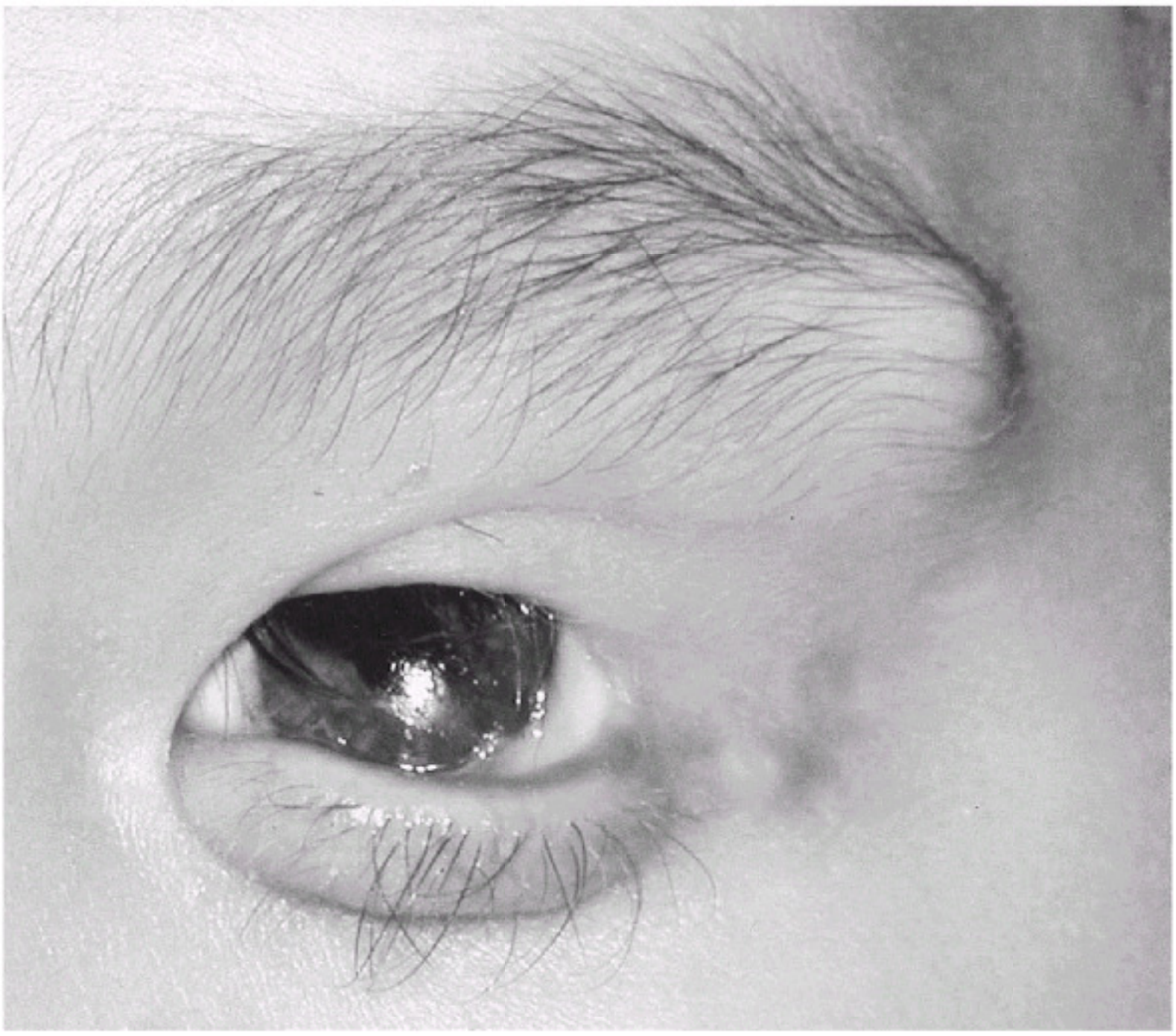


Figure 19.1 Clinical amophthalmos in the left eye. Patient presented with a severely contracted socket after attempted socket reconstruction.

Congenital Eyelid Coloboma

A congenital defect involving the absence of a portion of the eyelid margin is an eyelid coloboma (Fig. 19.2). Coloboma may affect either the upper or lower eyelids and may vary in size from a small eyelid marginal defect to a near complete absence of the eyelids. Coloboma more typically occur in the nasal aspect of the upper eyelid, and large eyelid coloboma can result in corneal exposure and ulceration.

The etiology of colobomas is varied. Abnormal migration patterns of ectoderm and mesoderm may cause abnormal development of the eyelid margin. Colobomas may also result from a mechanical disruption of eyelid development such as amniotic bands or facial clefts (Fig. 19.3). Eyelid colobomas can be seen in association with other abnormalities including dermoids, cleft lip, microphthalmia, and ocular colobomata. Coloboma of the upper lids occur commonly in

Goldenhar syndrome.

Treatment of upper eyelid coloboma should be directed at maintaining lubrication and protection for the ocular surface. Surgical correction is not emergent as long as the corneal surface is being protected. A larger coloboma may require more aggressive lubrication and perhaps occlusive dressing prior to surgical closure. For smaller colobomas surgical repair during the later half of the first year of life is preferable to allow for tissue growth. For defects less than 25% of the horizontal eyelid width, direct closure after excision of the defect is all that is required. The edges of the defect are excised to form a pentagonal defect and then the tarsus is closed with three interrupted absorbable sutures. The eyelid margin is closed with sutures anterior to, through, and posterior to the gray line. The skin is reapproximated with interrupted sutures (Fig. 19.4). Larger defects up to 40% of the eyelid margin can be closed by a lateral canthotomy and cantholysis with medial rotation of the lid. Larger eyelid defects often require a free tarsal conjunctival graft. Eyelid-sharing procedures (e.g., Hughes procedure), which occlude the line of sight, should be avoided in children as they will induce occlusion amblyopia. Because most eyelid colobomas causing corneal exposure are in the upper eyelid, a lateral canthotomy usually can be performed and the eyelid defect closed nasally as described above. If necessary, a temporal tarsal conjunctival sharing procedure can then be performed, taking care not occlude the visual axis.

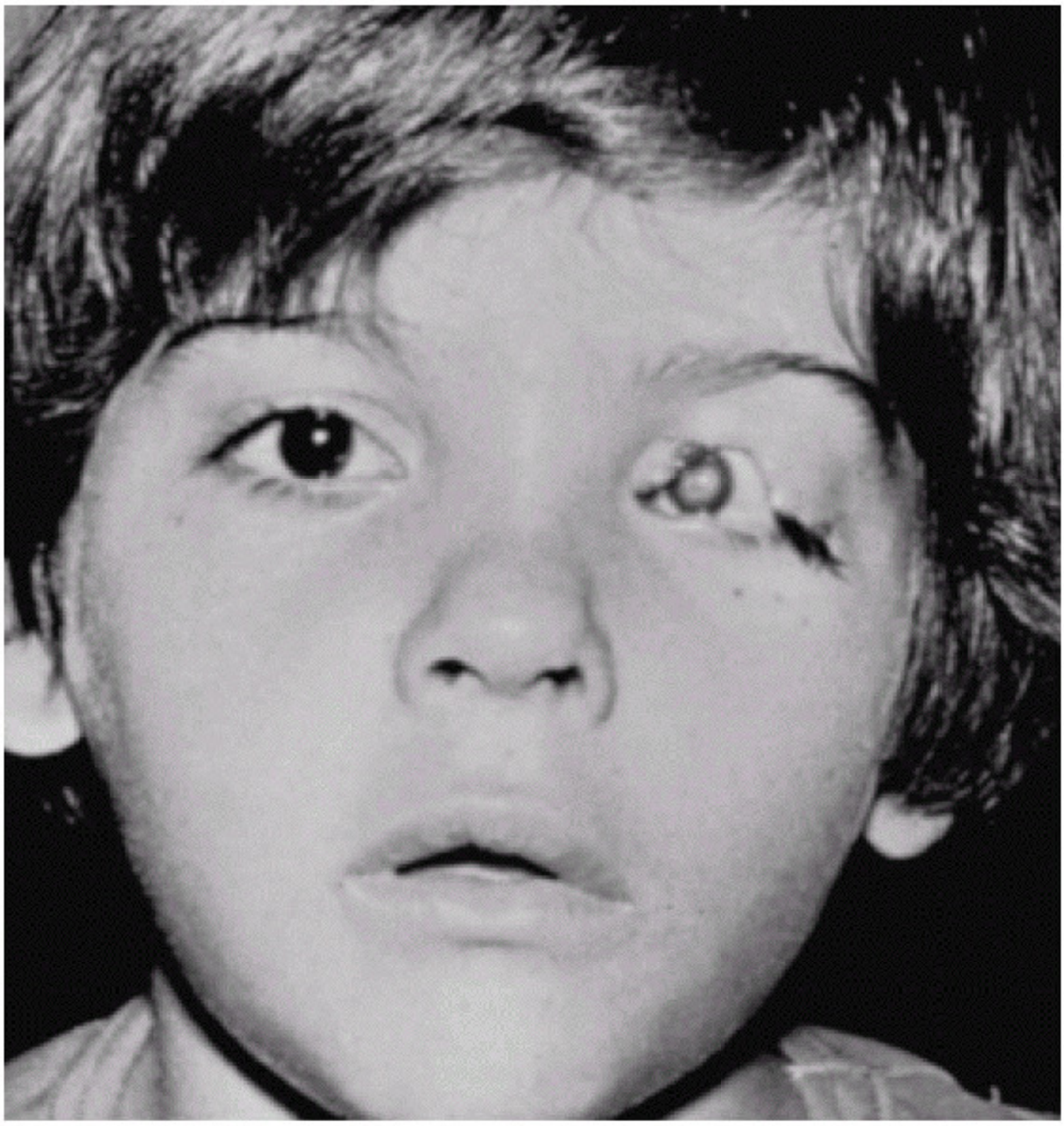


Figure 19.2 Untreated lid coloboma, resulting in corneal leukoma. (Courtesy of R. D. Harley, MD.)

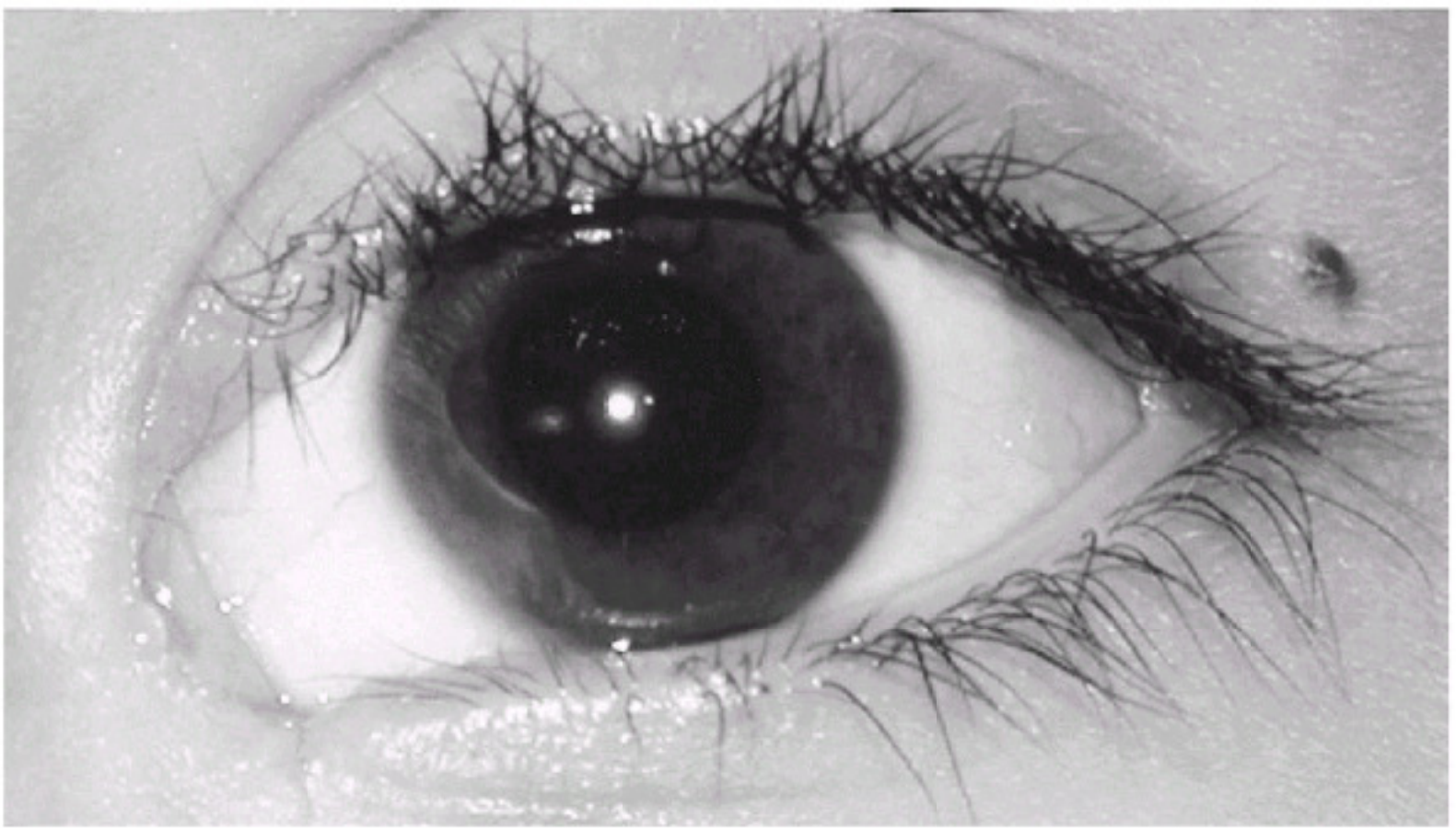


Figure 19.3 Small medial lower eyelid congenital cleft, resulting in canalicular atresia.

Pseudocoloboma

More commonly, pseudocoloboma of the lower lid are seen in craniofacial synostosis (Treacher Collins syndrome) (Figs. 19.5 and 19.6). With these pseudocolobomas the eyelid margin is intact, but there is a facial cleft laterally which results in an inferior and lateral displacement of the lower eyelid. Treacher Collins syndrome is caused by a first brachial arch abnormality. Ophthalmic findings include microphthalmos, iris coloboma, and absence of the puncta. Hypoplasia of the maxilla and zygoma are common with an antimongoloid slant to the palpebral fissures. Deformations of the external ear and hearing loss are associated with this syndrome. Simple soft tissue tightening and elevation of the lateral canthal tendon is frequently ineffective in correcting the lateral dystopia of the eyelid because there is often an absence of vertical and horizontal eyelid tissue. For this reason, transposition flaps from the upper to lower eyelids are useful in addition to resuspension of the lateral canthal tendon.

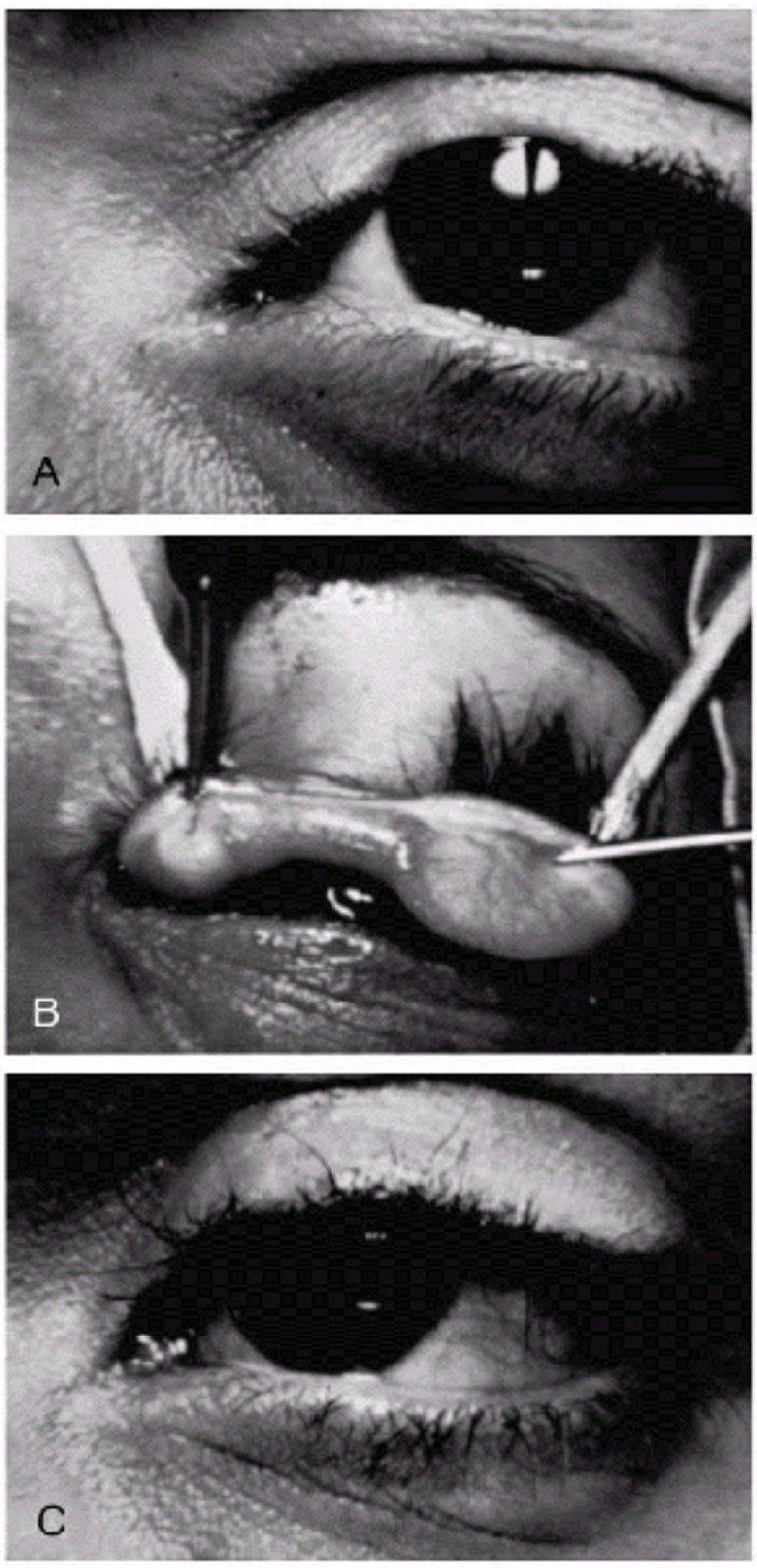


Figure 19.4 A: Congenital coloboma of the left upper lid. **B:** Lid everted to show absence of the tarsus in the area of the coloboma. **C:** Postoperative appearance.

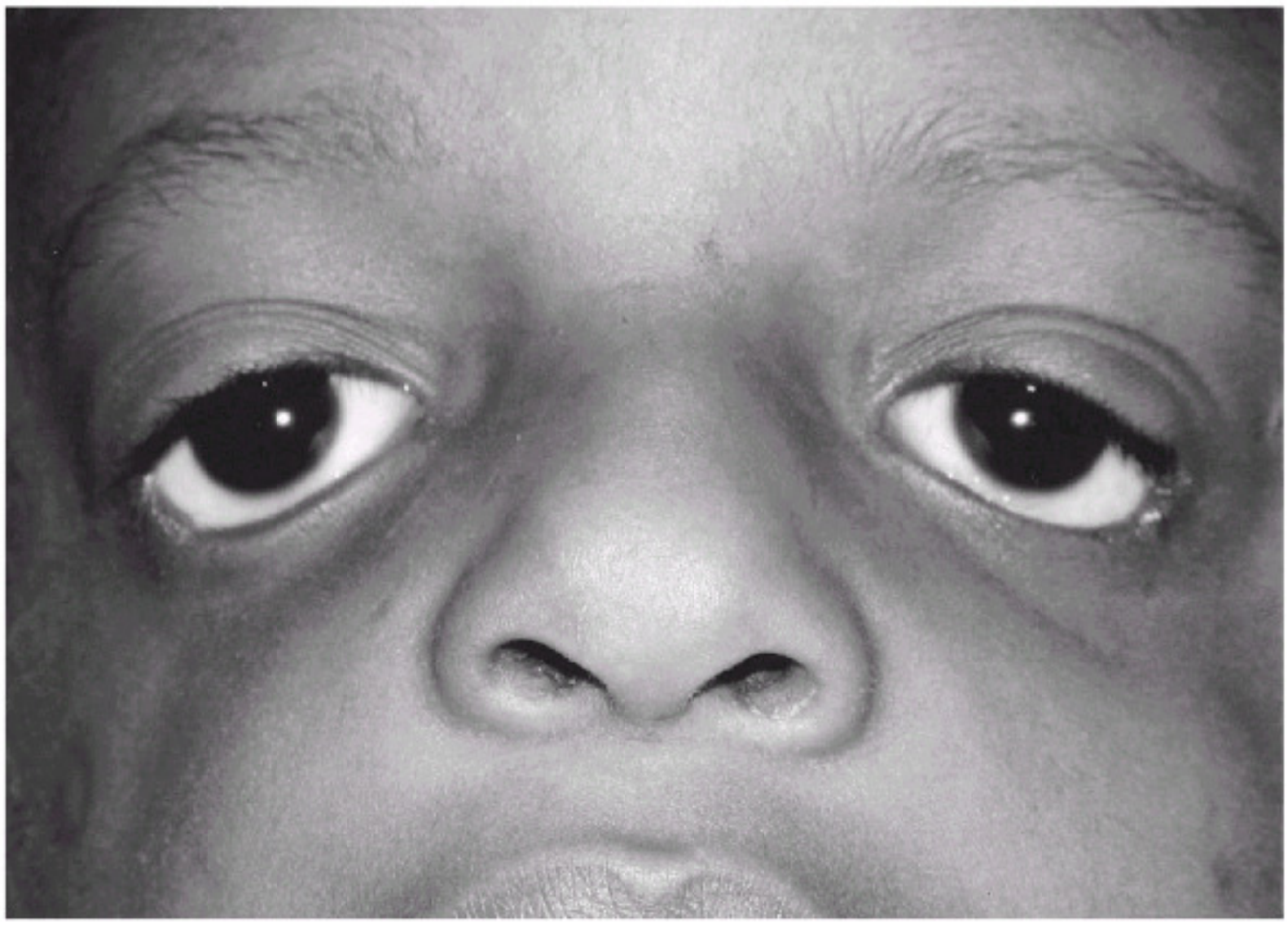


Figure 19.5 Pseudocolobomata of the lower eyelids associated with Treacher Collins syndrome.

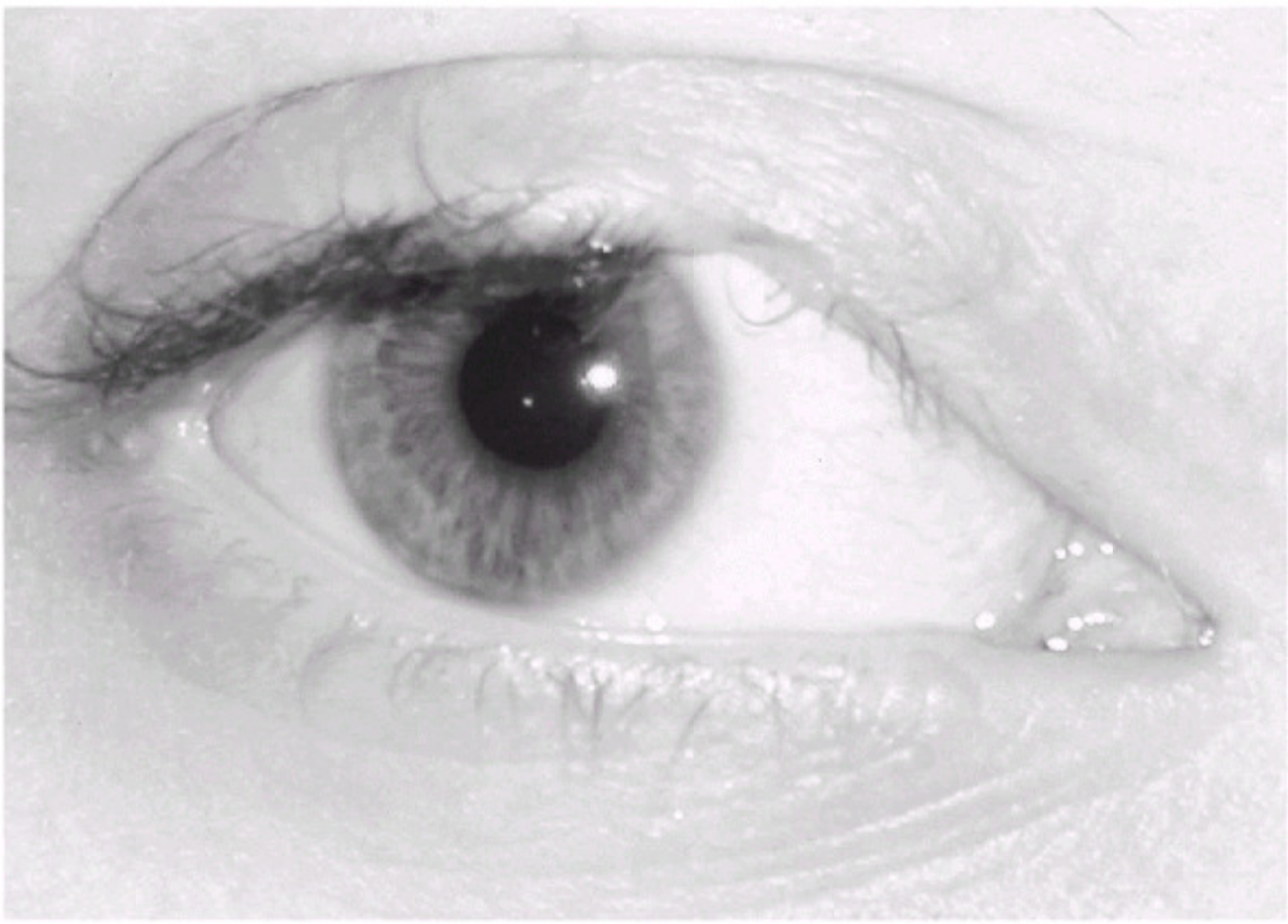


Figure 19.6 Pseudocoloboma of the upper eyelid caused by ischemic necrosis of the eyelid margin in a patient who had a hemangioma in that location.

Ankyloblepharon

Ankyloblepharon is caused by failure of eyelid separation or from an abnormality in the migration of the mesodermal elements of the eyelid (Fig. 19.7). Ankyloblepharon filiforme adnatum may be isolated, demonstrating fine bands of tissue between the upper and lower eyelids, or it may be seen with trisomy 18 or other chromosomal abnormalities (8,9). In addition, ankyloblepharon may be part of the Hay-Wells syndrome, which is characterized by congenital ectodermal dysplasia, alopecia, scalp infections, dystrophic nails, hypodontia, ankyloblepharon, and cleft lip and/or cleft palate (10). The treatment of ankyloblepharon is entirely surgical. The bands of the eyelid are separated, and the eyelid margins are reformed as necessary.

Distichiasis

Distichiasis occurs when a developmental abnormality results in cilia formation in association with metaplastic meibomian glands. This condition is often asymptomatic although

these lashes may cause superficial corneal irritation and abrasion. In an acquired form, distichiasis may occur with chronic eyelid inflammation such as blepharitis, trachoma, and Stevens-Johnson syndrome (Fig. 19.8).

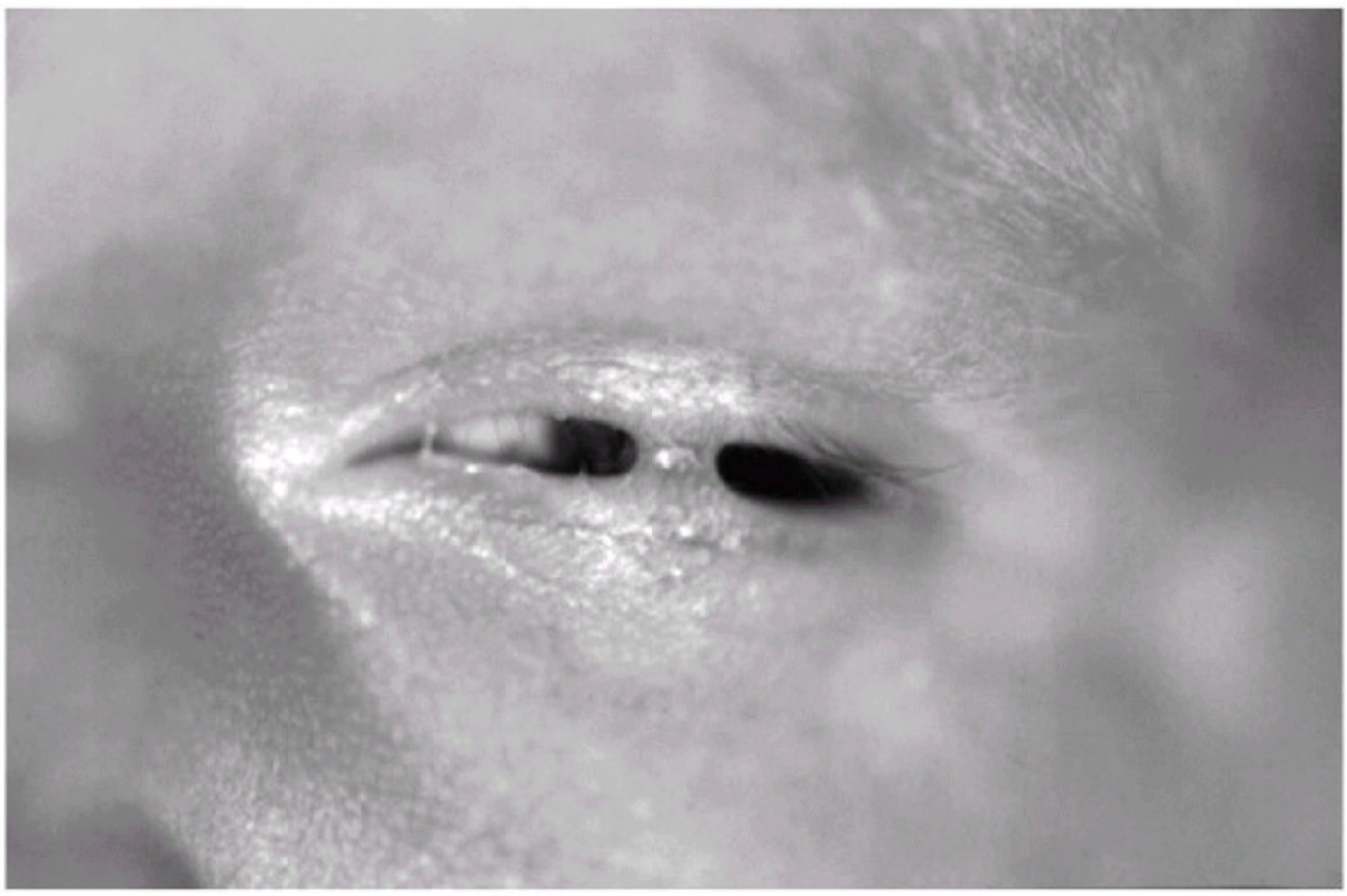


Figure 19.7 Ankyloblepharon in a newborn.

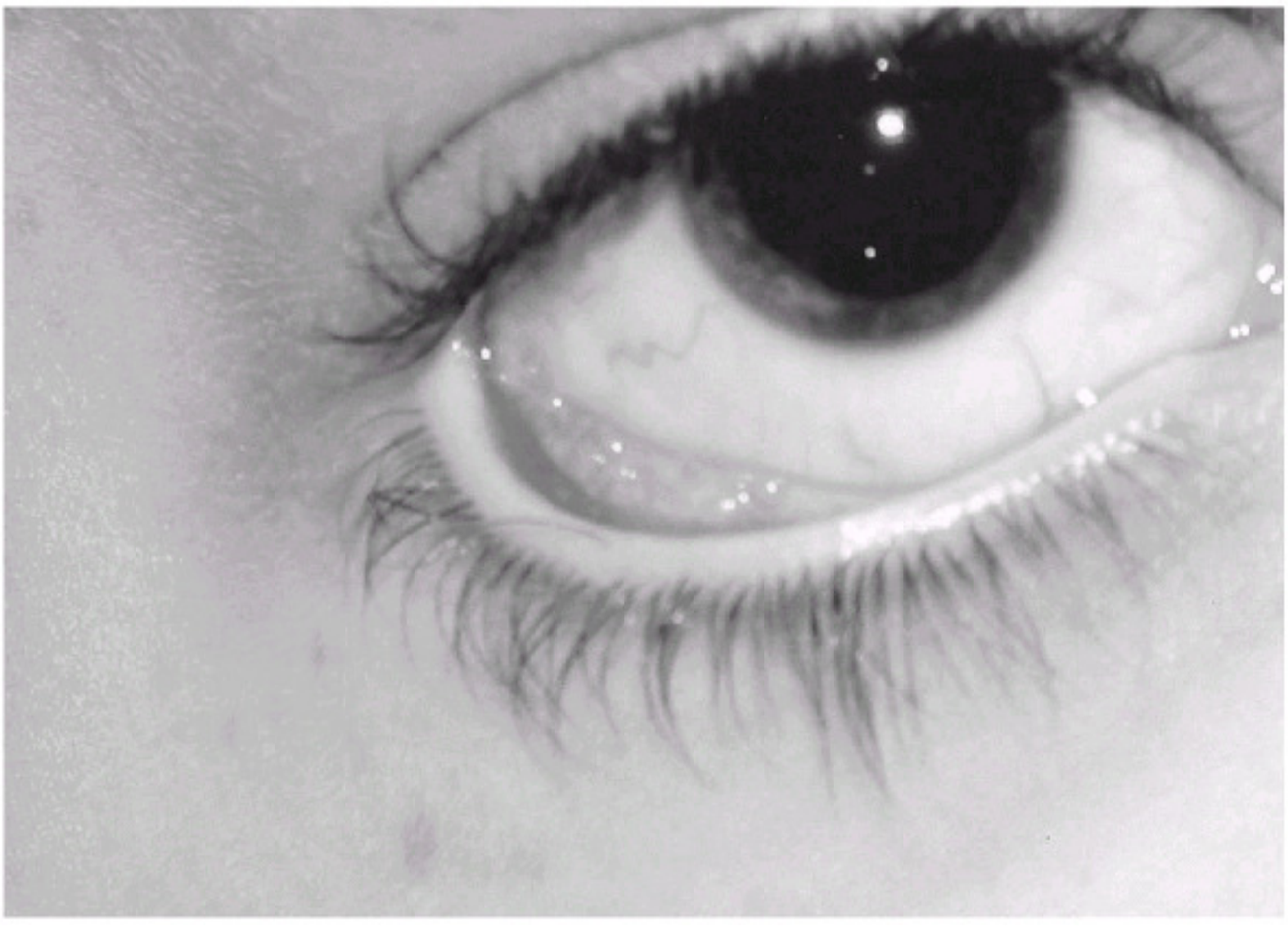


Figure 19.8 Acquired distichiasis. Eyelash in association with a meibomian gland orifice.

Trichiasis

Trichiasis refers to an acquired eyelash abnormality resulting from normally located but misdirected cilia. Chronic eyelid inflammation is the most common cause for trichiasis.

Treatment of eyelash abnormalities is not required in the absence of any abnormality of the corneal surface. Electrolysis or split thickness eyelid resections can be used to remove the lash follicles (11). In addition, direct excision of the lash follicles is possible.

Congenital Ectropion

Congenital ectropion is rarely found in isolation. When the lower eyelid is involved, it is often part of the blepharophimosis syndrome or Treacher Collins syndrome. Also, congenital eyelid ectropion may be seen in patients with neonatal erythroderma (collodion baby) (12). When secondary to an insufficiency in the vertical extent of the skin and orbicularis layers, a full thickness skin graft or transfer flap is usually required in addition to a lateral tightening of the eyelid.

Congenital Entropion and Epiblepharon

Epiblepharon results from an extra fold of pretarsal lower eyelid skin and orbicularis, which rotates the lower eyelid cilia and margin inward (Fig. 19.9). Epiblepharon is more common in Asian eyelids. With downward pressure over the excess skin, the eyelid margin assumes a normal appearance. This condition is typically self-limited and resolves with facial growth. Most children are relatively asymptomatic without corneal injury. If corneal surface changes occur with persistent corneal irritation, a small ellipse of subciliary skin and orbicularis muscle can be removed. Since lower eyelid retraction can result from excessive skin excision, only a minimal amount of skin is removed.

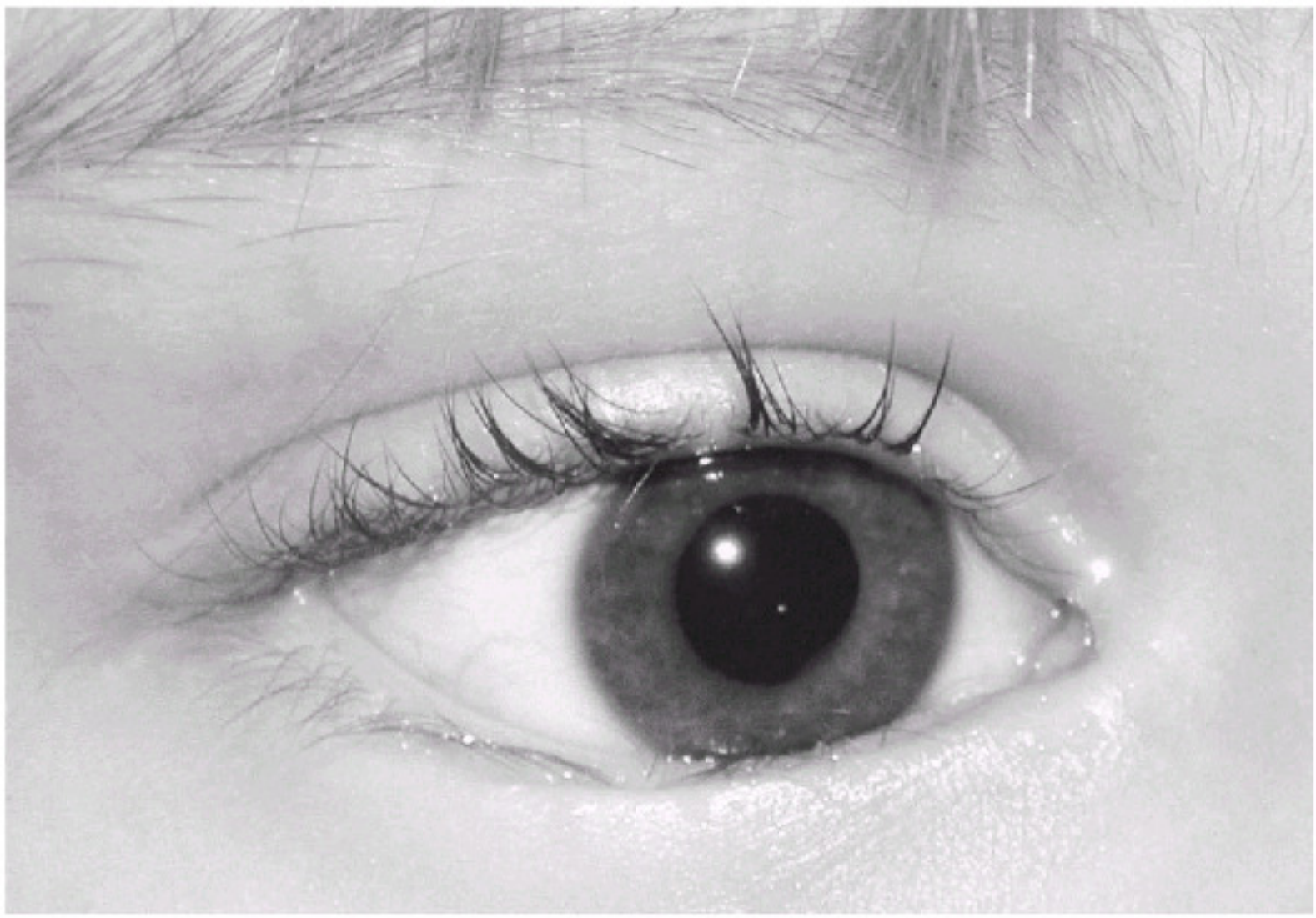


Figure 19.9 Epiblepharon, which typically resolves spontaneously.

Congenital lower eyelid entropion is caused when preseptal orbicularis overrides the pretarsal orbicularis (Fig. 19.10). In addition, there is laxity of the lower eyelid retractors, allowing a true inward rotation of the lower eyelid. Correction requires reattachment of the lower eyelid retractors to the lower border of the tarsus, elimination of horizontal eyelid laxity when present, and resection of overriding skin and orbicularis.

Congenital horizontal tarsal kink results in entropion of the upper eyelid and may be associated with congenital levator aponeurotic disinsertion. More important, corneal ulceration occurs in 50% of cases (13).

Congenital Eyelid Retraction

Congenital eyelid retraction, especially of the lower eyelid, may occur in isolation or secondary to structural anomalies, resulting in very shallow orbits and proptosis (Fig. 19.11). While some infants will have transient upper eyelid retraction, persistent superior scleral show in the absence of a

structural cause warrants a medical evaluation for thyroid or neurologic disease. Options to correct eyelid retraction are müllerectomy and levator recession. Spacer grafts are occasionally necessary.

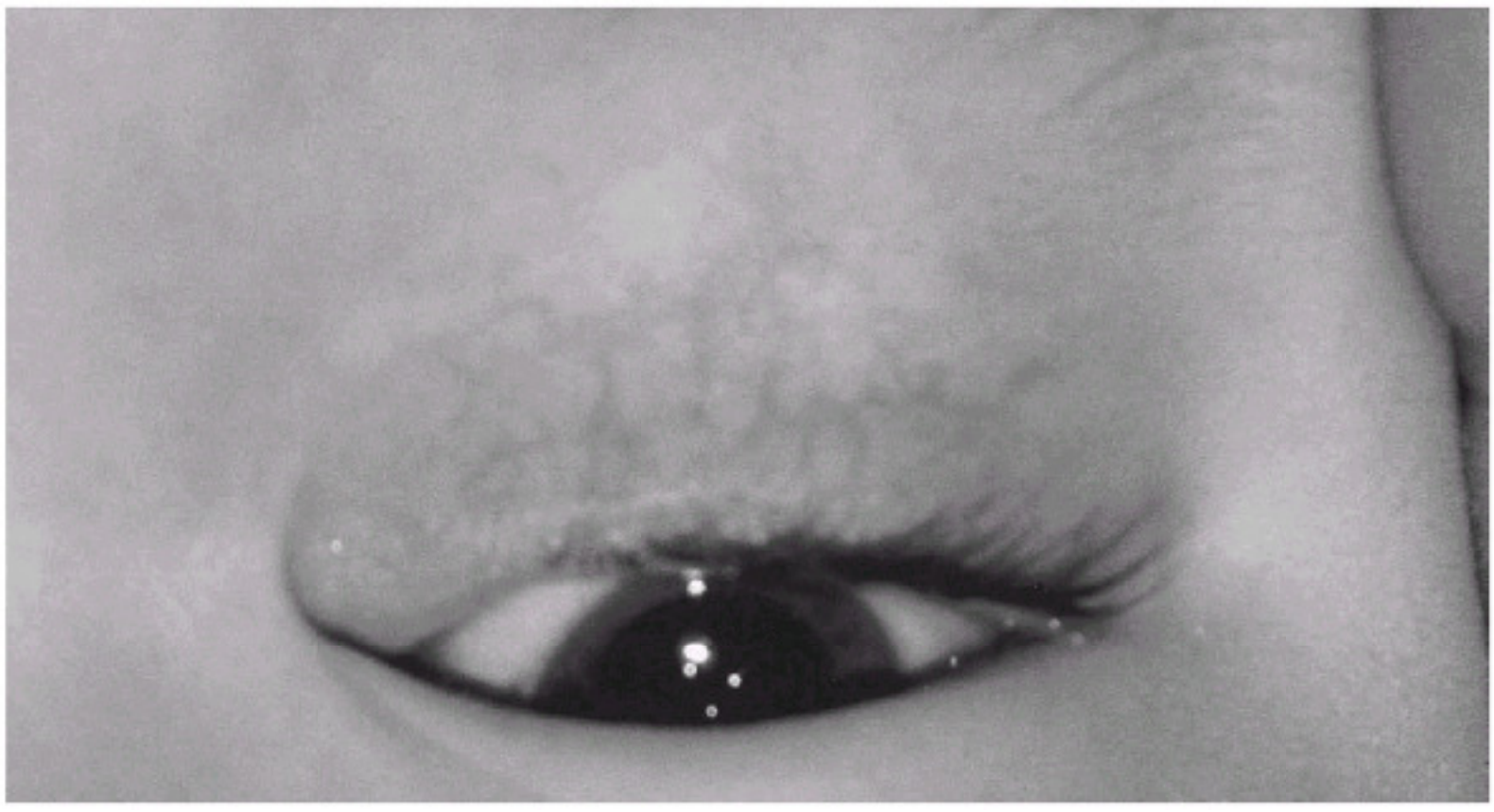


Figure 19.10 Lower eyelid entropion with inward rotation of the eyelid, necessitating surgical correction.

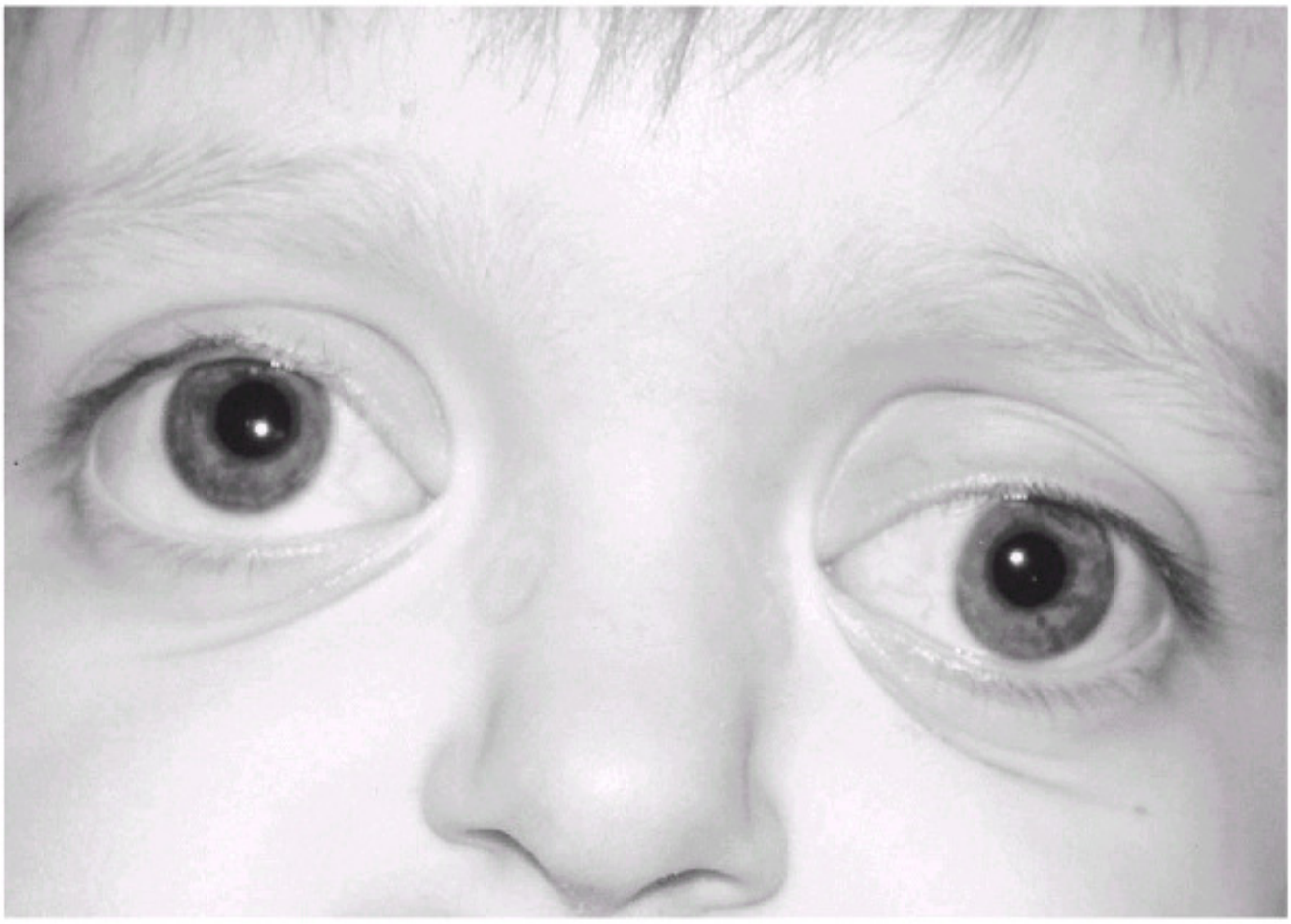


Figure 19.11 Lower eyelid retraction associated with shallow orbits and relative proptosis in a patient with Pfeiffer syndrome.

Euryblepharon

Euryblepharon is a condition characterized by increased vertical separation of the temporal aspect of the palpebral opening such that the palpebral conjunctiva is not in apposition with the eye (Fig. 19.12). The lateral canthus is usually displaced inferiorly. This condition is characterized by a lack of vertical skin height, and treatment requires a lateral canthoplasty as well as a skin graft into the lower eyelid to provide additional vertical height.

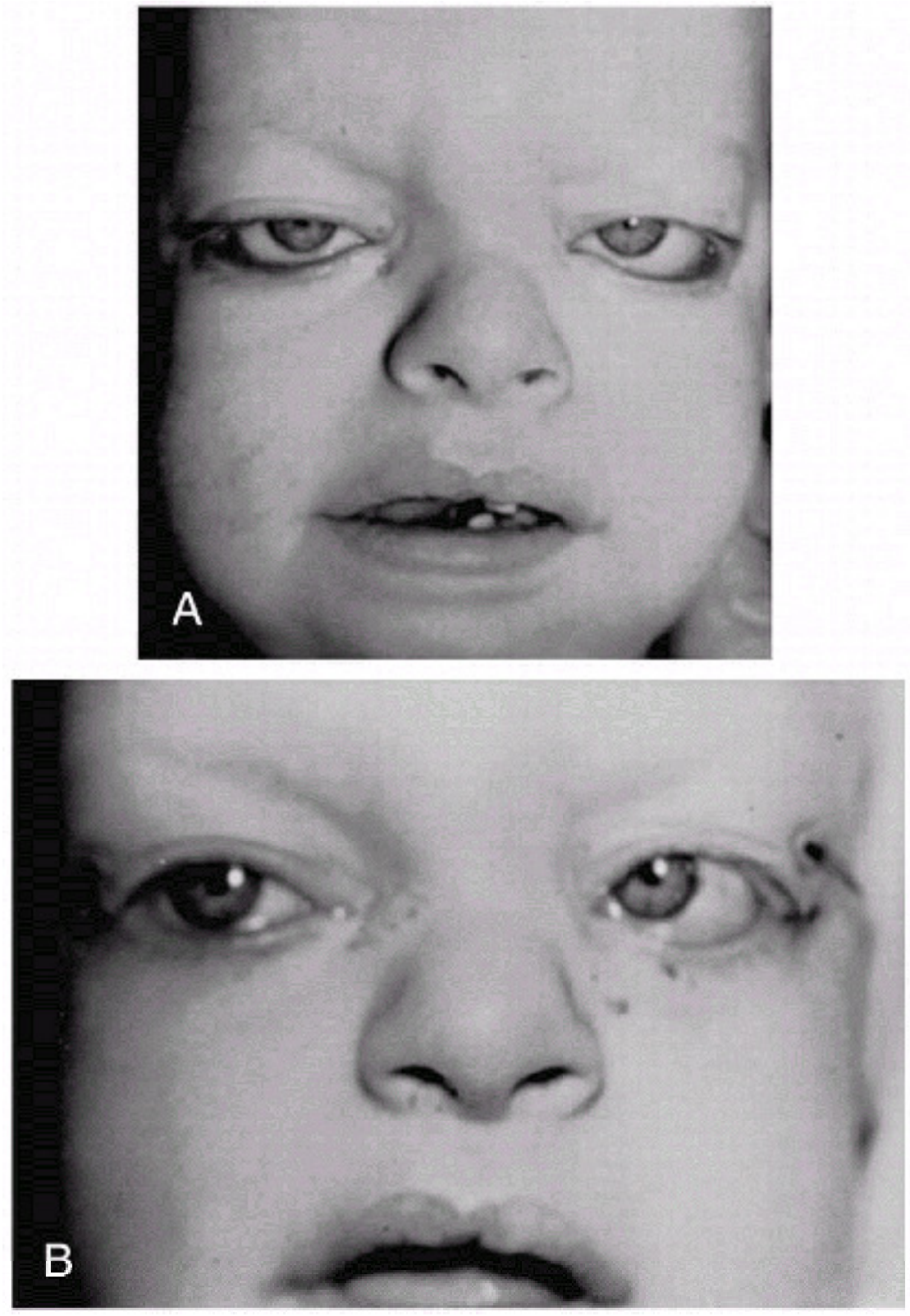


Figure 19.12 A: Euryblepharon with inferior displacement of the lateral canthus. **B:** Immediate postoperative appearance after a lateral canthoplasty.

Epicanthus

The epicanthus consists of a fold of skin in the medial canthal region overlying the medial canthal tendon. This condition can occur in isolation or it can be associated with multiple genetic disorders such as trisomy 21 and blepharophimosis syndrome. Epicanthal folds are generally classified as being one of four types: epicanthus supraciliaris, epicanthus inversus, epicanthus palpebralis, and epicanthus tarsalis.

Epicanthus tarsalis is the normal medial canthal structure seen in many Asian eyelids (Fig. 19.13). The eyelid fold arises in the region of the upper tarsal plate and extends to the skin of the medial canthus. Epicanthus inversus is seen in isolation and in patients with blepharophimosis syndrome. This occurs when the fold of skin begins in the lower eyelid tarsal region and extends up through the medial canthal region toward the brow. Epicanthus palpebralis occurs when a fold runs from the upper eyelid tarsal region to the lower border of the orbit. Epicanthus supraciliaris occurs when the fold arises in the brow and terminates in the area of the lacrimal sac.

Epicanthal folds can be corrected with a variety of techniques, including a YV plasty most simply (Fig. 19.14). In addition, the Mustarde (14) and Roveda techniques have been described.

Telecanthus

Telecanthus refers to a wide intercanthal distance, differentiated from hypertelorism, which describes an increased interorbital bony separation. Telecanthus is often associated with epicanthus and blepharophimosis. When associated with epicanthal folds, telecanthus may be corrected using the same procedures that are used to treat epicanthus. However, medial canthoplasty and/or transnasal wiring may be necessary in more severe cases.

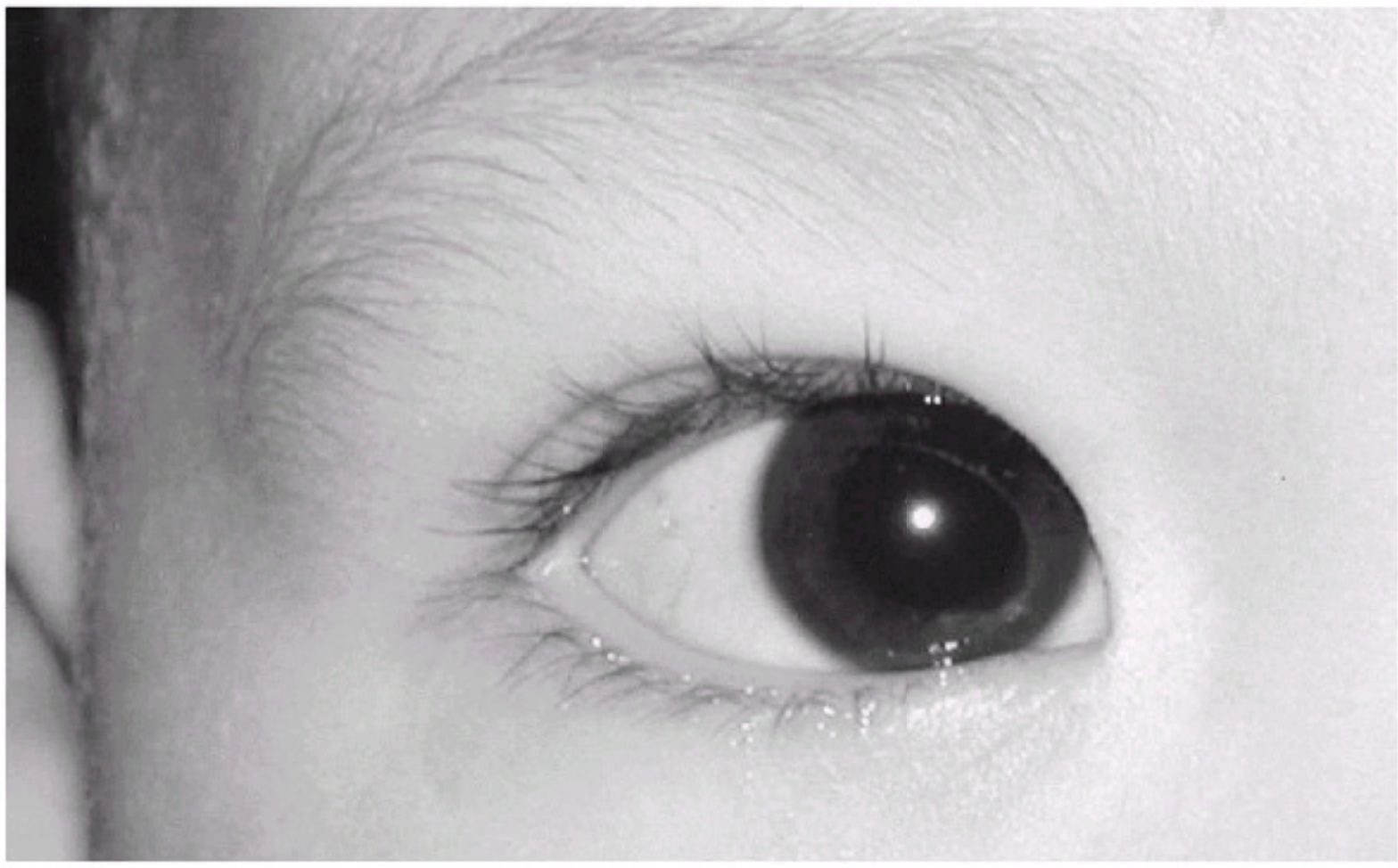
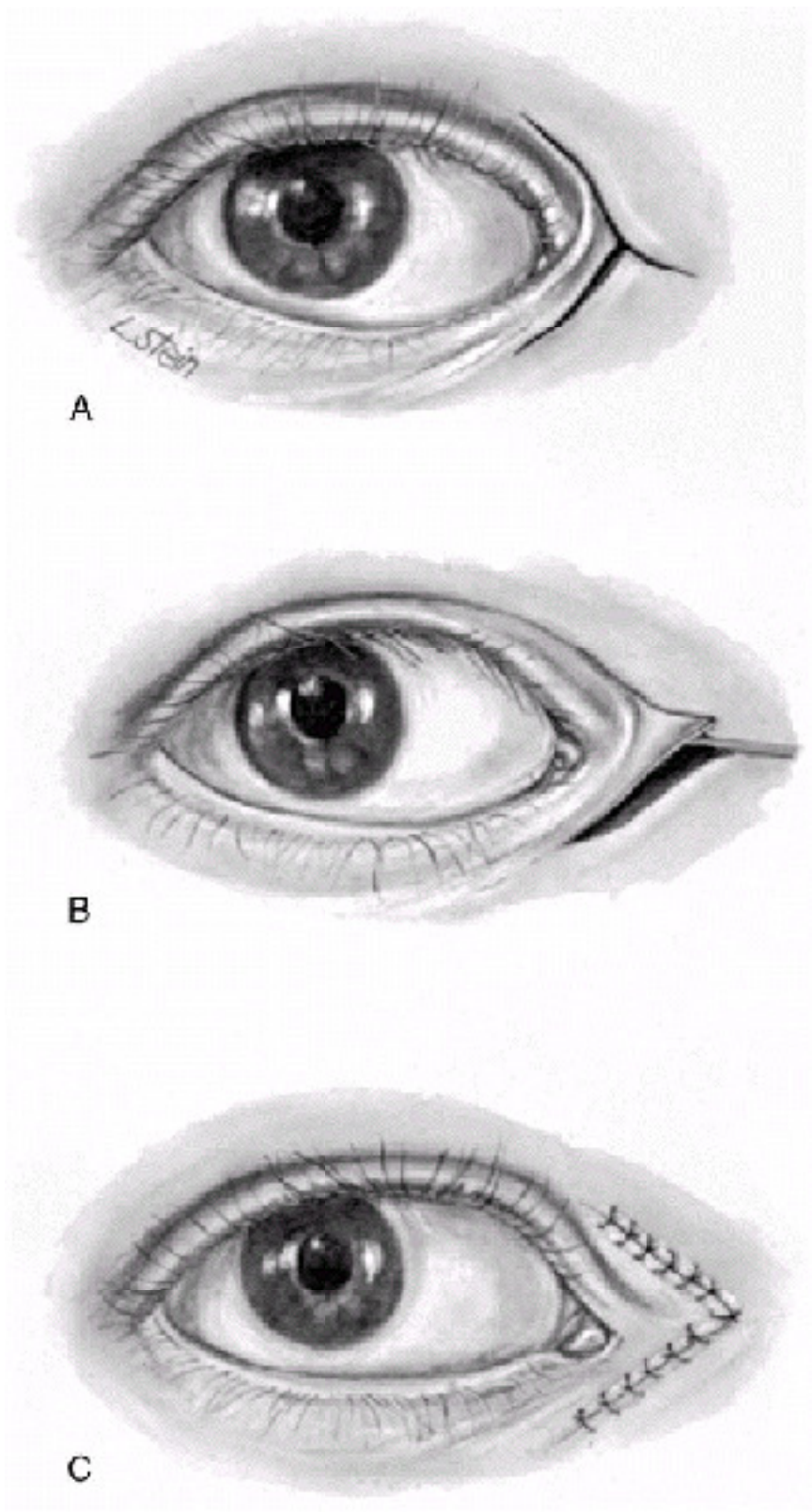


Figure 19.13 Epicanthal fold most consistent with epicanthus tarsalis.



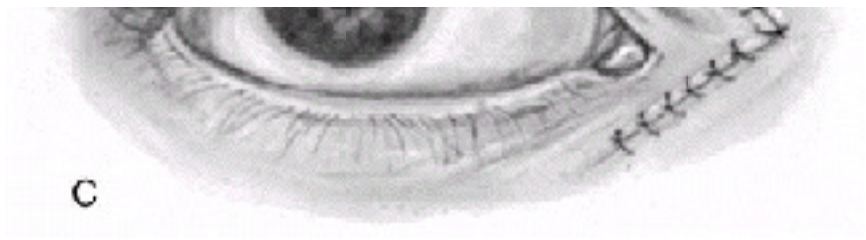


Figure 19.14 Surgery for epicanthus. **A:** Incision for preparing the skin flap. **B:** Undermining of skin to allow for movement of the tip. **C:** Skin sutures in a V-shape, flattening the epicanthal fold. The skin at the junction of the Y flap is rotated medially to the apex of the V, thus flattening the epicanthus.

Blepharoptosis

Ptosis of the child's upper eyelid is most often congenital. It is occasionally due to congenital myasthenia, congenital fibrosis of the extraocular muscles, syndromic associations, or acquired abnormalities such as loss of innervation to Müller or levator muscle. In addition, mechanical factors can contribute to ptosis, such as relative enophthalmos following an orbital fracture, tumor, or traumatic injury. Congenital ptosis of the upper eyelid is typically seen in association with abnormal development of the levator palpebral complex (Fig. 19.15). Although typically sporadic, familial ptosis has been linked to chromosome 1p (15). Perhaps abnormal neurologic innervation during development of the levator muscle results in abnormal development of the muscle complex, similar to what occurs in congenital fibrosis syndrome (16). Congenital ptosis occurs either unilaterally or bilaterally. Superior rectus muscle weakness can occur in association with congenital ptosis.

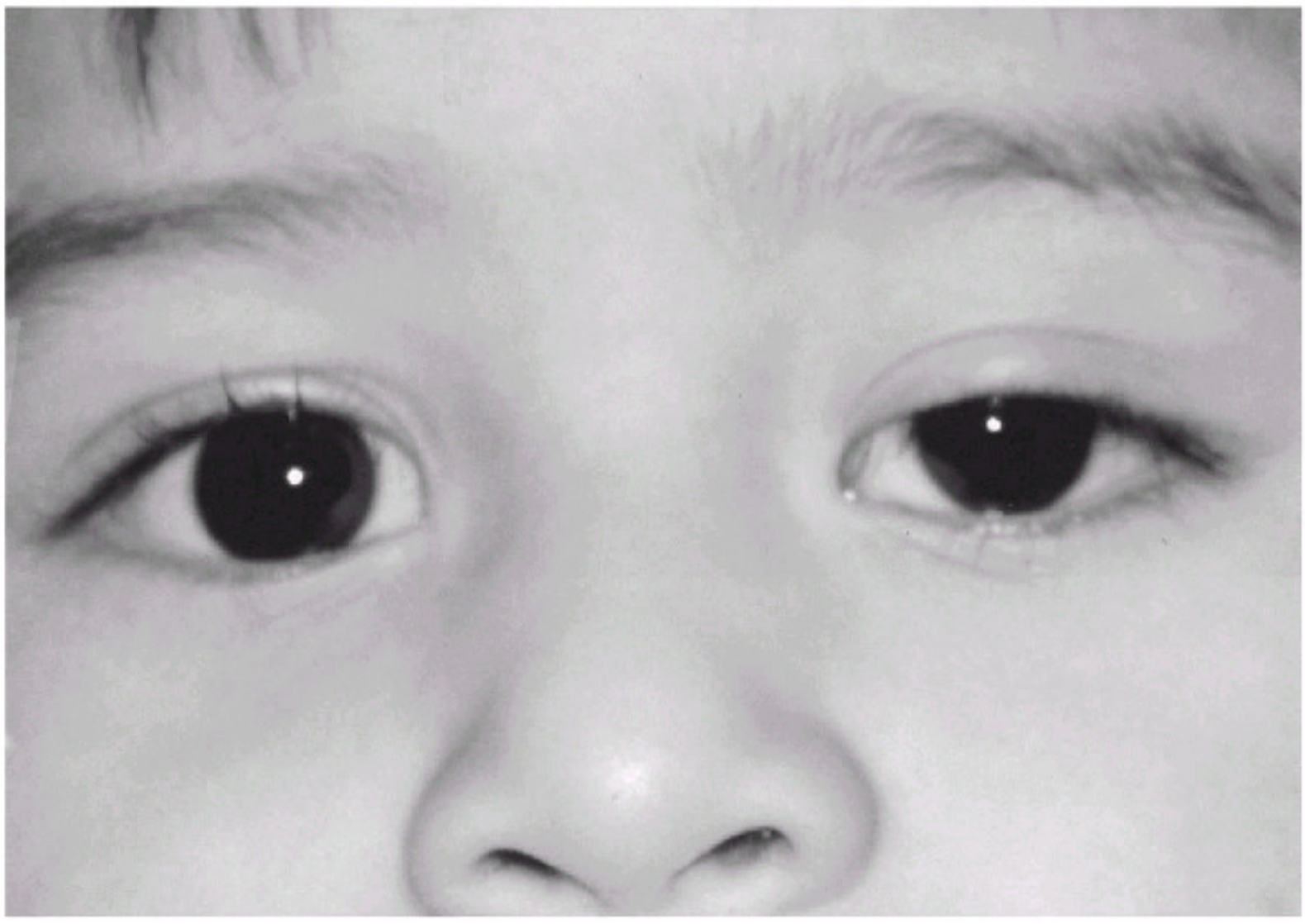


Figure 19.15 Congenital ptosis of the left upper eyelid.

Myogenic ptosis is also a potential cause of acquired ptosis in children. This is due to conditions such as muscular dystrophy and myasthenia gravis. Another unique type of congenital ptosis occurs in the Marcus Gunn jaw-winking phenomenon (Fig. 19.16). This is a result of aberrant innervation of the levator muscle with nerves normally directed to the muscles of mastication. Usually with contralateral jaw movement, the ptotic eye elevates. This is often noticed in infancy during feeding as the child seems to “wink” when nursing or taking a bottle.

Evaluation

Careful history should be taken as to the variability of the ptosis. Most patients with congenital ptosis will have a history of slight worsening with fatigue; however, they should not have large variability in the ptosis. Certainly alternating ptosis or a history of a normal eyelid position following sleep followed by significant ptosis when the patient is fatigued should raise a concern for myasthenia gravis. Evaluation of a patient with ptosis should include observation for signs of fatigue of the levator muscles. In a young child with poor cooperation, prolonged eyelid elevation to assess fatigability may not be possible. Tests which can be performed to establish the diagnosis of myasthenia gravis include the ice, rest, tensilon, and neostigmine tests. Tests for acetylcholine receptor antibodies are rarely positive in isolated ocular myasthenia gravis, especially in childhood; however, positive tests are strongly indicative of the presence of myasthenia gravis (17). A positive tensilon test, abnormal single-fiber electromyographic recordings, and therapeutic responses to anticholinesterase medicines or corticosteroids establish this diagnosis. If myasthenia is strongly suspected, then a trial of pyridostigmine bromide or corticosteroids is indicated.

Treatment of uncomplicated congenital ptosis requires measurement of the absolute amount of ptosis present in the primary position. Care should be taken to fix the brow

as patients with unilateral or bilateral ptosis often use their frontalis muscle to elevate the eyelids. The lid margin-reflex distance (MRD) should be measured. The MRD is the distance from a corneal light reflex to the upper eyelid margin with the patient's eyes in primary gaze. The amount of levator excursion also should be

measured. This can be difficult in younger children and infants. In congenital ptosis, the amount of ptosis inversely correlates with the amount of levator function. Repeat examination at separate visits helps the surgeon obtain reliable measurements of the true amount of ptosis and levator function. Levator excursion is measured by first firmly fixing the brow to immobilize the frontalis muscle. The amount of eyelid margin movement from full downgaze to full upgaze is then determined. A full examination of the extraocular muscles should be undertaken. In addition to specific examination of the superior rectus muscle, one should also check the Bell phenomenon (upward deviation of the eye during forced lid closure). A normal (present) Bell phenomenon is important because, after repair of congenital ptosis, lagophthalmos is common. A normal Bell phenomenon and normal superior rectus muscle function allow for protection of the cornea postoperatively (18). When superior rectus muscle function is reduced, a surgeon should be more conservative in the amount of surgery performed to correct the ptosis. In a younger child, reliable Schirmer testing is difficult. Examination of the tear film and careful evaluation of the cornea for any signs of exposure both pre- and postoperatively is necessary. In addition to evaluating the tear film, care should be taken to determine the corneal sensitivity. Certainly patients with diminished corneal sensitivity due to innervational abnormalities are at increased risk of exposure to keratopathy following surgery for correction of congenital ptosis. Corneal sensation can easily be determined using a simple wisp of cotton at the tip of a cotton-tip applicator applied to the corneal surface. Abnormal corneal sensitivity cautions the surgeon to avoid surgery or reduce the amount of ptosis correction.

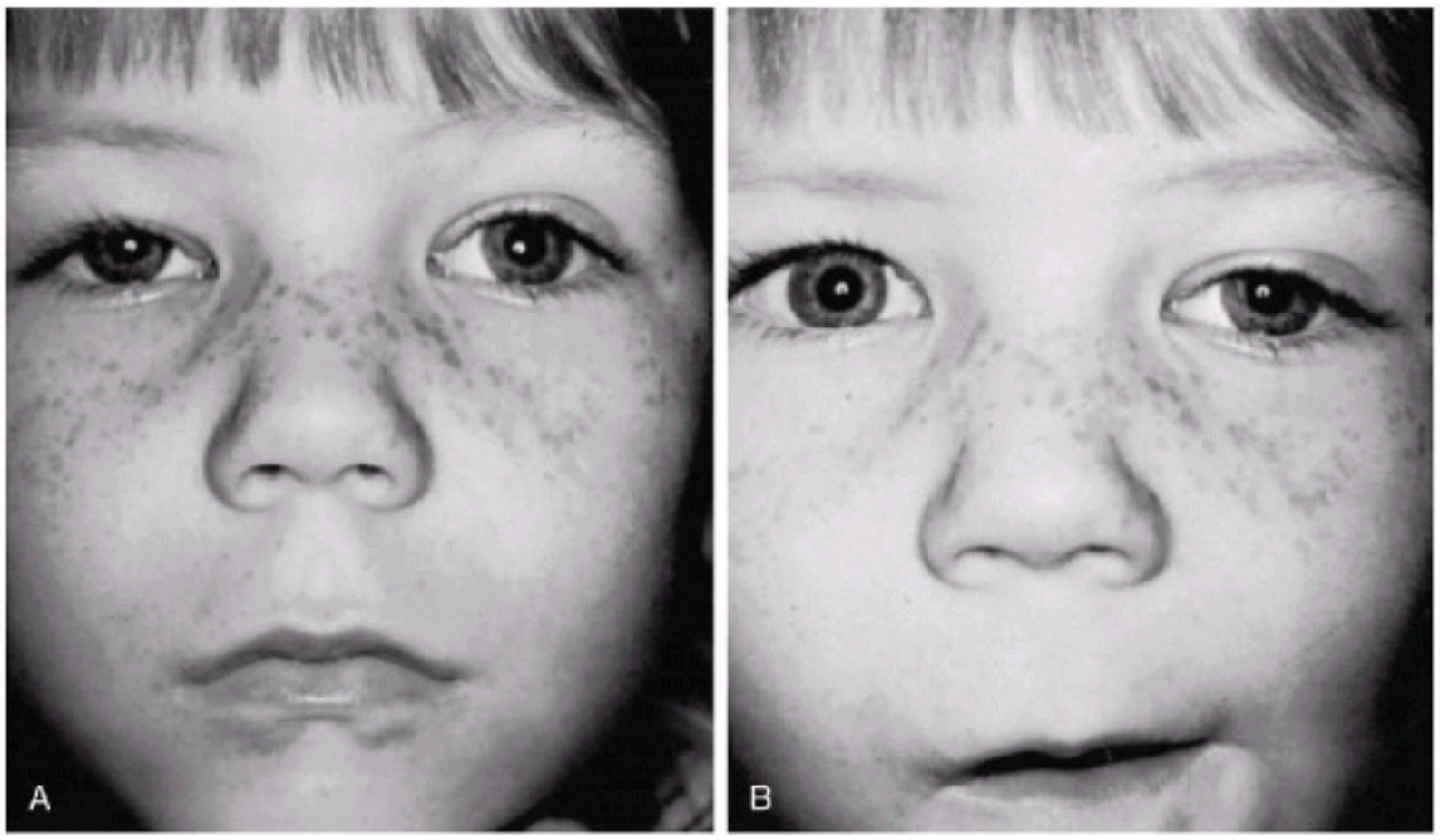


Figure 19.16 Right Marcus Gunn phenomenon demonstrated with jaw movement to the left. **A:** Before jaw movement. **B:** After jaw movement.

In patients with Marcus Gunn jaw-winking ptosis, the amount of eyelid retraction with movement of the jaw should be evaluated. In those patients with mild retraction, ptosis repair should be undertaken using standard amounts of surgery dependent on the degree of ptosis. An external levator resection is the usual procedure. If significant retraction is present, extirpation of the involved levator muscle combined with a frontalis suspension should be performed. Failure to extirpate the involved levator muscle will result in persistent wink.

In addition to measuring levator function, the eyelid should be assessed with its response to phenylephrine. One drop of 2.5% is instilled into the lower cul-de-sac in younger children and infants. The MRD is remeasured after approximately five minutes; if the eyelid elevates to a near normal position, tightening or resecting the Müller muscle could be considered for ptosis repair.

All patients with congenital ptosis require repeated visual acuity testing with determinations of refractive error. Amblyopia frequently occurs secondary to strabismus, induced astigmatism, and less commonly, occlusion of the line of sight (19). The presence of a chin elevation may allow for peripheral fusion but does not exclude the presence of amblyopia (20).

Timing of Surgical Intervention

In most situations, congenital ptosis is repaired when the child is 4 to 5 years old. Severe ptosis causing a significant chin-up position or occlusion amblyopia may be surgically repaired when recognized. Nevertheless, most ptosis-associated amblyopia is caused by induced astigmatism. If a

significant astigmatism develops, spectacle and amblyopia therapy should be instituted.

Surgical Procedures

There are several options for the surgical management of congenital ptosis. The main forms of treatment are external levator resection and frontalis suspension procedures. The Müller muscle procedures (Fasanella Servat and müllerectomy) may be used for correction in mild ptosis, particularly neurogenic ptosis associated with Horner syndrome.

Levator Muscle Procedures

Levator aponeurosis/muscle-shortening procedures are performed in cases of mild to moderate ptosis (Fig. 19.17). Although classic levator dehiscence can be encountered in the pediatric population, more commonly decreased levator excursion and levator muscle dysgenesis are encountered. Although a 1-mm resection generally elevates the eyelid 1 mm in adults, this is not true in most pediatric ptosis patients. A more generous resection is required in children and is dependent on the amount of levator function measured (Table 19.1).

The surgical approach is through the eyelid crease. Dissection is made initially through the skin, followed by the orbital septum. The underlying levator aponeurosis is exposed beneath the preaponeurotic fat. The levator aponeurosis is separated from the tarsal plate, and dissection in the plane between the Müller muscle and levator aponeurosis is carried out superiorly to expose and separate the levator tendon. In cases in which a large resection is anticipated, the lateral

and medial horns of the aponeurosis are cut. Three partial thickness permanent sutures are placed in the anterior tarsal surface 3 to 4 mm below the superior border of the tarsus. These sutures are then placed through the levator aponeurosis. Because the patient is usually under general anesthesia, the amount of resection needs to be determined prior to surgery. Sutures are tied with a single throw knot on the anterior surface of the aponeurosis and are replaced and retied until the surgeon is satisfied with the eyelid height and contour. Square knots are then tied, and levator tendon distal to the sutures is resected. The eyelid crease may be formed with separate sutures between the levator tendon and eyelid skin by incorporating bites

of the levator tendon into the skin closure, or the existing sutures may be brought through skin edges and retied on the skin surface.

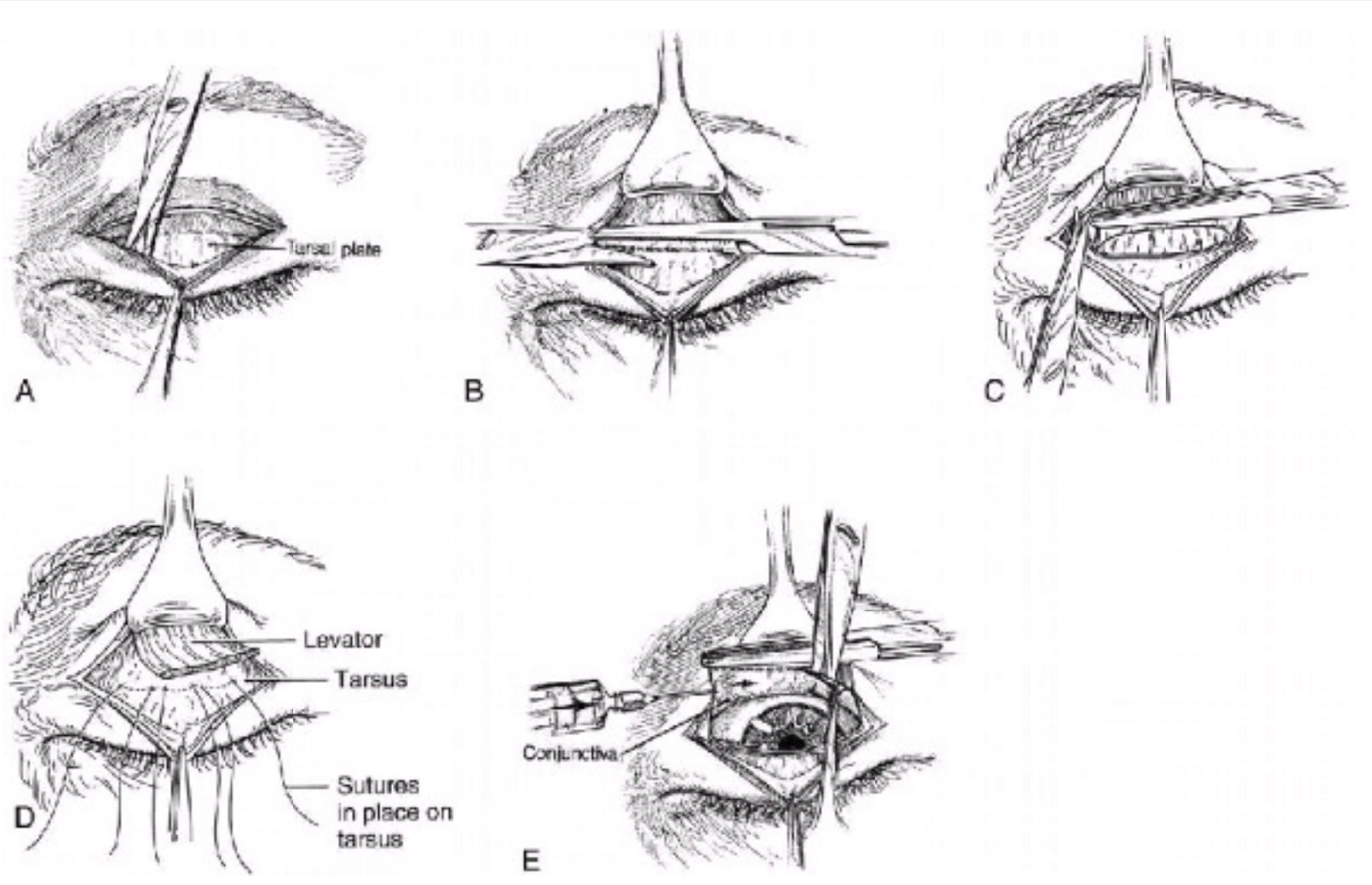


Figure 19.17 External levator procedure. **A:** The orbital septum has been opened, exposing the tarsus and levator tendon. **B:** Levator tendon dissected off the tarsus. **C:** The levator tendon is dissected off the Müller muscle. **D:** Reattachment of the tendon to the tarsus. **E:** After the final suture placement, the distal levator tendon is resected.

TABLE 19.1 PTOSIS REPAIR BASED ON LEVATOR MUSCLE FUNCTION AND AMOUNT OF PTOSIS

A. Poor levator muscle function (<4 mm) with severe ptosis (4 mm)

— Frontalis suspension procedure

B. Moderate levator muscle function (5-7 mm) with moderate ptosis (3 mm)

— external levator resection 17-20 mm

C. Moderate levator muscle function (5-7 mm) with mild ptosis (2 mm)

— external levator resection 12-15 mm

D. Moderate levator muscle function (8-10 mm) with mild ptosis (2 mm)

— external levator resection 10-12 mm

E. Good levator muscle function (10-13 mm) with mild ptosis (2 mm)

— external levator resection 6-9 mm

Frontalis Suspension

Frontalis suspension procedures are used in unilateral or bilateral cases of severe ptosis with extremely poor levator function (21) (Fig. 19.18). Autogenous fascia lata can be obtained from the leg of the child; typically, children are 3 to 4 years of age before an adequate length of fascia lata is obtainable. Banked irradiated fascia lata is available, but autogenous fascia lata has a lower rate of recurrent ptosis. Newer nonresorbable materials are available. These include Mersilene mesh, Supramid suture, and expanded polytetrafluoroethylene (ePTFE). Synthetic Supramid suture can be used for temporary elevation of the eyelid but may result in recurrent ptosis within 18 months (22). ePTFE is now available in strips specifically designed for use in ptosis repair (Fig. 19.19). A higher incidence of infection with similar material has been reported (23). Such infections are unusual if the eyelid skin incisions are closed with sutures and if patients are treated with antibiotics at the time of surgery and postoperatively.

In cases of severe unilateral ptosis, bilateral frontalis suspensions have been performed to provide a symmetric eyelid appearance, particularly in downgaze when lagophthalmos is most notable. However, if unilateral frontalis suspension is performed and postoperative asymmetry is an issue, the fellow normal eyelid can be subsequently operated. In cases of asymmetric bilateral ptosis requiring a frontalis suspension procedure on the more severely affected side, bilateral frontalis suspension will likely result in the best cosmetic result.

The double rhomboid technique provides excellent results (Fig. 19.19). The brow of the child is the most mobile section of the forehead and allows for both adequate elevation of the eyelid as well as good closure of the eyelid. Some surgeons prefer a central knot higher on the forehead. While this provides excellent contour and suspension to the upper lid, the more fixed superior forehead does not allow as much dynamic eyelid movement.

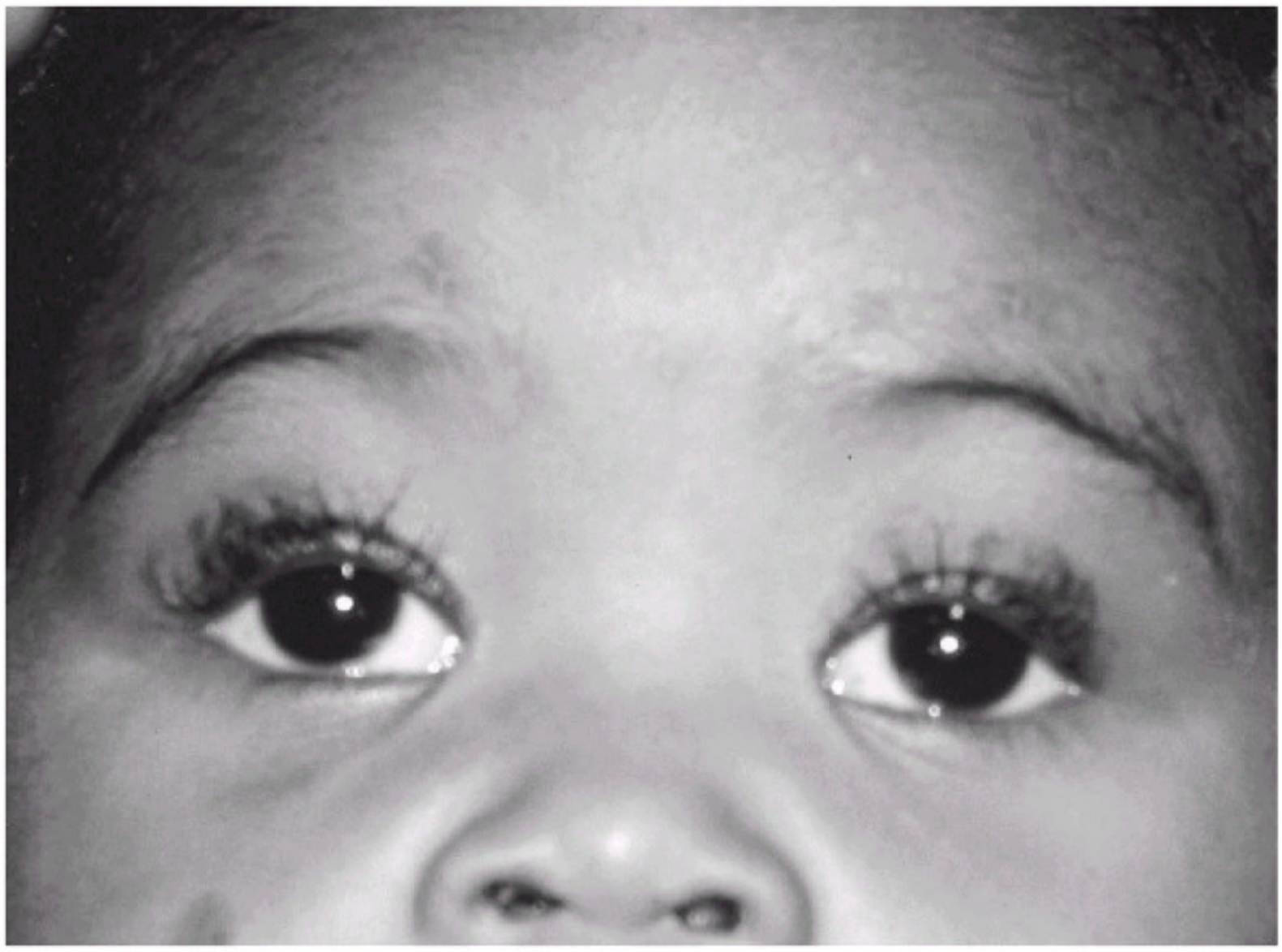


Figure 19.18 Postoperative appearance after bilateral frontalis suspension with expanded polytetrafluoroethylene.

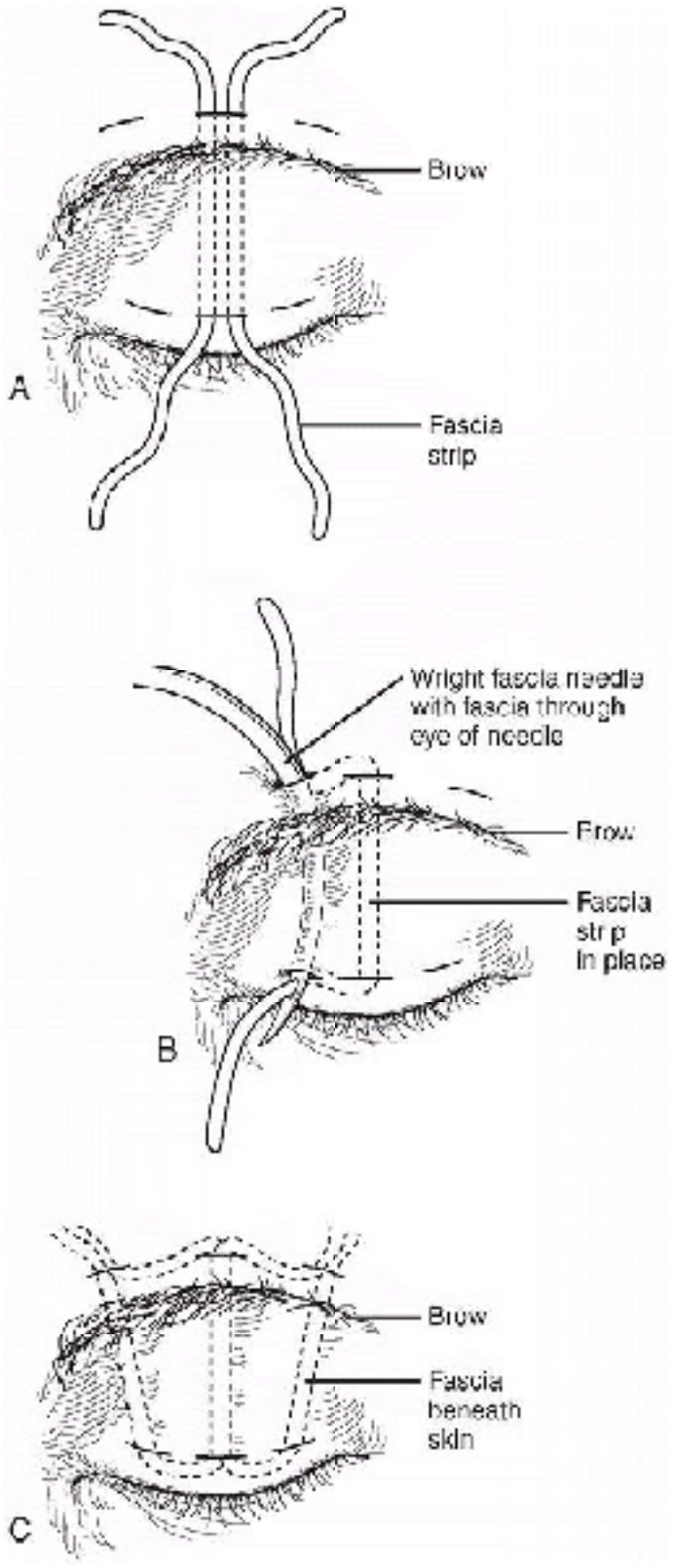


Figure 19.19 Double rhomboid technique for the frontalis suspension.

Tarsal Müller Muscle Procedures

Tarsal Müller muscle procedures result in good outcomes in those patients with excellent levator function and mild ptosis. A positive preoperative phenylephrine test suggests that a Müller muscle procedure will adequately elevate the eyelid. These procedures work particularly well for patients who have ptosis associated with congenital or acquired Horner syndrome.

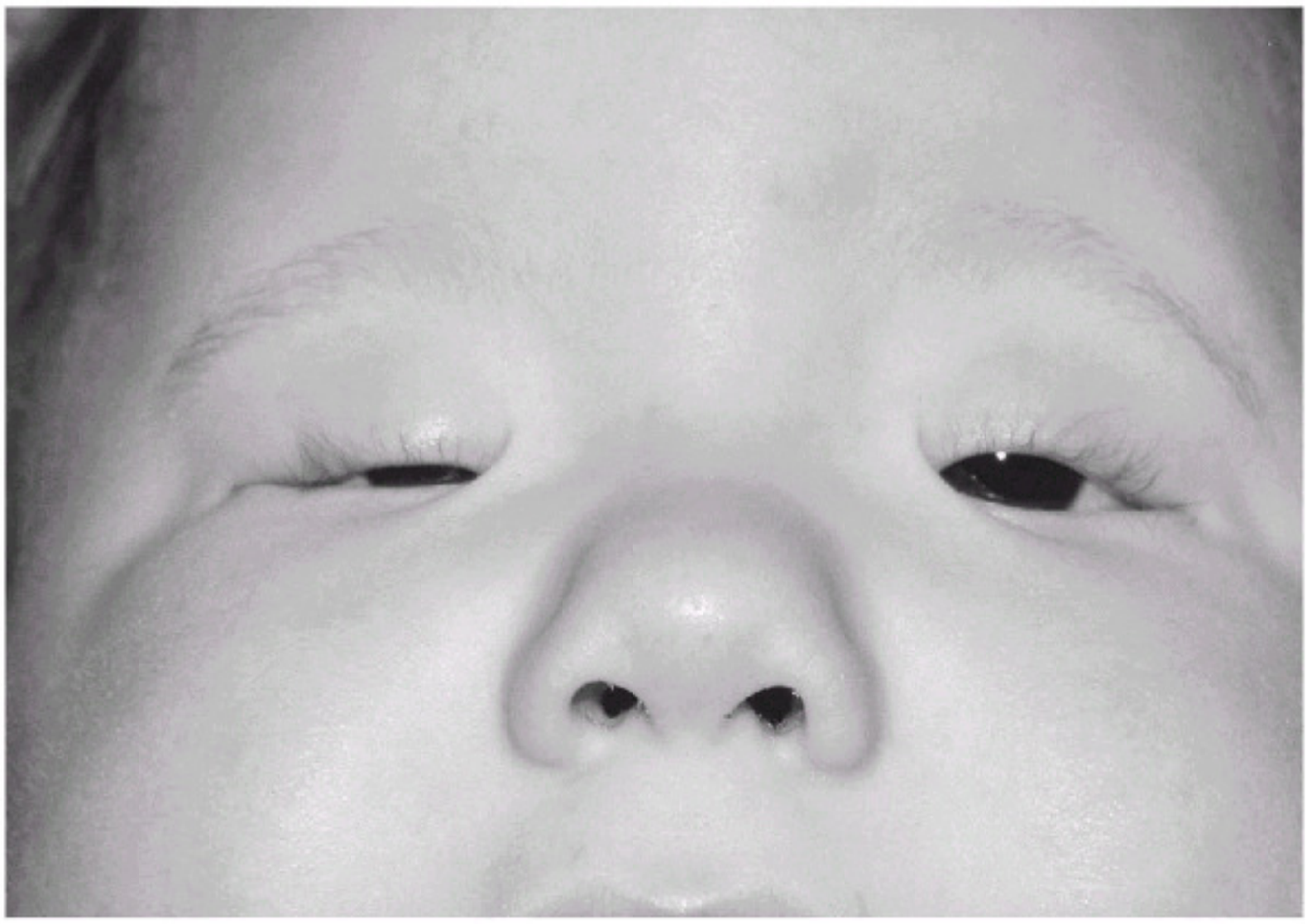


Figure 19.20 Blepharophimosis syndrome.

Complications of Ptosis Surgery

The primary complications of ptosis surgery are undercorrections, overcorrections, and corneal exposure problems. Other complications include abnormal lid crease, ectropion, entropion, conjunctival prolapse, infection, and bleeding. Blindness is a rare but devastating complication. Undercorrection is common in congenital ptosis, while overcorrection is unusual. Exposure keratopathy can be serious and should be investigated at all postoperative examinations. Lubrication with ointments and artificial tears should be used in all patients postoperatively until the corneal examination is stable.

Blepharophimosis Syndrome

Blepharophimosis syndrome is an autosomal-dominant condition with characteristic features including ptosis, epicanthus inversus, telecanthus, blepharophimosis (a short horizontal palpebral fissure length), and variable lower eyelid ectropion (Fig. 19.20). Each of the individual abnormalities is addressed surgically, either simultaneously or during separate sessions.

EYELID TUMORS

Benign Lesions

Capillary Hemangiomata

Capillary hemangiomata are the most common eyelid and orbital tumors in the infant. They are composed of abnormal capillaries with proliferation of endothelial cells. Clinically capillary hemangiomata present as superficial or deep lesions. Superficial lesions have a bright red appearance during the rapid growth phase and will blanche with compression, and deeper hemangiomata may give a reddish to purple hue to the overlying skin (Fig. 19.21). Capillary hemangiomata rapidly enlarge during the first several months of life and may continue to enlarge until 18 months of age; this rapid enlargement may lead to areas of necrosis or ulceration as the lesions outgrow their blood supply. These tumors are soft and compressible. Clinically, these lesions are more common in females and in those children born prematurely. Most hemangiomas regress completely without residua. Involution typically occurs slowly and is complete by 3 to 7 years of age. During the involutional stage, the reddish lesion will slowly change to gray, and the surface epithelium slowly changes to a more normal skin appearance. However, the skin may be thin with fine wrinkles. Hemangiomata on the eyelids can result in deformational abnormalities for the position and contour of the eyelid (Fig. 19.22).

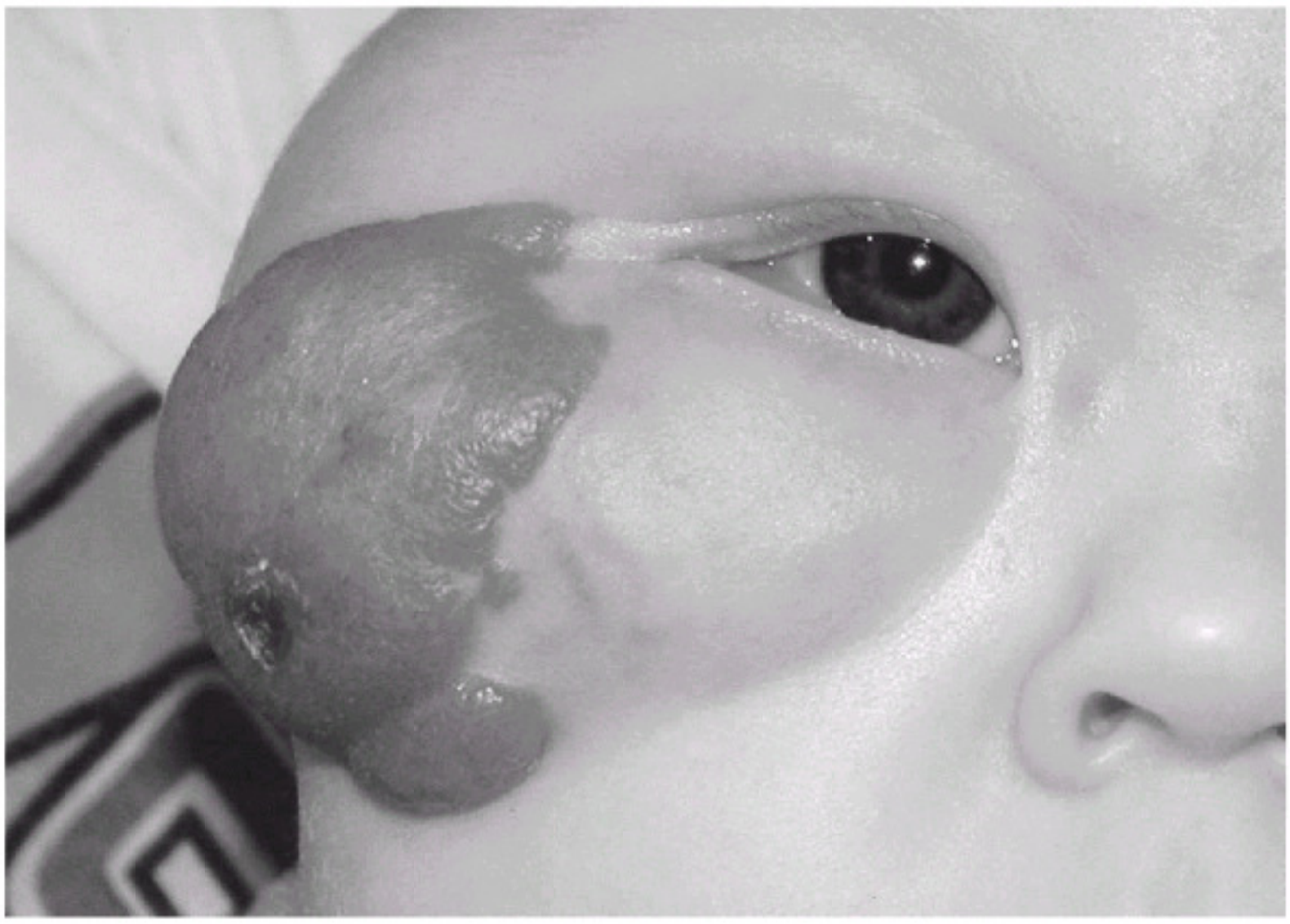


Figure 19.21 Large periocular capillary hemangioma. The most superficial components are bright red. Notice the small area of necrosis. The deeper portions of the tumor (medially) impart a gray hue to the overlying eyelid skin.

While larger tumors can cause occlusion amblyopia by blocking the visual axis, refractive amblyopia from induced astigmatism is more common. As little as 1.5 diopters of astigmatism increases the risk of amblyopia (24). Spectacle correction is frequently required along with amblyopia therapy.

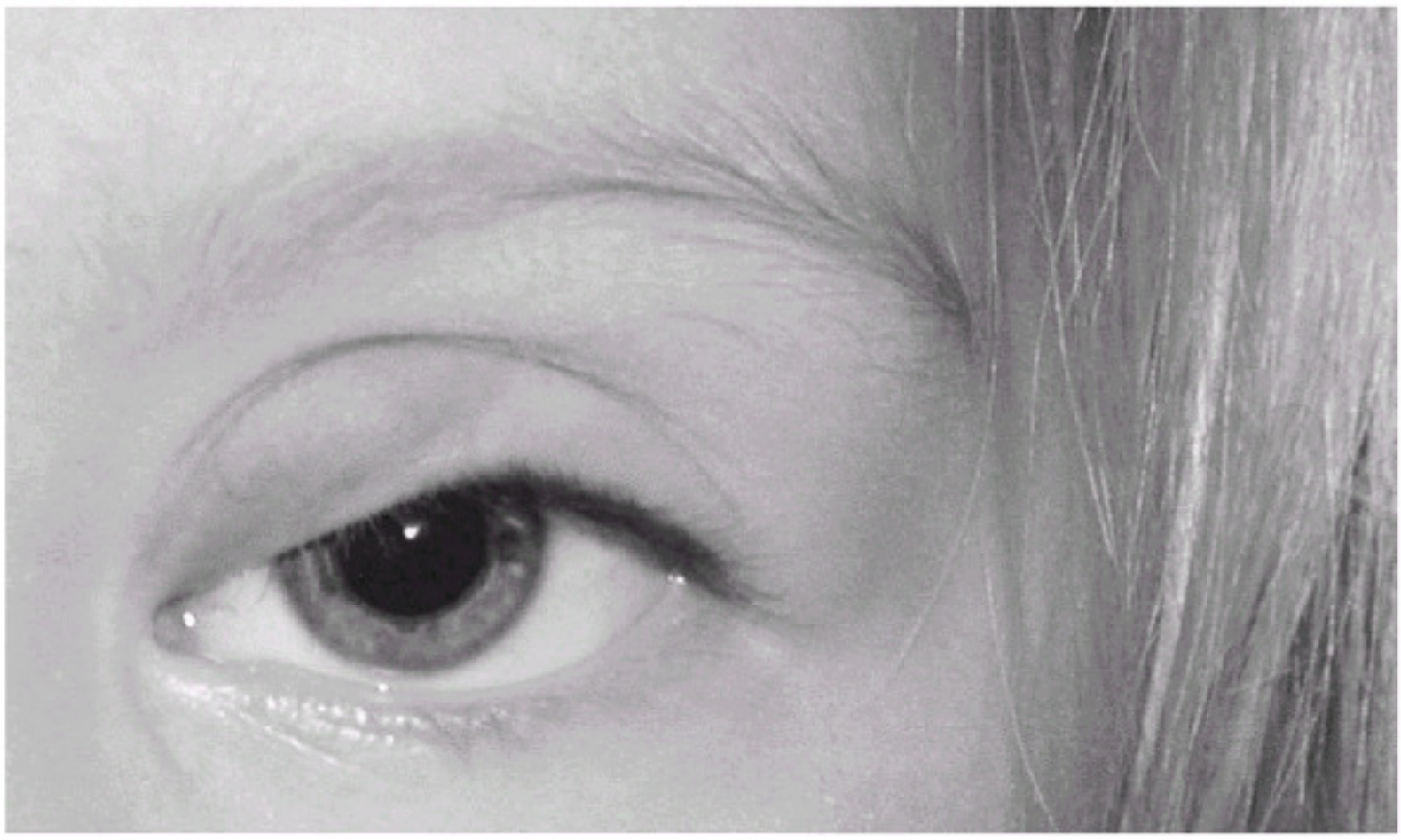


Figure 19.22 Regressing hemangioma with upper eyelid contour abnormality.

Evaluation

For larger lesions and lesions involving the orbit or when the hemangioma appearance is not typical, computed tomography (CT) or magnetic resonance imaging (MRI) are valuable imaging techniques. CT scanning demonstrates an enhancing soft tissue lesion with irregular borders. MRI is often better at differentiating capillary hemangiomata from lymphangiomata. MRI scanning may show the chocolate cysts of lymphangiomata that are not typical of capillary hemangiomata. An MRI of capillary hemangiomata shows characteristic flow voids.

Management

There are a number of management options for capillary hemangiomata. Most commonly observation alone is all that is required as these lesions typically involute spontaneously. Periocular capillary hemangiomata are more problematic as they have a higher incidence of amblyopia and eyelid deformities. As mentioned above, correction of any refractive error and appropriate amblyopia therapy are important in the management of the patient with periocular hemangiomata. In cases of occlusion amblyopia from large periocular hemangiomata, more aggressive intervention needs to be considered. Options to slow the growth or decrease the size of a periocular capillary hemangioma include intralesional corticosteroids, oral corticosteroids, topical corticosteroids, superficial laser ablation, surgical excision, and systemic interferon-alpha. In general, corticosteroid therapy is the primary modality used in the medical treatment of hemangiomata. Intralesional corticosteroid injections for periocular capillary hemangiomata were first described by Kushner (25). Typically a combination of long- and short-acting corticosteroids are injected in one or multiple sites into the lesion. The total steroid dosage per injection should be in the range of 3 to 5 mg/kg (26). Following injection with both long- and short-acting steroid agents, a repeat injection may be required in 4 to 6 weeks. If short-acting agents are used in isolation, then subsequent injections, if necessary, may be repeated at 2- to 4-week intervals. Complications of steroid injection include eyelid necrosis, subcutaneous fat atrophy, and very rarely, central retinal artery occlusion (26,27). The potential complication of retinal artery occlusion is extremely rare and might be minimized by injecting under low pressure, reducing the chance of retrograde flow of particulate steroid material. In addition, immediately before injection, the plunger of the syringe should be retracted to avoid direct intravascular injection. Additional complications that have been described include adrenal suppression (28). Children, pediatricians, and parents should be warned of this potential complication. Consideration should be given to measurement of circulating glucocorticoids. Despite these concerns, Addisonian crisis has not been reported following steroid injection for capillary hemangioma. Oral corticosteroids are used as either a primary modality by many practitioners or a secondary modality when intralesional steroid injections have produced little benefit. Many practitioners use oral corticosteroids as a first line of treatment with intralesional injection for those lesions requiring more aggressive intervention. Oral corticosteroids are administered at 1 to 4 mg/kg per day. The length of treatment depends on the size and response of the tumor. In general, it may last for 6 to 12 weeks with a tapering of the steroid dosage.

Alternatives include topical “betasol propionate,” although this treatment modality may not be as successful as oral or intralesional steroids (29). In more systemic life-threatening hemangiomata, interferon-alpha has been used. However, significant side effects, including neutropenia and neurologic toxicity, have been reported.

Finally, surgical excision of hemangiomata has been advocated for select cases (30). This may be better for small isolated lesions rather than large diffuse lesions. Excision is particularly useful for those lesions which are very anterior and well circumscribed. Since hemangiomata interdigitate with normal eyelid structures, surgical excision must be done with particular attention to the anatomy to avoid the creation of secondary problems such as ptosis. More commonly, surgery is used once total or near total regression of the hemangioma has occurred. Surgery may involve correction of eyelid crease abnormalities or ptosis, correction of eyelid contour abnormalities, or removal of excessive skin.

Lymphangioma

Lymphangioma is a tumor that presents in a fashion similar to capillary hemangioma. However, it typically does not show spontaneous involution. While more commonly involving the orbit, it can present as a mass of the eyelid or conjunctiva. Lymphangiomata are composed of endothelial-lined channels, collections of lymphocytes, and occasional blood-filled cysts. These lesions may increase in size with upper respiratory tract infections. More dramatic enlargement occurs with hemorrhage into a cyst. Management is challenging as complete surgical resection is rarely possible. Use of the carbon dioxide laser facilitates surgical excision of these lesions. Unlike capillary hemangiomata, corticosteroids are ineffective in the management of lymphangiomata.

Periocular Dermoid Cysts

Dermoid cysts occur most commonly in the periocular region overlying the frontozygomatic suture, frontolacrimal, or frontomaxillary sutures. These cysts are firm, smooth, nontender subcutaneous masses present from birth. The skin overlying the cysts is freely mobile, and the cyst is usually affixed to bone. Enlargement is typically slow. Rupture secondary to trauma can expose the cystic contents to the subcutaneous tissue and result in significant inflammation and permanent scarring. CT scans demonstrate the dermoid cyst to be a characteristically well-demarcated lesion. The surrounding bone frequently shows some molding around the cyst. Occasionally a lateral dermoid cyst may have a barbell appearance with an intraorbital and extraorbital component. CT scans are not necessary unless an internal cystic component is suspected.

Treatment of dermoid cysts is surgical excision performed at about 1 year of age. As children become more mobile, the risk of spontaneous rupture from trauma increases. Care should be taken to avoid rupture of the dermoid

cyst during surgery if possible. If rupture does occur, the surgeon needs to ascertain that complete removal of the contents of the cyst as well as the cyst capsule has been accomplished. Remnants of the dermoid can cause significant inflammatory reaction with fibrosis and scarring. Excision may be approached through either the eyelid crease incision or a sub- or suprabrow incision.

Plexiform Neuroma

Plexiform neuroma is most often seen in the setting of type 1 neurofibromatosis. The typical plexiform neuroma causes an S-shaped deformity of the upper eyelid. The lid may have a “bag of worms” sensation to palpation, resulting from the underlying nodular plexiform neuroma. A plexiform neuroma interdigitates with normal tissues and grows with age. Surrounding bone may show abnormalities, particularly absence or hypoplasia of the greater wing of the sphenoid. This tumor frequently causes mechanic ptosis with resultant astigmatism and amblyopia. If significant ptosis or induced astigmatism is present, surgical debulking of the eyelid components of the tumor may be necessary. However, recurrence is expected over time.

Nevi

The nevus develops as a benign proliferation of the epidermal melanocytes. In children, these can be congenital or acquired. Due to the fusion of the eyelids during fetal development, a nevus may be present on corresponding areas of both the upper and lower lids (kissing nevus). Nevi tend to be variable in color and size, but are typically tan colored with focal areas of increased pigmentation (Fig. 19.23). Surgical excision for cosmesis or because of a concern for malignant transformation may be considered. Larger lesions may require skin grafts, flaps, and occasionally multiple staged surgical procedures. Acquired nevi tend to occur after 6 months of age; these typically have pigmented spots within the lesion (Fig. 19.24).

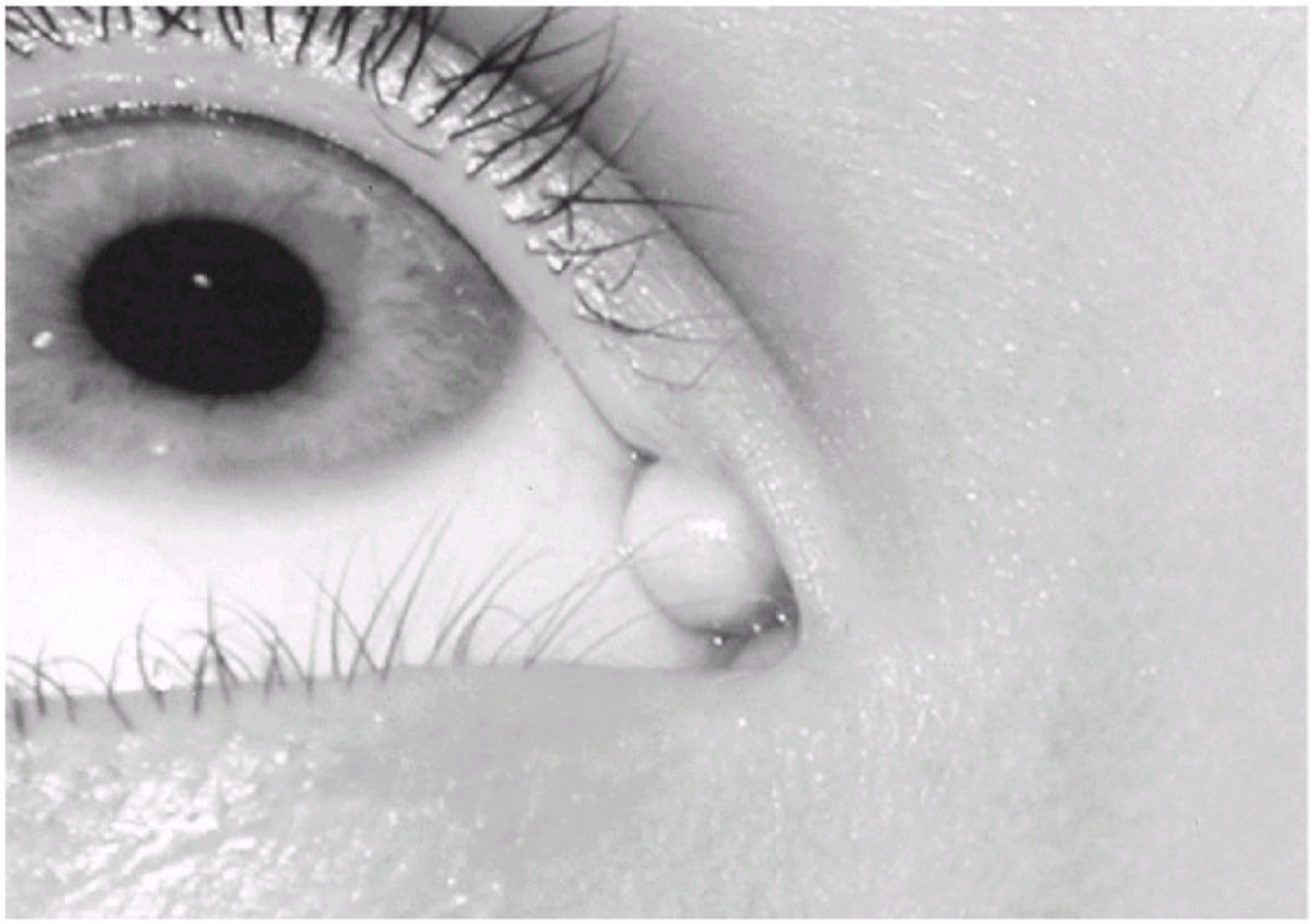


Figure 19.23 Pathologically confirmed congenital nevus of the medial upper eyelid.

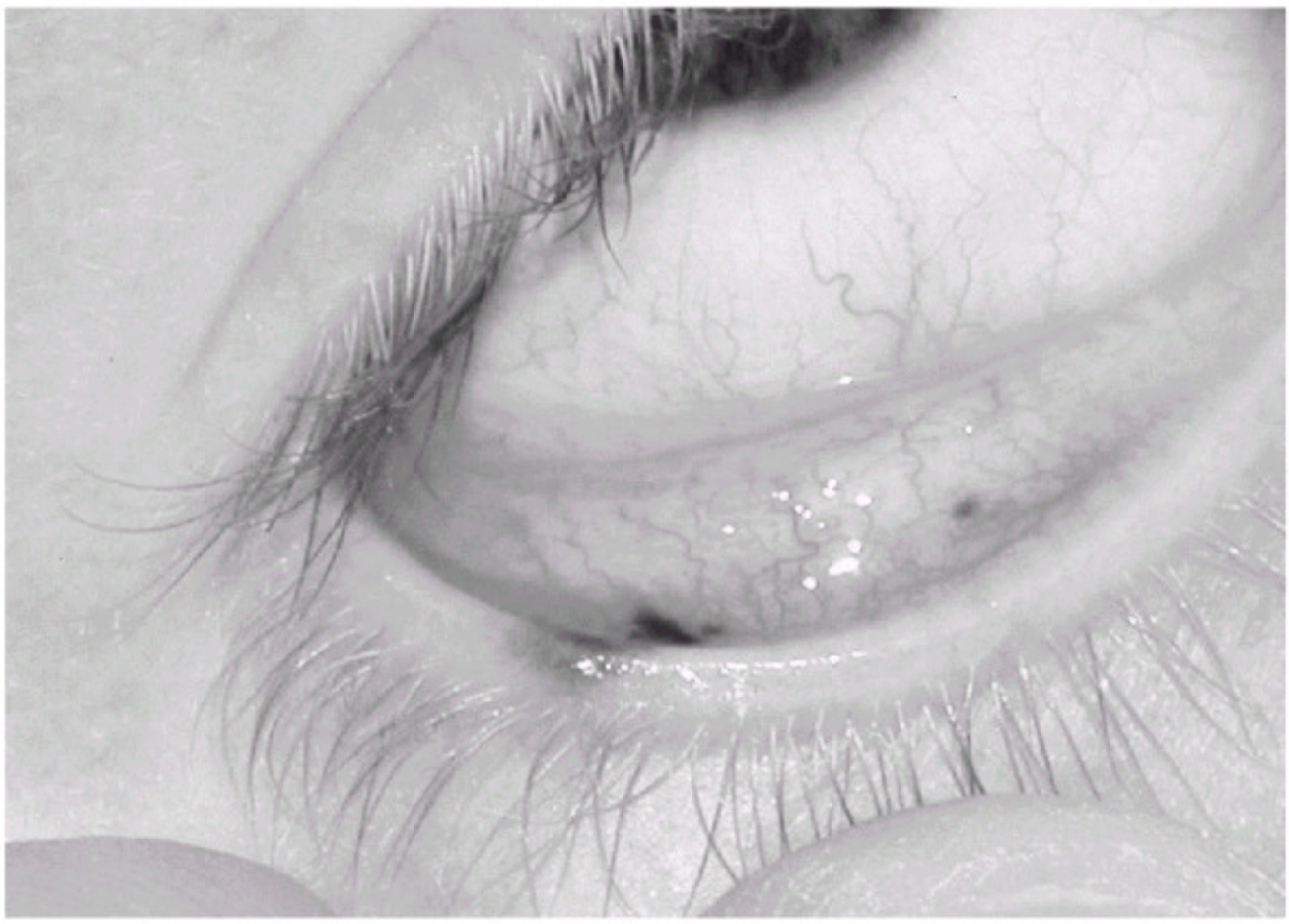


Figure 19.24 Acquired nevus in a 12-year-old white male. Pathology confirmed benign melanocytes.

One form of congenital pigmentation is that of oculodermal melanocytosis (nevus of Ota). The skin, as well as the ocular surface and conjunctiva, have a slate-gray pigmentation. The uvea of the affected eye may also have increased pigmentation. While more common in Asians, when seen in Caucasians, there is

an increased risk of uveal melanoma.

Giant Hairy Nevi

Giant hairy nevi are congenital, hairy, deeply pigmented melanocytic nevi. A 5% risk of malignant transformation into malignant melanoma is reported (31). Therefore, prophylactic excision of these nevi is performed.

Pilomatrixoma

Pilomatrixoma is a benign proliferation of hair matrix cells. These lesions tend to occur in children and have the appearance of a solid subcutaneous nodule.

Juvenile Xanthogranuloma

Juvenile xanthogranuloma is a proliferation of non-Langerhans cell histiocytes (Fig 19.25). These lesions in the skin are yellow-red, rounded papules and nodules. When they occur on the iris, they may be associated with spontaneous (atraumatic) hyphema. Since spontaneous resolution does occur, surgical excision of skin lesions is rarely necessary. Needle biopsy or anterior chamber aspiration have been used for iris lesions when the diagnosis is uncertain. Low-dose radiation has been used for recalcitrant iris lesions but seldom is necessary.

Chalazion

Chalazia are common lesions of the pediatric eyelid. A chalazion results when obstruction of a meibomian gland occurs,

resulting in rupture of the oil gland into the surrounding soft tissue and formation of a pseudocyst. The inflammatory reaction creates an erythematous nodule in the eyelid. Typical treatment includes warm compresses and eyelid hygiene. Topical antibiotic ointment may be used in combination with topical corticosteroids to reduce the inflammatory component of the chalazion. Intralesional corticosteroids are sometimes used. Care should be taken to avoid steroid injection into darkly pigmented skin as this may cause a focal area of hypopigmentation. For persistent chalazia, in which the inflammatory process is quiescent, incision and drainage may be necessary. For younger children, this is usually done under general anesthesia. A chalazion clamp is used and placed over the involved portion of the eyelid and the eyelid inverted. A number 11 or 15 Bard-Parker blade is used to vertically incise the tarsus from the palpebral conjunctival surface. Care is taken to avoid extending the incision to the lid margin as this could result in notching of the eyelid margin. A pseudocyst will typically extrude a gelatinous material when incised. A curette is used to remove the entire contents of the cyst. In larger lesions, excision of the pseudocyst wall is performed.

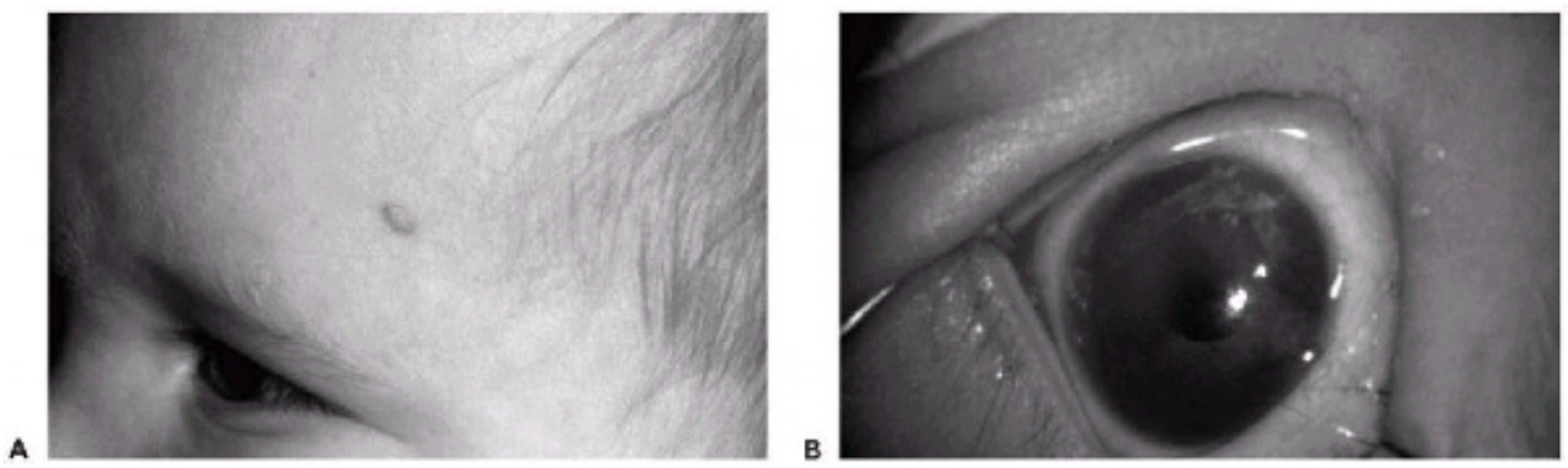


Figure 19.25 A: Juvenile xanthogranuloma (JXG) skin lesion. **B:** Spontaneous hyphema associated with JXG lesion of the iris.

Milia

Milia are cystic accumulations of keratin within the pilosebaceous units. These are extremely common in neonates and usually regress in the first 3 to 4 weeks of life. No treatment is required.

Pyogenic Granuloma

Pyogenic granulomas are bright red papules or nodules. They are common in children and can occur on any cutaneous or mucosal surface. These lesions are usually rapidly growing and bleed easily from minor trauma. When they occur in the periocular region, they are nearly always associated with a prior ocular injury, surgery, trauma, or with a chalazion. Larger lesions are simply excised and the base cauterized. Smaller lesions may respond to topical corticosteroids.

Syringoma

Syringomas are benign tumors of the eccrine duct structures. They are 1- to 3-mm translucent papules most commonly seen on the lower eyelid. The incidence is increased in Down syndrome.

Xanthelasma

Xanthelasma are typically yellow-colored papules and plaques seen on the upper eyelids near the medial canthus. While rare in the pediatric-age group, any child with xanthelasma deserves an evaluation for disorders of lipid metabolism.

Malignant Lesions

Malignant lesions are rare in the childhood eyelid. However, they may occur under certain circumstances. Basal cell carcinoma has been reported on the eyelids of children, but usually in association with nevus sebaceous, xeroderma pigmentosa, or basal cell nevus syndrome. Basal cell carcinomas have smooth pearly edges with telangiectases. The central area may necrose, leaving a raised rim.

Basal cell nevus syndrome is a autosomal-dominant disorder. In addition to basal cell carcinoma, jaw cyst, rib and vertebral abnormalities, calcification of the falx cerebri, agenesis of corpus callosum, palmer and plantar pits, ovarian fibromata, cardiac fibromata, and medulloblastomata occur. Additional ocular findings

include cataracts, glaucoma, coloboma, microphthalmia, and strabismus.

Squamous cell carcinoma is rare in children and is most typically seen in patients with xeroderma pigmentosa. Unlike basal cell carcinoma, squamous cell carcinoma can metastasize. Xeroderma pigmentosa is an autosomal-recessive disorder characterized by defective DNA repair under conditions of UV exposure.

INFECTIOUS EYELID DISORDERS

Preseptal Cellulitis

A common infectious eyelid disorder in children is preseptal cellulitis, an infectious process limited to the skin and

subcutaneous tissues anterior to the orbital septum. While the outcome is typically good in preseptal cellulitis, systemic sepsis and meningitis can occur. Preseptal cellulitis may be secondary to upper respiratory tract infections, sinusitis, or trauma (Fig. 19.26). Occasionally preseptal cellulitis results from an infection of a chalazion or spread from dacryocystitis. Abscess formation requiring surgical drainage can occur. Additionally, orbital and intracranial spread of the infection may occur. Patients with proptosis, pupillary changes, and limited extraocular motility should be evaluated for orbital cellulitis as these findings are not seen in patients with isolated preseptal cellulitis. Treatment of preseptal cellulitis includes antibiotics and surgical drainage of abscesses. Younger children and neonates should be admitted for intravenous antibiotics and monitoring. Older children with milder infections may be managed with oral antibiotics with close follow-up care. Common pathogens found in children with preseptal cellulitis include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenza*, and *Streptococcus epidermitis*. If a foreign body is suspected, then surgical removal of the foreign body is necessary for the infection to clear.

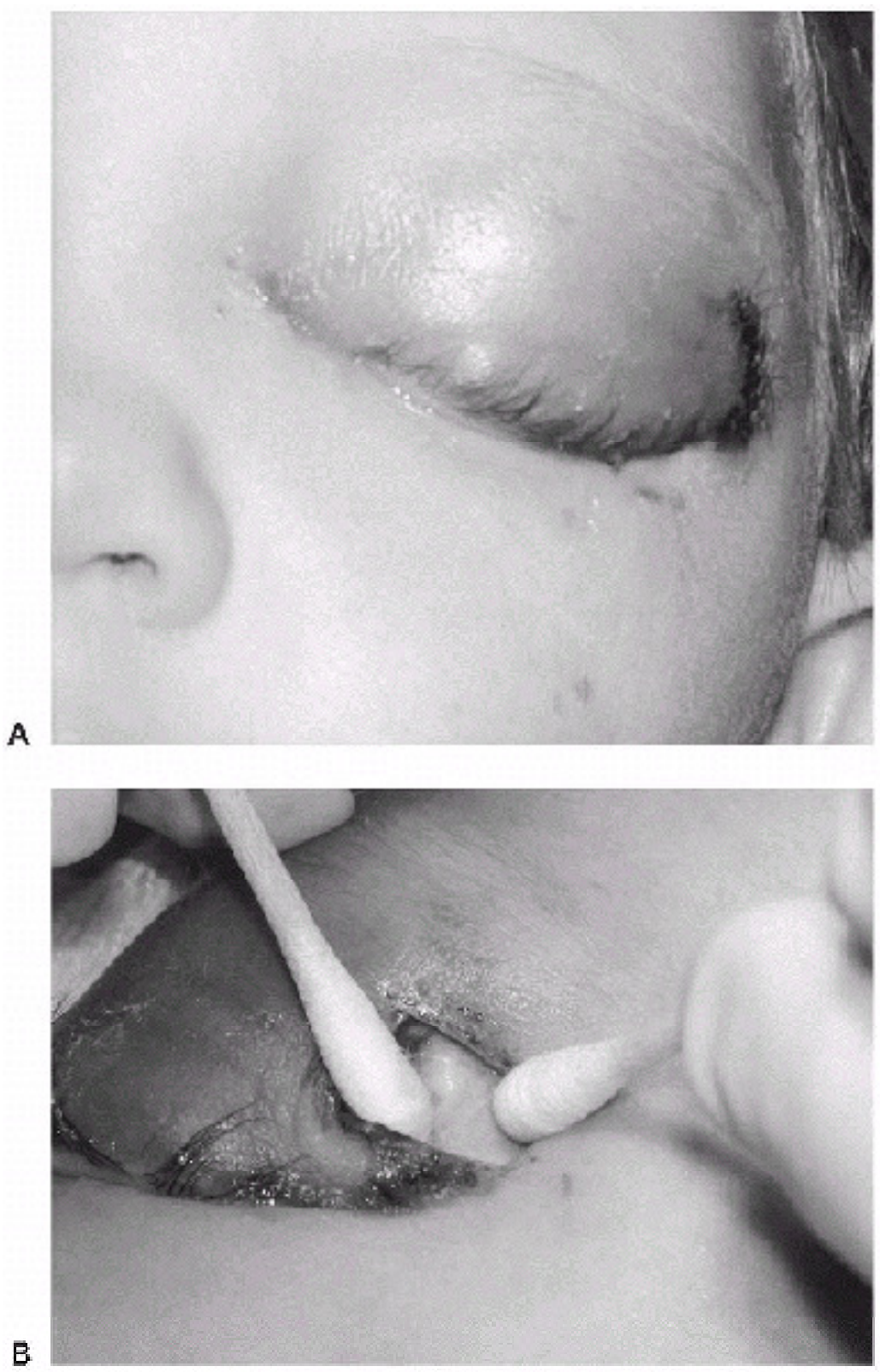


Figure 19.26 A: 4-year-old child with preseptal cellulitis several days after trauma. **B:** Lysis of sutures revealed a large abscess.

Necrotizing fasciitis is an infection caused by aerobic or anaerobic microorganisms which spreads rapidly through soft tissues. This condition has a high mortality rate. Typically these patients have signs of systemic toxicity with sepsis, organ failure, and respiratory failure. In the setting of necrotizing fasciitis, aggressive surgical debridement and broad-spectrum antibiotics are necessary.

Blepharitis

Chronic blepharitis is common in children and may result in chronic blepharoconjunctivitis, recurrent chalazia, loss of lashes (madarosis), and thickening of the lid

margins. Secondary corneal vascularization and scarring can result. Inflammation of the glands of the eyelid margin occurs with collarettes and crusting on the cilia. Treatment consists of warm compresses, tarsal massage, lid hygiene with baby shampoo scrubs, and topical erythromycin ointment three or four times daily. Treatment is continued for several weeks. Blepharitis may be chronic in children despite treatment. Oral erythromycin has been effective in children with severe blepharokeratitis (32). Oral tetracycline, minocycline, and doxycycline, while effective in adult blepharitis, are avoided in children due to the risk of dental enamel discoloration.

Herpes Simplex

When primary herpes simplex infection occurs in children, it is usually asymptomatic. Periocular involvement in primary herpes simplex infection usually manifests as vesicles on the eyelid margin. This infection is self-limited, but topical antibiotics may be used to prevent secondary bacterial infection. Latent herpetic infection may persist throughout life and be activated by many nonspecific stimuli. The most common ocular manifestation involves the cornea, but the lids may be involved in a recurrent infection. Herpetic blepharitis is characterized by the formation of vesicles that subsequently break down and ulcerate to form a yellowcrusted surface. Systemic administration of the antiviral agent acyclovir is beneficial.

Herpes Zoster

Herpes zoster ophthalmicus is unusual in childhood, but the upper or lower lids may be involved if the first or second division of the trigeminal nerve is affected. Vesicles occur at the inner half of the upper lid when the supratrochlear branch of the first division is involved, and along the side and tip of the nose if the nasociliary branch is involved. In the latter instance, severe keratitis and uveitis may occur. Systemic treatment with acyclovir is used along with antibiotic ointments to prevent secondary bacterial skin infections.

Molluscum Contagiosum

Molluscum contagiosum is a disorder caused by a poxvirus. The lesions are 2- to 4-mm papules, and they may be isolated

or multiple. In children, these lesions typically occur on the face, trunk, and extremities, including the eyelids. When present on the eyelids, they can be associated with chronic follicular conjunctivitis. Infection with this agent is self-limited and usually resolves in 6 to 18 months. When conjunctivitis is associated with molluscum contagiosum, the molluscum lesions near the lid margins should be excised or curetted. Asymptomatic children do not necessarily need treatment. However, if treatment is undertaken, simple excision or curettage of the surface of the lesions is all that is required.

Fungal Eyelid Infections

Eyelid infections due to fungi are unusual but may occur in immunocompromised individuals. Diagnosis requires a strong index of suspicion, proper culture with Sabouraud medium, and wet smears cleared with 10% potassium hydroxide. Pathogens include *Actinomyces*, *Nocardia*, *Candida*, and *Blastomyces*.

Pediculosis

Louse infections of the lids cause severe itching and irritation. The pubic louse has an affinity for the eyelids. Diagnosis is made easily on slit-lamp examination when the ova and adult crab louse are observed. Treatment consists of improving the patient's personal hygiene and application of a bland antibiotic ointment that suffocates the louse. Head and body antilouse shampoos are used along with home hygiene measures. It should be remembered that pediculosis is a sexually transmitted disease. A child presenting with pediculosis should prompt an evaluation for possible abuse.

Contact Dermatitis

The skin of the eyelids may resemble crepe paper, but it becomes markedly swollen after contact with inciting agents. The skin of the lids is red, itchy, and irritated. Common irritants include topical medications (e.g., atropine), cosmetics, nail polish, soaps, poison ivy, and sumac. Treatment consists of removal of the inciting substance. Symptomatic relief may be obtained by using systemic antihistamines and local corticosteroid preparations.

EYELID TRAUMA

The spectrum and management of periocular trauma is extensive. However, some common management issues should be considered. In any child who has sustained a periocular injury, the nature and history of the trauma should be elicited to the fullest extent possible. Blunt trauma with periocular ecchymosis will require careful evaluation of the eye and orbital structures. Even seemingly minor periocular trauma may be associated with orbital fractures and muscle entrapment in children (33). Therefore, ocular motility should be assessed and appropriate imaging studies performed when necessary. A thorough eye examination including a retinal examination should be included in the evaluation, as the history of the injury may be inconsistent with the physical findings.

Simple eyelid skin lacerations where a foreign body is not present and which do not involve the eyelid margin should be closed directly. Only the skin is closed, and care is taken to avoid vertical eyelid skin tension that can create eyelid retraction and abnormal eyelid contour. The orbital septum need not be closed for the same reason. Even in severe injuries, such as seen with dog bites, it is rare to have missing eyelid skin. When repairing complex skin lacerations where the anatomic relationships may at first not be obvious, start by suturing the skin where anatomic arrangement is recognized (Fig. 19.27). Closure of these areas will lead to a gradual recognition of the position of the remaining skin tissue so that proper reapproximation of the eyelid skin can be undertaken.

In cases in which the lid margin has been violated, the tarsus is closed primarily, followed by skin closure (Fig. 19.28). In full-thickness eyelid lacerations, the tarsus is closed with three interrupted 6-0 absorbable sutures. These

are preplaced and positioned such that a slight eversion of the lid margin occurs when the sutures are securely tied. Closure of the lid margin is performed with interrupted sutures. 7-0 chromic sutures with the tails cut close to the knots are usually used in younger children. These sutures resorb quickly and do not require general anesthesia to remove them. While the risk of corneal abrasion from the sutures at the margin is possible, scheduled application of antibiotic ointment seems preventative. In older children for whom in-office suture removal is possible, 8-0 black silk marginal sutures with the tails cut close to the knots work well without causing corneal surface irritation. Alternatively, the tails can be left long and draped over the anterior surface of the eyelid and then tied beneath superficial skin sutures. The skin can be closed with the surgeon's choice of absorbable or nonabsorbable suture depending on the child's age.

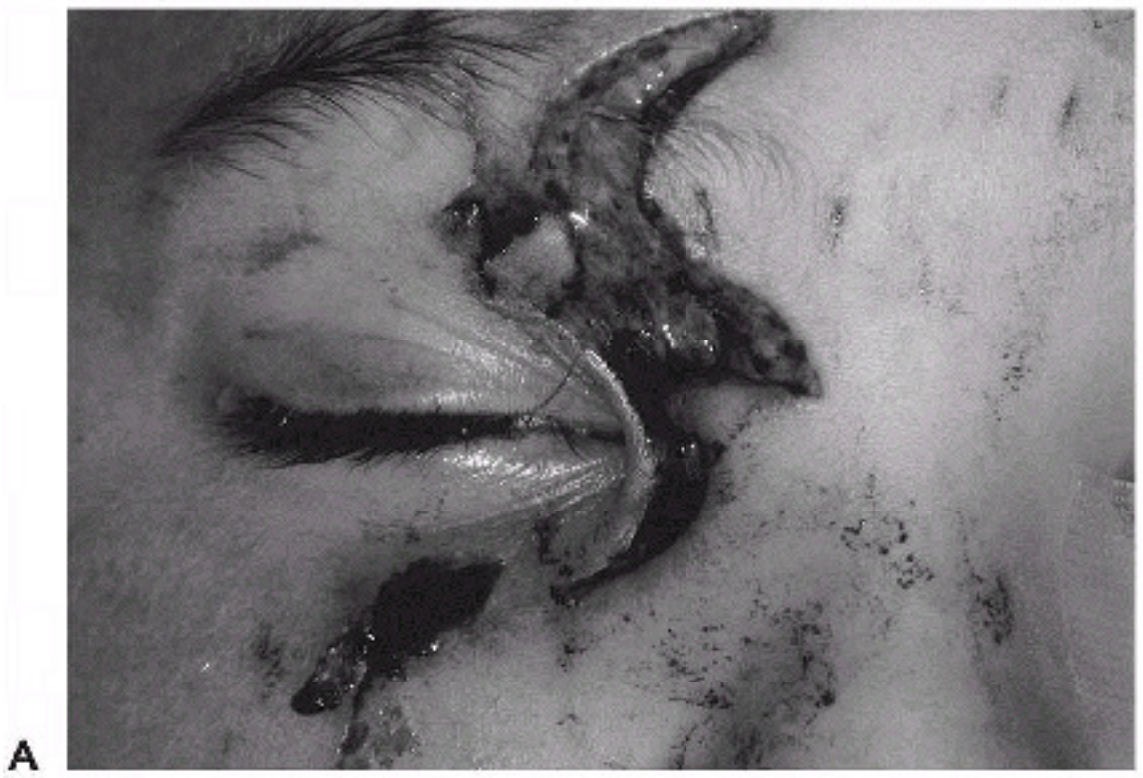


Figure 19.27 A: Complex medial canthal eyelid laceration. **B:** By first approximating the areas where the anatomic relationship is easily identified, (i.e., the brow cilia area and inferior laceration up to the medial canthal skin), the remaining anatomic relationships can be identified. The canaliculus and lacrimal sac were not involved.

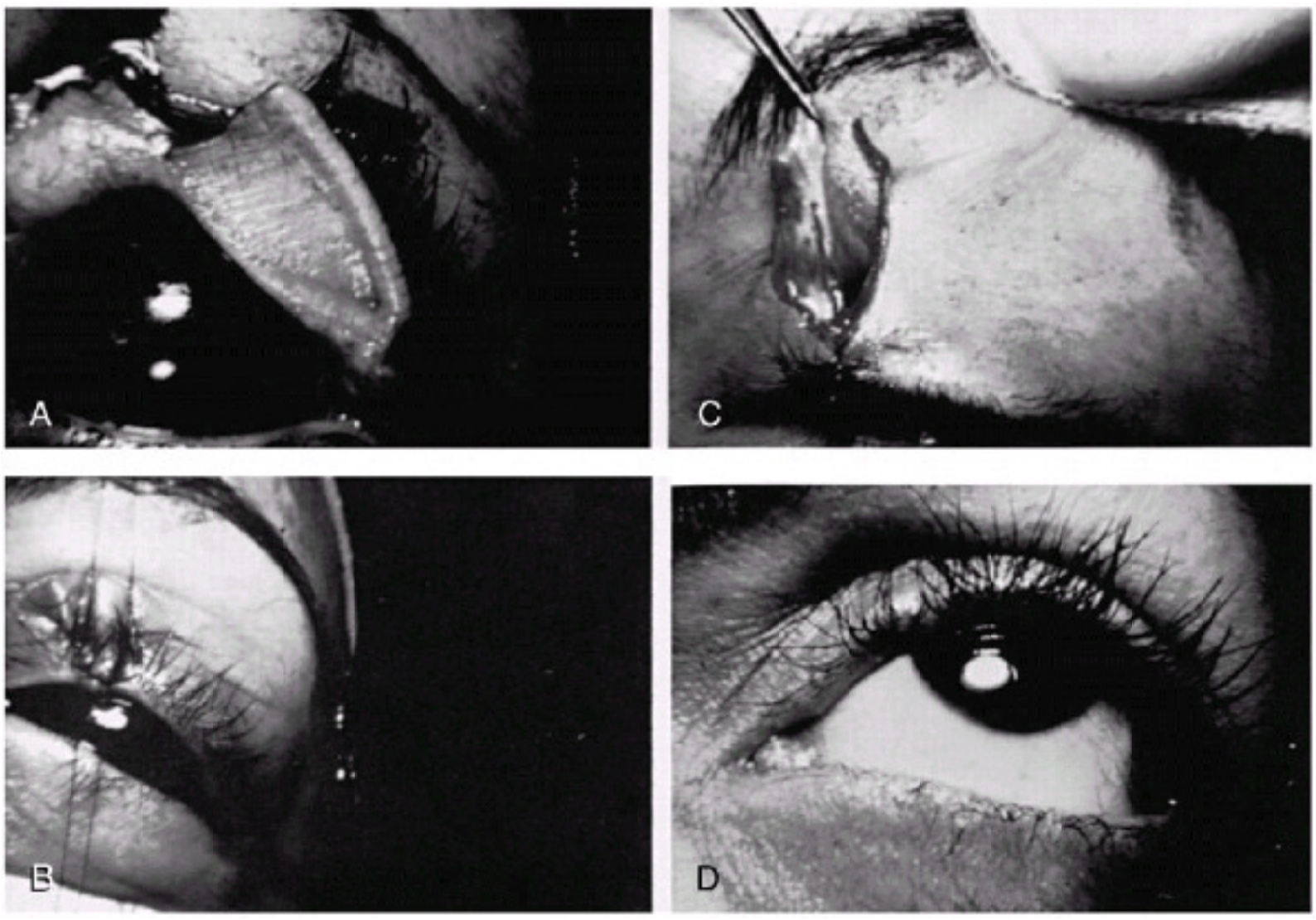


Figure 19.28 Repair of lid laceration. **A:** Vertical laceration through the lid border. **B:** Sutures at the anterior and posterior lid borders, and one in the area of the gray line. **C:** The remainder of the defect is closed in two layers. **D:** Postoperative appearance.

Trauma involving the lateral canthus will often require reapproximation of the lateral canthus with permanent Mersilene or prolene sutures through the periorbita of the lateral orbital rim. Medial canthal reconstruction with canalicular reconstruction can be managed with a Silastic intubation of the canalicular system. If the canaliculus is lacerated, careful inspection utilizing cotton-tipped applicators to retract the injured tissues will typically reveal the medial portion of the lacerated canaliculus that is recognized by the glistening epithelium. Typically, this is located more medially and more posteriorly than one might initially suspect. Avoid grasping the lacerated medial canthal area with toothed forceps when searching for the torn edge of the canaliculus. Sharp forceps create bleeding, shred tissues, and make location of the canaliculus more difficult. Once the canaliculus is located, Silastic intubation of the torn canaliculus is performed. The Ritleng introducer with Monoka monocanalicular stents or bicanalicular tubes easily facilitates intubation. Once the tube is in place, the epithelium of the canaliculus is closed with at least two 6-0 Vicryl sutures. These sutures are preplaced and then, with firm traction of the distal tube coming from the nares, the sutures are securely tied. The skin is then closed with either absorbable or nonabsorbable suture, depending on the child's age. Monocanalicular tubes self-seat in the punctum and do not require intranasal suture fixation. Similarly, a bicanalicular tube can be secured to itself within the lacrimal sac, thus avoiding intranasal fixation. Usually these tubes are removed in the office after 4 to 6 months.

Burn Injuries

Burns may result from caustic chemical exposure or materials from thermal injuries. Lye burns are more serious than acid burns. While base (alkali) penetrates deeply by causing protein dissolution, acid burns cause protein coagulation, which limits the depth of acid penetration. When caustic material comes into contact with the lids, the immediate treatment consists of a very thorough lavage with water. The cul-de-sacs should be included in the irrigation and all particulate matter should be removed. Scarring may lead to lagophthalmos, entropion, or ectropion. If scarring and contracture are severe, surgical lysis of the adhesions, excision of the scar tissue, and full-thickness skin grafting may be necessary.

REFERENCES

1. Piest KL. Embryology and anatomy of the developing face, In: Katowitz JA, ed. *Pediatric oculoplastic surgery*. New York: Springer-Verlag, 2002:11-30.

2. Dortzbach RK, Sutula FC. Involutional blepharoptosis. A histopathological study. *Arch Ophthalmol* 1980;98:2045-2049.

3. Jeong S, Lemke BN, Dortzbach RK, et al. The Asian upper eyelid: an anatomical study with comparison to the Caucasian eyelid. *Arch Ophthalmol* 1999;117:907-912.

4. Hawes MJ, Dortzbach RK: The microscopic anatomy of the lower eyelid retractors. *Arch Ophthalmol* 1982;100:1313-1318.

5. Jeffery AR, Ellis FJ, Repka MX, et al. Pediatric Horner syndrome. *J AAPOS* 1998;2:159-167.

6. Gossman MD, Mohay J, Roberts DM: Expansion of the human microphthalmic orbit. *Ophthalmology* 1999;106:2005-2009.

7. Slavotinek AM, Tifft CJ. Fraser syndrome and cryptophthalmos: review of the diagnostic criteria and evidence for phenotypic modules in complex malformation syndromes. *J Med Genet* 2002;39: 623-633.

8. Weiss AH, Riscile G, Kousseff BG. Ankyloblepharon filiforme adnatum. *Am J Med Genet* 1992;42:369-373.

9. Tuysuz B, Ilikkan B, Vural M, et al. Ankyloblepharon filiforme adnatum (AFA) associated with trisomy 18. *Turk J Pediatr* 2002; 44:360-362.

10. McGrath JA, Duijf PH, Doetsch V, et al. Hay-Wells syndrome is caused by heterozygous missense mutations in the SAM domain of p63. *Hum Mol Genet* 2001;10:221-229.

11. Vaughn GL, Dortzbach RK, Sires BS, et al. Eyelid splitting with excision or microhyfrecation for distichiasis. *Arch Ophthalmol* 1997;115:282-284.

12. Niemi KM, Kanerva L, Kuokkanen K, et al. Clinical, light and electron microscopic features of recessive congenital ichthyosis type I. *Br J Dermatol* 1994;130:626-633.

13. Sires BS. Congenital horizontal tarsal kink: clinical characteristics from a large series. *Ophthal Plast Reconstr Surg* 1999;15:355-359.

14. Mustarde JC. The treatment of ptosis and epicanthal folds. *Br J Plast Surg* 1959;12:252-258.

15. Engle EC, Castro AE, Macy ME, et al. A gene for isolated congenital ptosis maps to a 3-cM region within 1p32-p34.1. *Am J Hum Genet* 1997;60:1150-1157.

16. Engle EC. The molecular basis of the congenital fibrosis syndromes. *Strabismus* 2002;10:125-128.

17. Anlar B. Juvenile myasthenia: diagnosis and treatment. *Paediatr Drugs* 2000;2:161-169.

18. Carter SR, Meecham WJ, Seiff SR. Silicone frontalis slings for the correction of blepharoptosis: indications and efficacy. *Ophthalmology* 1996;103:623-630.

19. Harrad RA, Graham CM, Collin JR. Amblyopia and strabismus in congenital ptosis. *Eye* 1988;2:625-627.

20. McCulloch DL, Wright KW. Unilateral congenital ptosis: compensatory head posturing and amblyopia. *Ophthal Plast Reconstr Surg* 1993;9:196-200.

21. Crawford JS. Repair of ptosis using frontalis muscle and fascia lata. *Trans Am Acad Ophthalmol Otolaryngol* 1956;60:672-678.

22. Liu D. Blepharoptosis correction with frontalis suspension using a supramid sling: duration of effect. *Am J Ophthalmol* 1999;128: 772-773.

23. Wasserman BN, Sprunger DT, Helveston EM. Comparison of materials used in frontalis suspension. *Arch Ophthalmol* 2001;119: 687-691.

24. Weakley DR Jr. The association between nonstrabismic anisometropia, amblyopia, and subnormal binocularity. *Ophthalmology* 2001;108:163-171.

25. Kushner BJ. The treatment of periorbital infantile hemangioma with intralesional corticosteroid. *Plast Reconstr Surg* 1985;76: 517-526.

26. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. *N Engl J Med* 1999;341:173-181.

27. Kushner BJ. Hemangiomas in children. *N Engl J Med* 1999;341: 2018.

28. Goyal G, Watts P, Lane CM, et al. Adrenal suppression and failure to thrive after steroid injections for periocular hemangioma. *Ophthalmology* 2004;111:389-395.

29. Cruz OA, Zarnegar SR, Myers SE. Treatment of periocular capillary hemangioma with topical clobetasol propionate. *Ophthalmology* 1995;102:2012-2015.

30. Plager DA, Snyder SK. Resolution of astigmatism after surgical resection of capillary hemangiomas in infants. *Ophthalmology* 1997;104:1102-1106.

31. Lorentzen M, Pers M, Bretteville-Jensen G. The incidence of malignant transformation in giant pigmented nevi. *Scand J Plast Reconstr Surg* 1977;11:163-167.

32. Meisler DM, Raizman MB, Traboulsi EI. Oral erythromycin treatment for childhood blepharokeratitis. *J AAPOS* 2000;4:379-380.

33. Jordan DR, Allen LH, White J, et al. Intervention within days for some orbital floor fractures: the white-eyed blowout. *Ophthal Plast Reconstr Surg* 1998;14:379-390.

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20

Disorders of the Orbit

Daniel P. Schaefer

Orbital disease in the pediatric patient is a complex entity and must be approached in an organized, logical fashion to arrive at the best plan of evaluation, diagnosis, and finally, the appropriate treatment plan. The most common orbital diseases in childhood overlap little with those found in adults, but the method for the development of a differential diagnosis is similar. One should be able to develop an initial differential diagnosis based on the history and physical examination to elicit if the disease process is characterized by features of inflammation, infiltration, mass effect, or vascular changes; dynamics; and location of the disease process. The evaluation of the pathophysiologic changes should include motor and sensory effects. The presence or absence of pain is helpful in the development of a differential diagnosis. Pain is caused by a rapid increase of mass or pressure effect such as that seen with infection, inflammation, hemorrhage, or from bone or nerve involvement. Most neoplasms generally do not cause pain until late in their course. The progression of the disease process is important to establish since some processes occur in minutes (hemorrhage), hours to days (rhabdomyosarcoma, thyroid-related orbitopathy, neuroblastoma, granulocytic sarcoma, inflammation, or infection), weeks to months (chronic inflammatory conditions, benign neoplasm, or lymphoma), or months to years (dermoid, benign mixed tumors, neurogenic tumors, fibrous histiocytoma, or osteomas). Sometimes it is difficult for the patient or family to note the exact onset of symptoms, and old photos can be helpful in establishing the onset and progression of the disease process. Any past ocular, medical, and family history should be obtained. Systemic investigation is important in the assessment of the patient since endocrine, infectious, immunologic, vascular, and neoplastic diseases may have orbital involvement. Imaging techniques can then be employed to define the lesion as to location, contour, infiltrative effects, and effect on the adjacent orbital structures, such as vascularity, compression, and positional changes. Most patients will require an orbitotomy for the diagnosis or removal of the lesion.

ORBIT ANATOMY

The orbit is delineated by the bones of the face and skull; is surrounded by the brain, sinuses, and soft tissues of the face; and contains nerves, muscles, connective tissues, glandular structures, pigment cells, arteries, and veins (which contain red and white blood cells). All of these anatomic features may give rise to a primary orbital neoplasm or develop a disease process that extends into the orbit as a secondary orbital process. The bones that form the orbit are the frontal, zygomatic, maxillary, sphenoid, lacrimal, ethmoid, and palatine. Orbital tumors can be classified based on origin: Primary lesions originate from the orbit, and secondary lesions invade the orbit as with intracranial, paranasal, sinuses, and metastatic tumors.

In adults, the orbit is pyramidal in shape, with a total volume of 30 mL. The orbital roof is triangular and composed of the frontal bone and lesser wing of the sphenoid. The lateral wall, which is at a 45-degree angle to the medial wall, is composed of the greater wing of the sphenoid and the frontal and zygomatic bones. The thinner medial wall is composed of the maxillary, lacrimal, ethmoid, and lesser wings of the sphenoid bones. Finally, the orbital floor, which is also triangular in shape, is made up of the maxillary, zygomatic, and palatine bones. The growth of the orbit is believed to be completed sometime between 7 years of age and puberty. Loss of an eye before completion of the growth of the orbit is thought to retard its growth.

The orbit is surrounded by a number of sinuses. The ethmoid sinuses are located medially and are present at birth. The frontal sinus is superior to the orbit and is rarely well developed before 9 years of age. The maxillary sinus lies inferior to the orbit, is very small, and develops during childhood.

Evaluation of orbital disease should include a complete and thorough ocular examination, with special attention to inspection, color vision, ocular motility, pupillary function, position of the globe, palpation, exophthalmometry, and ophthalmoscopy. Optic nerve function should be evaluated and followed with color vision, visual fields, and occasionally visually evoked responses. These signs of orbital

disease are especially important and need to be carefully evaluated. The status and function of the cranial nerves, corneal and facial sensation, and facial tone and symmetry should be evaluated.

Photographic documentation of all abnormalities is helpful for observation and follow-up to compare for improvement or worsening of the disease process, and photos should be taken on all preoperative cases.

ORBITAL EXAMINATION

Proptosis

Proptosis is one of the main indicators of orbital disease. All patients need exophthalmometric readings to determine whether proptosis is present and to what degree. The exophthalmometer measures the anterior projection of the eye from the lateral orbital rim to the anterior surface of the cornea. The orbit is surrounded by bone, except anteriorly, so that any increase in volume from a mass, infection, or inflammation, for example, is expressed by the displacement of the globe anteriorly (axial proptosis), or nonaxial proptosis. Any asymmetry measuring more than 2 mm is significant (Fig. 20.1).

Displacement of the Globe

Evaluation of the displacement of the globe helps determine the location of the mass within the orbit. An orbital mass not centered within the orbit will displace the globe off its axis. The presence of axial or nonaxial globe displacement found on clinical exam will help in locating the mass that is displacing the globe and in developing the differential diagnosis. Superior tumors displace the eye inferiorly while intraconal processes usually cause axial proptosis, as seen with glioma, optic nerve meningioma, arteriovenous malformation, cavernous hemangioma, etc. Inferomedial displacement can result from dermoid cyst and lacrimal gland tumors. Inferolateral displacement can result from frontoethmoidal mucoceles, abscesses, osteomata, etc. Bilateral proptosis can result from idiopathic orbital inflammatory disease, Graves' disease, lymphoma, vasculitis, carotid cavernous fistula, cavernous sinus thrombosis, leukemia, and neuroblastoma. Knowledge of the position of the mass can often aid in the differential diagnosis.

Figure 20.1 Hertel exophthalmometer in use. Measurements are made from the lateral orbital rim to the anterior corneal surface.

Orbital hypertelorism is a wider than normal separation of the medial orbital walls. Telecanthus is a wide intercanthal distance in the presence of a normal interpupillary distance.

Palpation

The orbital rim should be palpated first for masses, and then the superior, lateral, inferior, and medial orbit. If a mass is noted, document its location, size, shape, tenderness, and consistency. Does the mass have a smooth consistency, separate from the surrounding orbital tissues, or is it fixed and infiltrating into adjacent tissues? Resistance to retropulsion of the globe, compared to the fellow side, may indicate a posterior or apex process. The regional lymph nodes should also be evaluated with palpation.

Motility

Orbital processes can affect motility, either by direct involvement of the muscles, deviation of the axis of the eye, or by involvement of the nerve. Inflammatory processes often cause pain with eye movement when the muscles or nerves are affected. Forced ductions help to distinguish between infiltrative and noninfiltrative myopathies. Hess motility examinations help to document the defect, as well as the progression or improvement of the disease process.

Pulsation may be secondary to an arterial vascular malformation in the orbit or the absence of orbital bone that allows the transmission of pulsation of the cerebrospinal fluid to the orbit, as seen with the absence of the sphenoid wing secondary to neurofibromatosis (NF), encephalocele, or surgical removal of the orbital roof. Palpate the radial pulse to ensure that the orbital pulsations are synchronous with it. If the flow through an orbital arterial vascular lesion is high, you may hear a bruit or feel a thrill, as with carotid cavernous fistulae, larger dural arteriovenous fistulae, and orbital arteriovenous malformations. Venous lesions of the orbit do not pulsate, but may enlarge with the Valsalva maneuver or with the head in a dependent position.

Visual Function

Evaluation of the visual pathways includes examination of visual acuities, color vision testing with color plates, red desaturation, visual fields, and pupillary reactions. All these factors can assist in the detection of visual loss due to an orbital process. Loss of color vision and abnormal pupillary reactions (afferent pupillary defects) are often the first signs of early visual loss. Visual field defects due to orbital apex lesions may present early as small paracentral scotomata and progress to centrocecal defects. Changes in the size of the pupil can be seen with tumors that invade or compress

the parasympathetic (third cranial nerve and ciliary ganglion) or sympathetic fibers that innervate the pupillary dilator muscles. Medial lesions may cause temporal visualfield defects due to compression of the optic nerve, and inferior sector defects or visual changes may arise from superior compression or compression of the nerve against superior structures.

Fundus Changes

Optic nerve pallor, elevation, or edema helps determine the duration of the process. Retinal striae or folds may be seen from a mass pressing on the posterior aspect of the globe.

Radiology Studies

Orbital imaging provides diagnostic information with increased specificity as to the location, nature, and progress of the orbital lesion, in addition to helping determine the best surgical approach to biopsy or excise the mass.

In the past, roentgenograms were a mainstay of orbital evaluations, but they now are rarely indicated because they add little to the information seen on computed tomography (CT) or magnetic resonance imaging (MRI). Roentgenograms are sometimes useful in the identification of bony defects, whether congenital or acquired. The continual advances in orbital imaging continue to improve soft-tissue detail, and consultation with the radiologist will assist in choosing the best imaging modality and techniques to help establish the diagnosis.

Ultrasonography uses high-frequency sound waves to produce echoes at the interface of acoustically different structures. Its advantages are that there is no radiation exposure and the test is easily available. Two-dimensional images of orbital tissues and lesion location, shape, and size can be obtained with B-scan. A-scan provides unidimensional images characterized by a series of spikes of varying height and width that demonstrate the particular echogenic characteristics of each tissue's reflectivity, structure, sound attenuation, location, size, borders, mobility, and compressibility. Useful information regarding the location, size, shape, tissue characteristics, and vascular features of orbital lesions can be obtained. Doppler echography will provide information as to the vascularity of the lesion. Poor resolution around the bone at the orbital apex makes this form of testing less useful. It is particularly helpful in identifying lesions adjacent to and involving the globe, such as scleritis and cystic lesions.

A very significant component of the evaluation of orbital disease involves CT and MRI scans. These studies can often identify the process, are critical in revealing its extent and location, and are much more useful than other modalities such as plain x-ray and ultrasonography of the orbit.

CT uses thin roentgen ray beams to obtain tissue density values, from which a computer forms detailed cross-sectional two-dimensional images of the body. These images can be axial, coronal, or sagittal, which allows a three-dimensional localization of the lesion. CT is the most valuable technique for delineating the shape, location, extent, and character of lesions in the orbit. The orbital fat is radiolucent on a CT scan, appearing black, and the intraconal fat gives a good contrast with adjacent soft-tissue structures, appearing gray; therefore, an excellent view of the orbital and bony structures is produced. The addition of contrast material gives further information regarding the lesion and enhances vascular structures. Spiral CT scanners produce higher quality images, have much faster scanning times (a few minutes per patient), and are less expensive than MRI scans. Contrast agents used in both CT and MRI scans help to give an estimate of the vascularity of the lesion and to identify or enhance the imaging of lesions that may otherwise not be seen well, such as enhancement of meningiomas, gliomas, rhabdomyosarcomas, and inflammatory lesions such as orbital inflammatory syndrome, sarcoidosis, varices, lymphangiomas, arteriovenous and lymphatic malformations, and hemangiomas.

MRI is based on the phenomenon exhibited by atomic nuclei with an odd number of either protons or neutrons, hydrogen proton density, and T1 and T2 relaxation times, which are specific for different tissues and tumors. MRI yields an excellent view of the optic nerve, orbital apex, orbitocranial junction, any process involving the brain since the bone is not visualized, organic foreign bodies, vascular tumors, or heterogeneous tumors. Gadolinium, in addition to intravenous contrast material, can be used to enhance some pathologic orbital processes. Fat suppression with gadolinium can be used to enhance orbital structures or processes. With this technique, the normally bright orbital fat will appear dark, allowing visualization of orbital structures and processes such as vascular tumors or inflammation. Surface coil technology enables excellent anatomic detail of the orbit with a good signal-to-noise ratio, even with thin slices. The orbital apex, cavernous sinus, and optic chiasm require a head coil. The advantages over CT scanning include no radiation exposure, no need for contrast material to visualize vascular structures, and better resolution of soft tissues. MRI is contraindicated in patients with metallic foreign bodies, metallic clips, or any ferromagnetic material. CT scanning still appears to be superior for the evaluation of bony structures, is cheaper and faster, and has a higher spatial resolution.

Arteriography can be used to study arterial lesions such as aneurysms or arteriovenous malformations. Selective injection, magnification, and subtraction techniques can increase visualization of the lesion. CT angiography and magnetic resonance angiography (MRA), allow noninvasive visualization of large- and medium-sized vessels of the arterial system but does not provide the fine detail that direct angiography does.

CONGENITAL ABNORMALITIES OF THE ORBIT

Anophthalmos and Microphthalmos

True anophthalmos occurs when the primary optic vesicle fails to grow out from the cerebral vesicle during early embryologic development. Anophthalmos most often is bilateral,

except for rare instances when one eye is microphthalmic and the other anophthalmic. The orbits and eyelids are usually small but well formed (Fig. 20.2). The conjunctival fornices are decreased in size, and the eye cannot be felt in the orbit on palpation. Histologically, no ocular tissue is present. Extraocular muscles may be present and well developed. Infants with true bilateral anophthalmos show an absence of the chiasm, small geniculate bodies, and small optic foramina. The socket and hypoplastic orbits should be treated with socket expansion with progressively enlarging conformers until a prosthesis can be placed. Tissue expanders can be placed in the orbit or subperiosteal and progressively expanded to enlarge the hypoplastic orbit for treatment of severe bony deformity or asymmetry. Dermis-fat grafts can also be placed, which may grow with the patient, producing a progressive socket expansion.

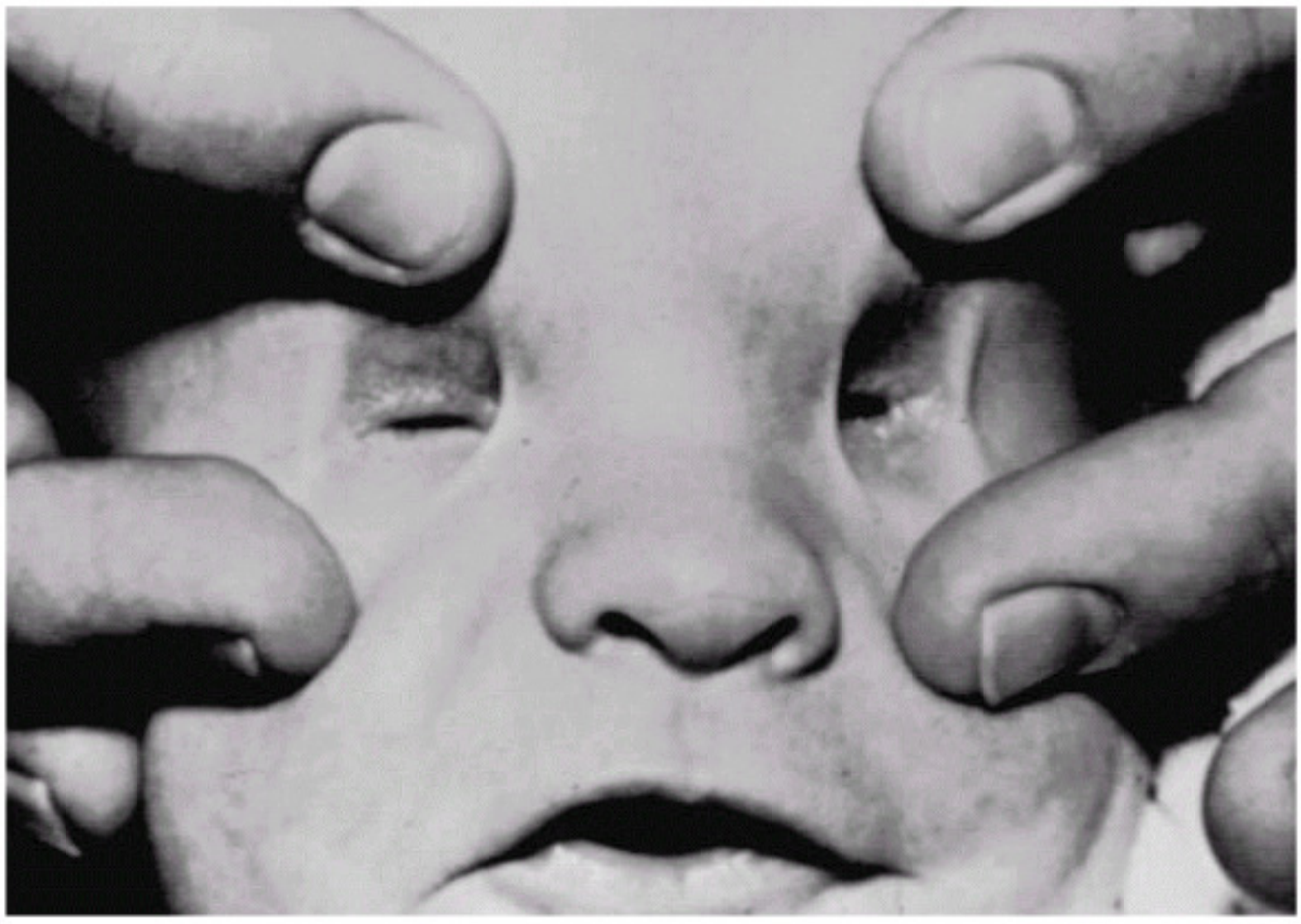

Figure 20.2 Anophthalmos with small orbits and no ocular tissues present. The eyelids are well developed.

Microphthalmos is usually a unilateral condition, and it occurs sporadically. The size of the eye varies with the severity of the defect. If colobomatous or if the choroidal fissure fails to close in the embryo stage, the condition may be associated with an orbital cyst. Failure of closure of the embryonic fissure can result in prolapse of neuroretinal tissue from a nonfunctioning globe, creating a cystic outpouching (Figs. 20.3 and 20.4). The cyst consists of an inner layer of primitive neuroretinal tissue that may contain retinal structures, photoreceptor differentiation, or rosette formation, and an outer layer continuous with the sclera with vascularized connective tissue and occasional cartilage. The size of the cyst varies and often is beneficial for stimulating normal growth of the orbital bone and eyelids. Occasionally the cyst can enlarge greatly, obscuring the microphthalmic globe; it may have to be removed to allow for the fitting of an ocular prosthesis. Occasionally the cyst may need repeated aspiration, resulting in a permanent cure. If excision is required, the cyst is excised, with closure of the scleral defect or enucleation of the nonfunctioning globe (Fig. 20.5). B-scan ultrasonography, CT, and MRI establish

the diagnosis, demonstrating a round or irregular cystic lesion adjacent to the microphthalmic globe (Fig. 20.6). Since both anophthalmos and microphthalmos are associated with hypoplastic orbits and small lids, treatment should be directed toward gradually expanding the lids and cul-de-sacs with progressively enlarging conformers. The lids will grow, stimulated by the conformers, in an attempt to achieve normal size. An ocular prosthesis may then be used for cosmesis. No definite association with systemic abnormalities has been identified in patients with microphthalmos with colobomatous cyst, except for occasional systemic anomalies in bilateral and familial cases of optic nerve and chiasmal glioma, trisomy and polycystic kidney, and Edward syndrome.

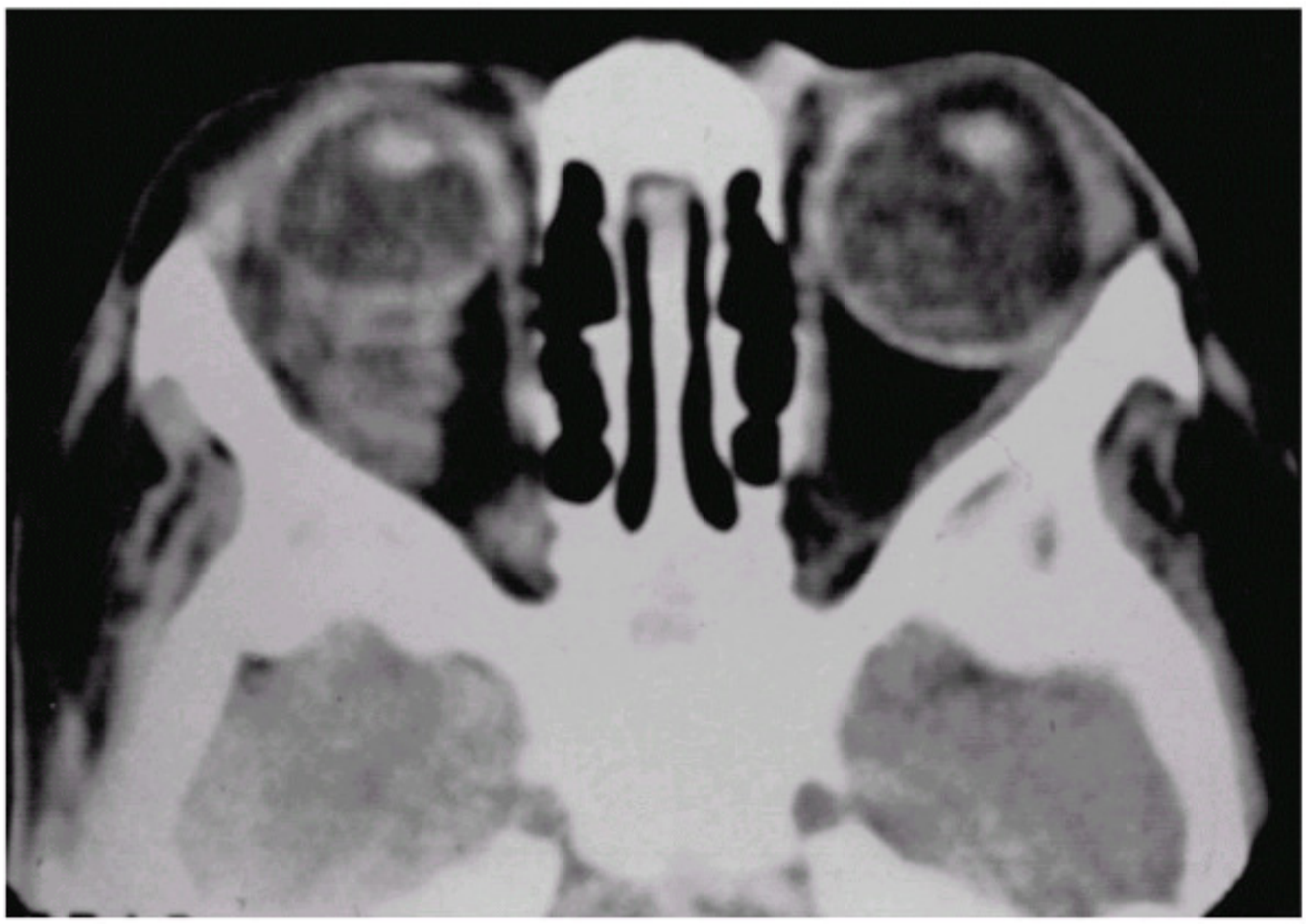

Figure 20.3 Axial computed tomography scan of microphthalmos with cyst. Note the small globe with cystic outpouching.

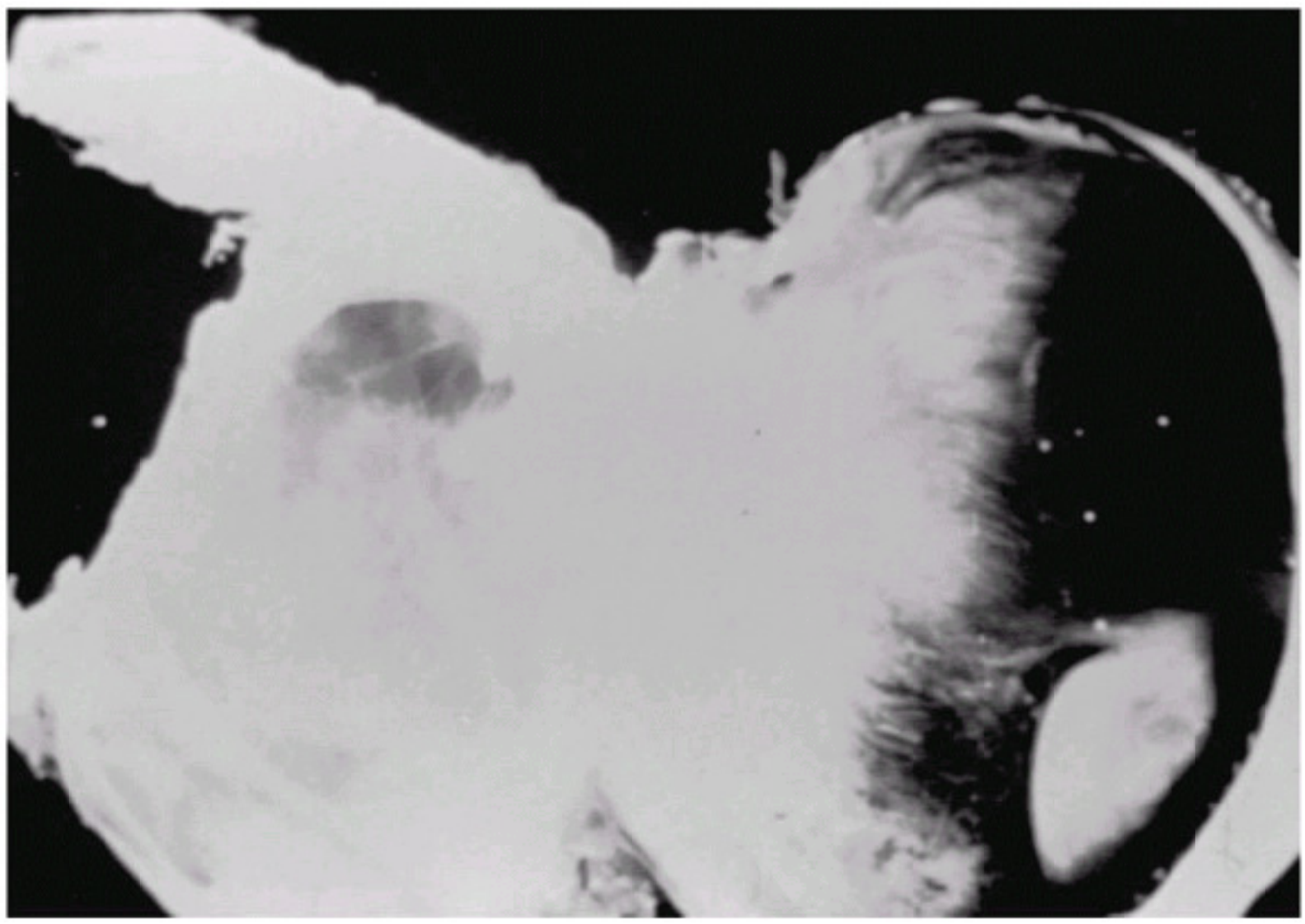

Figure 20.4 Pathologic specimen showing cystic prolapse of neuroretinal tissue from a nonfunctioning globe.

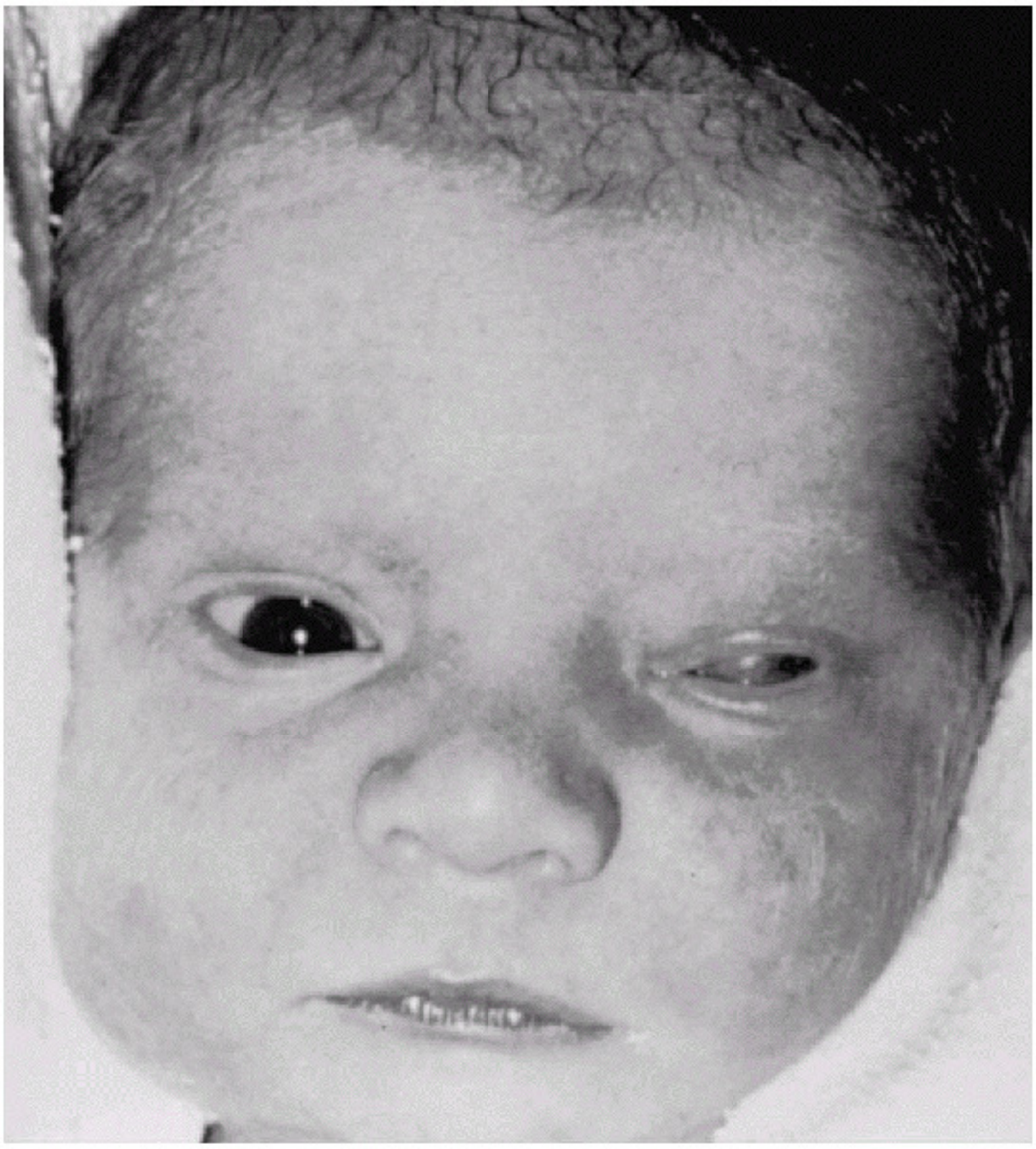

Figure 20.5 Microphthalmos with cyst in the left eye. Note that the cyst has enlarged and displaced the microphthalmic globe.

Cryptophthalmos

Cryptophthalmos is a rare condition that is usually bilateral. In this congenital abnormality of the eyelids, the globe is fused to the overlying skin. Cryptophthalmos has been divided into three types: complete, partial, and abortive. In complete cryptophthalmos, which is the most common, the eyelids are absent and the globe is entirely covered by skin extending from the brow to the cheek. In partial cryptophthalmos, the medial eyelid is replaced with a layer of skin fused to the globe, but the lateral portion of the eyelid is normal in structure and function. Abortive cryptophthalmos is characterized by a normal lower eyelid and an upper eyelid adherent to the superior portion of the globe. There is partial or complete absence of the eyebrow, eyelids, eyelashes, and conjunctiva with continuation of the forehead skin to the cheek over the eyes (Fig. 20.7). The hidden eye is usually abnormal, with a wide variety of ocular defects. The partially developed adnexa are fused to the anterior segment of the globe. These defects are thought to result from failure of the eyelid fold formation, which normally occurs in the seventh week of gestation. This condition is often associated with multiple congenital deformities such as cleft palate, syndactyly, dental malformations, nasal deformities, urogenital deformities, and hypoplasia of the facial and orbital bones. Histologically, the lids are abnormal with absent conjunctiva and diminished or absent orbicularis and levator muscles, tarsal plate, and sebaceous glands, making attempts at reconstruction difficult.

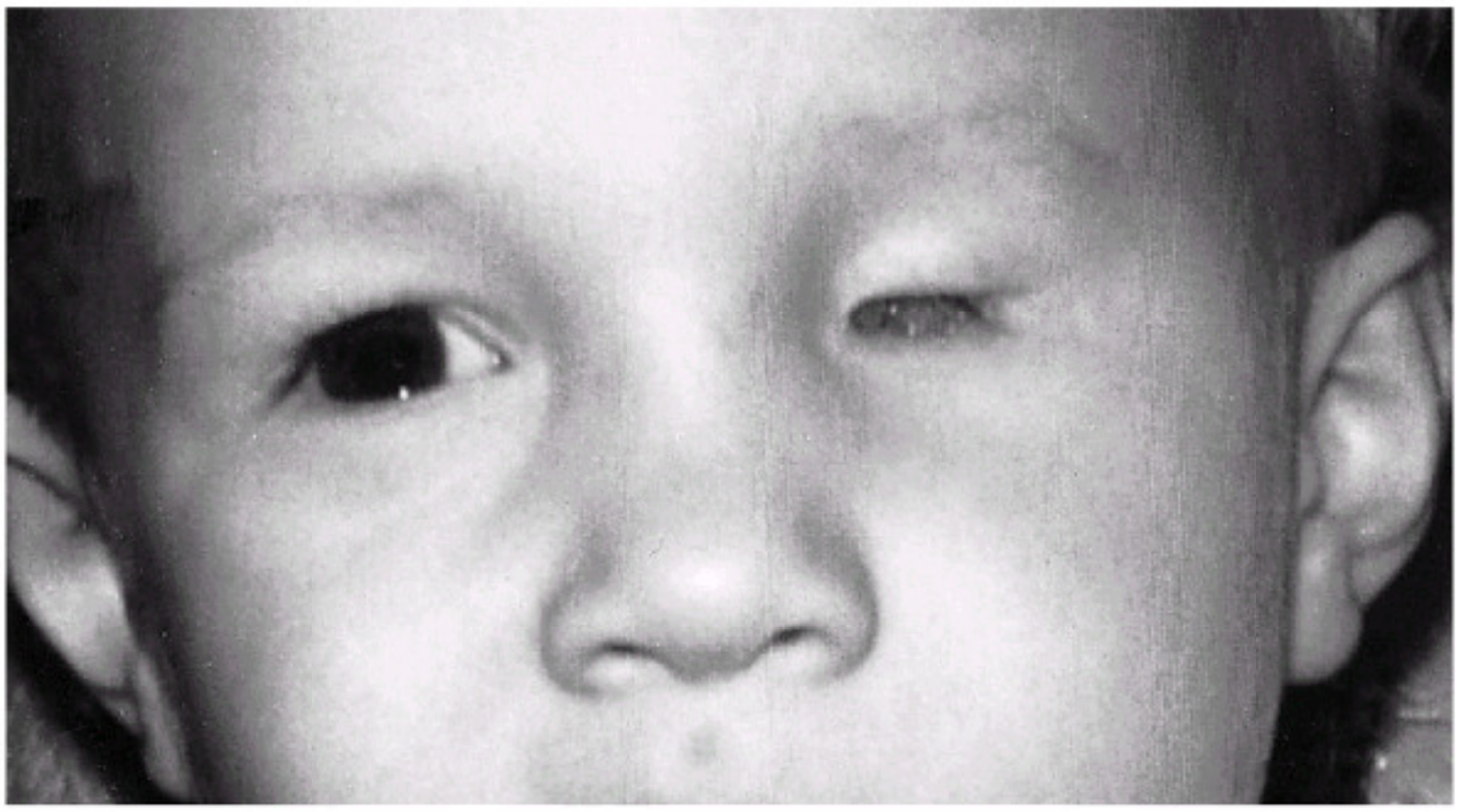

Figure 20.6 Microphthalmos demonstrating a hypoplastic orbit, decreased vertical and horizontal lengths of the eyelids, and hypoplasia of the malar area.

ORBITAL INFECTIONS

Orbital infections range from preseptal cellulitis to orbital abscesses. It is extremely important to know the features of these infections and their proper treatment due to the juxtaposition to the intracranial structures, which may lead to rapid and serious disease processes. The infections may occur from three primary sources: the majority are secondary to direct spread from an adjacent sinus; direct inoculation from trauma, skin infection, or postoperatively; or from a distant focus causing sepsis.

Preseptal Cellulitis

Preseptal cellulitis is much more common than orbital cellulitis in children. In a study of patients at a children's hospital, Weiss and colleagues found that 87% of children had preseptal cellulitis, while only 13% had orbital cellulitis. Preseptal cellulitis is characterized by eyelid swelling and edema, generally with more swelling of the upper eyelid (Figs. 20.8 and 20.9). If the cellulitis is severe, some chemosis may also be present. Since only the tissues anterior to the septum are involved, this process responds well to antibiotics. *Haemophilus influenzae, Staphylococcus aureus,* and streptococcal organisms are the main pathogens for which antibiotic coverage is required. Prior to the *H. influenzae* type B vaccine in 1985, the most common cause of preseptal cellulitis was *H. influenzae* infection in children under 5 years of age, and it was often associated with bacteremia and meningitis. Since then, infection with group A *Streptococcus* species is the predominant cause. Children with preseptal cellulitis often have a history of antecedent upper respiratory tract infections, recent lid trauma, insect bites, or infections, while preseptal cellulitis in adults is generally due to penetrating trauma or a cutaneous source.

Clinical evaluation and CT scanning appear to be the best methods to distinguish preseptal from orbital cellulitis. Proptosis and decreased motility seem to be the most significant signs that distinguish the two conditions. Chemosis is a less specific finding. Fever and an elevated white blood cell count with a left shift are nonspecific. On CT, preseptal cellulitis shows edema of the lids and subcutaneous tissue anterior to the orbital septum, whereas orbital cellulitis shows involvement of the tissue in the orbit itself (Fig. 20.10); however, this differentiation is usually made clinically. Rapid progression of preseptal cellulitis into the orbit can occur and therefore should be treated urgently.

Orbital Cellulitis

Orbital cellulitis requires prompt diagnosis and treatment to prevent visual or life-threatening complications. Orbital cellulitis in children is somewhat different from the disease in adults, but it is often directly related to sinusitis in both. Most commonly the ethmoid sinus and sometimes the maxillary sinus are involved in children. Upper respiratory tract infections interfere with clearance of secretions by the respiratory cilia, causing poor sinus drainage and predisposing children to sinus infections. The bones separating the orbit and sinuses are thin, allowing spread of the infection. The foramina, especially the ethmoid foramina, and

the valveless interconnecting venous system of the orbit and sinuses represent other routes for possible spread of infection from the sinuses to the orbit. Other causes of orbital cellulitis to be considered are trauma, foreign body, surgical, dacryoadenitis, panophthalmitis, dacryocystitis, or endogenous septicemia. Immunosuppressed or diabetic patients can develop fungal orbital cellulitis, with minimal or no clinical signs of inflammation because they can not mount a white blood cell response.

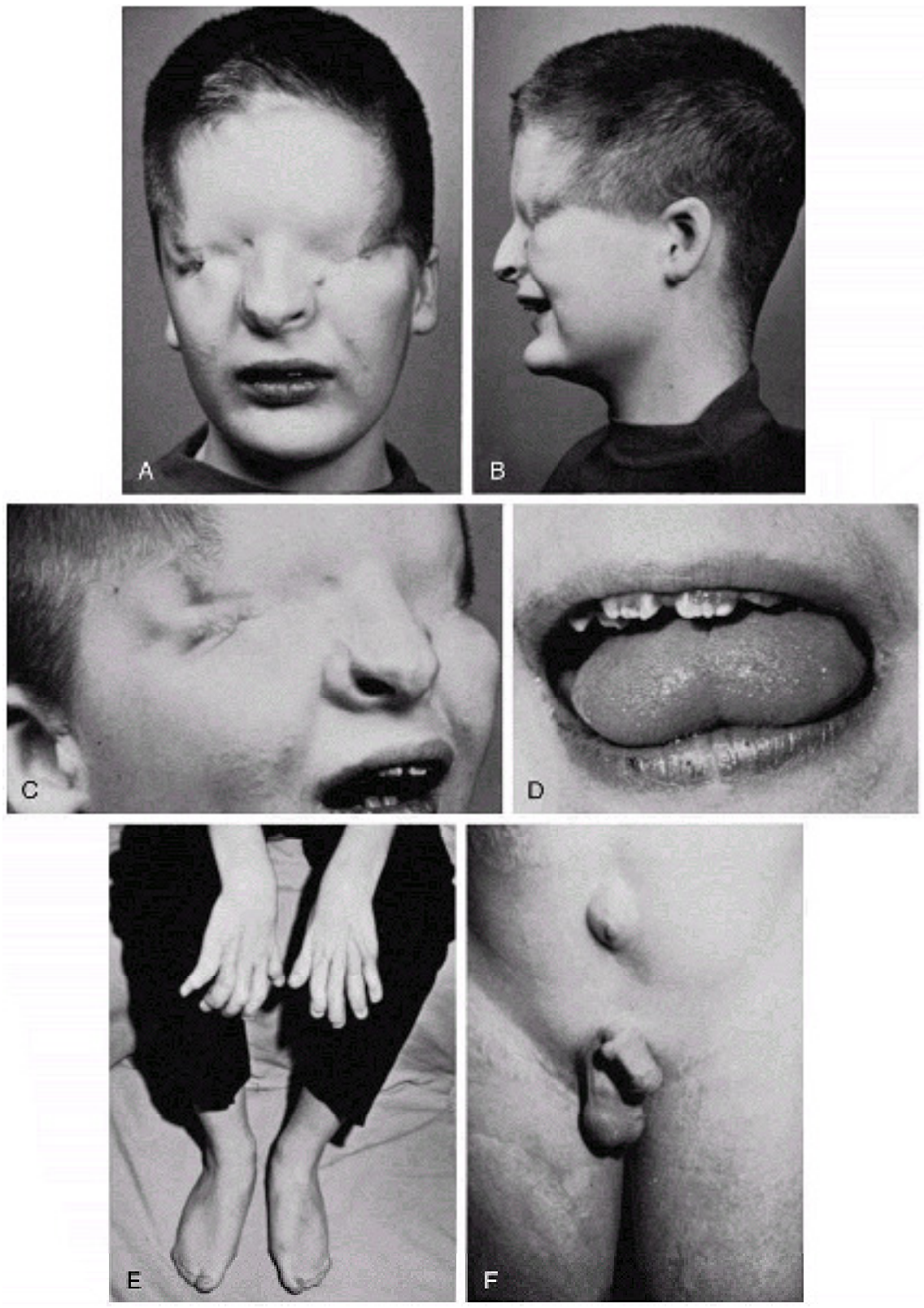

Figure 20.7 A: Cryptophthalmos associated with multiple congenital abnormalities. There is complete covering of the eyes with skin. The anterior segment is usually deformed. **B:** Side view. **C:** Associated notching of the right nostril and external ear deformity. **D:** Dental malformations associated with cryptophthalmos. **E:** Cryptophthalmos showing syndactyly of fingers and toes. Flexion deformity of fingers is postoperative. **F:** Cryptophthalmos associated with umbilical hernia and penis deformity. (Courtesy of Carl H. Ide, MD and Paul B. Wollschlaeger, MD.)

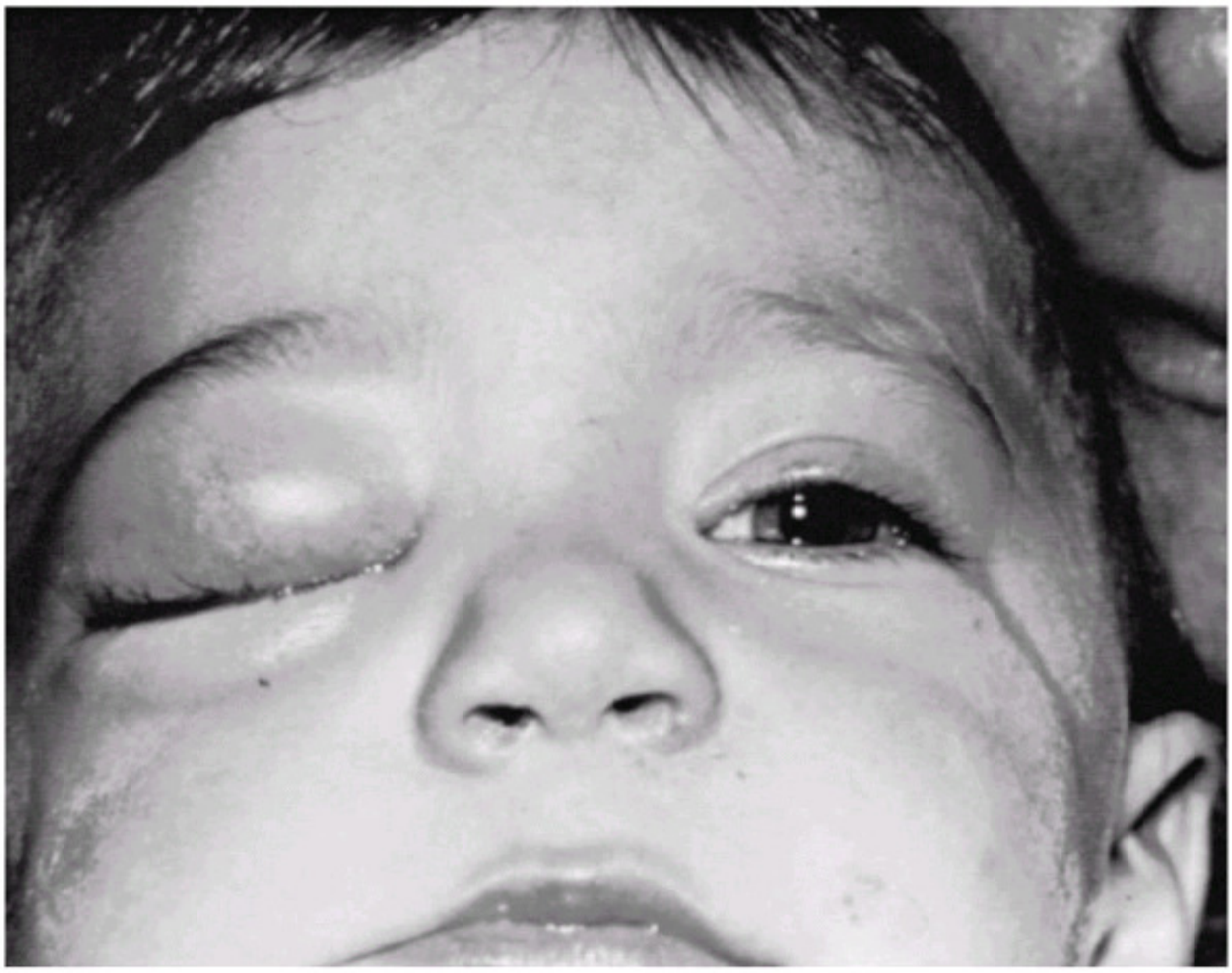

Figure 20.8 Preseptal cellulitis with eyelid swelling and edema.

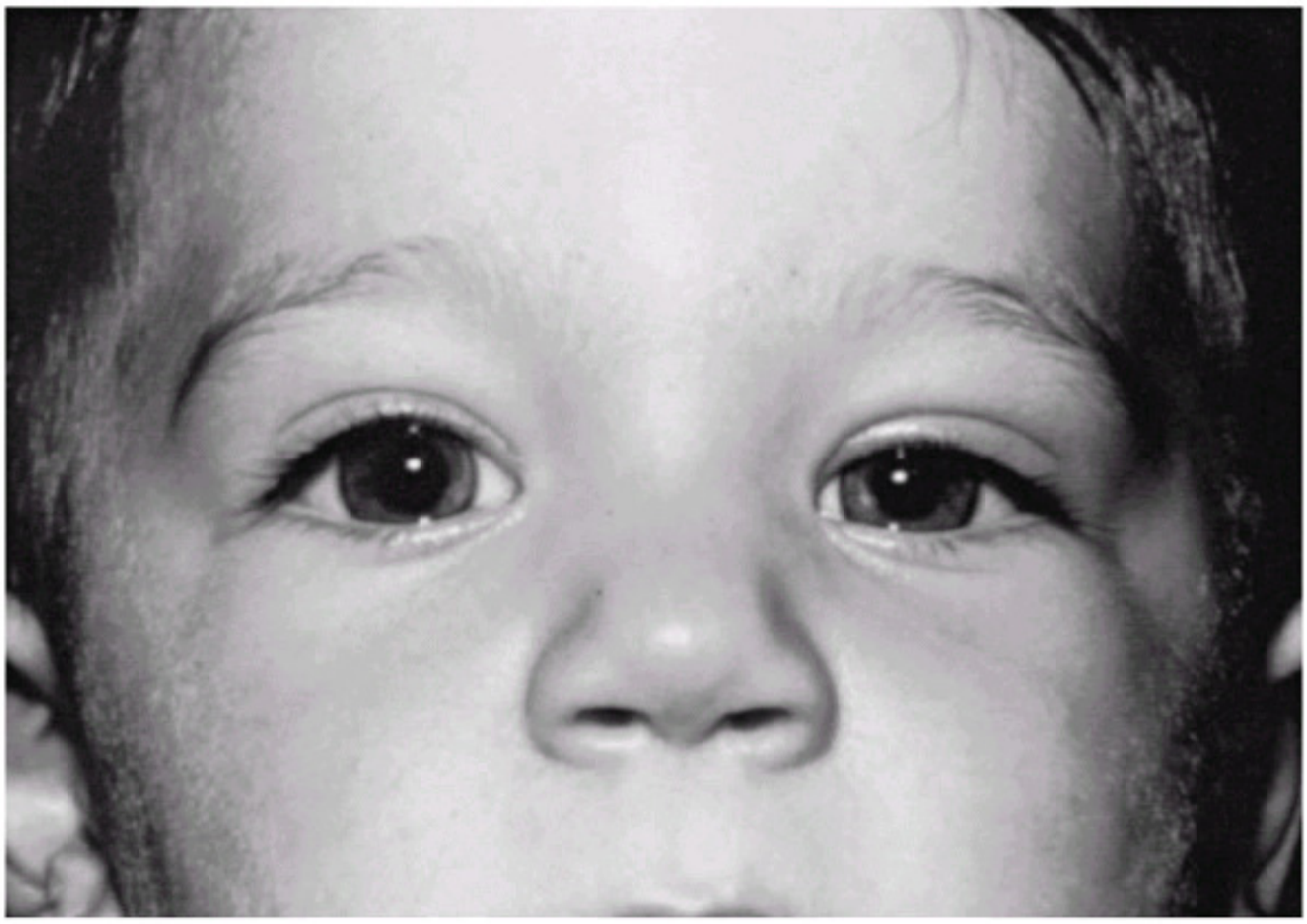

Figure 20.9 Resolved preseptal cellulitis after 2 days of oral antibiotics.

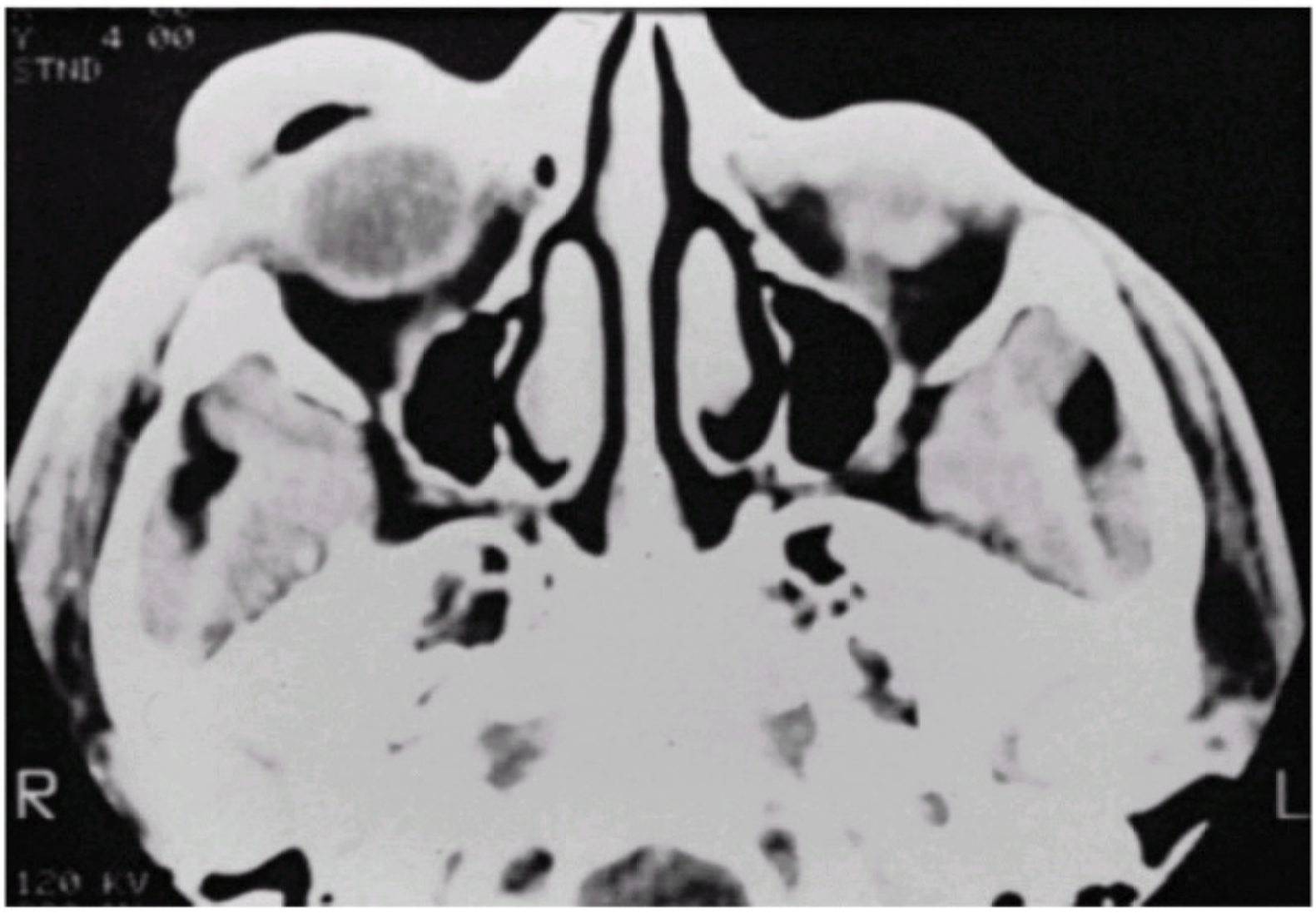

Figure 20.10 Axial computed tomography scan showing edema of the lids and subcutaneous tissues anterior to the orbital septum.

Signs of orbital cellulitis include lid edema, pain, decreased motility, proptosis, chemosis, decreased vision, orbital tension, and headache (Fig. 20.11). Decreased vision and pupillary abnormalities, afferent pupillary defect, or dilated pupil indicate involvement of the orbital apex and require aggressive treatment. Delayed treatment may result in an orbital apex syndrome, cavernous sinus thrombosis, possible blindness due to apical compression, cranial nerve palsies, brain abscess, and even death. Permanent visual loss can also result from direct optic neuritis or vasculitis. Spread via the vascular emissaries to the cavernous sinus can lead to cavernous sinus thrombosis, and spread through the diploic vessels to the intracranial cavity can lead to subdural empyema or intracranial abscesses. Recent past medical history is usually positive for an upper respiratory tract infection, but the symptoms may be mild. The child is sick, lethargic, tired, and febrile, which helps to differentiate this from orbital inflammatory disease. CT or MRI scan shows orbital involvement, location, and extent, and often reveals the accompanying sinus infection, which helps to secure the diagnosis of infection (Figs. 20.12 and 20.13). Most commonly, ethmoid sinusitis will be the cause, spreading into the orbit through the thin lamina papyracea.

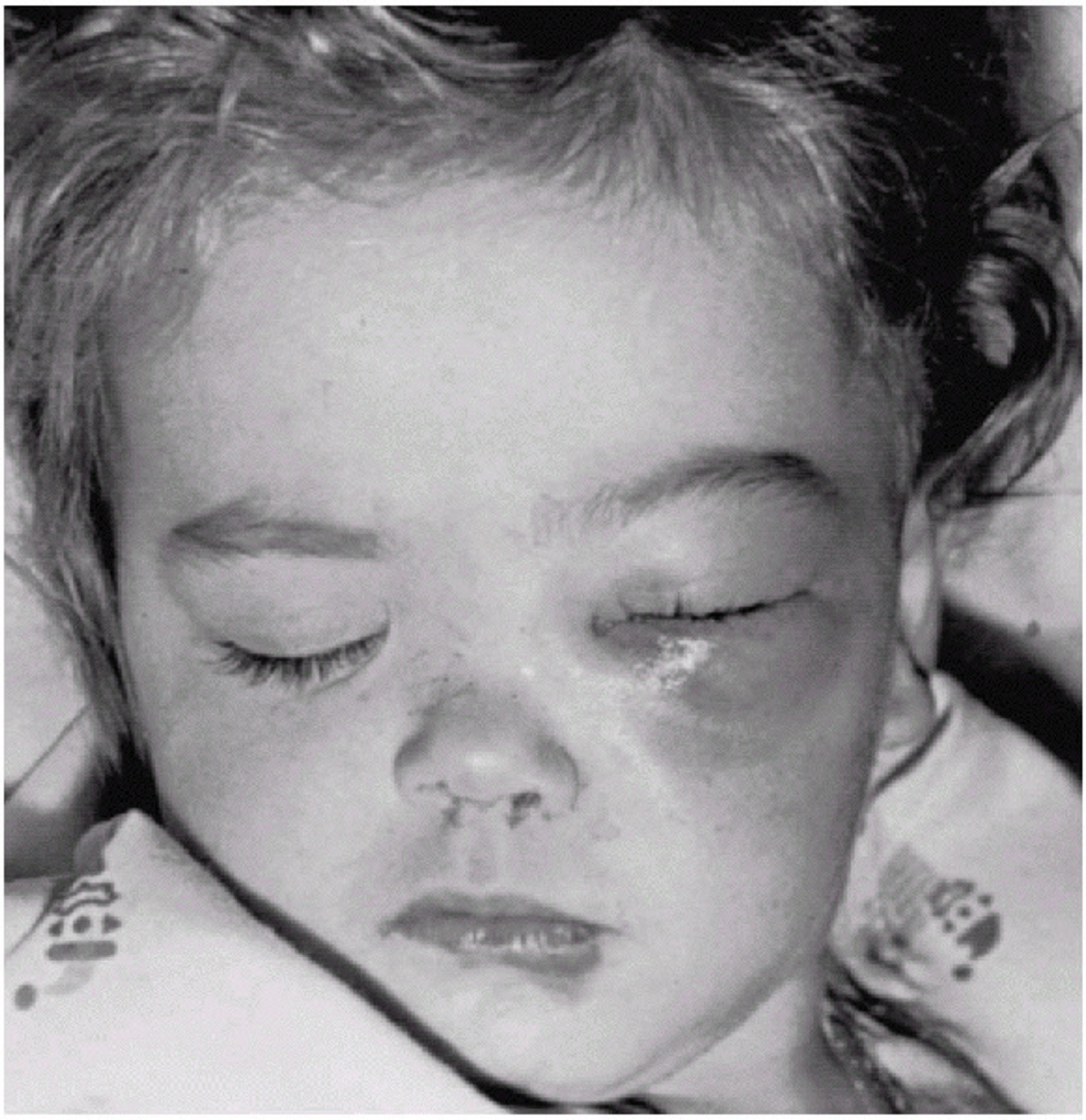

Figure 20.11 Orbital cellulitis secondary to *Haemophilus influenzae* infection. Of note is the ecchymotic bluish coloring. In addition to lid edema, the child had decreased motility, proptosis, chemosis, and decreased vision.

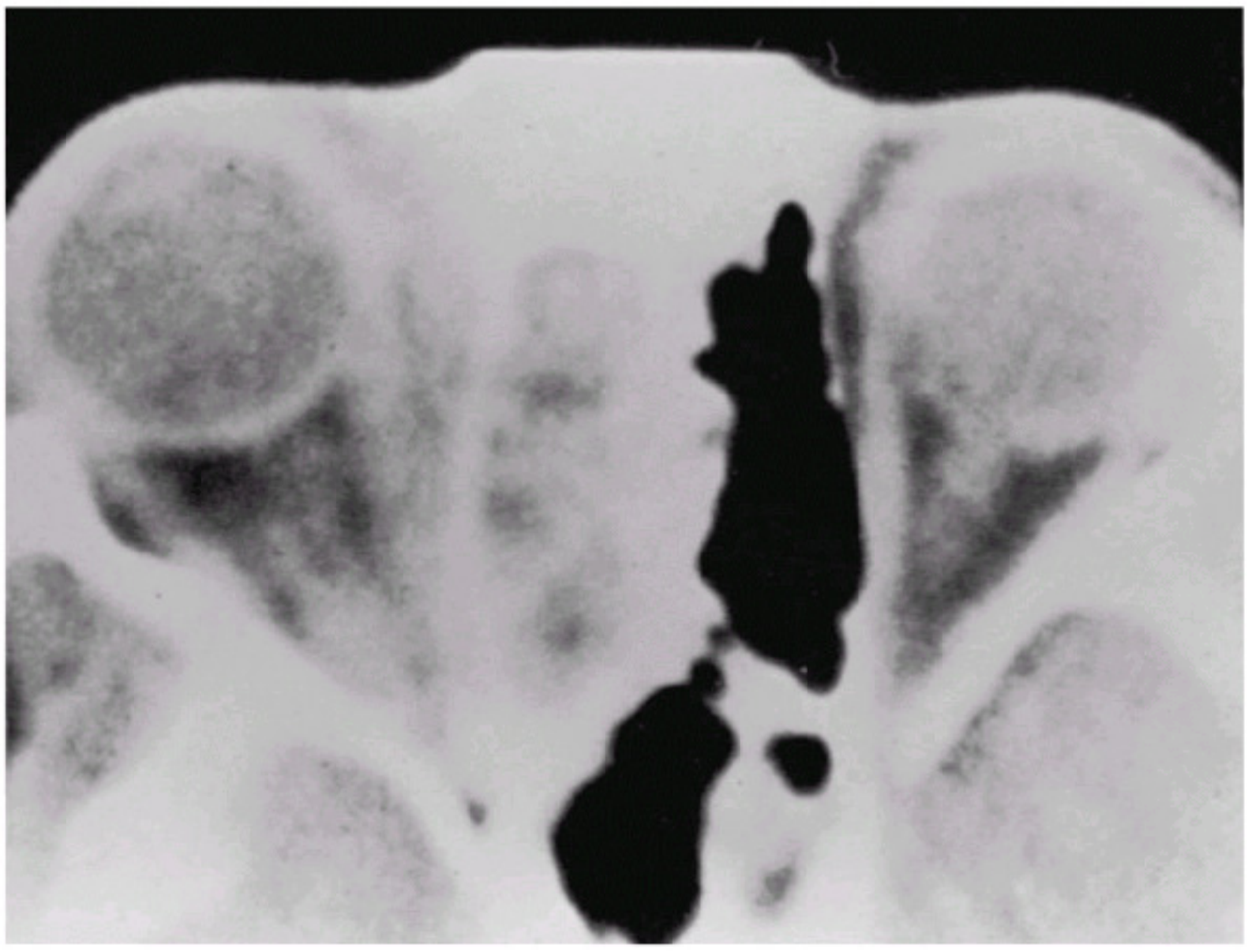

Figure 20.12 Axial computed tomography scan revealing ethmoid sinus disease spreading into the orbit.

In contrast to adults, the pathogens in orbital cellulitis in children tend to be due to a single aerobic organism, including *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *H. influenzae*, especially in children under 4 years of age, who do not have adequate humoral immunity to the polysaccharide-encapsulated bacteria. *H. influenzae* vaccines have lead to fewer cases of infection due to this organism. Other gram-positive and gram-negative organisms are possible causes. If foul smelling, anaerobic infections should be considered, especially if the wound has been contaminated by soil and bites. *Streptococcus pyogenes* may cause erysipelas, necrotizing fasciitis, or toxic shock, which requires very aggressive treatment. Antibiotic treatment should be targeted to cover the most likely infecting organisms. Since the disease process can threaten vision and life, high-dose intravenous antibiotics and nasal decongestants must be used.

Due to the delay in development of the sinuses in children, the most frequent locus of the disease is the ethmoidal sinus. Sinus drainage is less often required for children than for adults, but each case must be given individual consideration. The refractory nature of orbital abscesses in adults is probably due to multiple pathogens, including anaerobic bacteria. Close monitoring of vision, pupillary reaction, extraocular motility, and central nervous system (CNS) function must be carried out during the first 24 to 48 hours. If there is no evidence of improvement or if the condition becomes worse, surgical drainage of the infected sinus may be required. This may also indicate the presence of an orbital or subperiosteal abscess.

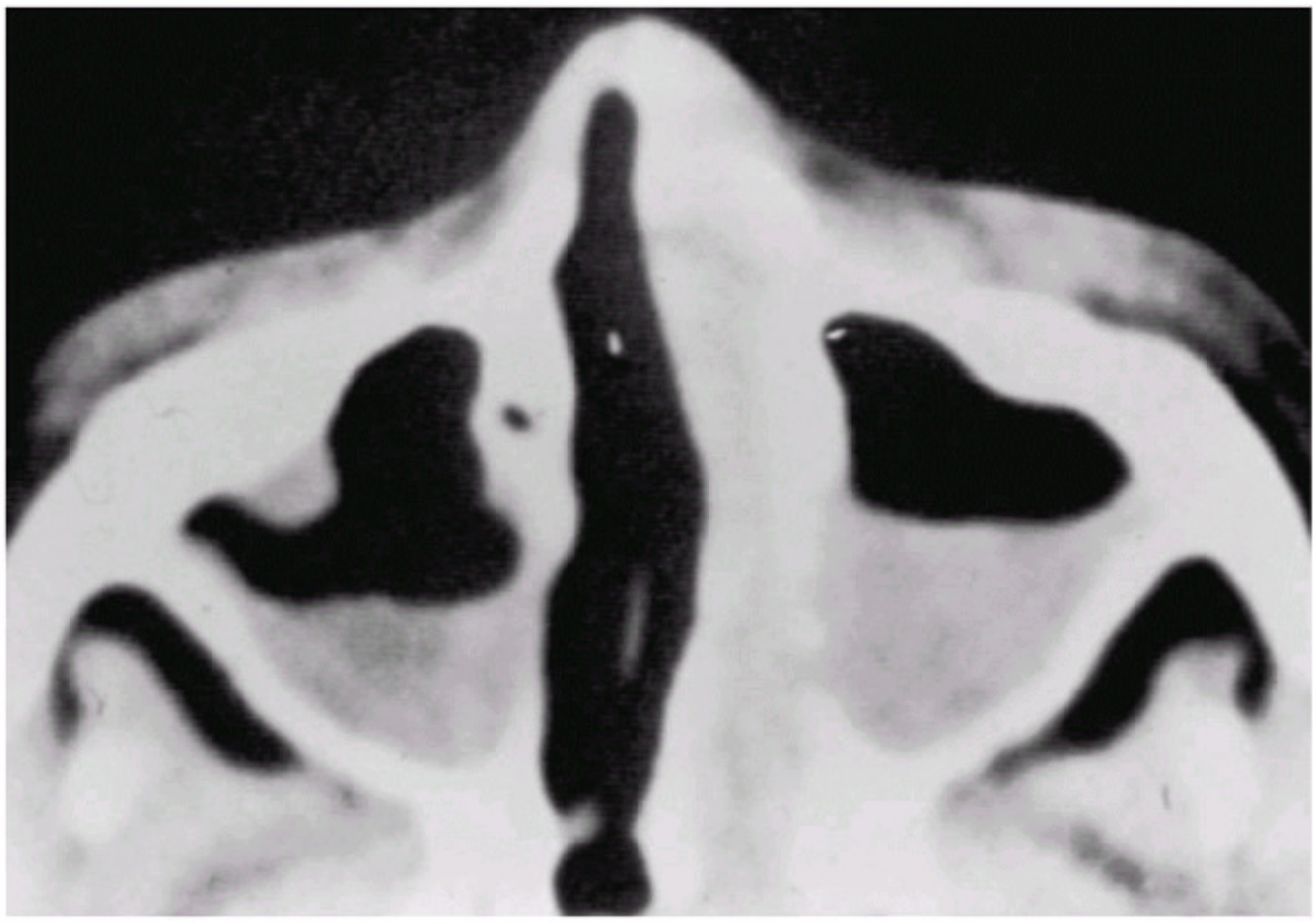

Figure 20.13 Maxillary sinusitis in a patient with orbital cellulitis.

Subperiosteal Abscess

Subperiosteal abscess formation involves the collection of purulent material between the periorbita and bony walls of the orbit, and can usually be identified by CT scan. The periorbital is tethered at the orbital suture lines so the abscess creates a smooth, dome-shaped elevation of the periorbital, with a homogeneous or heterogeneous collection. The signs are similar to those of orbital cellulitis but may also include nonaxial displacement of the globe and palpation of a fluctuant mass in the orbit. If this does not resolve on administration of intravenous antibiotics within 24 to 48 hours, or if there is a threat to the optic nerve, retinal function, suspicion of anaerobic infection, or very tense orbit with significant pain, drainage is indicated (Figs. 20.14 and 20.15). Infections of dental origin constitute an indication for surgical intervention because the presence of anaerobes should be anticipated.

Abscesses within the orbital tissues may also occur. These infections can extend more posteriorly, resulting in life-threatening consequences such as cavernous sinus thrombosis, meningitis, and intracranial abscesses. Clinically, third, fourth, and sixth cranial nerve palsies can occur bilaterally in cavernous sinus thrombosis. Systemic signs of toxicity are present, including sepsis, nausea, vomiting, meningeal signs, and altered levels of consciousness. When an abscess of the orbit or brain is identified, it requires immediate drainage to prevent serious complications.

Mucoceles and mucopyoceles of the sinuses are cystic structures that result from obstruction of the sinus excretory ducts, and are lined with respiratory epithelium, pseudostratified ciliated columnar epithelium with goblet cells. The continued expansion and erosion of the bones of the

orbital walls leads to orbital invasion (Fig. 20.16). The cysts are usually filled with thick mucoid secretions, a mucocele, or pus if infected, a mucopyocele. Most arise from the frontal or ethmoid sinuses, and they occur more frequently in adults. When they occur in children, there is an increased incidence of cystic fibrosis, for which these children should be evaluated. Treatment requires evacuation of the mucoceles and reestablishment of drainage of the sinus or obliteration of the sinus by mucosal stripping and packing with bone or fat.

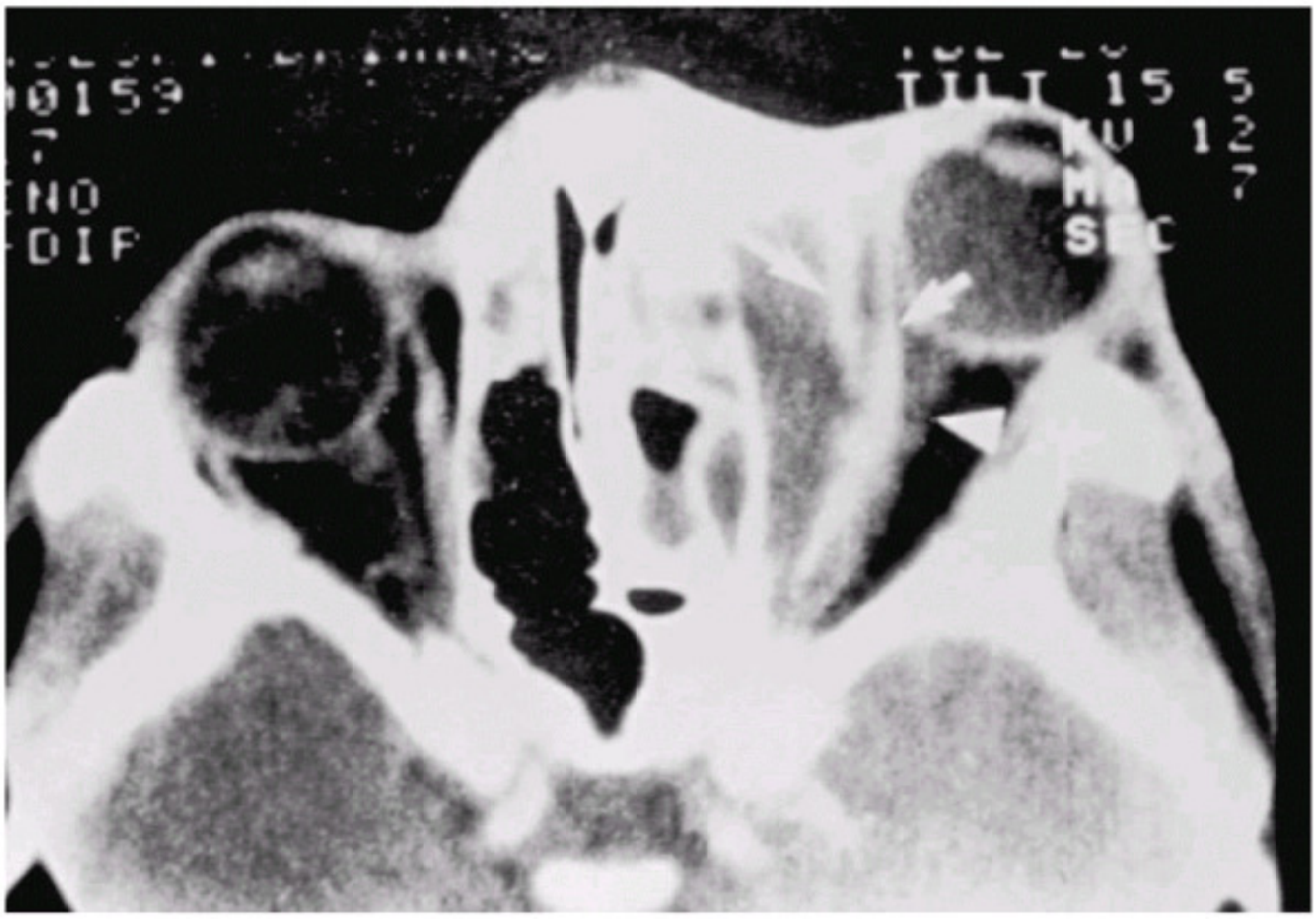

Figure 20.14 Axial computed tomography scan demonstrating a subperiosteal abscess.

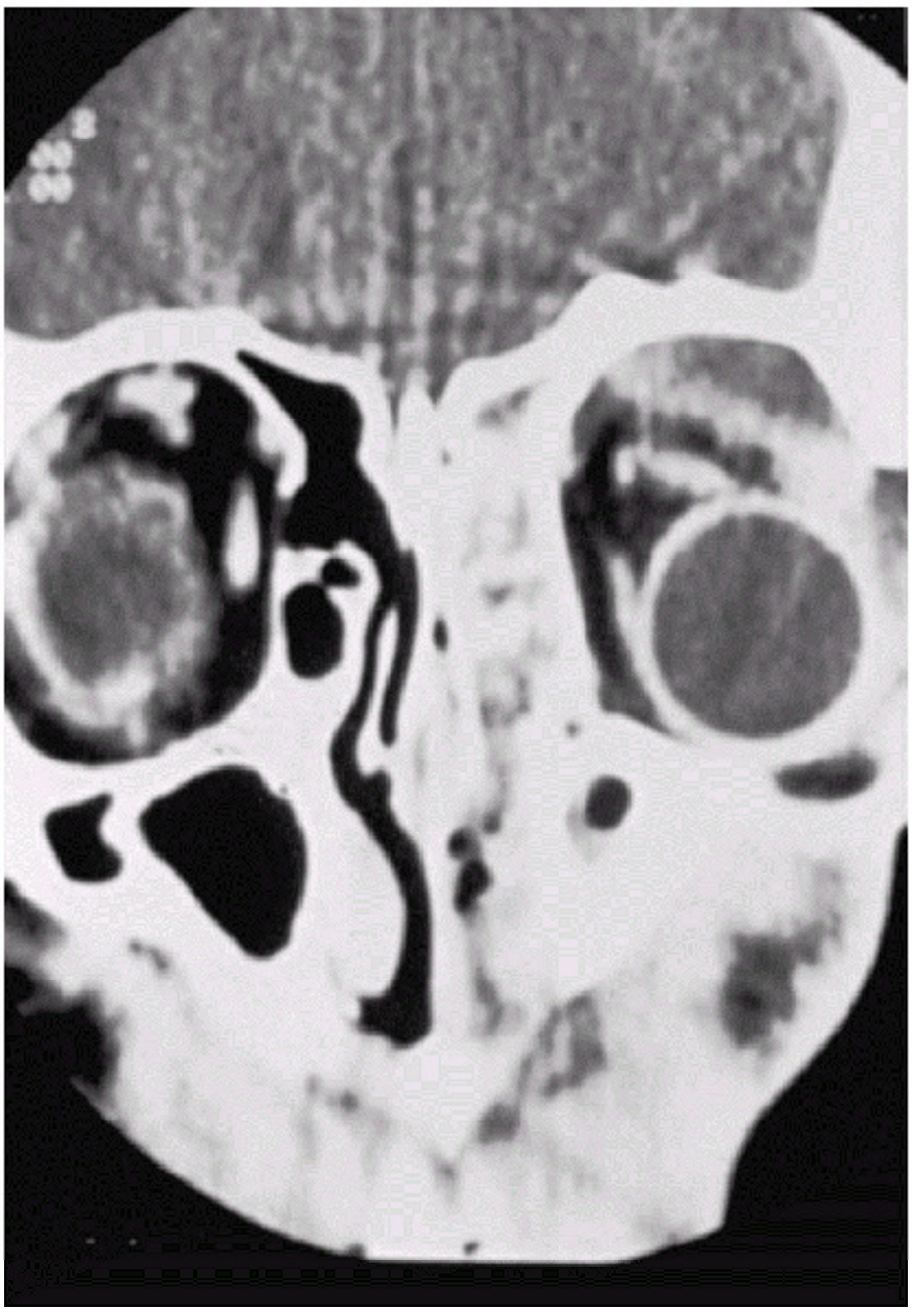

Figure 20.15 Coronal computed tomography scan demonstrating a superior subperiosteal abscess.

Dacryoadenitis

Dacryoadenitis is most often viral in nature, occasionally bacterial in origin, and very rare in children. Patients present with an inflamed, tender lacrimal gland, with adenopathy, fever, malaise, and leukocytosis (Fig. 20.17). CT scan shows diffuse lacrimal gland swelling without bony defects. It can be secondary to infectious mononucleosis, herpes zoster, mumps, trachoma, syphilis, tuberculosis, or sarcoidosis. It usually improves spontaneously, and since there is generally no bacterial involvement, antibiotics are rarely indicated. Systemic steroids frequently help to accelerate resolution of the process and keep the patient more comfortable. Dacryoadenitis can be difficult to distinguish from idiopathic lacrimal gland inflammation (pseudotumor). The presence of preauricular lymph nodes makes a diagnosis of viral dacryoadenitis more likely.

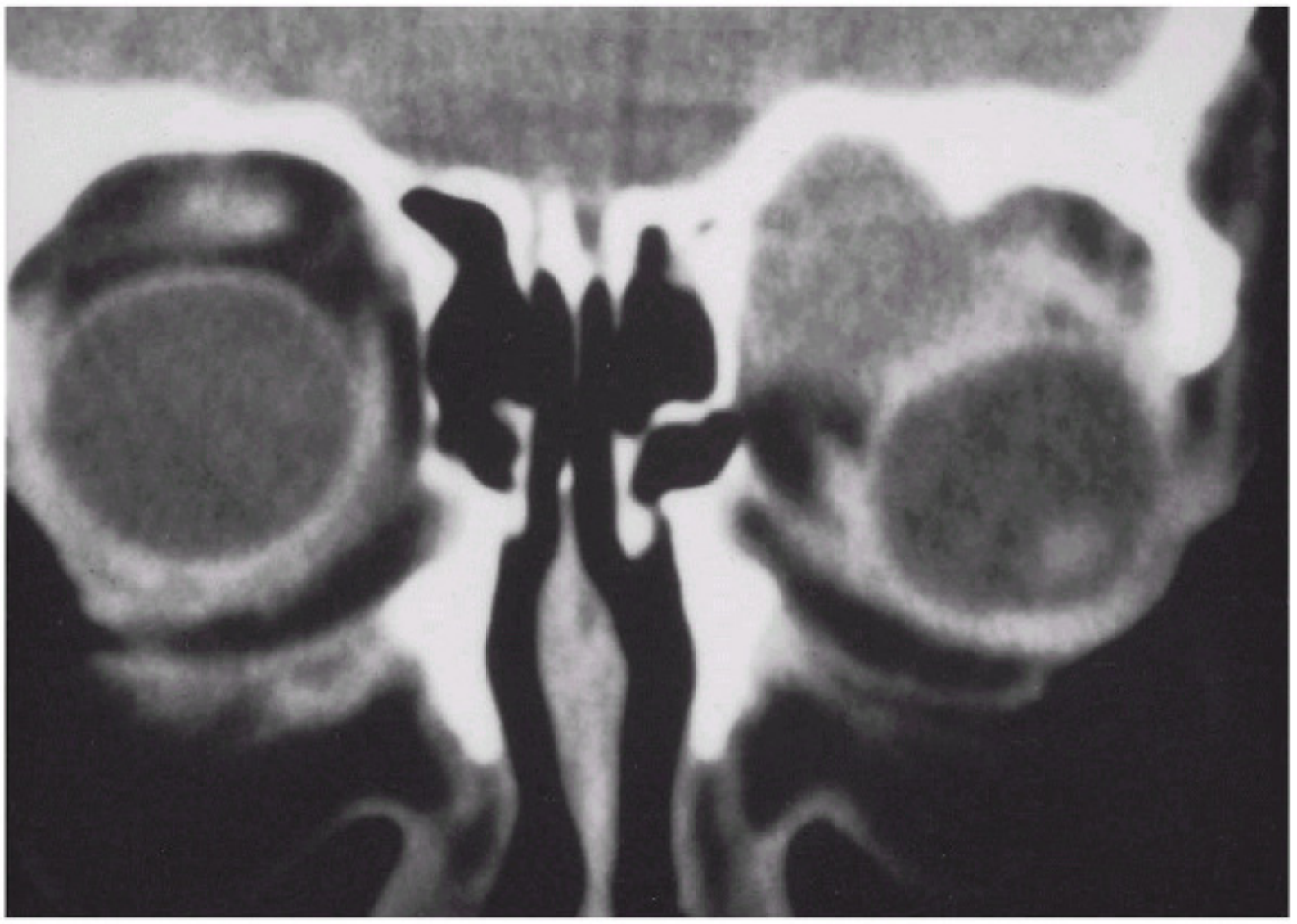

Figure 20.16 Mucocele involving the medial and superior orbit.

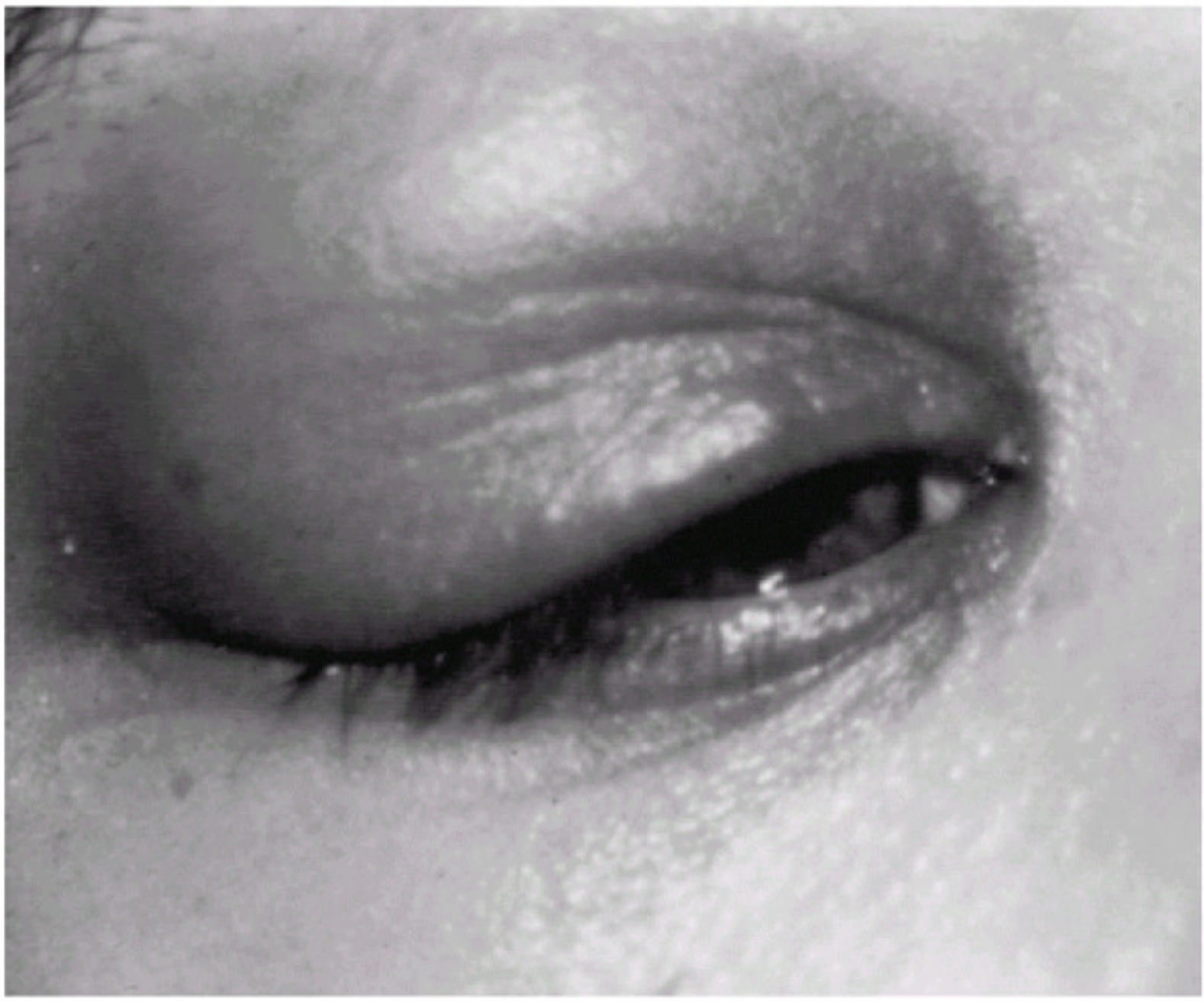

Figure 20.17 Dacryoadenitis with S-shaped lid deformity.

Dacryocystitis

Dacryocystitis is an infection of the lacrimal sac, which occurs in a chronic, indolent form and is most often seen in infants. They rarely develop a more acute process, with swelling, tenderness, and redness over the area of the lacrimal sac. Some stagnation of flow through the lacrimal sac results in infection and is often secondary to incomplete development of the lacrimal system in infants, just short of the nasal cavity. In most cases, it is caused by the persistence of a membrane at the valve of Hasner. This membrane will open spontaneously within the first year of life in more than 90% of patients. There frequently is persistent, chronic infection of the lacrimal sac, with symptoms of tearing, mucopurulent discharge, and chronic recurrent conjunctivitis (Fig. 20.18). Most commonly the organism involved is *H. influenzae* or *S. pneumoniae.* Other potential pathogens include staphylococci, *Klebsiella,* or *Pseudomonas.* Dacryocystitis rarely results in orbital cellulitis in children.

Acute dacryocystitis is treated with hot compresses and systemic antibiotics. This usually controls the infection but is not curative of the primary problem, the obstruction. The patient often requires probing and/or the placement of intubation tubes, balloon catheter dilation, or a dacryocystorhinostomy to prevent recurrent infections.

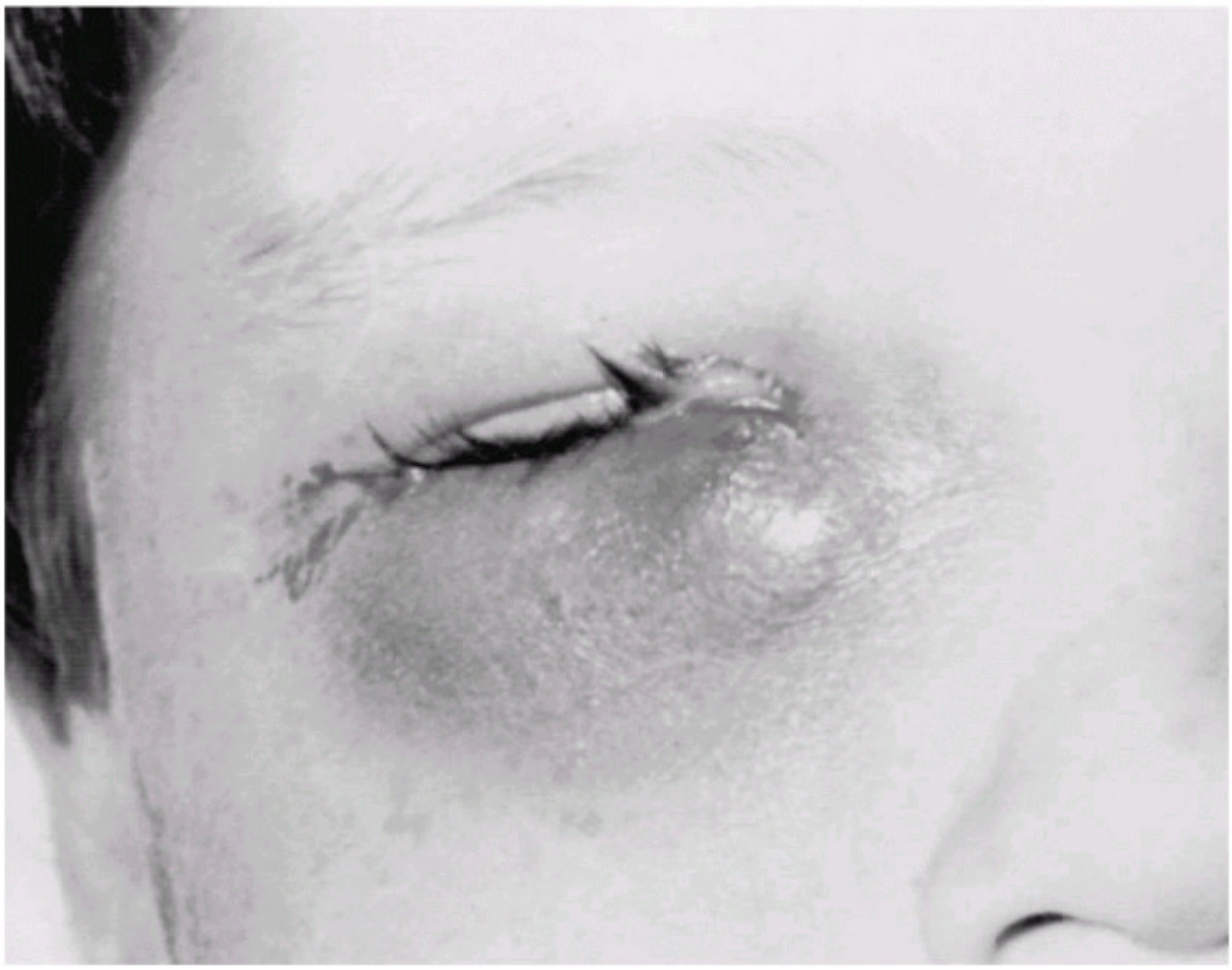

Figure 20.18 Acute dacryocystitis with preseptal cellulitis. The patient responded to antibiotics but required surgical dacryocystorhinostomy.

If a newborn presents with a mass in the medial canthus, one should consider a dacryocystocele or encephalocele. A dacryocystocele is located more inferior than most encephaloceles and is not associated with other abnormalities such as telecanthus. A CT scan should be performed if there is any question. A dacryocystocele develops when both the nasolacrimal duct and common internal punctum are closed in utero. The mucus produced within the sac has no drainage, and therefore produces a mass. Often it becomes infected within the first few days of life if not treated. Simple probing in the office is generally curative.

ORBITAL INFLAMMATION

Idiopathic inflammatory syndromes of the orbit (previously named pseudotumors) are often described histologically as pleomorphic inflammatory cellular responses and fibrovascular tissue reactions. This can be confusing clinically, posing a considerable diagnostic and therapeutic challenge. Idiopathic inflammatory syndrome of the orbit is a multifaceted disease with a wide spectrum of clinical, radiologic, and histopathologic presentations. Many classification schemes have been applied based on location of the inflammatory process, histopathologic characteristics, and stage of inflammation. There are highly variable clinical features, ranging from a diffuse to very focal process targeting specific orbital tissues, such as the lacrimal gland, extraocular muscles, and/or orbital fat. A diffuse inflammatory involvement is the most common presentation, followed by myositis, dacryoadenitis, and focal encapsulated mass. The disease process is localized to the extraocular muscles in 15% of patients. The process is typically characterized by an abrupt onset of pain, proptosis, and inflammatory signs and symptoms, such as swelling and erythema, depending on the location and degree of inflammation, fibrosis, and mass effect. Symptoms most commonly develop acutely in hours to days, occasionally subacutely over weeks, or chronically over a period of months. Pediatric idiopathic orbital inflammation differs from the adult presentation by an increased incidence of bilateral involvement, uveitis, disc edema, and eosinophilia. The orbital inflammatory processes can be nonspecific or specific. The pathogenesis has remained elusive despite several lines of evidence for an immune-mediated etiology. The frequency of the diagnosis of nonspecific orbital inflammatory syndromes is decreasing as the understanding of the pathogenetic and clinical manifestation increases. The character of presentation and temporal sequence should form the essential diagnostic framework. They classically present acutely or subacutely with signs of inflammation (pain, swelling, and redness), whereas chronic inflammation from granulomatous disease often presents with a mass effect or chronic bony destruction. It is important to separate these from lymphoproliferative disorders, which behave in a different fashion. The classifications of acute and subacute inflammations listed in Table 20.1 provide a framework for diagnosis and management.

Occasionally in children, a viral syndrome may precede the onset, and one must rule out infections. A bacterial orbital cellulitis may have severe pain, but the child is usually sick with fever, chills, lethargy, and the onset is generally over a few days. Most of these syndromes are managed with nonspecific, antiinflammatory medications, although biopsy is required in some instances if the lesion does not respond to treatment. The patients generally present with acute onset of orbital pain, restricted eye movement, proptosis, conjunctival vascular injection, chemosis, eyelid erythema, and soft-tissue swelling. Pain associated with eye movement is highly suggestive of idiopathic orbital inflammatory syndrome, especially myositis. Approximately one-third of children will present with bilateral involvement, and half will have headache, fever, vomiting, abdominal pain, and lethargy.

TABLE 20.1 ACUTE AND SUBACUTE INFLAMMATION OF THE ORBIT

	Anterior	Diffuse	Apical	Myositis	Lacrimal
Onset	Acute or subacute	Subacute remitting	Subacute	Acute or subacute	Acute or subacute
Pain	+	+	++	+	+
Ocular features	Good vision, ? EOM Injection/chemosis Uveitis Retinal detachment	Good vision, ? EOM Injection/chemosis Uveitis Retinal detachment	? Vision, ? EOM Mild proptosis	Good vision, ? EOM Injection/chemosis	S-shaped swollen lid Injection/chemosis
CT	Anterior irregular margins	Diffuse enhancement	Apical irregular infiltration	Muscle swelling and enlargement	Lacrimal gland swelling
Treatment	1 mg/kg/day prednisone	1 mg/kg/day prednisone	1 mg/kg/day prednisone	0.5 mg/kg/day prednisone	0.5 mg/kg/day prednisone
Outcome	Resolves	Recurrent	Clears in 1 to 2 months	Clears rapidly	Resolves

CT, computed tomography; EOM, extraocular movement; ?, decreased.

Nonspecific inflammations of the orbit have the clinical presentation of acute or subacute inflammatory symptoms and are composed of polymorphous infiltrations of inflammation, and their chemical byproducts produce pain, vascular dilation, and edema with or without systemic malaise. This is in contrast to the chronic or progressive infiltrative inflammations and granulomatous disease, which produce a mass effect associated with destruction and desmoplasia.

Idiopathic orbital inflammation is subclassified as to the anatomic target of involvement. The site of inflammation may present as a dacryoadenitis, myositis, sclerotenonitis, diffuse anterior inflammation, perioptic nerve inflammation, or superior orbital fissure and cavernous sinus, the so-called Tolosa-Hunt syndrome of painful ophthalmoplegia.

Anterior involvement presents with pain, proptosis, ptosis, lid swelling, chemosis, decreased motility, tense, warm, and tender tissues, and decreased vision, mainly involving the globe and adjacent structures. Associated findings may include uveitis, scleritis, papillitis, and even exudative retinal detachments. This syndrome is more common in children and young adults. Systemic evaluation in the younger age group may show an increased sedimentation rate and cerebrospinal fluid pleocytosis. The CT pattern depends on the tissues involved, dacryoadenitis, myositis, anterior or posterior orbit, etc. Characteristically, the CT shows diffuse anterior orbital infiltration, producing scleral and choroidal thickening, as well as some nerve sheath thickening (Fig. 20.19). Ultrasonography shows thickening of the sclera, with accentuation of Tenon space and doubling of the optic nerve shadow (the T sign) (Fig. 20.20). Differential diagnosis must include orbital cellulitis, ruptured dermoid cyst, hemorrhage within a vascular lesion, acute hemorrhage, rhabdomyosarcoma, metastatic neuroblastoma, collagen vascular diseases, and leukemic infiltrates. Histopathologically, the infiltration is characterized by a pleomorphic cellular infiltrate of lymphocytes, plasma cells, and eosinophils with variable degrees of reactive fibrosis. The fibrosis is more prominent as the process becomes more chronic. Treatment consists of oral prednisone, which generally results in a dramatic improvement of symptoms, especially pain, and resolution may be expected over several weeks. The systemic corticosteroids can then be slowly tapered. Recurrences occur more frequently in younger patients and require reinstitution of the corticosteroids and may require nonsteroidal antiinflammatory medications or rarely, immunosuppressive medications. Topical corticosteroid eye drops may help to decrease the superficial inflammatory and anterior chamber reactions. Lesions that do not respond to treatment necessitate orbital biopsy to determine the diagnosis. If the biopsy reveals a benign process, low-dose radiation to the orbit (1,000 to 2,000 Gy), antimetabolites, or alkylating agents such as methotrexate or cyclophosphamide, and continued corticosteroid therapy may occasionally be needed to control the disease process.

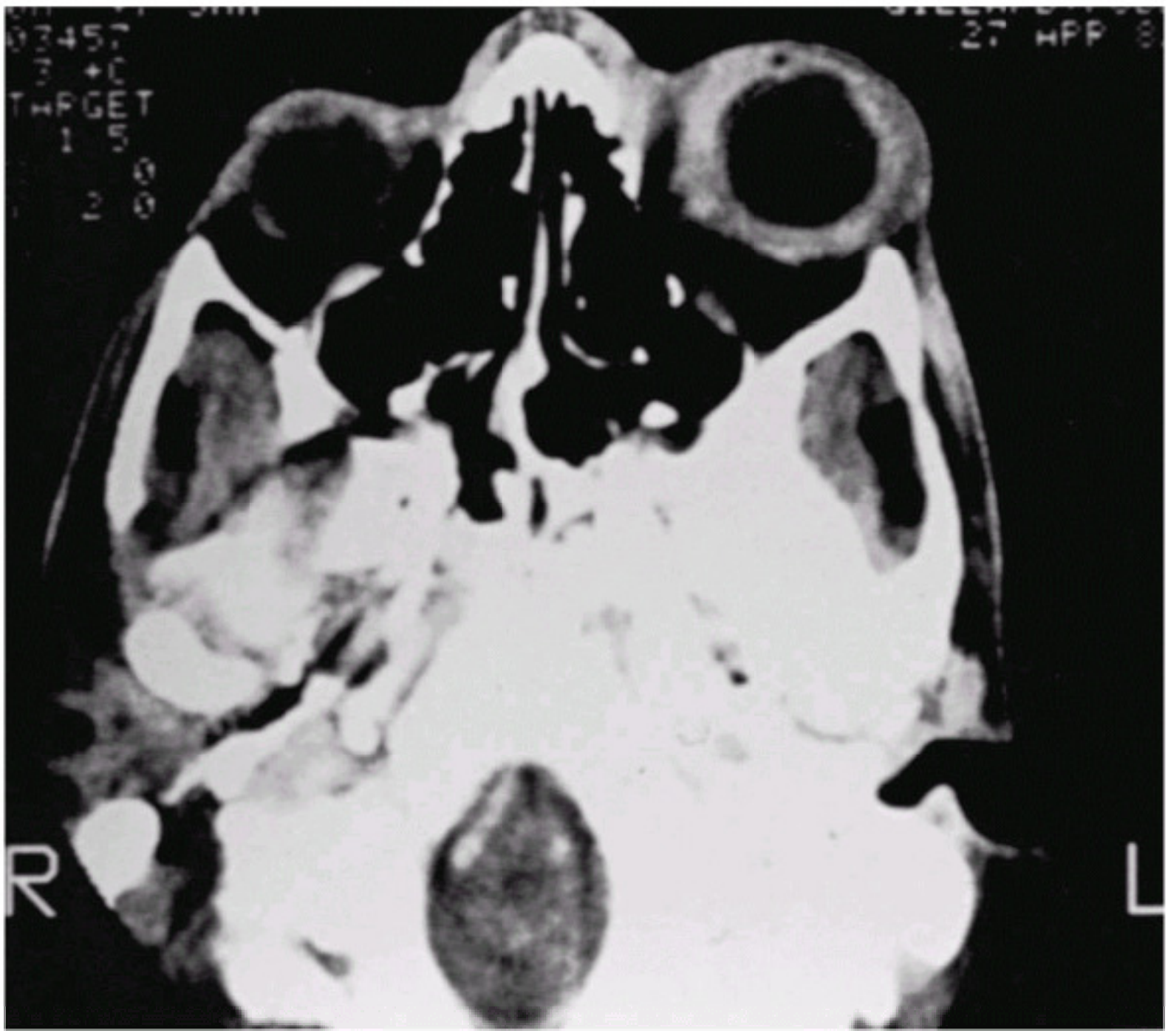

Figure 20.19 Idiopathic orbital inflammation showing scleral and choroidal thickening, known as the ring sign on computed tomography scan.

Diffuse inflammation is similar to anterior inflammation, but signs and symptoms are more severe, including limitation of ocular motility, papillitis, and exudative retinal detachment. CT and MRI scans show soft-tissue infiltration, involving the entire orbit from the apex to the posterior globe (Fig 20.21). Treatment with corticosteroids is

indicated, and a rapid response is usually seen; however, it is more difficult to taper the corticosteroids, and recurrences are more frequently seen than with anterior involvement.

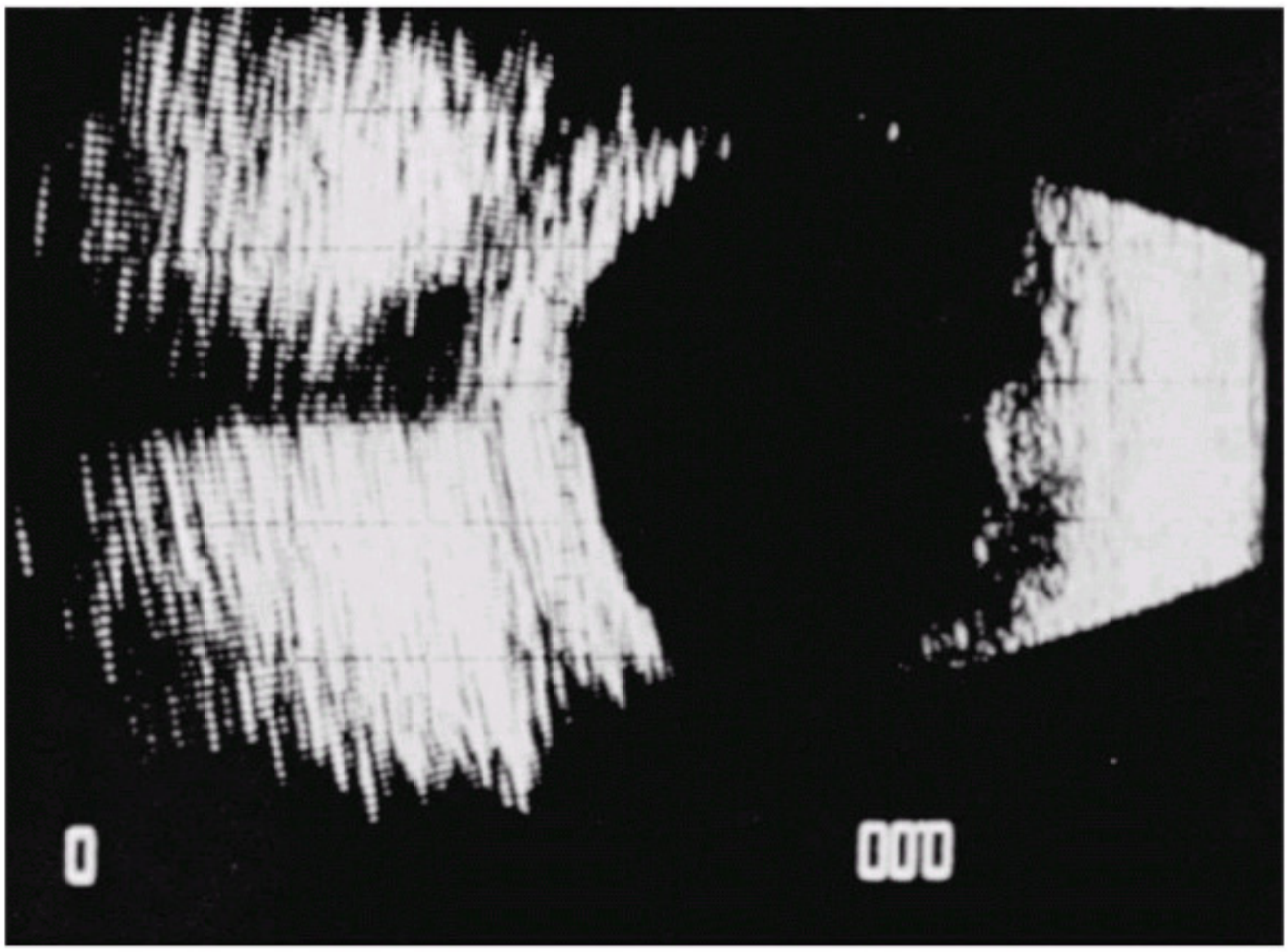

Figure 20.20 Idiopathic orbital inflammation with accentuation of Tenon space and doubling of the optic nerve shadow known as the T sign.

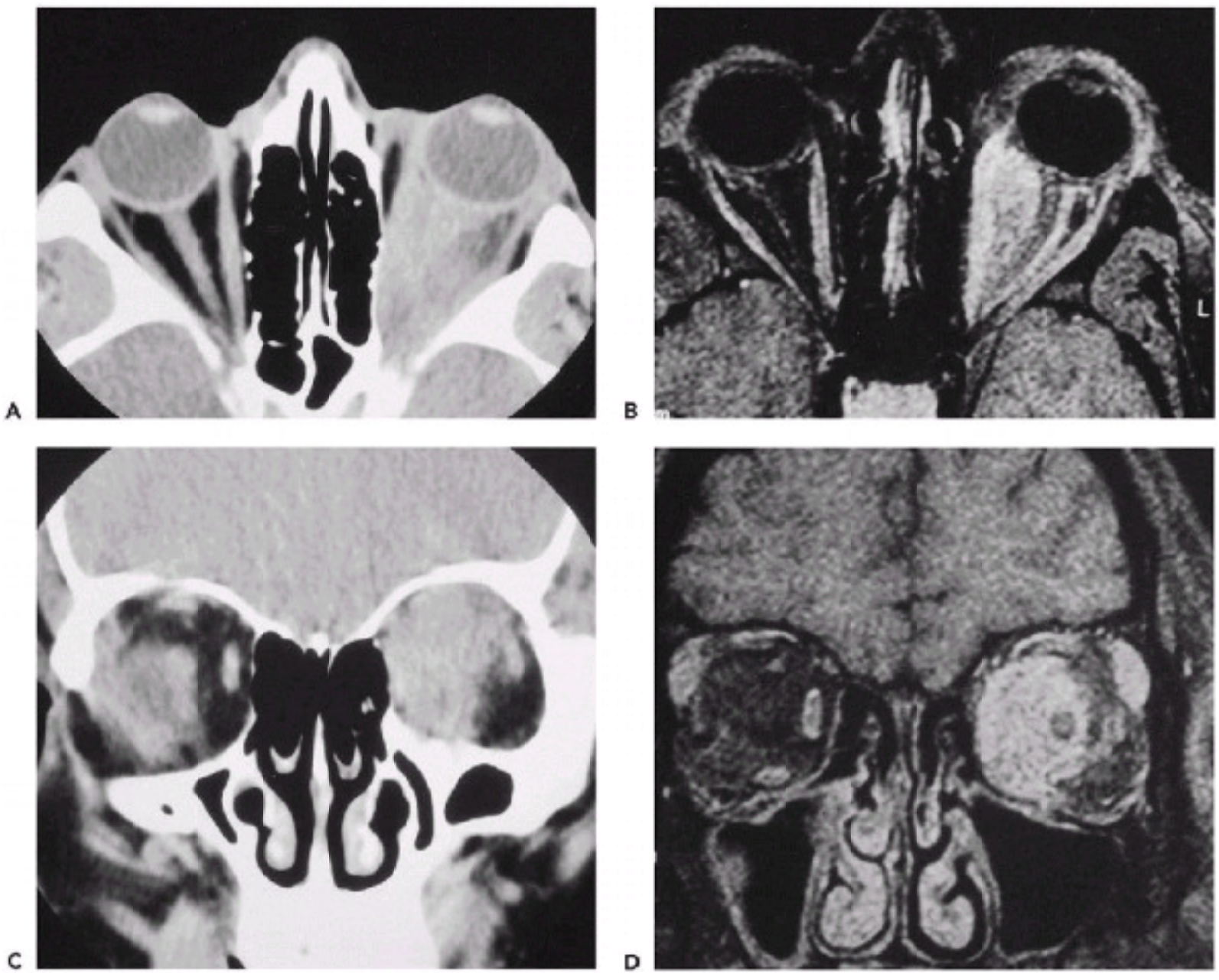

Figure 20.21 Idiopathic orbital inflammation. Patient presented with a 72-hour history of pain, proptosis, and diplopia. **A:** Axial computed tomography (CT) scan demonstrating a soft-tissue infiltrate involving the intraconal space, posterior globe, orbital apex, as well as enlargement of the lacrimal gland. The soft-tissue infiltration obscures the normal definition of the optic nerve. **B:** Magnetic resonance imaging (MRI) scan of the same patient demonstrating the soft-tissue infiltration but good definition of the optic nerve. **C:** Coronal CT scan of the same patient. **D:** MRI of the same patient.

Orbital myositis presents with pain on eye movement, retrobulbar pain, diplopia, swelling of the eyelids, localized injection, and/or chemosis over the affected muscle insertions, and occasionally proptosis. Eye movement is limited in the direction of the affected muscle, and pain is increased by movement in that direction. Forced ductions help to distinguish between infiltrative and noninfiltrative myopathies. CT shows enlargement of the affected muscle(s) with irregular margins (Fig. 20.22). The superior muscle complex is most commonly involved, followed by the medial rectus. The extraocular muscle tendons of insertion may be thickened in up to 50% of patients, in contrast with thyroid orbitopathy, in which the muscle tendon insertions are spared. The condition may be bilateral and can recur. Recurrent cases usually involve new muscles. Most cases have no systemic etiology, and a few will be associated with underlying immune disorders such as allergy, collagen vascular disease, Crohn disease, and rarely, paraneoplastic syndrome. Treatment is provided with oral prednisone 0.5 mg/kg daily. A good response is usually noted within several days in most patients. If they fail to respond or persist, biopsy should be performed. Patients with bilateral or multiple muscle involvement are more prone to recurrences and should be followed up and evaluated for associated systemic disease.

Apical orbital inflammation presents with pain, minimal proptosis, decreased vision, limitation of eye movements, and diplopia, often with minimal inflammatory

signs. CT shows irregular infiltration of the apex of the orbit, with possible extension along the muscles and nerves (Fig. 20.23). This process should rarely be treated nonspecifically without a very rigorous systemic evaluation, since a variety of disorders can present in this fashion. Lymphoma, secondary tumors from adjacent sinuses, sclerosing inflammation, fungal infections, metastases, Wegener granulomatosis, meningioma, mucormycosis, and Tolosa-Hunt syndrome should be ruled out. This process often requires a longer course of high-dose corticosteroids, usually 6 to 8 weeks, for complete resolution.

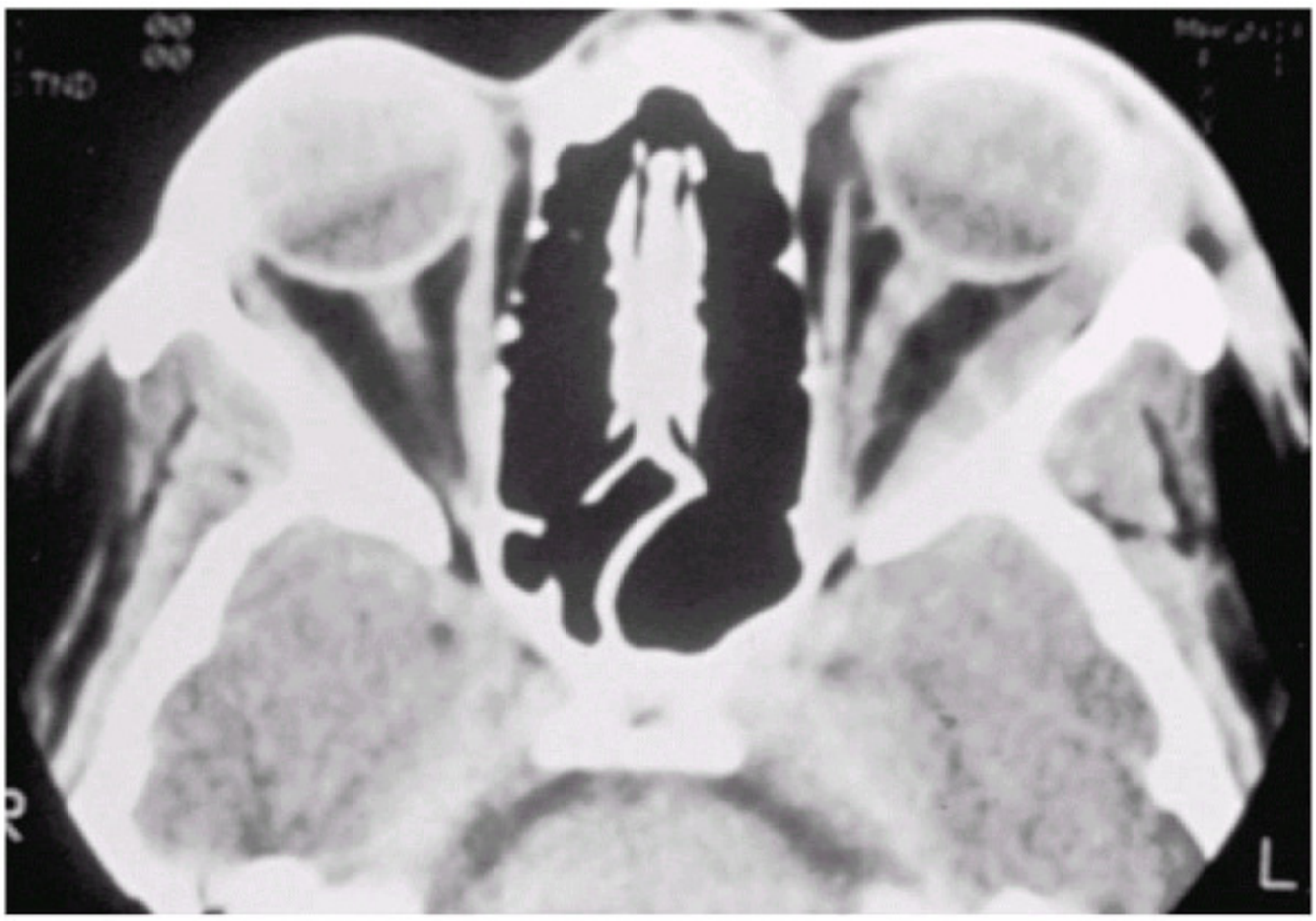

Figure 20.22 Axial computed tomography scan of a patient with myositis of the lateral rectus muscle resulting in decreased abduction.

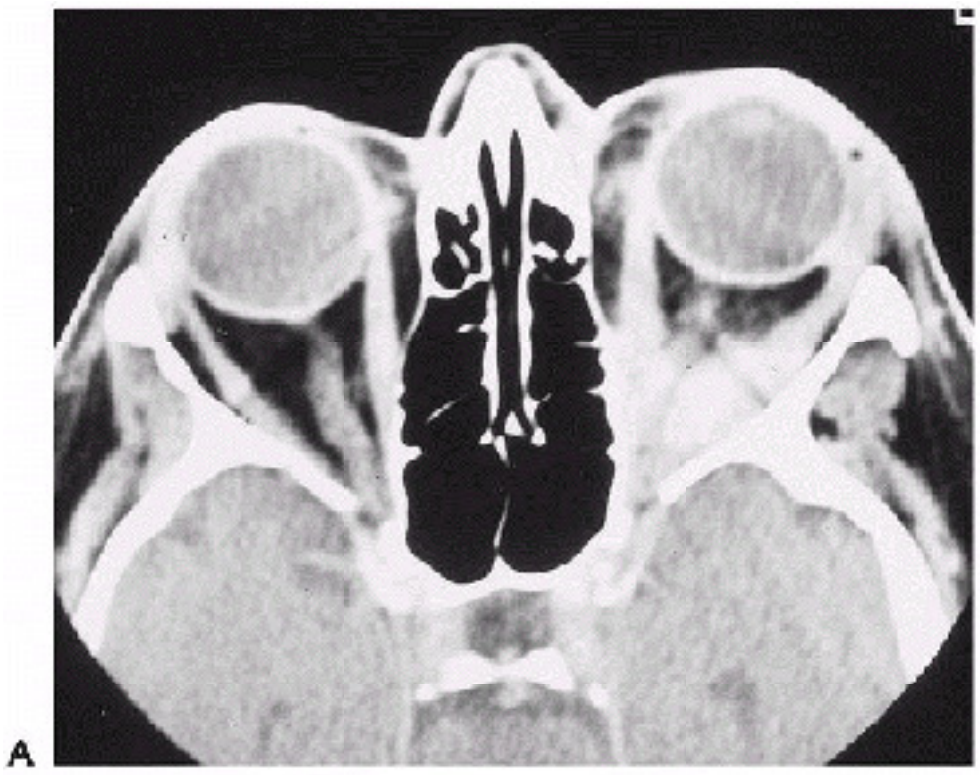

Figure 20.23 A: Axial computed tomography (CT) scan showing inflammatory infiltration of the orbital apex. **B:** Coronal CT scan demonstrating more involvement of the superior posterior orbit. The patient presented with minimal proptosis and limited motility in all directions.

Idiopathic lacrimal gland inflammation can be a nonspecific dacryoadenitis or can result from a multitude of causes, and evaluation for associated systemic disease for infections, lymphoma, sarcoid, Sjogren syndrome, sclerosing inflammation, hematopoietic malignancy, a myriad of autoimmune disorders, or Wegener granulomatosis should be performed. Viral and bacterial causes should also be ruled out. The patient presents with pain, tenderness, and injection of the superior temporal lid and conjunctiva, and pouting of the lacrimal ducts is noted on slit-lamp exam. The lid often demonstrates the classic S-shaped upper lid deformity and minimal displacement of the globe (Fig. 20.24). Unlike the previously described orbital inflammatory patterns, lacrimal gland inflammations can frequently be related to systemic syndromes and may have multiple causes. Therefore, when these inflammatory lesions do not respond to treatment, routine incisional biopsy through a percutaneous route to avoid the excretory ducts of the lacrimal gland is advocated. Idiopathic inflammation shows a polymorphous cellular infiltration with edema, vascular dilatation, and minimal destruction of the lacrimal gland. If there is destruction of the gland, then a rigorous evaluation for organ-specific immune disorders should definitely be performed. CT scan shows infiltration confined to the superior lateral orbit, an enlarged lacrimal gland with irregular margins that enhance with contrast, and often inferior

and medial displacement of the globe (Fig. 20.25). Once the diagnosis is confirmed histopathologically, treatment consists of oral prednisone.

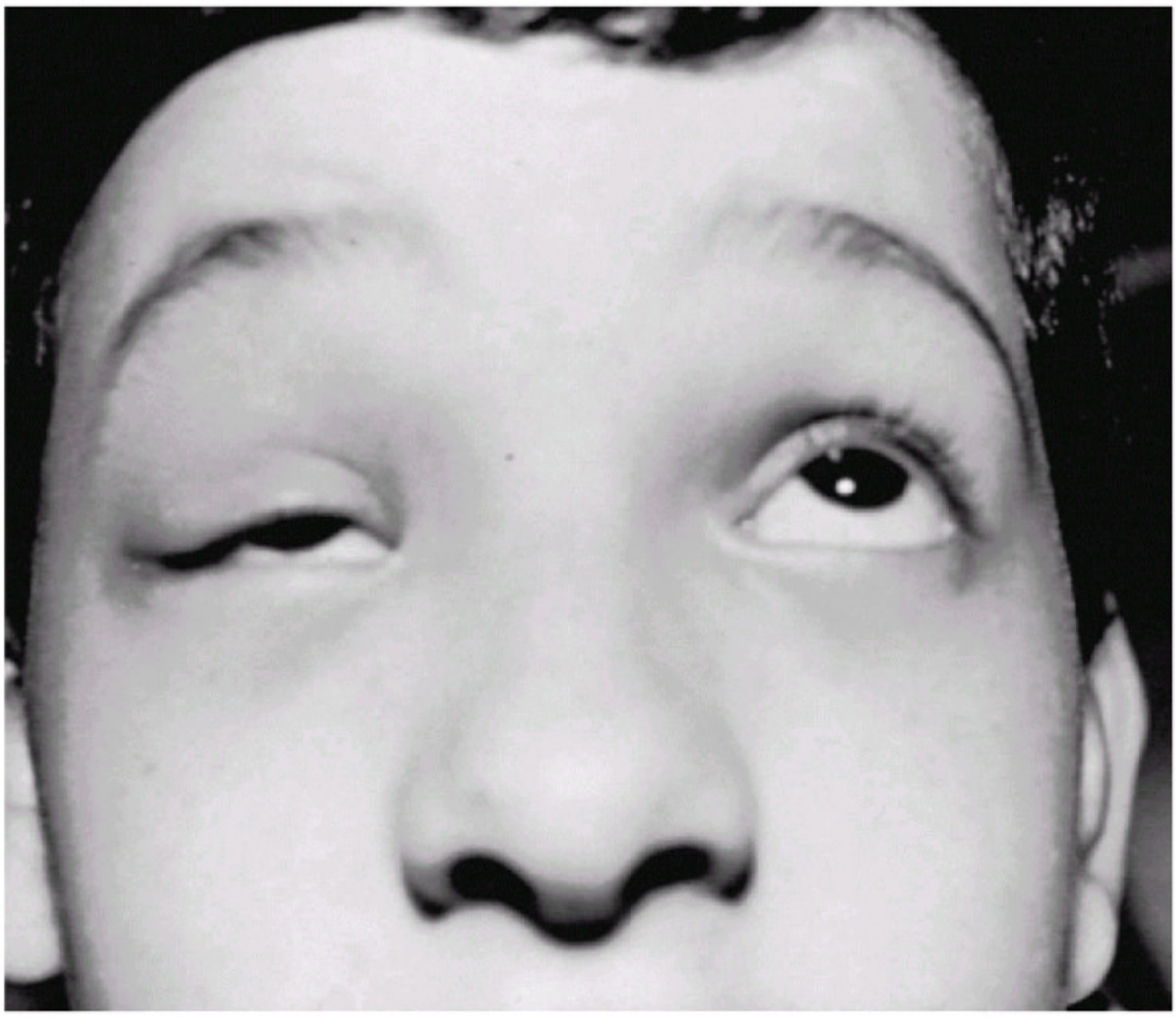

Figure 20.24 Patient with lacrimal gland inflammation. Note the decreased elevation and S-shaped deformity of the right upper lid.

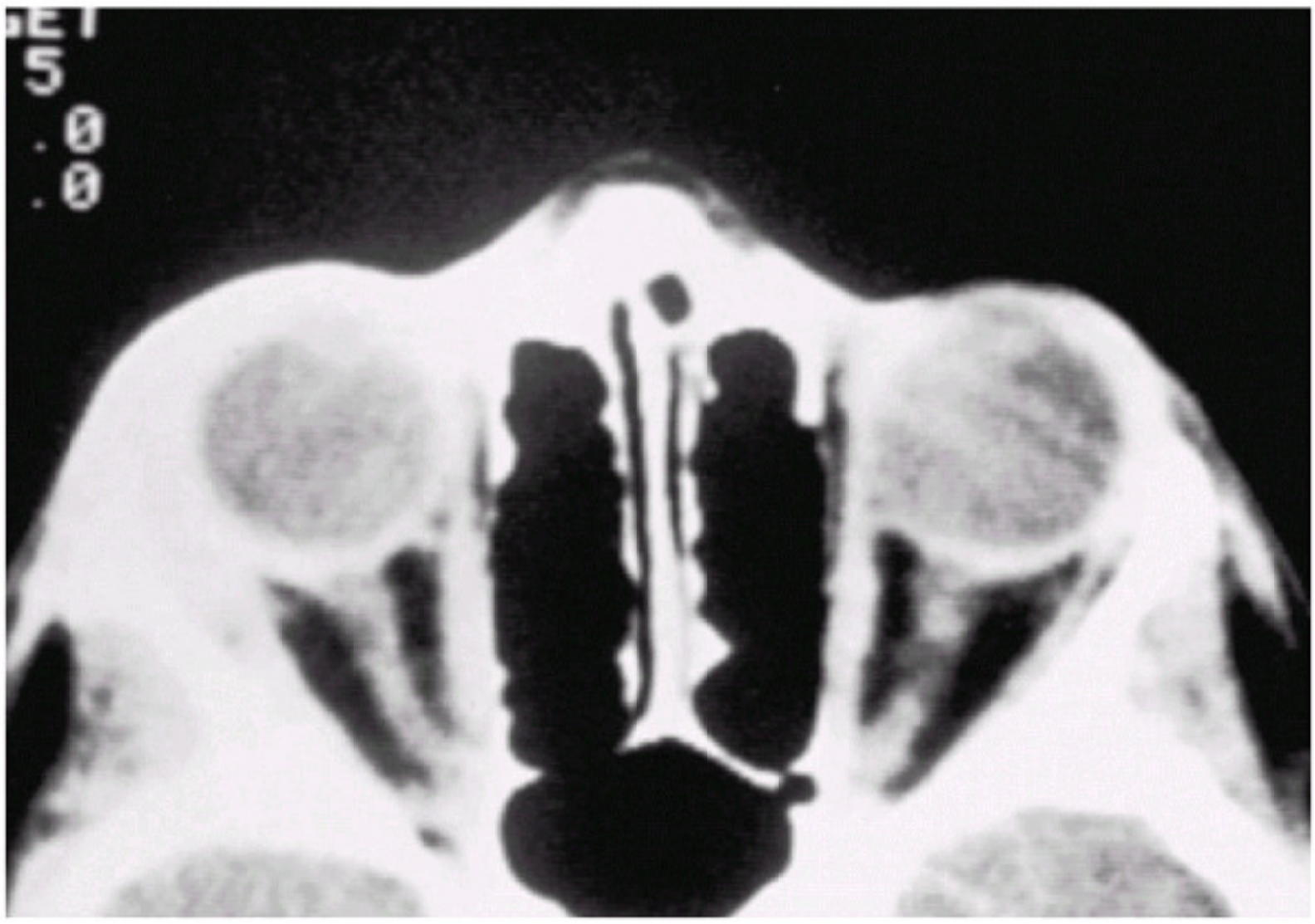

Figure 20.25 Axial computed tomography scan displaying an enlarged lacrimal gland.

ORBITAL TUMORS

The most common primary orbital tumors in the pediatric-age group include developmental cysts, vascular lesions, rhabdomyosarcomas, and neural tumors. Malignancy is a less common cause of proptosis than in the adult. Congenital abnormality, hamartoma (anomalous growth of tissue consisting only of mature cells normally found at the involved site, hemangioma, NF, and glioma), and choristoma (normal tissue in an abnormal anatomic location, dermoid cyst, epidermoid cyst, lipodermoid, and teratoma) are the most common. Rhabdomyosarcoma must be considered in any child presenting with a rapidly progressive proptosis. Fibro-osseous lesions arise within the orbital walls and impinge on orbital structures. Lacrimal gland tumors are rare but can be life-threatening neoplasms. Metastatic neoplasms include leukemia, neuroblastoma, and Ewing sarcoma. Secondary tumors can arise from the sinuses, intracranial fossa, eyelids, or globe.

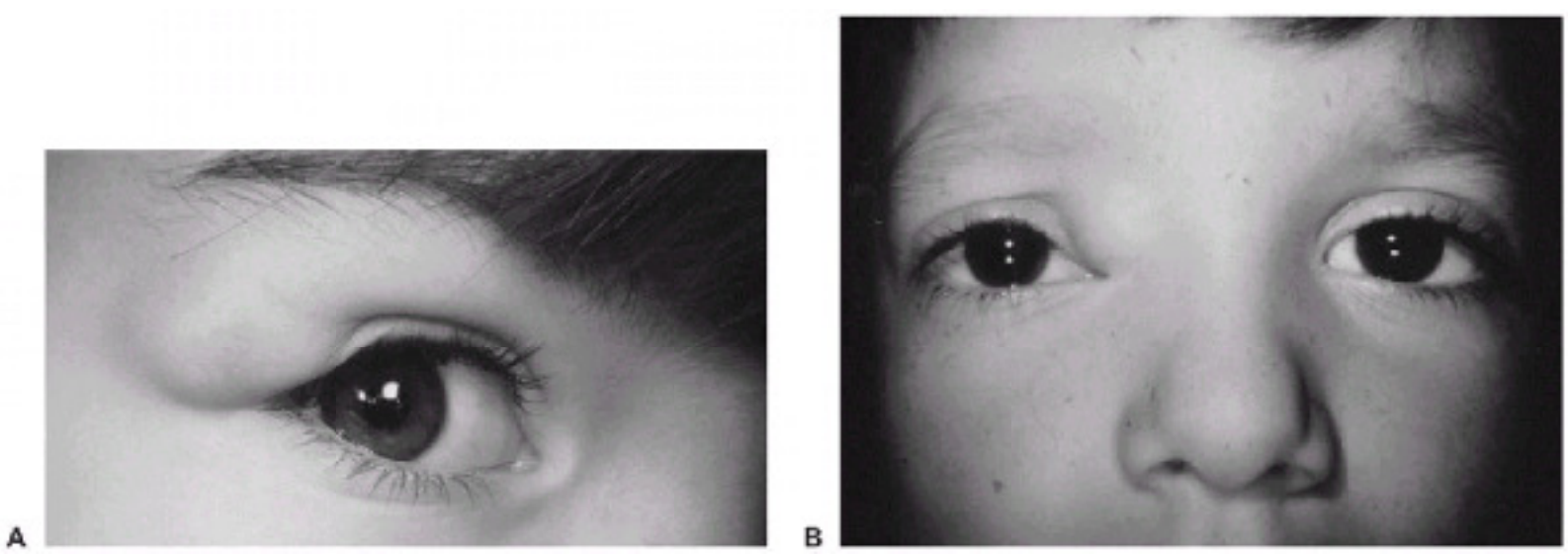

Figure 20.26 A: Dermoid cyst in the superotemporal orbit attached to the frontozygomatic suture. **B:** Dermoid cyst in the superonasal orbit, attached to the frontonasal suture line.

Congenital Developmental Cysts

Dermoid and Epidermoid Cysts

Dermoid and epidermoid cysts are congenital tumors composed of sebaceous material, hair follicles, and elastic fibers representing a “rest” of the primitive ectoderm in the area of the fetal cleft. A piece of skin is pinched off in a suture line where the tissue will gradually form a cyst. Since they are composed of tissues not normally found at their site of occurrence, these cysts are choristomata. A dermoid cyst will be lined with normal skin, keratinizing stratified squamous epithelium with various adnexal structures in the wall, including sebaceous glands, hair follicles, and eccrine sweat glands, and the contents of the cyst include

keratin, sebaceous secretions, and hair. A portion of the wall may be replaced by a giant cell foreign body granulomatous response, indicating previous rupture of the cyst. If the lining of the cyst does not contain skin appendages, it is an epidermoid cyst. Both will have the same clinical presentation and management. It is a cystic lesion that differs from the solid dermoid which occurs in the conjunctiva and cornea. The cyst can occur from any suture line. They are frequently attached to bone in the superior temporal aspect of the orbital margin, frontozygomatic suture, and frontonasal suture line (Fig. 20.26). Such cysts are firm, smooth, painless, oval masses on palpation, and may cause some bony erosion at the site of attachment. They may be freely mobile or may be fixed to the periosteum at the underlying suture, and may transilluminate. The more superficial cysts usually become clinically symptomatic in childhood, but the deeper orbital cysts may not become clinically symptomatic until adulthood. On CT, they have a low-density lumen, well-circumscribed round mass, and can exhibit

bony expansion and erosion (Figs. 20.27 and 20.28). Some may occur partly in the orbit and partly in the temporal fossa, connected through a defect in the bone of the zygomatic or frontal bone, the so-called dumbbell dermoid. Most anteriorly situated dermoid cysts can be excised easily through a skin crease incision, which hides the scar nicely, generally between the first and fifth year of life to prevent traumatic rupture. Treatment is desirable for more than just cosmetic reasons since even minor trauma may cause rupture of the cyst and result in a granulomatous reaction with secondary orbital and adnexal inflammation. A cryoprobe (Fig. 20.29) can be used to help manipulate the lesion. Every effort should be made to remove the tumor in one piece, employing meticulous dissection, since the contents of the dermoid cyst are irritating and result in lipogranulomatous inflammation of orbital tissues, and may lead to recurrences (Figs. 20.30 and 20.31). If the dermoid cyst is accidentally ruptured during removal, copious irrigation and removal of the entire cyst should be performed. Deep orbital dermoid cysts, such as those originating from the sphenozygomatic suture and extending along the orbital roof, may require a lateral orbitotomy or occasionally a transcranial approach to assist removal. These deeper cysts generally present in young adults as a slowly progressive,

painless proptosis (Fig. 20.32). These deeply located cysts may leak oil and keratin spontaneously or after trauma and present as an inflamed orbit with little pain. Longstanding cysts in the superior orbit may completely erode the orbital roof and become adherent to the dura mater.

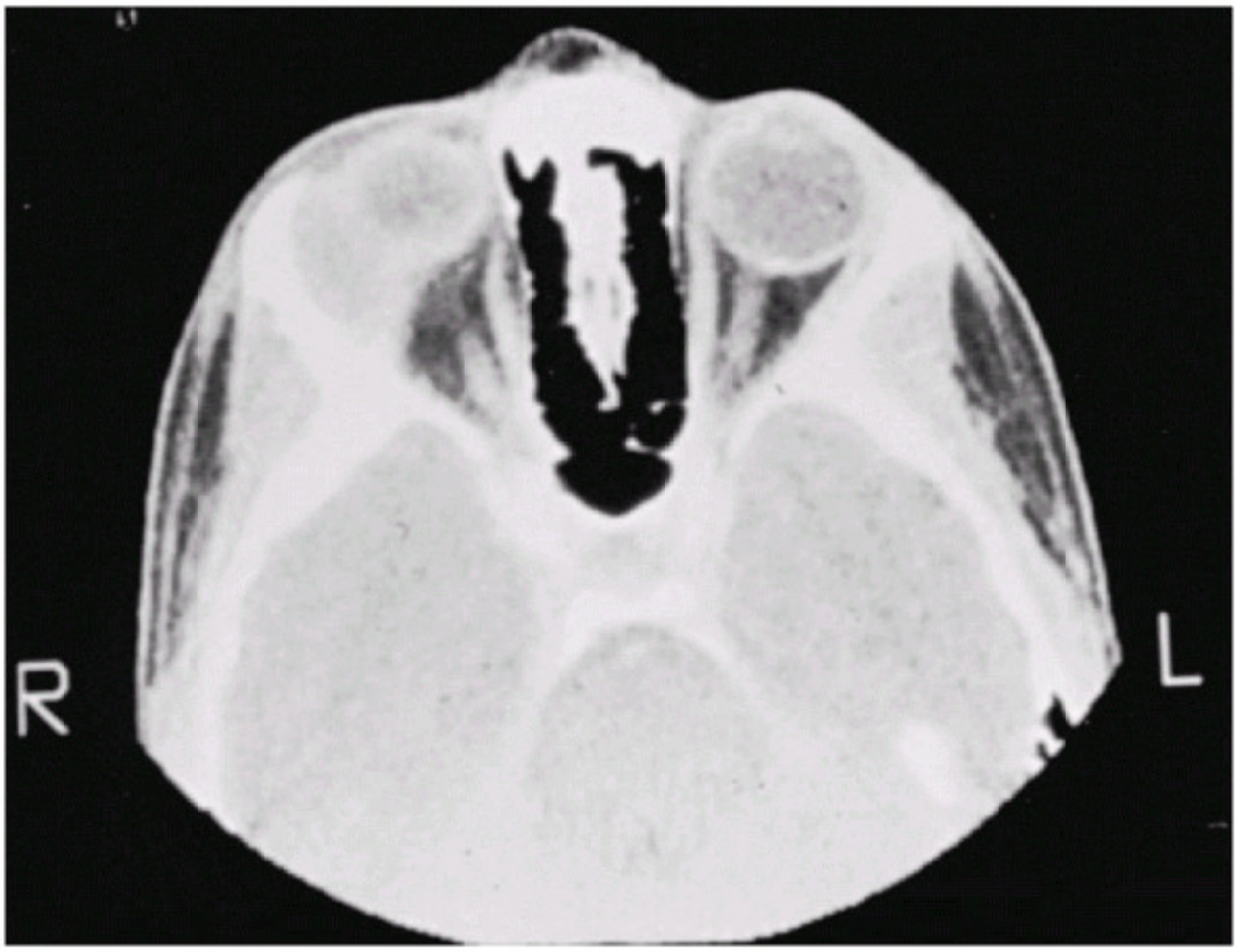

Figure 20.27 Axial computed tomography scan demonstrating a dermoid with evidence of bony fossa formation.

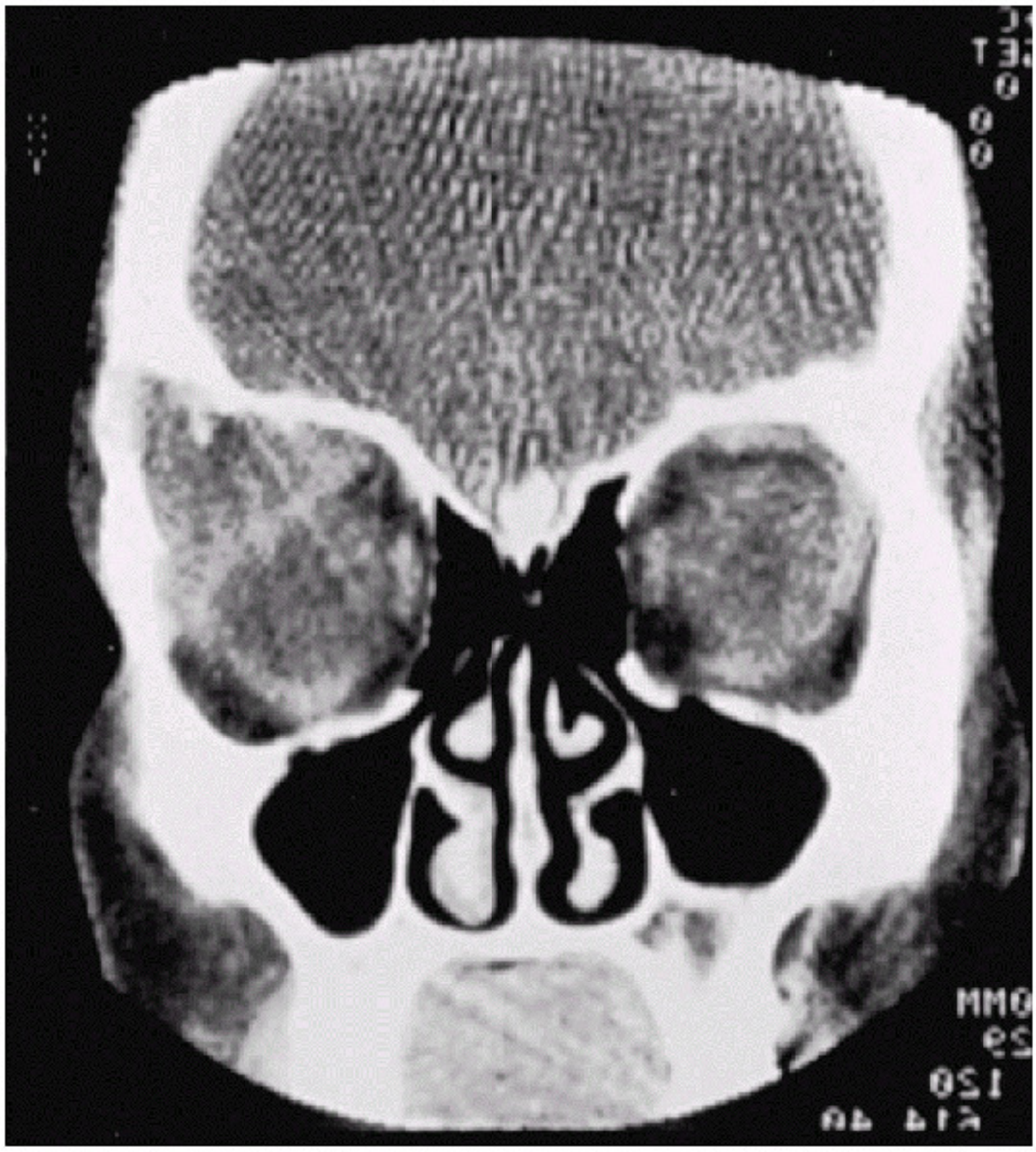

Figure 20.28 Coronal computed tomography scan of an orbital dermoid demonstrating bony fossa formation temporally.

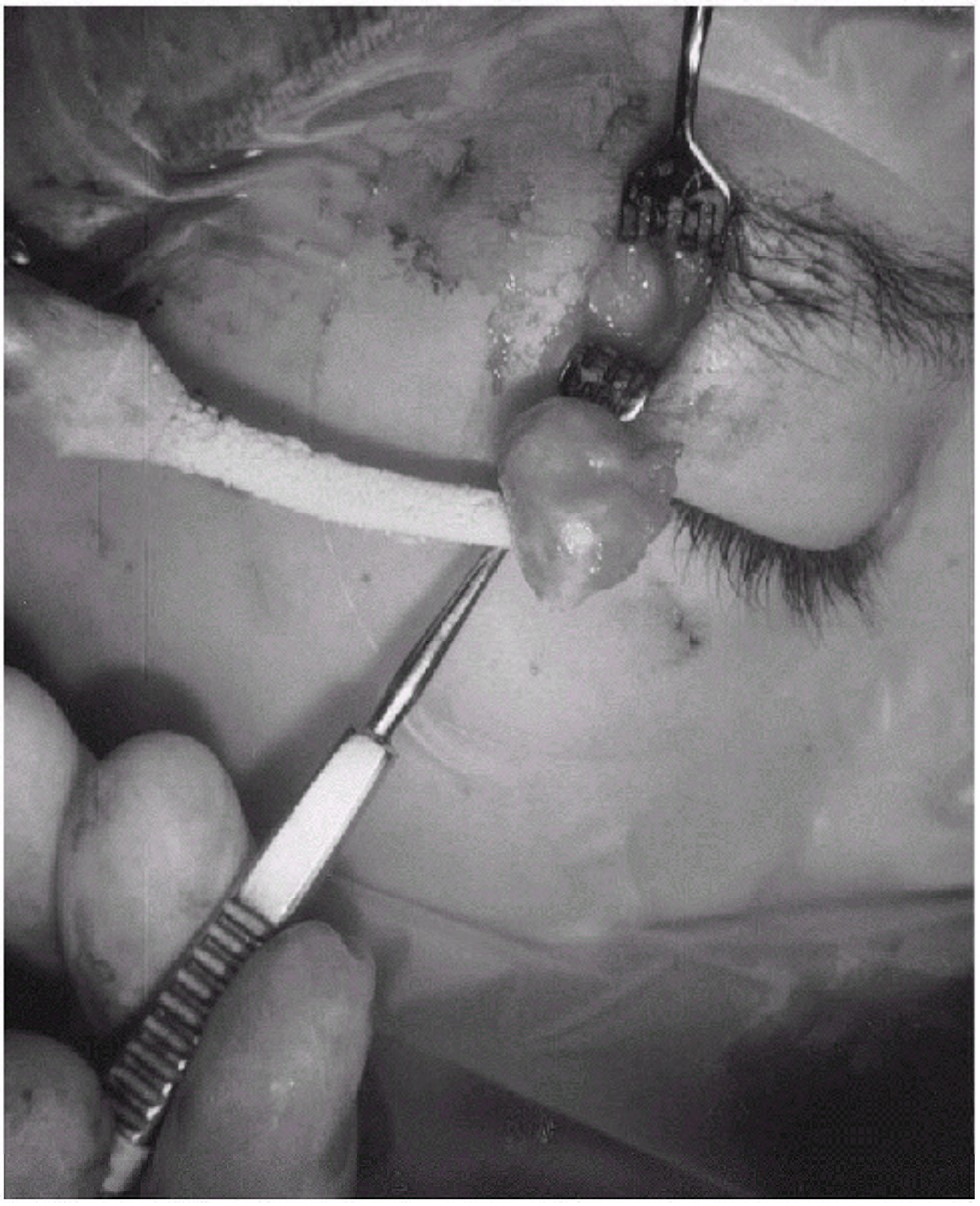

Figure 20.29 Use of a cryoprobe to assist in the removal of a superotemporal dermoid.

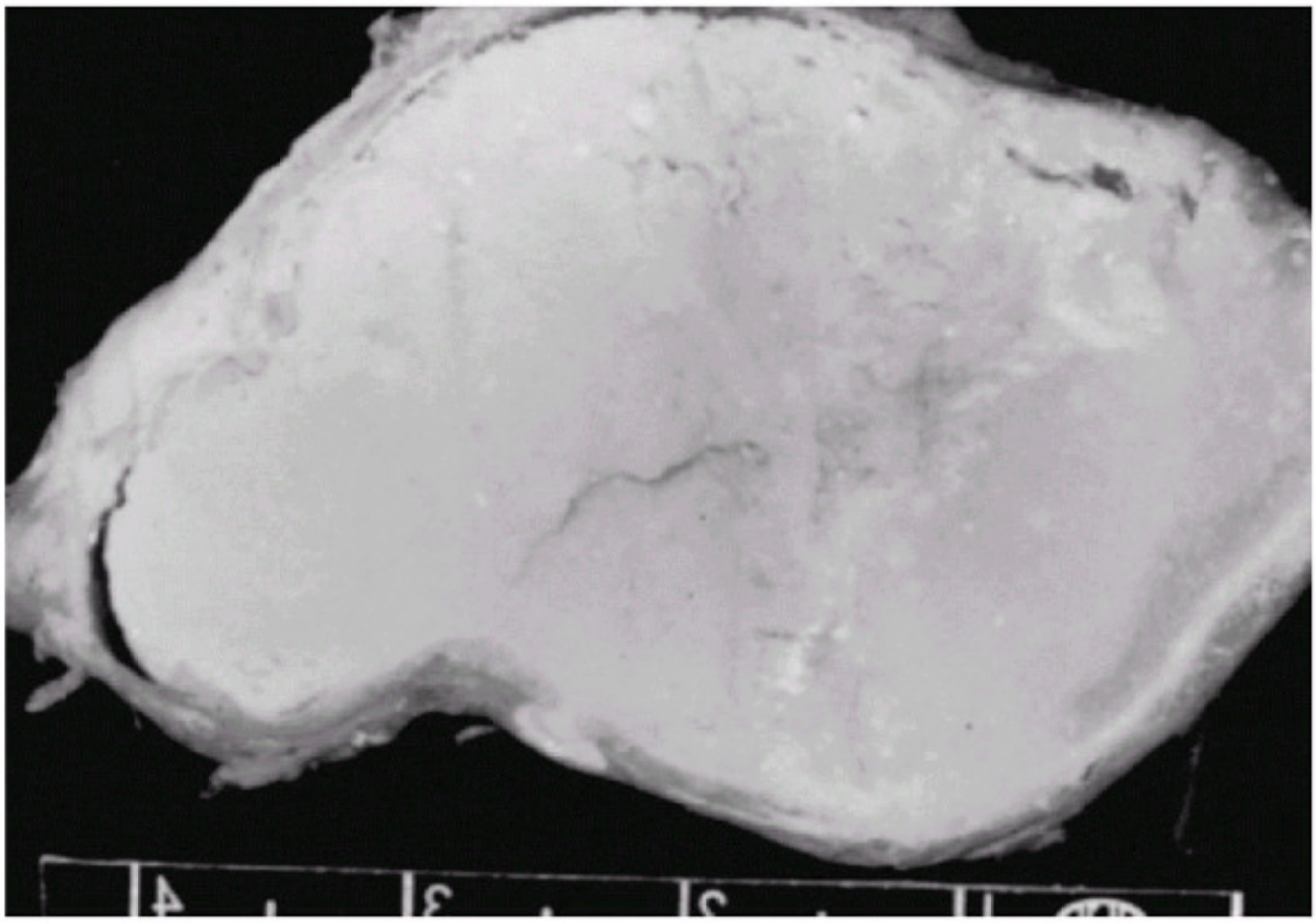

Figure 20.30 Gross section through a dermoid showing an intact capsule with yellowish amorphous material within.

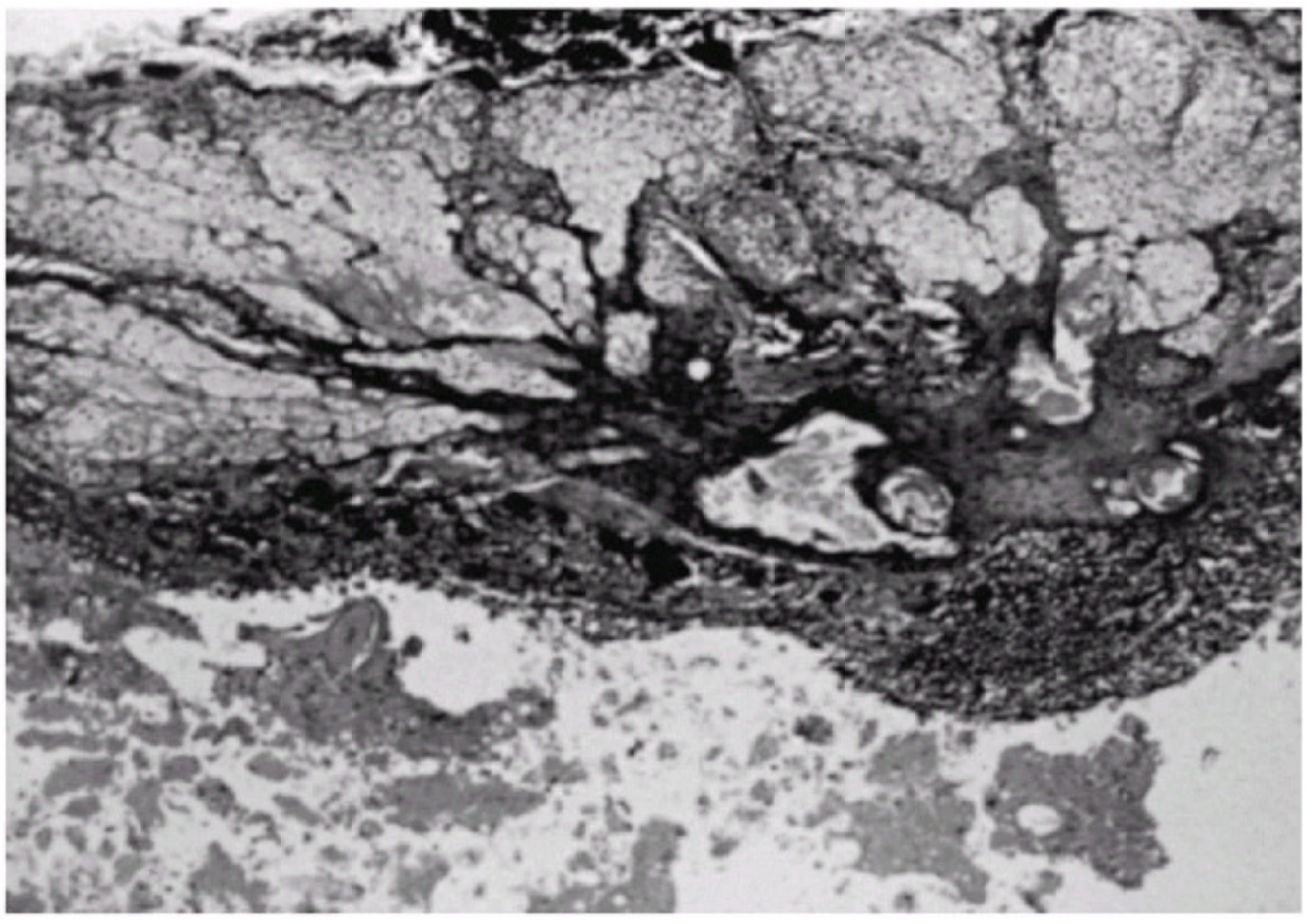

Figure 20.31 Histopathologically, the walls of the cyst contain sebaceous glands and an inflammatory infiltrate.

Lipodermoids are solid tumors which present subconjunctivally in the lateral orbit overlying the lateral rectus muscle and may have deep extensions that course

around the extraocular and levator muscles (Fig. 20.33). Only the anterior portion of these tumors should be excised, preserving the overlying conjunctiva if at all possible. Postoperative complications are common and include problems of motility if the excision is carried too posteriorly around the extraocular muscles, causing scarring and keratitis sicca secondary to damage to the lacrimal ducts. Mucosal grafts and careful microscopic dissection can improve surgical success.

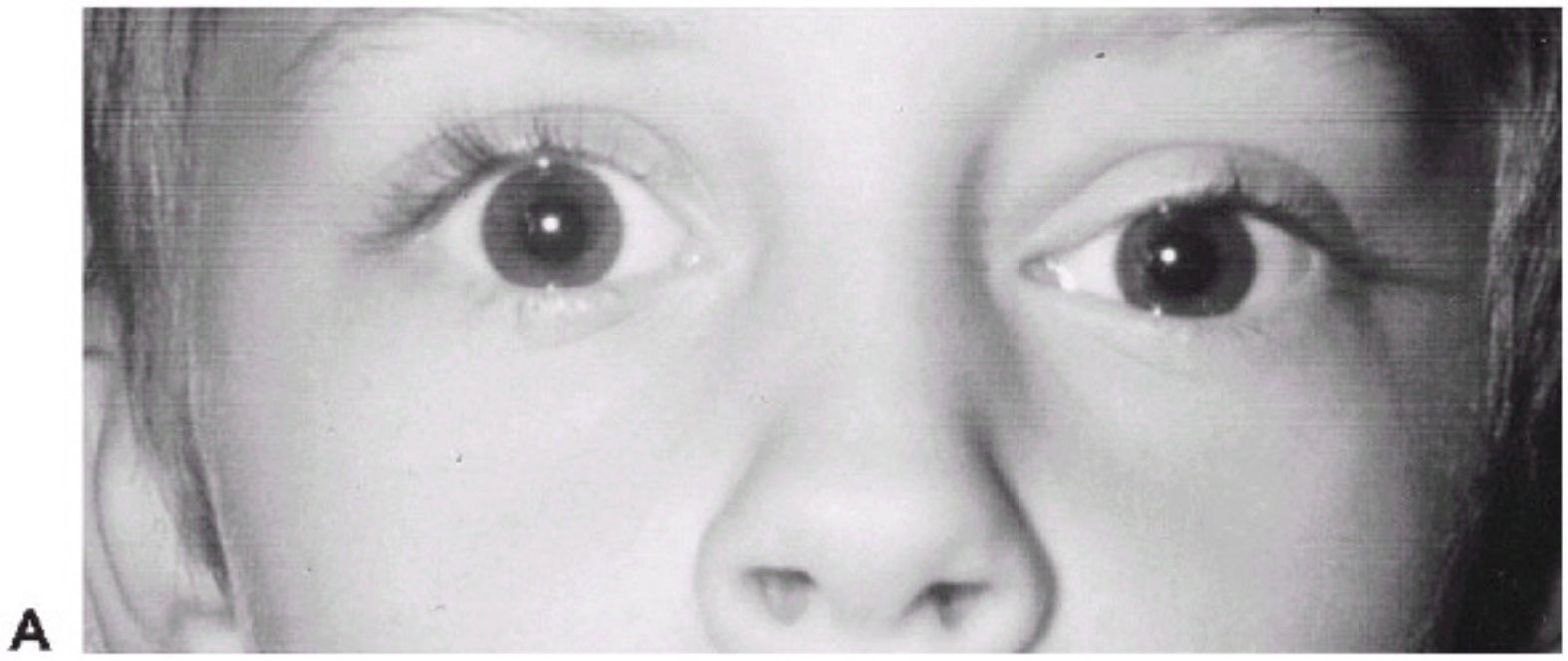

Figure 20.32 A: A deep orbit dermoid presenting as a gradual painless proptosis, as well as **(B)** an inferior displacement of the globe.

Figure 20.33 Lipodermoid overlying the lateral rectus muscle, superior lateral globe, and extending posteriorly. Note the hairs extending through the conjunctiva.

Conjunctival cysts of the orbit may be primarily choristomatous congenital rests or secondary after trauma or iatrogenic implantation of conjunctival epithelium. Following strabismus surgery, the cyst may be located near the insertion of the rectus muscle. After retinal detachment surgery, the cyst can arise posteriorly in the orbit, causing proptosis and affecting the rectus muscles. After enucleation, the cyst may cause difficulty retaining the prosthesis. The cysts are lined by nonkeratinized-stratified squamous epithelium, with or without goblet cells. The cysts are thin-walled, low-pressure lesions that generally conform to the orbital structures without creating significant mechanical disruption, such as motility disturbance, bone remodeling, or pain.

Teratomas

Teratomas are rare and typically grow rapidly after birth, causing destructive proptosis and exposure keratitis. They may also have a slow progressive course over several years. Teratomas are composed of tissue elements derived from two or more of the three primary embryonic cell layers, including ectoderm, endoderm, and mesoderm, and are thought to arise from pluripotent embryonic tissue. They most commonly occur in the testes, ovaries, and retroperitoneum, and rarely in the orbit. The tumors are usually cystic, and most are noted at birth but occasionally can present into adolescence. Most are benign and localized to the orbit, but rarely they can be highly malignant (Fig. 20.34). They may be sharply circumscribed and, if posterior to the globe, can cause substantial deformity and remodeling of the bone orbit. They are usually heterogeneous masses with calcification, adipose tissue, and occasional

bone formation. Orbital teratomas are usually multiloculated, cystic masses with solid areas. The affected eye is dwarfed by the extent of the tumor mass. The tumor is a choristoma and consists of skin, hair, sebaceous glands, cartilage, connective tissue, and epithelium (Fig. 20.35). All three layers may be represented: ectoderm, with keratinizing squamous epithelium and adnexal glandular structures; endoderm, with gastrointestinal mucosal and glandular tissues; mesoderm, with fibrous tissue, cartilage, fat, muscle, and/or bone; and neuroectoderm by mature brain. Some may be associated with brain and/or periorbital involvement and may be extensions of a primary teratoma from these sites. CT reveals large heterogeneous lesions with many cystic cavities and possible intracranial involvement (Fig. 20.36). Treatment consists of surgical excision, perhaps with a combined neurosurgical and orbital approach, with preservation of the globe whenever possible. Occasionally aspiration of the fluid from a large cyst may facilitate complete removal. Teratomas in other locations of the body have been known to undergo malignant transformation; those confined to the orbit are generally benign. Teratomas with malignant change are relatively resistant to chemotherapy and radiotherapy. Wide surgical excision is recommended.

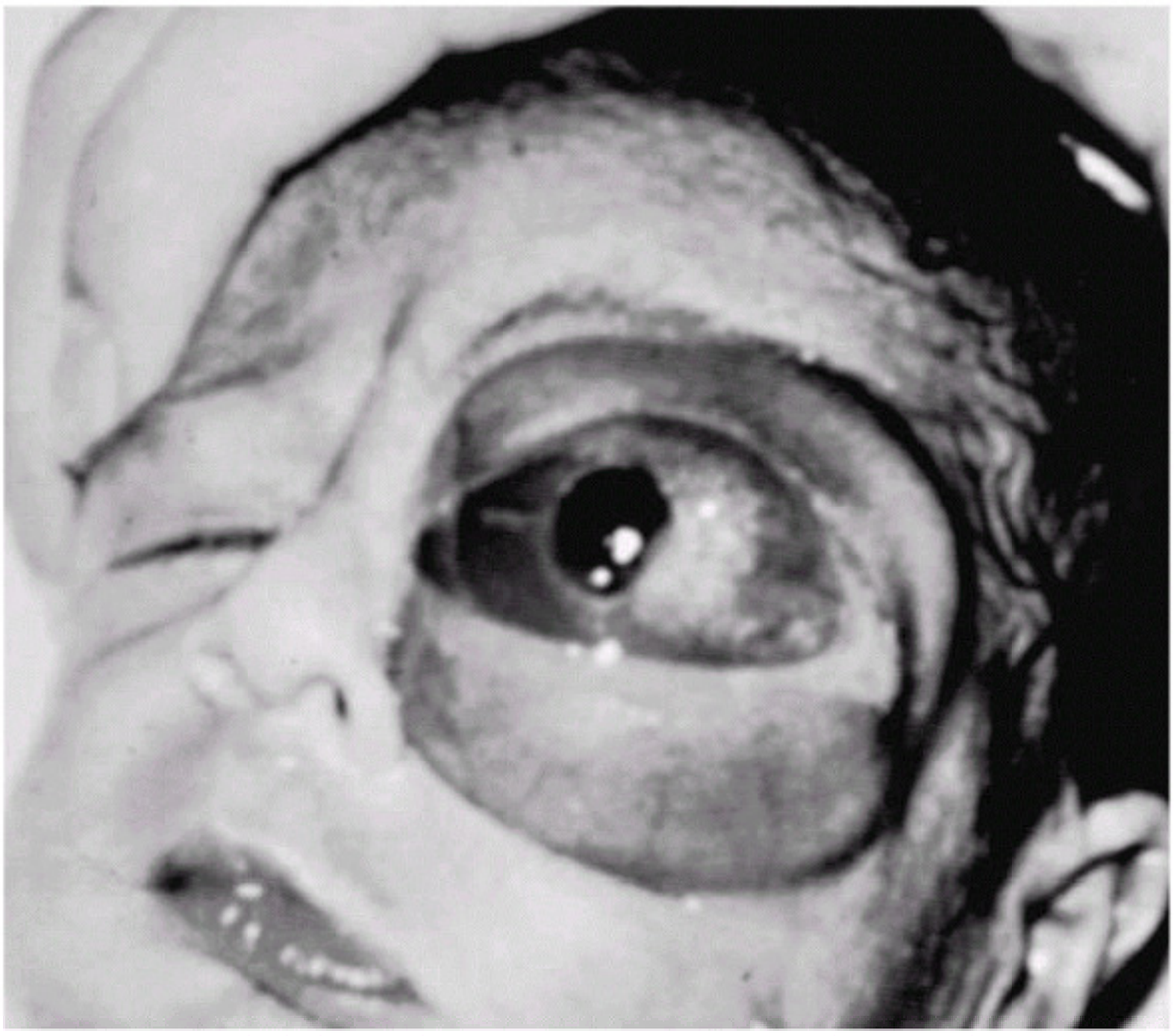

Figure 20.34 Teratoma producing massive exophthalmos at birth.

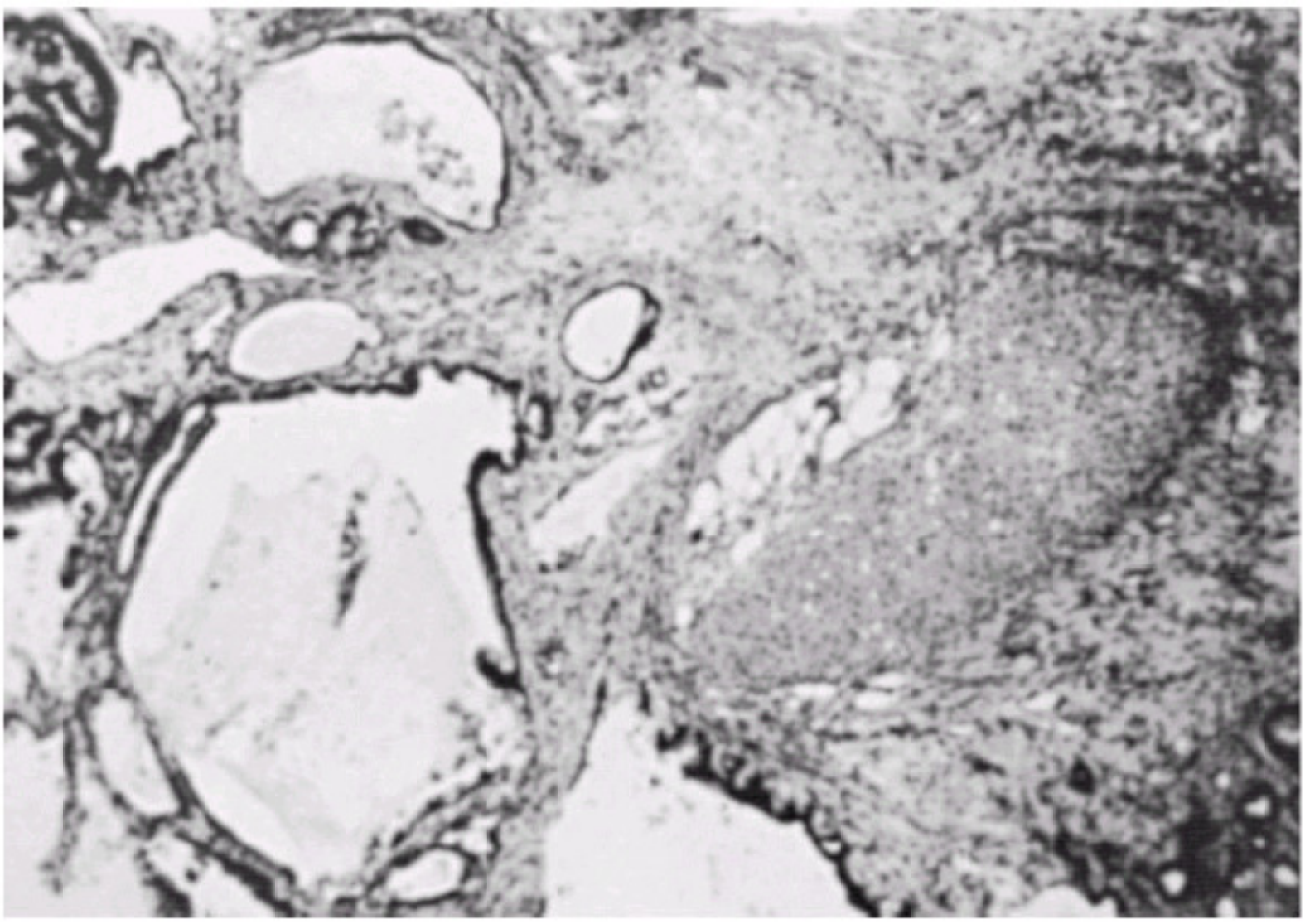

Figure 20.35 Teratoma displaying areas of cartilage formation, brain tissue, and epidermoid cysts.

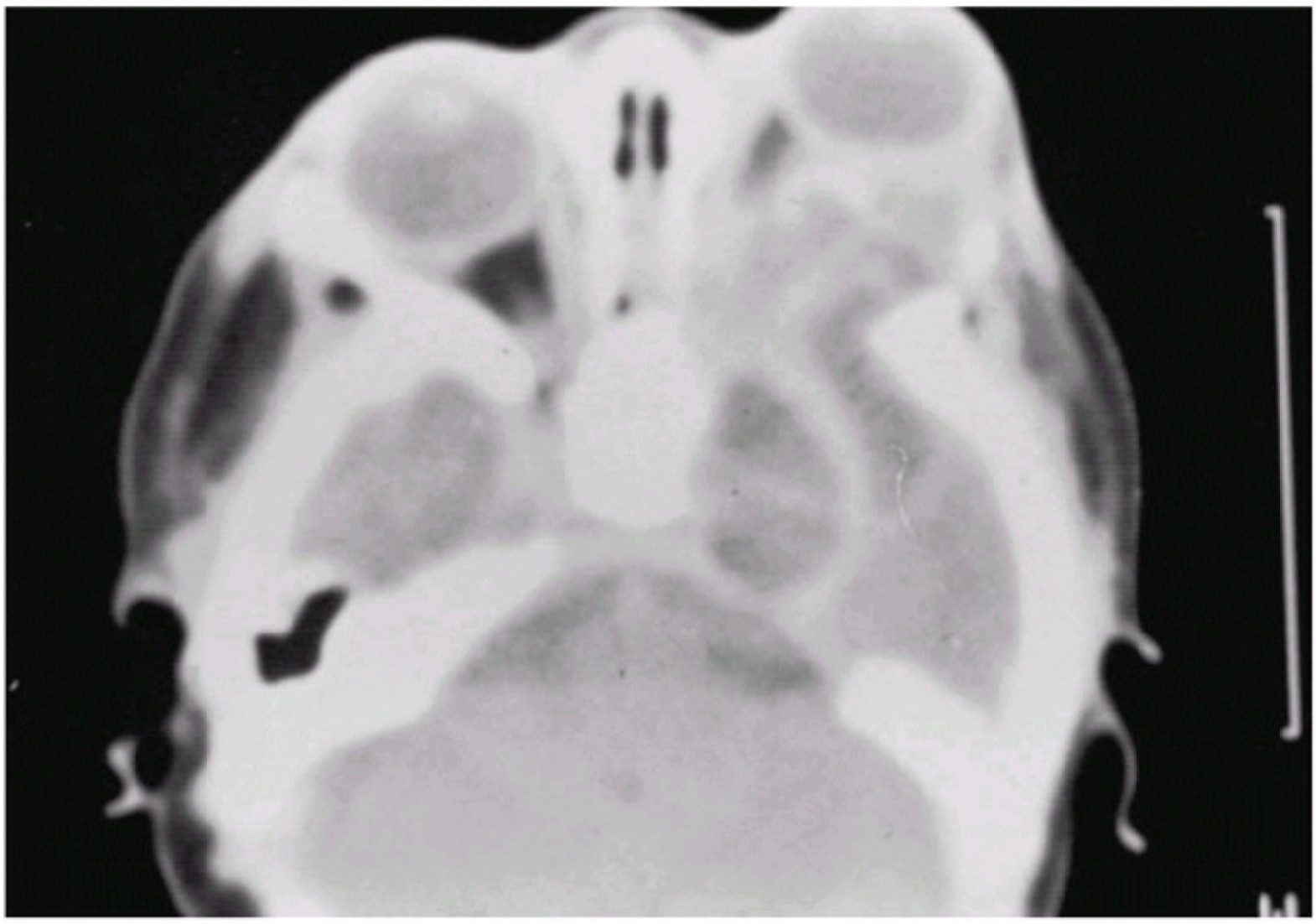

Figure 20.36 Axial computed tomography scan reveals a defect of the sphenoid bone with a large heterogeneous cystic mass extending from the orbit intracranially.

Capillary Hemangiomas

Capillary hemangiomas occur primarily in infants during the first year of life and are the most common periocular tumor of childhood. It is usually not present at birth but appears in the first week or two after birth, increasing its vascularization dramatically over the first 6 to 12 months of age (Fig. 20.37), with an infiltrative growth pattern that can involve all orbital structures. When the tumor involves the skin, it is commonly called a strawberry nevus because of the reddish coloration and irregularly dimpled surface (Figs. 20.38 and 20.39). The clinical appearance depends on the depth of the tumor under the skin. Most have both cutaneous and subcutaneous components. The subcutaneous portion can extend into the orbit causing displacement of the eye or proptosis. The lesions may be multiple and primarily involve the head and neck regions. When they occur in the eyelid and/or orbit, they may cause ptosis, globe displacement, proptosis, strabismus, or astigmatism; therefore, it is important to monitor these patients for amblyopia and perform a cycloplegic refraction. When amblyopia is present, occlusion therapy and glasses are indicated until treatment is completed. Capillary hemangiomas are soft and blanch on gentle pressure. Although benign, these tumors are unencapsulated and hypercellular but invasive lesions. Initially they are cellular lesions composed of proliferating capillaries with little intervening stroma with lumina that may be difficult to visualize. Later, the capillaries become dilated and filled with red blood cells, and fibrosis and fat are found in the stroma. They are composed of endothelial cells that form capillary-like spaces (Fig. 20.40).

When the orbit is involved, there may be a bluish discoloration or no skin changes, but they do present as a progressively enlarging mass. The rapid growth may suggest a rhabdomyosarcoma, but the diagnosis may be differentiated by

the presence of a soft mass that increases in size and assumes a blue or purplish discoloration when the child cries or strains, due to vascular engorgement (Figs. 20.41 and 20.42). The tumors most commonly occur in the superior aspect of the orbit. Lesions that involve the neck can compromise the airway and lead to respiratory obstruction. Multiple large visceral capillary hemangiomas can lead to sequestration of thrombocytes and red blood cells, causing a thrombocytopenia and bleeding diathesis, the Kasabach-Merritt syndrome.

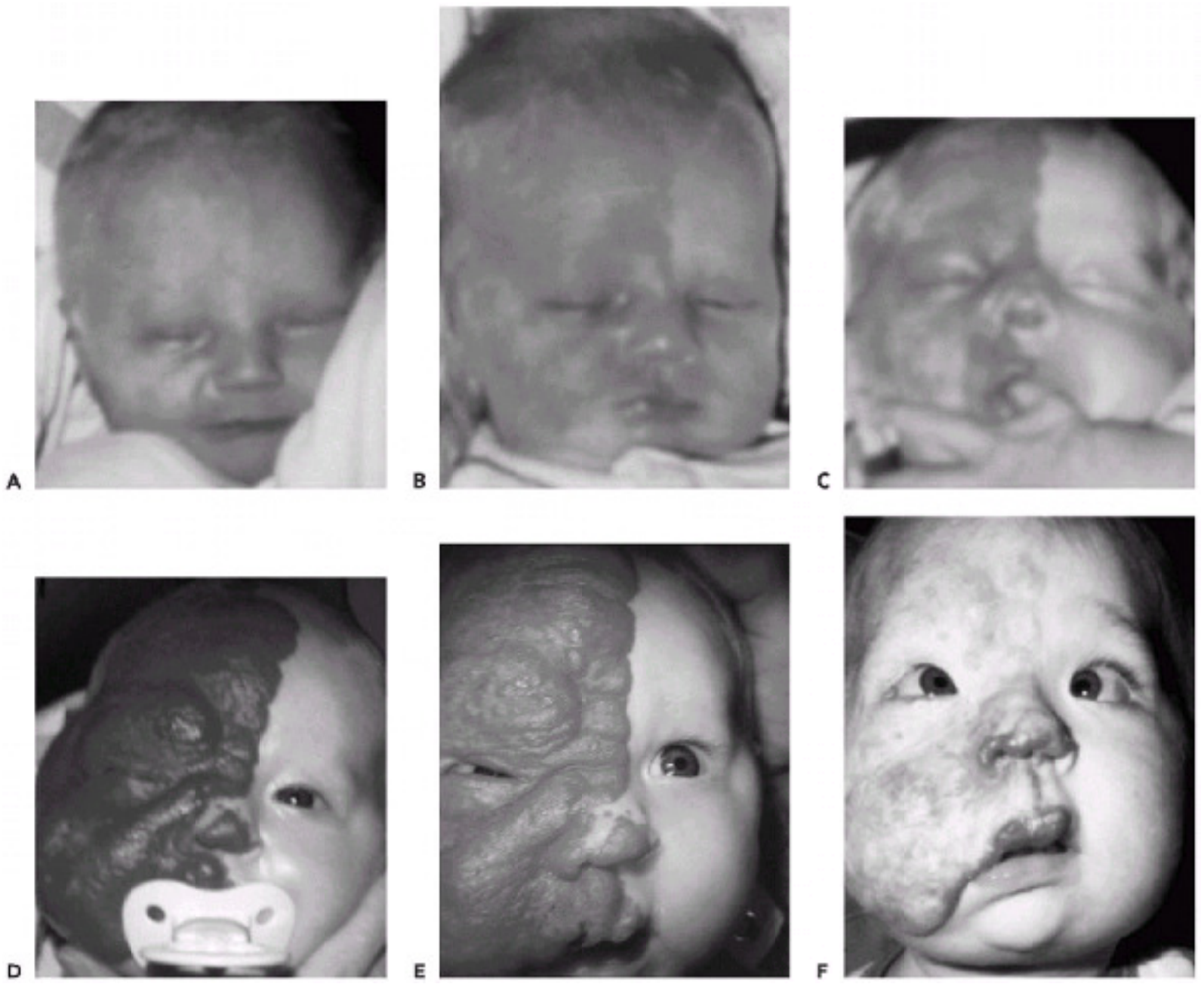

Figure 20.37 Evolution of a capillary hemangioma. **A:** 4 days old. **B:** 8 days old. **C:** 15 days old. **D:** 10 weeks old. **E:** 24 hours after first steroid injection. **F:** 1 year after intralesional injections and systemic steroids.

Capillary hemangiomas, if untreated, have an initial growth phase, usually for up to 6 to 12 months, a stable phase, and then a spontaneous involution phase, usually after 1 year up until age 8. They often increase remarkably in size during the first 6 months of life and then gradually diminish. The majority of the vessels disappear, but the larger veins persist. After the first year, these vascular tumors will involute, and 75% of the lesions resolve in the first 4 to 5 years of life. In rapidly proliferating lesions, ulceration, necrosis, bleeding, and infection can occur. As the growth becomes smaller, the reddish color fades to a light gray and the mass is less compressible.

When the skin is involved, a capillary hemangioma should be differentiated from a nevus flammeus, which may be part of the Sturge-Weber syndrome (encephalotrigeminal angiomatosis). A nevus flammeus is a deeper purple and does not blanch on pressure; it does not regress with age but grows with the child and is frequently accompanied by glaucoma on the side of the nevus and buphthalmos; CNS signs, such as seizures and contralateral hemiparesis due to the angiomatosis of the leptomeninges; and radiographic skull changes of intracranial calcification of the angiomatosis.

CT and MRI scans of these lesions demonstrate the margins

to vary from moderately well defined to infiltrating masses. They may involve any compartment, both intraconal and extraconal, preseptal and postseptal. Intravenous contrast causes a moderate to intense enhancement, which can be homogeneous or nonhomogeneous. On T1-weighted MRI, capillary hemangiomas have a low signal intensity compared to fat, and a high signal intensity to the extraocular muscles. On T2-weighted MRI, they have a high signal intensity with respect to fat and extraocular muscles, and there may be areas of flow voids (Fig. 20.41). Angiography will often demonstrate multiple small feeding vessels from both the ophthalmic artery and external carotid system.

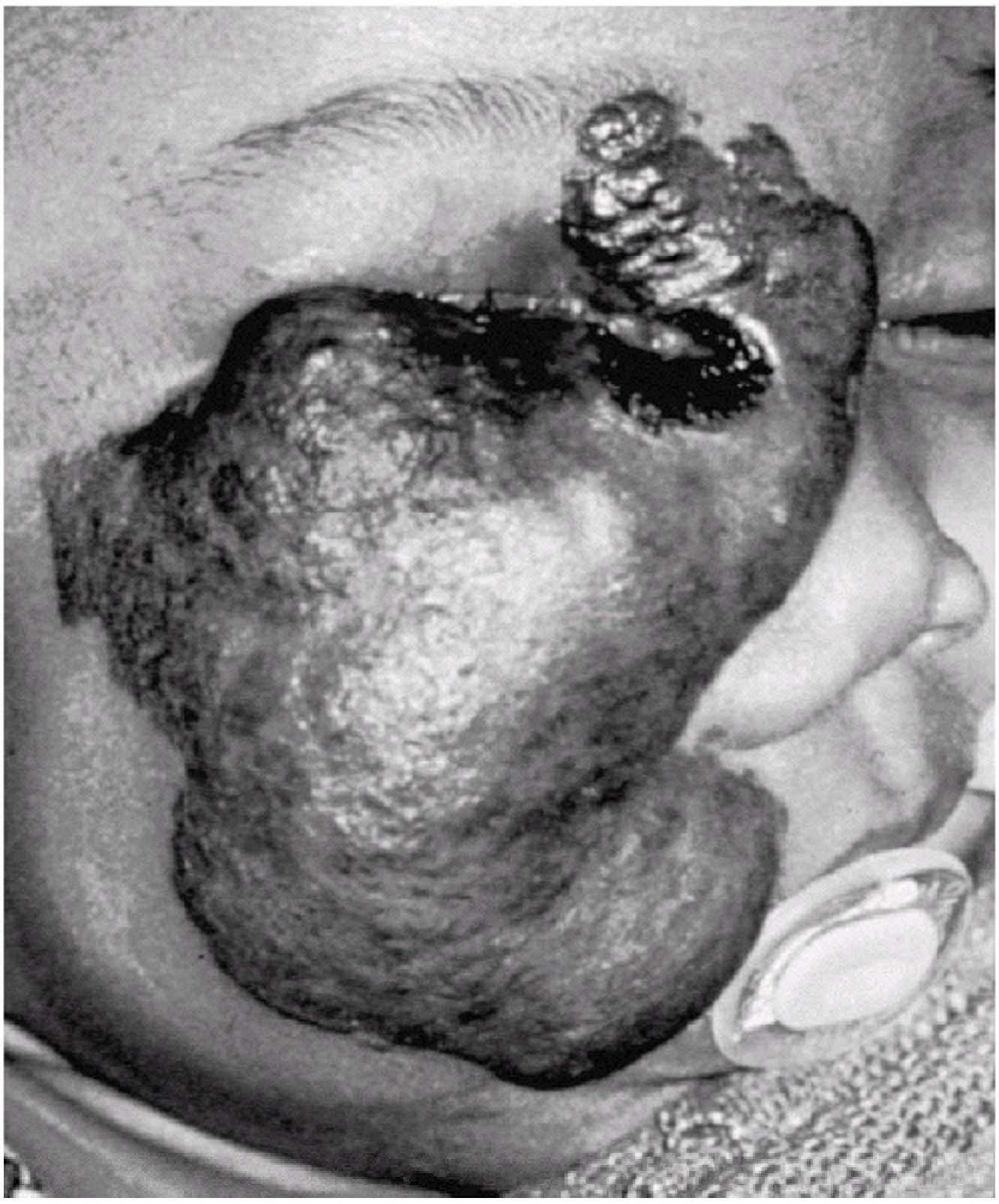

Figure 20.38 Large capillary hemangioma blocking the visual axis.

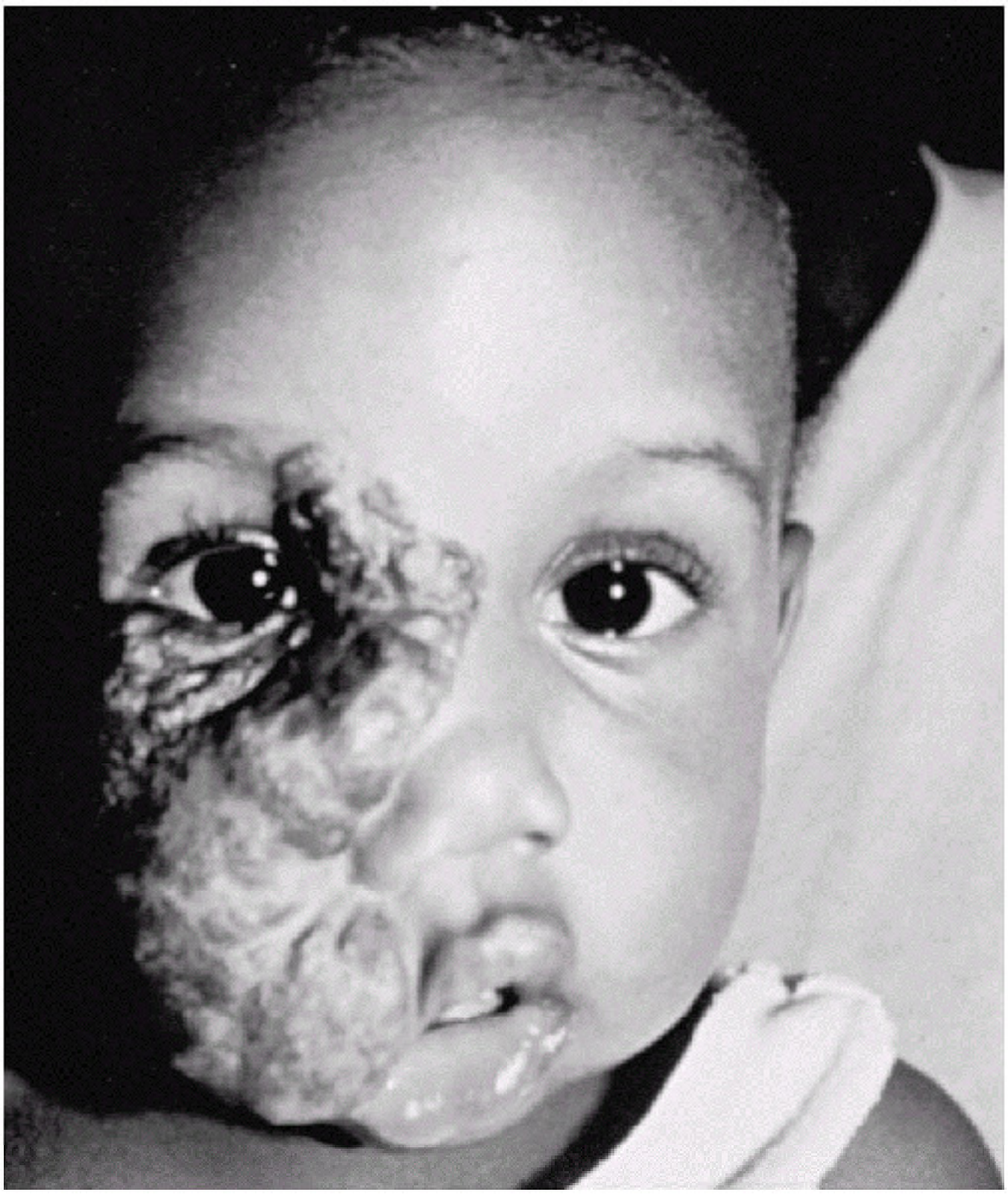

Figure 20.39 The same capillary hemangioma as in Figure 20.38 after intralesional steroid injection.

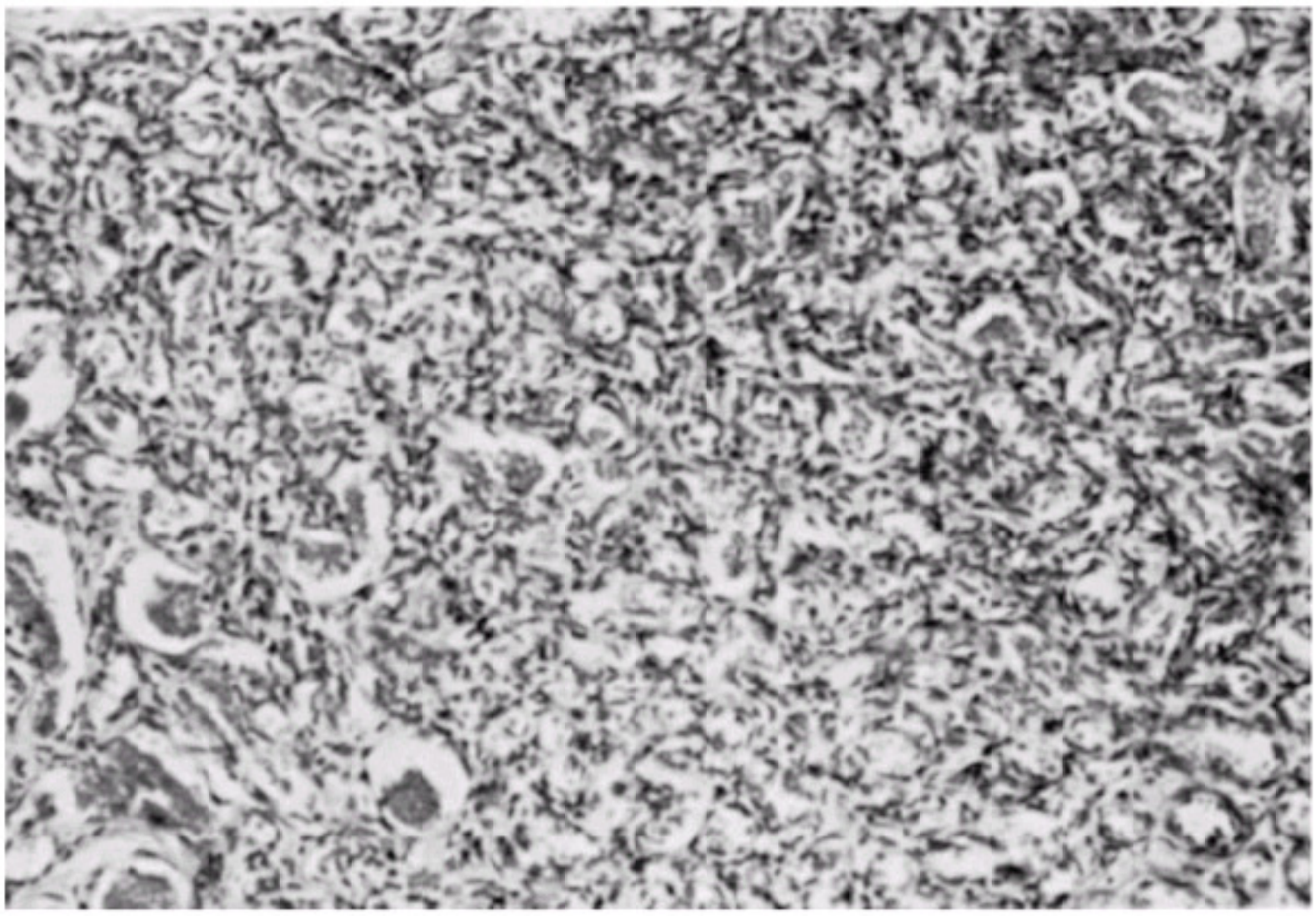

Figure 20.40 Hematoxylin-eosin stain demonstrating capillary-like spaces lined by endothelial cells.

Conservative treatment is usually best since there is a strong tendency for this kind of lesion to undergo spontaneous regression. Many are small, do not cause visual symptoms, and regress spontaneously. The therapeutic approach depends on location, rapidity of growth, deformities, destruction of tissue, and obstruction of vital functions. Treatment must be considered when complications develop, such as deprivation amblyopia, strabismus, or anisometropia, resulting from the swollen, closed lid. After the regression phase, if the lesion is flat, makeup can camouflage it. A variety of therapeutic options, depending on location, depth, and age, are available for lesions that require treatment; options include systemic, topical, and intralesional corticosteroids. The mechanism of action of steroids on these lesions is not fully understood, but they may stimulate vasoconstriction. The possible side effects of corticosteroids include gastritis, Cushing syndrome, retrobulbar hemorrhage, ocular penetration, retinal and/or choroidal embolization, and eyelid necrosis. Interferonalfa, an angiogenesis inhibitor has had some success for lesions not responding to steroids. Lasers and surgical procedures have limited application. Cutaneous laser therapy can reduce the remaining vessels significantly. If the lesion was significantly elevated, a crepe paper appearance to the skin may remain. Systemic and/or intralesional corticosteroids may be effective and should be tried with the help of a pediatrician. Cryotherapy and sclerosing solutions have limited usefulness. In rare instances of circumscribed lesions,

excision is indicated. There is no capsule surrounding these hemangiomas, but a safe excision can be performed with the appropriate use of cautery (Fig. 20.41).

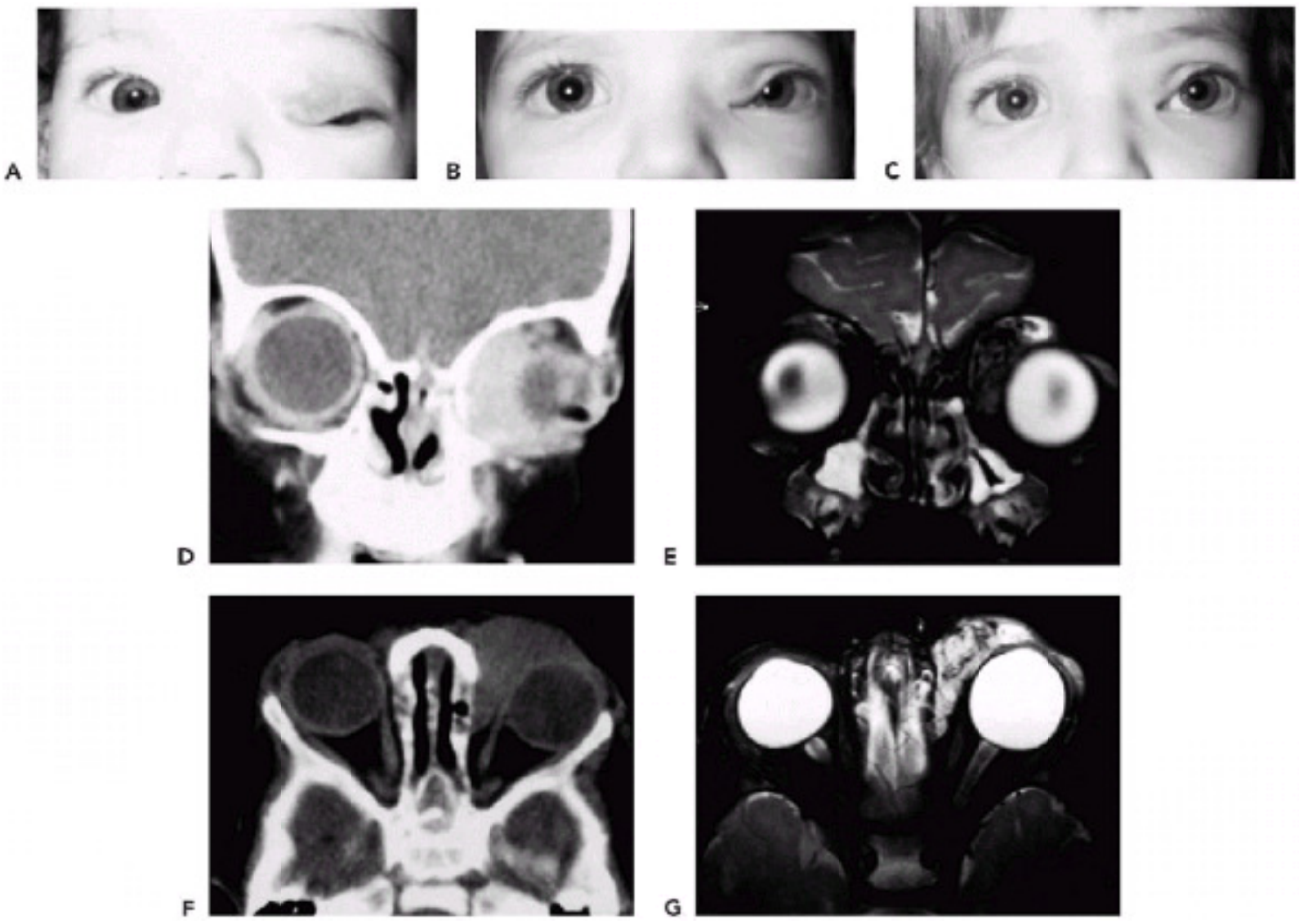

Figure 20.41 A: Deep capillary hemangioma of the left upper lid and orbit, with minimal overlying skin changes. **B:** 1 year after two intralesional steroid injections. **C:** 3 months after surgical excision of the capillary hemangioma. **D:** Coronal computed tomography (CT) scan demonstrating involvement of the medial and superior orbit. **E:** Coronal magnetic resonance imaging (MRI) scan demonstrating same lesion. **F:** Axial CT demonstrating the lesion. **G:** Axial MRI demonstrating the lesion.

Intralesional corticosteroids can be very helpful, especially for capillary hemangioma of the upper lid causing an amblyopia. A combination of a long-acting steroid (e.g., triamcinolone 40 mg/mL) and short-acting steroid (e.g., betamethasone 6 mg/mL) is injected directly into the lesion with a 23-gauge needle. The needle is placed into a few areas of the lesion, withdrawn first, and then injected. There is a small risk of embolization of the depot material into a vessel, which could result in a central retinal artery occlusion. Local complications secondary to steroid injections include eyelid necrosis, linear subcutaneous fat atrophy, local fat atrophy, and central retinal artery occlusion. Systemic complications of adrenal suppression, addisonian crisis, which can be life threatening, are more common, serious, and prolonged the younger the infant is. Rarely, failure to thrive has been reported following steroid injections. Pretreatment baseline measurements of cortisol and growth parameters, as well as poststeroid injection measurements, should be performed in conjunction with a pediatrician, especially one with endocrinology expertise. Most lesions will involute with one injection, but occasionally a second injection may be required if the response was not adequate. The corticosteroids probably act by rendering the tumor's vascular bed more sensitive to the body's circulating catecholamines. Side effects include necrosis of the overlying skin, subcutaneous fat atrophy, systemic growth retardation, and embolic visual loss.

For large hemangiomas, or orbital lesions, oral corticosteroids (e.g., prednisone 1 to 2 mg/kg/day) may be required. Systemic corticosteroids should be administered under the guidance of a pediatrician since the side effects and steroid dependence must be monitored. The response is often complete in 6 weeks, except in the growth phase when an increase in the size of lesion may be seen as the dose is tapered off. Smaller lesions that are refractory to corticosteroids may require surgical excision, but meticulous hemostasis must be obtained. The ophthalmologist should be aware that capillary hemangiomas in and around the orbit usually have a high blood flow derived from multiple

fine feeder arterial vessels from the internal and/or external carotid artery and are capable of bleeding profusely if surgical excision is performed.

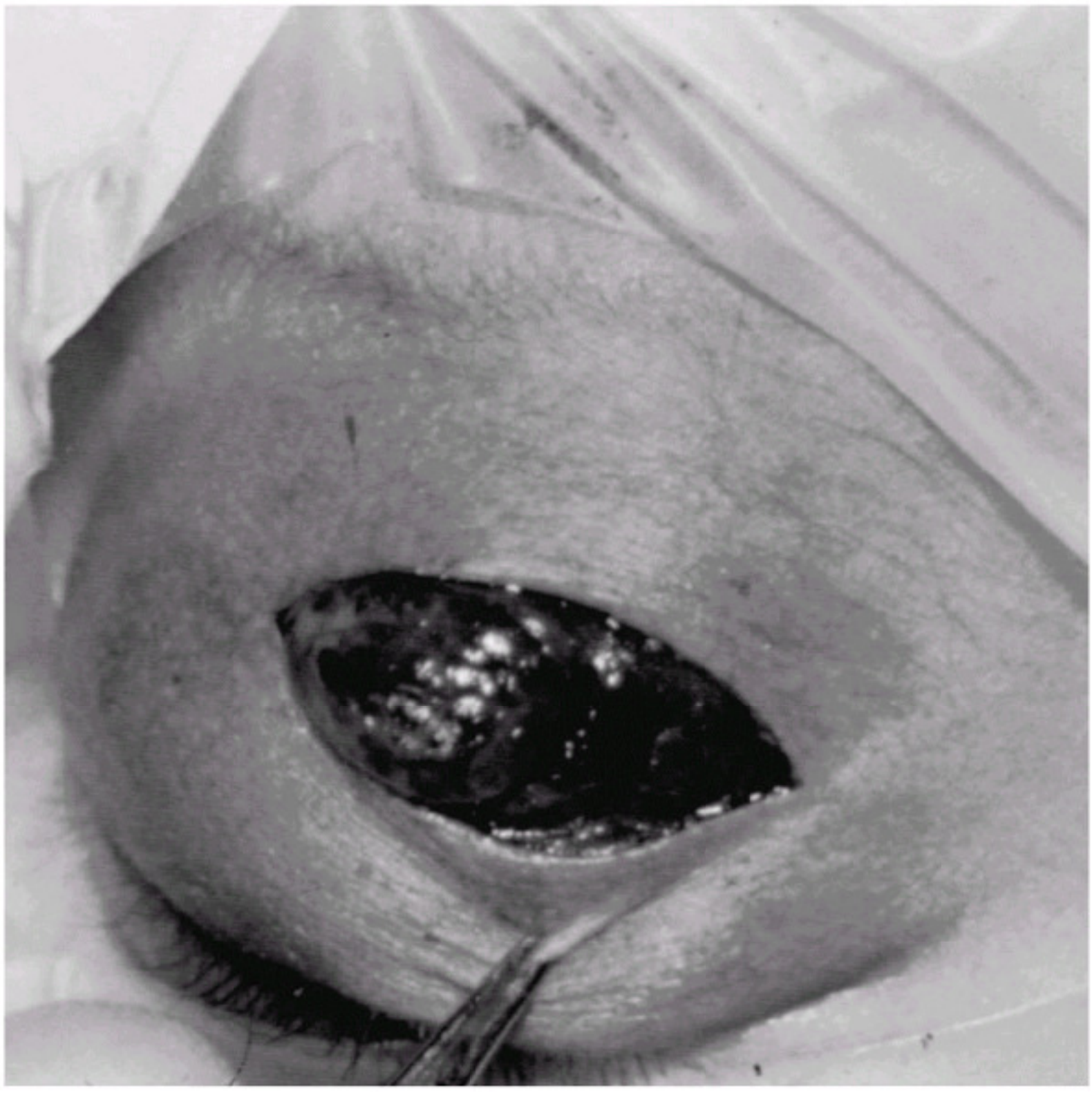

Figure 20.42 In cases of capillary hemangioma without overlying skin changes, biopsy is required to rule out rhabdomyosarcoma.

There are questionable benefits of systemic interferon and antifibrinolytic agents. Radiation therapy should not be used due to the potential secondary effects of cataract formation, bony hypoplasia, and future malignancy. Pulsed-dye laser therapy may improve the superficial component of these lesions, but the effect on the deeper component of these lesions is unclear. Sclerosing solutions should not be used due to the severe scarring that is created. Reconstructive or cosmetic surgery for skin redundancy and deformities should not be performed until complete resolution of the lesions is achieved.

When confined to the dermis, these lesions are termed superficial infantile capillary hemangiomas, the strawberry nevi. Their growth pattern and resolution are similar to capillary hemangiomas, and can occur anywhere on the body. As they involute, fine stellate areas of pale scarring may be noted in a previously vascular area, the herald spot.

Cavernous hemangiomas are the most common benign orbital tumor in adults.

Lymphangiomas

Lymphangiomas are typically diffuse, unencapsulated choristoma tumors that infiltrate normal tissues of the lid and orbit and usually become clinically apparent in the first decade of life. They are generally multilobular and easily compressible, and may involve the conjunctiva, eyelids, orbit, oropharynx and sinuses, and rarely spread intracranially. Proptosis tends to occur early and may appear shortly after birth. The natural progression is variable and unpredictable. Some are small and localized and slowly progressive, and others may diffusely infiltrate the orbital structures and enlarge relentlessly. They may be exacerbated by viral upper respiratory infection secondary to a response of the follicles of lymphoid tissues located in the interstitium. The female-to-male ratio is approximately 3:1, and the tumors show a predilection for the superior and inferior nasal aspects of the orbit.

Lymphangiomas contain a variable amount of reactive lymphoid tissue and tend to increase in size with upper respiratory tract infections, which is also a characteristic of other lymphoid tissues. Biopsy of rapidly expanding lesions of the orbit and lids is indicated to rule out a rhabdomyosarcoma. The histogenesis remains unclear, but they are thought to represent a combined vascular malformation with both venous and lymphatic components. Lymphangiomas are characterized by slow, indolent growth, with acute exacerbations occurring over minutes to a few hours secondary to spontaneous or traumatic hemorrhage. The thin walls of the lymphatic channels rupture spontaneously or with minor trauma, creating blood-filled cysts (the so-called chocolate cysts), which contain old, dark blood. Patients normally have pain due to the rapid distention of the orbital tissues. There is no connection with the lymphatic or vascular system so no pulsation is present. Patients may also have secondary induced ptosis, glaucoma, optic nerve compression, and strabismus, along with proptosis (Figs. 20.43, 20.44, and 20.45). Significant astigmatism may develop on the affected side because of the posterior pressure on the globe. Amblyopia can result in significant visual loss. Lymphangiomas are also found in other parts of the body such as the cheek, eyebrow, eyelids, roof of the mouth, and scalp. Involvement of the sinuses and oropharynx with these venous anomalies can result in severe nosebleeds.

CT demonstrates an unencapsulated infiltrative lesion that can extend across the orbital spaces into many tissues, with variable densities, creating a heterogeneous mass. Cystic spaces containing blood, plasma, or lymphatic tissue

may be present. This alternately solid and cystic component in a child's tumor is typical of a lymphangioma (Fig. 20.46). Noncontiguous intracranial vascular malformations have been reported in up to 25% of patients, and therefore imaging of the brain should be performed to detect these asymptomatic CNS lesions since they may subsequently bleed.

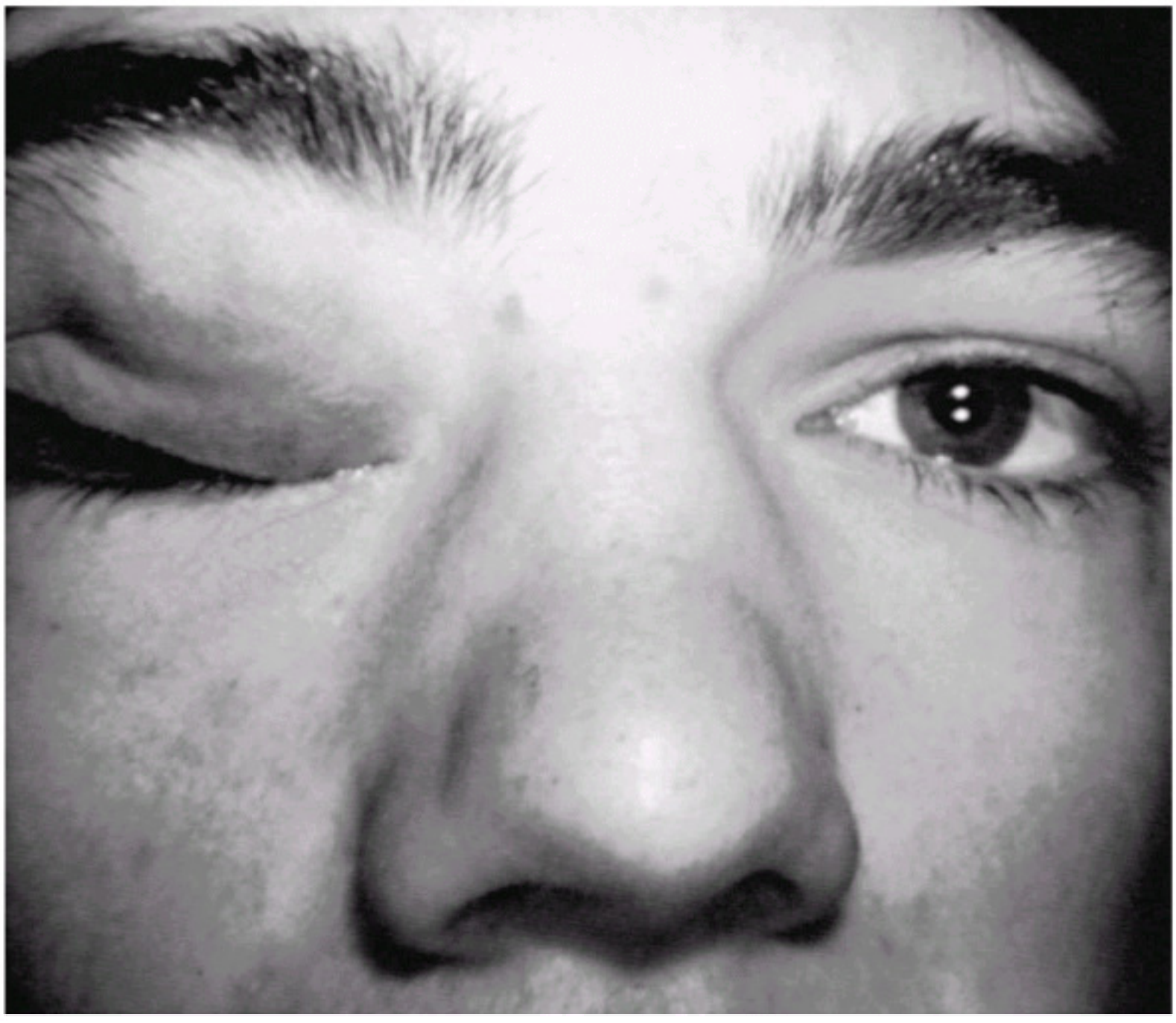

Figure 20.43 Lymphangioma of the superonasal orbit with associated ptosis and proptosis.

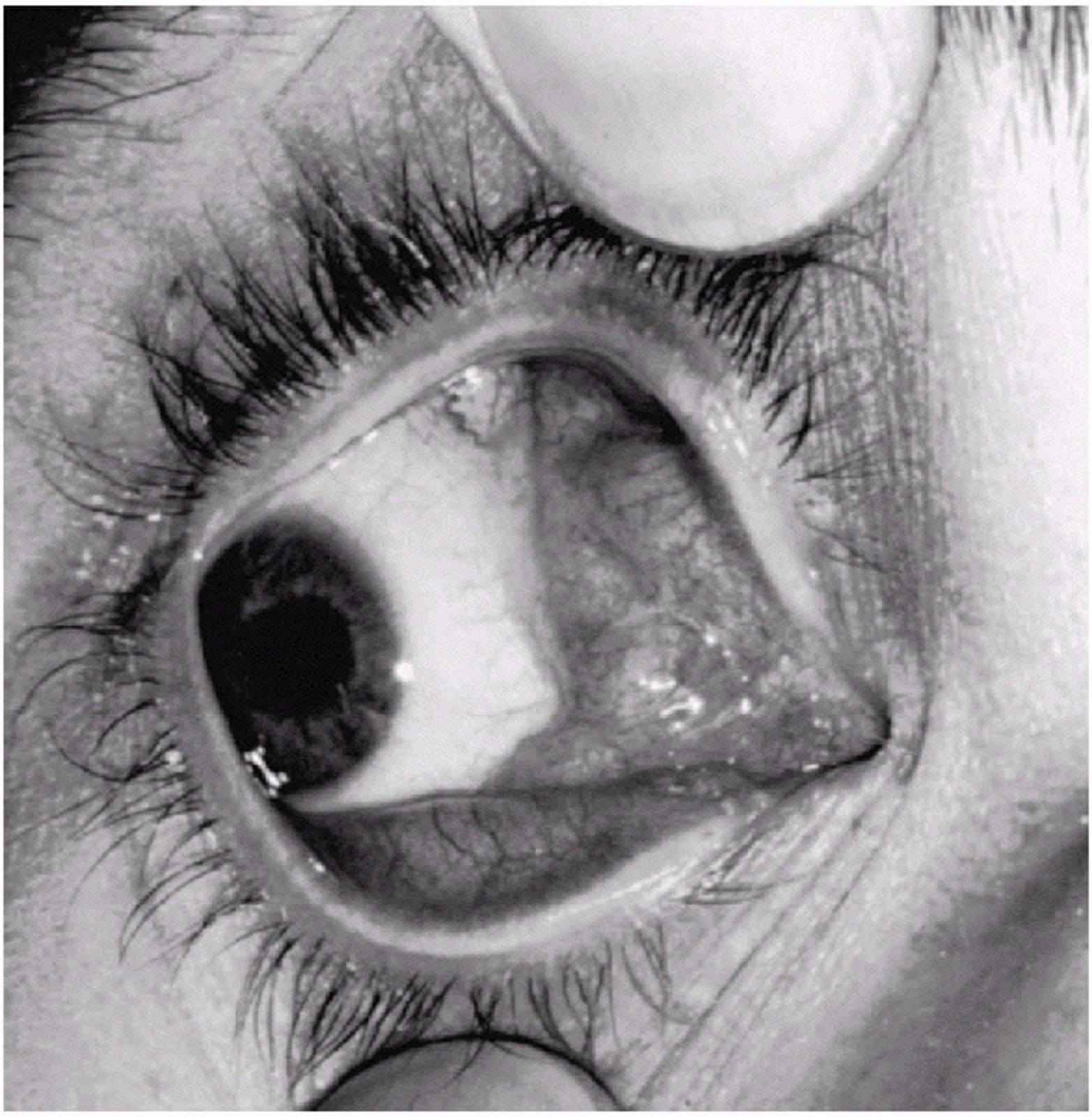

Figure 20.44 Lymphangioma with typical cystic conjunctival involvement.

Lymphangiomas are composed of irregularly sized and shaped dilated, serum-filled, thin-walled vascular channels lined with flattened endothelium in a loose fibrous stroma that contains bundles of smooth muscle and collections of lymphocytes. The endothelial spaces have no pericytes or smooth muscle in their walls. Scattered follicles of lymphoid tissues are located in the interstitium. The stroma has a variable amount of connective tissue that may exhibit evidence of scarring, hemosiderin deposition, and cholesterol clefts from previous hemorrhagic episodes. Thrombosis and calcification may be present. The tumors have an infiltrative growth pattern and are not encapsulated. The vascular channels are partially filled with proteinaceous and homogeneous eosinophilic fluid material (Fig. 20.47).

Figure 20.45 Lymphangioma, recurrent, with recent hemorrhage.

These tumors are often progressive from early childhood until midadolescence. Older patients appear to stabilize and have fewer of the acute manifestations commonly observed in children. The tumors do not regress, as do infantile capillary hemangiomas. There is no medical treatment available at present. Radiation therapy has been shown to be ineffective, which suggests that there is no significant lymphocytic composition in the tumor. Sclerosing solutions may add to the complications and should be avoided.

Complete surgical excision is not possible due to the infiltrative intertwining pattern of growth, and care should be taken to avoid damage to the normal functionally important orbital structures. Surgical debulking of the tumor is the best treatment presently known, but it is not always satisfactory and often requires repeated procedures; however, it may be considered when recurrent orbital hemorrhage compromises the globe or optic nerve, for marked proptosis and exposure complications, or when they cause a significant cosmetic deformity. Bleeding may result from minimal trauma with rupture of a component vessel, or possibly spontaneous hemorrhage from fragile neovascular tufts. Acute hemorrhage may cause optic nerve compression and require urgent surgical management. After hemorrhage, excision of the blood cyst is possible, but spontaneous regression is common. In emergency situations after hemorrhage into the cyst, causing visual compromise, aspiration of blood through a large bore needle or surgical excision is indicated. There is a high incidence of recurrent hemorrhage. Radical surgery is rarely advisable since the lesion is diffuse and does not respect tissue planes, but surgical debulking may be necessary to reduce the mass effect when recurrent orbital hemorrhage compromises the globe or optic nerve or when cosmetic deformity is significant. Postoperative drainage is recommended. The surrounding orbital tissues are occasionally scarred and interdigitate with the malformation, making differentiation of normal and abnormal tissues difficult during surgery. Bleeding is common, and one must guard against excising adjacent functioning normal structures. The patient and family must be informed of these possible and probable residual defects. The anteriorly located lesions are often diffusely infiltrative into the orbital tissue; some posterior lesions remain more localized and are more amenable to total or subtotal excision. Since the lesions do not respect tissue planes, portions of the tumor must be left to avoid damage to important normal structures. Fortunately the growth of most lymphangiomas is self-limited, but a few will continue to grow, becoming unsightly.

Systemic corticosteroids have been used with some success for symptomatic relief, loss of vision, motility dysfunction, decrease of inflammation and swelling, and pain relief. Systemic corticosteroids may cause a reduction of lymphoid hypertrophy, stabilizing the vasculature to decrease hemorrhage and fluid osmosis into the tissues, and causing the channels to involute, as seen with capillary hemangiomas. Corticosteroids used in children seems to

have a better effect on proptosis and mass effect than in the adult, possibly because the tumor mass is more actively enlarging, as seen in the treatment of capillary hemangiomata.

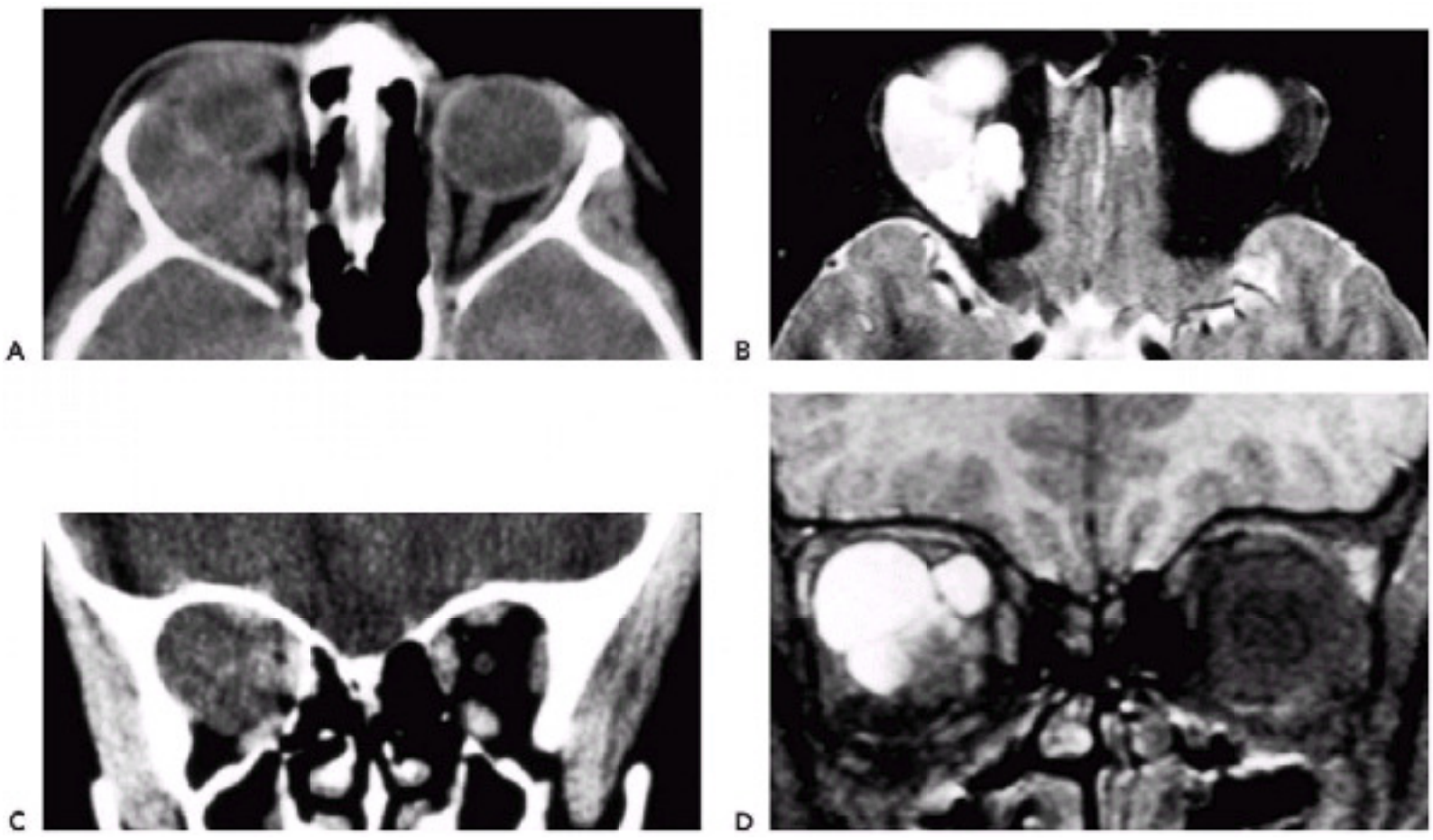

Figure 20.46 Axial and coronal computed tomography (CT) and magnetic resonance imaging (MRI) scans of a lymphangioma demonstrating a diffuse, infiltrating cystic lesion. **A:** Axial CT scan. **B:** Axial MRI of the same lesion. **C:** Coronal CT scan **D:** MRI scan of the same lesion.

Arteriovenous Malformations

Arteriovenous malformations are developmental anomalies of anastomosing arteries and veins without intervening capillaries. They can be spontaneous, caused by degeneration or traumatic fistulae, hemodynamically high or low flow, and angiographically direct or dural fistulae that flow in a retrograde fashion. Some may cause dilated corkscrew episcleral vessels (Fig. 20.48). Selective interventional radiographic occlusion of the feeding vessel may be followed by surgical excision.

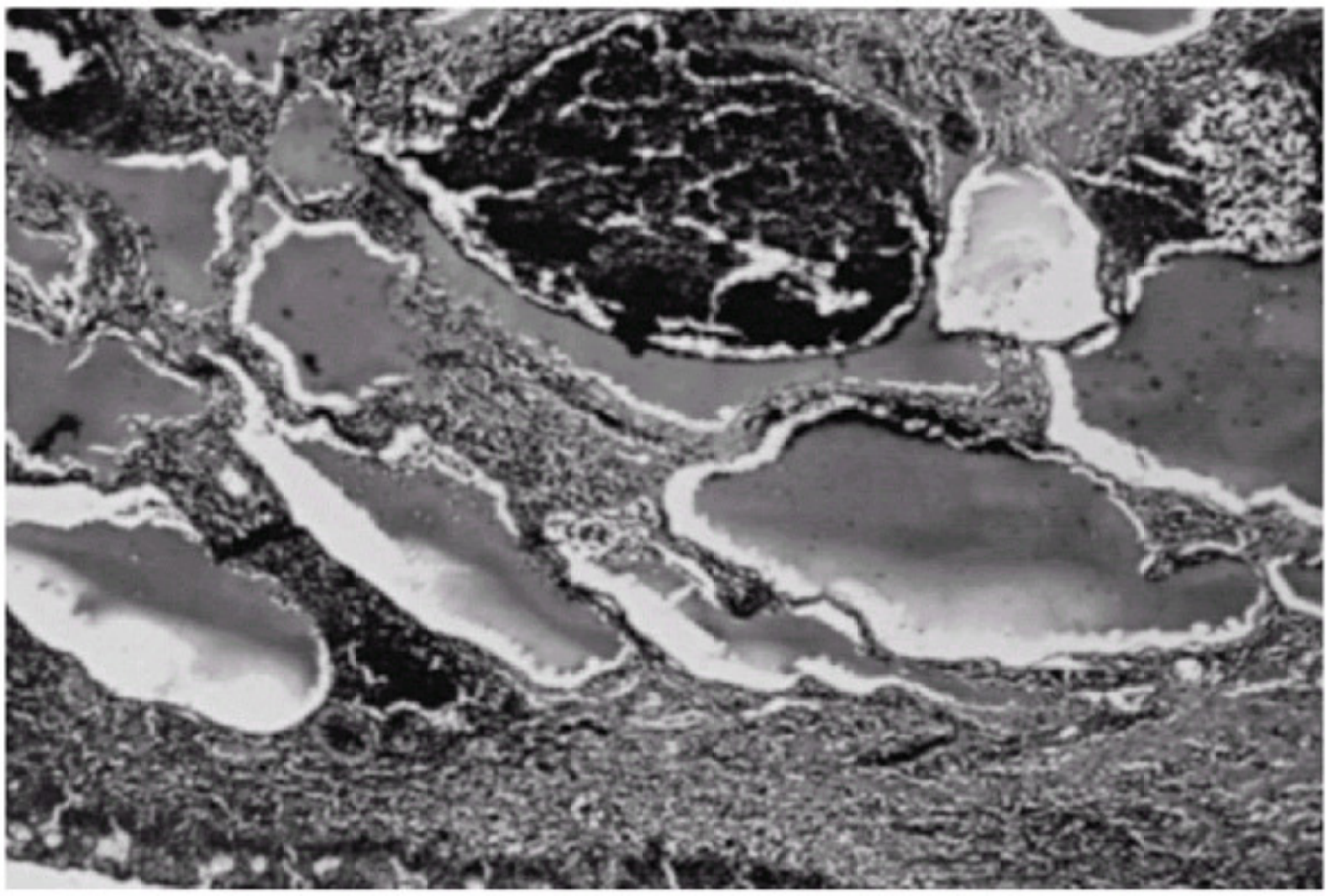

Figure 20.47 Hematoxylin-eosin stain of a lymphangioma revealing dilated, thin-walled vascular channels lined with endothelium. The stroma is filled with a lymphocytic infiltrate and connective tissue, with evidence of scarring and hemosiderin deposition from previous hemorrhages.

Carotid cavernous fistulae, which are communications of the internal carotid artery and cavernous sinus, are the most common malformations. The ophthalmic findings and symptoms depend on the site, degree of shunting, and volume of flow. High-flow fistulae may result in orbital edema, chemosis, increased episcleral venous and intraocular pressures, retinal vascular dilatation, retinal venous stasis, pulsatile exophthalmos, and bruits. The patient may have the characteristic corkscrew episcleral vessels with a bruit. There may be a pulsating proptosis present. Ocular damage is due to the ischemia caused by the diversion of arterial blood to the venous system, and the increased venous pressure in the cavernous sinus. Lateral rectus muscle palsy may be caused by a compression of sixth cranial nerve in the cavernous sinus. Low-flow shunts may present with lesser signs and symptoms of edema and vascular dilatation with or without an increase in the intraocular pressure. Interventional radiography with various embolic materials to occlude the feeding artery may be used in the treatment of these vascular lesions.

Dural carotid cavernous fistula is an abnormal connection between the meningeal branches of the internal and/or external carotid arteries and cavernous sinus. The communication

can be from the intracavernous branches of the internal carotid artery, meningeal hypophyseal, or artery of the inferior cavernous sinus, or from the external carotid artery, internal maxillary, and ascending pharyngeal, which provide the meninges in the region of the cavernous sinus. Up to 50% of dural carotid cavernous fistulae close spontaneously.

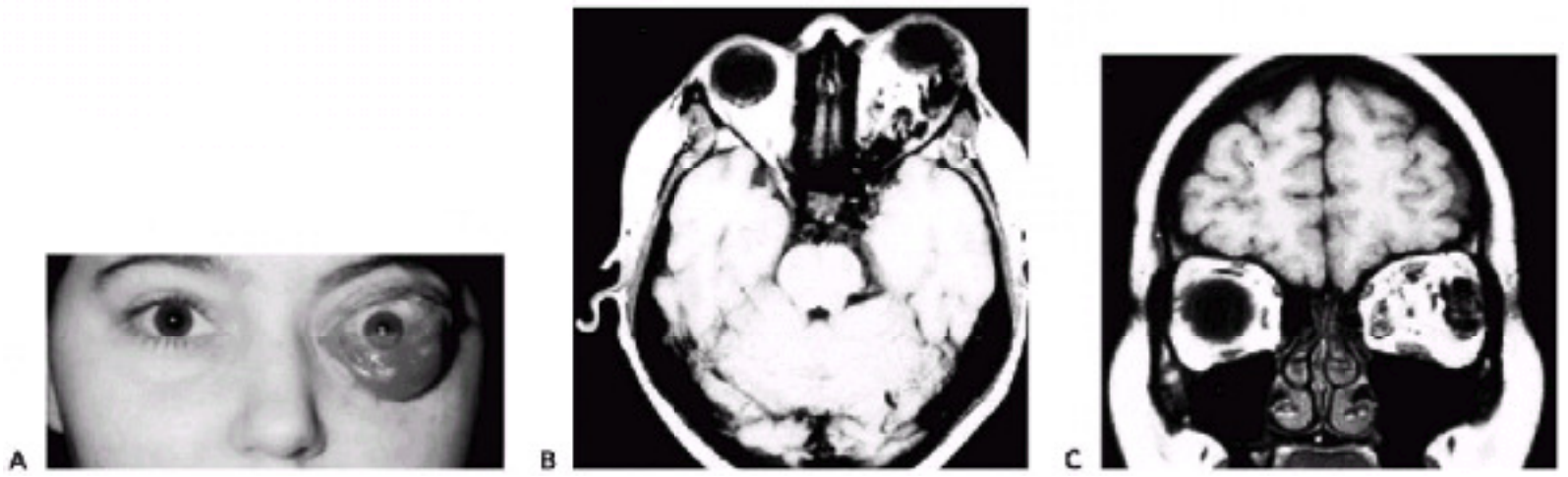

Figure 20.48 A hemodynamically high-flow arteriovenous malformation (A) causing a marked proptosis, conjunctival chemosis, exposure keratitis, and loss of vision. **B:** Axial magnetic resonance imaging (MRI) scan demonstrating marked orbital involvement, cavernous sinus, and brainstem. **C:** Coronal MRI scan of the same lesion.

CT and MRI scans may show dilatation of the superior ophthalmic vein, increase in the extraocular muscles, or enlargement of the cavernous sinus. Bilateral selective internal and external carotid angiography will identify the pathology; since the clinical presentation is not always on the side of the defect, there may be bilateral involvement. The scans will determine if the fistula is from the internal, external, or both carotid systems.

Orbital Varices

Varices are unusual vascular formations characterized by variable and transient proptosis increased by crying, coughing, sneezing, Valsalva maneuver, or placing the head in a dependent position for 5 seconds (Fig. 20.49). They occur primarily as dilations of preexisting venous channels. The proptosis may also be exaggerated with pressure on the jugular vein. Thromboses of elements within the varix produce episodes of swelling followed by shrinkage. Acute orbital hemorrhage may necessitate drainage. X-ray studies may indicate the presence of calcified thrombi, phleboliths, as a diagnostic aid. Contrast media studies of the orbital vessels may be the most useful in defining the extent of the lesion. Rapid spiral CT performed while decreasing the venous return, as during the Valsalva maneuver or dependent positioning, will demonstrate the characteristic enlargement of the engorged varix (Fig. 20.50). MRI, MRA, and Doppler echography may also demonstrate these lesions. Orbital venogram with direct injection, through proximal veins or intralesionally, may demonstrate ecstatic dysmorphic vessels flowing out through normal venous channels or, more commonly, saccular arrangement of malformed vessels extending out through multiple venous

outflow channels to the pterygopalatine fossa, face, and cavernous sinus. As with lymphangiomas, spontaneous orbital hemorrhage, strabismus, and optic nerve compression may occur. Treatment is usually conservative, except for lesions that threaten vision due to optic nerve or globe damage, pain, cosmesis, or progressive expansion. Complete excision is difficult because the varices often connect to the cavernous sinus through multiple channels, are tortuous with fragile, thin walls that tend to rupture and bleed excessively, and intertwine with normal orbital structures. Partial excision or embolization may provide adequate improvement of symptoms or reduce the vascularity of these lesions prior to surgical excision. The procedure includes intraoperative glue embolization combined with obstruction of outflow and followed by excision of the glued mass.

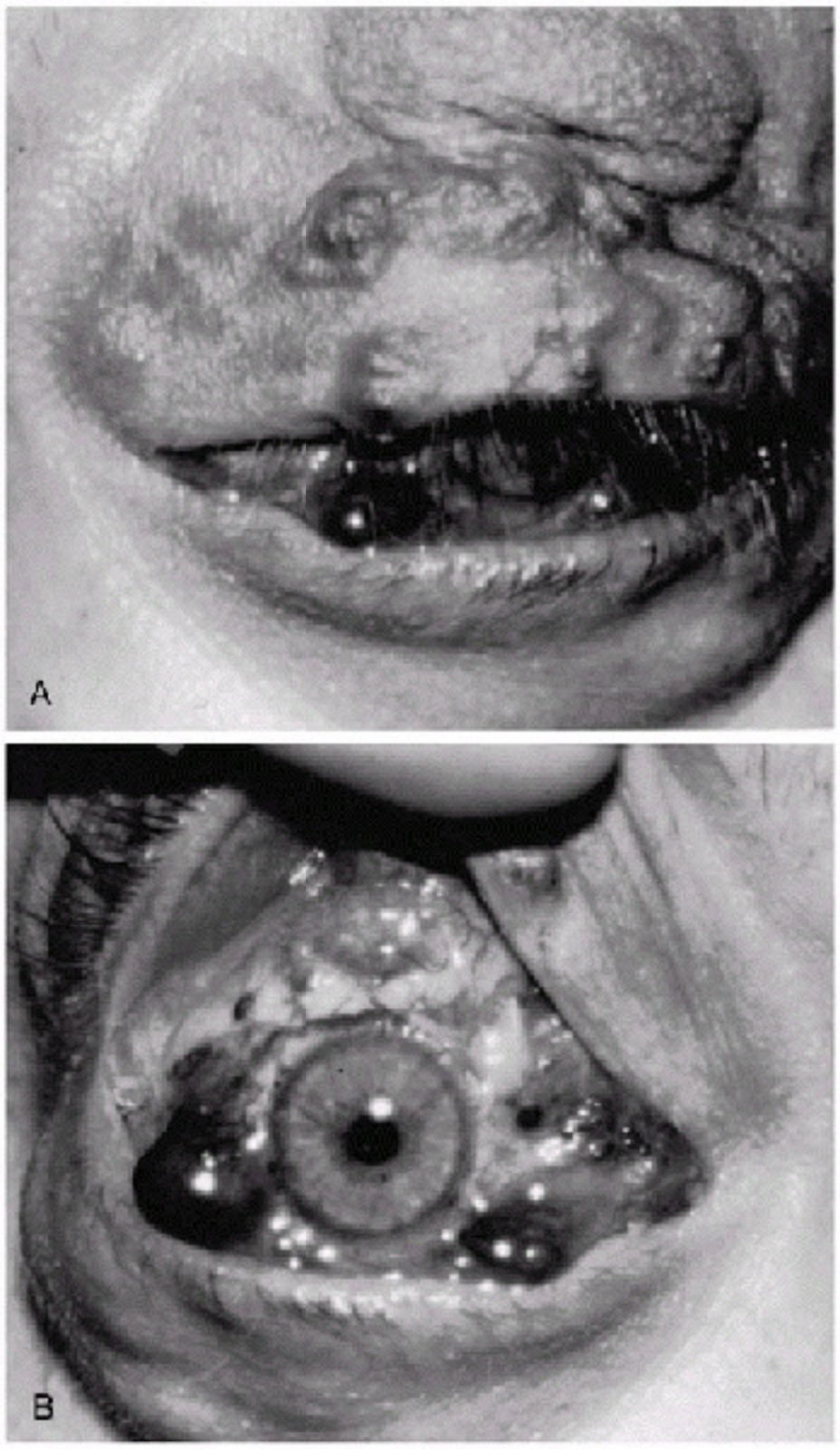

Figure 20.49 Orbital varices (A and B) consisting of numerous coiled vessels that increase in filling with crying, coughing, sneezing, or placing the head in a dependent position.

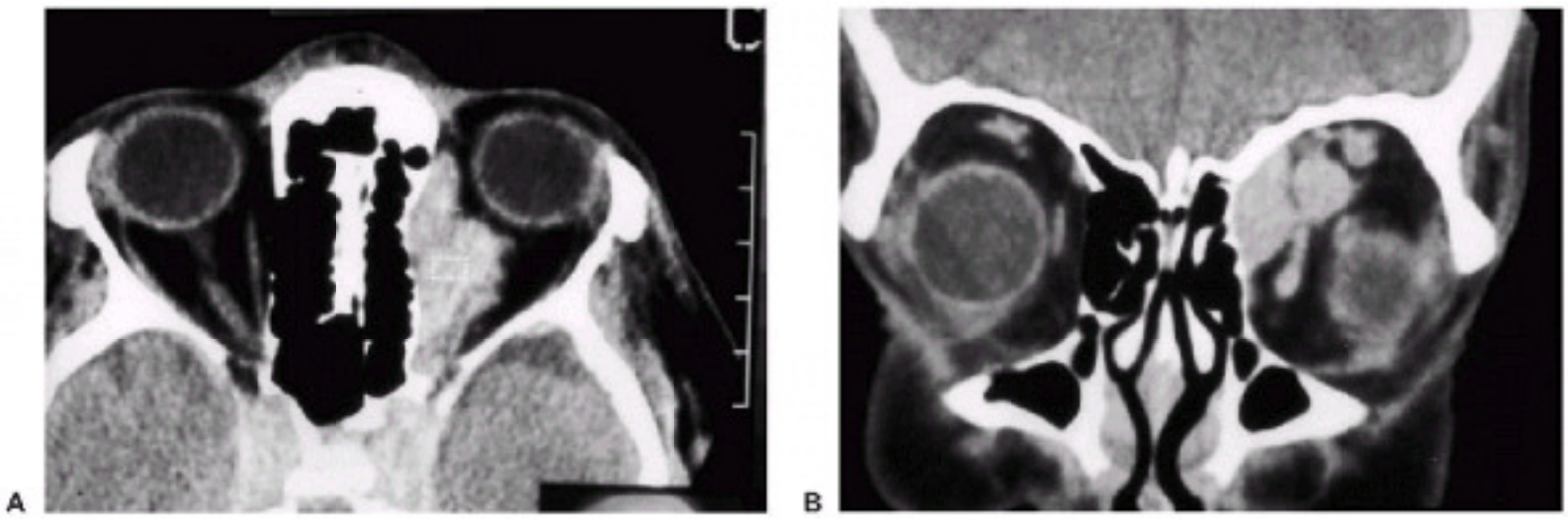

Figure 20.50 Orbital varix. **A:** Axial computed tomography (CT) scan of engorged varix. **B:** Coronal CT of same lesion demonstrating involvement of the superior medial orbit with dilated, ecstatic, dysmorphic, coiled vessels.

Orbital hemorrhages generally occur superiorly and result from trauma or spontaneously from vascular malformations. They should be allowed to reabsorb spontaneously unless there is visual compromise.

Rhabdomyosarcomas

Rhabdomyosarcomas are the most common malignant tumors of mesenchymal origin and also the most frequent orbital malignancy in children under 10 years of age, with the average age of onset 8 to 10 years old. They arise from undifferentiated pluripotent mesenchymal elements of the orbital soft tissues and not from the extraocular muscles. This mesenchymal tumor can originate from many different areas of the body including the orbit (10%), head and neck (25%), genitourinary tract (23%), and extremities (17%). It also originates in smaller percentages from the trunk, retroperitoneum, chest, perineum, and gastrointestinal tract. They can be embryonal, alveolar, botryoid, or pleomorphic in type.

Embryonal rhabdomyosarcoma is the most common histologic type, present in more than 80% of cases, and consists of loose fascicles of undifferentiated spindle cells with eosinophilic cytoplasm (Fig. 20.51). Embryonal rhabdomyosarcoma characteristically develops in the superior nasal orbit, displacing the eye down and outward, and is associated with a good survival rate of 94% (Figs. 20.52 and 20.53). The tumor may involve any part of the orbit and rarely arises from the conjunctiva. Electron microscopy and special stains may help identify striated muscle fibers. Cross-striations are often not visible on light microscopy but will be more apparent on electron microscopy. The most malignant form is alveolar, accounting for 9% of orbital rhabdomyosarcomas, with a predilection for the inferior orbit (Fig. 20.54), and histologically consists of rhabdomyoblasts arranged in an alveolar pattern with necrotic cells sloughing into the center. The pleomorphic, which is the least common and most differentiated form, occurs in older persons and has the best prognosis of 97% survival. The botryoid is a rare variant that appears grapelike and is not a primary tumor of the orbit, but invades the orbit from the paranasal sinuses or conjunctiva.

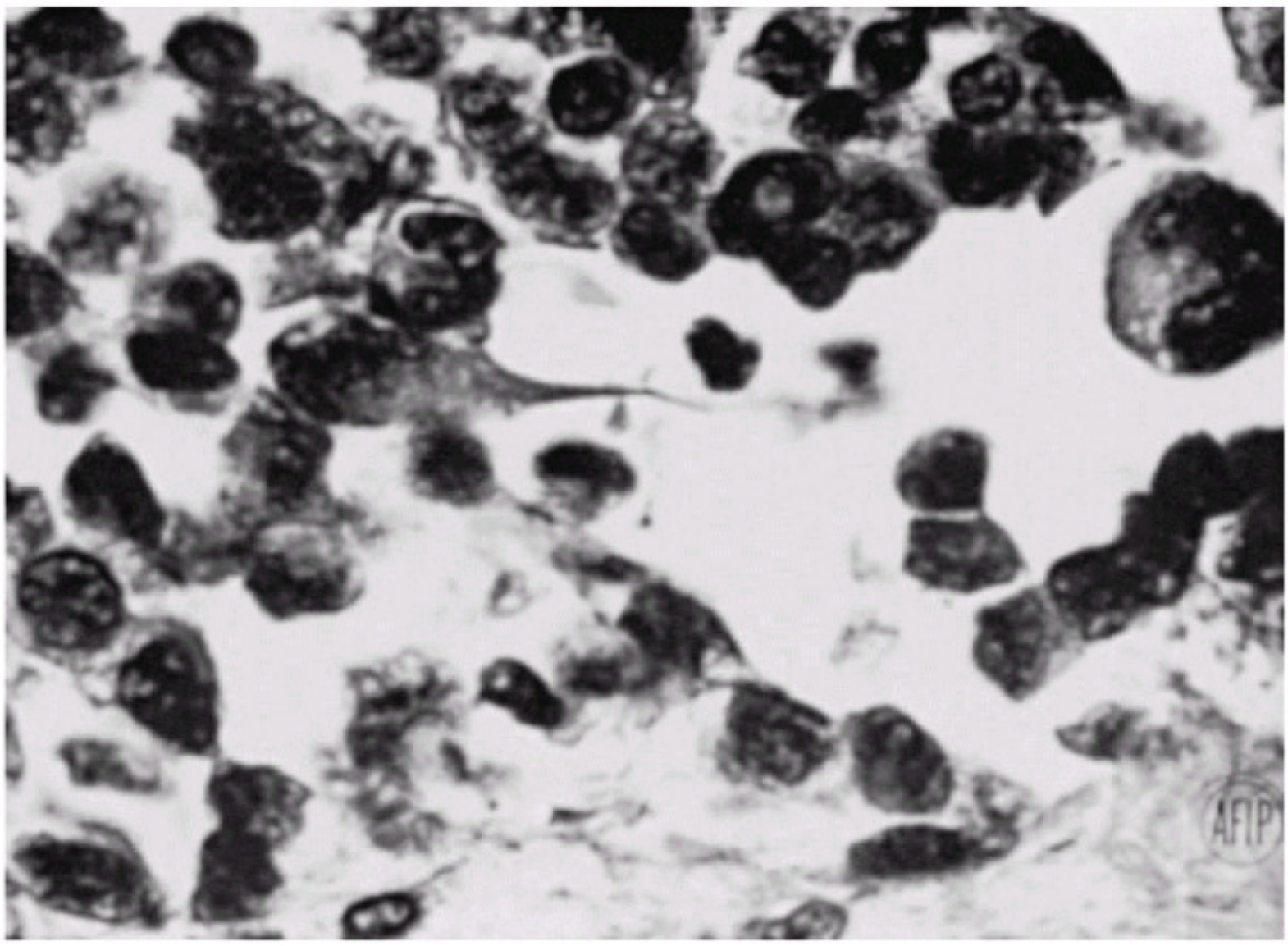

Figure 20.51 Hematoxylin-eosin stain of an embryonal rhabdomyosarcoma revealing strap cells with an eosinophilic cytoplasm.

Figure 20.52 A 6-year-old boy with a rhabdomyosarcoma of the superior orbit, resulting in a mechanic ptosis and down and outward displacement of the globe.

Preauricular and cervical lymph nodes should be examined for regional metastasis, followed by a chest x-ray or CT, bone marrow aspirate, biopsy, and lumbar puncture to evaluate for distant metastasis. The brain and lungs are primary sites for metastases. The tumor can also erode into the sinuses, causing nasal stuffiness and nosebleeds. CT reveals a well-circumscribed mass of homogeneous density and may cause areas of bone destruction, which are isodense in relation to normal muscle with moderate to marked contrast enhancement (Fig. 20.53). On MRI scans, they appear isointense or slightly hypointense compared to brain on T1-weighted images, and hyperintense on T2-weighted imaging. If the orbital bone is involved, especially the orbital roof, an MRI will be able to determine the extent of intracranial involvement.

When rhabdomyosarcoma is suspected, evaluation should proceed rapidly. Biopsy of the tumor by an anterior approach should be performed as soon as possible. Frequently the pseudocapsule allows complete removal of the rhabdomyosarcoma. Attempt to remove the entire lesion should be made; larger lesions should be debulked as extensively as possible. The smaller the volume of the residual tumor, the more effective the subsequent treatment is. Completely resected tumors with negative margins may not require radiation, whereas patients with microscopic residual orbital disease and/or lymph node metastases receive both chemotherapy and radiation. Once the diagnosis has been established, the patient should be referred to a pediatric oncologic center for systemic workup, checking for cervical and preauricular lymph nodes, chest radiography, bone marrow aspirate and biopsy, and lumbar puncture to rule out metastases, and then treating with radiation, followed by chemotherapy consisting of vincristine, doxorubicin hydrochloride, and cyclophosphamide. The side effects of radiation

in these children include cataracts, dermatitis, bony hypoplasia, dry eye syndrome, and keratitis, which must be watched for and treated as indicated.

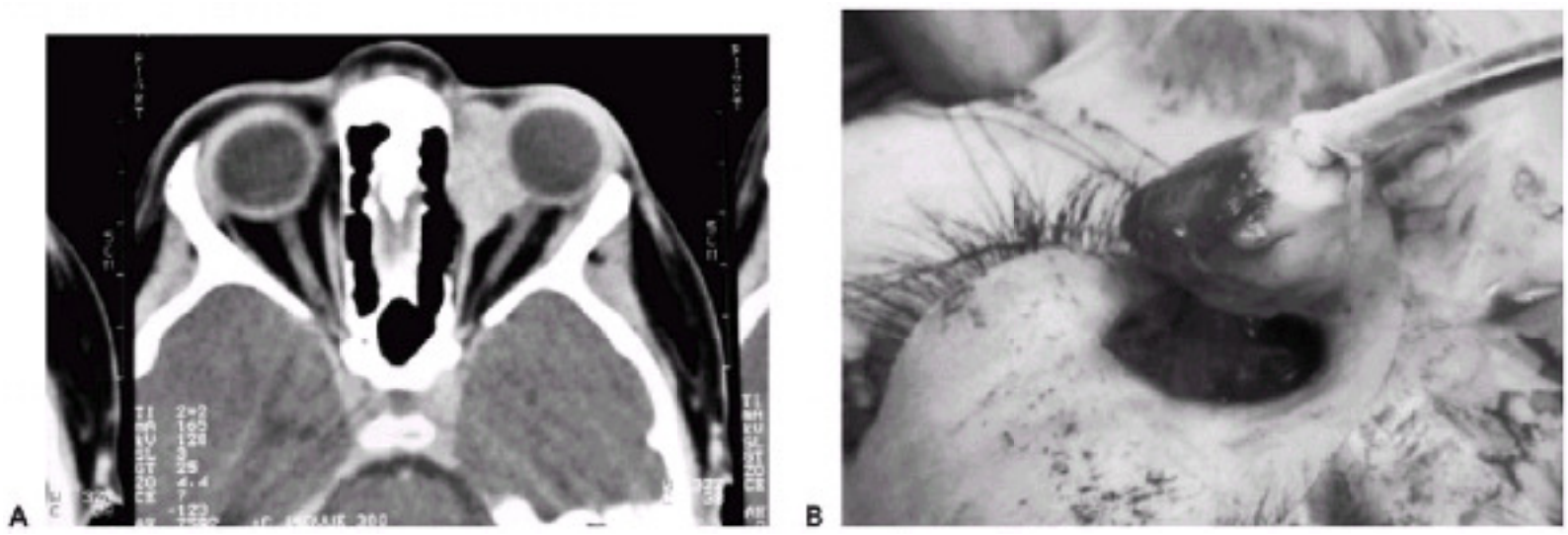

Figure 20.53 A: Computed tomography scan of the patient in Figure 20.52, demonstrating the involvement of the superior medial orbit and displacement of the globe. **B:** A cryoprobe may assist in mobilization and fixation of the tumor during excision.

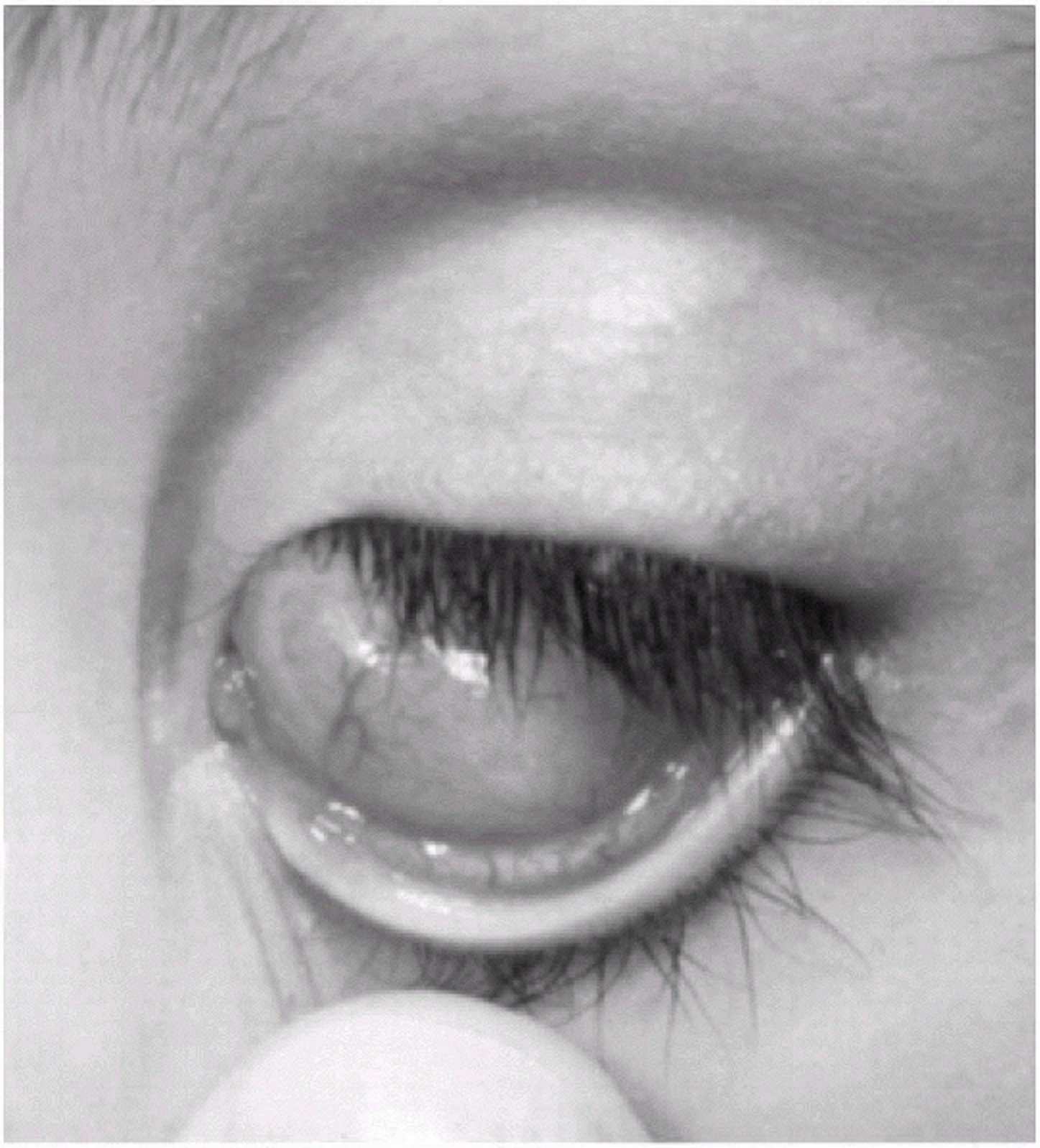

Figure 20.54 An alveolar rhabdomyosarcoma arising from the inferior orbit over a 10-day clinical course.

Any child presenting with a rapid onset of a painless proptosis over a period of several days to a few weeks should be considered to have a rhabdomyosarcoma until proven otherwise. There is often discoloration and edema of the eyelids. More than 70% will occur in the first decade of life, but this tumor may present from birth to the seventh decade. Frequently there is a vague history of trauma.

In a clinical study, 58 patients with orbital rhabdomyosarcoma were treated with irradiation alone or irradiation and chemotherapy, with follow-ups of 6 months to 14 years (mean 5.2 years). At present 74% are alive and 26% have died. Local control of the tumor was accomplished in 91% of cases. When local sinuses were invaded, the survival rate was 55%. Statistics from the Intergroup Rhabdomyosarcoma Study reveal a 3-year survival rate of 93% for children with localized orbital rhabdomyosarcoma. Chemotherapy appears to be of greatest value when disease is limited to the orbit. Irradiation or irradiation and chemotherapy should now be the treatment of choice for orbital rhabdomyosarcoma. Disfiguring orbital exenteration is now reserved for the rare radioresistant or drug-resistant tumor. The Intergroup Rhabdomyosarcoma Studies I-IV delivered a total dose of local radiation from 4,500 to 6,000 cGy over a 6-week period and systemic chemotherapy to eliminate microscopic cellular metastases with a survival rate of more than 90% if the tumor was confined to the orbit, compared with only a 25% to 35% survival rate in 1970. Prior to current treatment protocols, rhabdomyosarcoma of the orbit was managed with exenteration, a treatment currently reserved for rare cases of recurrence. There is a worse prognosis with tumor spread into the paranasal sinuses and meninges.

With a longer survivor rate of patients with rhabdomyosarcoma treated with chemotherapy and radiation, the incidence of second malignant neoplasms is increasing and includes acute nonlymphoblastic leukemia, leiomyosarcoma, adrenocortical carcinoma, epidermoid carcinoma, malignant melanoma, fibrillary astrocytomas, and osteogenic sarcoma. Any bone in the radiation field may be involved. These patients require lifelong follow-up with craniofacial examinations, as well as systemic evaluations.

Neural Tumors

Neurofibromas

Neurofibromas are slow-growing congenital tumors of the peripheral nerves, composed of proliferating Schwann cells within the nerve sheaths, with axons, endoneural fibroblasts, and mucin. Large plexiform neurofibromas may produce a slowly progressive proptosis and may also involve the lids (Figs. 20.55 and 20.56). Neurofibroma of the orbit may occur as an isolated lesion and can usually be excised without recurrence, or it represents part of a generalized disease (von Recklinghausen disease). Due to the variable expression of the mutations and the fact that the disease manifests in multiple tissues and organs, the NIH in 1990

established guidelines for the diagnoses of neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2). NF1 includes any two of the following: six or more café-au-lait spots, two or more neurofibromas or one plexiform neurofibroma, axillary or inguinal freckling, optic gliomas, osseous lesions, Lisch nodules, or a first-degree relative with NF1. NF2 includes either bilateral acoustic neuromas or a first-degree relative with NF2, in addition to either a unilateral eighth nerve palsy or two other lesions: neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity. A negative family history does not exclude the disease because half of all new cases of NF1 and even a greater proportion of NF2 cases present as new, sporadic mutations.

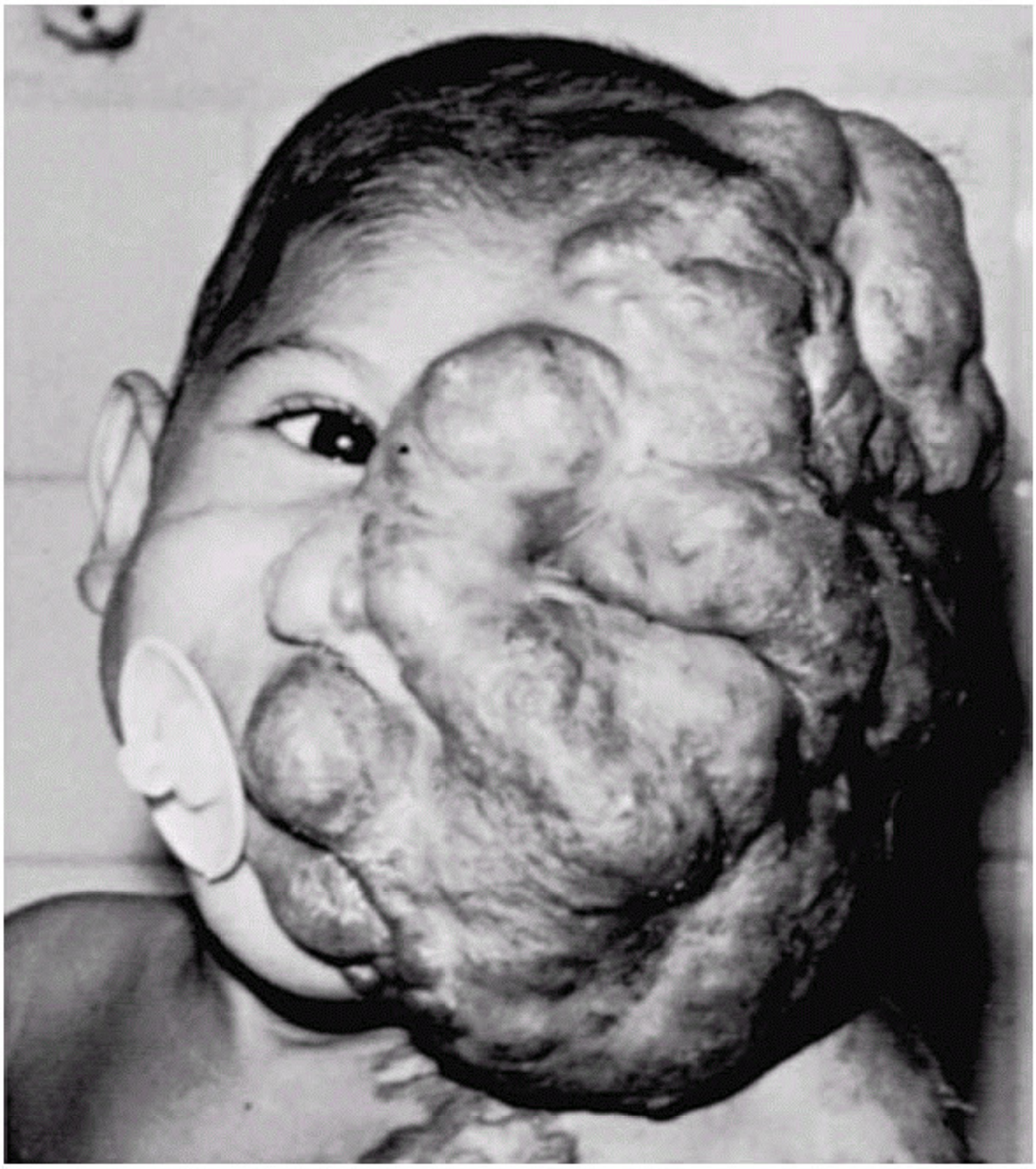

Figure 20.55 Extensive neurofibroma. (Courtesy of Monte A. Del Monte, MD.)

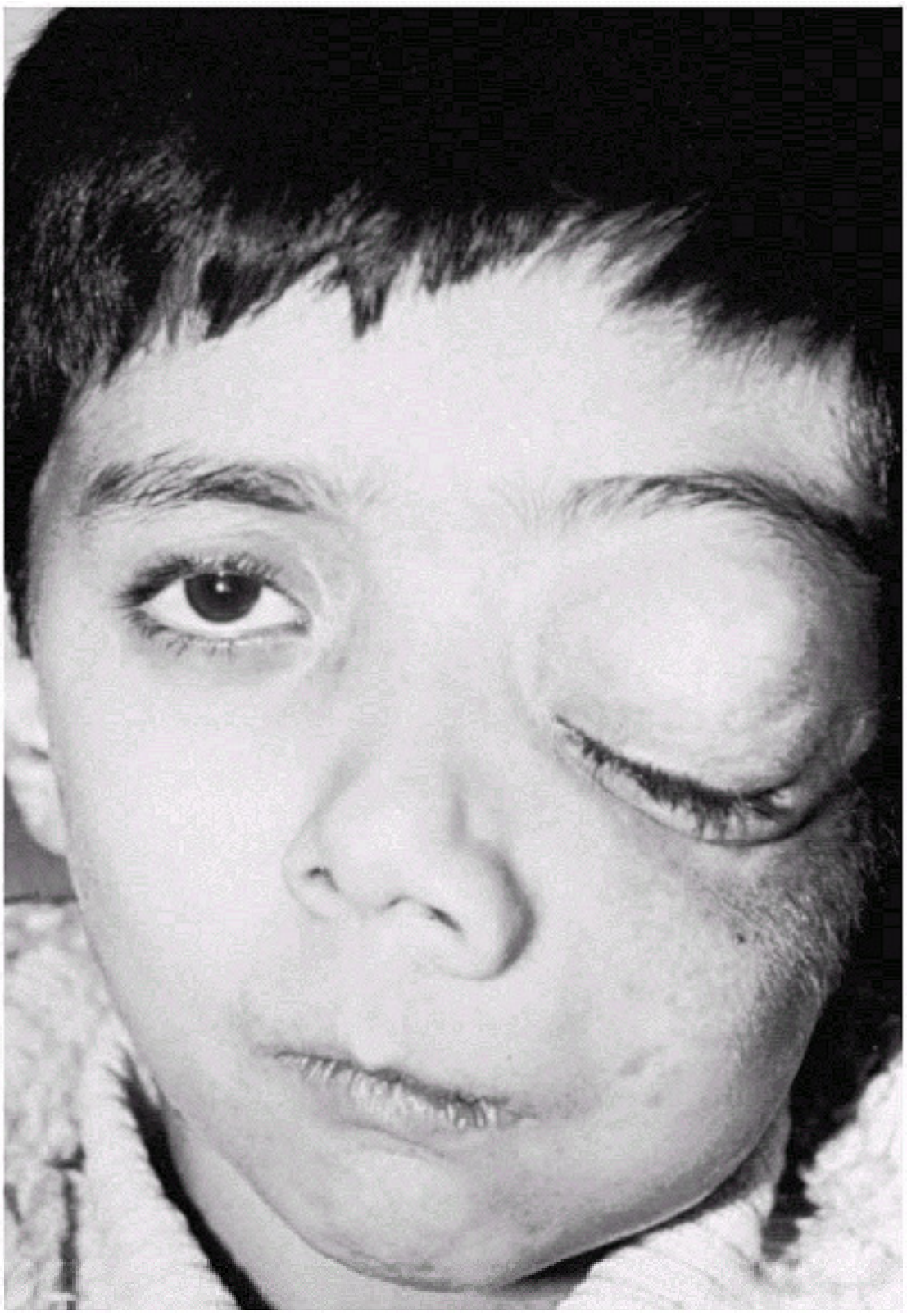

Figure 20.56 Neurofibroma of the left orbit, resulting in closure of the left eye.

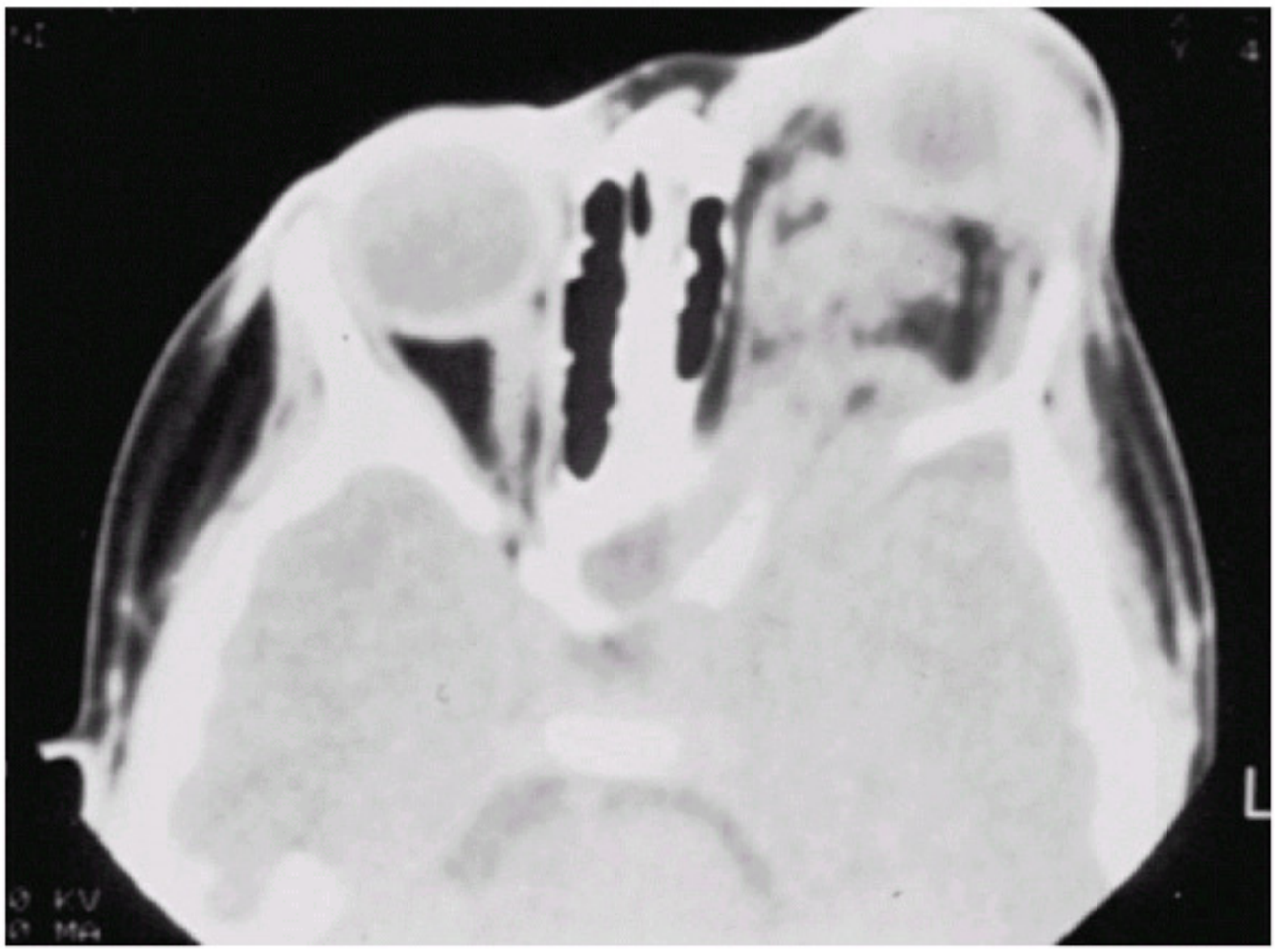

Figure 20.57 Axial computed tomography scan showing a neurofibroma infiltrating the posterior orbit and intracranial space through the dysplastic sphenoid bone.

Neurofibromatosis type 1, von Recklinghausen disease, is inherited as an autosomal-dominant gene with irregular penetrance, variable expressivity, and a high spontaneous mutation rate, with the defect localized to the long arm of chromosome 17. It is classified as a phakomatosis since the hamartomas involve the skin, eye, CNS, and viscera. It has multiple manifestations including Lisch nodules, café au lait spots, prominent corneal nerves, perilimbal neurofibromas, neurofibromas, glaucoma, megaloglobus, pigmentary hamartomas of the uveal tract, optic nerve and CNS tumors, and occasionally tumors of the spinal cord, sympathetic nerves, and adrenals. About one third of patients that present with optic nerve gliomas have NF1. NF2 has CNS meningiomas and, acoustic neuroma, and presenile lens opacities, and is ten times rarer than NF1. The defect is localized to the long arm of chromosome 22. Many of the typical characteristics are absent during infancy and develop only later in childhood and adolescence, and signs and symptoms often worsen during periods of high hormonal activity such as pregnancy and as the patient ages.

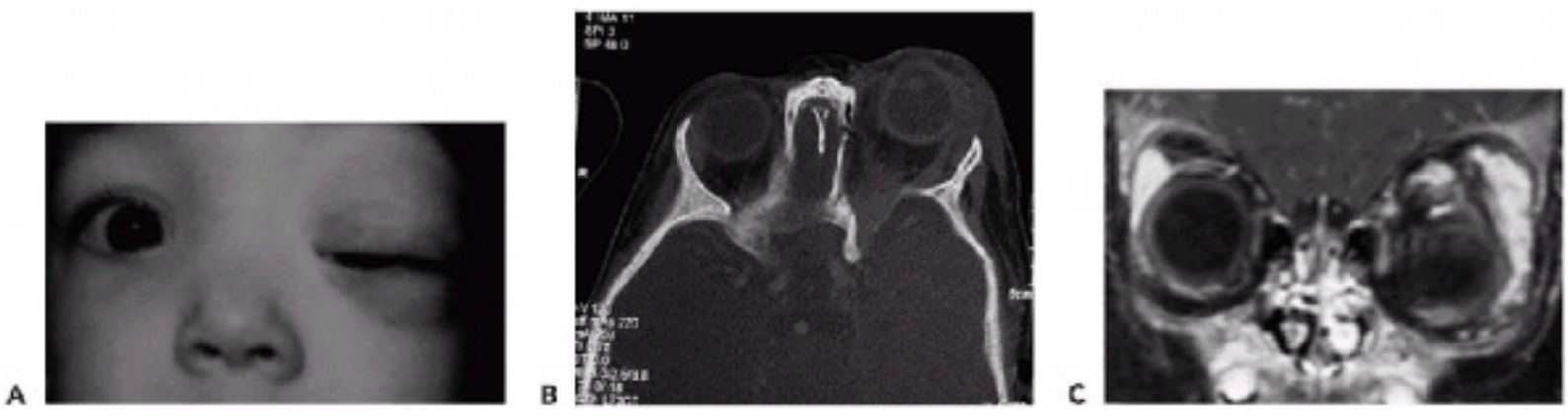

Figure 20.58 A: A 1.5-year-old girl with extensive neurofibromatosis involving the orbit, eyelids, and periorbita. **B:** Axial computed tomography scan demonstrating infiltration of the orbit and eyelids, with dysplasia of the sphenoid bone. **C:** Coronal magnetic resonance imaging scan of the same patient.

The association between neurofibroma and optic nerve glioma is well known. Palpation of plexiform neurofibromas, proliferations of Schwann cells within the nerve sheaths, in the lids produces a typical “bag of worms” feeling and may cause an S-shaped curvature of the upper eyelids. These tortuous, fibrous cords infiltrate normal tissues, making excision of the tumor difficult and often incomplete. The tumor can infiltrate all orbital tissues, making dissection and excision nearly impossible. The globe itself, including sclera, iris, ciliary body, cornea, and choroid, can be infiltrated, resulting in glaucoma and buphthalmos. Pulsation of the eye indicates an intracranial extension, usually secondary to a partial absence of the sphenoid bone (Figs. 20.57 and 20.58). Systemic NF manifests itself with anomalies such as café-au-lait spots, at least six that are more than 5 mm in diameter, which are caused by giant melanosomes that produce increased epidermal melanin and increase in number with age; axillary freckling; fibroma molluscum; dysplasia of the orbital walls; congenital glaucoma; iris nodules; and optic nerve gliomas. It is an autosomal-dominant disorder with variable expression.

On CT imaging, neurofibromas are contrast enhancing, irregular soft-tissue infiltrations. On MRI scans, they are heterogeneous and hypointense on T1-weighted

images and have a high-signal intensity on T2-weighted images with respect to orbital fat. They have variable enhancement with gadolinium and are best visualized with fat suppression.

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The management of plexiform neurofibromas is difficult and frustrating for the patient and family, as well as the ophthalmologist. The cosmetic results are often inadequate and temporary. The surgical management is repeated debulking and/or orbital bony surgery. The management of these lesions differs in adults and children. Rapid growth of neurofibromas typically occurs in children and adolescents, and they should be followed with close observation to allow timely intervention with appropriate surgical procedures. If there is normal development of the visual system, major surgical procedures should be delayed until the disease process has slowed, at which time a more permanent and definitive procedure may be performed. Radiotherapy is ineffective.

Patients with NF1 should be monitored for the early detection of optic nerve gliomas. The evaluation of the visual system in infants and young patients is difficult. Young children adapt well and rapidly to reduced vision, which emphasizes the importance of examining for other signs of an optic glioma, such as optic atrophy and MRI scans. Annual routine follow-up should be continued until the patient is at least 17 years old. The behavior of optic nerve gliomas can be quite variable, with visual loss occurring at a later age than previously reported. A negative evaluation and/or scan does not rule out later emergence of an optic nerve glioma. If an optic nerve glioma is detected, the decision to treat versus continuation of conservative management is complicated by reports of spontaneous regression in some patients as demonstrated by serial MRI scans and visual improvement. Therefore, the need for close and careful follow-up to establish progression before commencing treatment is indicated.

Neurilemomas

Neurilemomas (schwannomas) are slow-growing lesions that are derived from the sheath of the Schwann cells. The lesion is well encapsulated by the perineurium and is composed of orderly biphasic patterns of solid areas with nuclear palisading, Antoni A pattern, and myxoid areas, Antoni B pattern. Verocay bodies may be present and represent foci of nuclear palisading, fibrosis, hyalinization adjacent to blood vessels, and occasional xanthoma cells may also be seen. In contrast to neurofibromas, they are composed almost exclusively of Schwann cells and their processes. The proliferating Schwann cells within the perineural capsule compress the nerve of origin. They typically arise from the first division of the trigeminal nerve. Most patients will present with proptosis, motility disturbances, palpable mass, hypoesthesia, and occasional pain. CT and MRI scans generally demonstrate a smooth, elongated, circumscribed intra- or extraconal homogeneous mass denser than brain. On T1- and T2-weighted MRI scans, they are hyperintense to the gray matter and isointense with cerebrospinal fluid (Fig. 20.59). Complete excision is curative. Neurilemomas rarely undergo malignant changes.

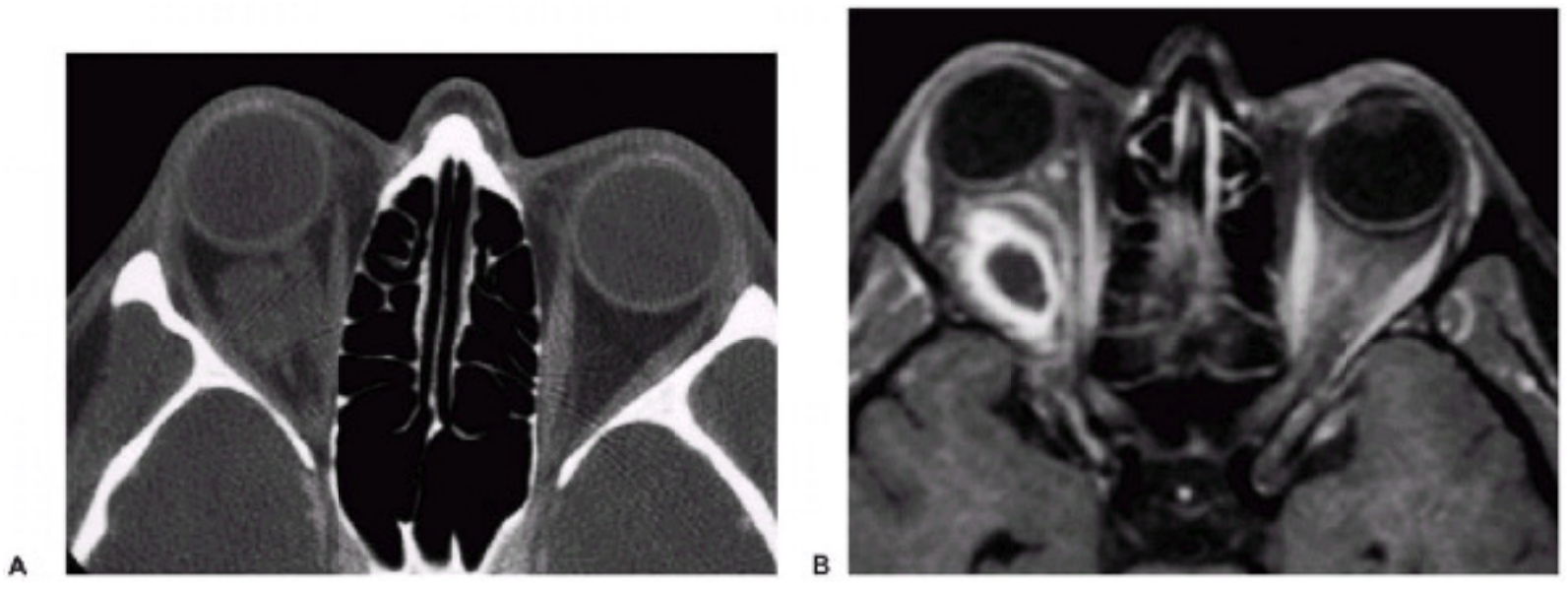

Figure 20.59 A: Axial computed tomography scan of a neurilemoma involving the lateral intraconal space with displacement of the optic nerve. **B:** Axial magnetic resonance imaging scan of the same lesion.

BONY DISEASES OF THE ORBIT

Fibrous Dysplasia of Bone

Fibrous dysplasia of bone manifests itself as a replacement of the normal bony medullary cavity with immature bone, fibrous hyperplasia, and osteoid, which replaces and distorts the medullary bone. It lacks osteoblasts, which prevents proper bone formation. It is a benign developmental disorder of the bone that can involve a single bone or be polyostotic. Most orbital lesions are monostotic but can involve multiple skull bones, not respecting the suture lines, and all bones may be involved. When the orbital bones are affected, the volume of the orbit is reduced. Proptosis and some swelling about the orbital margin are present, and most patients present with facial deformities, visual

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loss, or globe displacement (Fig. 20.60). The diagnosis is confirmed by radiographs showing a sclerotic lesion with a ground-glass appearance (Fig. 20.61). Histopathologic examination reveals bony trabeculae composed of woven bone within a fibrous stroma. These lesions often grow rapidly during early life and then stabilize after puberty, but occasionally they may progress into adulthood. The association of these polyostotic fibrous bony lesions with cutaneous pigmentation and endocrine disorders is known as McCune-Albright syndrome, which occurs largely in females and is also associated with sexual precocity and a postzygotic mutation in the G-protein. The etiology of fibrous dysplasia is unknown, and malignant transformation is very rare and usually associated with prior irradiation.

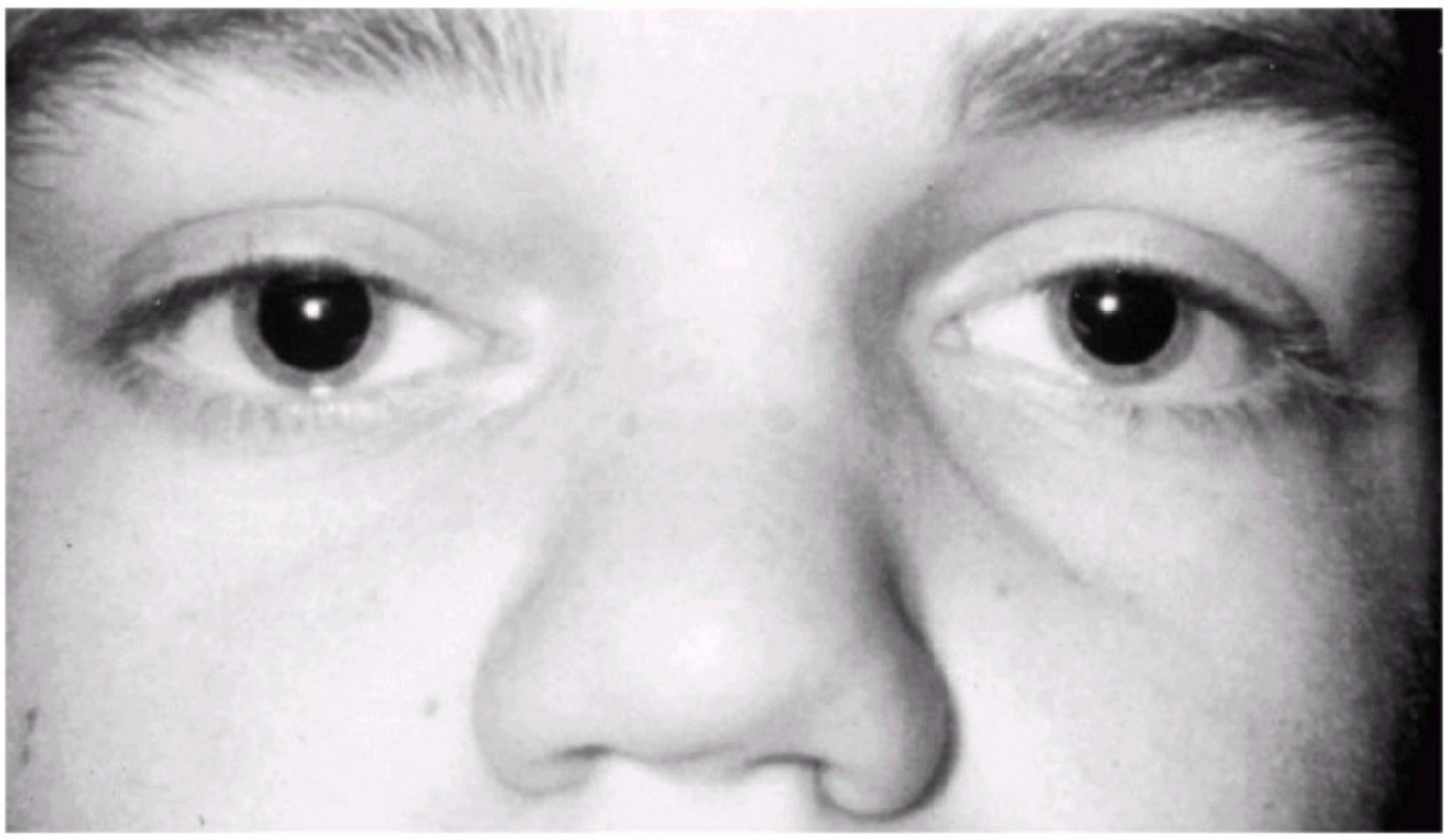

Figure 20.60 A 14-year-old boy with facial asymmetry, proptosis, and inferior displacement of the right orbit secondary to fibrous dysplasia.

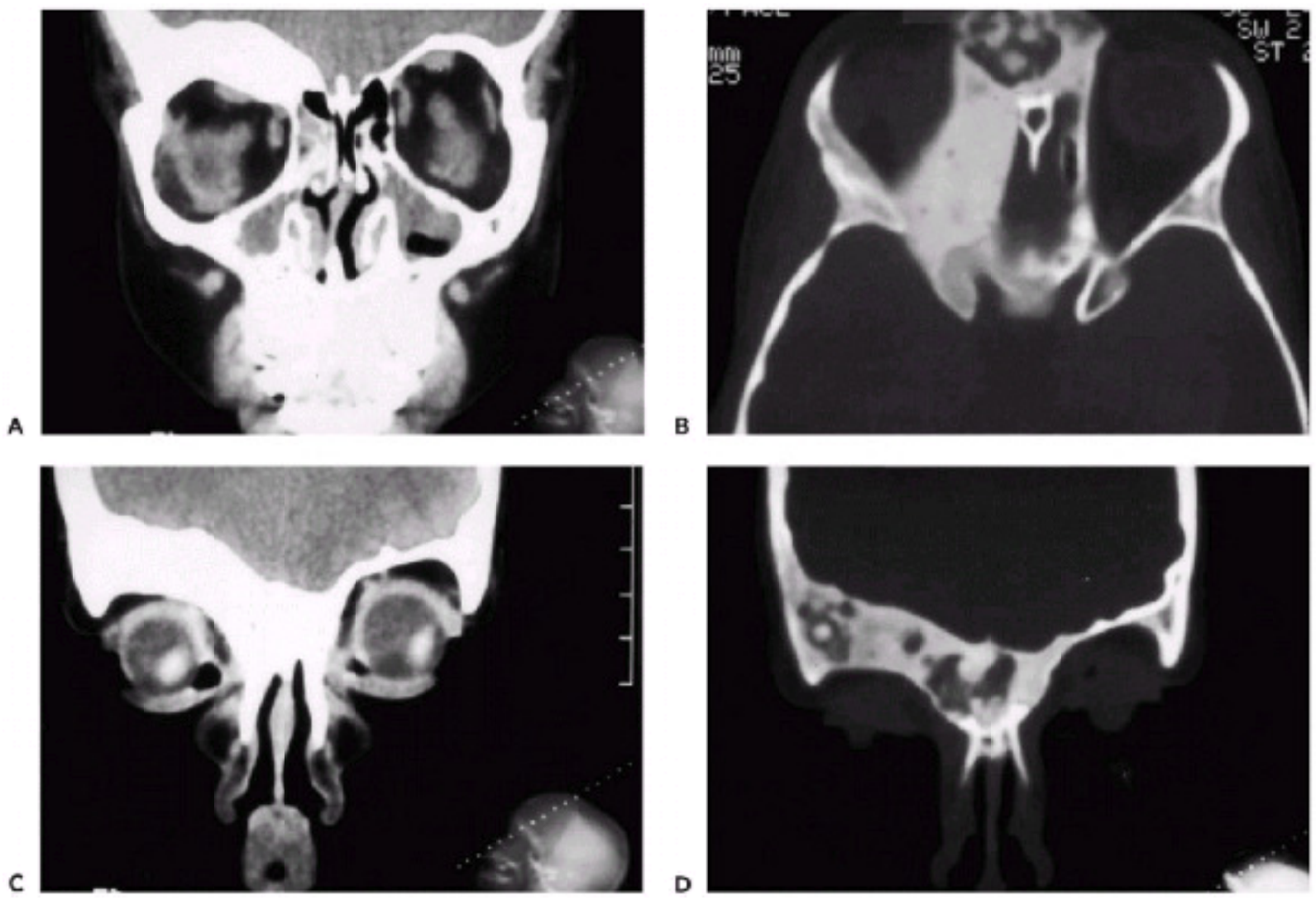

Figure 20.61 Fibrous dysplasia. **A:** Coronal computed tomography (CT) scan demonstrating sclerotic lesions involving the frontal and temporal bones. **B:** Axial CT scan demonstrating involvement of the frontal, ethmoid, and sphenoid bones, with a ground-glass appearance. **C:** Coronal view of the same patient. **D:** Coronal CT with bone density of the same patient.

The major clinical signs and symptoms vary according to the site and extent of bone involvement. Facial asymmetry, proptosis, and globe displacement are the most common presentations. A chronic visual loss from compression in the optic canal or at the chiasm can occur. Although rare, there can be rapid progression, increased pain, and infiltrative features, and one must rule out malignant transformation to osteosarcoma, fibrosarcoma, chondrosarcoma, and giant cell sarcoma.

Treatment is generally conservative with diagnostic imaging and regular observation, with intervention for gross deformity, functional deficits, pain, or sarcomatous transformation. If the lesion is well localized, resection, curettage with bone grafting, or contouring may be performed. Recently a more aggressive and earlier intervention, with a multidisciplinary craniofacial approach, is taken with removal of as much affected bone as possible and reconstruction as a one-stage procedure.

Ossifying Fibromas

Ossifying fibromas have been considered variants of fibrous dysplasia. They occur most frequently in the mandible and rarely in the orbit, with the frontal bone most commonly involved and then the ethmoid and maxillary bones. They exhibit more aggressive growth patterns, and total surgical excision is the treatment of choice. The tumor has a propensity for recurrence after incomplete excision, and therefore every attempt for a complete removal should be performed. Radiographs reveal a well-demarcated lesion with a sclerotic margin surrounding a less radiodense center. Pathologic examination reveals spicules of lamellar bone in a highly vascularized stroma. The spicules of bone are surrounded by osteoblasts resembling the psammoma bodies of meningioma.

Osteomas

Osteomas are seen occasionally in older children and generally arise from the bones of the paranasal sinuses, frequently the anterior ethmoid and frontal bones. The majority are solitary and asymptomatic, but they can enlarge to encroach on the orbital tissues, producing proptosis and globe displacement. Sphenoidal osteomas, though a rare site, may produce visual impairment, papilledema, and some ocular displacement. Radiologically, osteomas appear as well-circumscribed, sessile, or pedunculated, extremely dense masses that conform to the internal contour of the sinus of origin and may have a bosselated surface. Histopathologically, osteomas are composed of compact bone without a fibrovascular stroma. An uncommon autosomal-dominant syndrome of osteomas, soft-tissue tumors, peripheral congenital retinal pigment epithelial hypertrophy, and colonic polyposis with subsequent malignant transformation approaching 100%, is known as Gardner syndrome.

Chondroma

Chondromas are benign cartilaginous tumors that are usually asymptomatic and arise in the sinuses and nasal cavity, rarely from the orbit. These painless, slow-growing masses often arise near the orbital rim or trochlea. They are well-circumscribed dense masses on CT and MRI scans. Pathologically, they consist of lobulated mature hyaline cartilage, with mature chondrocytes within the cartilage, and variable fibrous or myxoid stroma. Excision is always curative.

Cholesterol Granuloma

Cholesterol granuloma is a foreign body response to crystallized cholesterol, which almost exclusively occurs in the diploe of the frontal bone overlying the lacrimal fossa, and occasionally in the zygoma. The pathogenesis is probably secondary to a traumatic intradiploic hematoma or a hemorrhage in a preexisting bony anomaly, and the breakdown of blood products leads to the deposition of cholesterol, cholesterol clefts, and a granulomatous response. The mass may occur over several weeks to years and may be associated with headache or pain. CT will demonstrate an osteolytic lesion with a density equivalent to brain, occasional intralesional bone fragments, which will eventually erode the inner and outer tables. Curettage is almost always curative.

Aneurysmal Bone Cysts

Aneurysmal bone cysts are benign cystic lesions that rarely arise in the skull, but more frequently in the metaphyses of long bones and in the spine; when they do involve the orbit, the frontal bone is the most frequent site of involvement. The pathogenesis is unknown, but 30% to 50% occur secondary to bone diseases, fibrous dysplasia, giant cell granuloma, giant cell tumor, osteoblastoma, osteosarcoma, intraosseous hemangioma, or reactive change to an arteriovenous malformation, and one should always rule these lesions out. The age range is from 11 months to 42 years, with the majority presenting in the second decade. Pathology generally demonstrates cavernous blood-filled spaces that lack endothelial lining, pericytes, or smooth muscle, but are surrounded by fibrous stoma that contains giant cells, hemosiderin-laden macrophages, lymphocytes, and trabeculae of osteoid and bone. CT will demonstrate a destructive or expansive lesion, with a central inhomogeneous patchy enhancement, with possible multiple fluid levels. Curettage is generally curative.

Giant Cell Granuloma

Giant cell granuloma or reparative granuloma is a benign granulomatous proliferation of questionable etiology, but thought to be a response to trauma and hemorrhage rarely involving the orbit. These lesions can arise in the maxillary, frontal, ethmoid, or sphenoid bones with equal frequency in an age group from 5 to 54 years of age. CT scans will demonstrate a destructive lesion with erosion of adjacent bone, with indistinct or sclerotic margins with moderate enhancement and inhomogeneous central matrix. The pathology demonstrates giant cells clustered around foci of hemorrhage, and the stroma contains ovoid and spindleshaped fibroblasts with a variable amount of fibrosis and evidence of old and new hemorrhages. Reactive bone formation of trabeculae of woven and lamellar bone, with or without an osteoblastic rim, is seen in 75% of cases. One must rule out Brown tumor of hyperparathyroidism, giant cell tumor, and aneurysmal bone cyst. This is important since giant cell granuloma is more aggressive and can undergo malignant transformation. Curettage is generally curative, with or without bone grafting. There is a higher rate of recurrence, but most will respond to a second curettage.

Brown Tumor

Brown tumor of hyperparathyroidism is a benign reactive proliferation that is histologically similar to giant cell granuloma and is associated with primary or secondary hyperparathyroidism, which causes increased osteoclastic activity

and focal areas of bone resorption and hemorrhage. The maxilla is more frequently involved than the frontal bone in the age group 10 to 70 years. These patients should be evaluated for abnormalities of serum calcium, phosphate, alkaline phosphatase, and parathormone levels, and a skeletal survey should be conducted. Treatment of the hyperparathyroidism often results in spontaneous resorption and healing of the bony lesion.

MALIGNANT LYMPHOMAS

The development of an orbital tumor in a child may be the first indication of leukemia or malignant lymphoma. True orbital lymphoma is rare in childhood, except for Burkitt lymphoma and, more recently, acquired immunodeficiency syndrome-associated lymphomas. A biopsy specimen confirms the presence of a malignant lymphomatous process, and careful systemic examination of the child is necessary to reveal the exact systemic involvement of the disease process. Acute leukemic disorders are more frequently encountered. Proptosis and ecchymosis about the lids may be the presenting sign. The acute and chronic leukemic disorders that involve the orbit are mainly of the lymphoid and myeloid groups. In childhood malignancies of the orbit, acute leukemia and granulocytic sarcoma are the causes of unilateral proptosis in approximately 10% of cases. Orbital leukemia will present bilaterally in 2% of cases. Soft-tissue hemorrhage is more common in the myeloid group.

Lymphoid proliferations present a diagnostic challenge because the biopsies are generally small, indolent courses, and neither cytologic nor architectural findings may be sufficient to distinguish between malignant and reactive processes. An experienced pathologist and flow cytometric immunophenotyping, in conjunction with clinical and histologic findings, increase the accuracy of the diagnosis, separating lymphomas from nonlymphomas.

Burkitt lymphoma is a high-grade undifferentiated lymphoma that affects African children between 2 and 12 years of age, with a median age of 7. It is endemic to Central Africa but also occurs sporadically worldwide. The sporadic cases are seen in the first three decades, with a median age of 11 years. There is a

predilection for the jaw, but it frequently involves the orbit and maxillary bone. Burkitt lymphoma is a malignant lymphoma of B-lymphocyte origin that was originally observed in endemic areas in Africa. There is evidence of a chromosomal translocation of the c-myc gene and cofactors involving the Epstein-Barr virus and states of chronic immune stimulation like malaria or human immunodeficiency virus (HIV) infection. The orbit becomes involved from upward extension of maxillary or mandibular tumors. This lymphoma disseminates rapidly from a solitary growth. It responds well to chemotherapy and adjuvant radiotherapy.

There is a wide spectrum of disease from benign lymphoid hyperplasia to malignant lymphoma. Histologically, benign lymphoid tumors have been reported to progress to systemic lymphomas. The Revised European-American Lymphoma classification lists five main subtypes of lymphomas: extranodal marginal zone B-cell lymphoma, 64% of cases; follicle center lymphomas, 10% of cases; diffuse large-cell B-cell lymphomas, 9% of cases; plasmacytoma, 6% of cases; and lymphoplasmacytic lymphoma, 5% of cases.

METASTATIC ORBITAL TUMORS

In children, metastatic tumors to the orbit occur more frequently than to the globe, in contrast to adults, where metastases to the choroid are more common. Neuroblastoma and Ewing sarcoma account for the majority of pediatric orbital metastases, then Wilms' tumor, chloroma, histiocytosis, testicular embryonal sarcoma, ovarian sarcoma, and renal embryonal sarcoma.

Leukemia

Leukemic infiltrates, unilateral or bilateral, to the orbit are not uncommon in the pediatric-age group. Acute lymphoblastic leukemia is the most common leukemia to involve the orbit. Primary leukemic orbital infiltrate, granulocytic sarcoma, or chloroma, are rare variants of myelogenous leukemia, acute myeloblastic leukemia, or chronic granulocytic leukemia entering the blast crisis. Orbital involvement may develop before, during, or after the occurrence of systemic leukemia. In children, there is a predilection for orbital and surrounding bone involvement presenting as a rapidly expanding tumor, with a mean age of onset of 7 years. Ten percent of cases are bilateral. It is also called a chloroma because the fresh specimen often exhibits a greenish hue due to the presence of myeloperoxidase. Generally the masses occur in the presence of systemic disease, but they may also present as isolated soft-tissue masses in the orbit without demonstrable bone marrow involvement. Chloroma, which presents as an orbital mass, is a greencolored tumor that may precede the development of granulocytic sarcoma (Fig. 20.62). The lesion is composed of immature cells, which stain positive for peroxidase granules or positive for cytoplasmic esterase by the Leder stain, which is positive in 75% of cases and indicate these granulocytic precursor cells (Figs. 20.63 and 20.64). Giemsastained touch preparations can detect Auer rods. The tumors may be well differentiated or poorly differentiated. There may be interspersed tingle body macrophages imparting a starry sky pattern. The single most sensitive and specific antibody for the detection of myeloid differentiation in paraffin sections is antimyeloperoxidase antibody. The diagnosis of granulocytic sarcoma is generally straightforward if there is a diagnosis of leukemia, but if there is no history of leukemia, this is often mistaken for a non-Hodgkin lymphoma, Ewing sarcoma, or Langerhans cell histiocytosis. The diagnosis requires a high index of suspicion and should always be confirmed by histochemical or immunohistochemical analysis. The prognosis is improved if chemotherapy is implemented before the development of systemic disease. If the lesion is large or vision is threatened, radiotherapy can be efficacious. The primary treatment is chemotherapy. Radiation therapy may further help to prevent

local recurrence, especially in the CNS. The prognosis is poor, but local irradiation and intensive chemotherapy initiated early in the disease process will improve the prognosis.

Figure 20.62 Granulocytic sarcoma presenting with a mass in the superior orbit, displacing the globe downward.

Neuroblastoma

Neuroblastoma arises from the adrenal medulla of infants and young children or from any cells of neural crest origin in the autonomic chain of postganglionic sympathetic nervous system of the cervical region, thorax, abdomen and/or pelvis, with the abdomen accounting for 72%. It is the most common solid tumor in children, accounting for 10% to 15% of pediatric cancers, and second to rhabdomyosarcoma as the most frequent orbital malignancy of childhood (90% of pediatric orbital malignancies). Most present before the age of 3; 90% occur in children younger than 5 years of age, but they can occur any time in the first two decades of life. When it metastasizes to the orbital bones, usually to the lateral wall, it produces periorbital hemorrhage, lid ecchymosis, and marked proptosis (Fig. 20.65). Metastases to the orbit occur with widespread disease in the abdomen, mediastinum, or neck. The diagnosis is usually established before orbital metastasis is evident. Children present with ocular signs in 8% of cases, and 20% of patients eventually have some ocular involvement. Ecchymosis of the lid without a history of trauma, bilateral in 40% of patients, with an abrupt proptosis may be the first sign of the disease. Decreased vision can occur from compression or direct invasion of the optic nerve. Metastasis to the eye can involve the choroid or iris. Patients then develop pallor, weight loss, and a palpable abdominal mass. An intravenous pyelogram demonstrates a kidney displaced by a mass. Congenital neuroblastoma of the mediastinal or cervical sympathetic ganglia may produce ipsilateral Horner syndrome with heterochromia. Any child presenting

with Horner syndrome should be evaluated for neuroblastoma. Other ophthalmic presentations may include opsoclonus or dancing eyes, which is a random, rapid conjugate eye movement seen in 2% to 4% of patients with neuroblastoma, myoclonus, or tonic pupils as a paraneoplastic process affecting the cerebellum.

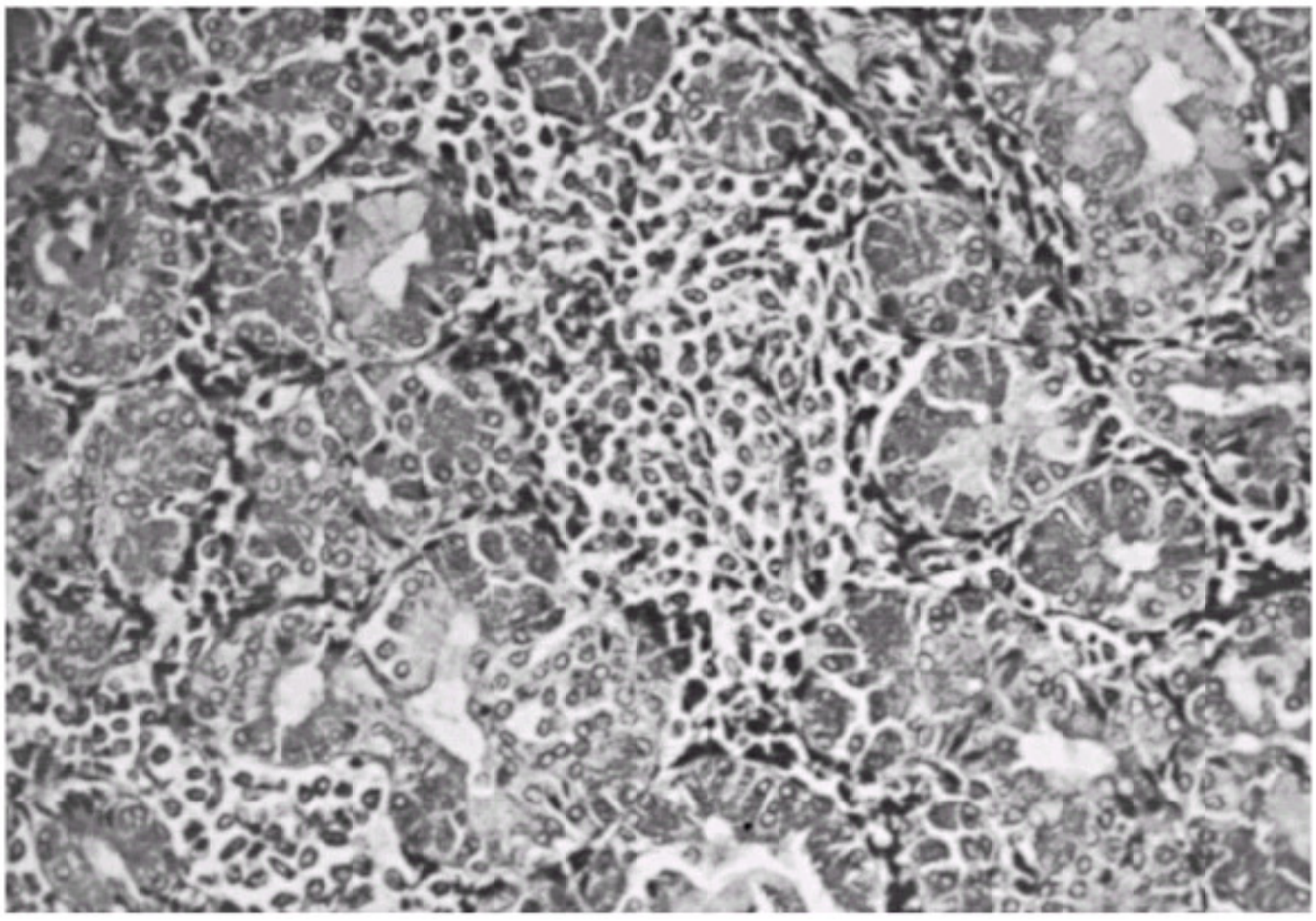

Figure 20.63 Hematoxylin-eosin stain revealing loose, immature cells infiltrating the lacrimal gland.

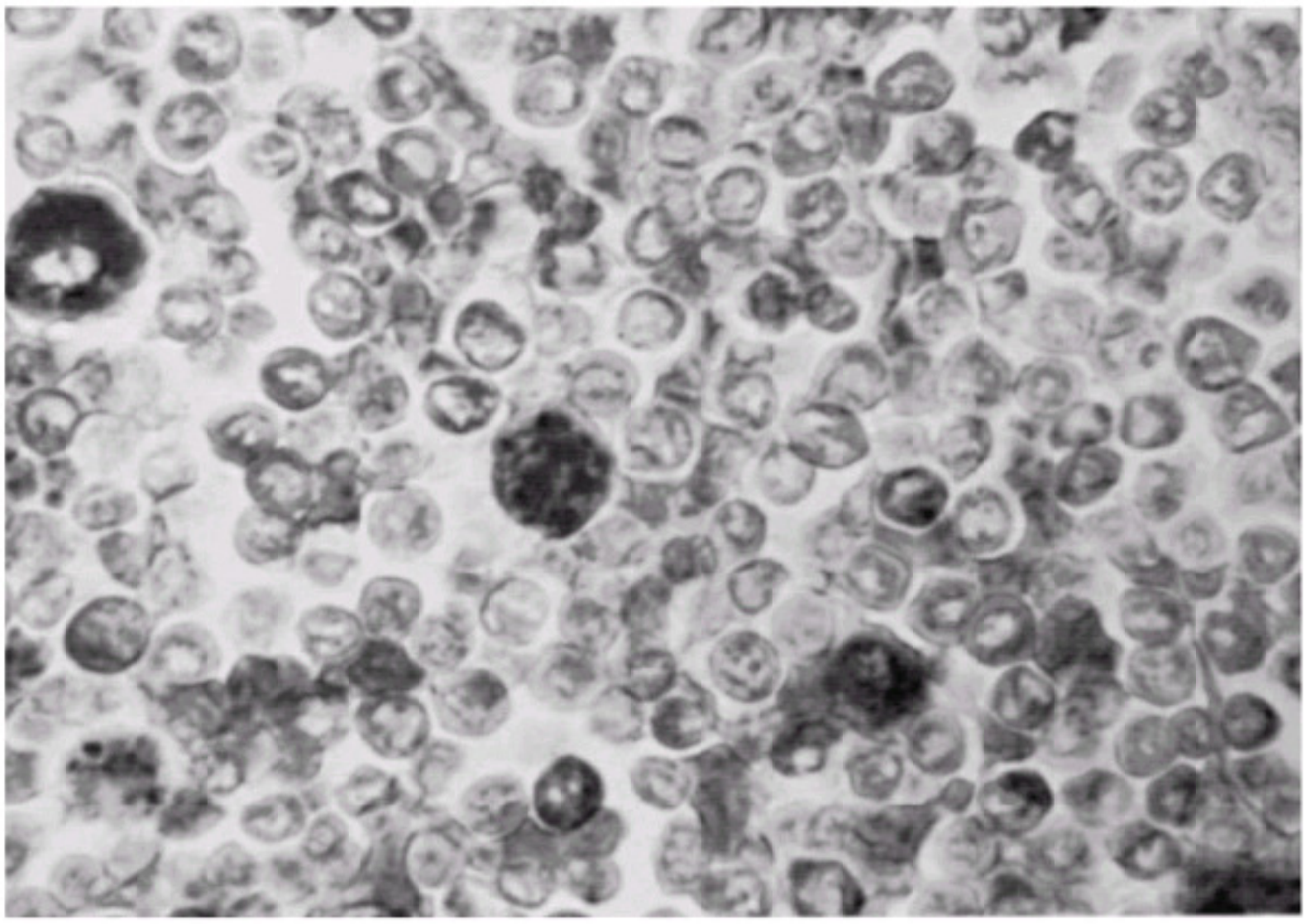

Figure 20.64 Leder stain demonstrating positive staining for cytoplasmic esterase, consistent with the peroxidase granules of granulocytic sarcoma.

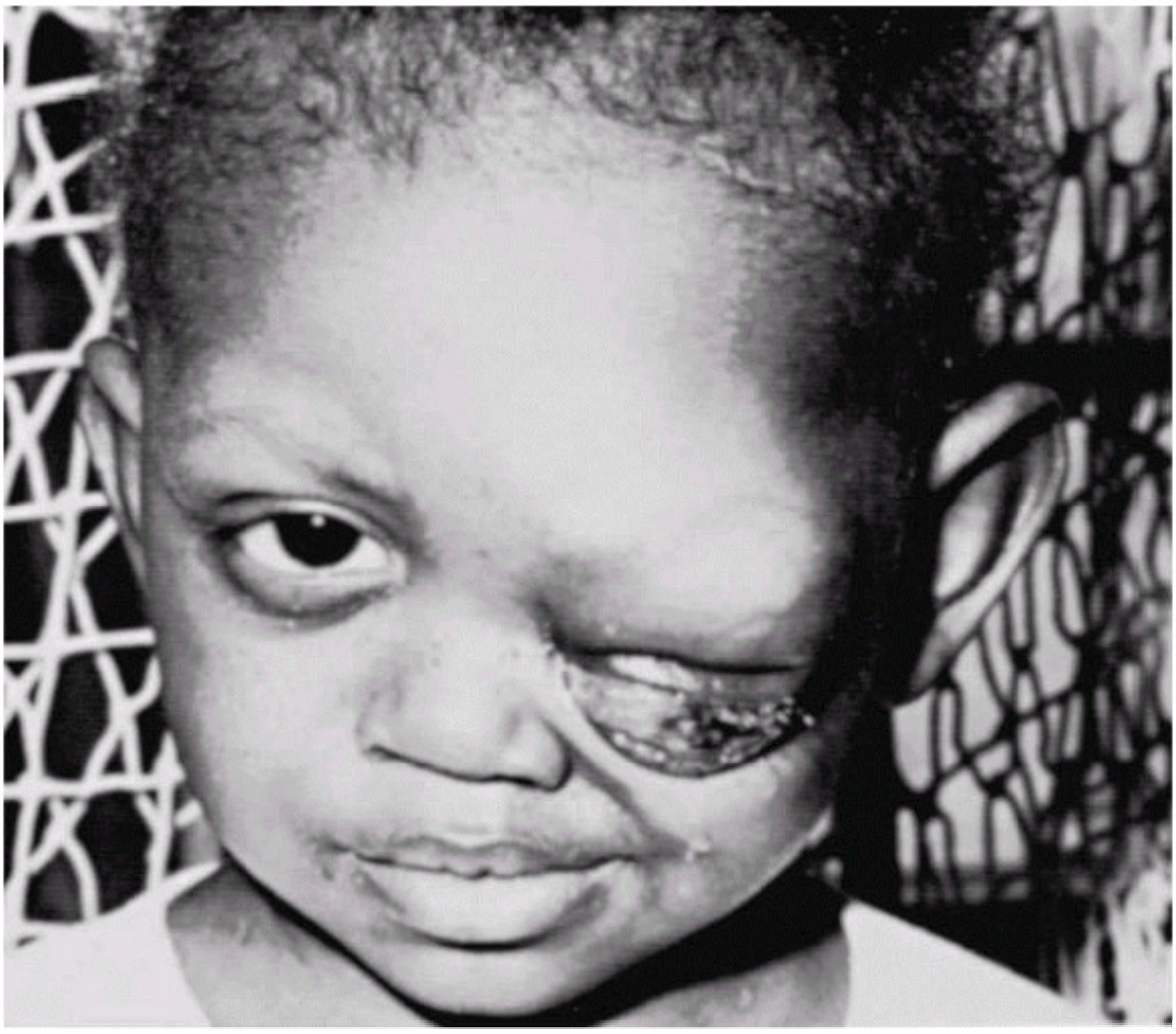

Figure 20.65 Metastatic neuroblastoma with proptosis of the left orbit and ecchymoses of both lower lids.

CT imaging, as well as bone scan and bone marrow biopsy, should be performed to find the primary lesion and metastasis. CT of the orbits often demonstrates bony destruction from the metastasis.

Clinical analysis of the urine for determination of catecholamine excretion can be especially important since catecholamines are often increased in neuroblastoma patients. About 90% of patients with such tumors have increased excretion of L-dopa, dopamine, norepinephrine, normetanephrine, homovanillic acid, and vanillylmandelic acid. As more reliance is placed on chemical testing, there should be correspondingly less need for surgical biopsy.

Treatment of orbital lesions includes surgical excision, radiation therapy with or without total body irradiation, autologous bone marrow rescue, and aggressive combination chemotherapy for disseminated disease.

SUGGESTED READINGS

Abramson DH, Ellsworth RM, Tretter P, et al. The treatment of orbital rhabdomyosarcoma with irradiation and chemotherapy. *Ophthalmology* 1979;86:1330-1335.

Alkemade PPH. Congenital teratoma of the orbit. *Ophthalmologica* 1976;173:274-285.

Brook I, Friedman EM, Rodriquez WJ, et al. Complications of sinusitis in children. *Pediatrics* 1980;66:568-572.

Brown BZ, Huffaker G. Local injection of steroids for juvenile hemangiomas which disturb the visual axis. *Ophthalmic Surg* 1982;13: 630-631.

Chang DA, Dallow RL, Walton DS. Congenital orbital teratoma: report of a case with visual preservation. *J Pediatr Ophthalmol Strabismus* 1980;17:88-95.

Cooling RJ, Wright JE. Arachnoid hyperplasia in optic nerve glioma: confusion with orbital meningioma. *Br J Ophthalmol* 1979;63: 596-599.

Davis JL, Parke DW II, Font RL. Granulocytic sarcoma of the orbit: a clinicopathologic study. *Ophthalmology* 1985;92:1758-1762.

Donaldson SS, Castroc JR, Wilbur JR, et al. Rhabdomyosarcoma of head and neck in children. *Cancer* 1973;36:26-35.

Dutton JJ. Optic nerve sheath meningiomas. *Surv Ophthalmol* 1992; 37:167-183.

Dutton JJ, Tawfid HA, DeBacker CM, et al. Multiple recurrences in malignant peripheral nerve sheath tumor of the orbit. *Ophthal Plast Reconstr Surg* 2001;17:293-299.

Fernbach SK, Naidich TB. CT diagnosis of orbital inflammation in children. *Neuroradiology* 1981;22:7-13.

Ferry AP, Abedi S. Diagnosis and management of rhino-orbital-cerebral mucormycosis. *Ophthalmology* 1983;90:1096-1104.

Friedman JM, Gutmann DH, MacCollin M, et al, eds. *Neurofibromatosis: phenotype, natural history and pathogenesis*, 3rd ed. Baltimore: Johns Hopkins University Press, 1999.

Gellady AM, Shulman ST, Ayoub EM. Periorbital and orbital cellulitis in children. *Pediatrics* 1978;61:272-277.

Goyal R, Watts P, Lane C, et al. Adrenal suppression and failure to thrive after steroid injections for periocular hemangioma. *Ophthalmology* 2004;11:389-395.

Grabb WC. Some anomalies of the head and neck. In: Grabb WC, Smith JW, eds. *Plastic surgery. A concise guide to clinical practice*. Boston: Little, Brown & Co., 1973, 115-130.

Green WR, Font RL, Zimmerman LE. Aspergillosis of the orbit. *Arch Ophthalmol* 1969;82:302-313.

Grossniklaus HE, Lass JH, Abramowsky CR, et al. Childhood orbital pseudotumor. *Ann Ophthalmol* 1985;17:372-377.

Haik B. Advances in the surgical management of capillary hemangiomas. In: Jakobiec FA, Sigelman J, eds. *Advanced techniques in ocular surgery*. Philadelphia: WB Saunders Co., 1984:659-666.

Haik B, Jakobiec FA, Ellsworth RM, et al. Capillary hemangioma of the lids and orbit: an analysis of the clinical pictures and therapeutic results in 101 cases. *Ophthalmology* 1979;86:760-789.

Handler SD, Raney RB. Management of neoplasms of the head and neck in children. I. Benign tumors. *Head Neck Surg* 1981;3: 395-405.

Handler SD, Savino PJ, Peyster RG, et al. Giant cell tumor of the ethmoid sinus: an unusual cause of proptosis in a child. *Otolaryngol Head Neck Surg* 1982;90:513-515.

Henderson JW. *Orbital tumors*, 2nd ed. New York: BC Decker, 1980.

Hiles DA, Pilchard WA. Corticosteroid control of neonatal hemangiomas of the orbit and ocular adnexa. *Am J Ophthalmol* 1971;70: 1003-1008.

Hooper R. Intracranial tumours in childhood. *Childs Brain* 1975;1: 136-140.

Hornblass A, Herschorn BJ, Stern K, et al. Orbital abscess. *Surv Ophthalmol* 1984;29:169-178.

Howard GM. Cystic tumors. In: Jones IS, Jakobiec FA, eds. *Diseases of the orbit*. Hagerstown, MD: Harper & Row, 1979, 1-10.

Hoyt WE, Joe S. Congenital teratoid cyst of the orbit. *Arch Ophthalmol* 1962;68:196-201.

Ide CH, Davis WE, Black SPW. Orbital teratoma. *Arch Ophthalmol* 1978;96:2093-2096.

Iliff WJ, Green WR. Orbital lymphangiomas. *Ophthalmology* 1979;86: 914-929.

Jakobiec FA, Font RL. Orbit. In: Spencer WH, ed. *Ophthalmic pathology. An Atlas and Textbook*, 3rd ed. Philadelphia: WB Saunders Co., 1986: 2461-2476.

Jakobiec FA, Jones IS. Vascular tumors, malformations and degenerations. In: Jones IS, Jakobiec FA, eds. *Diseases of the orbit*. Hagerstown, MD: Harper & Row, 1979:269-308.

Jones IS, Desjardins L. Management of orbital neurofibromatosis and lymphangiomas. In: Jakobiec FA, ed. *Ocular and adnexal tumors*. Birmingham, AL: Aesculapius Publishing, 1978:735-740.

Kennedy RE. Arterial embolization of orbital hemangiomas. *Trans Am Ophthalmol Soc* 1978;76:266-277.

Kennerdell JS, Dresner SC. The nonspecific orbital inflammatory syndromes. *Surv Ophthalmol* 1984;29:93-103.

Kennerdell JS, Maroon JC, Garrity JA, et al. Surgical management of orbital lymphangiomas with carbon dioxide laser. *Am J Ophthalmol* 1986;102:308-314.

Khalil M, Lindley S, Matouck E. Tuberculosis of the orbit. *Ophthalmology* 1985;92:1624-1627.

Knowles DM, Jakobiec FA, Jones IS. Rhabdomyosarcoma. In: Duane TD, Jaeger EA, eds. *Clinical ophthalmology*. Philadelphia: Harper & Row, 1985, 1-23.

Kobryn JL, Blodi FC, Weingeist TA. Ocular and orbital manifestations of neurofibromatosis. *Surv Ophthalmol* 1979;24:45-51.

Kohn R, Hepler R. Management of limited rhino-orbital mucormycosis without exenteration. *Ophthalmology* 1985;92:1440-1444.

Kushner BJ. Intralesional corticosteroid injection for infantile adnexal hemangioma. *Am J Ophthalmol* 1982;93:496-506.

Lewis RA, Gerson LP, Axelson KA, et al. von Recklinghausen neurofibromatosis. II. Incidence of optic gliomata. *Ophthalmology* 1984; 91:929-939.

Margo CE, Ragsdale BD, Perman KI, et al. Psammomatoid (juvenile) ossifying fibroma of the orbit. *Ophthalmology* 1985;92:150-159.

Mauriello JA, Flanagan JC. Management of orbital inflammatory disease: a protocol. *Surv Ophthalmol* 1984;29:104-116.

Moore AT, Buncic JR, Munro IR. Fibrous dysplasia of the orbit in childhood. *Ophthalmology* 1985;92:12-20.

Mottow LS, Jakobiec FA. Idiopathic inflammatory orbital pseudotumor in childhood. *Arch Ophthalmol* 1978;96:1410-1417.

Mottow-Lippa L, Jakobiec FA, Smith M. Idiopathic inflammatory orbital pseudotumor in childhood. *Ophthalmology* 1981;88: 565-574.

Nager FR, de Reynier JP. Das gehororgan bei den angeborenen kopfmissbildungen. *Pract Otorhinolaryngol (Basel)* 1948;10[Suppl 2]: 1-7.

Mulvihill JJ, Parry DM, Sherman JL, et al. NIH Conference. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). An update. *Ann Intern Med* 1990;113:39-52.

Oakhill A, Shah KJ, Thompson AG, et al. Orbital tuberculosis in childhood. *Br J Ophthalmol* 1982;66:396-397.

Robb RM. Refractive errors associated with hemangioma of the eyelids and orbit in infancy. *Am J Ophthalmol* 1977;83:52-58.

Robin JB, Schanzlin DJ, Meisler DM, et al. Ocular involvement in the respiratory vasculitides. *Surv Ophthalmol* 1985;30:127-140.

Rootman J. *Diseases of the orbit*. Philadelphia: JB Lippincott Co., 1988.

Sergott RC, Glaser JS. Graves' ophthalmopathy: a clinical and immunologic review. *Surv Ophthalmol* 1981;26:1-21.

Sergott RC, Glaser JS, Charyulu K. Radiotherapy for idiopathic inflammatory orbital pseudotumor. *Arch Ophthalmol* 1981;99:853-856.

Shields JA, Peyster RG, Handler SD, et al. Massive juvenile ossifying fibroma of maxillary sinus with orbital involvement. *Br J Ophthalmol* 1985;69:392-395.

Sires BS, Goins CR, Anderson RL, et al. Systemic corticosteroid use in orbital lymphangioma. *Ophthal Plast Reconstr Surg* 2001;17:85-90.

Smith BC, ed. *Ophthalmic plastic and reconstructive surgery*. St Louis: CV Mosby Co., 1987.

Stern J, DiGiacinto GV, Housepian EM. Neurofibromatosis and optic glioma: clinical and morphological correlations. *Neurosurgery* 1979;4:524-528.

Stern J, Jakobiec FA, Housepian EM. The architecture of optic nerve gliomas with and without neurofibromatosis. *Arch Ophthalmol* 1980;98:505-511.

Stewart WB, ed. *Ophthalmic plastic and reconstructive surgery*. San Francisco: American Academy of Ophthalmology, 1984.

Sutula FC, Glover AT. Eyelid necrosis following intralesional corticosteroid injection for capillary hemangioma. *Ophthalmic Surg* 1987; 18:103-105.

Thiagalingam S, Flaherty M, Dillson F, et al. Neurofibromatosis type 1 and optic pathway gliomas. *Ophthalmology* 2004;111:568-577.

Wolter JR. Diagnosis and management of orbital aspergillosis. *Ann Ophthalmol* 1976;8:17-20.

Waring GO, Roth AM, Rodrigues MM. Clinicopathologic correlation of microphthalmos with cyst. *Am J Ophthalmol* 1976;82:714-721.

Watters EC, Wallar PH, Hiles DA, et al. Acute orbital cellulitis. *Arch Ophthalmol* 1976;94:785-788.

Warnke RA, Weiss LM, Chan JKC, et al. Tumors of the lymph nodes and spleen. In: *Atlas of tumor pathology*, 3rd series, fascicle 14. Washington, DC: Armed Forces Institute of Pathology, 1995:387-410.

Weiss A, Friendly D, Eglin K, et al. Bacterial periorbital and orbital cellulitis in childhood. *Ophthalmology* 1983;90:195-203.

Wharam M, Beltangady M, Hays D, et al. Localized orbital rhabdomyosarcoma. *Ophthalmology* 1987;94:251-254.

Woog JJ, Albert DM, Solt LC, et al. Neurofibromatosis of the eyelid and orbit. *Int Ophthalmol Clin* 1982;22:157-187.

Wright JE. Orbital vascular anomalies. *Trans Am Acad Ophthalmol Otolaryngol* 1974;78:606-616.

Yip CC, Kersten RC, McCulley TJ, et al. Osteogenic sarcoma after orbital radiation rhabdomyosarcoma. *Ophthalmology* 2003;110: 1996-1999.

Zimmerman RA, Bilaniuk RT, Metzger RA, et al. Computed tomography of orbital facial neurofibromatosis. *Radiology* 1983;146: 113-116.

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Ocular Tumors of Childhood

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GENERAL CONSIDERATIONS

Several benign and malignant ocular tumors can occur in childhood. Tumors in the ocular region can lead to loss of vision, loss of the eye, and in the case of malignant neoplasms, loss of life. Therefore, it is important for the clinician to recognize childhood ocular tumors and to refer affected patients for further diagnostic studies and appropriate management. Some general concepts of childhood eye tumors will be reviewed, and the clinical manifestations of selected specific tumors of the eyelid, conjunctiva, intraocular structures, and orbit in children will be discussed. For more information on ocular tumors of childhood, the reader is encouraged to consult recent textbooks of ocular oncology that provide more details and cite numerous other references (1,2,3,4,5).

Clinical Signs of Childhood Ocular Tumors

The clinical characteristics of childhood ocular tumors vary depending on the location of the tumor: eyelids, conjunctiva, intraocular tissues, or orbit.

Eyelids and Conjunctiva

Eyelid and conjunctival tumors are generally quite evident, prompting an early visit to a physician. Since most tumors in the ocular area have characteristic features, an accurate diagnosis of eyelid and conjunctival tumors can usually be made with inspection alone. Therefore, additional diagnostic studies are not usually necessary.

Intraocular Tumors

Unlike tumors of the eyelids and conjunctiva, intraocular tumors are not readily visible. Infants and very young children do not complain of visual loss, and their visual acuity is difficult to assess. However, there are several features that should alert the pediatrician to consider the possibility of an intraocular tumor and prompt a timely referral.

Leukocoria

One of the more important signs of an intraocular tumor in children is leukocoria, or a white pupillary reflex (Fig. 21.1). There are many causes of leukocoria in children (6,7). The more common ones include congenital cataract, retinal detachment due to retinopathy of prematurity, persistent hyperplastic primary vitreous, and retinal telangiectasia with exudation (Coats disease). Retinoblastoma is probably the most serious cause of leukocoria in children. Any child with leukocoria should be referred promptly to an ophthalmologist for further diagnostic evaluation.

Strabismus

Most children with strabismus do not have an intraocular tumor. However, about 30% of patients with retinoblastoma present initially with either esotropia or exotropia, due to the tumor location in the macular area which disrupts the child's fixation. It is important that a retinal examination using the indirect ophthalmoscope be performed on every child with strabismus to exclude an underlying tumor.

Visual Impairment

An older child with an intraocular tumor may complain of visual impairment or may be found to have decreased vision on visual testing in school. This usually occurs from destruction of the central retina by the tumor or by the presence of vitreous hemorrhage, hyphema, or secondary cataract formation.

Orbital Tumors

Unlike tumors of the eyelid and conjunctiva, orbital tumors cannot be directly visualized. Therefore, they often attain

a relatively large size before becoming clinically evident. They generally present with proptosis or displacement of the eye. Pain, diplopia, and conjunctiva edema may also be early clinical features of an orbital tumor. Computed tomography (CT) and magnetic resonance imaging (MRI) have revolutionized the diagnosis and treatment of orbital tumors (8).

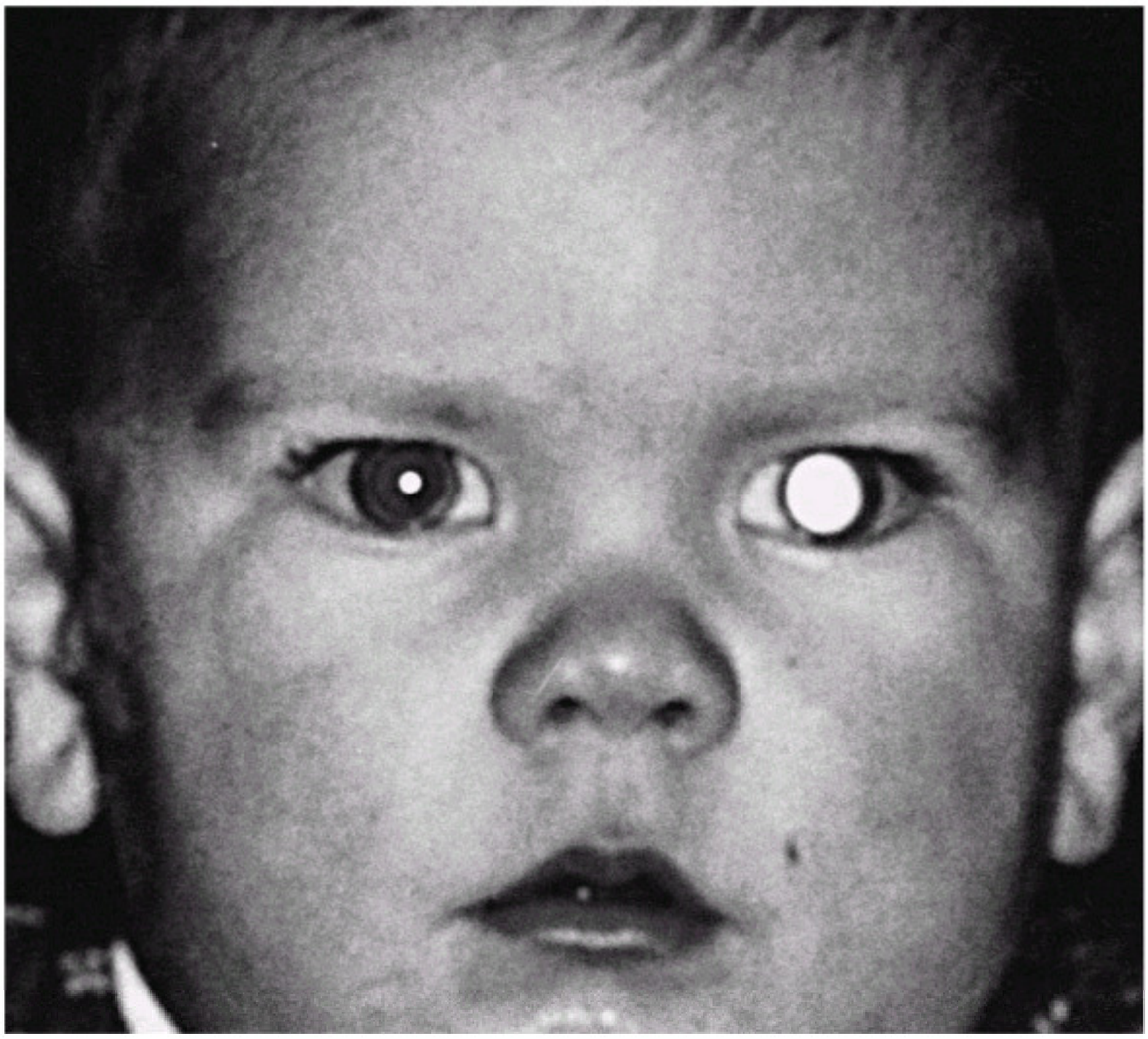


Figure 21.1 Leukocoria secondary to retinoblastoma.

Diagnostic Approaches

Although some atypical tumors can defy clinical diagnosis, most ophthalmic tumors in children can be accurately diagnosed by a competent ophthalmologist or ocular oncologist.

Eyelid and Conjunctiva

Most eyelid and conjunctival tumors are recognized by their typical clinical features, and special diagnostic studies are of little additional help (3). Smaller suspicious tumors in these tissues can be removed by excisional biopsy, and the diagnosis established histopathologically. Larger tumors, for which the resulting defect cannot be repaired primarily, are best diagnosed by incisional biopsy, and definitive treatment is withheld until a histopathologic diagnosis is established.

Intraocular Tumors

A number of intraocular tumors occur in children (2,4). Lesions of the iris can often be recognized with external ocular examination or slit-lamp biomicroscopy. Tumors of the retina and choroid can be visualized with ophthalmoscopy, which often reveals typical features depending on the type of tumor. Many small tumors are difficult to visualize and may only be detected by an experienced ophthalmologist using binocular indirect ophthalmoscopy. Ancillary studies such as fundus photography, fluorescein angiography, ocular ultrasonography, and occasionally CT or MRI are of supplemental value in establishing the diagnosis. Fine-needle aspiration biopsy has been employed in selected intraocular tumors of children (9). Such procedures in children often require general anesthesia.

Orbital Tumors

Some orbital tumors occur in an anterior location and can be recognized by their extension into the conjunctiva and eyelid area (5). This is particularly true of childhood vascular tumors such as capillary hemangiomata and lymphangiomata. Other tumors reside in the deeper orbital tissues and are less accessible to inspection, palpation, and biopsy. As mentioned earlier, CT and MRI have revolutionized orbital tumor diagnosis in children and have greatly improved the management of such cases (8). These imaging techniques can accurately localize and diagnose orbital masses and assist in proper management. Hence, “exploratory orbitotomy” is almost never necessary today.

Therapeutic Approaches

The treatment of an ocular tumor in a child also depends on the type, location, and size of the tumor.

Eyelid and Conjunctiva

True neoplasms of the eyelid and conjunctiva can be removed surgically by a qualified ophthalmologist or ocular oncologist (3). Inflammatory lesions that simulate neoplasia can be managed by antibiotics or corticosteroids, depending on the diagnosis. Some malignant neoplasms such as leukemias and lymphomata are best managed with a limited diagnostic biopsy followed by irradiation and/or chemotherapy.

Intraocular Tumors

The management of intraocular tumors is more complex (4). Certain benign intraocular tumors that are asymptomatic are usually managed by serial observation. Some symptomatic benign tumors can be treated with laser or cryotherapy, depending on the mechanism of visual impairment. Malignant tumors, such as retinoblastoma, sometimes require enucleation of the eye. In recent years, however, there has been a trend away from enucleation for retinoblastoma, with the increasing use of more conservative methods of management, such as laser photocoagulation, cryotherapy, and various radiotherapy techniques (10). Even more recently, there has been a trend toward using chemoreduction to reduce the tumor(s) to a small size so that enucleation and irradiation can be avoided. This subject is described later in this chapter.

Orbital Tumors

The treatment of an orbital tumor varies greatly with the clinical and histopathologic diagnoses (5). Benign vascular

tumors, such as capillary hemangioma and lymphangioma, can be managed by serial observation or patching treatment of the opposite eye to decrease the severity of associated amblyopia. Circumscribed tumors in the anterior orbit may be managed by excisional biopsy. Many malignant tumors, such as rhabdomyosarcoma and orbital leukemia, may require limited biopsy to establish the diagnosis, followed by irradiation or chemotherapy (1,5).

EYELID TUMORS

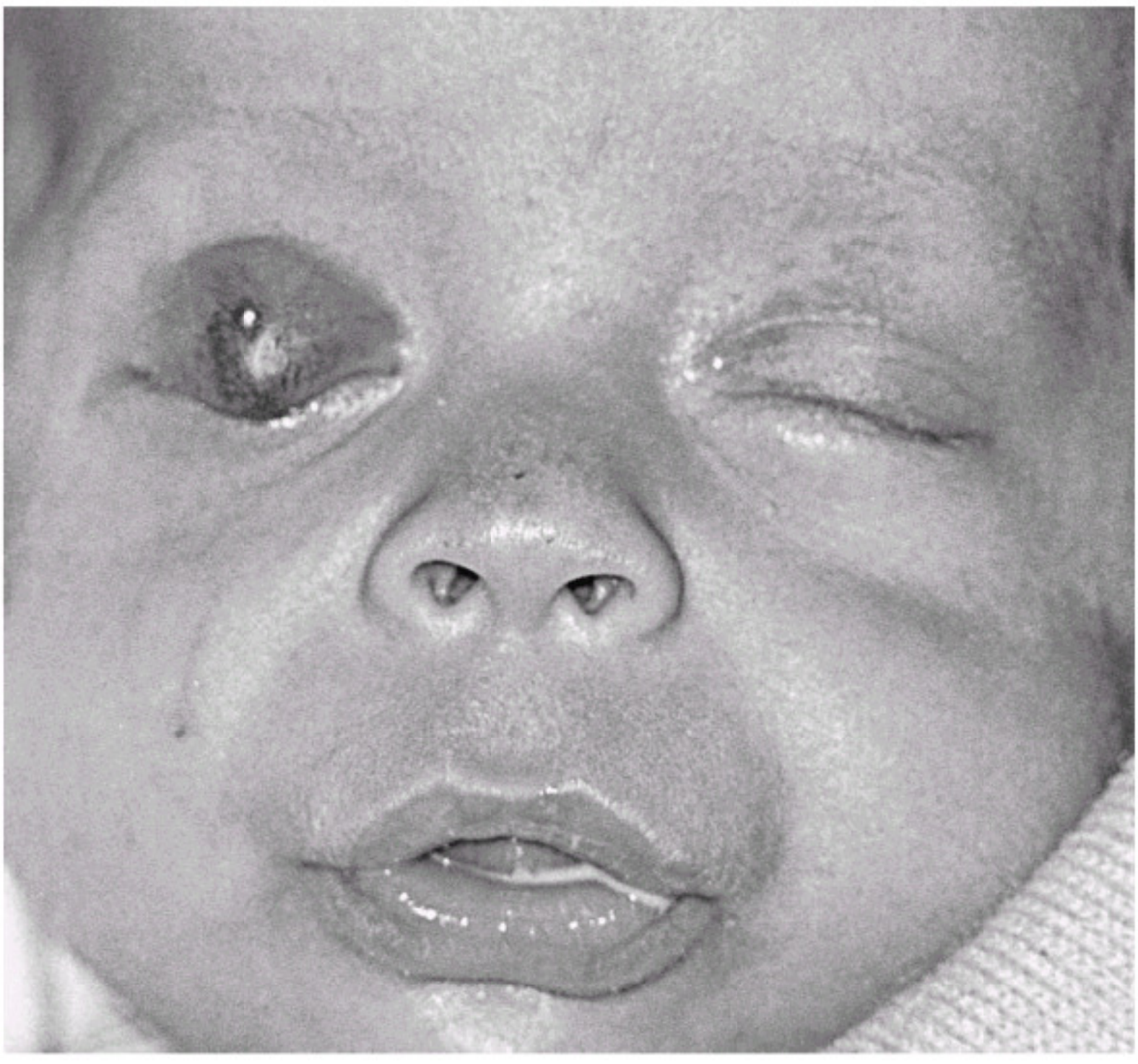
There are several pediatric cutaneous tumors that can affect the skin of the eyelids. These are covered in detail in textbooks of eyelid tumors (3). Only the more important ones will be considered here.

Capillary Hemangioma

Capillary hemangioma (or strawberry hemangioma) can occur on the eyelids as a reddish, diffuse or circumscribed mass (3,11) (Fig. 21.2). It usually has clinical onset at birth or shortly thereafter, tends to enlarge for a few months, and then slowly regresses. The main complications of this benign tumor are strabismus and amblyopia. In recent years the most frequently used treatment has been refraction, glasses for refractive error, patching of the opposite eye, and close follow-up. Oral corticosteroids or intralesional injection of corticosteroids may hasten regression of the tumor in some cases (12). More recently, there has been a trend toward complete surgical excision of those lesions that are relatively small and localized (13). Radiotherapy is almost never used today.

Facial Nevus Flammeus

Facial nevus flammeus is a congenital cutaneous vascular lesion that occurs in the distribution of the fifth cranial nerve (3). It may be an isolated entity or may occur with variations of Sturge-Weber syndrome. It is discussed in more detail in Chapter 22. Infants with this lesion have a higher incidence of ipsilateral glaucoma, diffuse choroidal hemangioma, and secondary retinal detachment. Affected infants should be referred to an ophthalmologist as early as possible to diagnose and treat these serious ocular conditions. Management of the cutaneous lesion includes observation, cosmetic make-up, or laser treatment.



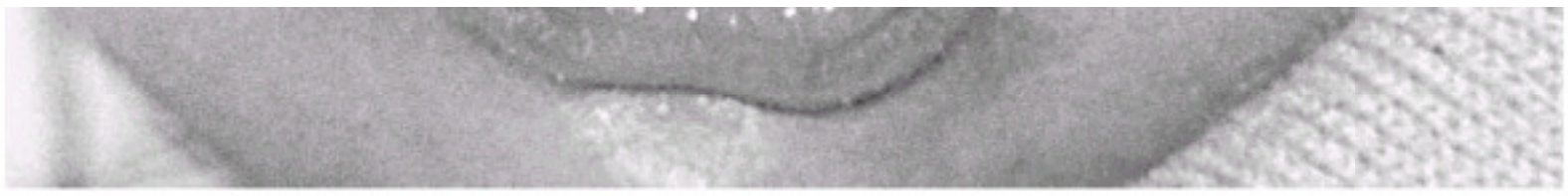


Figure 21.2 Capillary hemangioma of the eyelid.

Kaposi Sarcoma

A few years ago, when there was a higher incidence of acquired immunodeficiency syndrome (AIDS) in children, opportunistic neoplasms such as Kaposi sarcoma were diagnosed more frequently. In the last few years, however, it has become less frequent. Although the affected patient may have cutaneous lesions elsewhere, the eyelid can occasionally be the initial site of involvement. The lesion appears as a reddish-blue subcutaneous mass near the eyelid margin (Fig. 21.3). It generally responds best to chemotherapy and radiotherapy (3).

Basal Cell Carcinoma

Although basal cell carcinoma is primarily a disease of adults, it is occasionally seen in younger patients, particularly if there is a family history of basal cell carcinoma syndrome, as in nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome) (3). It generally occurs on the lower eyelid as a slowly progressive mass that frequently develops a central ulcer (rodent ulcer) (Fig. 21.4). Lesions near the eyelid margin often develop loss of eyelashes in the area of involvement. Treatment is local excision using frozen section control and eyelid reconstruction (3).

Melanocytic Nevus

A melanocytic nevus is a tumor composed of benign melanocytes. It can occur on the eyelid as a variably-pigmented

well-circumscribed lesion, identical to those that occur elsewhere on the skin. It does not usually cause loss of cilia. The blue nevus is often apparent at birth, whereas the junctional or compound nevus may not become clinically apparent until puberty. Transformation into malignant melanoma is rare and usually occurs later in life. Although most eyelid nevi in children can be safely observed, they are occasionally excised for cosmetic considerations or because of fear of malignant transformation (3).

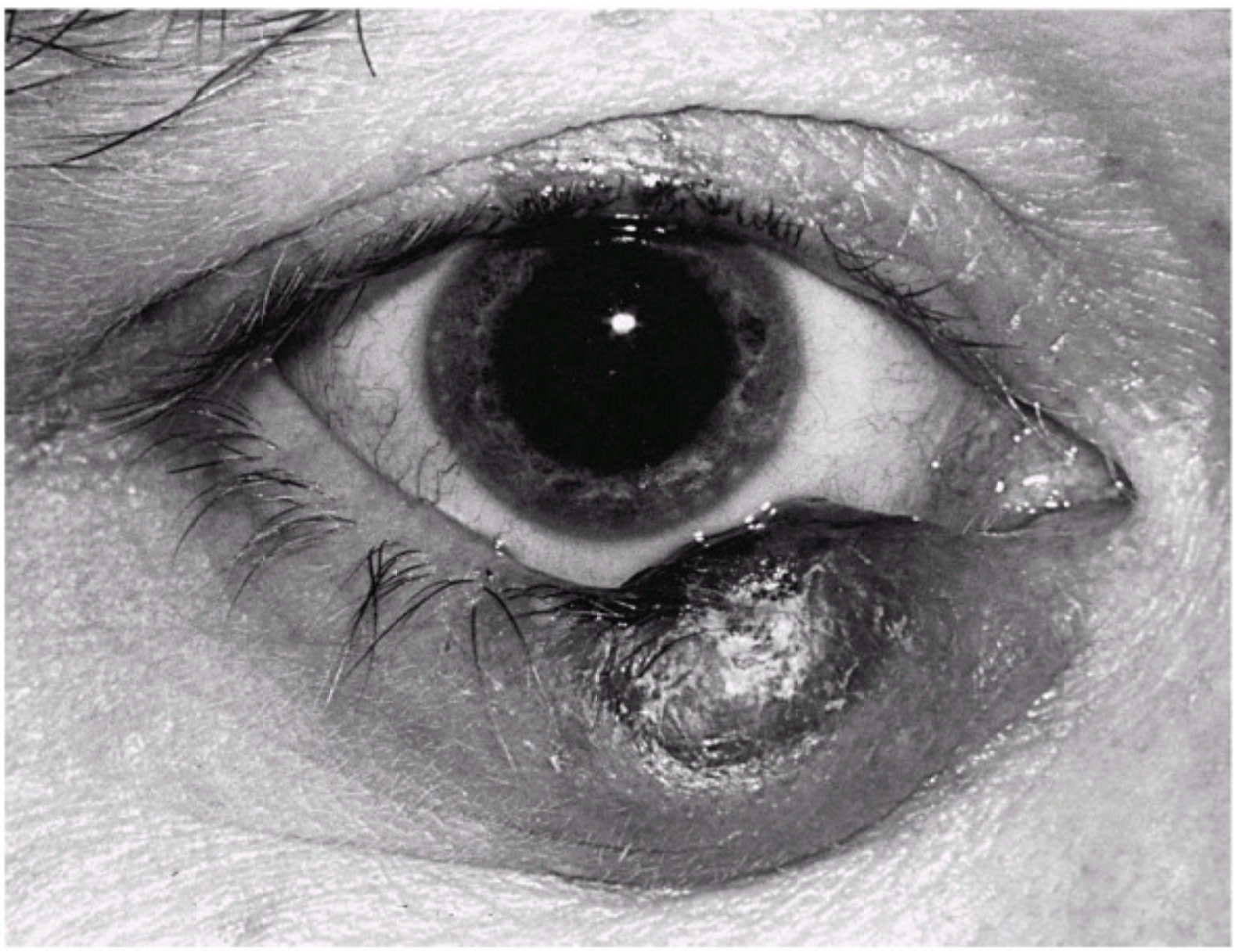


Figure 21.3 Kaposi sarcoma of the eyelid.

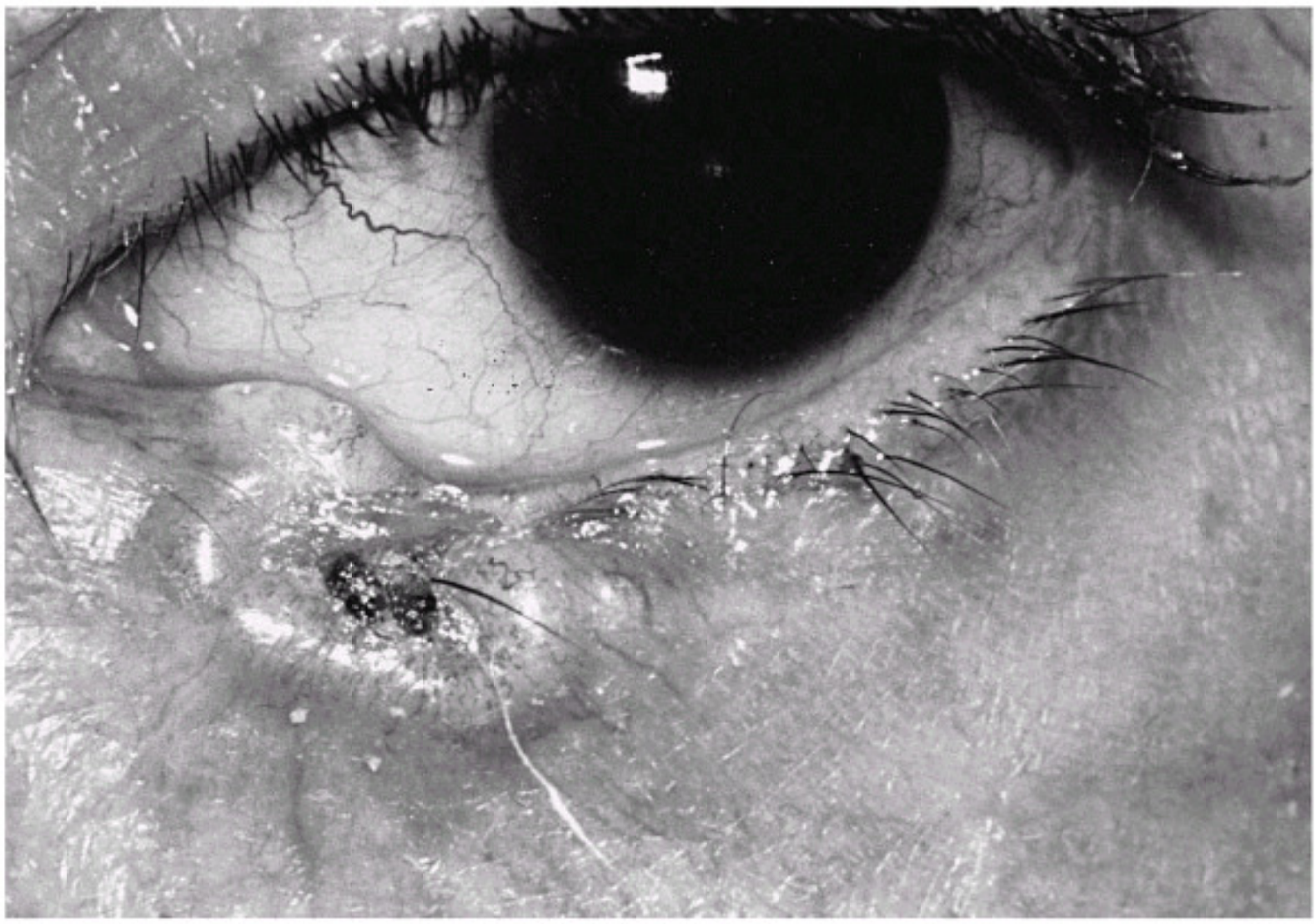


Figure 21.4 Basal cell carcinoma of the lower eyelid in a 17-year-old girl.

Neurofibroma

A neurofibroma can occur on the eyelid as a diffuse or plexiform lesion that is often associated with von Recklinghausen neurofibromatosis. In the earliest stages, the lesion produces a characteristic S-shaped curve to the upper lid. Larger lesions produce thickening of the eyelid with secondary blepharoptosis. Since these diffuse tumors are often difficult or impossible to completely excise, they should be managed by periodic observation or surgical debulking if they cause a major cosmetic problem (3).

Neurilemoma (Schwannoma)

Neurilemoma is a benign peripheral nerve sheath tumor that is composed purely of Schwann cells of peripheral nerves. It more commonly occurs in the orbit of young adults, but it can appear as a solitary eyelid lesion in children (3,14). Neurilemoma often occurs as a circumscribed solitary lesion (Fig. 21.5) unassociated with neurofibromatosis. It is a benign tumor that can be excised surgically.

Pilomatrixoma

Pilomatrixoma (“benign calcifying epithelioma of Malherbe”) is a benign neoplasm that arises from the matrix cells at the base of a hair (3,15). The term pilomatrixoma depicts its origin from the hair matrix cells. Pilomatrixoma is usually solitary, has a tendency to affect young individuals, and involves the periorbital region in 17% of cases (3). It has a tendency to involve the eyebrow or, less frequently, the eyelid as a subcutaneous red-to-blue mass that is fairly well circumscribed and firm or gritty on palpation.

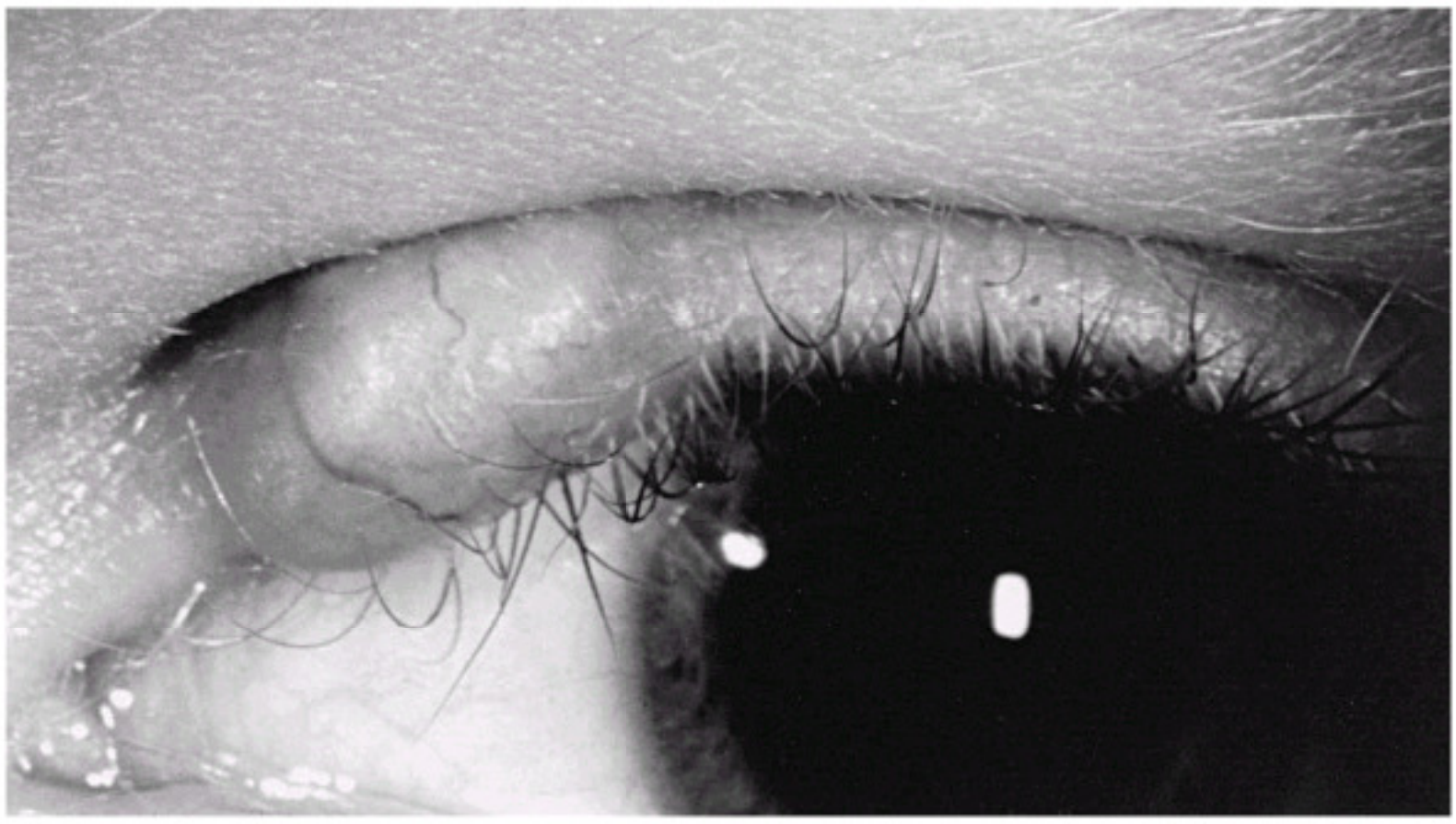


Figure 21.5 Neurilemoma of eyelid.

CONJUNCTIVAL TUMORS

The conjunctiva can be the site of origin of several tumors and pseudotumors that are discussed in detail in the literature (3).

Dermoid

Conjunctival dermoid is a congenital solid mass that occurs most often at the corneoscleral limbus inferotemporally (Fig. 21.6). It can occasionally be found over the central portion of the cornea. The round, yellow-white tumor often has fine hairs on its surface. Histopathologically, it is a choristomatous mass lined by keratinizing stratified squamous epithelium and containing dermal elements. The conjunctival dermoid is often a part of Goldenhar syndrome, a nonhereditary condition that is characterized by preauricular appendages, deafness, and vertebral anomalies (3,16,17).

Epibulbar Osseous Choristoma

Epibulbar osseous choristoma is a choristomatous malformation consisting of a focal deposit of mature bone on

the sclera beneath the conjunctiva. It most often occurs superotemporally as a hard fixed mass. This stationary lesion can be observed if it is asymptomatic or locally excised if it is symptomatic (3,18).

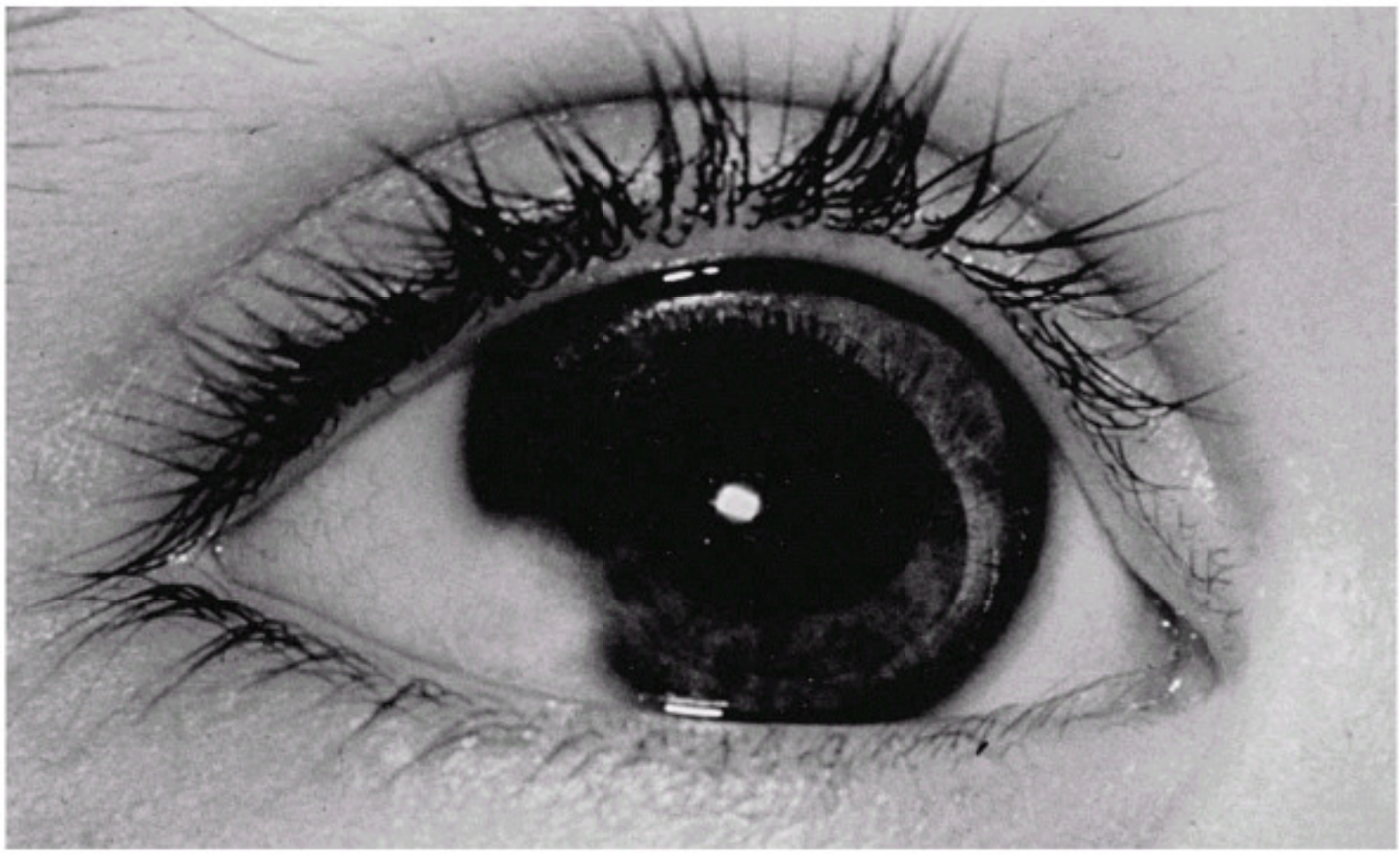


Figure 21.6 Limbal dermoid.

Complex Choristoma

A complex choristoma is a mass composed of a variety of ectopic tissues such as cartilage, lacrimal gland adipose tissue, and smooth muscle. It may assume a variety of clinical appearances on the conjunctiva, but it generally appears as a diffuse, fleshy thickening of the epibulbar tissues (Fig. 21.7). It is often seen in association with the nevus sebaceous of Jadassohn and arachnoid cysts as a part of organoid nevus syndrome (3,19,20). It is described and illustrated in Chapter 22.

Papilloma

Squamous papilloma can occur on the conjunctiva of young children as either a sessile vascular lesion or fleshy papillomatous mass. It is believed to be induced by human papillomavirus. If a conjunctival papilloma is not responsive to topical corticosteroids, then surgical excision and conjunctival cryotherapy is prudent. Oral cimetidine has been shown to be effective treatment for recurrent cases (21).

Nevus

Conjunctival nevus is a variably pigmented, cystic mass that occurs on the bulbar conjunctiva usually in the interpalpebral area (3,22) (Fig. 21.8). It usually becomes clinically apparent at about puberty and generally remains stable throughout life. In rare instances, a conjunctival nevus undergoes malignant transformation into malignant melanoma. Enlarging lesions are generally best managed by alcohol keratectomy, local excision, and supplemental cryotherapy (3,22).

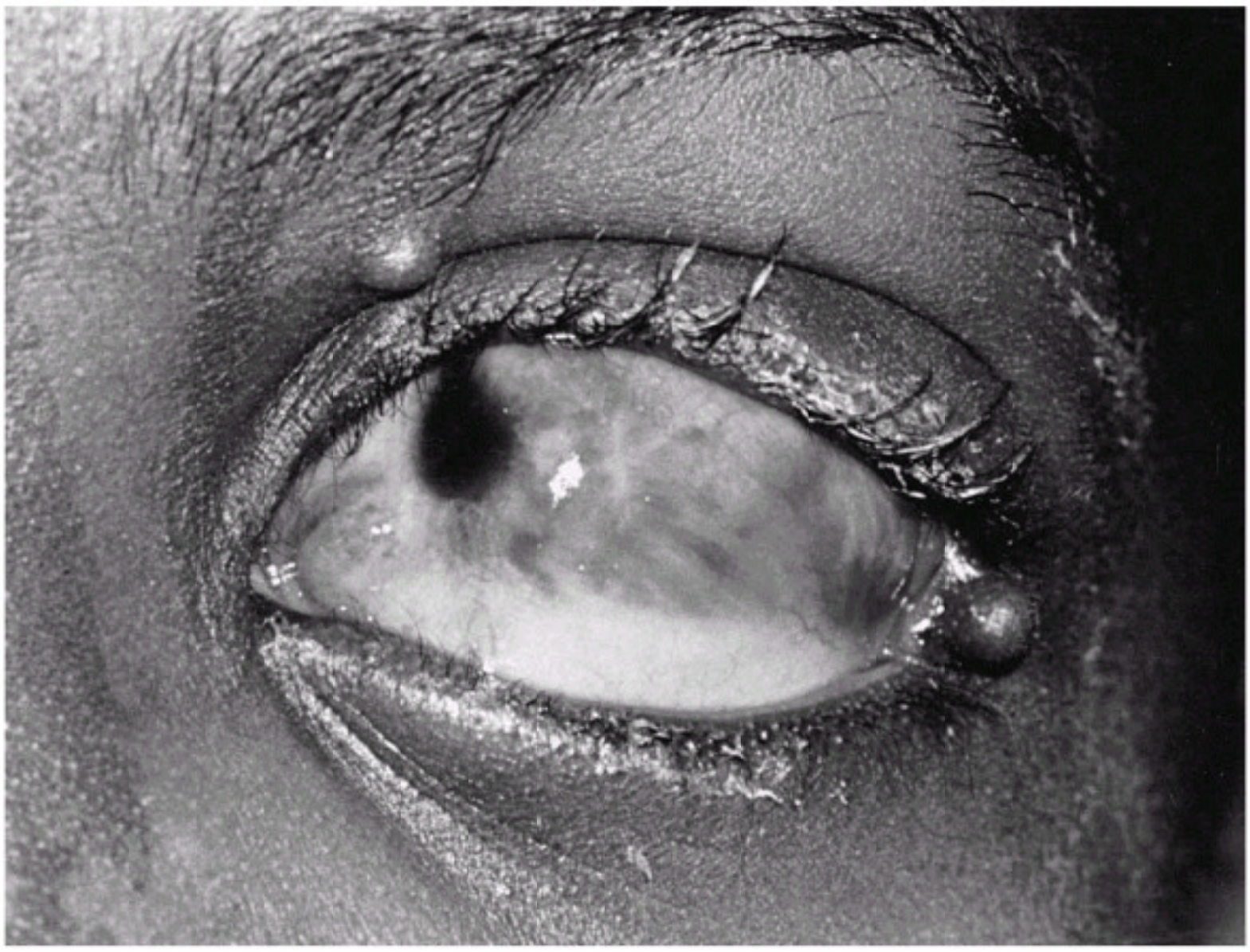


Figure 21.7 Complex choristoma of conjunctiva.

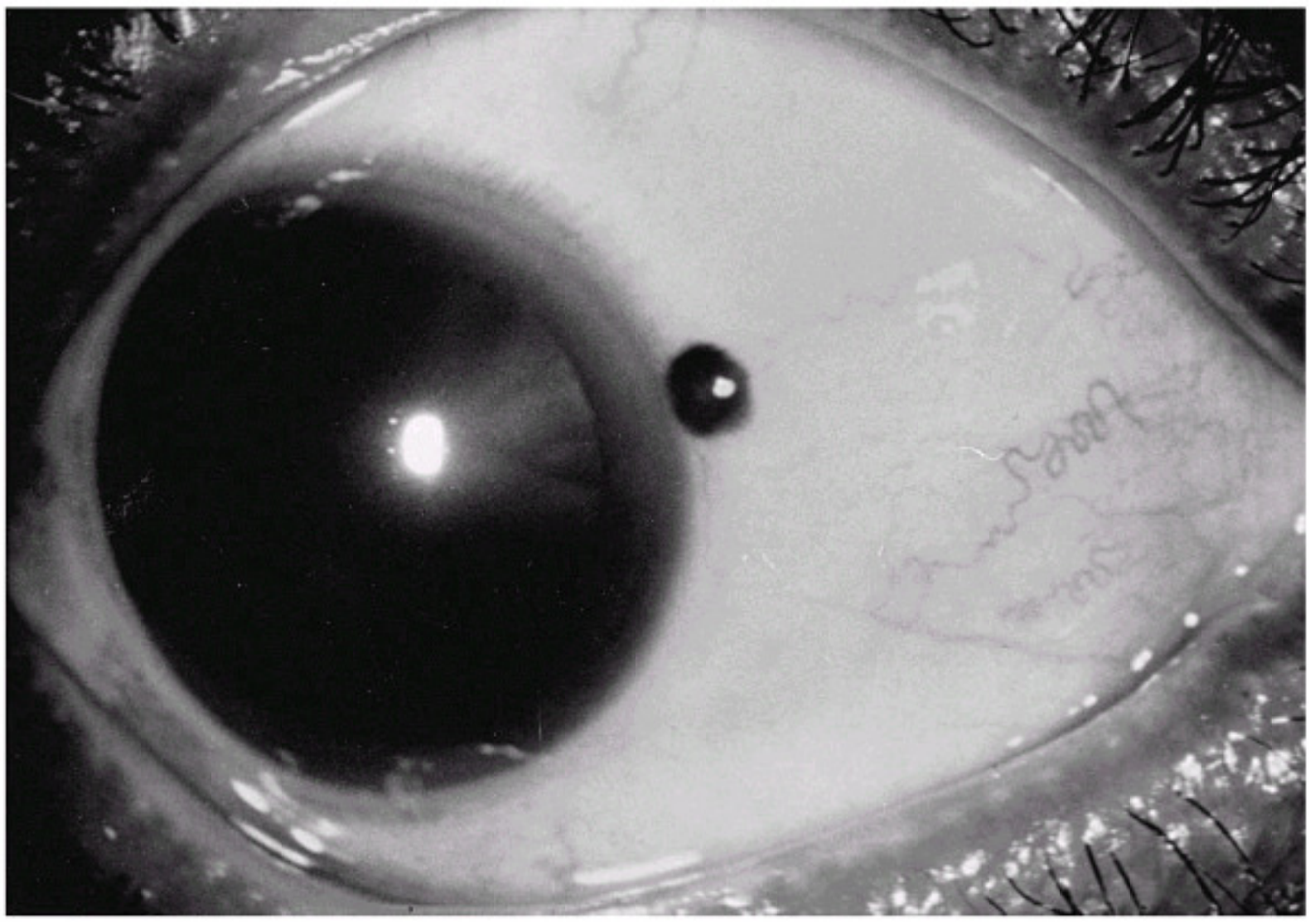


Figure 21.8 Conjunctival nevus.

Congenital Ocular Melanocytosis

Although it is not strictly in the conjunctiva, congenital ocular melanocytosis is included here because it is an important epibulbar lesion of childhood. It is a congenital, diffuse, patchy epibulbar pigmentation that is situated deep to the conjunctiva in the sclera (Fig. 21.9). There is usually diffuse pigmentation of the ipsilateral iris, causing heterochromia iridium. If the pigmentation extends onto the surrounding eyelid, it is called oculodermal melanocytosis, or nevus of Ota. Patients with congenital ocular melanocytosis have a higher incidence of malignant melanoma of the uveal tract, usually later in life (4,23). Occasionally a uveal melanoma occurs in a child with ocular melanocytosis (24). Hence, an ophthalmologist should perform a fundus examination every year.

Pyogenic Granuloma

Pyogenic granuloma is fleshy pink mass that can occur anywhere on the conjunctiva (Fig. 21.10). It develops fairly rapidly following surgical or nonsurgical trauma. Histopathologically, it is a proliferation of small blood vessels

with acute and chronic inflammatory cells. It is neither pyogenic nor granulomatous and hence, the term “pyogenic granuloma” is a misnomer. It can be treated with topical corticosteroids or resection (3).

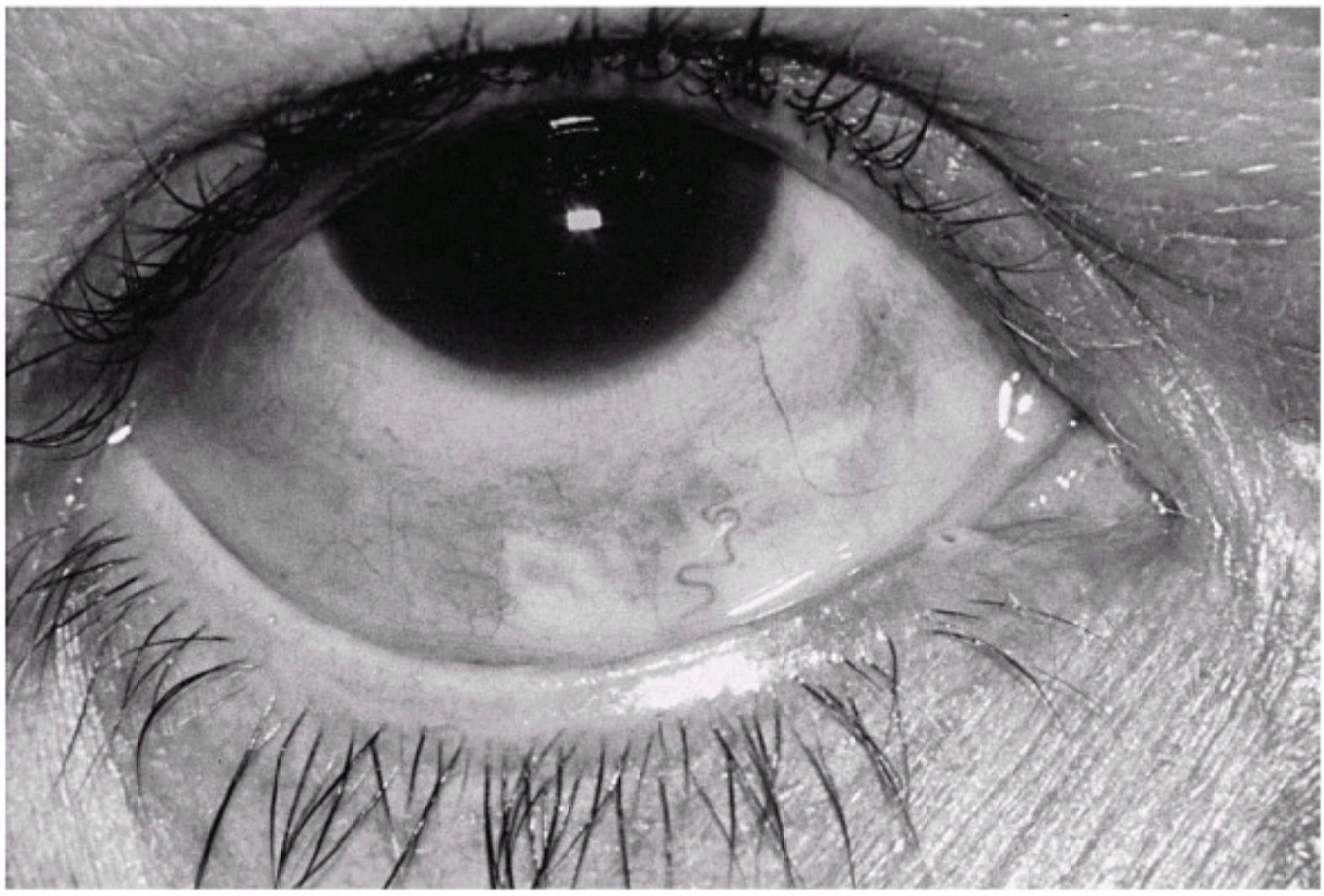


Figure 21.9 Congenital ocular melanocytosis.

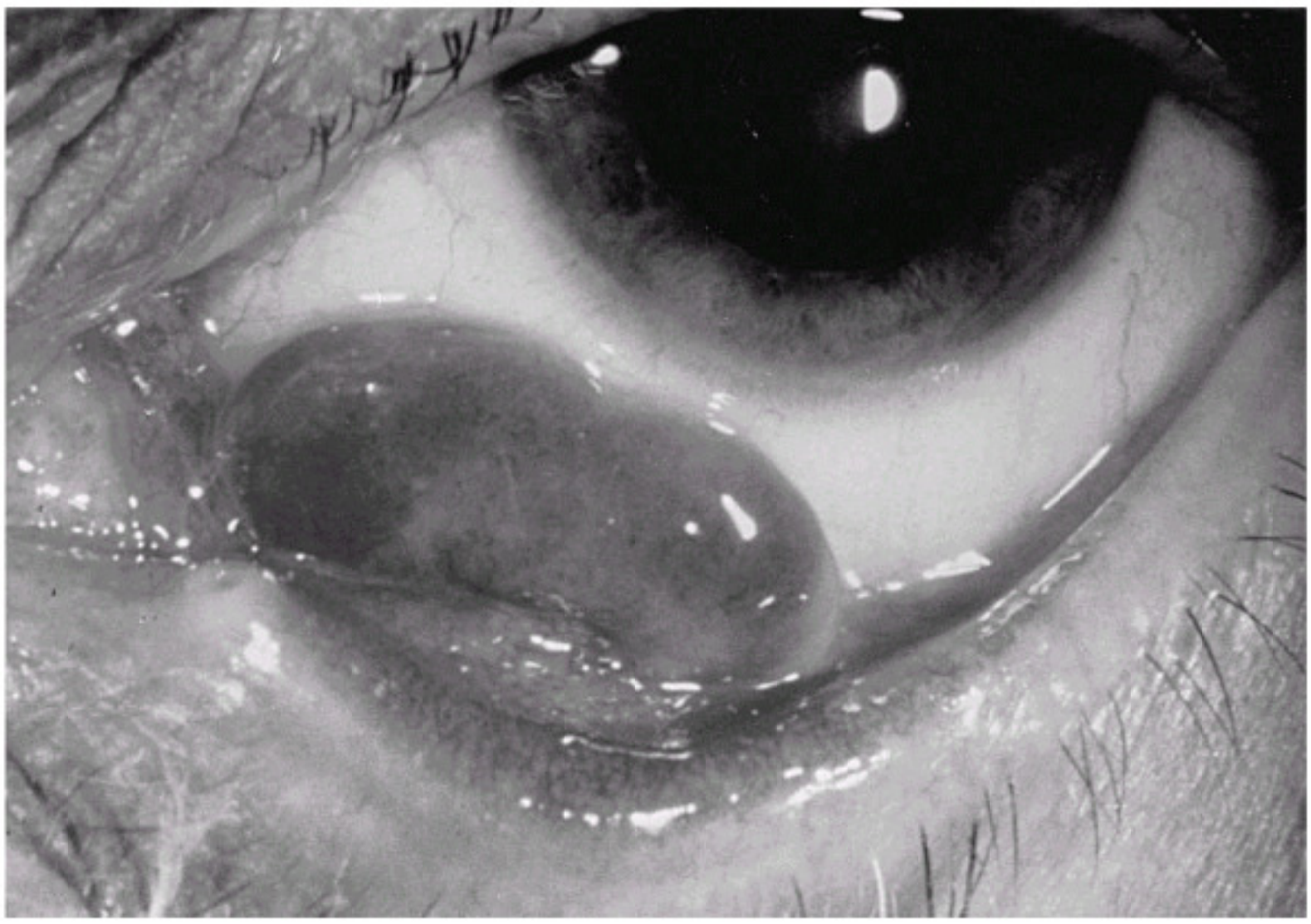


Figure 21.10 Pyogenic granuloma of the conjunctiva.

Kaposi Sarcoma

Kaposi sarcoma, described under eyelid tumors, can also occur in the conjunctiva in patients with AIDS (3). In the conjunctiva, it appears as a diffuse red mass that may be mistaken for hemorrhagic conjunctivitis (Fig. 21.11).

INTRAOCULAR TUMORS

Retinoblastoma

Retinoblastoma is the most common intraocular malignancy of childhood (2,3). It occurs in hereditary and nonhereditary forms (25). The hereditary form is usually bilateral and multifocal, whereas the nonhereditary form is unilateral and unifocal. The affected child usually presents with unilateral or bilateral leukocoria (Fig. 21.1), strabismus, or occasionally orbital cellulitis (26). Although it is usually diagnosed in children under 2 years of age, it can occur in older children (27) Small fundus tumors are gray-white in color (Fig. 21.12) and often show foci of chalkycolored calcification. Medium sized tumors are more elevated and have prominent dilated tortuous retinal blood vessels that feed and drain the tumor (3) (Fig. 21.13).

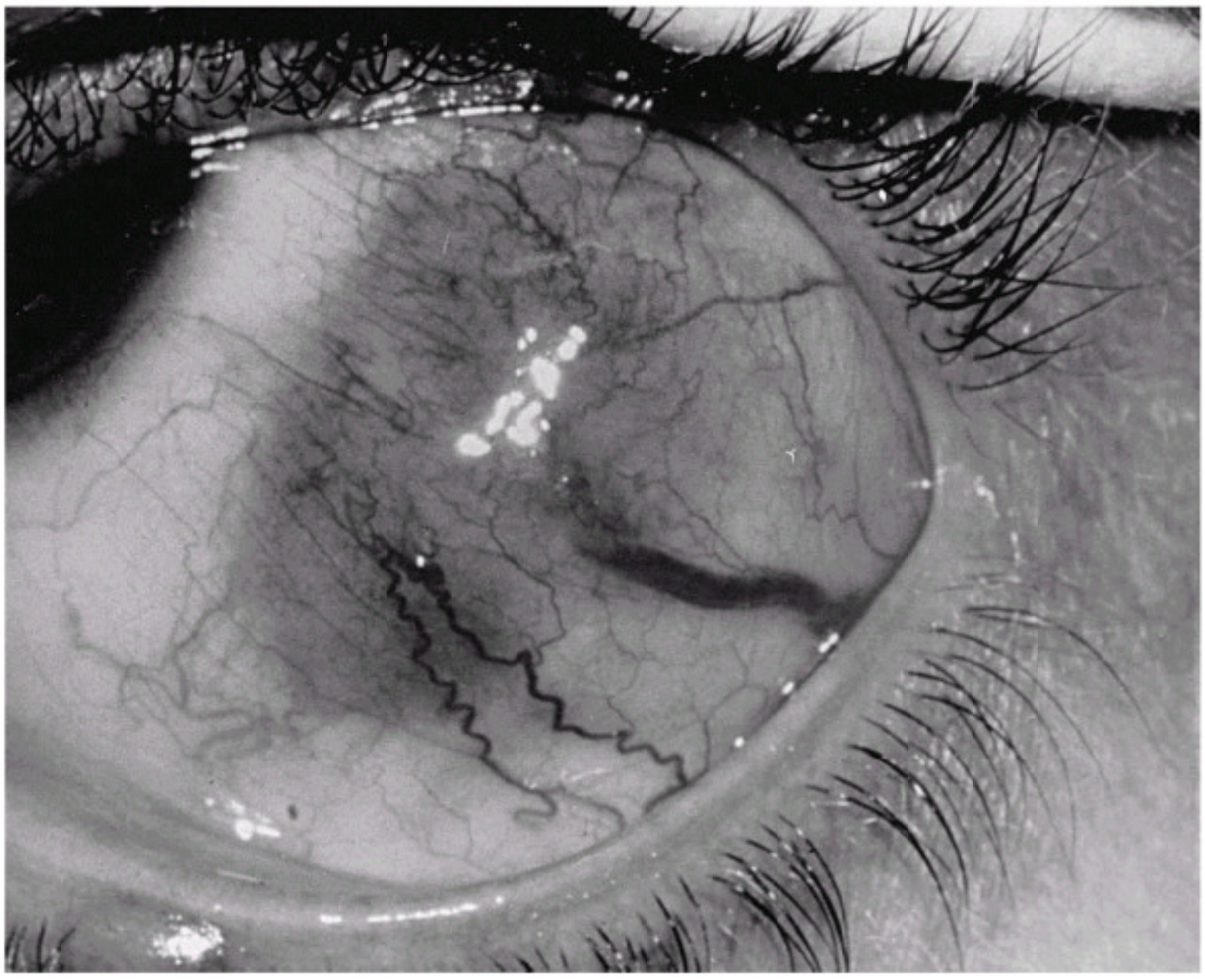


Figure 21.11 Kaposi sarcoma of the conjunctiva.

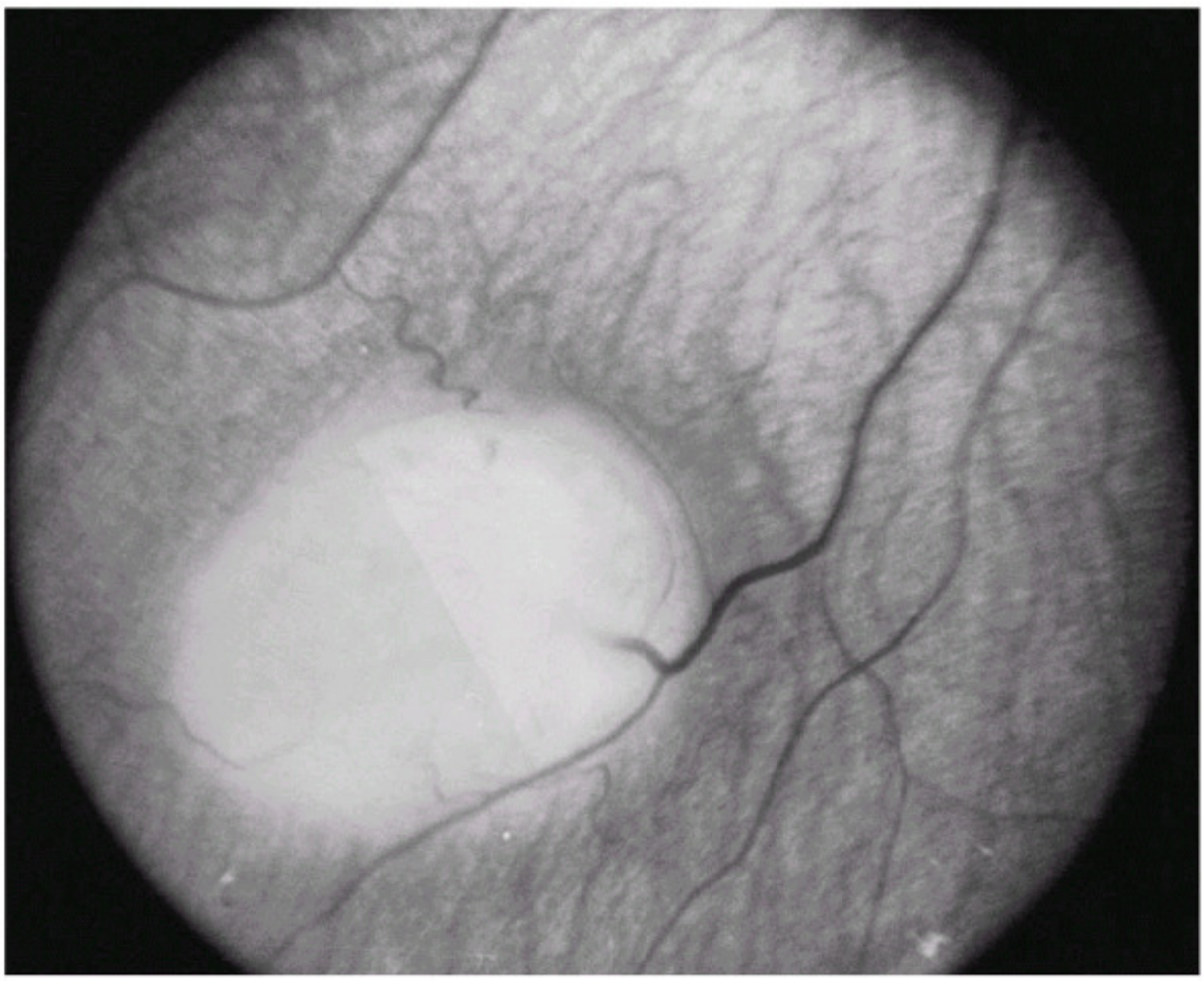


Figure 21.12 Fundus photograph of small retinoblastoma.

The diagnosis of retinoblastoma is best made by an experienced ophthalmologist using slit-lamp biomicroscopy and indirect ophthalmoscopy. Ancillary studies that may

provide diagnostic help are ultrasonography (Fig. 21.14) and CT (2,3) (Fig. 21.15).

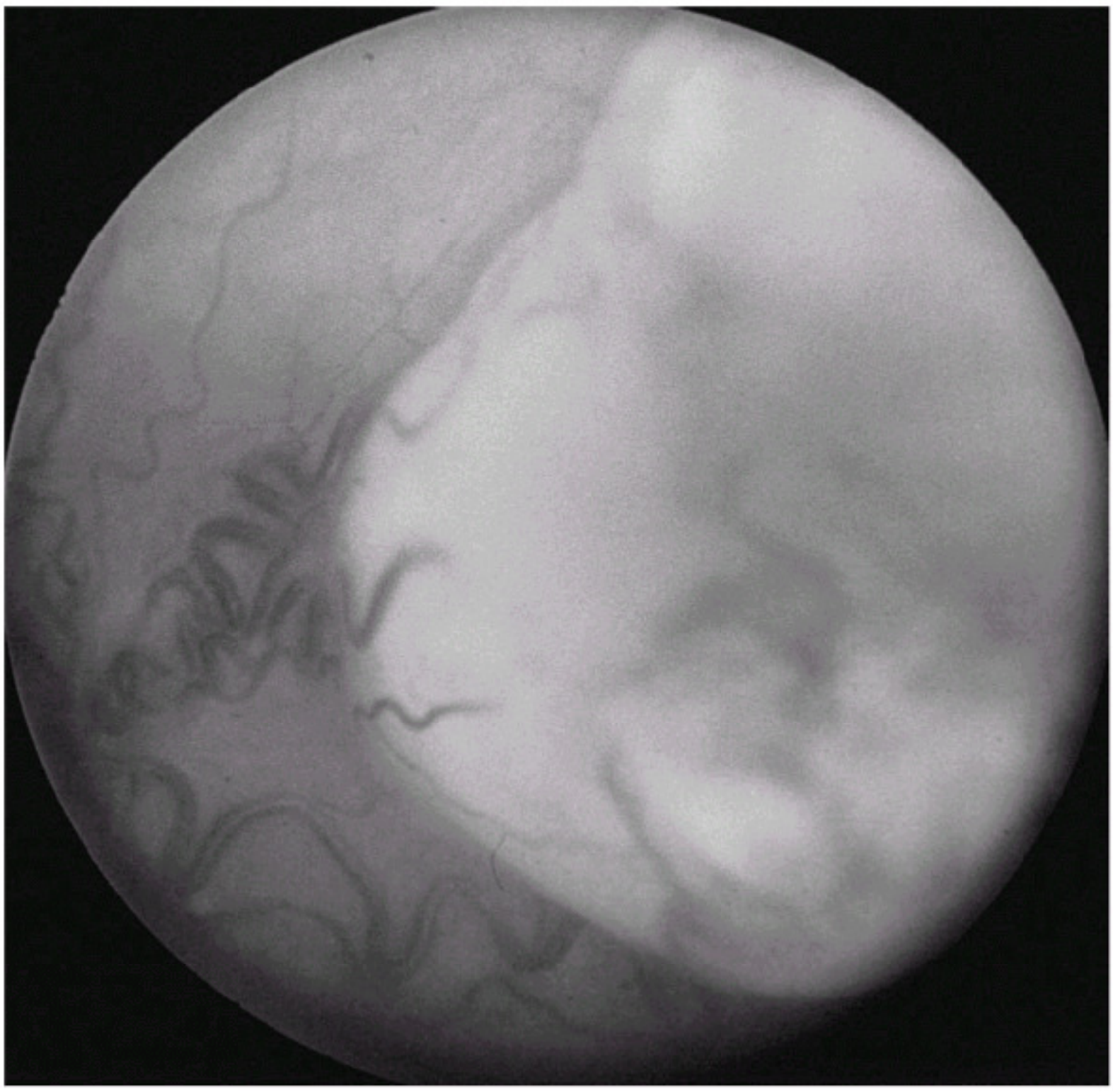


Figure 21.13 Fundus photograph of medium-sized retinoblastoma.

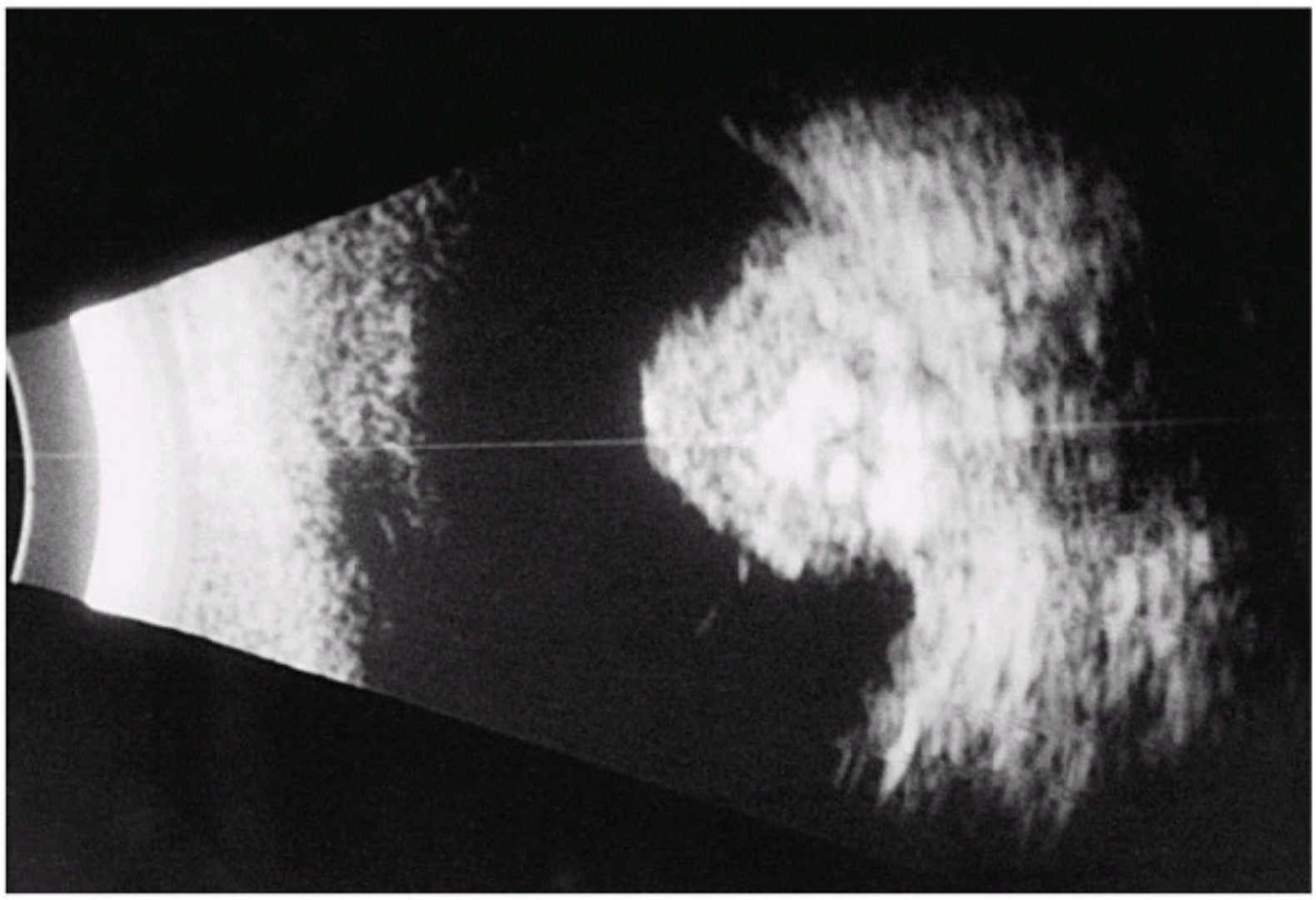


Figure 21.14 B-scan ultrasonogram of retinoblastoma.

The management of retinoblastoma is very complex and requires knowledge and experience (2,3). Treatment varies depending on number, size, and location of the tumors, and each case must be individualized depending on the clinical circumstances. More advanced tumors are managed by enucleation (Fig. 21.16). The hydroxyapatite implant has been used extensively in children and provides a good cosmetic appearance with fairly good motility of the implant (28) (Fig. 21.17). In recent years, fewer eyes have been enucleated because earlier diagnosis and improvements in conservative methods of management have been refined.

Less advanced tumors can be treated with external beam irradiation, cryotherapy, laser photocoagulation, or episcleral plaque brachytherapy (29,30,31,32). Recently techniques of chemoreduction and chemothermotherapy have been added to the treatment alternatives (33,34,35,36,37,38,39,40,41,42,43). With continued improvement of these techniques, it is anticipated that fewer eyes will require enucleation or external beam irradiation and that more patients will be managed with conservative methods.

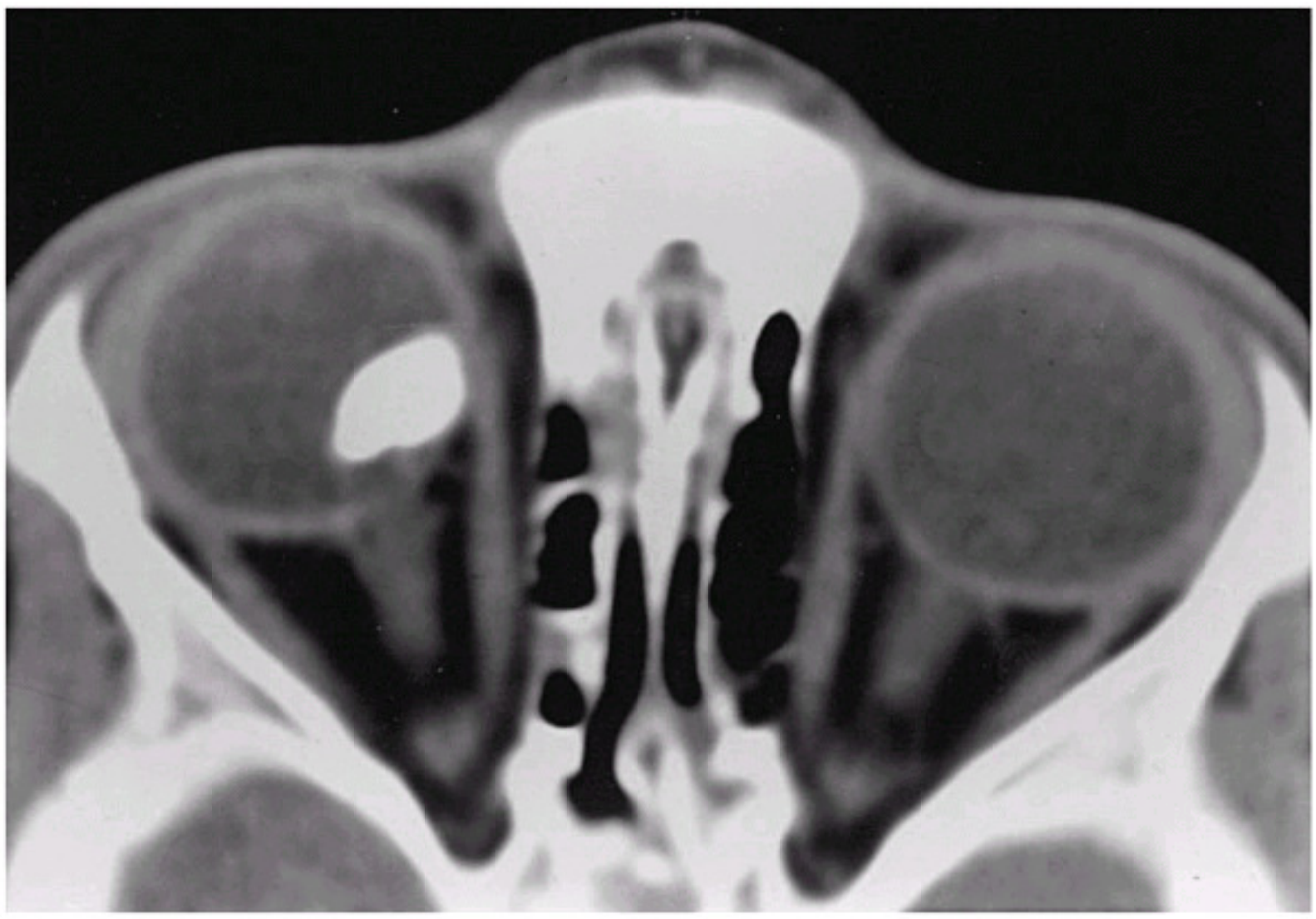


Figure 21.15 Axial computed tomography scan showing intraocular calcium in retinoblastoma.

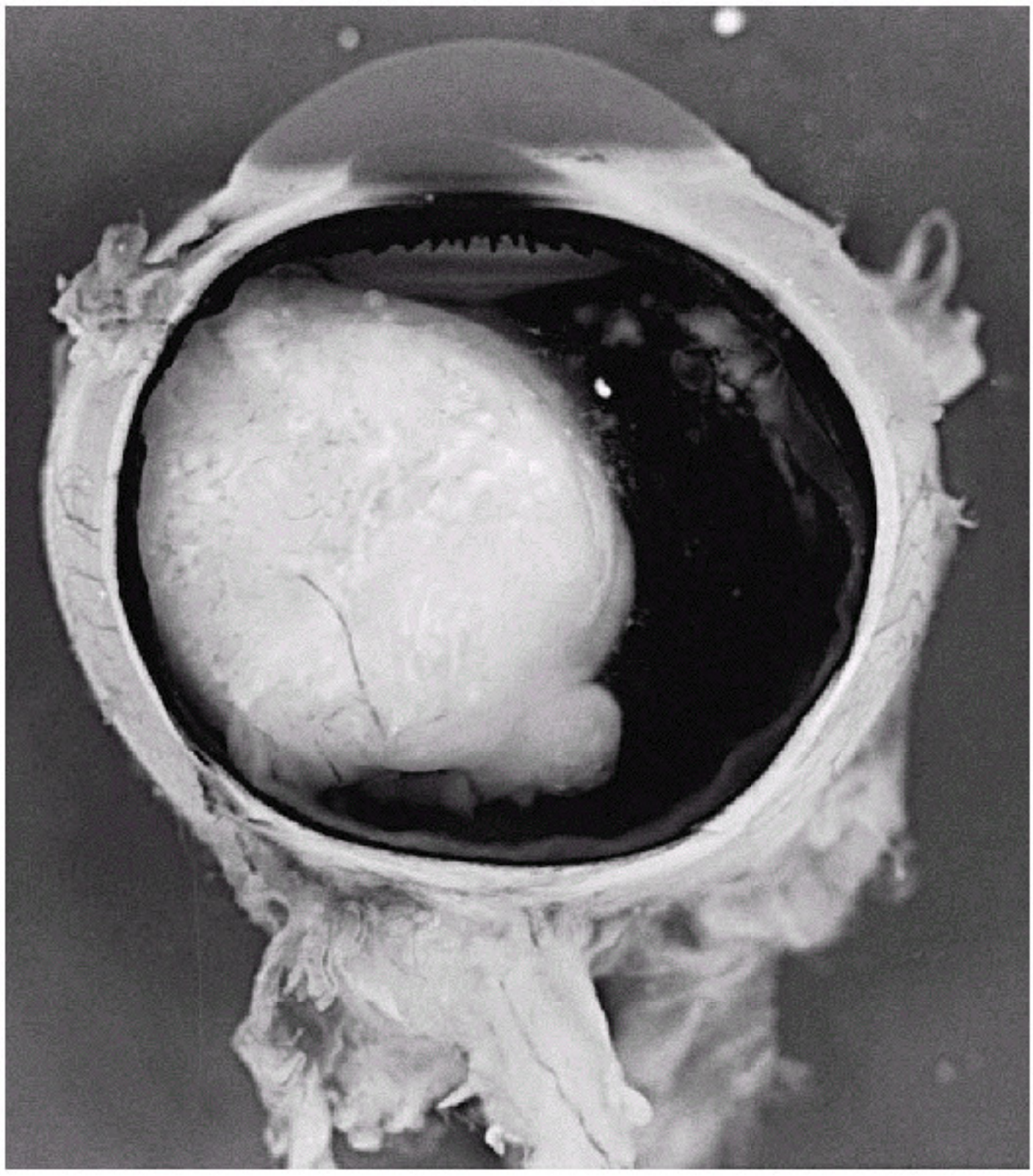


Figure 21.16 Gross section of enucleated eye showing retinoblastoma.

There have been several recent developments related to the genetics of retinoblastoma (25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44). The retinoblastoma gene is now recognized to be a recessive suppressor gene located on chromosome 13q14, and some affected children have other systemic features of 13q deletion syndrome. All family members of patients with retinoblastoma should be examined by an ophthalmologist.

Retinal Capillary Hemangioma

Retinal capillary hemangioma is a reddish-pink retinal mass that can occur in the peripheral fundus or adjacent to the optic disc (2,4). The tumor often has prominent dilated retinal blood vessels that supply and drain the lesion (Fig. 21.18). Untreated lesions can cause intraretinal exudation and retinal detachment. Fluorescein angiography shows early filling and intense late staining of the tumor (4). Patients with retinal capillary hemangioma should be evaluated for von Hippel-Lindau syndrome (VHL), an autosomal-dominant condition characterized by cerebellar hemangioblastoma, pheochromocytoma, hypernephroma, and other visceral tumors and cysts (4,45). If the tumor produces macular exudation of retinal detachment, it can be treated with laser or cryotherapy. The gene responsible for VHL has been localized to the short arm of chromosome 3 (45).

Retinal Cavernous Hemangioma

The retinal cavernous hemangioma typically appears as a globular or sessile intraretinal lesion that is composed of

multiple vascular channels with a reddish-blue color (4,46) (Fig. 21.19). It may show patches of gray-white fibrous tissue on the surface, but it does not cause the exudation that characterizes the retinal capillary hemangioma. Cavernous hemangioma is a congenital retinal vascular hamartoma that is probably present at birth. This tumor can be associated with similar intracranial and cutaneous vascular hamartomata, but the syndrome does not have the visceral tumors that characterize VHL syndrome. As a general rule, retinal cavernous hemangioma requires no active treatment. If vitreous hemorrhage should occur, laser or cryotherapy to the tumor can be attempted. If vitreous blood does not resolve, removal by vitrectomy may be necessary.

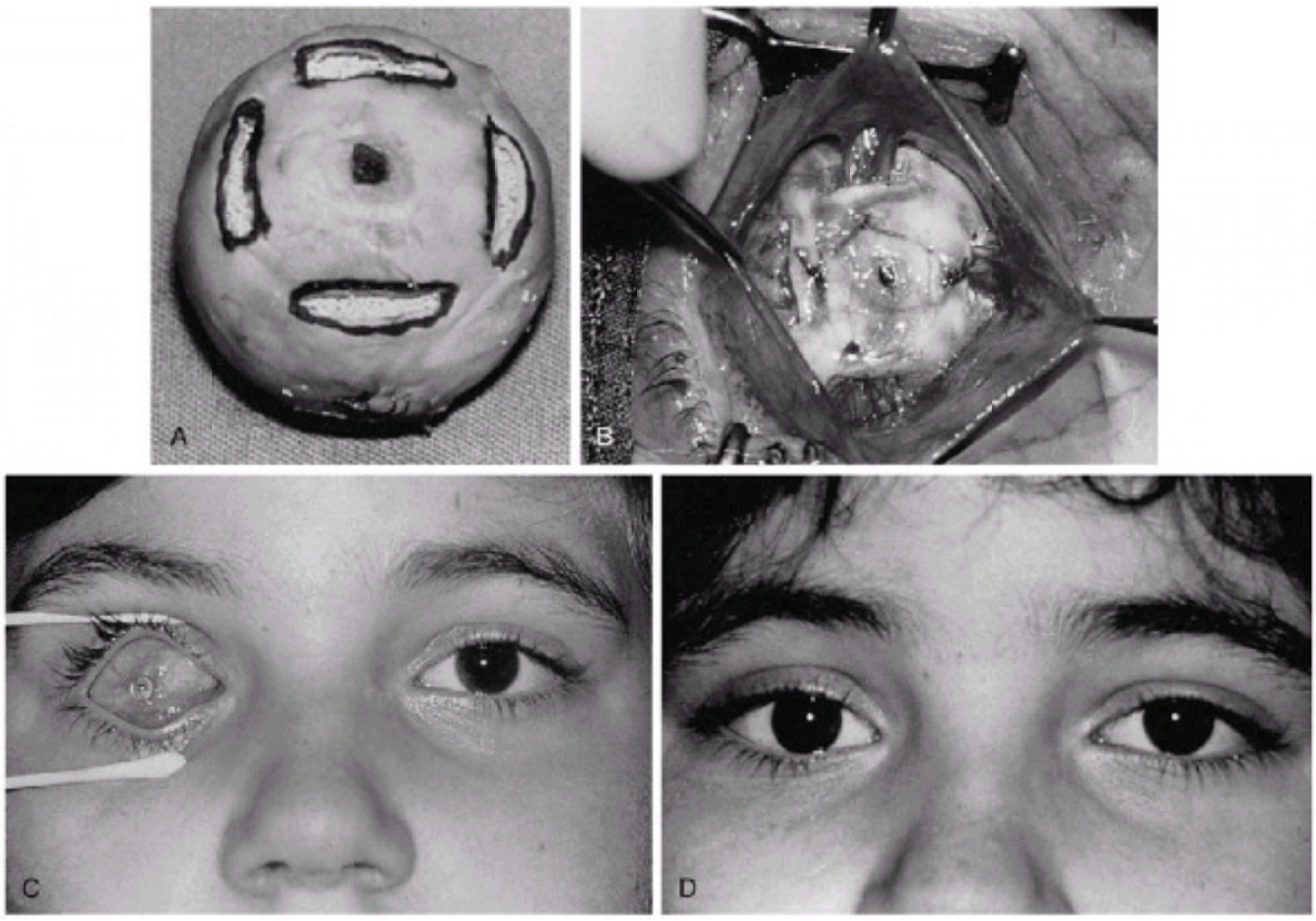


Figure 21.17 Hydroxyapatite implant following enucleation in a child. **A:** Round implant has been wrapped in donor sclera and grooves cut for placement of the rectus muscle insertions. **B:** Implant placed into socket after enucleation. **C:** anophthalmic socket showing plastic peg in place. **D:** Appearance of child showing excellent cosmetic results. Ocular motility was excellent.

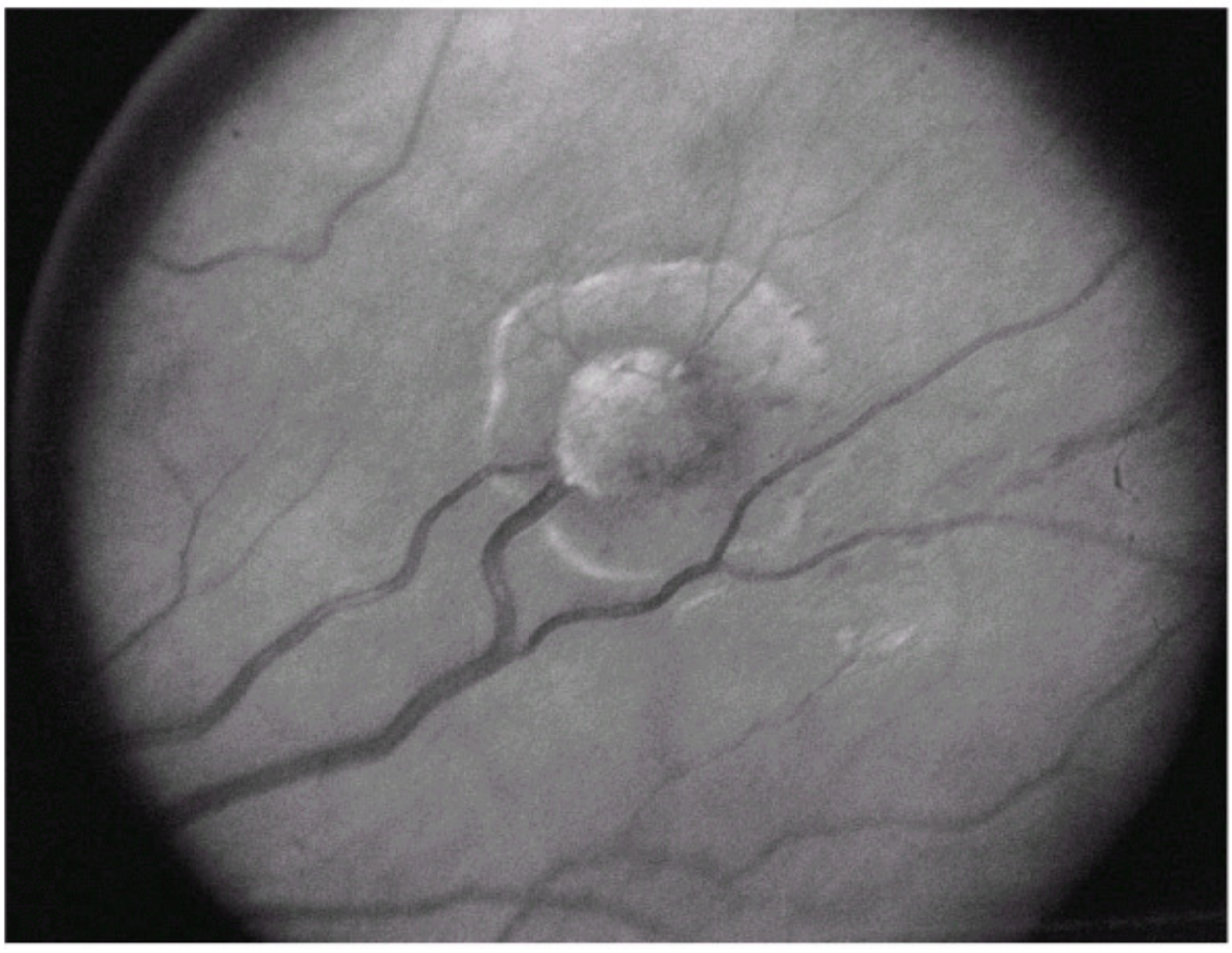


Figure 21.18 Retinal capillary hemangioma in a patient with von Hippel-Lindau syndrome.

Retinal Racemose Hemangioma

The retinal racemose hemangioma is not a true neoplasm but rather a simple or complex arteriovenous communication (2,4,47). It is characterized by a large, dilated, tortuous retinal artery that passes from the optic disc for a variable distance into the fundus, where it then communicates directly with a similarly dilated retinal vein that passes back

to the optic disc (Fig. 21.20). It can occur as a solitary unilateral lesion or it can be part of Wyburn-Mason syndrome, which is characterized by other similar lesions in the midbrain and sometimes the orbit, mandible, and maxilla (4). It does not appear to have a hereditary tendency.

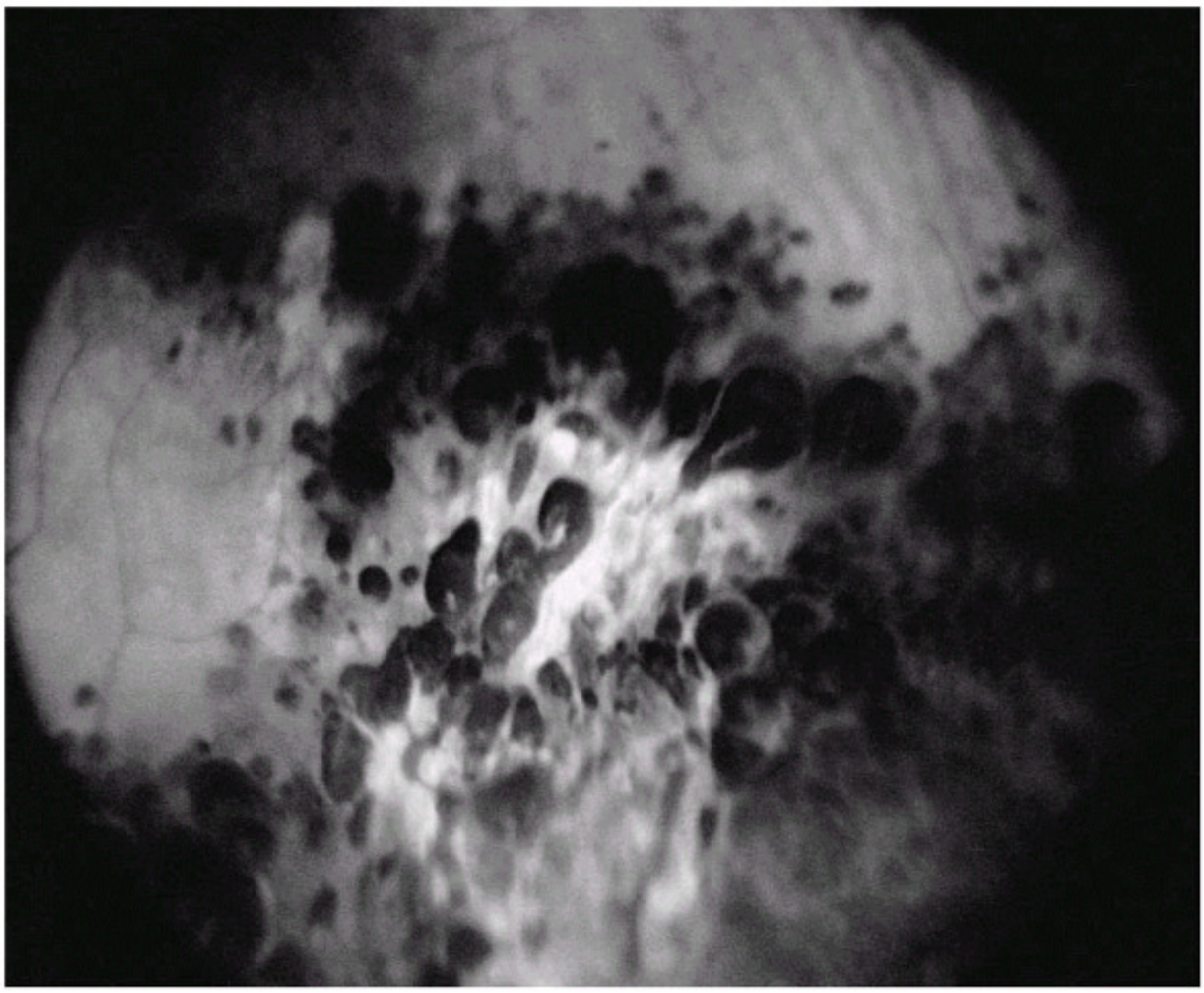


Figure 21.19 Retinal cavernous hemangioma.

Astrocytic Hamartoma of the Retina

Astrocytic hamartoma of the retina is a yellow-white intraretinal lesion that can also occur in the peripheral fundus or optic disc region (4). The lesion may be homogeneous or it may contain glistening foci of calcification (Fig. 21.21). Unlike retinal capillary hemangioma, it does not generally produce significant exudation or retinal detachment. Patients with astrocytic hamartoma of the retina should be evaluated for tuberous sclerosis, characterized by intracranial astrocytoma, cardiac rhabdomyoma, renal angiomyolipoma, pleural cysts, and other tumors and cysts. Although it is usually fairly stable, retinal astrocytic hamartoma can sometimes demonstrate aggressive growth (48).

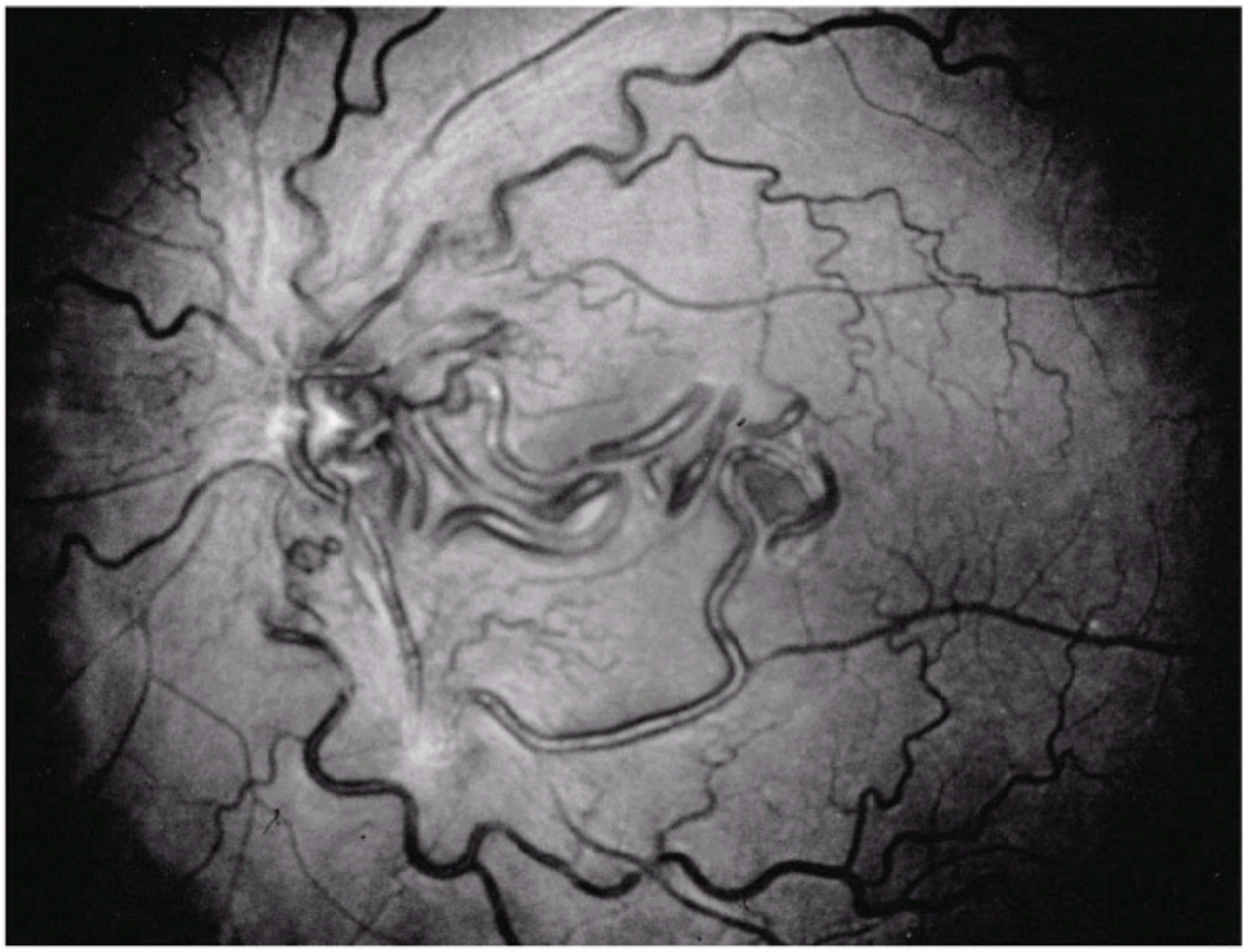


Figure 21.20 Retinal racemose hemangioma.

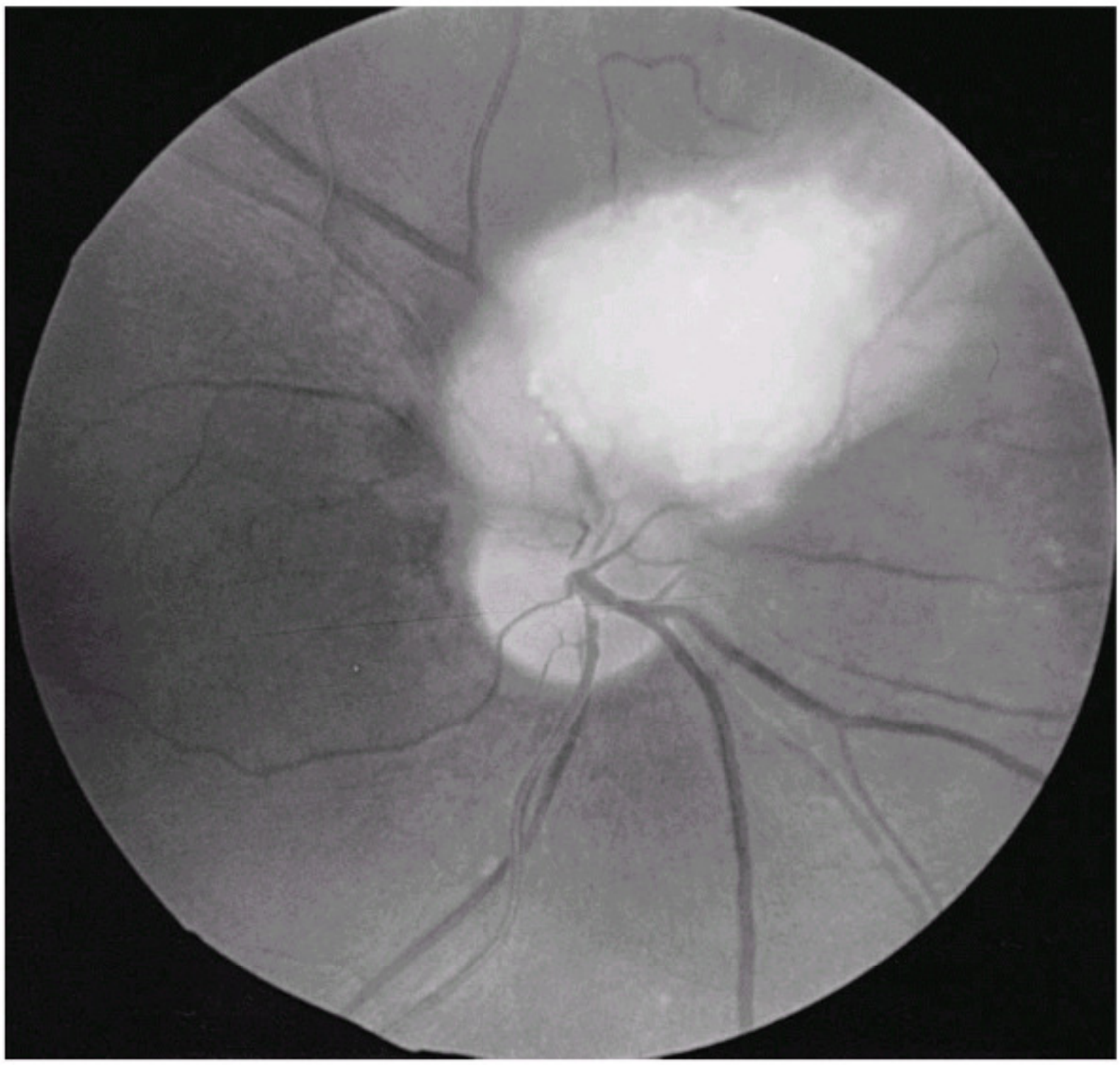


Figure 21.21 Retinal astrocytic hamartoma in a patient with tuberous sclerosis.

Melanocytoma of the Optic Nerve

Melanocytoma of the optic nerve is a deeply pigmented congenital tumor that overlies a portion of the optic disc (2,4,49) (Fig. 21.22). Unlike uveal melanoma that occurs predominantly in whites, melanocytoma occurs with equal frequency in all races. It must be differentiated from malignant melanoma.

Intraocular Medulloepithelioma

Medulloepithelioma is an embryonal tumor that arises from the primitive medullary epithelium or inner layer of

the optic cup (2,4,50,51). It generally becomes clinically apparent in the first decade of life and appears as a fleshy, often cystic mass in the ciliary body (Fig. 21.23). Cataract and secondary glaucoma are frequent complications. Although approximately 60% to 90% are cytologically malignant, intraocular medulloepithelioma tends to be only locally invasive and distant metastasis is exceedingly rare. Larger tumors generally require enucleation of the affected eye. It is possible that some smaller tumors can be resected locally without enucleation, although tumor recurrence frequently requires enucleation (51).

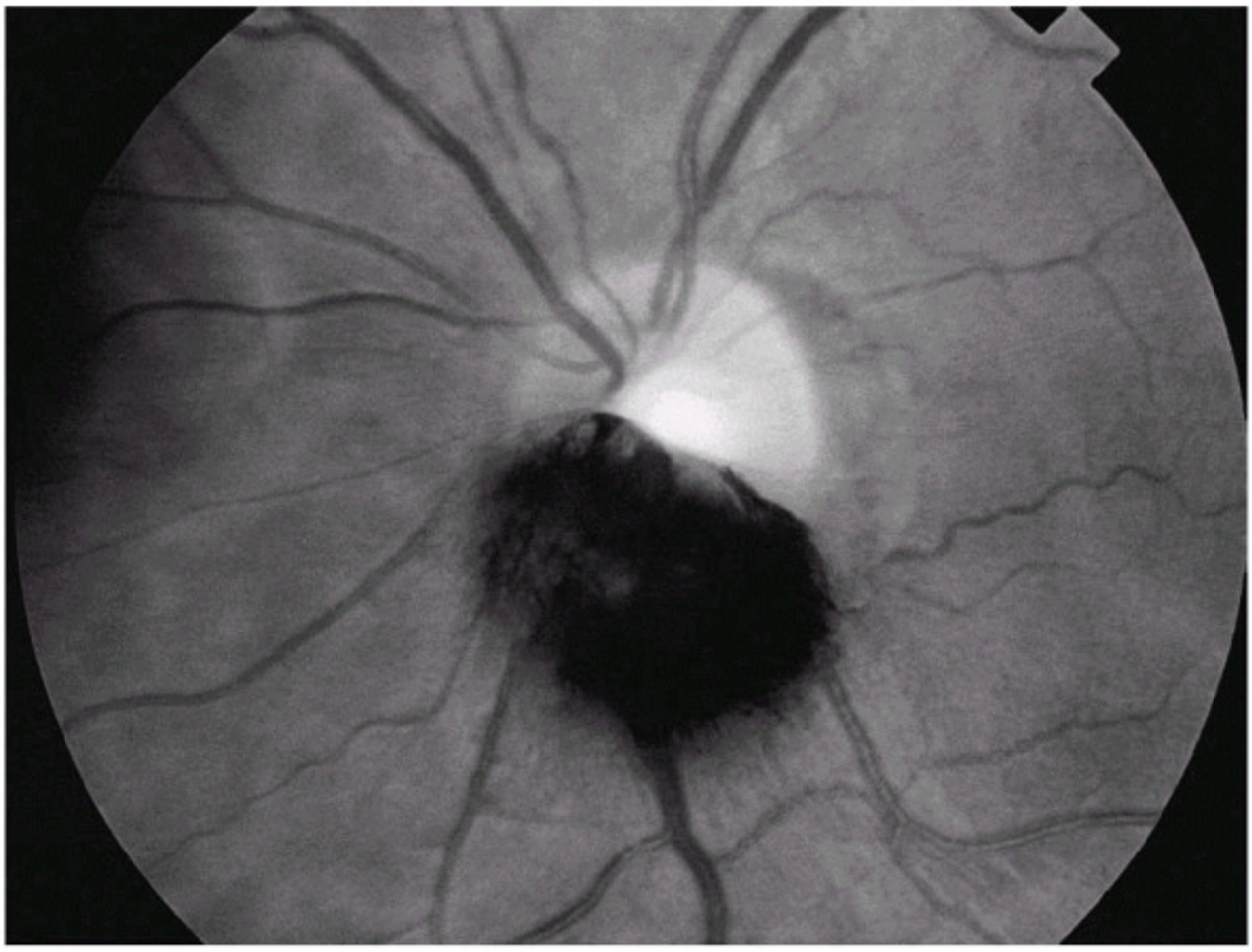


Figure 21.22 Melanocytoma of the optic disc.

Choroidal Hemangioma

Choroidal hemangioma is a benign vascular tumor that can occur as a circumscribed lesion in adults or as a diffuse tumor in children (2,4). The diffuse choroidal hemangioma usually occurs in association with ipsilateral facial nevus flammeus or variations of Sturge-Weber syndrome. Ipsilateral congenital glaucoma is a frequent association. Secondary retinal detachment often occurs. Affected children commonly develop amblyopia in the involved eye (2,4,52).

Choroidal Osteoma

Choroidal osteoma is a benign choroidal tumor that is probably congenital. Although it has been recognized in infancy, it may not be diagnosed clinically until young adulthood (2,4,53,54). It is more common in females. It consists of a plaque of mature bone that generally occurs adjacent to the optic disc (Fig. 21.24). It usually shows slow enlargement and choroidal neovascularization with subretinal hemorrhage as a frequent complication. The pathogenesis is unknown. Serum calcium and phosphorus levels are normal.

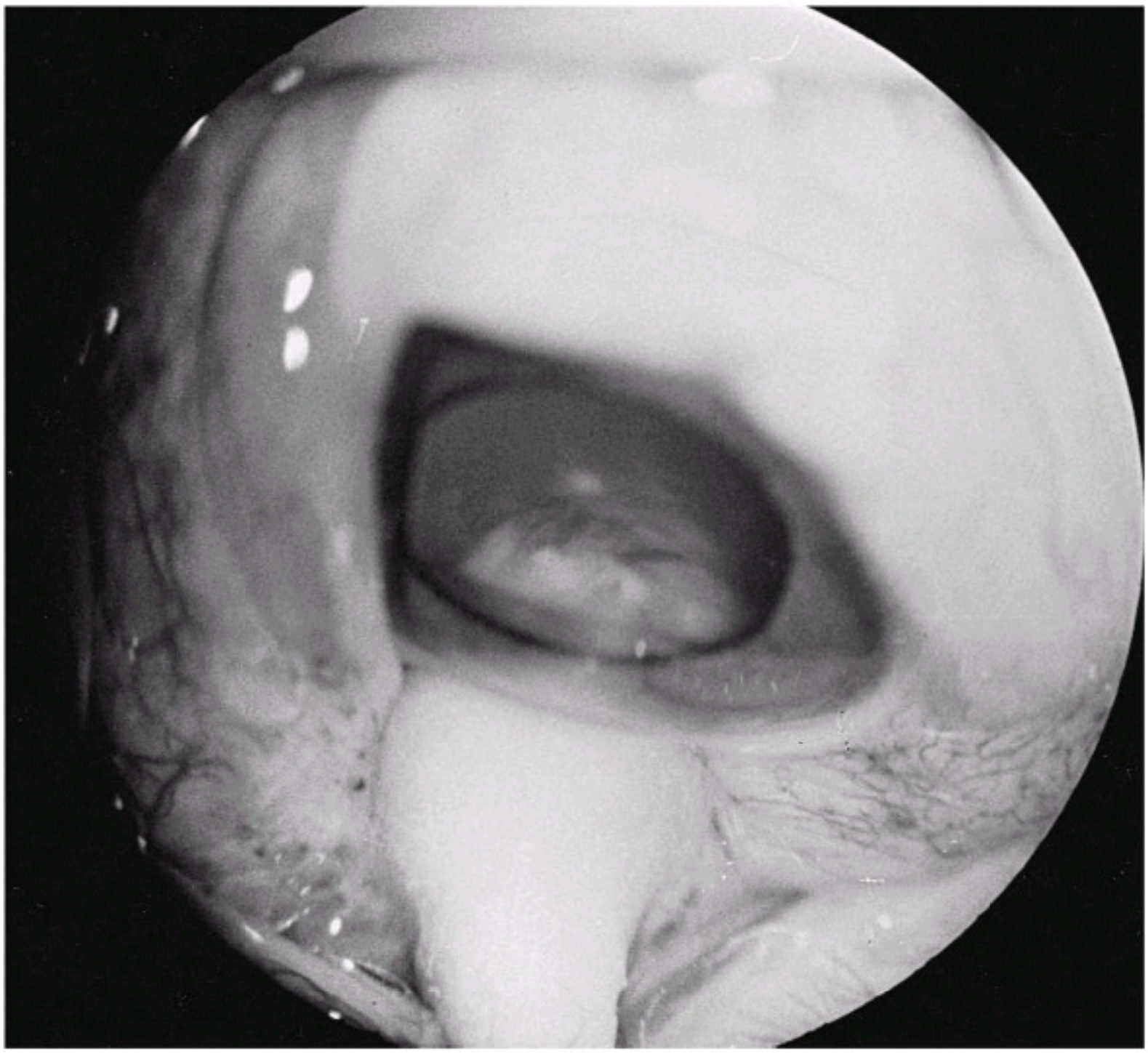


Figure 21.23 Medulloepithelioma (“diktyoma”) of the ciliary body.

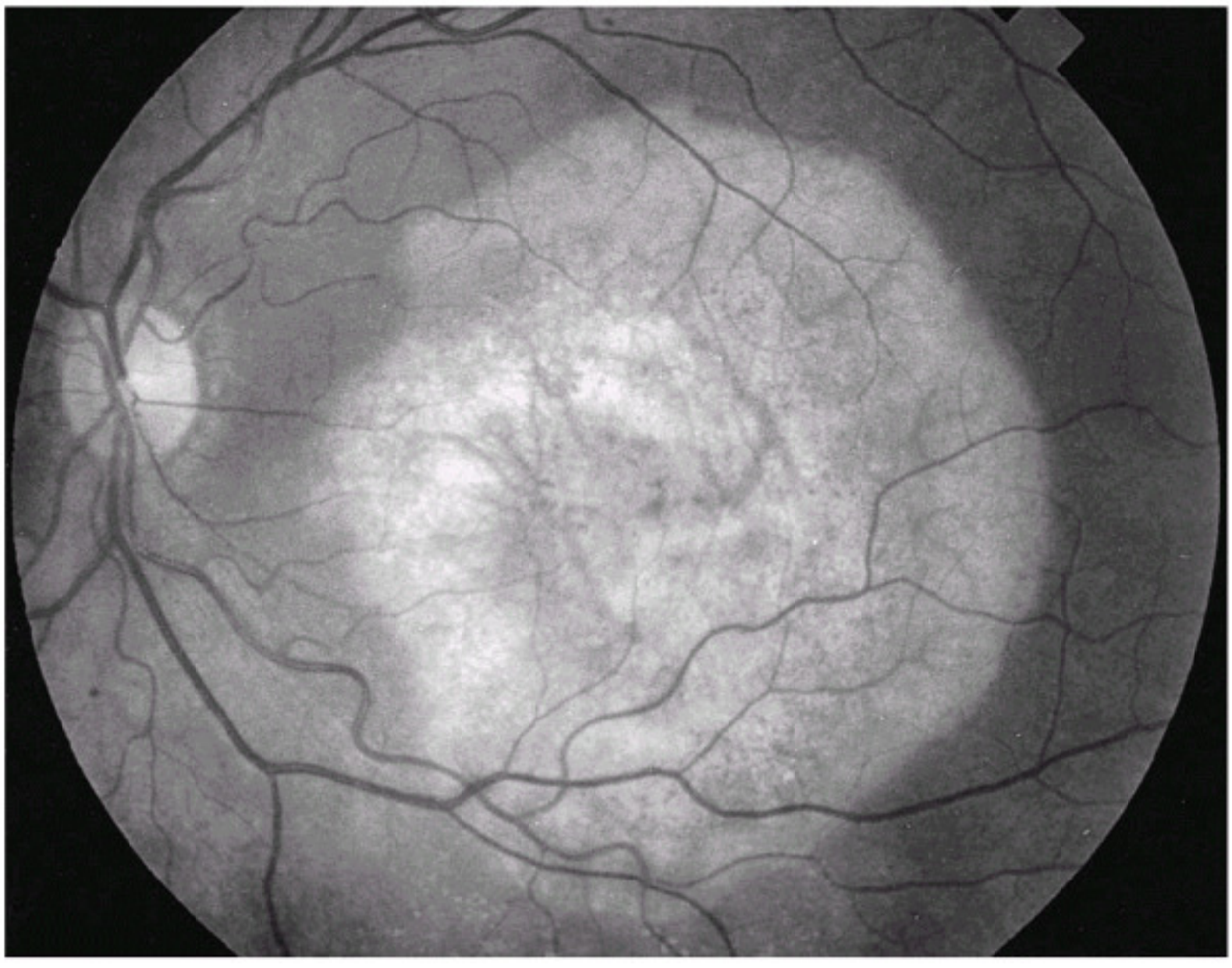


Figure 21.24 Choroidal osteoma.

Uveal Nevus

Uveal nevus is a flat or minimally elevated, variably pigmented tumor that may occur in the iris (Fig. 21.25) or choroid (Fig. 21.26). Although most likely congenital, it is usually asymptomatic and not recognized until later in life. Although most uveal nevi are stationary and nonprogressive, malignant transformation into melanoma can occur in rare instances (2,4).

An important variant of iris nevus is the presence of multiple bilateral slightly elevated melanocytic lesions of the iris, known as Lisch nodules. These lesions become clinically apparent at about age 5 years and are often the first sign of neurofibromatosis. This is further discussed in Chapter 22.

Uveal Melanoma

Although uveal melanoma is generally a disease of adulthood, it is occasionally diagnosed in children (55,56,57). It

is a variably pigmented elevated mass that shows slow progression. If it is not treated early, it has a tendency to metastasize liver, lung, and other distant sites. Most advanced tumors are treated by enucleation. Radiotherapy of local tumor resection can be employed for less advanced tumors.

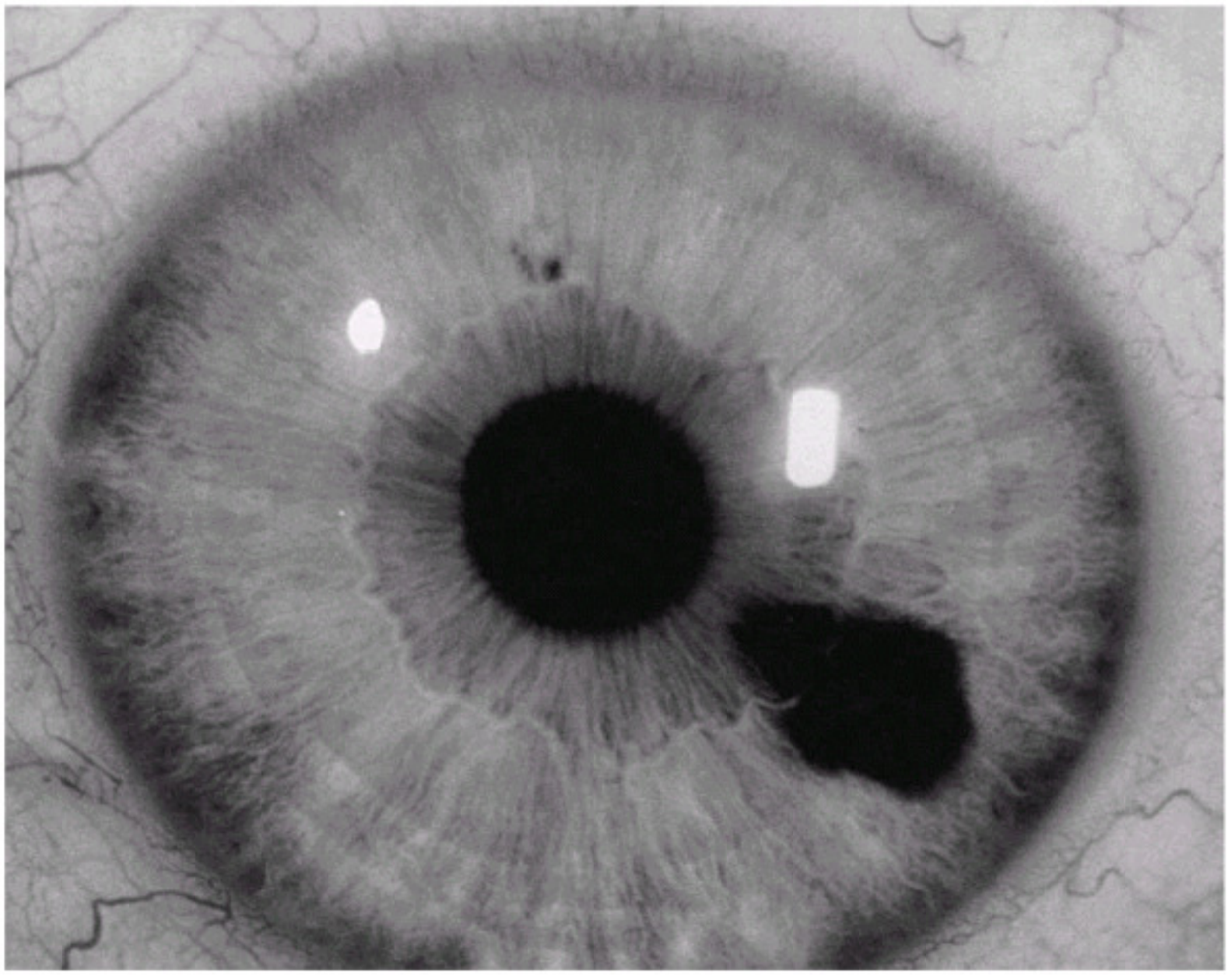


Figure 21.25 Iris nevus.

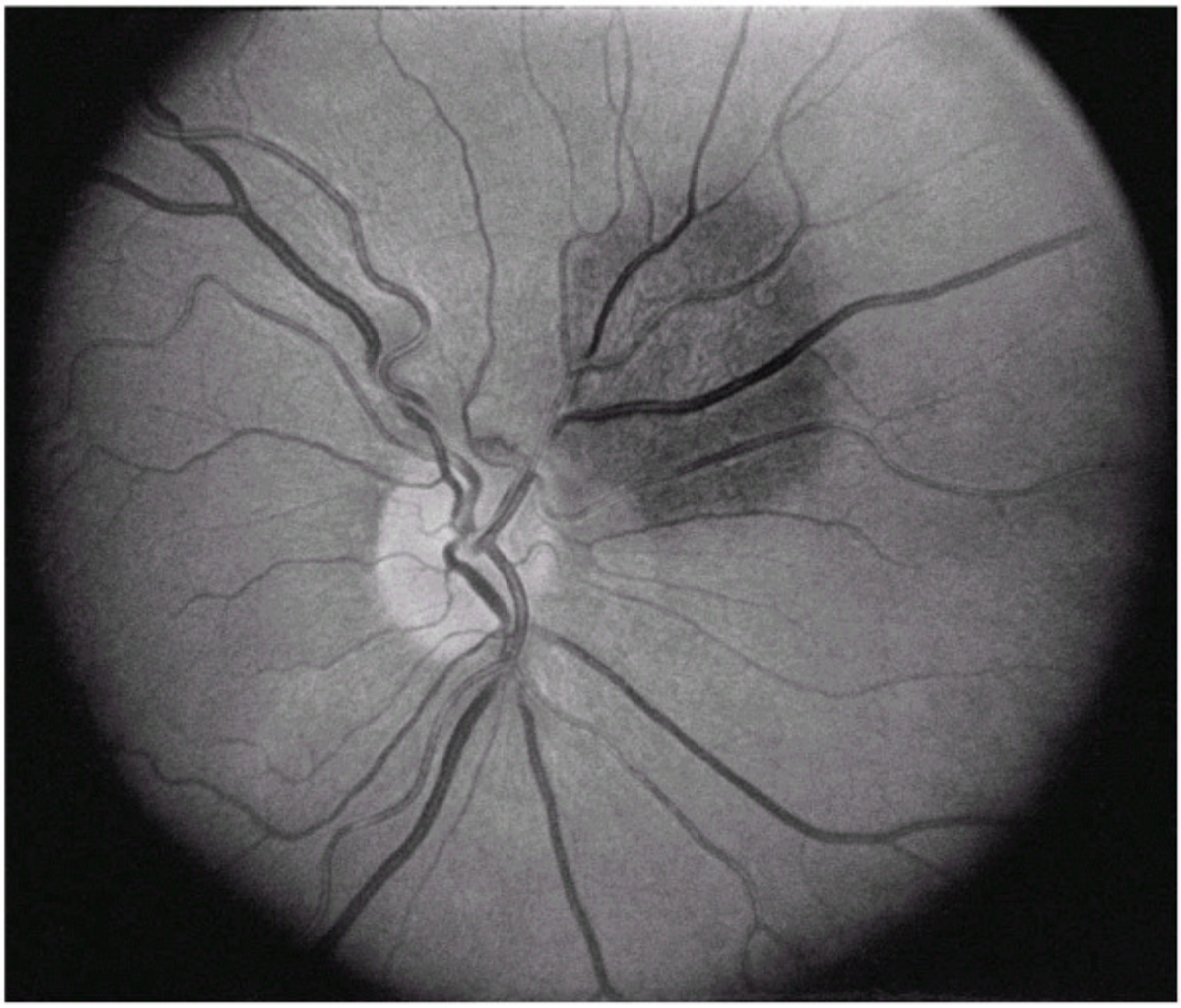


Figure 21.26 Choroidal nevus.

Congenital Hypertrophy of Retinal Pigment Epithelium

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is a well-circumscribed, flat, pigmented lesion (Fig. 21.27) that can occur anywhere in the fundus (58,59). It often shows depigmented lacunae within the lesion and a surrounding pale halo. It can occur as a solitary lesion or it can be part of a congenital grouped pigmentation (“bear tracks”). A recent report suggest that solitary CHRPE can spawn elevated nodular growth and undergo malignant transformation into adenocarcinoma (60,61). Similar pigmented lesions may be a marker for familial adenomatous polyposis and Gardner syndrome in which patients have a high likelihood of developing colonic cancer. However, those lesions have different clinical features than the multifocal variant of CHRPE (62).

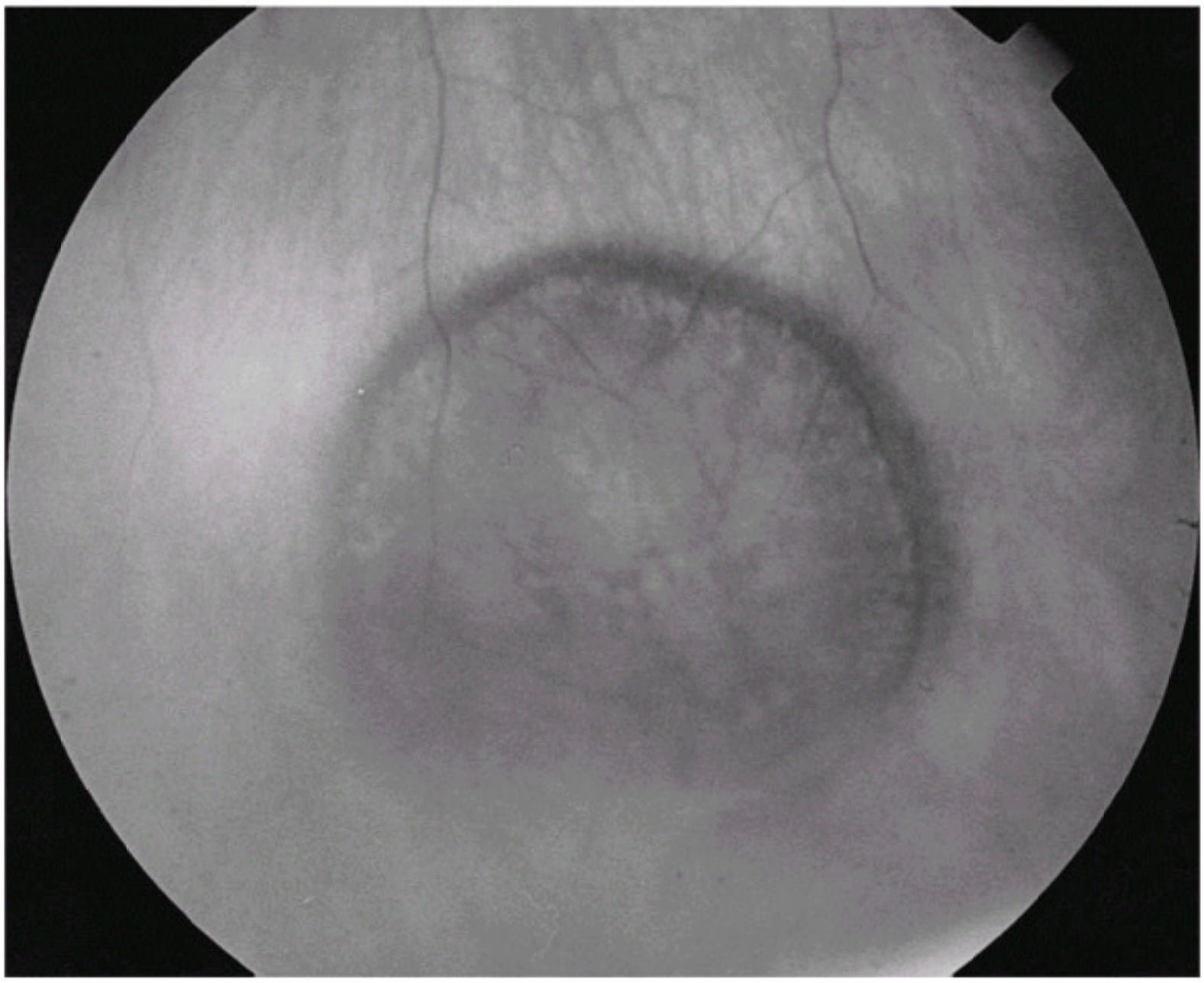


Figure 21.27 Congenital hypertrophy of the retinal pigment epithelium.

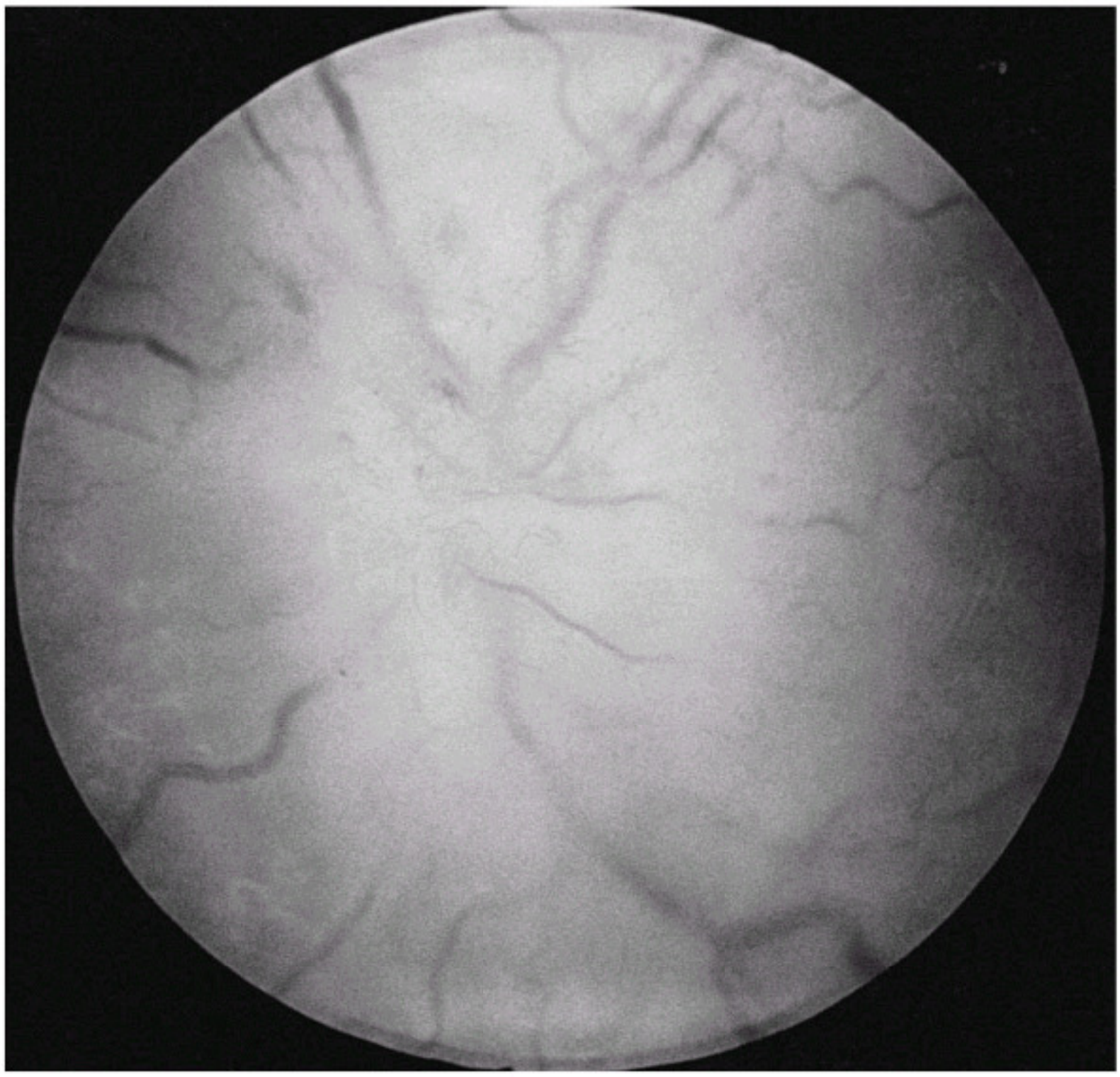


Figure 21.28 Leukemic infiltration of the optic nerve head.

Leukemia

Childhood leukemias can infiltrate the retina, optic disc, and uveal tract (2,4,63). Leukemia infiltration is characterized by a swollen optic disc (Fig. 21.28) and thickening of the retina and choroid, often with hemorrhage and retinal detachment. Intraocular leukemia is generally responsive to irradiation and chemotherapy, but they generally portend a poor systemic prognosis.

ORBITAL TUMORS

A variety of orbital neoplasms and related space-occupying lesions can affect the orbit in children (64,65). Orbital cellulitis secondary to sinusitis and inflammatory pseudotumors are more common than true neoplasms. Only about 5% of orbital lesions that come to biopsy prove to be malignant. Cystic lesions are the most common group, and vascular lesions are the second most common. This section covers orbital tumors and cysts; Chapter 20 contains discussions of orbital inflammatory and infectious conditions (65).

Dermoid Cyst

Several orbital cystic lesions can occur in children (66). Dermoid cyst is the most common noninflammatory

space-occupying orbital mass in children (1,5,66,67). It usually appears in the first decade of life as a fairly firm, fixed, subcutaneous mass at the superotemporal orbital rim near the zygomaticofrontal suture (Fig. 21.29). Occasionally, a dermoid cyst may occur deeper in the orbit unattached to bone (Fig. 21.30) Although it is sometimes stationary, the dermoid cyst does have a tendency to slowly enlarge. It can occasionally rupture, inciting an intense inflammatory reaction. Management is either serial observation or surgical removal of the mass (66).

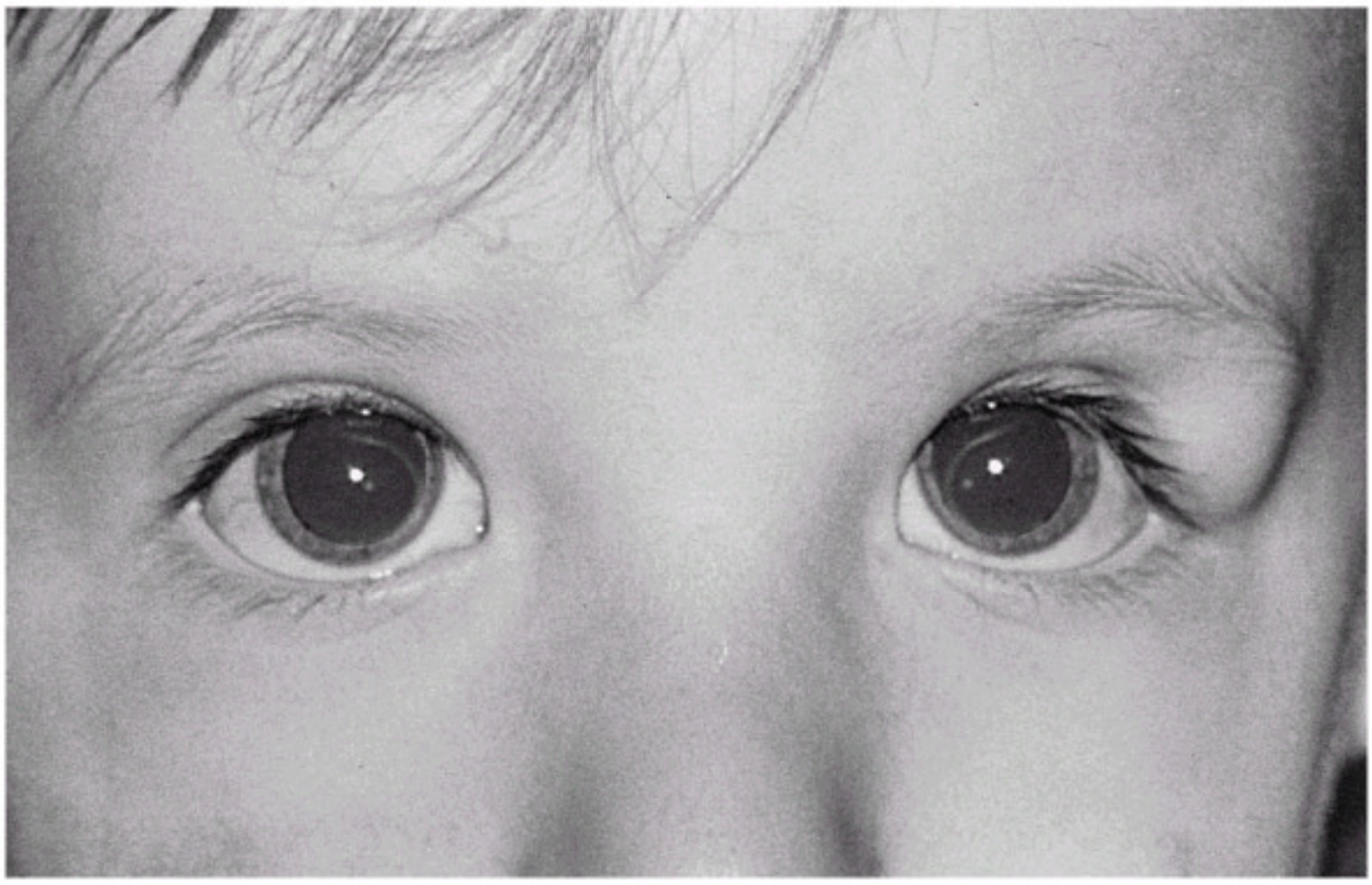


Figure 21.29 Dermoid cyst near the lateral orbital rim. Clinical appearance.

Teratoma

A teratoma is a cystic mass that contains elements of all three embryonic germ layers (1,5). An orbital teratoma causes proptosis which is generally quite apparent at birth. The diagnosis should be suspected by imaging studies. Larger orbital teratomas can destroy the eye. Smaller teratomas can be removed intact without sacrificing the eye, but larger ones that have caused blindness may require orbital exenteration.

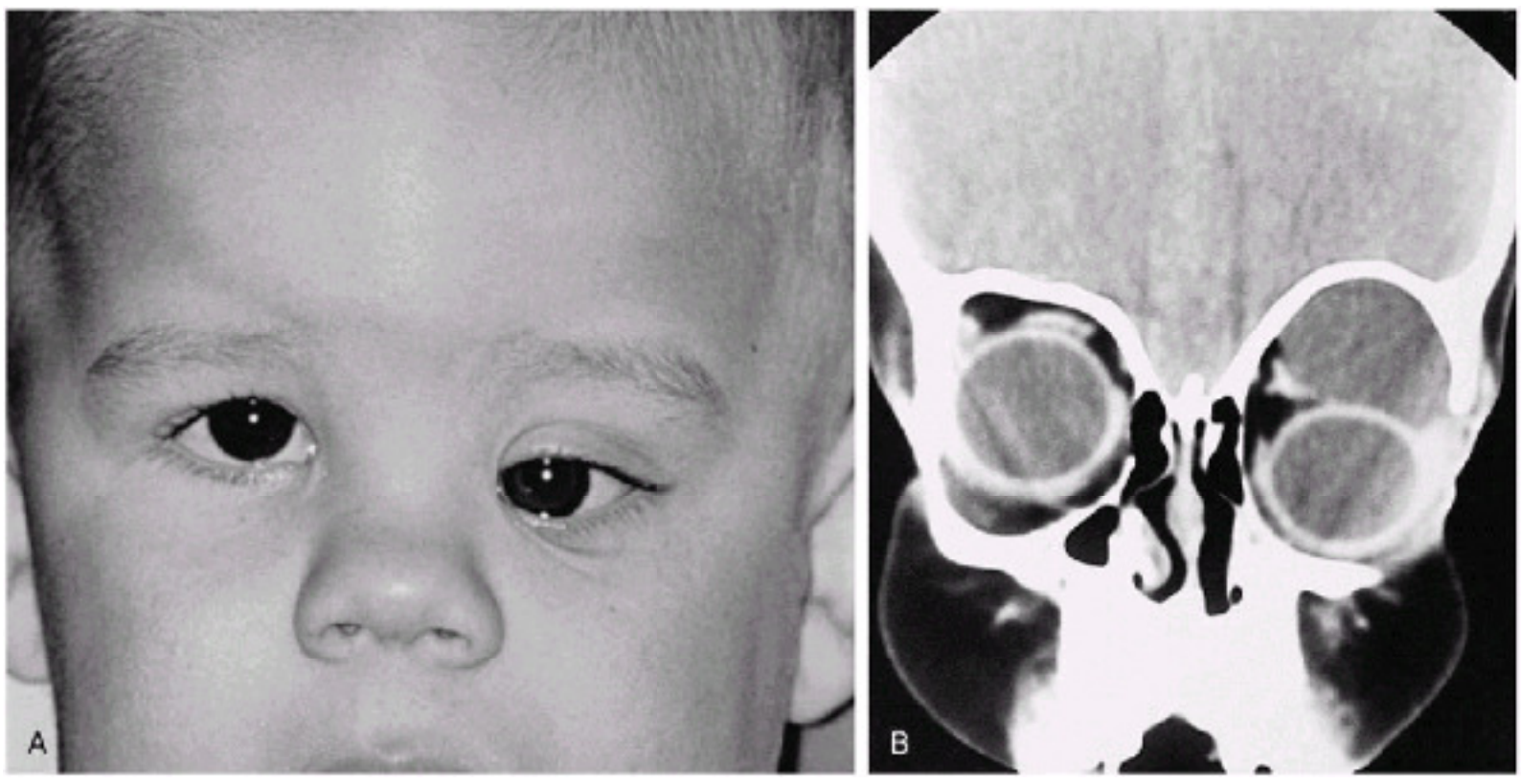


Figure 21.30 Giant orbital dermoid cyst in the deeper orbit. **A:** Clinical appearance. **B:** Axial computed tomography scan.

Capillary Hemangioma

Capillary hemangioma is the most common orbital vascular tumor of childhood (1,5,11). It usually is clinically apparent at birth or within the first few weeks of life. It tends to cause progressive proptosis during the first few months of life (Fig. 21.31), and then it becomes stable and slowly regresses. Orbital imaging studies show a diffuse, poorly circumscribed orbital mass that enhances with contrast material. The best management is refraction and treatment of any induced amblyopia with patching of the opposite eye. Local injection of corticosteroids or oral corticosteroids can hasten the regression of the mass and minimize the

complications (12). On occasion, local resection may be necessary (13).

Lymphangioma

Lymphangioma is an important vascular tumor of the orbit in children (1,5,68). It tends to become clinically apparent during the first decade of life. It may cause abrupt proptosis following orbital trauma, secondary to hemorrhage into the lymphatic channels within the lesion (Fig. 21.32). Such spontaneous hemorrhages, called chocolate cysts, may require aspiration or surgical evacuation to prevent visual loss from compression of the eye.

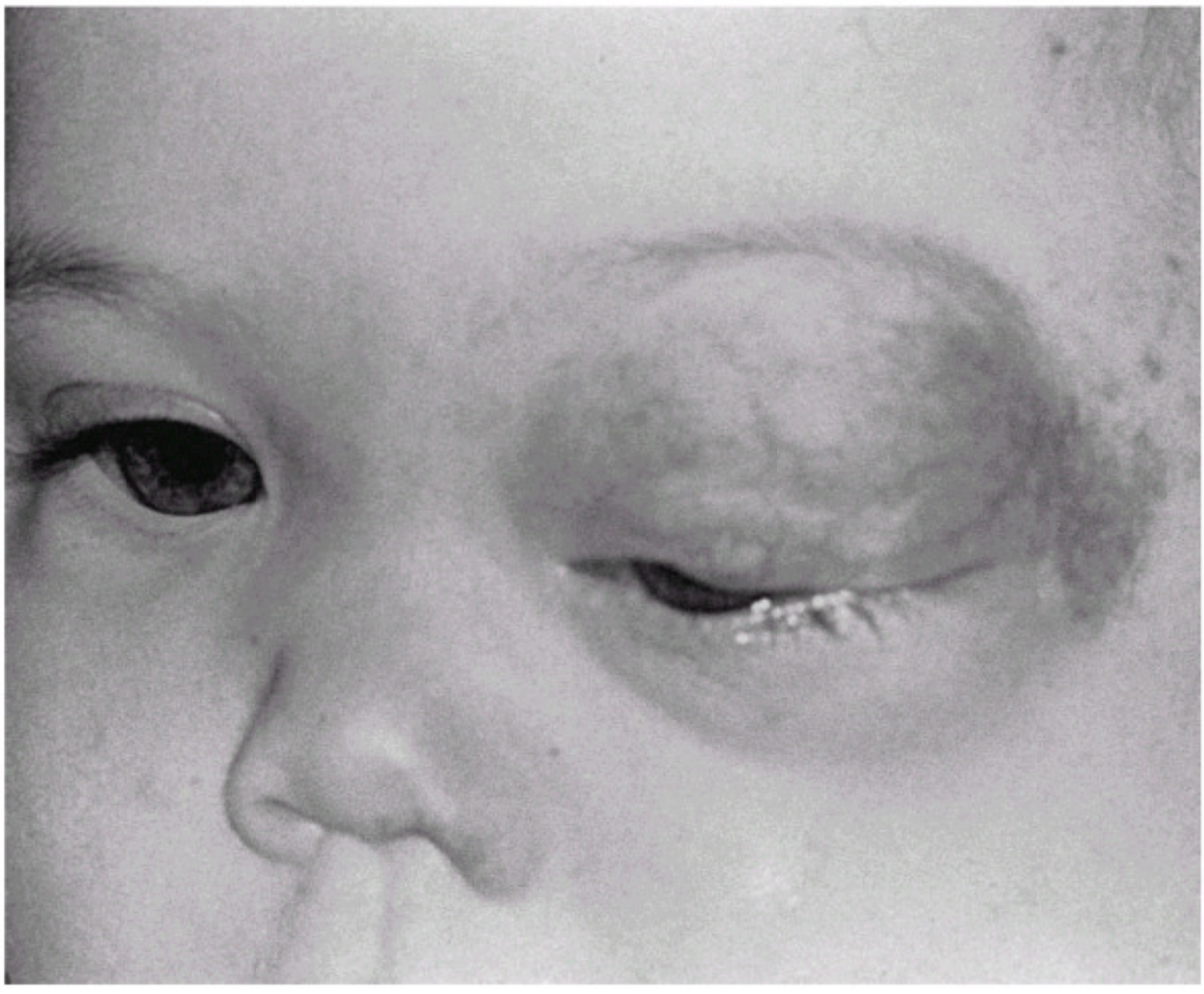


Figure 21.31 Orbital capillary hemangioma producing proptosis. Note the extension of the vascular tumor into the eyelids.

Juvenile Pilocytic Astrocytoma

Juvenile pilocytic astrocytoma (“optic nerve glioma”) is the most common orbital neural tumor of childhood (1,5,65). It is a cytologic benign hamartoma that is generally stationary or very slowly progressive (69). The affected child develops ipsilateral visual loss and slowly progressive axial proptosis (Fig. 21.33A). Orbital imaging studies show an elongated or oval-shaped mass which is well circumscribed because of the overlying dura mater (Fig. 21.33B). There is a greater incidence of this tumor in patients with neurofibromatosis (1,5,69). Since surgical excision necessitates blindness, the best management is periodic observation and surgical removal if there is blindness and cosmetically unacceptable proptosis. In cases that extend to the optic chiasm and are surgically unresectable, radiotherapy may be necessary (69).

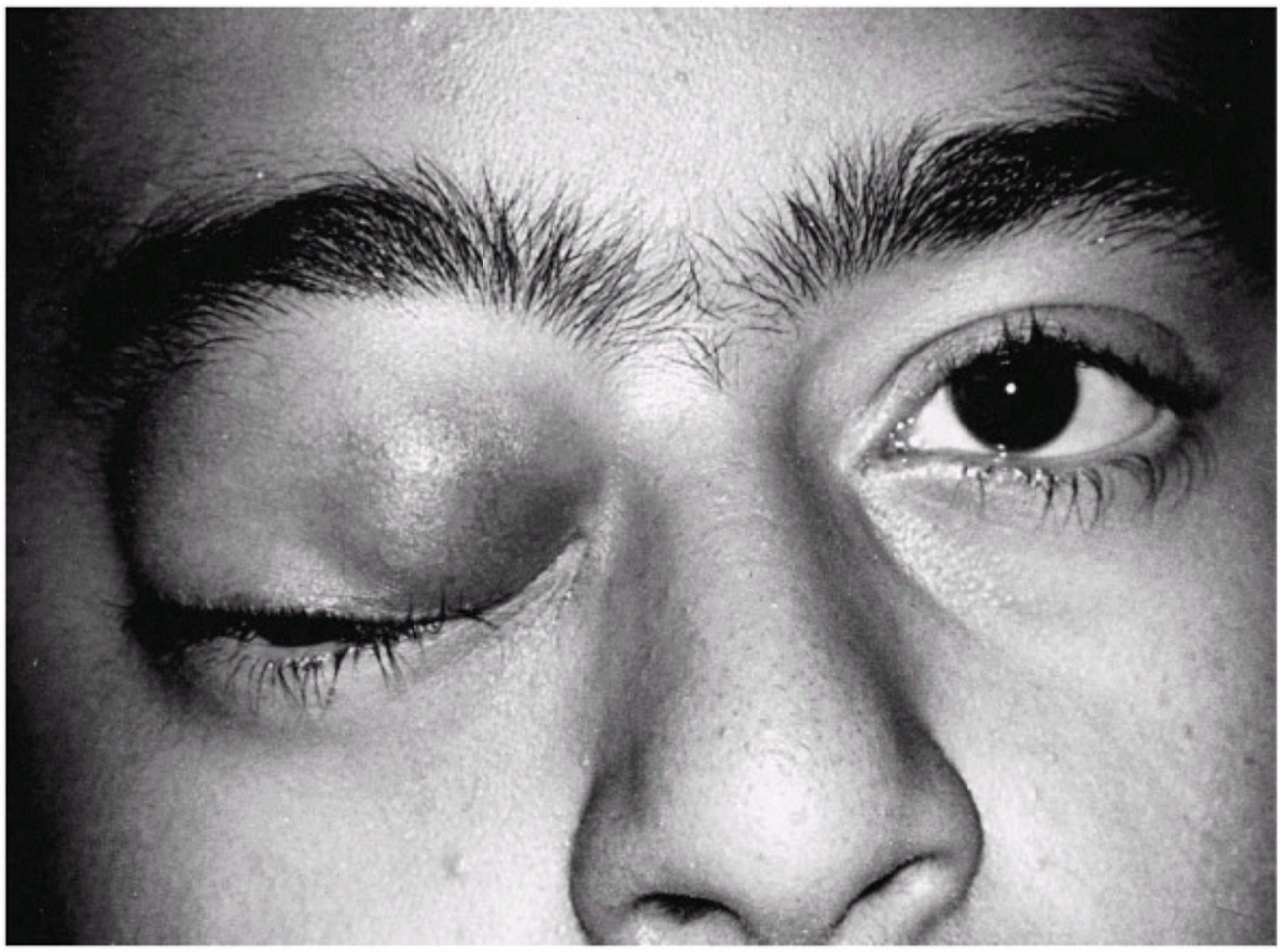


Figure 21.32 Orbital lymphangioma. The lesion recently expanded rapidly secondary to trauma-induced bleeding.

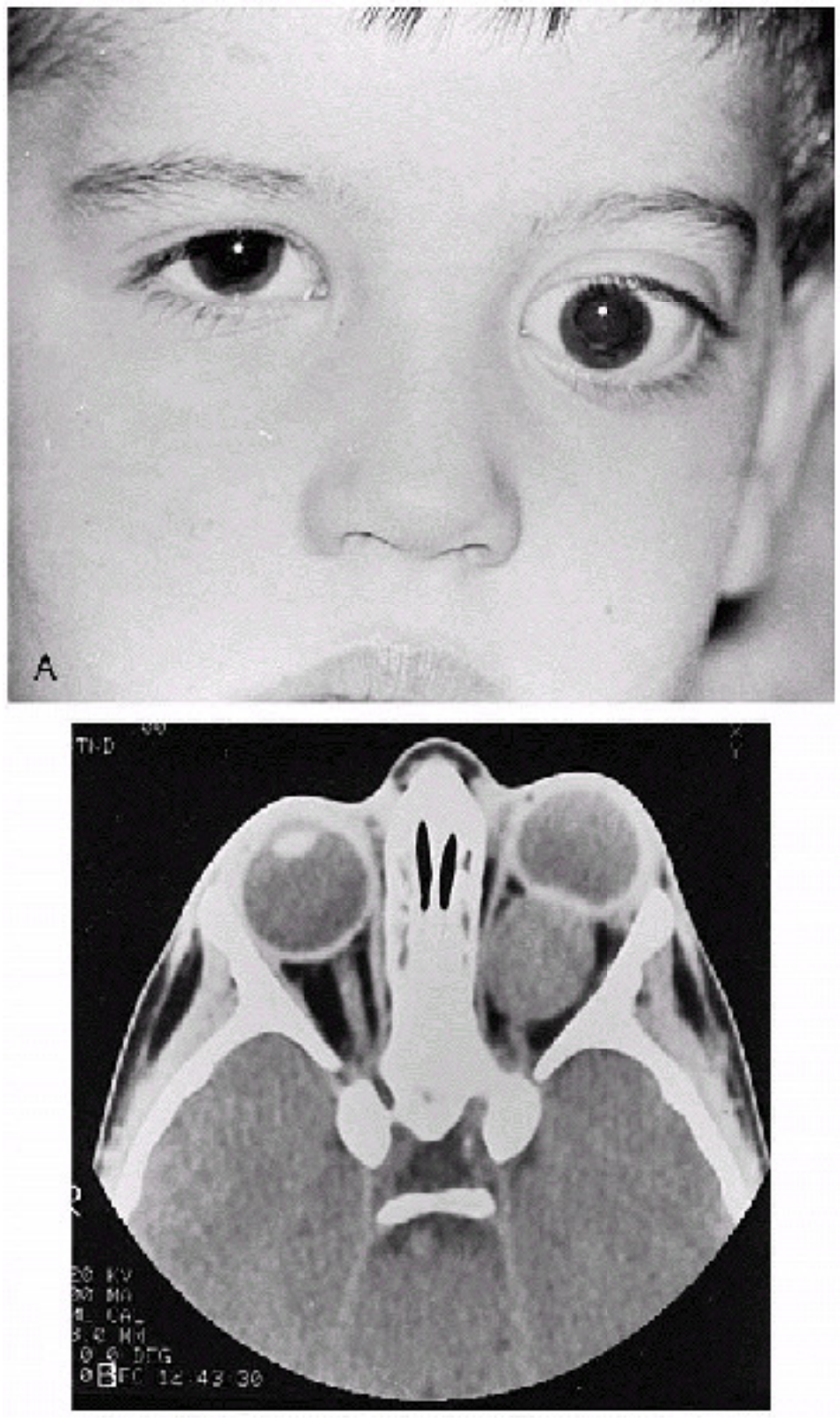


Figure 21.33 Juvenile pilocytic astrocytoma of optic nerve. **A:** Clinical appearance showing proptosis of left eye. **B:** Axial computed tomography scan.

Rhabdomyosarcoma

Rhabdomyosarcoma is the most important primary orbital malignant tumor of childhood (1,5,70,71). It usually occurs in the first decade of life with a mean age of eight years at the time of diagnosis. It causes fairly rapid proptosis and displacement of the globe, usually without pain or major inflammatory signs (Fig. 21.34A). Imaging studies show an irregular but fairly well-circumscribed mass usually in the extraconal anterior orbit (Fig. 21.34B). Although orbital exenteration was often employed in the past, more recent experience has suggested that the best cure is obtained by performing a biopsy to confirm the diagnosis and treating with combined irradiation and chemotherapy, using vincristine, cyclophosphamide and adriamycin.

Granulocytic Sarcoma ("Chloroma")

Granulocytic sarcoma is soft-tissue infiltration by myelogenous leukemia (1,5,72,73). Although leukemia usually appears

first in the blood and bone marrow, the orbit soft tissues may be the initial site to become clinically apparent. The child presents with a fairly rapid onset of proptosis and displacement of the globe. Confirmation of the orbital lesion can be made by biopsy and the condition treated by chemotherapy or low-dose irradiation.

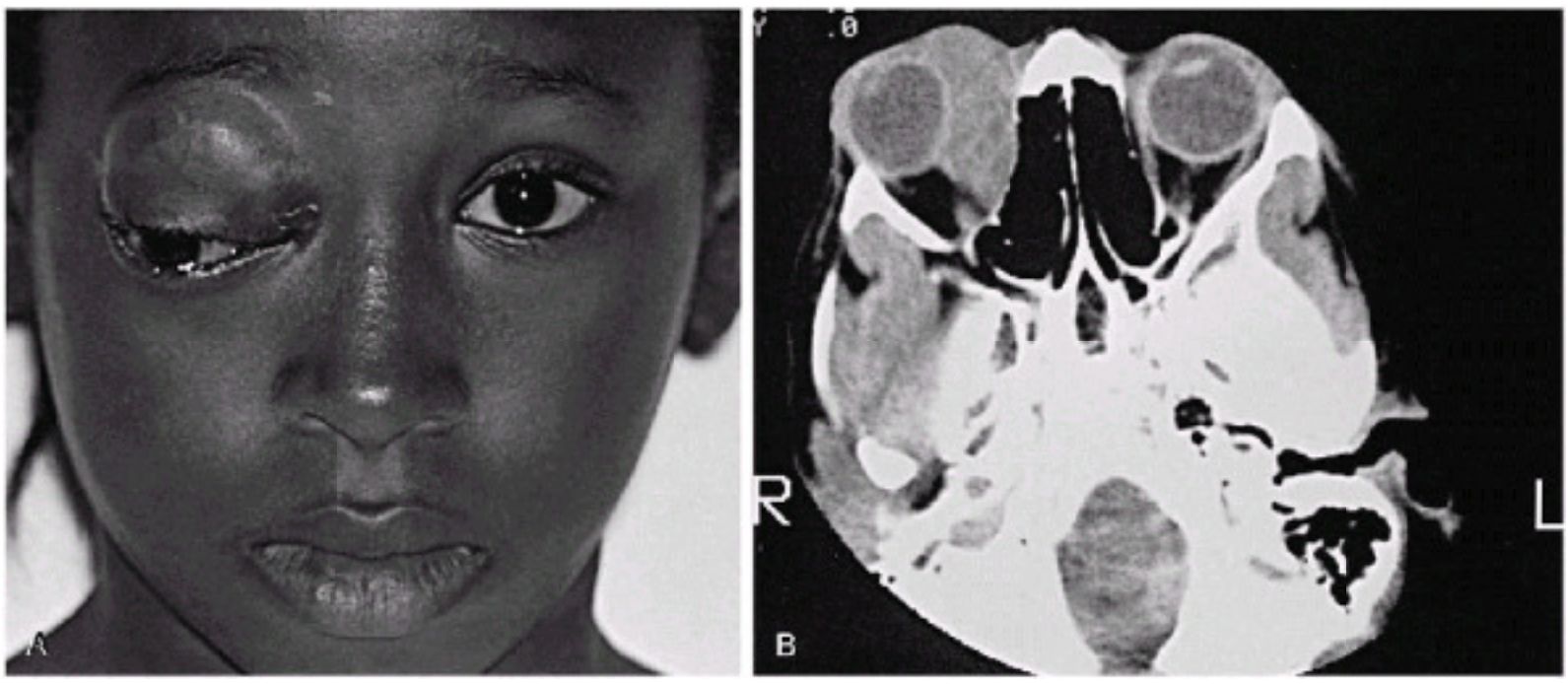


Figure 21.34 Orbital rhabdomyosarcoma. **A:** Clinical appearance showing proptosis and downward displacement of right eye. **B:** Computed tomography scan showing mass in superomedial orbit.

Lymphoma

The only important lymphoma to affect the orbit of children is Burkitt lymphoma. Although this tumor was originally recognized exclusively in African tribes, it is being recognized more often in patients with AIDS and as an American form in otherwise normal children (1,5,74).

Langerhans Cell Histiocytosis

Eosinophilic granuloma can affect the orbital bones as an intraosseous, bone-destructive inflammatory lesion. Although it can occur anywhere in the orbit, it most often occurs in the anterior portion of the frontal and zygomatic bones. Recent ultrastructural studies have suggested that the stem cell in eosinophilic granuloma and certain other tumors in the histiocytic X group in the Langerhans cell. Hence, the term Langerhans cell histiocytosis is becoming preferable (1,5,75).

Metastatic Neuroblastoma

Although orbital metastasis in children can occur secondary to Wilms' and Ewing tumors, metastatic neuroblastoma is the most common metastatic orbital of childhood (1,5,76). The majority of children with orbital metastasis of neuroblastoma have a previously diagnosed primary neoplasm in the adrenal gland. However, the orbital metastasis can be diagnosed before the adrenal primary in about 3% of cases.

REFERENCES

1. Shields JA. *Diagnosis and management of orbital tumors*. Philadelphia: WB Saunders Co., 1989.

2. Shields JA, Shields CL. *Intraocular tumors. A text and atlas*. Philadelphia: WB Saunders Co., 1992.

3. Shields JA, Shields CL. *Atlas of eyelid and conjunctival tumors*. Philadelphia: Lippincott Williams & Wilkins, 1999.

4. Shields JA, Shields CL. *Atlas of intraocular tumors*. Philadelphia: Lippincott Williams & Wilkins, 1999.

5. Shields JA, Shields CL. *Atlas of orbital tumors*. Philadelphia: Lippincott Williams & Wilkins, 1999.

6. Howard GM, Ellsworth RM. Differential diagnosis of retinoblastoma. A statistical survey of 500 children. I. Relative frequency of the lesions which simulate retinoblastoma. *Am J Ophthalmol* 1965; 60:610-618.

7. Shields JA, Parsons HM, Shields CL, et al. Lesions simulating retinoblastoma. *J Pediatr Ophthalmol Strabismus* 1991;28:338-340.

8. De Potter P, Shields JA, Shields CL, eds. *MRI of the eye and orbit*. Philadelphia: JB Lippincott Co., 1994.

9. Shields JA, Shields CL, Ehya H, et al. Fine needle aspiration biopsy of suspected intraocular tumors. The 1992 Urwick Lecture. *Ophthalmology* 1993;100:1677-1684.

10. Shields JA, Shields CL, Sivalingam V. Decreasing frequency of enucleation in patients with retinoblastoma. *Am J Ophthalmol* 1989; 108:185-188.

11. Haik BG, Karcioglu ZA, Gordon RA, et al. Capillary hemangioma (infantile periocular hemangioma). *Surv Ophthalmol* 1994;38: 399-426.

12. Kushner BJ. Intralesional corticosteroid injection for infantile adnexal hemangioma. *Am J Ophthalmol* 1982;95:496-506.

13. Aldave AF, Shields CL, Shields JA. Surgical excision of selected amblyogenic periorbital capillary hemangiomas. *Ophthalmic Surg Lasers* 1999;30:754-757.

14. Shields JA, Kiratli H, Shields CL, et al. Schwannoma of the eyelid in a child. *J Pediatr Ophthalmol Strabismus* 1994;31:332-333.

15. Shields JA, Shields CL, Eagle RC Jr, et al. Pilomatrixoma of the eyelid. *J Pediatr Ophthalmol Strabismus* 1995;32:260-261

16. Shields CL, Shields JA. Tumors of the conjunctiva and cornea. *Surv Ophthalmol* 2004;49:3-24.

17. Shields CL, Demirci H, Karatza E, et al. Clinical survey of 1643 melanocytic and nonmelanocytic conjunctival tumors. *Ophthalmology* 2004;111:1747-1754.

18. Shields JA, Eagle RC, Shields CL, et al. Epibulbar osseous choristoma. Computed tomography and clinicopathologic correlation. *Ophthalmic Practice* 1997;15:110-112.

19. Shields JA, Shields CL, Eagle RC Jr, et al. Ophthalmic features of the organoid nevus syndrome. *Trans Am Ophthalmol Soc* 1996;94: 65-86.

20. Shields JA, Shields CL, Eagle RC Jr, et al. Ophthalmic features of the organoid nevus syndrome. *Ophthalmology* 1997;104:549-557.

21. Shields CL, Lally MR, Singh AD, et al. Oral cimetidine (Tagamet) for recalcitrant, diffuse conjunctival papillomatosis. *Am J Ophthalmol* 1999;128:362-364.

22. Shields CL, Fasiudden A, Mashayekhi A, et al. Conjunctival nevi: clinical features and natural course in 410 consecutive patients. *Arch Ophthalmol* 2004;122:167-175.

23. Singh AD, De Potter P, Fijal BA, et al. Lifetime prevalence of uveal melanoma in Caucasian patients with ocular (dermal) melanocytosis. *Ophthalmology* 1998;105:195-198.

24. Gunduz K, Shields JA, Shields CL, et al. Choroidal melanoma in a 14 year-old patient with ocular melanocytosis. *Arch Ophthalmol* 1998;116:1112-1114.

25. Shields CL, Shields JA. Genetics of retinoblastoma. In: Tasman WS, Jaeger EA, eds. *Duane's Foundations of clinical ophthalmology*. Philadelphia: Lippincott Williams & Wilkins, 1991.

26. Shields JA, Shields CL, Suvarnamani C, et al. Retinoblastoma manifesting as orbital cellulitis. *Am J Ophthalmol* 1991;112:442-449.

27. Shields CL, Shields JA, Shah P. Retinoblastoma in older children. *Ophthalmology* 1991;98:395-399.

28. De Potter P, Shields CL, Shields JA, et al. Use of the orbital hydroxyapatite implant in the pediatric population. *Arch Ophthalmol* 1994;112:208-212.

29. Abramson DH, Marks RF, Ellsworth RM, et al. The management of unilateral retinoblastoma without primary enucleation. *Arch Ophthalmol* 1982;100:1249-1252.

30. Shields JA, Parsons H, Shields CL, et al. The role of cryotherapy in the management of retinoblastoma. *Am J Ophthalmol* 1989; 108:260-264.

31. Shields JA, Parsons H, Shields CL, et al. The role of photocoagulation in the management of retinoblastoma. *Arch Ophthalmol* 1990; 108: 205-208.

32. Shields CL, Shields JA, Cater J, et al. Plaque radiotherapy for retinoblastoma: Long term tumor control and treatment complications in 208 tumors. *Ophthalmology* 2001;108:2116-2121.

33. Shields CL, De Potter P, Himmelstein B, et al. Chemoreduction in the initial management of intraocular retinoblastoma. *Arch Ophthalmol* 1996;114:1330-1338.

34. Kingston JE, Hungerford JL, Madreperla SA, et al. Results of combined chemotherapy and radiotherapy for advanced intraocular retinoblastoma. *Arch Ophthalmol* 1996;114:1339-1343.

35. Gallie BL, Budning A, DeBoer G, et al. Chemotherapy with focal therapy can cure intraocular retinoblastoma without radiation. *Arch Ophthalmol* 1996;114:1321-1328.

36. Murphree AL, Villablanca JG, Deegan WF III, et al. Chemotherapy plus focal treatment in the management of intraocular retinoblastoma. *Arch Ophthalmol* 1996;114:1348-1356.

37. Shields CL, Shields JA, Needle M, et al. Combined chemoreduction and adjuvant treatment for intraocular retinoblastoma. *Ophthalmology* 1997;104:2101-2111.

38. Gunduz K, Shields CL, Shields JA, et al. The outcome of chemoreduction treatment in patients with Reese-Ellsworth group V retinoblastoma. *Arch Ophthalmol* 1998;116:1613-1617.

39. Shields CL, Honavar SG, Shields JA, et al. Factors predictive of recurrence of retinal tumor, vitreous seeds and subretinal seeds following chemoreduction for retinoblastoma. *Arch Ophthalmol* 2002;120:460-464.

40. Shields CL, Honavar SG, Meadows AT, et al. Chemoreduction plus focal therapy for retinoblastoma: factors predictive of need for treatment with external beam radiotherapy or enucleation. *Am J Ophthalmol* 2002;133:657-664.

41. Shields CL, Honavar SG, Meadows AT, et al. Chemoreduction for unilateral retinoblastoma. *Arch Ophthalmol* 2002;120:1653-1658.

42. Shields JA, Shields CL, De Potter P, et al. Bilateral macular retinoblastoma managed by chemoreduction and chemothermotherapy. *Arch Ophthalmol* 1996;114:1426-1427.

43. Shields CL, Santos C, Diniz W, et al. Thermotherapy for retinoblastoma. *Arch Ophthalmol* 1999;117:885-893.

44. Murphree AL, Benedict WF. Retinoblastoma: clues to human oncogenesis. *Science* 1984;223:1028-1033.

45. Singh AD, Shields CL, Shields JA. Major review: von Hippel-Lindau disease. *Surv Ophthalmol* 2001;46:117-142.

46. Gass JDM. Cavernous hemangioma of the retina. A neuro-oculocutaneous syndrome. *Am J Ophthalmol* 1971;71:799-781.

47. Archer DM, Deutman A, Ernest JT, et al. Arteriovenous communications of the retina. *Am J Ophthalmol* 1973;75:224-241.

48. Shields JA, Eagle RC Jr, Shields C, et al. Aggressive retinal astrocytomas in 4 patients with tuberous sclerosis complex. *Arch Ophthalmol*, in press.

49. Shields JA, Demirci H, Mashayekhi A, et al. Melanocytoma of optic disc in 115 cases: the 2004 Samuel Johnson Memorial lecture, part 1. *Ophthalmology* 2004;111:1739-1746.

50. Broughton WI, Zimmerman LE. A clinicopathologic study of 56 cases of intraocular medulloepitheliomas. *Am J Ophthalmol* 1978; 85:407-418.

51. Shields JA, Eagle RC Jr, Shields CL, et al. Congenital neoplasms of the nonpigmented ciliary epithelium. (medulloepithelioma). *Ophthalmology* 1996;103:1998-2006.

52. Stevenson RF, Morin JD. Ocular findings in nevus flammeus. *Can J Ophthalmol* 1975;10:136-139.

53. Gass JDM, Guerry RK, Jack RL, et al. Choroidal osteoma. *Arch Ophthalmol* 1978;96:428-435.

54. Shields CL, Shields JA, Augsberger JJ. Review: choroidal osteoma. *Surv Ophthalmol* 1988;33:17-27.

55. Barr CC, McLean IW, Zimmerman LE. Uveal melanoma in children and adolescents. *Arch Ophthalmol* 1981;99:2133-2136.

56. Shields CL, Shields JA, Milite J, et al. Uveal melanoma in teenagers and children. A report of 40 cases. *Ophthalmology* 1991;98: 1662-1666.

57. Singh AD, Shields CL, Shields JA, et al. Uveal melanoma in young patients. *Arch Ophthalmol* 2000;118:918-923.

58. Purcell JJ, Shields JA. Hypertrophy with hyperpigmentation of the retinal pigment epithelium. *Arch Ophthalmol* 1975;93: 1122-1126.

59. Shields CL, Mashayekhi A, Ho T, et al. Solitary congenital hypertrophy of the retinal pigment epithelium: Clinical features and frequency of enlargement in 330 patients. *Ophthalmology* 2003; 110:1968-1976.

60. Shields JA, Shields CL, Singh AD. Acquired tumors arising from congenital hypertrophy of the retinal pigment epithelium. *Arch Ophthalmol* 2000;118:637-641.

61. Shields JA, Shields CL, Eagle RC Jr, et al. Adenocarcinoma arising from congenital hypertrophy of the retinal pigment epithelium. *Arch Ophthalmol* 2001;119:597-602.

62. Shields JA, Shields CL, Shah P, et al. Lack of association between typical congenital hypertrophy of the retinal pigment epithelium and Gardner's syndrome. *Ophthalmology* 1992;99:1705-1713.

63. Schachat AP, Markowitz JA, Guyer DR, et al. Ophthalmic manifestations of leukemia. *Arch Ophthalmol* 1989;107:697-700.

64. Shields JA, Shields CL, Scartozzi R. Survey of 1264 patients with orbital tumors and simulating lesions: the 2002 Montgomery lecture, part 1. *Ophthalmology* 2004;111:997-1008.

65. Shields JA, Bakewell B, Augsberger JJ, et al. Space-occupying orbital masses in children: A review of 250 consecutive biopsies. *Ophthalmology* 1988;93:379-384.

66. Shields, JA, Shields CL. Orbital cysts of childhood—classification, clinical features, and management. *Surv Ophthalmol* 2004;49: 281-299.

67. Shields JA, Kaden IH, Eagle RC Jr, et al. Orbital dermoid cysts. Clinicopathologic correlations, classification, and management. The 1997 Josephine E. Schueler lecture. *Ophthal Plast Reconstr Surg* 1997;13:265-276.

68. Rootman J, Hay E, Graeb D, et al. Orbital-adnexal lymphangiomas. A spectrum of hemodynamically isolated vascular hamartomas. *Ophthalmology* 1986;93:1558-1570.

69. Dutton JJ. Gliomas of the anterior visual pathway. *Surv Ophthalmol* 1994;38:427-452.

70. Shields CL, Shields JA, Honavar SG, et al. The clinical spectrum of primary ophthalmic rhabdomyosarcoma. *Ophthalmology* 2001; 108:2284-2292

71. Shields JA, Shields CL. Rhabdomyosarcoma: review for the ophthalmologist. The 2001 Henry Dubins Lecture. *Surv Ophthalmol* 2003;48:39-57.

72. Font RL, Zimmerman LE. Ophthalmologic manifestations of granulocytic sarcoma (myeloid sarcoma or chloroma). *Am J Ophthalmol* 1975;80:975-990.

73. Shields JA, Stopyra GA, Marr BP, et al. Bilateral orbital myeloid sarcoma as initial sign of acute myeloid leukemia. *Arch Ophthalmol* 2003;121:138-142.

74. Edelstein C, Shields JA, Shields CL, et al. Non-African Burkitt's lymphoma presenting with oral thrush and an orbital mass in a child. *Am J Ophthalmol* 1997;124:859-860.

75. Demirci H, Shields CL, Shields JA, et al. Bilateral sequential orbital involvement in eosinophilic granuloma. *Arch Ophthalmol* 2002; 120:978-979.

76. Musarella M, Chan HSL, DeBoer G, et al. Ocular involvement in neuroblastoma. Prognostic implications. *Ophthalmology* 1984;91: 936-940.

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22

The Systemic Hamartomatoses (“Phakomatoses”)

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The systemic hamartomatoses (“phakomatoses”) comprise a group of syndromes with variable clinical manifestations that primarily affect the ocular region, central nervous system (CNS), skin, and sometimes viscera (1,2,3,4,5,6,7,8). Therefore, the recognition of the ocular or cutaneous features should prompt a referral to other specialists to evaluate the patient accordingly. This chapter discusses these oculoneurocutaneous syndromes with emphasis on their ophthalmologic and dermatologic manifestations. Other conditions that are not generally listed with the classic syndromes but that have similar ocular and dermatologic manifestations are also mentioned briefly.

GENERAL CONSIDERATIONS

Historical Aspects

The term “phakoma” was coined by Van der Hoeve in 1932 to indicate a mother spot or birthmark, a characteristic finding in many of these conditions (1). At that time, retinal and cerebellar hemangiomatosis (von Hippel-Lindau syndrome), neurofibromatosis (von Recklinghausen syndrome), and tuberous sclerosis (Bourneville syndrome) were grouped under this heading. Later, encephalofacial hemangiomatosis (EFH; Sturge-Weber syndrome), racemose hemangiomatosis (Wyburn-Mason syndrome), and cavernous hemangioma of the retina with cutaneous and central nervous system (CNS) involvement were grouped with these other conditions. As mentioned above, several other entities could be appropriately categorized with these classic oculoneurocutaneous syndromes.

Terminology

To better understand these syndromes, the clinician should be familiar with certain terms such as hamartia, hamartoma, chorista, and choristoma (3,4).

Hamartia and hamartoma are terms that refer to malformations that are composed of tissues that are ordinarily present at the location where they occur. A hamartia is a nontumorous anomaly composed of tissues that are normally present at the involved site, while a hamartoma is a tumorous malformation composed of tissues which are normally present at the involved site. Most of the entities discussed in this chapter are characterized by the presence of hamartomas. The term systemic hamartomatosis is used to designate multiple organ involvement. Examples of hamartomas include the vascular tumors that occur in patients with either retinocerebellar hemangiomatosis or EFH, and the glial and peripheral nerve tumors that occur with tuberous sclerosis or neurofibromatosis. These tumors develop in areas where vascular and neural tissues are normally present.

Chorista and choristoma, on the other hand, are terms that refer to malformations composed of elements that are not ordinarily present at the location where they occur. A chorista is a nontumorous anomaly composed of tissues which are not normally present at the involved site. The microscopic rests of ectopic lacrimal gland tissue that sometimes occur in the anterior chamber and deep orbit are examples of choristas. A choristoma is a tumorous malformation composed of tissues that are not normally present at the involved site. The classic example of a choristoma is the limbal dermoid, a tumor composed of dermal elements

that are not normally present in the bulbar conjunctiva or cornea.

A particular lesion may be classified as either a hamartoma or a choristoma depending on the organ involved (2,3). For example, a 5-mm nodule of mature bone would be classified as a hamartoma if it occurred on the superior orbital rim, but a similar mass of osseous tissue in the liver would be classified as a choristoma.

Heredity

Most of the hamartomatoses have an autosomal-dominant mode of inheritance, often with incomplete penetrance. Specific chromosomal abnormalities are continually being recognized in association with these entities. Notable exceptions are EFH (Sturge-Weber syndrome) and racemose hemangiomatosis (Wyburn-Mason syndrome) in which heredity does not appear to play a role and genetic abnormalities are not yet delineated. Although the hamartomatoses are generally hereditary, there is some controversy as to whether they are congenital, since they do not usually become clinically apparent until the teens or young adulthood.

Benign and Malignant Tumors

In general, the tumors that develop in these syndromes are benign. They differ from true neoplasms by virtue of the fact that they are anomalies of tissue formation, rather than tumors that arise from fully developed tissues. Furthermore, they are usually stationary or slowly progressive lesions that generally lack the capacity for the limitless proliferation seen with malignant neoplasms (3,4). Some of these syndromes, however, can be associated with malignant neoplasms. For example, there is an increased incidence of malignant schwannomas of the peripheral nerves in patients with neurofibromatosis (9). Hypernephroma occurs with greater frequency in patients with retinal capillary hemangiomatosis (3,4).

Formes Frustes and Combined Phakomatoses

It is common for patients with systemic hamartomatoses to only manifest some of the clinical features of a particular syndrome. This lack of complete expressivity is referred to as a forme fruste. Furthermore, patients can occasionally exhibit certain lesions characteristic of one entity and other lesions characteristic of another. For example, the café-au-lait spots seen in patients with neurofibromatosis can occasionally be seen in patients with tuberous sclerosis or EFH.

TUBEROUS SCLEROSIS COMPLEX (BOURNEVILLE SYNDROME)

Definition, Incidence, and Genetics

Tuberous sclerosis complex is a syndrome characterized by retinal astrocytic hamartomas cutaneous abnormalities, CNS astrocytomas, and internal tumors such as cardiac rhabdomyoma, renal angiomyolipoma, and other tumors (3,10). It is best known to produce a triad of adenoma sebaceum, epilepsy, and mental deficiency. The term “epiloia” (which implies epilepsy and “mindlessness”) have often been used to describe this condition, but the names tuberous sclerosis complex has become more widely accepted.

The incidence of tuberous sclerosis complex is about one in 10,000 (11). Although tuberous sclerosis complex is usually diagnosed clinically during the first few

years of life, it has occasionally been recognized in patients as young as 1 month or as old as 50 years. This syndrome has been identified in all races, and there is no sex predilection.

Most evidence suggests that tuberous sclerosis complex is transmitted by an autosomal-dominant mode with incomplete penetrance. In many cases with classic signs and symptoms, the family history is unremarkable and examination of family members is normal. Such patients are considered to be sporadic mutations. Recent reports have indicated that about half of the families show linkage to chromosome 9q34 and about half to chromosome 16p13 (11).

Ophthalmologic Features

The retinal astrocytic hamartoma is the characteristic fundus lesion of tuberous sclerosis complex. The smaller noncalcified tumor can be extremely subtle and appear only as ill-defined translucent thickening of the nerve fiber layer. A slightly larger tumor is more opaque and appears as a sessile white lesion at the level of the nerve fiber layer of the retina (Fig. 22.1). It may contain characteristic dense yellow, refractile foci of calcification that resemble fish eggs or tapioca. Although it is generally stable and does not usually cause serious complications, a recent report described four cases in which this tumor became highly aggressive and caused neovascular glaucoma that necessitated

enucleation (12). Histopathologically, these four tumors proved to be giant cell astrocytomas identical to the intracranial lesions seen with tuberous sclerosis complex (12).

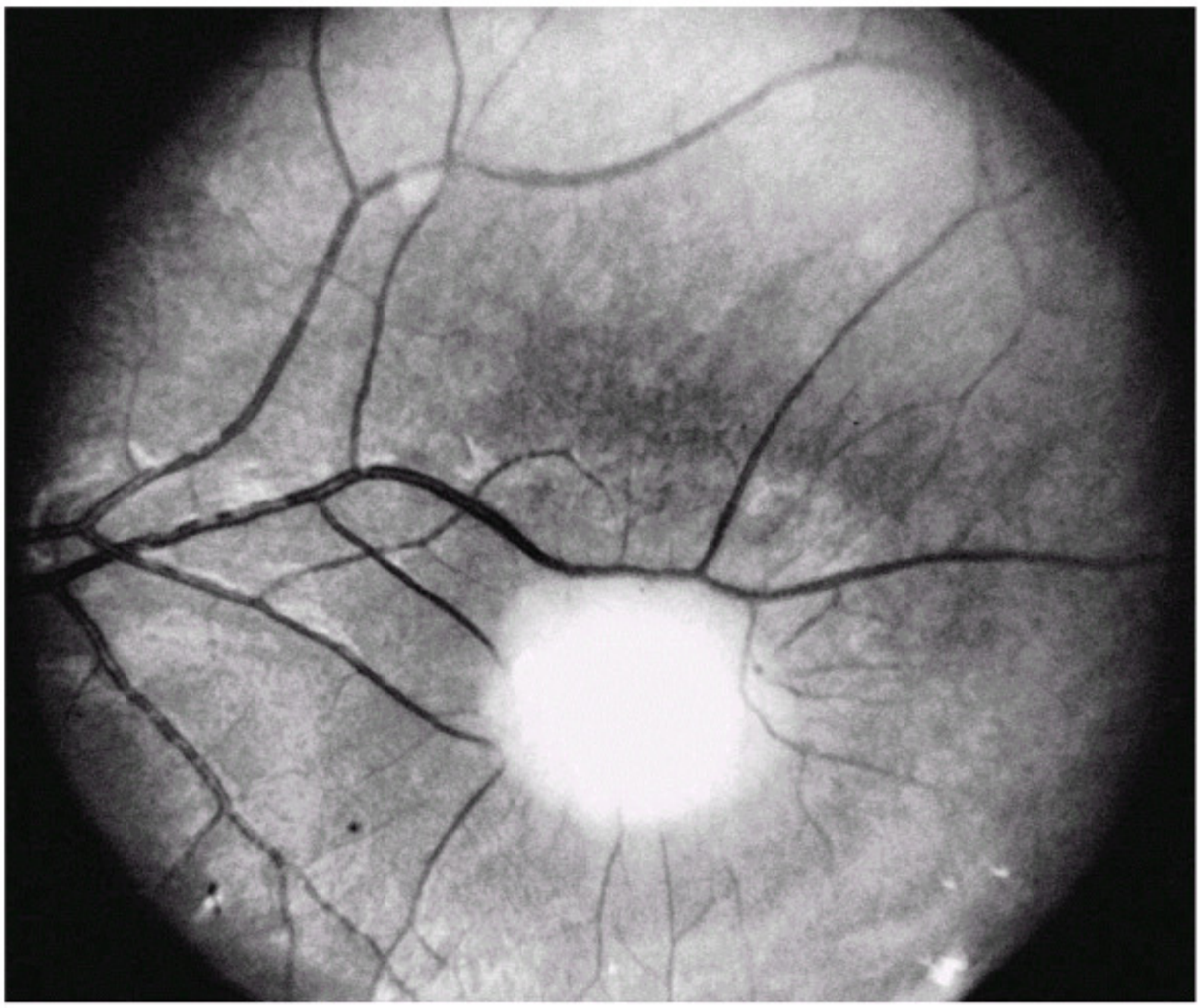

Figure 22.1 Retinal astrocytic hamartoma in patient with tuberous sclerosis.

Ancillary studies, such as fluorescein angiography and ultrasonography, can assist in the diagnosis. Fine-needle aspiration has been used to make a diagnosis in atypical cases (13).

The retinal astrocytic hamartoma shows rather typical pathologic features. It is located in the nerve fiber layer of the retina and is composed of fibrillary astrocytes. Foci of dystrophic calcification, sometimes resembling psammoma bodies, are frequently present in the tumor (2,3,4).

The uveal tract is rarely affected in tuberous sclerosis. A depigmented iris sector, seen in some affected patients, is believed to be the equivalent of depigmented cutaneous lesions (14,15).

Dermatologic Features

The main cutaneous manifestations of tuberous sclerosis complex include adenoma sebaceum, depigmented macules, and café-au-lait spots. Adenoma sebaceum is characterized clinically by multiple slightly elevated, rubbery, yellow-red papules. They are most often found on the face, frequently in a butterfly-shaped distribution (Fig. 22.2). They are composed microscopically of a benign proliferation of fibrous tissue and blood vessels (3,4). In reality, these tumors are angiofibromas, and the sebaceous gland hyperplasia appears to be a secondary change and is not part of the primary process. Consequently, the term “sebaceous adenoma” is a misnomer. Similar angiofibromas can occur beneath or adjacent to the fingernails or toenails in patients with tuberous sclerosis. These subungual fibromas, when present, are highly suggestive of tuberous sclerosis.

Figure 22.2 Facial appearance of patient showing subtle adenoma sebaceum associated with tuberous sclerosis.

Depigmented macules resembling vitiligo are commonly present on the skin of patients with tuberous sclerosis complex (3,4). Because these patches frequently assume a configuration of a leaf from the mountain ash tree, the characteristic lesion is often referred to as the ash leaf sign. These lesions are considered to be highly characteristic or even pathognomonic of tuberous sclerosis (16,17).

Other Features

The characteristic brain findings in patients with tuberous sclerosis complex include subependymal and cortical astrocytomas, sometimes with giant tumor cells (3,4,9,11,12). Both can demonstrate cystic and calcific changes, which account for the name tuberous sclerosis (“potato-like masses”). These lesions contribute to the seizures and mental deficiency. Contrary to early reports, mental deficiency is not necessarily a part of this syndrome. Many of the early reported patients were recruited from mental institutions where individuals with mental derangement were hospitalized. It is now recognized that many patients have only mild symptoms and signs and are of normal or near normal intelligence.

The renal lesions commonly predispose the patient to recurrent nephritis and elevated blood urea nitrogen. They have been shown histologically to be benign angiomyolipomas, with no tendency to undergo malignant transformation or to metastasize (18). The cardiac lesions have been shown to be rhabdomyomas, composed of large spider cells with prominent vacuoles containing glycogen (2,3,4). Some patients with tuberous sclerosis develop slowly progressive subpleural cysts which result from anomalous development of pulmonary tissue (19). These cysts can rupture, leading to spontaneous pneumothorax. Irregular cortical thickenings of bones, particularly the metatarsals and metacarpals, as well as hamartomas of the liver, thyroid, pancreas, testes, and other organs, have been reported (14).

Management

The majority of retinal astrocytic hamartomas are asymptomatic, are nonprogressive, and do not require treatment. Ocular examination should be performed yearly, and the patient followed for other manifestations of tuberous sclerosis. If there should be an associated retinal detachment that extends into the foveal area, then laser photocoagulation can be employed to bring about resolution of the subretinal fluid. The astrocytic hamartoma of the retina has an extremely low tendency to undergo malignant change and has no tendency to metastasize. The visual prognosis is also excellent, except in the rare instances in which exudation, retinal detachment, or vitreous hemorrhage occur.

Most of the cutaneous lesions of tuberous sclerosis complex require no treatment. Larger facial angiofibromas may require surgical excision for cosmetic

purposes.

NEUROFIBROMATOSIS (VON RECKLINGHAUSEN SYNDROME)

Definition, Incidence, and Genetics

Neurofibromatosis is an oculoneurocutaneous syndrome characterized by multisystem involvement that can lead to a wide variety of clinical symptoms and signs (20). Although a number of isolated reports during the nineteenth century described many of the clinical features of this syndrome, von Recklinghausen published a classic monograph in 1882 which provided a better understanding of this condition (21). The condition is now known as von Recklinghausen syndrome.

The frequency of a new mutation for neurofibromatosis is estimated to be about 1 in 2,500 to 3,000 live births (9). Neurofibromatosis is transmitted by an autosomal-dominant mode of inheritance with about 80% penetrance. About one-half of the cases occur as spontaneous mutations, and it is impossible to determine clinically which cases represent true mutations and which are inherited from a parent in whom the condition is not clinically expressed. More recently, neurofibromatosis has been subcategorized into types 1 and 2 (22). Type 1 is also known as peripheral neurofibromatosis or von Recklinghausen syndrome. It is characterized by many peripheral and cutaneous manifestations of the syndrome and is recognized to occur from an abnormality of chromosome 17. Type 2 is called central or bilateral acoustic neurofibromatosis. It is characterized by central neural tumors, early onset of posterior subcapsular cataract and is recognized to be related to an abnormality in chromosome 22. There appears to be considerable overlap between the two, and they are discussed collectively in this section.

Ophthalmologic Features

Neurofibromatosis has the most diversified ocular findings among the systemic hamartomatoses (2,3,4). One study summarized the ocular manifestations in 77 patients (23). These included abnormalities in the uveal tract (80%), eyelid (25%), cornea (25%), optic nerve (12%), retina (9%), and conjunctiva (4%). In addition, there is an increased incidence of glaucoma in patients with neurofibromatosis (24).

Eyelid involvement has been noted in 25% of patients with neurofibromatosis (23). The plexiform neurofibroma produces the typical S-shaped curvature to the upper eyelid, a finding which is believed to be highly characteristic of neurofibromatosis. In more advanced stages, the plexiform neurofibroma appears as a diffuse irregular nodular thickening of the eyelid that can produce atypical blepharoptosis.

Patients with neurofibromatosis have an increased incidence of congenital glaucoma (3,4,24). It appears to occur more commonly in patients who have neurofibromatous involvement of the eyelids or ipsilateral facial hemihypertrophy. It can be secondary to obstruction of aqueous outflow by diffuse neurofibromatous thickening of the trabecular meshwork, angle closure from forward displacement of the iris by a ciliary body tumor, or iris neovascularization. Patients with type 2 neurofibromatosis have recently been recognized to have early onset of posterior subcapsular cataract (22). The significance of this is unclear.

Uveal tract involvement has been recognized in about 80% of patients with neurofibromatosis (23). Multiple iris hamartoma, known as Lisch nodules, are the most common uveal abnormality (3,23). They occur in early childhood as discrete, multiple, lightly pigmented elevations of the anterior border layer (Fig. 22.3). These bilateral lesions appear to be relatively uncommon in children less than 5 years of age, but they show a marked increase in incidence after age 6 years. Histologically, Lisch nodules are focal aggregates of melanocytes and glial cells on the anterior border layer of the iris.

Similar hamartoma can occur in the choroid of patients with neurofibromatosis (3). It is most likely that these choroidal lesions are aggregates of cells similar to those which occur in the iris. The choroidal hamartoma probably represents a melanocytic nevus, which occurs with greater frequency in patients with neurofibromatosis. Other patients with neurofibromatosis have a diffuse thickening of the uveal tract due to an increased number of neurofibromatous and melanocytic elements. Another choroidal tumor which can occur in patients with neurofibromatosis is the neurilemoma (schwannoma). In patients with neurofibromatosis, the neurilemoma characteristically occurs as a diffuse thickening of the choroid, as described above. In rare instances, however, a circumscribed, elevated neurilemoma can occur in a patient with this syndrome. Most solitary neurilemoma of the choroid, however, are unassociated with neurofibromatosis (25). The astrocytic hamartoma that is classic for tuberous sclerosis occurs occasionally in patients with neurofibromatosis. There are also cases of combined hamartoma of the retinal pigment epithelium in patients with neurofibromatosis type 2 (3,4). At least three patients with neurofibromatosis who developed choroidal melanoma have also been seen (unpublished observations).

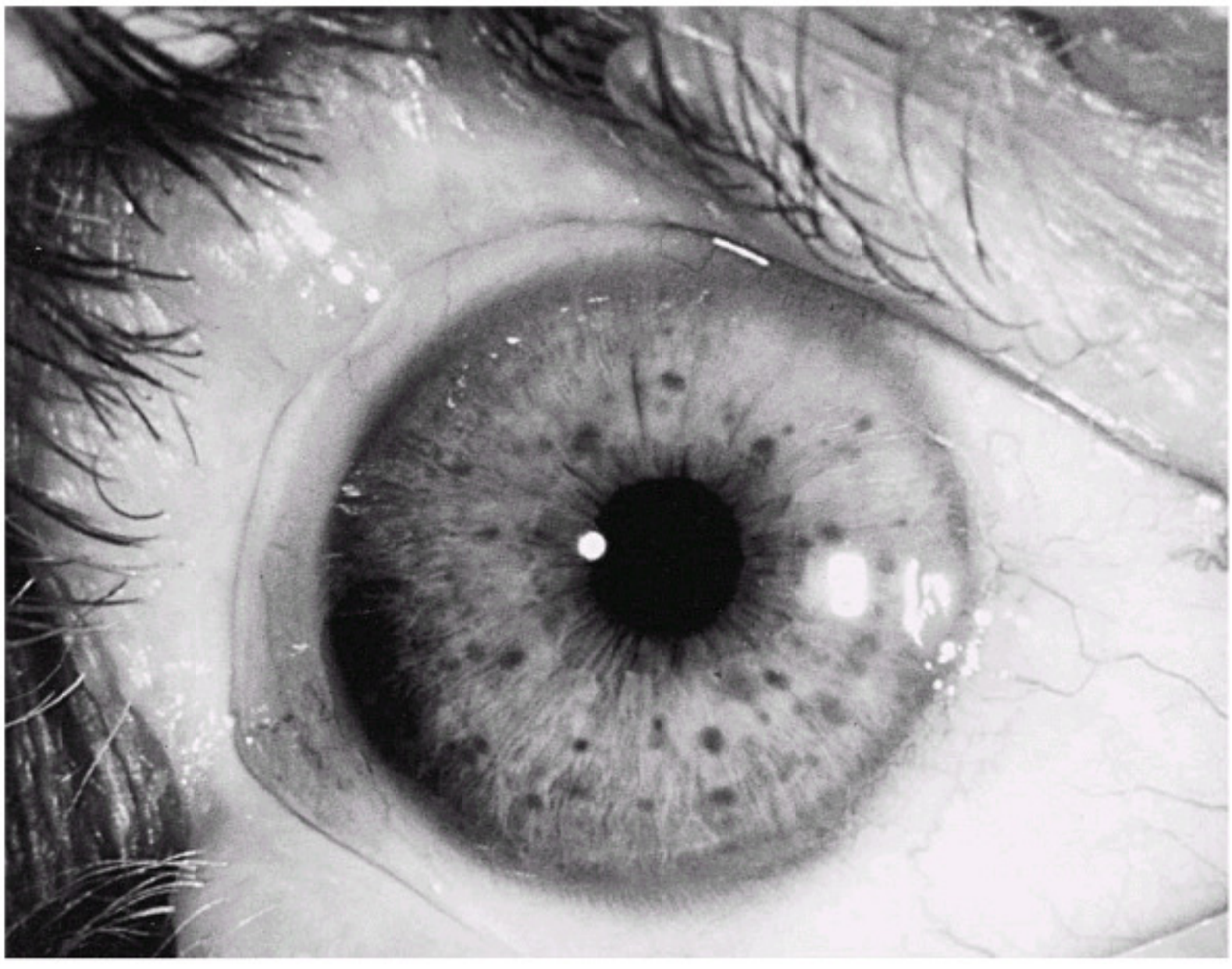

Figure 22.3 Lisch nodules of iris in patient with neurofibromatosis.

The orbital portion of the optic nerve can be involved with optic nerve pilocytic astrocytoma (glioma) or meningioma. In patients with pilocytic astrocytoma, the reported incidence of neurofibromatosis has ranged from 9% to 30% (3,4,26). The juvenile pilocytic astrocytoma of the optic nerve is a slowly progressive lesion that can lead to proptosis, optic atrophy, and visual loss. Young children with this tumor may present with optic disc edema and signs of retinal venous obstruction. Histologically, the juvenile pilocytic astrocytoma is composed of well-differentiated astrocytes (22). The treatment of pilocytic astrocytoma of the optic nerve is controversial and depends on the location and extent of the disease. Some require no treatment, some need irradiation or chemotherapy, and others require surgical excision (27).

Plexiform neurofibromata, histopathologically similar to those that appear on the skin, can also occur in the orbits of patients with neurofibromatosis. As mentioned earlier, the plexiform neurofibroma is considered to be pathognomonic of neurofibromatosis. However, they are not pathognomonic of this syndrome; multiple localized neurofibromas have been observed in a patient with no evidence of von Recklinghausen disease (28). Neurilemomas (schwannomas) can also develop in the orbits of patients with neurofibromas. They arise from the Schwann cells of the ciliary nerves (29).

Dermatologic Features

The most important cutaneous manifestations of neurofibromatosis include benign nerve sheath tumors, pigmented macules (café-au-lait spots) (Fig. 22.4) and nevi. Most of these skin lesions become clinically apparent at puberty, although in some instances they have been noted at birth. The benign cutaneous and subcutaneous nerve sheath tumors (neurofibromas and schwannomas) can occur anywhere on the skin and may be particularly pronounced in the facial area (Fig. 22.5). They characteristically enlarge very slowly over many years and can lead to massive hemihypertrophy of the extremities or face. Such proliferation has been called elephantiasis neuromatosa.

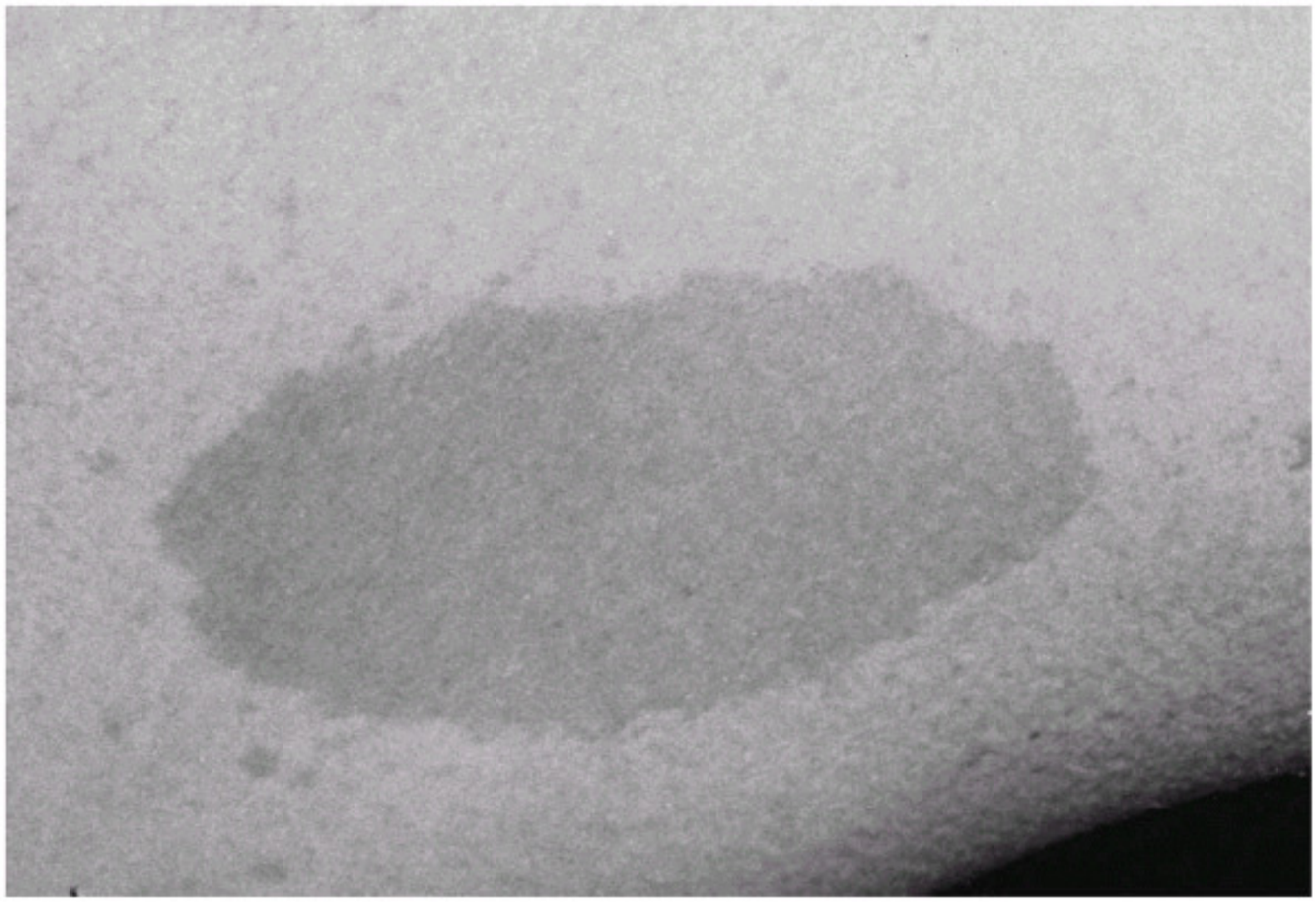

Figure 22.4 Pigmented cutaneous macule (café-au-lait spot) on the hand of a patient with neurofibromatosis.

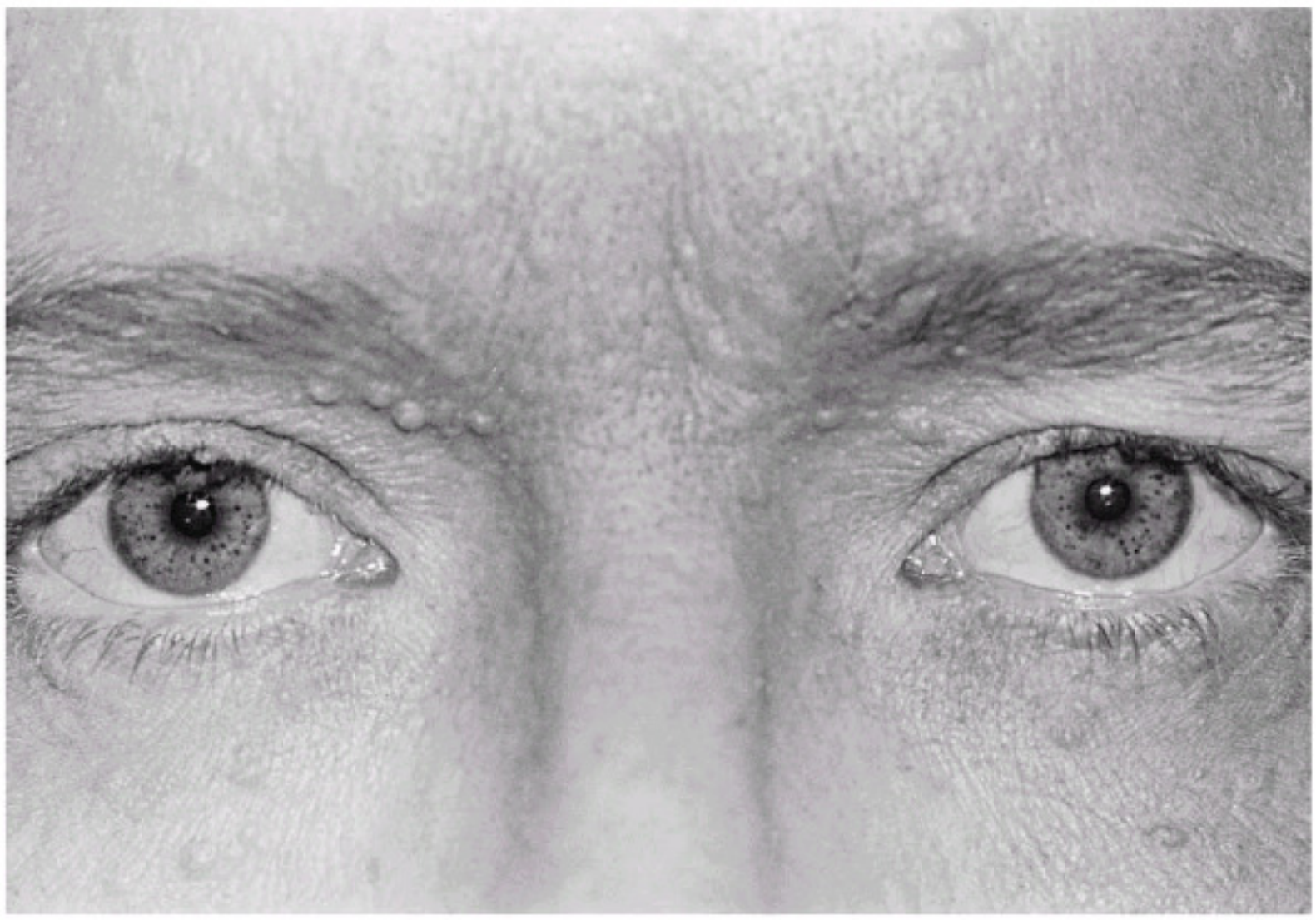

Figure 22.5 Facial nerve sheath tumors in a patient with neurofibromatosis.

The pigmented macule (café-au-lait spot) is characterized clinically as a patch of light brown pigmentation with fairly well-defined borders (Fig. 22.4). It can occur anywhere on the skin and can assume a variety of sizes and configurations. Café-au-lait spots are highly characteristic of neurofibromatosis, and it has been suggested that any person with six or more of these lesions larger than 1.5 cm must be presumed to have neurofibromatosis, even in the absence of a positive

family history (3). Histologically, the café-au-lait spot is characterized by hyperpigmentation of the basal layer of the otherwise normal epidermis.

Other Features

The CNS manifestations of neurofibromatosis vary with the size and extent of the associated tumors (3,20). Acoustic neuromas, particularly bilateral, are considered to be pathognomonic of type 2 neurofibromatosis (22). Other associated tumors include gliomas in the region of the third ventricle, pituitary tumors, and spinal cord meningiomas.

A number of other benign and malignant systemic tumors have been associated with neurofibromatosis. Sarcomas occasionally arise from the peripheral nerve sheaths, either *de novo* or from preexisting cutaneous tumors. Malignant peripheral nerve sheath tumors are said to occur in up to 29% of patients (29). There seems to be an increased incidence of breast, genitourinary, and gastrointestinal tumors, and cutaneous melanoma (3). Patients with neurofibromatosis are recognized to have a slightly higher incidence of pheochromocytoma (30) and malignant melanoma of the uveal tract (31).

Management

The management of neurofibromatosis varies with the location and extent of the disease. Treatment can be very complex, and all of the therapeutic ramifications cannot be discussed here.

RETINOCEREBELLAR HEMANGIOMATOSIS (VON HIPPEL-LINDAU SYNDROME)

Definition, Incidence, and Genetics

A capillary hemangioma can occur in the retina (von Hippel disease) or in both the retina and cerebellum (von Hippel-Lindau disease). In 1895 von Hippel reported the clinical findings of so-called retinal angiomatosis (32) and in 1926 Lindau studied cerebellar lesions and pointed out their relationship to the retinal tumors previously described by von Hippel (33). Consequently, the combination of retinal and cerebellar involvement has been called von Hippel-Lindau (VHL) syndrome. The definition of VHL syndrome has now been expanded to include all of the clinical manifestations of this intriguing condition (4,34,35).

VHL syndrome is recognized to be a hereditary disorder, with an autosomal-dominant mode of inheritance and incomplete penetrance. Many cases which are seen by the ophthalmologist, however, occur as spontaneous mutations with no apparent family history of the disease. Probably about 20% of cases have a positive family history (35). The exact frequency of familial occurrence is not known because many cases are lowly penetrant and express only subtle subclinical features of the syndrome. The condition has recently been recognized to be related to a partial deletion of the short arm of chromosome 3 (34,35,36).

Ophthalmologic Features

The ocular manifestations of VHL syndrome are not as diversified as they are in the other systemic hamartomatoses (3,4,35). The capillary hemangiomas of the retina or optic disc are the only intraocular hamartomas which are known to occur with this syndrome. When associated with VHL syndrome, the retinal and optic disc tumors are often multiple and are bilateral in more than half of the cases (3,35). The diagnosis of the ocular lesions is usually made in the second or third decade of life.

The ophthalmoscopic appearance of a capillary hemangioma varies with the location of the lesion in the fundus. In the earliest stages, a tumor in the peripheral retina is often subtle and difficult to identify ophthalmoscopically. As the tumor enlarges, it appears as a distinct red nodule with a typical dilated tortuous afferent artery and efferent vein (Fig. 22.6). The dilated blood vessels extend from the optic disc to the tumor and can be recognized immediately upon ophthalmoscopic examination of the posterior fundus. A capillary hemangioma of the optic disc does not usually develop the well-defined feeding and draining blood vessels that characterize the peripheral lesion (3,4). A retinal capillary hemangioma can assume either an exudative form or vitreoretinal form. These two forms are described in greater detail in the literature (3).

Histopathologically, the capillary hemangioma consists of a proliferation of retinal capillaries that usually replace the full thickness of the sensory retina (3,36). With light microscopy, there appears to be a benign proliferation of both endothelial cells and pericytes. It has recently been demonstrated that the clear “stromal cell” which characterizes the capillary hemangioma may be the cell of origin for the neoplasm, but the exact nature of these cells is still not known (36). In the end stages, there may be a total retinal detachment with massive gliosis of the retina, cataract, and phthisis bulbi.

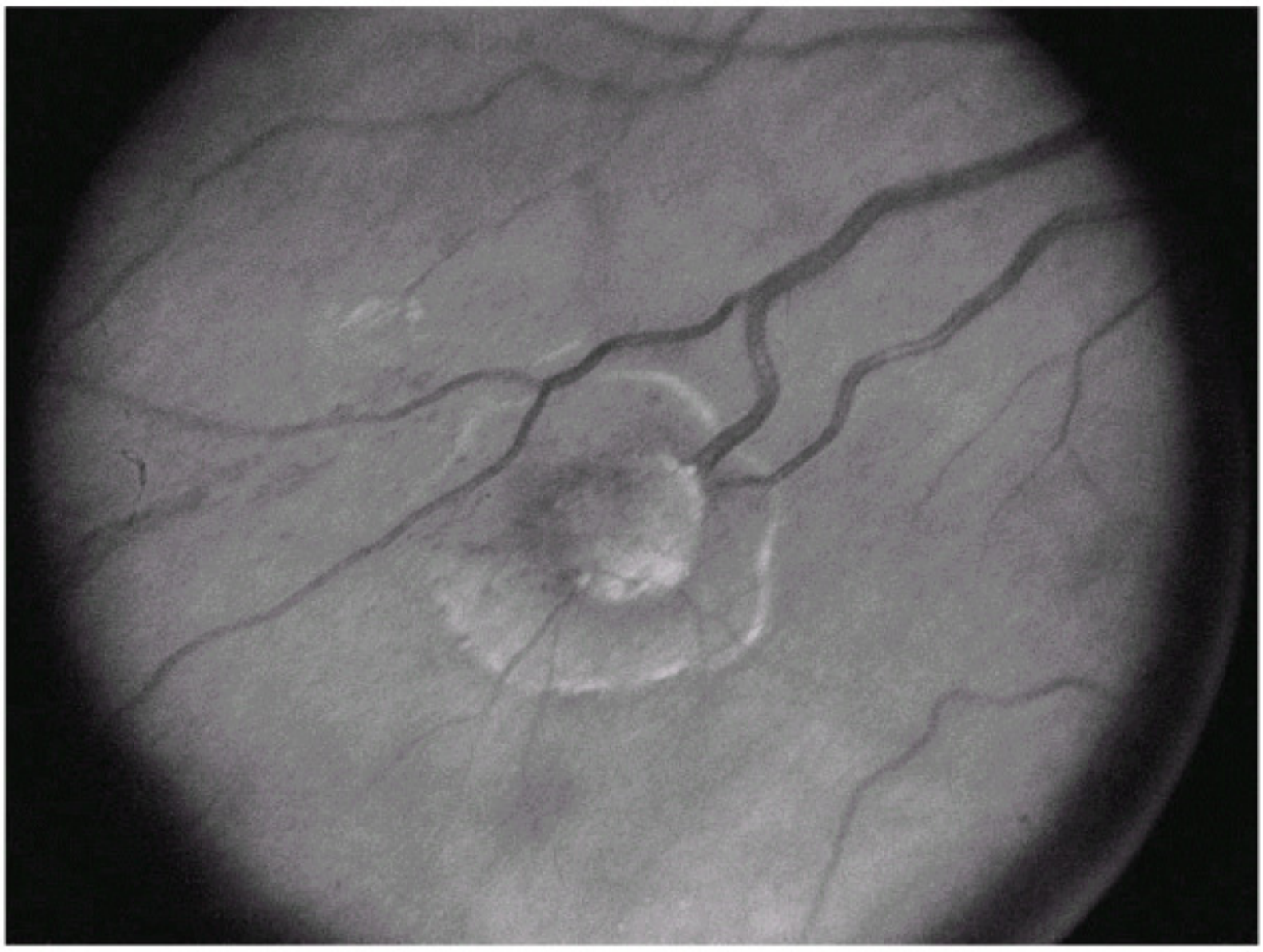

Figure 22.6 Retinal capillary hemangioma in a patient with von Hippel-Lindau syndrome.

Fluorescein angiography is the most helpful ancillary study in confirming the diagnosis. In the arterial phase, the tumor fills rapidly by way of the feeding retinal artery and shows numerous fine capillaries within the tumor. In the venous phase, the lesion shows marked hyperfluorescence as the dye leaks from the capillaries. In the late phase, fluorescein leaks from the tumor into the overlying vitreous (3).

Dermatologic Features

In contrast to the other systemic hamartomatoses, VHL syndrome usually has no major cutaneous involvement. Congenital cutaneous hemangiomas have been observed on rare occasions.

Other Features

The cerebellar hemangioblastoma is the classic CNS lesion in VHL syndrome. It can be small and asymptomatic, but it usually enlarges slowly and can eventually produce profound cerebellar signs and symptoms. The cerebellar symptoms usually occur in the fourth decade of life, and patients with known ocular disease should have periodic neurologic evaluation to detect early onset. Identical lesions can occasionally occur in the medulla oblongata and spinal cord.

The cerebellar hemangioblastoma is best diagnosed with computed tomography or magnetic resonance imaging. Like retinal capillary hemangioma, it characteristically has large blood vessels that supply and drain the lesion. The vascular tumor frequently occurs within a cerebellar cyst. Histologically, the tumor is a hemangioblastoma with features similar to the vascular tumor which occurs in the retina (1).

Various systemic hamartomas can occur in patients with VHL syndrome (3,35,37,38). These include hypernephroma, pheochromocytoma, renal cyst, and pancreatic and epididymal cysts (37). A detailed medical and family history should be taken on all patients with retinal capillary hemangioma and, if indicated, appropriate studies be undertaken to detect any of the systemic components of VHL syndrome.

Management

No active treatment may be necessary for small asymptomatic retinal tumors because some of them remain stable for many years and some even regress spontaneously. The patient should be examined periodically and treatment instituted if the tumor grows or if there is progressive accumulation of exudation or subretinal fluid. In such instances, several methods of treatment have been advocated, including argon laser and cryotherapy (3,39). If a capillary hemangioma has caused an extensive retinal detachment with subretinal exudation, a vitrectomy and/or scleral buckling procedure may be necessary to reattach the retina. Plaque radiotherapy has been used for selected tumors with extensive retinal detachment.

ENCEPHALOFACIAL HEMANGIOMATOSIS (STURGE-WEBER SYNDROME)

Definition, Incidence, and Genetics

Encephalofacial hemangiomatosis (EFH) is frequently referred to as Sturge-Weber syndrome. In 1879 Sturge described a syndrome composed of a facial hemangioma with ipsilateral buphthalmos and contralateral seizures (40). He speculated that an associated intracranial angioma may have been present. In 1884 Milles established the association of a choroidal hemangioma with this condition (41). Later Weber studied the clinical manifestations in greater detail, and the fully expressed entity became known as Sturge-Weber syndrome (42). Sturge-Weber syndrome is now recognized to consist of a facial hemangioma,

buphthalmos, seizures, and radiographic evidence of intracranial calcification (43). Most patients, however, have a forme fruste rather than the entire syndrome. In contrast to the other systemic hamartomatoses, there is no recognizable hereditary pattern associated with Sturge-Weber syndrome. It is apparently very rare for more than one member of a family to demonstrate the clinical manifestations. There is no predisposition for gender or race.

Ophthalmologic Features

The ocular findings associated with Sturge-Weber syndrome include eyelid involvement with nevus flammeus, prominent epibulbar blood vessels, glaucoma, retinal vascular tortuosity, and diffuse choroidal hemangioma (44).

The facial hemangioma can frequently involve the eyelids. Although it is usually unilateral (Fig. 22.7), bilateral involvement occasionally occurs. Involvement of the upper eyelid has a high association with ipsilateral glaucoma. Prominent tortuous epibulbar blood vessels, in both the conjunctiva and episclera, are common findings. Glaucoma is more common in patients with Sturge-Weber syndrome than it is in the other systemic hamartomatoses. In a study of 50 patients with nevus flammeus, there was an 8% overall incidence of glaucoma. If the facial hemangioma involved both the first and second division of the trigeminal nerve, the incidence was 15% (44). The glaucoma occurs unilaterally on the side of the facial hemangioma. As mentioned earlier, the chances of glaucoma are greater if the hemangioma involves the upper eyelid. Occasionally patients have shown bilateral involvement of the upper eyelid with bilateral glaucoma. It may gradually lead to extensive cupping of the optic disc and blindness. Patients with facial nevus flammeus who developed complete blindness from unrecognized glaucoma have been observed. The associated glaucoma can be either congenital or juvenile.

The only important abnormality of the uveal tract in patients with Sturge-Weber syndrome is the diffuse choroidal hemangioma. Patients with this tumor usually have a bright red pupillary reflex in the involved eye as compared with the normal contralateral eye. This phenomenon, which is due to the light reflex from the highly vascularized

tumor in the posterior pole, has been called the “tomato catsup” fundus (45). The choroidal hemangioma is usually unilateral, but bilateral cases associated with bilateral facial nevus flammeus have been recognized (46). It is extremely rare for the diffuse choroidal hemangioma to occur as an isolated finding without the facial nevus flammeus or some of the other manifestations of Sturge-Weber syndrome. The diffuse tumor is usually diagnosed when the affected patient is young (median age 8 years) because either the associated facial hemangioma prompts a fundus examination or visual impairment occurs from hyperopic amblyopia or from a secondary retinal detachment. The diffuse choroidal hemangioma can produce a total retinal detachment and neovascular glaucoma. Histopathologically, the lesion is a diffuse thickening of the choroid consisting of variable sized venous channels (47).

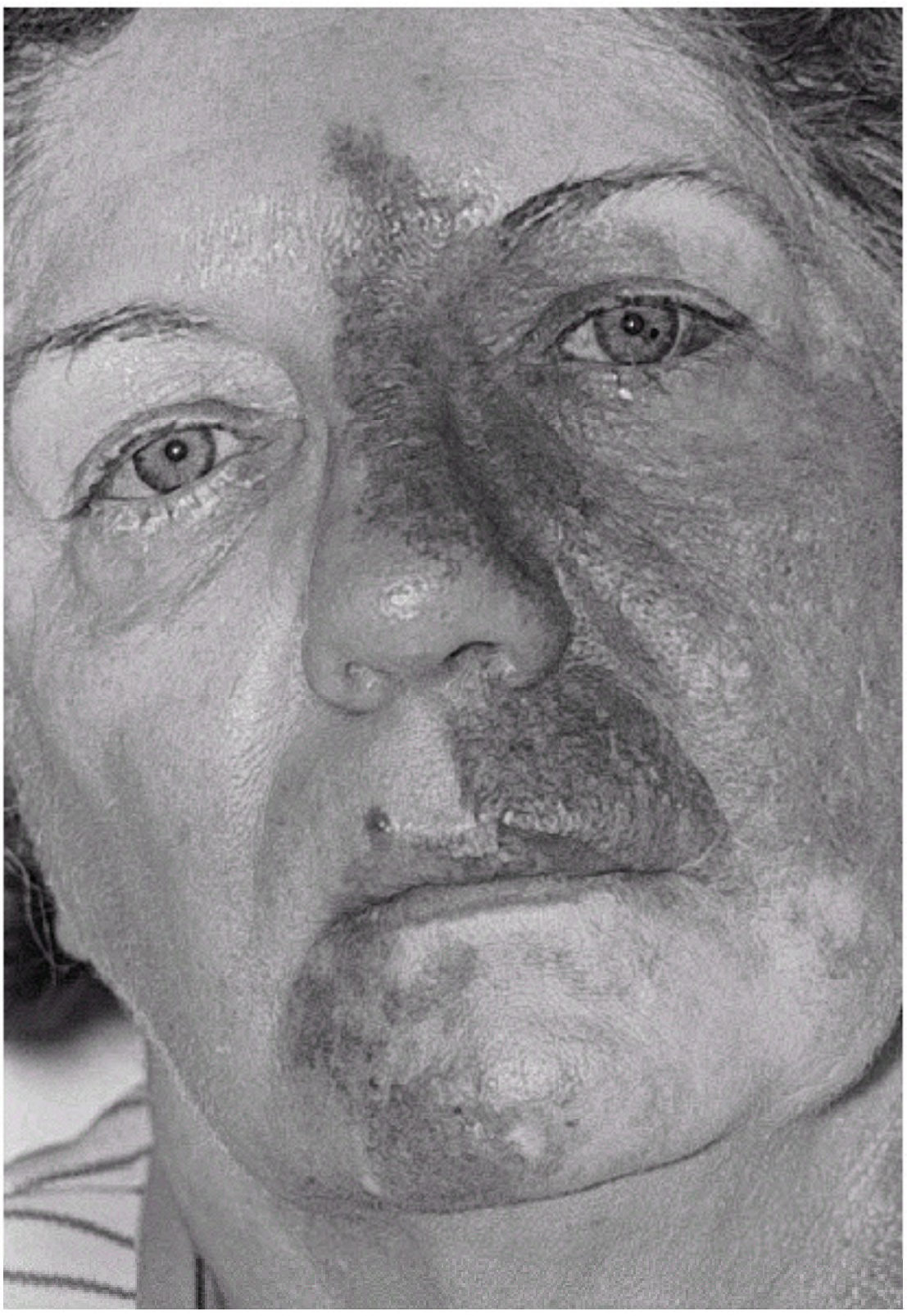

Figure 22.7 Facial nevus flammeus associated with Sturge-Weber syndrome.

The precise incidence of the diffuse choroidal hemangioma in patients with facial nevus flammeus syndrome has not been determined. The incidence of choroidal

hemangioma appears to be higher in patients who have both facial nevus flammeus and leptomeningeal hemangiomatosis.

Dermatologic Features

The classic skin lesion of Sturge-Weber syndrome is the facial hemangioma, often referred to as nevus flammeus or port wine stain (3,4). Although it classically occurs in the cutaneous distribution of the fifth cranial nerve (Fig. 22.7), it can have many variations, ranging from minor involvement of the first division of the nerve to massive involvement of all three divisions. It sometimes crosses the midline in an irregular pattern and is occasionally bilateral. Histologically, the cutaneous lesion is a cavernous hemangioma consisting of dilated, congested veins with a thin endothelium (3).

Other Features

The typical CNS change associated with Sturge-Weber syndrome is a diffuse leptomeningeal hemangioma that is ipsilateral to the facial hemangioma (2,3,4). It is characteristically most pronounced in the occipital region. The adjacent cerebral cortex can show secondary calcification that appears on skull x-rays as a radiopaque double line, which has been called the “railroad track” sign. The calcific process often progresses during the first 20 years of life but usually becomes stable in adulthood. Convulsions, which frequently occur, are characteristically localized to the side contralateral to the CNS involvement (3,4).

Management

The management of the diffuse choroidal hemangioma can be very difficult, and it varies with the extent of the tumor. In some cases, the tumor is only minimally elevated and may require no treatment. A thicker tumor that is located beneath the fovea can be initially managed by refraction, correction of hyperopic refractive error, and treatment of associated amblyopia. A small secondary retinal detachment can be treated with laser photocoagulation, but more extensive retinal detachment may require irradiation, which is often very effective in management (48). Another option is retinal detachment surgery combined with laser or cryotherapy to preserve vision and prevent neovascular glaucoma. A subfoveal tumor eventually causes cystoid macular edema, making the visual prognosis much worse. Treatment of the glaucoma can be difficult and should be undertaken by an ophthalmologist who is experienced in the management of complicated glaucoma problems.

The cutaneous lesions seen with Sturge-Weber syndrome can be managed by cosmetics to cover the defect or by laser treatment to the affected area. Both of these methods can improve the cosmetic appearance.

RACEMOSE HEMANGIOMATOSIS

Definition, Incidence, and Genetics

Racemose hemangioma of the midbrain and ipsilateral retina is called Wyburn-Mason syndrome (3,4). In contrast to the other oculoneurocutaneous syndromes, it has few skin changes except for occasional small facial hemangiomas. The ocular and CNS changes, however, may be quite striking. Wyburn-Mason first recognized this relationship in 1943 (49). He estimated that intracranial aneurysms were present in 81% of known cases of retinal arteriovenous aneurysms. Conversely, he estimated that retinal arteriovenous aneurysms occurred in about 70% of cases of midbrain arteriovenous aneurysms (49).

Like Sturge-Weber syndrome, this congenital condition does not appear to be familial and does not exhibit a hereditary pattern. The characteristic arteriovenous communications can range from very subtle asymptomatic lesions to more extensive ones which form tumor-like masses, often referred to as racemose or cirsoid hemangiomata (3,4).

Ophthalmologic Features

The classic ocular finding is the racemose hemangioma of the retina (50,51,52). Similar vascular malformations can occur in the orbit and adjacent structures. These retinal arteriovenous communications have been divided into three groups (50). Group I is characterized by interposition of an abnormal capillary plexus between the major vessels. It is not a true tumor, and the affected patient is generally asymptomatic. Group II is typified by a direct arteriovenous communication without interposition of capillary or arteriolar elements (Fig. 22.8). The dilated blood vessels in this group may superficially resemble a capillary hemangioma of the retina, but no tumor, exudation, or retinal detachment is present. In general, these patients have few visual symptoms, but they may have associated cerebral arteriovenous malformations.

Group III is characterized by a more extensive and complex arteriovenous communication which is often associated with visual loss. The fundus changes in this group are similar to those described by Wyburn-Mason (49), and the affected patient has a high incidence of CNS lesions. In

this group, the most striking feature is one or more dilated arteries that emerge from the optic disc, pass for a variable distance into the retina, form distinct arteriovenous communications, and then pass back to the optic disc as large veins. There is characteristically no exudation or retinal detachment. Although these lesions are believed to remain stationary indefinitely, remarkable changes have been observed in the distribution of the blood vessels over several years. Branch retinal vascular obstruction can occasionally occur (53,54).

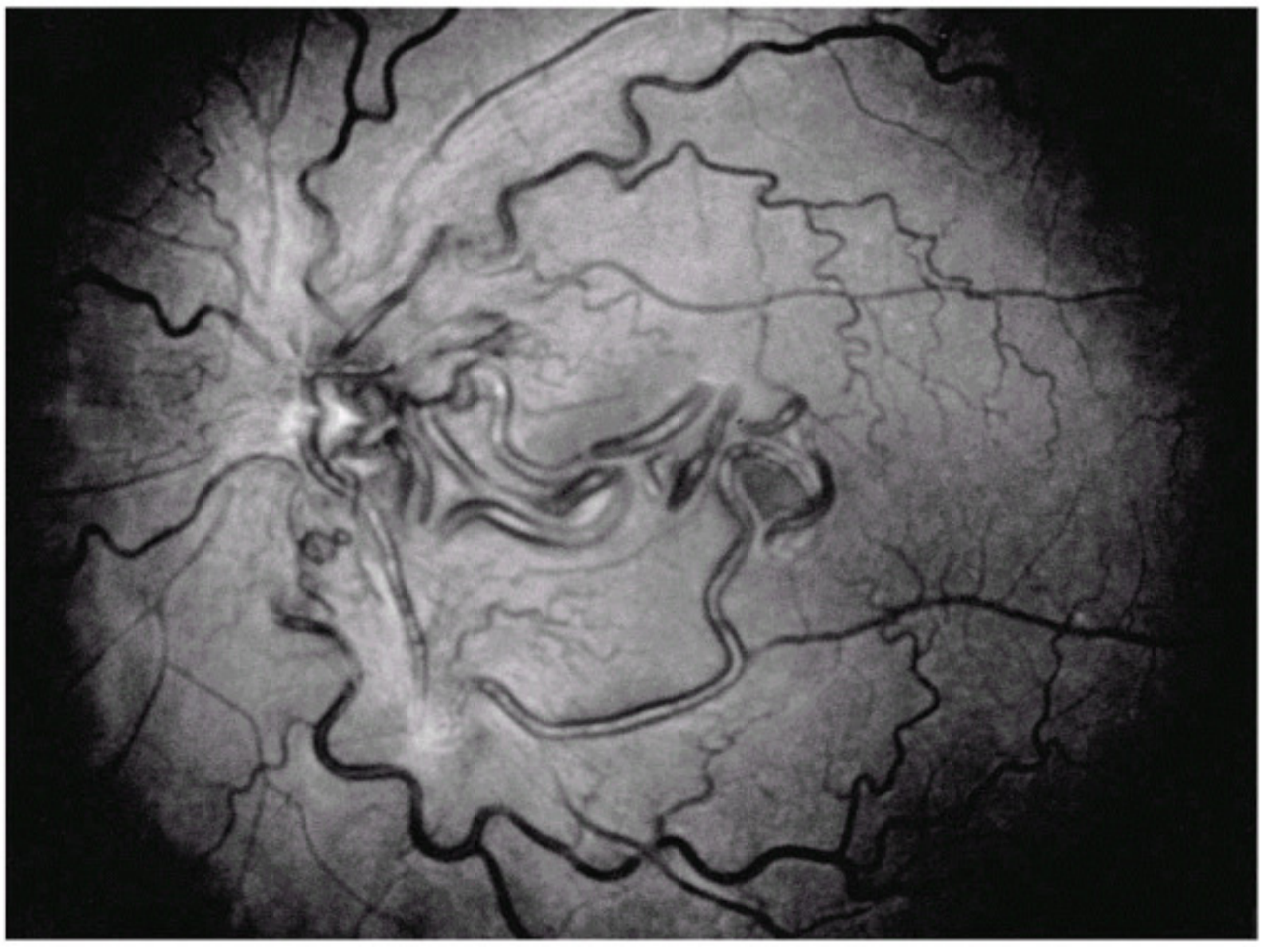

Figure 22.8 Retinal arteriovenous communication in Wyburn-Mason syndrome.

Dermatologic Features

There are no significant cutaneous changes associated with racemose hemangiomatosis, except for the rare occurrence of small facial angiomas.

Other Features

The seizures that occur with Wyburn-Mason syndrome are probably related to the CNS vascular malformations. Spontaneous intracranial hemorrhages, secondary to the vascular anomaly in the midbrain, can lead to a variety of neurologic symptoms and signs. Intracranial hemorrhage occurs more frequently than intraocular hemorrhage. The bones of the skull can frequently be involved with the vascular malformation. When the mandible or maxilla are involved, abnormal bleeding can follow dental work. One patient with a large retinal racemose hemangioma who has a history of massive hemorrhage following tooth extraction has been observed.

Management

In general, no dermatologic or ophthalmic treatment is necessary for retinal racemose hemangiomatosis. The retinal lesion generally cannot be treated. If it produces persistent vitreous hemorrhage, then the blood can be removed by vitrectomy. Panretinal photocoagulation may be necessary for neovascular complications of retinal vein obstruction.

RETINAL CAVERNOUS HEMANGIOMATOSIS WITH CUTANEOUS AND CENTRAL NERVOUS SYSTEM VASCULAR MALFORMATIONS

Although not historically grouped with the phakomatoses, the cavernous hemangioma of the retina has been recognized to be frequently associated with skin and CNS changes and should perhaps be considered one of the systemic hamartomatoses (3,55,56,57).

Definition, Incidence, and Genetics

The syndrome of cavernous hemangiomas of the retina, CNS, and skin may be diagnosed at any age and seems to be more common in women than in men. The retinal and skin tumors are frequently asymptomatic, but the CNS hamartomas can sometimes produce dramatic clinical symptoms. In many instances, there is an autosomal-dominant mode of inheritance.

Ophthalmologic Features

The only ocular manifestation of this syndrome is the retinal cavernous hemangioma. Ophthalmoscopically, the retinal lesions appear as a cluster of dark venous intraretinal aneurysms (3,4,44,45,46) (Fig. 22.9). There is no feeder artery and usually no yellow exudation, but white fibroglial tissue is characteristically present on the surface of the tumor. In some instances, the tumor can be largely obscured by this surface fibroglial tissue. It can be found in the peripheral

retina or on the optic disc. It is usually nonprogressive but, on rare occasions, may show minimal enlargement over a long period of time. The main complication of retinal cavernous hemangioma is vitreous hemorrhage. Some larger cavernous hemangiomas can be associated with severe fibrogliosis that can cause dragging of the retina with displacement of the macular area. Histopathologically, the cavernous hemangioma appears as many large-caliber veins that usually

arise in the inner portions of the retina.

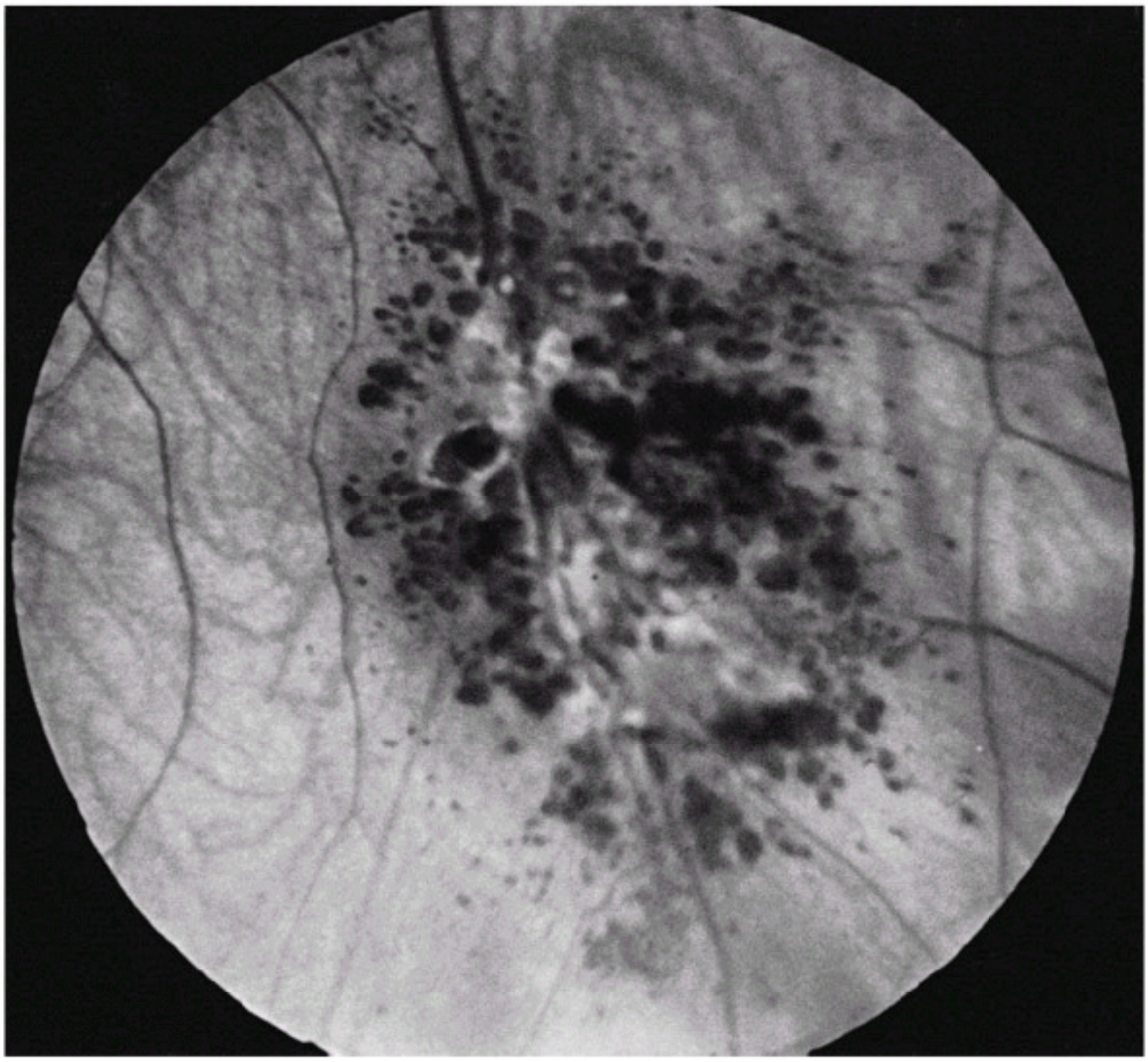

Figure 22.9 Retinal cavernous hemangioma.

The most important diagnostic ancillary test for a cavernous hemangioma of the retina is fluorescein angiography, which produces results that are highly characteristic, if not pathognomonic, of this condition. During the arterial phase, the vascular channels comprising the lesion remain hypofluorescent. In the late venous phase, fluorescein begins to slowly enter the vascular spaces. In later angiograms, fluorescein is contained within the venous aneurysms of the lesion, and there is minimal, if any, leakage of dye into the surrounding tissues. The fluorescein pools in the plasma in the superior portion of each vascular space, while the blood collects in the inferior portion of each aneurysm. This produces the characteristic fluorescein-blood interface in the late angiograms which is very characteristic of a cavernous hemangioma of the retina.

Dermatologic Features

The hemangiomas of the skin in this syndrome are quite variable in their appearance and distribution on the body. The lesions occur most commonly on the back of the neck. Involvement of the eyelids is rare.

Other Features

Various types of seizures can occur in patients with this syndrome. They appear to be secondary to similar vascular malformations in the CNS. Patients have been seen who presented initially with diplopia due to paresis of extraocular muscles, presumably secondary to bleeding into the oculomotor nuclei (45). It is likely that many patients have vascular lesions in the CNS that remain subclinical throughout life.

Management

Dermatologic Disease

The cutaneous hemangiomas seen with this condition are generally small and asymptomatic and require no aggressive treatment.

Ophthalmologic Disease

Most cavernous hemangiomas of the retina are asymptomatic and stable and require no treatment. Since they rarely progress or produce visual symptoms, they usually can be managed by periodic observation. Vitreous hemorrhage can be an occasional complication of the larger lesions. If this should occur, either cryotherapy or photocoagulation can be used to treat the tumor, but the value of such treatment is still unproved. A low-energy radioactive plaque has been employed in one case of a large retinal cavernous hemangioma with recurrent vitreous hemorrhage, and no further vitreous hemorrhage occurred.

ORGANOID NEVUS SYNDROME

Definition, Incidence, and Genetics

Organoid nevus syndrome (ONS) is an oculoneurocutaneous condition characterized by the sebaceous nevus of Jadassohn, cerebral atrophy, epibulbar complex choristoma, posterior scleral cartilage, and occasionally other features (58,59). Although the sebaceous nevus of Jadassohn is a well-known dermatologic entity, the full blown syndrome is uncommon and the exact incidence is unknown. It is generally a sporadic condition with familial occurrence being extremely rare.

Ophthalmologic Features

Although there are several ophthalmic features of ONS, the two most important ones are the epibulbar complex choristoma and posterior scleral cartilage. The epibulbar complex choristoma is a fleshy lesion of the conjunctiva that often extends onto the cornea (Fig. 22.10). It is composed histopathologically of a dermolipoma that contains variable combinations of ectopic lacrimal gland and hyaline cartilage. The posterior scleral cartilage produces a peculiar yellow-white discoloration of the fundus in the area of involvement. Since the cartilage produces a pattern similar to bone with ultrasonography and computed tomography, it has sometimes been misinterpreted as a choroidal osteoma.

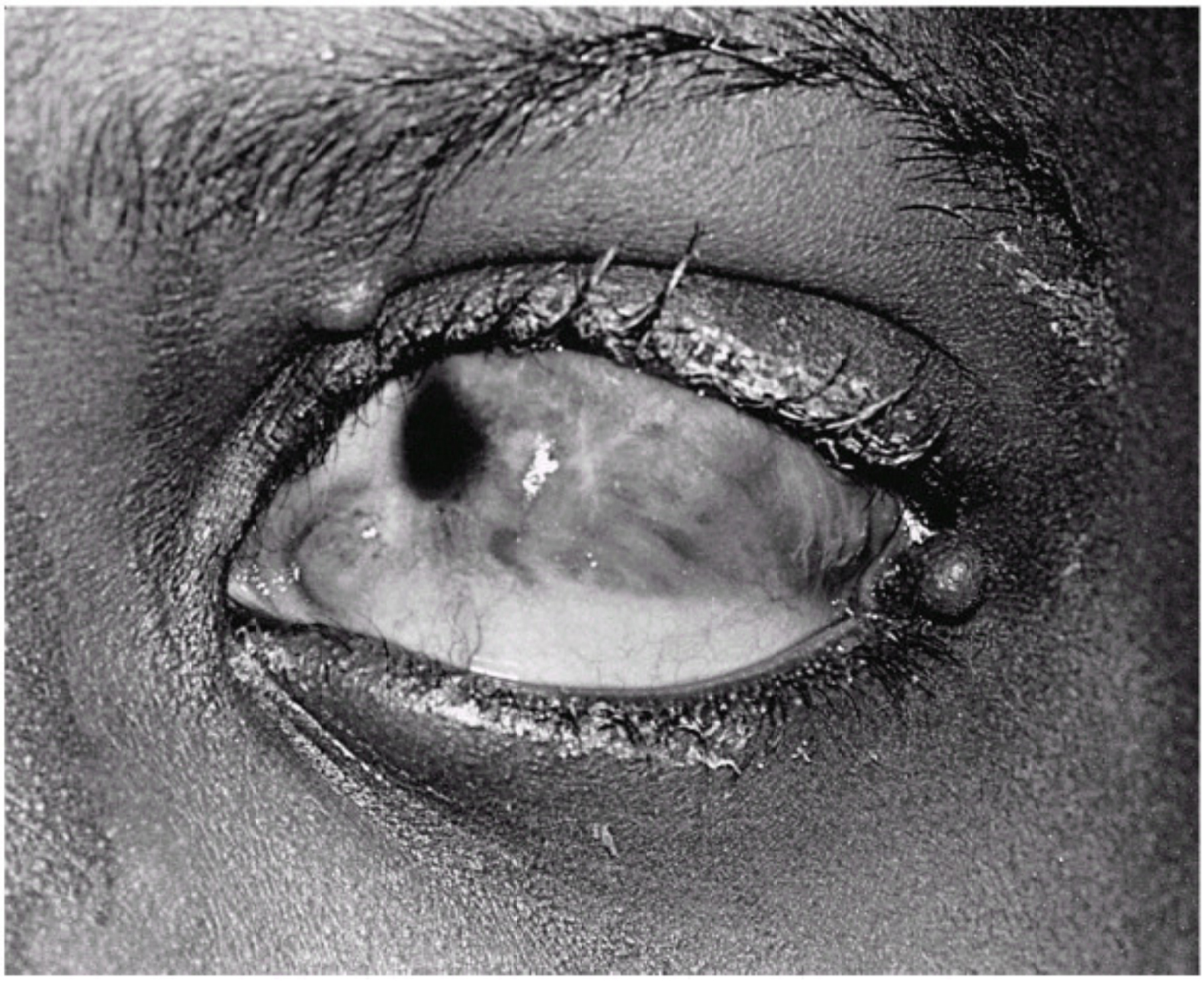

Figure 22.10 Epibulbar complex choristoma in a patient with organoid nevus syndrome.

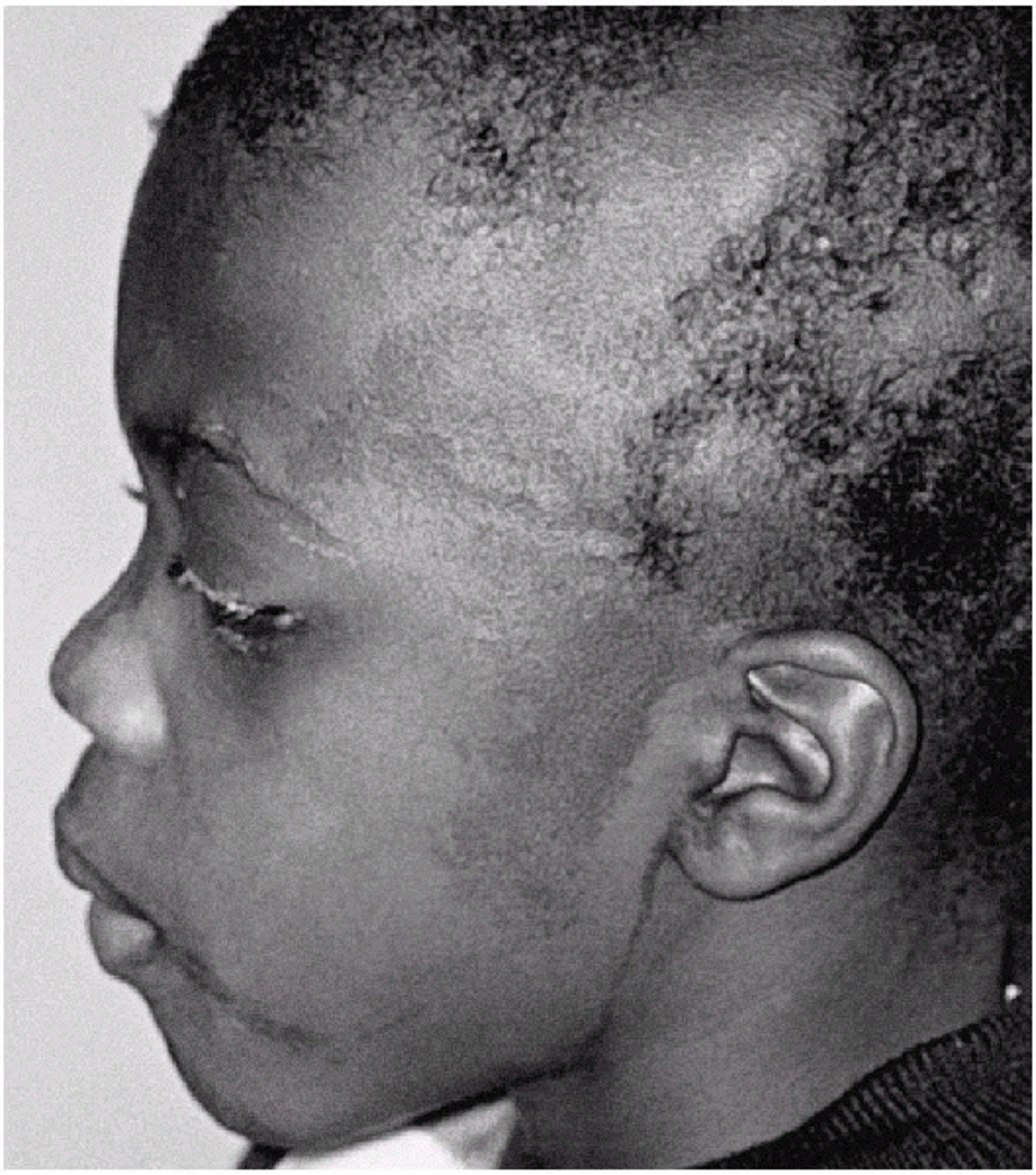

Figure 22.11 Nevus sebaceous of Jadassohn in patients with epibulbar choristoma shown in Figure 22.10. Note the alopecia.

Dermatologic Features

The main dermatologic feature of ONS is the sebaceous nevus of Jadassohn. It appears as a geographic yellow-brown lesion that often involves the preauricular region and extends onto the scalp where it is associated with alopecia (Fig. 22.11).

Other Features

Patients with ONS can develop seizures, due mainly to enlarging subarachnoid cysts in the CNS. Rarely the affected patient can have various cardiac and renal abnormalities.

Management

The epibulbar choristoma generally remains fairly stationary and can be safely observed in many instances. Larger or progressive lesions, however, may require surgical excision. There is no treatment of the fundus lesion. The sebaceous nevus requires close follow-up and surgical resection when possible, since basal cell carcinoma or other adnexal tumors can develop in about 20% of cases.

OTHER CONDITIONS RELATED TO PHAKOMATOSES

Other oculoneurocutaneous conditions that are sometimes loosely classified with the phakomatoses include ataxia telangiectasia (Louis-Bar syndrome), oculodermal melanocytosis, Klippel-Trenaunay-Weber syndrome, and diffuse neonatal hemangiomatosis. These associations are discussed in the literature (3) but are beyond the scope of this discussion.

COMBINED SYSTEMIC HAMARTOMATOSES

Because systemic hamartomatoses are derived from primitive neuroectoderm or mesectoderm, one would expect to see various combinations of these syndromes. The numerous reports on such overlap between these conditions are beyond the scope of this chapter, but some of them are mentioned in a recent textbook (1). Neurofibromatosis has been seen in association with von Hippel and Sturge-Weber syndromes. Tuberous sclerosis has been reported in association

with a lesion that the authors interpreted as a retinal hemangioma and with Klippel-Trenaunay-Weber syndrome. Sturge-Weber syndrome has occurred in association with oculodermal melanocytosis. There have been reports of retinal capillary hemangiomas associated with neurofibromatosis. Oculodermal melanocytosis has been seen in association with neurofibromatosis. Optic nerve glioma has been reported in a patient with von Hippel-Lindau disease (60).

SUMMARY

The systemic hamartomatoses, or phakomatoses, are characterized by hamartias and hamartomas which can involve the eye, skin, CNS, and occasionally viscera. Although these syndromes all represent congenital abnormalities of tissue formation, the lesions may not become clinically apparent until later in life.

The conditions which are presently included in this classification are: (a) tuberous sclerosis (Bourneville syndrome); (b) neurofibromatosis (von Recklinghausen syndrome); (c) retinocerebellar capillary hemangiomatosis (VHL syndrome); (d) encephalofacial cavernous hemangiomatosis (Sturge-Weber syndrome); (e) racemose hemangiomatosis (Wyburn-Mason syndrome); (f) retinal, cutaneous, and CNS cavernous hemangiomatosis; and (g) ONS. Several other syndromes are occasionally included under this category as well. The ocular, cutaneous, and CNS manifestations of these entities have been emphasized.

REFERENCES

1. Van der Hoeve J. The Doyne memorial lecture. Eye symptoms in phakomatoses. *Trans Ophthalmol Soc UK* 1932;52:380-401.

2. Font RL, Ferry AP. The phakomatoses. *Int Ophthalmol Clin* 1972; 12:1-50.

3. Shields JA, Shields CL. Systemic hamartomatoses (“phakomatoses”). In: Shields JA, Shields CL, eds. *Intraocular tumors. A text and atlas*. Philadelphia: WB Saunders Co., 1992:513-539.

4. Shields JA, Shields CL. The systemic hamartomatoses (“phakomatoses”). In: Mannis MJ, Macsai MS, Huntley AC, eds. *Eye and skin disease*. Philadelphia: Lippincott-Raven, 1996:367-380.

5. Shields JA, Shields CL. *Atlas of eyelid and conjunctival tumors*. Philadelphia: Lippincott Williams & Wilkins, 1999.

6. Shields JA, Shields CL. *Atlas of intraocular tumors*. Philadelphia: Lippincott Williams & Wilkins, 1999.

7. Shields JA, Shields CL. Vascular and hemorrhagic lesions. In: Shields JA, Shields CL, eds. *Atlas of orbital tumors*. Philadelphia: Lippincott Williams & Wilkins, 1999:45-74.

8. Ebert EM, Albert DM. The phakomatoses. In: Albert DM, Jakobiec FA. eds. *Principles and practice of ophthalmology*. Philadelphia: WB Saunders Co., 2000:5120-5146.

9. Crowe FW, Schull WJ, Neel JV. *A clinical, pathologic and genetic study of multiple neurofibromatosis*. Springfield, IL: CC Thomas Co., 1956.

10. Bourneville D. Sclereuse tubereuse des circonvolution cerebrales. Idiote et epilepsie hemiphlegique. *Arch Neurol (Paris)* 1880;1: 81-91.

11. Kwiatkowski DJ, Short MP. Tuberous sclerosis. *Arch Dermatol* 1994;130:348-354.

12. Shields JA, Eagle RC Jr, Shields C, et al. Aggressive retinal astrocytomas in 4 patients with tuberous sclerosis complex. *Arch Opthalmol*, in press.

13. Shields JA, Shields CL, Ehya H, et al. Atypical retinal astrocytic hamartoma diagnosed by fine needle biopsy. *Ophthalmology* 1996; 103:949-952.

14. Kranias G, Romano PE. Depigmented iris sector in tuberous sclerosis. *Am J Ophthalmol* 83:758-759.

15. Lucchese NJ, Goldberg MF. Iris and fundus pigmentary changes in tuberous sclerosis. *J Pediatr Ophthalmol Strabismus* 1981;18:45-46.

16. Gold AP, Freeman JM. Depigmented nevi; the earliest sign of tuberous sclerosis. *Pediatrics* 1965;35:1003-1005.

17. Lagos JC, Gomez MR. Tuberous sclerosis. Reappraisal of a clinical entity. *Mayo Clin Proc* 1967;42:26-49.

18. Farrow GM, Harrison EG Jr, Utz DC, et al. Renal angiomyolipoma. A clinicopathologic study of 32 cases. *Cancer* 1968;22:564-570.

19. Reed WB, Nickel WR, Campion G. Internal manifestations of tuberous sclerosis. *Arch Dermatol* 1963;87:715-728.

20. Brasfield RD, Das Gupta TK. von Recklinghausen's disease: a clinicopathological study. *Ann Surg* 1972;175:86-104.

21. von Recklinghausen FD. *On multiple fibromas of the skin and their relationship to multiple neuromas*. Berlin: Hirschwald, 1882.

22. Kaiser-Kupfer MI, Freidlin V, Dariles MB, et al. The association of posterior capsular lens opacities with bilateral acoustic neuromas in patients with neurofibromatosis type 2. *Arch Ophthalmol* 1989; 107:541-544.

23. Lewis RA, Riccardi VM. von Recklinghausen neurofibromatosis. Incidence of iris hamartoma. *Ophthalmology* 1981;88:348-354.

24. Grant WM, Walton DS. Distinctive gonioscopic findings in glaucoma due to neurofibromatosis. *Arch Ophthalmol* 1968;79: 127-134.

25. Shields JA, Sanborn GE, Kurz GH, et al. Benign peripheral nerve tumor of the choroid. *Ophthalmology* 1981;88:1322-1329.

26. Lewis RA, Gerson LP, Axelson KA, et al. von Recklinghausen neurofibromatosis. II. Incidence of optic gliomata. *Ophthalmology* 1984;91:929-935.

27. Shields JA. *Diagnosis and management of orbital tumors*. Philadelphia: WB Saunders Co., 1989.

28. Shields JA, Shields CL, Lieb WE, et al. Multiple orbital neurofibromas unassociated with von Recklinghausen's disease. *Arch Ophthalmol* 1990;108:80-83.

29. Wander JV, Das Gupta TK. Neurofibromatosis. *Curr Probl Surg* 1977;14:1-81.

30. Hume DM. Pheochromocytoma in the adult and in the child. *Am J Surg* 1960;99:458-496.

31. Wiznia RA, Freedman JE, Mancini AD, et al. Malignant melanoma of the choroid in neurofibromatosis. *Am J Ophthalmol* 1978;86: 684-687.

32. von Hippel E Jr. Vorstellung eines patienten mit einem sehr ungewohnlichen aderhautleiden. *Ber Versamml Ophthalmol Gesellsch* 1895;24:269.

33. Lindau A. Studien uber kleinhirncystein. Bau, pathogenese und beziehungen zur angiomatose retinae. *Acta Pathol Microbiol Scand* 1926;3(suppl 1):1-28.

34. Latif F, Tory K, Gnarrra J, et al. Identification of the von Hippel-Lindau tumor supressor gene. *Science* 1993;260;1317-1320.

35. Singh AD, Shields CL, Shields JA. Major review: Von Hippel-Lindau disease. *Surv Ophthalmol* 2001;46:117-142.

36. Chan CC, Vortmeyer AO, Chew EY, et al. VHL gene deletion and enhanced VEGF gene expression detected in the stromal cells of retinal angioma. *Arch Ophthalmol* 1999;117:625-630.

37. Hardwig P, Robertson DM. Von Hippel-Lindau disease: a familial, often lethal, multi-system phakomatosis. *Ophthalmology* 1984;91: 263-270.

38. Price EB Jr. Papillary cystadenoma of the epididymis. A clinicopathologic analysis of 20 cases. *Arch Pathol* 1971;91:456-470.

39. Shields JA. Response of retinal capillary hemangioma to cryotherapy. *Arch Ophthalmol* 1993;111:551.

40. Sturge WA. A case of partial epilepsy apparently due to a lesion of one of the vasomotor centers of the brain. *Trans Clin Soc Lond* 1879;12:162-167.

41. Milles WJ. Naevus of the right temporal and orbital region; naevus of the choroid and detachment of the retina in the right eye. *Trans Ophthalmol Soc UK* 1884;4:168-171.

42. Weber FP. Right-sided hemihypertrophy resulting from right-sided congenital spastic hemiplegia with a morbid condition of the left side of the brain revealed by radiogram. *J Neurol Psychopathol (London)* 1922;37:301-311.

43. Alexander GL, Norman RM, eds. *The Sturge-Weber syndrome*. Bristol, England: J Wright, 1960.

44. Stevenson RF, Morin JD. Ocular findings in nevus flammeus. *Can J Ophthalmol* 1975;10:136-139.

45. Susac JO, Smith JL, Scelfo RJ. The “tomato catsup” fundus in Sturge-Weber syndrome. *Arch Ophthalmol* 1974;92:69-70.

46. Lindsey P, Shields JA, Goldberg RE, et al. Bilateral nevus flammeus and bilateral choroidal hemangiomas. *Retina* 1981;1:88-95.

47. Witschel H, Font RL. Hemangioma of the choroid. A clinicopathologic study of 71 cases and a review of the literature. *Surv Ophthalmol* 1976;20:415-431.

48. Chao A, Shields CL, Krema H, et al. Plaque radiotherapy for choroidal hemangioma with total retinal detachment and iris neovascularization. *Retina* 2001;21:682-684.

49. Wyburn-Mason R. Arteriovenous aneurysm of midbrain and retina, facial naevi and mental changes. *Brain* 1943;66:163-203.

50. Archer DM, Deutman A, Ernest JT, et al. Arteriovenous communications of the retina. *Am J Ophthalmol* 1973;75:224-241.

51. Cameron ME. Congenital arterio-venous aneurysm of the retina. *Br J Ophthalmol* 1958;42:655-666.

52. Cameron ME, Greer CH. Congenital arterio-venous aneurysm of the retina. A post mortem report. *Br J Ophthalmol* 1968;52: 768-772.

53. Mansour AM, Wells CG, Jampol L, et al. Ocular complications of arteriovenous communications of the retina. *Arch Ophthalmol* 1989;107:232-236.

54. Shah GK, Shields JA, Lanning R. Branch retinal vein obstruction secondary to retinal arteriovenous communication. *Am J Ophthalmol* 1998;126:446-448.

55. Gass JDM. Cavernous hemangioma of the retina. A neuro-oculocutaneous syndrome. *Am J Ophthalmol* 1971;71:799-814.

56. Goldberg RE, Pheasant TR, Shields JA. Cavernous hemangioma of the retina. A four generation pedigree with neurocutaneous involvement. *Arch Ophthalmol* 1979;97:2321-2324.

57. Lewis RA, Cohen MH, Wise GN. Cavernous hemangioma of the retina. A report of three cases and a review of the literature. *Br J Ophthalmol* 1975;59:422-434.

58. Shields JA, Shields CL, Eagle RC Jr, et al. Ocular manifestations of the organoid nevus syndrome. *Trans Am Ophthalmol Soc* 1996; 94:65-86.

59. Shields JA, Shields CL, Eagle RC Jr, et al. Ophthalmic features of the organoid nevus syndrome. *Ophthalmology* 1997;104:549-557.

60. Nau J, Shields CL, Shields JA, et al. Optic nerve glioma in a patient with von Hippel-Lindau syndrome. *J Pediatr Ophthalmol Strabismus* 2003;40:57-58.

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23

Ocular Abnormalities in Childhood Metabolic Disorders

Avery H. Weiss

DISORDERS OF AMINO ACID METABOLISM

Albinism

Albinism represents a group of inherited disorders characterized by a congenital reduction of melanin pigment in the developing eye. Specific changes in the eye and visual system result from this pigmentary defect and are common to all types of albinism. Although the reduction in melanin synthesis can be localized to the eye (ocular albinism [OA]), it is much more likely to involve the skin, hair, and eye (oculocutaneous albinism [OCA]) (Fig. 23.1; see Color Plate VA). Affected individuals show hypopigmentation of skin and hair with characteristic eye involvement. Therefore, the diagnosis is usually made on the basis of the clinical findings (1).

Melanin is exclusively produced by a relatively small population of melanocytes with two embryonic origins. Melanocytes deriving from the neural crest migrate to and settle in the skin, hair, and eye (choroid and iris). Melanocytes in the retinal pigment epithelium (RPE) originate from the outer layer of neuroectoderm that makes up the optic vesicle. Production of melanin occurs in specialized intracytoplasmic organelles known as melanosomes. These membrane-bound organelles contain the enzymes needed to convert tyrosine to melanin. Hydroxylation of tyrosine to dihydroxyphenylalanine is mediated by tyrosinase. Then additional enzymes, including tyrosinase-related proteins 1 and 2, regulate subsequent oxidative steps in the pathway, resulting in the synthesis of eumelanin and pheomelanin, the two major forms of melanin (1).

Proteins other than the family of tyrosine enzymes are involved in melanogenesis. The OCA2 locus in humans (pink eye dilution gene in mice) encodes for a transmembrane protein important for the synthesis of melanin (2). Mutations within this locus are associated with OCA2 and a subset of patients with Prader-Willi and Angelman syndrome. This locus has been mapped to chromosome l5q. The genes associated with Chédiak-Higashi (*CHS1*) and Hermansky-Pudlak (*HPS1*, *HPS2*, *HPS3*, and *HPS4*) syndromes encode for proteins involved in the biogenesis and trafficking of melanosomes and other lysosomal-related organelles. Combined abnormalities of melanosomes, along with lysosomal and other lysosomal-related organelles (platelet-dense granules, basophil granules, major histocompatibility complex class 2 compartments), in these genetic disorders demonstrate the shared properties of these organelles (3).

Congenital nystagmus with an abrupt onset during the first 3 months of life is usually the presenting clinical sign. The nystagmus is pendular initially but can become jerk type as fixation improves. Severity frequently varies with horizontal gaze position being least at the null point and therefore prompting a compensatory head turn to optimize visual acuity. Unstable fixation and immature tracking behavior lead to vision concerns. Although acuity development can be delayed, most older children have 20/40 to 20/200 acuities.

Iris hypopigmentation is an important diagnostic finding observed in almost all albinism patients. Incident light reflected from within the eye can penetrate the iris in albinism, owing to reduced melanin in the posterior pigmented layer. Diffuse iris defects can be grossly detected by transscleral illumination using a light source placed on the bulbar

conjunctiva, but punctate defects are subtle and best appreciated at slit-lamp examination (4) (see Color Plate VB).

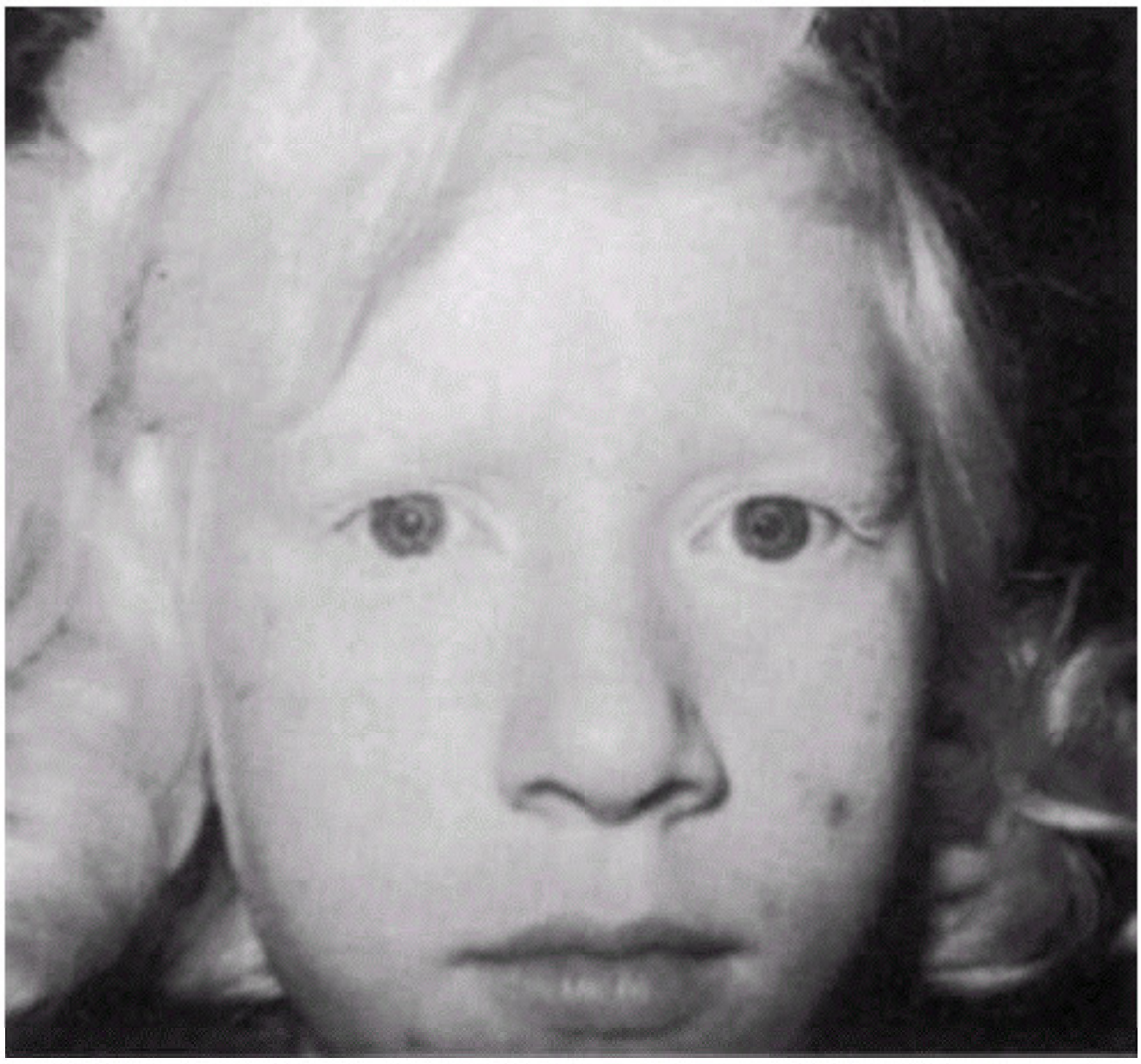


Figure 23.1 Oculocutaneous albinism. The skin, hair, and irides of this black child are hypopigmented.

Fundus pigmentation is typically commensurate with skin pigmentation but in albinism, the fundus is hypopigmented. Loss of melanin pigmentation within the RPE allows for direct visualization of the underlying and prominent choroidal vessels (Fig. 23.2). The macula, unlike the peripheral retina, contains luteal (carotenoid) pigments. Since the luteal pigments are intact in albinism, the hypopigmentation is more conspicuous in the peripheral retina than the macula. Functionally, the RPE is intact, and the full-field electroretinogram (ERG) is normal.

The hallmark of albinism is macular hypoplasia (see Color Plate VC). The normal eye is characterized ophthalmoscopically by the presence of a concave depression in the region of the macula, owing to the lateral displacement of the inner retinal layers. In albinism, the macula is coplanar with the surrounding retina, causing loss of the macular and foveal light reflexes, and blood vessels may course through this normally avascular structure. As a result of the loss of ganglion cells originating from the fovea, the optic disc contains fewer axons and its diameter tends to be small but within the normal range.

The visual pathways are abnormal in albinism. Melanin plays an important developmental role in the routing of optic nerve axons. Normally the ratio of fibers that project to the contralateral hemisphere versus those that project to the ipsilateral hemisphere is 53:47. In albinism, the ratio is increased since axons from the temporal retina are routed contralaterally rather than ipsilaterally. This leads to altered binocular representation of the visual scene in which spatial correspondence in the retina is not maintained in the visual cortex. If the two retinal images are not in precise cortical registration, then binocular interactions cannot develop normally, and stereopsis is severely reduced or absent. Because stereopsis provides a feedback signal that helps to establish and maintain eye alignment, albinos frequently have strabismus. Misrouting of optic axons can be demonstrated with a lateralizing visually evoked potential (VEP). The response to a pattern-onset stimulus presented monocularly is recorded with electrodes offset to the right and left of the midline. Asymmetries in amplitude between the two hemispheres is indirect evidence of abnormal decussations. Using a pattern stimulus, the VEP asymmetry can be detected in patients with albinism (4).

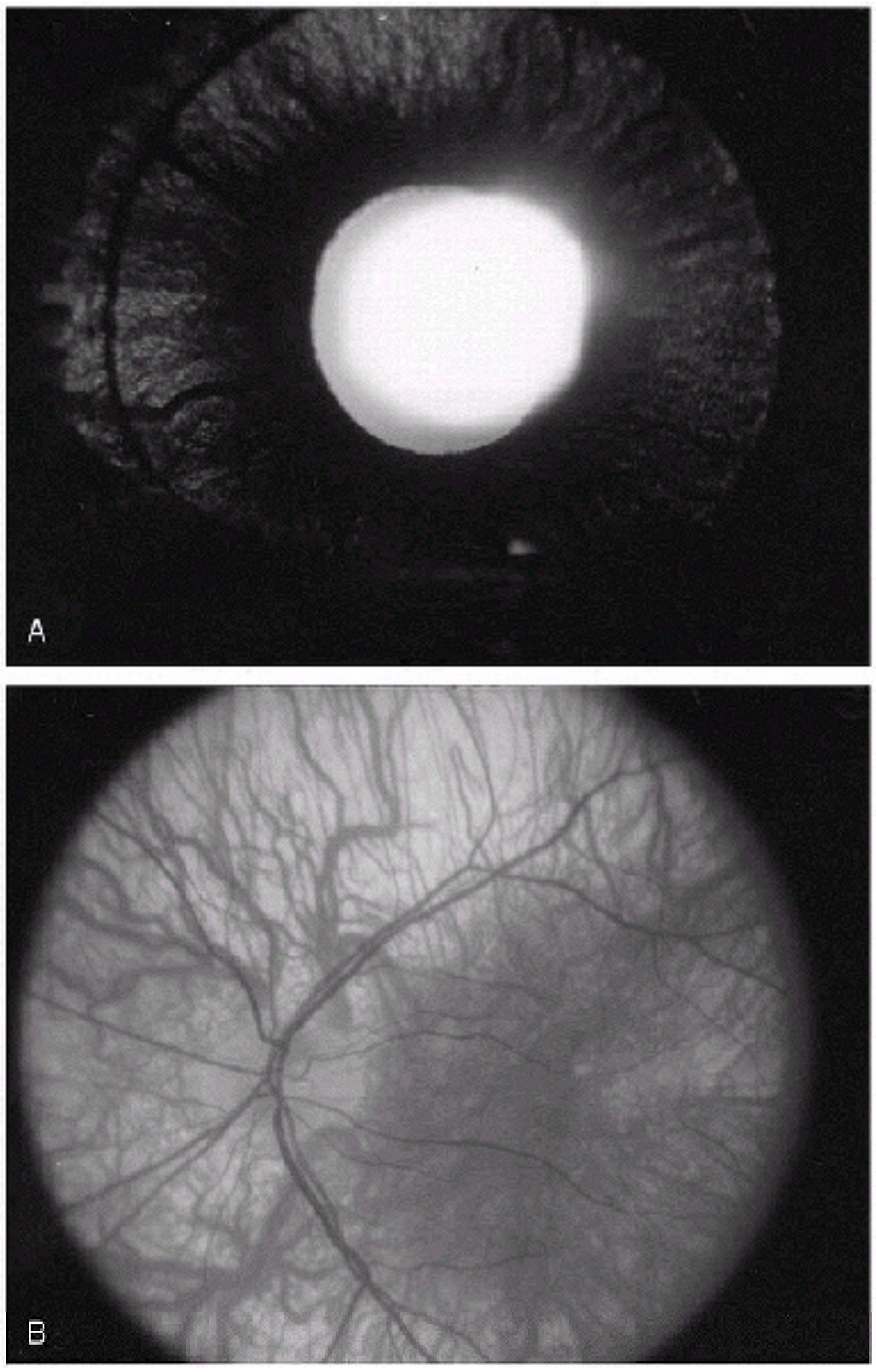


Figure 23.2 Ocular fundus in albinism. Pertinent findings include absence of macular reflex and blonde fundus. In (**A**) and (**B**), the choroidal vessels are abnormally prominent because overlying pigment epithelium is hypopigmented. **A:** Slit-lamp photograph shows diffuse iris transilluminations. **B:** Fundus in albinism showing absence of retinal pigmentation and hypoplastic macula.

Because the various types of albinism share overlapping clinical features, albinism is most reliably classified by the underlying molecular defect (Table 23.1) In OCA1A, there is a complete lack of tyrosinase activity. Individuals with OCA1A are usually diagnosed at birth on the basis of having white scalp hair, white skin, and blue irides, especially in dark-complexioned families. Nystagmus, reduced acuity, and strabismus may be the initial manifestations in lightcomplexioned families in whom pigmentary differences are less conspicuous. The skin and hair remain white throughout life, visual acuity ranges from 20/100 to 20/400, and no melanin pigmentation develops within the iris or retina.

In OCA1B, tyrosinase activity is reduced or temperature dependent (5). Although affected individuals have white or light yellow hair and white skin at birth, the skin, hair, and eyes acquire pigmentation by the age of 1 to 3 years.

At slit-lamp examination, peripapillary clumps or radial spokes of pigmentation become evident, along with fine granular pigmentation of the retina. Despite these pigmentary changes, there is typically no improvement in visual acuity.

TABLE 23.1 CLASSIFICATION OF ALBINISM

Clinical condition	Molecular defect
Oculocutaneous albinism type 1 (OCA1)	
OCA1A	No tyrosinase activity
OCA1B	Reduced tyrosinase activity
Yellow OCA	Reduced tyrosinase activity
Minimal pigment OCA	Reduced tyrosinase activity
Temperature-sensitive OCA	Temperature-sensitive tyrosinase
Oculocutaneous albinism type 2 (OCA2)	
OCA2	P gene mutation
Brown OCA	P gene mutation
Prader-Willi syndrome	P gene mutation
Angelman syndrome	P gene mutation
Oculocutaneous albinism type 3 (OCA3)	
OCA3	Tyrosinase-related protein 1
Oculocutaneous albinism type 4 (OCA4)	Membrane-associated transporter gene
Oculocutaneous albinism associated with systemic disease	
Hermansky-Pudlak	HPS1, HPS2, HPS3, HPS4
Ocular albinism type 1	
OA1	G-protein coupled membrane receptor
OA1 with sensorineural deafness	Unknown

Individuals with OCA2 have a defective P protein with normal tyrosinase activity (2). The *OCA2* gene encodes for the P protein, which is an integral component of the melanosomal membrane. These individuals produce some melanin but predominantly yellow pheomelanin rather than black-brown eumelanin. The phenotype is determined by the relative amounts of pigmentation of skin, hair, and eyes, which can range from minimal to near normal. In general, the pigmentary deficiency is less severe than that observed in OCA1A but can overlap with that in OCA1B. Scalp hair and skin coloration vary from off-white to blond to brown. The ocular findings are identical except for the increased amounts of iris and retinal pigmentation. Visual acuity ranges from 20/30 to 20/400 but is usually near the 20/200 level (1).

Prader-Willi syndrome (PWS) and Angelman syndrome (AS) have hemizygous deletions within chromosomal locus 15q where the OCA2 gene colocalizes (1,6). Individuals with PWS and AS can have hypopigmented skin and hair, but the ocular features of albinism are usually lacking. When the ocular findings of albinism are found, affected individuals are reported to have an *OCA2* gene mutation of the nondeleted chromosome (7). Prader-Willi syndrome is characterized by hypotonia, obesity, mental retardation, hypogonadism, short stature, and small hands and feet. The diagnosis of AS should be suspected in any albino with microcephaly, developmental delay, inappropriate laughter, and seizures. Craniofacial stigma include flat occiput, thin upper lip, prominent jaw, and widely spaced teeth.

OA has an X-linked inheritance pattern and is less prevalent than OCA. Affected males have normal skin and hair pigment along with ocular features of albinism. Despite normal skin appearance, light and electron microscopy demonstrates aggregates of abnormal melanosomes within keratinocytes and melanocytes in affected males and carrier females. The ocular findings include congenital nystagmus, reduced visual acuity (20/40 to 20/200) hypopigmentation of the iris and retina, and foveal hypoplasia. In individuals with dark complexions, the iris and retinal pigmentary changes can be subtle or absent, and there is less severity of

foveal hypoplasia and reductions in visual acuity. The *OA1* gene encodes a G-protein-coupled membrane receptor that localizes to melanosome membranes (8). The obligate ligand for the putative OA1 receptor has not been identified but is likely important to melanosome function.

Previous studies reported an autosomal-recessive OA (OA2), with normal skin and hair pigmentation in a sibship. King proposes that this phenotype is consistent with the OCA1B or OCA2 spectrum (1). To date, no additional autosomal gene locus has been linked to OCA or OA.

OA is rarely associated with sensorineural deafness and vestibular dysfunction. Inheritance is autosomal dominant. Some patients have heterochromia iridis and a prominent white forelock, suggesting overlap with Waardenburg syndrome. Therefore, a digenic interaction between MITF, a transcription factor linked to Waardenburg syndrome, and OA has been proposed (9).

OCA can appear as part of a multisystem disease in which the melanocyte and other intracellular organelles are affected. The classic example is Hermansky-Pudlak syndrome, which includes a group of genetic disorders resulting from abnormal formation of certain membrane-bound organelles. To date, four genotypes have been identified, HPS1, HPS2, HPS3, and HPS4 (3,10,11). The gene for type 2 HPS encodes for the ß3A subunit of adaptor complex 3, known to assist in vesicle formation in the trans-Golgi network (12). The functional roles for the remaining gene products are unknown. This group of autosomal-recessive disorders consists of OCA in association with lysosomal accumulation of ceroid lipofuscin, and deficient platelet function. Progressive accumulation of ceroid lipofuscin leads to interstitial fibrosis and granulomatous colitis. A bleeding diathesis can occur as a result of a deficiency of platelet storage granules or dense bodies. Reduction or absence of these granules, which contain serotonin, adenine nucleotides, and calcium, results in defective platelet aggregation. Easy bruisability, of soft tissues especially, and prolonged bleeding time in individuals of Puerto Rican descent are characteristic features.

Chédiak-Higashi is another multisystem disease associated with albinism. Patients with this disorder have the typical features of albinism, and skin biopsy reveals the

presence of abnormally large melanosomes. In addition, they have an associated immune defect, increased susceptibility to lymphoproliferative disorders, and presence of larger intracytoplasmic granules in leukocytes and other tissues. Defective chemotaxis and decreased bactericidal activity predispose these children to bacterial infections. The diagnosis is usually suspected on the basis of the clinical finding and presence of abnormal granules in their leukocytes. Most patients die by the second decade of life from an overwhelming infection or malignancy.

Alkaptonuria

Alkaptonuria is a rare autosomal-recessive disease resulting from a deficiency of the enzyme that degrades homogentisic acid (HGA), an intermediary product in the metabolism of phenylalanine and tyrosine. The gene encoding for this enzyme, homogentisate 1,2-dioxygenase, is mutated (13). Accumulation of HGA and its metabolites in cartilage and other connective tissues (ochronosis) leads to arthritis, joint destruction, and cardiac-valve calcification. The earliest pigmentation changes involve the eyes and ears, but not until patients reach their twenties. Patches of pigmentation are usually found in the sclera in front of the extraocular muscles but can be detected in the conjunctiva or cornea (14). Ochronotic pigmentation of many internal areas of the body (cartilage, tendons, and ligaments) can be quite striking. Arthritis is a long-standing complication of alkaptonuria and is the major cause of disability. Clinically, it resembles ankylosing spondylitis involving the spine and large joints, leading to lumbosacral ankylosis with limitation of motion (15). There is no effective therapy.

Cystinosis

Cystinosis is an autosomal-recessive disorder with an estimated incidence of 1 case per 150,000 live births. It is a lysosomal storage disorder resulting from defective transport of cystine across lysosomal membranes (16). Cystine is the homodimer of the amino acid cysteine, which is generated by protein catabolism. Cystinosin, a selective transmembrane protein, transports cystine out of the lysosome. Mutations in the gene encoding for cystinosin (*CTNS*) impair cystine transport, resulting in accumulation at levels of 5 to 500 times normal—levels that initiate crystallization and cell damage (17). The most common mutation is a 57,257-bp deletion that can be detected by polymerase chain reaction (18). The kidney is particularly susceptible to cystine toxicity, resulting in kidney damage beginning in the first year of life. By comparison, central nervous system (CNS) damage does not become evident before the patient's third decade (19).

The term *cystinosis* includes infantile and late-onset nephropathic forms and a benign nonnephropathic form. The most common and clinically important type is the infantile nephropathic form. Infants with cystinosis are typically normal at birth. Beginning at about 6 months of age, development slows, linear growth falls, and the child suffers from isolated or repeated episodes of acidosis and dehydration owing to polyuria. Urinalysis reveals excessive losses of glucose, amino acids, phosphate, calcium, bicarbonate, and other small molecules (Fanconi syndrome). Progressive glomerular damage usually leads to renal failure in untreated patients by 10 years of age (16). Phosphaturia can lead to hypophosphatemic rickets. Accumulation of cystine crystals in other tissues causes hypothyroidism, diabetes mellitus, and delayed onset of puberty. Patients with treated nephropathic cystinosis can develop late complications such as distal myopathy, swallowing difficulties, hepatomegaly, and computed tomography (CT) evidence of cortical atrophy and calcifications (19).

Late-onset cystinosis is clinically similar to the infantile form except for the delayed onset and slower progression of the disease. Patients may have preserved renal function into the third decade, and growth delay is mild. Accumulation of corneal crystals is slower. Patients with nonnephropathic disease have isolated ocular involvement. Molecular testing reveals the presence of mutations with residual activity of the cystine transporter (20).

The eye, like the kidney, is predisposed to cystine-related damage. Although they are not present at birth, cystine crystals can be found in the cornea of patients with nephropathic cystinosis by 1 year of age (Table 23.2). Slit-lamp detection of corneal crystals is an easy way to help confirm the diagnosis and should be done in all patients with Fanconi syndrome or renal failure of uncertain etiology. These refractile crystals first appear in the anterior third of the cornea, but with increasing age, they occupy its entire thickness and become densely packed (Fig. 23.3). With continued buildup of cystine crystals, the cornea becomes opacified, resulting in decreased vision and the need for corneal transplantation in some patients. Cystine crystals are abundant on the conjunctiva, but there are relatively fewer on the surface of the iris, lens capsule, and trabecular meshwork.

Photophobia and secondary blepharospasm are significant problems for most patients with cystinosis and can be disabling in some patients. Symptomatic children often wear heavily tinted sunglasses and brimmed hats to avoid undue levels of light exposure. The severity of photophobia is somewhat correlated with the density of corneal cystinosis rather than the corneal epithelium which tends to be intact. Possible reasons for the photophobia include a tear deficiency, subtle corneal inflammation, and glare (21).

Increased long-term survival of patients with cystinosis has led to the emergence of late ocular sequelae (22). The most important sequelae are due to progressive cystine accumulation in the retina. Decreases in visual acuity, color vision loss, and pigmentary disturbances of the macula and peripheral retina have been described (Table 23.3). Visual testing shows elevation of dark-adaptation thresholds and variable reduction in the rod- and cone-mediated ERGs. Severe visual loss and even blindness can occur in patients who go untreated for years. Progressively increasing deposits of cystine crystal can be detected in most ocular tissues, including extraocular muscles and the optic nerve.

Replacement of electrolytes, calcium, carnitine, and glucose due to renal losses, kidney transplantation, and oral

cysteamine are the mainstays of systemic treatment. Several studies have documented the ability of cysteamine to preserve renal function and to prevent growth retardation (23,24). However, cystine crystals continue to accumulate in the cornea, indicating that the drug does not achieve adequate levels in this avascular tissue. To overcome this delivery problem, topical cysteamine was formulated and found to be highly successful in removing cystine crystals from the cornea. Cysteamine eye drops (0.5%) administered as often as hourly are well tolerated and dramatically reduce the intense photophobia and blepharospasm that accompany cystine accumulation (25).

TABLE 23.2 CORNEAL OPACITIES AS AN IMPORTANT OCULAR FINDING

Age at onset	Disorder	Major systemic signs
3 to 12 months	Tyrosinosis type II	Keratitis, photophobia, hyperkeratosis (palms/soles)
	Cystinosis	Renal Fanconi syndrome, failure to thrive
		Storage symptoms
	Hurler (MPS type I-H)	Coarse facies
	Scheie (MPS type I-S)	Hepatosplenomegaly
	a-mannosidosis (infantile)	Bone changes
	Maroteaux-Lamy syndrome	Cardiomyopathy
	I-cell disease	Inguinal hernias
	Steroid sulfatase deficiency	X-linked ichthyosis
1 to 6 years	Morquio syndrome (MPS type IV)	Bone changes, dwarfism
	Mucolipidosis type IV	Psychomotor retardation, retinal degeneration
	a-mannosidosis	Mental deterioration, cataract
	Tangier disease	Yellow tonsil, hypocholesterolemia
	LCAT deficiency	Hemolytic anemia, lipoprotein abnormalities
Late childhood, adolescence to adulthood	Fabry disease	Abdominal pain, painful neuropathy, angiokeratoma
	Galactosialidosis	Cherry-red spot, angiokeratoma, neurologic deterioration
	Wilson disease	Kayser-Fleischer ring, hepatic dysfunction, extrapyramidal signs

LCAT, lecithin-cholesterol acyltransferase; MPS, mucopolysaccharidosis.

Modified from Saudubray JM, Charpentier C. Clinical phenotypes: diagnosis/algorithms. In: Scriver CR, Beaudet AL, Sly WC, et al, eds. *The metabolic and molecular basis of inherited disease,* 8th ed. New York: McGraw-Hill, 2001 : 1374, with permission.

Modified from Saudubray JM, Charpentier C. Clinical phenotypes: diagnosis/algorithms. In: Scriver CR, Beaudet AL, Sly WC, et al, eds. *The metabolic and molecular basis of inherited disease,* 8th ed. New York: McGraw-Hill, 2001 : 1374, with permission.

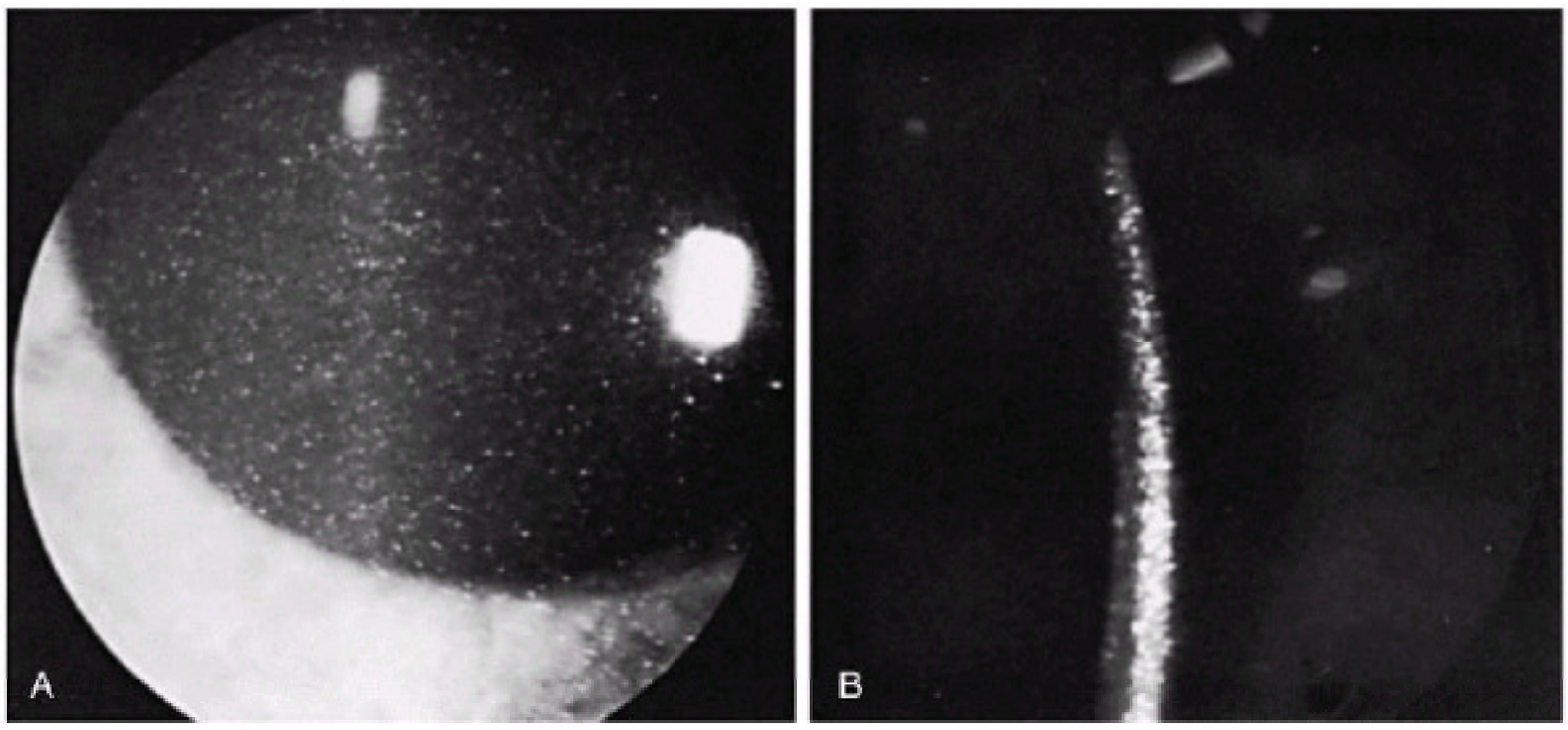


Figure 23.3 A: Cornea of an 8-year-old girl with cystinosis, seen in direct illumination. The crystals are too small to see with the naked eye but are readily visible with proper magnification. **B:** Slit-beam view of the cornea shown in (**A**). The refractile, iridescent crystals are scattered throughout the stroma but are most dense in the anterior two-thirds.

TABLE 23.3 PIGMENTARY DISTURBANCE OF THE RETINA AS AN IMPORTANT MANIFESTATION

Abetalipoproteinemia
Carbohydrate glycoprotein deficiency syndrome
Cystinosis
Hyperornithinemia
Refsum disease
Mitochondrial disorders
Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency
Mucopolysaccharidosis (types I, IV, VI, VIII)
Peroxisomal disorders
Primary hyperoxaluria (PH1)
Zellweger syndrome
Infantile phytanic acid storage
Neonatal adrenoleukodystrophy
Acyl-CoA oxidase deficiency
Primary hyperoxaluria (PH2)

CoA, coenzyme A.

Hyperornithinemia (Gyrate Atrophy of the Choroid and Retina)

Gyrate atrophy of the choroid and retina is a retinal degeneration related to a deficiency of ornithine aminotransferase (OAT). As a result, 10- to 20-fold elevations of ornithine accumulate in plasma, cerebrospinal fluid (CSF), and aqueous humor. More than 50 different mutations of the gene encoding for OAT have been identified to date (26). The functional gene has been mapped to chromosome 10q26. Gyrate atrophy occurs worldwide, but its prevalence is much higher in the Finnish population.

Clinically, the disease begins with myopia, night blindness, and contracted visual fields in the first decade of life (27). Examination of the fundus reveals punctate or circular patches of chorioretinal atrophy in the retinal periphery (Table 23.3). With increasing age, the lesions become larger and more numerous, gradually coalescing and forming confluent areas of chorioretinal atrophy with scalloped margins posteriorly (Fig. 23.4). Near puberty, increased pigment appears at the back edge of the chorioretinal lesions and in the posterior pole. Posterior subcapsular cataracts are present in patients by the end of their second decade. Visual loss parallels the fundus changes, showing slowly progressive contraction of the visual field until blindness occurs in the third to seventh decades. Likewise, the ERG progressively deteriorates until the response to light becomes extinguished.

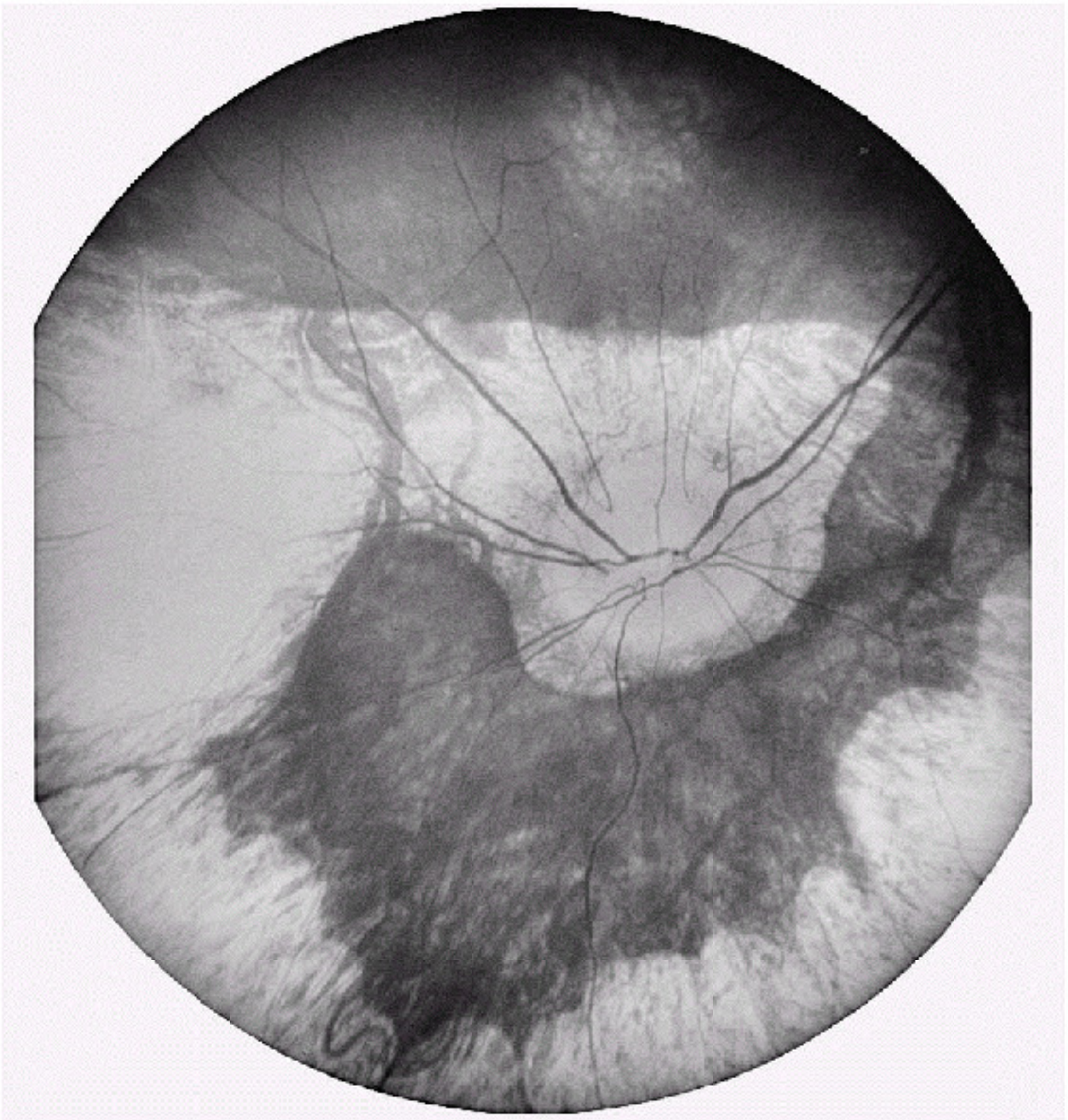


Figure 23.4 Peripheral fundus in gyrate atrophy of the retina and choroid. Areas of pigment epithelial atrophy enlarge and coalesce with time.

Various therapies have been tried to prevent or delay the onset of blindness. Initially pharmacologic doses of vitamin B6, a cofactor for OAT activity, were given in an attempt to stimulate the enzyme. This strategy failed in all but a small percentage of patients (28,29). A second strategy involved creatine supplementation based on the fact that ornithine is a potent inhibitor of creatine biosynthesis. Creatine supplementation appeared to have no beneficial effect (30).

Another strategy called for an arginine-restricted diet with the intent of lowering plasma ornithine levels. The effect of long-term reduction of ornithine accumulation is still controversial. Some authors report slowed progression of the retinal degeneration while others observe continued progression (31,32,33).

Primary Hyperoxaluria

Primary hyperoxaluria (PH) is a rare autosomal recessive disorder characterized by increased synthesis and toxic accumulation of oxalic acid. Failure of either of two enzymes to detoxify glyoxalate, an oxidation product of glycine, leads to its increased conversion to oxalate. PH type 1 (PH1), which is the most common type, is due to a deficiency of the liver-specific peroxisomal enzyme alanineglyoxylate aminotransferase (34). PH type 2 (PH2) is

caused by a defect in the more widespread cytosolic enzyme D-glycerate dehydrogenase/glyoxylate reductase (35). Because oxalate cannot be metabolized further, elevated levels accumulate in the urine, leading to the formation of stones and resulting in nephrocalcinosis in the kidney, and eventually renal failure. In PH1, oxalate crystals can accumulate in extrarenal tissues including bone, heart, nerves, joint, and teeth (oxalosis). In general, PH2 is a milder disease, and there is no evidence of systemic oxalosis.

Retinopathy is the major clinical finding in the eye, but histopathologically oxalate crystals are deposited throughout the ocular tissues (36,37). Initially, multiple crystalline deposits (100-200 microns) with a vascular distribution are found in the posterior pole out to the equator. Later, ringlets of pigmentation may surround the crystals and coalesce in the macula, forming a black geographic lesion (Table 23.3). Visual acuity is relatively good when the optic disc is normal but reduced when there is optic atrophy (37). Fluorescein angiography initially shows multiple areas of hypofluorescent centers (oxalate crystal) surrounded by hyperfluorescent rings (atrophic RPE). Later angiography can show small-vessel occlusion and localized subretinal neovascularization.

TABLE 23.4 CATARACT AS AN IMPORTANT MANIFESTATION OF METABOLIC DISEASE

Age at onset	Disorder	Major important features
Congenital (at birth)	Lowe syndrome	Hypotonia, renal disease
	Zellweger syndrome and variants	Dysmorphia, hypotonia, seizures
	Rhizomelic chondrodysplasia punctata	Dwarfism, bone changes
Newborn (1 to 4 weeks)	Galactosemias	Liver disease, failure to thrive, *Escherichia coli* sepsis
	Gal-1-UDP transferase deficiency	
	Epimerase deficiency	
Infancy (1 month to 1 year)	Galactosemia	Isolated
	Galactokinase deficiency	
	Oligosaccharidoses	Coarse facies, hepatosplenomegaly
	Sialidosis	
	a-mannosidosis	
	Nonketotic hypoglycemia	Seizures, developmental delay
Childhood (1 to 15 years)	Hypoparathyroidism and pseudohypoparathyroidism	Bone changes, hypocalcemia
	Diabetes mellitus	Hyperglycemia
	Wilson disease	Chronic hepatitis, neurologic involvement
	Neutral lipid storage disease (OMIM 275630)	Ichthyosis, hepatosplenomegaly, myopathy
	Sjogren-Larson	Ichthyosis, mental retardation, spastic paraplegia
Adulthood (>15 years)	Galactosemia (heterozygotes)	Isolated
	Hyperornithinemia	Myopia, night blindness, chorioretinal atrophy

	Hyperornithinemia	Myopia, night blindness, chorioretinal atrophy
	Fabry disease	Renal failure, angiokeratoma
	Cerebrotendinous xanthomatosis	Xanthoma, neurologic dysfunction, low intelligence

Gal-1-UDP transferase, galactose-l-uridine diphosphate transferase.

Modified from Endres W, Shin YS. Cataract and metabolic disease. *J Inherit Metab Dis* 1990;13 : 509-516, with permission from Kluwer Academic Publishers.

The diagnosis is usually based on the presence of increased urinary excretion of oxalate and glyoxylate in PH1, and of oxalate and glycerate in PH2. Enzyme assay of biopsied tissue or molecular testing is necessary to confirm the diagnosis. Treatment is directed at reducing exogenous oxalate intake, administration of pharmacologic doses of pyridoxine (essential cofactor for aminotransferases), or enzyme replacement by liver transplantation. The associated renal failure is managed in the short term with renal dialysis and in the long term with kidney transplantation (38).

Galactosemia

The galactosemias are a group of three inherited disorders characterized by an inability to metabolize galactose. The main source of galactose is milk, which contains lactose, a disaccharide composed of glucose and galactose. Galactose

is primarily converted to glucose by sequential enzymatic activity of galactokinase, galactose-1-phosphate uridyl transferase (Gal-1-UDP transferase), and uridine diphosphate (UDP)-galactose-4-epimerase. Decreased activity of any one of these enzymes is a cause of galactosemia. The gene for each galactose enzyme has been characterized, and numerous mutations have been identified (39,40,41).

Patients with Gal-1-UDP transferase deficiency, the most common form of galactosemia, typically present in infancy with failure to thrive. Vomiting and diarrhea begin with milk ingestion. Jaundice and unconjugated hyperbilirubinemia are the earliest signs of hepatic dysfunction, followed by hepatomegaly and abnormal liver function tests. Untreated, the liver disease can progress to cirrhosis. Aminoaciduria and proteinuria are evidence of renal tubular dysfunction, and there is a higher incidence of *Escherichia coli* sepsis. A minority of patients present later in life with developmental delay, hepatomegaly, and cataracts (42).

Cataract is the major ocular complication (Table 23.4). The cause of the cataract is most likely related to the accumulation of galactitol in the lens. In the presence of lenticular aldose reductase, galactose is reduced to galactitol, which is impermeable to cellular membranes, leading to its intracellular accumulation. Increased intracellular levels of galactitol create an osmotic gradient causing the lens to imbibe water, which in turn leads to hydropic degeneration of lens fiber cells. The earliest observable lens change is an increased refractive power of the fetal lens nucleus, giving the appearance of an “oil drop.” This is usually followed by development of a zonular or nuclear cataract (43).

The mainstay of treatment is elimination of galactoserich foods from the diet. Long-term studies indicate that dietary elimination of galactose can reverse or delay the development of cataracts and liver disease, but it has no ameliorative effect on the damage to the CNS and ovaries (44). Children with galactosemia are often delayed in acquisition of language skills, mildly retarded, and girls suffer from ovarian failure.

Patients with galactokinase deficiency have cataracts but no evidence of hepatic or renal disease, or mental retardation (45). Because cataracts may be the first and only abnormality, it is important to routinely screen for galactosemia in infants and children who develop cataracts (46). Homozygous deficiency of galactokinase is associated with the zonular cataracts that typically develop in the first year of life. By comparison, the causal relationship between partial galactokinase deficiency and cataracts is less clear. Individuals with reduced galactokinase activity seem to have a higher prevalence of cataracts than those with normal galactokinase activity. Cataracts that develop later in life can be nuclear or subcapsular. Rarely pseudotumor cerebri has been reported.

There are two forms of the UDP-galactose-4-epimerase deficiency. In the benign form, the child is normal and the epimerase deficiency is limited to red blood cells and leukocytes. With generalized loss of epimerase activity, the clinical presentation resembles transferase deficiency with vomiting, weight loss, hepatomegaly, hypotonia, aminoaciduria, and galactosuria. Cataracts have not been noted in either form of this rare disorder (44,47).

DISORDERS OF LIPID METABOLISM: FAMILIAL HYPERCHOLESTEROLEMIA

Familial hypercholesterolemia (FH) is one of the most common metabolic diseases and a frequent cause of coronary arteriosclerosis. The amount of low-density lipoprotein (LDL), the major cholesterol-carrying lipoprotein in human plasma, is the major determinant of cholesterol levels. This spherical particle consists of an inner core of cholesterol esters surrounded by an outer layer of phospholipids and apolipoprotein B (apoB) (48). LDL is the obligate ligand for the LDL receptor (LDLR), which is located on cell surface of hepatocytes. After binding to the receptor, LDL is internalized and then degraded in lysosomes, releasing free cholesterol into the intracellular cholesterol pool. The intracellular concentration of cholesterol provides the feedback signal that controls transcription of LDLR. When the intracellular cholesterol level is low, transcription of LDLR is upregulated; when levels are high, transcription is downregulated (48). Hepatic stores of cholesterol are influenced by intestinal absorption and reexcretion of dietary cholesterol, and excretion into bile. Recent studies indicate that intestinal absorption is mediated by ATPbinding cassette transporter G5 (ABCG5), and excretion is mediated by another ABC transporter, ABCG8 (49,50).

Four monogenic disorders that cause LDL to accumulate in plasma are known, and their underlying molecular defects have been characterized. Each of these disorders is characterized by hypercholesterolemia with cholesterol deposits in skin and tendons, premature atherosclerosis, and coronary heart disease. The most common is FH. Heterozygous patients exhibit hypercholesterolemia in the first decade of life, corneal arcus and tendon xanthoma in their teens, and generalized atherosclerosis by their thirties (48). Homozygotes develop all of these complications in early childhood and can die from a myocardial infarction in childhood. The second disorder is familial ligand-defective apoB-100. The clinical manifestations are similar to but not as severe as those seen in heterozygous FH (51). The third disorder is sitosterolemia in which there is increased absorption of dietary cholesterol and plant phytol, and reduced excretion of these sterols into bile. Mutations of the ABC transporters (ABCG5 and ABCG8) have been identified in this disorder (49,50). The fourth disorder is autosomal-recessive hypercholesterolemia (ARH), in which intracellular processing of the LDL-LDLR complex is altered (52). Children and young adults with ARH, like homozygotes with FH, have severe hypercholesterolemia, coronary heart disease, and cholesterol-laden skin deposits.

The major ocular manifestations of FH are palpebral xanthomata (xanthelasmata) and corneal arcus (53). Xanthelasmata appear as orange-yellow plaques within the eyelid skin. Corneal arcus is caused by cholesterol deposits in the periphery of the stroma where it is separated from the limbus by a narrow zone of clear cornea (Fig. 23.5; see Color Plate VD). The presence of xanthelasmata or corneal arcus in a young person is associated with a higher incidence of hypercholesterolemia, but they can be found in normal individuals (54). The diagnosis is suspected on finding an elevated plasma cholesterol and normal triglycerides, and confirmed by molecular testing.

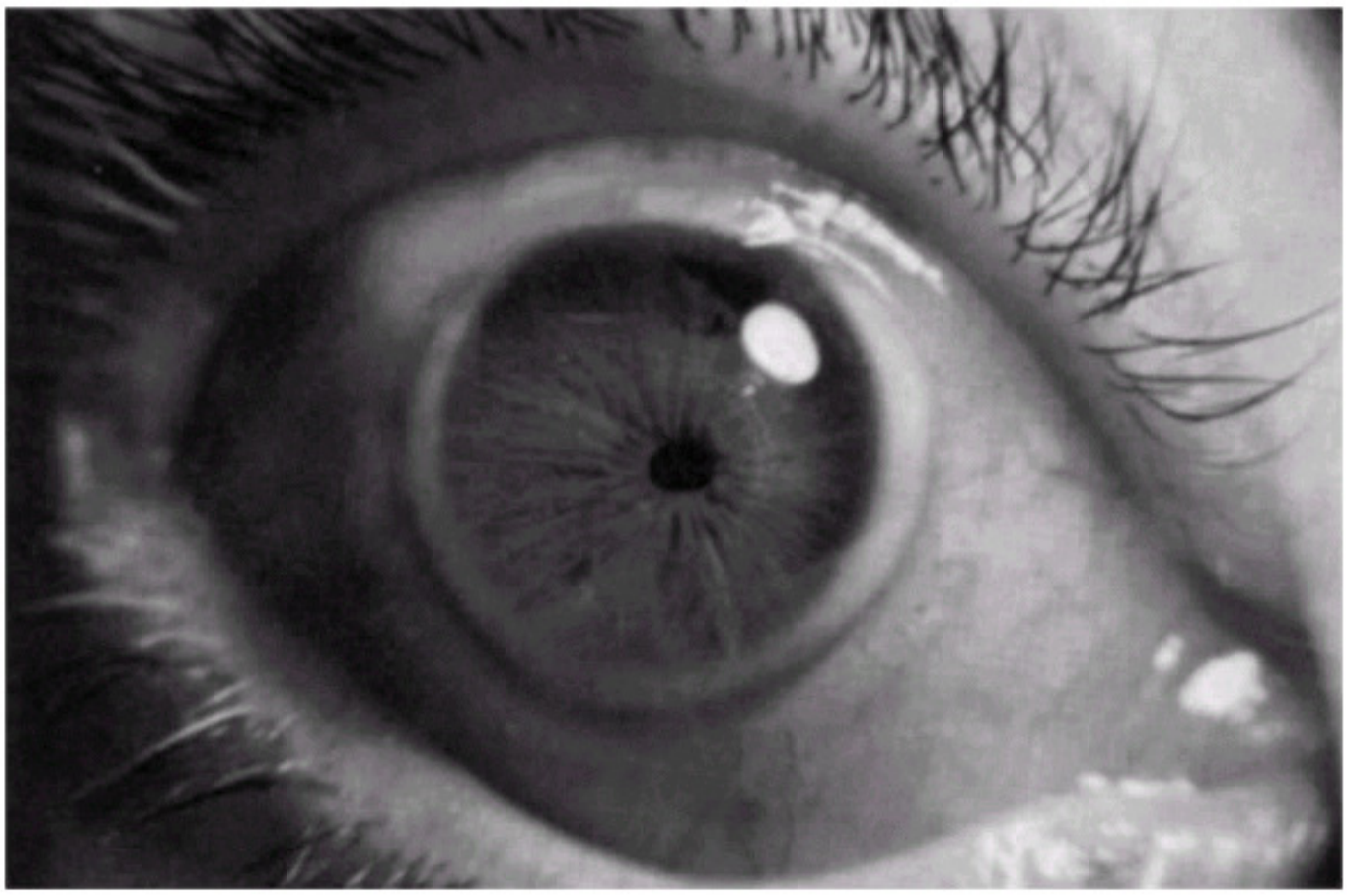


Figure 23.5 Arcus senilis. The severe degree of corneal arcus seen here is uncommon even in the elderly. When observed in those under 40 years of age, arcus may be a sign of hypercholesterolemia.

DISORDERS OF LIPOPROTEIN METABOLISM

Cholesterol, triglycerides, and other lipids are transported in body fluids by lipoproteins classified according to increasing density (Table 23.5). A lipoprotein is a particle consisting of a central core of hydrophobic lipids surrounded by a shell of polar lipids and apolipoproteins. The apolipoproteins are synthesized and secreted by the liver and intestine. They have two roles: solubilizing hydrophobic lipids and serving as shuttles and sinks for lipids moving to and from specific cells and tissues.

Tangier Disease

Tangier disease is characterized by a deficiency of high-density lipoproteins (HDL) and accumulation of cholesterol esters in the reticuloendothelial system and other tissues. HDL transport cholesterol and phospholipids from peripheral tissues to the liver (reverse cholesterol transport). Extracellular lipid efflux is initially dependent upon shuttling of cholesterol from endocytotic vesicles to the cellular surface by ABC1 (55). In Tangier disease, the ABC1 gene is mutated, and intracellular lipids can not be exported (56,57). Deficiency of HDL leads to reduced total serum cholesterol, usually below 125 mg/dL while plasma triglycerides are normal or elevated. These findings together with lipoprotein electrophoresis showing absence of HDL are pathognomonic of Tangier disease.

The classic findings of Tangier disease include yellowcolored tonsils, hepatosplenomegaly, peripheral neuropathy, and orange-brown spots of the rectal mucosa (58). Corneal opacities are noted in 25% to 50% of patients. A diffuse or dot-like haze of the central cornea develops with advancing age, owing to the continued accumulation of cholesterol esters. Conjunctival biopsies reveal intracellular lipid droplets outside of lysosomes, which helps to distinguish Tangier disease from Niemann-Pick and other lysosomal diseases. Additional ocular findings include orbicularis oculi weakness and secondary ectropion (59,60).

TABLE 23.5 MAJOR LIPOPROTEINS AND THEIR LIPID AND PROTEIN COMPONENTS

Lipoprotein	Major core lipid	Apoproteins
Chylomicron	Dietary triacylglycerols	ApoE, CII, B-48
Very low density lipoprotein	Endogenous triacylglycerides	ApoE, CII, B-100
Low-density lipoprotein	Endogenous cholesterol esters	ApoE, B-100
High-density lipoprotein	Endogenous cholesterol esters	Apol, AII

Familial Lipoprotein Lipase Deficiency

Familial lipoprotein lipase deficiency is a rare autosomal-recessive disorder in which there is defective clearance of chylomicrons from plasma and a corresponding increase in triglyceride levels. Lipoprotein lipase is responsible for the hydrolysis of chylomicrons and very-low-density lipoprotein (VLDL) triglyceride release of fatty acids to tissues for energy. The diagnosis is usually based on a history of failure to thrive, recurrent abdominal pain or pancreatitis, and detection of elevated triglycerides after overnight fasting. Hepatomegaly and eruptive xanthomata are evidence of extravascular phagocytosis of chylomicrons by hepatic and skin macrophages. Ocular manifestations are limited to the retinal vessels, which take on a pink color known as “lipemia retinalis” when triglyceride levels are above 2,000 mg/dL (Fig. 23.6; see Color Plate VE). The color changes reflect altered scattering of light owing to the massive presence of chylomicrons. Visual acuity is normal, and the retinal vascular changes are reversible. Treatment is restriction of dietary fat.

Abetalipoproteinemia

Abetalipoproteinemia is a rare autosomal-recessive disorder characterized by a defect in the assembly or secretion of plasma lipoproteins that contain apoB. This results in the failure to form chylomicrons in the intestine and VLDL in the liver. Critical to the assembly of apoB is microsomal triglyceride transfer protein (MTP), which facilitates the transport of triglyceride, cholesterol ester, and phospholipid between membranes. Individuals with abetalipoproteinemia lack MTP activity and have mutations in the MTP gene (61,62). Because these lipoproteins transport cholesterol and triglycerides, plasma levels of both lipids are greatly reduced. The inability to form chylomicrons leads to the abnormal accumulation of triglycerides in the intestinal mucosa and malabsorption of fat and fat-soluble vitamins.

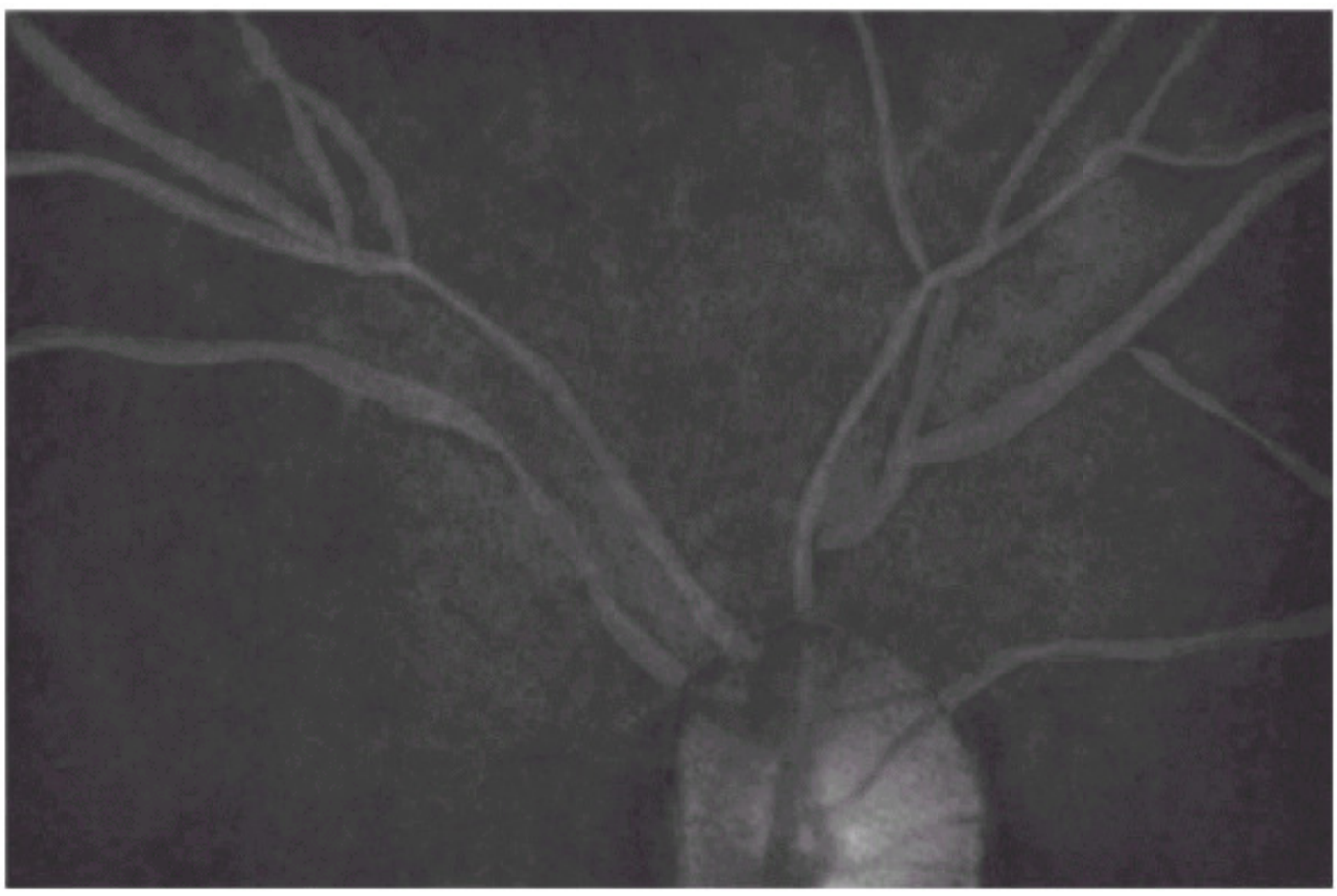


Figure 23.6 Lipemia retinalis. The marked fundus changes in this 23-year-old black man with fat-induced hyperlipemia (type 1 hyperlipoproteinemia) cleared within several days after ingestion of fat was stringently limited.

Chronic diarrhea owing to fat malabsorption is the initial clinical manifestation in infancy and early childhood. The presence of “star-shaped” erythrocytes (acanthocytes) in the peripheral blood is highly characteristic. This peculiar shape of red blood cells is related to the abnormal lipid composition of their membranes. Severe anemia can result from the secondary deficiency of iron and folate. Neurologic disease begins during the teenage years with decreased deep tendon reflexes and loss of vibratory and proprioceptive senses, followed by ataxic gait. Progressive spinocerebellar degeneration peripheral neuropathy, along

with myopathic changes, can lead to generalized weakness and confinement to a wheelchair by the third decade (51).

Retinal degeneration is considered one of the cardinal manifestations of abetalipoproteinemia (Fig. 23.7). In the original reports, progressive visual loss, especially night blindness; pigmentary disturbances of the retina; and reductions in the ERG were noted (Fig. 23.3). More recently, it has become generally accepted that the neurologic disease and degenerative pigmentary retinopathy are secondary to a deficiency of vitamin E and therefore preventable. Presumably the high levels of polyunsaturated fatty acids in the outer retina and inadequate levels of vitamin E predispose the retina to oxidative damage. Several studies have shown that the retinal degeneration and neurologic disease is preventable with administration of large oral doses of vitamin E (63,64). Long-standing studies of patients on oral vitamin E reveal normal vision, subtle pigmentary disturbances limited to the retinal equator and/or macula, and normal ERGs. Angioid streaks are a rare manifestation of abetalipoproteinemia, predisposing affected individuals to the development of subretinal neovascular membranes and sudden visual loss (65).

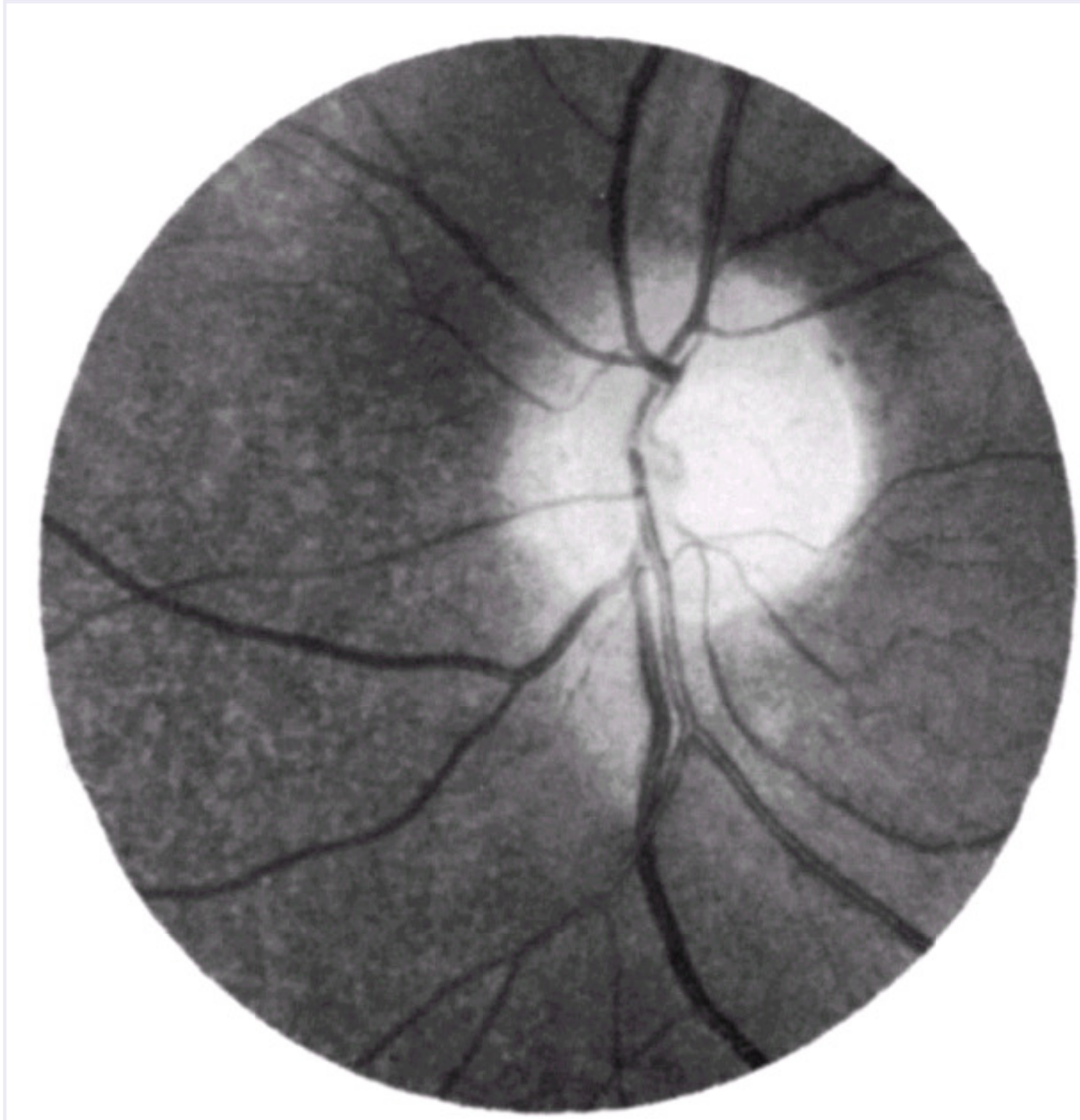


Figure 23.7 Granular mottling of retinal pigment epithelium in abetalipoproteinemia. Electroretinography reveals diminished or absent signals in such eyes.

Horizontal ophthalmoplegia occurs in approximately one-third of affected patients. It is characterized by an acquired exotropia, with progressive medial rectus paresis, decreased saccadic velocities, and dissociated nystagmus of the adducting eye (66). One reported patient had ptosis with eyelid synkinesis and anisocoria, findings consistent with aberrant regeneration and peripheral involvement of the oculomotor nerve (67). However, reduced saccadic velocities implicate the brainstem burst generator, and histopathology shows myopathic changes

Lecithin-Cholesterol Acyltransferase Deficiency and Fish-Eye Disease

Lecithin-cholesterol acyltransferase (LCAT) is a plasma enzyme that transfers a fatty acid from lecithin to cholesterol. Esterified cholesterol can then be used in the synthesis of cell membranes and other cellular components. It normally circulates in the plasma bound to HDL and LDL. Deficiencies of LCAT limit the available pool of cholesterol esters and lysolecithin required for membranogenesis and other synthetic pathways. Consequently, elevated levels of free cholesterol and lecithin accumulate in serum and various tissues. Serum levels of total cholesterol and triglycerides can be normal or high (68).

The major findings of LCAT deficiency are anemia, proteinuria, renal failure, early-onset atherosclerotic changes, and corneal opacities (68). The corneal changes are found in all patients from early childhood (Table 23.2). They appear centrally as numerous, minute gray dots distributed throughout the corneal stroma. Along the peripheral cornea, the opacities are more confluent, forming a ring of opacification resembling a corneal arcus. Slit-beam views of the cornea can reveal a sawtooth configuration to the anterior and posterior corneal surfaces (crocodile shagreen) attributed to degenerative changes of stromal collagen. Histopathologic studies reveal the presence of vacuoles containing electron-dense particles within the Bowman layer and stroma (69). Heterozygotes appear to have a higher

incidence of arcus-like corneal lesions.

Fish-eye disease is a rare autosomal-recessive disease with main clinical manifestations of corneal opacifications (the eye resembling the eye of a boiled fish) and hypertriglyceridemia. It is caused by a selective functional loss of

LCAT activity associated with HDL but not LDL. Serum levels of HDL are 10% of normal, whereas levels of LDL and VLDL are elevated. Furthermore, their lipid composition is abnormal: HDL contains relatively high amounts of free cholesterol, whereas LDL and VLDL contain relatively high amounts of cholesterol esters. Interestingly, neither patients with fish-eye disease nor familial LCAT deficiency in whom HDL levels are severely reduced show an increased incidence of atherosclerotic heart disease (68).

Patients with fish-eye disease have pronounced corneal opacities but no renal or hematologic abnormalities, unlike those with familial LCAT deficiency (Table 23.2). These opacities can cause progressive visual loss, for which corneal transplantation is sometimes required (68,70).

Sphingolipidoses

The sphingolipidoses are a group of inherited disorders caused by defects in the degradation of various sphingolipids resulting in their excessive intralysosomal accumulation (Fig. 23.8). Sphingolipids are found in cellular membranes of all tissues but are enriched in membranes of brain and nervous tissue. Beginning with sphingosine as the basic backbone, the various kinds of sphingolipids are formed by the sequential addition of a fatty acid (ceramide), one or more sugar residues (cerebroside), and sialic acid (ganglioside). Because the sphingolipid composition differs across tissues, the clinical phenotype can vary widely, depending on the nature and severity of the enzyme defect.

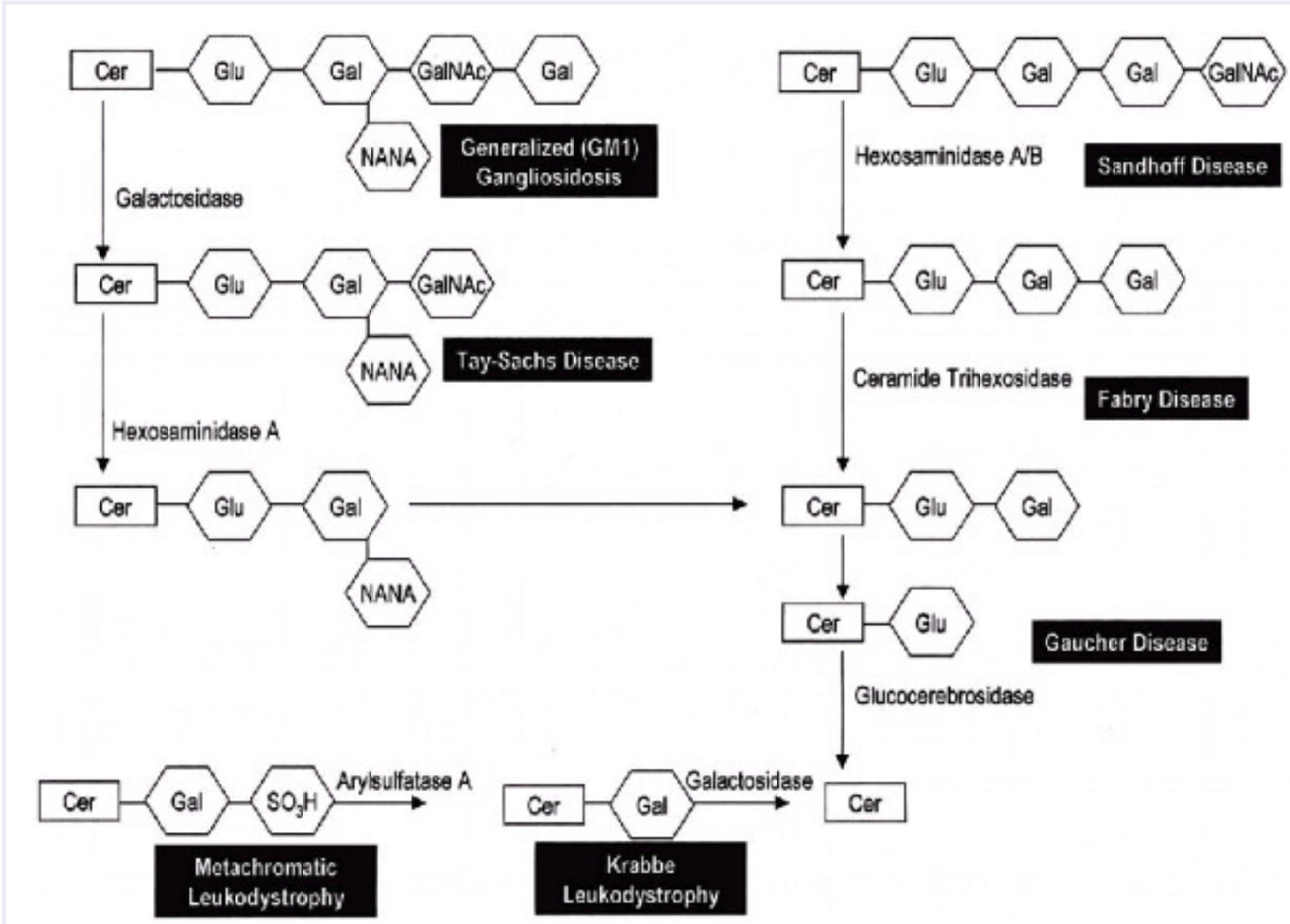


Figure 23.8 Metabolic pathways for sphingolipid metabolism. Cer, ceramide; Glu, glucose; Gal, galactose; Glc Nac, N-acetyl-glucosaminyl; NANA, N-acetyl neuraminic acid.

G_{M2} Gangliosidoses (Tay-Sachs Disease and Sandhoff Disease)

Lysosomal degradation of G_{M2} gangliosides requires three genetically distinct proteins: hexosaminidase A (HexA), hexosaminidase B (HexB), and G_{M2} activator. Hexosaminidase is a dimeric enzyme composed of alpha and beta chains encoded by the genes *HexA* and *HexB*, respectively. Mutations of these genes cause Tay-Sachs disease and Sandhoff disease. Clinical phenotypes associated with deficiency of HexA and HexB vary widely, ranging from infantile onset with rapidly progressive neurologic deterioration and death to adult-onset slowly progressive neurologic disease compatible with prolonged survival. However, Tay-Sachs and Sandhoff diseases are clinically indistinguishable and therefore considered together. Defective activity of the G_{M2} activator is rarely diagnosed and clinically is indistinguishable from both infantile Tay-Sachs and Sandhoff diseases (71).

TABLE 23.6 METABOLIC DISORDERS WITH MACULAR CHERRY-RED SPOTS

Disorder	Frequency of occurrence
G_{M2} gangliosidosis	
Tay-Sachs disease	All cases
Sandhoff disease	Most cases
G_{M1} gangliosidosis	50%
Niemann-Pick disease (type A)	50%
Metachromatic leukodystrophy	Occasional cases
Farber disease	Variable
Sialidosis (type 1)	All cases
Sialidosis (type 2)	Variable
Galactosialidosis	Variable
Disorders with macular halos	
Niemann-Pick disease (type B)	10% of cases

Infants with acute G_{M2} gangliosides due to HexA deficiency (Tay-Sachs disease) or HexB deficiency (Sandhoff disease) are normal at birth. At 3 to 5 months of age, motor weakness is detected, and the startle reaction to sudden sounds is exaggerated. Between 6 and 10 months of age, the failure to achieve, or loss of, gross motor skills becomes more obvious. After 10 months of age, there is rapid neurologic deterioration associated with severe visual loss and increasing seizures. Death caused by aspiration or bronchopneumonia ensues between 2 and 4 years of age (71).

The earliest and most important ocular finding from a diagnostic viewpoint is the cherry-red spot (Table 23.6). Ophthalmoscopically, the normal-appearing fovea stands out against the background of the peripheral retina in which the ganglion cells are swollen with sphingolipids (Fig. 23.9; see Color Plate VF). Progressive lipid accumulation leads to ganglion cell damage, resulting in severe visual loss, optic atrophy, and extinguished VEP (71,72). Abnormalities of eye movements have been noted long after blindness occurred (73).

Subacute G_{M2} gangliosidosis is characterized by the progressive loss of motor and cognitive skills between 2 and 10 years of age. Seizures, increasing spasticity, and generalized neurologic deterioration predominate between 10 and 15 years of age until death occurs from intercurrent infection. Typically, a macular cherry-red spot is not found, but visual loss from optic atrophy or retinal degeneration can develop late in the disease.

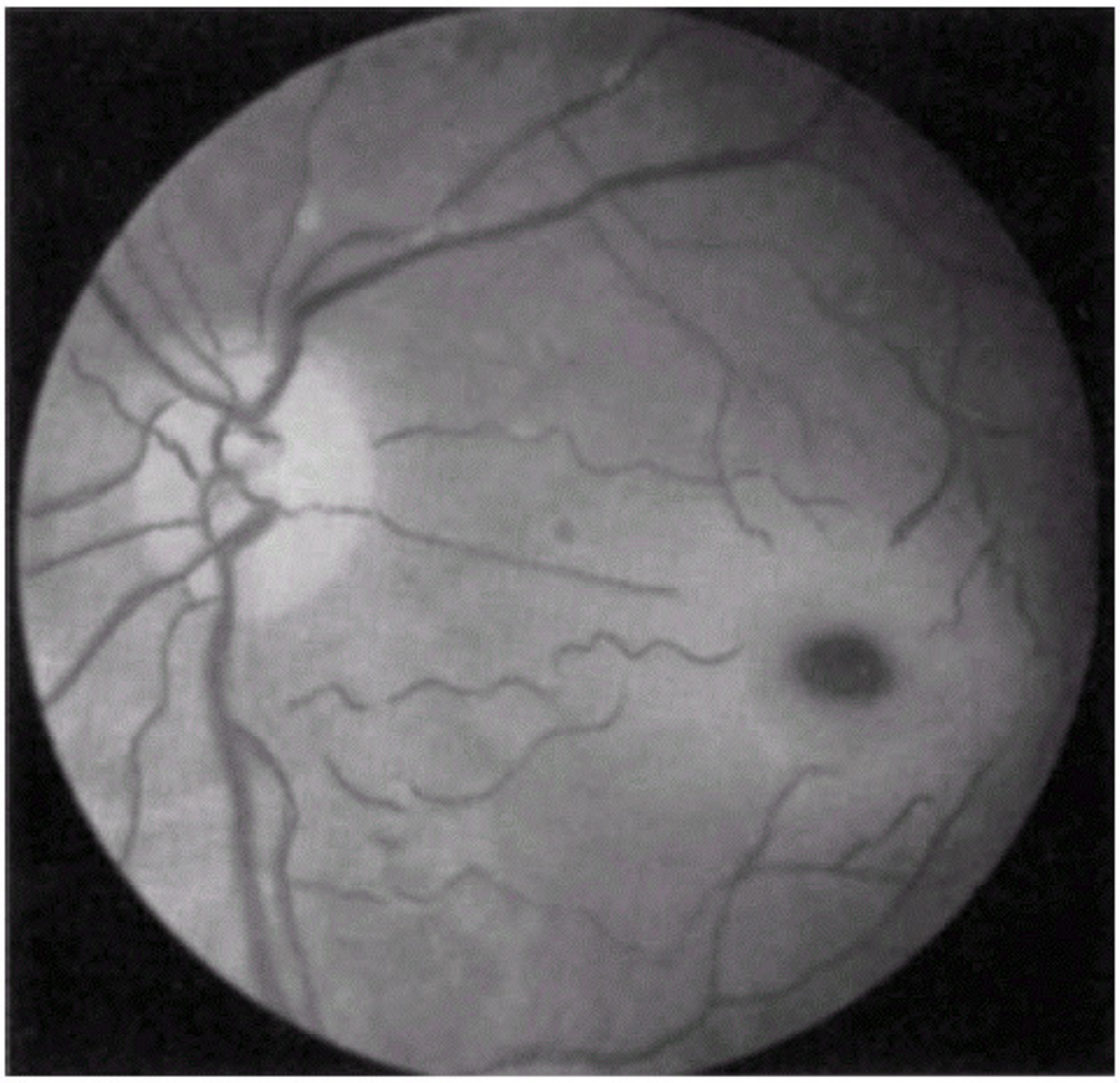


Figure 23.9 Cherry-red spot seen in the fundus of an infant with Tay-Sachs disease. There is optic atrophy, indicating that the disease is in its late stages.

Chronic G_{M2} gangliosidosis has its onset in adolescence or adulthood during which there is an insidious onset of progressive dystonia, spinocerebellar degeneration, motor neuron disease, and psychoses. Visual acuity is normal, and the fundi are unaffected.

G_{M1} Gangliosidosis

G_{M1} gangliosidosis is a rare storage disease with autosomal-recessive inheritance caused by ß-galactosidase deficiency. This enzyme deficiency leads to the accumulation of G_{M1} ganglioside within the brain and complex carbohydrates within soft tissues, bone, and viscera. On the basis of age of onset, it can be classified clinically into infantile, late infantile/juvenile, and chronic/adult types (74).

The infantile type is the most common and is usually recognized because of the combined presence of neurologic abnormalities, coarse facial features, and hepatomegaly. Psychomotor delay is present at birth or develops within 3 to 6 months of age. Neurologic deterioration is rapid, leading to seizures, blindness, spastic rigidity, and death before 2 years of age. Generalized skeletal dysplasia is often present. Visual loss develops early, and macular cherry-red spots are found in at least 50% of patients. Subtle corneal clouding may occur owing to the stromal accumulation of keratan sulfate. Strabismus, nystagmus, and optic atrophy have been noted. Peripheral blood smear shows vacuolated lymphocytes, and foamy histiocytes are found in the bone marrow, liver, spleen, and lymph nodes (74).

In juvenile G_{M1} gangliosidosis, neurologic deterioration begins in the first or second year of life with gait disturbance, progressive stiffness, and mental regression. Seizures are common, and patients expire between 3 and 10 years of age. Many patients have skeletal dysplasia, but facial dysmorphism and visceromegaly are not present. Visual acuity is appropriate for age, and the fundi are normal (74).

Adult G_{M1} gangliosidosis is a chronic disease with onset between 3 to 30 years of age that is mainly found in Japan. Initial clinical manifestations are gait or speech disturbance with progressive dystonic posturing. Mental deterioration is mild, and there are pyramidal signs. Facial dysmorphism is mild, and there is no visceromegaly. Cherry-red spots are not observed, but corneal opacities can occur (74).

Fabry Disease

Fabry disease is a lysosomal storage disorder caused by a deficiency of the enzyme a-galactosidase A. As a result, the substrate ceramide trihexoside accumulates within vascular endothelial cells, leading to ischemia and infarction, especially of the kidney, heart, and brain (Fig. 23.10). Parenchymal deposition of ceramide in podocytes causes proteinuria, and cardiomyopathy and conduction abnormalities in cardiomyocytes (Fig. 23.10). Inheritance is X-linked. The

encoding gene, which maps to the × chromosome, has been fully characterized (75).

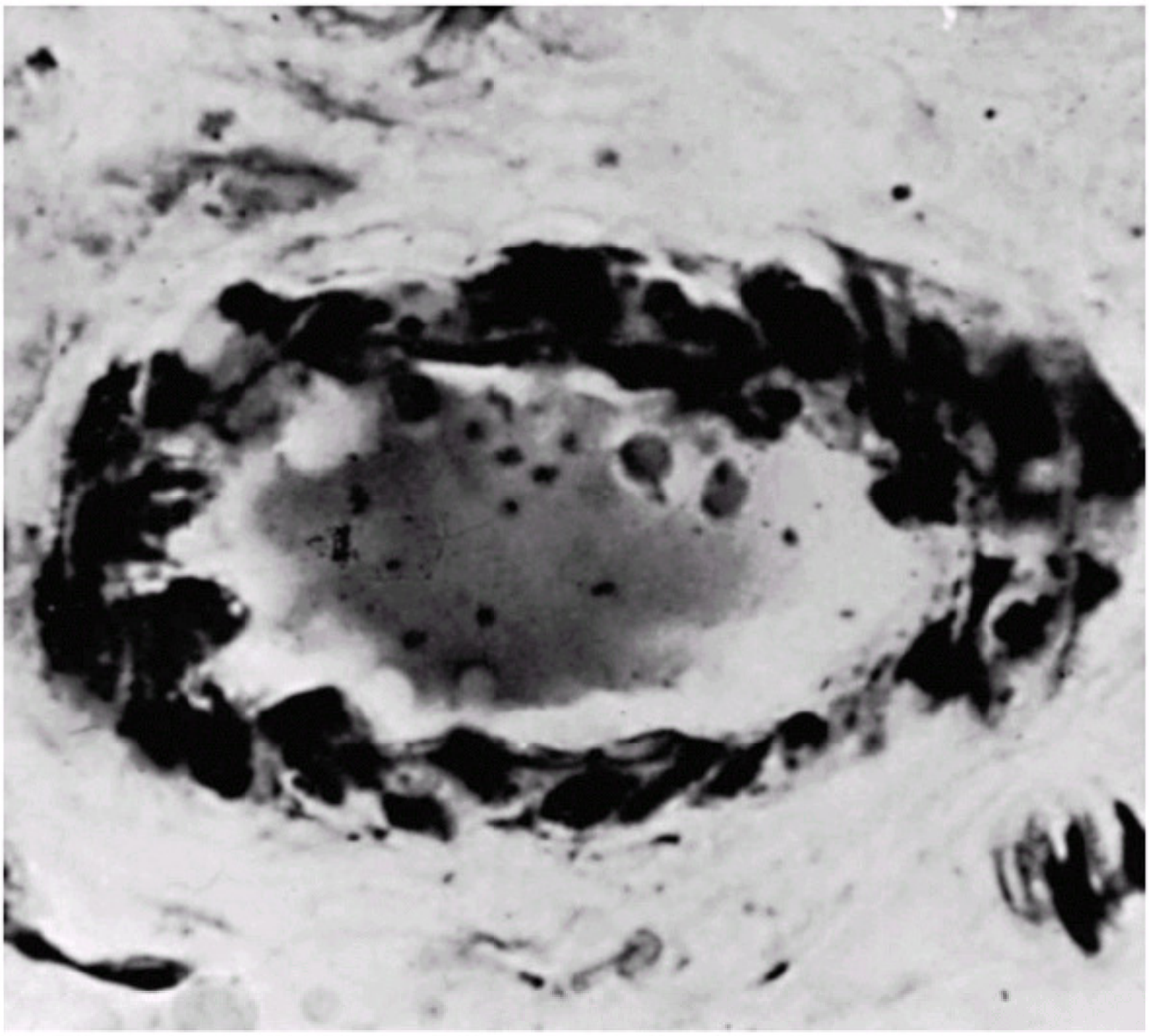


Figure 23.10 Sudan black-stained conjunctival tissue demonstrates the glycolipid material present in the media of small blood vessels in Fabry disease (× 1,000).

Typically, affected males present in childhood or adolescence with painful extremities (acral paresthesias); fever lasting a few minutes to a few days; heat, cold, and exercise intolerance; and GI problems. Examination of the skin reveals angiokeratomata (Fig. 23.11; see Color Plate VIA), which are red or blue-black nodules and are found between the umbilicus and knees. In adulthood, cardiac disease becomes problematic owing to angina, myocardial infarction, and arrhythmias. Proteinuria is found early, but there is progressive renal impairment with onset of renal failure between the third and fourth decades of life. Patients are also at risk for cerebrovascular events including thrombosis, transient ischemic attacks, and focal neurologic deficits (diplopia, hearing loss, and vestibular hypofunction). Female carriers may be asymptomatic or present with fullblown systemic disease. The diagnosis is established by demonstration of deficient a-galactosidase A activity in serum, white cells, or even tears (76). In the past, premature demise usually resulted from renal failure or widespread small-vessel occlusive disease of the heart or brain (76).

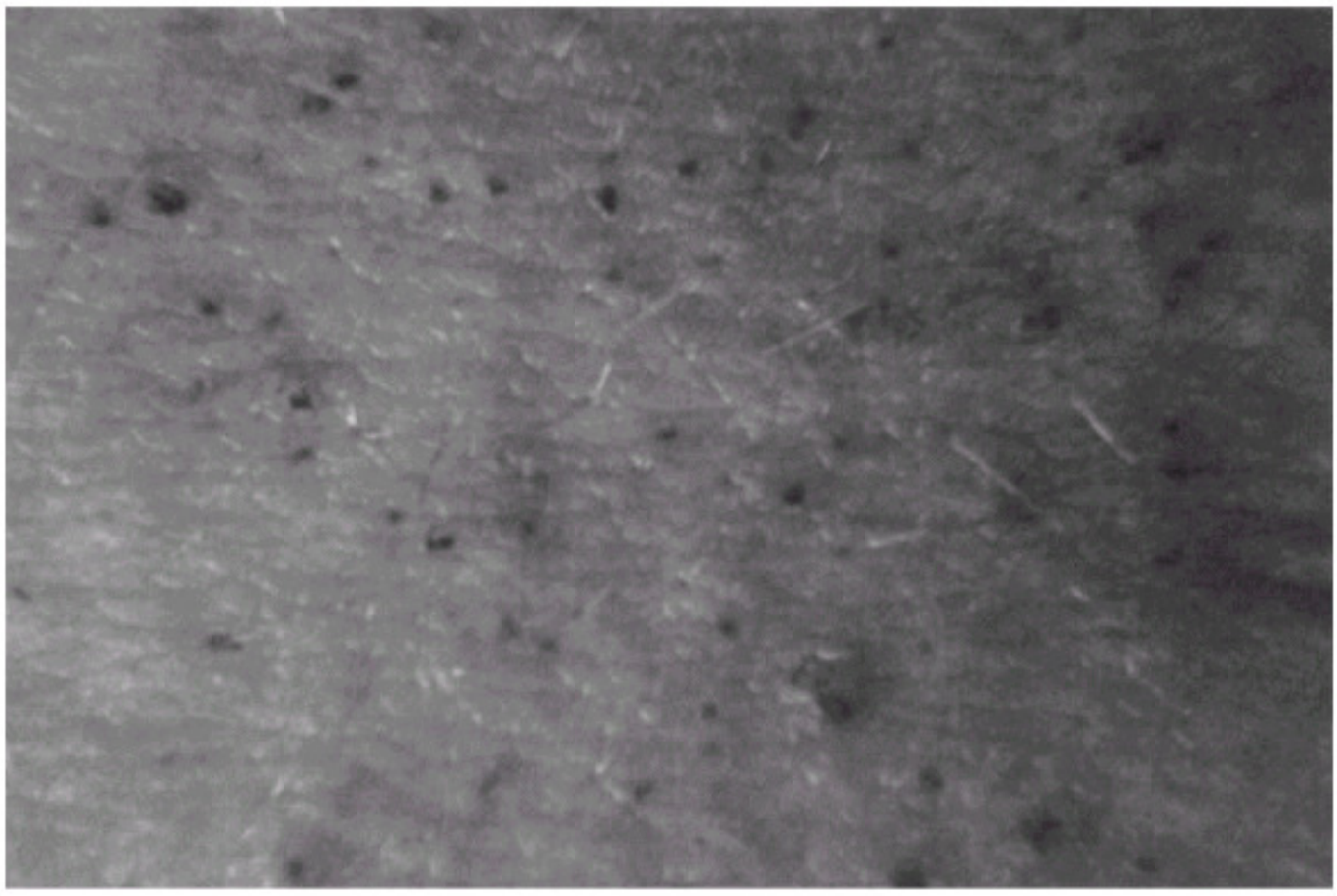
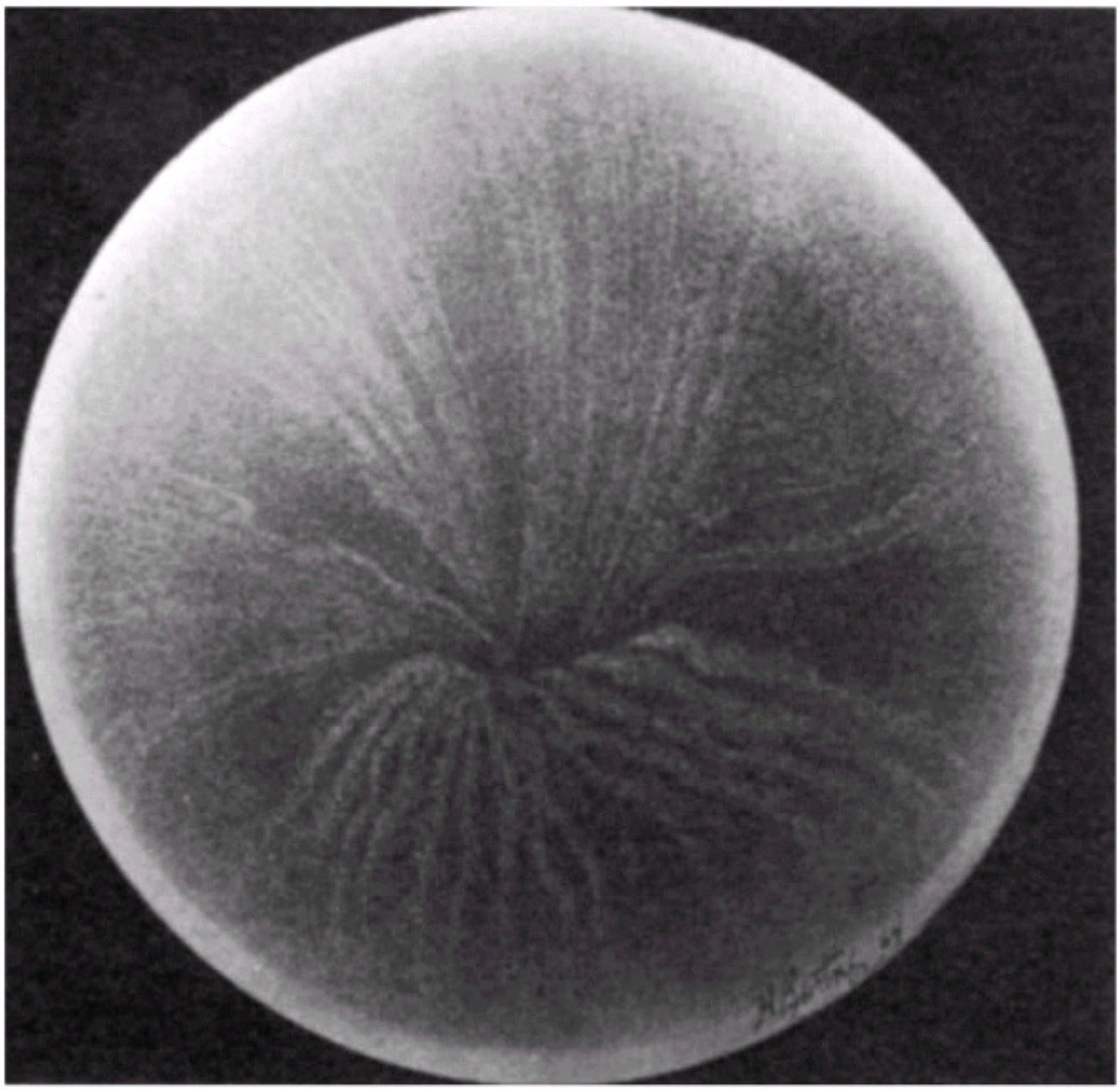


Figure 23.11 Skin lesions, the “angiokeratomata” of Fabry disease, most prominent in the bathing suit area.



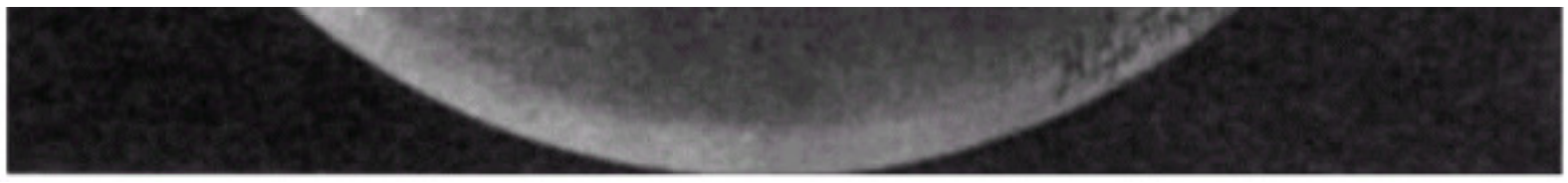


Figure 23.12 Cornea of a female carrier of Fabry disease, showing the whorl-like changes in the epithelium.

Ocular involvement is present early in life and helps in making the diagnosis. Slit-lamp examination reveals characteristic changes of the cornea and lens. Yellowish deposits extend from a central vortex to the periphery, giving the corneal epithelium a whorl-like appearance (Fig. 23.12). The opacities may be the only clinical finding in asymptomatic female carriers (77). Similar deposits are found in patients on long-term chloroquine or amiodarone. Inspection of the lens reveals granular opacities within the inferior portion of the anterior capsule or on the posterior capsule (Fig. 23.13; see Color Plate VIB). The granular deposits align linearly and radiate from a central region of the posterior capsule, giving rise to a characteristic spoke-like opacity in about 50% of affected males and a smaller percentage of carrier females. The vessels of the conjunctiva and retina, like vessels elsewhere, are often dilated and tortuous (Fig. 23.14; see Color Plate VIC). With superimposed renal failure and hypertension, retinal vascular complications, including central retinal artery occlusions, can occur (78).

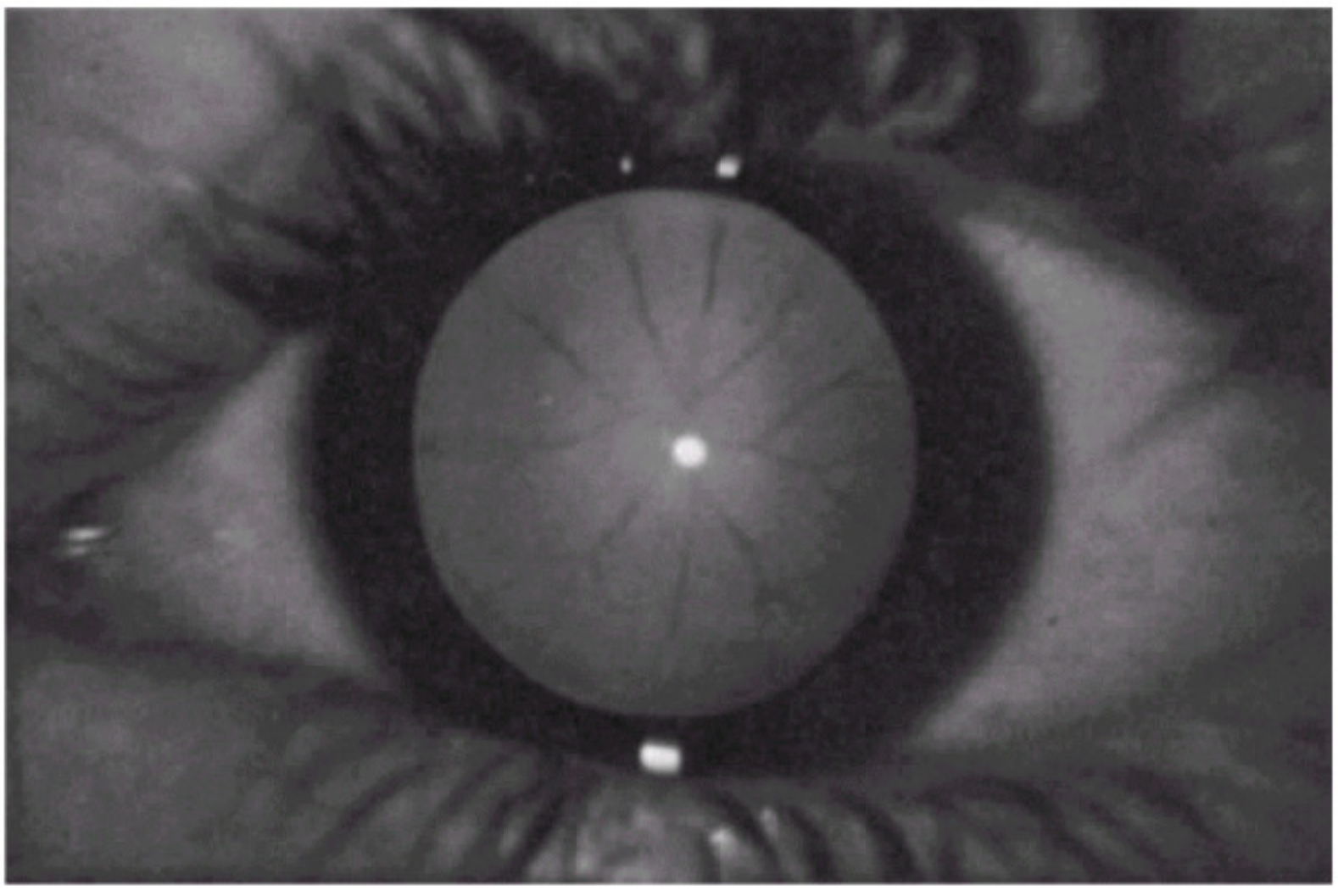


Figure 23.13 Cataract noted in the posterior capsular area of the lens in about 50% of patients with Fabry disease. Carriers may also show this capacity, which is best seen by retroillumination.

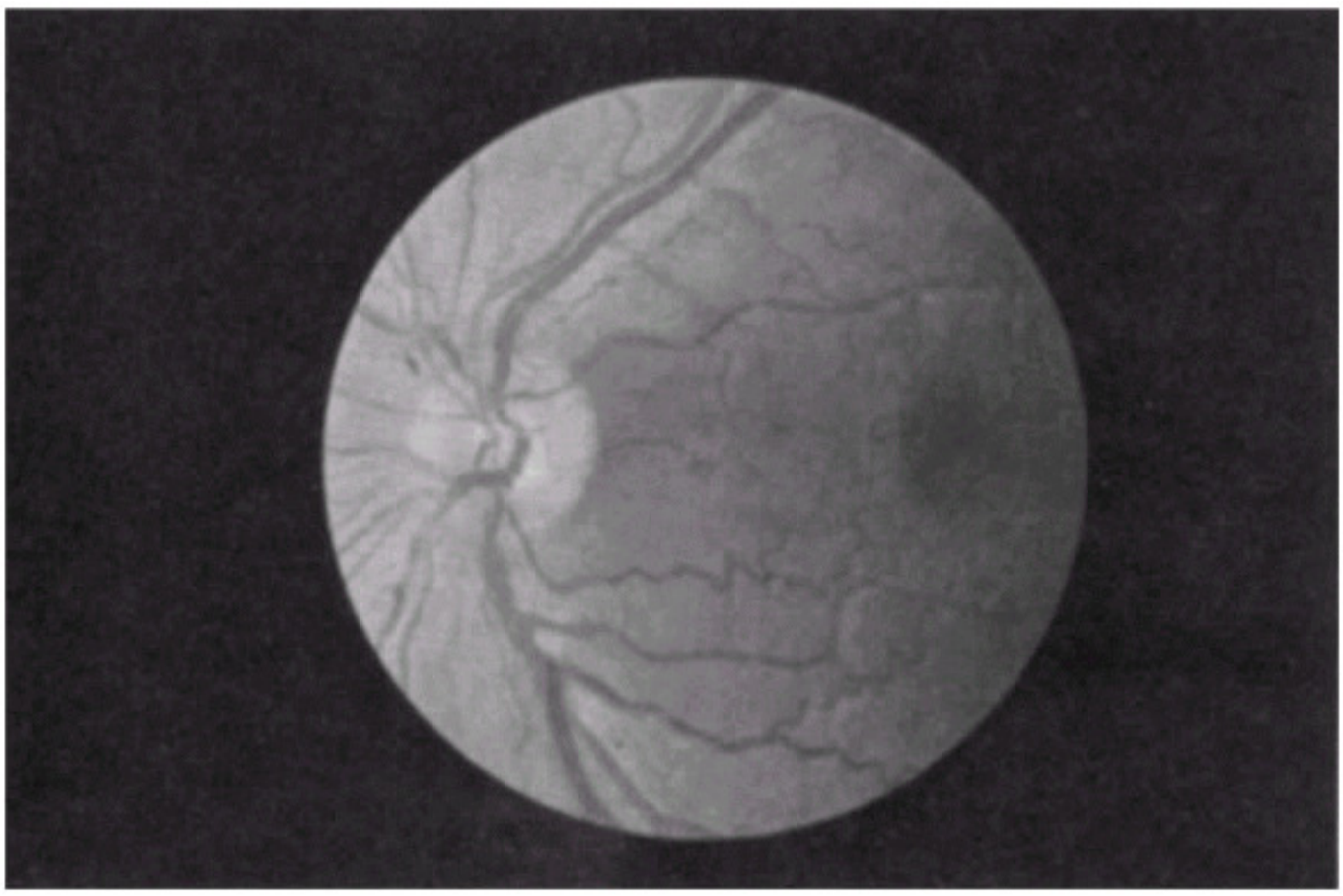


Figure 23.14 Characteristic retinal vessel tortuosity of a 22-year-old man with Fabry disease.

Treatment with enzyme replacement (recombinant a-galactosidase A) is now available for patients with Fabry disease. Two recent clinical trials have conclusively shown that with therapy the deposits of ceramide trihexoside in the kidney, heart, and skin, and neuropathic pain are reduced, and there is improved renal function and cardiac conduction (79,80).

Metachromatic Leukodystrophy

Metachromatic leukodystrophy (MLD) is an autosomal-recessive disorder caused by a deficiency of arylsulfatase. This lysosomal enzyme removes the sulfate moiety from cerebroside sulfate, a glycolipid that is mainly found in myelin sheaths of the nervous system. Levels of arylsulfatase A activity are correlated with symptomatic disease, age of onset, and rapidity of neurologic deterioration (81). Approximately 0.5% to 2.0% of the population have arylsulfatase A activities of 5% to 15% but are asymptomatic. Molecular testing reveals loss of a polyadenylation signal that encodes for a glycosyl subunit, resulting in a smaller, less efficient enzyme. Mutations associated with no enzyme activity (type I) are associated with early onset and rapidly progressive disease. In comparison, mutations with residual arylsulfatase A are associated with late onset of milder disease (82). Histologic studies of the central and peripheral nervous systems show demyelination and loss of white matter and the presence of metachromatic material in macrophages.

Three clinical forms of MLD can be distinguished according to age at onset: infantile (1 to 2 years), juvenile (3 to 16 years), and adult (older than 16 years). Affected infants initially present with loss of acquired motor skills, hypotonia, and depressed deep tendon reflexes that progress to hypertonia with exaggerated reflexes, along with ataxia, truncal titubations, nystagmus, and optic atrophy (82). Prior to cellular death, swelling and opacification of the ganglion cells filled with cerebroside can lead to a cherry-red spot or grayness of the macula (83,84). Within a few years, the blind unresponsive quadriplegic infant with decerebrate or decorticate rigidity dies, usually from pneumonia (81). Bone marrow transplantation has limited success in the treatment of late infantile disease (85).

Patients with late-onset MLD present with cognitive and behavioral disturbances, and peripheral neuropathy including optic atrophy. Brain magnetic resonance imaging (MRI) scans show loss of white matter, especially periventricular white matter. Protein levels are elevated in the CSF. The diagnosis is confirmed by the demonstration of metachromatic lipids in tissue specimens (including conjunctiva), reduced arylsulfatase activity (including tears), or a mutated arylsulfatase A allele.

Multiple sulfatase deficiency is an extended form of MLD in which there is a deficiency of arylsulfatase, steroid sulfatase, and various sulfastases that degrade glycosaminoglycans. In addition to the neurologic manifestations of infantile MLD, these children have mucopolysaccharidosislike features, coarse facial features, hepatosplenomegaly, skeletal anomalies, and ichthyosis. Besides optic atrophy, cherry-red spot, or grayness of the macula, the eye findings may include retinal degeneration, corneal opacities, and equatorial lens opacities (83,86).

Krabbe Disease (Globoid Cell Leukodystrophy)

Krabbe disease is an autosomal-recessive disorder caused by a deficiency of galactocerebrosidase, the lysosomal enzyme that cleaves galactose from ceramide. The onset is usually between 3 to 6 months of age, although later onset in childhood and adulthood is reported. The infantile-onset form accounts for 85% to 90% of cases. Early signs include irritability, hypersensitivity to sensory stimuli, spasticity and seizures, followed by regression of psychomotor development and generalized neurologic deterioration (87). Optic atrophy and blindness are prominent early signs (88). Macular cherry-red spots have been noted in one patient. CSF protein is elevated. Neuroimaging studies show diffuse cerebral atrophy, hypodensity of white matter, and abnormal signal intensity of white matter on T2-weighted images. Histologically, there is extensive loss of myelin and the presence of globoid cells, which are macrophages distended with galactocerebroside. Disease progression is rapid and patients rarely survive beyond 2 years of age.

The late-onset forms have a more insidious onset, progress over a period of years, and account for 10% to 15% of cases. Children may present with decreased visual acuity due to optic atrophy along with spastic or ataxic gait disturbance, loss of fine motor skills, and deterioration in school performance (87). Allogeneic bone marrow transplantation can slow disease progression and reverse the central nervous manifestations, especially in patients with presymptomatic infantile-onset disease or late-onset disease (89).

Gaucher Disease

Gaucher disease is the most common sphingolipidosis having an estimated prevalence of 1 in 4,000 among the general population and 1 in 850 among

Ashkenazic Jews. It is caused by a deficiency of glucocerebrosidase and results in the accumulation of glucocerebroside in liver, spleen, bone, brain, and sometimes other tissues (90). Clinically, three types have been delineated: nonneuropathic (type 1), acute neuropathic (type 2), and subacute neuropathic (type 3).

Type 1 is the most common and represents the mildest form of the disease. It is characterized by progressive hepatosplenomegaly and structural skeletal changes. Splenic sequestration and displacement of the bone marrow often lead to anemia and coagulation abnormalities. Bone involvement can be mild or severely debilitating. Radiographic findings include the Erlenmeyer flask deformity of the distal femur, aseptic necrosis, and pathologic fractures. Although the splenomegaly and bone complications may appear in early life, the course of the disease is slowly progressive and patients survive into adulthood. Infants with type 2 disease develop marked hepatosplenomegaly by 6 months of age, show progressive neurologic deterioration, and usually die before 2 years of age. In type 3 disease, the severity of involvement is between that for types 1 and 2, and patients can survive beyond their second decade (90).

Ocular manifestations are usually related to the accumulation of lipid within macrophages and neurons of the tissues. White deposits, presumably filled with undigested glucocerebroside, have been noted on the surface of the cornea, trabecular meshwork, iris, and retina and within the vitreous (91,92). The retinal spots are usually seen in type 3 disease but have been reported in severe type 1 disease (Fig. 23.15). Fundus abnormalities include perimacular grayness, but the typical cherry-red spot of the macula is not found. Premature onset of pingueculae on the conjunctiva has been reported, but histologic studies have revealed elastic degeneration rather than lipid-laden macrophages. Neuroophthalmic manifestations are sequelae of CNS involvement in type 2 and type 3 disease. Abnormalities of eye movements can be a prominent neurologic finding and, in conjunction with the visceromegaly, should bring Gaucher disease to mind. Decreased saccadic velocity detected by eye movement recording is often the first sign of neurologic involvement, followed by a horizontal gaze palsy (93). These findings indicate that there is early involvement of the saccadic burst neurons, abducens motoneurons, and parapontine reticular formation. The diagnosis of Gaucher disease is usually made on the basis of the clinical findings, and demonstration of Gaucher cells in the bone marrow is confirmed by enzymatic or molecular testing. In the past the only therapy was symptomatic correction of the hematologic or skeletal complication. Enzyme replacement is now recommended for children with type 1 Gaucher disease (94,95). Treatment reduces the amount of storage material in liver and spleen, improves the red blood cell and platelet counts, and increases bone mineralization and remodeling.

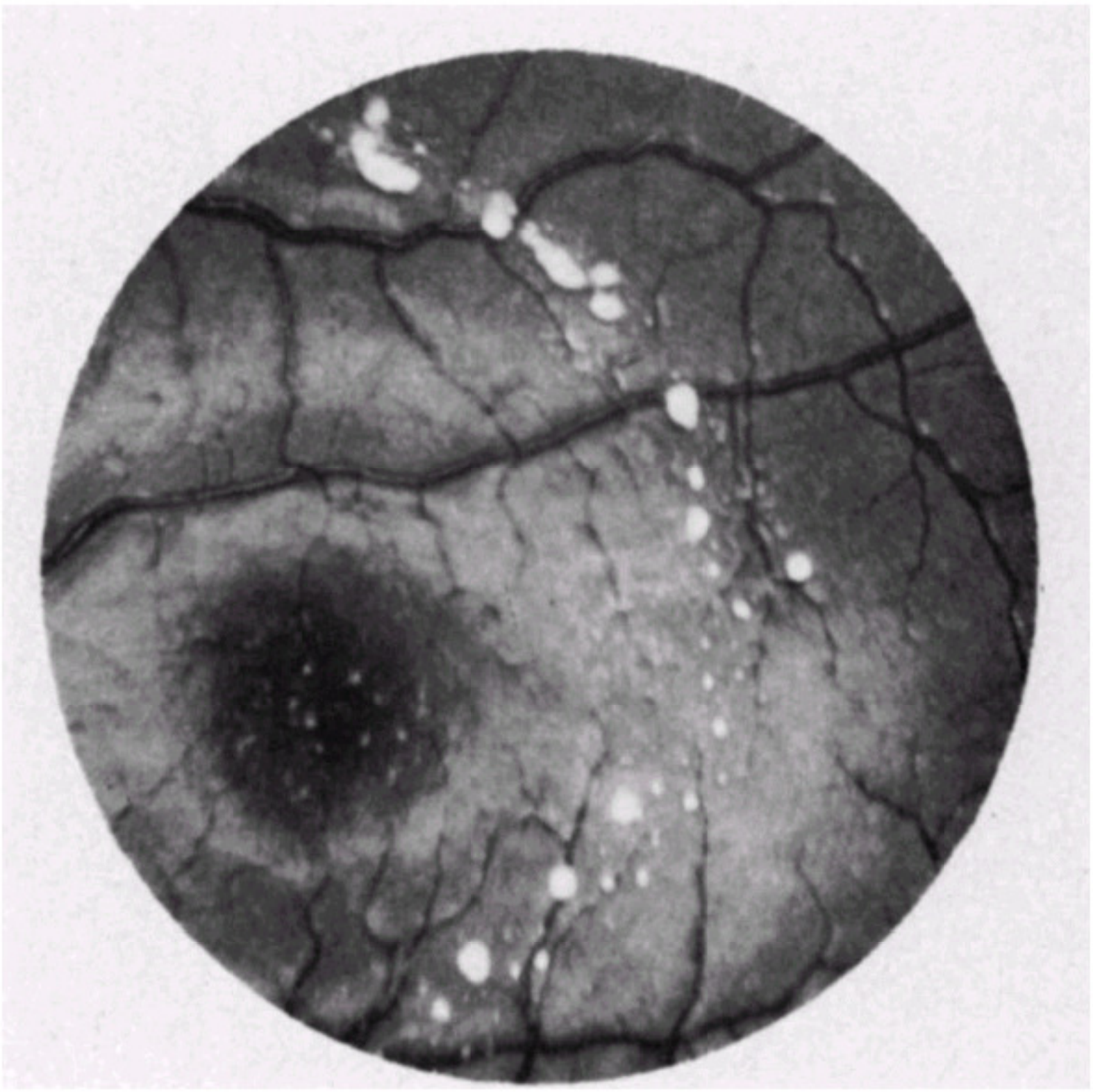


Figure 23.15 Characteristic white spots in or on the retina in a patient with juvenile neuronopathic Gaucher disease.

Niemann-Pick Disease

Niemann-Pick disease (NPD) includes a heterogeneous group of disorders separable on the basis of clinical phenotype and genetic defect into types A, B, C1, and C2. Each of these variants is an autosomal-recessive disorder characterized by variable involvement of the CNS and visceromegaly. NPA and NPB are due

to a deficiency of acid sphingomyelinase (ASM). NPC1 and NPC2 result from a defect in intracellular transport of cholesterol from the lysosome to plasma membrane.

Acid sphingomyelinase cleaves sphingomyelin into ceramide and phosphocholine. As a result of the ASM deficiency in NPA and NPB, sphingomyelin accumulates in macrophages in the spleen, liver, lymph nodes, and lung. Histopathology reveals cells having a foamy cytoplasm representing storage material that stains for lipid. Wright stain gives the cytoplasm a striking blue appearance referred to as the sea-blue histiocyte (96).

Niemann-Pick type A (NPA) is the most common subtype of NPD and, like Tay-Sachs disease, has a higher prevalence among Ashkenazic Jews. Typically newborns are normal, but during the first few months of life, feeding problems, hepatosplenomegaly, and failure to thrive become evident. By 6 months of age, the infant loses motor and cognitive skills and thereafter, the emaciated appearance with protuberant abdomen and spastic rigidity dominates the clinical picture. Although respiratory symptoms are minimal, chest radiographs show alveolar infiltrates. Death usually occurs by 3 years of age. The major ocular finding in NPA is the macular cherry-red spot, present in 50% of affected infants (72). The cherry-red spot in NPD is related to sphingomyelin accumulation in the lysosomes of retinal ganglion cells (Fig. 23.16). Vision is retained until optic atrophy develops late in the disease. Walton and co-workers (97) have reported subtle lens opacities and peculiar corneal opacification that can progress in some cases.

Niemann-Pick type B (NPB) is a milder disease because there may be no neurologic deficits or only mild ataxia (96). However, storage material accumulates in the brain. Although residual ASM activity of 2% to 10% of normal is reported in some individuals, it is not significantly correlated with disease severity. Affected patients are found to have splenomegaly, pancytopenia secondary to hypersplenism, or pulmonary disease related to lipid-laden histiocytes filling the alveoli. Longevity usually depends on the severity of lung involvement. A distinctive macular halo is

thought to be pathognomonic of NPB, but it is found in only 10% of cases (98). It is variably described as a concentric ring of gray deposits or crystalloid opacities centered on the foveola. Intraretinal localization of the opacities is uncertain, but the preservation of good visual acuities for as long as 20 years is consistent with sparing of the photoreceptors.

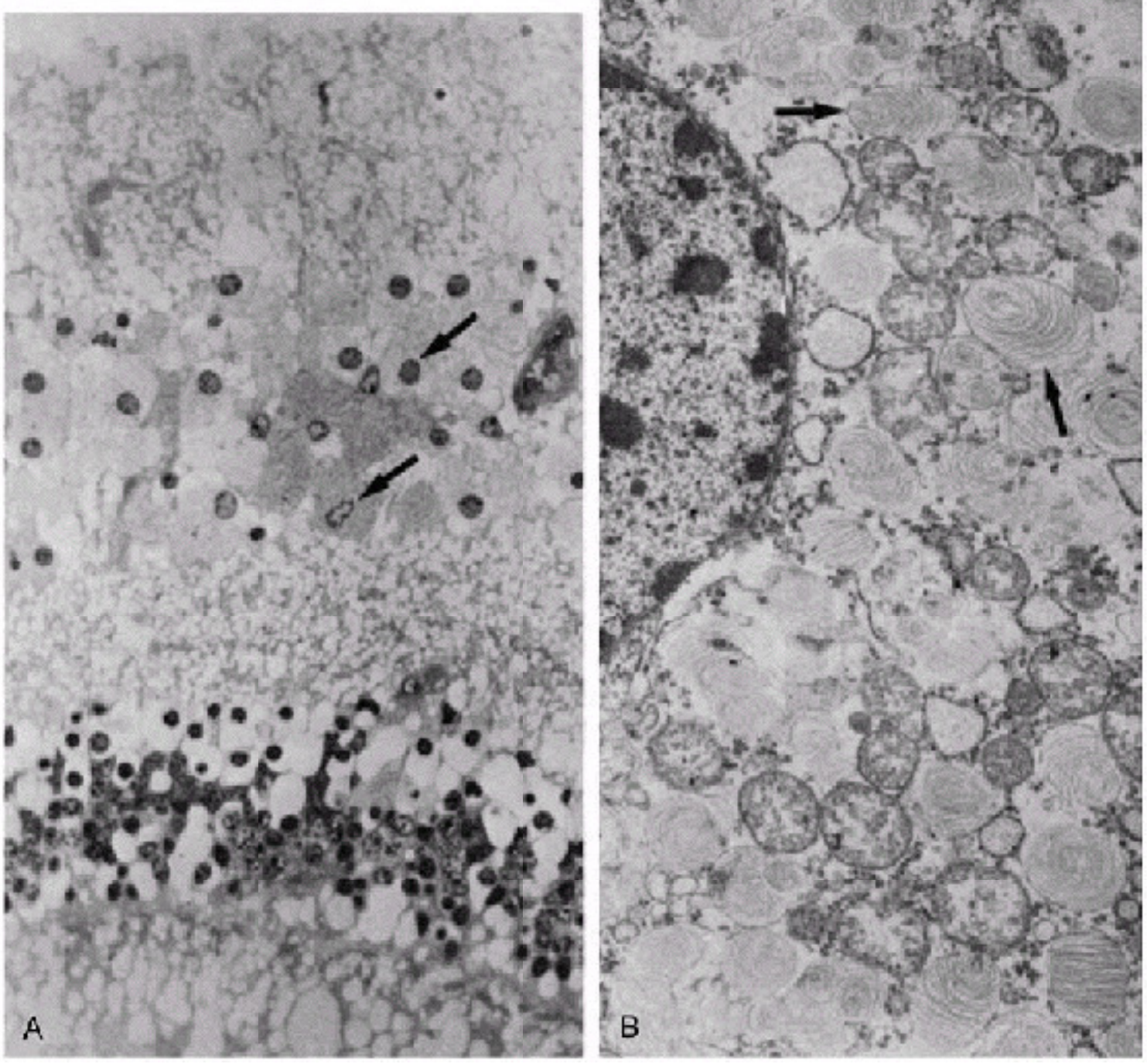


Figure 23.16 A: Light photomicrograph of the retina in a patient with Niemann-Pick disease, showing ganglion cells distended with lipid inclusions (**arrows**) (3-µm section stained with toluidine blue, × 1,000). **B:** Electron micrograph of a retinal ganglion cell containing membrane-bound lamellar inclusions characteristic of Niemann-Pick disease (**arrows**) (× 15,000).

Niemann-Pick C1 (NPC1) is characterized by the accumulation of cholesterol within lysosomes, resulting from its defective transport from the lysosome to plasma membrane. Two proteins encoded by different genes are responsible for this intracellular movement of cholesterol (99,100,101). Mutations of NPC1 account for

95% of NPC cases, and mutations of NPC2 for the remaining 5%. The clinical phenotype is somewhat correlated with the specific gene mutation.

The clinical phenotype is highly variable in terms of age of onset and disease progression. Some patients have an acute onset in infancy with early demise, and others do not become symptomatic until adolescence or adulthood. Most patients are normal until 1 to 2 years of age after which they develop progressive neurologic signs (102). Neither cherry-red spots nor macular halos are observed. The hallmark of type C disease is a vertical ophthalmoplegia in conjunction with ataxia/athetosis and foam cells in the bone marrow—a triad known as the DAF syndrome. Vertical saccades are slow and hypometric whereas horizontal saccades are normal initially but a total ophthalmoplegia develops with disease progression (103).

Treatment is currently limited to symptomatic relief and liver transplantation in individual patients. Enzyme replacement with recombinant sphingomyelinase for NPA and NPB and hematopoietic stem cell transplantation hold great promise based on preliminary evidence in mouse models of NPD.

Farber Disease

Farber disease (disseminated lipogranulomatosis) is an autosomal-recessive disorder caused by a deficiency of lysosomal acid ceramidase (104). As a result, ceramide accumulates in macrophages within various tissues. The clinical triad of subcutaneous nodules around joints and over pressure points, progressive arthropathy, and laryngeal hoarseness

is virtually diagnostic of this disease (Fig. 23.17). The lungs, liver, heart, and lymph nodes may also be involved. Motor impairment and mental deterioration may result when ceramide accumulates in neurons. There are several phenotypes having variable involvement of the CNS. In the classic type, there is progressive neurologic deterioration, and death occurs within the first few years of life. Without CNS involvement, there is still progressive joint deformity, but longevity is significantly prolonged. Although few patients have been treated, hematopoietic stem cell transplantation causes regression of the granuloma and dramatically increases joint mobility (105).

Figure 23.17 Nodular thickening of the wrists in a patient with Farber lipogranulomatosis.

The major ocular finding is a macular cherry-red spot owing to subtle opacification of the surrounding retina. Histopathologic studies of the retina have shown the presence of intracytoplasmic lipid vacuoles containing curvilinear tubular structures known as “Farber bodies” (106). Granulomatous nodules on the eyelid, skin, and conjunctiva can be prominent in some patients. Nodular opacities in the cornea and lens are less frequent findings.

Mucopolysaccharidosis

The mucopolysaccharidoses (MPS) are caused by deficiency of enzymes catalyzing the stepwise degradation of glycosaminoglycans (mucopolysaccharides). Specifically, the catabolism of dermatan sulfate, keratan sulfate, heparan sulfate, or chondroitin sulfate is involved individually or in combination. There are six types of mucopolysaccharidoses distinguished on the basis of clinical features and specific enzyme deficiency (107). Ocular findings are common in MPS-I, MPS-IV, MPS-VI, and MPS-VII.

Mucopolysaccharidosis (MPS) type I includes three clinical phenotypes linked by a common deficiency of a-Liduronidase. At the severe end of the spectrum is Hurler syndrome (MPS-IH), with onset between 6 and 24 months of age and characterized by the development of coarse facial features, enlarged tongue, hepatosplenomegaly, stiff joints, and cardiac disease (coronary artery disease, endocardial fibroelastosis). Developmental delay and progressive deterioration become obvious after 2 years of age. Affected children seldom live to 10 years of age. Bone x-ray studies show a constellation of findings referred to as dysostosis multiplex. At the mild end of the spectrum is Scheie syndrome (MPS-IS) in which coarse facies, joint stiffness, and aortic valve disease predominate, but stature and intelligence are normal. In Hurler/Scheie syndrome, the clinical phenotype is intermediate between MPS-IH and MPS-IS (107).

Detection of corneal opacities is the main reason that the ophthalmologist is asked to evaluate patients with MPS (Table 23.2). Functionally, the opacifications are consistent with normal vision or only mild reductions until corneal clouding becomes severe. Additional ophthalmic involvement is mostly related to the abnormal accumulation of glycosaminoglycans within various parts of the eye. Excessive accumulation in the trabecular meshwork is associated with glaucoma (108) and retinal degeneration (109), both of which can lead to blindness (Table 23.3). Another potentially blinding complication is indirectly related to increased intracranial pressure presumably due to infiltration of the meninges and defective resorption of CSF (110). Sustained increases in intracranial pressure are frequently associated with ventricular enlargement and progressive optic atrophy.

Morquio syndrome is caused by an individual's inability to degrade keratan sulfate, resulting from either a deficiency of N-acetylgalactosamine 6-sulfatase (MPS-IVA) or ß-galactosidase (MPS-IVB). Both types are characterized by short trunk dwarfism, skeletal deformities, normal intelligence, and fine corneal

deposits that progress with advancing age (107).

Maroteaux-Lamy syndrome is characterized by defective degradation of dermatan sulfate resulting from a deficiency of arylsulfatase B. The clinical phenotype resembles that of Hurler syndrome except that mental development is normal. Corneal opacities are obvious and can interfere with vision (111).

Mucopolysaccharidosis (MPS) type VII (Sly syndrome) exhibits a wide clinical spectrum and is caused by a deficiency of ß-glucuronidase. Patients with early-onset disease present with hepatosplenomegaly, dysostosis multiplex, and developmental delay. Corneal opacities are variably present. Children with onset after 4 years of age have milder disease with normal intelligence and clear corneas (107).

Enzyme replacement with alpha-L-iduronidase is one treatment option for Hurler syndrome (112). Weekly administration reduces hepatic storage, increases degradation of glycosaminoglycans, and ameliorates some aspects of clinical disease. Stem cell transplantation provides an attractive alternative because it delivers enzyme inside and outside the blood compartment. Allogeneic bone marrow transplantation has been shown to increase longevity and improve systemic health in patients with various types of MPS (113,114). Long-term ophthalmologic follow-up indicates partial resolution of corneal clouding in some patients, but ERGs show progressive deterioration (115).

DISORDERS OF GLYCOPROTEIN

Glycoproteins are ubiquitous proteins to which oligosaccharide chains are covalently linked through the hydroxyl

groups of serine or threonine or through the free amino group of asparagine. Degradation of glycoproteins is accomplished by a series of lysosomal enzymes. Deficiency or faulty intracellular trafficking of any one of these enzymes results in the abnormal accumulation of storage material and specific clinical manifestations. Each of these disorders has an autosomal-recessive mode of inheritance. Affected patients have a Hurler-like phenotype with coarse facial features, visceromegaly, and dysostosis multiplex, but increased amounts of oligosaccharides are found in the urine. The most relevant clinical features of each of these disorders are outlined in Table 23.7.

TABLE 23.7 CLINICAL FEATURES OF MANNOSIDOSIS, FUCOSIDOSIS, AND SIALIDOSIS[a]

Disorder	Age of onset	Facies	Dysostosis multiplex	Neurologic	Hepatosplenomegaly	Eye findings
a-mannosidosis						
Type I	3 to 12 months	Coarse	+++	Mental retardation	+++	Cataracts, corneal opacities
Type II	1 to 4 years	Coarse	++	Mental retardation	++	Cataracts, corneal opacities
ß-mannosidosis	<1 to 6 years	Some dysmorphism	±	Mental retardation	-	-
Fucosidosis						
Type I	3 to 18 months	Mild coarsening	++	Mental retardation, seizures	++	Infrequent
Type II	1 to 2 years	Mild coarsening	++	Mental retardation	++	Tortuous conjunctival vessels
Sialidosis						
Type I and type II	8 to 25 years	Normal	-	Myoclonus, seizures, neuropathy	-	Blindness, cherry-red spot
Congenital	*In utero*	Coarse	+++	Mental retardation	++	
Infantile	0 to 12	Coarse	+++	Mental	±	Cherry-red

Infantile	0 to 12 months	Coarse	+++	Mental retardation	±	Cherry-red spots
Juvenile	2 to 20 years	Mild coarsening	++	Myoclonus, mental retardation	-	Reduced acuity, cherry-red spots
Aspartylglycosaminuria	1 to 5 years	Coarse, sagging skin	+	Mental retardation	-	Lens opacities

[a]Other important findings include the presence of vacuolated lymphocytes and angiokeratoma.

±, borderline; +, mild; ++, moderate; +++, severe.

Modified from Thomas GH. Disorders of glycoprotein degradation: a-mannosidosis, ß-mannosidosis, fucosidosis, and sialidosis. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001 : 3507-3534, with permission.

Sialidosis

Sialidosis is a rare lysosomal storage disease due to an inherited deficiency of sialidase, the enzyme that cleaves sialic acid residues from oligosaccharides. As a result, there is tissue accumulation and increased urinary excretion of sialylated oligosaccharides and glycoproteins (116). Two clinical variants are distinguished on the basis of age of onset and disease severity. Type I sialidosis is a late-onset mild form characterized by normal facies, cherry-red spot with decreased visual acuity, and myoclonus or gait disturbance (117,118). Visual loss is progressive and likely related to progressive optic nerve disease. As ganglion cells atrophy, the cherry-red spot may fade. The myoclonus initially involves the limbs but can become generalized and disabling with disease progression.

Type II sialidosis is the dysmorphic form in which early onset and disease severity are correlated with lower levels of residual sialidase activity. Congenital sialidosis type II patients present at birth with hydrops fetalis, ascites, hepatosplenomegaly, stippled epiphyses, and early demise. Individuals with infantile or childhood-onset have coarse facial features, visceromegaly, dysostosis multiplex, and developmental delay. Cherry-red spots, punctate lens opacities, myoclonus, and ataxia are observed in older children who survive into the second decade. Vacuolated lymphocytes and foam cells in the bone marrow are found in type II but not in type I (116).

The diagnosis is confirmed by the detection of sialylated oligosaccharides in the urine and reduced activity of lysosomal sialidase. The gene coding for sialidase was cloned, and mutations have been identified in individuals with sialidosis (119). Some of these mutations may affect active site residues, but others affect surface sites that are likely important for interaction with other lysosomal enzymes. Recent evidence indicates sialidase is part of a multienzyme complex including cathepsin A (protective protein), ß-galactosidase (120), and others.

Galactosialidosis

Galactosialidosis is associated with a combined deficiency of neuraminidase and ß-galactosidase secondary to a deficiency of cathepsin A (121). The conformational structure of this lysosomal protein is important for the protection and maintenance of the catalytic activity of both of the other enzymes (122). All patients have a Hurler-like phenotype, and three clinical phenotypes are recognized on the basis of age of onset.

The early infantile form is associated with nonimmune fetal hydrops, coarse facial features, hepatosplenomegaly, proteinuria that progresses to renal failure, cardiomegaly with heart failure, and early death. The late infantile form has features similar to those of the early infantile form except that heart involvement is characterized by thickening of aortic and mitral valves, and longevity is longer. Approximately 60% of reported patients, mostly Japanese, have the juvenile/adult form. Unlike the infantile forms, neurologic involvement is common and includes generalized seizures, myoclonus ataxia, and mental retardation with progressive deterioration. Skeletal changes are mild, and there is no visceromegaly (119). Ocular findings are common to all three forms and include cherry-red spots with progressive acuity loss, corneal clouding, and punctate lens opacities (119,123). Histopathologic studies reveal intracytoplasmic inclusions within retinal ganglion and amacrine cells that lead to severe loss of these cell types. The cherry-red spot may fade as the ganglion cells atrophy. In support of the anatomic changes, pattern VEPs show severely reduced amplitudes, and full-field ERGs demonstrate a reduction in the b-wave (124).

Mannosidosis

Mannosidosis is a lysosomal disorder caused by a deficiency of a-mannosidase, the enzyme that cleaves mannose from the oligosaccharide chain of glycoproteins. Consequently, mannose-rich oligosaccharides accumulate in numerous tissues. In soft tissues, this leads to coarse features, macroglossia, hypertrophic gums, and hernias. Abnormal storage in the CNS results in mental deterioration and hearing loss. Hepatosplenomegaly is common. Dysostosis multiplex and thickened calvarium are the predominant skeletal changes. Vacuolated lymphocytes are found in the peripheral blood and foam cells in the bone marrow. The severity of disease varies with age at onset. In infantile onset (type I), clinical signs appear rapidly, and death often occurs between 3 and 10 years of age. The milder juvenile form (type II) is characterized by normal early development with appearance of mental deterioration and hearing loss in childhood or later (117). Ocular manifestations are most apparent in the lens where mannose-rich glycoproteins have been found. In type I, a spoke-like opacity of the posterior cortex is highly characteristic (125). In type II, punctate opacities are scattered throughout the lens (126). On occasion, anteriorly located opacities have been noted in the lens and cornea. Electron microscopy of skin and conjunctiva shows membrane-bound vacuoles in fibroblasts, suggestive of lysosomal storage disease.

I-Cell Disease (Mucolipidosis II)

I-cell disease was initially named after the abundant intracytoplasmic inclusions noted on microscopy. Although cells are filled with storage material in mucolipidosis II and III, lysosomal enzymes are paradoxically present at elevated levels in serum and other body fluids (127). To better understand this paradox, it is necessary to briefly review intracellular sorting and trafficking of proteins. Lysosomal enzymes, like many other proteins, are synthesized in ribosomes and then translocated to the endoplasmic reticulum, where mannose side chains are added. These glycoproteins are then transferred to the Golgi apparatus, where the terminal mannose is phosphorylated, a reaction catalyzed by N-acetyl-glucosaminyl (Glc Nac) phosphotransferase. A second enzyme, phosphodiesterase, then

cleaves off the N-acetylglucosamine, leaving mannose-6-phosphate. Exposure of the mannose-6-phosphate marker allows the protein to be recognized by specific receptors and translocated to lysosomes. The lack of this obligate marker results in these proteins being diverted from lysosomes to the plasma membrane for extracellular secretion. The activity of Glc Nac phosphotransferase activity is absent in mucolipidosis II and reduced in mucolipidosis III. Cell types dependent on the mannose-6-phosphate marker are therefore deficient in multiple lysosomal enzymes. Although all cells are deficient in phosphotransferase activity, certain cell types still accumulate lysosomal enzymes, suggesting there are alternative targeting pathways (127).

I-cell disease is characterized by the early onset of coarse facial features, dysostosis multiplex, psychomotor retardation and reduced linear growth. Deficiency of lysosomal enzymes leads to the progressive accumulation of mucopolysaccharides in bones and soft tissues, especially skin, ears, and gingiva. With advancing age, joint immobility, cognitive deficits, and cardiomegaly progress, and respiratory infections become more frequent. Most children die of cardiorespiratory complications before 8 years of age (127). Corneal clouding is a late manifestation, in contrast to Hurler syndrome (128).

Mucolipidosis III/Pseudo-Hurler Polydystrophy

Mucolipidosis III is a much milder disease than mucolipidosis II owing to residual phosphotransferase activity. Onset of involvement is between 2 and 4 years of age. Stiffness of the hands and shoulders is a common manifestation. By 6 years of age, claw-hand deformity, scoliosis, and short stature are apparent, and there is mild mental retardation. Coarsening of facial features, skin thickening, and corneal clouding become evident with increasing age. Carpel tunnel syndrome and progressive destruction of the joints, especially the hip joint, are disabling. Milder disease with slower progression allows survival into adulthood (127). Ophthalmologic manifestations are due to the accumulation of storage material causing axial hyperopia (increased scleral thickness), puffiness of the eyelids, and fine discrete opacities of the corneal stroma that progress but do not compromise vision. Optic nerve head swelling can result from mechanical compression due to accumulation of storage

material within the scleral canal or meninges. Nonspecific tortuosity of retinal vessels and surface wrinkling maculopathy are reported, but ERGs are normal (128).

The diagnosis of mucolipidosis II and III is based on demonstration of increased levels of hexosaminidase B, iduronate sulfatase, and arylsulfatase A in the serum and deficient levels of these enzymes in the lysosomes of cultured fibroblasts. Alternatively, the level of phosphotransferase activity can be directly measured. To date molecular testing is limited to the detection of mutations in the phosphotransferase gamma subunit (129).

Mucolipidosis IV

Mucolipidosis IV is an autosomal-recessive neurodegenerative disease characterized by ophthalmologic and neurologic abnormalities. On the basis of electron microscopic evidence of membrane-bound storage material, it was first considered to be a mucolipidosis. Recent evidence indicates that type IV is caused by mutations in the mucolipin gene, which encodes a novel transient receptor potential (TRP) channel (130, 131). The TRP family of channel proteins are implicated in a variety of cellular functions, including calcium entry into epithelial cells, stabilization of membranes, and transport of lipids to lysosomes.

Affected individuals present in infancy with hypotonia, developmental delay, and corneal epithelial haze. More than 80% are Ashkenazi Jews. Brain MRI scans show a dysplastic corpus callosum and white matter demyelination early, and cerebellar atrophy later. All patients have constitutive achlorhydria with elevated serum gastrin levels. Delay in establishing the diagnosis is related to the nonspecificity of the clinical findings (132,133).

Bilateral corneal clouding and strabismus often bring these children to an ophthalmologist in the first year of life. Fundus examination reveals optic nerve pallor, retinal vascular attenuation, and retinal pigmentary abnormalities that progress with increasing age (134,135). Pradhan and colleagues (136) documented progressive amplitude reduction for the photopic and scotopic ERG, suggesting a rodcone dystrophy. The scotopic ERG is electronegative at the highest stimulus intensity (137). Progressive corneal opacification can contribute to visual loss. Keratoplasty fails to correct the problem as the corneal opacification recurs when the epithelium of the donor graft is replaced by host stem cells. Nystagmus and cataract (posterior subcapsular and nuclear) have been noted in a minority of patients (135). Histopathologic studies of conjunctiva obtained by biopsy or topical swab show characteristic lysosomal inclusions on microscopy.

Carbohydrate-Deficient Glycoprotein Syndromes

The carbohydrate-deficient glycoprotein syndromes include a heterogeneous group of genetic disorders characterized by defective addition of oligosaccharides to the asparagine moiety of glycoproteins. These N-linked glycoconjugates are an important feature of various serum transport proteins (apolipoprotein B, transferrin) hormones (thyroid-stimulating hormone), lysosomal enzymes, and circulating proteins (immunoglobulin G). As a result of the large number of potentially defective proteins, affected individuals have multisystem disease, and there are multiple phenotypes (137).

Type 1A, due to a deficiency of phosphomannomutase, is the most common form (138). Infants typically present with axial hypotonia, hyporeflexia, and abnormal eye movements, probably related to cerebellar hypoplasia (139,140). Later psychomotor retardation, stroke, microcephaly, retinal dystrophy, and stroke-like episodes (50%) become more apparent. Although pigmentary retinopathy is found only in some patients, full-field ERG demonstrates abnormalities in all patients (141). The rod response is severely reduced or extinguished; the cone response is variably reduced and delayed. Older children can present with ataxia, mental retardation, and skeletal deformities. Additional signs are unusual distribution of subcutaneous fat, inverted nipples, and growth delay. Cerebellar hypoplasia is a prominent feature. Diagnosis is usually confirmed by isoelectric focusing of transferrin with demonstration of charge and mass changes.

DISORDERS OF PEROXISOMES

Peroxisomes are membrane-bound organelles that are found in virtually all eukaryotic cells and catalyze a variety of anabolic and catabolic functions. These functions include the biosynthesis of plasmalogens and bile acids, and a- and ß-oxidation of long-chain fatty acids and related compounds. Disorders of peroxisomes are divided into defects of organelle assembly that are associated with multiple enzyme deficiencies or defects of single enzymes (142). Recent studies have identified a family of matrix and membrane peroxin proteins that are involved in the biogenesis of peroxisomes. To date, mutations in 11 different PEX genes have been characterized in humans (143). Defects in the importation of peroxisomal proteins lead to metabolic disturbances and excessive accumulation of substrates that are responsible for the clinical manifestations. A mutation in PEX1 is found in 65% of patients with peroxisomal biogenesis disorders (PBD) (144). Inheritance is autosomal recessive. Despite their genotypic diversity, PBDs share the following clinical characteristics: facial dysmorphism (large fontanel, shallow orbits, low or broad nasal bridge, anteverted nostrils), psychomotor retardation, hypotonia, hearing loss, and retinal degeneration (Fig. 23.8).

Cerebrohepatorenal Syndrome of Zellweger

Zellweger syndrome is the most severe phenotype, characterized by facial dysmorphism (Fig. 23.18), severe hypotonia, neonatal seizures, neuronal migration defects, and hepatomegaly. Brain MRI scans demonstrate cortical dysplasia, neuronal heterotopia, and dysmyelination with early loss of cerebellar white matter. Most infants die before 1 year of age. Histopathology reveals the absence of peroxisomes, along with the presence of small (microgyria) and thickened (pachygyria) cerebral convolutions and multiple renal cysts. Biochemical abnormalities include reduced levels of plasmalogens, defective oxidation, and accumulation

of very long-chain fatty acids (VLCFA) and phytanic acid, and accumulation of bile and its intermediates (142).

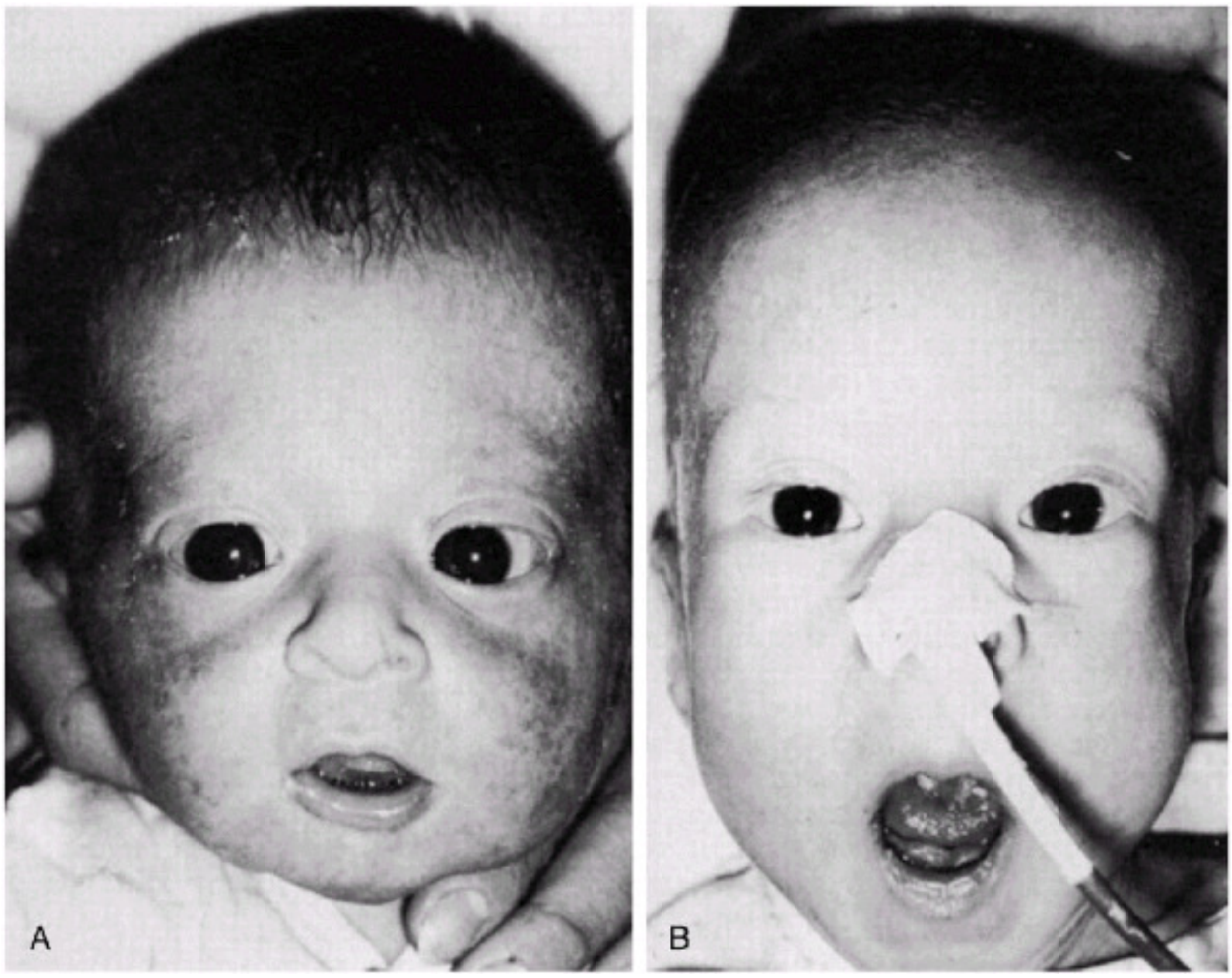


Figure 23.18 A and **B:** Two infants with Zellweger cerebrohepatorenal syndrome, showing characteristic high forehead, shallow orbits, and broad nasal bridge.

Ocular involvement is common (145,146). Abnormalities of the anterior segment include corneal clouding, cataract, congenital glaucoma, and Brushfield spots (Fig. 23.19). In the posterior segment, there can be a dysplastic or atrophic optic disc and disturbance of retinal pigmentation (147). The ERG is extinguished, but the striking clinical features distinguish Zellweger syndrome from Leber congenital amaurosis and other early-onset retinal dystrophies.

Infantile Refsum Disease

Infantile Refsum disease is the mildest phenotype among the peroxisomal biogenesis disorders. The concurrence of sensorineural deafness, pigmentary degeneration of the retina, and elevated phytanic acid are the hallmarks of this disorder (142). It is distinguished from adult Refsum disease by the presence of facial dysmorphism, mental retardation, hepatomegaly, and severe reduction of peroxisomes. The levels of phytanic acid and VLCFA are increased, and other peroxisomal metabolites are elevated. All patients develop retinal degeneration. The fundus can be normal or with early-onset involvement, there can be visual loss, congenital nystagmus, pigmentary mottling of the macula, and optic disc pallor. The ERG demonstrates severe reduction of the rod- and cone-mediated responses (148). Because of the relatively mild systemic involvement, the ophthalmologist plays an important role in making the diagnosis.

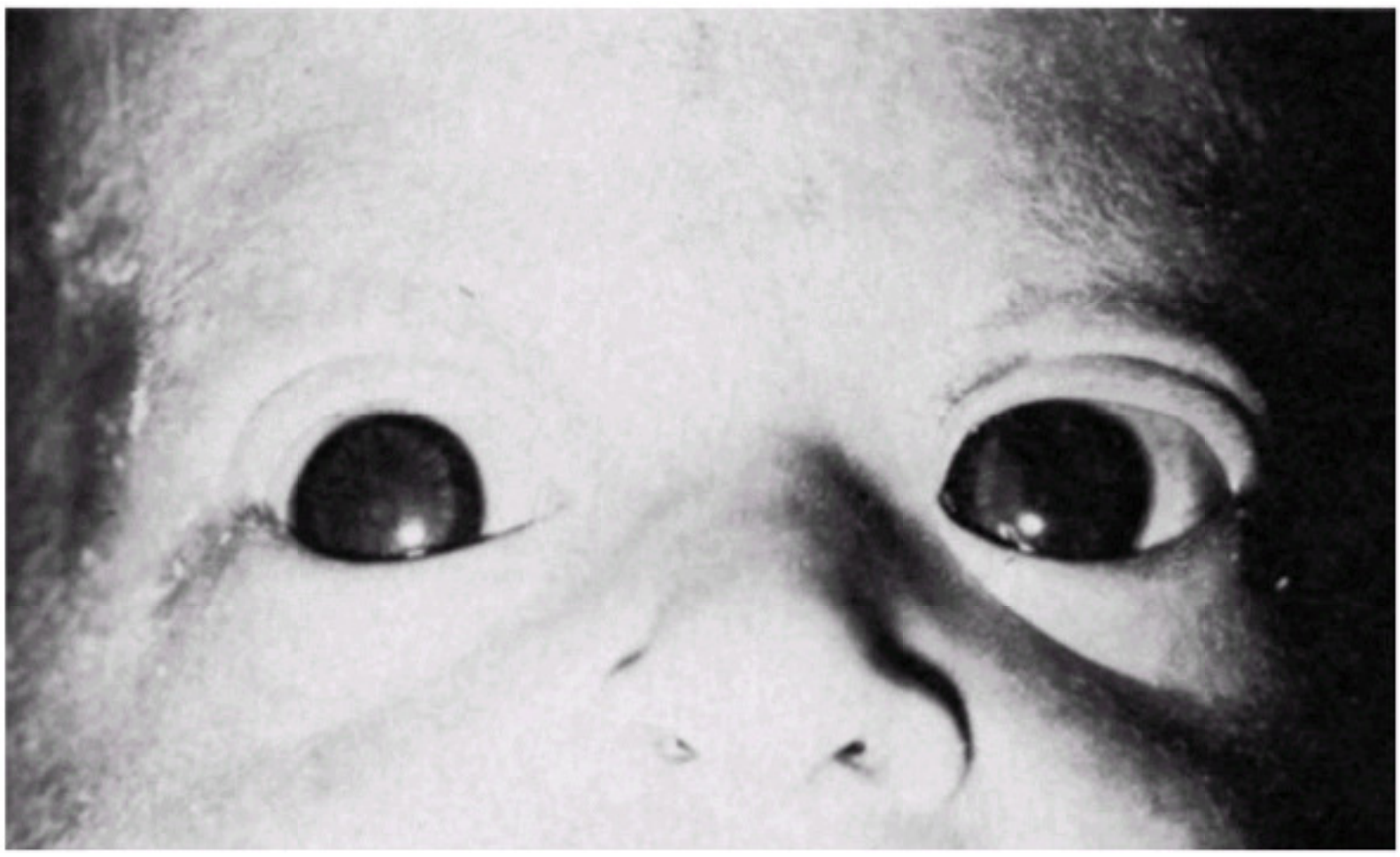


Figure 23.19 Infant with Zellweger syndrome and bilateral congenital cataracts. A full surgical iridectomy is present superiorly in the left eye.

Adrenoleukodystrophy

The term adrenoleukodystrophy is used to describe two genetically distinct diseases characterized by CNS demyelination, adrenal insufficiency, and abnormally high levels of VLCFA in tissues and body fluids (149,150). The X-linked type has normal-appearing peroxisomes, but there is impaired function of VLCFA coenzyme A (CoA) ligase. This protein is a member of the ABC transmembrane transporter protein superfamily and possibly transports VLCFA into peroxisomes (151). Clinically, there are three distinct phenotypes: cerebral (35% to 40%), adrenomyeloneuropathy (30% to 35%), and isolated Addison disease (152).

The cerebral form of X-linked adrenoleukodystrophy has its onset between 4 and 8 years of age. Early development is normal, and behavioral changes and difficulties performing in school are the most common initial symptoms.

Then there is progressive neurologic deterioration leading to a vegetative state within 6 months to 10 years. More than 90% of patients have clinical or biochemical evidence of adrenal insufficiency. Brain CT or MRI scans demonstrate progressive demyelination of the periventricular white matter in the posterior parietal and occipital regions. The diagnosis is confirmed by the detection of abnormally high levels of VLCFA in plasma, red cells, and fibroblasts (150). Treatment consists of adrenal hormone replacement, bone marrow transplantation for early-onset disease, and Lorenzo's oil (glyceryl trioleate-trierucate).

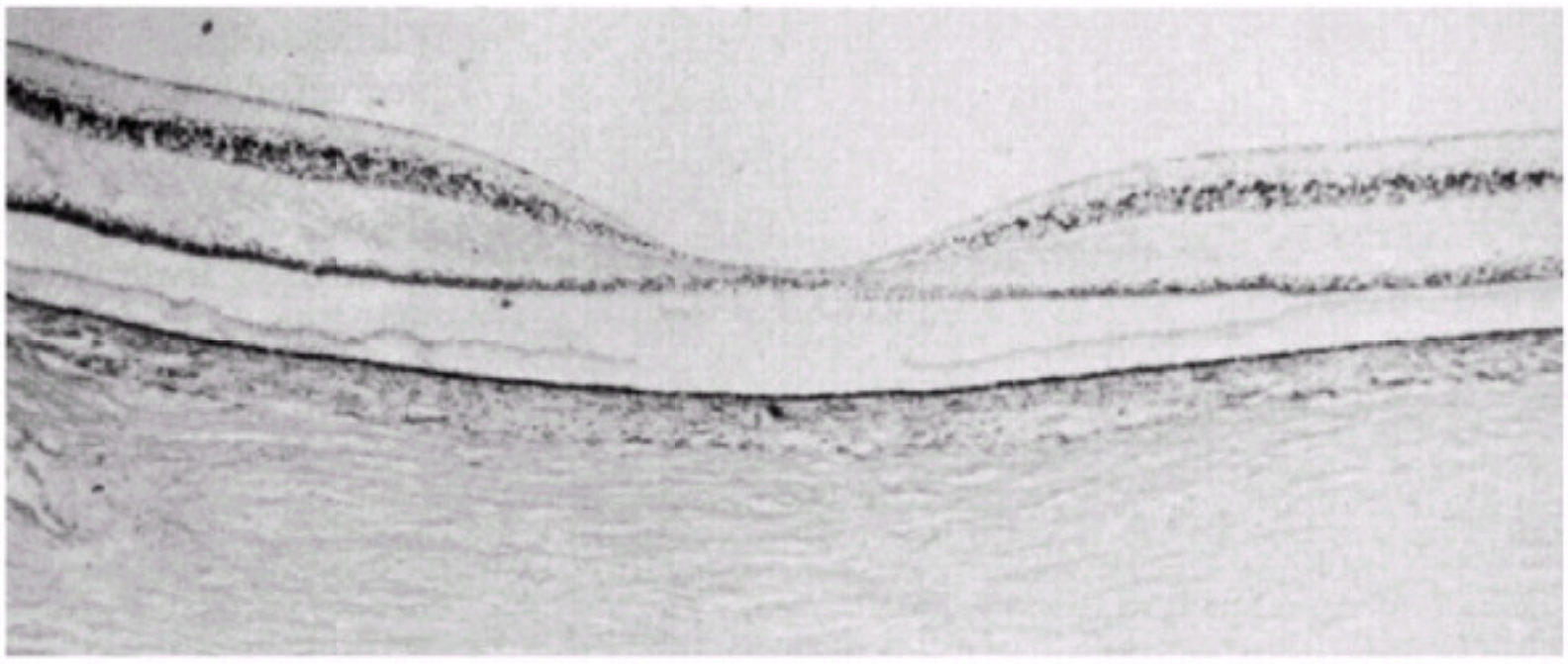


Figure 23.20 Section of the retinal fovea in a patient with childhood adrenoleukodystrophy, showing loss of ganglion cells; the bipolar and photoreceptor layers are intact (×60).

Ocular abnormalities become evident 6 months to 6 years after the onset of systemic involvement (152). Visual acuity may initially be 20/20 but can rapidly deteriorate to no light perception. Although the fundi are frequently normal in appearance, most patients later develop optic atrophy, and some show pigmentary

mottling of the macula and midperipheral retina (Fig. 23.20). Ocular histopathology shows marked degeneration of photoreceptor cells, including the macula (153). Visual field defects vary with the severity of optic nerve and posterior visual pathway involvement. Strabismus is common, and acquired pendular nystagmus has been reported (154).

The second type of adrenoleukodystrophy is one of the peroxisomal biogenesis disorders in which the number and size of peroxisomes are diminished, the function of multiple peroxisomal enzymes is impaired, and inheritance is autosomal recessive. Affected individuals present in infancy with hypotonia, failure to thrive, and seizures. Dysmorphic facial features may or may not be present. Later psychomotor delay and blindness, secondary to progressive optic atrophy, become evident. Additional ocular findings include focal pigmentary disturbances in the peripheral retina and visible clumps of macrophages in the vitreous. The clinical course varies from early death to survival into the midteens. The diagnosis is confirmed by showing absence of hepatic peroxisomes, reduced plasmalogen levels, and increased plasma levels of VLCFA and other peroxisomal metabolites.

Refsum Disease

Refsum disease is a rare autosomal-recessive disorder caused by a defect in the a-oxidation of phytanic acid (155). Most patients have a mutation of phytanoyl-CoA hydroxylase, a peroxisomal protein catalyzing the first step in a-oxidation (156). A subset of patients have mutations in PEX7, which is required for targeting to the peroxisome (157). In homozygotes, phytanic acid accumulates to high levels accounting for 5% to 30% of the total plasma lipids, compared with 0.3% in normal individuals. Heterozygotes have intermediate levels and are largely asymptomatic. It is believed that accumulation of phytanic acid leads to its incorporation into lipid membranes, displacing normal straight-chain fatty acids. Incorporation of this multiplebranched molecule may distort membrane structure and impair cellular function. Clinically, there are four cardinal features—retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, and elevated CSF protein. Additional systemic manifestations can include deafness, ichthyosis, epiphyseal dysplasia, and cardiomyopathy. Although the onset of disease may occur between the first and fifth decade, most patients have symptoms by 20 years of age (158).

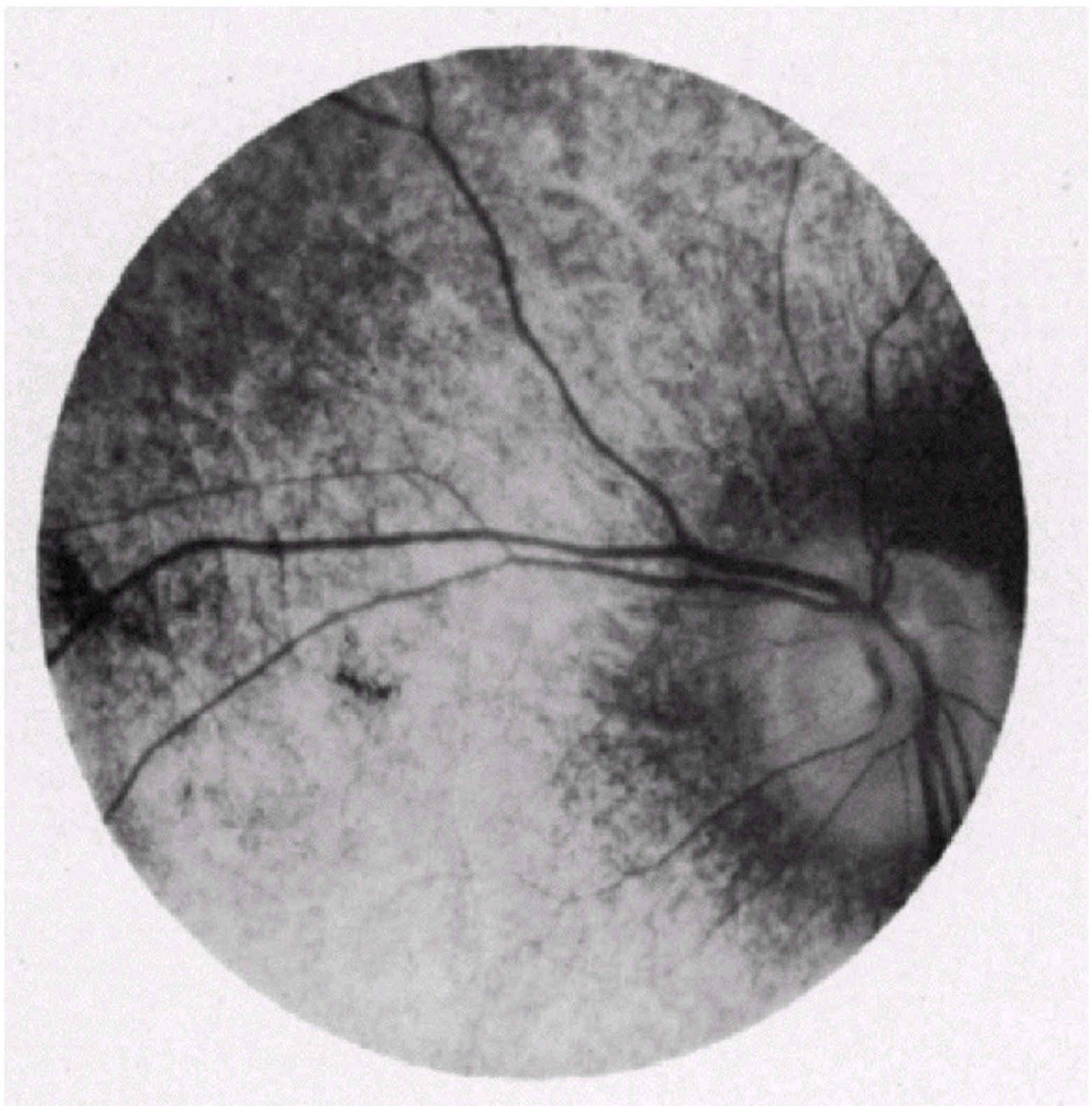
All patients have retinitis pigmentosa with visual field loss that begins in the midperiphery and marches centrally and peripherally, leaving a central island of intact vision (158,159). Nystagmus, secondary to cerebellar involvement, can develop in Refsum disease, unlike patients with typical retinitis pigmentosa. Ophthalmoscopy reveals a diffuse pigmentary retinopathy and attenuation of retinal vessel caliber early in the disease and secondary optic atrophy in later stages (Fig. 23.21). The ERG shows predominant loss of rod function. Pupillary miosis and poor pupillary dilation have been repeatedly noted (159). Cataracts, typically posterior subcapsular, develop in midlife. Treatment is elimination of phytanic acid and its precursor, phytol, from the diet (158,160,161). The basis for this successful therapy is that phytanic acid is exclusively of exogenous origin (dairy products) and not endogenously synthesized. Dietary compliance can prevent progressive visual loss but does not restore visual deficits already incurred.

DISORDERS OF COPPER METABOLISM

Wilson Disease

Wilson disease is an autosomal-recessive disorder caused by a genetic defect of the copper ATP transporter (ATP7B),

which plays a role in copper distribution in the liver, brain, and kidney (162). Recent evidence indicates that a copper chaperone (Atox1) first transfers copper from the cytosol to ATP7B through protein-protein interactions. Then the copper-transport protein delivers the metal to the secretory pathway for incorporation into copper-dependent enzymes or to the membrane for exportation from the cell. Mutations of the protein lead to a deficiency of copper-dependent enzymes, like ceruloplasmin, and to excretion into bile (163,164). Copper accumulates to toxic levels in liver, brain, and other tissues, where it presumably stimulates the production of reactive oxygen species and disrupts cell metabolism.



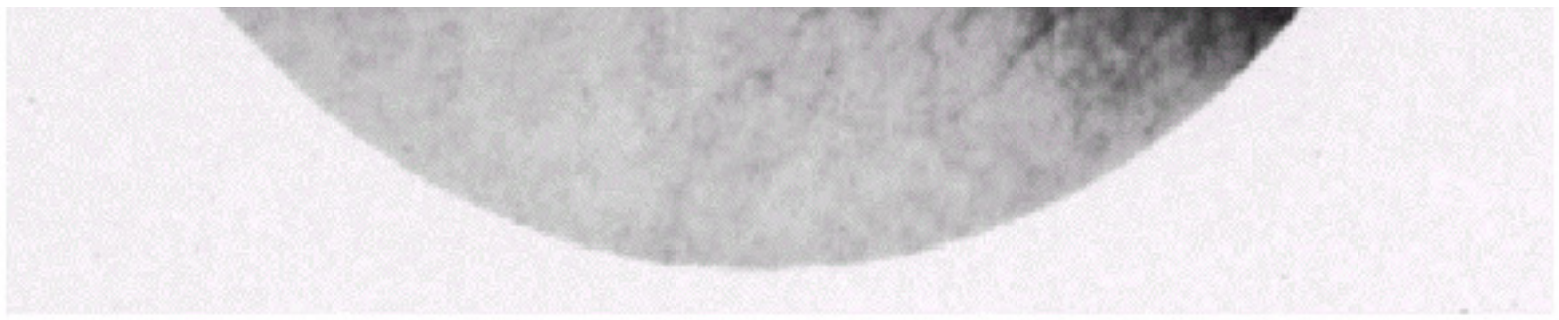


Figure 23.21 Pigmentary retinopathy in a patient with Refsum disease. Note the narrow retinal vessels.

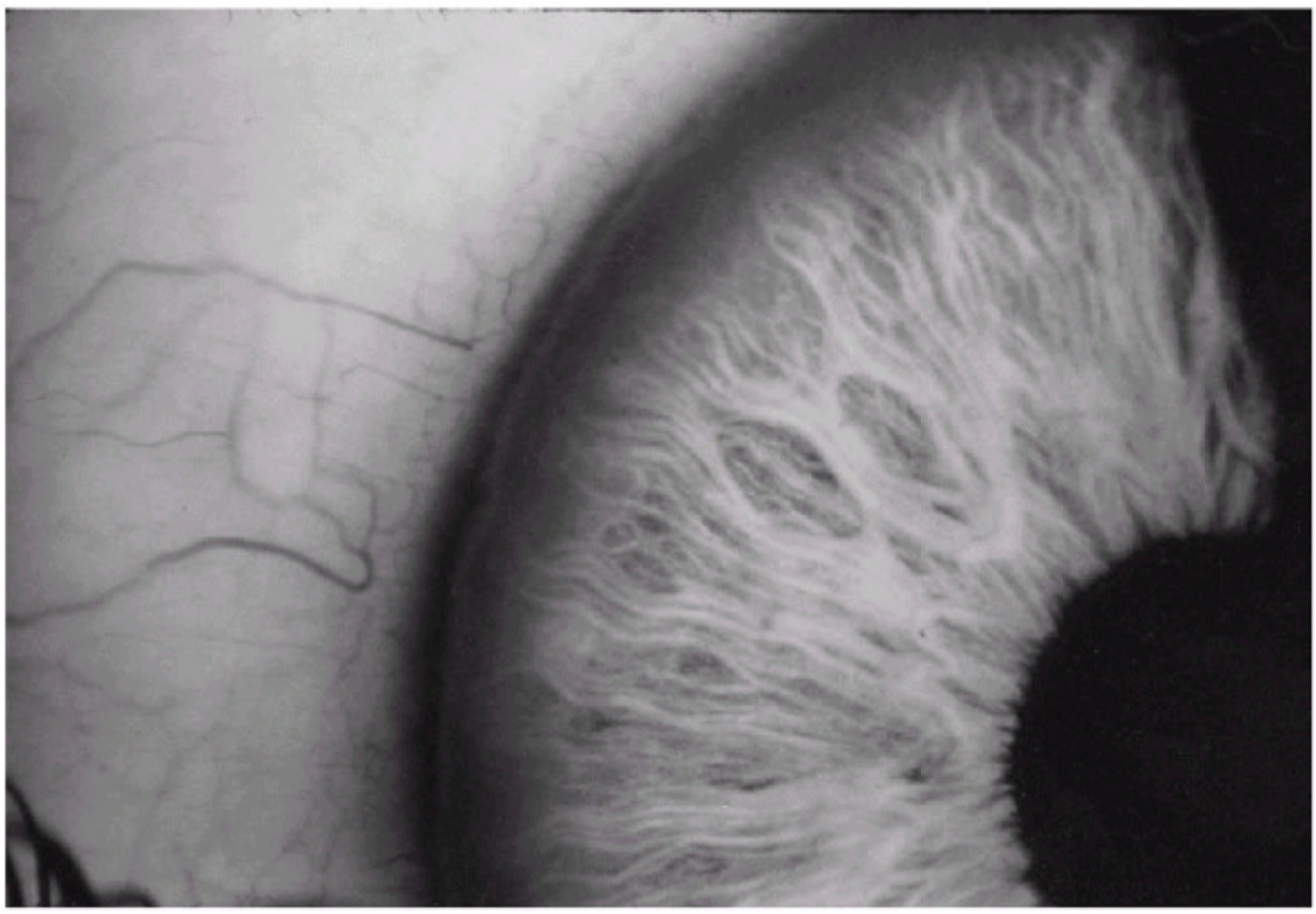


Figure 23.22 Slit-lamp photograph of the cornea reveals prominent Kayser-Fleischer ring in a patient with Wilson disease.

Patients with Wilson disease present with liver disease, neurologic signs, or both (165). Liver involvement may develop at any age beyond 6 years and can be mild or fulminant, rapidly progressing to hepatic failure and death. Of particular importance, Wilson disease is the most common cause of chronic or recurrent liver disease in childhood. Neurologic signs are unusual before 12 years of age. Dysarthria, incoordination of voluntary movements, tremor, and choreoathetosis are early extrapyramidal signs of neurologic involvement. Deterioration in intellectual function and behavioral disturbances are usually late manifestations. Brain MRI scans reveal cortical and subcortical signal abnormalities, especially in the basal ganglia. Additional extrahepatic manifestations include hemolytic anemia, joint disease, and defects of renal tubular acidification.

The Kayser-Fleischer ring is the most important ophthalmologic sign in Wilson disease (165). It is a green-to-brown granular deposit located within the Descemet membrane at the corneal periphery (Fig. 23.22). It first appears at the superior and inferior limbus but then progresses to involve the entire circumference of the cornea. In advanced cases, the ring can be seen on gross inspection but is best seen with slit-lamp examination in its early stage. The Kayser-Fleischer ring is present in nearly 100% of patients with neurologic disease and in 70% to 95% of patients with liver disease. Although the Kayser-Fleischer ring is considered to be pathognomonic of Wilson disease, it occurs in primary biliary cirrhosis and other chronic liver diseases.

Cataract is another ocular manifestation of Wilson disease (165). Copper accumulates in a spoke-like pattern on the anterior lens capsule, in a pattern resembling a sunflower (Fig. 23.23). The sunflower cataract is present in only 10% to 20% of patients with Wilson disease and does not affect vision.

Neurologic involvement in Wilson disease largely spares the ocular motor system. Versions are normal and pathologic nystagmus is not observed. Electrooculographic recordings have demonstrated slow saccades and pursuits with reduced gain (166, 167). Additionally, loss of accommodation

and accommodative convergence interferes with near vision and can be very problematic (168). MRI scans demonstrate abnormalities in the midbrain, where the neural centers for accommodation and convergence are located (169).

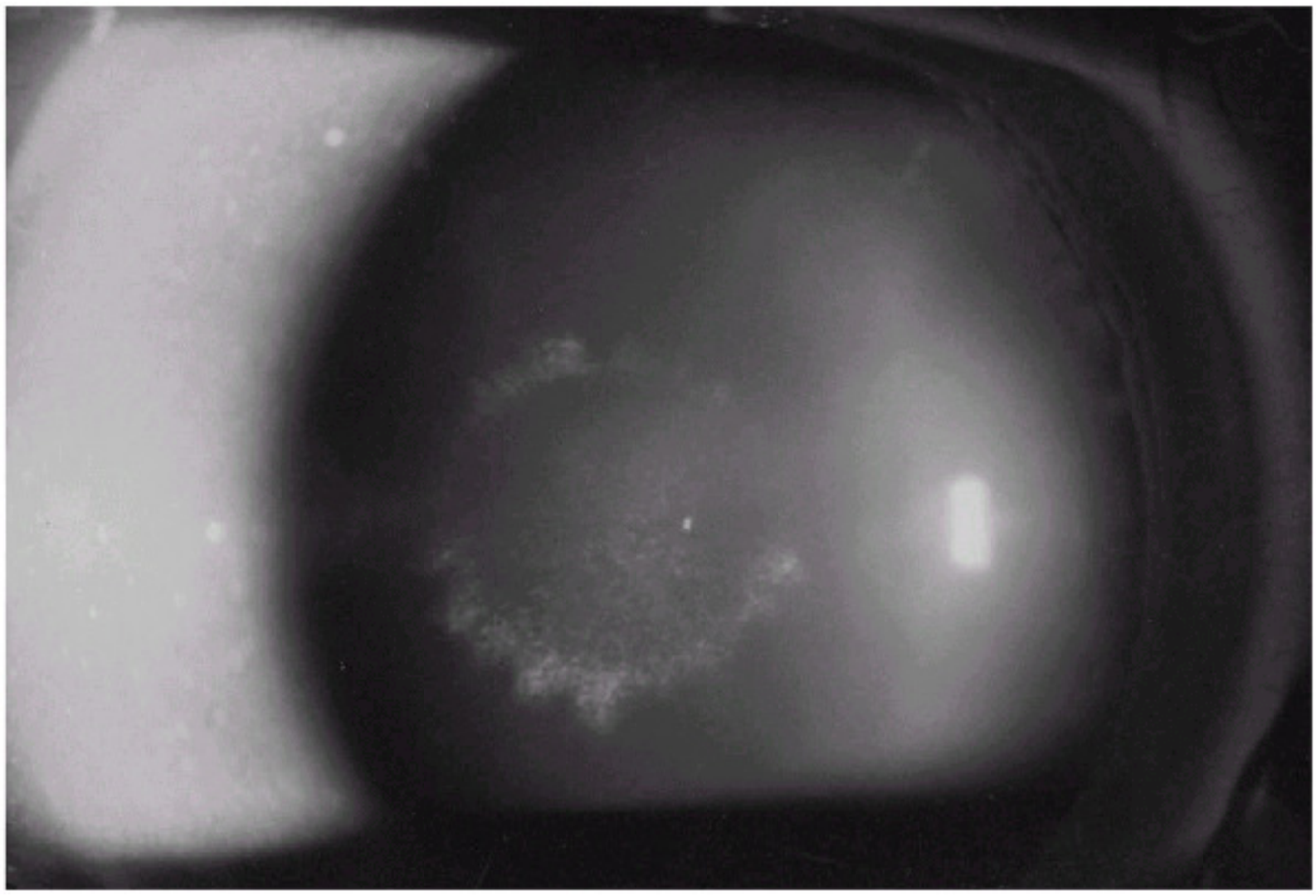


Figure 23.23 Slit-lamp photograph shows a “sunflower cataract” in Wilson disease.

Laboratory studies are necessary to confirm the diagnosis. Serum copper and ceruloplasmin levels are low, whereas urinary copper excretion is high. The observed levels, however, are variable, especially in younger patients with hepatic disease. Therefore, liver biopsy is the most reliable method for documenting increased copper accumulation.

Treatment is directed at reducing tissue stores of copper using copper chelators. Penicillamine has been the copper chelator of choice, but long-term follow-up shows neurologic deterioration in 50% of patients. Preliminary evidence indicates that tetrathiomolybdate, an alternative copper chelator, is associated with a lower incidence of neurologic deterioration (170). Liver transplant is well tolerated in patients with end-stage liver disease (165).

Menkes (Steely-Hair) Syndrome

Menkes syndrome is an X-linked recessive disorder of intracellular transport of copper due to mutations in the ATP7A gene (171). Absorption of copper is normal, but defective transport from the cytosol into the trans-Golgi network leads to reduced activity of copper-dependent enzymes, such as cytochrome oxidase, superoxide dismutase, tyrosinase, and lysyl oxidase (165). Deficiency of each of these enzymes is associated with specific clinical manifestations. The encoded protein also mediates translocation of copper from the Golgi to the plasma membrane, facilitating copper efflux. Therefore, mutations of ATP7A also lead to toxic intracellular accumulation of copper and low serum levels of copper and ceruloplasmin.

Although infants are normal at birth, failure to thrive, seizures, and rapid neurologic deterioration dominate the clinical picture by 3 months of age (165,172). The presence of sparse “kinky” hair, generalized hypopigmentation (due to tyrosinase deficiency), and pudgy cheeks are characteristic. Most infants die by 1 year from progressive neurologic deterioration or cerebrovascular events (165,173). Histopathologic studies of the brain reveal focal neuronal loss and reactive gliosis in the cerebral cortex and cerebellum, thought to be related to increased vulnerability to free-radical injury (due to superoxide dismutase deficiency) and reduced metabolic capacity (due to cytochrome oxidase deficiency). Arterial vessels are tortuous with regions of abnormal narrowing and dilation resulting from defective elastic lamina, probably due to defective collagen crosslinking by lysyl oxidase (165). Microscopically, hair shafts are twisted (pili torti) and fragmented (trichorrhexis nodosa), and vary in diameter (monilethrix). Ocular abnormalities are common in Menkes disease (173). Visual acuity can be subnormal for age despite a normal-appearing optic nerve and retina (except for peripheral hypopigmentation). Flash VEPs were normal in 50% of affected infants with reduced vision, implicating delays in visual maturation. Longitudinal studies in one infant showed a progressive decrease in the amplitude of the ERG (predominantly the b-wave) and VEP. Furthermore, the presence of optic atrophy in some patients, histopathologic evidence of ganglion cell loss, and progressive ERG reductions suggest a retinal or optic nerve basis, whereas the progressive neurodegeneration and reduced VEPs in other patients suggest a cortical basis (174,175,176). An increased prevalence of strabismus and gaze-evoked and rotary nystagmus are likely related to CNS involvement. Additional findings include myopia, ptosis with miosis (attributable to deficiency of dopamine-beta-hydroxylase), aberrant eyelash orientation, blue irides, and iris transillumination (174).

The diagnosis is usually based on the detection of low serum copper and ceruloplasmin levels. Documentation of increased copper content in intestinal mucosa and other tissues helps to confirm the diagnosis. Treatment is limited

to the parenteral administration of copper, which raises serum copper levels but does not prevent the cerebral or retinal degeneration (165).

REFERENCES

1. King RA, Hearing VJ, Creel DJ, et al. Albinism. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular bases of inherited disease*, 8th ed. New York: McGraw-Hill, 2001: 5587-5627.

2. Rinchik EM, Bultman SJ, Horsthemke B, et al. A gene for the mouse pink-eyed dilution locus and for human type II oculocutaneous albinism. *Nature* 1993;361:72-76.

3. Huizing M, Gahl WA. Disorders of vesicles of lysosomal lineage: the Hermansky-Pudlak syndromes. *Curr Mol Med* 2002;2: 451-467.

4. Creel DJ, Summers CG, King RA. Visual anomalies associated with albinism. *Ophthalmic Paediatr Genet* 1990;11:193-200.

5. King RA, Townsend D, Oetting W, et al. Temperature-sensitive tyrosinase associated with peripheral pigmentation in oculocutaneous albinism. *J Clin Invest* 1991;87:1046-1053.

6. King RA, Wiesner GL, Townsend D, et al. Hypopigmentation in Angelman syndrome. *Am J Med Genet* 1993;46:40-44.

7. Horsthemke B, Dittrich B, Buiting K. Imprinting mutations on human chromosome 15. *Hum Mutat* 1997;10:329-337.

8. Schiaffino MV, d'Addio M, Alloni A, et al. Ocular albinism: evidence for a defect in an intracellular signal transduction system. *Nat Genet* 1999;23:108-112.

9. Morell R, Spritz RA, Ho L, et al. Apparent digenic inheritance of Waardenburg syndrome type 2 (WS2) and autosomal recessive ocular albinism (AROA). *Hum Mol Genet* 1997;6:659-664.

10. Gahl WA, Brantly M, Kaiser-Kupfer MI, et al. Genetic defects and clinical characteristics of patients with a form of oculocutaneous albinism (Hermansky-Pudlak syndrome). *N Engl J Med* 1998; 338:1258-1264.

11. Anderson PD, Huizing M, Claassen DA, et al. Hermansky-Pudlak syndrome type 4 (HPS-4): clinical and molecular characteristics. *Hum Genet* 2003;113:10-17.

12. Bonifacino JS, Gahl WA. A new variant of Hermansky-Pudlak syndrome due to mutations in a gene responsible for vesicle formation. *Am J Med* 2000;108:423-427.

13. Fernandez-Canon JM, Granadino B, Beltran-Valero de Bernabe D, et al. The molecular basis of alkaptonuria. *Nat Genet* 1996; 14:19-24.

14. Kampik A, Sani JN, Green WR. Ocular ochronosis: clinicopathological, histochemical and ultrastructural studies. *Arch Ophthalmol* 1980;98:1441-1447.

15. Phornphutkul C, Introne WJ, Perry MB, et al. Natural history of alkaptonuria. *N Engl J Med* 2002;347:2111-2121.

16. Gahl WA, Thoene JG, Schneider JA. Cystinosis: a disorder of lysosomal membrane transport. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:5085-5108.

17. Town M, Jean G, Cherqui S, et al. A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. *Nat Genet* 1998;18:319-324.

18. Forestier L, Jean G, Attard M, et al. Molecular characterization of CTNS deletions in nephropathic cystinosis: development of a PCR-based detection assay. *Am J Hum Genet* 1999;65:353-359.

19. Theodoropoulos DS, Krasnewich D, Kaiser-Kupfer MI, et al. Classic nephropathic cystinosis as an adult disease. *JAMA* 1993;270: 2200-2204.

20. Gahl WA, Thoene JG, Schneider JA. Cystinosis. *N Engl J Med* 2002;347:111-121.

21. Katz B, Melles RB, Schneider JA. Corneal sensitivity in nephropathic cystinosis. *Am J Ophthalmol* 1987;104:413-416.

22. Kaiser-Kupfer MI, Caruso RC, Minkler DS, et al. Long-term ocular manifestations in nephropathic cystinosis. *Arch Ophthalmol* 1986;104:706-711.

23. DaSilva VA, Zurbrugg RP, Lavanchy B, et al. Long-term treatment of infantile nephropathic cystinosis with cysteamine. *N Engl J Med* 1985;313:1460-1464.

24. Gahl WA, Reed GF, Thoene JG, et al. Cysteamine therapy for children with nephropathic cystinosis. *N Engl J Med* 1987;316: 971-977.

25. Kaiser-Kupfer MI, Fujikawa L, Kuwabara T, et al. Removal of corneal crystals by topical cysteamine in nephropathic cystinosis. *N Engl J Med* 1987;316:775-779.

26. Valle D, Simell O. The hyperornithinemias. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 7th ed. New York: McGraw-Hill, 1995: 1147-1185.

27. Kaiser-Kupfer M, Ludwig D, DeMonasterio R, et al. Gyrate atrophy of the choroid and retina: early findings. *Ophthalmology* 1985;92:394-401.

28. Weleber R, Kennaway N. Clinical trial of vitamin B, for gyrate atrophy of the choroid and retina. *Ophthalmology* 1981;88: 316-324.

29. Hayasaka S, Saito T, Nakagima H, et al. Clinical trials of vitamin B, and protein supplementation for gyrate atrophy of the choroid and retina. *Br J*

Ophthalmol 1985;69:283-290.

30. Vannas-Sulonen K, Sipila I, Vannas A, et al. Gyrate atrophy of the choroid and retina. A five-year follow-up of creatine supplementation. *Ophthalmology* 1985;92:1719-1727.

31. Kaiser-Kupfer M, Caruso R, Valle D. Gyrate atrophy of the choroid and retina: chronic reduction of ornithine slows retinal degeneration. *Arch Ophthalmol* 1991;109:1539-1548.

32. Valle D, Walser M, Brusilow S, et al. Gyrate atrophy of the choroid and retina: amino acid metabolism and correction of hyperornithinemia with an arginine-restricted diet. *J Clin Invest* 1980; 65:371-378.

33. Vannas-Sulonen K, Simell O, Spilia I. Gyrate atrophy of the choroid and retina: the ocular disease progresses in juvenile patients despite normal or near normal plasma ornithine concentration. *Ophthalmology* 1987;94:1428-1433.

34. Purdue PE, Lumb MJ, Fox M, et al. Characterization and chromosomal mapping of a genomic clone encoding human alanine: glyoxylate aminotransferase. *Genomics* 1991;10:34-42.

35. Cramer SD, Ferree PM, Lin K, et al. The gene encoding hydroxypyruvate reductase (GRHPR) is mutated in patients with primary hyperoxaluria type II. *Hum Mol Genet* 1999;8:2063-2069.

36. Meredith TA, Wright JD, Gammon JA, et al. Ocular involvement in primary hyperoxaluria. *Arch Ophthalmol* 1984;102:584-587.

37. Small KW, Letson R, Scheinman J. Ocular findings in primary hyperoxaluria. *Arch Ophthalmol* 1990;108:89-93.

38. Hoppe B, Langman CB. A United States survey on diagnosis, treatment, and outcome of primary hyperoxaluria. *Pediatr Nephrol* 2003;18:986-991.

39. Stambolian D, Ai Y, Sidjanin D, et al. Cloning of the galactokinase cDNA and identification of mutations in two families with cataracts. *Nat Genet* 1995;10:307-312.

40. Maceratesi P, Daude N, Dallapiccola B, et al. Human UDP-galactose 4' epimerase (GALE) gene and identification of five missense mutations in patients with epimerase-deficiency galactosemia. *Mol Genet Metab* 1998;63:26-30.

41. Tyfield L, Reichardt J, Fridovich-Keil J, et al. Classical galactosemia and mutations at the galactose-1-phosphate uridyl transferase (GALT) gene. *Hum Mutat* 1999;13:417-430.

42. Holton JB, Walter JH, Tyfield LA. Galactosemia. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. McGraw-Hill: New York, 2001: 1553-1588.

43. Stambolian, D. Galactose and cataract. *Surv Ophthalmol* 1988; 32:333-349.

44. Waggoner DD, Buist NBM, Donnell GV. Long-term prognosis in galactosemia: results of a survey of 350 cases. *J Inherit Metab Dis* 1990;13:802-815.

45. Bosch AM, Bakker HD, van Gennip AH, et al. Clinical features of galactokinase deficiency: a review of the literature. *J Inherit Metab Dis* 2002;25:629-634.

46. Gitzelmann R. Hereditary galactokinase deficiency, a newly recognized cause of juvenile cataracts. *Pediatr Res* 1967;1:14-23.

47. Sardharwalla IB, Wraith JE, Bridge C, et al. A patient with severe type epimerase deficiency galactosemia. *J Inherit Metab Dis* 1988; 11:249-251.

48. Goldstein JL, Hobbs HH, Brown MS. Familiar hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:2863-2913.

49. Berge KE, Tian H, Graf GA, et al. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science* 2000;290:1771-1775.

50. Lee MH, Lu K, Hazard S, et al. Identification of a gene, *ABCG5*, important in the regulation of dietary cholesterol absorption. *Nat Genet* 2001;27:79-83.

51. Kane JP, Havel RJ. Disorders of the biogenesis and secretion of lipoproteins containing the B lipoproteins. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. McGraw-Hill: New York, 2001: 2717-2752.

52. Garcia CK, Wilund K, Arca M, et al. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. *Science* 2001;292:1394-1398.

53. Fredrickson DS, Levy RL. Familiar hyperlipoproteinemia. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. *The metabolic basis of inherited*

disease, 3rd ed. New York: McGraw-Hill, 1972: 545.

54. Macaraeg PVJ Jr, Lasagna L, Snyder B. Arcus not so senilis. *Ann Intern Med* 1968;68:345-354.

55. Oram JF. Molecular basis of cholesterol homeostasis: lessons from Tangier disease and ABCA1. *Trends Mol Med* 2002;8: 168-173.

56. Francis GA, Knopp RH, Oram JF. Defective removal of cellular cholesterol and phospholipids by apolipoprotein A-I in Tangier Disease. *J Clin Invest* 1995;96:78-87.

57. Brooks-Wilson A, Marcil M, Clee SM, et al. Mutations in *ABC1* in Tangier disease and familial high-density lipoprotein deficiency. *Nat Genet* 1999;22:336-345.

58. Assman G, von Eckardstein A, Brewer HB Jr. Familial high-density lipoprotein deficiency: Tangier disease. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 7th ed. New York: McGraw-Hill, 1995: 2053-2072.

59. Chu FC, Kuwabara T, Cogan DG. Ocular manifestations of familiar high-density lipoprotein deficiency (Tangier disease). *Arch Ophthalmol* 1979;97:1926-1928.

60. Pressley TA, Scott WJ, Ide CH, et al. Ocular complications of Tangier disease. *Am J Med* 1987;83:991-994.

61. Wetterau JR, Aggerbeck LP, Bouma ME, et al. Absence of microsomal triglyceride transfer protein in individuals with abetalipoproteinemia. *Science* 1992;258:999-1001.

62. Sharp D, Blinderman L, Combs KA, et al. Cloning and gene defects in microsomal triglyceride transfer protein associated with abetalipoproteinaemia. *Nature* 1993;365:65-69.

63. Muller DPR, Lloyd JK. Effect of large oral doses of vitamin E on the neurologic sequelae of patients with abetalipoproteinemia. *Ann N Y Acad Sci* 1982;393:133-144.

64. Runge P, Muller DPR, McAllister J, et al. Oral vitamin E supplements can prevent the retinopathy of abetalipoproteinemia. *Br J Ophthalmol* 1986;70:166-173.

65. Dieckert JP, White M, Christmann L, et al. Angioid streaks associated with abetalipoproteinemia. *Ann Ophthalmol* 1989;21: 173-175.

66. Yee RD, Cogan DG, Zee DS. Ophthalmoplegia and dissociated nystagmus in abetalipoproteinemia. *Arch Ophthalmol* 1976;99: 571-575.

67. Cohen DA, Bosley TA, Savino PJ, et al. Primary aberrant regeneration of the oculomotor nerve. *Arch Neurol* 1985;42:821-823.

68. Santamarina-Fojo S, Hoeg JM, Assman G, et al. Lecithin cholesterol acyltransferase deficiency and fish eye disease. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001: 2817-2833.

69. Bethel W, McCulloch C, Ghash M. Lecithin cholesterol acyltransferase deficiency: light and electron microscopic findings from two corneas. *Can J Ophthalmol* 1975;10:494-501.

70. Carlson CA, Philipson B. Fish-eye disease: A new familial condition with massive corneal opacities and dyslipoproteinemia. *Lancet* 1979;2:921-922.

71. Gravel RA, Kaback MM, Proia RL, et al. The G_{M2} gangliosidoses. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:3827-3876.

72. Cogan DG, Kuwabara T. The sphingolipidoses and the eye. *Arch Ophthalmol* 1968;79:437-452.

73. Musarella MA, Raab EL, Rudolph SH. Oculomotor abnormalities in chronic G_{M2} gangliosidoses. *J Pediatr Ophthalmol Strabismus* 1982;19:80-89.

74. Suzuki Y, Oshima A, Nanba E. a-galactosidase deficiency (ß-galactosidosis): G_{M1} gangliosidosis and Morquio B disease. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:3775-3809.

75. Desnick RJ, Ioannou YA, Eng CM. a-galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:3733-3774.

76. Johnson DL, Del Monte MA, Cotlier F. Fabry's disease: diagnosis by a-galactosidase A activity in tears. *Clin Chim Acta* 1975;63: 81-90.

77. Weingeist TA, Blodi FC. Fabry's disease: ocular findings in a female carrier. *Arch Ophthalmol* 1971;85:169-176.

78. Sher NA, Reiff W, Letson RD, et al. Central retinal artery occlusion complicating Fabry's disease. *Arch Ophthalmol* 1978;96: 815-817.

79. Eng CM, Guffon N, Wilcox WR, et al, for the International Collaborative Fabry Disease Study Group. Safety and efficacy of recombinant human

alpha-galactosidase A—replacement therapy in Fabry's disease. *N Engl J Med* 2001;345:9-16.

80. Desnick RJ, Brady R, Barranger J, et al. Fabry disease, an underrecognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. *Ann Intern Med* 2003;138:338-346.

81. Polten A, Fluharty AL, Fluharty CB, et al. Molecular basis of different forms of metachromatic leukodystrophy. *N Engl J Med* 1991;324:18-22.

82. von Figura K, Gieselman V, Jaeken J. Metachromatic leukodystrophy. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:3695-3724.

83. Quigley HA, Green WR. Clinical and ultrastructural ocular histopathologic studies of adult-onset metachromatic leukodystrophy. *Am J Ophthalmol* 1976;82:472-479.

84. Libert J, van Hoof F, Toussaint D. Ocular findings in metachromatic leukodystrophy: an electron microscopic and enzyme study in different clinical and genetic variants. *Arch Ophthalmol* 1979;97:1495-1504.

85. Krivit W, Shapiro E, Kennedy W, et al. Treatment of late infantile metachromatic leukodystrophy by bone marrow transplantation. *N Engl J Med* 1990;322:28-32.

86. Bateman JB, Philipart M, Isenberg S. Ocular features of multiple sulfatase deficiencies and a new variant of metachromatic leukodystrophy. *J Pediatr Ophthalmol Strabismus* 1984;21:133-139.

87. Suzuki K, Suzuki Y, Suzuki K. Galactosylceramide lipidosis: globoid-cell leukodystrophy (Krabbe disease). In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *Metabolic and molecular basis of inherited disease*, 7th ed. New York: McGraw-Hill, 1995: 2671-2692.

88. Brownstein S, Meagher-Villenure K, Polomero RC, et al. Optic nerve in globoid leukodystrophy (Krabbe's disease)—ultrastructural changes. *Arch Ophthalmol* 1978;96:864-870.

89. Krivit W, Shapiro EG, Peters C, et al. Hematopoietic stem-cell transplantation in globoid-cell leukodystrophy. *N Engl J Med* 1998;338:1119-1126.

90. Beutler E, Grabowski GA. Gaucher disease. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001: 3635-3668.

91. Cogan D, Chu EC, Gittinger J, et al. Fundal abnormalities in Gauchers disease. *Arch Ophthalmol* 1980;98:2202-2203.

92. Sasaki T, Tsukahara S. A new ocular finding in Gaucher's disease: a report of two brothers. *Ophthalmologica* 1985;191:206-209.

93. Harris CM, Taylor DS, Vellodi A. Ocular motor abnormalities in Gaucher Disease. *Neuropediatrics* 1999;30:289-293.

94. Barton NW, Brady RO, Dambrosia JM, et al. Replacement therapy for inherited enzyme deficiency—macrophage targeted glucocerebrosidase for Gaucher's disease. *N Engl J Med* 1991;324: 1464-1470.

95. Charrow J, Andersson HC, Kaplan P, et al. Enzyme replacement therapy and monitoring for children with type 1 Gaucher disease: consensus recommendations. *J Pediatr* 2004;144:112-120.

96. Schuchman EH, Desnick RJ. Niemann-Pick disease types A and B: acid sphingomyelinase deficiencies. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:3589-3610.

97. Walton DC, Robb RM, Crocker AC. Ocular manifestations of group-A Niemann-Pick. *Am J Ophthalmol* 1978;85:174-180.

98. Cogan DG, Chu FC, Barranger JA, et al. Macular halo syndrome: variant of Niemann-Pick disease. *Arch Ophthalmol* 1983;101: 1698-1700.

99. Carstea ED, Morris JA, Coleman KG, et al. Niemann-Pick C1 disease gene: homology to mediators of cholesterol homeostasis. *Science* 1997;277:228-231.

100. Davies JP, Chen FW, Ioannou YA. Transmembrane molecular pump activity of Niemann-Pick C1 protein. *Science* 2000;290: 2295-2298.

101. Naureckiene S, Sleat DE, Lackland H, et al. Identification of *HE1* as the second gene of Niemann-Pick C disease. *Science* 2000; 290:2298-2301.

102. Patterson MC, Vanier MT, Suzuki K, et al. Niemann-Pick disease type C: a lipid trafficking disorder. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:3611-3633.

103. Cogan DG, Chu EC, Reingold DB, et al. Ocular motor signs in some metabolic diseases. *Arch Ophthalmol* 1981;99:1802-1808.

104. Moser HW, Linke T, Fensom AH, et al. Acid ceramidase deficiency: Farber lipogranulomatosis. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The*

metabolic and molecular basis of inherited disease, 8th ed. New York: McGraw-Hill, 2001:3573-3585.

105. Vormoor J, Ehlert K, Groll AH, et al. Successful hematopoietic stem cell transplantation in Farber disease. *J Pediatr* 2004;144: 132-134.

106. Zarbin MA, Green WR, Moser HW, et al. Farber's disease: light and electron microscopic study of the eye. *Arch Ophthalmol* 1985; 103:73-80.

107. Neufeld EE, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001: 3421-3452.

108. Canton LB, Disseler JA, Wilson EM II. Glaucoma in the Maroteaux-Lamy syndrome. *Am J Ophthalmol* 1989;108:426-430.

109. Caruso RC, Kaiser-Kupfer ML, Muenzer J. Electroretinographic findings in the mucopolysaccharidoses. *Ophthalmology* 1986;93: 1612-1616.

110. Collins MLZ, Traboulsi EL, Maumenee IH. Optic nerve swelling and optic atrophy in the systemic mucopolysaccharidoses. *Ophthalmology* 1990;97:1445-1449.

111. Kenyon KR, Topping TM, Green WR, et al. Ocular pathology of the Maroteaux-Lamy syndrome (systemic mucopolysaccharidosis type VI): histologic and ultrastructural report of two cases. *Am J Ophthalmol* 1972;73:718-741.

112. Wraith JE, Clarke LA, Beck M, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). *J Pediatr* 2004;144:581 -588.

113. Krivit W, Peters C, Shapiro EG. Bone marrow transplantation as effective treatment of central nervous system disease in globoid cell leukodystrophy, metachromatic leukodystrophy, adrenoleukodystrophy, mannosidosis, fucosidosis, aspartylglucosaminuria, Hurler, Maroteaux-Lamy, and Sly syndromes, and Gaucher disease type III. *Curr Opin Neurol* 1999;12:167-176.

114. Staba SL, Escolar ML, Poe M, et al. Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. *N Engl J Med* 2004;350:1960-1969.

115. Gullingsrud EO, Krivit W, Summers CG. Ocular abnormalities in the mucopolysaccharidoses after bone marrow transplantation. Longer follow-up. *Ophthalmology* 1998;105:1099-1105.

116. Thomas GH. Disorders of glycoprotein degradation: a-mannosidosis, ß-mannosidosis, fucosidosis, and sialidosis. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001: 3507-3534.

117. Goldberg MF, Cotlier E, Fischenschler LG. Macular cherry-red spot, corneal clouding and beta-galactosidase deficiency. *Arch Intern Med* 1971;128:387-398.

118. Sogg RL, Steinman L, Rathien B, et al. Cherry-red spot-myoclonus syndrome. *Ophthalmology* 1979;86:1861-1874.

119. Pshezhetsky AV, Richard C, Michaud L, et al. Cloning, expression and chromosomal mapping of human lysosomal sialidase and characterization of mutations in sialidosis. *Nat Genet* 1997;15: 316-320.

120. Lukong KE, Landry K, Elsliger MA, et al. Mutations in sialidosis impair sialidase binding to the lysosomal multienzyme complex. *J Biol Chem* 2001;276:17286-17290.

121. d'Azzo A, Andria G, Strisciuglio P, et al. Galactosialidosis. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:3611-3633.

122. Rudenko G, Bonten E, Hol WG, et al. The atomic model of the human protective protein/cathepsin A suggests a structural basis for galactosialidosis. P*roc Natl Acad Sci U S A* 1998;95:621-625.

123. Usui T, Sawaguchi S, Abe H, et al. Late-infantile type galactosialidosis. Histopathology of the retina and optic nerve. *Arch Ophthalmol* 1991;109:542-546.

124. Usui T, Abe H, Takagi M, et al. Electroretinogram and visual evoked potential in two siblings with adult form galactosialidosis. *Metab Pediatr Syst Ophthalmol* 1993;16:19-22.

125. Arbisser AI, Murphree AL, Garcia CA. Ocular findings in mannosidosis. *Am J Ophthalmol* 1976;82:465-471.

126. Letson RD, Desnick RI. Punctate lenticular opacities in type II mannosidosis. *Am J Ophthalmol* 1978;85:218-223.

127. Kornfeld S, Sly WS. I-cell disease and pseudo-Hurler polydystrophy: disorders of lysosomal enzyme phosphorylation and localization. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:3469-3482.

128. Libert J, van Hoof F, Farriaux JP, et al. Ocular findings in I-cell disease (mucolipidosis type II). *Am J Ophthalmol* 1977;83: 617-628.

129. Raas-Rothschild A, Cormier-Daire V, Bao M, et al. Molecular basis of variant pseudo-Hurler polydystrophy (mucolipidosis IIIC). *J Clin Invest* 2000;105:673-681.

130. Bargal R, Avidan N, Ben-Asher E, et al. Identification of the gene causing mucolipidosis type IV. *Nat Genet* 2000;26:118-123.

131. Sun M, Goldin E, Stahl S, et al. Mucolipidosis type IV is caused by mutations in a gene encoding a novel transient receptor potential channel. *Hum Mol Genet* 2000;9:2471-2478.

132. Amir N, Zlotogora J, Bach G. Mucolipidosis type IV: clinical spectrum and natural history. *Pediatrics* 1987;79:953-959.

133. Chitayat D, Meunier CM, Hodgkinson KA, et al. Mucolipidosis type IV: clinical manifestations and natural history. *Am J Med Genet* 1991;41:313-318.

134. Riedel KG, Zwaan J, Kenyon KR, et al. Ocular abnormalities in mucolipidosis IV. *Am J Ophthalmol* 1985;99:125-136.

135. Smith JA, Chan CC, Goldin E, et al. Noninvasive diagnosis and ophthalmic features of mucolipidosis type IV. *Ophthalmology* 2002;109:588-594.

136. Pradhan SM, Atchaneeyasakul LO, Appukuttan B, et al. Electronegative electroretinogram in mucolipidosis IV. *Arch Ophthalmol* 2002;120:45-50.

137. Jaeken J, Stibler H, Hagberg B. The carbohydrate-deficient glycoprotein syndrome. A new inherited multisystemic disease with severe nervous system involvement. *Acta Paediatr Scand Suppl* 1991;375:1-71.

138. Jaeken J, Artigas J, Barone R, et al. Phosphomannomutase deficiency is the main cause of carbohydrate-deficient glycoprotein syndrome with type I isoelectrofocusing pattern of serum sialotransferrins. *J Inherit Metab Dis* 1997;20:447-449.

139. Petersen MB, Brostrom K, Stibler H, et al. Early manifestations of the carbohydrate-deficient glycoprotein syndrome. *J Pediatr* 1993;122:66-70.

140. Stark KL, Gibson JB, Hertle RW, et al. Ocular motor signs in an infant with carbohydrate-deficient glycoprotein syndrome type Ia. *Am J Ophthalmol* 2000;130:533-535.

141. Andreasson S, Blennow G, Ehinger B, et al. Full-field electroretinograms in patients with the carbohydrate-deficient glycoprotein syndrome. *Am J Ophthalmol* 1991;112:83-86.

142. Gould SJ, Raymond GV, Valle D. The peroxisome biogenesis disorders. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:3181-3217.

143. Moser AB, Rasmussen M, Naidu S, et al. Phenotype of patients with peroxisomal disorders divided into sixteen complementation groups. *J Pediatr* 1995;127:13-22.

144. Reuber BE, Germain-Lee E, Collins CS, et al. Mutations in *PEX1* are the most common cause of peroxisome biogenesis disorders. *Nat Genet* 1997;17:445-448.

145. Cohen SMZ, Green WR, De la Cruz ZC, et al. Ocular histopathologic studies of neonatal and childhood adrenoleukodystrophy. *Am J Ophthalmol* 1983;95:82-96.

146. Hittner HM, Kretzer FL, Mehta RS. Zellweger syndrome: lenticular opacities indicating carrier status and lens abnormalities characteristic of homozygotes. *Arch Ophthalmol* 1981;99:1977-1982.

147. Garner A, Fielder AR, Primavesi R, et al. Tapetoretinal degeneration in the cerebro-hepato-renal (Zellweger's) syndrome. *Br J Ophthalmol* 1982;66:422-431.

148. Weleber RG, Tongue AC, Kennaway NG, et al. Ophthalmic manifestations of infantile phytanic acid storage disease. *Arch Ophthalmol* 1984;102:1317-1321.

149. Moser HW, Moser AE, Singh I, et al. Adrenoleukodystrophy: survey of 303 cases: biochemistry, diagnosis and therapy. *Ann Neurol* 1984;16:628-641.

150. Moser HW, Smith KD, Watkins PA, et al. X-linked adrenoleukodystrophy. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:3257-3301.

151. Moses J, Douar AM, Sarde CO, et al. Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters. *Nature* 1993;361:726-730.

152. Traboulsi EI, Maumenee IH. Ophthalmologic manifestations of X-linked childhood adrenoleucodystrophy. *Ophthalmology* 1987; 94:47-52.

153. Glasgow BJ, Brown HH, Hannah JB, et al. Ocular pathologic findings in neonatal adrenoleukodystrophy. *Ophthalmology* 1987;94:1054-1060.

154. Kori AA, Robin NH, Jacobs JB, et al. Pendular nystagmus in patients with peroxisomal assembly disorder. *Arch Neurol* 1998;55: 554-558.

155. Herndon JH Jr, Steinberg D, Uhlendorf BW. Refsum's disease: defective oxidation of phytanic acid in tissue cultures derived from homozygotes and heterozygotes. *N Engl J Med* 1969;281: 1034-1038.

156. Jansen GA, Hogenhout EM, Ferdinandusse S, et al. Human phytanoyl-CoA hydroxylase: resolution of the gene structure and the molecular basis of Refsum's disease. *Hum Mol Genet* 2000; 9:1195-1200.

157. van den Brink DM, Brites P, Haasjes J, et al. Identification of *PEX7* as the second gene involved in Refsum disease. *Am J Hum Genet* 2003;72:471-477.

158. Wanders RJ, Jakobs C, Skjeldal OH. Refsum disease. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001: 3303-3321.

159. Refsum S. Heredopathia atactica polyneuritiformis. Phytanic acid storage disease (Refsum's disease) with particular referral to ophthalmological disturbances. *Metab Ophthalmol* 1977;1: 73-79.

160. Hansen E, Bachen NL, Flagge T. Refsum's disease: eye manifestations in a patient treated with low phytol, low phytanic acid diet. *Acta Ophthalmol (Copenh)* 1979;57:899-913.

161. Dickson N, Mortimer JG, Faed JM, et al. A child with Refsum's disease: successful treatment with diet and plasma exchange. *Dev Med Child Neurol* 1989;31:92-97.

162. Bull P, Thomas GR, Rommens JM, et al. The Wilson's disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. *Nat Genet* 1993;5:327-337.

163. Petrukhin K, Fischer SG, Piratsu M, et al. Mapping, cloning and genetic characterization of the region containing the Wilson disease gene. *Nat Genet* 1993;5:338-343.

164. Walker JM, Huster D, Ralle M, et al. The N-terminal metal-binding site 2 of the Wilson's disease protein plays a key role in the transfer of copper from Atox1. *J Biol Chem* 2004;279: 15376-15384.

165. Culotta VC, Gitlin JD. Disorders of copper transport. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill, 2001, pp 3105-3126.

166. Goldberg MF, Van Noorden GK. Ophthalmologic findings in Wilson's hepatolenticular degeneration. *Arch Ophthalmol* 1966; 75:162-170.

167. Kirkham TH, Kamin DF. Slow saccadic eye movements in Wilson's disease. *J Neurol Neurosurg Psychiatry* 1974;37:191-194.

168. Klingele TG, Newman SA, Burde RM. Accommodation defect in Wilson's disease. *Am J Ophthalmol* 1980;90:20-24.

169. McCrary JA III. Magnetic resonance imaging diagnosis of hepatolenticular degeneration. *Arch Ophthalmol* 1987;105:277.

170. Brewer GJ, Hedera P, Kluin KJ, et al. Treatment of Wilson disease with ammonium tetrathiomolybdate. III. Initial therapy in a total of 55 neurologically affected patients and follow-up with zinc therapy. *Arch Neurol* 2003;60:379-385.

171. Vulpe C, Levinson B, Whitney S, et al. Isolation of a candidate gene for Menkes disease and evidence that it encodes a potential heavy metal binding protein. *Nat Genet* 1993;3:7-13.

172. Menkes JH, Atter M, Steigleder GK, et al. A sex-linked recessive disorder with retardation of growth, peculiar hair, and focal cerebral and cerebellar degeneration. *Pediatrics* 1962;89:764-779.

173. Hsich GE, Robertson RL, Irons M, et al. Cerebral infarction in Menkes' disease. *Pediatr Neurol* 2000;23:425-428.

174. Gasch AT, Caruso RC, Kaler SG, et al. Menkes' syndrome: ophthalmic findings. *Ophthalmology*. 2002;109:1477-1483.

175. Wray SH, Kuwabara T, Sanderson P. Menkes' kinky-hair disease: a light and electron microscopic study of the eye. *Invest Ophthalmol* 1968;15:138-148.

176. Levy NS, Dawson WW, Rhodes BJ, et al. Ocular abnormalities in Menkes kinky-hair syndrome. *Am J Ophthalmol* 1974;77: 319-325.

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24

Pediatric Neuroophthalmology

Robert C. Sergott

Denise Hug

Neuroophthalmology is a hybrid subspecialty integrating the uncompromising logic of neurology with the unswerving precision of ophthalmology. Pediatric neuroophthalmology adds yet another dimension to this discipline by mandating the keen observation skills and finesse of pediatrics.

Neuroophthalmic disorders in the pediatric population, although not as common as in their adult counterparts, are equally crucial to patients' ultimate visual and neurologic health. Very subtle initial symptoms may indicate major intracranial pathology. Prompt diagnosis and management is the best method to prevent the most somber and permanent visual and neurologic sequelae.

The diseases encountered in pediatric neuroophthalmology are similar to those in adult situations in that the same broad categories—neoplastic, infectious, inflammatory, vascular, metabolic, and congenital—must be considered. However, in pediatric neuroophthalmology, the frequency of the various diseases is weighted toward congenital and neoplastic entities.

The clinician evaluating these patients must define the onset and progression of the present problem, and secure detailed prenatal, birth, growth and development, and family histories. The amount of history obtained directly from the child obviously depends on his or her age and mental status. Primary and secondary historical details must always be elicited from mothers, fathers, grandparents, and siblings who may have witnessed the patient's behavior.

In this chapter, pediatric neuroophthalmic problems are approached as the patients and their parents report them to clinicians—by their symptoms. Each symptom complex is analyzed anatomically so that a coherent comprehensive differential diagnostic approach may be formulated.

VISUAL LOSS

Children rarely complain of unilateral loss of vision, usually adapting to the deficit rather than admitting to any interference with their activities. A decrease of visual acuity in one eye is most often detected on screening examinations performed by pediatricians, school nurses, and general ophthalmologists.

After the most common problems of strabismus and anisometropic amblyopia have been excluded, and if no anterior segment pathology can be found, concern must arise that a neuroophthalmic disorder is present. The optic nerve is the initial neuroanatomic structure of the afferent visual system and should occupy the first position in the differential diagnostic analysis.

The physical findings of unilateral optic nerve disease are identical for children and adults. Decreased central visual acuity associated with a central scotoma, an acquired dyschromatopsia, and an afferent pupillary defect (Marcus-Gunn pupil) are observed in varying degrees, depending on the severity of the optic neuropathy.

Bilateral optic neuropathies in some ways present a more difficult diagnostic challenge. Again, children rarely complain of decreased vision, preferring the strategy of adaptation. When visual loss is mild and bilateral, routine screening examinations reflect symmetric loss of vision, implicating poor attention and lack of cooperation. Also, with bilateral optic neuropathies, dyschromatopsias may be symmetric, mimicking congenital color blindness. Finally, with bilateral, symmetric disease, the only pupillary finding is a sluggish reaction to direct light stimulation, which is more difficult to appreciate than an afferent defect.

Once the diagnosis of an optic neuropathy or bilateral optic neuropathies has been established, the exact etiology must be determined. It is recommended that congenital defects of the optic nerve be considered first since their discovery may spare children extensive neuroradiologic investigations.

OPTIC NERVE HYPOPLASIA

Optic nerve hypoplasia may present to the pediatric ophthalmologist during the evaluation of unilateral visual

loss or during the assessment of strabismus or nystagmus. Sometimes the patient is referred for further evaluation because of the unusual appearance of the optic disc. In the latter circumstances, the clinician must regard the hypoplastic optic nerve as more than a passing funduscopic curiosity. Rather, the disc anomaly may be the harbinger of associated significant central nervous system (CNS) and endocrinologic abnormalities.

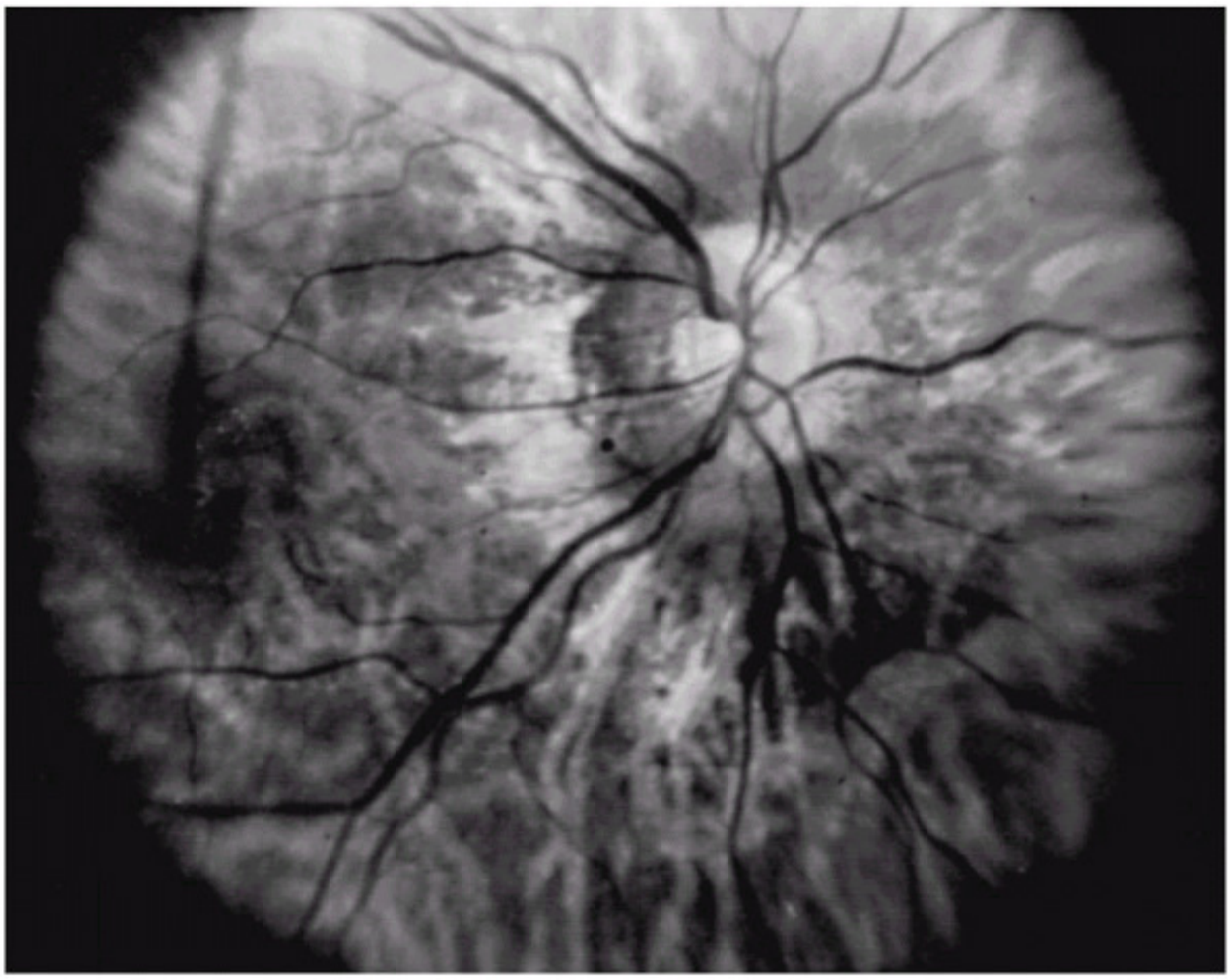

Figure 24.1 Marked optic disc hypoplasia. The optic disc is approximately one-half the normal size and is surrounded by a peripapillary yellowish border.

Hypoplastic optic nerves may be unilateral or bilateral. Likewise, they may affect central visual acuity profoundly or produce only visual field changes ranging from nasal defects to nerve fiber layer defects and generalized constriction (1). When the optic nerve is strikingly hypoplastic (Fig. 24.1), the funduscopic diagnosis is elementary. However, detailed evaluation of the optic nerve with higher magnification may be necessary to evaluate subtle findings of optic nerve hypoplasia (Fig. 24.2).

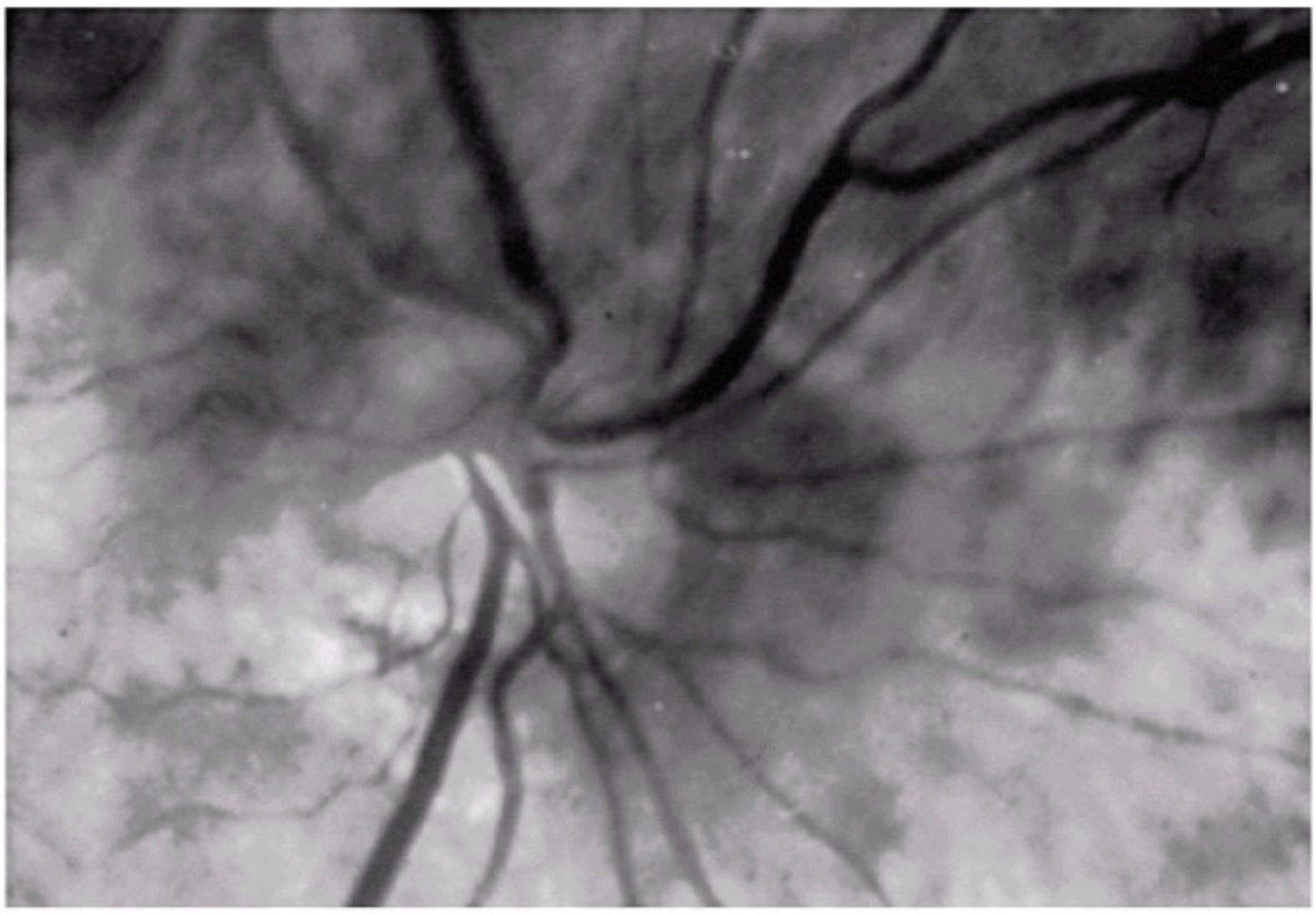

Figure 24.2 More subtle hypoplasia of the optic disc than shown in Figure 24.1. The lower border of the disc is truncated. The patient presented with a superior visual field defect that was initially believed to represent a chiasmal lesion.

TABLE 24.1 FUNDUSCOPIC CRITERIA FOR DIAGNOSIS OF OPTIC NERVE HYPOPLASIA

Small optic disc
Peripapillary halo surrounds disc (“double-ring” sign)
Combined size of small disc and halo roughly approximate size of a normal disc
Normal or slightly tortuous, nondilated vessels
Decreased foveal reflex
Decreased thickness of retinal nerve fiber layer

Six fundoscopic features (Table 24.1) should be sought in contemplating the diagnosis of optic nerve hypoplasia. First, by definition, the disc must be small. Second, the disc is surrounded by a peripapillary yellowish border that encircles the entire disc to form a halo. This halo constitutes the “double-ring” sign that has been invariably associated with this diagnosis. On the basis of the histopathologic study of Mosier and colleagues (2), the outer portion of the double ring is the junction between sclera and lamina cribrosa where the choroid is discontinuous. The inner ring is demarcated by termination of the retinal pigment epithelium, with the whitish appearance of the inner ring attributed to glial and connective tissue around the retinal vessels.

The third criterion for the funduscopic diagnosis is that the dimensions of the hypoplastic nerve and peripapillary halo roughly approximate the size of a normal optic disc. The remaining three criteria involve the retina and include (a) normal or slightly tortuous, nondilated retinal vessels; (b) decreased foveal reflex; and (c) decreased thickness of the retinal nerve fiber layer. Pathologic studies have revealed decreased numbers of retinal ganglion cells, as well as thinning of the nerve fiber layer, thereby confirming the ophthalmoscopic observations of the retina (3).

It is important to remember that the appearance of the optic nerve is not always predictive of the ultimate visual acuity. In unilateral or asymmetric disease, there can be a superimposed component of amblyopia which is amenable to conventional amblyopia treatment (4,5).

Etiology

No single, unifying pathophysiologic concept has evolved to explain optic nerve hypoplasia, although an increasing number of reports have associated maternal use of a variety of therapeutic and “recreational” drugs with this optic nerve disorder. In the “recreational” category, lysergic acid diethylamide (LSD) and ethanol (as part of the fetal alcohol syndrome) have been implicated (6). In the therapeutic category, anticonvulsants, corticosteroids, diuretics, meperidine, protamine zinc insulin, and cold medications have all been reported to be associated with this optic nerve abnormality (7). Likewise, younger mothers and mothers with diabetes mellitus may have children with a higher incidence of optic nerve hypoplasia (8). Recent genetic studies have implicated the homeobox gene *HESX1/hesx1*

in septooptic dysplasia. The data suggest that this gene plays an important role in forebrain and pituitary development (9,10,11,12).

Ocular and Central Nervous System Associations

Optic nerve hypoplasia may exist as a totally isolated congenital defect, but it has also been reported with almost every other congenital ocular abnormality ranging from ocular motor palsies to microphthalmos to blepharophimosis. Moreover, a variety of neurologic abnormalities and syndromes have been associated with hypoplastic optic nerves. Some of these disorders, such as hydranencephaly and anencephaly, preclude continued growth and development. However, the classic association with midline CNS deficits is consistent with a normal life expectancy.

de Morsier (13,14) described a variety of sagittal midline defects, including agenesis of the anterior commissure and septum pellucidum, as well as malformation of the chiasm (Figs. 24.3 and 24.4). de Morsier coined the term “septooptic dysplasia” for these defects, but it was Hoyt and coworkers (15) who stressed the syndrome of septooptic dysplasia with growth retardation secondary to hypopituitarism. Detection of this syndrome is critical because the endocrine abnormalities can be life threatening. In addition, growth retardation is reversible if growth hormone therapy is initiated before epiphyses close. Likewise, encephaloceles are common in these patients, and this brain tissue in the sphenoid sinus can easily be mistaken for an abnormality and biopsied.

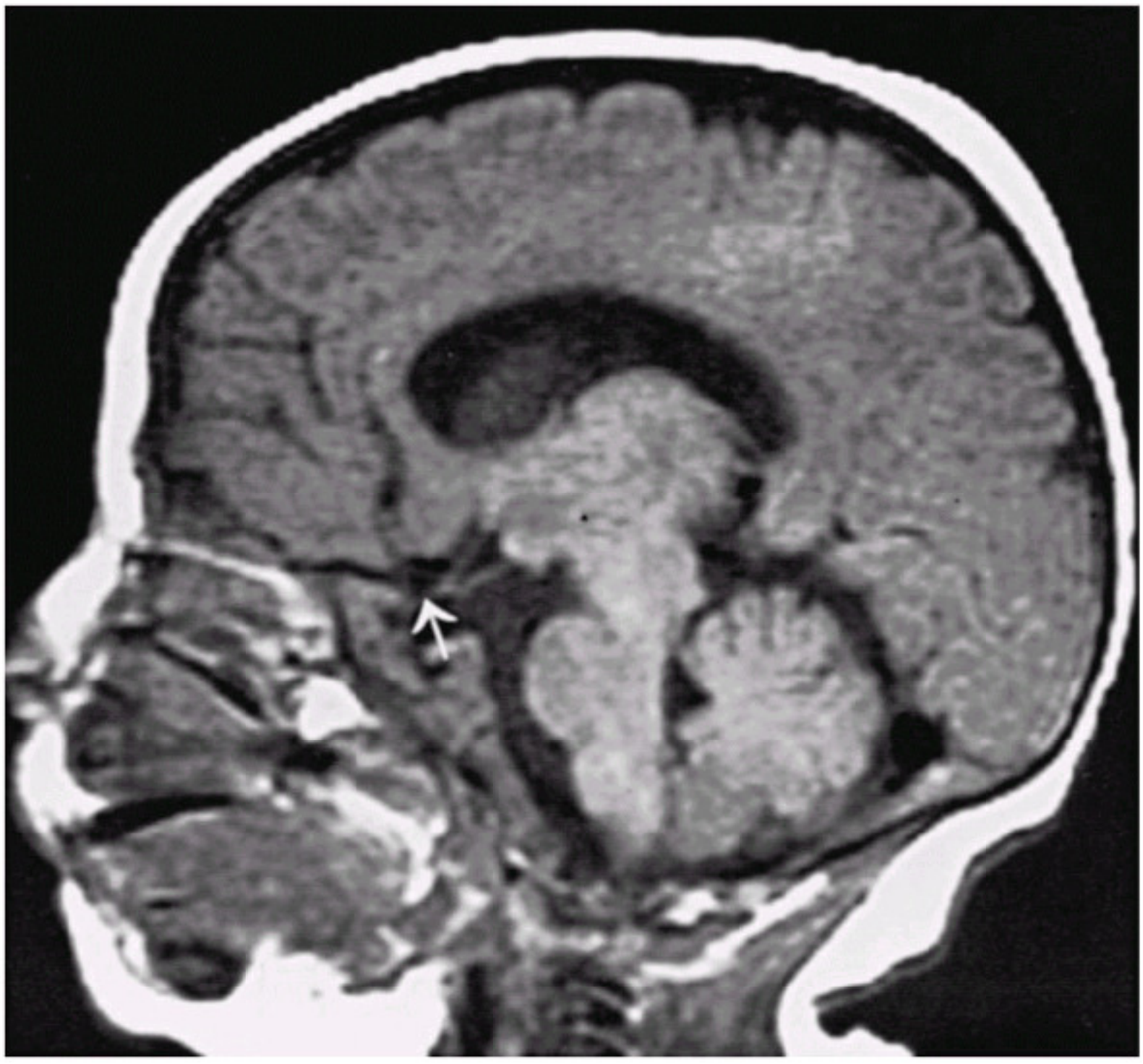

Figure 24.3 Sagittal magnetic resonance imaging scan of a patient with de Morsier syndrome (septooptic dysplasia). The pertinent neuroradiologic features are hypoplastic optic nerves (*arrow*), as well as agenesis of the anterior commissure and septum pellucidum. (Courtesy of Robert Grossman, MD.)

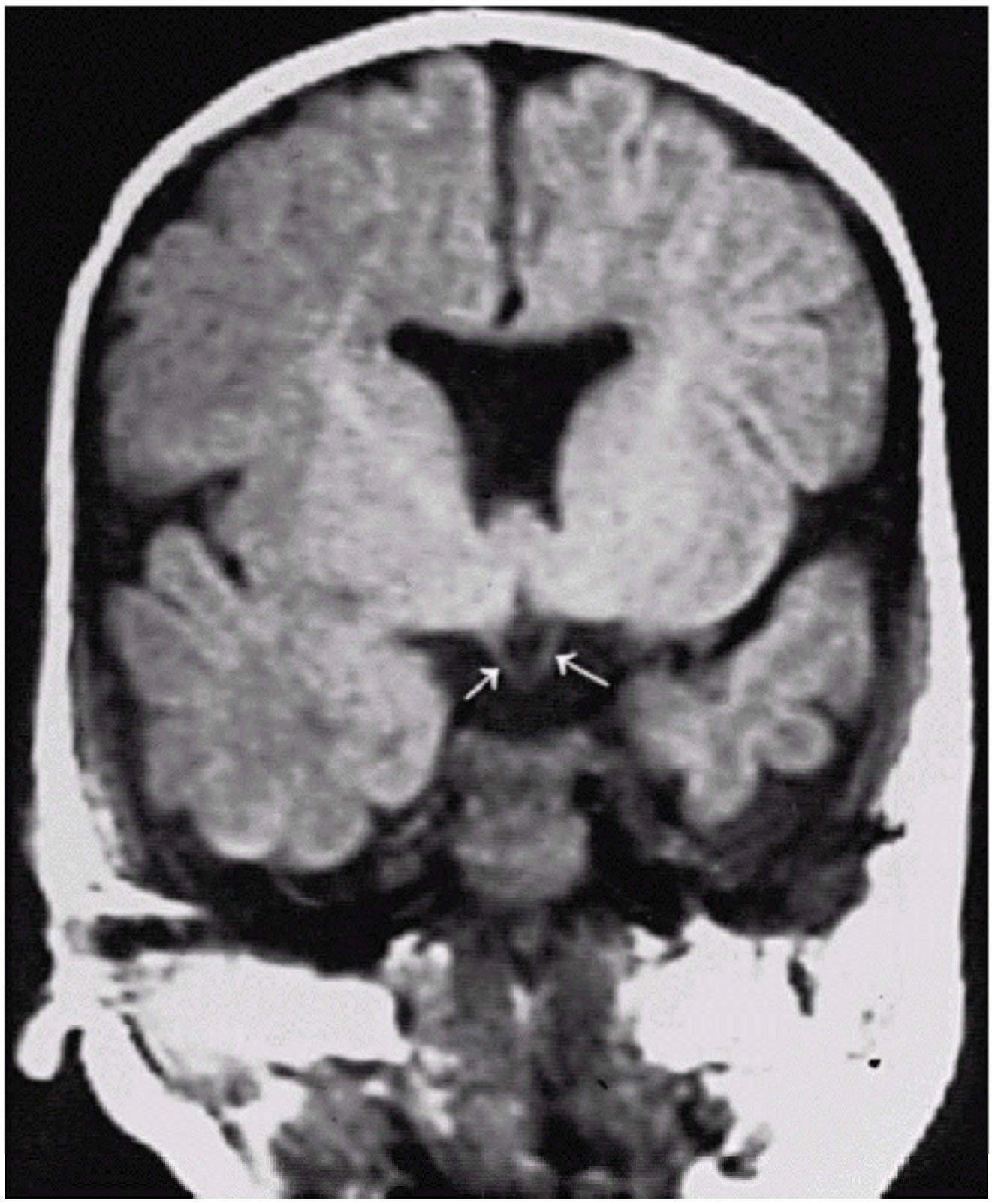

Figure 24.4 Coronal magnetic resonance imaging scan of the patient in Figure 24.3. Arrows denote hypoplastic optic nerves.

OPTIC NERVE DYSPLASIA

Dysplasia of the optic nerve refers to a collection of clinical entities ranging from the morning glory syndrome and coloboma to megalopapillae and tilted optic discs. Of these, the morning glory syndrome and coloboma are discussed here because they may produce central visual loss in the pediatric-age group. The other disorders usually are associated with visual field defects and are discussed in the section concerning visual field abnormalities.

The morning glory syndrome (Fig. 24.5) is a rare disc anomaly first described by Kindler (16). The optic disc is funnel shaped, distorted, and of a larger size than normal. The chorioretinal pigment encircling the disc is prominent and elevated in the shape of an annulus. Patients often are neurologically and ophthalmologically normal; however, as with other varieties of optic disc hypoplasia and dysplasia, basal encephaloceles have been associated with the morning glory syndrome.

Patients with this syndrome often lose vision because of a nonrhegmatogenous retinal detachment involving the posterior pole. The prognosis for visual rehabilitation with traditional vitreoretinal surgical procedures is poor. However, Irvine and coworkers (17) and Chang and associates (18) reported some success in repairing these detachments when optic nerve sheath decompression surgery was performed simultaneously with vitreoretinal surgery. This surgical finding implies that the retinal detachment develops because cerebrospinal fluid (CSF) within the subarachnoid

space around the optic nerve percolates around the dysplastic disc tissue into the subretinal space.

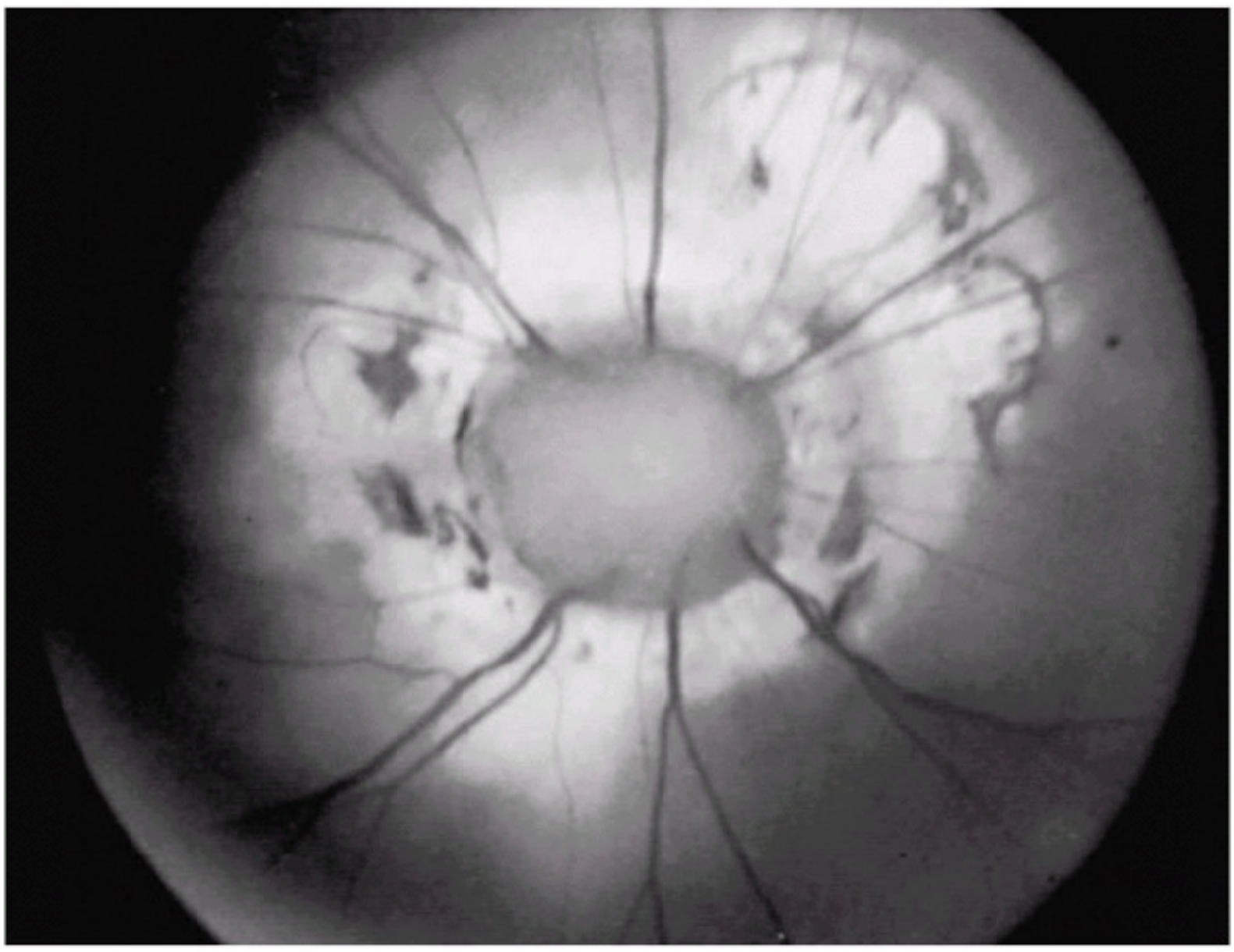

Figure 24.5 Morning glory syndrome of the optic disc. The disc is funnel shaped, distorted, and larger than normal size. The chorioretinal pigment surrounding the disc is shaped like an annulus.

Coloboma are the other major variety of dysplastic optic disc anomalies that may present in childhood with visual loss (Fig. 24.6). A coloboma is a developmental malformation resulting from partial or anomalous closure of the embryonic fissure. An optic nerve coloboma may exist independently or be associated with colobomatous defects in the retina and choroid, depending on which portion of the embryonic fissure fails to close. If the proximal portion of the fissure fails to close in the correct manner, the retina and choroid are involved primarily. When the more distal segment of the fissure remains open, the nerve and its meningeal sheath are affected with a colobomatous defect.

Patients with optic disc coloboma frequently have reduced visual acuity but occasionally may have only field defects. Reduction in the nerve fiber layer is observed in the affected eyes, and the foveae may be hypoplastic. Significant refractive errors and anisometropia are common in optic nerve coloboma and should be addressed (19,20). Patients with optic nerve coloboma are also at risk for retinal detachment, which has been reported to occur as early as 5 months of age (21).

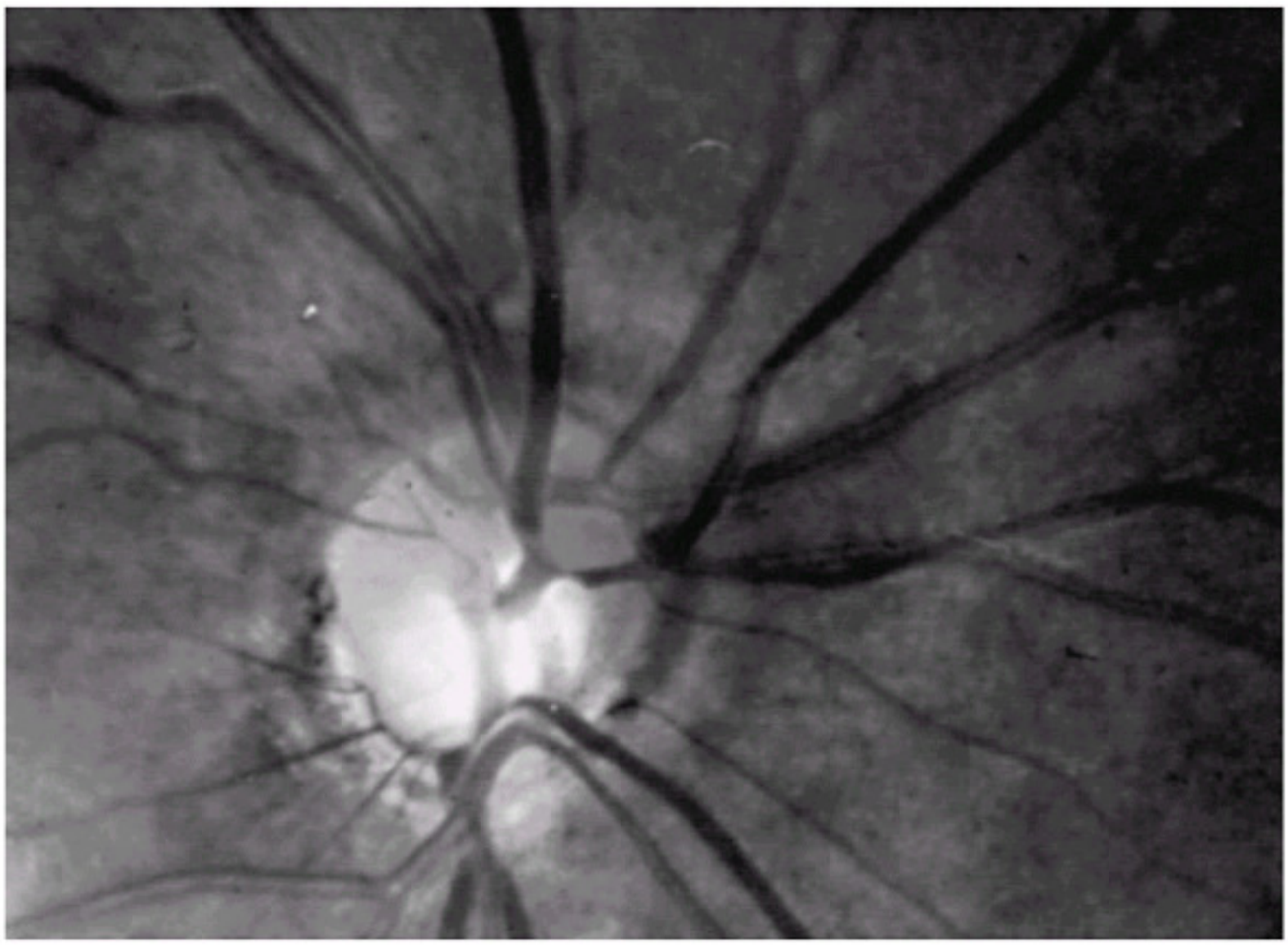

Figure 24.6 Optic disc coloboma, which was not associated with a corresponding colobomatous defect in the retina and choroid.

As in optic nerve hypoplasia, optic nerve coloboma may occur in isolation or associated with other neurologic or systemic syndromes. Coloboma are most notably seen in CHARGE (*c*oloboma, *h*eart disease, *a*tresia choanae, *r*etarded *g*rowth and development) association and renal-coloboma syndrome.

DOMINANT OPTIC ATROPHY

Dominant optic atrophy (DOA) is the most common bilateral hereditary condition of the optic nerve encountered in the pediatric population. Recent studies have shown that mutations in the *OPA1* gene cause dominant optic atrophy linked to chromosome 3q27-q29 (22,23,24). Patients often present in childhood after failing school screening examinations. Acute visual loss has not been described in this disease. Some patients may not come to medical attention until adulthood.

Because the visual deficits may be mild (20/40 to 20/200 range) and because children frequently do not report visual changes, the exact incidence and onset of DOA remains uncertain. The current consensus now favors an onset at about 10 years of age.

In 1959 Kjer (25) published his classic monograph describing 19 Danish families with DOA. He attempted to use the presence of nystagmus as a distinguishing feature between what he believed were two forms of DOA. However, Waardenburg and coworkers (26) considered that nystagmus was too nonspecific a finding to be used reliably to separate these two supposed entities. Review of the literature favors the position of Waardenburg. Kline and Glaser (27) described 24 individuals in four pedigrees without nystagmus or other extraocular motility abnormalities.

This study may represent the best description of the clinical profile of DOA. In this series, best corrected visual acuity ranged from 20/25 to 20/400. In six of the 12 patients, the two eyes had identical acuity, and there was a one-line difference between the two eyes in two patients. The remaining four patients had greater than a two-line difference between eyes, one individual having 20/30 in the right and 20/200 in the left.

Visual field deficits for DOA are noteworthy for four characteristics: (a) elongated blind spots, (b) cecocentral scotoma, (c) mild temporal depression to central isopters (I-2-E and I-3-E) are rarely encountered, and (d) normal peripheral isopters (I-4-E or larger). Progressive loss of acuity and visual field have been described rarely in DOA. Such deterioration is so unusual that thorough diagnostic investigation is advocated in this circumstance, so that “progressive DOA” becomes a diagnosis of exclusion.

The color vision deficits in DOA are fascinating and often provide a helpful diagnostic point in distinguishing DOA from other optic neuropathies. Ishihara and

provide excellent screening methods for detecting dyschromatopsias for DOA, but only the Farnsworth-Munsell 100-hue examination precisely defines the defects. In Kline and Glaser's (27) series, a tritan (yellowblue) error was found in 15 of 22 eyes. In five of these 15 eyes, a deutan or protan axis was also identified with the tritan abnormality. The remaining seven eyes displayed a generalized dyschromatopsia without an identifiable axis. This tritan dyschromatopsia for DOA is significant because it violates Koellner's rule (i.e., disease of receptor and bipolar layer of the retina results in decreased blue-yellow sensitivity, and disease of the retinal ganglion cells and visual pathways anterior to the lateral geniculate body produces red-green dyschromatopsia). To date, no explanation for the unusual tritan axis in DOA has been provided.

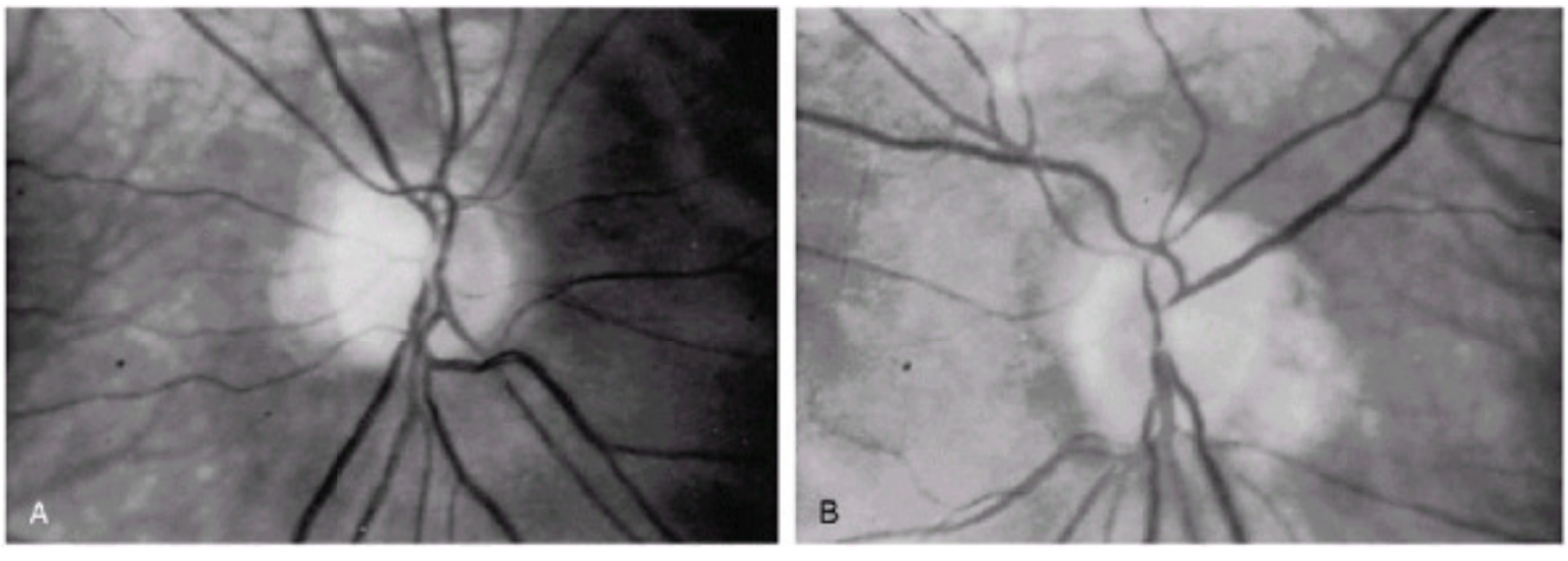

Figure 24.7 A and **B:** Dominant optic atrophy demonstrating pallor of the temporal aspect of both discs with focal excavation of the temporal portion of the nerves. (Courtesy of Joel S. Glaser, MD.)

The appearance of the optic nerve in DOA has been controversial. There is agreement that pallor of the temporal segment of the disc occurs routinely and that diffuse pallor does not occur, but no consensus has been reached regarding other features of the optic nerve appearance. Kline and Glaser (27) believed strongly that most eyes (16 of 22 in their series) demonstrate focal temporal excavation (Fig. 24.7). This excavation can be so pronounced that the temporal portion of the disc may be on a different plane compared with the nasal aspect. The degree of temporal excavation is highly variable, and this variability may explain why different clinicians have had the strong opinions that no “pathognomonic” disc appearance exists.

TABLE 24.2 DIAGNOSTIC CRITERIA FOR DOMINANT OPTIC ATROPHY

Autosomal-dominant inheritance pattern (may be necessary to examine asymptomatic family members)
Insidious onset, often around 10 years of age
Bilateral, symmetric visual loss, although asymmetric loss is well described
Mild-to-moderate reduction in visual acuity
Central and cecocentral scotomata with normal peripheral isopters
Tritan dyschromatopsia with possibly superimposed protan and deutan defects; rarely, generalized dyschromatopsia may be present
Temporal disc pallor with possible triangular temporal excavation of disc

Adapted from Kline LB, Glaser JS. Dominant optic atrophy: the clinical profile. *Arch Ophthalmol* 1979;97:1680-1686 and from Smith DP. The assessment of acquired dyschromatopsia and clinical investigation of the acquired tritan defect in dominantly inherited juvenile atrophy. *Am J Optom* 1972;49 : 574-588, with permission.

No correlation has yet evolved between the degree of visual loss and severity of dyschromatopsia or optic disc appearance. No treatment is currently available for DOA, but with proper diagnostic evaluation, these patients may be spared extensive neuroradiologic investigation and possibly years of antiglaucomatous therapy.

Kline and Glaser (27) modified the criteria for the diagnosis of DOA as first proposed by Smith. These criteria are listed in Table 24.2.

OPTIC NEURITIS

During the last 30 years, only three studies have investigated thoroughly the entity of optic neuritis in the pediatric age group (28,29,30). The lack of published clinical material reflects the unusual occurrence of CNS demyelinating disease in children. Characterized neuropathologically by preserved axonal structure associated with destroyed myelin, invading lymphocytes and macrophages, and reduced numbers of oligodendrocytes, optic neuritis has a peak age incidence of 20 to 40 years.

In contrast with the adult form of this disease, optic neuritis in children has three special characteristics: (a) bilateral simultaneous involvement is much more

common in children than in adults, (b) between 70% and 80% of children demonstrated optic disc edema compared with

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approximately 30% of adults with this disorder (Fig. 24.8), and (c) association with multiple sclerosis (MS) is much lower in children than adults. In the above studies, only 17% of the patients went on to develop widespread CNS demyelination (MS) in a follow-up lasting 3 to 12 years. In adults, 40% to 80% of the patients develop MS. Optic neuritis in children is most often associated with postinfectious etiology with symptoms of febrile or flu-like illness preceding the optic neuritis by days to weeks. In addition, infectious, systemic inflammatory and postimmunization causes are all possible.

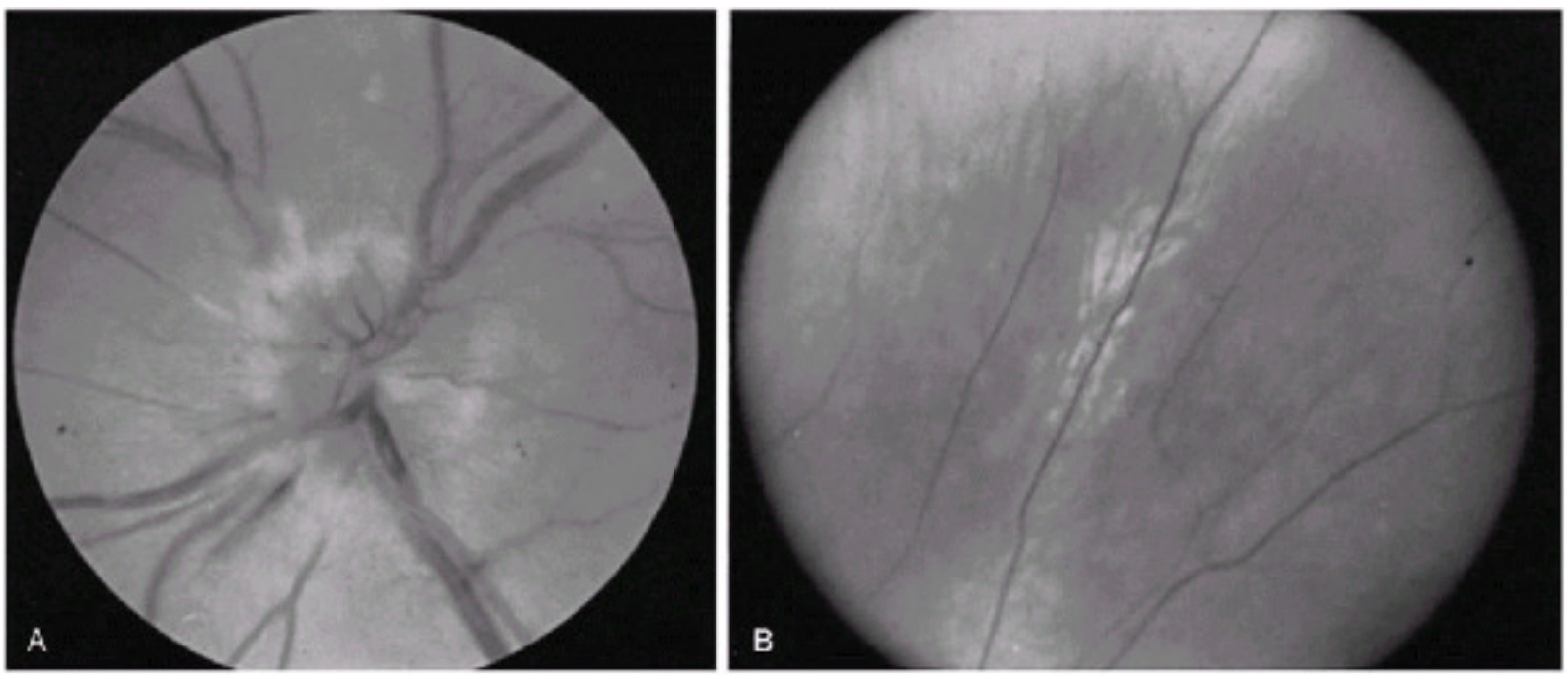

Figure 24.8 A: Inflammatory papillitis developing after a nonspecific viral illness. The optic disc is diffusely edematous with exudates and small streak hemorrhages in the peripapillary area. **B:** The temporal peripheral retina of the patient shown in (**A**). The perivascular sheathing of this retinal vessel developed 3 months after the acute papillitis.

If optic neuritis is suspected, neuroimaging should be performed to rule out intracranial mass or evidence of hydrocephalus. Underlying infectious causes, as well as increased intracranial pressure, are ruled out by performing a lumbar puncture.

Treatment of optic neuritis in the pediatric population remains controversial. There has been no controlled study to determine the role of systemic corticosteroids in the treatment of pediatric optic neuritis. The Optic Nerve Treatment Trial (31,32) showed faster visual recovery and decreased risk of developing MS when patients were treated with high-dose intravenous steroids followed by oral steroids. Optic neuritis in children is certainly a clinically different disease so it is difficult to apply these results to children. But given that the vision loss is often bilateral and profound and that a subset of these children go on to develop MS, it is difficult to find fault in the use of systemic corticosteroids.

PAPILLITIS AND MACULAR STAR

During the past several years, there has been growing recognition and interest in a syndrome of edema of the optic nerve head (“papillitis”) associated with macular exudate (“macular star,” “hemimacular star,” or “neuroretinitis”). This entity actually dates back to 1916 and Leber's original report (33). Although Leber incorrectly hypothesized that the disorder was a primary retinal disease, he provided an exceedingly accurate clinical profile and description.

Using fluorescein angiography, Gass (34) demonstrated that the optic disc changes developed prior to or simultaneously with the macular exudate. Children and teenagers usually present with unilateral loss of vision, although cases of bilateral involvement have been described. Approximately 50% of patients present with retrobulbar pain worsened by eye movement, similar to optic neuritis associated with MS. However, patients with papillitis and neuroretinitis do not have an increased risk of MS or future episodes of clinically significant demyelination (35).

Most cases of papillitis with a macular star are “idiopathic” and are theorized to be “postviral.” In contrast, several specific causes have been found, and the clinician should investigate the patient for these diagnoses. Even though some of these specific diagnoses are systemic diseases, the papillitis and neuroretinitis may be a unilateral rather than bilateral process. The differential diagnosis includes (a) cat-scratch fever (36), (b) Epstein-Barr virus (37), (c) mumps (38), (d) hepatitis B (39), (e) Lyme disease (40), (f) syphilis (41), (g) toxoplasmosis (42), and (h) sarcoidosis (43).

DEVIC DISEASE

Devic disease (neuromyelitis optica) is a variety of CNS demyelinating disease confined to both optic nerves and the spinal cord. Children and adults may be affected with

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this disorder, which produces bilateral visual loss and transverse myelitis. The visual loss is always bilateral, but it may begin in one eye and involve the second eye several days later (44). Paraplegia from transverse myelitis quickly follows. In addition to white matter lesions, the gray matter of the spinal cord may be involved.

Compared with those who have MS, patients with Devic disease demonstrate a much more elevated CSF protein concentration, as well as increased numbers of inflammatory cells in the spinal fluid. Recovery of vision and neurologic function in Devic disease is highly variable.

SCHILDER DISEASE

Bilateral optic neuritis without visual improvement may be the first manifestation of Schilder disease, a rare and relentlessly progressive widespread demyelinating disease (myelinoclastic diffuse sclerosis) (45). Schilder disease may present as an intracranial mass, mimicking tumor or abscess, on magnetic resonance imaging (MRI) (46,47,48). The disease usually develops before 10 years of age and is rapidly fatal within 1 to 2 years. However, there have been several reported cases which have responded to corticosteroid treatment (46,49,50). The disease is not inherited and has an equal male-to-female incidence. The neuropathologic features are indistinguishable from those of MS.

PAPILLEDEMA

The diagnosis and management of papilledema in pediatric neuroophthalmology should be on an emergent basis. Papilledema is defined as bilateral, though possibly asymmetric, optic disc edema caused by increased intracranial pressure (Fig. 24.9).

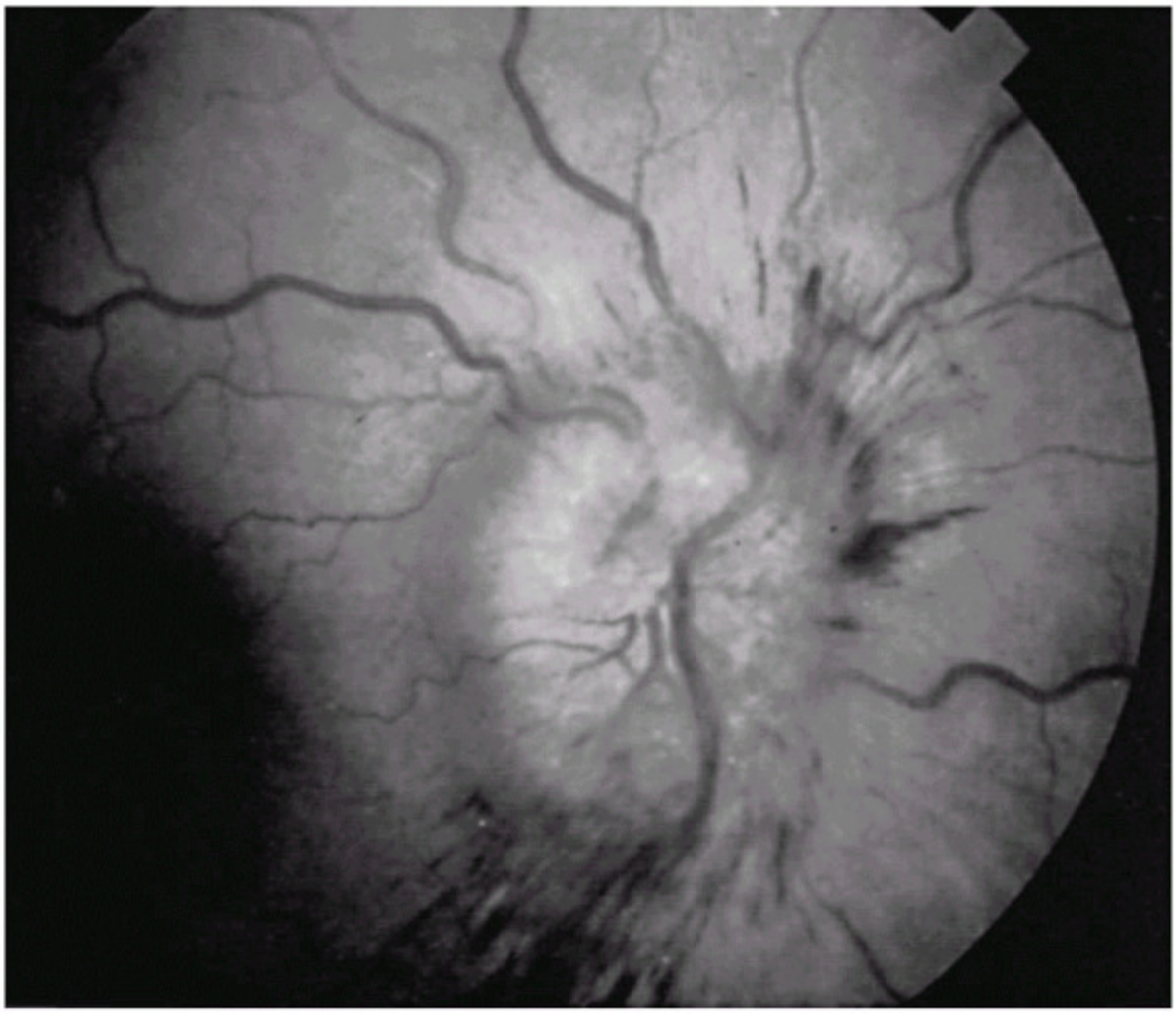

Figure 24.9 Acute papilledema with streak peripapillary hemorrhages, distention of the retinal venous system, and marked optic disc edema. Note the absence of a central cup.

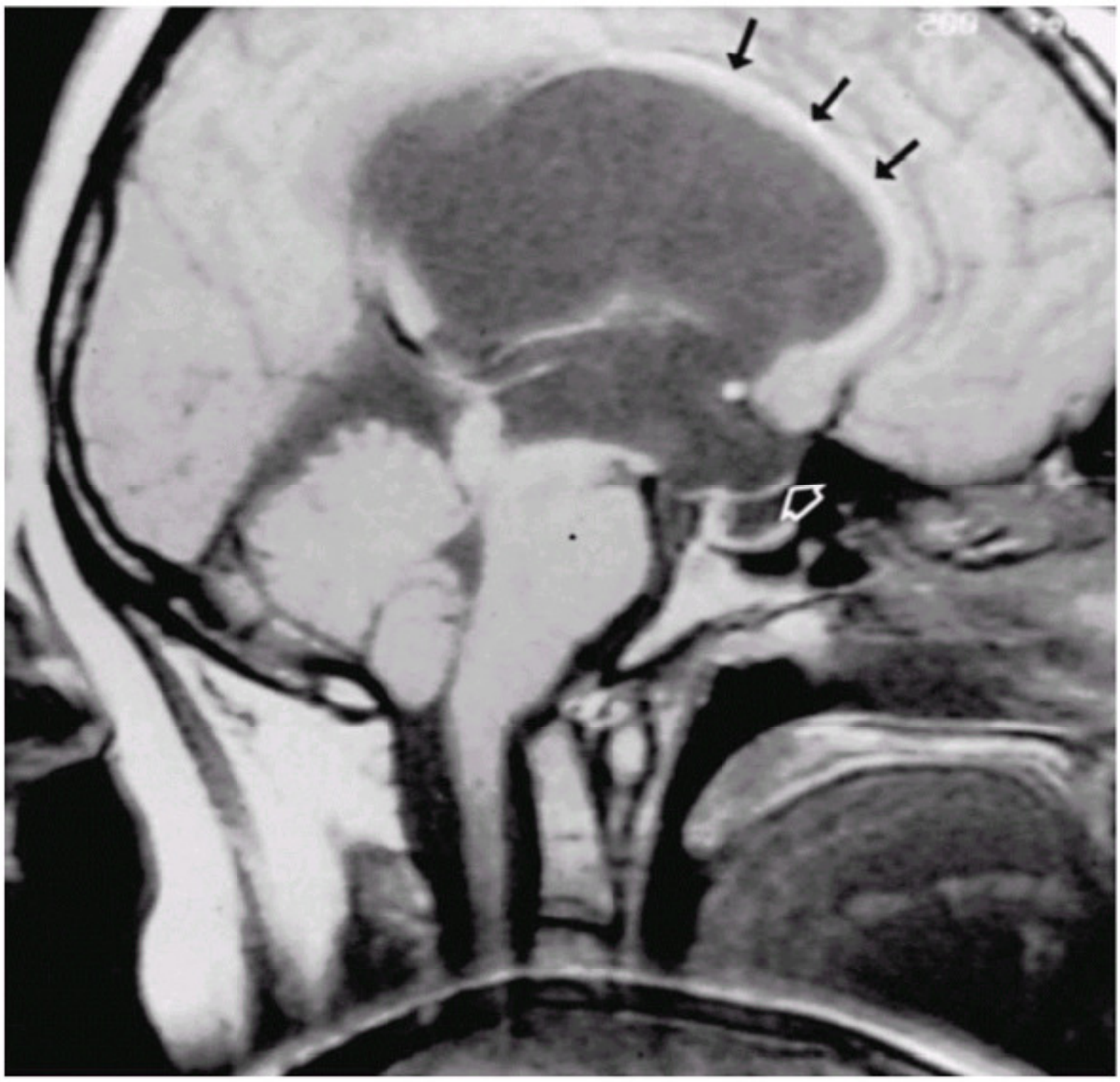

Figure 24.10 Sagittal magnetic resonance imaging scan of obstructive hydrocephalus. The lateral ventricles are massively distended, resulting in thinning of the corpus callosum (*black arrows*). The third ventricle is distended, producing distortion of the optic chiasm (*white arrowhead*).

In children, the most common cause of papilledema is an intracranial mass lesion producing obstructive hydrocephalus (Fig. 24.10). Because such lesions may result in sudden transtentorial herniation and death, it is vital to initiate prompt and proper management for these children. Moreover, chronic bilateral papilledema of any cause may progress to optic atrophy and bilateral blindness. Papilledema is therefore a neuroophthalmic finding that has both life- and vision-threatening implications.

Symptoms

Headache caused by increased intracranial pressure and transient obscuration of vision (TVO) are the most common presenting symptoms of papilledema. The headaches are of a dull, aching quality involving the entire head, although sometimes more discomfort is felt at the posterior aspect of the skull and upper cervical area. The headaches are usually worse on awakening in the morning and subside in the evening. Nausea and vomiting may accompany increased intracranial pressure headaches, but usually only after the headache pattern has been established. Coughing, sneezing, and any type of Valsalva maneuver exacerbate the headaches.

TVOs are the most common visual symptoms produced by papilledema. These events occur without warning, and vary from blurring of the environment to total blindness. TVOs usually involve both eyes simultaneously, but unilateral events occur in some patients. Increasing frequency and severity of TVOs have been a forewarning of impending permanent visual deficits, according to Meadows (51). Rush (52) and Miller (53) do not believe that increasing

TVOs necessarily foreshadow permanent visual loss. The mechanism of TVO is unknown, although the observation by Cogan (54) of precipitation of these events by change in posture suggests some role for alteration of blood flow or optic nerve CSF fluid dynamics in their etiology.

Double vision because of unilateral or bilateral sixth nerve palsies is another disturbance related to increased intracranial pressure and papilledema. The sixth nerve is compressed against a branch of the basilar artery by the increased intracranial pressure. Relief of the increased intracranial pressure produces resolution of the sixth nerve palsy.

No specific histopathologic type of mass lesion or intracranial abnormality invariably produces papilledema. The specific and varied pediatric neurooncologic and neurosurgical problems that may have papilledema as one of their presenting manifestations are discussed later.

On occasion, it has been theorized that infants may not develop papilledema because of their distensible skulls and open fontanelles. However, there are numerous examples of papilledema in infants, and thus the histologic development of the skull does not preclude the development of papilledema.

Papilledema Diagnosis by Ultrasonography

In children with head trauma and metabolic disorders, the examination of the optic nerve may be difficult. Helmke and Hansen (55) demonstrated that ultrasonography can detect dilation of the optic nerve sheath meninges caused by acute elevations of intracranial pressure. Therefore, in pediatric patients with suspected increased intracranial pressure in whom the optic nerve cannot be visualized, ultrasonography may help to establish the diagnosis of papilledema.

Treatment

Pediatric ophthalmologists confronted with a patient who has papilledema have a dual challenge. First, they must ensure that immediate high-resolution neuroradiologic studies (computed tomography [CT] and MRI scans) are performed. If an intracranial mass is discovered, appropriate inpatient neurologic and neurosurgical care must be initiated. Increased intracranial pressure is first reduced medically with acetazolamide and corticosteroids, provided that the elevated intracranial pressure has not produced significant vomiting. Antiseizure prophylaxis with a loading dose of phenytoin, followed by the appropriate maintenance dose, may also be considered.

If a ventriculoperitoneal shunting procedure should be performed to reduce the intracranial pressure before direct operative attack on the mass lesion remains a neurosurgical decision. Successful reduction of the intracranial pressure does not ensure that the papilledema will not permanently damage the patient's vision. Thus, the second part of the dual challenge to the pediatric ophthalmologist involves trying to protect against visual loss (56). As mentioned earlier, reduction in intracranial pressure does not prevent permanent loss of vision. Some patients even lose vision suddenly after neurosurgical decompression of the primary intracranial process (“post-decompression blindness”) (57). The mechanism of this phenomenon is unknown.

Some intracranial mass lesions are not totally resectable, but these children may survive for extended periods with advanced chemotherapeutic and radiation therapy regimens. However, the quality of their lives may be significantly impaired because of visual loss due to chronic papilledema. Because of the possibility of seeding distant sites with the primary tumor, CSF shunting procedures are not usually recommended. Surgical decompression of the meningeal sheath of the intracranial optic nerve may offer an effective treatment for vision in children with a good survival prognosis, despite a nonresectable central nervous mass lesion producing chronic papilledema (56).

PSEUDOTUMOR CEREBRI

Pseudotumor cerebri is a term used when a patient has signs and symptoms of increased intracranial pressure without evidence of intracranial mass or hydrocephalus. It is helpful to think of pseudotumor cerebri in two separate categories: idiopathic versus secondary. Once the diagnosis of pseudotumor has been made, one must make every effort to rule out an underlying cause. The causes are quite variable and include: dural sinus thrombosis, malnutrition, aplastic anemia, lupus, Addison disease, exogenous hormone use/withdrawal, medication/vitamin ingestion, and Lyme disease.

Pseudotumor cerebri in prepubescent children differs from the adult form in several important ways. The male: female ratio is equal in these children. Obesity is not associated with pseudotumor cerebri in young children, spontaneous remission is more common, and finally, response to oral corticosteroids is possibly better. Pseudotumor cerebri in pubescent and postpubescent children seems to follow adult disease in that there is a female predominance and it appears to have a relationship with obesity (58,59). Just like adults, children with chronic papilledema are at risk for permanent vision loss. Because of the risk of vision loss, these children must be treated and followed carefully.

The ophthalmoscopic diagnosis of chronic papilledema may be one of the most difficult in the whole field of ophthalmology (Fig. 24.11). Because of the lack of hemorrhages and exudates, the casual observer may overlook this physical finding. An awareness of the possibility of chronic papilledema is especially critical since testing to confirm severe constriction of the visual fields is difficult in younger children. Here again, much reliance has to be placed on the family's observations of the patient's visually oriented behavior.

When progressive loss of visual function can be documented in a patient with chronic papilledema, medical and/or surgical intervention is indicated. Obviously, if an underlying cause is present, it must be treated. It is important to initiate medical intervention until the underlying etiology is resolved. If corticosteroids and diuretics are ineffective, surgery with a lumboperitoneal shunt or optic nerve sheath decompression is necessary. Both procedures are effective in treating chronic papilledema (60,61,62).

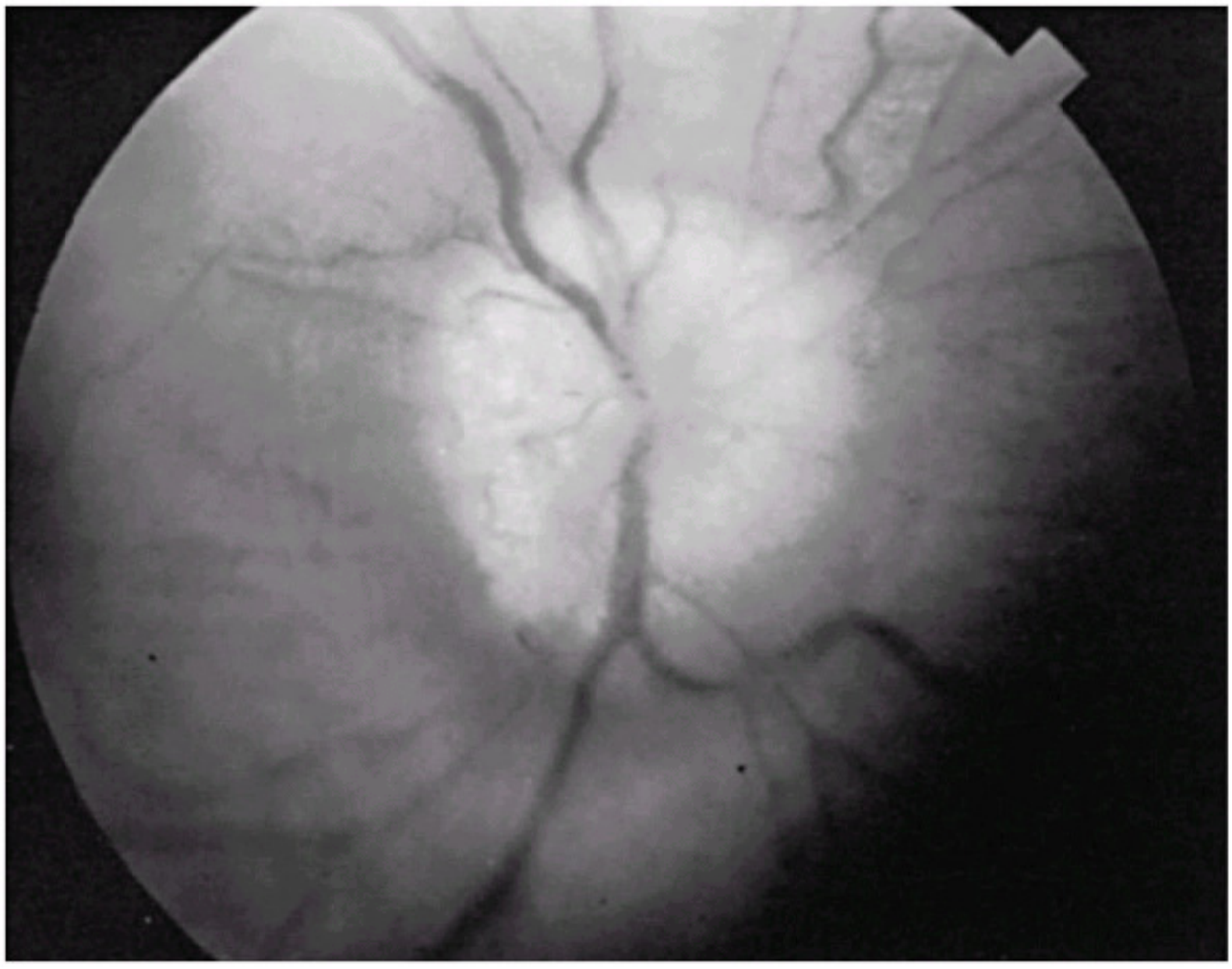

Figure 24.11 Chronic papilledema represents one of the most difficult funduscopic diagnoses. As the papilledema becomes more chronic, the disc begins to resemble the appearance of a congenitally anomalous disc. The disc is elevated without a central cup, and the peripapillary hemorrhages and exudates have disappeared.

LEBER OPTIC NEUROPATHY

Leber optic neuropathy rarely has its onset in adulthood, the disease being found predominantly in pediatric- and adolescent-age groups. Although Leber initially described the disease as appearing between the ages of 18 and 23, numerous reports now exist documenting its occurrence before age 10 and after age 30.

Leber optic neuropathy is a maternally inherited disorder and has a 9:1 male-to-female ratio. Approximately 50% of males and 10% of females with the genetic defect develop the optic neuropathy. The majority of cases of Leber optic neuropathy are associated with point mutations in the mitochondrial genome responsible for complex 1 (NADH:ubiquinone oxidoreductase). These genes are referred to as the ND genes, and the point mutations are as follows: G11778A in *ND4*, G3460A in *ND1*, and T14484C in *ND6*. Not all patients with Leber optic neuropathy have one of these mutations. Currently *ND6* is considered a hot spot because at least 7 different point mutations in this gene have been found in pedigrees with Leber optic neuropathy. The importance of genetic testing is not limited to the diagnosis of Leber optic neuropathy. It is also important because the different major point mutations have different clinical phenotypes and prognosis (63,64,65).

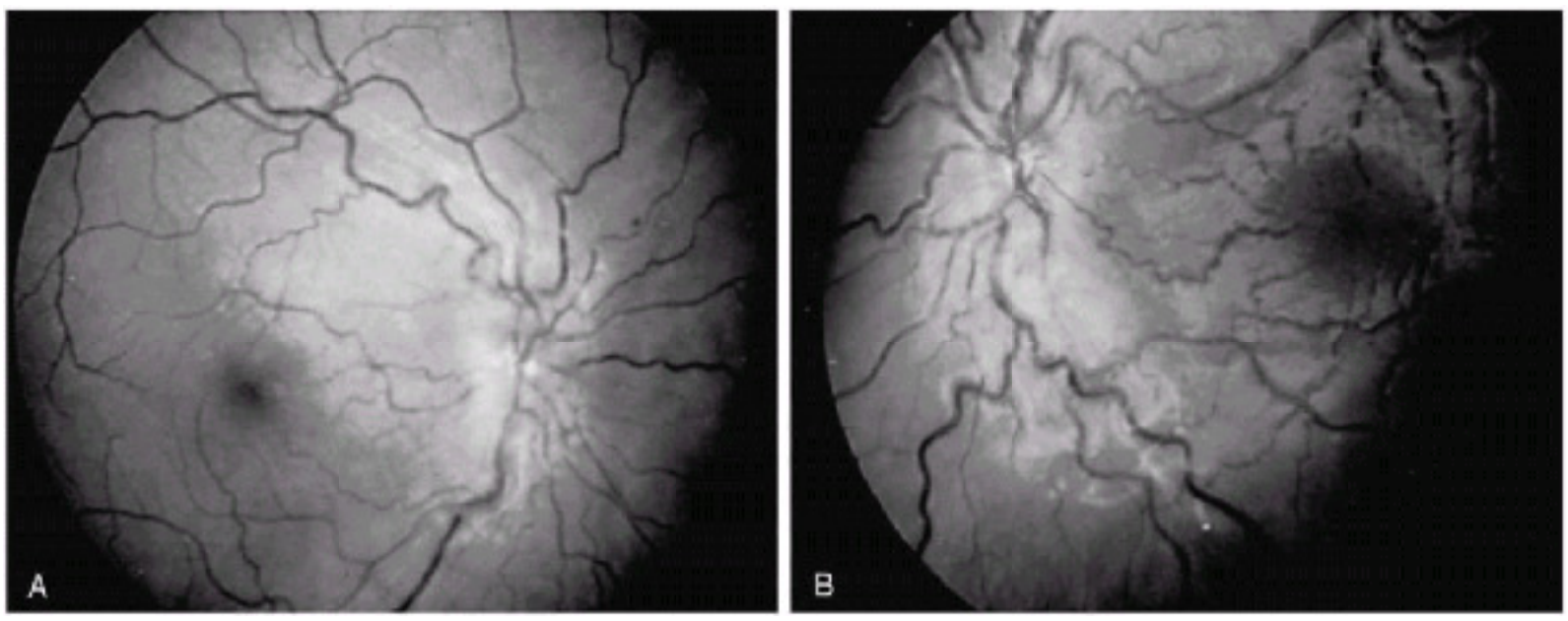

Figure 24.12 A and **B:** Hyperemic discs of a 17-year-old boy with Leber optic neuropathy.

Presentation

The presenting symptoms of Leber optic neuropathy are virtually indistinguishable from those of optic neuritis. Patients report a blur or shadow in their central vision. The onset may be unilateral or bilateral. When one eye is first involved, the second eye invariably becomes affected within several days to weeks; exceptional cases are described with intervals of 3, 8, 12, and 14 years before the second eye became involved.

Smith and colleagues (66) postulated that a typical funduscopic picture exists for acute Leber optic neuropathy. They described pronounced telangiectatic microangiopathy in the circumpapillary region associated with hyperemia of the disc and swelling of the nerve fiber layer surrounding the disc (Fig. 24.12). Fluorescein angiography reveals that the peripapillary disc vasculature is dilated but does not leak dye. The discs eventually become pale, with subsequent loss of the retinal nerve fiber layers.

Most patients with Leber disease have only optic nerve disease, but there are well-documented cases of more diffuse neurologic involvement (67). However, no specific pattern of involvement elsewhere in the CNS has yet emerged. Two patients with electrocardiographic abnormalities have also been described (68), but again this seems more the exception than the rule.

Treatment

A small percentage of patients with Leber optic neuropathy demonstrate spontaneous visual improvement. To date, it is impossible to predict who will regain visual function and to what degree. At the present time, no therapeutic regimen has been documented to be effective.

OPTIC NERVE GLIOMA

Optic nerve glioma usually occur before the age of 20 years. Seventy-five percent of these lesions present before the patient is more than 10 years old (69). More than 90% of optic nerve glioma are diagnosed by age 20.

These tumors present with loss of vision, strabismus, and optic nerve pallor or swelling, perhaps combined with a central retinal vein obstruction. In rare instances, an ocular ischemic syndrome with corneal edema, iritis, iris neovascularization, and glaucoma may be evident. As with chiasmal glioma, optic nerve glioma may be the initial manifestation of neurofibromatosis. The incidence of optic nerve glioma and neurofibromatoses is not well established—some investigations reporting a 10% association and others an almost 80% frequency.

CT and MRI scanning establish the diagnosis of optic nerve gliomata (Figs. 24.13 and 24.14). Like chiasmal glioma, these tumors of the optic nerves have an extremely variable natural history: some patients experience a very benign course in contrast to others who have rapidly growing neoplasms (69,70,71).

Proper treatment of optic nerve glioma is confounded by this variable natural history. Complete surgical excision often requires a craniotomy and results in an excellent survival rate. However, the challenge is to determine which patients need this extensive treatment. The role of radiation therapy is equally ambiguous.

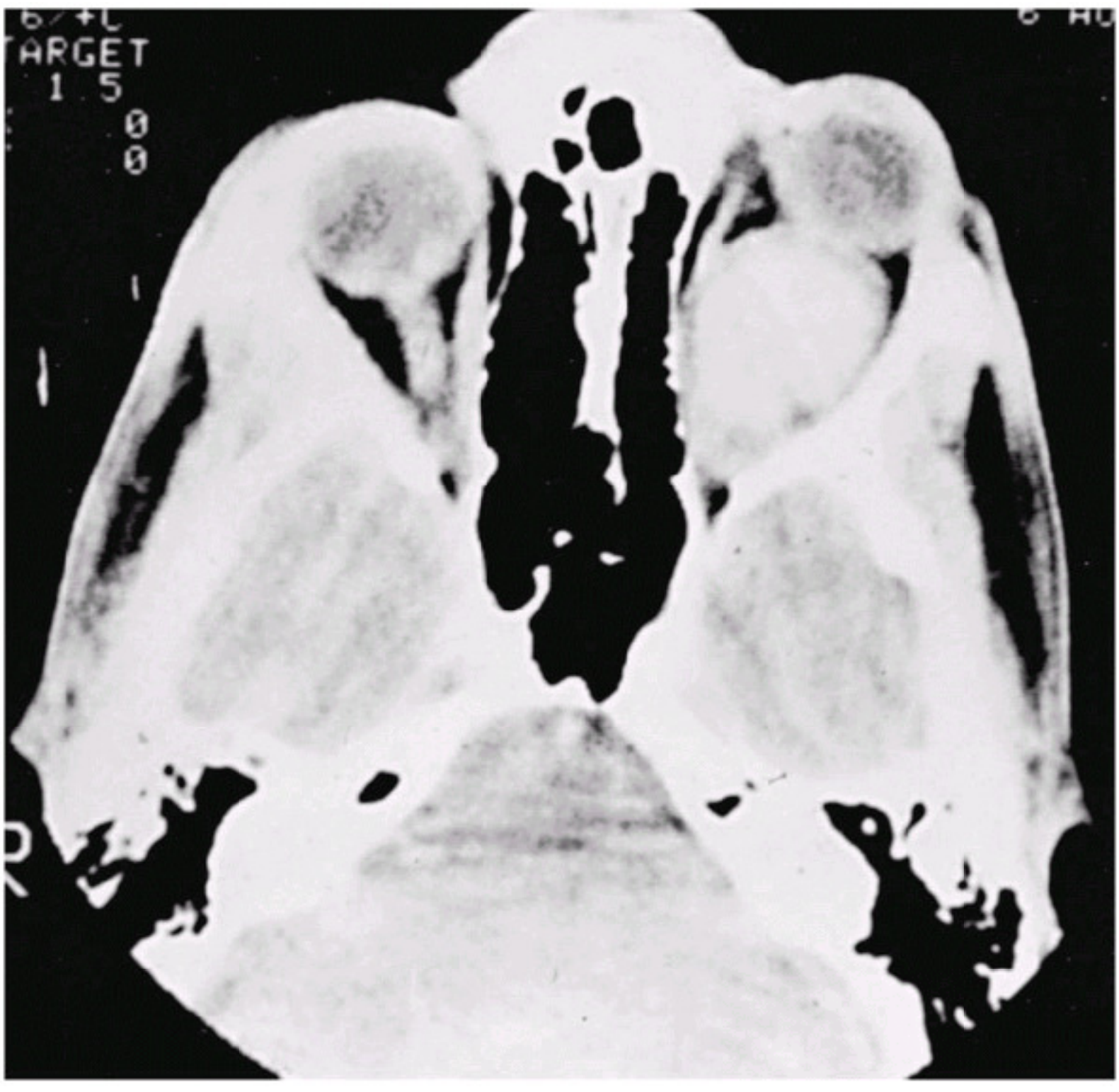

Figure 24.13 Axial computed tomographic scan demonstrating a left retrobulbar mass that proved to be a glioma.

CHIASMAL SYNDROMES

Pathologic processes in and around the optic chiasm present with decreased visual acuity. The presenting symptoms and initial ophthalmologic findings are virtually identical to those described previously for optic neuropathies. Patients with chiasmal syndromes classically develop a temporal hemianopic defect in one or both visual fields. However, it is always difficult to demonstrate these defects in young children even by confrontation techniques. On rare occasions, parents may report that the patient bumps into objects consistently on one side or ignores toys or individuals in a single temporal hemifield. Because nerve fibers from the papillomacular bundle compose 80% of the chiasm, patients with these problems most commonly present with impaired central vision.

Disorders of the optic chiasm are diseases of compressive tumors. Inflammatory, demyelinating disease of the chiasm is extraordinarily rare and must be a diagnosis of absolute exclusion. A chiasmal syndrome, whether in infants, grade-school children, or adolescents, means a neoplasm. Ischemia of the chiasm does not occur in the pediatric-age group and probably does not exist in adolescents or adults. Traumatic chiasmal syndromes do not present with a cryptic history. The most common tumors that produce chiasmal syndromes are considered next.

Craniopharyngioma

In the general population, craniopharyngioma make up 3% of all intracranial tumors. In contrast, these tumors are the most common tumors not originating from glial cells in children and adolescents. In the pediatric population, they constitute between 8% and 13% of all intracranial tumors (72,73).

Developing from squamous cells in the vicinity of the infundibular stem and adenohypophysis, these tumors are believed to be remnants of the Rathke pouch, a structure usually destined for atrophy in prenatal life. Because of their histologic source, craniopharyngioma are always found in the suprasellar cistern, although they may invade any surrounding structures. When the tumors infiltrate and extend into the third ventricle, the flow of CSF is blocked, resulting in papilledema and obstructive hydrocephalus.

Although ophthalmologists rarely see children with craniopharyngioma without visual problems, some patients initially present with failure to maintain growth and development, diabetes insipidus, precocious puberty, or obesity. These associated findings may be crucial diagnostic clues to the pediatric ophthalmologist evaluating the patient with subtle visual findings and may guide the diagnostic investigation toward craniopharyngioma.

Optimal management of craniopharyngioma remains controversial. Surgical resection is still the mainstay therapy, but the issue of total resection versus subtotal resection followed by radiotherapy has not been answered. A recent

study showed that local recurrence rates were halved with subtotal resection plus postoperative radiotherapy at 10 years, but there was no significant difference in overall survival (74). Despite the benign histologic appearance of these neoplasms, they frequently demonstrate locally invasive malignant behavior. Local recurrences are common but with current surgical, stereotactic, and local chemotherapy techniques, survival is good (75,76,77,78,79).

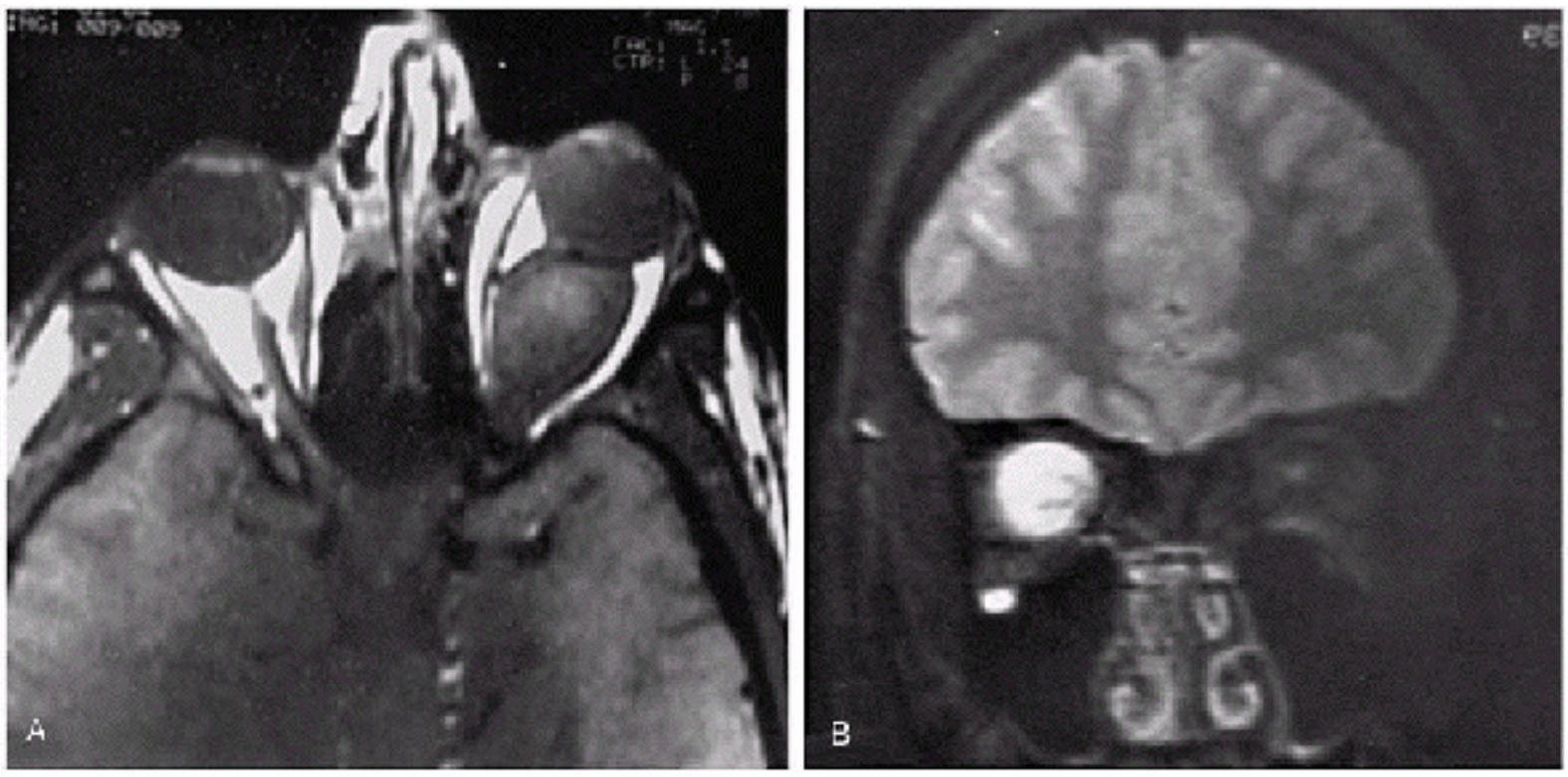

Figure 24.14 A: T1-weighted magnetic resonance imaging (MRI) scan of the optic glioma illustrated in Figure 24.13. The mass involves the entire intraorbital optic nerve. **B:** T2-weighted MRI scan demonstrating the high-intensity glioma tissue enveloping the entire optic nerve. Note the faint shadow of the optic nerve in the opposite orbit. **C:** Chronic optic disc edema with an optociliary shunt vessel associated with an optic glioma.

Optic Chiasmal Glioma

Gliomas constitute the other main neoplasm of the optic chiasm in the pediatric-age group. Histologically, these lesions are similar to optic nerve glioma. However, compared with their counterparts within the optic nerve, the chiasmal lesions are more likely to display an exophytic component. As discussed earlier, glioma of the visual pathways in children make up 3% to 5% of all childhood brain tumors, with a median age of onset at less than 5 years. Boys and girls are equally affected. Ten percent to 20% of these patients have neurofibromatosis.

Perhaps because of the young age at onset and initial subtle symptoms, a long diagnostic delay is common. Patients frequently present with strabismus, and the diagnosis of chiasmal glioma often is not established until several surgical procedures for strabismus have failed to correct the

ocular misalignment. Several clinicians reported monocular nystagmus similar to spasmus nutans as the presenting sign of patients with chiasmal glioma (80,81,82). Because of this association, detailed neuroimaging studies of the chiasm should be considered in any patient with unilateral ocular oscillatory movement. It may be impossible to distinguish clinically between “benign” spasmus nutans and the eye movement disorder associated with these tumors. Eye movement recording techniques are usually impractical in very young children.

The older the patient, the more likely are the presenting signs of chiasmal glioma to be related to decreased visual function rather than to strabismus or monocular nystagmus. The visual loss is usually of slow onset, but abrupt unilateral and bilateral loss of vision due to hemorrhage into the glioma have been described by Maitland and associates (83). Optic disc hypoplasia has been reported in 10% to 20% of patients with chiasmal glioma.

CT and MRI scans are the mainstay in the diagnosis of chiasmal glioma. Whether or not the lesion is solely intrinsic within the chiasm is the crucial question that must be answered by neuroradiologists. For purely intrinsic lesions, surgical biopsy is not required. In comparison, intrinsic lesions with an extrinsic component usually should be biopsied because (a) it may be difficult to determine whether the lesion is indeed a glioma by neuroimaging studies and (b) removal of a large exophytic component or surgery for an extrinsic cyst may improve vision.

The treatment of chiasmal glioma has been controversial because the natural history of these lesions is not as well understood as once thought. Hoyt and

Baghdassarian (84) described 18 patients with chiasmal glioma and found progressive visual loss in only eight of 36 eyes. A subsequent report on the same patients confirmed the relatively benign visual course of these lesions (85). It appears that glioma associated with neurofibromatosis have a more indolent course and often do not require treatment (86,87).

A long-term mortality analysis of patients with chiasmal glioma disclosed that 54% died during a median follow-up period of 20 years (88). The five patients in this series who died of the tumor had done so by 1969, the date of the original study. Only one patient died between 1969 and 1986 from the effects of the chiasmal glioma. Radiation therapy was used for 11 of the 16 patients who died. Only three of the surviving 12 patients received radiation therapy.

However, some patients with chiasmal glioma clearly have a grim visual and systemic prognosis. The children who seem to have the worst prognosis are those who have hypothalamic and/or thalamic involvement (89). Children with chiasmal glioma must be followed carefully, both clinically and with serial neuroimaging. Treatment options include resection, radiation, and chemotherapy. However, it is impossible to know the best way to treat these children.

NYSTAGMUS

Probably no other physical finding evokes as much frustration and confusion for clinicians as nystagmus. This rhythmic, oscillatory, involuntary movement of the eyes engenders this uncertainty because nystagmus is uncommon and difficult to examine. Any intermittent or continuous *new-onset* nystagmus requires first-class neuroimaging studies. In this section, the most important types of nystagmus that provide localizing neuroophthalmic diagnostic information are considered.

Seesaw Nystagmus

Seesaw nystagmus is characterized by a conjugate, pendular, somewhat torsional movement of the eyes with a superimposed vertical movement. The extorting eye rises and the contralateral, intorting eye falls. The nystagmus is seen best in primary gaze and in downgaze.

Seesaw nystagmus localizes to the diencephalon owing to lesions within the pathway from the zona incerta to the interstitial nucleus of Cajal (90). Large parasellar tumors producing bitemporal hemianopsias and compression in the area of the third ventricle are the most common causes of seesaw nystagmus. This variety of nystagmus may also be seen after major craniocerebral trauma and with lesions in the upper midbrain.

Convergence-Retraction Nystagmus

Convergence-retraction nystagmus is an exquisitely localizing type of nystagmus that indicates a pathologic condition in the midbrain. Always associated with a complete or partial paralysis of upgaze, convergence-retraction nystagmus is elicited by attempted upgaze and is produced by cofiring of extraocular muscles, resulting in retraction. In fact, true convergence is not present (convergence being a smooth eye movement) because the eye movements in this condition are opposed adducting saccades. Moreover, this eye movement is not true nystagmus since it is initiated by saccades.

When convergence-retraction nystagmus coexists with large pupils that are unreactive to direct light stimulation with light-near dissociation and upper eyelid retraction, this constellation of clinical findings is known as Parinaud syndrome (91).

In the pediatric-age group, the most common cause of convergence-retraction nystagmus is a pineal gland tumor. The other most important cause is failure of a ventriculoperitoneal shunt (92). In shunt failure, convergence-retraction nystagmus and the other manifestations of Parinaud syndrome may develop before pronounced ventricular enlargement is evident on neuroimaging studies.

Upbeat Nystagmus

Two types of upbeat nystagmus are described: upbeat on upgaze and upbeat on downgaze. The upbeat on upgaze variety (type I) is a large-amplitude nystagmus present in the primary position and increasing with upgaze. Type I is associated with midline cerebellar findings and is localized to the anterior vermis of the cerebellum (93).

In contrast, type II consists of small-amplitude upbeat nystagmus that decreases in upgaze and increases in downgaze. Type II upbeat nystagmus is associated with intrinsic medullary disease (94).

Downbeat Nystagmus

Localizing the disease process to the cervicomedullary junction, downbeat nystagmus is defined as nystagmus in primary position with the fast phase beating downward (95). MRI scans of the posterior fossa, brainstem, and cervical spinal cord are the diagnostic procedure of choice for patients with downbeat nystagmus.

Downbeat nystagmus is most frequently associated with Arnold-Chiari malformations, platybasia with basilar impression, and lower brainstem demyelination or ischemia (96,97). When downbeat nystagmus occurs with generalized cerebellar findings, the diagnosis of spinocerebellar degeneration must be considered.

Periodic Alternating Nystagmus

Periodic alternating nystagmus (PAN) is a horizontal jerk nystagmus that periodically changes directions. Usually the eyes beat in one direction for approximately 90 seconds and then go into a null phase before beginning to move in the opposite direction. This process is continuous while patients are awake and often persists during sleep.

PAN may coexist with downbeat nystagmus, and the differential diagnosis and anatomic localization for these types of nystagmus are virtually identical. PAN has been described with primary cerebellar tumors, demyelinating disease, Arnold-Chiari malformations, and ischemia (98,99). PAN is also seen in idiopathic congenital nystagmus and albinism (100,101).

OPSOCLONUS

Opsoclonus defines back-to-back saccades going in various directions and composed of varying amplitudes. The saccades frequently have curved or oblique paths. Opsoclonus is believed to be caused by a disorder of inhibitory control of “pause neurons” within the pons. The pause neurons are thought to inhibit “burst neurons” within the pause. Therefore, opsoclonus seems to represent chaotic saccades caused by unchecked burst cells (102).

Although opsoclonus may very rarely be observed in otherwise healthy infants, it must be considered a sign of posterior fossa dysfunction until proved otherwise.

Coxsackie B, cytomegalovirus, and *Haemophilus influenzae* meningitis in children have all been associated with opsoclonus. However, the most important cause in apparently healthy children is occult neuroblastoma, and this should be the first diagnostic concern (103).

NEUROOPHTHALMIC DISORDERS OF OCULAR MOTILITY

For the practicing ophthalmologist, the easiest approach to simplify the complex pediatric neuroophthalmic problems of eye movements is to determine whether the patient has a problem moving one eye or both eyes. Through this differential diagnostic approach, the clinician can focus on specific disorders without

overlooking relatively rare problems.

Bilateral Ophthalmoplegia

When the patient is unable to move both eyes completely, the ophthalmologist must adhere to a strict, anatomically based differential diagnostic scheme (104) (Table 24.3). The astute clinician must examine eye movements and search for associated findings such as lid abnormalities, proptosis, and pupillary asymmetries in order to arrive at the correct diagnosis. Often the associated physical findings rather than the eye movements themselves represent the critical clinical observations.

MYASTHENIA SYNDROMES

It is recommended that the differential diagnostic approach be initiated at the neuromuscular junction, where myasthenia gravis is definitely the most common abnormality. Caused by a failure of impulse conduction between the nerve and muscle, myasthenia gravis assumes more varied forms in the pediatric population than in adults. These additional myasthenia syndromes are especially important in newborn infants. Although some of these myasthenic syndromes are rare, the pediatric ophthalmologist may be able to make a lifesaving diagnosis.

Transient Neonatal Myasthenia

This syndrome is defined as a myasthenic condition developing temporarily in newborn infants of mothers with myasthenia gravis (105). The condition affects approximately 12% of infants of myasthenic mothers.

Almost 80% of patients manifest weakness during the first day of life, and symptoms often develop a few hours after birth. Limited eye movements, ptosis, and orbicularis oculi weakness occur in 15% of patients. The most common initial symptoms are weakness, poor feeding, and hypotonia.

The syndrome usually persists for about 15 to 20 days, but occasionally lasts only 1 week or lingers for almost 2 months. If the diagnosis is not made and proper treatment is not instituted, death may occur from respiratory failure.

Improvement of symptoms after intramuscular or subcutaneous injection of 0.1 mg of edrophonium chloride establishes the diagnosis. Orally administered pyridostigmine bromide, provided that swallowing is not too severely impaired, may be necessary until spontaneous remission occurs.

Congenital Myasthenia

In contrast to transitory neonatal myasthenia, congenital myasthenia affects infants whose mothers have never been and never will be affected by myasthenia gravis (106). Symptoms are predominantly ophthalmic, with bilateral

ophthalmoplegia, ptosis, and orbicularis oculi weakness usually developing shortly after birth. The systemic musculature is often spared clinically evident weakness. However, electromyography often detects evidence of impaired systemic neuromuscular transmission.

TABLE 24.3 BILATERAL OPHTHALMOPLEGIA: DIFFERENTIAL DIAGNOSIS

Anatomic site	Etiology	Pupil	Pain	Diagnostic aids	Comments
Neuromuscular junction	Myasthenia Botulism	N	-	Edrophonium test	Orbicularis weakness, transient signs
Muscle vasculature	Arteritis	±	Headache	Erythrocyte sedimentation rate	Polymyalgia rheumatica, ischemic neuropathy
Muscles	Graves ophthalmopathy	N	Foreign body sensation	Forced ductions, CT scan, thyroid function tests	Lid retraction, proptosis, congestion
	Chronic progressive external ophthalmoplegia	N	-	Diplopia, rare	Family history
	Mucormycosis	±	+	Culture, CT	Life threatening, diabetics
Cranial nerve	Diabetic-vascular	Usually NS	±	Glucose tolerance test	Pain limited, 10 days
	Multiple sclerosis	±	-	CSF electrophoresis	Cranial neuropathies, rare
	Polyradiculitis (Fischervariant-Guillain Barré)	±	-	CSF protein	Postinfectious, subacute ataxia
	Neurosyphilis	±	-	CSF and serum VDRL	History of syphilis
	Diphtheria	±	-	Culture	
Cavernous sinus	Pituitary apoplexy	+	++	Skull series, CT	Field defects variable, mimics optic neuritis
	Metastasis	±	+	CSF protein, cells	Severe persistent pain
Interpeduncular cistern	Basilar artery				
	a. Aneurysm	+	±	CT, arteriogram	May mimic posterior fossa tumor

	a. Aneurysm	+	±	CT, arteriogram	May mimic posterior fossa tumor
	b. Occlusion	+	-	Clinical signs	Coma
Skull base	Tumor, primary	±	±	CT, CSF	Slow evolution
	Chronic inflammation	-	-	CT, CSF	Slow evolution
	Meningeal carcinomatosis	±	-	CSF	Consecutive palsies
Brainstem	Wernicke encephalopathy	-	-	Alcoholism	Thiamine administration
	Dorsal midbrain syndromes	+	-	CT	Lid retraction, convergence retraction nystagmus
	Whipple disease	±	-	CSF protein, cells	Uveitis, peripheral neuropathy, gastrointestinal symptoms
	Progressive supranuclear palsy	-	-	-	Dementia, dystonic rigidity

CSF, cerebrospinal fluid; CT, computed tomography; N, normal; VDRL, venereal disease reference laboratory.

From Sergott RC, Glaser JS, Berger LJ. Simultaneous, bilateral diabetic ophthalmoplegia: report of two cases and discussion of differential diagnosis. *Ophthalmology* 1984;91:18-22. Published courtesy of *Ophthalmology.*

Because mothers are never affected but siblings in the same family often demonstrate similar findings, congenital myasthenia is believed to have a genetic basis. Forty-two percent of patients present before 2 years of age, and more than 60% before the age of 20 (107).

Congenital myasthenia gravis results from functional or structural abnormalities at the myoneural junction (108). Unlike juvenile myasthenia gravis, the congenital form is not immune mediated. Therefore, plasmapheresis and systemic immunosuppression are not beneficial. Some types of congenital myasthenia gravis respond to anticholinesterase inhibitors while other types fail to respond. Thymectomy is recommended only if a neoplasm is suspected.

In addition to diagnosing congenital myasthenia, the pediatric ophthalmologist must monitor these patients for amblyopia due to paralytic strabismus. Standard occlusion therapy should be instituted when amblyopia is suspected.

Juvenile Myasthenia

Juvenile myasthenia refers to the syndromes of limited ocular disease or generalized systemic weakness that are virtually identical in presentation, pathogenesis, course, and

treatment to the adult form of the disease (109). Patients always present after 1 year of age, and more than 75% of cases develop after age 10. Ptosis, diplopia, and facial diplegia are common presentations, and ophthalmologists must not become so entranced with the ophthalmic manifestations that they overlook subtle but potentially life-threatening bulbar symptoms of dysarthria, dysphagia, fatigue, shortness of breath, or nocturnal regurgitation of salivary secretions. Some children, usually between 2 and 10 years of age, develop an acute “malignant” variety of myasthenia gravis with acute bulbar symptoms progressing to acute respiratory failure within 24 hours.

Pathogenesis

The weakness and fatigue produced by myasthenia result from impaired neuromuscular transmission because of a reduced number of acetylcholine receptors (AChR) at the neuromuscular junction. Abnormalities of the thymus gland occur in 75% of myasthenia patients, and the common association of other diseases with a probable immunopathogenesis such as Graves disease, Hashimoto thyroiditis, rheumatoid arthritis, pernicious anemia, and systemic lupus erythematosus provided the first indication that myasthenia also had an immune basis.

The occurrence of transient neonatal myasthenia in some infants of mothers with myasthenia suggested that transplacental passage of antibody produced the disease. Since then, anti-AChR antibodies have been detected in the serum of children and adults with myasthenia.

Three different mechanisms for antibody-mediated damage and the eventual reduction of AChR have been postulated: (a) blockage of the receptors' active sites, (b) destruction of the AChRs in a complement-dependent reaction, and (c) enhancement of the degradation rate of AChRs by cross-linking of the receptors with antibodies (110,111). Which of these mechanisms predominates in a particular patient is unknown.

INFANTILE BOTULISM

Because infantile botulism may present predominantly with ptosis before the development of paralysis and respiratory failure, it is possible to misdiagnose the condition as myasthenia. The critical differential diagnostic feature is enlarged pupils that respond poorly to direct light stimulation, which develops only with botulism and never with myasthenia. Ophthalmoplegia is relatively rare with botulism. Since the disease has such a fulminant onset, patients rarely present initially to a pediatric ophthalmologist. However, because of the combination of ptosis and pupillary dilation, an eye doctor may be the first physician to consider the diagnosis, even in the intensive care unit setting.

In adults, botulism develops from ingested food contaminated with toxin of *Clostridium botulinum.* A different pathogenesis exists for infants, for whom a history of honey ingestion or soil eating is obtained from the family. The honey and soil contain *C. botulinum* organisms that colonize the immature gut and produce toxin which is absorbed into the circulation (112). Diffuse autonomic dysfunction and hypotonia develop and progress to coma within 6 to 8 hours of the onset of symptoms. If proper respiratory support and intensive care are provided, the infants often improve spontaneously.

THIRD NERVE PALSY

Paralysis of the third cranial nerve in children demands a different diagnostic approach from that for the same clinical condition in adults. The best, and virtually only, clinical studies examining the problem in the pediatric population are those of Miller (113) and Harley (114).

Both studies reported an approximate 45% incidence of congenital third nerve palsies. It is helpful to think about cranial nerve III palsies in terms of congenital versus acquired. Congenital third nerve palsies are usually indicative of a developmental anomaly or birth trauma, although rare cases of third nerve neuroma have been reported (115). On the other hand, acquired third nerve palsies are often an ominous sign. Miller (113) found that the etiology of third nerve palsy includes: congenital 43%, trauma 20%, infection/inflammation 13%, tumor 10%, aneurysm 7%, and ophthalmic migraine 7%.

In congenital oculomotor nerve palsy, the pupil may or may not be involved, and both studies found a high incidence of aberrant regeneration developing in these patients.

Three of the patients with congenital third nerve palsies in Miller's study developed cyclic oculomotor palsy. This condition is usually diagnosed in the first year of life. It is characterized by complete oculomotor palsy with cyclic spasm of the affected muscles. During the spastic phase, the eye adducts, the lid elevates, and the pupil constricts. The spastic phase usually lasts less than 1 minute and is followed by the paretic phase. The alternating spasms and paralysis usually continue during sleep (116). In addition to being associated with congenital third nerve palsy, patients may have a history of an orbital or basilar skull fracture or meningitis.

Seven of Harley's 32 patients developed third nerve palsies in association with migraine headaches (“ophthalmoplegic migraine”). In very young patients, no history of migraine is available from the child but should be sought from parents or siblings.

The ophthalmoplegia is clinically indistinguishable from any other third nerve palsy and may develop at any time during the course of the headache, including the period after the pain has resolved. A history of cyclic vomiting, motion sickness, and vertigo suggests the diagnosis of ophthalmoplegic migraine. The ophthalmoplegia usually resolves within several weeks, although permanent ptosis, mydriasis, and oculomotor defects are described. When the pupil is involved and no definitive migraine history can be elicited, cerebral angiography may be necessary to exclude an aneurysm.

FOURTH NERVE PALSY

As for oculomotor paresis, Harley's series provides some of the best data regarding trochlear nerve palsies in children

(114). Twelve of the 18 patients had congenital fourth nerve palsies, seven being unilateral and five bilateral fourth nerve paralysis. Five patients demonstrated a trochlear nerve palsy after head trauma, and one manifested this problem after encephalitis.

SIXTH NERVE PALSY

The most common isolated cranial nerve palsy affecting ocular motility in childhood is a sixth nerve paresis. At one time, the key to the diagnosis and management of this condition was ascertaining the “isolated” nature of the problem; i.e., no other neurologic or ophthalmic signs or symptoms present. However, the studies of Harley (114) and Robertson and associates (117) found a 33% and 10% incidence, respectively, of neoplastic disease presenting with an isolated sixth nerve palsy. Many of these are brainstem glioma, which have a bleak prognosis regardless of the time of diagnosis, but some supratentorial and cerebellar lesions may first involve a sixth nerve palsy; delay in diagnosis can adversely affect the prognosis. In the era of MRI scanning, the risk-to-benefit ratio of an MRI is minimal, and this approach is now advocated in cases of sixth nerve palsy in children.

Unlike optic neuropathies for which the management is often dictated by whether the visual loss followed an acute, subacute, or slowly progressive cadence, the development of diplopia is invariably reported by patients as an acute event. Patients do not experience “a little double vision”—they either have true binocular diplopia or they do not. While the diplopia may be intermittent or constant, it is not similar to visual loss, which may worsen in hours, days, weeks, or months. Therefore, sixth nerve palsies can be judged to be acute or chronic only in retrospect. By this retrospective analysis, it has been determined that a benign, self-limited sixth nerve palsy syndrome exists for children. It has been suggested that this clinical syndrome is the sequela of a viral infection (118).

When a sixth nerve palsy is associated with ipsilateral ear and facial pain, a diagnosis of Gradenigo syndrome may be made. This condition is usually caused by middle ear infection, but tumors have presented with this constellation of findings, especially when hearing is preserved.

MISCELLANEOUS NEUROOPHTHALMIC SYNDROMES IN CHILDREN

Kearns-Sayre Syndrome

Kearns-Sayre syndrome is a form of chronic progressive external ophthalmoplegia (CPEO) with many associated abnormalities, including heart block and pigmentary degeneration of the retina (119). In addition to the symmetric ophthalmoplegia, ptosis, and orbicularis oculi weakness, patients invariably have short stature, a myopathy of skeletal muscle (ragged-red fibers), and elevated CSF protein. Other associated abnormalities may include hearing loss, peripheral neuropathy, cerebellar ataxia, pendular nystagmus, corticospinal tract dysfunction, corneal opacity, and problems with corticosteroid glucose and calcium metabolism.

Defects in pyruvate metabolism within the muscular and neural tissues of these patients have been suggested as a possible underlying etiology to explain the widespread problems. In contrast to adults with CPEO who are relatively healthy, children with Kearns-Sayre syndrome may be ill owing to the diffuse myopathy, neuropathy, encephalopathy, and endocrine disturbances. Moraes and coworkers (120) reported mitochondrial DNA deletions in both the adult CPEO syndrome and pediatric Kearns-Sayre disorder. Decreased activities of enzymes within the mitochondrial respiratory chain were found, but an exact correlation between the genetic, biochemical, and clinical manifestations remains to be established.

Ocular Motor Apraxia

Encompassing a congenital syndrome as well as several acquired varieties, ocular motor apraxia may present initially to the pediatric ophthalmologist. The entity is defined as the ability to initiate saccades in response to certain visual reflexes (such as vestibular or optokinetic stimulation), but a failure to initiate saccades on command.

Cogan (121) first described congenital ocular motor apraxia, which usually comes to attention during infancy. After several months, the child develops typical horizontal thrusting head movements for the eyes to change their object of fixation. The congenital syndrome is confined to horizontal eye movements, but the acquired condition involves both horizontal and vertical saccades. As the patient with congenital ocular motor apraxia becomes older, the eye movements improve and the head movements become less noticeable (122). This spontaneous improvement led Cogan to postulate that this entity may represent a developmental delay rather than a total absence of the pathways for horizontal voluntary saccades. Acquired ocular motor apraxia has been associated with virtually any disorder known to affect the initiation of voluntary saccades. According to Leigh and Zee (123), acquired ocular motor apraxia may be seen with Huntington chorea, Gaucher disease, olivopontocerebellar degeneration, atypical Niemann-Pick disease, Mobius syndrome, ataxia-telangiectasia, posterior fossa tumors, and bilateral frontoparietal lesions.

Spasmus Nutans

The triad of nystagmus, head nodding, and atypical head positions constitutes spasmus nutans (124). This poorly understood entity begins before 1 year of age and usually resolves spontaneously within 1 to 2 years. However, using eye movement recordings, Gottlob and colleagues (125) found that the nystagmus persisted in some patients up to 12 years of age. The nystagmus is frequently asymmetric, and unilateral forms have been described. The typical eye movement abnormality is a high-frequency, small-amplitude horizontal nystagmus. The nystagmus of spasmus nutans

is clinically indistinguishable from that associated with gliomata of the afferent visual system. Therefore, many ophthalmologists obtain an MRI for all patients before establishing the diagnosis of spasmus nutans. Young and associates (126) report a relatively high incidence of strabismus and amblyopia in the eye with the greater nystagmus; because of this, these children should be followed carefully.

Mobius Syndrome

The concurrence of facial diplegia with a horizontal eye movement problem should raise the possibility of Mobius syndrome. The horizontal eye movement difficulties range from an isolated sixth nerve paralysis to a complete horizontal gaze palsy. In addition, there may be tongue atrophy, head and neck deformities, and chest and extremity abnormalities. A developmental defect in and around the abducens nuclei has been suggested as a cause.

Cerebral Ataxia and Optic Atrophy

Although cerebellar ataxia has been associated with numerous neurologic syndromes, Nicolaides and coworkers (127) have defined what appears to be a new syndrome of ataxia with optic atrophy, as well as several other manifestations. All three patients demonstrated early normal development until cerebellar ataxia occurred following a febrile illness in infancy. In addition, the patients had generalized hypotonia, areflexia, flexor plantar responses, pes cavus, and progressive optic atrophy, as well as sensorineural hearing loss. The syndrome of cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural deafness has been designated as CAPOS syndrome. It has been postulated that CAPOS syndrome has either an autosomal-dominant or maternal mitochondrial inheritance pattern.

REFERENCES

1. Frisen L, Holmegaurd L. Spectrum of optic nerve hypoplasia. *Br J Ophthalmol* 1978;62:7-15.

2. Mosier MA, Lieberman MF, Green WR, et al. Hypoplasia of the optic nerve. *Arch Ophthalmol* 1978;96:1437-1442.

3. Whinery RD, Blodi FC. Hypoplasia of the optic nerve: a clinical and histopathologic correlation. *Trans Am Acad Ophthalmol Otolaryngol* 1963;67:733-738.

4. Kushner BJ. Functional amblyopia associated with organic ocular disease. *Am J Ophthalmol* 1981;91:39-45.

5. Kushner BJ. Functional amblyopia associated with abnormalities of the optic nerve. *Arch Ophthalmol* 1984;102:683-685.

6. Hoyt CS. Optic disc anomalies and maternal ingestion of LSD. *J Pediatr Ophthalmol* 1978;15:286-289.

7. Hoyt CS, Billison FA. Maternal anticonvulsants and optic nerve hypoplasia. *Br J Ophthalmol* 1978;62:3-6.

8. Peterson RA, Walton DS. Optic nerve hypoplasia with good visual acuity and visual field defects. *Arch Ophthalmol* 1977;95: 254-258.

9. Tajima T, Hattorri T, Nakajima T, et al. Sporadic heterozygous frameshift mutation of HESX1 causing pituitary and optic nerve hypoplasia and combined pituitary hormone deficiency in a Japanese patient. *J Clin Endocrinol Metab* 2003;88:45-50.

10. Thomas PQ, Dattani MT, Brickman JM, et al. Heterozygous HESX1 mutations associated with isolated congenital pituitary hypoplasia and septo-optic dysplasia. *Hum Mol Genet* 2001;10: 39-45.

11. Dattani ML, Martinez-Barbera J, Thomas PQ, et al. Molecular genetics of septo-optic dysplasia. *Horm Res* 2000;53:26-33.

12. Dattani MT, Martinez-Barbera JP, Thomas PQ, et al. Mutations in the homeobox gene *HESX1/Hesx1* associated with septo-optic dysplasia in human and mouse. *Nat Genet* 1998;19:125-133.

13. de Morsier G. [Studies on malformation of cranio-encephalic sutures. III. Agenesis of the septum lucidum with malformation of the optic tract.] *Schweiz Arch Neurol Psychiatr* 1956;77: 267-292.

14. de Morsier G. Median cranioencephalic dysraphias and olfactogenital dysplasia. *World Neurol* 1962;3:485-500.

15. Hoyt WG, Kaplan SL, Grumbach MM, et al. Septooptic dysplasia and pituitary dwarfism. *Lancet* 1970;1:893-894.

16. Kindler P. Morning glory syndrome: unusual congenital optic disc anomaly. *Am J Ophthalmol* 1970;69:376-384.

17. Irvine AR, Crawford JB, Sullivan JH. The pathogenesis of retinal detachment with morning glory disc and optic pit. *Retina* 1986; 6:146-150.

18. Chang S, Haik BG, Ellsworth RM, et al. Treatment of total retinal detachment in morning glory syndrome. *Am J Ophthalmol* 1984; 97:596-600.

19. Olsen TW. Visual acuity in children with colobomatous defects. *Curr Opin Ophthalmol* 1997;8:63-67.

20. Olsen TW, Summers CG, Knobloch WH. Predicting visual acuity in children with colobomas involving the optic nerve. *J Pediatr Ophthalmol Strabismus* 1996;33:47-51.

21. Daufenbach DR, Ruttum MS, Pulido JS, et al. Chorioretinal colobomas in a pediatric population. *Ophthalmology* 1998;105: 1455-1458.

22. Thiselton DL, Alexander C, Taanman JW, et al. A comprehensive survey of mutations in the OPA1 gene in patients with autosomal dominant optic atrophy. *Invest Ophthalmol Vis Sci* 2002;43: 1715-1724.

23. Pesch UE, Leo-Kottler B, Mayer S, et al. *OPA1* mutations in patients with autosomal dominant optic atrophy and evidence for semi-dominant inheritance. *Hum Mol Genet* 2001;10: 1359-1368.

24. Johnston RL, Seller MJ, Behnam JT, et al. Dominant optic atrophy. Refining the clinical diagnostic criteria in light of genetic linkage studies. *Ophthalmology* 1999;106:123-128.

25. Kjer P. Infantile optic atrophy with dominant mode of inheritance: a clinical and genetic study of 19 Danish families. *Acta Ophthalmol (Copenh)* 1959;164(Suppl 54):1-147.

26. Waardenburg PJ, Franceshetti A, Klein D, eds. *Genetics and ophthalmology*, vol. 2. Assen, Netherlands: Van Gorcum, 1953: 1623.

27. Kline LB, Glaser JS. Dominant optic atrophy: the clinical profile. *Arch Ophthalmol* 1979;97:1680-1686.

28. Kennedy C, Carroll FD. Optic neuritis in children. *Arch Ophthalmol* 1960;63:747-755.

29. Meadows SP. Retrobulbar and optic neuritis in childhood and adolescence. *Trans Ophthalmol Soc UK* 1969;89:603-638.

30. Rollinson RD. Bilateral optic neuritis in childhood. *Med J Aust* 1977;2:50-51.

31. Beck RW, Cleary PA. Optic neuritis treatment trial. One-year follow-up results. *Arch Ophthalmol* 1993;111:773-775.

32. The Optic Neuritis Study Group. Visual function 5 years after optic neuritis. Experience of the Optic Neuritis Treatment Trial. *Arch Ophthalmol* 1997;115:1545-1552.

33. Leber T. Die pseudonephritischen netzhauterkrankungen die tetinitis dtellata: die purtschershe netzhautaffektron nach schwerer dchadelverletzung. In: Graef AC, Saemisch T, eds. *Graefe-saemisch handbuch der gesamten augenheilkundle*, 2nd ed. Leipzig, Germany: Ergelmann, 1916:1319-1339.

34. Gass JD. Diseases of the optic nerve that may simulate macular disease. *Trans Am Acad Ophthalmol Otolaryngol* 1977;83: 763-770.

35. Parmley VC, Scheffman JS, Maitland CG, et al. Does neuroretinitis rule out multiple sclerosis? *Arch Neurol* 1987;44:1045-1048.

36. Dreyer RF, Hapen G, Gass JD, et al. Leber's idiopathic stellate neuroretinitis. *Arch Ophthalmol* 1984;102:1140-1145.

37. Frey T. Optic neuritis in children: infectious mononucleosis as an etiology. *Doc Ophthalmol* 1973;34:183-188.

38. Maitland CG, Miller NR. Neuroretinitis. *Arch Ophthalmol* 1984; 102:1146-1150.

39. Farthing CF, Howard RS, Thin RN. Papillitis and hepatitis B. *Br Med J (Clin Res Ed)* 1986;292:1712.

40. Lesser RL, Kormehl EW, Pachrer AR, et al. Neuroophthalmologic manifestations of Lyme disease. *Ophthalmology* 1990;97: 699-706.

41. Fewell AG. Unilateral neuroretinitis of syphilitic origin with a striate figure in the macula. *Arch Ophthalmol* 1932;8:615.

42. Roach ES, Zimmerman CF, Troost BT, et al. Optic neuritis due to acquired toxoplasmosis. *Pediatr Neurol* 1985;1:114-116.

43. Miller NR. *Walsh and Hoyt's clinical neuro-ophthalmology*, 4th ed. Baltimore: Williams & Wilkins, 1995:4487-4489.

44. Scott GI. Neuromyelitis optica. *Am J Ophthalmol* 1952;35: 755-764.

45. Poser CM, Van Bogaert L. Natural history and evolution of the concept of Schilder's diffuse sclerosis. *Acta Psychiatr New Scand* 1956;31:285-331.

46. Kurul S, Cakmakci H, Dirik E, et al. Schilder's disease: case study with serial neuroimaging. *J Child Neurol* 2003;18:58-61.

47. Fitzgerald MJ, Coleman LT. Recurrent myelinoclastic diffuse sclerosis: a case report of a child with Schilder's variant of multiple sclerosis. *Pediatr Radiol* 2000;30:861-865.

48. Garell PC, Menezes AH, Baumbach G, et al. Presentation, management and follow-up of Schilder's disease. *Pediatr Neurosurg* 1998;29:86-91.

49. Afifi AK, Follett KA, Greenlee J, et al. Optic neuritis: a novel presentation of Schilder's disease. *J Child Neurol* 2001;16: 693-696.

50. Pretorius ML, Loock DB, Ravenscroft A, et al. Demyelinating disease of Schilder type in three young South African children: dramatic response to corticosteroids. *J Child Neurol* 1998;13: 197-201.

51. Meadows SP. The swollen disc. *Trans Ophthalmol Soc UK* 1959; 79:121-143.

52. Rush JA. Pseudotumor cerebri. *Mayo Clin Proc* 1980;55:541-546.

53. Miller NR, ed. *Walsh and Hoyt's clinical neuro-ophthalmology*, 4th ed. Baltimore: Williams & Wilkins, 1982:193.

54. Cogan DG. Blackouts not obviously due to carotid occlusion. *Arch Ophthalmol* 1965;73:461-462.

55. Helmke K, Hansen HC. Fundamentals of transorbital sonographic evaluation of optic nerve sheath expansion under intracranial hypertension. II. Patient study. *Pediatr Radiol* 1996;26: 706-710.

56. Sergott RC. Diagnoses and management of vision-threatening papilledema. *Semin Neurol* 1986;6:176-184.

57. Beck RW, Greenberg HS. Post-decompression optic neuropathy. *J Neurosurg* 1988;63:196-199.

58. Balcer LJ, Liu GT, Forman S, et al. Idiopathic intracranial hypertension: relation of age and obesity in children. *Neurology* 1999; 52:870-872.

59. Cinciripini GS, Donahue S, Borchert MS. Idiopathic intracranial hypertension in prepubertal pediatric patients: characteristics, treatment, and outcome. *Am J Ophthalmol* 1999;127:178-182.

60. Lee AG, Patrinely JR, Edmond JC. Optic nerve sheath decompression in pediatric pseudotumor cerebri. *Ophthalmic Surg Lasers* 1998;29:514-517.

61. Burgett RA, Purvin VA, Kawasaki A. Lumboperitoneal shunting for pseudotumor cerebri. *Neurology* 1997;49:734-739.

62. Eggenberger ER, Miller NR, Vitale S. Lumboperitoneal shunt for the treatment of pseudotumor cerebri. *Neurology* 1996;46: 1524-1530.

63. Luberichs J, Leo-Kottler B, Besch D, et al. A mutational hot spot in the mitochondrial ND6 gene in patients with Leber's hereditary optic neuropathy. *Graefes Arch Clin Exp Ophthalmol* 2002; 240:96-100.

64. Fauser S, Luberichs J, Besch D, et al. Sequence analysis of the complete mitochondrial genome in patients with Leber's hereditary optic neuropathy lacking the three most common pathogenic DNA mutations. *Biochem Biophys Res Commun* 2002;295: 342-347.

65. Chinnery PF, Brown DT, Andrews RM, et al. The mitochondrial ND6 gene is a hot spot for mutations that cause Leber's hereditary optic neuropathy. *Brain* 2001;124:209-218.

66. Smith JL, Hoyt WF, Susac JO. Ocular fundus in acute Leber's optic neuropathy. *Arch Ophthalmol* 1973;90:349-354.

67. McLeod JG, Low PA, Morgan JA. Charcot-Marie-Tooth disease with Leber's optic atrophy. *Neurology* 1978;28:179-184.

68. Rose FC, Bowden AN, Bowden PMA. The heart in Leber's optic atrophy. *Br J Ophthalmol* 1970;54:388-393.

69. Chutorian AM, Schwartz JF, Evans RA, et al. Optic gliomas in children. *Neurology* 1964;14:83-95.

70. Miller NR, Iliff WJ, Green WR. Evaluation and management of gliomas of the anterior visual pathways. *Brain* 1974;97:743-754.

71. Kanamori N, Shibuya M, Yoshida J, et al. Long-term follow-up of patients with optic glioma. *Childs Nerv Syst* 1985;1:272-278.

72. Banna M, Hoore RD, Stanley P, et al. Craniopharyngioma in children. *J Pediatr* 1973;83:781-785.

73. Koos WT, Miller MH. *Intracranial tumors of infants and children*. Stuttgart, Germany: Georg Thieme Verlag, 1971.

74. Stripp DC, Maity A, Janss AJ, et al. Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. *Technol Int J Radiat Oncol Biol Phys* 2004; 58:714-720.

75. Selch MT, DeSalles AA, Wade M, et al. Initial clinical results of stereotactic radiotherapy for the treatment of craniopharyngiomas. *Med Cancer Res Treat* 2002;1:51-59.

76. Kalapurakal JA, Goldman S, Hsieh YC, et al. Clinical outcome in children with craniopharyngioma treated with primary surgery and radiotherapy deferred until relapse. *Pediatr Oncol* 2003; 40:214-218.

77. Varlotto JM, Flickinger JC, Kondziolka D, et al. External beam irradiation of craniopharyngiomas: long-term analysis of tumor control and morbidity. *Int J Radiat Oncol Biol Phys* 2002;54: 492-499.

78. Isaac MA, Hahn SS, Kim JA, et al. Management of craniopharyngioma. *Cancer J* 2001;7:516-520.

79. Fisher PG, Jenab J, Goldthwaite PT, et al. Outcomes and failure patterns in childhood craniopharyngiomas. *Childs Nerv Syst* 1998;14:558-563.

80. Donin JF. Acquired monocular nystagmus in children. *Can J Ophthalmol* 1967;2:212-215.

81. Kelly TW. Optic glioma presenting as spasmus nutans. *Pediatrics* 1970;45:295-296.

82. Schulman JA, Shults TA, Jones JR. Monocular vertical nystagmus as an initial sign of chiasmal glioma. *Am J Ophthalmol* 1987;87: 87-90.

83. Maitland CG, Ahiko S, Hoyt WE, et al. Chiasmal apoplexy: report of four cases. *J Neurosurg* 1982;56:118-122.

84. Hoyt WF, Baghdassarian SA. Optic glioma of childhood: natural history and rationale for conservative management. *Br J Ophthalmol* 1969;53:793-798.

85. Glaser JS, Hoyt WF, Corbett J. Visual morbidity with chiasmal glioma. *Arch Ophthalmol* 1971;85:3-12.

86. Tow SL, Chandela S, Miller NR, et al. Long-term outcome in children with gliomas of the anterior visual pathway. *Pediatr Neurol* 2003;28:262-270.

87. Allen JC. Initial management of children with hypothalamic and thalamic tumors and the modifying role of neurofibromatosis—1. *Pediatr Neurosurg* 2000;32:154-162.

88. Imes RK, Hoyt WF. Childhood chiasmal gliomas: update on the fate of patients in the 1969 San Francisco study. *Br J Ophthalmol* 1986;70:179-182.

89. Khafaga Y, Hassounah M, Kandil A, et al. Optic gliomas: a retrospective analysis of 50 cases. *Int J Radiat Oncol Biol Phys* 2003; 56:807-812.

90. Daroff RB. See-saw nystagmus. *Neurology* 1965;15:874-877.

91. Gay AJ, Brodkey J, Miller JE. Convergence-retraction nystagmus: an electromyographic study. *Arch Ophthalmol* 1963;70.453-458.

92. Cobbs WH, Schatz NJ, Savino PJ. Midbrain eye signs in hydrocephalus. *Trans Am Neurol Assoc* 1978;103:130.

93. Daroff RB, Troost BT. Upbeat nystagmus. *JAMA* 1973;225:312.

94. Schatz NJ, Schlezinger NS, Berry RG. Vertical upbeat nystagmus on downward gaze: a clinical pathologic correlation. *Neurology* 1975;25:380.

95. Cogan DG. Downbeat nystagmus. *Arch Ophthalmol* 1968;80: 757-768.

96. Cogan DG, Barrows JL. Platybasia and the Arnold-Chiari malformation. *Arch Ophthalmol* 1954;52:13-29.

97. Zee DS, Friendlech AR, Robinson DA. The mechanism of downbeat nystagmus. *Arch Neurol* 1974;30:227-237.

98. Baloh RW, Honrubia V, Konrad HR. Periodic alternating nystagmus. *Brain* 1976;99:11-26.

99. Towle PA, Romanul F. Periodic alternating nystagmus: first pathologically studied case. *Neurology* 1970;20:408.

100. Gradstein L, Reinecke RD, Wizov SS, et al. Congenital periodic alternating nystagmus. Diagnosis and management. *Ophthalmology* 1997;104:918-928.

101. Abadi RV, Pascal E. Periodic alternating nystagmus in humans with albinism. *Invest Ophthalmol Vis Sci* 1994;35:4080-4086.

102. Cogan DG. Ocular dysmetria: flutter-like oscillations of the eyes and opsoclonus. *Arch Ophthalmol* 1954;51:318-335.

103. Ellenberger C Jr, Keltner JL, Stroud MH. Ocular-dyskinesia in cerebellar disease: evidence for the similarity of opsoclonus, ocular dysmetria, and flutter-like oscillations. *Brain* 1972;95: 685-692.

104. Sergott RC, Glaser JS, Berger LJ. Simultaneous bilateral diabetic ophthalmoplegia: report of two cases and discussions of differential diagnosis. *Ophthalmology* 1984;91:18-22.

105. Namba T, Brown SB, Grob D. Neonatal myasthenia gravis: report of two cases and review of the literature. *Pediatrics* 1970;45: 488-504.

106. Levin PM. Congenital myasthenia in siblings. *Arch Neurol* 1949; 62:745-748.

107. Namba T, Brunner NG, Brown SB, et al. Familial myasthenia gravis: report of 27 patients in 12 families and review of 164 patients in 73 families. *Arch Neurol* 1971;25:49-60.

108. Engel AG, Walls TJ, Nagel A, et al. Newly recognized congenital myasthenic syndromes. I: congenital paucity of synaptic vesicles and reduced quantal release. II: high-conductance fast-channel syndrome. III: abnormal acetylcholine receptor (AChR) interaction with acetylcholine. IV: AChR deficiency and short channelopen time. *Prog Brain Res* 1990;84:124-137.

109. Millichap JG, Dodge PR. Diagnosis and treatment of myasthenia gravis in infancy, childhood, and adolescence. *Neurology* 1960; 11:1007-1014.

110. Drochman DB. Present and future treatment of myasthenia gravis. *N Engl J Med* 1987;316:743-745.

111. Fambrough DM, Drochman DB, Satyamurti S. Neuromuscular junction in myasthenia gravis: decreased acetylcholine receptors. *Science* 1973;182:293-295.

112. Arnon SS, Midura TF, Clay SA, et al. Infant botulism: epidemiological, clinical and laboratory aspects. *JAMA* 1977;237: 1946-1951.

113. Miller NR. Solitary oculomotor nerve palsy in childhood. *Am J Ophthalmol* 1977;83:106-111.

114. Harley RD. Paralytic strabismus in children: etiology, incidence, and management of the third, fourth, and sixth nerve palsies. *Ophthalmology* 1980;87:24-43.

115. Norman AA, Farris BK, Siatkowski RM. Neuroma as a cause of oculomotor palsy in infancy and early childhood. *J AAPOS* 2001; 5:9-12.

116. Loewenfeld H, Thompson HS. Oculomotor pareses with cyclic spasms: a critical review of the literature and new case. *Surv Ophthalmol* 1975;20:81-124.

117. Robertson DM, Hanes JD, Rucker CW. Acquired sixth nerve pareses in children. *Arch Ophthalmol* 1970;83:574-579.

118. Knox DL, Clark DB, Schuster EF. Benign VI nerve palsies in children. *Pediatrics* 1967;40:560-564.

119. Kearns TP, Sayre GP. Retinitis pigmentosa, external ophthalmoplegia, and complete heart block. *Arch Ophthalmol* 1958;60: 280-289.

120. Moraes CT, DiMauro S, Zeviani M, et al. Mitochondrial DNA deletions in progressive external ophthalmoplegia and Kearns Sayre syndrome. *N Engl J Med* 1989;320:1293-1299.

121. Cogan DG. A type of congenital ocular motor apraxia presenting jerky head movements. *Trans Am Acad Ophthalmol* 1952;56: 853-862.

122. Cogan DG, Chu FC, Reingold D, et al. A long-term follow-up of congenital ocular motor apraxia. *Neuroophthalmology* 1980;1: 145-147.

123. Leigh RJ, Zee DS. *The neurology of eye movement*. Philadelphia: FA Davis Co., 1983.

124. Norton EWD, Cogan DG. Spasmus nutans: a clinical study of 20 cases followed two years or more since onset. *Arch Ophthalmol* 1954;152:442-446.

125. Gottlob I, Wizov SS, Reinecke RD. Spasmus nutans. A long-term follow-up. *Invest Ophthalmol Vis Sci* 1995;36:2768-2771.

126. Young TL, Weis JR, Summers CG, et al. The association of strabismus, amblyopia, and refractive errors in spasmus nutans. *Ophthalmology* 1997;104:112-117.

127. Nicolaides P, Appleton RE, Fryer A. Cerebellar ataxia, are flexia, pes cavus, optic atrophy and sensorineural hearing loss (CAPOS): a new syndrome. *J Med Genet* 1996;33:419-421.

128. Smith DP. The assessment of acquired dyschromatopsia and clinical investigation of the acquired tritan defect in dominantly inherited juvenile atrophy. *Am J Optom* 1972;49:574-588.

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25

Nystagmus

Mitchell B. Strominger

Nystagmus is a rhythmic oscillation of one or both eyes. It can be transiently evoked physiologically or persistently manifested as a nonspecific sign of abnormality. Developmental and hereditary anomalies of the eye and central nervous system (CNS) or even toxicity of pharmacologic agents can all be associated with nystagmus. Nystagmus can also arise from an inherited or idiopathic defect in fixation, gaze holding, or the vestibular apparatus.

HISTORY

When patients with nystagmus are evaluated, the history is extremely important to determine the etiology. The history should detail when the nystagmus was first noted and if it changed over time. Also important is whether it is constant throughout the day, changes depending on visual attentiveness, or is associated with a face turn or head movement. The prenatal history is explored for intrauterine infections, especially toxoplasmosis or rubella. A maternal history of anticonvulsant or psychogenic drug use or gestational diabetes may suggest optic nerve hypoplasia (ONH). The birth history is directed towards prematurity, neonatal asphyxia with cerebral hypoxia, and known neurologic problems, especially intraventricular hemorrhage and hydrocephalus, or developmental delay.

The family history gives information as to a possible hereditary factor. Other family members with nystagmus suggests congenital motor efferent nystagmus. A family history of night blindness or color deficiency suggests congenital stationary night blindness (CSNB) or achromatopsia. For the latter condition, the family history may be especially important, because not every child with achromatopsia shows photophobia in the first few months of life (1). The family's ethnic background may suggest a metabolic condition, such as Tay-Sachs disease, or a lipofuscinosis.

EXAMINATION

Examination of the symmetry of the face, the position of the ears, dental anomalies, skin tags, and pigmentation is helpful in identifying a developmental syndrome or albinism. The visual acuity is tested binocularly first and then monocularly, at distance and near fixation, and with and without any idiosyncratic head position. In infants, the ability to fixate on and follow moving objects and the use of visual clues is noted. The ability to optically elicit ocular movements using an optokinetic nystagmus tape or drum should also be noted. In the absence of the latter, there is a high likelihood that vision is grossly defective.

The characteristic of the nystagmus waveform should be noted, although this can change during the first year of life (2). It is described by its plane, amplitude, frequency, and symmetry. The plane of oscillation may be principally horizontal, vertical, oblique, or rotary (torsional). The amplitude may be fine (less than 5 degrees), medium (5 to 15 degrees), or large (greater than 15 degrees). If the oscillations are of similar speed in either direction, it is classified as a pendular nystagmus. A nystagmus is considered jerk if there is a biphasic rhythm with a fast phase in one direction, followed by a slow phase in the opposite direction. The frequency should be noted as high, low, or in cycles per second (Hz). A slit lamp or ophthalmoscope can be used to magnify ocular movements. Electronystagmography allows a more exact and permanent objective recording.

The nystagmus is observed for an extended period to determine whether it regularly changes direction with time, suggesting periodic alternating nystagmus (PAN); if both eyes move conjugately; if the pattern changes with eye position; and if the frequency or amplitude varies. Nystagmus that remains horizontal on vertical gaze suggests a diagnosis of congenital motor nystagmus, latent nystagmus (LN), PAN, or peripheral vestibular nystagmus (3).

The pupillary response is then observed for a paradoxic pupillary dilation with decreased illumination. The immediate pupil response on decreasing illumination after light adaptation is noted. An immediate constriction during the first 20 seconds, followed by a slow dilation after 1 minute, would be most typical of CSNB, achromatopsia, or ONH. However, a similar response has been reported in some patients with Leber congenital amaurosis (LCA), Best disease, albinism, and retinitis pigmentosa (1,3).

Examination of the eye should detect any severe bilateral ocular abnormality. Obvious bilateral anterior segment malformation, such as dysgenesis, congenital cataracts, or congenital glaucoma, does not usually cause a diagnostic problem. The irides are examined for transillumination defects that would suggest albinism. An obvious posterior pole abnormality, such as cicatricial retinopathy of prematurity (ROP), retinoblastoma, or coloboma, is also easily recognized. A blunted foveal reflex would suggest albinism. Finally, the optic nerve is examined for pallor, hypoplasia, or increased cupping.

A clinical dilemma arises when an ocular malformation either does not exist or is very subtle. Conditions such as LCA, achromatopsia, CSNB, hereditary optic atrophy, mild ONH, and ocular albinism may be difficult or impossible to detect on clinical examination alone. In such cases, an electroretinogram (ERG) should be performed.

NYSTAGMUS ASSOCIATED WITH NEUROLOGIC DISORDERS

Acquired Fixation Nystagmus

Posterior fossa disease may bring about a jerk or pendular, horizontal or vertical nystagmus and oscillopsia on attempted fixation. Fixation nystagmus is usually associated with demyelinating disease of the brainstem (3). Rarely it occurs congenitally in association with an afferent or efferent visual pathway disorder. It diminishes when fixation is abolished.

Convergence-Retraction Nystagmus

Variable bursts of sustained convergence and retraction of the eyes on attempted upgaze suggest a midbrain disorder. Co-contraction of all the extraocular muscles causes retraction with convergence because of the greater strength of the medial rectus muscles. In infants, one would suspect congenital aqueductal stenosis, in children a pinealoma or obstructive hydrocephalus, and in older adults a vascular accident in the tectal or pretectal area. Parinaud syndrome is convergence-retraction nystagmus in association with vertical eye movement palsies, pupillary abnormalities, lid retraction, and accommodative spasm (4,5).

Seesaw Nystagmus

Seesaw nystagmus is a unique vertical-torsional oscillation of both eyes in which one eye rises and intorts and its fellow eye falls and extorts. The nystagmic movement is usually pendular, and the disjunctive vertical movement alternates to provide the seesaw effect. This disorder may be congenital, but most patients have large, extrinsic parasellar tumors (i.e., craniopharyngioma) expanding within the third ventricle and compressing the brainstem. Acquired oscillopsia and bitemporal hemianopsia are associated findings (6,7). Rarely a jerk waveform presents with an intrinsic focal brainstem lesion in the lateral medulla or

mesodiencephalon (8). Other causes include severe head trauma, syringobulbia, and multiple sclerosis.

Periodic Alternating Nystagmus

PAN is a horizontal jerk nystagmus in which the direction of the fast phase changes spontaneously and cyclically with an intervening neutral period. A typical cycle lasts 1 to 6 minutes. A sequence of jerk waveforms in one direction converts to a neutral period of pendular waveforms, followed by jerk waveforms in the opposite direction. Alternating head turns may accompany the jerk nystagmus periods. PAN appears to result from a spatial and temporal shift in the null zone (9). PAN usually remains horizontal in vertical gaze. It may prevail during sleep and may coexist with downbeat nystagmus, both of which suggest an abnormality in the caudal medulla (10). Up to one-third of patients with albinism demonstrate PAN (9). Acquired PAM, which has different characteristics than the congenital form, occurs most commonly with disease involving the midline cerebellum. Inhibitory pathways that use gammaaminobutyric acid (GABA) in the nodulus and uvula control the time course of rotationally induced nystagmus (11). Experimental injury in monkeys activates a repair mechanism that reverses the direction of the induced nystagmus, thus producing the oscillations of PAN (12,13). Baclofen, a GABA agonist, can be effective in treating PAN (14).

Downbeat Nystagmus

Downbeat nystagmus is recognized by a deficit in downward pursuit whereby the eyes drift upward, and a corrective saccade returns the eyes to the primary position. It is maximal in downgaze and lateral gaze and when the head is erect or hyperextended. A rare congenital form has been identified. It is usually hereditary, self limited, and associated with good vision and a normal neurologic examination. A compensatory chin-down head posture is sometimes noted which does not require surgery. An acquired hereditary form of downbeat nystagmus may precede spinocerebellar degeneration (15). More commonly, downbeat nystagmus is acquired. Oscillopsia is usually present. Structural lesions at the craniocervical junction produce compression of the caudal brainstem. These lesions should be investigated with sagittal magnetic resonance imaging (MRI). Cerebellar ectopia due to the Arnold-Chiari malformation is often discovered (Fig. 25.1). Basilar impression, platybasia, dolichoectasia of the vertebrobasilar arteries, and cerebellar degeneration are other well-known causes. Alcohol, lithium, tranquilizers, and anticonvulsants may also give rise to this condition (16,17,18).

Upbeat Nystagmus

A vertical vestibular or smooth pursuit deficit similar in type but opposite in direction to downbeat nystagmus is thought to cause upbeat nystagmus, which may increase or convert to downbeat nystagmus with convergence. It may occur congenitally as a variant of congenital nystagmus (CN) with anterior visual pathway disease (19). Acquired forms occur with lesions of the brainstem (mainly the pontomesencephalic junction, rostral medulla, or caudal pons), cerebellar vermis, or after meningitis (20,21).

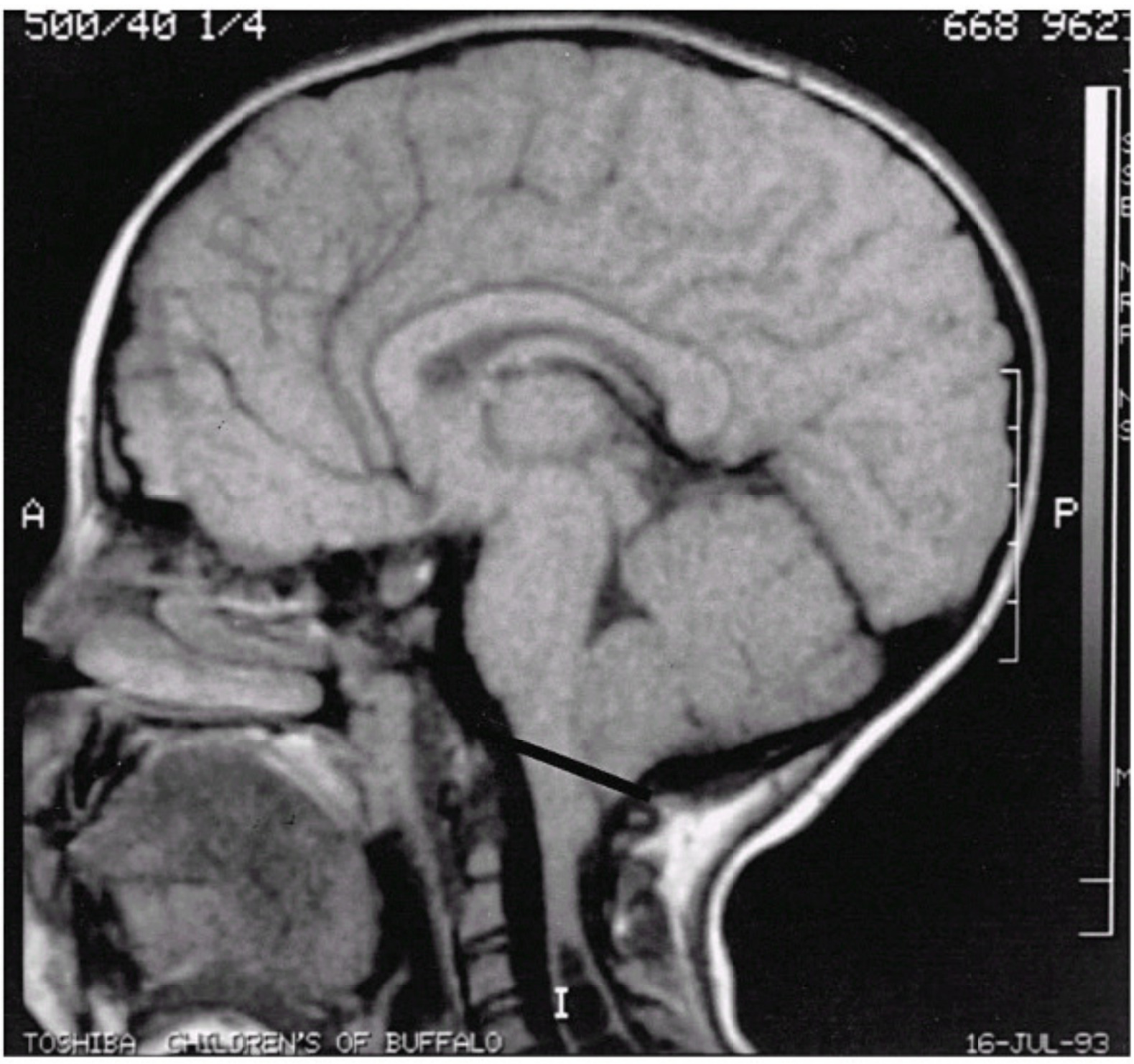

Figure 25.1 Arnold-Chiari malformation. Sagittal magnetic resonance imaging scan of type I Arnold-Chiari malformation with mild cerebellar tonsillar herniation below line. Note associated syrinx in cervical cord.

Gaze Paretic Nystagmus

Parietooccipital, cerebellar, and brainstem lesions that affect the conjugate gaze mechanism cause a gaze paretic nystagmus. The dysfunction is similar to endpoint nystagmus except that it occurs in a less extreme position of gaze and is of greater amplitude. In addition, patients recovering from gaze palsy often go through a phase when they cannot maintain an eccentric gaze and the eyes drift slowly back to the primary position. A corrective saccade repositions the eyes eccentrically. The nystagmus fast phase is in the direction of gaze. Barbiturates and phenytoin can cause a similar nystagmus (22).

Central Vestibular Nystagmus

A lesion of the vestibular nuclei or its pathways produces a horizontal and rotary jerk nystagmus on lateral gaze, usually to the side opposite the lesion. It may be bidirectional, beating to the left on left gaze and to the right on right gaze, and may become vertical on vertical gaze. Vertigo, tinnitus, and deafness are not usually associated. The nystagmus may be chronic if the underlying cause cannot be corrected. It is usually a sign of demyelinating disease, vascular accident, encephalitis, or tumor (23,24).

Peripheral Vestibular Nystagmus

Lesions of the labyrinth or eighth nerve cause a horizontal and rotary jerk nystagmus on lateral gaze opposite the side of the lesion. Vertigo may be marked, and tinnitus and deafness occur in concert. Visual fixation decreases the intensity of the nystagmus and vertigo, which lasts minutes, days, or weeks. Central pathways eventually compensate even if the underlying cause remains. Common causes are Meniere disease, infectious or vascular disorders, and trauma (25,26).

NYSTAGMUS ASSOCIATED WITH OCULAR DISORDERS

Visual loss, or the lack of visual development, within the first 2 years of life is usually associated with nystagmus. After 6 years of age, visual loss usually does not result in nystagmus. Between 2 and 6 years of age, visual loss is variably associated with nystagmus. Acquired monocular visual loss, due to an anterior visual pathway tumor or other ocular disorder, may be associated with a fine, rapid, monocular nystagmus (27,28). Nystagmus is usually not present in patients with cortical blindness because of the retention of visual input to the brain via the extrageniculostriate visual system (29).

Table 25.1 lists the ocular conditions associated with

nystagmus. Disorders are divided into those with and without strabismus. The latter are subdivided into spasmus nutans and nystagmus due to afferent abnormalities. A distinction between afferent “sensory” and efferent “motor” nystagmus is maintained in this chapter, although there is eye movement recording evidence that CN is probably a single entity regardless of associated sensory abnormalities (30). The afferent abnormalities include all the nonstrabismic ocular conditions associated with nystagmus, of which those without obvious ocular abnormalities are the major focus of this chapter. Also, causes of searching versus pendular nystagmus are differentiated but most likely they represent a spectrum with the former having visual input worse than 20/200 leading to a larger amplitude, lower frequency, pendular nystagmus with shorter foveation times.

TABLE 25.1 OCULAR CONDITIONS ASSOCIATED WITH NYSTAGMUS

I. Nonstrabismic ocular conditions associated with nystagmus

A. Afferent conditions with obvious bilateral malformation, dysgenesis, or tumor

1. Ocular coloboma

2. Congenital cataract

3. Congenital glaucoma

4. Retinoblastoma

5. Cicatricial retinopathy of prematurity

6. Iridocorneal dysgenesis

7. Aniridia

8. Persistent hyperplastic primary vitreous

9. Retinal dysplasia

10. Congenital toxoplasmosis

11. Congenital “macular coloboma”

B. Spasmus nutans

C. Afferent conditions without obvious ocular malformation, dysgenesis, or tumor

1. Conditions typically associated with searching nystagmus

a. Leber congenital amaurosis

b. Bilateral optic nerve hypoplasia/atrophy

2. Conditions typically associated with pendular nystagmus

a. Albinism

i. Ocular albinism

ii. Oculocutaneous albinism

b. Achromatopsia

c. Congenital stationary night blindness

d. Macular disorders

i. Congenital retinoschisis

i. Congenital retinoschisis

II. Strabismus associated with nystagmus

A. Nystagmus blockage syndrome

B. Latent nystagmus

C. Manifest latent nystagmus

Modified from Catalano RA, Calhoun JH. Ocular conditions associated with nystagmus. In: Reinecke RD, ed. *Ophthalmology annual, 1988*. New York: Raven Press, 1988 : 90, with permission.

Figure 25.2 therefore demonstrates a simplified algorithm for examining a child or infant with nystagmus. In this algorithm, the nature of the nystagmus is used to direct the workup. If the nystagmus is asymmetric, rapid, and pendular, the workup is that for spasmus nutans; if it is symmetric and searching, the workup is directed toward severe retinal and optic nerve disorders; if it is symmetric and pendular and not periodic and alternating, diagnosis is directed toward albinism, isolated cone dysfunction, or macular abnormalities. Congenital motor nystagmus is a diagnosis of exclusion, with a reasonably good visual prognosis.

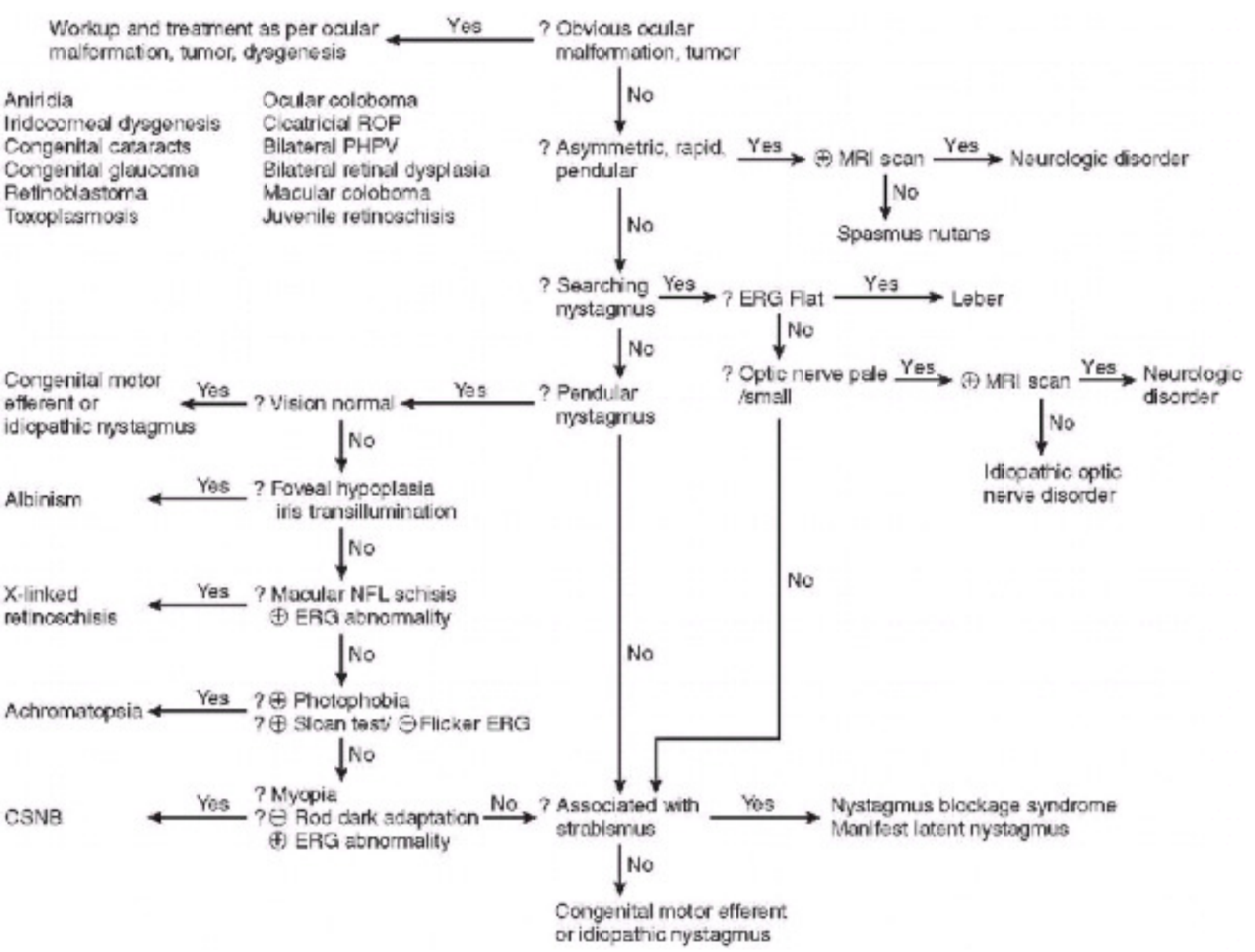

Figure 25.2 Algorithm for the workup of an infant with nystagmus. ?, Positive; [circled minus], negative; ERG, electroretinogram; ROP, retinopathy of prematurity; PHPV, persistent hyperplastic primary vitreous; NFL, nerve fiber layer; CSNB, congenital stationary night blindness.

Nonstrabismic Ocular Conditions Associated with Nystagmus

Afferent Conditions with Obvious Ocular Malformation

Any congenital or perinatal condition that results in occlusion of the visual axis, distortion of the retinal image, or malformation of the sensory retina or optic nerve can result in nystagmus. Although electronystagmography may show complex or varied waveforms, the type of nystagmus is often related to the severity of the visual impairment. A moderate disruption in vision may result in pendular nystagmus, whereas a more severe form of the same disorder may produce a searching nystagmus. Although this may be

helpful prognostically, ocular malformations usually are readily recognized. The more common ocular malformations in which nystagmus may be a prominent sign include bilateral coloboma (31), congenital cataracts (32), congenital glaucoma (33), retinoblastoma (34), bilateral cicatricial ROP (35), iridocorneal dysgenesis (36), aniridia (37), persistent hyperplastic primary vitreous (38), bilateral retinal dysplasia (39), congenital toxoplasmosis with macular involvement (40), and congenital macular colobomata (41).

Spasmus Nutans

The classic triad of signs in spasmus nutans includes (a) monocular or dissociated, pendular, small-amplitude, rapid (high-frequency) nystagmus; (b) head nodding; and (c) an anomalous head position. However, there are numerous reports of children who have spasmus nutans without head nodding or head tilt (42). Spasmus nutans is usually acquired between 4 and 8 months of age and clinically ceases spontaneously by 3 years of age. It can, however, be variable in its onset and duration. Nystagmus may persist subclinically into the first decade of life; eye movement recordings in older children have demonstrated persistent asymmetric, fine, pendular nystagmus. Approximately one-third of patients may develop normal acuity and stereopsis (43). The head nodding is a compensatory vestibuloocular reflex to suppress the nystagmus (44).

A similar clinical presentation has been noted in children with chiasmatic glioma (45), subacute necrotizing encephalopathy (46), the retinal disorders of achromatopsia (47), CSNB (48), and rod dystrophy (49). Associated clinical findings may be helpful in distinguishing CNS disorders from spasmus nutans. These include any signs of optic neuropathy (decreased vision, afferent pupil defect, optic disc pallor, or atrophy), vertical or seesaw nystagmus, diencephalic syndrome (failure to thrive, diabetes insipidus, excessive appetite), and increased intracranial pressure with hydrocephalus. Eye movement recordings do not differentiate spasmus nutans patients with or without CNS disease (50). Electroretinography should be considered to identify patients with underlying retinal disease (49). In the absence of associated signs, however, spasmus nutans is usually considered a diagnosis of exclusion. Older age at onset (older than 2 years old) should raise suspicion, and it is usually prudent to obtain neuroimaging (high-resolution computed tomography [CT] or preferably, MRI) to rule out an intracranial process in children presenting with acquired, asymmetric, rapid, and pendular nystagmus.

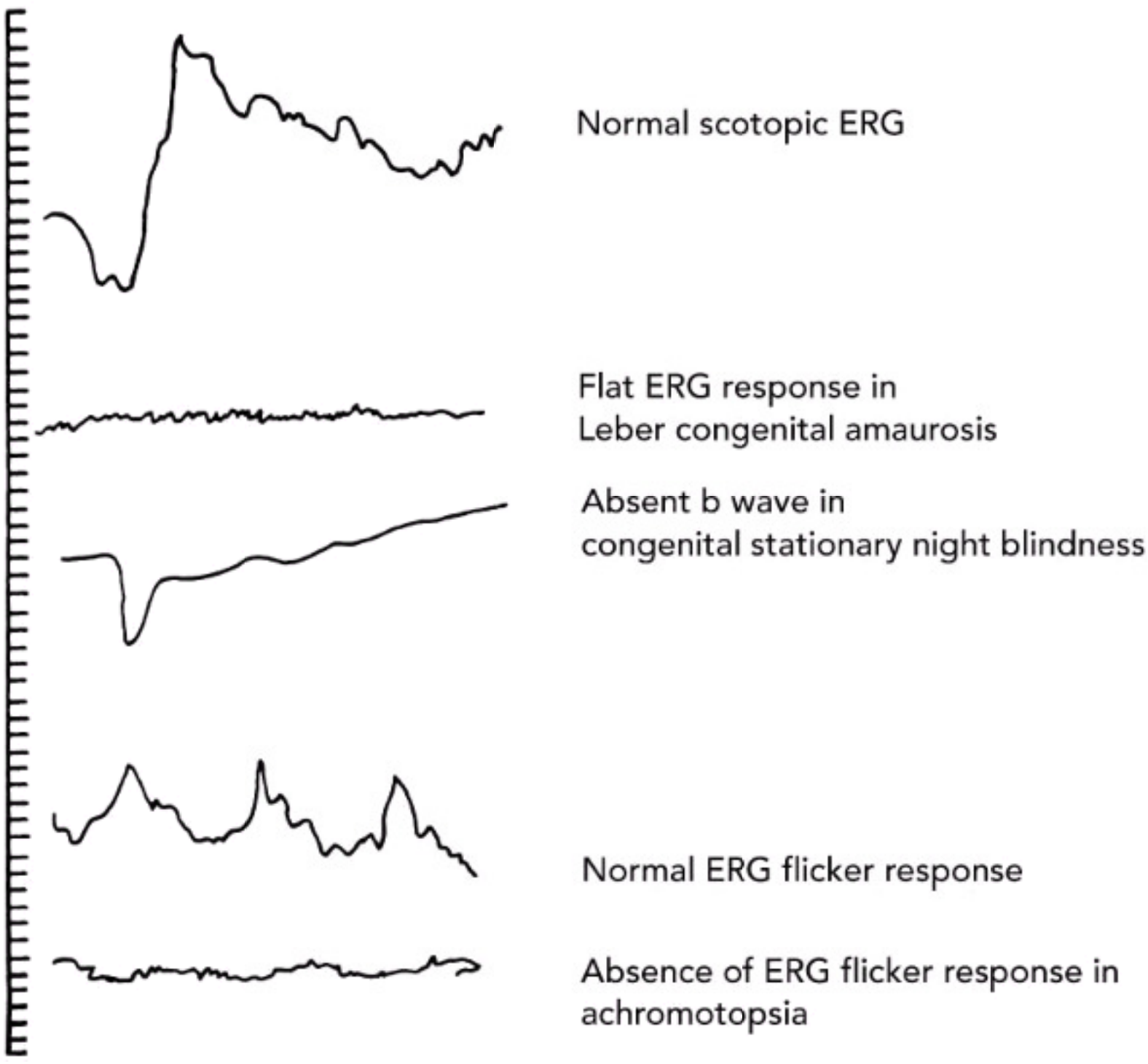

Figure 25.3 Electroretinographic findings in an infant with nystagmus.

Afferent Conditions without Obvious Ocular Malformation

Conditions Typically Associated with Searching Nystagmus

Leber Congenital Amaurosis. This autosomal-recessive disorder is characterized by diminished vision starting at or shortly after birth. It has been mapped in five families of North African origin to chromosome 17p13 (51). Acuity is less than 20/200 in up to 95% of affected individuals, and a searching nystagmus is present in 75% (52). The pupils are poorly reactive, and many children exhibit the oculodigital sign (habitual eye rubbing). The fundus is usually normal in infancy. Pigmentary disturbances of the peripheral retina develop during childhood in most patients, along with optic disc pallor and arteriolar attenuation (53). A markedly reduced or absent response to the ERG is noted in virtually all patients (Fig. 25.3). As many as 15% of patients may have mental retardation (53). Other systemic associations include medullary cystic kidney disease, cardiomyopathy,

and skeletal abnormalities (53,54). Neurologic and skeletal abnormalities usually are not present in patients with LCA with greater than 5 diopters of hyperopia. This may be useful in planning an educational program for these children (55).

A variety of ocular conditions, including keratoconus, keratoglobus, macular coloboma, disc edema, cataract, and strabismus, have been associated with LCA. Histopathologic studies have shown the outer retinal layers to be primarily affected (56). It is unclear whether LCA is a progressive photoreceptor degeneration or abiotrophy (53).

Optic Nerve Hypoplasia. ONH is a congenital, nonprogressive condition characterized by a paucity of axons within the optic nerve and diminished ganglion cell layer of the retina (57). It is included under conditions without obvious ocular malformations because it is sometimes difficult to observe the optic nerve completely in an infant with nystagmus. Ophthalmoscopically, ONH is recognized by a small, pale nerve head. Classically, it is surrounded by a ring of white sclera and a second pigmented or nonpigmented ring outlining the scleral rim, giving rise to the term double-ring sign (Fig. 25.4). The retinal vessels usually appear relatively normal, but the retina may be deeply red in color because of the thinness of the nerve fiber layer.

Severe bilateral ONH results in a searching nystagmus, whereas mild, unilateral ONH may not have visual symptoms. In one study, 78% of those with bilateral involvement, poor vision, and nystagmus had additional ocular abnormalities, compared with 21% of patients with unilateral ONH (58). Delayed development is the most frequent nonocular disorder, followed by hypopituitarism, cerebral palsy, and epilepsy (59).

In 1956 de Morsier (60) noted an association of bilateral ONH with absence of the septum pellucidum and dysplasia of the anterior third ventricle and corpus callosum. Subsequent investigators have associated hypopituitarism with this disorder (61). Rarer systemic associations include midline facial defects and abnormalities of the cerebral cortex, brainstem, and cerebellum (62). Associated ocular malformations include microphthalmos, coloboma, aniridia, and strabismus.

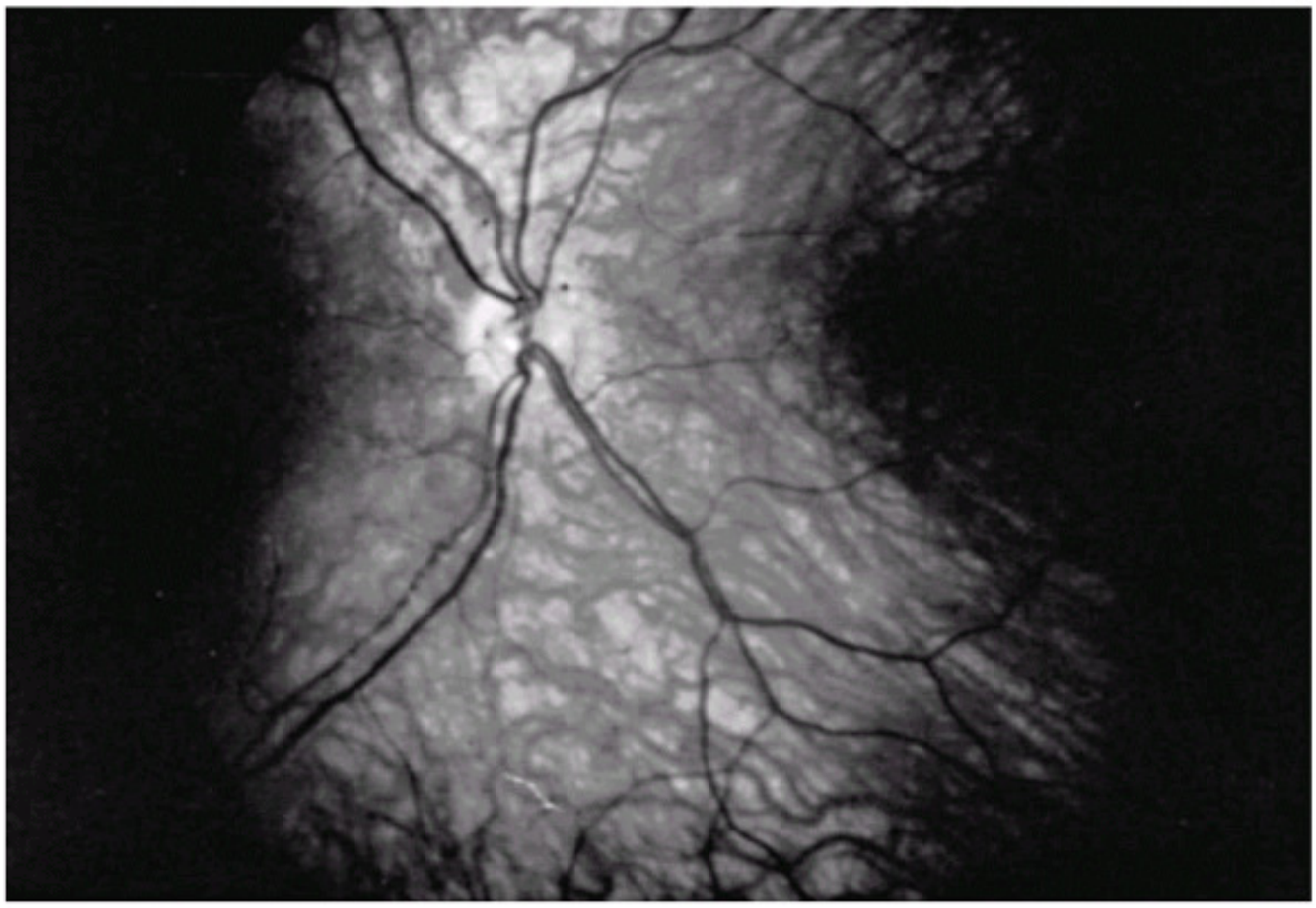

Figure 25.4 Optic nerve hypoplasia. Note the small optic nerve head and the surrounding ring outlining the scleral rim (double-ring sign).

ONH is believed to result from a defect in the differentiation of retinal ganglion cell axons. It has been associated with embryonic insults at or after 6 weeks of gestation with maternal ingestion of quinidine (63) and with anticonvulsants (64). It is more common in children of severely diabetic and of adolescent mothers (59).

Neuroimaging with MRI is recommended in all children with bilateral ONH, and some practitioners would also consider it in unilateral cases if other midline craniofacial anomalies are present. Cerebral hemispheric abnormalities, along with posterior pituitary ectopia, are predictive of hypopituitarism and neurodevelopmental delays (65). Endocrine consultation should also be obtained to monitor growth.

Afferent Conditions Associated with Pendular Nystagmus

Pendular nystagmus is usually associated with a moderate disruption of vision. In the absence of obvious ocular abnormalities, examination is first directed toward the detection of foveal hypoplasia (Fig. 25.5) or iris transillumination (Fig. 25.6), which is highly suggestive of albinism. Schisis of the nerve fiber layer of the macula in boys suggests X-linked retinoschisis. In the absence of obvious macular disorders in infants, electrophysiologic examination may be helpful diagnostically.

Albinism

Albinism is a genetically determined disturbance in melanogenesis with hypopigmentation of the skin, hair, and eyes. All forms of true albinism are characterized by reduced visual acuity, hypoplasia of the macula, nystagmus, and excessive decussation of most temporal retinal ganglion cell axons through the chiasm to the contralateral

geniculate and cortex. Multiple inheritance patterns (autosomal recessive and X-linked) have been noted for true albinism (66). It is apparent that there are

multiple abnormal alleles of the genes responsible for melanogenesis. The result is that several different genotypes may have a similar phenotypic expression for albinism.

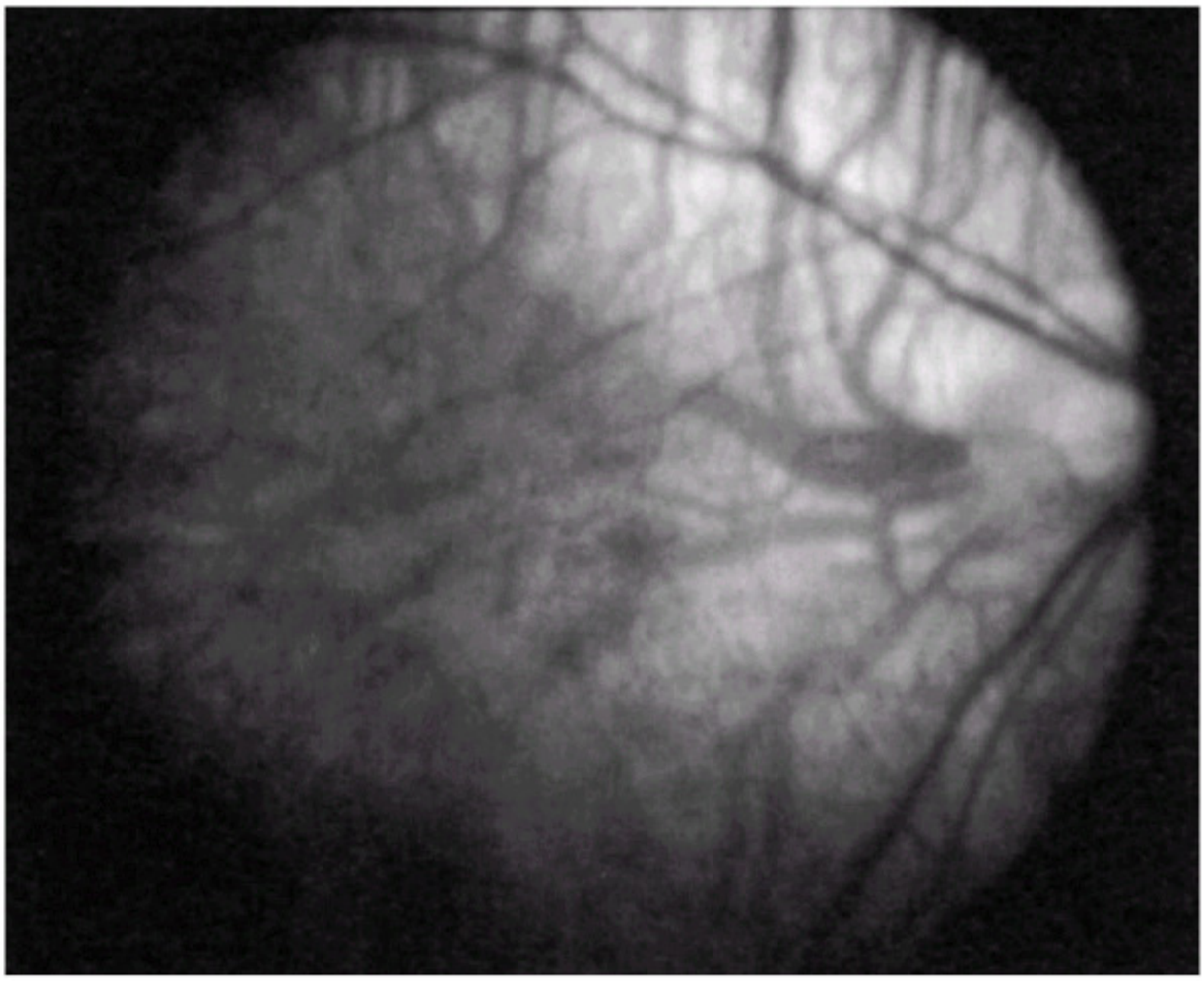

Figure 25.5 Fundus of a patient with albinism. Note the hypopigmented appearance of the background and the absence of a clearly defined fovea (foveal hypoplasia).

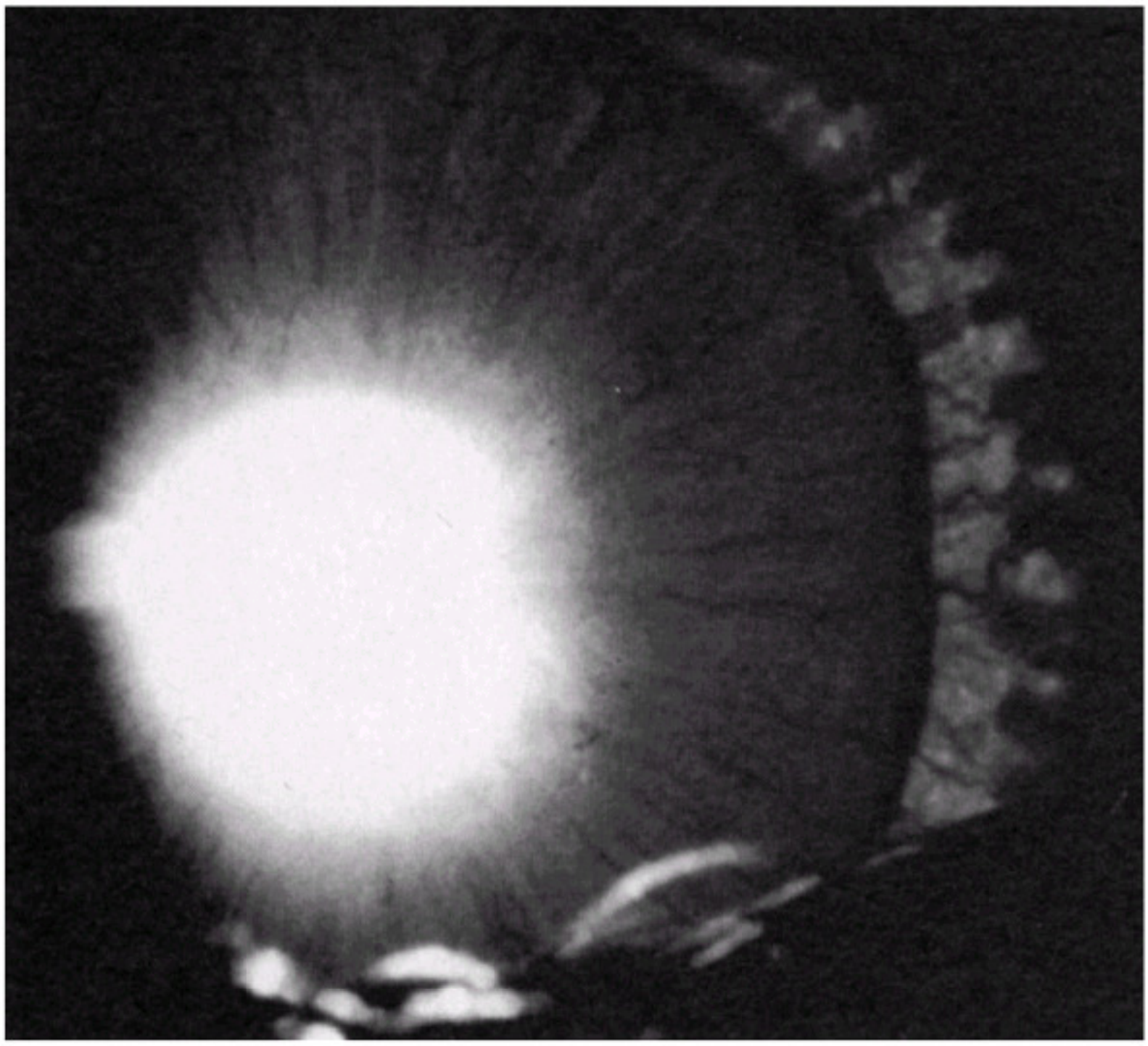

Figure 25.6 Iris transillumination in a patient with albinism as demonstrated by slit-lamp retroillumination. Note the lens edge as seen through the hypopigmented iris.

Tyrosinase is the enzyme responsible for the initial steps of melanin synthesis. The autosomal-recessive form of oculocutaneous albinism (OCA) has a defect in the gene which produces an inactive form of the enzyme. This gene is located on chromosome 11q14-21 (67). The hair bulb incubation test demonstrates the presence or absence of tyrosinase activity and provides biochemical evidence for heterogeneity, but alone it cannot separate the various forms of albinism known to exist. Clinical, biochemical, and ultrastructural criteria are now used to distinguish each form of albinism (68). Tyrosinase-negative OCA is considered type 1 and has four subtypes. Tyrosinase-positive OCA is type 2, which is caused by separate mutations at the P locus on chromosome 15q11.2-q12 (69). Type 3 OCA is described in African and African-American individuals. It is characterized by light brown skin and hair, moderate tanning ability, and blue-gray irides with transillumination defects. Tyrosinase is found in normal quantity but exhibits reduced tyrosine hydroxylase activity (70). A precise diagnosis is essential for counseling the family about the implications of the disease and the heritable pattern. Prenatal diagnosis of OCA by electron microscopic study of desquamated skin cells also is now possible (71).

Clinical management relates to protecting the skin and maximizing vision. Albinos may have delayed visual maturation, only gradually becoming visually attentive after 2 to 3 months of age. They also often have high refractive errors and may benefit significantly from correction. Near acuity is relatively better than far (convergence dampens their nystagmus), and most albinos can read small print without low-vision aids. Therefore, most are mainstreamed into the normal school system. Adequate protection of the skin by ultraviolet barriers and clothing is necessary because of an increased risk of skin cancer.

It is important to recognize two special subtypes of albinism because they may have life-threatening complications. The Chédiak-Higashi syndrome (chromosome 1q43) is a lethal condition in which albinism is associated with a defect in cellular immunity (T cells) as well as leukocytes. Neutrophils show reduced migration and deficient chemotaxis and bactericidal capacity. Children have an increased susceptibility to gram-positive infections. Patients surviving infections often die of malignant lymphoreticular infiltration of the tissues (70,72,73). Hermansky-Pudlak syndrome (chromosome 10q23.1-q23.3) is an association of OCA with hemorrhagic diathesis and a ceroid-like accumulation in the reticuloendothelial cells; it is unusually prevalent in Puerto Ricans. The bleeding tendency is low, but there have been reported deaths from hemorrhage. There is a qualitative defect in platelets, and aspirin and cyclooxygenase inhibitors should be avoided because they may convert a mild bleeding disorder into a severe one. Additional associations include the development of restrictive lung disease in the third and fourth decades, ulcerative colitis, kidney disease, and cardiomyopathy (70,74,75).

Achromatopsia (Rod Monochromatism)

Achromatopsia is a rare congenital, autosomal-recessive disorder with a prevalence of only 3 in 100,000 (76). The locus for this disorder has been mapped to chromosome 2q11 (77) and chromosome 8q (78) It is characterized by a complete loss of color vision, diminished visual acuity of 20/100 to 20/400, photophobia, and typically an oblique pendular nystagmus of small amplitude and high frequency. The small amplitude of this nystagmus may make clinical detection difficult, but it differentiates this disorder from albinism, in which the nystagmus is of larger amplitude (79). Other characteristics are a decrease in amplitude in the dark and a change in waveform from pendular in childhood to a jerk waveform in adults (47).

Histopathology has demonstrated that the cone photoreceptors in the retina are either missing or severely maldeveloped. Because of severe photophobia, children with this disorder may prefer to play outside at dusk and may have better vision in dim illumination (hemeralopia) (80). The most reliable diagnostic test for infants is the ERG. In achromatopsia, the ERG flicker response is absent (Fig. 25.2) and the photopic single-flash response is reduced. The scotopic response

is normal. In this disorder, photophobia and nystagmus may diminish and even disappear after the age of 15, but the visual acuity does not improve (80,81).

A form of incomplete rod monochromatism also exists. Because blue cones are involved minimally or not at all, this has also been called blue-cone monochromatism. The inheritance appears to be X-linked. Visual acuity is in the 20/60 range, nystagmus is minimal, and photophobia is absent. Unlike achromatopsia, this condition appears to progress slowly to macular scarring and cone dysfunction. It is distinguished from achromatopsia by color-plate discrepancies in which blue-cone monochromats can distinguish between blue-green and purple-blue, but achromats

cannot. In addition, differences in the eye movement response to optokinetic stimuli moving from the nasal to temporal field (achromats respond poorly) can be used to distinguish these two conditions. Since blue cones probably represent only a small portion of all retinal cones, the ERG is just as abnormal in this disorder as in complete achromatopsia. However, patients with blue-cone monochromatism show a peak illumination sensitivity near 440 nm, whereas patients with rod monochromatism demonstrate a peak sensitivity near 504 nm (82,83).

Congenital Stationary Night Blindness

CSNB is a heritable disorder in which the predominant complaint of affected individuals is night blindness. It is characterized by a normal fundus appearance, normal daylight visual fields, absence of rod dark adaptation, and lack of progression.

Multiple inheritance patterns have been identified in CSNB: autosomal dominant, autosomal recessive, and X-linked. Decreased vision, myopia, and nystagmus is seen only in some autosomal-recessive variants and never in patients with autosomal-dominant CSNB (84,85).

In X-linked CSNB, visual acuity ranges between 20/30 and 20/100. Myopia of between 3.50 and 11.0 diopters is usually present. Patients with acuities worse than 20/60 have an obvious pendular nystagmus, but electronystagmography can occasionally detect nystagmus when the acuity is better (80). Color vision is normal or, at worst, only mildly abnormal, differentiating this disorder from achromatopsia. The prime diagnostic tool in infants is the ERG, in which there is a reduction or absence of any positive response (b-wave) to scotopic testing (Fig. 25.2). Clinically and genetically, two subtypes have been defined with the distinction being a mildly abnormal cone function with undetectable rod activity in type 1, and residual rod activity with a more significantly abnormal cone ERG in type 2 (86). The elucidation of the molecular basis has identified the matrix protein nyctalopin in type 1, and a subunit of a retina-specific calcium channel in type 2 (87,88). Both are predicted to function at various levels of retinal signal transduction. In addition, some young patients with X-linked CSNB demonstrate an initial “paradoxic” pupillary constriction in darkness (89).

Oguchi disease is a related autosomal-recessive congenital stationary disorder with diminished night vision. Unlike CSNB, there is a peculiar homogeneous yellow to grayishwhite discoloration of the fundus, and only occasionally mildly abnormal vision in the range of 20/25 to 20/50. The abnormal coloration usually disappears after 2 to 3 hours of dark adaptation and begins to reappear after about 10 minutes of light exposure. The appearance and reappearance of abnormal coloration with light suggests a disorder of retinal pigment kinetics. Normal rhodopsin kinetics, however, have been found in one patient. The ERG in Oguchi disease is similar to that in CSNB in demonstrating an absent b wave. In Oguchi disease, however, the ERG picture may become less abnormal after prolonged dark adaptation (84,90).

X-Linked Juvenile Retinoschisis

This recessive disorder is characterized by a cleavage of the retina at the level of the nerve fiber layer. Its prevalence ranges from 1 in 5,000 to 1 in 25,000 and is considered the most common cause of juvenile macular degeneration in males. Therefore, examination of male relatives is important to help confirm the diagnosis and provide genetic counseling. Expressivity is variable with visual acuity ranging from nearly normal to light perception. Typically the vision is between 20/50 and 20/100 and gradually diminishes to about 20/200 with increasing age (80). Four of five patients presenting at younger than 2 years of age had nystagmus in a survey of the United Kingdom (91). Vitreous veils with or without retinal vessels occur in less than 50%. Vitreous hemorrhage from rupture of these vessels may be the presenting symptom (92). Although bilateral elevated bullous schisis cavities involving the fovea may occur in infancy, the most frequent finding is a stellate maculopathy representing foveal schisis. Clinically, this maculopathy can look very similar to cystoid macular edema (CME) and often is misdiagnosed as such. It can be differentiated from CME by the lack of leakage on fluorescein angiography. A high rate of spontaneous reattachment with retinal pigment demarcation lines is reported (91). The ERG is again useful diagnostically; the b-wave, both scotopic and photopic, is usually reduced. The gene has been localized to the Xp22 region (93). The abnormality appears to be a dysfunctional adhesive protein secreted by the photoreceptor and bipolar cells, and transported by Müller cells into the inner retina (94). At present, no effective treatment is available.

Strabismic Ocular Conditions Associated with Nystagmus

Nystagmus Blockage Syndrome

Nystagmus blockage syndrome (NBS) is a particular type of CN in which it is believed that a sustained adduction effort, resulting in esotropia, occurs to dampen the nystagmus. The incidence of NBS in esotropic patients has been variably reported as between 4% and 10%. NBS is characterized by an inverse relationship between the angle of esotropia and the amplitude of nystagmus. Typically the nystagmus is most pronounced in abduction. Further, on occlusion of one eye, the fellow eye fixates in adduction, often accompanied by an ipsilateral face turn. The angle of esotropia increases when a prism with its base out is placed before the fixating eye and the pupil does not constrict when the eye assumes its adducted position (demonstrating that no accommodative mechanisms are at play). The nystagmus usually begins in early infancy. Overaction of the inferior oblique muscles and dissociated vertical deviations occur less frequently in NBS than in essential infantile esotropia (95,96).

Latent and Manifest Latent Nystagmus

LN describes a conjugate congenital jerk nystagmus evoked by occlusion of one eye. The fast phase is toward the viewing (nonoccluded) eye. The slow phase has decreasing velocity away from the fixating eye (97). Alternate occlusion of the eyes results in reversal of the nystagmus direction.

The amplitude of the nystagmus increases with gaze directed to the side of the fixating eye (Alexander's law). Nystagmus intensity (amplitude times frequency) is greater when viewing with the amblyopic eye (98). Binocular vision is always better than monocular vision in LN (99). Most cases of clinical LN are actually manifest LN (MLN) such that eye movement recordings detect small amplitudes of nystagmus under binocular conditions (97). It is currently hypothesized that LN is due to an imbalance in the input to a defective nucleus of the optic tract (100,101). Occasionally LN may be acquired spontaneously or following minor head trauma in adulthood causing oscillopsia (102).

MLN is a condition in which abnormal visual input from one eye, usually due to amblyopia, causes latent nystagmus to become manifest. All patients with MLN have strabismus and esotropia, dissociated vertical deviation or both, but this alone does not cause the nystagmus (103). Like LN, the fast phase of the nystagmus is always in the direction of the fixating eye. Quantitative oculography is useful in distinguishing NBS and CN from MLN with esotropia. The latter is much more common, although combinations of waveforms are frequently noted (97). Successful conversion of MLN to LN has been described following amblyopia therapy and with surgical or optical alignment. It is not known whether the decrease in nystagmus intensity is a result of improved binocular vision or vice versa (98).

Some patients with uniocular infantile blindness have a horizontal nystagmus in their contralateral, structurally sound eyes. This nystagmus has the characteristics of LN. Kushner (104) suggested that this syndrome represents a manifest nystagmus of the latent type in patients who have inherited a genetic predisposition for congenital strabismus.

Congenital Motor, Efferent, or Idiopathic Nystagmus

CN is characterized by a conjugate, mainly horizontal, principally jerk nystagmus even on up- and downgaze. Although difficult to identify clinically, a torsional component may be present (105). The nystagmus may be present at birth but typically develops during infancy (106). The waveform can be age dependent. Most commonly, it is of large-amplitude “triangular” in the first few months of life, then pendular, and eventually jerk at about 1 year of age (107). There is often a position of least nystagmus that is called the null zone, which may be straight ahead or in any position of gaze. Away from the null zone, the fast phase is in the direction of gaze (Alexander's law). If the null zone is in eccentric position, a compensatory face turn or abnormal head position may be necessary to decrease the nystagmus and improve the visual acuity. This is not characteristic of CN in that an abnormal compensatory head posture can occur with any cause of nystagmus. Away from the null zone and with fixation attempts, increased attention, or anxiety, the nystagmus amplitude increases. Convergence can dampen the nystagmus, and the nystagmus is abolished during sleep (108). Typically the vision in CN is relatively good, from 20/20 to 20/70, and most patients do not complain of oscillopsia. This is probably secondary to a foveation period during which the waveform is “flattened” when the eye is closest to the target. A common associated finding is inversion of the optokinetic reflex. With optokinetic drum testing, the quick phase is directed in the same direction as the drum rotates rather than in the opposite direction (14).

It is important to make this diagnosis as early as possible because of its implications for reasonably good vision and to avoid undue anxiety for the family. The absence of oscillopsia, inversion of the optokinetic reflex, relatively good vision, and occasionally the family history are helpful in diagnosis. The diagnosis is much easier to make in children who are old enough for vision and color vision testing. Vision better than 20/100 excludes LCA and achromatopsia, the absence of myopia excludes CSNB, a normal fundus examination excludes macular and optic nerve disorders, and the absence of iris transillumination and a normal fovea exclude all types of albinism.

NYSTAGMUS TREATMENT

Regardless of the type of nystagmus, the goal of treatment is to improve vision, eliminate anomalous (compensatory) head positions, and abolish any oscillopsia. Dampening the nystagmus amplitude, increasing the foveation period, and broadening the null zone can improve acuity in some CN patients. Using optical, medical, and surgical modalities, some of these goals have been achieved, and ongoing research continues to improve upon the armamentarium.

Optical treatment begins by obtaining the best refraction and spectacle prescription. Contact lenses have been reported to increase foveation time by increasing convergence and accommodative effort or by a sensory feedback mechanism on the eyelids leading to reduced nystagmus (109). A system of a high-minus contact lens in conjunction with a high-plus spectacle lens was designed to stabilize retinal images. Unfortunately, this was only effective when the patient was stationary and viewing monocularly, although initial problems posed by rigid contact lenses have been overcome by soft, gas-permeable lenses (110,111). Prisms can be used to shift the null zone if there is a small (less than 15-degree) turn or to “fine tune” surgical results (112). Base-out prisms can also induce accommodative convergence and sometimes need to be combined with myopic correction. In those cases in which a convergent mechanism is spontaneously maintained, base-out prisms can help realign the visual axis or improve head posture.

Several medications have made an impact on specific nystagmus types. A decrease in the oscillopsia of acquired pendular and downbeat nystagmus has been reported with intravenous scopolamine (113). Gabapentin, an anticonvulsant with GABAergic properties, has been shown to improve visual acuity (114). Other GABAergic agents, including clonazepam, valproic acid, and isoniazid, help some patients. Upbeat or downbeat nystagmus responds to clonazepam (115). Baclofen, a GABA agonist, has been used successfully to abolish periodic alternating nystagmus and oscillopsia, although the congenital form is less responsive

(14,116). Seesaw nystagmus has improved with alcohol and clonazepam (117,118). With all of these agents, their benefit must be weighed against the potential CNS side effects, especially drowsiness.

Botulinum toxin can be used to achieve a “pharmacoparesis” with improved vision in CN (119) and to decrease oscillopsia in acquired nystagmus (120,121,122). Approaches include retrobulbar injection or direct injection into the horizontal muscles of one or both eyes. Injections need to be repeated every few months, and potential complications include ptosis, diplopia, continued oscillopsia, and patient acceptance. Success has been mixed, with some patients requiring multiple consecutive injections (121,122) and others not obtaining satisfactory results (123).

Anderson (124) and Kestenbaum (125) originally described the surgical management of congenital motor nystagmus to shift the null zone to the primary position and eliminate a compensatory head posture. Dell'Osso and Flynn (112) demonstrated visual improvement using this technique by broadening the null region and reducing the nystagmus intensity (amplitude times frequency) on motility recordings. With the early surgical amounts, however, there still existed a residual head posture (126), and “augmented” surgery (larger bilateral recession/resection on the horizontal muscles) was advocated (127,128). A gaze deficit can be created with aggressive surgery, but it is accepted by most patients (128). When strabismus is present with an abnormal head posture, surgery on the fixating eye is performed to eliminate the head position, and the fellow eye is surgically compensated for the strabismic angle (129).

Large retroequatorial recessions of all four horizontal rectus muscles have been proposed for patients with a central null zone to improve vision and decrease the nystagmus amplitude (130,131). Some patients report an improvement in their visual function, although objective change using eye movement recordings have been minimal. This surgery appears to work well in PAN (132). More recently, Dell'Osso (133) suggested and then demonstrated in patients (134) that simply detaching the extraocular muscle, dissecting the perimuscular fascia, and then reattaching to the original site on the globe can improve foveation times and subjective visual acuity in patients with CN. This is thought to be due to an alteration in proprioceptive input from palisade organs that lie in proximity to the attachment points of the extraocular muscles.

Most cases of acquired nystagmus with oscillopsia are not amenable to neurosurgery with one notable exception. Downbeat nystagmus due to Arnold-Chiari malformation responds to suboccipital decompression and can also prevent further neurologic deficits (135).

SUMMARY

Nystagmus is a nonspecific sign that may occur physiologically or pathologically. The approach to diagnosing and managing infants presenting with nystagmus includes family, perinatal, and nystagmus history; ophthalmologic examination; and when appropriate, electrophysiologic and neuroradiologic examinations. If there is an obvious ocular abnormality severe enough to impair visual function, management and counseling specific for the disorder are appropriate.

In the absence of obvious ocular malformation, the workup is governed by the nature of the predominant ocular oscillation. If the nystagmus is asymmetric, rapid, and pendular, CT or MRI scan is usually indicated to rule out an intracranial process. If no CNS disorder is present, the presumptive diagnosis for asymmetric, high-frequency nystagmus is spasmus nutans. Searching nystagmus implies a severe retinal or optic nerve disorder, and the first step is to obtain an ERG to rule out LCA, along with careful inspection of the optic nerves. If the discs appear pale or other CNS signs are present, neurologic examination and neuroradiologic imaging are performed. If the nystagmus is symmetric and pendular, a careful search is made for foveal hypoplasia and iris transillumination, which would suggest albinism. In the absence of these, electrophysiologic studies and careful ophthalmoscopy may detect an isolated cone or macular abnormality. Congenital motor (efferent) nystagmus is essentially a diagnosis of exclusion with a relatively good visual prognosis.

REFERENCES

1. Hoyt CS. The apparently blind infant. *Trans New Orleans Acad Ophthalmol* 1986;34:478-488.

2. Jan JE, Farrell K, Wong PK, et al. Eye and head movements of visually impaired children. *Dev Med Child Neurol* 1986;28:285-293.

3. Walsh FB, Hoyt WE. *Clinical neuro-ophthalmology*, 3rd ed. Baltimore: Williams & Wilkins Co., 1969.

4. Huber A. *Eye symptoms in brain tumors*, 2nd ed. St. Louis: CV Mosby Co., 1971

5. Smith JL, Zieper I, Gay AJ, et al. Nystagmus retractorius. *Arch Ophthalmol* 1959;62:864-867.

6. Daroff RB. See-saw nystagmus. *Neurology* 1965;15:874-877.

7. Fein JM, Williams RDB. See-saw nystagmus. *J Neurol Neurosurg Psychiatr* 1969;32:202-207.

8. Halmagyi GM, Hoyt WF. See-saw nystagmus due to unilateral mesodiencephalic lesion. *J Clin Neuroophthalmol* 1991;11:79-84.

9. Abadi RV, Pascal E. Periodic alternating nystagmus in humans with albinism. *Invest Ophthalmol Vis Sci* 1994;35:4080-4086.

10. Baloh RW, Honrubia V, Konrad HR. Periodic alternating nystagmus. *Brain* 1976;99:11-26.

11. Cohen B, Helwig D, Raphan T. Baclofen and velocity storage: a model of the effects of the drug on vestibulo-ocular reflex in the rhesus monkey. *J Physiol* 1987;393:703-725.

12. Cohen B, Henn V, Rapham T, et al. Velocity, storage, nystagmus, and visual-vestibular interaction in humans. *Ann N Y Acad Sci* 1981;374:421-433.

13. Leigh RJ, Robinson DA, Zee DS. A hypothetical explanation for periodic alternating nystagmus: instability in the optokineticvestibular system. *Ann N Y Acad Sci* 1981;374:619-635.

14. Halmagyi GM, Rudge P, Gresty MA, et al. Treatment of periodic alternating nystagmus. *Ann Neurol* 1980;8:609-611.

15. Brodsky MC. Congenital downbeat nystagmus. *J Pediatr Ophthalmol Strabismus* 1996;33:191-193.

16. Wertenbaker C, Henkind P, Keltner JL, et al. Downbeat nystagmus. *Surv Ophthalmol* 1981;25:263-269.

17. Halmagyi GM, Rudge P, Gresty MA, et al. Downbeating nystagmus: a review of 62 cases. *Arch Neurol* 1983;40:777-784.

18. Jacobson DM, Corbett JJ. Downbeat nystagmus associated with dolichoectasia of the vertebrobasilar artery. *Arch Neurol* 1989;46:1005-1008.

19. Good WV, Brodsky MC, Hoyt CS, et al. Upbeating nystagmus in infants: a sign of anterior visual pathway disease. *Binoc Vis Q* 1990;5:13-18.

20. Daroff RB, Troost BT. Upbeat nystagmus. *JAMA* 1973;225:312.

21. Fisher A, Gresty M, Chambers B, et al. Primary position upbeating nystagmus: a variety of central positional nystagmus. *Brain* 1983;106:949-964.

22. Abel LA, Dell'Osso LF, Daroff RB. Analog model for gaze evoked nystagmus. *IEEE Trans Biomed Eng* 1978;25:71-75.

23. Brandt T, Daroff RB. The multisensory physiological and pathological vertigo syndrome. *Ann Neurol* 1980;7:195-203.

24. Leigh RJ, Zee DS. *The neurology of eye movements*. Philadelphia: FA Davis Co., 1983.

25. Zee DS, Preziosi TJ, Proctor LR. Bechterew's phenomenon in a human patient. *Ann Neurol* 1982;12:495-496.

26. Reker U. Peripheral-vestibular spontaneous nystagmus: analysis of reproducibility and methodologies. *Arch Otorhinolaryngol* 1980;226:225-237.

27. Zee DS, Friendlich AR, Robinson DA. The mechanism of downbeat nystagmus. *Arch Neurol* 1974;30:227-237.

28. Donin JF. Acquired monocular nystagmus in children. *Can J Ophthalmol* 1967;2:212-215.

29. Perenin MT, Ruel J, Hecaen H. Residual visual capacities in a case of cortical blindness. *Cortex* 1980;16:605-612.

30. Hertle RW, Dell'Osso LF. Clinical and ocular motor analysis of congenital nystagmus in infancy. *J AAPOS* 1999;3:70-79.

31. Pagon RA. Ocular coloboma. *Surv Ophthalmol* 1981;25:223-236.

32. Beutler E, Matsumoto F, Kuhl W, et al. Galactokinase deficiency as a cause of cataracts. *N Engl J Med* 1973;288:1203-1206.

33. deLuise VP, Anderson DR. Primary infantile glaucoma (congenital glaucoma). *Surv Ophthalmol* 1983;28:1-19.

34. Ellsworth RM. Retinoblastoma. In: Duane TD, Jaeger EA, eds. *Clinical ophthalmology*. Philadelphia: Harper & Row, 1988.

35. Flynn JT. An international classification of retinopathy of prematurity. Clinical experience. *Ophthalmology* 1985;92:987-994.

36. Townsend WM. Congenital corneal leukomas. I. Central defect in Descemet's membrane. *Am J Ophthalmol* 1974;77:80-86.

37. Nelson LB, Spaeth GL, Nowinski TS, et al. Aniridia: a review. *Surv Ophthalmol* 1984;28:621-642.

38. Haddad R, Font RL, Reiser E. Persistent hyperplastic primary vitreous. A clinicopathologic study of 62 cases and review of the literature. *Surv Ophthalmol* 1978;23:123-134.

39. Francois J. Incontinentia pigmenti (Bloch-Sulzberger syndrome) and retinal changes. *Br J Ophthalmol* 1984;68:19-25.

40. Schlaegel TR. Toxoplasmosis. In: Duane TD, Jaeger EA, eds. *Clinical Ophthalmology*. Philadelphia: Harper & Row, 1988.

41. Moore AT, Taylor DS, Harden A. Bilateral macular dysplasia ("colobomata") and congenital retinal dystrophy. *Br J Ophthalmol* 1985;69:691-699.

42. Weissman BM, Dell'Osso LF, Abel IA, et al. Spasmus nutans: a quantitative prospective study. In: Keller EL, Zee DS, eds. *Adaptive process in visual and oculomotor systems*. New York: Pergamon Press, 1986.

43. Gottlob I, Wizov SS, Reinecke RD. Spasmus nutans: a long-term follow-up. *Invest Ophthalmol Vis Sci* 1995;36:2768-2771.

44. Gottlob I, Zubcov A, Wizov SS, et al. Head nodding is compensatory in spasmus nutans. *Ophthalmology* 1992;99:1024-1031.

45. Albright AL, Schlabassi RJ, Slamovitis TL, et al. Spasmus nutans associated with optic gliomas in infants. *J Pediatr* 1984;105:778-780.

46. Sedwick LA, Burde RM, Hodges FJ. Leigh's subacute encephalomyelopathy manifesting as spasmus nutans. *Arch Ophthalmol* 1984;102:1046-1048.

47. Gottlob I, Reinecke RD. Eye and head movements in patients with achromatopsia. *Graefes Arch Clin Exp Ophthalmol* 1994;232:392-401.

48. Gottlob I, Wizov SS, Reinecke RD. Quantitative eye and head movement recordings of retinal disease mimicking spasmus nutans. *Am J Ophthalmol* 1995;119:374-376.

49. Smith DE, Fitzgerald K, Strass-Isern M, et al. Electroretinography is necessary for spasmus nutans diagnosis. *Pediatr Neurol* 2000; 23:33-36.

50. Gottlob I, Zubcov A, Catalano RA, et al. Signs distinguishing spasmus nutans (with and without central nervous system lesions) from infantile nystagmus. *Ophthalmology* 1990;97: 1166-1175.

51. Camuzat A, Rozet J, Dollfus H, et al. Evidence of genetic heterogeneity of Leber's congenital amaurosis (LCA) and mapping of LCA1 to chromosome 17p13. *Hum Genet* 1996;97:798-801.

52. Noble KG, Carr RE. Leber's congenital amaurosis. A retrospective study of 33 cases and a histopathological study of one case. *Arch Ophthalmol* 1978;96:818-821.

53. Lambert SR, Taylor D, Kriss A. The infant with nystagmus, normal appearing fundi, but an abnormal ERG. *Surv Ophthalmol* 1989;34:173-186.

54. Roizenblatt J, Cunha LAP. Leber's congenital amaurosis with associated nephronophthisis. *J Pediatr Ophthalmol Strabismus* 1980; 17:154-158.

55. Wagner RS, Caputo AR, Nelson LB, et al. High hyperopia in Leber's congenital amaurosis. *Arch Ophthalmol* 1985;103: 1507-1509.

56. Mizuno K, Takei Y, Sears ML, et al. Leber's congenital amaurosis. *Am J Ophthalmol* 1977;83:32-42.

57. Lloyd L, Buncic JR. Hypoplasia of the optic nerve and disc. In: Smith JL, ed. *Neuroophthalmology focus*. New York: Masson Publishing, 1980:85-96.

58. Skarf B, Hoyt CS. Optic nerve hypoplasia in children. Association with anomalies of the endocrine and CNS. *Arch Ophthalmol* 1984;102:62-67.

59. Margalith D, Jan JE, McCormick AQ, et al. Clinical spectrum of congenital optic nerve hypoplasia: review of 51 patients. *Dev Med Child Neurol* 1984;26:311-322.

60. de Morsier G. [Studies on malformation of cranio-encephalic sutures. III. Agenesis of the septum lucidum with malformation of the optic tract.] *Schweiz Arch Neurol Psychiatr* 1956;77: 267-292.

61. Hoyt WE, Kaplan SL, Grumbach MM, et al. Septooptic dysplasia and pituitary dwarfism. *Lancet* 1970;2:893-894.

62. Frisen L, Holmegaard L. Spectrum of optic nerve hypoplasia. *Br J Ophthalmol* 1978;62:7-15.

63. McKinna AJ. Quinine-induced hypoplasia of the optic nerve. *Can J Ophthalmol* 1966;1:261-266.

64. Hoyt CS, Billson FA. Maternal anticonvulsants and optic nerve hypoplasia. *Br J Ophthalmol* 1978;62:3-6.

65. Brodsky MC, Glasier CM. Optic nerve hypoplasia: clinical significance of associated central nervous system abnormalities on magnetic resonance imaging. *Arch Ophthalmol* 1993;111:66-74.

66. O'Donnell FE, King RA, Green WR, et al. Autosomally recessively inherited ocular albinism. *Arch Ophthalmol* 1978;96:1621-1625.

67. Barton DE, Kwon BS, Francke U. Human tyrosinase gene, mapped to chromosome 11 (q14-21), defines second region of homology with mouse chromosome 7. *Genomics* 1988;3:17-24.

68. Witkop CJ Jr. Inherited disorders of pigmentation. *Clin Dermatol* 1985;3:70-134.

69. Ramsay M, Colman M, Stevens G, et al. The tyrosinase-positive oculocutaneous albinism locus maps to chromosome 15q11.2-q12. *Am J Hum Genet* 1992;51:879-884.

70. Boissy RE, Norland JJ. Molecular basis of congenital hypopigmentary disorders in humans: a review. *Pigment Cell Res* 1997; 10:12-24.

71. Eady RAJ, Gunner DB, Garner A, et al. Prenatal diagnosis of oculocutaneous albinism by electron microscopy of fetal skin. *J Invest Dermatol* 1983;80:210-212.

72. Blume RS, Wolff SW. The Chédiak-Higashi syndrome: studies in four patients and a review of the literature. *Medicine* 1972;51: 247-280.

73. Brahmi Z. Nature of the natural killer cell hyporesponsiveness in the Cheédiak-Higashi syndrome. *Hum Immunol* 1983;6:45-52.

74. Hermansky R, Pudlak P. Albinism associated with hemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow. *Blood* 1959;14:162-169.

75. Schinella RA, Greco MA, Barton LC, et al. Hermansky-Pudlak syndrome with granulomatous colitis. *Ann Intern Med* 1983;92: 20-23.

76. Verriest G. [Color vision deficiency.] *Bull Soc Ophtalmol Fr* 1969; 69:901-927.

77. Abour NC, Zlotogora J, Knowlton RG, et al. Homozygosity mapping of achromatopsia to chromosome 2 using DNA pooling. *Hum Mol Genet* 1997;6:689-694.

78. Milunsky A, Huang X-L, Milunsky J, et al. A locus for autosomal recessive achromatopsia on human chromosome 8q. *Clin Genet* 1999;56:82-85.

79. Yee RD, Baloh RW, Honrubia V. Eye movement abnormalities in rod monochromacy. *Ophthalmology* 1981;88:1010-1018.

80. Krill AE. *Hereditary retinal and choroidal diseases. Vol. 2. Clinical characteristics*. Hagerstown, MD: Harper & Row, 1977.

81. Carr RE. Electrodiagnostic tests of the retina and higher centers. In: Harley RD, ed. *Pediatric ophthalmology*, 2nd ed. Philadelphia: WB Saunders Co., 1983:189-206.

82. Berson EL, Sandberg MA, Rosner B, et al. Color plates to help identify patients with blue cone monochromatism. *Am J Ophthalmol* 1983;95:741-747.

83. Yee RD, Farley MK, Bateman JB, et al. Eye movement abnormalities in rod monochromatism and blue cone monochromatism. *Graefes Arch Clin Exp Ophthalmol* 1985;223:55-59.

84. Carr RE. Congenital stationary night blindness. *Trans Am Ophthalmol Soc* 1974;72:448-487.

85. Hittner HM, Borda RP, Justice J. X-linked recessive congenital stationary night blindness, myopia, and tilted discs. *J Pediatr Ophthalmol Strabismus* 1981;18:15-20.

86. Miyake Y, Yagasaki K, Horiguchi M, et al. Congenital stationary night blindness with negative electroretinogram. A new classification. *Arch Ophthalmol* 1986;104:1013-1020.

87. Bech-Hansen NT, Naylor MJ, Maybaum TA, et al. Loss-of-function mutations in a calcium-channel alpha subunit gene in Xp11.23 cause incomplete X

linked congenital stationary night blindness. *Nat Genet* 1998;19:264-267.

88. Pusch CM, Zeitz C, Brandau O, et al. The complete form of X-linked congenital stationary night blindness is caused by mutations in a gene encoding a leucine-rich repeat protein. *Nat Genet* 2000;26:324-327.

89. Barricks MF, Flynn JT, Kushner BJ. Paradoxical pupillary responses in congenital stationary night blindness. *Arch Ophthalmol* 1977;95:1800-1804.

90. Wilder H. Oguchi's disease. *Am J Ophthalmol* 1953;36:718-719.

91. George NDL, Yates JRW, Bradshaw K, et al. Infantile presentation of X-linked retinoschisis. *Br J Ophthalmol* 1995;79:653-657.

92. Balian JV, Falls HF. Congenital vascular veils in the vitreous: hereditary retinoschisis. *Arch Ophthalmol* 1960;63:92-101.

93. Sieving PA, Bingham EL, Roth MS, et al. Linkage relationship of X-linked juvenile retinoschisis with Xp22.1-p22.3 probes. *Am J Hum Genet* 1990;47:616-621.

94. Mooy CM, van den Born LI, Paridaens DA, et al. Hereditary X-linked juvenile retinoschisis: a review of the role of Muller cells. *Arch Ophthalmol* 2002;120:979-984.

95. Dell'Osso LF, Ellenberger C, Abel IA, et al. The nystagmus blockage syndrome. Congenital nystagmus, manifest latent nystagmus, or both? *Invest Ophthalmol Vis Sci* 1983;24:1580-1587.

96. von Noorden GK, Wong SY. Surgical results in nystagmus blockage syndrome. *Ophthalmology* 1986;93:1028-1031.

97. Dell'Osso LF, Schmidt D, Darroff RB. Latent, manifest latent, and congenital nystagmus. *Arch Ophthalmol* 1979;97:1877-1885.

98. Zubcov AA, Reinecke RD, Gottlob I, et al. Treatment of manifest latent nystagmus. *Am J Ophthalmol* 1990;110:160-167.

99. Evans DE, Biglan AW, Troost BT. Measurement of visual acuity in latent nystagmus. *Ophthalmology* 1981;88:134—138.

100. Tusa RJ, Mustari MJ, Burrows AF, et al. Gaze-stabilizing deficits and latent nystagmus in monkeys with brief, early-onset visual deprivation: eye movement recordings. *J Neurophysiol* 2001;86: 651-661.

101. Mustari MJ, Tusa RJ, Burrows AF, et al. Gaze-stabilizing deficits and latent nystagmus in monkeys with early-onset visual deprivation: role of the pretectal NOT. *J Neurophysiol* 2001;86: 662-675.

102. Gresty MA, Metcalfe T, Timms C, et al. Neurology of latent nystagmus. *Brain* 1992;115:1303-1321.

103. Dell'Osso LF, Traccis S, Abel LA. Strabismus: a necessary condition of latent and manifest latent nystagmus. *Neuroophthalmology* 1983;3:247-257.

104. Kushner BJ. Infantile uniocular blindness with bilateral nystagmus. A syndrome. *Arch Ophthalmol* 1995;113:1298-1300.

105. Abadi RV, Dickinson CM. Waveform characteristics in congenital nystagmus. *Doc Ophthalmol* 1986;64:153-167.

106. Gottlob I. Infantile nystagmus. Development documented by eye movement recordings. *Invest Ophthalmol Vis Sci* 1997;38: 767-773.

107. Reinecke RD, Guo S, Goldstein HP. Waveform evolution in infantile nystagmus: an electro-oculo-graphic study of 35 cases. *Binoc Vis* 1988;31:191-202.

108. Dell'Osso L, Daroff RB, Troost BT. Nystagmus and saccadic intrusions and oscillations. In: Duane TD, Jaeger EA, eds. *Clinical ophthalmology*. Philadelphia: Harper & Row, 1988.

109. Allen ED, Davies PD. Role of contact lenses in the management of congenital nystagmus. *Br J Ophthalmol* 1983;67:834-836.

110. Leigh RJ, Averbuch-Heller L, Tomsak RL, et al. Treatment of abnormal eye movements that impair vision: strategies based on current concepts of physiology and pharmacology. *Ann Neurol* 1994;36:129-141.

111. Yaniglos SS, Leigh RJ. Refinement of an optical device that stabilizes vision in patients with nystagmus. *Optom Vis Sci* 1992;69: 447-450.

112. Dell'Osso LF, Flynn JT. Congenital nystagmus surgery: a quantitative evaluation of the effects. *Arch Ophthalmol* 1979;97: 462-469.

113. Barton JJS, Huaman AG, Sharpe JA. Muscarinic antagonists in the treatment of acquired pendular and downbeat nystagmus: a double-blind, randomized trial of three intravenous drugs. *Ann Neurol* 1994;35:319-325.

114. Averbuch-Heller L, Tusa RJ, Fuhry L, et al. A double-blind controlled study of gabapentin and baclofen as treatment for acquired nystagmus. *Ann*

Neurol 1997;41:818-825.

115. Currie JN, Matsuo V. The use of clonazepam in the treatment of nystagmus-induced oscillopsia. *Ophthalmology* 1986;93: 924-932.

116. Gradstein L, Reinecke RD, Wisov SS, et al. Congenital periodic alternating nystagmus. Diagnosis and management. *Ophthalmology* 1997;104:918-928.

117. Frisen L, Wikkelso C. Posttraumatic seesaw nystagmus abolished by ethanol ingestion. *Neurology* 1986;36:841-844.

118. Cochin JP, Hannequin D, Domarcolino C, et al. [Intermittent see-saw nystagmus abolished by clonazepam.] *Rev Neurol (Paris)* 1995;151:60-62.

119. Carruthers J. The treatment of congenital nystagmus with botox. *J Pediatr Ophthalmol Strabismus* 1995;32:306-308.

120. Helveston EM, Pogrebniak AE. Treatment of acquired nystagmus with botulinum A toxin. *Am J Ophthalmol* 1988;106:584-586.

121. Repka MX, Savino PJ, Reinecke RD. Treatment of acquired nystagmus with botulinum neurotoxin A. *Arch Ophthalmol* 1994; 112:1320-1324.

122. Ruben ST, Lee JP, O'Neal D, et al. The use of botulinum toxin for the treatment of acquired nystagmus and oscillopsia. *Ophthalmology* 1994;101:783-787.

123. Tomsak RL, Remler BF, Averbuch-Heller L, et al. Unsatisfactory treatment of acquired nystagmus with retrobulbar injection of botulinum toxin. *Am J Ophthalmol* 1995;119:489-496.

124. Anderson JR. Causes and treatment of congenital eccentric nystagmus. Br J Ophthalmol 1953;37:267-281.

125. Kestenbaum A. [New operation for nystagmus.] *Bull Soc Ophtalmol Fr* 1953;6:599-602.

126. Mitchell PR, Wheeler MB, Parks MM. Kestenbaum surgical procedure for torticollis secondary to congenital nystagmus. *J Pediatr Ophthalmol Strabismus* 1987;24:87-93.

127. Nelson LB, Ervin-Mulvey LD, Calhoun JH, et al. Surgical management for abnormal head position in nystagmus: the augmented modified Kestenbaum procedure. *Br J Ophthalmol* 1984;68: 796-800.

128. Scott WE, Kraft SP. Surgical treatment of compensatory head position in congenital nystagmus. *J Pediatr Ophthalmol Strabismus* 1984;21:85-93.

129. Cooper EL, Sandall GS. Surgical treatment of congenital nystagmus. *Arch Ophthalmol* 1969;81:473-480.

130. Helveston EM, Ellis FD, Plager DA. Large recession of the horizontal recti for treatment of nystagmus. *Ophthalmology* 1991;98: 1302-1305.

131. von Noorden GK, Sprunger DJ. Large rectus muscle recessions for the treatment of congenital nystagmus. *Arch Ophthalmol* 1991;109:221-224.

132. Reinecke RD. Retroequatorial placement of horizontal recti. *J Pediatr Ophthalmol Strabismus* 1996;33:201-202.

133. Dell'Osso LF. Extraocular muscle tenotomy, dissection, and suture: an hypothetical therapy for congenital nystagmus. *J Pediatr Ophthalmol Strabismus* 1998;35:232-233.

134. Hertle RW, Dell'Osso LF, FitzGibbon EJ, et al. Horizontal rectus tenotomy in patients with congenital nystagmus: results in 10 adults. *Ophthalmology* 2003;110:2097-2105.

135. Pedersen RA, Troost BT, Abel LA, et al. Intermittent downbeat nystagmus and oscillopsia reversed by suboccipital craniectomy. *Neurology* 1980;30:1239-1242.

136. Catalano RA, Calhoun JH. Ocular conditions associated with nystagmus. In: Reinecke RD, ed. *Ophthalmology annual, 1988*. New York: Raven Press, 1988:90.

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26

Ocular Trauma and Its Prevention

Robert A. Catalano

Ocular trauma is a significant cause of visual loss in children. According to the 2000 Annual Report of the United States Eye Injury Registry (consisting of non-mandatory reports of serious, potentially vision-threatening trauma from 41 states), eye injury is the leading cause of monocular blindness in the United States. The majority (57%) of these injuries occur in individuals under age 30. Based on a recent European study, the highest proportion of severe eye injuries in children occurs in the home (40%), followed by injuries sustained playing sports or due to a motor vehicle accident. In children younger than age 6, domestic accidents (scissors, pencils, or other sharp objects) were the principal cause; in older children, toys, stone, and ball injuries predominated (1). This study and others (2,3,4) revealed a substantial male preponderance and noted that most severe injuries in children are accidental and caused by another child.

Estimates place the cost for the projected 227,000 hospital days for eye trauma at $175 to $200 million (5). These costs are exclusive of any forced career changes or other economic loss suffered by injured patients, which compound enormously over a lifetime, especially for pediatric patients.

In contrast with other causes of childhood visual loss, such as from congenital and/or hereditary diseases in which current treatments are often ineffective, victims of ocular trauma can often benefit greatly by prompt treatment. Even greater benefit can result, if ocular trauma is prevented, which is readily attainable in the pediatric population.

HISTORY

Although most ophthalmological office examinations for children require only a brief history, when ocular trauma is apparent or suspected, a complete and detailed history is essential, especially when a responsible adult did not observe the injury. In many cases, it is this initial history that is the most accurate and unbiased. Extra care and attention to detail is required to detect prevarication or other attempts at deception; for example, the child may have sustained the trauma engaged in a proscribed behavior, a “supervising” adult may have been involved in the injury, or the visual loss, if any, may have predated the injury. In addition, careful documentation of all historical and objective findings, with detailed drawings or photographs, if indicated, can be crucial for purposes of determining civil liability and/or suspected child abuse.

When the patient's chief complaint is trauma, the usual sequence of questions for history taking must be greatly expanded. Precise determination of the time and place of the onset of symptoms or signs must be made. A foreign body sensation that began when the child was near a construction site prompts a search for a different type of object than if the symptoms began in a wooded area. When the inciting event is not obvious, and the symptoms and signs did not begin at a distinct time, inquiry must be made of activities in the preceding hours, days, or even weeks.

The child's precise activity at the time of injury and the site where it occurred must be determined. Whether or not the child was wearing glasses, using high-speed motorized equipment, and whether or not anyone was hammering are examples of the level of detail that must be documented. If a wild animal inflicted the injury, the animal should undergo pathological examination of its brain to look for signs of rabies infestation. When such examination is impossible, consultation with local health officials should be sought to determine the need for rabies prophylaxis. Domesticated animals may be observed for 10 days to look for signs of disease.

The general medical history must also be determined. Known medical problems, hospitalizations, prior ocular and nonocular surgeries, current medications of all types, medicinal allergies, and family history must all be explored.

In addition, patients with open wounds must have their tetanus prophylaxis history reviewed and reimmunization administered, if necessary.

EXAMINATION

Despite the critical need for as complete an examination as possible to make an accurate diagnosis, initial efforts must be directed to the more important goal of preventing further injury. In the case of a ruptured globe, a more complete examination is always obtained with the child anesthetized in the operating room at significantly less risk of causing further injury. Further complicating an already difficult situation is the consideration that a pediatric ocular trauma patient is likely to be in some degree of discomfort, reducing what may be an already low level of cooperation. Extra efforts at cajoling or bribery, additional pairs of strong hands, a papoose board, local nerve block, sedation, or even anesthesia may be required alone or in combination for proper diagnosis and treatment.

Special Studies

Additional modalities of examination may be required in some instances. When motorized equipment or high-speed impacts (e.g., hammering) were involved at the time of the injury, a foreign body, either in the globe or orbit, must be suspected. Plain radiographic films and noncontrast computed tomography (CT) (6,7) may be required for accurate and precise localization. An intraocular foreign body should also be considered whenever a ruptured globe is suspected.

If a clear view of the fundus is not obtained, ultrasonography should be considered to assess retinal integrity. However, the diagnostic possibility of a ruptured globe is a contraindication to the use of ultrasound. In that instance, any pressure on the globe may further disrupt the anatomy (causing retinal and/or uveal prolapse), and the nonsterile probe raises the risk of infection. For closed-globe injuries, ultrasound biomicroscopy is particularly superior to other methods in the evaluation of the zonular status, angle recession, cyclodialysis, and the detection of small superficial and intraocular foreign bodies (8).

Protection from Further Injury

When definitive treatment for the injury will occur later, the injured eye and adnexa should be protected from further inadvertent trauma. With lid lacerations, foreign bodies, and suspected ruptured globes, a standard eye shield should be taped to the orbital rim to protect the globe and lids. When ophthalmic supplies are unavailable, a disposable Styrofoam coffee cup can be cut about 2.5 cm (1 inch) from its base and used for the same purpose.

From a systemic standpoint, a child with a possibly ruptured globe may be agitated, nauseated (from a vasovagal reflex), or both. Mild sedation, along with an antiemetic, may be indicated to prevent further damage. If there is concern that the child may pull off a protective eye shield, elbow or other restraints may be necessary.

When a ruptured globe is repaired under general anesthesia, a nondepolarizing agent should be used (9). Depolarizing agents (e.g., succinylcholine) transiently raise intraocular pressure and possibly further extrude intraocular contents.

BIRTH AND PRENATAL TRAUMA

Although unusual, newborns can sustain ocular injuries. The most widely recognized finding associated with birth trauma is a vertically oriented rupture of Descemet's membrane, which is often accompanied by a hazy cornea. Horizontal Descemet's ruptures (Haab's striae) result more commonly from the high intraocular pressure of congenital glaucoma. Although direct contact of forceps with the cornea is usually implicated, periocular compression is also a possible mechanism of injury (10).

With time, epithelial edema fades, leaving a vertical line at the level of Descemet's membrane. This line is visually insignificant. However, true ruptures of Descemet's membrane can lead to very large degrees of astigmatism that can result in anisometropic amblyopia (11). The initial corneal haziness can act as a form of occlusion, which can induce axial myopia and exacerbate the anisometropia (12). The use of a rigid contact lens to neutralize the astigmatism and aggressive occlusion therapy can possibly improve the visual prognosis (13).

Perinatal periocular ecchymoses (14), lid (15), canalicular (16) laceration, ptosis (17), corneal edema (14), hyphema (14), and multiple retinal hemorrhages (14) have also been reported. Injuries to the lid that cause ptosis are potentially very serious because the ptosis may cause an axial myopia (12), which can lead to an anisometropic amblyopia.

In addition to corneal injury, forceps delivery may rarely result in choroidal ruptures, even in the absence of external signs of injury (18). Finally, ocular adnexal birth injury by a fetal monitoring scalp electrode has been reported occasionally (19).

Ocular injury can also occur prenatally, during amniocentesis. Despite ultrasound control, injury to the fetus occurs in 3% of cases (20), usually resulting in cutaneous scars. Ocular perforation may also occur, with varying degrees of visual disability (Fig. 26.1) (21,22).

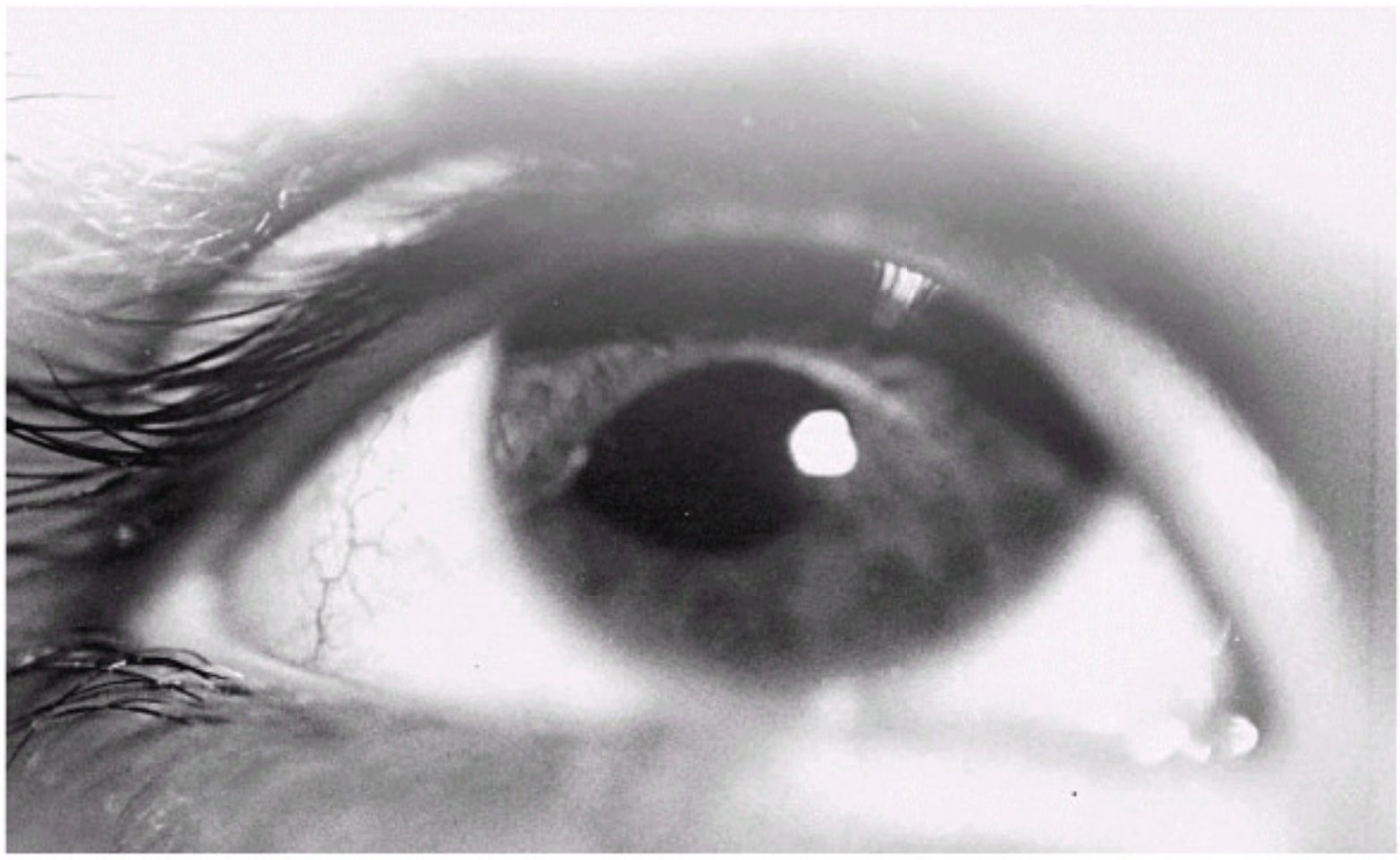

Figure 26.1 Penetrating injury from amniocentesis.

INJURIES TO THE LIDS AND ADNEXA

Ecchymosis of the Eyelid

Most orbital contusions, due to blunt injuries, cause soft tissue damage with little or no disability. Blunt trauma, however, can be associated with a blowout or other orbital fractures, hyphema, angle recession, iridodialysis, retinal edema, and retinal breaks. Deep orbital bleeding can cause compression of the optic nerve or ophthalmic artery. Examination of the peripheral retina, using scleral depression, may have to wait until orbital edema subsides. The examination should not be delayed, however, in patients with symptoms suggestive of a retinal tear.

The distribution of hemorrhage can occasionally foretell a serious orbital injury. Blood under the superior conjunctiva suggests an orbital roof fracture, especially when accompanied by significant eyelid edema and ecchymosis (23). Basilar skull fractures are sometimes associated with a ring-like distribution of periorbital blood. Hemorrhage in the lower lid and inferior orbit may signal an orbital floor fracture (Fig. 26.2).

Blunt trauma can also result in ptosis secondary to a hematoma of the eyelid or levator palpebrae muscle. A permanent ptosis can result if the aponeurosis is stretched or torn. Fingers or hooks caught under the upper eyelid often result in this type of injury.

Treatment of lid ecchymosis consists of cold compresses for the initial 24-hour period, followed by warm compresses as needed.

Lid Laceration

In addition to obvious causes of lacerations from injury with sharp objects and animal bites, lid lacerations can be caused by strong blows with blunt objects, such as an elbow in a competitive basketball game. The initial evaluation of a lid laceration of any etiology is directed at the integrity of the globe; vision-threatening ocular injuries take precedence over those involving only the lids, where delayed repair may still give an excellent cosmetic and functional result. With lacerations involving the medial portion of the lid, the status of the canaliculi should be determined to the greatest extent possible without risking further injury.

Figure 26.2 Eyelid and periorbital ecchymosis and limitation of upward gaze resulting from a blowout fracture.

There is no clear consensus concerning prophylactic treatment with antibiotics for lid lacerations. Although standard surgical practice may suggest use of antibiotics in other injuries, they may not be necessary with lid lacerations due to the rich blood supply of the lids.

Most children who sustain ophthalmic trauma are not sufficiently cooperative to allow for local or regional anesthetic techniques. Regardless of the level of cooperation, general anesthesia is mandatory whenever related injuries require its use, as in an ocular laceration.

Primary, edge-to-edge closure remains the mainstay of treatment for lid lacerations. Nonrepair of a torn canaliculus may be considered when only one canaliculus is involved (24), but when both canaliculi are involved, intubation of the canaliculi with Silastic tubing looped and brought out through the lower opening of the nasolacrimal duct increases the chance of functional success. Subsurface absorbable sutures are then used around the cut edges of the canaliculi before the cutaneous edges are repaired. Even with a complete history, a thorough search for a retained foreign body should be made at the time of repair of any laceration. The reader is referred elsewhere (25) for detailed, specific recommendations on treatment, which are beyond the scope of this chapter.

ORBITAL TRAUMA

Blowout Fracture of the Orbital Floor

Orbital apex, lateral wall, and Le Fort type III fractures have a greater association with severe ocular injuries than blowout fractures of the orbital floor, but they occur less commonly (26). The term *direct orbital floor fracture* describes an orbital floor fracture associated with an orbital rim fracture. Much greater force is needed to fracture the orbital rim than to fracture the orbital floor. The term *indirect orbital floor fracture* describes an isolated orbital floor fracture and is known more commonly as a *blowout fracture*. Two theories have been developed to explain the pathogenic mechanism of a blowout fracture. The first maintains that these fractures result when the intraorbital pressure is suddenly elevated by a nonpenetrating blunt force. The orbital tissues are compressed, and the weakest part of the orbit, the 0.5-mm-thick orbital floor just below the inferior rectus muscle, becomes the avenue of decompression (Fig. 26.3). A more recent theory suggests that a blunt force applied to the inferior orbital rim compresses the bone and causes a buckling of the orbital floor. Orbital floor fractures are common when objects larger than the orbital opening, such as a ball, a fist, or the dashboard of an automobile, impact the orbit, particularly the inferior lateral orbit. *Macaca* monkey experiments have suggested that forces greater than 2 joules (J) are needed to produce an orbital floor fracture,

and that orbital wall fractures fail to protect the globe from rupture (27).

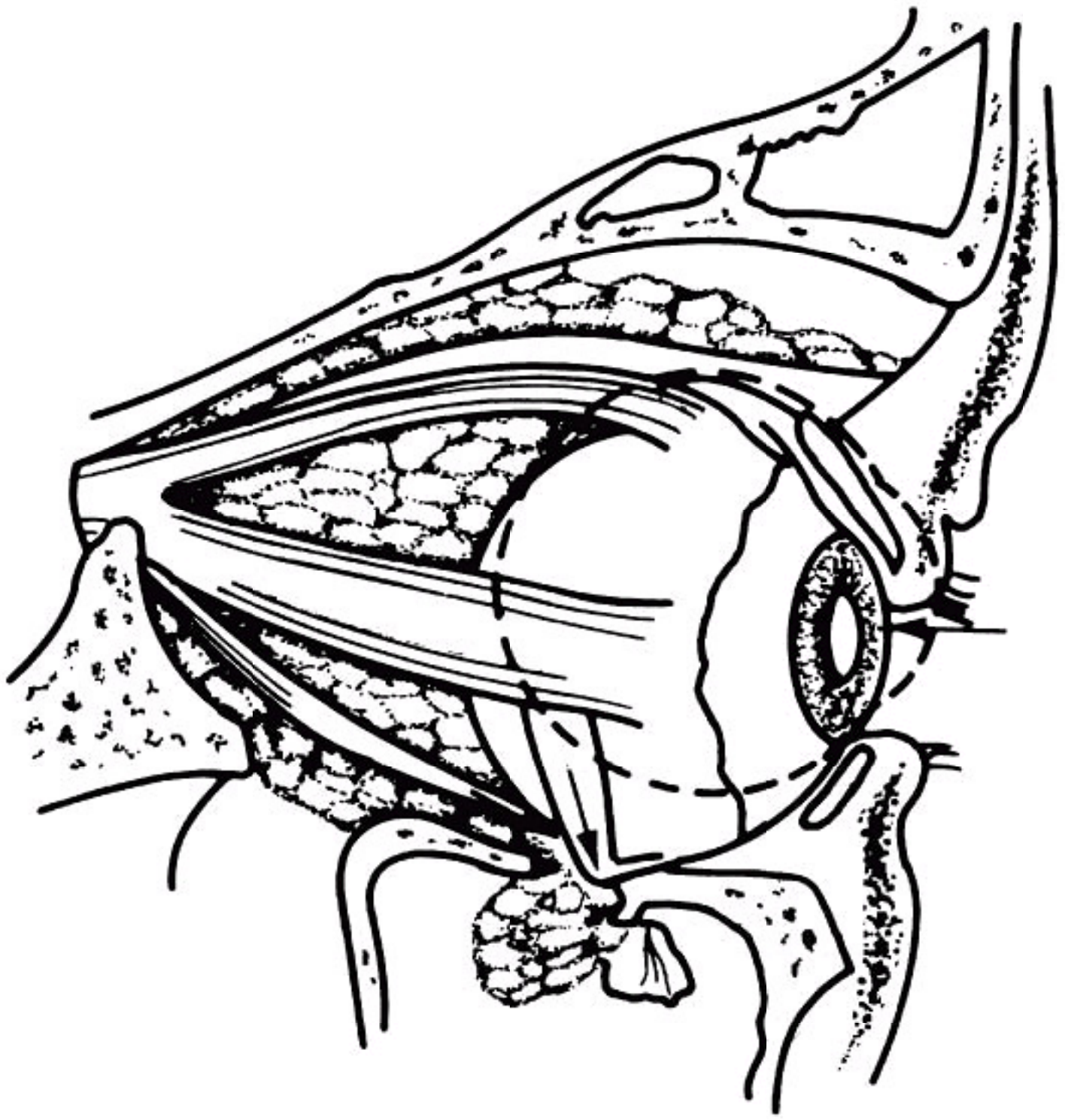

Figure 26.3 Schematic to demonstrate a blowout fracture of the orbital floor. The dotted line indicates the normal position of the globe. The small opening into the maxillary sinus entraps the inferior rectus and oblique muscles. (From Catalano RA, ed. *Ocular emergencies*. Philadelphia: **WB** Saunders Co, 1992, with permission.)

The most apparent clinical sign of an orbital floor fracture is a limitation of upward gaze (Figs. 26.2 and 26.4). A concomitant limitation of downward gaze, however, is a more certain indication of inferior rectus or oblique muscle entrapment. Entrapment is more likely to occur when an articulated bone fragment acts like a trap door, restricting the movement of the inferior rectus or oblique muscle (28). This occurs most frequently with small, indirect orbital floor fractures, and most commonly the inferior rectus muscle, posterior to its adventitial connection to the inferior oblique muscle, is involved. Additional signs are lid ecchymosis, epistaxis, orbital emphysema, and hypesthesia of the ipsilateral cheek and upper lip, which results from disruption of the infraorbital nerve as it traverses the orbital floor. Enophthalmos results from expansion of the orbital volume and is an overt sign of an orbital floor fracture. It occurs more commonly with direct orbital floor fractures but it may not become apparent until orbital edema resolves. Exophthalmos from orbital edema, hematoma, or inflammation is more likely to be present acutely.

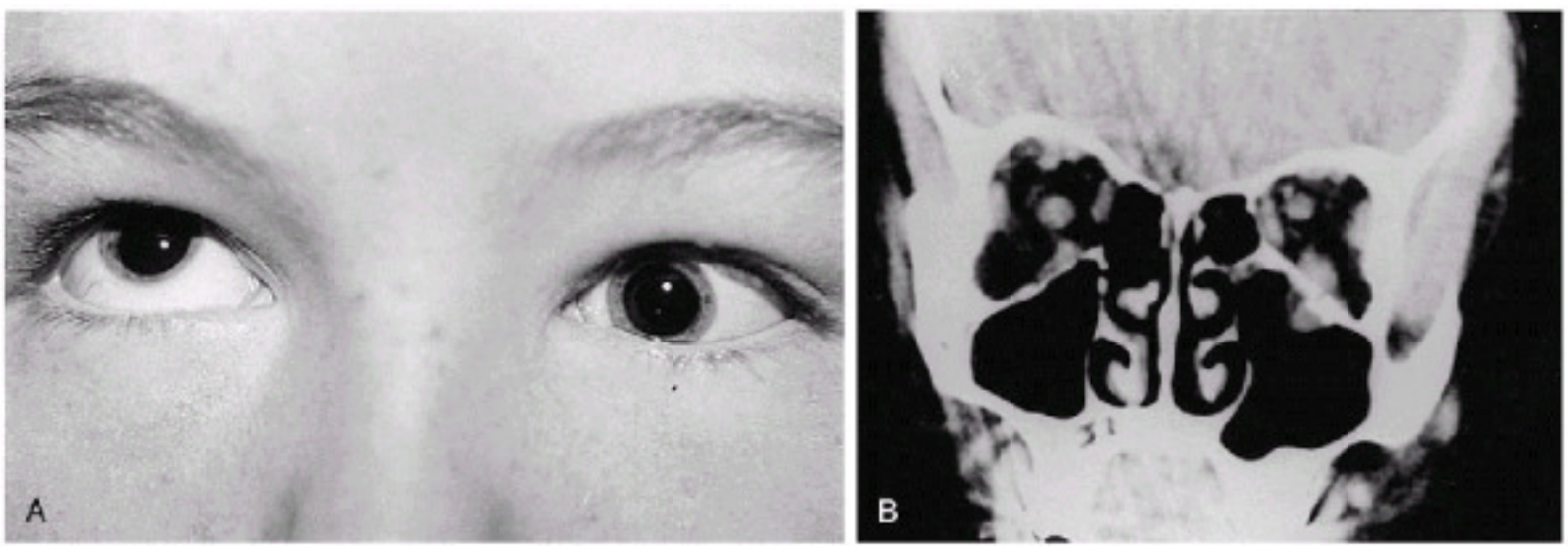

Figure 26.4 Blowout fracture of the left eye in a 12-year-old girl who was kicked in the eye by a classmate. A: Limitation of upgaze. B: Coronal CT scan showing tissue entrapment.

The best imaging techniques to visualize an orbital floor fracture are plain film radiography and CT scanning. The optimal plain film projection is the Waters' view because it best demonstrates the orbital floor and maxillary sinus (Fig. 26.5). An orbital floor fracture is suggested by the prolapse of orbital contents into the maxillary sinus, an air-fluid level in the sinus, or orbital emphysema. Although the Waters' view is suggested for screening, direct, coronal 1.5- to 2-mm CT scanning should be obtained, if surgical repair is contemplated, because this provides more soft tissue and bone fragment detail.

The indications for surgical repair of a blowout fracture are controversial (29). The radiographic presence of fracture alone is not an indication for surgery and is not the sole finding of infraorbital hypesthesia. Generally accepted indications for repair include a motility disturbance due to extraocular muscle entrapment (within 30 degrees of the primary position) or enophthalmos. In pediatric patients, symptoms of entrapment of the inferior rectus muscle include pain, nausea, and vomiting. Surgical repair rapidly relieves these symptoms (30). Surgical intervention for a limitation of motility is based on true mechanical restriction, suggested by persistent positive forced traction testing and confirmed radiography. It should be remembered, however, that techniques other than floor fracture repair (prisms, strabismus surgery) might be effective in relieving diplopia. Enophthalmos of greater than 2 mm generally requires repair, because it is usually cosmetically unacceptable. Because the necessary exposure of an orbital floor fracture places pressure on the globe, the presence of a penetrating ocular injury is an absolute contraindication to orbital floor repair.

The timing of surgical repair is also controversial. A

blowout fracture never needs emergent treatment. Most ophthalmologists agree that surgery can be safely delayed for 10 to 14 days without risking the development of scarring or fibrosis. The passage of several days is usually needed to allow orbital swelling to subside enough to perform an adequate clinical examination. An indication for early surgical repair may be the presence of enophthalmos in the acute stage of an orbital floor fracture. Orbital edema and hematoma mask usually the early appearance of enophthalmos; its acute presence indicates a substantial extrusion of orbital contents into the maxillary sinus.

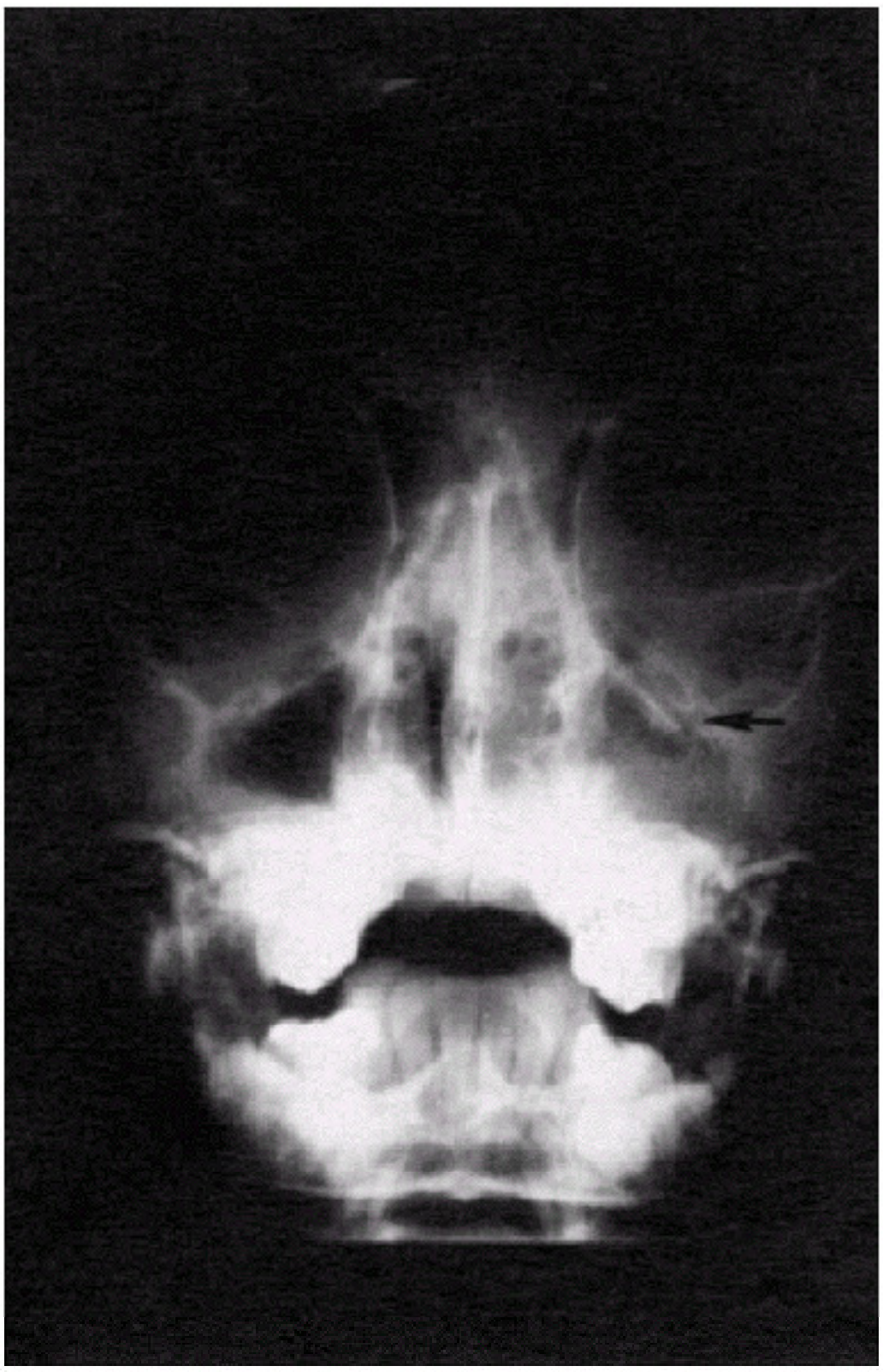

Figure 26.5 Waters' view demonstrating blowout fracture of the orbital floor. (From Catalano RA, ed. *Ocular emergencies*. Philadelphia: WB Saunders Co, 1992, with permission.)

Additional therapeutic measures in the acute setting are antibiotic prophylaxis to prevent an orbital cellulitis, nasal decongestants, and ice packs.

INJURIES TO THE GLOBE

Injuries to the Conjunctiva and Sclera

A *subconjunctival hemorrhage* commonly accompanies blunt trauma (Fig. 26.6). In the absence of other injury, an affected patient is treated with reassurance alone. The hemorrhage may appear to become larger over the first several days. This occurs as gravity and the weight of the eyelid smooths out blood clots that can dissect under normal conjunctiva. Rarely, if ever, does a subconjunctival hemorrhage rebleed. The blood gradually resorbs over 2 to 3 weeks.

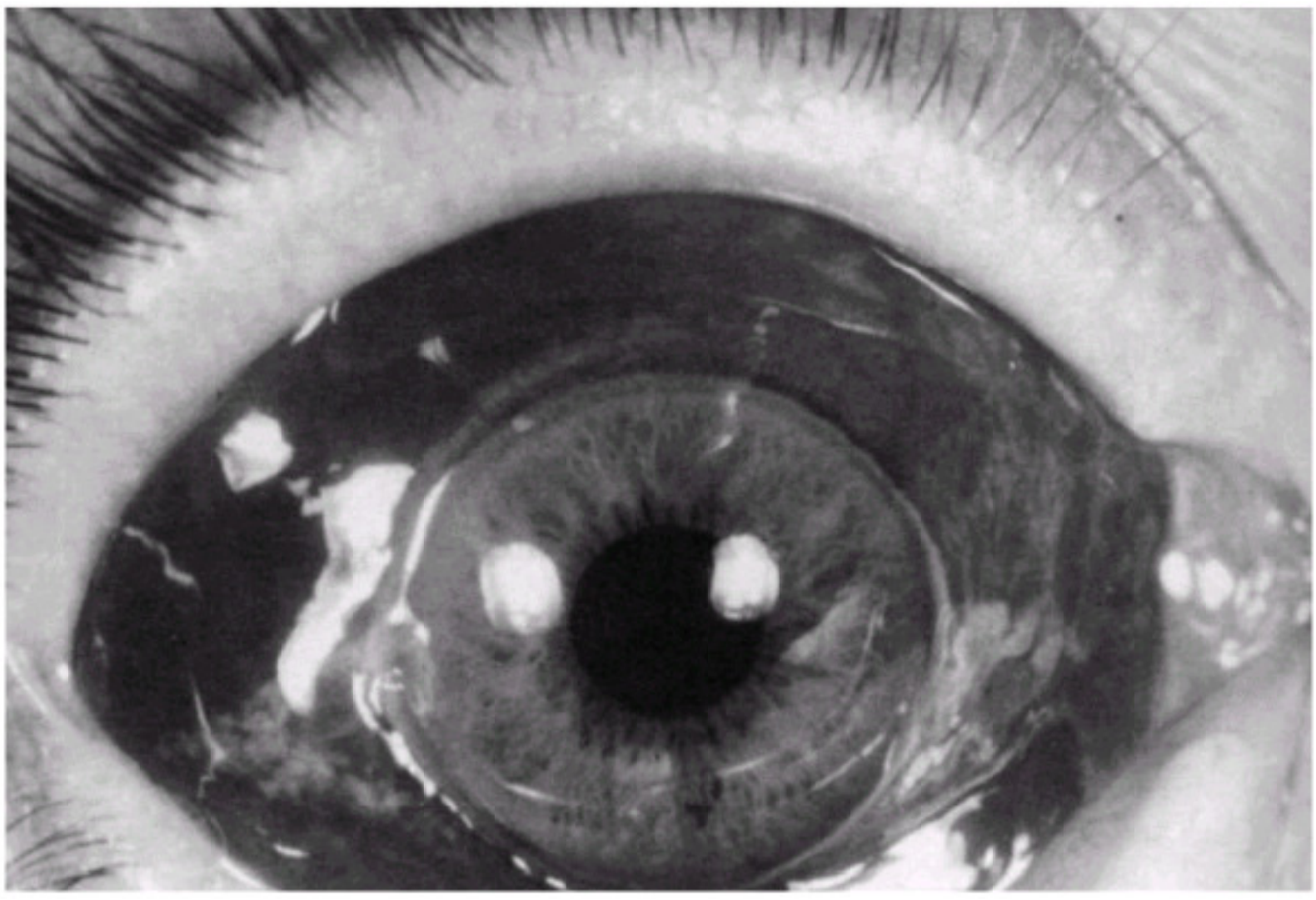

Figure 26.6 Traumatic subconjunctival hemorrhage. (From Catalano RA, ed. *Ocular emergencies*. Philadelphia: WB Saunders Co, 1992, with permission.)

Conjunctival edema (*chemosis*) can accompany a minor injury. However, its presence raises the suspicion of scleral rupture or a retained foreign body. Air under the conjunctiva (*emphysema*) suggests fracture through the ethmoid or maxillary sinus. Emphysema appears cystic and causes crepitus on palpation.

A *laceration of the conjunctiva* is especially common when a sharp object, such as a fingernail or glass, strikes the eye. In addition to conjunctival hemorrhage, prolapse of whitish-appearing Tenon's tissue or orbital fat may be evident. A complete examination to rule out an occult scleral laceration or retained foreign body is necessary. If sliding the conjunctiva does not allow adequate visualization, blunt dissection and inspection of the sclera are performed under anesthesia, if necessary. Ophthalmoscopy through maximally dilated pupils and ultrasound are used to rule out an intraocular foreign body. These measures are usually sufficient to exclude a more serious injury. However, the physician should not hesitate to conduct an examination under anesthesia or obtain imaging studies, if uncertainty exists. Small conjunctival lacerations do not need suturing, but lacerations greater than 6 mm should be closed with absorbable suture (e.g., 7-0 plain gut), taking care not to incorporate Tenon's tissue in the wound. One should also respect the normal anatomical relationship of the caruncle and semilunar fold in the repair. The unrepaired conjunctival defect heals within 2 to 3 weeks.

Occult scleral rupture can occur with blunt trauma, especially at the limbus and just posterior to the rectus muscle insertions, where the sclera is weakest (31). In addition to a bullous conjunctival hemorrhage and chemosis, signs of rupture include an asymmetrical reduction in intraocular pressure, shallowing or deepening of the anterior chamber, irregularity or peaking of the pupil, hyphema, decreased visual acuity, and subconjunctival pigmentation. The last is due to prolapsed uveal tissue at the site of rupture. In suspected cases, as much as a 360-degree conjunctival peritomy

should be performed (incising the conjunctiva at the limbus and retracting it posteriorly to expose the underlying sclera), with particular attention directed to the area under the rectus muscle insertions.

Corneal Foreign Bodies and Abrasions

Corneal and conjunctival foreign bodies are relatively common causes of acute ocular pain and foreign body sensation. Although a multitude of different objects can lodge in the cornea and/or conjunctiva, a history of proximity to a car with a raised hood or a construction site immediately raises one's suspicion. Although inert objects may cause little or no secondary changes, organic material can produce a severe reaction (Fig. 26.7).

The cornea and bulbar conjunctiva are examined directly with or without magnification. The palpebral conjunctiva of the lower eyelid and the inferior cul-de-sac can be examined by pulling down the lower eyelid and having the patient look up. Examination of the palpebral conjunctiva of the upper eyelid and the upper cul-de-sac is more difficult. “Double eversion” of the upper eyelid may be required. A single eversion of the upper eyelid can be achieved by gently grasping the eyelid at the lash line and pulling it down while placing minimal counterpressure at the upper border of the eyelid with a cotton-tipped applicator. The patient should be instructed to look down during the procedure. Elevation of the lid margin, counterpressure at the upper border, and gentle lid rotation usually everts the lid (Fig. 26.8). “Double eversion” of the upper eyelid is accomplished by substituting a Desmarres retractor for the cotton-tipped applicator and pulling the eyelid forward as it is rolled around the retractor (Fig. 26.9). A careful search for a foreign body is then made of both the palpebral conjunctiva and the cul-de-sac. Upper

lid eversion produces discomfort, which can be minimized by instructing the patient to look down continually.

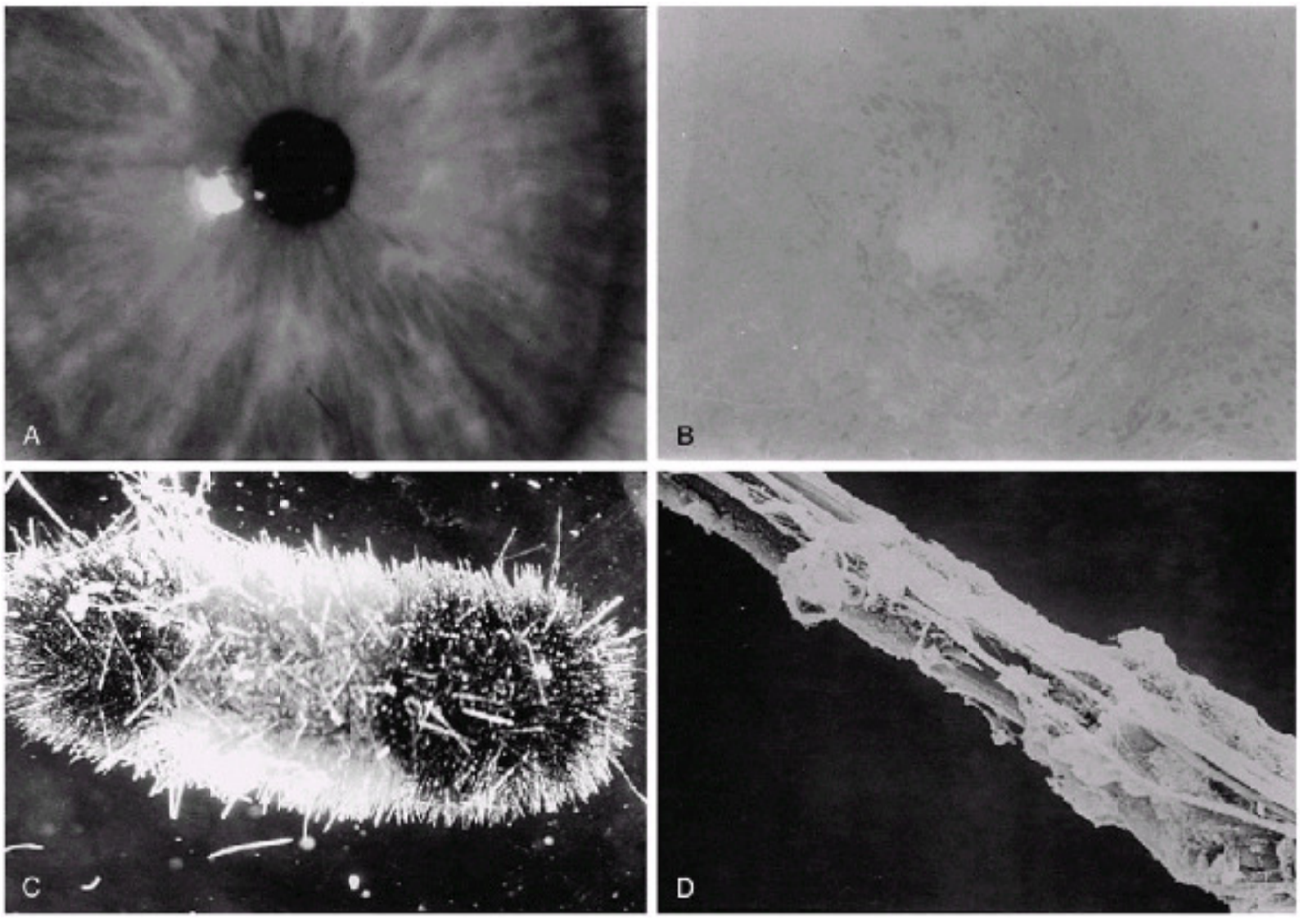

Figure 26.7 Four-year-old boy with caterpillar-hair (seta)-induced keratoconjunctivitis. A: Apical corneal infiltrates. B: Conjunctival foreign body granuloma (hematoxylin-eosin stain). C: Caterpillar with setae. D: Seta (scanning electron micrograph > 1000). (Courtesy of George G. Hohberger, MD, Mayo Clinic, with permission.)

If a foreign body is found, it can usually be easily removed. Adequate anesthesia is obtained with topical anesthetics (proparacaine 0.5% or tetracaine 0.5%). One drop is usually adequate, but additional applications at intervals of 3 to 5 minutes may be necessary. Young children may require generous amounts of vocal reassurance, or, if it is unsuccessful, heavy sedation or a brief general anesthesia.

Before the removal of a foreign body in the conjunctiva, the underlying sclera should be examined to rule out a

penetrating injury. If the conjunctiva, as well as the retained foreign body, is not easily movable over the underlying sclera, or, if the foreign body appears fixed to deeper structures of the globe, an accompanying scleral injury should be suspected. Further manipulations and treatment should be carried out in the operating room, under the operating microscope.

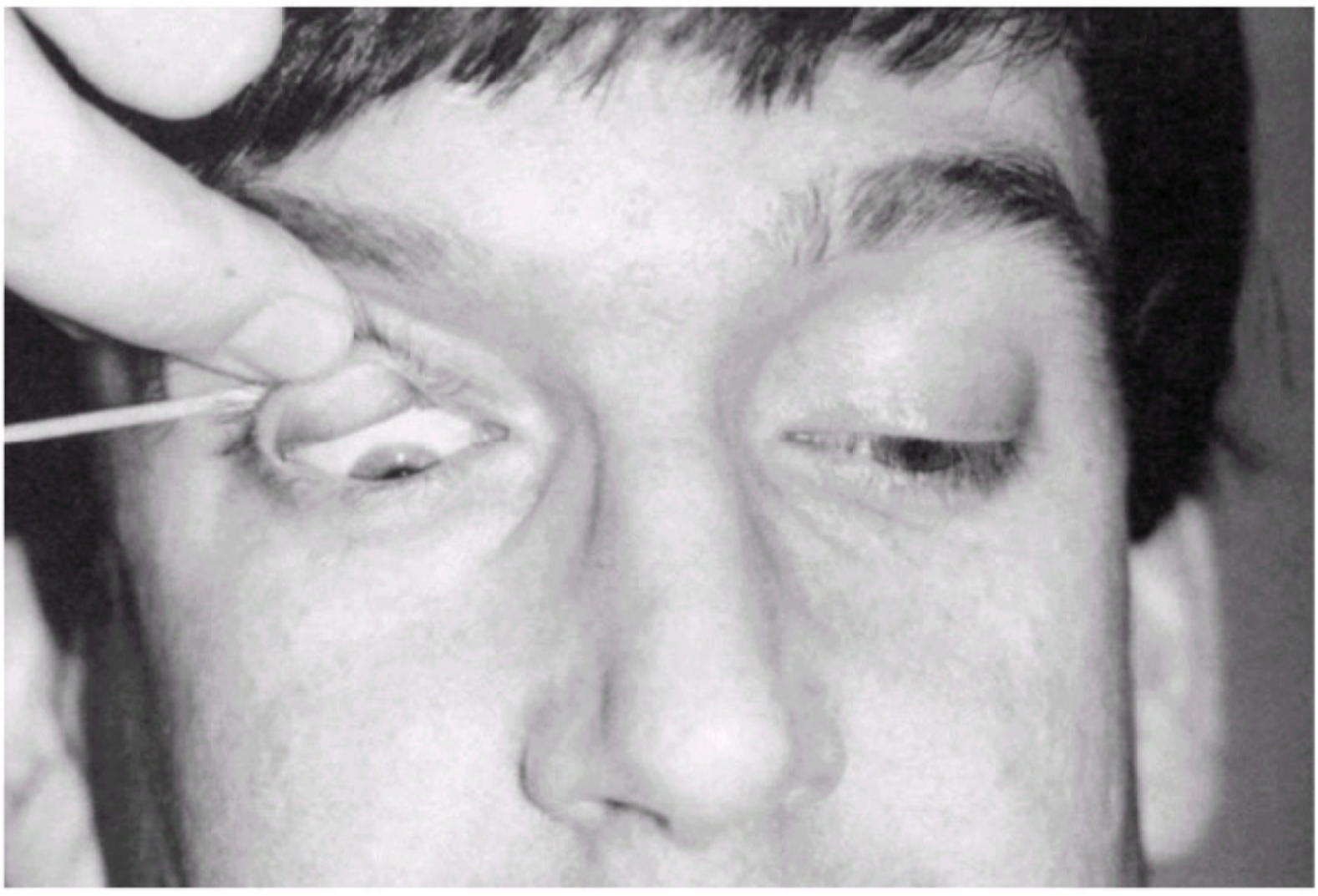

Figure 26.8 Eversion of upper eyelid with cotton applicator. (From Catalano RA, ed. *Ocular emergencies*. Philadelphia: WB Saunders Co, 1992, with permission.)

If the foreign body appears to be adherent to only the cornea or conjunctiva, it can be removed with a foreign body spud, fine forceps (jewelers or tying forceps), or the edge of a medium-bore needle (22-gauge). This is best done at the slit lamp with the physician's hand resting on the patient's cheekbone. This position lessens the chance of striking the globe with a sharp object; any movement of the patient is automatically followed by the physician's hand (Fig. 26.10). Many foreign bodies can also be removed by applying a bland ophthalmic ointment (Lacri-Lube, Duratears) to the end of a cotton-tipped applicator and swabbing the foreign body, a safer approach to use when a slit lamp is not available. Although this technique removes loose or recently occurring foreign bodies, it is less effective with foreign bodies that have been present for a longer duration and have become more adherent. Once a conjunctival foreign body is removed, further treatment is usually not indicated. Once a corneal foreign body is removed, the treatment should follow the guidelines outlined later for corneal abrasions.
Iron-containing corneal foreign bodies often leave a deposit of rust that may spread into the deeper layers of the cornea. The residual rust often resolves with time but can cause persistent foreign bodylike complaints. The rust ring can be scraped with a dull object, like a foreign body spud, or removed with a mechanical corneal bur (a battery-operated low-speed drill).

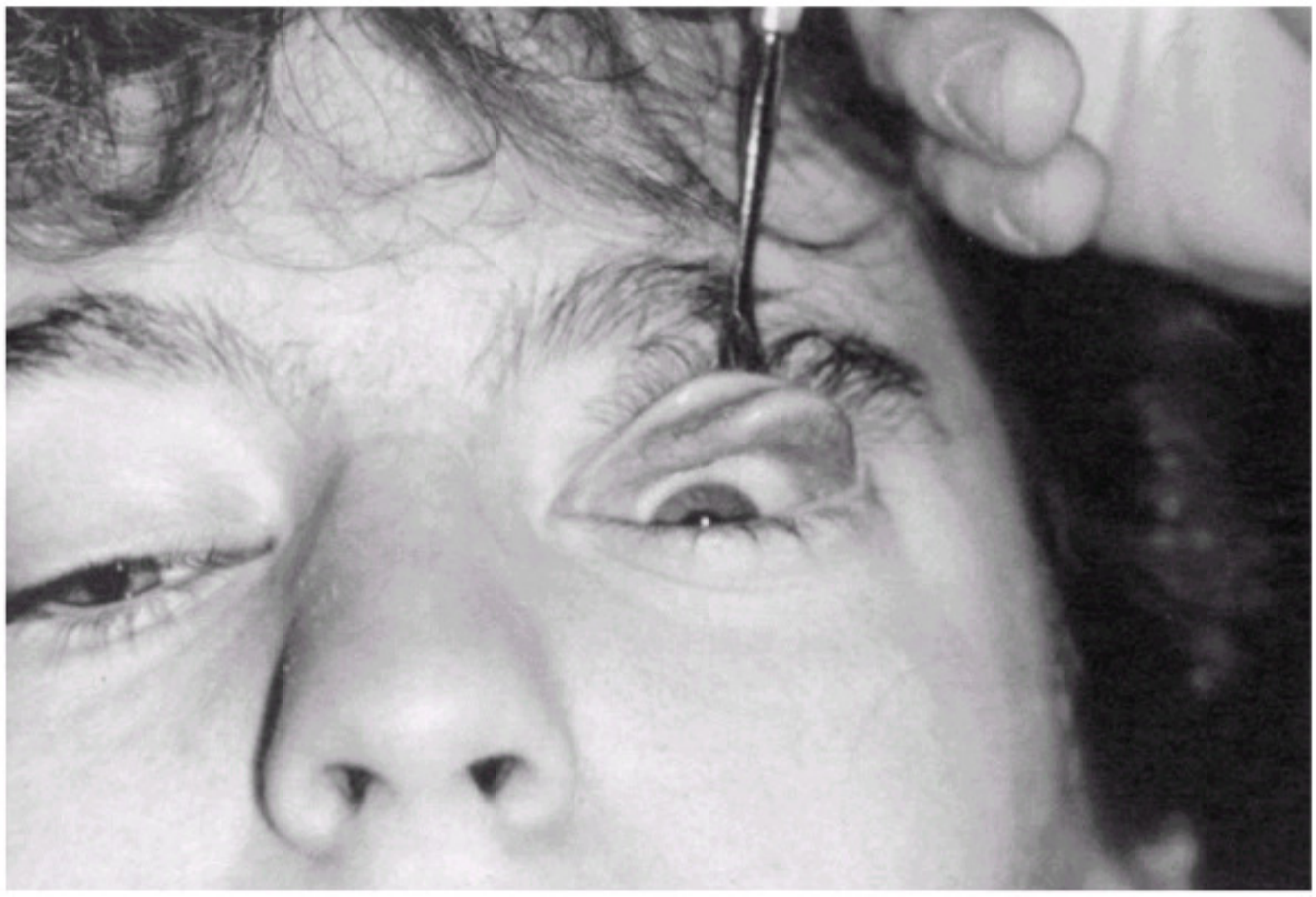

Figure 26.9 “Double” eversion of upper eyelid with Desmarre's retractor. (From Catalano RA, ed. *Ocular emergencies*. Philadelphia: WB Saunders Co, 1992, with permission.)

Figure 26.10 Method to remove foreign body at the slit lamp. The foreign body is approached obliquely from the side, lessening the chance of striking the globe with a sharp object. (From Catalano RA, ed. *Ocular emergencies*. Philadelphia: WB Saunders Co, 1992, with permission.)

A corneal abrasion is one of the most common ocular complaints seen in an emergency setting. The epithelium covering the cornea is distinct in morphology and function from the conjunctival epithelium, with which it is continuous. When the corneal epithelium is scratched, abraded, or denuded, it exposes the underlying basement layer and superficial corneal nerves. This is accompanied by pain, tearing, and photophobia. Extensive abrasions can also cause a significant drop in visual acuity because the underlying layers do not offer the same smooth, reflective surface as the normal corneal epithelium.

The diagnosis can usually be made by penlight alone, when the usual smooth, glistening tear film overlying the epithelium is disrupted. If possible, slit-lamp confirmation to determine the depth of the abrasion is indicated. Minute amounts of fluorescein dye, with or without the use of a cobalt-60 filtered light source, can also be used for confirmation and exact delineation.

The treatment of corneal abrasions is directed at promoting healing and relieving pain. Small abrasions can be treated with frequent applications of topical antibacterials (drops or ointment 4 times a day) with or without immobilization of the lid with a patch. Larger abrasions usually require lid immobilization for comfort, although a recent study demonstrated no difference in the rate of healing or in reported discomfort with or without eye patching (32). Applying a small ribbon of 2.5-cm (1-inch) tape horizontally across the lash margin may be a simpler yet effective method of stabilizing the lid (Fig. 26.11) without patching. Patients with larger abrasions should be followed until epithelial healing has occurred. Topical anesthetics result in almost immediate relief of pain but are toxic to the epithelium. There is no indication for their prolonged use. Ophthalmic nonsteroidal antiinflammatory drugs are a better choice to reduce the pain associated with simple corneal abrasion, and they do not delay healing (33).

Injuries to the Iris

Blunt ocular contusion can injure the iris sphincter muscle, resulting in pupillary constriction (*traumatic mio*sis) during the first several hours, followed by dilation (*traumatic mydriasis*). Patients present with pain, photophobia, perilimbal conjunctival injection, and anisocoria. An accommodative spasm or paralysis may be associated, resulting in blurred vision and difficulty with near tasks. Signs include inflammatory or pigment cells in the anterior chamber (*traumatic iritis*) and iris sphincter tears, both of which are recognizable on slit-lamp examination. Additionally, the pupil does not constrict to light stimulation as briskly as the unaffected *eye* or dilate as rapidly when the illumination is reduced. Pharmacological testing with pilocarpine 1% usually demonstrates reduced sensitivity, which is useful in distinguishing traumatic mydriasis from parasympathetic denervation (e.g., Adie's pupil), in which the iris is suprasensitive.

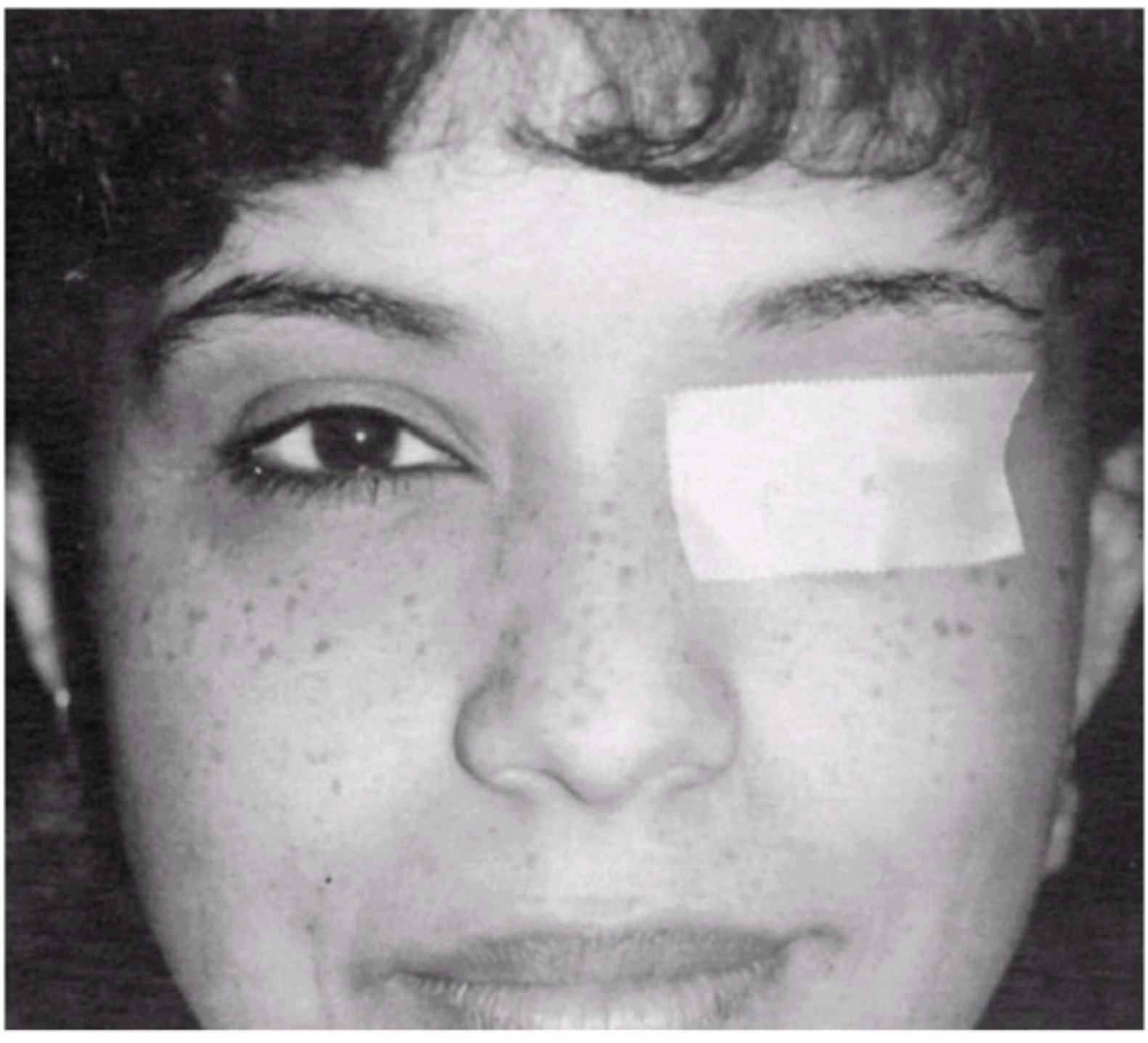

Figure 26.11 Immobilization of eyelids with 1-inch tape across eyelid margins. (From Catalano, RA, ed. *Ocular emergencies*. Philadelphia: WB Saunders Co, 1992, with permission.)

In addition to direct contusion injury to the iris, mydriasis can be caused by traumatic injury to the ciliary ganglion (a rare complication of orbital floor fractures). Miosis can be a component of traumatic Horner's syndrome, due to injury of the carotid plexus, cervical ganglion, cervical spine, or brainstem. Accompanying features of this syndrome are ipsilateral ptosis (lid droop), anhidrosis (decreased sweating), and relative enophthalmos (recession of the eye within the orbit).

A direct blow to the eye may also cause a cellular reaction in the anterior chamber (a traumatic iritis), which may be difficult to distinguish from a microhyphema. A hyphema is characterized by red blood cells in the anterior chamber, as opposed to the white blood cells of iritis. Allowing the patient to sit quietly for several minutes allows the cells, which can be dispersed with patient movement, to layer, possibly making correct identification easier. The diagnosis is always hyphema when both red and white blood cells are present in the anterior chamber, which is actually typical. Other disorders in the differential diagnosis of traumatic iritis include long-standing, untreated corneal abrasions and traumatic retinal detachments, both of which can result in a secondary anterior chamber reaction. Pigment in the anterior vitreous (tobacco dust) is seen also in retinal detachments.

The treatment of traumatic mydriasis or miosis is supportive. Mild degrees of traumatic iritis may be treated with cycloplegia alone (e.g., cyclopentolate 1% or 2%, 4 times a day) for relief of spasm and pain. More severe iritis should also be treated with a topical corticosteroid (e.g., prednisolone acetate 0.125% or 1%, 3 or 4 times a day). Corticosteroids reduce the formation of anterior and posterior synechiae (abnormal adhesions of the iris to the cornea and lens, respectively). Both medications are tapered over several days.

Disinsertion of the iris at its root (*iridodialysis*) is characterized by polycoria (the appearance of multiple pupils) and a D-shaped pupillary aperture (Fig. 26.12). Its occurrence is usually accompanied by hyphema. Rare iris injuries include iris atrophy and iridoschisis (a split within the iris stroma). Patients with an iris injury often experience glare and photophobia and may have diplopia. A tinted contact lens or a dyed lens with an artificial pupil (available through Narcissus Eye Research Foundation, Daly City, CA) can reduce these symptoms and conceal the cosmetic deformity. Sphincterotomy with the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser (in aphakic and pseudophakic eyes) or argon laser (phakic eyes) may clear the central visual axis and improve visual acuity in patients with an eccentric pupil. Surgical repair of sphincter lacerations and tears can be accomplished by using the suture technique

described by McCannel (34) or by using a scleral tunnel incision and double-armed 10-0 polypropylene suture (35).

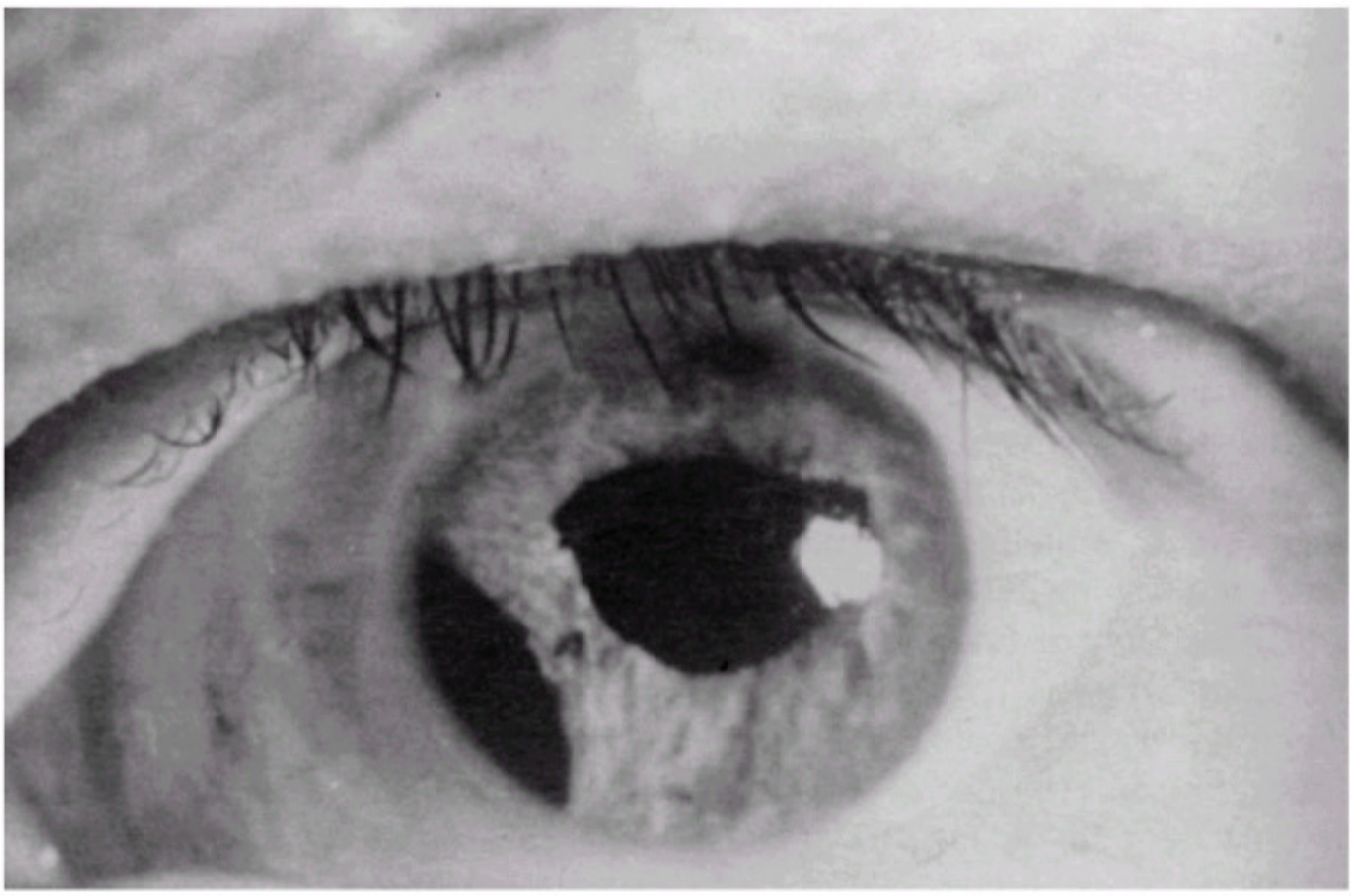

Figure 26.12 Iridodialysis. (From Catalano RA, ed. *Ocular emergencies*. Philadelphia: WB Saunders Co, 1992, with permission.)

Any iris abnormality should be clearly documented because other physicians may mistake pupillary asymmetry or irregularity as a sign of third cranial nerve dysfunction, related to uncal herniation.

Traumatic Hyphema

Blunt ocular injury causing a tear in the face of the anterior ciliary body is the most common cause of hyphema (bleeding into the anterior chamber) (Fig. 26.13). If a history of trauma is not elicited in a child with hyphema, one should suspect leukemia, hemophilia, juvenile xanthogranuloma, retinoblastoma, a fictitious history by the child, or child abuse. Hyphemas that occur following intraocular surgery resorb usually within days without sequelae, but the physician should be cognizant of a consequent rise in intraocular pressure.

Most patients with hyphema present with pain, and young children may be somnolent (36). The history should elicit the mechanism of injury and any complicating factors, such as a bleeding disorder, anticoagulant therapy, kidney or liver disease, or sickle cell disease or trait. A careful examination is mandatory, because one third of hyphema patients have other ocular injuries (37). Hyphemas are graded at presentation based on the amount of blood present in the anterior chamber

(Table 26.1). Gonioscopy in the early stages may reveal the site of bleeding and can confirm the presence of angle recession.

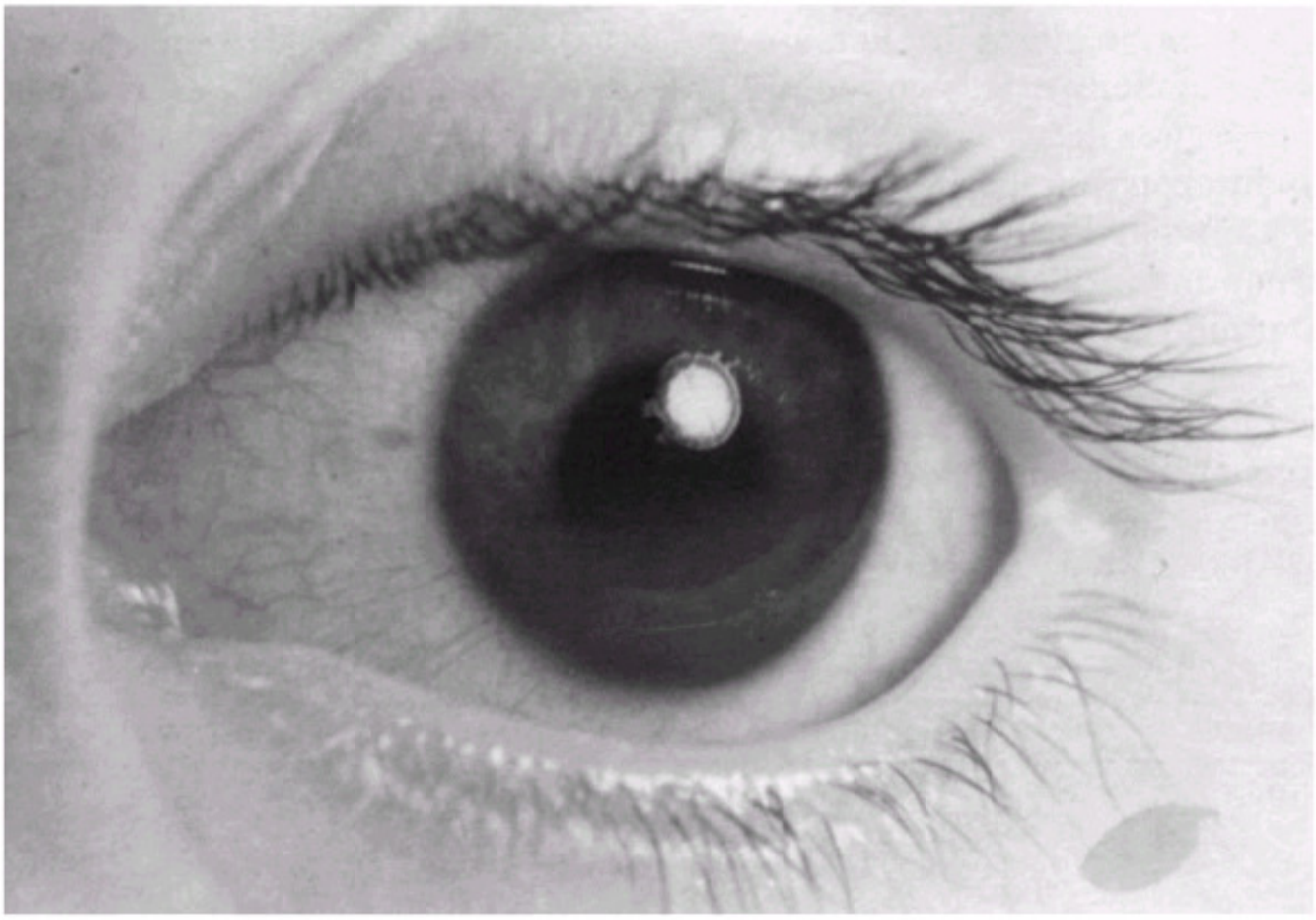

Figure 26.13 Hyphema. (From Catalano RA, ed. *Ocular emergencies*. Philadelphia: **WB** Saunders Co, 1992, with permission.)

The management of traumatic hyphema is variable and controversial (38,39). There is no consensus as to whether patients should be at strict bed rest or allowed limited ambulation and whether they can watch television or read. There is also no agreement as to the efficacy of hospitalization, occlusion of one or both eyes, patching of the traumatized eye, cycloplegics, topical corticosteroids, and antifibrinolytic agents (40). Community standards often dictate hospitalization policies. Randomized trials comparing treatment modalities have not been performed, although there are reports in the literature that the outpatient management of traumatic hyphemas, even in the pediatric population, results in rebleed rates within the range reported for hospitalized children (41,42).

Hospitalization should be considered based on the patient's age (toddlers are unlikely to be easily constrained at home), probability of noncompliance (immature patients or those without assistance at home), and the likelihood of developing complications (patients with sickle cell disease or trait or those with elevated intraocular pressure at presentation). Patients with a rebleed are more likely to develop complications and should be hospitalized. Risk factors for this may be the presence of high intraocular pressure and low vision at the time of first examination (43). In one study, African American children appeared to be at greater risk for developing a secondary hemorrhage, unrelated to the presence of sickle cell hemoglobinopathy (44). In another study, the presence of posterior segment injuries was more directly related to a poor visual outcome rather than the occurrence of secondary hemorrhage (45).

Antifibrinolytic agents (aminocaproic acid, tranexamic acid) may be used in populations with high rebleed rates (lower socioeconomic status, urban, younger age, delayed time from injury to admission) (46,47). The side effects of nausea, vomiting, postural hypotension, tinnitus, lethargy, raised intraocular pressure (48), and hematuria should also

be considered when making this decision. Contraindications include pregnancy and a cardiac, hepatic, renal, or intravascular clotting disorder. Relative contraindications include sickle cell disease or trait and total hyphema, because these agents reduce the rate of resorption of blood. Suggested treatment of traumatic hyphema is presented in Table 26.2, and indications for surgical evacuation of the clot are reviewed in Table 26.3.

TABLE 26.1 GRADING OF HYPHEMA

Grade	Percentage of Anterior Chamber Filled with Blood
Microscopic	Circulation of red blood cells only, no layering
I	<33%
II	33%-50%
III	50%-95%
IV	100% (total or “eight ball” hyphema)

TABLE 26.2 TREATMENT OF HYPHEMA

Suggested Orders	Comment
Hospitalization	Young children and elderly; all patients with rebleeds.
Bed rest	Reliable adults and older children with microhyphema may be treated with bed rest at home, if community standards allow. They should be examined daily for 5 additional days, refrain from any activity, and return immediately, if any pain or decrease in vision occurs. With the head of the bed elevated 30 degrees; bathroom privileges with assistance.
Sedation as needed	Lorazepam (Ativan): *Adults and older children:* 2-3 mg/dl q 8-12 hr PO. Chloral hydrate: *children:* 50 mg/kg tid. *Younger children:* consult with pediatrician.
Laxative of choice	Adults only.
Shield involved eye	Patch only if there is an associated corneal abrasion.
Eye rest	May watch television at a distance, no prolonged reading or near visual tasks.
Cycloplegia	Atropine 1% topically tid to qid.
Topical steroids	Prednisolone acetate 1% q 2-6 hr, if a fibrinous anterior chamber reaction develops.
No aspirin products	Use acetaminophen with or without codeine for analgesia.
Antiemetic, as	Prochlorperazine (Compazine): *Adults:* 10 mg IM q 8 hr, or 25-mg

Antiemetic, as needed	Prochlorperazine (Compazine): *Adults:* 10 mg IM q 8 hr, or 25-mg suppository q 12 hr; *children:* 0.13 mg/kg body weight IM, or 2.5-mg suppository bid to tid. Promethazine hydrochloride (Phenergan): *Adults:* 25-mg IM, or suppository q 4-6 hr; *children:* 1.1 mg/kg (maximum dose, 25 mg). The safety of these medications in children less than 9 kg or =2 yr in age has not been established.
Antiglaucoma medications	For elevations of intraocular pressure >40 mm Hg at presentation, or >30 mm Hg for 2 weeks or more subsequently (20 mm Hg in those with sickle cell trait or disease): *First-line:* Topical ß-blocker (e.g., levobunolol or timolol 0.25% tid). *Second-line:* Acetazolamide 250 mg PO tid. (In sickle cell use, methazolamide [Neptazane] 50 mg bid to tid.) *Third-line:* Mannitol 1-2 g/kg IV over 45 min once every 24 hr.
Antifibrinolytic agents	Aminocaproic acid (Amicar): Use based on community standards and patient presentation (see text); dose is 50 mg/kg PO q 4 hr (maximum 30 g/dl). *If no rebleeding occurs:* halve dose on day 3 and discontinue on day 4. Be cognizant that intraocular pressure may rise suddenly on cessation of use. *If rebleeding occurs:* continue Amicar for 5 additional days, check clotting studies, bleeding time, platelet count.
Laboratory studies	Complete blood count; clotting studies, platelet count, and liver function tests, if history of bleeding disorder. Baseline creatinine and blood urea nitrogen (BUN) if aminocaproic acid is to be used. Sickle cell prep, hemoglobin electrophoresis in black patients.
Surgical evacuation of clot	See Table 26.3 for indications.

hr, hours; PO, per eye; qid, four times a day; tid, three times a day.

Rebleeds occur usually occur from the second to the fifth day following injury. They are frequently of greater magnitude than the original hemorrhage and more likely to be associated with elevated intraocular pressure. An increase in size of the hyphema, particularly the presence of bright red blood over darker, clotted blood, confirms this occurrence. Secondary hemorrhage significantly reduces the visual prognosis (49). If rebleeding does not occur,

cycloplegic agents and steroids are tapered beginning on the sixth day after injury, with the rapidity of tapering based on the presence of anterior chamber inflammation. Antiglaucoma medication may have to be continued indefinitely. The patient should continue to refrain from strenuous exercise and wear an eye shield at night for an additional 2 weeks. Normal activities can resume 1 month after injury. A dilated fundus examination with scleral depression and gonioscopy should be performed 1 month after injury. Patients with *recession of the anterior chamber angle* should be examined annually. These patients are at increased risk for glaucoma, which can occur years after the injury.

TABLE 26.3 INDICATIONS FOR SURGICAL EVACUATION OF CLOT IN HYPHEMA

Indication	Comment
Elevated intraocular pressure (IOP); unresponsive to medical therapy	IOP >50 mm Hg for 5 days
	IOP >35 mm Hg for 7 days
	IOP >25 mm Hg for 1 day in patients with sickle cell disease or trait or preexisting glaucoma
Corneal bloodstaining	At the first sign of bloodstaining, regardless of TOP or grade of hyphema
	If IOP >25 mm Hg and total hyphema to prevent bloodstaining
Prolonged clot duration	Persistent total hyphema >5 days
	Persistent small hyphema >10 days

IOP, intraocular pressure.

Injuries to the Lens

Cataract or lens subluxation secondary to ocular contusion injuries is often associated with severe posterior segment sequelae and poor visual outcomes (50). Trauma is the most common cause of *dislocation of the lens* (Fig. 26.14). Other causes include congenital dislocation, systemic syndrome (e.g., Marfan's, homocystinuria), inflammation, and buphthalmos.

Traumatic dislocation results when contusion-induced equatorial expansion of the eye disrupts the zonule. A complete rupture results in a free-floating (“luxated”) lens; partial severance results in a “subluxated” lens. Symptoms of dislocation are fluctuating vision, glare, monocular diplopia, and decreased vision, the last resulting from functional aphakia or induced astigmatism.

A partial dislocation is occasionally difficult to diagnose. The pupil should be dilated and the lens examined using retroillumination at the slit lamp. The zonules can often be seen with a gonioscopy lens. Visualization of vitreous between broken zonules or seeing the edge of the lens within the pupil confirms the diagnosis. Additional signs are shallowing (or deepening) of the anterior chamber, iridodonesis (movement of the iris with ocular movement), and phacodonesis (fine movement of the lens on ocular movement). Patients with a dislocated lens are always evaluated for other signs of ocular injury.

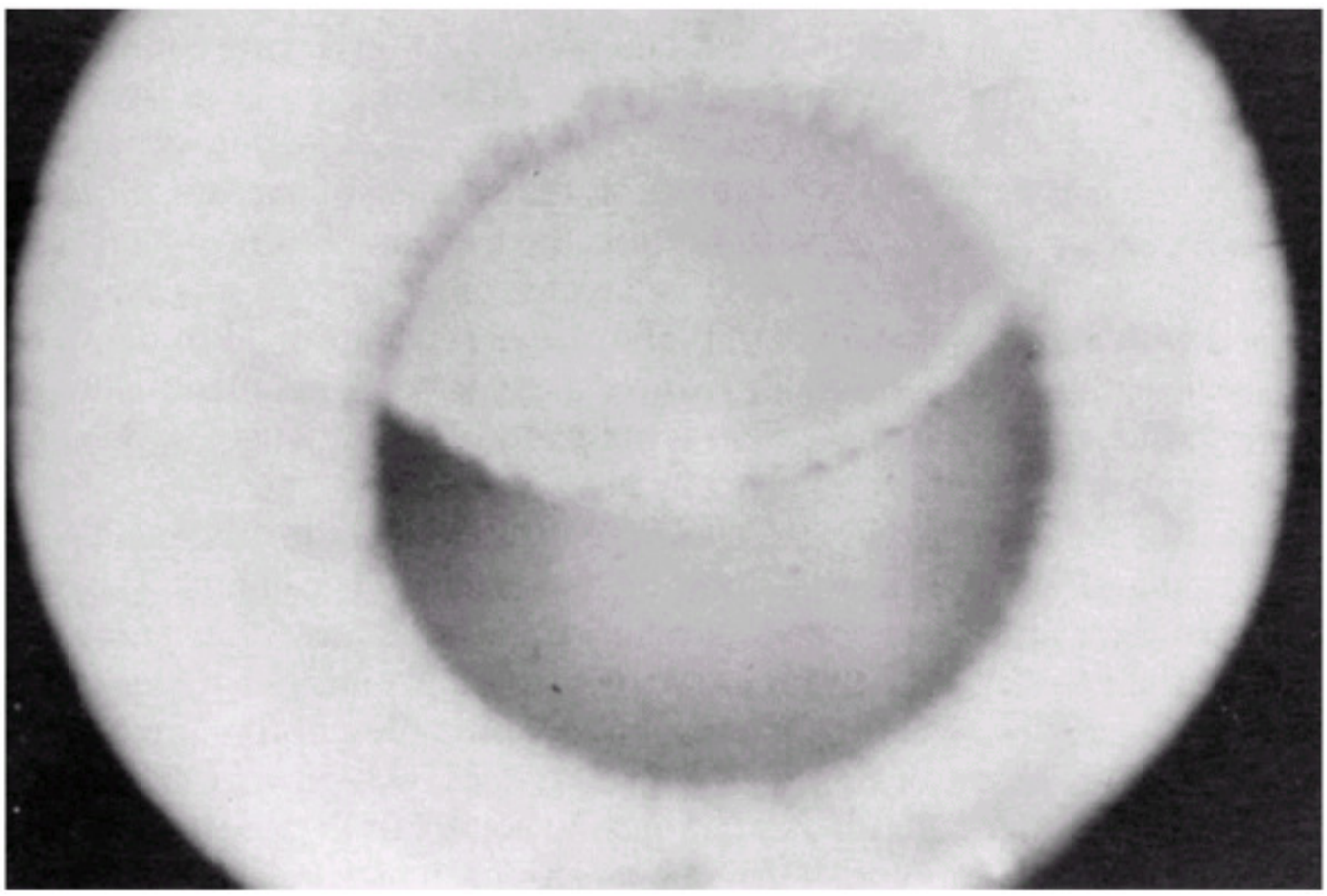

Figure 26.14 Traumatic dislocation of the ocular lens. (From Catalano RA, ed. *Ocular emergencies*. Philadelphia: WB Saunders Co, 1992, with permission.)

Complications of dislocated lenses include refractive disorders, pupillary block glaucoma, and lenticular-corneal touch. Incomplete rupture of the zonule causes the lens to be drawn to the side of the intact zonular fibers. If the lens is dislocated out of the visual axis, functional aphakia results. If the edge of the lens lies on the visual axis, astigmatism and monocular diplopia can result. Pupillary block occurs when the dislocated lens occludes the pupillary aperture. An anteriorly dislocated lens can also touch the posterior cornea, damaging the endothelial cells. Rarely, nonpupillary block glaucoma can result from misdirection of aqueous humor or anterior displacement of the lens-iris diaphragm. This is suggested by shallowing of the central anterior chamber, absence of lens movement, and myopic shift in refraction. Nonpupillary block is treated with cycloplegic-mydriatic agents to relax the ciliary body and allow for posterior movement of the lens-iris diaphragm. As with any disorder simulating malignant glaucoma, iridectomy and miotics may worsen this condition.

A noncataractous, dislocated lens may be stable and asymptomatic for years. The patient, however, should be forewarned of the symptoms of pupillary block glaucoma and advised to wear eye protection for sports and hazardous labor. Contact lenses can be used to correct an induced aphakic or astigmatic refractive error. These are preferable to spectacles because they produce less image size disparity with the normal eye (aniseikonia). Pupillary dilation or constriction occasionally improves visual acuity. Patients treated with miotics should be informed of the possibility of pupillary block glaucoma. Patients treated with mydriatics should be warned of possible dislocation of the lens into the anterior chamber and corneal decompensation. In some cases, the Nd:YAG laser can be used to lyse the remaining zonules, achieving a clear aphakic visual axis. Indications for surgical removal of a dislocated lens include pupillary block, corneal touch, inflammation, and decreased vision.

A *contusion cataract* results when the lens capsule is ruptured by a direct or contrecoup injury. In addition to lenticular opacification (Fig. 26.15), affected patients present with decreased vision, elevated intraocular pressure, and/or intraocular inflammation. The rapidity of cataract formation depends on whether the lens capsule was ruptured. In the absence of rupture, a cataract may not develop for months; with rupture, the lens can become hydrated and cataractous within hours. Not every cataract is progressive; a small rent may self-seal with the development of a fibrous plaque at the site of the injury. When the visual acuity is not appreciably reduced and glaucoma or inflammation is not present, the preferred management is observation. Miotics may be helpful in reducing glare and diplopia induced by focal opacities.

As with subluxated lenses, the evaluation should include an assessment of associated injuries, as well as the location and extent of lens injury. The status of the posterior capsule and presence of any zonular rupture (dislocation of the lens) are the two most important factors in surgical planning. The lens capsule can usually be assessed at the slit lamp, but, occasionally, a fibrinous reaction in the anterior chamber, or opacification of the lens, prevents an adequate assessment. A water-bath ultrasound may be helpful in these instances. If the posterior capsule is ruptured, a pars plana approach may be prudent to minimize the risk of nuclear dislocation into the vitreous.

Any injury to the lens may also produce amblyopia from occlusion or anisometropia in very young children (under age 9). Removal of an only partially cataractous lens or a subluxated lens, whose edge is in the pupil, may become necessary, if its persistence is thought to be a more potent amblyogenic factor than surgical aphakia or pseudophakia.

Even in patients in their late teens, progressive axial myopia associated with traumatic glaucoma can occur (51). Lens-induced glaucoma can result from two mechanisms other than pupillary block. High-molecular weight-lens proteins liberated by trauma (lens particle glaucoma) can block the trabecular meshwork. Additionally, denatured lens material from a cataractous lens can leak through an intact lens capsule and be engulfed by macrophages that clog the anterior chamber angle (*phacolytic glaucoma*). Lens-induced glaucoma is suspected when a break in the lens capsule and fluffy white particles in the anterior chamber and chamber angle are seen on slit-lamp examination. Phacolytic glaucoma is suspected by the presence of iridescent particles, cells, and protein flare. Similar particles may be present on the surface of the lens capsule and in the anterior chamber angle, open usually on gonioscopic examination. Phacolytic glaucoma can be confirmed by the presence of macrophages filled with lens material on microscopic examination of aqueous humor obtained by paracentesis. Both problems are treated with corticosteroids (e.g., prednisolone acetate 1% every 6 hours in lens-induced glaucoma and as frequently as every hour in phacolytic glaucoma); antiglaucoma medications (e.g., timolol or levobunolol 0.5% every 12 hours; acetazolamide 500 mg initially, followed by 250 mg every 6 hours; or mannitol 1 to 2 g/kg intravenously over 45 minutes); and topical cycloplegia (e.g., cyclopentolate 1% every 8 hours). Cataract extraction is performed after the intraocular pressure has been brought under control (usually within 24 to 36 hours).

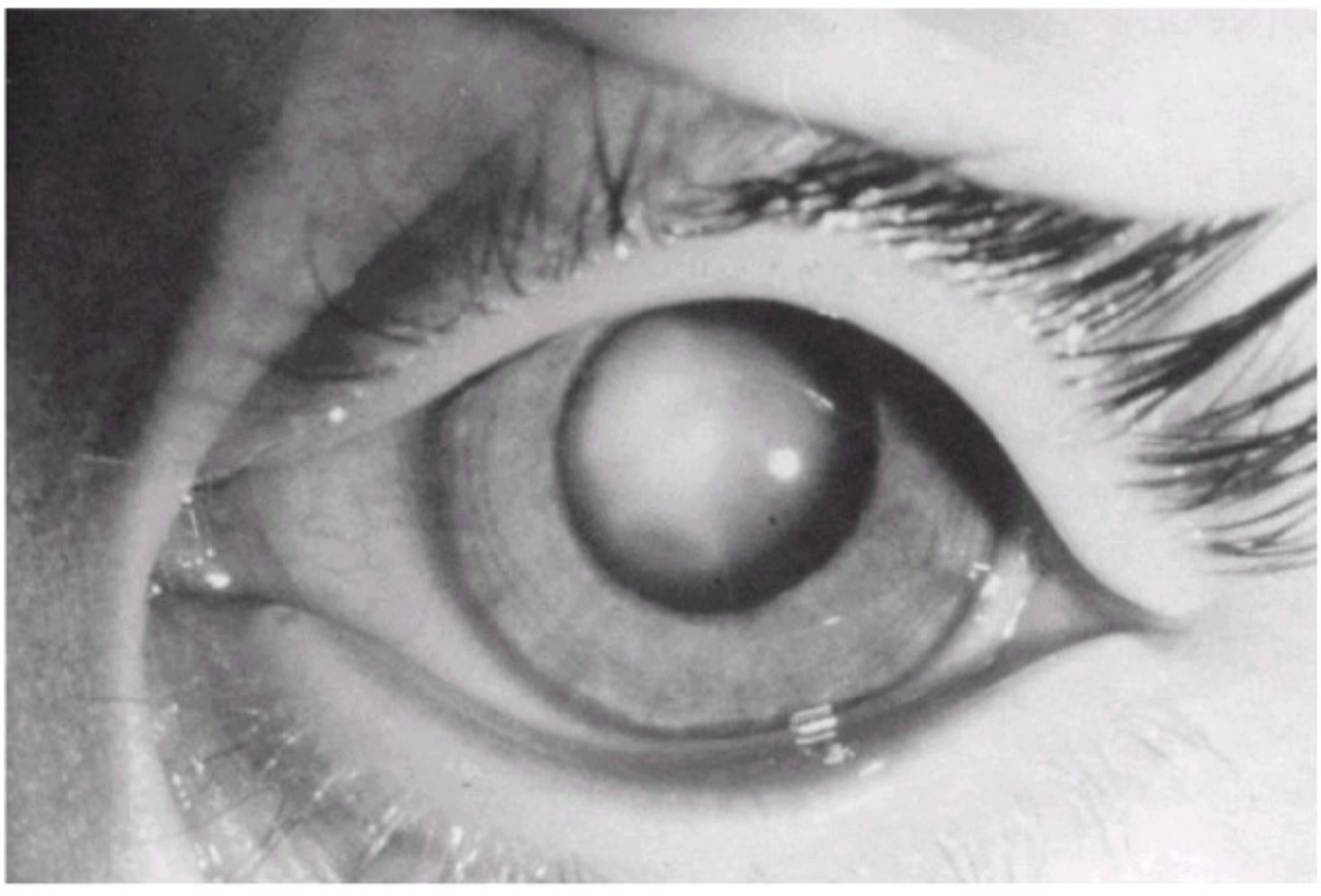

Figure 26.15 Contusion cataract. (From Catalano RA, ed. *Ocular emergencies*. Philadelphia: WB Saunders Co, 1992, with permission.)

Injuries to the Posterior Pole of the Eye

Severe blows to the eye can result in a myriad of posterior pole injuries ranging from intraretinal hemorrhages; retinal edema, tears, detachment, and dialysis; choroidal and chorioretinal ruptures; and avulsion of the optic nerve head. The latter results usually in total loss of vision; the severity of other posterior pole injuries is correlated with involvement of the fovea.

Severe trauma can result in a concussive injury to axonal transport. This disruption in the nerve fiber layer is termed *commotio retinae* when it occurs in the retinal periphery and traumatic macular edema (Berlin's edema), if it involves the macular region. In either case the affected retina takes on a gray, translucent appearance. With macular edema the foveal reflex is lost. Intraretinal hemorrhages may be concomitant, if the retinal capillary circulation is disrupted. These may break through into the vitreous over several days, obscuring the view of the underlying retina. Mild *commotio retinae* and traumatic macular edema may resolve over a few days, but, when associated with intraretinal hemorrhages, these disorders may result in retinal atrophy, pigment scarring, and atrophic holes. In the absence of other injuries the treatment is supportive. The patient should be instructed to wear dark sunglasses to prevent exacerbating light damage to the retina. Small atrophic holes do not usually cause a retinal detachment. Even large macular holes may spontaneously resolve (52). Larger holes, however, often portend retinal tissue loss and, consequently, a less favorable prognosis (53).

Choroidal and chorioretinal ruptures are less common than traumatic macular edema and *commotio retinae*. They occur when greater force impacts the eye, causing significant distortion of the globe and stretching of the choroid. Larger ruptures result in subretinal hemorrhage, which obscures visualization of the underlying choroid. With time the hematoma resorbs, and the rupture becomes visible as a white concentric streak, which actually represents exposure

of the underlying sclera. Visual disability is related to the presence or absence of foveal involvement, and a late complication is the development of choroidal neovascularization. In one study, the proximity of the rupture to the center of the fovea and the length of the rupture were associated with the subsequent development of neovascularization (54).

Retinal tears and retinal dialysis are usually consequent to severe impact directly over the retina of a small object with considerable force such as that from a pellet gun. They typically involve the ora or equator and may require cryotherapy or surgery to prevent recurrent detachment.

Optic nerve head avulsion represents the most severe of blunt ocular injuries. It results when a blunt, small object strikes the globe from the infratemporal margin and severely compresses it against the orbital roof (55). The affected eye presents with a brisk afferent pupillary defect and no light perception to trace light perception in the temporal field. Widespread retinal infarction occurs, which is manifest by preretinal hemorrhages obscuring the optic disc, florid blot retinal hemorrhages, marked swelling of the retina, and a cherry red spot at the macula. Vitreous hemorrhage develops within a few hours. No treatment is useful, and recovery does not occur.

Indirect damage to the optic nerve may occur after blunt trauma to the forehead (56). Patients may present with acute loss of vision and an afferent papillary defect. The recent optic nerve trauma did not demonstrate a proven benefit of either megadose corticosteroids or optic canal decompression in these patients (57). The decision on how to treat paitents with indirect optic nerve trauma should be made on an individual patient basis.

Corneal and Corneoscleral Lacerations

Lacerations of the globe can be caused by injuries with sharp objects or by high-energy blunt objects smaller than the orbital opening. Many injuries of the latter type occur in sports and recreation (e.g., with a fast-moving ball in a racket sport) and are entirely preventable.

The goals of therapy are the restoration of normal anatomy and the prevention and treatment of complicating factors, such as infection and glaucoma. In young children, however, a significant complicating condition can be amblyopia, and the ultimate visual outcome is heavily dependent on its management (58,59).

Standard ophthalmic surgical practices prevail in the management of pediatric corneal and corneoscleral lacerations. A complete systemic evaluation to look for other injuries should be undertaken, especially if other injuries would preclude prompt treatment of the ocular injury or require concomitant treatment while the patient is anesthetized. Treatment with broad-spectrum antibiotics as a prophylactic measure should be initiated immediately.

Fibrin glue and cyanoacrylate tissue adhesive are both effective in closing corneal perforations up to 3 mm in diameter (60). If surgery is required, small-filament nonabsorbable suture (e.g., 10-0 nylon) is used to obtain watertight edge-to-edge closure. Any uncontaminated extruded uveal tissue can be repositioned in most cases. Retinal detachments and tears are generally repaired secondarily. Specific recommendations of surgical technique are beyond the scope of this chapter.

Obvious lenticular injury strongly suggests primary lensectomy, although restoring ocular integrity is of primary importance. Subsequent cataract extraction with intraocular lens implantation, even when combined with a penetrating keratoplasty, may still allow for excellent results (59).

The surgical repair should be undertaken as soon as possible. However, in a general hospital, careful consideration must be given to whether or not repair is scheduled as an emergency in the middle of the night or as an urgent case the next day. When the usual complement of a skilled ophthalmic operating room staff is not available for an emergency repair, delaying the repair until skilled staff is available may provide the best results. A delayed repair (up to 36 hours) has not been shown to be a poor prognostic factor (61).

CHILD ABUSE

Despite many years of heightened awareness, both socially and politically, physical abuse and neglect of children remain an all too frequent and tragic occurrence today. A 1995 survey by the National Committee to Prevent Child Abuse reported 996,000 confirmed cases of child abuse nationwide from over 3 million reports (62). Of the 1,215 fatal episodes, almost 82% occurred in children under age 5 years and 41% in children under age 1 year.

All states require health professionals to report child abuse, even if it is only suspected, because the statutes generally protect the reporting professional acting in good faith. A thorough ophthalmological examination can often provide early evidence of child abuse. This condition should be high on the list of systemic conditions whose successful management requires input from ophthalmologists for improved outcome. However, almost no other area of multidisciplinary management demands more caution in interpretation of findings, because *many* of the ophthalmic manifestations seen in child abuse can have other causes. A governmental agency's declaration of “confirmed” child abuse supported by an examining ophthalmologist's interpretation of typical signs can save a child's life, if it is correct (63), or tragically tear a family apart, if in error (64).

Child abuse cuts across all racial and socioeconomic strata, although many North American-trained ophthalmologists are biased by their training in municipal hospitals to believe child abuse occurs mostly in the inner-city minority population. There is no typical profile of an abusive parent or guardian.

Insight into the ophthalmological examination in a suspected case of child abuse is required in several ways. When a history of trauma is omitted or denied, it is incumbent on the ophthalmologist to look for nontraumatic causes for findings that could also be due to trauma; for example, when retinal hemorrhages are present, causes such as infection, anemia, and platelet disorders, should be investigated. A similar situation occurs with a “spontaneous” hyphema; the lack of cutaneous lesions consistent with juvenile xanthogranuloma

should raise the index of suspicion. A more difficult situation is when a parent or guardian furnishes a history of trauma, but the findings are inconsistent with the events of the admitted injury, such as a traumatic cataract allegedly sustained by injury from another toddler.

Nonaccidental injury of children takes usually one of two forms: either the abuse results in obvious injuries (e.g., burns, bone fractures, cutaneous lacerations) or the child was violently shaken, resulting in thoracic compression as well as cranial injury from rapidly reversing head movements. Ophthalmic manifestations (e.g., hemorrhages) can occur in either case.

External and Anterior Segment Manifestations

Injuries affecting the adnexae and anterior segment are noted less frequently in child abuse than vitreoretinal and optic nerve findings. However, the presence of these anterior segment abnormalities strongly suggests severe injury and poor visual prognosis (65).

Direct blows to the head and face can cause hyphema, corneal abrasion, lens subluxation and/or cataract, subconjunctival hemorrhage, lid laceration, and ecchymosis. Nonaccidental chemical injuries may cause cutaneous burns, conjunctivitis, and/or keratitis (66,67,68).

While periorbital injuries, such as burns, abrasions, and lacerations, can be consistent with or even suggest intentional injury, anterior segment trauma (corneal abrasion, hyphema, ectopia lentis, and some cataracts) is usually more nonspecific, prompting a careful search for other evidence of injury. Exceptions to the nonspecificity of these injuries include traumatic types of cataracts (Vossius' ring and anterior or posterior subcapsular rosettes) (69) and ectopia lentis. Lens dislocations from nonaccidental trauma have been reported in all directions except upward, which is the usual direction of displacement in Marfan's syndrome, one of the leading causes of nontraumatic ectopia lentis (70).

Posterior Segment Manifestations

Retinal and/or vitreous hemorrhages are the most commonly recognized posterior manifestations of child abuse (Fig. 26.16) (71,72). They occur in 6% to 24% of all abused children and are even more common (50% to 80%) in the shaken baby syndrome (65,73). They take usually the form of superficial (flame-shaped) hemorrhages in the posterior pole but can affect deeper layers and more peripheral locations as well. The intensity of hemorrhage correlates with the severity of neurological injury (74) but does not appear to be related to sustained elevated intracranial pressure, elevated intrathoracic pressure, direct tracking of blood from the intracranial space, or direct impact trauma (75). Retinal hemorrhages in children under age 3 years should suggest nonaccidental trauma, because their occurrence due to true accidental trauma is uncommon (76). Further, the presence of any retinal or optic nerve sheath hemorrhage in an infant, in the absence of an appropriate explanation for these findings, should raise suspicion of child abuse (77). Cardiopulmonary resuscitation, employed in the most severe cases of child abuse or neglect, is recognized as only an infrequent cause of the retinal hemorrhages seen in some of these children (78,79). Significant vitreous hemorrhage is a poor prognostic sign for vision in abused children (80), but the major cause of vision loss in child abuse is brain injury (81).

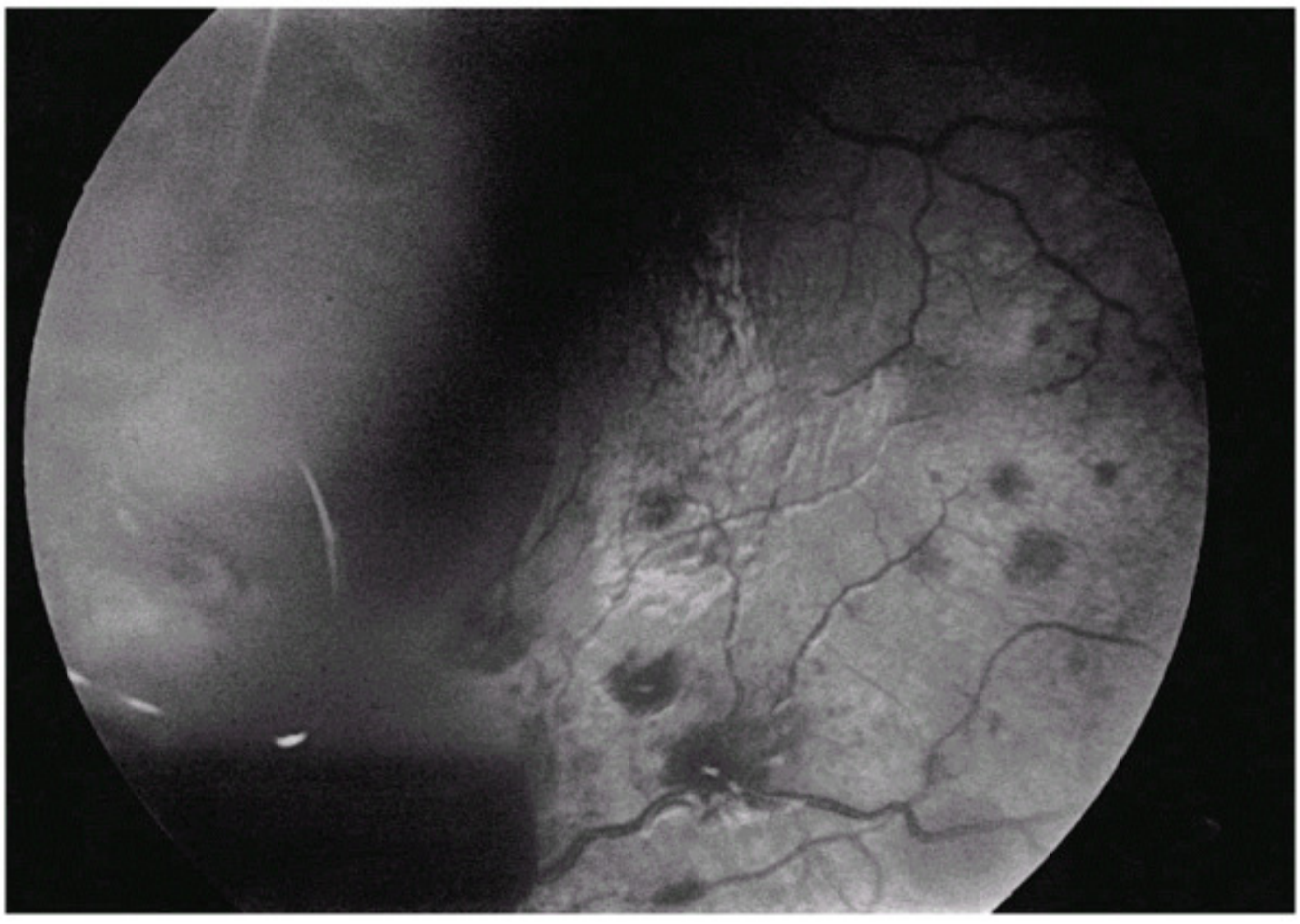

Figure 26.16 Retinal, preretinal, and vitreous hemorrhages in an infant with confirmed physical abuse.

Almost all other forms of retinal trauma can be seen also in child abuse. Retinal detachment, dialysis, vitreoretinal traction (82), perimacular folds (82,83), and avulsion have all been reported in abused children. Traumatic retinoschisis, similar in appearance to a preretinal hemorrhage but occurring in deeper layers, is common in shaken babies and is more suggestive of this etiology than the other nonspecific entities just mentioned (84). Optic nerve sheath hemorrhages are also possible (85), and, in fact, are indicative of trauma when found on postmortem examination (86).

SPORTS AND OTHER RECREATIONAL INJURIES

At best, ocular trauma sustained in a recreational setting is a minor inconvenience, requiring interruption of the offending activity; at worst, it can produce a potentially blinding injury (87), which, in many cases, is preventable. Athletic injuries can occur by contact with another player, contact with the ball (or puck, shuttlecock, etc.), or interaction with the playing surface. Based on data from the U.S. Consumer Products Safety Commission, there were an estimated 30,630 (product-related) sports and recreational eye injuries in 2002, with more than 14,000 of them occurring in individuals younger than age 15. The distribution of injuries among various sports is age-dependent (Table 26.4). Basketball and baseball lead the list because of their widespread distribution and popularity and

respective inherent risks. Racket sports also represent a significant threat (88) owing to the high speeds of the ball and close distances involved. The incidence of sports-related ocular injuries

ries has decreased since 1994, with the notable exception of golfing injuries (89). Notably, the latter often cause severe ocular trauma (90).

TABLE 26.4 ESTIMATED SPORTS AND RECREATIONAL EYE INJURIES BY AGE GROUP IN 2002

Activity	No. of Estimated Injuries	Age (yr)				
		<5	5-14	15-24	25-64	>65
Basketball	6,552	66	1,684	3,184	1,605	13
Baseball	2,756	164	1,677	593	322	0
Football	2,087	6	664	931	486	0
Bicycling	2,048	223	503	303	1,019	0
Racket sports*	1,894	0	544	666	684	0
Swimming	1,772	257	943	186	386	0
Golf	1,272	74	385	0	730	83
Ball sports†	1,196	61	713	184	161	77
Playground equipment	1,033	385	633	0	15	0
Softball	960	83	436	67	274	100
Soccer	954	6	283	136	529	0
Hockey‡	601	12	429	61	99	0
Volleyball	312	0	6	189	117	0
Total selected activities	23,437	1,337	8,900	6,500	6,427	273
Other activities¶	7,193	977	3,049	1,303	1,754	110
TOTAL	30,630	2,314	11,949	7,803	8,181	383

* Racket sports include racquetball, tennis, squash, paddleball, badminton, and handball.

† Ball sports include unspecified ball sports.

‡ Hockey includes ice, field, street, and roller hockey.

¶ Other activities include all other sports and recreation-related product codes.

From U.S. Consumer Products Safety Commission: Product Summary Reports—Eye Injuries

From U.S. Consumer Products Safety Commission: Product Summary Reports—Eye Injuries Only—Calendar Year 2002. US Consumer Product Safety Commission, Directorate for Epidemiology; National Injury Information Clearinghouse; National Electronic Injury Surveillance System; Product Summary Reports.

Ocular injuries from basketball occur from mostly contact with other players (91), because the ball is much too large to make direct contact with the globe. Injuries, such as corneal abrasion, lid laceration, and traumatic iritis, generally predominate (92).

In baseball, however, injuries occur from mostly the ball or related equipment (93). The ball is small enough to injure the globe and moves much more rapidly, putting the young and/or novice player at risk for significant injury, especially if unprotected. Hyphema, orbital contusion and/or fractures, and corneal abrasions predominate. The peak age for baseball injuries corresponds to the time when baseball is introduced in both an organized (Little League) and an ad hoc fashion. This comes at a time when a young player may be able to hit a ball hard to cohorts who may lack the reflexes and/or skill to safely handle it. The potential for injury from “soft” baseballs (which are 15% to 20% of major league ball hardness) is still significant, and use of these balls still requires protective eyewear (94).

Soccer-related eye injuries are less common and, for unknown reasons, tend to occur in the superotemporal quadrant. Most result from being struck by a kicked ball (95).

Because of their potential in severity, fireworks lead the list of significant injuries (96) sustained during nonathletic recreation. A 1995 report in the Morbidity and Mortality Weekly Report from the Centers for Disease Control (CDC) noted that (an estimated) 20% of the 12,000 patient visits to U.S. emergency rooms for fireworks-related injuries were for ocular trauma (97). Most of the injuries occurred on or around Independence Day, and 54% of the injuries took place despite adult supervision (98). Although not a protective factor with fireworks injuries, adult supervision has been shown to reduce ocular injuries in children caused by air guns (99).

Even nonstrenuous recreational activity can result in ocular injuries when insufficient care is exercised. Fishhook ocular injuries are potentially serious, because they can produce penetrating and/or perforating wounds (100,101). The prognosis with prompt treatment, however, is excellent (102). Finally, the incidence of injuries from certain activities changes with the activity's popularity. Ocular injuries from pellet guns are decreasing, but paintball-gun ocular injuries are increasing. The latter are often severe and occur usually when the participants are not wearing eye protection (103).

Although not a sport, laser pointers are at times maliciously pointed at other individuals. Fortunately, one recent study did not demonstrate consistent, long-term damaging effects from transient ocular exposure to laser pointer beams. The commonest physical sign was punctate epitheliopathy, and commonest symptom was ocular discomfort (104).

PREVENTION

Ocular injuries in children are largely preventable (4,105,106). Over 82% of the injuries (for all ages and all

activities) in the United States Eye Injury Registry (107) occurred when no ocular protection of any kind (protective goggles or standard or prescription spectacles) was in place, implying that a large measure of protection can be obtained by simply increasing the prevalence of protective eyewear, especially for risky activities (sports, recreation, and occupation). It has been estimated that the universal use of protective eyewear for sports and recreation can reduce ocular injuries by 90% (108). Ocular protection can be chosen from a large variety of commercially available styles (109).

Injuries occurring outside of sports, recreation, and occupational activities are difficult to guard against, because protective eyewear is not used for activities of daily living. Eyewear should be the mainstay of preventive efforts for sports and recreational injuries, especially those with significant inherent risk of ocular injury. Current published guidelines (110) recommend protective eyewear for all athletes, even those engaged in “low-risk” activities. It should be mandatory for participants who are functionally oneeyed or who have had prior ocular surgery and/or trauma.

“Street wear” spectacles with standard plastic (CR-39) lenses will provide some measure of protection and are appropriate for low-risk activities with low incidence of injury. Activities with significant risk for ocular injury from an object (a ball or puck), other equipment, or another player require the use of at least sports goggles with polycarbonate lenses (which provide more impact resistance than CR-39 lenses) or even full-face protection.

Although the most significant risk for ocular injury is posed by those sports and recreational activities that combine a high inherent risk of injury coupled with large numbers of participants, the use of sports goggles with polycarbonate lenses can prevent the majority of injuries.

REFERENCES

1. Tomazzoli L, Renzi G, Mansoldo C. Eye injuries in childhood: a retrospective investigation of 88 cases from 1988 to 2000. *Eur J Ophthalmol* 2003;13:710.

2. Kaimbo WK, Spileers W, Missotten L. Ocular emergencies in Kinshasa. *Bull Soc Belge Ophtalmol* 2002;284:49.

3. Cascairo MA, Mazow ML, Prager TC. Pediatric ocular trauma: a retrospective study. *J Pediatr Ophthalmol Strabismus* 1994;31:312.

4. Nelson LB, Wilson TW, Jeffers JB. Eye injuries in childhood: demography, etiology, and prevention. *Pediatrics* 1989;84:438.

5. Tielsch JM, Parver LM. Determinants of hospital charges and length of stay for ocular trauma. *Ophthalmology* 1990;97:231.

6. Jankovic S, Zuljan I, Sapunar D, et al. Clinical and radiological management of wartime eye and orbit injuries. *Mil Med* 1998; 163:423.

7. Davis PC, Newman NJ. Advances in neuroimaging of the visual pathways. *Am J Ophthalmol* 1996;121:690.

8. Ozdal MP, Mansour M, Deschenes J. Ultrasound biomicroscopic evaluation of the traumatized eyes. *Eye* 2003;17:467.

9. Libonati MM. General anesthesia. In: Tasman W, Jaeger EA, eds. *Duane's clinical ophthalmology*. Philadelphia: Lippincott-Raven Publishers, 1995;6(1):6.

10. Hofmann RF, Paul TO, Pentelei-Molnar J. The management of corneal birth trauma. *J Pediatr Ophthalmol Strabismus* 1981;18: 45.

11. Angell LK, Robb RM, Berson FG. Visual prognosis in patients with ruptures in Descemet's membrane due to forceps injuries. *Arch Ophthalmol* 1981;99:2137.

12. Hoyt CS, Stone RD, Fromer C. Monocular axial myopia associated with neonatal eyelid closure in human infants. *Am J Ophthalmol* 1981;91:197.

13. Stein RM, Cohen EJ, Calhoun JH, et al. Corneal birth trauma managed with a contact lens. *Am J Ophthalmol* 1987;103:596.

14. Jain IS, Singh YP, Grupta SL, et al. Ocular hazards during birth. *J Pediatr Ophthalmol Strabismus* 1980;17:14.

15. Sachs D, Levin PS, Dooley K. Marginal eyelid laceration at birth. *Am J Ophthalmol* 1986;102:539.

16. Harris GJ. Canalicular laceration at birth. *Am J Ophthalmol* 1988; 105:322.

17. Crawford JS. Ptosis as a result of trauma. *Can J Ophthalmol* 1974; 9:244.

18. Estafanous MF, Seeley M, Traboulsi EI. Choroidal rupture associated with forceps delivery. *Am J Ophthalmol* 2000;129:819.

19. Lauer AK, Rimmer SO. Eyelid laceration in a neonate by fetal monitoring spiral electrode. *Am J Ophthalmol* 1998;125:715.

20. Isenberg SJ. Ocular trauma. In: Isenberg SJ, ed. *The eye in infancy*, 2nd ed. St. Louis: Mosby, 1994: 488.

21. Admoni MM, BenEzra D. Ocular trauma following amniocentesis as the cause of leucocoria. *J Pediatr Ophthalmol Strabismus* 1988;25:196.

22. Isenberg SJ, Heckenlively JR. Traumatized eye with retinal damage from amniocentesis. *J Pediatr Ophthalmol Strabismus* 1985; 22:65.

23. Messinger A, Radkowski A, Greenwald MJ, et al. Orbital roof fractures in the pediatric population. *Plast Reconstr Surg* 1989; 84:213.

24. Smit TJ, Mourits MP. Monocanalicular lesions: to reconstruct or not. *Ophthalmology* 1999;106:1310.

25. Karesh JW. The evaluation and management of eyelid trauma. In: Tasman WB, Jaeger EA, eds. *Duane's clinical ophthalmology*. Philadelphia: Lippincott-Raven Publishers, 1996;5(75):5.

26. Read RW, Sires BS. Association between orbital fracture location and ocular injury: a retrospective study. *J Craniomaxillofac Trauma* 1998;4:10.

27. Green RP, Peters DR, Shore JW, et al. Force necessary to fracture the orbital floor. *Ophthalmic Plast Reconstr Surg* 1990;6:211.

28. Bansagi ZC, Meyer DR. Internal orbital fractures in the pediatric age group: characterization and management. *Ophthalmology* 2000;107:829.

29. Dutton J. Management of blow-out fractures of the orbital floor. *Surv Ophthalmol* 1991;35:279.

30. Egbert JE, Kersten RC, Kulwin DR. Pediatric orbital floor fracture: direct extraocular muscle involvement. *Ophthalmology* 2000;107: 1875.

31. Yanoff M, Fine BS. *Ocular pathology*, 2nd ed. Philadelphia: Harper & Row, 1982:185.

32. Michael JG, Hug D, Dowd MD. Management of corneal abrasion in children: a randomized clinical trial. *Ann Emerg Med* 2002; 40:67.

33. Weaver CS, Terrell KM. Evidence-based emergency medicine. Update: do ophthalmic nonsteroidal anti-inflammatory drugs reduce the pain associated with simple corneal abrasion without delaying healing? *Ann Emerg Med* 2003;41:134.

34. McCannel MA. A retrievable suture idea for anterior uveal problems. *Ophthalmic Surg* 1976;7:98.

35. Brown SM. A technique for repair of iridodialysis in children. *J AAPOS* 1998;2:380.

36. Coats DK, Paysse EA, Kong J. Unrecognized microscopic hyphema masquerading as a closed head injury. *Pediatrics* 1998; 102:652.

37. Shingleton BJ. Eye injuries. *N Engl J Med* 1991;325:408.

38. Crouch ER. Traumatic hyphema. *J Pediatr Ophthalmol Strabismus* 1986;23:95.

39. Romano PE. Pro steroids for systemic antifibrinolytic treatment for traumatic hyphema. *J Pediatr Ophthalmol Strabismus* 1986;23: 92.

40. Kraft SP, Christianson MD, Crawford S, et al. Traumatic hyphema in children. *Ophthalmology* 1987;94:1232.

41. Coats DK, Viestenz A, Paysse EA, et al. Outpatient management of traumatic hyphemas in children. *Binocul Vis Strabismus Q* 2000;15:169.

42. Shiuey Y, Lucarelli MJ. Traumatic hyphema: outcomes of outpatient management. *Ophthalmology* 1998;105:851.

43. Rahmani B, Jahadi HR. Comparison of tranexamic acid and prednisolone in the treatment of traumatic hyphema. A randomized clinical trial. *Ophthalmology* 1999;106:375.

44. Lai JC, Fekrat S, Barron Y, et al. Traumatic hyphema in children: risk factors for complications. *Arch Ophthalmol* 2001;119:64.

45. Cho J, Jun BK, Lee YJ, et al. Factors associated with the poor visual outcome after traumatic hyphema. *Korean J Ophthalmol* 1998;12:122.

46. Rahmani B, Jahadi HR, Rajaeefard A. An analysis of risk for secondary hemorrhage in traumatic hyphema. *Ophthalmology* 1999; 106:380.

47. Goldberg MF. Antifibrinolytic agents in the management of traumatic hyphema. *Arch Ophthalmol* 1983;101:1029.

48. Dieste MC, Hersh PS, Kylstra JA, et al. Intraocular pressure increase associated with epsilon-aminocaproic acid therapy for traumatic hyphema. *Arch Ophthalmol* 1988;106:383.

49. Agapitos PJ, Noel L-P, Clarke WN. Traumatic hyphema in children. *Ophthalmology* 1987;94:1238.

50. Greven CM, Collins AS, Slusher MM, et al. Visual results, prognostic indicators, and posterior segment findings following surgery for cataract/lens subluxation-dislocation secondary to ocular contusion injuries. *Retina* 2002;22:575.

51. Graul TA, Kim CS, Alward WL, et al. Progressive axial myopia in a juvenile patient with traumatic glaucoma. *Am J Ophthalmol* 2002;133:700.

52. Yamada H, Sakai A, Yamada E, et al. Spontaneous closure of traumatic macular hole. *Am J Ophthalmol* 2002;134:340.

53. Yeshurun I, Guerrero-Naranjo JL, Quiroz-Mercado H. Spontaneous closure of a large traumatic macular hole in a young patient. *Am J Ophthalmol* 2002;134:602.

54. Secretan M, Sickenberg M, Zografos L, et al. Morphometric characteristics of traumatic choroidal ruptures associated with neovascularization. *Retina* 1998;18:62.

55. Hillman JS, Myska V, Nissim S. Complete avulsion of the optic nerve: a clinical, angiographic and electrodiagnostic study. *Br J Ophthalmol* 1975;59:503.

56. Anderson RL, Panje WR, Gross CE. Optic nerve blindess following blunt forehead trauma. *Ophthalmology* 1982;89:445-455.

57. Leven LA, Beck RW, Joseph MP, et al. The treatment of traumatic optic neuropathy: the international optic nerve trauma study. *Ophthalmology* 1999;106:1268-1277.

58. Dana MR, Schaumberg DA, Moyes AL, et al. Outcome of penetrating keratoplasty after ocular trauma in children. *Arch Ophthalmol* 1995;113:1503.

59. Vajpayee RB, Angra SK, Honavar SG. Combined keratoplasty, cataract extraction, and intraocular lens implantation after corneolenticular laceration in children. *Am J Ophthalmol* 1994;117: 507.

60. Sharma A, Kaur R, Kumar S, et al. Fibrin glue versus N-butyl-2-cyanoacrylate in corneal perforations. *Ophthalmology* 2003;110: 291.

61. Barr CC. Prognostic factors in corneoscleral lacerations. *Arch Ophthalmol* 1983;101:919.

62. Lung CT, Daro D. Current trends in child abuse reporting and fatalities: the results of the 1995 annual fifty state survey. Chicago: National Committee to Prevent Child Abuse, 1996.

63. Marcus DM, Albert DM. Recognizing child abuse. *Arch Ophthalmol* 1992;110:766.

64. Weissgold DJ, Budenz DL, Hood I, et al. Ruptured vascular malformation masquerading as battered/shaken baby syndrome: a nearly tragic mistake. *Surv Ophthalmol* 1995;39:509.

65. Annable WL. Ocular manifestations of child abuse. In: Reece RM, ed. *Child abuse: medical diagnosis and management*. Philadelphia: Lea & Febiger, 1994:138-149.

66. Meadow R. Munchausen syndrome by proxy. *Arch Dis Child* 1982;57:92.

67. Rosenberg DA. Web of deceit: a literature review of Munchausen syndrome by proxy. *Child Abuse Negl* 1987;11:547.

68. Taylor D. Recurrent non-accidentally inflicted chemical eye injuries to siblings. *J Pediatr Ophthalmol Strabismus* 1976;13:238.

69. Cordes FC. *Cataract types*. Rochester, MN: American Academy of Ophthalmology and Otolaryngology, 1961:91-95.

70. Levin AV. Ocular manifestation of child abuse. *Ophthalmol Clin North Am* 1990;3:249.

71. Harley RD. Ocular manifestations of child abuse. *J Pediatr Ophthalmol Strabismus* 1980;17:5.

72. Kaur B, Taylor D. Fundus hemorrhages in infancy. *Surv Ophthalmol* 1992;37:1.

73. Caffee J. The whiplash shaken infant syndrome: manual shaking by the extremities with whiplash-induced intracranial and intraocular bleedings, linked with residual permanent brain damage. *Pediatrics* 1974;54:396.

74. Wilkinson WS, Han DP, Rappley MD, et al. Retinal hemorrhage predicts neurologic injury in the shaken baby. *Arch Ophthalmol* 1989;107:1472.

75. Morad Y, Kim YM, Armstrong DC, et al. Correlation between retinal abnormalities and intracranial abnormalities in the shaken baby syndrome. *Am J Ophthalmol* 2002;134:354.

76. Buys YM, Levin AV, Enzenauer RW, et al. Retinal findings after head trauma in infants and young children. *Ophthalmology* 1992; 90:1718.

77. Marshall DH, Brownstein S, Dorey MW, et al. The spectrum of postmortem ocular findings in victims of shaken baby syndrome. *Can J Ophthalmol* 2001;36:377.

78. Goetting MG, Sowa B. Retinal hemorrhage after cardiopulmonary resuscitation in children: an etiologic reevaluation. *Pediatrics* 1990;85:585.

79. Kanter RK. Retinal hemorrhage after cardiopulmonary resuscitation or child abuse. *J Pediatr* 1986;108:430.

80. Matthews GP, Das A. Dense vitreous hemorrhages predict poor visual and neurological prognosis in infants with shaken baby syndrome. *J Pediatr Ophthalmol Strabismus* 1996;33:260.

81. Kivlin JD, Simons KB, Lazoritz S, et al. Shaken baby syndrome. *Ophthalmology* 2000;107:1246.

82. Massicotte SJ, Folberg R, Torczynski E, et al. Vitreoretinal traction and perimacular folds in the eyes of deliberately traumatized children. *Ophthalmology* 1991;98:1124.

83. Gaynon MW, Koh D, Marmor MF, et al. Retinal folds in the shaken baby syndrome. *Am J Ophthalmol* 1988;106:423.

84. Greenwald MJ. The shaken baby syndrome. *Semin Ophthalmol* 1990;5:202.

85. Lambert SR, Johnson TE, Hoyt CS. Optic nerve sheath and retinal hemorrhages associated with the shaken baby syndrome. *Arch Ophthalmol* 1986;104:1509.

86. Budenz DL, Farber MG, Mirchandani HG, et al. Ocular and optic nerve hemorrhages in abused infants with intracranial injuries. *Ophthalmology* 1994;101:559.

87. Larrison WI, Hersh PS, Kunzweiler T, et al. Sports-related ocular trauma. *Ophthalmology* 1990;97:1265.

88. Elman MJ. Racket-sports ocular injuries. *Arch Ophthalmol* 1986; 104:1453.

89. Rubin SE, Catalano RA. Ocular trauma and its prevention. In: Nelson LB, Harley RD, Lampert R, eds. *Harley's pediatric ophthalmology,* 4th ed. Philadelphia: WB Saunders, 1998:496.

90. Jayasundera T, Vote B, Joondeph B. Golf-related eye injuries. *Clin Experiment Ophthalmol* 2003;31:110.

91. Zagelbaum BM, Starkey C, Hersh PS, et al. The National Basketball Association eye injury study. *Arch Ophthalmol* 1995;113:749.

92. Zagelbaum BM. Sports-related eye trauma: managing common injuries. *Physician Sports Med* 1993;21:25.

93. Zagelbaum BM, Hersh PS, Donnenfeld ED, et al. Ocular trauma in major-league baseball players. *N Engl J Med* 1994;330:1021.

94. Vinger PF, Duma SM, Crandall J. Baseball hardness as a risk factor for eye injuries. *Arch Ophthalmol* 1999;117:354.

95. Capao FJA, Fernandes VL, Barros H, et al. Soccer-related ocular injuries. *Arch Ophthalmol* 2003;121:687.

96. Dhir SP, Shishko MN, Krewi A, et al. Ocular fireworks injuries in children. *J Pediatr Ophthalmol Strabismus* 1991;28:354.

97. Serious eye injuries associated with fireworks—United States, 1990—1994. *MMWR Morb Mortal Wkly Rep* 1995;44:449.

98. Smith GA, Knapp JF, Barnett TM, et al. The rocket's red glare, the bombs bursting in air: fireworks-related injuries to children. *Pediatrics* 1996;98:1.

99. Enger C, Schein OD, Tielsch JM. Risk factors for ocular injuries caused by air guns. *Arch Ophthalmol* 1996;114:469.

100. Aiello LP, Iwamoto M. Perforating ocular fishhook injury. *Arch Ophthalmol* 1992;119:1316.

101. White ME, Owens SD, Dooley CD, et al. Fishing related eye injuries: a report of 27 cases. *Invest Ophthalmol Vis Sci* 1990;31: 21.

102. Aiello LP, Iwamoto M, Guyer D, et al. Surgical management and visual prognosis of penetrating ocular fishhook injuries. *Ophthalmology* 1992;99:862.

103. Hargrave S, Weakley D, Wilson C. Complications of ocular paintball injuries in children. *J Pediatr Ophthalmol Strabismus* 2000;37:338.

104. Sethi CS, Grey RH, Hart CD. Laser pointers revisited: a survey of 14 patients attending casualty at the Bristol Eye Hospital. *Br J Ophthalmol* 1999;83:1164.

105. Gothwal VK, Adolph S, Jalali S, et al. Demography and prognostic factors of ocular injuries in South India. *Aust N Z J Ophthalmol* 1999;27:318.

106. Strahlman E, Elman M, Daub E, et al. Causes of pediatric eye trauma. *Arch Ophthalmol* 1990;108:603.

107. United States Eye Injury Registry (2000). *Eye trauma: epidemiology and prevention*. Retrieved February, 2004, from the World Wide Web: http://www.useironline.org

108. Jeffers JB. An on-going tragedy: pediatric sports-related eye injuries. *Semin Ophthalmol* 1990;5:216.

109. Easterbrook M. Eye protection in racquet sports. *Clin Sports Med* 1988;7:253.

110. American Academy of Pediatrics Committee on Sports Medicine and Fitness, American Academy of Ophthalmology Committee on Eye Safety and Sports Ophthalmology. Protective eyewear for young athletes. *Pediatrics* 1996;98:311.

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27

Role of the Ophthalmologist in Learning Disorders

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The study of learning disabilities has advanced greatly over the past decade. Development of neuropsychological testing techniques, neuroanatomical findings that underlie learning problems, and treatment/intervention programs has increased interest in this area of research. Learning involves visual and auditory perception and processing. The ophthalmologist should be knowledgeable in these areas but should realize that, despite the increase in understanding these concepts, continued questions and areas of controversy still exist.

In past years, most ophthalmologists read or were told that treatment of the disorders affecting children with dyslexia and other learning disabilities fell outside the field of ophthalmology because the brain, not the eyes, is the main organ subserving the process of thinking and learning (1,2,3). Because dyslexia, for example, implied an inability to understand the written word, the definitive diagnosis and therapy was placed in the hands of educators and clinical psychologists, not ophthalmologists. The role of the ophthalmologist was merely to rule out an eye disease as the first step in determining the reason for a learning disorder (LD) before referring the child back to the pediatrician or family physician for further evaluation and referral. This process exists today and is quite inefficient because most primary care doctors lack the subspecialty knowledge and resources to act on the educational or psychology reports on behalf of the child and family. Teachers and schools are experts in education and teaching, not the neuroscience of learning, and as a rule do not understand all the nuances involved in the central nervous system pathophysiology of these individuals. Ophthalmology in the past has stressed “reading” disabilities only and not viewed the subject universally, considering the other types of learning disorders. Comorbidity was often not taken into consideration. Optometry has tried to fill this void of effective services for learning disabled individuals. Ophthalmology must now take the lead.

This limited role for ophthalmologists in “treating” or, rather, “advising” children with learning disabilities and their parents is presently being displaced by a move toward a more interdisciplinary approach. A true paradigm shift for ophthalmology must take place. The pediatric ophthalmologist is often the first expert to whom the pediatrician refers a child who is suspected of having a learning disorder. Educating ophthalmologists in both the medical and nonmedical conditions and situations that could affect learning will help ensure that individuals receive appropriate, effective, and timely remedial treatment to reach their full potential. The public believes that “Eye MDs” are experts in visual perception and visual processing as well as visual function and ocular pathology. Ophthalmologists must provide these services.

In this chapter we examine the deficiencies that cause a child to be a poor reader and learner; look at the correctable defects that may make the child's marginal skills more usable; mention the educational, psychological, and medical remedies; and finally, review the claims of those who believe that they have the secret of the “quick fix.” We will define the neuropsychological categories of learning disorders and define vision therapy and show how and why it is not the effective and efficient tool for learning disability remediation that it is claimed to be. Finally, a practical plan of how an ophthalmologist can advise and effectively help the affected individuals and their families seek appropriate remedial treatment will be presented.

CLASSIFICATION OF LEARNING DISORDERS

Of animals' characteristics, reading the written word is uniquely human. Butterflies migrate, bees dance, and most animals have behavioral codes that allow some communication, but only in the present tense or, at most, with a minimal delay. We place so much value on this ability to read and, subsequently, learn that illiteracy is an international intellectual indicator of a country. In a nation, such as the United States, in which the education system is dependent on mastery of reading with emphasis on appropriate progression in such skills, any reading deficit brands the child and the child's parents as underachievers of the first order. Because an entire school class may have its rating based on the class average reading performance, a child who underachieves not only is a disappointment to the child's parents but also reflects on the teacher's abilities. Reading is the most important functional tool that we utilize to mediate learning. Listening, touching, smelling, and tasting are the other sensory modalities with which we learn.

Even the ability to perform the mathematical task 2 + 2 = 4 is not generally perceived to be on a plane with the ability to read the statement “Two plus two is equal to four.” The child who is slow to grasp the mathematical skill is readily excused, and calculators and computers are expected to minimize such problems. This often causes educators, pediatricians, and other professionals to delay in diagnosing such individuals with a learning disability. However, the child who is deficient in correctly identifying the word “cat” as an animal with certain characteristics, and who cannot repeatedly identify it without error, is quickly thrust into the role of the underachiever, and the parents are soon called to the school for a conference.

The conference with the teacher and parents is typically not the first clue that the child is a poor reader or learner. With the advent and widespread watching of the television show *Sesame Street* by the preschooler, many children learn the alphabet and have some word knowledge well before they begin school. The child who has not picked up any reading skills before first grade is often quietly held suspect by the parents, especially if they have had the opportunity to compare his or her performance with other siblings or playmates.

Depending on the difficulty the child has in learning to read, the first conference with the parents may not be too threatening. However, after several conferences the parents typically begin their route of physician visits with the hope that some correctable defect can be found and repaired, so that they can get on with the education of the child. It is this “quick fix” attitude that causes so much trouble for the child and provides a ripe opportunity for costly therapy of unproved effectiveness. As in any medical condition, without a correct diagnosis, the cure is difficult, if not impossible, to obtain. So the same applies to educational and learning processing disorders. It is necessary to diagnose the specific type of learning and reading dysfunction before an effective remediation plan can be formulated and implemented.

Learning disabilities can be defined as “a generic term that refers to a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or mathematical abilities. These disorders are presumed to be due to central nervous system dysfunction and may occur in conjunction with other handicapping conditions (e.g., mental retardation, psychological problems) and environmental circumstances (e.g., poor instruction) (4). The literature reveals that about 7% to 15% of all school-aged children have been diagnosed with a learning disability (5).

Koller (6) has classified eye involvement in learning disabilities into two main groups: the first consists of two types: (a) those individuals with purely medically and surgically treated ophthalmic disorders that may temporarily or chronically affect learning in school through annoyance and distraction (DSM-IV: Axis III—general medical conditions) and (b) those with conditions not purely ophthalmic that traditionally have fallen into the fields of the cognitive sciences and education (DSM-IV: Axis I). The second group of conditions can be subdivided into four traditional neuropsychological types of learning disorders: (a) developmental speech and language disorders, (b) nonverbal learning disorders, (c) attention disorders—ADD and ADHD, and (d) pervasive developmental disorders (PDD), also termed *autism spectrum disorders* (ASD). In this chapter we will not discuss those conditions in group one but will mention them now with the understanding that they provide mostly annoying symptoms that create inattention and distraction but are not direct causes of a learning or reading disorder. They may cause intermittent or constant blurry vision, itchy eyes, a foreign body sensation, diplopia, other visual phenomena, tearing, photophobia, and headache. The conditions include: ocular allergy, heterophorias and tropias, amblyopia, nystagmus, and migraine.

The ophthalmologist should be familiar with the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV). Medicine, in general, is moving

toward an interdisciplinary mode and thus ophthalmologists must look to other medical disciplines to understand the ocular and visual consequences of disease of another organ system that might affect the visual system. The brain, mediating visual processing and visual perception, is one such system. The social reasons for deficient learning in school, such as dysfunctional family environment, poor instruction, foreign first-language, and severe psychiatric disease are not directly associated with eye abnormalities (DSM-IV, axes II and IV).

Language-Based Learning Disorders

A variety of obstacles can inhibit reading, such as blindness, insufficient intellect, lack of attention, and negative motivation. Surprisingly, mildly reduced vision and even poor distant vision per se seldom prevent the acquisition of reading skills. Numerous examples can be cited of the partially sighted person excelling in professions demanding the most required reading, such as law or philosophy. The motivation factor is a major one for the patient with any kind of handicap to reading. The demand for reading in our society is so overwhelming that all but the severely impaired eventually manage to attain at least marginal skills.

The belief that visual disabilities lead to poor academic achievement is superficially so logical that authors often cannot resist making such a conclusion, in spite of the absence of firm supporting evidence (7). Most physicians who have had any experience with poor readers are quick to point out that in both good and poor readers there is the same incidence of systemic and ocular problems. This was elegantly studied by Helveston et al (8), who documented that academic performance, including reading, had no correlation with any vision function tested, including visual acuity, muscle balance, preferred eye and hand, color vision, refraction, sensory and motor function, and a writing and drawing task (9,10). The temptation to blame visual parameters remains so strong that considerable credence is given to claims that minor obstacles to reading—such as modest impairments of visual acuity, mild nystagmus, poor coordination, cerebral palsy with good cerebration, strabismus, or even modest visual field defects—are legitimate causes of poor reading ability.

TABLE 27.1 MAJOR FINDINGS FROM NICHHD-SUPPORTED RESEARCH PROGRAMS

Research Domain	Findings	Research Group
Definition of learning disabilities	A definition must be developed within a longitudinal developmental perspective unbiased by a priori assumptions reflected in current definitions.	Bowman Gray School of Medicine, Yale University
	Exclusionary definitions using discrepancy criteria appear invalid, particularly in the area of basic reading skills.	Yale University, Ontario Institute for Studies in Education
Reading and language-related processes	Reading disabilities affect at least 10 million children in the United States.	Yale University
	Epidemiological studies indicate that as many women as men manifest dyslexia; however, schools identify four times as many boys as girls.	Bowman Gray School of Medicine, University of Colorado, Yale University
	Reading disabilities reflect a persistent deficit rather than a developmental lag. Longitudinal studies show that of those children who are reading disabled in the third grade, approximately 74% remain disabled in the ninth grade.	Yale University, Ontario Institute for Studies in Education
	Distinguishing between disabled readers with and without an IQ achievement discrepancy appears invalid. Children with and without discrepancies show similar information processing, genetic, and neurophysiological profiles.	University of Colorado, Bowman Gray School of Medicine, Yale University, Ontario Institute for Studies in Education
	Children with reading disability differ from one another *and* from other readers along a continuous distribution. They *do* not aggregate	Yale University, Bowman Gray School of Medicine,

	Children with reading disability differ from one another *and* from other readers along a continuous distribution. They *do* not aggregate together to form a distinct “hump” separate from the normal distribution.	Yale University, Bowman Gray School of Medicine, University of Colorado, Ontario Institute for Studies in Education
	The ability to read and comprehend depends on rapid and automatic recognition and decoding of single words. Slow and inaccurate decoding are the best predictors of deficits in reading comprehension.	Yale University, Bowman Gray School of Medicine, University of Colorado, Johns Hopkins School of Medicine
	The ability to decode single words accurately and fluently is dependent on the ability to segment words and syllables into phonemes. Deficits in phonological awareness reflect the core deficit in dyslexia.	Yale University, University of Colorado, Bowman Gray School of Medicine, University of Miami, Johns Hopkins School of Medicine
	The best predictor of reading ability from kindergarten and first-grade performance is phoneme segmentation ability.	Bowman Gray School of Medicine, Yale University
Attention	A precise classification of disorders of attention is not yet available. A classification methodology that assesses internal and external validity of dimensional and categorical models must be applied to this issue.	Yale University
	Disorders of attention and reading disability often coexist, but the two disorders are distinct and separable.	Bowman Gray School of Medicine, Yale University
	Disorders of attention occur more frequently and exacerbate the severity and cognitive morbidity of reading disabilities. Because disorders of attention and reading disabilities often co-occur, more men are typically identified as reading disabled, sparingly inflating the sex ratio in favor of males.	Bowman Gray School of Medicine, University of Miami
Genetics	A multiple regression procedure has been developed that allows for the analysis of the genetic etiology of individual differences in component language and reading skills. This methodology can assess differential genetic and environmental effects.	University of Colorado
	There is strong evidence for genetic etiology of reading disabilities, with deficits in phonological awareness reflecting the greatest degree of heritability.	University of Colorado
	There appears to be at least one type of	University of

	There appears to be at least one type of reading disability that can be linked to the HLA region of chromosome 6, reflecting a possible association with autoimmune disorders.	University of Colorado, University of Miami
Neuroanatomy, neurophysiology, neuroimaging	Several types of brain pathology, including microdysgenesis (ectopias), cell loss, and abnormalities of the corpus callosum are present in a number of strains of mice. There is a similarity between the brain lesions seen in the mouse model and in humans with dyslexia.	Beth Israel Hospital and Harvard Medical School
	At the microscopic level, atypical neural organization in dyslexic individuals is suggested by absence of the normal left-greater-than-right asymmetry in the region of the posterior temporal planum.	Beth Israel Hospital and Harvard Medical School
	The phenotypic expression of dyslexia is related to anomalous organization of tissue and processing systems subserved within the posterior left hemisphere.	Beth Israel Hospital and Harvard Medical School, Bowman Gray School of Medicine
	Regional blood studies indicate that deficiency in word recognition skills is associated with less-than-normal activation in the left temporal region.	Bowman Gray School of Medicine
	PET studies indicate that dyslexic adults have greater-thannormal activation in the occipital and prefrontal regions of the cortex.	University of Miami
Intervention	Disabled readers do not readily acquire the alphabetic code due to deficits in phonological processing. Thus, disabled readers must be provided highly structured programs that explicitly teach application of phonological rules to print.	Bowman Gray School of Medicine
	Longitudinal data indicate that systematic phonics instruction results in more favorable outcomes for disabled readers than does a context emphasis (whole-language) approach.	Bowman Gray School of Medicine

HLA, human leukocyte antigens; PET, positron emission tomography. From Lyon GR. Research initiatives in learning disabilities: contributions from scientists supported by the National Institute of Child Health and Human Development. *J Child Neurol* 1995;10:S120-S126.

A poor reader who has inherent difficulty in learning the skills of reading might be expected to be handicapped excessively with ocular problems that would be minor to the good reader. This is not the case. Minor problems do not seem to hinder the poor reader more than the good reader. If it were otherwise, the poor reader would have an excess of minor problems compared with the good reader. No such excess of minor or major ocular problems has been found, although sporadic, poorly controlled reports continue to surface that suggest otherwise.

The signal advancement in the field of dyslexia was the establishment by Congress in 1968 of a mandated interest in dyslexia carried out by the National Institute of Child Health and Human Development. Presently, centers have been established for the study of the condition and progress is being made, as summarized in Table 27.1. Nationally recognized centers for the study of this vexing problem are helpful and, perhaps, will eventually lead to appropriate remedial measures and to standardization of diagnostic criteria such that moving across state borders does not suddenly invoke a “cure” for the condition because differing criteria for

poor readers are used (11). In the previous edition of this book (Chapter 25), Reinicke (12) enumerates the data showing that refractive errors, ocular motility disorders, including convergence insufficiency exophoria, accommodation, stereopsis, peripheral vision defects, tinted lenses, and drug therapy all do not influence one's ability to read and, subsequently, learn (13). In 1896, the onset of dyslexia in a 45-year-old man was described in detail by Hinshelwood, who attributed the term “dyslexia” to Professor Berlin as used in Berlin's 1887 monograph. It was not until Orton's (14) seminal article on word blindness in schoolchildren that the educational aspects of dyslexia became well known. Orton detailed dyslexia as treatable by tutorials in reading, emphasizing that the term “word

blindness” should not be used. Eventually, Orton was memorialized in the society bearing his name (see later section, Role of the Ophthalmologist).

Shaywitz et al (15), authors of one of the most important articles on dyslexia, found that, contrary to expectations, reading problems did not follow a bimodal distribution, rather a normally distributed bell-shaped curve. A bimodal distribution would be expected, if the poor reading were a biologically based specific disorder. Their conclusions make sense: First, reading difficulties are part of a continuum; second, dyslexia is not all-or-none; and, finally, dyslexia can be quantified and predicted with a normally distributed model. This is an important feature to stress to the parents and their child with poor reading ability.

There has been much confusion in the neuropsychological, educational, medical, optometric, and lay communities as to the definition of *dyslexia*. For the current chapter we will define dyslexia as “the unexpected difficulty in learning to read and spell” (16). The term *unexpected* means that the child (or adult) has the requisite other skills (i.e., intellectual functioning, peripheral nervous system functioning) and educational opportunities to be able to learn how to read. There are multiple subtypes of dyslexia, which has caused additional confusion in the field. Dyslexia is considered a language-based disorder because a significant number of affected individuals have subtle language findings on neuropsychological testing and a clear association with left hemisphere dysfunction (17).

Types

There are four types of dyslexia described in the literature: (a) dysphonic dyslexia, (b) surface dyslexia, (c) mixed dyslexia, and (d) deep dyslexia. Note that the nomenclature for these conditions may differ, depending on the source (18).

Dysphonic dyslexia (a deficit in phonological processing) is the most common type. It occurs in two thirds of all children who have a reading disorder. The basic cognitive deficit associated with this condition is the difficulty processing information through auditory channels. This leads to an inability to process the sound-symbol relationships needed to learn how to read. For example, these individuals have trouble sounding out novel words that they are confronted with due to difficulty making the association between the written letter symbol and the sound that is associated with each letter. They tend to rely more on the “visual images” of words and will either “read” novel words as words that they already know that closely resemble the novel word (typically have a similar beginning and possibly ending sound). For example, reading “should” as “said” is perceived due to the visual similarity of letter. These children reverse letters while writing and also spell words with letters that are out of order because of the difficulty with understanding the sound-symbol relationship (“grage” for “garage”).

Surface dyslexia accounts for approximately 14% of the reading disabilities and is characterized by difficulty visualizing words to the point where reading can become fluent (18). These individuals tend to rely more heavily on the sound-symbol relationships while reading and thus need to “break down” every word, rather than having an automaticity to reading. These children often make errors on simple words that they have seen before because they struggle to create a “sight vocabulary” or series of words that they memorized (“the”; “is”; “and”). This type of reading disability has sometimes been labeled “orthographic” processing disorder.

Mixed dyslexia involves both the dysphonic and orthographic aspects of reading. These children typically have extreme difficulty learning how to read, because they do not have strong phonological processing and visual processing to compensate for their weaknesses. The prognosis for fluent reading in these children is typically not good (18).

Deep dyslexia, the fourth type of dyslexia, is a very rare form of reading disability. The child struggles with both the phonological and the visual-spatial aspects of reading and begins to rely more heavily on semantic word knowledge. These children are better able to read words that are meaningful (mostly nouns) and have difficulty reading words that cannot be easily imagined (i.e., “thus,” “an”). They will also make semantic reading errors such that they may read the word “daddy” as “father” (19).

Etiology and Neuropathology of Dyslexia

There is evidence that dyslexia can develop in two ways. The first is underlying genetic factors, and the second is due to prenatal and/or perinatal exposure. Gene-linkage genetics research has discovered that chromosomes 6 and 15 are associated with dyslexia. In addition, a rare cause of dyslexia is an abnormal sex chromosome number 47, XXY. Studies reveal that somewhere between 35% and 40% of all dyslexic individuals have a first-degree relative with the condition.

Environmental causes, such as birth weight, gestational age, neonatal distress, and complications during pregnancy can all contribute to the onset of developmental dyslexia.

Various studies have shown that the normal asymmetry of the planum temporale being larger in the left hemisphere does not exist in dyslexics (20,21,22,23). Feifer and DeFina (18), in 2000, hypothesized that the abnormal development of the planum temporale of the left hemisphere may be responsible for the phonological processing deficits seen in the dysphonic dyslexic individuals. A second common finding of individuals with dyslexia is heterotopias in the left angular gyrus (24). These focal ectopias and dysplasias are typically believed to be as a result of abnormal cellular migration during the second trimester of fetal development (25). Feifer and DeFina believe that deficits in the left angular gyrus may be the genesis of the orthographic aspects of dyslexia in that the visual-spatial aspects of reading may be disrupted in this region (i.e., where visual-spatial meets language) (18). Shaywitz (26) has shown that PET-scan imaging reveals less metabolic activity in the left hemisphere in patients with dyslexia.

TREATMENT OF LANGUAGE-BASED LEARNING DISABILITIES AND DYSLEXIA

Language-based learning disabilities are typically treated through direct intervention with a speech/language therapist

(pathologist) and through compensatory strategies. There are training methodologies available in which the clinician can teach compensatory strategies to these individuals, often working with the teachers and school systems.

Shaywitz (26) wrote that most of the remedial systems devised to treat dyslexia have several commonalities and involve systemic and direct instruction in the areas of (a) phonetic awareness, (b) phonics, and (c) fluency. Treatment should involve and should be provided in the context of an enriched language environment. Several remedial systems for dyslexic children include the Orten-Gillingham System, the Wilson Reading System, and the Lindamood-Bell Phoneme Sequencing Program. All of these systems have intensive training programs with certification for their clinicians and are based on evidence-based research. Parents should be directed toward one of these experts for dyslexic remediation (26).

NONVERBAL LEARNING DISABILITIES

The concept of nonverbal learning disabilities (NLD) is relatively recent when compared to other learning disability diagnostic categories. In 1967 Johnson and Myklebust (27) described a pattern of learning difficulties that included problems with (a) spatial orientation, (b) interpretation of nonverbal communication, (c) body image, (d) right-left confusion, (e) visual-spatial-motor organization, and (f) social perceptions. These children subsequently have been found to have difficulty with arithmetic. NLD is thought to be a result of right hemisphere dysfunction with some frontal lobe involvement (28,29,30). Rourke (31) believes that the underlying pathology is lack of development of the brain's white matter, which affects the right hemisphere more so than the left. The diagnosis of NLD occurs usually later in a child's academic career. Reading disorders are typically diagnosed in first or second grade. Difficulty with math is often excused in early grades, and comprehension problems arise more often in later elementary or junior high years. The need for higher order concept formation and social skills increases in junior high school. Psychosocial deficits develop as these children grow older. Well-developed verbal and reading skills, however, are frequently observed in these

children and adults. Comprehension of written material (context) is problematic with inability to appreciate inferential meaning. Spoken inflection and body language are also hard for these individuals to understand.

If diagnosed earlier, occupational therapy to improve motor and sensory deficits is the most effective therapy. At times, therapy must be coordinated with a homework tutor, reading specialist, and/or a physical therapist, if other and more complex aspects of NLD are identified. Numerous treatment strategies have been tried over the years; however, utilizing current repetitive, standard rehabilitation science techniques seem, at present, to be best.

The idea is to teach organizational skills by enhancing motor awareness, planning, action, and, finally, motor memory. By organizing these motor parameters efficiently, one can therefore possibly extrapolate these developed organizational skills to higher cognitive and executive functions involving nonmotor learning. If one learns to organize motor function, it is possible to organize thoughts. Rehabilitation science has long been effective to training individuals after closed head trauma, brain surgery, and strokes to compensate for the damaged brain function by utilizing areas of the brain previously not involved in the function of the injured area. Thus, a stroke patient can learn to speak or walk again over time. The brain has great synaptic regenerative power. Thus, NLD patients can be trained to organize better, improve math skills, and even appreciate nonverbal cues to a greater extent (32). Social skill training is important for these NLD individuals as well.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

The diagnosis of attention deficit and attention deficit/hyperactivity disorders (ADD; ADHD) is established by the criteria listed in the DSM-IV (33), with behavior repeated over time. Controversy still exists over the true existence and definition of these two diagnoses as a separate category of learning disabilities. The DSM-IV codes the disorder based on three typologies: (a) predominantly inattentive type, (b) predominantly hyperactive-impulsive type, and (c) combined type. In addition, it acknowledges that several conditions (i.e., pervasive developmental disorder, schizophrenia, etc.) can have similar presentations, but that these conditions cannot be the sole explanation of the patient's behavior concerns (33).

ADHD is a very prevalent condition and has been reported to occur in about 3% to 5% of all school-aged children (34). The disorder also tends to affect more boys at a rate of somewhere between 2:1 and 9:1 (33,34). The subtypes have recently been studied. Nadeau et al (35) noted that girls manifest ADD more often by being hyper-talkative rather than hyperactive. Also, Faraone et al (36) reported that the inattentive type of ADHD tends to occur in girls and is more prevalent in older children. The hyperactive-impulsive type (which seems to be the least diagnosed) and combined type were more prevalent in younger children. Interestingly, Faraone et al. proposes that the disorder may have, at least in some children, a developmental pathway in which hyperactivity and impulsivity are more prevalent earlier in the course of the disorder, with inattention being more noticeable later in the child's life. This would be disorganized rather than hyperactive and impulsive (37). The exact anatomical and neurophysiological etiology of ADD/ADHD is as yet not proven. Many theories exist (38,39,40). Genetic studies have shown an increased risk of ADHD in children who have parents with ADHD, thus, supporting the biological basis of the condition (41). The Committee on Quality Improvement (Subcommittee on Attention Deficit/Hyperactivity Disorder) of the American Academy of Pediatrics published its clinical practice guidelines, *Diagnosis and Evaluation of the Child with Attention Deficit/Hyperactivity Disorder*, which emphasizes to pediatricians the DSM-IV criteria for diagnosing ADHD and observing the typical behaviors in more than one setting,

location, and situation over time (42). Research involving the study of academically efficient individuals with ADHD, compared to those afflicted who are scholastically inefficient, was suggested. Perhaps the latter group has more than one comorbid condition.

Psychostimulants have been traditionally incorporated as the primary treatment for children with ADHD. The three most prescribed agents are methylphenidate, pemoline, and dextroamphetamine (43). Methylphenidate is prescribed about 71% of the time (44). They have been shown to improve behavior in school as well as at home (45). Treatment should be under the direction of a pediatric neurologist, developmental pediatrician, pediatric psychiatrist, or pediatrician.

PERVASIVE DEVELOPMENTAL DISORDERS

Pervasive developmental disorders (PDD), also referred to in the literature as autism spectrum disorders (ASD), include a wide variety of conditions that impact the normal course of child development and influence learning. The basic characteristics of these children are that they display severe and persistent impairments in (a) reciprocal social interaction skills; (b) communications skills; or (c) the presence of stereotyped behavior, interests, and activities (33). These individuals lack social reciprocity, have a limited but intense range of interests, and exhibit repetitive actions. Reciprocal social interaction deficits can be observed with children who fail to develop and maintain peer relationships, lack of cooperative play/interactions, lack of social reciprocity, and impairment in nonverbal behaviors of social meaning (i.e., eye contact, facial expression, body postures). An individual with high functioning PDD can exhibit many NLD characteristics. A DSM-IV designation of ASD-NOS (autism spectrum disorder—not otherwise specified) is often used for these patients. These children often look normal and may be initially difficult to identify. Eventually, however, inferential and conceptual learning usually becomes too great in later elementary years, and these children will then require more educational, social, and vocational support. A child with communication deficits may lack communication in any form (i.e., both spoken and gestural), may lack the ability to initiate or sustain a conversation, and/or may use stereotyped or idiosyncratic communication patterns. Finally, these children tend to demonstrate restricted interests in activities (baseball statistics, train schedules, doll collections). Inflexibility and the need for routine and/or repetitive motor patterns are also characteristic (33). The differential diagnosis of most children with “classic autism” is made prior to school age, typically before the third birthday.

The incidence of autism in the normal population ranges from 2 to 4 per 10,000 (33) to 1 per 1,000 (46). Several studies have shown that there is about a 3% chance of having an autistic sibling when another sibling has been diagnosed with the condition (47). Genetic transmission is multifactorial (48). Studies have revealed an initial smaller head circumference with an accelerated growth before age 14 months due to increased white matter in the frontal lobes (49). Reduced cerebellar size, along with increased neuronal density in the limbic system, are consistent findings (50). Positron emission tomography (PET) imaging studies confirm lower activation levels in frontoparietal regions as well as in the neostratum and thalamus (51).

Asperger's syndrome is a type of PDD that is less fully understood than classic autism. Children with this disorder have the impaired social interactions and restricted, repetitive patterns of behavior/interests but typically develop language in a more “normal” fashion. These children do not usually demonstrate delays in language acquisition and may score within normal limits on tests of language skills. However, they may have difficulty with pragmatic language, which impedes functional and social skills (52). They do have higher IQs than autistic children.

Definitive diagnosis and treatment of pervasive developmental disorders should be in the hands of a qualified pediatric psychiatrist and knowledgeable pediatrician, as well as occupational and physical therapists, who are well schooled in diagnosing and treating children with PDD/ASD (53).

THE ROLE OF THE PEDIATRIC OPHTHALMOLOGIST

The initial step in educating ophthalmologists is to introduce to the ophthalmology community pediatric psychiatry, educational and neuropsychology, occupational therapy, and educational science in all of its forms relating to learning disorders in children and adults (54). (An appendix to this chapter outlines briefly what an ophthalmologist in general practice and those in a pediatric practice should know about learning disorders.) The next step is to make the diagnosis and treatment of children and adults with learning disabilities more efficient by developing a system for classifying disorders that is oriented toward ophthalmologists. Such a system is described in Chapter 11 in “Clinical Practice Guidelines Redefining the Standards of Care for Infants, Children, and Families with Special Needs” (55).

EYE-MD OFFICE SUSPICION OF A CHILD WITH A LEARNING DISORDER

Children with language-based disorders, such as dyslexia, can often be suspected during a routine eye examination. Early identifying characteristics include unusual difficulty learning numbers, letters, and colors without evidence of eye disease. The ophthalmologist should refer these individuals to a knowledgeable neuropsychologist or speech and language pathologist for further testing to identify all of the language disorders existing in any particular case and then to recommend diagnosis-specific therapy. A licensed certified reading teacher and a homework tutor may both be required, with additional therapy and monitoring by the speech and language specialist and neuropsychologist, as is necessary.

Appropriate diagnostic studies establish the all toomissed

nonverbal learning disorder. The ophthalmologist can suspect NLD by giving the young patient a simple visual memory test (Foss) in the office (56,57). It takes only 1 to 2 minutes to perform (Fig. 27.1). Other characteristics of NLD can be obtained via the history. Trouble with math, difficulty with inferential meaning and context comprehension as well as interpersonal skill dysfunction all point to a possible NLD diagnosis. These individuals can be rapid readers but often do not fully understand what they read. Occupational therapy is the treatment path that is most efficient for NLD children. At times, therapy must be coordinated with a homework tutor, reading specialist, and/or a physical therapist, if other, more complex aspects of NLD are identified. Numerous treatment strategies have been tried before; utilizing current repetitive, standard rehabilitation science techniques seem, at present, to be best.

It is with NLD individuals that some optometric vision training techniques appear to be helpful. These therapies are partially based on occupational and physical therapy principles as well as standard rehabilitation science. Adults, after strokes, as well as all-aged individuals after accidental closed head trauma or brain tumor resection, are taught to use the uninjured functioning parts of their brain to compensate for loss of normal use of an injured or damaged brain area, despite the fact that the area of the brain assuming the new function was never intended to do so. Stroke patients learn to read, write, talk, and navigate once again, despite permanent brain damage to the areas previously programmed to maintain those particular functions. A similar model exists for children with naturally occurring brain dysfunction, such as children with NLD. These children are born with inefficient or inadequate brain programming and processing.

Laterality training and eye-hand coordination strategies, such as is advocated by “vision therapists,” can help to improve those parameters by positive reinforcement. To what direct extent learning itself, in a classroom or at home, is enhanced in all cases has yet to be shown via evidence-based and value-based science, using a masked or doublemasked controlled study. Published papers reviewed by the authors to date are anecdotal or retrospective/prospective reviews of measurement parameters or performance, while other remedial methods are often being simultaneously carried out (58).

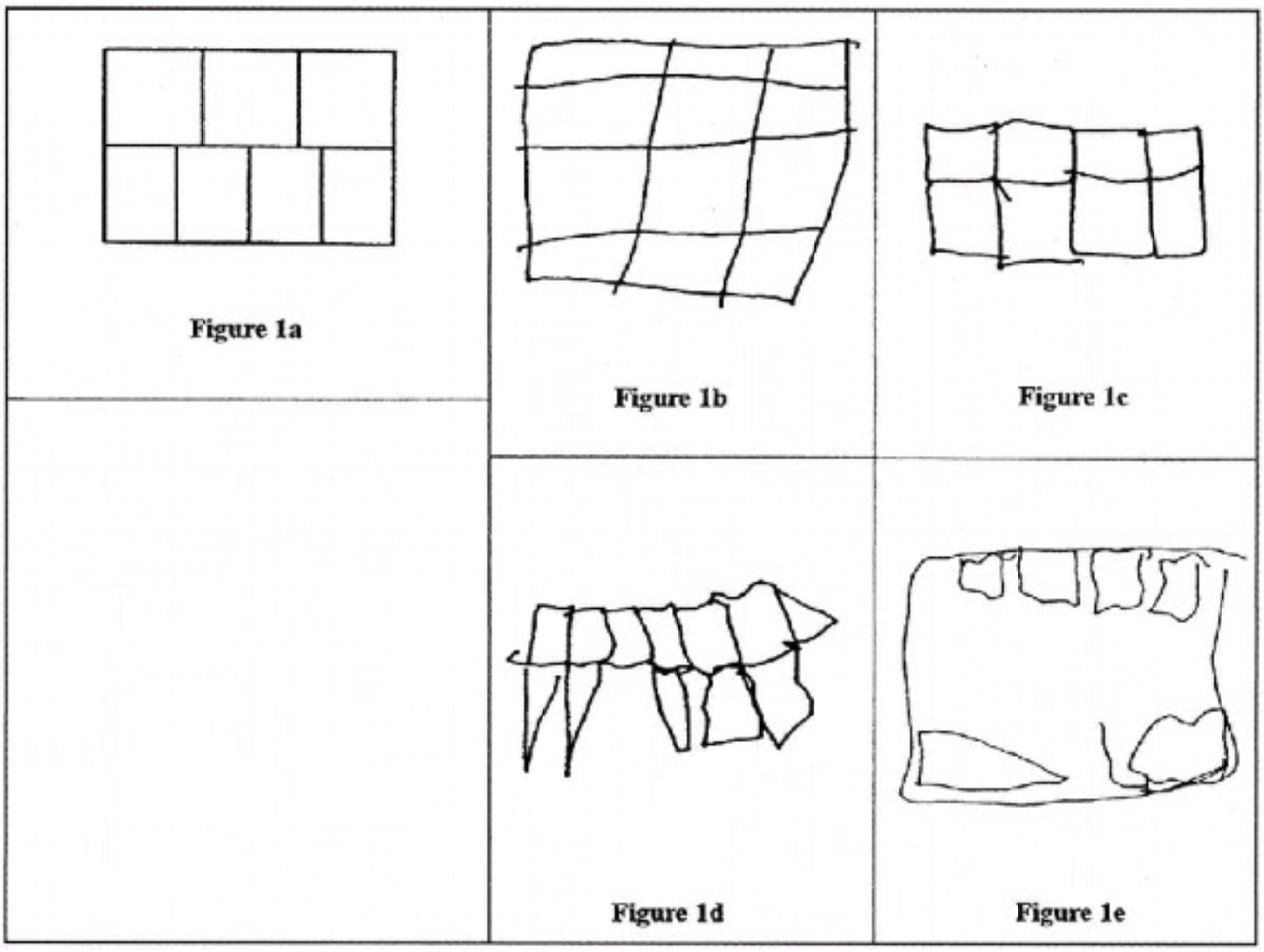

Figure 27.1 A diagnostic tool for categorizing nonverbal learning disabilities in school-aged children 6 to 12 years old. (A) A simple pattern is presented to a child for 15 seconds. The child is then asked to draw the pattern from memory. Figures *B* and *C* are examples of acceptable normal variations in children's drawings. Figures *D* and *E* represent variations that indicate a possible nonverbal learning disorder.

Optometric vision training consists of two unrelated therapies. The first is related to classic orthoptics to enhance binocular function, which optometry believes can influence reading and learning. The second is termed *developmental optometry* and consists of many different kinds of exercises involving hand-eye and body coordination. This treatment process is based primarily on occupational therapy principles. These optometric “therapies” are designed to improve visual information processing (59). Although orthoptic exercises may improve fusional vergence parameters and perhaps decrease reading fatigue, it has little effect on any of the aforementioned brain-mediated learning disorders. As far as “developmental vision therapy” is concerned, however, there may be some beneficial effects of certain visual/spatial/motor exercises for individuals with NLD. The treating optometrist wishes to develop motor awareness, motor planning, motor integration, and motor memory of the differences between the right and left sides of the body, using occupational therapy methods. When an individual achieves organizational efficiency through repetitive, organized visual motor tasks, it may be possible to translate the organizational skills into higher cognitive organizational ability and hence improve learning efficiency. Developmental optometry techniques have no therapeutic value for children with dyslexia, attention disorders, or pervasive developmental disorders. Again, NLD accounts for less than 15% of all LD patients (54).

ADD/ADHD

It is necessary for the pediatric ophthalmologist to identify the behavior by listening and observing while the child is in the examination chair and then referring appropriately. The pediatric neurologist, pediatric developmental specialist, family physician or pediatrician, or pediatric psychiatrist can all typically provide treatment. The characteristics to look for when suspecting a patient has ADD/ADHD are listed in the Appendix IV.

PDD/ASD

The pediatric ophthalmologist can often identify an individual with Asperger's syndrome or other PDD by history and observation of the child's behavior in the examination chair. Lack of eye contact is often the initial complaint and reason for referral to the Eye-MD (53). The ophthalmologist learns information about a lack of social relatedness and peer interaction from the family and patient history. This can also provide information concerning a limited but intense range of interest or other behaviors peculiar to individuals with autistic spectrum disorders. Definitive diagnosis and treatment should be provided by experienced and certified neuropsychologists, pediatric psychiatrists, and developmental pediatricians. Help is secondarily available from speech and language pathologists as well as occupational and physical therapists (see Appendix).

CONCLUSION

In the 21st century, medical science is progressing rapidly toward an interdisciplinary model that requires the physician to think “outside the box,” so to speak, and learn about other specialties and available diagnostic and therapeutic possibilities. Complementary and alternative medicine is gaining popularity. Neuroscience, genetics, and digital technology (high tech) are slowly coming together in the research arena and will likely propel our knowledge rapidly forward in our understanding of visual perception and brain processing during the next half century. Our patients feel that we are the experts in visual perception and processing as well as ocular pathology and visual function. We should be able to counsel them as to how to solve their perceived “eye” problem affecting their learning ability. We should tell them that the eye is merely a “camera,” while it is the brain that perceives and processes the information that the camera eye provides. By knowing the various ways the brain may mis-process information causing a learning disorder, the ophthalmologist can be a primary source of directing these families to the appropriate professional best trained and equipped to help them achieve their optimal learning potential. Many professional disciplines must work together to achieve that goal.

REFERENCES

1. Hartstein J. *Current concepts in dyslexia*. St. Louis: Mosby, 1971.

2. Gable JL. *Visual disorders in the handicapped child*. San Mateo, CA: Marcel Dekker, 1984.

3. Miller NR. Neuro-ophthalmologic topographic diagnosis of tumors and related conditions. In: Miller NR, ed. *Walsh & Hoyt's clinical neuro-ophthalmology*, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 1988:1137-1242.

4. National Joint Committee on Learning Disabilities. Learning Disabilities: issues on definition. *J Learn Disabil* 1987;20:107-108.

5. Gaddes WH, Edgell D. Learning disabilities and brain function, 3rd ed. New York: Springer-Verlag, 1993.

6. Koller HP. An ophthalmologist's approach to visual processing/learning differences. *J Pediatr Ophthalmol Strabismus* 2002;39(3): 133-142.

7. Webber GY. Visual disabilities—their identification and relationship with academic achievement. *J Learn Disabil* 1980;13:13.

8. Helveston EM, Weber JC, Miller K, et al. Visual function and academic performance. *Am J Ophthalmol* 1985;99:346.

9. Coleman HM. The West Warwick visual perception study. Parts I and II. *J Am Optom Assoc* 1972;43:452, 532.

10. Hoffman LG. Incidence of vision difficulties in children with learning disabilities. *J Am Optom Assoc* 1980;51:447.

11. Lyon GR. Research initiatives in learning disabilities: contributions from scientists supported by the National Institute of Child Health and Human Development. *J Child Neurol* 1995;10: S120-S126.

12. Reinicke RD. Role of the ophthalmologist in reading disorders. In: Nelson LB, Olitsky S, eds. *Harley's pediatric ophthalmology*. Philadelphia: Lippincott Williams & Wilkins, 1998:499-507.

13. Menaker SJ, Breton ME, Breton ML, et al. Do tinted lenses improve the reading performance of dyslexic children? *Arch Ophthalmol* 1993;111:213-218.

14. Orton ST. “Word blindness” in school children. *Arch Neurol Psychol* 1925;14:581.

15. Shaywitz SE, Escobar MD, Shaywitz BA, et al. Evidence that dyslexia may represent the lower tail of a normal distribution of reading ability. *N Engl J Med* 1992;326:145.

16. Pennington BF. Diagnosing learning disorders. A neuropsychological framework. New York: Guilford Press, 1991.

17. Shaywitz BA, Fletcher JM, Shaywitz SE. Defining and classifying learning disabilities and attention deficit/hyperactivity disorder. *J Child Neurol* 1995;10[Suppl 1]:S50-S57.

18. Feifer SG, DeFina PA. The neuropsychology of reading disorders: diagnosis and intervention workbook. Middletown, MD: School Neuropsych Press, 2000.

19. McCarthy RA, Warrington EK. Cognitive neuropsychology: a clinical introduction. New York: Academic Press, 1990.

20. Lovett M. Developmental reading disorders. In: Feinberg T, Farah M, eds. *Behavioral neurology and neuropsychology*. New York: McGraw Hill, 1997:773-787.

21. Hynd G, Semrud-Clikeman M. Brain morphology in developmental dyslexia and attention deficit/hyperactivity disorder. *Arch Neurol* 1990;47(8):919-926.

22. Larsen J, Hoion T, Lundberg I, et al. MRI evaluation of the size and symmetry of the planum temporale in adolescents with developmental dyslexia. *Brain Lang* 1990;39(2):289-301.

23. Galaburda AM, Corsigkia J, Rosen GD, et al. Planum temporale asymmetry: reappraisal since Geschwind and Levitsky. *Neuropsychologia* 1987;25:853-868.

24. Goldberg E. Gradiental approach to neocortical functional organization. *J Clin Exp Neuropsychol* 1989;11(4):489-517.

25. Kolb B, Wishaw IQ. *Fundamentals of human neuropsychology*, 5th ed. New York: WH Freeman and Company, 2003.

26. Shaywitz S. *Overcoming dyslexia*. New York: Alfred A. Knopf, 2003.

27. Myklebust HR, Johnson DJ. *Learning disabilities: educational principles and practices*. New York: Grune & Stratton, 1967.

28. Bannatyne A. Diagnosis: a note on recategorization of the WISC scaled scores. *J Learn Disabil* 1974;7:272-274.

29. Foss JM. Nonverbal learning disabilities and remedial interventions. *Ann Dyslexia* 1991;41:129-131.

30. Johnson D, Myklebust HR. Nonverbal disorders of learning. In: *Learning disabilities educational principles and practices*. New York: Grune & Stratton, 1967.

31. Rourke BP. *Syndrome of nonverbal learning disabilities: neurodevelopmental manifestations*. New York: Guilford Press, 1995.

32. Goldberg KB, Moss E, Dadario B, et al. *Information processing and personality in children and adolescents with nonverbal learning disabilities*. Philadelphia: Society for Personality Assessment, 2001.

33. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association, 1994.

34. Barkley R. *Attention deficit hyperactivity disorder: a handbook for diagnosis and treatment*. New York: Guilford Press, 1990.

35. Nadeau KG, Littman EB, Quinn PO. *Understanding girls with attention deficit hyperactivity disorder*. Silver Spring, MD: Advantage Books, 1999.

36. Faraone SV, Biederman J, Weber W, et al. Psychiatric, neuropsychological, and psychosocial features of DSM-IV subtypes of attention-deficit/hyperactivity disorder: results from a clinically referred sample (Diagnostic and Statistical Manual of Mental Disorders—IV). *J Am Acad Child Adolesc Psychiatry* 1998;37(2): 185-193.

37. Seidman LJ, Beiderman J, Weber W, et al. Neuropsychological function in adults with attention-deficit hyperactivity disorder. *Biol Psychiatry* 1998;44(4):260-268.

38. Heilman KM, Voeller KKS, Nadeau SE. A possible pathophysiologic substrate of attention deficit hyperactivity disorder. *J Child Neurol* 1991;6[Suppl]:S76-S81.

39. Kolb B, Wishaw IQ. *Fundamentals of human neuropsychology*, 5th ed. New York: WH Freeman and Company, 2003.

40. Hynd GW, Semrud-Clikeman, Lorys AR, et al. Corpus callosum morphology in attention deficit-hyperactivity disorder: morphologic analysis of MRI. *J Learn Disabil* 1991;24:141-146.

41. Zametkin AJ. The neurobiology of attention-deficit hyperactivity disorder: a synopsis. *Psychiatr Ann* 1989;19(111):584-586.

42. American Academy of Pediatrics. Clinical practice guideline: diagnosis and evaluation of the child with attention deficit/hyperactivity disorder. *Pediatrics* 2000;105(5):1158-1170.

43. Greenhill LL. Childhood attention deficit hyperactivity disorder: a synopsis. *Psychiatr Ann* 1989;19(11):584-586.

44. Greenhill LL, Halperin JM, Abikoff H. Stimulant medications. *J Am Acad Child Adolesc Psychiatry* 1999;38(5):503-511.

45. Musten LM, Firestone P, Pisterman S, et. Al. Effects of methylphenidate on preschool children with ADHD: cognitive and behavioral functions. *J Am Acad Child Adolesc Psychiatry* 1997;36:1407-1415.

46. Happe F, Frithy U. The neuropsychology of autism. *Brain* 1996; 119:1377-1400.

47. Smalley SL, Asarnow RF, Spence MA. Autism and genetics: a decade of research. *Arch Gen Psychiatry* 1988;45:953-961.

48. Pennington BF. *Diagnosing learning disorders: a neuropsychological framework*. New York: Guilford Press, 1991.

49. Courchesne E, Carper N. Evidence of brain overgrowth in the first year of life in autism. *J Am Med Assoc* 2003;290(3):337-344.

50. Courchesne E, Yeung-Courchesne R, Press GA, et al. Hypoplasia of cerebellar vermal lobules VI and VII in autism. *N Engl J Me*d 1988;318:1349-1354.

51. Horowitz B, Rumsey J, Grady C, et al. The cerebral metabolic landscape in autism. *Arch Neuro*l 1988;45:749-755.

52. Miller JN, Ozonoff S. The external validity of Asperger disorder: lack of evidence from the domain of neuropsychology. *J Abnorm Psycho*l 2000;109(2):227-238.

53. Greenspan SI, Weider S. *The child with special needs*. Reading, MA: Perseus Books, 1998.

54. Koller HP, Goldberg KB. A guide to visual and perceptual learning disabilities. *Curr Concepts Ophthalmo*l 1999;7:24-28.

55. The Interdisciplinary Council in Developmental and Learning Disorders. *Clinical guidelines: redefining the standards of care for infants, children and families with special needs*. Bethesda, MD: ICDL Press, 2001.

56. Foss JM. Nonverbal learning disabilities and remedial interventions. *Ann Dyslexia* 1991;41:128-140.

57. Atzmon D, Nemet P, Ishay A, et al. A randomized prospective masked and matched comparative study of orthoptic treatment versus conventional reading and tutoring for reading disabilities in 62 children (including pro and con editorial comments by Drs. Herdenbergh and Cibis Tongue). *Binocul Vis Eye Muscle Surg Q* 1993;8(2):91-106.

58. Scheiman MM, Rouse MW. Optometric management of learningrelated vision problems. St. Louis: Mosby, 1994.

59. Koller HP. How does vision affect learning? *J Ophthalmic Nurs Tech* 1996;338(1):12-18.

Appendix

Visual Perception and Learning Differences in Pediatric Ophthalmology: What the Ophthalmologist Needs to Know About Learning Disabilities in Clinical Practice

From Koller HP. An Ophthalmologist's Approach to Visual Processing/Learning Differences. Interdisciplinary Council on Development and Learning Disorders (ICLD) Guidelines Manual. Bethesda, MD: ICLD Press, 2000.

I. **Ophthalmic Causes of Temporary Learning Impairment and Inefficiency**
   A. Strabismus, amblyopia, and refractive errors
      1. Decompensated accommodative esotropia with secondary diplopia
      2. Secondary ocular cranial nerve palsies (n. III, IV, VI)
      3. Uncorrected congenital vertical strabismus with abnormal face and head positions
      4. Bilateral very high ametropias, such as bilateral amblyopia of high hyperopia
      5. Bilateral occlusion amblyopia, such as after congenital cataract surgery
      6. Associated untreated “A” and “V” syndromes
      7. Convergence insufficiency exotropia/phoria in certain individuals
   B. Nystragmus of moderate to severe degree causing significant vision loss
   C. Pediatric ocular diseases that can affect learning via visual and emotional effects
      1. Severe juvenile rheumatoid arthritis and related ocular inflammations
      2. Congenital glaucoma with vision loss
      3. Congenital cataracts and major corneal opacities with vision loss and nystragmus
      4. Significant unilateral and/or bilateral ocular trauma with vision loss
      5. Ocular and adnexal neoplasms with secondary disfigurement and vision loss
      6. Severe chronic ocular infections such as HSV-I with vision loss
      7. Congenital and degenerative retinal diseases affecting the macula

II. **Neuro-ophthalmic Causes of Temporary or Intermittent Learning Impairment and Inefficiency**
   A. Brain tumors causing a change in personality and behavior in a pediatric patient
   B. Migraine syndromes
      1. Acephalgic pediatric migraine with visual disturbances and variable vision in school
      2. Ophthalmic migraine in childhood
      3. Ophthalmoplegic migraine
      4. Classic migraine in the older student
   C. Optic nerve disease with significant visual impairment

III. **Systemic Diseases Associated with Vision and Neurologic Dysfunctions Potentially Affecting Learning**
   A. Metabolic and endocrinic disorders

B. Blood dyscrasias affecting the eye and brain
C. Metastatic neoplastic disease to the eye and/or brain

IV. **The Ophthalmologist's Role in Examining a Child and Advising the Family of a Defect** in visual processing and/or learning is to rule out the presence of eye disease or related systemic disorder and to refer the pediatric patient to the proper professionals for more definitive diagnoses and subsequent treatment(s). In order to effectively do this, a classification of non-ophthalmic learning disorders will now be outlined.

A. Learning disabilities (differences)
1. Developmental speech and language based disorders (epidemiology)
a. Articulation disorders
b. Expressive language disorders
c. Receptive
1. Dyslexia—phonologic processing disorder
a. genetics
b. pathophysiology
c. remediation
d. early preschool identifying characteristics
2. Other receptive language disorders
2. Nonverbal learning disabilities (epidemiology)
a. Definition
b. Characteristics and affected areas of learning
1. visual-spatial perception
2. visual memory
3. psychomotor coordination
4. complex tactile-perceptual skills
5. reasoning
6. concept formation
7. mathematical abilities
8. psychological behavioral difficulties
9. good verbal and reading skills
c. Early identification traits
d. Differential diagnosis

e. Methods of treatment. What exactly is optometric vision training?
f. Rationale of therapy based on the traditional closed head trauma/stroke rehabilitation model
3. Attention deficit hyperactivity disorder (epidemiology)
a. Definition
b. Characteristics (DSM-IV) and diagnostic criteria observable during an eye exam
1. squirms in seat, fidgets with hand and/or feet
2. unable to remain seated when required to do so
3. easily distracted
4. blurts out answers before a question is finished
5. difficulty following instructions
6. unable to sustain attention in work activities
7. interrupts or intrudes on others
8. does not appear to listen
9. loses items for tasks such as toys, pencils, and books
10. often engages in dangerous activities without considering the consequences
c. Subclassification
1. inattention
2. impulsivity
3. hyperactivity
d. Differential diagnosis
1. Tourette's syndrome
2. conduct disorder
3. oppositional defiant disorder
4. other tic disorders
e. Treatment and community support
1. pediatric neurologist
2. pediatric developmental specialist
3. pediatric psychiatrist
4. special education teacher or tutor
5. various support groups
4. Pervasive developmental disorders/autistic spectrum disorders (PDD/ASD)
a. Definition
b. Characteristics: defects in social relatedness and language/communication skills
c. Subclassifications
1. Asperger's syndrome (chief eye symptom is “lack of eye contact”)
2. Rett syndrome
3. classic autism
4. unclassified PDD/ASD
d. Referral and treatment options
e. Micro and primary dyskinetic strabismus as a presenting sign of PDD
f. Hyperlexia

V. **Patient Support Groups for Learning Disabled (LD) Individuals**

A. CHADD (Children and Adults with ADD)
B. CEC (Children's Educational Counsel)
C. ASLHA (American Speech, Language and Hearing Association)
D. LDAA (Learning Disabilities Association of America)
E. PERC (Parents Educational Resource Center)
F. The Orten Dyslexia Society
G. AHA (American Hyperlexia Association)
H. HALO (Health Achievement Learning Opportunities Centers)

VI. **Role of the Pediatric and Comprehensive Ophthalmologist Concerning Individuals with Learning Disabilities**

A. Identify and treat any eye or eye-related systemic disease or abnormality.

B. By observation and careful history, identify which broad category of learning differences the patient likely has and convey that impression to the pediatrician, the family, and any other interested parties. These children have often been through many psychological tests, tutoring, and other attempts at remediation without a definitive diagnosis or combination of diagnoses. Suggest a comprehensive neuropsychologic/educational evaluation from a qualified, credentialed neuropsychologist when all interested parties agree.

C. Help the family by giving them a direction in which to proceed so that the child with non-ocular learning differences can start to achieve his full potential. Not every individual with learning disabilities requires every possible specialist These professionals include:

1. Pediatric neurologist
2. Pediatric psychiatrist
3. Pediatric developmental specialist
4. Pediatric endocrinologist
5. Pediatric geneticist
6. Pediatric otolaryngologist
7. Pediatric ophthalmologist
8. Speech and language pathologist (audiologist)
9. Neuropsychologist
10. Educational psychologist
11. Educator with special education credentials
12. Reading tutor
13. Physical therapist
14. Occupational therapist
15. Pediatric social worker
16. School placement expert (educator)
17. Disabilities attorney
18. Family physician or general pediatrician

D. A specialized attorney is often beneficial for helping families receive federal LD benefits to which they are entitled under the terms of the Individuals with Disabilities Education Act (IDEA) and Americans with Disabilities Act (ADA).

E. When the answer the question, “Is the child's reading and/or learning problem in school due to his eyes?” is “No,” the ophthalmologist must explain why it is not and offer a positive and constructive method to direct those families toward obtaining the proper and appropriate care. The public still believes that eye specialists are knowledgeable in the field of visual perception as well as visual function.

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28

Working with Visually Impaired Children and Their Families

Marilyn A. Moller

Rose D. Skolnick

Whenever a child is diagnosed as having a significant visual impairment, both the parents and the child face a variety of challenges. Not the least of these is their need for facts and counsel concerning the medical, educational, social, and psychological aspects of vision loss. Add to this the needs of the child as he or she grows into awareness of what it means to be blind or partially sighted, and it becomes clear that there must be a professional who is willing and able to be the linchpin in the support system for child and family alike. It is therefore crucial that the ophthalmologist to whom such families turn be fully knowledgeable with regard to the impact of visual impairment on development, educational options, community resources, and a wide variety of other information essential to these children and their parents.

DEFINITIONS

Educational and governmental agencies generally use the federal definition of blindness and visual impairment in determining eligibility for services. Although they are nearly 3 decades old, they have such broad acceptance that they continue to be virtually universally used.

Legal blindness is defined as “visual acuity of 20/200 or worse in the better eye with correction, or a visual field that subtends to an angle of not greater than 20 degrees” (1). Obviously, students who fall within these limitations frequently have considerable useful vision and will often still be able to use print as their major means of learning.

Partially sighted students are those who “have visual acuity above 20/200 but worse than 20/70 in their better eye with correction” (1).

Both of these categories of children are covered by the term “visually impaired.” Although the term “visually handicapped” was used for many years, “visually impaired” is now the preferred term and is now widely used.

ATTITUDES

Studies have shown that blindness is second only to cancer in the degree of dread with which it is regarded by the American public (2). Although no studies have been done that have added the acquired immune deficiency syndrome (AIDS) to the list of dreaded events, it is likely that blindness remains very high on society's list of fears.

In addition, society has instilled into its members deepseated feelings about the blind, including myths of helplessness, special acuity of senses, punishment for evil, and so on (3). Thus, the practitioner must first develop an informed and positive manner with regard to the visually impaired before attempting to help parents deal with their own complex feelings regarding their visually impaired child.

Furthermore, if the onset of blindness or visual impairment occurs after approximately age 4, the child will require considerable assistance in handling the complex set of feelings that the traumatic event engenders. The stages of adjustment to the onset of significant visual impairment closely parallel those of adjustment to terminal illness: rejection, bargaining, anger, depression, and, finally, acceptance. In blindness, however, the depression stage can often

last months or even years (4) unless professional assistance is given during the adjustment process.

Further adjustment problems arise if there is disfigurement or if the child *looks* different. The albino child, especially the African-American albino, and the family have particular adjustment problems. Elementary school children almost always encounter some teasing. The support of educational professionals can provide valuable assistance, as can encouraging the child to develop a special interest at which to excel. Studies have repeatedly found that in children with major visual impairments, the development of a positive self-concept is significantly delayed (5). The support of parents, schools, and the medical profession can be vital in helping the child and family in this crucial area.

Professional counseling may prove very valuable for the entire family unit. In addition, peer support groups, such as the National Association of Parents of the Visually Impaired (NAPVI) and its local chapters, can be most helpful. Similar groups have been formed for the parents of children with cataracts, retinitis pigmentosa, and the like. These groups form a support network for parents, allowing them to share their feelings with people who have had similar problems and to share solutions that have been found.

VISUALLY IMPAIRED CHILDREN AS PATIENTS

Although there is no one “right way” to treat or interact with blind and partially sighted children, a few basic guidelines may make the interaction a more positive and rewarding experience both for the child who is a patient and for the practitioner. When working with the visually impaired infant be sure to:

- Talk softly to the infant before touching or picking him or her up. In this way he or she will begin to associate the human voice with anticipated change.
- Read the infant's total body for responsiveness, not just his or her eyes and visual signals.
- Be especially gentle when touching the infant, because he or she has no visual clues to expect impending contact.

When working with preschool and early elementary grade schoolchildren who are blind or partially sighted, it may be helpful to keep these guidelines in mind:

- Address the child by his or her name when entering the room, even if you are just passing through.
- Tell the child *exactly* what you are going to do *before* you do it, then tell him or her again as you conduct the procedure exactly what is happening.
- Warn the child when there will be discomfort (failure to do so may result in the child's coming to associate all contact with the ophthalmologist with discomfort, rather than isolating the specific instances when this occurs).
- Let the child touch or examine instruments and equipment whenever possible because he or she cannot do so visually.
- Use the child's name when you want a specific response from him or her. Blind children do not have the visual cues that others do to know immediately that a person is speaking directly to them.
- If the child must be moved from one treatment room or office to another, describe the route as you take it and explain why the move is necessary, then orient the child to the new situation.
- Avoid discussing the child's condition in front of him or her unless you want the child to have this information. Facial expression often does not reveal all that he or she understands or takes in.
- As children approach and enter adolescence, be attuned to whether the child needs to discuss issues related to the progress of vision loss or to heredity.

Young people need this information, and the ophthalmologist is often the sole source of these facts.

If most of these suggestions seem like simple common sense, that is exactly the case! Working effectively with blind and visually impaired children (and adults, for that matter) entails nothing more than thoughtfulness and consideration, and an awareness of the limitations their vision loss places on them (6).

As the child grows older and enters adolescence, the ophthalmologist is the key resource for accurate and complete information about the diagnosis, prognosis, and genetics of the youngster's eye condition. Studies have shown that as few as 34% of visually impaired teenagers could identify their diagnosis, and certainly even a smaller percentage could give more complete information (7).

EARLY YEARS

The years between birth and age 5 are as crucial in the development of blind and partially sighted children as they are in the nonhandicapped population. Research has repeatedly demonstrated that the visually impaired child is developmentally delayed even when there are no other handicapping conditions (8). Gross motor activities, such as reaching and walking, may be delayed by several months owing to the absence of the usual visual enticements. In a landmark study in 1968, Cratty (9) demonstrated that body image and sensory integration are also significantly delayed.

For these reasons, it is crucial that the environment of the visually impaired child be rich in sensory experiences. If there is any usable vision, the child should be encouraged to employ it. Bright colors should abound, and the child's vision and attention should be directed to them (“Look at the ball”). Blind children should be encouraged to explore their environment tactually. There are many toys on the market that have interesting sounds and textures. All visually impaired children should be given specific help in developing such skills as jumping, hopping, and running.

Until ages 4 or 5 the visually impaired child is not usually aware of any sensory deficit. Some time during the fourth or fifth year the child becomes aware that others have an ability that he or she lacks. This can be dealt with

in a matter-of-fact way and is usually much more difficult for the parent than for the child.

Another problem that frequently arises during the early years is the development of “blindisms,” or strange behavioral mannerisms. These may include rocking, light gazing, exaggerated finger play, eye gouging, and a variety of other behaviors that society considers bizarre. Traditional thought has held that these behaviors are an attempt to provide self-stimulation in an environment that is sensorally deprived. Others contend that these behaviors are not unique to visually impaired children and can be effectively treated by the same behavior modification techniques used to eliminate other objectionable behaviors, such as thumb sucking and nail biting. Parents may need assistance in developing a program that will extinguish the behavior while not placing too much emphasis on it.

Studies have indicated that partially sighted and blind children both develop play skills much more slowly than do their sighted peers. In addition, unless provisions for additional stimulation and social interaction are made, their play is less imaginative and more stereotypical than that of sighted children (10). Thus, most blind and partially sighted children, who are not otherwise handicapped, can benefit greatly from nursery school and kindergarten experiences with nonhandicapped children. With a caring teacher the child can generally be accommodated in such a program. This provides vital socialization skills and a necessary foundation for later educational experiences.

GENERAL EDUCATIONAL BACKGROUND

Until the late 18th century, education of the visually impaired was virtually nonexistent because of the prevailing belief that it was impossible to educate those without vision. A movement then began in western Europe that resulted in the establishment of private, state-supported schools for the blind. Concurrently, experimentation was underway that eventually resulted in the development of the Braille system of reading for the blind.

The United States adopted the same schooling system, which became the practice until shortly after World War II. At that time, the great increase in visually impaired children (largely a result of retinopathy of prematurity [ROP]) resulted in the establishment of public school classes for the visually impaired, which existed first in large metropolitan centers, such as New York and Philadelphia.

These self-contained programs continued to proliferate through the mid-1970s. Some large public school systems were including blind and partially sighted children in regular education programs, but this practice (called “mainstreaming”) did not come into popular acceptance until the passage of the landmark Education of All Handicapped Children Act (PL 94-142) in November 1975. Since, school systems throughout the country have greatly expanded their services to blind and partially sighted students and to those otherwise handicapped children who also have significant visual impairments.

A variety of program options is available to the visually impaired child in the public school setting (8). Full-time classes exist in which the child spends the entire school day in small classes (8 to 12 students) of visually impaired children taught by specially-certified teachers. Resource room programs are those in which the child spends part of the day with a specially trained teacher of the visually impaired who provides individualized instruction, and the remainder of the school day in a regular classroom with nonhandicapped children. Itinerant programs are those in which the child is mainstreamed for the vast majority of his or her education but is seen by a special teacher on a regular schedule for individual instruction. This itinerant vision consultant generally has many students in several schools within a district and travels from school to school serving the children on an as-needed basis. Placement in the traditional state-supported schools (which generally offered residential programs) is usually now reserved for severely multihandicapped, visually impaired children whose needs cannot be met in the public school setting (11).

Parents should be in touch with local school officials several months before their child becomes of school age. During this pre-enrollment period the school obtains from pediatricians, ophthalmologists, and parents the necessary information for making an appropriate placement and planning an appropriate program.

Ophthalmologic information that the school needs to ensure the child's eligibility for services to the visually impaired includes details of visual acuity (both near and distant), diagnosis, prognosis, treatment plan, and any necessary activity restrictions. The physician should *strictly refrain* from making *any* education recommendations whatsoever. The exact nature of the educational placement, whether or not a child is to be taught Braille, and other fundamentally educational decisions, *should remain a matter between school personnel and parents*.

Before enrollment, the school should conduct a thorough individualized psychological assessment of the child. Parents should insist on their right to have this examination conducted by a professional trained in the testing of visually impaired children. Research has repeatedly shown that testing by individuals unfamiliar with the special instruments and techniques used in the evaluation of visually impaired children produces grossly distorted assessment results (12). Psychological instruments specifically designed for blind and severely visually impaired children should be employed when appropriate; the Perkins-Binet intelligence scale for the visually handicapped is in common use, as is the Caillier-Azusa scale for the deaf-blind. In addition, adjustments are made in the time allowed for tasks and in the omission of certain tasks in the Wechsler intelligence scale for children who are highly visual in nature.

Once this information has been collated, the school conducts a Child Study Evaluation Team meeting in which parents should participate. During this meeting a placement is recommended. Subsequently, an individualized educational program (IEP) is drawn up in which specific educational goals and objectives are described for each child. Parents have specific rights with regard to approval of programs and placements, and they should become encouraged to be familiar with these rights and to exercise them when appropriate.

The education of blind and partially sighted children has many common factors, but there are enough differences in subject content for these two facets of the education of the visually impaired to be treated separately in the sections that follow.

EDUCATION OF BLIND CHILDREN

The education of blind children should contain all of the elements essential to the good education of any child. Above and beyond this, the education of blind

children must include certain additional subjects, unique aids and devices, and large measures of individualized instruction.

Educationally, blindness has more to do with the inability to use vision as the major learning channel than it has with the specific visual acuity. Thus, in this section the blind child can be considered as one who is unable to read the printed word with efficiency, rather than one whose vision falls below a certain acuity.

The readiness stage of learning generally encompasses kindergarten and the early months of first grade. During these months, certain essential preliminary skills basic to reading are learned. In the case of the blind child, this readiness phase emphasizes fine motor tasks and the development of tactile sensitivity. When the child is able to recognize small shapes, to differentiate between rough and smooth, and to follow a line of small figures across a page from left to right and to find the next line, he or she is ready to begin to learn the letters of the Braille alphabet.

The Braille system bears no relationship to a raised Arabic alphabet, but, rather, is based on a system using a sixdot “cell.” There are three dots on the left numbered vertically one, two, and three and three dots on the right numbered four, five, and six. All Braille symbols are made from combinations of these dots. Children learn to recognize the letters of the alphabet and the numerals tactually, while their sighted peers are learning to recognize the Arabic symbols visually.

The textbooks used for reading and for other subjects are Braille copies of the textbooks used by sighted elementary grade schoolchildren. Blind students learn to write Braille during their early elementary school years on a small, typewriter-like device called a Braille writer (Fig. 28.1).

Numerous other subjects are added to the curriculum of a blind child. Prime among these is listening. Contrary to popular belief, the blind are not automatically possessed of additional keenness in the other senses. Rather, it is necessary for them to develop greater tactile and auditory acuity. Therefore, listening is taught from the very earliest years as a special subject. Research has demonstrated that if listening is an integral part of blind children's education from early years, it ultimately will become their most efficient means of acquiring information (10). Listening skills run the continuum from simple auditory discrimination of different sounds through the following of complex directions to the use of accelerated or compressed speech in recorded textbooks.

Daily living skills are taught as a special subject. These skills may include dressing (buttoning, buckling, zippering, tying, and so on), eating, personal hygiene, use of the telephone, handling money, and a wide variety of other dayto-day activities. The mastery of all of these skills is essential to full independence as an adult.

Figure 28.1 A Braille writer. Any combination of the six keys is pressed simultaneously to make one Braille letter, number, or symbol.

Orientation and mobility include the entire range of skills necessary for independent travel. Orientation refers to such skills as laterality and directionality. Mobility refers to travel, both with a sighted guide and a white cane. Students first learn to locate familiar objects within the classroom and school and then progress to travel outdoors and on public transportation, even in the heart of a busy city.

Blind students should learn keyboarding as soon as their sighted peer begins to write. No modifications are necessary on a standard computer keyboard. Students learn the touch system in much the same way as do their sighted peers. The teaching of keyboarding skills in the early elementary grades provides an excellent foundation and corollary to computer literacy instruction.

Subjects such as art, physical education, and music should certainly be included in the blind student's curriculum. An entire system of Braille notation is available in music, and adaptations can easily be made in the other subject areas so that the blind student can be included in activities.

Talking calculators, relief maps, three-dimensional models, and a wide variety of other aids and devices may be used to help the blind child to acquire the same concepts and skills as nonhandicapped youngsters.

EDUCATION OF PARTIALLY SIGHTED CHILDREN

For educational purposes, partially sighted children are those who, although visually impaired, can use printed materials as their major reading method.

These youngsters are taught by fundamentally the same methods as are their sighted peers. Large-print materials are used for textbooks. Many of the subjects taught to blind

children are also included (some in a modified form) in the curriculum of the partially sighted. The skills and subjects taught depend to a large degree on the extent of the visual impairment.

Figure 28.2 A visually impaired student using a computer with the standard typewriter keyboard but with the monitor modified appropriately for his visual needs. Closed-circuit TV systems (CCTVs) work the same way.

Vision utilization is often taught on an individual basis. The inclusion of this area is meant to teach the partially sighted child to use residual vision in the most efficient and extensive manner possible. In the very early stages of this skill, DayGlo fluorescent colors and materials may be used to elicit visual attention. In the later stages of development, such skills as visual closure and figure-ground discrimination are taught. Although it is not possible to generate physical improvement in acuity, it has been demonstrated repeatedly that children can be taught to make more efficient use of their residual vision. The extensive course in orientation and mobility given to blind children is generally unnecessary for their partially sighted counterparts; however, children with impaired vision often need some specific instruction in gaining independent travel skills. The same basic rule applies in the area of daily living activities. The intensity and duration of instruction may be less, but some assistance may be necessary in gaining skills.

Developing legible handwriting is often a problem for partially sighted children, who therefore should also have keyboarding included in the curriculum. As for all children, computer skills are an essential component of a good education.

Physical education skills are particularly crucial for partially sighted children, who generally possess the basic ability to achieve physical fitness and develop recreational sports skills. However, a physical education program specifically tailored to the needs of such children is crucial to the ultimate development of these abilities. Emphasis should be placed on individual sports endeavors, such as gymnastics and swimming, rather than on more difficult team sports, such as softball and basketball (13).

A wide variety of magnification aids may also be used to facilitate the education and independence of the partially sighted child. These tools may range from the simple handheld magnifier to the telescope and ultimately to sophisticated closed-circuit television systems that enlarge printed material (Fig. 28.2).

MULTIHANDICAPPED CHILDREN

The problems of visually impaired children who are also handicapped in other ways are intensified beyond measure. Mentally handicapped children are also more handicapped by their visual impairment than are children of normal intelligence. So it is with all other handicaps that these are added to visual impairment.

It is vital when working with multihandicapped children and their families to view the *whole* child. The handicaps must not be viewed separately but dealt with as aspects of the whole child. Early intervention is crucial in working with the multihandicapped, visually impaired child. Speech and language therapy, physical therapy, and other appropriate interventions should be sought at the earliest opportunity. Furthermore, in determining educational placement, differential diagnosis must be made. Placement and programming should certainly address all handicaps, but primary attention should be given to the most significant handicapping conditions, not the most obvious. Undue stress should not be placed on the visual handicap, and developmental delays or other problems should not be attributed solely to this deficit.

THE EXPANDING ROLE OF TECHNOLOGY

The role of technology in the education and daily life of blind and visually impaired individuals cannot be overstated. Recent advances in technology have enabled this population to have access to virtually all print media and

the World Wide Web (Internet) as well as to perform almost all tasks related to school and work performance.

The legal definition of assisted technology is “any item, piece of equipment or product system, whether acquired commercially off the shelf, modified or

customized, that is used to increase, maintain, or improve functional capabilities of individuals with disabilities" (PL 100-407, PL 101-476).

It cannot be stressed too much that a careful evaluation of student needs and abilities (physical and intellectual) is essential prior to the purchase of any assisted technology. The match between student needs and developmental levels and assisted technology is crucial to successful use. An assisted technology evaluation to determine the exact technology that would be most useful for an individual student should be performed by a qualified professional as part of a Learning Media Assessment that also includes a functional visit evaluation. Under *no circumstances* should corporate representatives of any product, no matter how excellent the product itself may be, conduct such evaluations.

In determining which technology best suits an individual student, always consider "low-tech." A simple snowball magnifier may be a better choice for some students than a complex closed-circuit television enlargement system. The following factors should be considered when recommending assisted technology for individual students:

- Age of the student
- Motivation to successfully use technology
- Responsibility for care and use of the technology
- Cognitive ability
- Prerequisite skills necessary (keyboarding, use of function keys, ability to use synthetic speech, knowledge of Braille, ability to follow multiple step direction sequences, ability to memorize at least ten key commands)
- Secondary limitations in fine motor skills
- Viability of the technology for other uses, such as games, social interaction, etc.

In evaluating the technology itself, a number of factors must be included. Among them are:

- How flexible is the hardware/software (e.g., can it be used for more than one purpose and more than one person at a time)?
- Can it be used by sighted and visually impaired individuals interchangeably?
- How does the program hardware handle graphics?
- Does the system lose its flexibility as peripherals/extra pieces are added?
- Can the computer be easily adapted so that a variety of methods can be used for input and output (e.g., Braille, voice, disk, CD-ROM)?
- Does the speech synthesizer work with all hardware and software being used?
- What is the voice quality? Can the voice output be modified to refine the pronunciation of words?
- For word processing programs, is the editing flexible?
- Are repair and upgrade services *readily* available?

In the rapidly expanding world of technology, it is literally impossible to provide a comprehensive and current list of available options. However, the information below provides a basic overview of the technology available to meet the needs of blind and visually impaired students.

LARGE PRINT ACCESS

Screen Magnification Software

ZoomText magnifies text to provide screen enlargement from 2 × to 16 ×. ZoomText Xtra! uses the sound card built into your PC to provide a screen reader with magnification. A Level 3 version is being developed that will add scanning, OCR, form-filling and printing.

InLarge (Macintosh) enlarges the screen or specific areas of the screen from 2 × to 16 ×, with the ability to invert the screen to white on black.

Other screen enlargers: LP WIN, Lunar.

Magnification Systems: Closed-Circuit Televisions (CCTV)

Closed-circuit television is a form of electronic magnification that uses either a handheld, zoom lens camera that is manually scanned over text or a mounted zoom lens camera attached to a viewing table. CCTVs generally enlarge text from 2 × to 16 × the original size with monitors ranging in size from 5 to 21 inches. Most newer versions have automatic focus and allow the user to reverse text to white or black. Other common features are color, split image, and line makers and PC access.

Commonly used models include: Aladdin Genie, ClearView, Spectrum, Rainbow, and ViewPoint. There are several portable, handheld CCTVs available, such as Elite, Magni Cam, Ovac, and Big Picture.

Scanning Systems

Scanning systems come in either stand alone or computer access models. They allow text to be scanned and either spoken or enlarged or both. Scanned files can be saved as computer files where they can be read or converted to Braille. Examples of scanning systems are: Open Book, Kurzweil Reader, Reading Edge, VERA, and Expert Reader.

Speech Access

Talking Word Processors

The simplest form of speech access is a talking word processor. Many come in both Macintosh and PC versions and are appropriate for younger children as well as adults. Programs, such as Intellitalk and Write Out Loud, are good tools for school-age children. They provide features, such as the ability to read each letter, word, sentence or paragraph, as text is entered and have a variety of male and female voices from which to choose.

More sophisticated speech programs often require a separate speech synthesizer in the form of hardware, such as

DECtalk, Keynote Gold, Artic Synthetic Phonix, or DoubleTalk, whereas others provide speech through a separate software application, such as DEC Access 32, Flextalk, Eloquence, or Microsoft SDK. These are primarily available for PC use only.

Screen Readers

Screen readers, such as JAWS (Job Access With Speech), Window Eyes, Winvision 97, and Outspoken for Windows, provide keyboard commands that enable the blind user to independently navigate through the desktop of the computer to select and use program and features. Most screen readers no longer require the use of a hardware synthesizer.

Braille Access

Braille Translation Programs

Braille translation software provides a means by which to convert printed test into speech and Braille. Duzbury, Mega Dots, and NFB Trans are the most widely used of these programs.

Braille Embossers

Braille embossers can be used with any Braille translation program to generate a Braille hard copy of text. They range from smaller personal models to larger professional models. Popular models include: Braille blazer, Juliet, Tomeo, Thiel, and Versa Point.

Braille Displays

Braille displays are also referred to as “refreshable braille.” They can be used to access computers in conjunction with screen readers to navigate the computer desktop and to read and edit computer files. Some commonly used models are Braille Wave, Alva, Braille Window, and Navigator.

Portable Devices

All portable devices mentioned allow the user to create, save, edit files and store data, keep an address book, appointment book, and have calculators.

- Braille 'n Speak, Braille Lite, Braille Wave, and Aria—Braille keyboard, speech output, and optional refreshable Braille
- Type 'n Speak, Keynote Companion—QWERTY keyboards and speech output

CONCLUSION

Of necessity this chapter has emphasized the ways in which visually impaired children are different from their normally sighted peers. However, it should be remembered that such children are more like “normal” youngsters than they are different from them. It is crucial that blind and partially sighted children be treated as *whole* individuals and that their unique talents and abilities be kept more in mind than their disabilities. It is to be hoped that the ophthalmologist can play a key role in seeing that these girls and boys are seen and treated not as visually impaired children but as children who *happen* to be visually impaired.

REFERENCES

1. Federal Regulations PL 94-142. Washington, DC: US Government Printing Office, November 29, 1975.

2. Lambert RM, West M. Psychology of adjustment to blindness. *J Vis Impair Blind*. 1981;75:193-196.

3. Hatlen PH. In support of specialized programs for blind and visually impaired children. *J Vis Impair Blind*. 1987;81:7-10.

4. Eichel VL. Mannerisms of the blind: a review of the literature. *J Vis Impair Blind*. 1978;72:125-130.

5. Cook-Clampert D. The development of self-concepts in blind children. *J Vis Impair Blind*. 1981;75:233-238.

6. Harrell L. *Touch the baby, blind and visually impaired children as patients*. New York: American Foundation for the Blind, 1984.

7. Sacks SZ, Corn AL. Students with visual impairments: do they understand their disability? *J Vis Impair Blind*. 1996;90:412-422.

8. Daugherty KM, Moran ME. Neuropsychological learning and developmental characteristics of the low vision child. *J Vis Impair Blind*. 1982;76:398-406.

9. Cratty J. *Body image of the blind*. New York: American Foundation for the Blind, 1968.

10. Parsons S. Function of play in low-vision children. *J Vis Impair Blind*. 1986;80:777-782.

11. McIntire JC. The future role of residential schools for the blind. *J Vis Impair Blind*. 1985;79:161-163.

12. Lukoff IF. *Attitudes toward blindness*. New York: American Foundation for the Blind, 1976.

13. Short FX, Winnick JP. The influence of visual impairment on physical fitness. *J Vis Impair Blind*. 1986;80:729-732.

Supplemental Resources

Alliance for Technology Access
2175 East Francisco Blvd, Suite L.
San Rafael, CA 94901
(800) 266-5592
http://www.ataccess.org

American Foundation for the Blind
15 W. 16th Street
New York, NY 10011
(212) 620-2000

American Printing House for the Blind
P.O. Box 6085
Louisville, KY 40206-0085
(800) 223-1839 FAX: (502) 899-2274
http://www.aph.org E-mail: info@aph.org

Ann Morris Enterprises, Inc.
890 Fams Court
East Meadow, NY 11554-5101
(800) 454-3175 FAX: (516) 292-2522
http://www.annmorris.com

Blind Related Links (http://seidata.com/~marriage/rblind.htmlQadaptech) (another list of links to blindness related information)

Council for Exceptional Children
1920 Association Drive
Reston, VA 22091
(703) 720-3660

Independent Living Aids, Inc.
27 East Mall
Plainview, NY 11803
(800) 537-2118 FAX: (516) 752-3135
http://www.independentliving.com E-mail: indlivaids@aol.com

Library of Congress Division for the Blind and Physically Handicapped
1291 Taylor Street
NW Washington, DC 20213
The Lighthouse, Inc.
111 East 59th Street
New York, NY 10022-1202
(800) 829-0500 FAX: (718) 786-5620
http:www.lighthouse.org

The Low Vision Gateway (http://www.lowvision.org) (includes low vision aids, books, educational resources, Braille information, and much more)

LS&S Group, Inc.
P.O. Box 673
Northbrook, IL 60065
(800) 468-4789 FAX: (847) 498-1482
http://www.lssgroup.com E-mail: LSSGRP@aol.com

Maxi Aids & Appliances for Independent Living
42 Executive Blvd
P.O. Box 3209
Farmingdale, NY 11735
(800) 522-6294 FAX: (516) 752-0689
http://www.maxiaids.com E-mail: sales@maxiaids.com

National Association for Parents of the Visually Impaired
P.O. Box 317
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(608) 452-0606

Resources for Parents and Teachers of Blind Kids (http://home.earthlink.net/~deedaze) (an incredible site, overflowing with useful information)

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Medicolegal Issues in Pediatric Ophthalmology

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This chapter will consider the legal implications of several common situations pertinent not only to ophthalmology, but to all areas of medicine. Included are: informed consent, medical malpractice, liability in the consultation setting, and medical records. The discussion is based on review of legal opinions and commentary and on the author's personal experience as a reviewer and expert in medical malpractice cases. Several informative writings that have appeared in the *New York Law Journal* and the *Journal of Legal Medicine,* as well as representative selections from a vast amount of material available on the LexisNexis database, have been consulted. This report is an overview and may not be applicable in every situation. It is not intended to be specific advice on any private legal matter.

INFORMED CONSENT

Battery

The development of the informed consent doctrine begins with consideration of battery, one of the oldest forms of disfavored conduct. It consists of unpermitted, unprivileged, intentional contact with another person. The contact need not result in bodily harm; the intended contact itself is the harm.

In the medical context, it is legally well established that everyone of sufficient age and soundness of mind has the right to decide what is to be done to his or her body, even when survival is implicated (1). Treatment with no consent at all, actual or implied (2), treatment substantially different from that to which the patient consented (3,4), or unauthorized substitution of one treater for another (5) come within the definition of battery, especially when invasive procedures are involved. That an unpermitted medical treatment may be lifesaving or curative, except in situations in which consent would be implied (discussed in following text), is not a defense to battery. The following actual case (6) is illustrative:

> A physician determined that a patient required surgery on the right ear. The patient gave informed consent to the procedure. With the patient under general anesthesia, the surgeon operated on the left ear, which at the subsequent trial he said required the same treatment. Although the operation was performed properly, there were complications resulting in harm. The patient took an easier route than proving negligence by obtaining a verdict of battery, despite the surgeon's best intentions.

In this case, consent did not extend to surgery on the other ear, despite the similarity in indications. Had life or hearing been immediately threatened, the result might have been otherwise. A point of practical significance is that as an intentional tort, battery is not within the scope of the physician's malpractice liability coverage, and there is the possibility of punitive damages.

Although any consent effectively precludes a claim of battery, the concepts of autonomy and the right of choice are now legally recognized to require more (7,8,9,10).

Informed Consent

The consent process flows naturally from the “partnership” between physician and patient; however, when this does not occur, serious legal consequences may result.

A claim of lack of informed consent usually accompanies an allegation of medical malpractice for wrongful diagnosis or treatment (discussed later). It is a claim that can win for a plaintiff even when evidence of malpractice is weak. Lack of informed consent differs importantly from malpractice in not requiring that the treatment be a departure from the standard of care. The elements of the claim are that the health care provider did not disclose the risks and benefits of the proposed treatment and of alternative treatments; that with full information, a reasonable person in the patient's position would have declined the treatment; and that the treatment *even when appropriate and carried out skillfully,* was a substantial factor causing the patient's injuries (11). That the physician acted entirely in good faith is not a defense. Expert testimony is usually required to establish what the patient should have been told, but jurisdictions are divided on whether it is required as to what the patient would have decided, if properly informed (12).

Malpractice addresses the patient's interest in competent care, while lack of informed consent implicates the interest in self-determination (9). In contrast to the Canadian position that consent requires only broad discussion (13), at least some American courts have held that this would be a nullity, that is, there is either informed consent for treatment or no consent at all, and therefore battery (14,15). However, almost all courts scrutinize the adequacy of informed consent under principles of negligence.

Disclosure

Adequacy of disclosure is assessed by one of two standards, depending on the jurisdiction. Whether either one is breached is a question for the jury. One refers to what a reasonable physician would consider important to the patient's decision (the “reasonable practitioner” standard) (16). The other is whether the physician has disclosed what a reasonable person in the patient's position would want to know to make a considered decision (the “prudent patient” standard) (14,17).

Ideally, these should coincide, but in practice they are differing legal concepts. The reasonable practitioner standard tends to ignore the concept of patient autonomy to decide what is acceptable, regardless of the type and likelihood of the risks involved. Some British courts have held that this does not include the right to any disclosure of an alternative treatment considered by the patient's own doctor to be contraindicated (18,19). Although the law has progressed from this type of paternalism, it remains as the standard in about half of the states.

The reasonable patient standard emphasizes the patient's right of choice and is more within the knowledge and experience of the average juror deciding informed consent claims. However, it has been criticized as focusing on the mind of a hypothetical “reasonable patient” and not focusing on the particular plaintiff (7,14). Again, an actual case (20) is instructive:

> A young woman agreed to surgery for her injured knee. In preparation for the procedure, the surgeon referred her for an arthrogram

(arthroscopy was not yet in vogue) to a radiologist, who included among the disclosed risks the possibility of an adverse inflammatory reaction to the injected contrast medium. This occurred and was incorrectly diagnosed as a joint infection by another orthopedic surgeon. Continuous infusion of antibiotics into the patient's knee for the supposed joint infection led to that very outcome.

At trial, the radiologist could not produce the patient's signed consent for the arthrogram, but his sworn testimony as to his invariable custom and practice of holding a thorough informed consent conversation persuaded the jury that he had indeed carried out this process. The first orthopedic surgeon, who was not responsible for performance of the arthrogram or for holding the informed consent dialogue for this procedure with the patient, and whose diagnosis and proposed treatment were entirely within the standard of care, was found by the jury on the basis of the patient's testimony to have omitted informing her that, with or without the risks of the arthrogram, intensive physical therapy without surgery was a treatment option, and that she would have elected it.

There are important lessons in this case. First, the radiologist could have been defended much more easily had his consent form been available. He won because he could convincingly describe a thorough conversation outlining the risks, benefits, and the limited alternatives to achieve visualization of the interior of the joint. Second, each participant in a treatment must describe his or her own aspect of it, but not that of any other participant. Discussing the pros and cons of the proposed surgery were not part of the radiologist's obligation. Likewise, the orthopedic surgeon was not required to make disclosure about the arthrogram. The jury found him liable for not presenting an alternative to the operation that the patient testified she would have elected.

Must all risks be disclosed? The law requires disclosure only of *material,* not trivial, risks that are reasonably foreseeable (14). “One in a million” occurrences, risks obvious to a lay person and those that clearly would not result in refusal of treatment had they been disclosed constitute other exceptions. As in malpractice, these situations turn on their particular fact contexts.

There is also an allowance for risks whose disclosure, in the physician's best judgment, would be emotionally harmful. Since assertion of this defense is clearly self-serving and not accepted by all courts, it is best avoided.

Some courts (21,22) and commentators (23) have considered the degree of the physician's experience with a treatment to be a material risk factor requiring disclosure, but other courts have stated that information regarding the skill and experience of a doctor is not relevant to understanding the risks of the treatment itself (15). Other potential concerns that have led to similar debate involve personal medical

(24) and financial interest (25) factors that could affect the treating physician's skill and judgment.

A proper, informed consent dialogue requires that the patient receive the information in ordinary terms and in his or her customary language, translated, if necessary. There must be the opportunity to decide free of duress, although this does not prevent the physician from offering a recommendation based on expertise and judgment. Disclosure should always include the possibility of no treatment at all and the anticipated consequences of that course.

Documentation

Commentators (26) have been critical of the informed consent process as concentrating more on avoidance of physician liability than on truly educating patients so that they might make self-determined medical decisions. They point to the consent form for support of this proposition, suggesting that it converts what was intended as a process of dialogue and discussion into a one-shot paper signing, as though decision making were a discrete event in time rather than a series of interactions as more information becomes available. Studies (27) have shown that this latter model of informed consent, by giving the patient a greater sense of control, encourages compliance with treatment. To date this view has not prevailed either in customary medical encounters or in the courts.

Minors and Incapacitated Persons

For both adults and minors requiring emergency life- or function-preserving treatment, the law implies full consent, except where it is clear from prior information that this has affirmatively been refused. This exception also applies to the extension of a planned surgical procedure on an anesthetized patient because of circumstances becoming evident only during the course of the operation.

In our practices, sometimes we are confronted with an unaccompanied minor presenting for routine examination. Even without invasive treatment, the examination represents “contact” for which the physician has no permission, especially for the use of cycloplegic drugs.

Parents or a legal guardian are responsible for health care decisions for an underage child. Many states allow adolescents to consent for purposes such as obtaining contraceptive devices, prenatal care, or screening and treatment for sexually transmitted diseases. Minors who are married, pregnant, parents, self-supporting, or a member of the military (so-called emancipated minors) are generally fully able to give consent in all health matters.

Unless the child fits into one of these categories, the best course in this situation would be to require written authority or consent by telephone. The latter requires a good faith belief that the appropriate person at the remote location has been contacted. In urgent, but not emergency situations, relatives or an adult sibling are deemed to have this authority without formal delegation.

Persons whose ability to understand and choose appropriately is questionable, unless already under judicially decreed guardianship, may require psychiatric consultation (28).

Informed Consent for Research Subjects

Courts have evolved from the strong presumption that all nontraditional practices are outside the standard of care (29,30) to a recognition that investigation requires a different analysis (31). Initially, clinical research was largely unregulated, and ethical matters—such as consent and safety monitoring—remained in the hands of the investigators. In the 1970s, certain research abuses led to congressional action to protect human subjects (32,33). The resulting regulations meticulously spell out the informed consent requirements and provide that they be monitored by local institutional review boards (33).

In addition, there is an in-between category of “innovative therapy,” a single or limited number of unproven interventions, such as an off-label use of a drug, intended to solve an immediate clinical problem in an individual patient when the usual treatment options have not been effective or appropriate (10,34). Penalization for the treatment of amblyopia, now well accepted, was at one time such an innovation. Without prior formal study of safety and efficacy, these nonvalidated practices also expose patients to greater risk, and it has been urged, but not required, that their use should be within the framework of a research protocol.

The principal difference between treatment in the clinical and research settings is the difference in objectives. The informed consent process must recognize that such studies are done to develop new knowledge, which only later may be valuable to a broader population of patients (10,35). The purpose of the trial is not to make the individual subject well, although this may occur fortuitously.

The investigator's first loyalty is to the protocol, not to the patient (10). Subjects may have to forego all treatment or an adjustment in dosage, or may experience unexpected and unpleasant side effects. It is entirely possible that the subject will not be told of treatment alternatives outside the experimental protocol that could be elected by declining to participate (10,35,36). If the patient enrolls solely because of hoped-for benefits, any informed consent process has failed.

Recently, there has been a trend toward lawsuits for harm to research subjects (37), including an action for enrolling premature infants into a high oxygen study without parental knowledge and consent (38). Courts formerly analyzed informed consent mostly under the standard for conventional treatment but now claim to recognize, although not consistently, that loss of the right to personal dignity is a separate and unique wrong to which traditional malpractice and informed consent principles do not fully apply (8,39).

The main informed consent safeguards are that the patient know that he or she is an experimental subject and possibly a control (40), that the effects of the treatment are not entirely known, and that withdrawal from the study is permissible. Other items to include are the names of those individuals responsible for

subject protection, whether there is a Data and Safety Monitoring Board and that the study will be discontinued if the treatment convincingly shows an adverse effect, and a statement of the subject's rights and that they may not be waived, and the study's

privacy policy. Some authors (41) have stated that for informed consent to be complete, discussion of risks should include remotely suspected as well as known risks, because in this special context it is the patient, not the investigator, who determines which risks are material to the decision to participate. Informed consent authority for minors and adolescents follow similar rules to those applicable to the usual clinical situation.

To summarize, informed consent should be thought of as a process, not as a paper. The document is helpful to memorialize what should have occurred before the patient's signature is obtained. The process should be appropriate whether the setting is one of conventional clinical practice or of an investigative study, and requires disclosure of information and its implications to a person with capacity who understands what is disclosed and voluntarily makes a decision. This is sound both legally and ethically.

MEDICAL MALPRACTICE

The term “malpractice” describes professional negligence. “Medical” in most jurisdictions refers not only to the conduct of physicians, but to other health care disciplines as well, such as dentistry and podiatry.

The elements of negligence are the existence of a duty, breach of that duty, harm directly and proximately (i.e., no intervening cause) resulting from the breach, and damages caused by the harm to be compensated by a financial award. The duty is to conform to the standard of care in diagnosis and treatment. The injured plaintiff must prove the first three elements through the testimony of expert witnesses from the discipline in question. Damages can be directly shown as to past items and expertly forecast into the future.

Malpractice is not the same as harm from acceptable care done skillfully. It is well known that reasonable errors in judgment can occur in diagnosis when signs and symptoms may be sufficiently indicative of more than one disorder or when one treatment chosen from several that are acceptable is ineffective or gives an adverse result. Such occurrences more usually involve issues of informed consent, discussed elsewhere in this chapter.

Standard of Care

Cases in all jurisdictions have defined the standard in the following general way: “The doctor must possess a reasonable degree of knowledge and ability expected of the average doctor, under the same or similar circumstances in the community where he or she practices” (42).

Expert testimony is required to acquaint a jury with the appropriate standard of care. Note that this definition refers to the “average” doctor, not to the most learned and skillful. The standard is that which existed on the date of the alleged occurrence, not as modified by later discoveries or improved technology. The physician's “community” formerly meant his or her immediate professional environment, but at present is greatly enlarged due to the ease of intercommunication of medical knowledge.

A distinction is made between the standard for the comprehensive ophthalmologist and that for the subspecialist. If the physician attempts to practice beyond the limits of his or her customary involvement, the standard of the entered discipline will prevail.

Breach

Rarely, a physician holding a valid license to practice will be found to not possess the necessary knowledge and skill. Malpractice claims are usually based on a physician's failure to employ the conceded skills. Incorrect diagnosis based on an inadequate examination, failure to order the appropriate ancillary studies (laboratory tests, imaging, etc.) or to request an indicated consultation, or poorly chosen treatment are typical allegations. Here, too, expert testimony is required to establish a breach. Where more than one treatment is acceptable, there is no obligation that it should be the preference of the majority of the discipline or of the testifying expert.

Abandonment of the patient by the doctor during a course of care is another type of breach, which is typically highly disfavored by juries. A physician-patient relationship can be terminated by the physician for any reason or no reason, provided it is done with adequate notice and an offer to refer the patient's record to a succeeding physician. Abandonment applies only when the patient is under an active course of care, which does not include merely a series of checkup visits. A child on an occlusion program for amblyopia, and whose vision is periodically checked and the regimen adjusted, is probably under active treatment, whereas a child undergoing interval vision checks once occlusion is discontinued is probably not. Similarly, the child with juvenile rheumatoid arthritis (JRA) and uveitis, and whose status is periodically evaluated and given therapy when indicated, can be considered under treatment, but, perhaps, not the child known to have JRA and no uveitis. There is no “bright line” for these determinations. They are fact-specific and subject to a jury's assessment.

Failure to deal properly with noncompliance and “no show” patients can lead to a claim of abandonment. There should be documentation of such instances and attempts, preferably repeated, to address the situation. Abandonment will not be construed when the withdrawal is instigated by the patient or by mutual consent.

Many states recognize a “best judgment” rule in determining the standard of care. The following case illustrates this concept:

> A premature infant received supplementary oxygen at a rate of 6 liters per minute and ordered by the neonatologist to be reduced to 4 liters per minute after 12 hours, because the doctor was aware of the potentiality of retinopathy of prematurity at the higher level. The flow was not reduced as ordered, and the infant became blind. The neonatologist was found to have malpracticed for failure to assure that the order was carried out, even though 6 liters per minute were within the general standard at the time of the occurrence (43).

Under the “best judgment” rule, there is an individual standard to which a doctor is expected to conform when

personal knowledge and experience dictate rejection of that of the general discipline.

Harm

Breach of the standard of care must be proven, again by expert testimony, to have caused harm other than an outcome that was reasonably foreseeable even with acceptable care, and which would not have occurred, except for the offending conduct as the direct (proximate) cause or as a substantial contributing factor. In addition, some states recognize a “lost chance doctrine,” under which a patient with a disorder having a poor chance for a successful outcome in any event, can overcome the proximate cause hurdle by attempting to prove that the physician's negligence diminished even further the opportunity for a good result (44).

Damages

Harm caused by malpractice is compensated by an award of money for such items as medical and related expenses, lost wages, and so forth. Intangible damages (“pain and suffering”), the subject of much controversy, cannot be precisely estimated. They are left to jury determination and can be adjusted (higher or lower) by the court when judged to be unreasonable.

The amount of damages will be reduced by the percentage of fault attributable to the patient's own conduct. This is known as “comparative negligence.” Formerly and still retained in a few jurisdictions, *any* degree of culpable plaintiff conduct could entirely eliminate an award of damages.

Promises

Although not the same as malpractice, plaintiffs occasionally sue successfully for an unfulfilled promise of cure or of a specific result. The physician should studiously avoid expressed promises and any discussion that could be so construed. Promises relied upon by the patient in accepting treatment can be viewed as making a contract, breach of which giving rise to damages. The strategic advantages of such a suit include the lack of necessity for expert testimony and a longer statute of limitations than for malpractice. Expressing confidence in an outcome based on reliable evidence (“therapeutic assurance”) that falls short of a promise is the safer course.

LIABILITY OF THE CONSULTANT

Consultation occurs with great frequency in the practice of pediatric ophthalmology. The pediatric ophthalmologist is called upon by the pediatrician or family physician for diagnosis and treatment of ocular conditions beyond their expertise. When faced with a problem involving endocrine disturbances, neurological, or complicated reconstruction, among others, the pediatric ophthalmologist is obliged to request comparable assistance.

The possibility of liability for malpractice arises when the physician breaches a duty of competent care of the patient, and the patient is harmed as a direct result of the breach. Before this duty can be breached, there must be a determination that it existed in the first place. For this reason, referral and consultation should be distinguished, because they have different legal implications. The key determination is the intention of the various parties.

In a consultation, one physician requests an evaluation by another with the intention of obtaining suggestions for diagnosis or therapy for a patient who, by common intention and until indicated otherwise, will continue under the first doctor's care. Some courts have said that even though the consultant examines the patient, discusses the findings, and charges a fee, these do not establish a physician-patient relationship between consultant and patient. Other courts have held that the relationship does exist, but these cases usually concern hospital-based activities, such as pathology (45) and imaging interpretation (46)—where, although the physician in these activities may not have had direct contact with the patient, it was understood by all concerned that the service was necessary and for the patient's benefit (47,48). Reliance on such an opinion on the part of the attending physician is an important factor in the determination (48).

In contrast, when one physician refers the patient to another not for advice only, but for diagnosis and continuing care by the second doctor, a succeeding physician-patient relationship comes into being. Although often imprecisely called a consultation, this is more accurately characterized as a referral, because it is intended to transfer responsibility for care. This is the more common mechanism of patient acquisition by the pediatric ophthalmologist.

There are other scenarios that establish neither status. One doctor asking for another doctor's advice about a case not personally familiar to the latter and occurring on the golf course, at the scrub sink, in the hospital cafeteria, or collectively at grand rounds (49) or in a panel discussion, does not easily fit within the concept of physician-patient relationship, particularly because it is beyond any contemplated intention on the part of the patient. On the other hand, when the patient seeks a “second opinion” on his or her own initiative, clearly, there is intent to create a relationship.

There are other special situations in which the law will imply the necessary relationship. When a patient requiring urgent care comes to a hospital emergency department or a hospitalized patient requires consultation services, perhaps, leading to a referral as described previously, the law of many states holds that the patient can rely on his or her being provided for by the physician officially designated to do so, if there is communication about the patient to that physician. This will be determined by an official oncall schedule, if one is maintained, or by a rotation system agreed to or otherwise understood between the hospital and its associated community of ophthalmologists. It is widely held to be a departure from the standard of care for the designated physician not to personally attend a patient where findings communicated to him or her would call for such personal effort (50). Serving as a supervisor of

physicians in training creates a comparable obligation (51). Some degree of meaningful input into the patient's management is necessary (52,53). Harm resulting from the failure to personally attend the patient is actionable as malpractice.

What is the obligation of the requesting physician? A referral contemplates ongoing care by the succeeding ophthalmologist, and, if this occurs, the relationship of the referring doctor and the patient is severed. In a consultation, the original ophthalmologist continues in attendance. What is the required response to the consultant's advice by the requesting doctor?

The advice may be accepted, preferably with documentation indicating that it is reasonable to do so upon careful consideration of all circumstances. However, rejecting the advice is also permissible, provided there is documented evidence that the consultant's recommendations were at least considered, and, preferably, adding the reasons why they were not followed.

THE MEDICAL RECORD

Appropriate medical care includes the creation and maintenance of adequate records. These are necessary for one's own guidance rather than reliance on memory, and for the information of succeeding physicians. Proper records can be extremely helpful as evidence of acceptable care in the event of a malpractice claim.

Ownership

Medical records are normally retained in the custody of the physician or hospital, but this, by itself, does not determine ownership. The general legal interpretation, supporting enacted statutes, is that the doctor owns the physical record document and the patient is the owner of the information it contains.

Content

A well-composed medical record should contain the patient's complaints, the examination findings, a working diagnosis and plan—revisable, if necessary—and at least a partial differential diagnosis. Laboratory and imaging results (although the images may be stored separately), consultation reports, and similar items should also be included, as well as follow-up studies, notation of missed appointments and of attempts to reschedule, description of other forms of noncompliance, such as failure to follow the treatment regimen, and records of telephone conversations. It is preferable to keep financial notations out of the medical record, because these are not relevant to most purposes for which other individuals might scrutinize such potentially sensitive information.

Format

There is no standard arrangement for the medical record. Each doctor is free to employ any layout that facilitates his or her own personal system for rapid and efficient review of the data.

Preprinted record forms have the advantage of providing prompts for the acquisition and entry of information. A potential disadvantage is that an unfilled space, even if superfluous to the examination on a given occasion, can be displayed in front of a jury as an instance of alleged carelessness.

Alterations

In a litigation context, alterations to a medical record present the problem of physician credibility, particularly when the changes serve to exculpate the physician. It is critically important that changes not be made after the filing of a lawsuit, because this will be exploited in front of a jury. Handwriting experts employ sophisticated methods to identify the maker and timing of alterations in a written record, and recovery of deleted data from a computer is technologically possible.

Alterations of the record under circumstances that clearly do not suggest an intention to conceal damaging information is both medically sound and legally permissible. Initially, unrecorded examination findings or revision of one's initial diagnosis and treatment plan, on the basis of post-visit reflection outside of the

hurried conditions of a working session, are indicated in the interest of good medicine.

The appropriate method to change a written record is to delete material by drawing a line through it, such that the deleted material remains ascertainable. Deletion by erasure or painting over should be avoided. The desired change or any new material should be placed directly above the deletion, if there is space, or nearby with marks to indicate the place of insertion. As an alternative, a narrative entry in the next available place in the record, which refers back to the material being altered and describes the change, is appropriate. This is the only proper way to correct a computerized record without suppressing the removed information. With either method, the date and time of the new entries should be indicated.

REFERENCES

1. *Schloendorff v. Society of New York Hospital,* 105 N.E. 92 (N.Y. 1914).

2. *Mink v. University of Chicago,* 460 F. Supp. 713 (N.D. Ill. 1978).

3. *Cobbs v. Grant,* 502 P.2d 1 (Cal.1972).

4. *Gaskin v. Goldwasser,* 520 N.E.2d 1085 (Ill. App. Ct. 1988).

5. *Tom v. Lenox Hill Hosp.,* 627 N.Y.S.2d 874 (N.Y. App. Div. 1995).

6. *Mohr v. Williams,* 104 N.W. 12 (Minn. 1905).

7. Grant H. Morris, *Dissing Disclosure: Just What the Doctor Ordered,* 44 Ariz. L. Rev. 313-371 (2002).

8. *Lugenbuhl v. Dowling,* 701 So.2d 447 (La. 1997).

9. Roger L. Jansson, *Researcher Liability for Negligence in Human Subject Research: Informed Consent and Researcher Malpractice Actions,* 78 Wash. L. Rev. 229-263 (2003).

10. E. Haavi Morreim, *Medical Research Litigation and Malpractice Tort Doctrines: Courts on a Learning Curve,* 4 Hous. J. Health L. & Policy 1-86 (2003).

11. Thomas A. Moore, *Informed Consent, part 2,* N.Y.L.J., Oct. 3, 1995, at 3, col. 3.

12. Thomas A Moore, *Update on Informed Consent,* N.Y.L.J., June 5, 2001, at 7, col. 1.

13. *Marion's Case,* 175 C.L.R. 218 (1992).

14. *Canterbury v. Spence,* 464 F.2d 712 (D.C. Cir. 1972).

15. *Duttry v. Patterson,* 771 A.2d 1255 (Pa. 2001).

16. *Natanson v. Kline,* 350 P.2d 1093 (Kan. 1960).

17. *Cooper v. Roberts,* 286 A.2d 647 (Pa. Sup. Ct. 1971).

18. *In re W,* 3 W.L.R. 758 (1992).

19. *In re J,* 3 W.L.R. 507 (1992).

20. *Shkolnick v. Hosp. for Joint Diseases,* 211 A.D.2d 347 (1995).

21. *John v. Kokemoor,* 545 N.W.2d 495 (Wisc. 1996).

22. *Barriocanal v. Gibbs,* 697 A.2d 1169 (Del. 1997).

23. Emmanuel O. Iheukwumere, *Doctor, Are You Experienced? The Relevance of Disclosure of Physician Experience to a Valid Informed Consent,* 18 J. Contemp. Health L. & Policy 373-419 (2002).

24. *Faya v. Almaraz,* 620 A.2d 327 (Md. 1993).

25. *Moore v. Regents of Univ. of California,* 793 P.2d 479 (Cal. 1990).

26. Victor Ali, *Consent Forms as Part of the Informed Consent Process: Moving Away from "Medical Miranda",* 54 Hastings L. J. 1575-1591 (2003).

27. Greenfield S, Kaplan S, Ware JE Jr: Expanding patient involvement in care: effect on patient outcomes. *Ann Int Med* 1985;102: 520-528.

28. *Lynn v. Hugo,* 272 A.D.2d 38 (N.Y. 2000).

29. *Jackson v. Burnham,* 39 P. 577 (Colo. 1895).

30. *Owens v. McCleary,* 313 Mo. 213 (1926).

31. *Fortner v. Koch,* 261 N.W.2d 762 (1935).

32. *National Research Act of 1974, Pub. L. No. 93-348, 88 Stat. 342 (1974).*

33. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research,* U.S. Dep't of Health, Educ. & Welfare, Pub. L. No. (OS) 78-042 (1978).

34. Dale H. Cowan, *Innovative Therapy v. Experimentation,* 21 Tort & Ins. L. J. 619-633 (1986).

35. Karine Morin, The standard of disclosure in human subject experimentation. *J Leg Med* 1998;19:157-221.

36. Robert J. Levine, *Uncertainty in Clinical Research,* 16 Law, Med. & Health Care 174-182 (1988).

37. *Grimes v. Kennedy Krieger Institute,* 782 A.2d 832 (Md. 2001)

38. *Burton v. Brooklyn Doctors Hospital,* 88 A.2d 217 (N.Y. App. Div. 1982).

39. *Kus v. Sherman Hosp.,* 644 N.E.2d 1214 (Ill. App. Ct. 1995).

40. *Salgo v. Leland Stanford Jr. Univ. Board of Trustees,* 317 P.2d 170 (Cal. Ct. App. 1957).

41. Beecher H. Ethics and clinical research. *N Eng J Med* 1966;274: 1354-1360.

42. Pike v. Honsinger, 55 N.Y. 201 (1898).

43. *Toth v. Community Hosp.,* 22 N.Y.2d 973(1968).

44. *Herskovits v. Group Health,* 664 P.2d 609 (Wash. 1983).

45. *Walters v. Rinker,* 520 N.E.2d 468 (Ind. Ct. App. 1988).

46. *Dougherty v. Gifford,* 826 S.W.2d 668 (Tex. App. 1992).

47. *Phillips v. Good Samaritan Hosp.,* 416 N.E.2d 646 (Ohio Ct. App. 1979).

48. *Bovara v. St. Francis Hosp.,* 700 N.E.2d 143 (Ill. App. Ct. 1998).

49. *Sawh v. Schoen,* 215 A.D.2d 291(N.Y. 1995).

50. *Thomas v. Corso, 265 Md. 84* (1972).

51. *Moeller v. Hauser,* 237 Minn. 368 (1952).

52. *McKinney v. Schlatter,* 692 N.E.2d 1045 (Ohio 1997).

53. *Oja v. Kin,* 581 N.W.2d 739 (Mich. 1998).

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30

The Evolution of Strabismus Surgery

Norman B. Medow

There is pictorial evidence of strabismus dating as far back as 2nd century BC, in both Egypt and in China (1). Whether these reported observations are artistic flaws or actual strabismus is unclear. No written evidence from this period remains.

Susruta, the 2nd century Hindu physician whose works were translated into English between 1914 and 1917, made no mention of strabismus in his extensive writings. Both the Edwin Smith Papyrus (2) (circa 1500 BC) (Fig. 30.1) and the Ebers Papyrus mention strabismus. The Romans, Celsus (25 BC-50 AD) as well as Galen (131 AD-210 AD), both commented on strabismus. Although Galen was born in Greece, he and Celsus had large practices in Rome. Galen described both acquired (presumably paralytic) and congenital (i.e., nonparalytic) strabismus (3). Heredity as a cause of strabismus was recognized early. Hippocrates (460 BC-370 BC) commented on it as well as did others. Earlier theories revolved around evil spirits and the idea that a mother may have ingested something that caused the strabismus. Spells and witches' curses were also invoked as causal. One theory was a belief that a muscle cramp occurred after prolonged staring at an object or at light, leading to the deviation (4).

The earliest treatments for strabismus included the use of purges and potions, which, coupled with prayer and incantations, would hopefully remove the evil humors or spirits that were causing the deviation. The Ebers Papyrus suggested that equal parts of turtle brains and spices would cure the strabismus (2).

Strabismus masks were first reported to have been used by Paul of Aegina (5) (625-690). No diagram or report of his masks remains. One of his other ideas was to attach purple flocks of material to the lateral canthus of a patient whose eyes turned outward, for example, so that the eye could then be forced to look and fixate at the wool swatches, thereby correcting the deviation. This innovative technique puts Paul of Aegina in the forefront of being considered the *father of orthoptics.*

In 1540 Ambroise Pare (6) (Fig. 30.2) resurrected the earlier use of masks and described a mask that covered the hemi-face from the forehead to just below the nose and had apertures for the eyes. Looking through these apertures would force the eyes to straighten. The mask was held in place by four ribbons that were tied behind the head.

George Bartisch (7) (1535-1606), in his famous book *Ophthalmodouleia* (1583), described full-face masks that were slipped over the head, similar to the balaclava ski mask with eye openings set in either a convergent or divergent fashion—convergent for use with exotropia or divergent for use with esotropia. History reports that these and a variety of later masks provided little help for the strabismus patient. This form of therapy still persists today. Today it is found in the use of spectacles that have binasal or bitemporal occlusion in an attempt for vision training advocates to improve esotropia or exotropia. Its effective use is similarly questionable.

The causes of strabismus occupied many for more than 200 years. Irregularities of the cornea, lens, and retina were all invoked as causes for strabismus.

Amblyopia, as a term, was first used in the late 1700s. Georges-Louis Leclerc, Comte de Buffon (4) (1707-1788), described, in 1748, that most often only one eye deviates at a time while the other eye fixates on the object of regard. This concept was new at the time, but today is quite clear and acceptable. He felt that strabismus was caused by unequal power of the eyes, the less powerful eye being the one that deviates. He recommended that the stronger eye be occluded in an effort to strengthen and straighten the deviating eye. Buffon's work was used throughout Europe, in both France and England. Erasmus Darwin (8) (1731-1802), Charles Darwin's grandfather, believed that the better eye should be covered for most of the day. Like Buffon, his success was limited. His failure was due, in part, to undetected refractive errors, which may have been present and, not corrected, led to the unsuccessful occlusion methods used at the time.

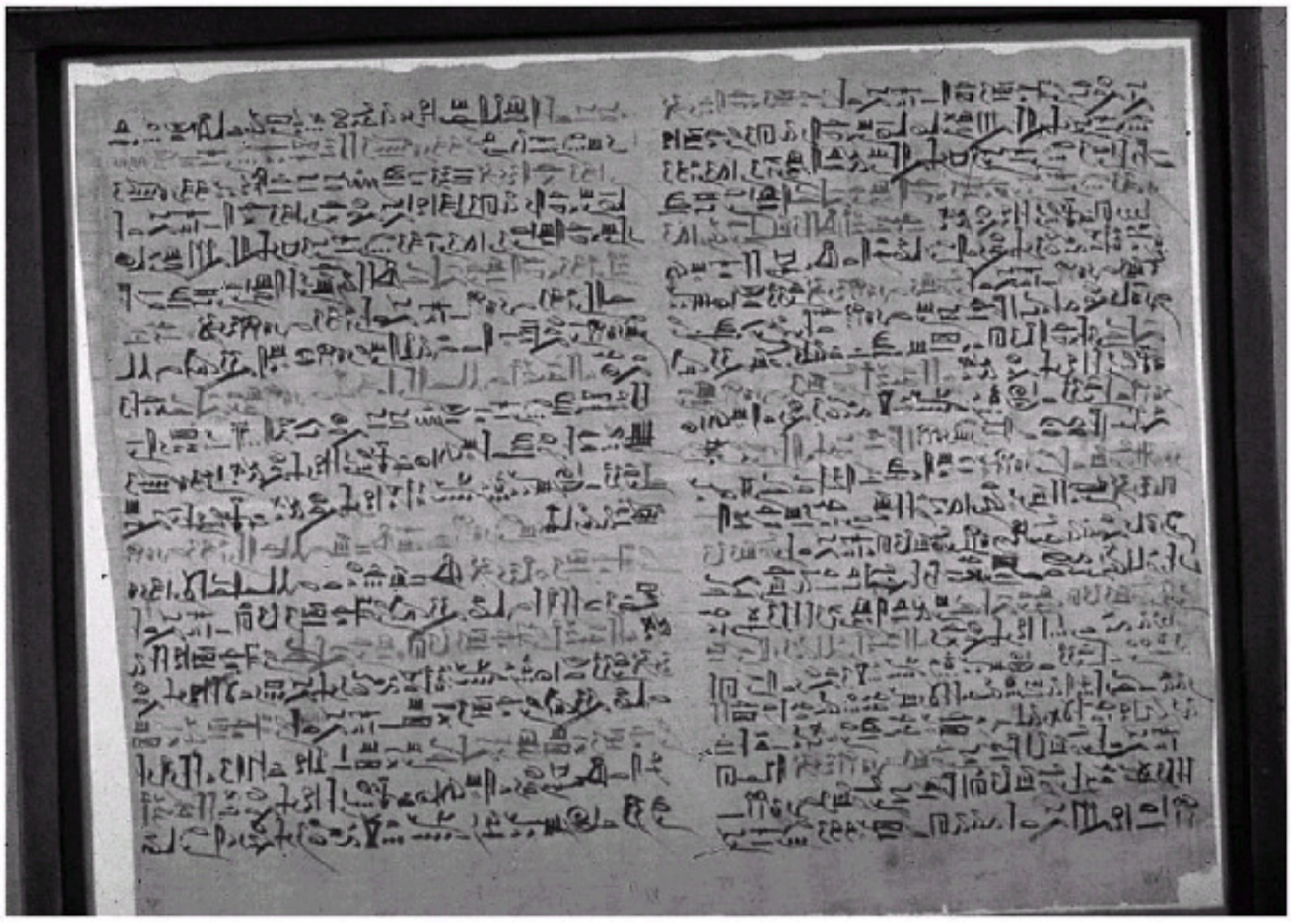


Figure 30.1 Edwin Smith Papyrus.

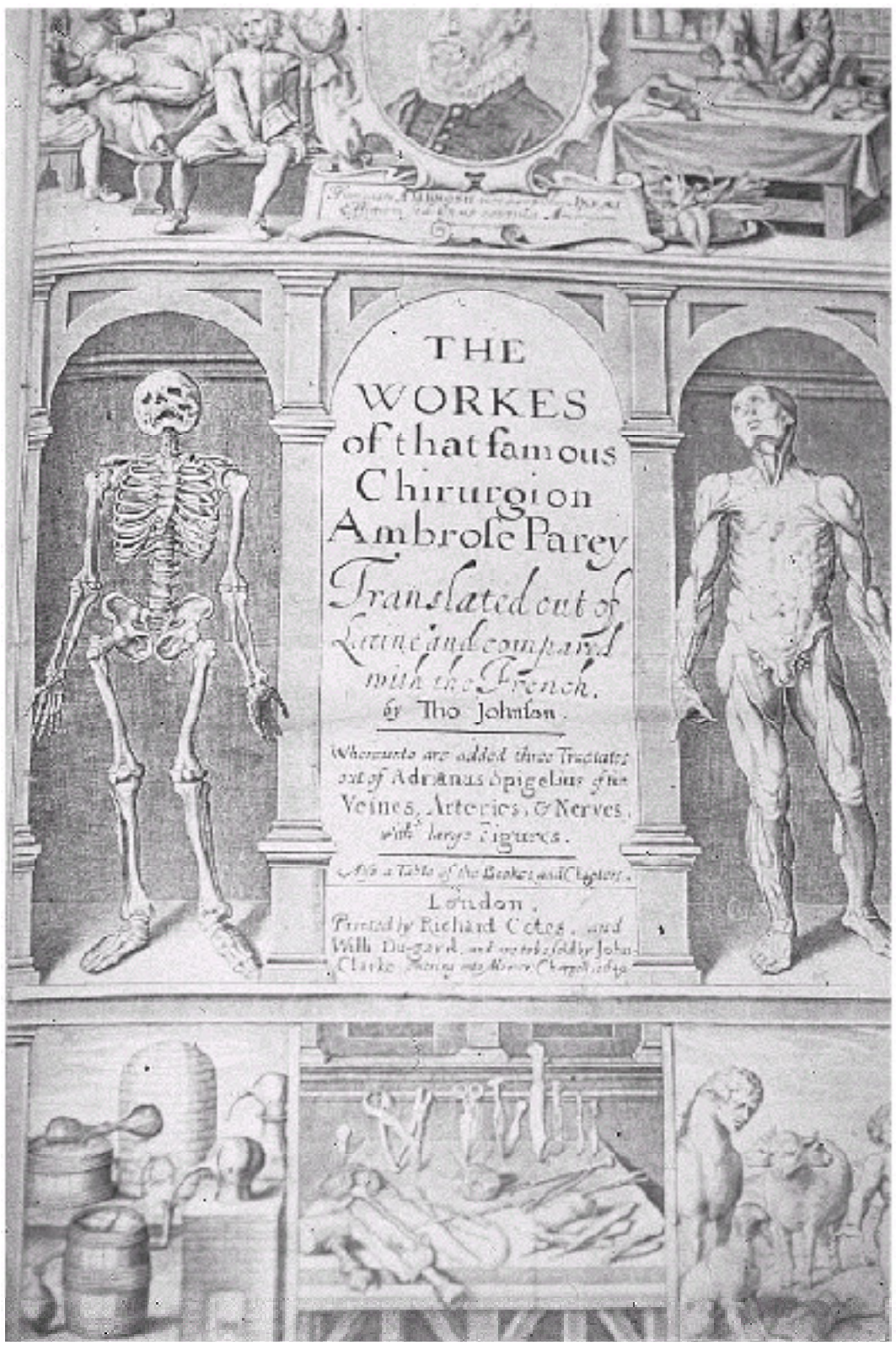


Figure 30.2 Ambroise Pare. (From Pare A. The works from the Latin and compared with the French. In: Johnson TH, ed. London: Cotes and Young, 1649:583, with permission.)

Surgery for strabismus had an inauspicious beginning. Chevalier John Taylor (9) was one of history's great exaggerators (Figs. 30.3 and 30.4). Taylor was one of the most extravagant of all of the traveling quacks—a charlatan supreme and a figure chosen by history to play a major role in the evolution of strabismus surgery. Given this, the entire ophthalmic legacy has Chevalier Taylor involved in cataract, glaucoma, and strabismus. Taylor trained in London at some of the best institutions of the time. Rather than choose a traditional route, that is, working in a hospital or in private practice, Taylor become an itinerant surgeon traveling throughout Europe with a large retinue, including satisfied patients, musicians, and a large stack of press releases and public relations managers. Taylor gave himself the title *Chevalier,* proving the strength of his self-laudatory skills. Although his main interest was cataract surgery, he became convinced that strabismus could be cured. He was bright and a very good observer. He recognized that in many strabismus cases, the deviated eye had substantial vision and could pick up fixation if the dominant eye was covered. He was also very aware of human nature and realized that people could easily be fooled. When he arrived in town and examined potential surgical patients, he always chose patients who had some vision in the deviating eye, noting that the deviating eye could pick up fixation if the straight eye were covered. He usually performed surgery in a town square surrounded by a select circle of his people as well as many of the town's folk. The following was his method, recorded by many observers of the time. Taylor passed a fine needle with a silk thread through a portion of the conjunctiva of the deviating eye a few millimeters from the limbus, usually inferiorly on the globe, probably between the medial rectus and the inferior rectus of the eye. He then made a loop with the silk thread, tied it and pulled on the conjunctiva, elevating it from the globe and then excised a small portion of the conjunctiva with scissors.

The surgery was nowhere near the medial rectus or the inferior rectus. Once the conjunctiva had been cut, he immediately applied a patch to the nondeviating eye, commenting immediately to all that the deviating eye picked up fixation. It was straight—a miracle! Taylor explained that the eye deviated because nerve filaments between the muscles of the eye were, in some way, imbalanced. To restore balance it was necessary to weaken the muscles that dominated the strabismus by cutting the nerve filaments that went to the muscles. He theorized that by doing this, the patient's strabismus would be cured. Cutting a nerve filament to the muscle is interesting; however, even with a sound theory, the location of these nerve filaments was nowhere near the muscles. Following this superb show, Taylor would leave town in his carriage that displayed his famous motto, *qui dat videre, dat vivere* (“He who gives sight gives life”). This motto was prominently displayed on the side of his carriage and on all of his publications. By the time the patch came off and the deviation returned, Taylor was long gone from the site of his latest surgical adventure.

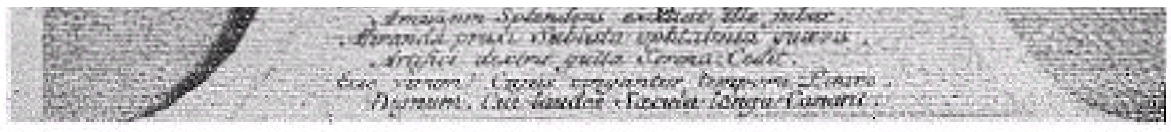
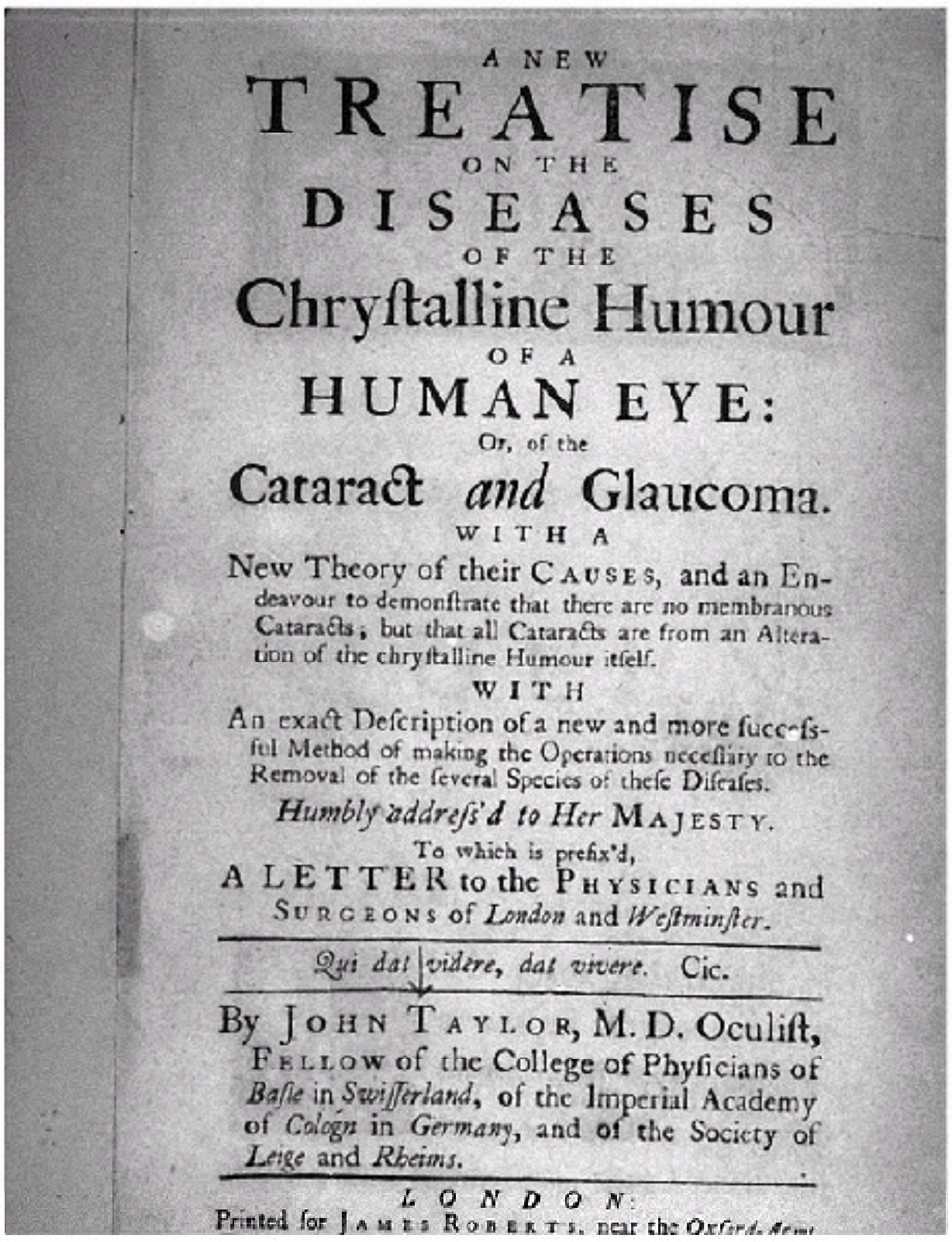


Figure 30.3 Chevalier John Taylor (1703-1772). (From James RR. *Studies in the history of ophthalmology in England.* London: Cambridge University Press, 1933, with permission.)

Following the escapades of John Taylor, a number of legitimate advances were made, ultimately leading to strabismus surgery being performed for the first time on October 26, 1839, at 3 o'clock in the afternoon. By that time John Taylor had been dead for 67 years.

Johann Friedrich Dieffenbach (10) (1792-1847) was born in February 1792 in Konigsberg, Prussia (Figs. 30.5, 30.6 and 30.7). After studying theology for a few years, he returned to Konigsberg to study medicine. At the time of his medical studies, his primary interest was in the transplantation of hair, an area still of rich interest in modern medical thoughts. After studying with Dupuytren, Magendie, and Larrey, Dieffenbach received his medical degree at the University of Wartburg in 1822. He became a gifted and innovative surgeon, beloved by his students and patients. His popularity is exemplified by this song that was sung by children through Berlin at the time:



A NEW
TREATISE
ON THE
DISEASES
OF THE
Chryſtalline Humour
OF A
HUMAN EYE:
Or, of the
Cataract *and* Glaucoma.
WITH A
New Theory of their CAUSES, and an Endeavour to demonſtrate that there are no membranous Cataracts; but that all Cataracts are from an Alteration of the chryſtalline Humour itſelf.
WITH
An exact Deſcription of a new and more ſucceſsful Method of making the Operations neceſſary to the Removal of the ſeveral Species of theſe Diſeaſes.
Humbly addreſs'd to Her MAJESTY.
To which is prefix'd,
A LETTER to the PHYSICIANS and SURGEONS of *London* and *Weſtminſter*.
Qui dat videre, dat vivere. Cic.
By JOHN TAYLOR, M. D. Oculiſt,
FELLOW of the College of Phyſicians of *Baſle* in *Swiſſerland*, of the Imperial Academy of *Cologn* in *Germany*, and of the Society of *Leige* and *Rheims*.
LONDON:
Printed for JAMES ROBERTS, near the *Oxford*

Figure 30.4 Title page from John Taylor: a new treatise on the diseases of the crystalline humor of a human eye.

Weirkennt nicht Doktor Dieffenbach den doktor der doktoren? Er schneidet arm und beine ab, macht neue nas und ohren.

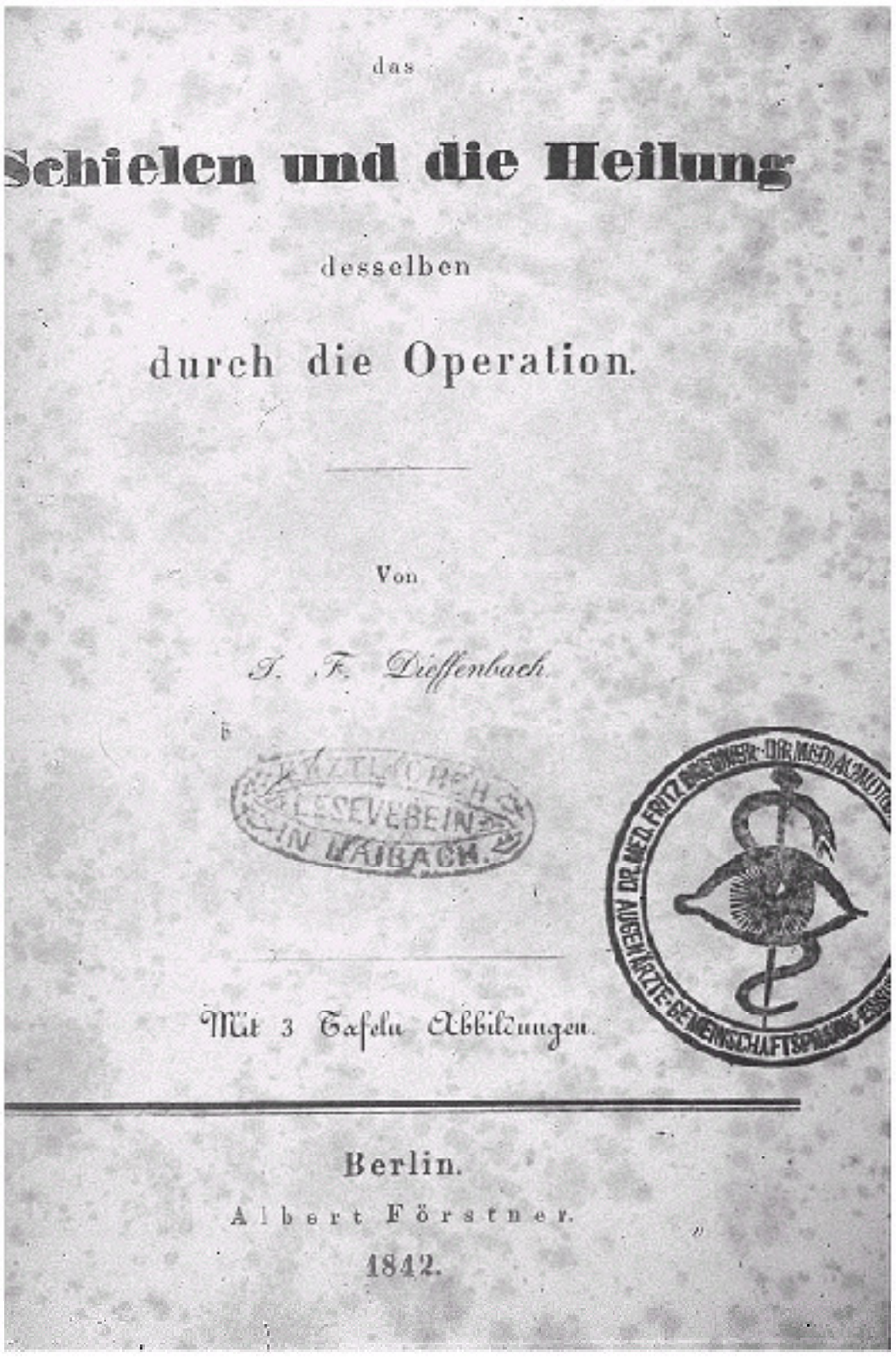
The translation for this is “Who does not know Doctor Dieffenbach, doctor of doctors? He cuts off arms and bones and makes new noses and ears.” Dieffenbach was an extremely innovative surgeon. Because of his innovations in the area of plastic and reconstructive surgery, he has been called “the father of cosmetic surgery.” His surgery for nasal reconstruction, although modified, is widely used today.

In the 1830s Louis Stromeyer (11) (1804-1876), professor of surgery at Hanover and a colleague of Dieffenbach, proposed subcutaneous severing of the achilles tendon for the correction of clubbed foot. This operation was highly

successful and was widely practiced. Dieffenbach learned of this operation from Stromeyer and successfully used it in Berlin. In addition, Dieffenbach and Stromeyer both performed tenotomies to improve torticollis. In 1838 Professor Stromeyer (11) proposed performing myotomy of the ocular muscles for the

correction of strabismus, and, to this end, he experimented on cadaver eyes. In 1839, stimulated by Stromeyer's suggestion, Dieffenbach performed a myotomy of the medial rectus muscle of a 7-year-old boy (12). In 1842 Dieffenbach recorded his experience in 1,200 cases of strabismus operations and noted that if the tendon was severed, the results were better than if the muscle was cut. He also showed that adhesions were often formed, resulting in a variety of postoperative abnormal deviations (13). In this book, he explained that all six muscles of the eye could be operated on, describing specific instruments for performing strabismus surgery.

Figure 30.5 Diefenbach JF. Print 1831. (From Dieffenbach JF. *Ueber das schieien in die heilung desselben durch die operation.* Berlin, Germany: Albert Forsner, 1842, with permission.)


das

Schielen und die Heilung

desselben

durch die Operation.

Von

J. F. Dieffenbach.

Mit 3 Tafeln Abbildungen.

Berlin.

Albert Förstner.

1842.

Figure 30.6 Title page from Dieffenbach JF. *Ueber das schieien in die heilung desselben durch die operation.* Berlin, Germany: Albert Forsner, 1842, with permission.

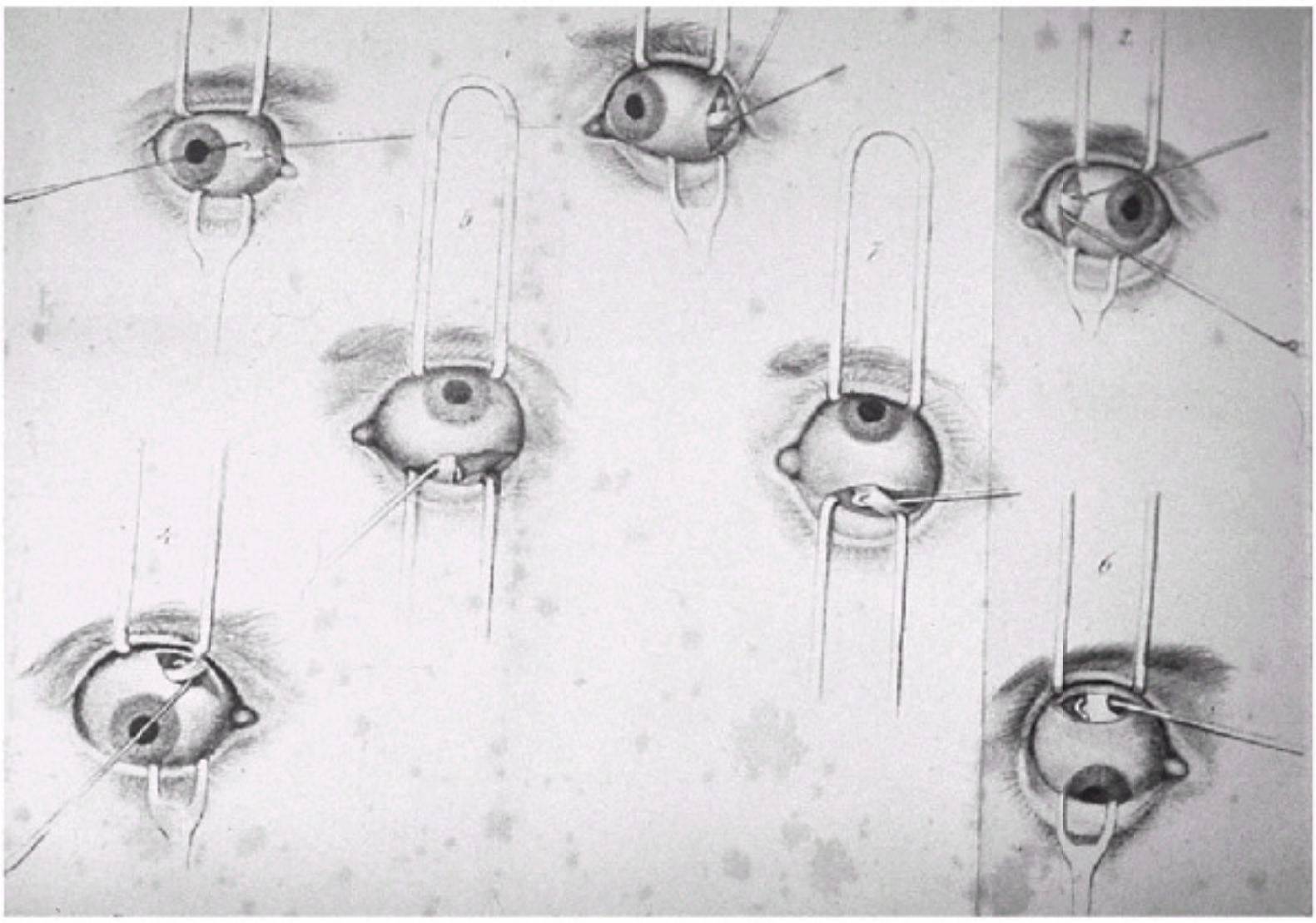


Figure 30.7 Isolation of the individual muscles. (From Dieffenbach JF. *Ueber das schieien in die heilung desselben durch die operation.* Berlin, Germany: Albert Forsner, 1842, with permission.)

In May 1840 Florent Cunier (1812-1853), a well-known Belgian physician, reported that his operation on the lateral rectus muscle was first performed on October 29, 1839 (14). Thus, an argument ensued, and still does in some quarters, as to who performed the first strabismus operation. History has granted the priority for strabismus surgery to be in the hands of Dieffenbach—October 26, 1839, at 3 o'clock in the afternoon, with six observers present (13). News of the success of this operation was heralded across Europe and the Atlantic so that by 1841 French, English, and American surgeons had all used Dieffenbach's technique. Edward Duffin (1800-1874) of London offered one of the first English reports on strabismus surgery (15), and John Homer Dix (1810-1884), in 1841, published a book on his experience with this new mode of treatment (16). Both Duffin and Dix wrote books about their experience before Dieffenbach's book in 1842. Duffin's book does not contain his own personal experience but a composite of the experience of the surgeons in England. Dix, on the other hand, reports his personal experience with this procedure. He first performed this operation on September 9, 1840. His 1841 book is the first American book written on this subject.

Much has changed since Dieffenbach's first strabismus operation, but his seminal surgical technique justifies our referring to him as the “father of strabismus surgery.” The use of muscle surgery spread like wildfire, with hundreds of surgeons around the world performing and modifying this technique. Frederick August von Ammon (17) (1799-1861) first described a myectomy, and Dieffenbach talked about myotomy.

After the rapid advance of strabismus surgery, complications of this procedure became noted. Overcorrection, in which an esotropia was converted to an exotropia or in which a myotomy or tenotomy had not been completed, left the eye oftentimes more deviated than before. What we now call a consecutive exotropia, namely exotropia occurring after esotropia surgery, was then termed a “Dieffenbacher.” These occurrences prompted new surgeries to be developed. One was an attempt to find the medial rectus and to advance it. This technique was performed by Dieffenbach, but his results were not completely successful. He did note that the muscle must have reattached at some place, but his attempts to find it and to suture it back in place failed. Another attempt at this operation was performed by George Critchett (18) (1817-1882) in the 1850s.

Our current attempts at finding a lost medial rectus muscle are also oftentimes disappointing. Attempts to use traction sutures labeled the Faden operation were performed by a number of people, including William Robert Wilde (19) (1815-1876) in Scotland. Jules Renee Guerin (1801-1886) is given credit in 1842 for having found a previously myotomized medial rectus muscle, putting a suture through it and reattaching it to the globe, thus, in effect, advancing a previously recessed medial rectus muscle. It remained for better instruments to be developed and better techniques for isolating the muscle and then for suturing the muscle back on the globe, rather than performing free tenotomies of any of the muscles. Most of the earlier procedures were aimed at horizontal muscle surgery, and only infrequently were the vertical or oblique muscles approached. In these early days it was difficult to approach a contracted or strongly adducted eye. Surgery was performed under nonsedative anesthesia with the patient generally seated before the surgeon. Assistance was necessary to keep the patient calm, and the surgeon had to be adept and speedy in his operation. General anesthesia was not used until the late 1840s, when ether was introduced. For the most part, surgery remained an option of last resort. Sutures in the late 1800s and early 1900s were thick and had to be removed. Needles were not sharp and often had a cutting edge, making their passage through the sclera risky. Our spatula needles of today are finely honed and specifically made for use in strabismus surgery. The basis for today's strabismus surgery was developed during the early years, as mentioned previously. Much has changed since then; however, much has remained the same. Resect or advance a muscle to strengthen it, recess, perform a myotomy or tenotomy, use expanders or extirpate a muscle to weaken it—the more things change, the more they stay the same!

REFERENCES

1. von Noorden. *The history of strabismology.* Oostende, Belgium: JP Wayenborgh, 2002:6.

2. Joachim H. *The Ebers papyrus.* Berlin, Germany: University Press, 1890:68.

3. Hirschberg J. *History of ophthalmology,* vol 7. In: Blodi F, transl./ed. Bonn, Germany: Verlag, JP Wayenborgh, 1985:5327-5335.

4. Keiner GB. *New viewpoints on the origins of squint.* The Hague, Netherlands: Martinus Nijhoff, 1951:2-6.

5. Wood C. *American encyclopedia of ophthalmology,* vol 2. Chicago: Cleveland Press, 1916:1323-1324.

6. Pare A. *The works from the Latin and compared with the French.* In: Johnson TH, ed. London, England: Cotes and Young, 1649: 583.

7. Bartisch G. *Ophthalmodouleia.* Dresden, Germany: Mathies Stocker, 1583:25-28.

8. Darwin E. *Zoonomia.* London, England: J Johnson, 1801.

9. James RR. *Studies in the history of ophthalmology in England.* London: Cambridge University Press, 1933:132-216.

10. Goldwyn RM. Johann Friedrich Dieffenbach (1794-1847). *Plast Reconstr Surg* 1968:42;19-28.

11. Stromeyer GF. *Bietrage Zur Operativen Orthopedik.* Hanover, Germany: Helwig, 1838:79.

12. Dieffenbach JF. An die schielen und die heilung. *Berlin Med Zeitung* 1839;46:27.

13. Dieffenbach JF. *Ueber das schieien in die heilung desselben durch die operation.* Berlin, Germany: Albert Forsner, 1842.

14. Cunier F. Sur la myotomie appliquee au traitment du strabisme. *Ann d Oculistique* 1840;3:122-125.

15. Duffin E. *Practical remarks on the new operation for the cure of strabismus or squinting.* London, England: John Churchill, 1840.

16. Dix JH. *Treatise on strabismus or squinting, and the new model of treatment.* Boston: D Clapp Jr, 1841.

17. von Ammon FA. Zur heilung des strabismus durch die myotomie. *Ammons Monatsschrift F Medizin* 1840;3:321-333.

18. Critchett G. Practical remarks on strabismus, with some novel suggestions respecting the operation. *Lancet* 1855;1:507-509.

19. Wilde WRE. Description of a case of severe trichiasis and convergent strabismus of both eyes—with an account of the mode of applying ligatures on the recti muscles of the eye. *Dublin J Med Sci* 1845;(Nov):201-206.

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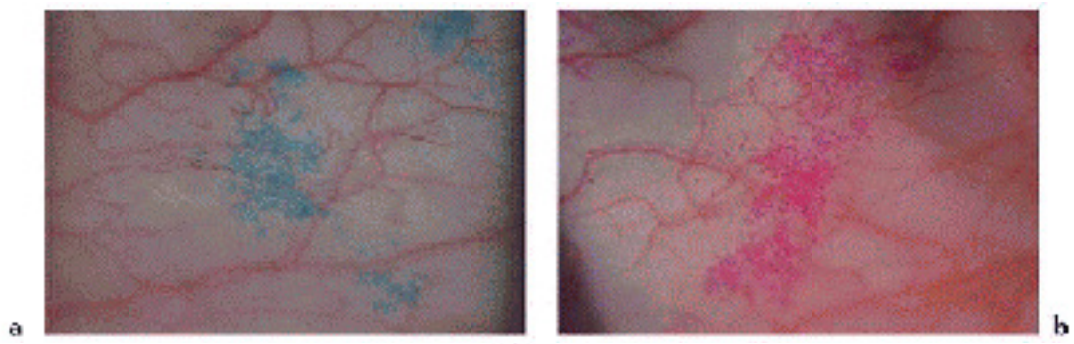
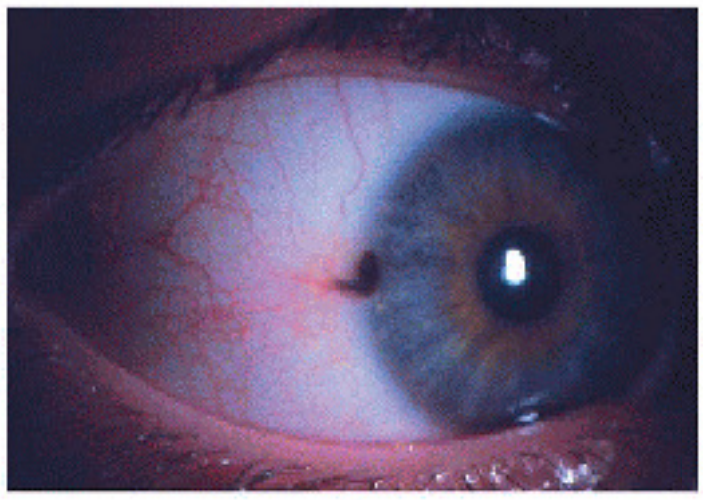
Color Plates

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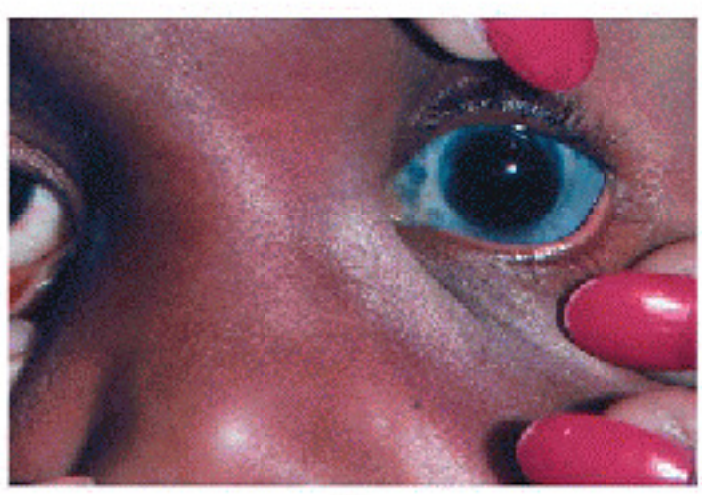
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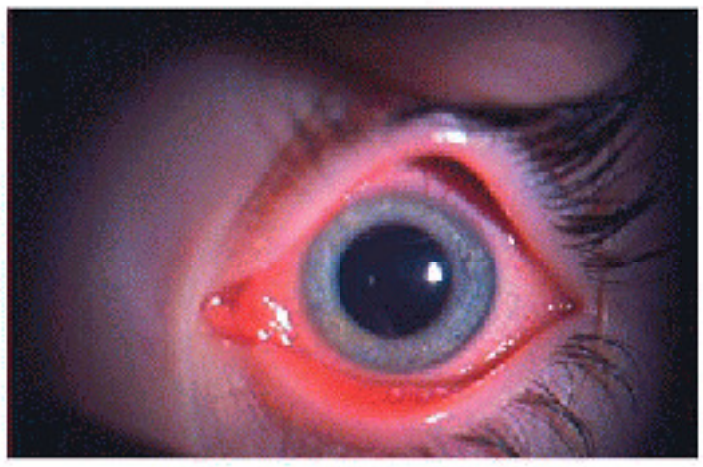
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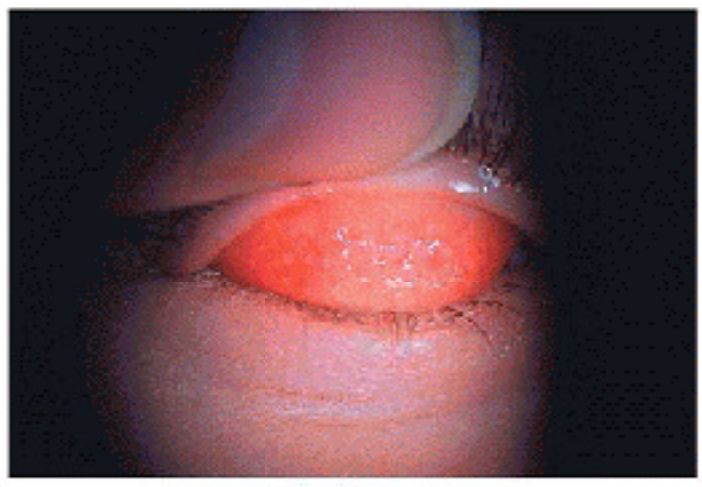
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Plate I. A: Lissamine green (*a*) versus rose bengal stain (*b*). **B:** Nevus. **C:** Congenital glaucoma with ocular melanosis. **D:** Pharyngeoconjunctival fever. **E:** Vernal keratoconjunctivitis.

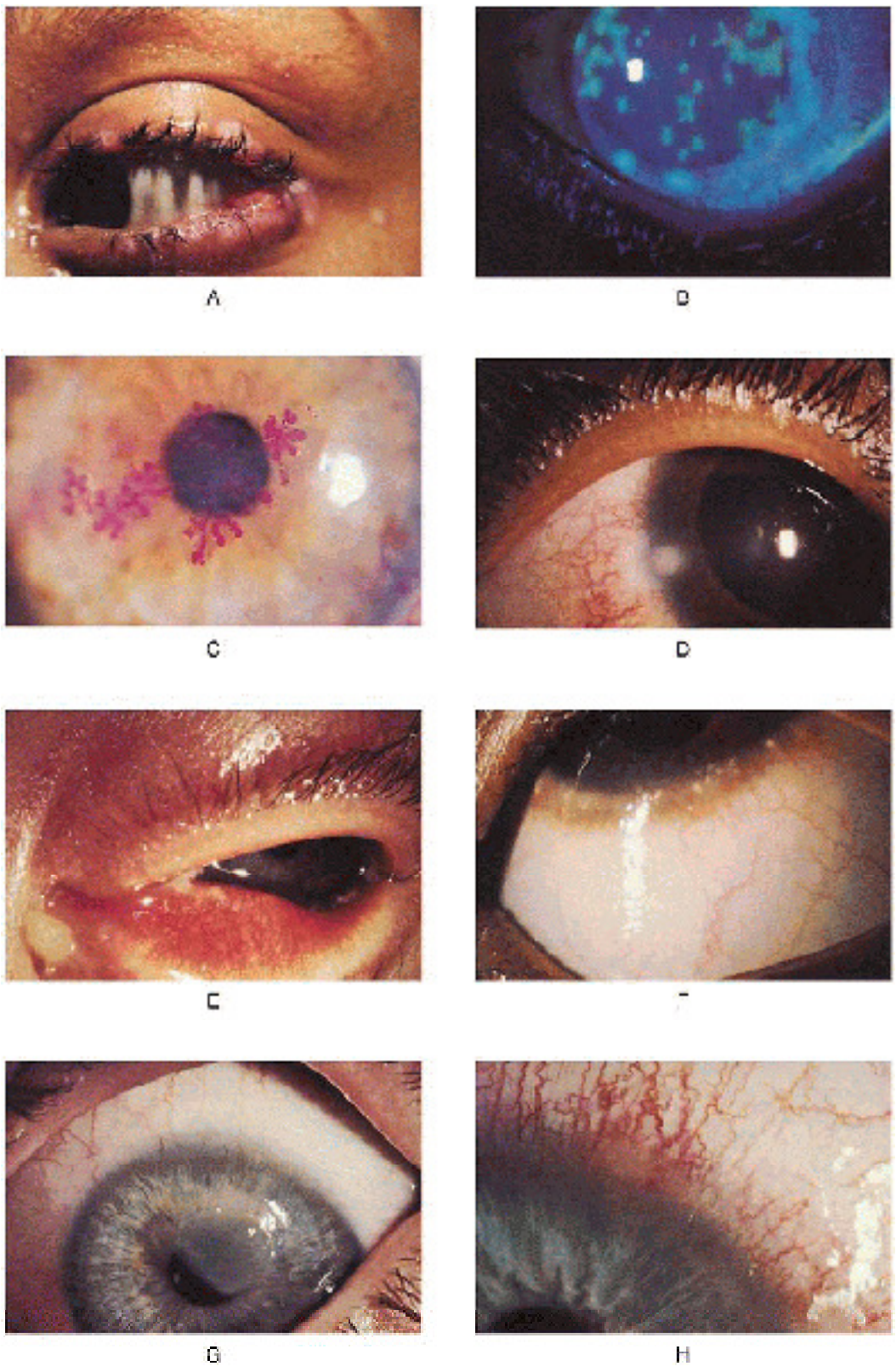
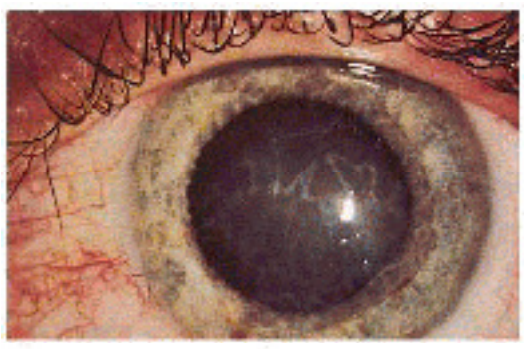


Plate II. A: Staphylococcal blepharitis with keratitis involving the lower and upper lids. **B:** Primary herpes virus infection of the cornea and conjunctiva with numerous dendritic figures (fluorescein stain). **C:** Herpes simplex keratitis ulceration of the cornea (rose Bengal stain). **D:** Active chickenpox and limbal involvement with stromal inflammatory changes. **E:** Inclusion conjunctivitis of the newborn; no corneal changes were noted. **F:** Limbal vernal conjunctivitis with minimal vascularization but lymphoid hypertrophy at the limbus. **G:** Corneal shield ulcer in vernal conjunctivitis. **H:** Phlyctenular conjunctivitis with phlyctenules at the limbus.



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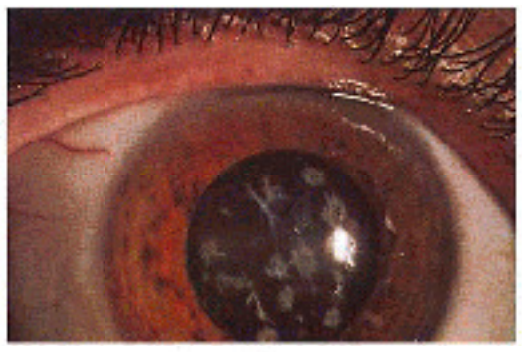

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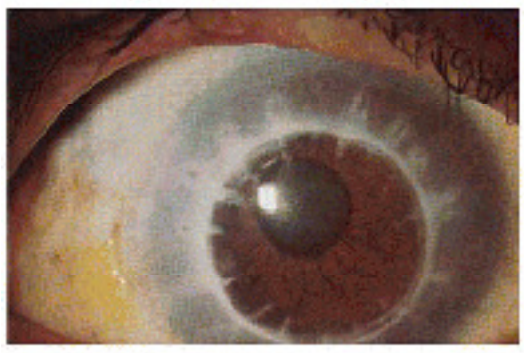

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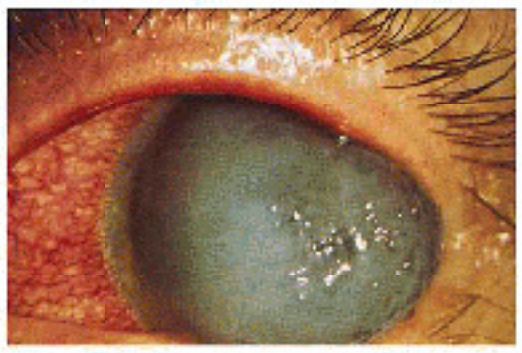

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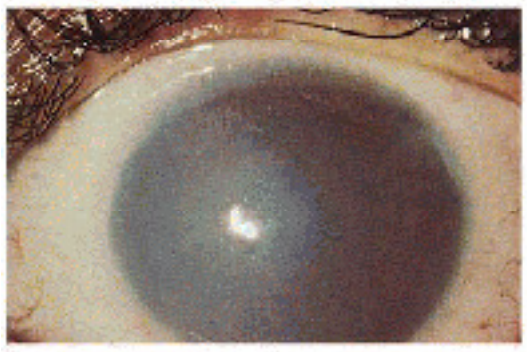

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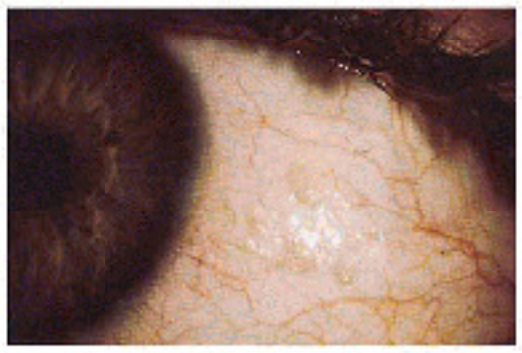

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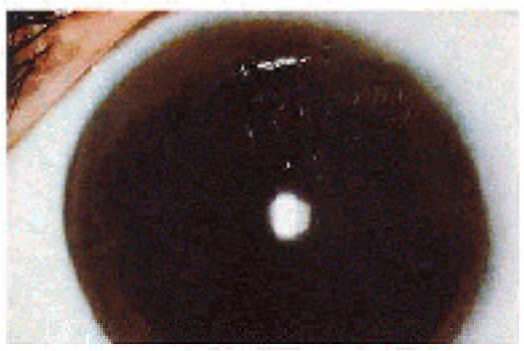
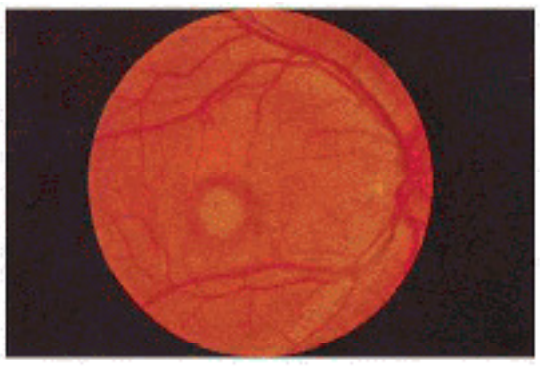


G

H

Plate III. A: Reis-Bucklers corneal dystrophy involving the superficial cornea, epithelium, Bowman's membrane, and sub-Bowman's stroma. Note the irregular astigmatism, as shown by the reduplicated light reflex. **B:** Granular corneal dystrophy in the early part of the third decade. This was first seen during the late teen years. **C:** Hereditary corneal dystrophy with a clear, penetrating corneal implant. **D:** Marked hydrops in a patient with Down syndrome who had keratoconus. **E:** corneal clouding and thickening in Hurler disease. **F:** Bitot spot of the conjunctiva adjacent to the cornea. Note the glistening area, which represents degenerated epithelial cells. **G:** Kayser-Fleischer ring in Wilson disease. This orangebrown ring is noted for 360 degrees around the periphery. **H:** Slit lamp view of Kayser-Fleischer ring in Wilson disease to show the deposition in the region of Descemet's membrane in the cornea.



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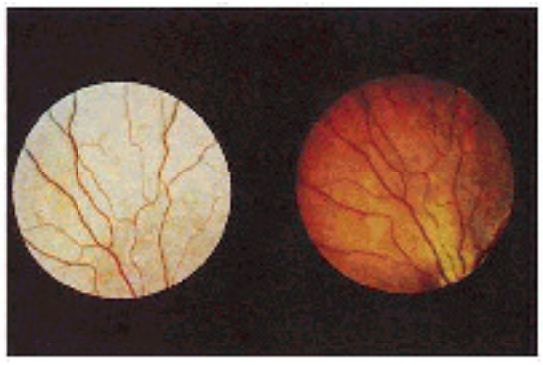

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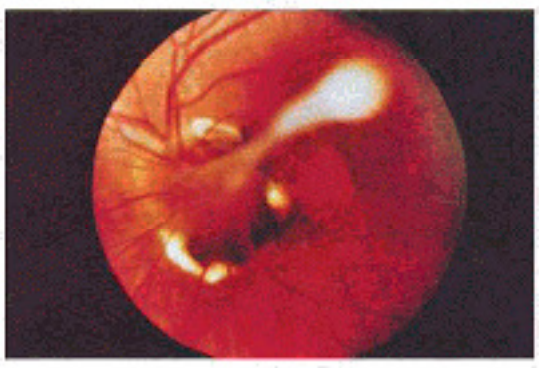

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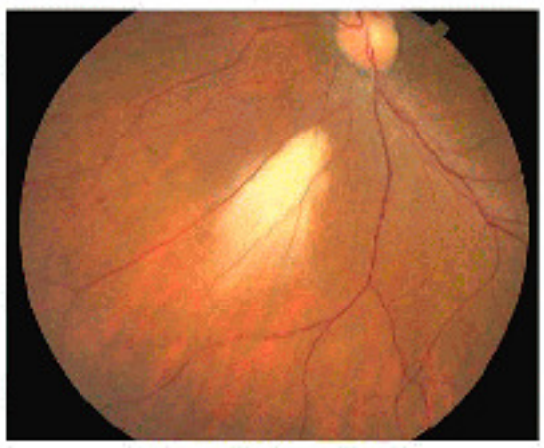

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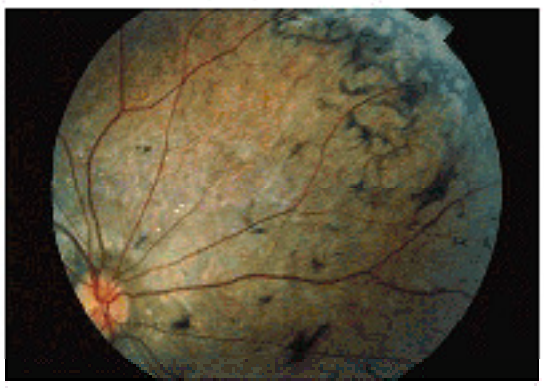

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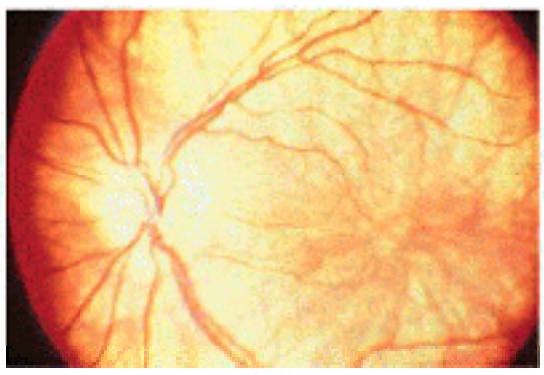
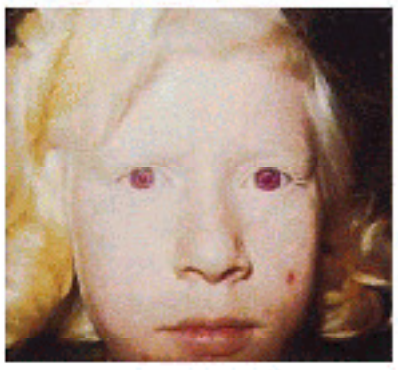


F

Plate IV. A: Vitelliform macular degeneration with egg-yolk appearance. **B:** Oguchi disease and light-adapted retina (*left*) and dark-adapted retina exhibiting the Mizuo phenomenon (*right*). **C:** Persistent hyperplastic vitreous emanating from the disc. **D:** Myelinated nerve fibers with feather-like appearance away from the optic nerve. **E:** Bietti's crystalline retinopathy with crystals in retinal layers associated with bone spicules. **F:** Decreased pigmentation in the retinal pigment epithelium and choroids associated with albinism.



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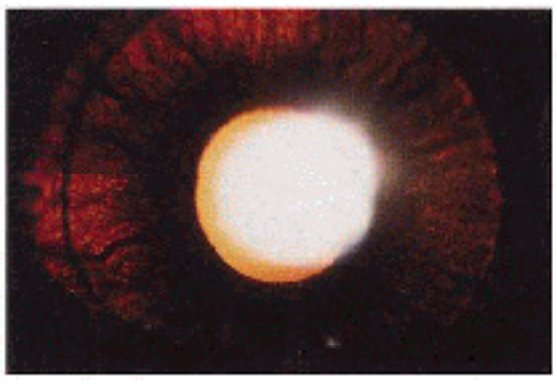

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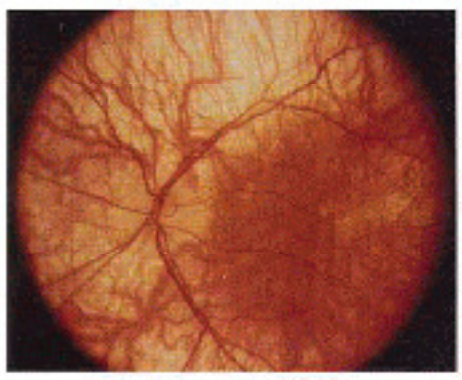

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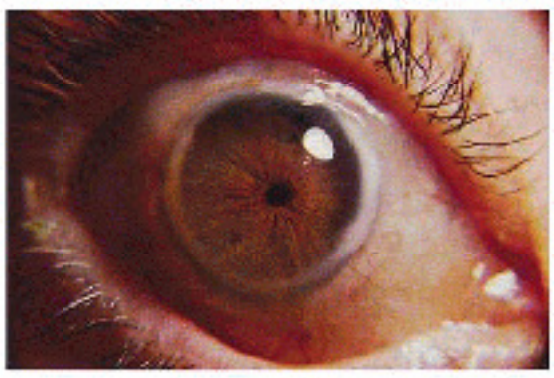

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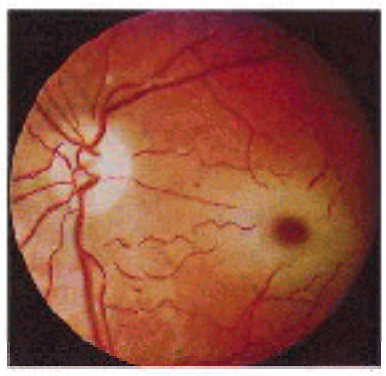
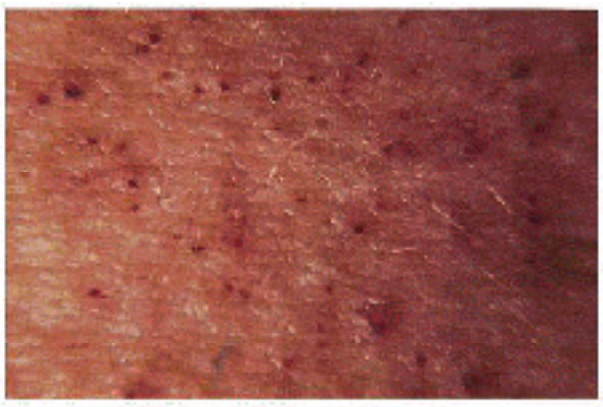


F

Plate V. A: Oculocutaneous albinism. **B:** Diffuse iris transillumination. **C:** Pigmentary dilution of the posterior pole. Note there is macular hypoplasia. **D:** Arcus senilis. The severe degree of corneal arcus seen here is uncommon even in the elderly. When observed in those under 40 years of age, arcus may be a sign of hypercholesterolemia. **E:** Lipemia retinalis. The marked fundus changes in this 28-year-old black male with fat-induced hyperlipemia (Type I hyperlipoproteinemia) cleared within a few days after ingestion of fat was stringently limited. **F:** Fundus of an adult with Tay-Sachs disease. There is optic atrophy, indicating that the disease is in its late stages.



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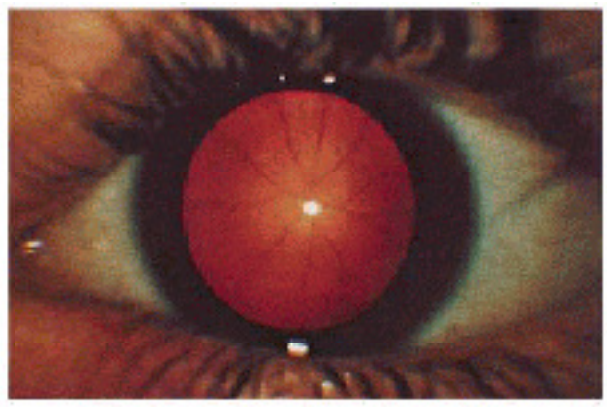

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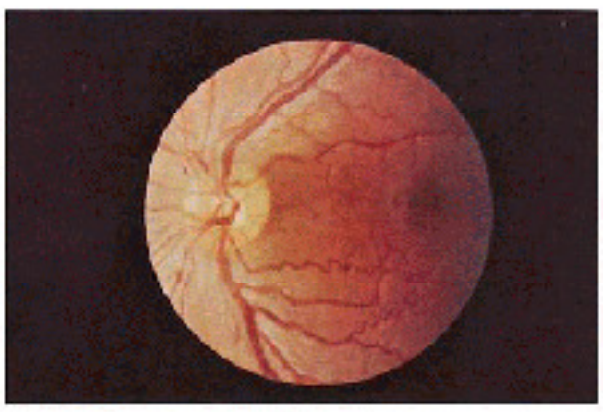

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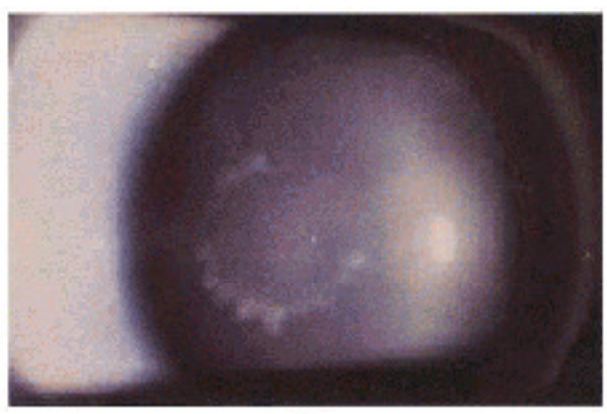

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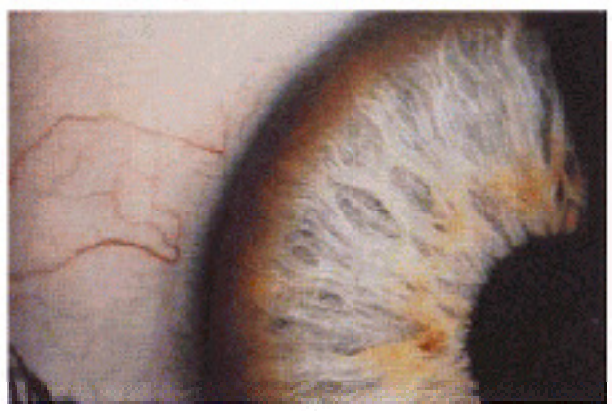

E

Plate VI. A: Skin lesions, the “angiokeratoma” of Fabry disease, most prominent in the bathing suit area. **B:** Cataract noted in the posterior capsular area of the lens in about 50 percent of patients with Fabry disease. Carriers may show this opacity, which is best seen by means of retroillumination. **C:** Characteristic retinal vessel tortuosity in a 22-year-old male with Fabry disease. **D:** Prominent Kayser-Fleischer ring in a patient with Wilson Disease. **E:** Sunflower cataract in Wilson disease.