CROSS SECTION OF OPHTHALMOLOGY
Spasm reactor?
Brief summary. Side effects: Blurring of vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur on higher dosage levels, rarely on usual dosage. Administer with caution to patients with incipient glaucoma or urinary bladder neck obstruction or in prostatic hypertrophy. Contraindicated in patients with acute glaucoma, advanced renal or hepatic disease or a hypersensitivity to any of the ingredients.
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DuPont Guerry, III, M.D., D. Med. Sc., F.A.C.S.
Professor and Chairman, Department of Ophthalmology
1953–1973
Medical College of Virginia, Health Sciences Division of
Virginia Commonwealth University, Richmond, Virginia
Cross Section of Ophthalmology

This issue of the MCV/Q is dedicated to Dr. DuPont Guerry, III, to honor his decisive influence on the development of the Department of Ophthalmology of the Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, during his 20 years as chairman of the department. It is with our deep regret that he has decided to resign from this position, although he will remain actively involved in all phases of the department's programs, and, one hopes, for many years to come.

The content of this issue covers various areas in this specialty and represents contributions by former and present residents trained under Dr. Guerry, and full-time staff members. For this reason the title, "Cross Section of Ophthalmology," was chosen.

My thanks are extended to Dr. Fairfield Goodale, editor of the MCV/Q, and his staff for making it possible to publish these collected papers as a special issue in tribute to Dr. Guerry, on this particular occasion.

Doctor DuPont Guerry, III, was born August 16, 1912, in Greenville, South Carolina. After graduation from Furman University, Greenville, South Carolina, where he received his baccalaureate degree, he attended the University of Virginia, School of Medicine, Charlottesville, Virginia. There he completed his medical training with an M.D. degree in 1938 and subsequently spent one year of internship at the University of Virginia Hospitals. He then enrolled in a residency program in otolaryngology at the Manhattan Eye, Ear, Nose and Throat Hospital from 1939 through 1941, followed by a residency in ophthalmology at the Institute of Ophthalmology, Presbyterian Hospital, Columbia University, New York, from 1941 until 1944. In 1944, he received his Doctor of Medical Sciences (ophthalmology) degree from the same university. Doctor Guerry is a Diplomate of the American Board of Otolaryngology as well as the American Board of Ophthalmology. In 1944, he joined the faculty of the Medical College of Virginia, Richmond, Virginia, where he has remained active ever since. He was appointed Professor and Chairman of the Department of Ophthalmology of MCV in 1953 and has remained in this position until his present announcement to resign from his chairmanship.

Doctor Guerry holds memberships in professional and honorable societies too numerous to be listed here and has been author and co-author of many scientific publications.

In 1965, he accepted the responsibility to serve on the editorial staff of the American Journal of Ophthalmology, and he was appointed to the American Board of Ophthalmology in 1969.

One of his greatest contributions in the field of ophthalmology has undoubtedly been his instrumental influence on the development of light coagulation treatment for many ocular diseases and the recognition of its clinical significance. He performed the first treatment of this kind in the United States in 1958. It is a therapy which has progressed to the point where ocular diseases formerly not amendable to any therapy, can now be successfully treated and vision preserved—a goal to which he has dedicated his work and life.

WALTER J. GEERAETS, M.D.
Professor of Ophthalmology
Medical College of Virginia
Corneal Opacification in Infancy

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Corneal opacification in the newborn and in infancy is often not sufficiently recognized, and its importance in the diagnosis of a more complicated systemic disease can easily be overlooked.

A quick search in the standard textbooks for this specific topic is often unrewarding because only a few textbooks would devote more than a few paragraphs on the subject (23).

The purpose of this paper is to present a systematic classification of the more important conditions that can manifest as corneal opacification in early infancy and to state its differential diagnostic significance.

CAUSES OF CORNEAL OPAFICATION IN INFANCY:

I. Congenital Malformations
   1. Anterior chamber cleavage syndromes
      a. Congenital central anterior synechiae
      b. Rieger's syndrome
      c. Axenfeld's syndrome
      d. Peters' anomaly
      e. Congenital anterior staphyloma
   2. Sclerocornea
   3. Congenital glaucoma
   4. Dermoid tumors

II. Birth Trauma

III. Corneal Dystrophy
    Congenital hereditary corneal dystrophy

IV. Inflammatory Processes
   1. Interstitial keratitis
   2. Herpes simplex
   3. Riley-Day syndrome
   4. Rubella syndrome

V. Inborn Errors of Metabolism
   1. Mucopolysaccharidoses
      a. Hurler's (type I)
      b. Scheie's (type V)
      c. Maroteaux-Lamy (type VI)
   2. Lowe's syndrome

VI. Chromosomal Aberrations
   1. Mongolism (Down's syndrome)
   2. Trisomy 13–15 (Patau's syndrome)

   I. Congenital Malformations.
   1. Anterior chamber cleavage syndrome: In his second Edwin B. Dunphy lecture, Reese made a plea toward simplification in the nomenclature of a group of various clinical syndromes, congenital in nature, characterized by varying degrees of iridocorneal adhesions, iris and iridocorneal angle changes, and marked prominence of the Schwalbe's line (posterior embryotoxon) with or without accompanying corneal opacities and glaucoma. He suggested calling these groups the anterior chamber cleavage syndrome, believing that these various syndromes represent varying degrees of involvement due to a "faulty cleavage" of the anterior chamber during its developmental stage.
      a. Congenital central anterior synechiae: Reese and Ellsworth (27) consider this condition the most severe form of anterior chamber cleavage abnormality. This is clinically characterized by central corneal opacification, with or without edema, occurring at the site of the adhesions of the iris to the posterior surface of the cornea. The iris adhesion may be focal or circumferential involving the iris collarette or, less commonly,
CHING: CORNEAL OPAQUE IN INFANCY

Fig. 1—Congenital central anterior synechiae showing dense central corneal opacification with central synechiae bridging from the iris collarette. (Courtesy of M. M. Parks, M.D.)

points peripheral to the collarette (fig. 1). The cornea may have a ground glass appearance in the early stages due to edema caused by defects in Descemet's membrane formed by the iris adhesions. If there is no accompanying glaucoma or if the glaucoma is controlled, the defect in Descemet's membrane is sealed, and the cornea clears somewhat, leaving a well demarcated scar. Thus, clinically some patients will show progression of the opacification and in some, clearing of the opacification.

Glaucoma was present in 70% of Reese and Ellsworth's cases. Although most of their cases had narrow angles accompanying the forward displacement of the iris due to the adhesions to the cornea, the glaucoma was probably related to the cleavage defects in the angle rather than the narrow angles (27, 3, 20). The condition is bilateral in 80% of the cases (27), and the involvement is usually symmetrical in the two eyes.

Therapy depends on the extent of the anomaly. Glaucoma control, if present, and improvement of visual acuity are the goals of therapy in such cases.

b. Rieger's syndrome: This syndrome was first described and termed dysgenesis mesodermais corneae et irides (28). Some authors consider this syndrome different from the anterior chamber cleavage syndrome of Reese and Ellsworth on the basis that central corneal opacities are not common in Rieger's syndrome. It is probably transmitted as an autosomal dominant gene with high penetrance. Primary ocular findings consist of hypoplasia of the anterior leaf of the iris, iridocorneal angle adhesions, and posterior embryotoxon. The first feature mentioned above is considered by many investigators as the sine qua non of the syndrome. Associated abnormalities include high degrees of myopia, hyperopia, and astigmatism. Strabismus may be present with exotropia occurring more often than esotropia (13, 1, 15, 31).

c. Axenfeld's syndrome: This syndrome was first described by Axenfeld in 1920 (2), as consisting of a prominent, thickened, and centrally displaced Schwalbe's line. He termed this specific feature posterior embryotoxon. Currently, most authors describe Axenfeld's syndrome as a milder form of Rieger's syndrome with only posterior embryotoxon and iridocorneal angle adhesions (fig. 2b), with or without glaucoma (5) (fig. 2a).

d. Peters' anomaly: As described by Peters in 1906, this syndrome consists of a well defined defect of the deepest stromal layer of the cornea and Descemet's membrane and a
central corneal opacity occurring with or without adhesions or remnants of adhesions to the iris (fig. 3).

Although this syndrome is considered by most investigators as belonging to anterior chamber cleavage syndrome (13), recent studies question this. Brown and Nakashishii (22) published a report on the electronmicroscopic study of a patient with Peters' anomaly. They described the finding of Bowman's membrane defect in addition to the defect in Descemet's membrane, thus favoring Alkemeade's (1) suggestion that Peters' anomaly is not strictly a part of an anterior chamber cleavage defect because the portion of the cornea involved does not normally develop during the formation of the anterior chamber embryologically. Of the reported cases, 80% are bilateral. The occurrence of glaucoma is frequently encountered. Less frequently associated abnormalities include anterior polar cataract and other forms of congenital cataract, microphthalmos, and sclerocornea.

e. Congenital anterior staphyloma: This condition is characterized by a conical protrusion of a diffusely scarred, usually opacified cornea, lined by iris internally (fig. 4). Most authors consider this a part of the anterior chamber cleavage syndrome, although others have ascribed this condition to intrauterine inflammation. This condition can be bilateral or unilateral. The cornea of the affected eye is usually severely damaged with the iris adherent to the cornea. The lens is usually cataractous and the ciliary body is atrophic.

2. Sclerocornea: This condition is defined as a congenital anomaly in which the cornea assumes an opaque appearance approaching that of the sclera. Sclerocornea commonly occurs in conjunction with cornea plana, although it can occur as an isolated congenital anomaly as described by Rollet in 1933 (30). The scleralization may involve the whole or part of the cornea (fig. 5). It can occur in either eye or both eyes. Generally, the cornea is vascularized but can be differentiated from interstitial keratitis by the absence of inflammation and the conspicuous presence of arcades of superficial scleral vessels that extend into the opacified area. Associated ocular findings include nystagmus, strabis-
mus, glaucoma, microphthalmos and microcornea, embryotoxon, cornea plana, and aniridia. Associated systemic manifestations include malformation of the skin, face, and ears; mental retardation and cerebellar dysfunction; cryptochidism, and brachycephaly (10).

Treatment varies depending on the degree of corneal scleralization and the associated abnormalities. Paufique (24) reported treatment with keratoplasty in 1952.

3. Primary congenital glaucoma: Primary congenital glaucoma is the most common hereditary glaucoma of childhood. The disease is diagnosed in over 60% of cases within the first six months of life and in over 80% of cases within the first year (15). There is a small difference in sex incidence with the males predominating in 65% of cases. Unilateral involvement is seen in 25–30% of the cases (31). The anomaly of congenital glaucoma is inherited as an autosomal recessive gene with approximately 80% penetrance (31). Although most cases show this mode of inheritance, clinically in a significant number of cases, the condition does exhibit a sporadic character (31).

Photophobia is probably the earliest symptom in infantile glaucoma. This is due to irritation of the corneal nerve endings from stretching of the cornea due to the increased intraocular tension. Blepharospasm and epiphora are also early signs and symptoms of the condition and should arouse the suspicion of pediatricians and ophthalmologists seeing the patient for the first time. Unfortunately, these findings are occasionally dismissed as physiologic for the age of the patients, passed unnoticed, or mistaken for a less serious condition such as a blocked naso-lacrimal system, especially in the absence of moderately advanced changes such as corneal edema and corneal enlargement. In blocked tear ducts, the nostril in the same side is usually dry unless there is coincidental rhinitis. The finding of epiphora with nasal discharge on the same side should make the physician look closer at the eyes.

More often, when these patients are first seen, definite pressure related changes are already present including ground glass looking cornea (fig. 6a), buphthalmos (fig. 6b), tears in Descemet’s membrane, and deep anterior chamber. Cupping of the disc, which is now recognized as an early sign of the condition, has been shown to be reversible to a certain degree with the control of the intraocular tension (31). Late changes include bullous keratopathy of the cornea, optic atrophy, and even phthisis bulbi.

Seemingly unrelated organ system anomalies are also relatively common. Pyloric stenosis, deafness, mental deficiency, and cardiac anomalies have been described (31). Congenital cataract can be found occasionally.
The importance of early diagnosis and prompt therapy, either medical or surgical, cannot be over-emphasized. A variety of surgical procedures have been used to control the intraocular tension in these patients. Of these, the procedure of choice at the present time is goniotomy. This procedure is aimed at opening the superficial layer of the trabecular meshwork to allow better aqueous drainage into Schlemm’s canal. The exact mechanism of its pressure lowering effect is still unsettled.

Of the newer procedures, the external trabeculotomy [Harms and Dannheim. Epicritical Consideration of 300 Cases of Trabeculotomy of Extern; quoted by Shaffer and Weiss (31)] and the external trabeculectomy (16) hold promise in the treatment of this condition, especially in cases where dense opacities of cornea precluding anterior chamber visualization are present. However, long-term results from both procedures are still forthcoming.

4. Dermoid tumors: Dermoid tumors can either be cystic or solid. They are congenital misplacements and represent inclusions of epidermal and associated connective tissues during the closure of the fetal clefts. When occurring in the cornea (fig. 7), they may be composed of fibrofatty masses with projecting hairs (12). They are also most commonly located in the inferotemporal quadrant when occurring in the cornea. When involvement of the cornea is severe, they can easily be mistaken for sclerocornea and microcornea. When coincidental ear abnormalities are noted, search for associated vertebral column and other abnormalities should be made because of the possibility of Goldenhar syndrome (9). Excision is generally the rule in the management of this condition.

II. Birth Trauma. A few ocular abnormalities at birth have been ascribed to birth trauma (7), and corneal injury is one of them. These injuries commonly result from compression of the globe between the roof and superior margin of the orbit and poorly applied forceps. Cases of corneal injuries occurring in non-forceps delivery have also been described. Lloyd reported that this condition is more common in the left eye. This occurrence has been explained on the basis of the relative frequency of left occiput anterior (LOA) presentation at delivery (7).

Clinically, these patients may present with varying degrees of corneal injury. Transient diffuse corneal opacity can occur due to edema from the direct trauma. Permanent diffuse corneal opacity can occur due to secondary inflammation in the anterior chamber with keratic precipitate formation. Permanent opacity due to rupture of Descemet’s membrane and overlying cornea may exist. Cyst formation and formation of glassy membranes in the anterior chamber have also been reported. The appearance of Descemet’s tears is also characteristic of corneal injuries. These tears are usually parallel to one another in a vertical or oblique direction; whereas, tears that occur in congenital glaucoma are usually horizontal in direction.

The usual sequelae of these injuries are amblyopia, strabismus, myopia, astigmatism, endothelial dystrophy, and bullous keratopathy.

III. Corneal Dystrophy.

Congenital hereditary corneal dystrophy. This condition was originally described by Laurence in
1863 as corneitis interstitialis in utero. However, its true clinical character was determined by Franceschetti and Babel in 1945 as bilateral, symmetrical corneal dystrophy present at birth. Maumenee speculated that the possible mechanism for abnormal corneal hydration in these patients could be either an abnormal embryonic development of the corneal stroma itself, or a congenital form of endothelial dystrophy. More recently, Kenyon, et al. (14) performed electronmicroscopic studies on a patient with congenital hereditary dystrophy. They speculated that the disease starts as a primary degeneration of the corneal endothelium as early as the fifth month of gestation, later progressing peripherally. The clinically apparent clouding of the cornea is due to diffuse stromal and epithelial edema occurring secondarily.

Clinically, patients present with a diffusely cloudy, ground glass appearing cornea at birth or soon after. The cloudiness is usually denser in the axial region and in the superficial layers of the stroma. Epithelial edema may be present in some cases, but epithelial bullae are rarely seen. Vascularization usually does not occur. These patients rarely exhibit photophobia or any evidence of inflammation in the eye. Pearce (25) reported the occurrence of congenital nystagmus in patients with this condition. Penetrating keratoplasty has been tried in cases with some success (fig. 8).

IV. Inflammatory Processes.

1. Interstitial keratitis: Interstitial keratitis in itself is nonspecific and denotes an inflammation of the deeper portion of the cornea. It is caused by a multitude of etiologic agents including Treponema pallidum, M. tuberculosis, and M. Leprae. Syphilitic interstitial keratitis is usually not present at birth and may develop during the early adolescent period. The latter two can occur early in life but are relatively rare. The condition is almost always bilateral with the second eye manifesting the same process within a month or two of the onset.

Clinically, the condition usually starts as a uveitis and keratitis with early development of endothelial bedewing and keratitic precipitates. Then the stroma develops edema which is later followed by vascularization. At this point, the cornea has a ground glass appearance. The cornea gradually clears, especially with treatment, but leaves residual signs like ill defined areas of deep corneal haze, mostly axial, and attenuated vessels in the deep layers of the stroma later turning into "ghost vessels." These ghost vessels are blood vessels devoid of blood and are best seen during slit lamp examination.

Treatment consists of topical steroids, mydriatics, and specific therapy of the underlying infectious process.

2. Herpes simplex: Herpes simplex is the most common cause of keratitis in children. The infection can occur very early, even shortly after birth. The incidence and severity of this condition appears to be increasing, especially with the increasing use of local and systemic steroids.

The infection may involve mainly the epithelium or the stroma of the cornea. In both forms, the cornea may have a hazy appearance because of inflammatory infiltration and edema when severe. Epithelial forms such as discrete dendritic ulcers or diffuse epithelial lesions may be seen. Stromal lesions can have a disciform pattern and may occur with or without epithelial ulcers. The onset is usually acute with pain and intense photophobia. Decrease in corneal sensation is a common finding. Anterior uveitis is a frequent complication.

The current treatment of choice is either epithelial debridement or IDU (Idoxuridine) in epithelial lesions and IDU combined with cautious use of topical steroids in stromal forms. Cycloplegics are used to provide comfort to the patient.

3. Riley-Day syndrome: This syndrome was first described by Riley and co-workers in 1949 (29). It is a central autonomic nervous system dysfunction that occurs predominantly in children of Jewish parentage.
The patients may present in early infancy with retarded development and weight gain, difficulty in swallowing, and frequent bouts of respiratory infection with an exaggerated febrile response. The child shows marked indifference to pain, poor motor coordination, postural hypertension, cold hands and feet, emotional instability, dysarthria, and profuse sweating.

Most of the ocular problems of these children result from reduced or absent tear formation during crying, in spite of the presence of normal lacrimal glands, and from corneal anesthesia due to absence of corneal nerves.

Clinically, the corneal involvement may occur in varying degrees of severity (17) and can appear as a severe central corneal ulceration resembling neuroparalytic keratitis. Keratomalacia in a mild form may resemble exposure keratitis in its location and appearance, and a faint scarring resembling etched glass in the lower cornea may be present.

Dunnington, in 1954 (6), described three cases of familial dysautonomia, one of which was brought to the physician because of corneal haziness noted by the parents. Early diagnosis of the condition is important since it will allow for early treatment and prevention of the many complications.

Diagnosis is based upon the findings of the absence of tear formation, corneal anesthesia, exodeviation, miosis induced by 2.5% metacholine, elevated ratio of urinary homovanillic acid to vanillyl mandelic acid, absence of intradermal histamine flare, myopia, anisometropia, ptosis, and anisocoria.

Treatment consists of parenteral antibiotics and supportive measures systemically, and artificial tears and bland ophthalmic ointments to prevent drying of the cornea. Topical antibiotics and tarsorrhaphy may be indicated in some cases.

4. Rubella syndrome: Gregg (11) first emphasized the relation between maternal rubella and multiple infantile anomalies. The syndrome results from maternal infection with rubella during the early part of pregnancy. The rubella virus can be cultured from the infant for many months from the time of birth.

Early corneal opacification can occur as a result of the glaucoma, breaks in the Descemet's membrane with edema probably due to previous episodes of acute elevations of intraocular tension, and transient edema probably due to accompanying intraocular inflammation. Sometimes only a transient corneal haze is noted.

Systemic abnormalities include malformation of the heart, hearing defects, mental retardation, and dental defects.

Affected children may present with one or more of the following ocular findings: cataracts (bilateral in 75%), glaucoma, peripheral "salt and pepper" retinopathy, central retinal pigmentaion, subnormal ERG, hypoplasia of iris with small pupils, vitreous haze, nystagmus, microphthalmos, and waxy atrophy of the optic disc.

V. Inborn Errors of Metabolism.

1. Mucopolysaccharidoses: This is a group of inherited metabolic disorders of mucopolysaccharide metabolism resulting in deposition of the substance in various parts of the body. Of the six syndromes already described in the literature, only three are associated with early corneal opacification.

Recent biochemical studies on these groups of conditions have revealed enzyme deficiencies. Some authors [O'Brien, San Filippo Syndrome: Profound Deficiency of Alpha Acetyl Glucosaminidase Activity in Organs and Skin Fibroblast from Type B Patients. (In Press) and Matalon and Dorfman] have actually pinpointed the actual enzyme responsible in some of these diseases, thus opening the horizon for more extensive clinical studies.

a. Hurler's syndrome (type I): This syndrome is transmitted as an autosomal recessive gene. Besides early corneal clouding, ocular changes include pigmentary retinal degeneration with an abnormal ERG. Histopathologically, the corneal clouding is explained by the presence of corneal corpuscles in the stromal connective tissue distended with the acid mucopolysaccharide. The corneal corpuscles are also surrounded by a thick rim of electron opaque homogenous material which permeates Bowman's membrane.

Other clinical findings include gargoylody physical characteristics, mental retardation, parchment-like skin, deformities of the fingers, hepatosplenomegaly, frequent upper respiratory tract infections, and cardiac decompensation leading to congestive heart failure.

Laboratory tests reveal increased urinary excretion of chondroitin sulfate B and heparitin sulfate.

Treatment of this condition with plasma infusion has been reported by some authors with limited success (4).
TABLE 1.
DIFFERENTIAL CHARACTERISTICS OF SYSTEMIC MUCOPOLYSACCHARIDOSIS

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Type</th>
<th>Transmission</th>
<th>Cornea</th>
<th>ERG</th>
<th>Substance increased in urine</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurler's</td>
<td>I</td>
<td>autosomal recessive</td>
<td>early clouding</td>
<td>affected</td>
<td>chondroitin sulfate B, heparitin sulfate</td>
<td>skeletal deformities, hepatosplenomegaly, infantilism, mental deficiency</td>
</tr>
<tr>
<td>Hunter's</td>
<td>II</td>
<td>sex-linked recessive</td>
<td>not cloudy</td>
<td>affected</td>
<td>chondroitin sulfate B, heparitin sulfate</td>
<td>dwarfism, hepatosplenomegaly, deafness, mental deficiency</td>
</tr>
<tr>
<td>San Fillipo's</td>
<td>III</td>
<td>autosomal recessive</td>
<td>not cloudy</td>
<td>affected</td>
<td>heparitin sulfate</td>
<td>mental deficiency, seizures, mild gargoyles features</td>
</tr>
<tr>
<td>Morquio's</td>
<td>IV</td>
<td>autosomal recessive</td>
<td>grossly cloudy by age 10</td>
<td>not affected</td>
<td>kerato sulfate</td>
<td>dwarfism, skeletal deformities, decreased muscle tone</td>
</tr>
<tr>
<td>Scheie's</td>
<td>V</td>
<td>autosomal recessive</td>
<td>early clouding</td>
<td>affected</td>
<td>chondroitin sulfate B</td>
<td>aortic valvular disease, thickened joints</td>
</tr>
<tr>
<td>Maroteaux-Lamy's</td>
<td>VI</td>
<td>autosomal recessive</td>
<td>early clouding</td>
<td>not affected</td>
<td>chondroitin sulfate B</td>
<td>normal cardiovascular status usually</td>
</tr>
</tbody>
</table>

2. Lowe's syndrome: This syndrome was first described by Lowe and co-workers in 1952 (18). The disease is probably transmitted as a sex-linked recessive gene since all the cases reported thus far have been in boys. The essential enzyme or protein abnormalities are unknown.

Systemic abnormalities include vitamin D resistance rickets, aminoaciduria, proteinuria; mental, psychomotor, and growth retardation; cryptorchidism; and musculoskeletal abnormalities including hypotonia and hyporeflexia.

Besides corneal opacities, ocular changes consist of nystagmus, glaucoma, malformation of anterior chamber angle and iris, and cataracts.

VI. Chromosomal Aberrations.

1. Mongolism (Down's syndrome): This condition is due to trisomy of the 21 chromosome, although involvement of the 22 chromosome has been claimed by other authors. This disease probably results from maternal primary nondisjunction related to age dependent factors. Corneal changes include hypertelorism, oblique eyelid fissures, epicanthus, blepharitis, ectropion, nystagmus, convergent strabismus, high myopia, hyperopia,
color blindness, Brushfield’s spots, blepharocon-junctivitis, and cataracts. Other ocular findings are keratoconus, acute corneal hydrops, corneal edema, corneal ectasia, and corneal leukoma. The systemic findings in this condition are well known and will not be discussed here.

2. Trisomy 13–15 (Patau’s syndrome): As the name denotes, this syndrome occurs as a result of trisomy of any of the 13–15 chromosomes. Ocular changes are best seen histologically. There is usually disorganization of the globe. The anterior chamber and iris are usually not well defined, and retinal dysplasia is a frequent finding. Microphthalmus and atrophy of the optic nerve and ganglion cell layer of the retina are common findings. Intraocular cartilage has been reported in half of the cases studied. Uveal colobomas are also frequent.

The importance of this condition to our discussion lies in the fact that the cornea (fig. 9c) may appear poorly defined and may resemble the sclera or it may be opaque as part of the microphthalmia and poorly developed eyes.

Systemic abnormalities (figs. 9a and 9b) include harelip, cleft palate, polydactyly, umbilical hernia, and malformation of the heart and central nervous system. Children affected seldom survive for more than a few weeks.

Conclusion. There are many conditions that can present with corneal opacification in infancy. Some are vision-threatening conditions that require early diagnosis and prompt treatment; others, although not posing any immediate deleterious effect on vision, may serve as important differential diag-

Fig. 9a—External features of trisomy 13–15. (Courtesy of D. S. Friendly, M.D.)

Fig. 9b—Polydactyly in trisomy 13–15.

Fig. 9c—Photograph of a trisomy 13–15 patient showing microphthalmos and a poorly differentiated partially opaque cornea.
nastic points in the diagnosis of more serious systemic diseases.

Undoubtedly, the list presented can be expanded to include other conditions. Only the more important and relatively common conditions were included.

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Cogan-Guerry Microcystic Corneal Epithelial Dystrophy: A Clinical and Electron Microscopic Study

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Over the past two decades various authors have described changes such as "fingerprint lines," grayish-white microcysts, and geographic or map-like patterns in the corneal epithelium of apparently healthy eyes. As further papers have been published on these types of corneal changes, they have appeared to be very similar in clinical presentation, clinical course, and histopathology.

In 1950, Guerry described the ocular findings of two patients with "peculiar wavy lines, extremely fine in character" which were best seen by retro-illumination (2). Their whorl-like pattern appeared similar to fingerprints and were located in or near the epithelium. Vision was 20/20 in both eyes. A histologic study was not performed.

Cogan et al. in 1964, described five cases, two with histopathologic correlation, that had "grayish-white, discrete but sometimes confluent spheres, measuring usually 0.1-0.5 mm in diameter and situated in the superficial portion of the cornea (1)." If present in the pupillary area, a slight reduction of vision may have been present, and these changes were usually found in asymptomatic healthy eyes. Histologic examination revealed discrete intraepithelial cysts which contained pyknotic nuclei and cytoplasmic debris. A thickened anomalous basement membrane within the epithelial layers was also seen. All the cases reported were in women, an etiology could not be found, and the condition was described as "benign and usually asymptomatic."

In 1966, Guerry reported nine cases of microcystic dystrophy of the corneal epithelium similar to that described by Cogan and found associated with the grayish-white dots "many irregular, faintly gray configurations varying in size from a millimeter or so to several millimeters . . . The border of these map-like areas appeared a darker gray than did the background (3)." In one case, corneal epithelium was obtained for histopathological examination. The pathological changes were similar to those reported by Cogan et al. The author stressed that these map-like or geographic changes could easily be missed unless diffuse illumination was used. These changes seemed to appear more frequently in women since seven of the nine cases reported were females.

In 1966, Wolter et al. reported an additional case of microcystic dystrophy (5) and in 1972, Trobe et al. reported a series of 35 patients which manifested some combination of the dot, fingerprint, or map-like patterns (4). The histopathology in these 35 patients was the same as that reported by Cogan et al., and Guerry. Ocular pain in the form of foreign
body sensation was the presenting symptom of 54% of the patients in their series, and the treatment the authors felt to be most successful was hypertonic sodium chloride ointment. When the pain persisted, mechanical debridement and pressure dressing were effective.

The purpose of this paper is to present a case of microcystic corneal epithelial dystrophy with light and electron microscopic studies of the pathological corneal epithelium.

Case Report. A 44-year-old married caucasian female secretary was first seen during October, 1971, with the complaint of blurred vision in the left eye for the last four months.

Past medical history revealed a normal ocular examination during March, 1970. Vision at that time in the right eye was correctable to 20/15 with a −1.25 sphere. Vision OS was correctable to 20/15 −2 with a −1.25 −0.75 ax 135 sphero-cylinder. For many years, she gave a history of an occasional foreign body sensation of short duration in the right eye upon awakening which never required medical treatment. She had recently been examined by another ophthalmologist who found decreased vision in the left eye but no pathology to explain it.

Ocular examination at the time of complaint of blurred vision OS revealed a vision OD of 20/15 with correction and a vision OS of 20/25, described as very distorted by the patient, with a −1.75 −1.25 ax 115 correction. Both corneas revealed pooling of fluorescein solution on the surface but no staining. The irregular fluorescein pattern on the right cornea was a superior temporal small area and on the left cornea a large apical area (fig. 1). In these areas on the cornea, the image of the Placido disc and the keratometer mires were also distorted. Slit lamp examination by direct illumination appeared normal; however, retro-illumination revealed superficial thin gray lines producing a geographic pattern on the cornea. Mild central corneal guttata was present in both eyes. Corneal sensation and Schirmer tear test were normal in both eyes. The intraocular pressure by applanation was 18 mm Hg OU. The retina and disc were unremarkable in each eye; however, the view of the left posterior pole was distorted because of the corneal pathology.

The patient symptomatology remained unchanged as did the geographic or map-like corneal areas during follow-up visits. During this time small, round microscopic, epithelial grayish deposits surrounding the geographic area were visualized in the right cornea. These deposits remained, but they changed in location, size, and number.

Four months after the patient’s initial visit, she elected to undergo corneal epithelial curettage of the left eye since the blurred vision bothered her during work. The corneal epithelium was scraped after 4% cocaine ophthalmic solution was instilled for anesthesia. The peripheral epithelium required more manipulation for removal than the central epithelium which lifted off easily. The eye was patched with antibiotics, cycloplegic drops, and pressure dressing. Re-epitheliation occurred in three days without complication.

Over the past eight months, the corneal lesion of the right eye has persisted with only slight variation.
The left cornea appears normal with direct and retro-illumination. Vision OS with the patient's original corrective lens is 20/15.

Materials and Methods. After removal of the corneal epithelium in one piece it was immediately fixed in 10% formalin, dehydrated in increasing concentrations of ethanol, and embedded in paraffin. Sections were cut 8μ thick and stained with hematoxylin and eosin, Masson's trichrome, and by the periodic acid-Schiff reaction. When approximately half of the epithelium had been sectioned and stained in this way, an examination of the fine structure became desirable, as an afterthought. The remaining epithelium was de-paraffinized, osmicated, and re-embedded, partly in Epon, partly in Durcupan ACM, according to the method described by Zimmerman et al. (6). Sections approximately 1μ thick were mounted on glass slides and stained with toluidine blue. Thin sections 80-100 μ thick were collected on unfilmed copper grids and stained with uranyl acetate for 6–8 minutes and lead citrate for 10 minutes. The sections were viewed with a RCA 3-G electron microscope and photographed on Kodak EM film #4498.

Results and Comments. Light Microscopy. The paraffin and 1μ epoxy sections showed apparently normal corneal epithelium with an anomalous basement membrane (fig. 2), as described first by Cogan et al. (1) and confirmed and extended by Guerry (3). In some areas the thickened basement membrane extended into the epithelium between the deeper layers of the cells. In a few sections the basement membrane appeared interrupted with the loose ends forming a knob or curl. Several cysts of different sizes located at different levels were found. Some were underneath the insinuated basement membrane and a few immediately under the surface. (figs. 3 and 4). These cysts contained cell debris.

Electron Microscopy. Before the findings on the ultrastructural level are reported, the limitations of the applied method should be mentioned. Because of the unusual tissue preparation outlined in materials and methods, a certain degree of artifactual change of the tissue can be assumed to have taken place, primarily in the cytoplasm. The empty spaces...
which are normally present in the corneal epithelium, particularly in the cytoplasm of the surface cells, appeared enlarged and more numerous. Since the tissue was fixed immediately after removal, post mortem changes are very unlikely. However, it is not possible to determine whether the appearance of the cytoplasm is due primarily to the preparation of the tissue or due to the pathologic condition, that is, the dystrophy. Therefore, no conclusions will be made about the fine structure of the cytoplasm, the mitochondria, and the Golgi apparatus. On the other hand, the granular or rough endoplasmic reticulum (rER), fibrils, and desmosomes appeared to be normal. For these reasons, this preliminary ultrastructural study is limited mainly to the two characteristic features of the dystrophy, namely the microcysts and the thickened basement membrane.

The cysts ranged in size from 5μ to 50μ. A portion of such a cyst underlying the aberrant basement membrane is shown in figure 5. It contains a homogeneous substance, surrounded by the same dense material that forms the border of the cysts (fig. 6). No definite membrane enclosing the cysts can be recognized.

If this fact could be confirmed in a future exclusively ultrastructural study, it would mean that these cysts are not true membrane bound cysts which by some mechanism migrate to the surface, but instead represent pseudocysts, that is, holes, with some debris from degenerated cells, which are transported to the surface with the surrounding cells. Whether those cysts seen underneath the aberrant basement membrane remain “trapped” or also reach the surface, and how they “escape” is not known. Similarly, it should be interesting to know whether the aberrant basement membrane also moves to the surface with the cells that are constantly formed in the basal layer. A slit lamp examination at regular intervals could perhaps provide an answer.

A relatively small cyst, about the size of a single cell, is seen in figure 7. This illustration also shows that, although cell membranes are not prominent, cisternae of rER, interdigitating cell processes, intercellular spaces, and desmosomes are intact and normal. Also visible is the difference in the density of the cytoplasm between wing cells and surface cells.

The basement membrane is shown at high magnification in figure 8. Two slightly different regions can be recognized. The anterior portion has a marbled appearance, with fibrous material surrounded by irregular strands of a homogeneous sub-

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Fig. 5—Portion of corneal epithelium showing thickened and insinuated basement membrane (BM) and border of a microcyst containing homogeneous material (16,000X). IS—intercellular spaces, D-desmosomes, F-fibrils, G-glycogen, C-cyst.

Fig. 6—Portion of microcyst with homogeneous material. No membrane surrounding cyst can be seen (25,000X).
stance. The posterior portion consists of tufts of fibrous material. The thickness of the anomalous membrane ranges from 2 µ to 6 µ, that is, approximately 100 times the regular thickness of the normal basement membrane.

Previous histopathological case reports of this dystrophy have demonstrated reduplication of the basement membrane (1, 3) but not actual loss of basement membrane as seen in this patient's epithelium. This loss of basement membrane does not appear to be an artifact since the edges of the remaining membrane are curled and interdigitated between the corneal epithelial cells. This loss of basement membrane may be due to a degenerative process and could produce some of the debris containing "cysts."

**Diagnosis.** The corneal changes when mild are very difficult to recognize as has been pointed out by the authors. The most useful examination procedure to detect these corneal changes is to apply topical fluorescein to the lower cul-de-sac, have the patient blink a few times, and then hold the lids open for 30 to 60 seconds to allow the fluorescein to pool. The dystrophy pattern then becomes very apparent when viewed with the slit lamp and blue light. It should be noted that this pooling of fluorescein is entirely different from the break up of tear film in sicca problems which is also seen with the lids held open.

In summary, microcystic epithelial dystrophy of the cornea as described by Cogan and Guerry has become a well documented clinical entity. In this paper, a case report and preliminary electron microscopic findings of a patient with this dystrophy were presented. This case showed a thickened, two-layered basement membrane which was completely missing in some areas. The second characteristic change was that of cystic epithelial areas containing debris. The possible significance of these findings...
and a diagnostic technique for detection of these corneal changes were discussed.

REFERENCES


Cryopreserved Corneal Tissue: A Practical Guide to Its Use

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The use of cryopreserved corneal tissue stored at $-179^\circ$ C in liquid nitrogen for up to six months has become more popular during the past two years. This seems to be a useful technique for the future, not only because it will allow a better utilization of the still sparsely available corneal tissue, but also because it will make the life of the corneal surgeon easier, by allowing him to schedule his transplants during routine operating time rather than in the evenings or during holidays.

This paper will not deal with the actual technique of cryopreservation and the studies done to insure us of the viability of the corneal endothelium if the technique of cryopreservation has been scrupulously followed. Neither will we discuss the actual results obtained when using cryopreserved tissue. Our personal experience with this type of tissue is limited to only a handful of cases, meaningless for statistical purposes, and we would have to rely solely on published results or personal communications from other corneal surgeons.

What we will explain in detail is the technique we have developed to actually use cryopreserved tissue in the operating room. Anyone who has followed the development of this type of transplant material has heard and read how important it is to follow exactly certain steps, but nowhere in the literature is there a guide as to how, in practice, the different steps are to be carried out. We know of no other procedure in ophthalmology where absolute adherence to the strictest set of guidelines is absolutely necessary.

Earlier attempts to use frozen corneal tissue frequently failed because the absolute need for a very exacting thawing process had not been recognized. The time element for proper thawing is counted in seconds, which makes meticulous preparation and a carefully thought out technique absolutely necessary if we are to achieve clear grafts.

The cornea has been preserved in a solution of sucrose and dimethylsulfoxide (DMSO) and albumin, and it is well known that DMSO is toxic to the warm endothelium; therefore, DMSO is added during the freezing process in an ice bath and does not injure the endothelial cells when it is frozen and kept frozen in the storage cannister. When thawing, the process has to be done rapidly, but not so rapidly that the DMSO can injure the endothelium. Once the cornea has been thawed it is placed in 25% salt-poor albumin at which time the metabolism of the cornea starts again. It can be kept in that solution for a maximum of 10 minutes, but should be placed in the recipient eye as soon as possible so that the normal metabolites can start repairing some of the damage done to the endothelial cells, even with the best freezing technique, and a fatal process of anoxia will not further damage the endothelial cells.

Surgical Technique.

1. The cornea arrives in the operating room from the eye bank in a widemouthed thermos bottle. On the top tiny holes have been made to allow some venting of the liquid nitrogen which fills half of the thermos bottle. Taped to the side of the thermos is a long forceps which permits pick up of the plastic vial floating freely in the nitrogen and which contains the
Fig. 1—Removal of plastic vial from widemouthed thermos filled with liquid nitrogen.

Fig. 2—Plastic vial open, showing the inner vial with frozen cornea and suture.

small glass tube with the frozen cornea and preservative (fig. 1).

2. The patient is prepared in the usual fashion with the surgeon wearing two pairs of gloves. The surgeon then removes one pair of gloves, drapes the patient, and gives the usual O'Brien and retrobulbar blocks for the routine ocular anesthesia. The operating microscope has been positioned and focused either before the preparation of the patient or at the end of this step #2.

3. The surgeon will have to do the critical thawing himself unless he can rely on an assistant who is totally familiar with the procedure and will not deviate one iota from the course to be outlined. For our purposes here, we will assume that the surgeon himself will want to be in charge of this most important step. While still wearing the gloves, the surgeon steps out of the operating room either into the utility room or into the wash up area, opens the thermos, and picks up the plastic bottle floating in the nitrogen. While a circulating nurse closes the thermos again, the surgeon wraps the plastic bottle in a towel and opens it. As there may be liquid nitrogen inside the plastic bottle, the precaution of using a towel in opening it is necessary to prevent accidental spilling of the nitrogen onto the surgeon’s face, which could happen with a rapid warming up (fig. 2).

4. The small glass tube is removed from the outer plastic vial and is placed either in a water bath or under the faucet (if previously it has been established that the temperature is 60°) for exactly 50 seconds. The glass vial is rotated slowly during this 50-second warming process so that the water reaches all areas of the glass vial. It is important not to move the glass vial too rapidly as the thawing ice crystals could damage the endothelium. At the end of 50 seconds, a small ice ball should remain attached to the center of the cornea, and this is allowed to thaw at room temperature, which usually takes about 20 to 30 seconds. If, after removal from the hot water, there is no ice ball, the thawing has been too fast, the so-called thermal runaway has occurred, and the cornea is not suitable for a penetrating keratoplasty (fig. 3).

5. The preserving fluid bathing the cornea is now poured off and 1 to 1.5 cc of 25% salt-poor albumin is added to the cornea. The glass tube is brought back to the operating room and placed on a sterile towel in an ice bath (fig. 4).

6. The surgeon will now remove his gloves, put on gown and fresh gloves, place the bridle suture, and trephine the recipient eye with a Castroviejo trephine of whatever
Fig. 3—Cornea being thawed for 50 seconds under 60°C water.

Fig. 4—Thawed preserving fluid being poured off and albumin being added.

Fig. 5—Cornea, endothelial side up, being placed on the punch.

Fig. 6—Castroviejo trephine is being fastened to the punch head.
Fig. 7—Cutting of the graft by pushing down the plunger of the punch.

size the surgeon has decided beforehand. It is important to note that the cut has to be made with a Castroviejo trephine and no other. The corneal button, after having been cut completely, is left in the recipient eye.

7. The thawed out cornea with its small suture in the scleral rim still attached is now removed from the glass tube with albumin and placed, endothelial side up, in the corneal punch. The suture is cut, and the plastic ring is placed over the cornea for better fixation (fig. 5).

8. The corneal punch is built in such a fashion that any size Castroviejo trephine can be screwed into its top. The same trephine

used on the recipient eye should now be fastened to the top of the corneal punch (fig. 6).

9. The punch is lowered by pressing with both thumbs over the top which should allow a clean cut of the cornea (fig. 7).

10. The trephined button is then placed inside the recipient bed after the previously cut recipient button has been removed. The transfer from the punch to the eye can be accomplished with any spatula or lens loop.

11. The previously described steps 3 through 10, can be easily accomplished in less time than the 10 minutes maximum in which the thawed cornea can remain in albumin.

Special Measure in Aphakia. Obviously in those cases where a Bonacoloto-Flierenga ring has to be used and possibly an anterior vitrectomy needs to be done, the time limit of 10 minutes is too short for comfortable operating, and the technique has to be changed slightly. In those cases, we advise, after draping of the patient, that the surgeon put on gown and gloves, anesthetize the patient, and then suture the ring in place. The proper thawing can then be carried on as outlined, and after the surgeon returns to the O.R. with the cornea in albumin, he should change gown and gloves and proceed as described.

In summary, the thawing of the cryopreserved cornea needs to be done in 50 seconds, and the thawed cornea has to be inside the recipient eye within 10 minutes. These facts require a completely thought out technique with which the surgeon needs to be thoroughly familiar in every minute detail before he ever attempts to use cryopreserved tissue.
Cytomegalovirus Infection of the Eye in a Case of Renal Homotransplantation

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Ocular involvement in cytomegalic inclusion disease, a viral infection usually seen in infants, is rarely seen in adults (4) except as a terminal infection complicating diseases such as malignant lymphoma and leukemia (1). In infants, chorioretinitis and the frequent finding of intracranial calcification make clinical differentiation from toxoplasmosis difficult (5). This report presents a case of cytomegalic inclusion disease involving the eyes of an adult who had received a renal homotransplant.

Case History. An 18-year-old white man was treated at another hospital in March for chronic renal failure. Renal biopsy revealed chronic glomerulonephritis. Serum calcium was low to normal, and inorganic phosphorus was elevated. Treatment consisted of vitamin D 200,000 units b.i.d. and calcium gluconate 1½ grains t.i.d. Three months later extensive calcification of major vessels was detected radiographically. Serum calcium was 17 mg per 100 ml. In August, the patient was admitted to Medical College of Virginia Hospital. His blood pressure was 160/104, the pulse 104, the respirations 20, the temperature 99°F, and the weight 103 pounds. The hemoglobin was 9.8 g per 100 ml, the creatinine clearance 0.5 ml per minute, the total protein 5.8, the albumin 2.9, and the globulins 2.9 g per 100 ml. Radiographs showed demineralization of all bones. Hemodialysis was performed. Cystoscopic examination revealed an anomalous left ureteral orifice. In October, the patient underwent bilateral ureteronephrectomy, posterior bladder neck resection, and splenectomy. A kidney taken from his father was transplanted. Azathioprine 175 mg, prednisone 60 mg, and actinomycin D 200 mg per day were given. Urine excretion was adequate. Urine culture yielded S. aureus, coagulase positive, which responded to antibiotics. In November, a low grade fever began which progressed to a spiking pattern and persisted until death. Blood cultures were sterile. Numerous antibiotics, and Mycostatin® had no effect. On December 15, a chest radiograph showed pulmonary infiltration. The peripheral white cell count was abnormally low, and azathioprine was discontinued. One week before death the serum urea nitrogen reached its minimum value of 19 and creatinine 0.8 mg per 100 ml. There was no clinical evidence of ocular disease. The patient was thought to have “transplantation” pneumonia and died in December, approximately nine months after his admission. The autopsy findings included chronic pyelonephritis, nephrolithiasis, bacterial microabscesses of pancreas, heart, and kidneys as well as cytomegalic inclusion disease of the lungs.

Gross and Histologic Examination of Eyes. Each globe measured 25 × 24 × 24 mm and was cut in the vertical plane and showed no gross lesions. Microscopically the ciliary body and iris showed no lesions. The retina of the posterior segment was involved by a few small white plaques in a few places. The lesion was most prominent in the choriocapillaris and vascular layer of the choroid, but it did extend to Bruch’s membrane in several areas. In these areas the infiltrate was sparse and consisted of plasma cells, a few neutrophils, pigment laden macrophages, and nuclear debris. Cellular composition was similar in all nodules, but some were distinctly related to small vessels in the choriocapillaris and the vascular layer of the choroid. These areas did not contain un-
equivocal inclusion bodies. However, there were typical basophilic inclusions surrounded by a halo in swollen endothelial cells of the choroid (figs. 1 and 2). Many smaller basophilic inclusions were seen in the cytoplasm of the endothelial cells. In a few areas the necrosis extended into the retina between the outer plexiform and inner nuclear layers, and in some they involved the entire thickness of the retina. The optic nerve contained many similar areas of necrosis, but the optic nerve head was uninvolved (fig. 3).

Comment. Bilateral chorioretinitis caused by cytomegalovirus was seen in this patient. Immunosuppressive therapy necessary for his kidney transplant seemed a contributory factor to the disease. As described by de Venecia and co-workers, the ophthalmoscopic appearance of cytomegalic inclusion disease is distinctive (2). This patient had no symptoms referred to the eyes. While certainly not unexpected in view of the pulmonary cytomegalovirus pneumonia, this seems to be a rare development in the eyes of transplant patients. The incidence of ocular cytomegalovirus in transplant patients may be higher, however, since the eyes are not routinely removed at autopsy. The optic nerve showed lesions in the present case. These were similar to those seen in the choroid. Schneck (3) described probable cytomegalovirus infection which showed similar nodules in the brains of 12 of 34 patients who expired following renal transplantation. In 2 of these 12 cases intranuclear inclusions were found.

Ocular lesions in infants were described by Smith as peripheral involvement of choroid and retina (5). However, retinal involvement in adult cytomegalic inclusion disease was usually described at the posterior pole. The lesions in this case were in this location but mainly damaged the choroid with relatively slight destruction of the retina.

Intranuclear inclusions were difficult to find. This is not unusual. The reason is not clear but perhaps related to the extensive necrosis. The endothelial cells of the vessels of the choroid were swollen, and several contained basophilic intranuclear inclu-
sions. In spite of the fairly extensive focal areas of necrosis, the patient had no symptoms referable to the eyes.

In summary, an adult who had a renal homograft transplantation died of cytomegalovirus pneumonia. Examination of the eyes showed a chorioretinitis with typical cells and inclusion bodies.

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The Effect of Electrical Current on the Crystalline Lens*

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Development of lenticular opacities from lightning was first described by St. Ives (21) in 1722. Even today cataract formation by this mode is a rarity. However, the development of cataracts from accidental exposure to artificially generated electricity has become more frequent and has assumed some medico-legal importance. Cataract secondary to artificially generated electrical current was first described by Desbrieres and Bargy (6) in 1905. Since that time numerous cases have been reported in the literature. The nature of the current producing cataracts varied. However, alternating current of 50 to 60 cycles per second was responsible for the majority of cataracts detailed in the literature. Since all cases resulted from accidental contact with a commercial power source, amperage would seem to be high while voltage varied considerably from 60,000 v in a case of Becker (1) to 220 v by Cavka (3), Horton (11), and Godtfredsen (8). The extent and the severity of the injury in many instances was not related to the voltage. However, data on exposure time are sparse and often unreliable so that the total amount of electrical energy received is, in most instances, a matter of speculation only. An excellent summary of the cases described in the literature up to 1961 is provided by Long (19). Since then a number of additional case reports have appeared in the literature reporting cataractous changes following accidental exposure from 240 to 5,000 v (18, 9, 17, 12, 14). The case of Klima (14) and co-workers is interesting as the accident caused severe bilateral iritis followed by typical electrical cataracts with no visible burn anywhere on the body surface. Koskenoja and Runeberg (15) were sufficiently concerned about the problem of electrical cataracts to examine 237 psychiatric patients who had received up to several hundred therapeutic shock treatments, but they did not discover any traumatic lens changes in this group.

The experimental production of electrical cataracts in animals was first successfully attempted by Hess (10) in 1888. He subjected rabbits and cats to multiple electrical discharges (6 to 20) at short intervals from Leyden jars in the head region close to the eye. He observed miosis, anemia of the iris, conjunctival chemosis, and corneal opacification. Lens opacities were observed by him in enucleated eyes as early as 2 to 4 hours after exposure.

These experiments were repeated in 1900 by Kiribuchi (13) who produced reversible lens opacities after 30 to 50 shocks of 1-second duration using a voltage of 70 to 160 v. Similar experiments were conducted by Kuwabara (16), Pastega (20), Frese (7), and Croci (5). The latter produced opacities in 7 of 20 animals using a power source producing 10,000 to 100,000 v with a very low amperage.

In 1936, Comberg (4) attempted to clarify if electrical cataracts are caused by iritis or if they are the result of direct passage of electrical current through the lens. He placed electrodes on the anterior pole of the cornea and the posterior pole of the proptosed globe and used multiple (up to 60) discharges from Leyden jars as a power source. Fourteen of 15 animals shocked by this technique developed lenticular opacities. In 7 animals the

* This study was sponsored by the Medical Department of Reynolds Metals Company, Inc., Richmond, Virginia.
opacities progressed over the observation period, in 5 instances they remained stationary, while in 2 animals the cataracts regressed. He could observe such opacities as early as 30 minutes after shocking which led him to believe that the electric current itself, rather than the anterior uveitis, was responsible for the lens changes.

Bellows and Chinn (2) noted that isolated beef lenses subjected to high voltage current showed a marked decrease in water uptake when immersed in distilled water. They speculated on the possibility of an injury to the lens epithelial cells being responsible for the reduced swelling of exposed lenses; however, they did not reach any definite conclusions as to the mechanism of the production of electrical cataracts.

An excellent experimental study to determine the amount of energy necessary to produce electrical cataracts was described in 1963 by Long (19). He exposed proposted rabbit eyes to 200 shocks of .2 seconds each at intervals of 4 seconds using a 50 v alternating current. Total exposure time was 40 seconds, and total energy delivered to the eye was 50 times .1466 a or 7.25 watt-seconds for a total of 291 watt-seconds. The slightest amount of current in his experiment to produce minimal cataractous changes was 100 shocks of .25 second at 14 v, representing a total energy of 50.7 watt-seconds. Long (19) also gives an excellent description of the clinical and histological appearance of the experimental lens opacities.

We were prompted in this study by the fact that all previous experimental studies used a multiple repetitive shocking arrangement, something which would be unlikely to occur in any type of industrial or household accident. The aim of this study was to produce lenticular opacities by a single electrical shock of short duration such as is most commonly seen in accidental contact with electrical current. By keeping the exposure time short, the thermal effect upon the eye from electricity was avoided. Survival rate of the animals was acceptable up to 500 v shocks. Anterior segment uveitis was minimal lasting only from several hours to three days, and corneal opacities were extremely rare when resistance was kept low by keeping the shaved lower lid of the globe adequately moistened with normal saline. Physiology was preserved by maintaining the globe in situ rather than using a proptosing device.

Experimental Apparatus. In order to study the effects of single electrical shock upon rabbit lenses, a pulse variable voltage source was built. This is operated on 120 v AC, 60 Hz and has a 0 to 120 v variable transformer connected across the primary of a 120 to 560 v center-tapped step-up transformer. The separate windings of the primary and secondary of this transformer provide isolation of the output circuits from the power line. Either of two output ranges, 0 to 280 v or 0 to 560 v, may be selected by a switch which also determines the appropriate scale on the 0 to 300 and 0 to 600 v RMS voltmeter. The duration of the pulse is preset on an interval timer with manual reset and has a range of 0 to 6 seconds. It is initiated by a push-button operated relay. Pulse current, as well as pulse duration, are measured across a 10 ohm .5% shunt in series with the output circuit. Leads with clip-on connectors are used for making contact to the experimental animal. Pulse current and time are measured with the Tectronex type 549 storage oscilloscope which is calibrated to 100 ma peak current per centimeter on vertical sweep and 100 msec per centimeter on the horizontal sweep. The unit is housed in a metal cabinet with the voltmeter, timer, and controls on a sloped front panel which has provisions for plugging in the oscilloscope and clip-on leads. The cabinet is grounded (fig. 7).

Lens Changes Following Electroshock. Mature Dutch rabbits weighing from 1,600 to 2,500 g were used for all experiments. The earliest changes were observed beneath the anterior capsule consisting of an accentuation of the rabbit lens vertical suture line. The area around the sutures assumed a feathery outline thus making the vertical sutures stand out more clearly (figs. 1 and 2). As this feathery appear-

Fig. 1—Accentuation and feathery appearance of anterior suture line.
ance diminished, there appeared a large number of anterior subcapsular vacuoles in the same area, often clustered around the suture line. These vacuoles, in most instances, increased in number up to two weeks after the shock. Following this in the low amperage shock, they became stationary and very seldom regressed so that there was only an occasional anterior vacuole visible (figs. 3 and 4). In the more heavily shocked animals after two weeks, the vacuoles were gradually replaced by superficial ring-shaped, scale-like opacities. The density of the opacities increased for about four weeks, after which time the opacities showed little or no change over the observation period of four months (figs. 5 and 6).

Contrary to the findings of Long, no changes were observed in our experiments in the posterior capsule, and in no instance did any of the opacities progress to involve more than the immediate anterior subcapsular area.

Long (19) reported lens changes by his multiple shock technique with an average of 291 watt-seconds. The slightest exposure to produce such changes was given by him as 50.7 watt-seconds.

In total, 32 animals were shocked in our experiments with exposure times ranging from 100 to 400 msec and voltages of 150 to 500 v AC. Peak amperage as read on the storage oscilloscope varied from a high of 900 ma to a low of 100 ma. The peak amperage was converted to RMS amperage by multiplication with a .707 factor.

Twenty-six of the animals survived for the observation time and are summarized in our findings. Total power applied to each eye was calculated as watt-seconds. It appeared from a tabulation of the
results that only the total amount of energy delivered was significant in terms of the extent of the opacities developed. Results were divided into three groups. In the first group no biomicroscopically visible changes were observed. In the second group minimal changes consisting of anterior suture feathering, with or without anterior subcapsular vacuoles, occurred which either regressed or remained stationary. The third group developed a typical anterior scale-like opacity covering variable parts of the lens.

**Group I:** Eight animals receiving a single shock of 1.06 to 12.15 watt-seconds developed no visible lens changes.

**Group II:** Ten animals receiving single shock exposures of 6.2 to 26.6 watt-seconds developed minimal lens changes. Eight of these remained stationary over the observation period while 2 regressed to the point where, after 12 weeks, no changes could be detected by slit lamp examination. The lowest powers with which changes were observed were 6.2 and 7.07 watt-seconds.

**Group III:** Eight animals receiving single shocks of 22.98 to 79.54 watt-seconds developed typical anterior subcapsular lens opacities which involved a major portion of the pupillary area when the eyes were maximally dilated. The data for all animals are summarized in Table 1.

In summary, the cataractogenic properties of electric current were studied. Previous observations dealing with this subject utilized a multiple shock technique—something which is unlikely to occur in any accidental exposure. This study focused on the production of lens changes in rabbit eyes following single exposures of measured electric current. The biomicroscopic characteristics of these changes were described. Minimal lens changes were produced by single shock exposures ranging from 6–26 watt-

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**Table 1.**

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<th>MINIMAL CHANGES</th>
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seconds while typical electrical cataracts were produced by current of 23–80 watt-seconds. Exposure times were usually 250 msec or less since the survival rate of animals subjected to longer exposures made such studies unfeasible.

Author’s note: The author acknowledges the technical advice and assistance of Messrs. Raymond Ruffin and Harry Mueller of the Department of Biophysics.

REFERENCES


Radiation Cataract: Biomicroscopic Observations in Rabbit, Monkey, and Man*

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The great variation in dose levels of ionizing radiation required to produce lens changes in various species has not been adequately explained, nor has an acceptable theory been postulated.

Single exposures of rabbit and monkey (Macaca mulatta) eyes to 1 Mev/x-irradiation and to 20 and 100 Mev/protons beam energy have required enormous dose differences to produce minimal lens changes in the two species, and the latent period after exposure and first observable lens changes was equally remarkable.

The term "cataract" has been purposely avoided in this text because of the variation in definition by various investigators and/or clinicians. It should, therefore, be understood that the most minute changes described can be regarded as a sensitive "biological dosimeter" in radiation damage to the lens, though the changes certainly would not affect vision.

The type or configuration of lens changes in these two species was quite different. This can be understood on the basis of the structural differences of their crystalline lenses based on the location of the suture lines.

On the other hand, lens changes in the monkey and those described in man are very similar. However, following irradiation, the latent period and dose requirements to produce lens changes also vary to a great extent.

Figure 1 illustrates the in vivo lens changes in the rabbit after ionizing radiation, arbitrarily classified in grades of severity based on biomicroscopic findings. Such changes were similar for x-ray and proton irradiation, although dose requirements to produce such changes varied with the energy and dose level (fig. 2). A brief description of the various degrees of observed lens changes follows.

Grade 0: Double contoured white horizontal suture lines in posterior subcapsular areas, fading into a fine haze towards the center of the lens. No coarse or medium sized dots and no more than five dots present.

Grade 1: Same as 0, but moderate number of fine dust-like dots and a few larger dots, white and sharply outlined in the posterior cortex along both sides of the suture lines. The suture line shows branching mainly on the two ends but also along the entire course. Less than five coarse dots along the posterior suture lines.

Grade 2: Any features described under 0 or 1, but in addition, one or two white linear opacities near the suture lines and oriented in the direction of the individual lens fibers in that particular area. Coarse dots range up to 10.

Grade 3: Same as 2, but up to 30 linear opacities and/or increase in larger dots.

Grade 4: The suture line is branched but shows, in addition, interruptions in continuity, besides the features described in 3, and up to 50 and above coarse opacities.

Grade 5: Increasing number of hard white dots and linear opacities. Beginning of a haziness in the posterior cortex.

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LENS CHANGES
WHOLE LENS IRRADIATION

Fig. 1—Schematic drawing of observed lens changes in the Dutch rabbit eye after whole lens irradiation. The number underneath each drawing represents the grade of lens changes (see text). Zero represents the initial appearance of all lenses used in the study. One shows changes which occur with age. Two through 9 show lens changes, in order of increasing severity, which developed in irradiated lenses during the observation period.

**Grade 6:** Same as in 5, but more pronounced haziness. Suture line still double contoured with branching.

**Grade 7:** Suture lines in some areas thickened and dense white but partially still double contoured. Haziness in posterior cortex increased with radiating pattern particularly in central portion of the posterior cortex.

**Grade 8:** Double-contoured suture lines have disappeared leaving only dense thick white fragments in the posterior cortex within the veil-like haziness and numerous heavy dot-like opacities and occasional vacuoles. There were no changes in the lens periphery (biomicroscopically). Few dot-like opacities might be located in anterior cortex.

**Grade 9:** Same as in 8; however, all changes are somewhat more anterior with respect to the posterior capsule. The earlier suture lines appear to have contracted into a thick rock-like mass with a rough cratered surface. The veil-like haziness extends from this mass in a somewhat posterior direction toward the periphery.

From the *in vivo* study it was concluded that the effect of proton irradiation for the two energy levels (20 Mev, 100 Mev) in producing lens changes is significantly greater than the effect caused by 1 Mev x-radiation. Also, exposure to the higher LET 20 Mev proton beam results in more pronounced lens changes as compared with effects after a lower LET 100 Mev proton irradiation at identical dose levels and single exposure (fig. 3). The similar biomicroscopic appearance of such lens changes may indicate that the pathogenesis is the same for the two types of irradiation. Onset of first detectable lens changes after proton beam exposure was approximately the same as observed after x-ray exposure; however, the progression of lens changes to more severe degrees appeared slower for the former. No further progressions were noted after 12 months post irradiation at which time a “plateau” was reached which was not reversible over several years of follow-up examinations.

Latent periods between day of exposure and first detectable lens changes in rabbits varied slightly with beam energy and dose levels but fell in a time span of two-and-a-half to four months post irradiation in the case of single dose exposure. For fractionated doses, one exposure per month for a total
of 10 months, and two proton beam energies (20 and 100 Mev), the latent time is illustrated in figure 4. The final degree of lens changes for these two modes of radiation is presented in figure 5.

Comparing the grades of final lens changes after single radiation exposure with those observed after equal total doses, but administered in fractionation of 1 exposure per month over a 10-month period, it was obvious that the lens changes produced after single exposures were significantly more severe than those developed after fractionated exposures. This can be expected and has long been recognized and attributed to a biological repair mechanism in the case of protracted irradiation. It can be equally well understood that the rate of progression in lens changes is slower after fractionated exposures than after single exposures. The final degree of severity of lens changes was found to be equal if the total fractionation given was about twice that of single exposures, that is, 500 R x-ray given over 10 months caused about the same effect as 250 R x-ray given as a single dose. This observation also holds true for protracted and single proton beam irradiation within the limits of the experimental model used in this study.

From preliminary observations, these lens changes in the Rhesus monkey were arbitrarily categorized into seven severity grades and illustrated in figure 6. Grade 0 represents the normal, non-irradiated lens. Only animals with grade 0 prior to irradiation were used in this investigation.

**Grade 0**: Normal clear lens with occasional few fine and thin irregular lines on the posterior capsule due to vitreous adhesions. Besides some mild cortical haziness sometimes appearing with aging of the animal, no other age-related lens changes.

**Grade 1**: Few fine glistening dots in the posterior subcapsular region.

**Grade 2**: Fine crystalline appearing precipitates
Fig. 6—Schematic drawing of observed lens changes in the Rhesus monkey eye after whole lens irradiation. Grade 0 represents the initial appearance of all lenses used in this study. Grades 1 through 7 show lens changes as they developed with time and various modes of radiation exposure.

Located in the posterior subcapsular region were increased in number in the presence of a few small vacuoles. Lens otherwise clear.

Grade 3: Posterior subcapsular generalized haziness with many small, dense, dot-like opacities and a moderate number of fine vacuoles. Several areas showed more dense haziness.

Grade 4: Similar findings as in Grade 3, but the fine opacities appear in greater number and accumulate particularly in the posterior pole region.

Grade 5: Dense posterior, “typical” radiation cataract (referred to in literature as early radiation cataract). Many vacuoles primarily within posterior pole region of doughnut-shaped circular but irregular lens opacities. From this area in radiating fashion general haziness in which many fine crystalline appearing dots are interspersed. Anterior cortex still free of changes.

Grade 6: Posterior and anterior subcapsular cortical haziness and densities in radiating fashion with many whitish dot-like opacities and vacuoles of various sizes.

Grade 7: Mature cataract in which many vacuoles can still be seen in the anterior cortex. Difficult to distinguish from any other type of mature cataract if progression has not been followed, mainly through the stages of Grade 5 and 6.

Again, there were no obvious differences in the appearance of those changes after x-ray and proton irradiation though the dose requirements for the different modes of radiation, that is, beam energy and type of radiation to produce similar severity grades, varied.

From the accumulated data over a two-and-a-half-year observation period, no lens changes were detected after proton (100 Mev beam energy) exposure and 250 rads single dose. Of three animals exposed to 500 rads, only one lens showed Grade 1 changes at the two-and-a-half-year examination date. Of three animals which received 750 rads, one did not show any observable changes, while two presented Grade 1, which in one animal progressed to Grade 2 at the three-year examination follow-up. In three animals which had received 1,000 rads single exposure, only one showed Grade 1 changes two years post exposure which progressed to Grade 3 over the following six months. One animal which did not present any changes on the examination date at two and one-half years progressed rapidly to a Grade 5 at the time of three years post irradiation; one animal of this group presented Grade 1 changes at the two-and-a-half-year examination without further progression at this time. Because of the possible rapid progression after first minimal changes have become manifest, biomicroscopic examination is at present scheduled in three-month intervals.

Because of the different manifestations of lenticular changes in these two species (monkey and rabbit), comparison of energy and dose levels are made only for the first detectable minimal lens changes.

Results of protracted radiation and its effect on monkey lenses are at present under investigation and no conclusive statements can be made at this time. Based on the observations made on rabbit lenses, however, it can be assumed that a similar additive or accumulative effect will finally be noted.

A cataractogenic dose for x-ray exposure in man has been quoted in the literature with 250 to 500 rads. However, in present studies of patients receiving irradiation treatment from a Cobalt-60 source for various malignancies, where one or both eyes received considerable dose levels, no lens changes have been observed in 27 patients out of a total of 28 over a two- to four-year observation time. In all cases, dose levels to which the lenses were exposed had been carefully determined by dosimetry for each exposure area. Those dose levels to the lens ranged from 480 rads to 6,850 rads given over a six- to eight-week period in fractionated doses of 100 to 200 rads daily for five days per week. The only patient who has developed a char-
characteristic radiation cataract to date is an 8-year-old girl. She received two series of therapeutic radiation in a four-year span (3,965 and 3,200 rads) in 1966 and 1970 respectively. Unfortunately, the parents did not bring the child for reexamination on a regular basis, so the posterior subcapsular lens changes had become quite prominent and typical for ionizing radiation exposure at the time the child was seen two months after final x-radiation in 1970. Hence, the exact latent period and the appearance of first observable minimal lens changes are not known. Certainly this observation confirms earlier statements that the age of the patient when radiation exposure took place plays an important role, that is, with younger age more severe lens changes can be expected with equal dose levels.

Because of the great variance of apparent dose requirements for production of lens changes in man, Rhesus monkeys, and Dutch rabbits, as mentioned above, it was felt that in vitro studies on cultured lens epithelial cells of the three species may allow greater insight on a cellular level into the mechanism involved following equal doses of x-ray exposure of the cultured cells at various times after the original explant was made.

To use such a model, it was necessary to establish that lens epithelial cultures could be maintained over long periods of time, and to study the normal, non-exposed cells of the three species, with regard to their morphological appearance and growth rate. These observations on cultures have been carried out over a four-and-a-half-year period and are described and illustrated in the following article.

Author's note: The author would like to acknowledge the extensive experimentation on the physical aspects of instrumentation design and dosimetry carried out on all animal studies by Dr. William T. Ham, Jr., Chairman, Department of Biophysics, and his staff, and to Dr. Richard King, Chairman, Division of Radiotherapy, and his staff. The author is grateful to these colleagues for making patients available who had received radiation treatment in which the lens received appreciable x-ray doses, and to Mr. Robert Howells for carrying out exact dosimetry in these patients. My thanks are also due to Dr. Thomas Nooney for his assistance in patient evaluation and clinical follow-up examinations.

BIBLIOGRAPHY


(Other pertinent literature is listed in the above mentioned papers.)
Observations of Lens Epithelium in Cell Cultures*

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The following investigation had been conducted to evaluate lens epithelial cells *in vitro* as a potentially suitable model for future studies of chronic low dose ionizing radiation effects on this cell type *in vitro*. Since there is a great range of dose requirements to produce *in vivo* radiation cataract in man, monkeys, and rabbits, and an equally wide range in time from radiation exposure until the first minimal lens changes can be biomicroscopically detected (3), it may be assumed that *in vitro* comparison of cells derived from these three species may provide some explanation for the *in vivo* differences. While controlled low dose acute or chronic ionizing radiation exposures and subsequent examinations can easily be achieved in animal experimentation, such data are more difficult to obtain from the human lens for obvious reasons. Thus, very minute lens changes can be quite accurately detected through biomicroscopic observation in the rabbit and monkey eye, but they may easily escape attention during routine clinical examination of the human lens after accidental or therapeutic exposure to ionizing radiation. Such minor lens changes are not expected to interfere with visual acuity, thus, the exposed person would not be aware of them. In addition, there is no established pattern for these very early changes in human lenses on which even a trained observer could base his criteria. Moreover, exact dosimetry is more difficult on human lenses, and scheduled follow-up examinations are frequently not kept by patients having undergone therapeutic radiation involving the eye.

The required radiation dose level for production of early *in vivo* lens changes in rabbits and humans deviates at least by one order of magnitude. Also, the latent periods after irradiation until lens changes become manifest vary greatly between the two species. It was hoped that *in vitro* observations of epithelial explants from human, monkey, and rabbit lenses would provide information whether this wide range of clinically observed dose requirements holds true *in vitro* systems as well.

It is for those reasons that normal behavior of human, monkey, and rabbit lens epithelial cells *in vitro*, that is, without irradiation, had to be compared to form a base line for further investigation. These observations were focused primarily on morphological changes of the three cell strains which possibly might have occurred over the period of observation due to the environment in which the cells of the different species were grown. Thus, if after a prolonged time in *in vitro* milieu, cells of different species would become indistinguishable from one another, as compared with initial findings after explantation, this model of experimentation would not be applicable to the purpose of studying radiation effects. On the other hand, if species specific characteristics remained unchanged from the original explants, the model could be accepted as valid and would possibly allow some guarded extrapolation to *in vivo* systems.

**Literature Review.** Attempts to grow lens epithelium from different species *in vitro* had been made by numerous investigators, however, little has been reported on long-term cultivation of lens epithelium. It should be noted that during the early days of tissue culture, terminology often varied from one author to the next so that it is frequently difficult to know exactly what is meant by some of the terms.
In our experiments we adhered closely to the nomenclature recommended by the Tissue Culture Association at their 17th annual meeting, May 31–June 3, 1966, San Francisco, California.

In 1922, Fischer, by repeating explantation of different tissues from chick embryo eyes, recorded that his attempts to grow lens epithelium in vitro were unsuccessful. He did succeed in growing epithelium but felt it was from the iris fragments adherent to the lens capsule and not lens epithelium.

In 1926, Kirby reported on various experiments in cultivating lens epithelium of chick embryo. When culturing the anterior one-third of 52-hour-old chick embryo eyes for 72 hours at 37.5°C in homogeneous medium consisting of equal parts of adult chicken plasma and chick embryo extract using the concave slide method of Carrel, he observed differentiation of the posterior portion of the lens vesicle. Kirby subsequently (experiment No. III) attempted to avoid Fischer's uncertainty regarding the source of the outgrowth by first incubating the intact chick embryo lens 24 hours and observing no growth from adherent tissue; he then opened the capsule ("cuticula") and obtained epithelial outgrowth in two of four attempts. In his experiment No. IV, lens epithelium was explanted on the point of a needle within an embryonic tissue juice plasma clot medium at 37.5°C. After 12–24 hours, lens epithelial cells began to migrate and to divide. Kirby also demonstrated that lens epithelium could be cultivated in media containing extract from the embryonic eye alone and also from other embryonic tissue after the eyes had been removed. He stated at one point that one strain was carried through "17 generations in six weeks." However, his exact meaning is not quite clear and most likely referred to replications since he reported that the cultures almost doubled in size every 48 hours.

In 1929, Kirby, Estey, and Tabor in another study using lens epithelium of the chick embryo in vitro demonstrated that during a period of eight months, 174 of 294 original explants (59%) showed active growth after 48 hours, that is, survived after the "first transfer." One hundred twelve (38%) survived the "second transfer," and 56 (19%) of the original explants survived the "third transfer." They reported that it was possible to carry a single strain through by 112 passages over a period of seven months. The medium was changed every 48 hours. They also concluded that cultures of chick embryo lens epithelium were more successful in the regular culture media than when the various constituent inorganic salts were increased more than 25% over the normal. Tyrode's medium with a pH of 8.2 was markedly toxic, but it was possible to revive certain debilitated cultures of lens epithelium by placing them in normal media for several passages.

In 1932, Kirby, Estey, and Wiener studied the effect of changes in the nutrient medium on chick embryo lens epithelium cultured in vitro. They observed that glucose proved toxic to the cells when the concentration exceeded 578 mg per 100 ml. Levulose 1660 mg per 100 ml and galactose 333 mg per 100 ml caused growth retardation or cellular death as did acetone (40 mg%) and betahydroxybutyric acid (120 mg%).

In 1948, Ida Mann reported her experiments on about 70 cultures of mouse lens epithelium. Lenses of young mice up to 10 days old were used first but proved difficult to explant without infection, while those from embryo mice of the same strain were grown successfully. In her study, the culture medium used was composed of rat serum, Tyrode's solution, and mouse embryo extract. Cellular differentiation was observed around 10 days; after that very few cultures survived. No culture remained alive after 12 days, and no further stage of differentiation could be observed. The first stage of differentiation was an increase in the cytoplasm and movement of the nucleus to one side. This resembled the process of normal differentiation of lens epithelial cells into lens fibers in the intact lens where the nucleus moves to the side of the cell next to the capsule. The cell then elongated forming a lens fiber with the nucleus eventually equidistant from the two ends. In a later stage, the voluminous clear cytoplasm apparently flattened in a few cells so that the cell became bluntly pointed at both ends with the nucleus remaining applied to one side of the central part of the elongated portion of the cells.

In 1958, Mamo and Leinfelder described the characteristics of lens epithelial growth in culture derived from 5–7-day-old chick embryos and human cataractous lenses. A small number of human lens epithelium specimens was obtained from donor eyes of the eye bank and from the eyes of stillborn infants. The media used in their study were Tyrode's solution, Tyrode's solution without sodium bicarbonate (glucosol), and supernatant fluid of centrifuged embryonic extract of 7–8-day-old chick embryos mixed with equal parts of glucosol solution. The lens capsule, approximately 3 mm in diameter, was laid flat
on the plasma covered wall of a roller tube. Rotation of the tube (9 rev per hour) provided a slow washing action thus promoting adequate exchange of food materials and waste products between fluid and cells. The cultures were kept at 37°C. Evidence of growth observed in cultures of chick lens epithelium occurred in about 12 hours while in human lens epithelium it took about 48 hours. If the culture was maintained without changing the supernatant fluid, human lens epithelium survived for approximately three weeks. No evidence of differentiation of lens epithelium into lens fibers was observed in their study. They found that human lens epithelium grew earlier and more quickly in tissue culture if the explant was obtained from a normal lens. In cultures of chick embryo lenses, the explants became discolored after a few days by gradual accumulation of fat within the cells, followed by progressive loss of a distinguishable cell pattern. The authors also observed that outgrowth had been established. Adult human lens epithelium seemed to be more resistant and less easily destroyed than that derived from the chick embryo.

In 1959, Van der Veen and Heyen reported the continuous culture of lens epithelium from a 3-month-old male calf. The explants, anterior lens capsule with attached epithelium in small fragments, were supplied with 2 ml of growth medium consisting of Hank’s solution, 30% calf serum inactivated at 56°C for 30 minutes, 0.5% lactalbumin hydrolysate, 5,000 U penicillin and 5 mg DHS per 100 ml. These cells were cultured in two screw-cap bottles of 200 ml size without plasma at 36°C. Four milliliters of fresh growth medium per flask were added after seven days without removing the old media. After that, 75% of the culture medium was "renewed" every seven days for two weeks and then every third and fourth day. Initial outgrowth from some explants was noted four weeks after primary explantation. After another month, isolated, transparent islands of cells were observed with further growth progressing at a very slow rate. After eleven weeks the cells were transferred by mechanical detachment. Hereafter, the growth rate increased, and three subcultures were made at intervals of two weeks. Later on, cells were detached by using 0.2% Versene and 0.5% Trypsin to initiate two other sublines. Proliferation continued for eight months at a constant rate. Each culture was then divided into two to four subcultures after 10–14 days incubation. One strain of cells was maintained through 44 passages for two years. Microscopic observation did not reveal any characteristic cell type. Some cells were polygonal, others pyramidal or irregular in shape. The nuclei were oval and contained several nucleoli. Under phase-contrast microscopy, intercellular bridges were regularly observed. Dividing lens cells were rarely seen. The authors attributed this to a probable short period for the completion of mitosis. Their attempts to cultivate the cells in a growth medium with less than 20% calf serum and to adapt the cells to a medium containing heterologous serum failed consistently. With their method, they succeeded in subculturing cells from the two calves lenses, maintaining them through 18 subcultures for one year. No differences in morphology or growth were observed in the three strains of calf lens epithelium. Three other attempts by these investigators to grow lens cells in continuous culture were unsuccessful.

In 1960, Bryan, Leinfelder, and Meltzer studied the effects of gases upon cell growth of human lens epithelium. The cultures were maintained as monolayers in silicon-stoppered T-60 flasks. The nutrient employed was composed of 4 − 4 − 2 Tyrode's BSS, pooled horse serum and embryonic extract respectively and 200 U penicillin and 200 µ gm streptomycin per milliliter added. The medium was changed at least once a week, and the flasks were shaken to provide space for new growth. With different gas mixtures, (95% O₂ + 5% CO₂; 95% N₂ + 5% CO₂; 95% air + 5% CO₂ and 100% O₂ at 1 lt per minute) the pH varied. The temperature was kept at 37.5°C. The cell strains (human lens epithelium, embryonic chick heart fibroblasts, and Earle's L-strain) demonstrated the ability to proliferate in an environment low in O₂. Growth was determined by initial cell count compared with that after four days. Of the three cell strains tested, only the lens epithelium in which the pH of the medium was increased did not show a significant decrease in growth. However, the cells showed more proliferation at a pH of 7.2 (95% O₂ ± 5% CO₂) than the control at a pH of 7.6.

In 1965, Tamura reported his experimental results of long-term cultures of rabbit lens epithelium. He used medium 199 from Chiba Serum Co. Ltd. at pH 7.2 containing LAH (0.25%) (Difco Co.) and calf serum (10%). A suspension of the minced tissue of the lens capsule was centrifuged, and the sediment was cultured at 37°C on coverslips in T-form culture bottles. The medium was changed every five to seven days. The cells grew in a monolayer with a rather low growth rate; cell duplication
from the operating room were kept in sterile media. A small portion of the lens capsule with adherent lens epithelium was used for initial electrophoretic analysis. The remainder was flattened out, divided into two parts, and each placed on one of two 2.5 × 2.5 cm glass slides within a 5 cm diameter Petri dish. MEM was then added to cover the explants to about 1 mm above the surface. For the first three days the medium was changed every day and then twice a week until a satisfactory growth was evident. After a period of about two to three weeks, the original explants were removed for further electrophoretic studies. When cell growth filled almost the entire surface of the slides, one half of the culture was again electrophoretically evaluated. The other half was kept for subculturing or for continuous observation without subculturings. In case of accumulation of metabolic waste products and cellular debris, the cultures were washed as required with MEM without subsequently altering the usual medium change schedule.

A complementary series of cultures was grown in Rose chambers for greater ease of handling, especially during time-lapse photography. Only human and rabbit lenses, cataractous and non-cataractous, were used. Explants of lens capsules were made essentially as described; they were divided and placed into separate chambers for parallel observation. One variation consisted in withholding the first medium change until at least a week had elapsed since explantation. Thereafter, the medium was changed every five to seven days. As a rule, explants remained in their original chambers rather than being transferred to another Rose chamber, although this was done in some cases.

**Subculturing.**

1. **Trypsinization:** Standard procedure for trypsinization, as described by Puck (9), was modified for preparing subcultures in this study. Trypsin 1-300² made up in GKN to a 0.25% solution was added to the Petri dish after removal of the medium. The cultures were then incubated at 37°C for 15 minutes with occasional gentle agitation. An equal volume of growth medium was then added and cooled to room temperature to stop the trypsin action. The cells were gently pipetted three to four times to break up larger clumps. The cell suspension was then diluted with growth medium and transferred into the Petri dishes. Growth medium was added in an amount sufficient to cover the cells to about 1 mm, and the cultures were incubated at 37°C in 5% CO₂ in air. The medium was changed after three days when

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1 Grand Island Biological Company

2 Nutritional Biochemicals Company
most of the cells had attached to the glass surface. Thereafter, the medium was changed twice weekly.

Trypsinization of Rose chamber cultures was accomplished using a similar technique by injecting the trypsin into the chamber through the silicone gasket and drawing off the cell suspension into a syringe in the same manner after adequate incubation. In fact, suspensions with cell concentrations sufficient for growth could be obtained from moderately or heavily populated Rose chamber cultures utilizing only a vigorous injection, agitation, and withdrawal of medium without trypsin or versene, thereby reducing the cellular trauma of transfer.

2. Mechanical transfer of an original explant: When adequate cell growth was obtained, usually about one to two weeks following explantation, the original explants were transferred to new Petri dishes to produce a new population of cells. This procedure was repeated up to 10 times with continuous good results in obtaining new starting cell growth. Cultures were observed regularly by phase contrast microscopy. Time-lapse photographic records were also made under phase contrast on cultures grown in Rose chambers. Cover slips from both Petri dish and Rose chamber cultures at various ages were stained with H & E for more careful study of mitoses, intracellular detail, and comparative morphology.

3. Photography: Phase contrast photomicrographs were taken with oblique illumination to obtain a more “three-dimensional” effect of the cells (figs. 1 and 2).

Results. Lens epithelial cultures of three species were observed in this study: 1) human, 2) monkey, and 3) rabbit. The human lens epithelium was obtained from a) cataractous lenses, b) from clear dislocated lenses, and c) from donor eyes received from the Eye Bank. Rabbit lenses were taken from embryonic, adult, and x-ray irradiated eyes. There was a total of 92 original human, 19 monkey, and 38 rabbit lens epithelium explants cultured in Petri dishes, and 27 human and 18 rabbit explants in Rose chambers.

There were no observable differences in the morphological characteristics of the cells and of the growth pattern among the various specimens, regardless of whether the epithelium was obtained from cataractous or clear human lenses or from the three different sources of rabbit lens epithelium. Consequently, with the exception of varying time intervals in the appearance of some morphological changes for the different species, no effort is made to describe the results of these cultures separately. This aspect will be discussed under “conclusion.”

Some of the original cultures and subcultures were lost for reasons such as pH and temperature changes in the incubator and fungal contamination of the culture medium. Because these “accidental” losses were due to external influences, they are not included in the overall evaluation.

The principal differences between this study and those described in the literature review were in the culture medium used, the frequency of exchanging the culture medium, the difference of techniques including the type of culture chambers, and the methods of examination.

Evidence of growing lens epithelial cells was...
observed within the first 10 days after explantation for human, one to seven days for rabbit, and one to two days for monkey lenses. At this time most of the cells appeared to be flat and of an epithelial type with some showing mitotic figures seen in stained preparations. Others were more of a spindle or fibroblastic type. Further outgrowths from the primary explants were observed in about 3–14 days for human, 2–14 days for rabbit, and 3–6 days for monkey lens epithelium.

Once started, the outgrowing cells steadily multiplied, ultimately forming a relatively solid monolayer which often covered the entire cover slip. At the same time, cells of the explant and those in the monolayer closer to the explant often exhibited a rounding up of their central areas and engulfment of birefringent droplets which became smaller with time and appeared finally as small black intracytoplasmic granules. These cells then became spherical in shape and detached from the glass surface. Thus, a confluence of multiplication and migration with cell degeneration was common. Degenerative changes tended to occur in focal areas, characterized by progressive intracellular granulation, vacuolization, and inclusion of oil droplets. The initial vacuoles were small and isolated but later became confluent. These areas appeared less transparent and at times showed discoloration. Nuclear fragmentation was frequently seen, after which the cells shrank with apparent contraction of the cytoplasm; they often detached from the glass. Cells at the periphery of the culture were usually fibroblastic and frequently isolated, or they formed a loose network with intercellular bridges. In the more closely packed central areas, cells formed a flattened polygonal epithelioid layer, much more quiescent and indistinct. In most Rose chamber preparations the cell borders became indefinite, the nuclei ill-defined, and intracellular detail less clear. Time-lapse photographic studies showed continued, though less vigorous, intracellular activity, however.

Thus, morphology within one cell culture ranged from round epithelial to fusiform and fibroblastic shapes. It appeared to be a matter of cell location (environment) as much as age which disposed cells to present one form or another. In addition, all cultures showed numerous multinucleated cells, sometimes with up to 18 nuclei, surrounded by a disproportionately large amount of cytoplasm (fig. 18a).

Cells from human lenses had a slower rate and were less resistant to such trauma as pH fluctuation, trypsinization, or mechanical transfer and often appeared less active in general than those from rabbits and monkeys. No differences could be detected between cultures from cataractous and normal lenses with regard to the onset of outgrowth, growth rate, vulnerability, and morphology of the cells. All cultures grown in Petri dishes showed after several months a tendency to elongation of the cells into a form which closely resembled the formation of lens fibers. This was enhanced in areas where cells were tightly crowded. No such transition was noted, however, in the Rose chamber cultures of either species. Figures 3 through 17 show several forms of observed lens shapes at various times regardless from which species the cultures derived.

**Conclusion.** Growth of lens epithelial cells *in vitro* has been described previously by several
Fig. 5—Loose network of peripherally located cells with cytoplasmic bridges.

Fig. 6—The cytoplasmic bridges have become more fiber-like after subculturing.

Fig. 7—More densely packed fibroblastic appearance of rabbit lens epithelial culture four months after first subculture.

Fig. 8—Monolayered cell growth of monkey lens epithelial cell culture nine months after original explant.

Fig. 9—Cultured cells organized in bundles.

Fig. 10—More distinct appearance of fiber-like organization.
Fig. 11—Two years after original explantation the cells have organized in a directional fashion.

Fig. 12—Three-year-old culture of rabbit lens epithelial cells resembling lens fibers.

Fig. 13—Cell degeneration with several vacuoles six months after explant was placed in Petri dish (human lens epithelium).

Fig. 14—Birefringent droplets and small black intracytoplasmic granules.

Fig. 15—Small "oil droplets" in degenerating cells.

Fig. 16—Degenerating focal area of cells with many cytoplasmic black granules in otherwise normal culture, three days after seventh transfer of cultured rabbit cells.
investigators. Their techniques and results varied considerably. In 1959, Van der Veen and Heyen reported that in their study no cells grew in medium containing heterologous serum or less than 20% homologous (calf) serum. In the present study, all epithelial cells from human, rabbit, and monkey lenses did grow in a medium containing heterologous serum (calf) without adding homologous serum. Also, their observation that division of cells was rarely seen could not be confirmed in our study since mitoses could be demonstrated with time-lapse cinematography, and different states of mitosis were seen in all stained preparations (figs. 18b and 18c). Furthermore, long-term continuous cultures without subculturing of cells from primary explants have been kept alive for over four-and-a-half years.

The present study thus confirmed that lens epithelial cells can be maintained in vitro with mitotic activity and differentiation over several years. No distinct differences in cellular morphology of the cells derived from human, rabbit, and monkey were noted over the entire observation period. All cultures contained multinucleated cells, though in varying numbers. Human lens epithelium seemed to be less resistant to experimental trauma than that of rabbit, a fact which was particularly obvious after trypsinization, but less pronounced after mechanical transfer of cells for subculture.

Whether this cell type represents a suitable in vitro model to carry out comparative studies on radiation effects is somewhat questionable because of the relatively slow multiplication rate of these cells, for this fact would require prolonged observation
times over which experimental artefacts could easily be introduced.

In summary, a method for in vitro culturing of lens epithelial cells from human, rabbit, and monkey has been described. The lens epithelium grown in vitro was carried on for successive generations. The cultures of rabbit and human lens epithelium were maintained for more than four and a half years and those of monkey lens epithelium for over three years. No definite differences in cellular morphology for the three species were observed. Mitotic activity and differentiation of the lens epithelium resembling lens fibers were demonstrated in all cultures. A review of the pertinent literature is presented.

Author's note: The initial pilot studies on the cell cultures were to a large extent carried out by Drs. Nongnart Romayananda and Michael Hines. Extensive technical assistance in all phases of this investigation was rendered by Mr. Vernon Jones.

REFERENCES


An Optical Approach to Aid Cerebral Hemiplegics

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Introduction. Communication is the process by which information is received, interpreted, and retained; however, communication often breaks down as a result of brain injury. It has been estimated (10) that there are 400,000 adults in the United States with some degree of communication loss from stroke, and each year another 20,000 people become similarly afflicted. The ability to transmit and/or receive information depends on visual and auditory comprehension and retention, reading comprehension, visual motor facility, and speech. These areas are so interrelated that a collapse in one often causes a breakdown in a closely connected ability (6).

One of the major factors contributing to a stroke patient's communication disorder is a visual field disturbance. A common problem incurred by stroke patients is that of homonymous hemianopsia. A schematic drawing of the central visual pathways (fig. 1) indicates that fibers from the temporal half of the retina of the right eye pass through the optic chiasm and, without crossing, pass to the lateral geniculate body of the right side. The nasal fibers from the left retina decussate in the optic chiasm and enter the optic track of the right cerebral hemisphere. There they join the uncrossed fibers from the temporal half of the right eye, and then pass to the lateral geniculate body. Thus, the termination of the nasal fibers is contralateral. As seen in figure 1, a large lesion of the occipital lobe on the right side blocks impulses from both eyes which results in left lateral homonymous hemianopsia; “half-blindness” because the geometric half of the visual field is involved; “homonymous” since the corresponding halves of each retina are blinded; “left lateral” because nothing to the left side is seen, and because the disturbance is named for the side of the visual field defect and not for the side of the “retinal blindness.”

Background. For over a half century, various attempts have been made to aid the patient with homonymous hemianopsia. Duke-Elder (3) refers to the early work of Braunschweig (1920) and Strebel (1923) to enlarge the visual field by bending the light rays. In 1926, Weiner (9) reported the application of a prism as a mirror using the property of total internal reflection. In 1929, Young (11) successfully employed a reflecting prism to the spectacle correction of a 34-year-old female who had suffered permanent right homonymous hemianopsia with macular sparing during her eighth month of pregnancy. Young stated, “… it seems remarkable that this patient, who was at first almost helpless, now drives an automobile.” The patient objected to the unsightliness of the prism. In 1949, Bell (1) used a small mirror appliance for patients with homonymous hemianopsia, but the number of successful cases was not reported. Burns and coworkers (2) reported a clinical evaluation of six patients with a similar defect; three were successful wearers of the mirror device. In 1955, Duszynski (4) recommended dichroic mirrors, also called “beam splitters” because they transmit certain spectral regions and reflect the remainder. However, the brightness difference between the direct field and the reflected image, together with the very conspicuous size—as large as a spectacle lens—were not appreciated by the wearers. No statistics on the results were quoted in his paper.

Three patients with long-term hemianopsia were fitted with a mirror device by Walsh and Smith (8) in 1966. Duszynski (4) showed what he described as, “… a conventional type of hemianopsia mirror”
**NOONEY: CEREBRAL HEMIPLEGICS**

Total congruous hemianopsia due to indicated lesion side.

![Schematic drawing of the central visual pathways showing homonymous hemianopsia as a result of a lesion in the occipital cortex on the right side.](image)

Fig. 1—Schematic drawing of the central visual pathways showing homonymous hemianopsia as a result of a lesion in the occipital cortex on the right side.

(manufactured by ‘The House of Vision’). However, these items were made only rarely and by special order according to the same manufacturers (5). The mirrors were made of glass in the past and were a source of potential danger to a partially sighted individual.

Although some previous efforts have been made to develop an optical aid for hemianopic patients, no large scale attempt seems to have been undertaken, and only a few patients have received the benefits of such a device. Apparently, little has been done with specific reference to the large number of hemianopes in our medical centers, institutions, and nursing homes who are so disadvantaged by this portion of their illness that rehabilitative achievement is unusually difficult and unnecessarily prolonged.

**Rationale.** A patient with the type of lesion shown schematically in figure 1 often suffers concurrent left hemiparesis, left hemianesthesia, and even agnosia for the left half of space, that is, inability to recognize or tendency to ignore the left side of space, including the left side of his own body. The portion of his body which he cannot feel or see may be cause for disruption of body-image and function.

Many patients are seen in the Medical College of Virginia Hospitals who have hemiplegia and hemianopsia. The development of patient awareness in the hemianopic field has been a most difficult problem. This condition seriously impedes the rehabilitation of the hemiplegic patient to such an extent that he must often remain in institutional care without ever developing enough facility to live in his own home, a foster home, or a home for the aged.

It should be understood that this is not an attempt to mediate sharp visual acuity in the retinal periphery, for acute visual perception is a function of the fovea centralis and drops off markedly a few degrees outside the macula in the normal eye. Visual perception and awareness of movement in the peripheral retina is of importance in the phylogenetic development of the vertebrate eye, and it is primarily this movement-seeing capacity which can be transferred to the functionally normal portion of the retina by this optical device.

**Specific Aims.**

1. To develop a series of plastic mirrors which can be mounted to a patient’s spectacle frame as an aid to cerebral hemiplegics with homonymous hemianopsia.
2. To provide a clinical service for patients so afflicted within a broad geographical area. To our knowledge there is no such service available in the entire middle Atlantic region.
3. To adapt a particular device tailored to each patient, depending on his particular needs, thus expanding his binocular visual field as early as possible in the rehabilitative phase. While hemianopsia is a defect of the binocular field, incomplete or sector defects may also be treated by this device if the visual depression is a troublesome source of field restriction as, for example, a lower quadrant lateral hemianopsia on either side.
4. To provide the needed refractive correction made of plastic lenses so that the attached mirror device will not be a burden to the patient, but on the contrary, will be a real
source of added protection from hazard to the blind side and thus improve his perceptive faculty and spatial orientation.

Results and Discussion. Patients are available for this study at various levels of disability, not only from the MCV Hospitals, but from other institutions and from the private sector. In a pilot study, 12 patients with homonymous hemianopsia with central fixation sparing have benefited by one of our mirror prototypes. There has not been the opportunity for long-term follow-up to date, but the encouraging results may be exemplified by briefly discussing some of the observed clinical results.

Case 1: A middle-aged female patient with a left homonymous hemianopsia following a cerebral accident had lost all of her communicative ability and kept her head turned toward the right side about 25° with agnosia for the left side. A mirror was attached to a pair of plastic spectacles without her exact prescription lenses, since her refractive error could not be readily determined. Within a short span of a week or two the patient began to carry her head in the straight forward position and became aware of her surroundings on the blind side.

Case 2: A 67-year-old female stroke patient, blind in the right eye and with complete temporal field loss in the left eye, was treated with a mirror small enough so that it did not interfere either with central fixation or with the intact left nasal field. Due to the patient’s post cataract left spectacle lens her visual field was further depressed. Yet, she adapted quickly to the mirror device, and for the first time since the cerebral vascular accident she could avoid obstacles to her left side.

Case 3: A young teen-age girl had a similar field loss, that is, light perception (without light projection) in the right eye, and complete temporal hemianopsia with macular sparing in the left eye, due to a severe head injury. The increased visual awareness was sufficient for her to obtain a driver’s license from the State Division of Motor Vehicles.

Case 4: A 22-year-old male college student with left homonymous hemianopsia and binocular macular sparing adjusted quickly to the optical mirror, and he, also, was able to complete the requirements of the Division of Motor Vehicles for a Virginia driver’s license.

Case 5: The subjective improvement in visual field expansion with the help of this appliance, which in turn aids in the total rehabilitative process, can be shown in this particular patient. An adult male was brought to occupational therapy after having been fitted with one of the mirror devices, and for the first time he was able to sandpaper a whole section of a piece of 10" x 10" wood, that is, he could see both left and right sides of the working surface. Previously, he had always stopped at the center line and waited for one of the therapy personnel to come to his table and rotate the board 180°; he would then complete the remaining side. Figure 2 shows one of the mirror prototypes made larger than normal for photographic purpose.

An optical (mirror) device to project the mirror image of the blind field into the seeing half-field enables a patient to be aware of both sides of his environment and thus helps to expedite the usually long convalescent period. Hypalgesia and hypesthesia also slow the recovery process, but being able to see a paretic limb aids in the restoration of function. Information presented to the side of the “retinal blindness” through the mirror device has been helpful to all of the homonymous hemianopsia patients treated thus far. They soon learned to properly project the image to the correct side. Some investigators (7) have not had satisfactory results with such devices; however, this has not been our experience. Some patients have indicated that getting used to the device is similar to an automobile driver using the rear view mirror, that is, the person

Fig. 2—Image of a left eye through one of the mirror prototypes which aids the homonymous hemianopsia patient to be aware of his environment on the blind side.
adapted to the image projection. Thus, the patient enjoys fuller visual fields, which in turn improves his total functioning capabilities and reduces the possibility of accidents due to the lack of visual perception and recognition of motion in the area of the visual field loss.

The success of our pilot study has led to professional support from the Virginia Commission for the Visually Handicapped, the Virginia Department of Vocational Rehabilitation, the Department of Public Health of Richmond, Virginia, and the Veterans Administration Prosthetics and Sensory Services, as well as various departments of the School of Medicine at the Medical College of Virginia, Virginia Commonwealth University. A three-year expanded study is planned. Results will be disseminated in report form to the sponsoring and supportive agencies, referring physicians, and to the appropriate literature.

In summary, research has been directed to the design and development of an optical aid for patients suffering from hemiplegia caused by a cerebral hemorrhage, thrombosis, embolism, tumor, injury, and so forth, and to follow their visual rehabilitation up to a three-year convalescence. Hemianopsia frequently accompanies intracranial lesions, with a common type being homonymous hemianopsia, or blindness in the same half of the visual field of both eyes. A lesion on the right side of the brain causes a left homonymous hemianopsia so that the patient cannot see to the left of the mid-line without turning his head to the left side (fig. 1). An optical mirror permits the projection of the mirror image of the blind field into the seeing half-field to make the patient aware of both sides of his surroundings and thus helps to shorten the long recovery period (fig. 2). Hypalgesia and hypesthesia also delay convalescence, but awareness of the paretic side provides functional reinforcement. Then as the patient becomes rehabilitated, even if not completely and the homonymous hemianopsia remains, he will be able to carry on with his restricted field of vision, for example, see passing automobiles and other objects of danger which are projected onto his non-functioning side of the retina. A small plastic mirror attached externally to the patient's spectacle frame causes only minimal interference in the remaining usable field of vision and expands the binocular visual field.

Author's note: The author is greatly indebted to Mr. K. H. Duncan of S. K. Design and Manufacturing Company for making the mirror prototypes used in this study.

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Experimentally Induced Coloboma in the Golden Hamster: A Preliminary Report

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Introduction. The appearance of a coloboma of the iris must have been known long before Walther (15) introduced the term in 1821 since the condition is easily visible. The word coloboma is derived from the Greek and means the part which is taken away in mutilation or injury or the part that is lacking, that is, a defect. In coloboma iridis, therefore, a section of the iris is lacking, often bilaterally. After the invention of the ophthalmoscope by von Helmholtz in 1851, it could be seen that the defect is not restricted to the iris but that lens, retina, choroid, and optic nerve can also be involved. However, little was known about the etiology. A fault in the closure of the “choroid fissure” was first mentioned as the cause of the congenital defect by von Ammon (1) in 1831. At that time the pigment epithelium, the most obviously involved layer, was believed to be part of the choroid, and the cleft was, therefore, called choroid fissure. This is a misnomer since the defect lies primarily in the neural retina and the pigment epithelium, both derived from neuroectoderm. The choroid, a derivative of mesoderm, has not formed at the time of the fissure closure and becomes involved only secondarily. The most commonly employed term now is embryonic fissure.

Various investigators have proposed different theories regarding the cause of the retarded closure or non-closure of the embryonic fissure: lack of degeneration of mesoderm in the fissure (8), inflammation of the optic vesicle (3), pressure from an unusual amount of cerebrospinal fluid (4), abnormally large lens (2), and maternal toxins or malnutrition (10). The actual formation of a coloboma was first observed and described by von Hippel (6) who was able to successfully breed a colobomatous male rabbit and to obtain affected offspring. He found that 18% of the embryos had the same malformation. From his extensive and detailed studies he concluded that the congenital abnormality was hereditary and that all previously postulated theories should be abandoned. Still, opinions differed as to which tissue was primarily involved in coloboma formation. Some researchers (8, 6) believed that the mesodermal tissue within the fissure kept the margins from fusing. Others (12, 13, 7) considered an increase in the mitotic activity of the inner layer of the neuroectodermal optic cup and the subsequent eversion of this layer to be the cause of a non-fusion of the fissure margins. This latter theory is today the most widely accepted one, since the mesodermal tissue seems to disappear from the fissure area before the margins approach each other, prior to actual fusion.

One way to study a congenital defect, besides the breeding of an affected animal, is to induce the abnormality in laboratory animals, a method widely used in teratology. As described in a review article by Tuchmann-Duplessis and Mercier-Parot (14), colobomata have been produced in laboratory animals by means of various teratogenic agents (Table 1).

The golden hamster has also been used in experiments employing teratogens (9, 11); colobomata, however, have not been reported.

The present study represents the second part of a more comprehensive investigation of the morphogenesis of the normal and abnormal embryonic...
TABLE 1.

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<tr>
<th>Teratogenic Agent</th>
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<tr>
<td>X-rays</td>
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<td>Vitamin A Excess</td>
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fissure. The first part, an electron microscopic study of the normal closure, has already been completed (5). The second part consists of the attempt to induce colobomata by means of hypo- and hyper-vitaminosis A. If both attempts are successful, the resulting colobomata will then be compared with one another as well as with the sequence of events in the normal closure. It is hoped that this investigation will permit some insight into the cellular phenomena that lead to a congenital coloboma.

Materials and Methods. In the first attempt of this study 25 female golden hamsters, ranging in age from 2 to 6 months, were bred. The middle of a 30-minute mating period was considered time zero. On the 8th day of pregnancy they were given 1 ml with 25,000 IU of vitamin A (US Vitamin and Pharmaceutical Comp.) by stomach tube. Six females, serving as controls, received 1 ml of the carrier solution (sorethytan ester). On the 14th day of pregnancy the animals were sacrificed with sodium pentobarbital. Twenty litters with a total of 204 embryos were obtained from the experimental animals and 6 litters from the control group. The embryos from 15 females were placed in Kahle’s fixative for two days and stored in 70% ethanol. The eyes were dissected from the embryos, dehydrated in a graded series of alcohol, aniline and toluene, and embedded in paraffin. Serial sections, made in the equatorial plane, were stained with hematoxylin and eosin. The eyes of the remaining embryos were prepared for electron microscopy. These were fixed in glutaraldehyde (3%) for 1 hour, postfixed in osmium tetroxide (2%) for 1½ hours, dehydrated in acetone, and embedded in Durcupan ACM.

In the second attempt of this study nine female hamsters were used. Exactly seven days after mating they were given 40,000 IU of vitamin A. On the 14th day of pregnancy the females were sacrificed and the embryo eyes processed and embedded in Durcupan ACM as described above. Equatorial sections 1-2 μ thick were stained with toluidine blue for light microscopic examination.

Results. The first attempt to induce a non-closure of the embryonic fissure by means of hypervitaminosis A was unsuccessful. In addition to some malformations of the mandible and maxilla and a few cases of exencephaly, 124 embryos showed bilateral or unilateral exophthalmos, however, sectioning revealed that all eyes were normal in size and structure (fig. 1). The protrusion was caused by an abnormally shallow orbit, that is, only tissue derived from mesoderm was affected. Since organs derived from neuroectoderm are usually susceptible to the influence of teratogenic agents at a slightly earlier period of development, the time of treatment with vitamin A was changed to seven days after mating. In three females no living embryos but only resorption sites were found. The remaining six females produced 52 embryos, 18 of which had abnormal eyes upon gross examination.

The recent study of the developing fissure in the normal eye showed that it is formed during the 10th day of gestation. The space between its margins is filled with vascular (hyaloid artery) and mesenchymal tissue. The fissure closes during the 12th day, after which no trace of it is left. At that age the eye is approximately 500-600 μ in diameter.

At 14 days (fig. 2), the size of the eye is about 1 mm. The pigment epithelium is thin and heavily pigmented, the retinal layer is quite thick and shows beginning differentiation into inner and outer neuroblastic layer.

Exophthalmic eye with open fissure. Gross examination showed already that the pigmented layer did not form a full circle, that is, a portion in the inferior area was missing or unpigmented.

Equatorial sections (fig. 3) show an eye approximately 750 μ in diameter, with an open fissure containing only traces of mesenchymal cells and small
blood vessels. Although the eye is protruding and "open," that is, without lids and, therefore, appears to be larger, it is actually smaller than the normal eye. This fact demonstrates the influence of an open fissure on the growth of the eye. The exophthalmic eye without coloboma, as obtained in the first attempt with vitamin A, grows normally; the one with the induced open fissure does not. Also obvious is the fact that the neuroretina has separated from the pigment epithelium. This is most likely not an artefact due to shrinkage during fixation as is frequently seen in paraffin sections. In glutaraldehyde-fixed eyes the two layers normally remain attached (fig. 2). At the fissure the inner layer is everted. It seems to have grown faster and has become folded upon itself, thus forming part of the outer layer. The pigmented epithelium is much thicker than normal and shows obliquely running streaks (arrows), possibly aberrant nerve fibers. Equatorial epoxy section. Toluidine blue (100 ×).

Fig. 1—Horizontal section through the head of a 14-day hamster embryo. The right eye is normal; the exophthalmic left eye is not covered by lids but is otherwise normal. Paraffin section. Hematoxylin and eosin (15 ×).

Fig. 2—Equatorial section through a normal eye of a 14-day hamster embryo. IL—inner layer (neural retina); OL—outer layer (pigment epithelium) (75 ×).

Fig. 3—Eye of a 14-day hamster embryo following treatment with excess vitamin A after seven days of gestation. The embryonic fissure (EF) has not closed, the neural retina is everted at the fissure and forms part of the outer layer. The pigment epithelium is thicker than normal and shows obliquely running streaks (arrows), possibly aberrant nerve fibers. Equatorial epoxy section. Toluidine blue (100 ×).
development. Sectioning revealed an optic cup much smaller than normal (fig. 4), approximately 250 μ in diameter as compared to about 1,000 μ of a normal eye. The two layers of the optic cup—presumptive neural retina and pigment epithelium—are of similar thickness, that is, the inner layer is much thinner than in normal eyes of this age. The cells of the outer layer contain many pigment granules. Some pigment granules are also present in the retinal layer. The fissure is open, about as wide as on the 10th day when the fissure is being formed by invagination of the optic vesicle. The tissue within and around the cup shows little organization, that is, there is no indication of a formation of lens and choroid. From this first examination the impression is gained that the optic cup developed until it reached a stage similar to that of a normal eye on the 9th or 10th day and that at this stage the normal process became greatly disturbed.

Comments. From these preliminary observations final conclusions cannot be drawn at this time. The results show, however, that a high dose of vitamin A acts as teratogen capable of inducing a typical coloboma in the golden hamster. It will be of interest to compare the induced coloboma with a hereditary one which is being investigated at present (C. Jackson, personal communication, 1972).

This study is being continued and extended by beginning with the younger stages of development, comparable to those examined in the normal eye, and by studying the formation of a coloboma on the ultrastructural level.

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Genetic Counseling in Retinitis Pigmentosa

VAN B. NOAH, M.D.

During his lifetime the practicing ophthalmologist will see more than a few retinitis pigmentosa cases. It is his responsibility not only to diagnose and prognosticate this eye disease, but also to set aside a little time in which to advise the patient and his family on its genetic aspects.

Retinitis pigmentosa has been established as a definite hereditary disorder. Therefore, the most important factor to consider for accurate counseling is the family history. Unfortunately, for one reason or another, this is not always available, and the investigator may need to rely on the nature and severity of the disease, examination of other members of the family, and the presence of other disorders. Pseudoretinitis pigmentosa caused by inflammation or drugs should be ruled out.

Family pedigrees of typical retinitis pigmentosa exist for nearly every known mode of genetic transmission. Over 90% of these pedigrees are concerned with an autosomal recessive gene, while 3% to 6% are related to an autosomal dominant gene. X-linked genes constitute 1% to 3% and may be recessive, intermediate, or dominant.

It is important to recognize the mode of transmission in individual cases. Unless this is done, no reliable eugenic advice can be forthcoming.

The autosomal recessive mode of inheritance is characterized by an unrevealing family history, although a history of consanguinity may be discovered (opinions vary, but this could be as high as 40%). This form of the disease is serious, with complete blindness by age fifty to sixty usually the rule. Parents of affected individuals are phenotypically normal.

Also characteristic of the recessive gene is the frequent association with other disorders. Such co-existing anomalies may offer a clue to the recessive nature of this gene when family history is lacking. The relationship of retinitis pigmentosa to any congenital anomaly is too great to be explained by mere coincidence. Most notable are afflictions of the aural, metabolic, genitourinary, musculoskeletal, and central nervous systems. Ten to 40% of retinitis pigmentosa is associated with sensorineural hearing defects alone, either congenital or acquired and with or without mutism. Deafness may be late or incomplete, and in such instances it is manifested initially by loss of the higher frequency sounds. Indeed, approximately 10% of all children with this type of hearing defect will later show signs of retinitis pigmentosa. The penetrance of the involved gene for hearing loss varies among the members of a pedigree of retinitis pigmentosa. Probably a single gene with pleiotropic action is responsible for this close association, and not a situation of polygenic heredity. Of particular interest is the fact that approximately 13% of heterozygotes demonstrate slight loss of hearing; thus an audiometric examination of non-affected members as well as affected members of a pedigree may prove valuable in determining recessiveness.

The CNS associations comprise mostly diencephalic-hypophyseal manifestations. Epilepsy may be present, as well as mental retardation, EEG abnormalities, and psychiatric disorders (most notably, recurrent depressive episodes, schizophrenia, and paranoia). Metabolic disorders are usually those of the lipidoses.

Many of these genetic combinations form very interesting and well-recognized syndromes:

*Usher's Syndrome*—retinitis pigmentosa deaf-mutism

*Hallgren's Syndrome*—retinitis pigmentosa, congenital deafness, vestibulocerebellar ataxia, schizophrenia-like symptoms, mental deficiency

*Refsum's Syndrome*—atypical retinitis pigmentosa, polyneuritis, spinocerebellar ataxia

*Cockayne's Syndrome*—retinitis pigmentosa, dwarfism, deafness

*Bassen-Kornzweig Syndrome*—atypical retinitis pigmentosa, acanthocytosis, Friedreich's ataxia
Spielmeyer-Vogt Syndrome—retinitis pigmentosa, multiple CNS manifestations
Kearns-Sayre Syndrome—retinitis pigmentosa, heart block, progressive ophthalmoplegia externa
Laurence-Moon-Bardet-Biedl Syndrome—retinitis pigmentosa, obesity, hypogonadism, polydactyly, mental retardation
Hurler's Syndrome (and other mucopolysaccharidoses)—retinitis pigmentosa, corneal haze, gargoylism

The autosomal recessive form of retinitis pigmentosa is also associated with other eye disorders. Myopia of over two diopters is present in 30 to 40%. Keratoconus and glaucoma occur more frequently than in the normal population.

The autosomal dominant mode of transmission is usually more benign and much later in onset. Related congenital anomalies are not common; hearing loss is rare. Complicated cataracts are, however, more common than in the recessive form. At least three consecutive generations of affected individuals should be elicited from the family history to firmly establish this mode of inheritance. But this gene is not always regular; it may skip one or more generations, although such an occurrence is rare. According to most genetic investigators, mutations do not occur. This form of retinitis pigmentosa is apparently on the increase because of the gene's dominant nature and because "survival of the fittest" hardly holds true in today's society. Since one-half of an affected person's offspring (without regard to sex) will similarly be affected, prevention of such requires sterilization or abstinence from procreation. Proper thinking on the part of most should dictate their not bringing into the world others who inevitably would go blind. Counseling should be guided by this philosophy.

Pseudodominance refers to that situation where an affected individual (with recessive genes) mates with a heterozygous person, resulting in one-half of offspring affected. Such circumstances could easily fool the investigator into believing a dominant gene to be responsible. Consanguinity is almost always the rule in these cases.

The X-linked mode of inheritance is, as previously mentioned, of three types. Generally these modes are manifested by retinitis pigmentosa of the severest order. Of these, the X-linked recessive is the most frequent. In nearly 100% of such cases there is myopia of greater than two diopters. The X-linked dominant is very rare and typically abortive with little pigment. In this instance the female carrier is herself affected, usually at a later age. The X-linked intermediate form is equally rare. Of particular interest is the so-called "tapetoretinal reflex" in the female carrier, a brilliant silvery scintillation more pronounced in the macular area but covering the entire fundus in many cases. The affected males may have choroidal sclerosis in addition to the pigmentary degeneration. Female carriers should be made aware that half of their male offspring will be affected. Affected males should realize that all of their daughters will be carriers.

In offering genetic counseling, one would be wise to realize that patients and members of their families prefer that probability figures be expressed as "odds." Fraser Robert's yardstick, specifically that one of 40 random pregnancies will yield a child with one or more congenital anomalies, should suggest to the physician that absolute assurance might not be a sound policy. The autosomal dominant and X-linked modes of transmission are easily recognized in most instances, and the subsequent counseling is rather straightforward.

Most counseling will, of course, be concerned with the autosomal recessive gene. Here one would do well to remember an important statistic. The frequency of affected homozygous persons within the human population is one in twenty thousand. If "p" is the frequency of the normal gene and "q" the frequency of the defective gene, then p + q = 1. Squaring both sides gives p^2 + 2pq + q^2 = 1, which is the binomial equation of probability. Here, p^2 is the frequency of normal homozygotes, 2pq of normal heterozygotes, and q^2 of affected homozygotes. Since q^2 = 1/20,000, then q = 1/141, this being the frequency of the defective gene. The frequency of heterozygotes is thus 2pq = (2)(1/141) (1/141), or 1/71. This means that the probability that an affected individual married to a normal person with no family history of the disease will give birth to an affected child is (1/2)(1/71), or one chance out of 142. The probability that a known heterozygote married to a normal person will have an affected child is (1/4)(1/71), or one chance out of 284. These odds are more than favorable, and the physician is not justified in recommending that such individuals should not rear children. Eugenically speaking, such needless advice would serve only to reduce very slightly the frequency of the defective gene, and at the sacrifice of the happiness derived from a new face in the home.
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The purpose of this paper is to briefly review the factors involved in acuity changes in diabetes mellitus and to report findings suggesting a new concept, namely, diurnal fluctuations in acuity that are not associated with hypoglycemic episodes.

Decreased acuity in diabetes may be due to:
A. Non-diabetic causes common to the general population
B. Factors secondary to diabetes:
   1. refractive changes secondary to blood glucose changes
   2. cataracts, juvenile or senile
   3. diabetic retinopathy
   4. hypoglycemia
   5. diurnal fluctuations, probably due to blood glucose changes

A sudden onset of myopia should always arouse a suspicion of diabetes mellitus (2). The changes may be as great as two to three diopters or sufficient to change acuity from 20/20 to 20/200 or less. The most dramatic changes usually occur in undiagnosed diabetes and may cause serious diagnostic confusion as summarized by the editor’s comment on D. M. Watkin’s article (7), “Diabetes Mellitus in an Internist”:

“Myopia was a presenting complaint only 10 days after a... normal postprandial blood sugar. The significance of the myopia was not appreciated by the ophthalmologist who prescribed glasses. The neurologist interpreted the leg cramps as a sign of multiple sclerosis, and the otolaryngologist somehow favored a diagnosis of brain tumor.” Typically, the acute myopia develops during the onset of the disease and may progress over several months with intermittent exacerbations. Hypermetropia typically occurs during the treatment period and tends to clear over a period of three to four weeks (6). Myopia therefore results from increased blood sugar, and hypermetropia results from returning the blood glucose level toward normal. These refractive changes may occur suddenly but invariably resolve slowly over several weeks or months.

Theories to explain the refractive variations have included changes in the axial length of the globe, changes in the refractive index of the aqueous or vitreous, accommodative paresis, and accommodative spasm. Rosenstein showed that atropine cycloplegia does not change the refractive findings (quoted by Mattos), (4). That the axial length, or vitreous or aqueous alterations were not involved was proven by Elschnig who reported on myopia in a diabetic with unilateral aphakia (quoted by Mattos), (5). He found no refractive changes in the aphakic eye, thus excluding axial length, vitreous or aqueous changes as etiological factors. Duke-Elder first explained the lens alterations that occur. With hyperglycemia the osmotic pressure of the aqueous decreases and fluid infiltrates into the lens making it more spherical and resulting in myopia. With decreases in the blood sugar the flow of fluid is reversed.

The cataracts that occur in diabetes may be of the juvenile or snowflake type or typical senile. The snowflake cataracts appear suddenly in early uncontrolled juvenile diabetics and resolve with good diabetic control. The acuity changes with cataracts are slow, and when snowflake cataracts clear, the acuity improvement is slow.

Advanced diabetic retinopathy may not result in any decreased acuity, and conversely, minimal diabetic retinopathy involving the macula may seriously impair the vision. Decreased acuity in diabetic retinopathy may be due to macular edema, macular...
exudates, macular hemorrhages, gliotic masses overlying the macula, retinal detachment, vitreous hemorrhages, or a combination of these factors. Generally, there is no correlation between the severity of the retinopathy and the visual acuity. In any case there are no rapid fluctuations of acuity with diabetic retinopathy, even though the disease is characterized by remissions and exacerbations in its early stages.

Acuity decreases secondary to hypoglycemia are usually associated with dizziness, diplopia, micropsia, macropsia, and central scotomas. The blood glucose is usually 60 mg% or less, and the disturbance may be secondary to the cerebral effects of hypoglycemia. The onset occurs suddenly and responds in minutes after the ingestion of glucose.

In following diabetics in the out-patient ophthalmology clinic, it was observed that some patients complained of decreased visual acuity at certain consistent times of the day, with a duration of 1 to 3 hours. Some stated they could not read in the morning. Others noted their acuity was decreased in the afternoon. A few stated they would not drive at certain times of the day because of visual difficulties. History and chart review did not reveal any correlation with poor control or hypoglycemic episodes. The following findings were tabulated from patients with this complaint of fluctuating acuity.

These findings were tabulated from approximately 150 diabetics questioned over a year-and-a-half period. Most of the patients had diabetic retinopathy of various stages. The incidence of confirmed fluctuating acuity was 8% or one in every 12 diabetics. Only those with an elicited history of daily acuity changes were examined for this finding. It is possible that others have this variation, but the change is not sufficient to be a complaint for their acuity needs. Being aware of the variation will also depend on whether the patient's activities such as reading, sewing, and so forth, require good acuity. The incidence might well be higher if all diabetics were examined for this finding regardless of their history. In some patients the second daily examination may not have coincided exactly with the time of greatest acuity deficit.

Seven of the patients had decreased afternoon acuity and five had decreased morning acuity. The change varied from one Snellen line to five lines in three patients with an average change of three lines.

Seven of the patients wore refractive corrections. Since the pinhole acuity was in most instances the same as the best corrected acuity, it can be assumed that the change that occurs in these patients is in the lens. None of the patients could relieve symptoms by the ingestion of glucose, and none had associated symptoms of hypoglycemia such as dizziness, diplopia, micropsia, macropsia, or scotomas. Also, the symptoms usually lasted from 1 to 3 hours and sometimes occurred only a short time after a meal.

It is a well-documented fact that the acute refractive changes that occur in early diabetes are usually of weeks or months in duration and that the changes are secondary to fluid flow into or out of

<table>
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<tr>
<th>Age</th>
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<th>A. M. Acuity</th>
<th>P. H.</th>
<th>P. M. Acuity</th>
<th>P. H.</th>
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<td>O. S. 20/100</td>
<td>20/30</td>
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DD Disease duration
PH Pinhole acuity
CF Count fingers
HM Hand motion

Four patients in which this complaint was elicited failed to show any A. M. to P. M. variation.
the lens. No reports could be found in the literature referring to diurnal variations in acuity in well-controlled diabetics. The only exception found that was not associated with actual hypoglycemia was O. Lippmann's correspondence (3) on D. M. Watkin's article (7) in which he reports on myopic changes in a 38-year-old brittle diabetic: "Her myopia increased and decreased within minutes after blood sugar variations. She used the variation of her visual acuity as a substitute for a blood sugar test for many months. Her visual observations were confirmed several times by blood sugar tests." Even a well-controlled diabetic obviously does not have the same level of blood glucose throughout the day. The glucose levels rise after meals and may fall almost to hypoglycemic levels at other times of the day, producing a marked difference between high and low glucose levels, even though two-hour postprandial determinations are in a range classified as good control. It is conceivable that this acceptable variation between high and low levels could cause sufficient fluid shifts in the lens to produce diurnal variations in acuity. It was interesting that the patients in this series stated that the time of decreased acuity was consistent from day to day. The capsule of the lens in a normal healthy state maintains fairly stable molecular concentrations, and fluid changes are normally slow. When, however, the lens is repeatedly subjected by changing osmotic pressures to fluid shifts, it is reasonable that normal diffusion and active transport of fluid mechanisms are stressed and that fluid shifts could then occur more rapidly.

It is important that ophthalmologists be aware of this diurnal variation of acuity in diabetics and its probable incidence. If a patient is examined at a time of best acuity, no refractive correction would be recommended. Sugar ingestion to relieve symptoms might be inadvertently and erroneously advised. Conversely, if the patient is examined at a time of greatest acuity deficit, refractive correction would probably be prescribed, and a reversal of his diurnal variation from A.M. to P.M., or P.M. to A.M. would result. Examination by different ophthalmologists at different times of the day could result in markedly contradictory findings.

In summary, the factors involved in acuity changes in diabetics are briefly reviewed with emphasis on the rate of acuity variations. Twelve patients with a consistent history of diurnal acuity variations were examined, and an average variation of three Snellen lines was found. The incidence of this confirmed complaint was 8% of the number of patients questioned. The mechanism is assumed to be rapid fluid changes in the lens secondary to daily glucose fluctuations, in contradistinction to the slow fluid shifts causing myopia and hyperopia in early diabetics. It is postulated that the rapid changes occur due to damage of the normal lens mechanisms by repeated stress or insult inflicted by recurrent adjustments to osmotic pressure changes. The clinical importance of the entity is emphasized.

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Some Therapeutic Considerations in Diabetic Retinopathy

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With the increasing emphasis on photocoagulation therapy in diabetic retinopathy, its potentials and, most probably, the beneficial effects such therapeutic modality may have in arresting or even improving diabetic retinopathy, one should realize the limitations, the present lack of factual knowledge, and the theories underlying such treatment. One should also keep in mind that light—including laser—coagulation of the retina is still employed selectively in quite a number of other pathological fundus conditions with time-proven effectiveness though it no longer receives the same wide general attention that its use in diabetic retinopathy receives today. Other ocular conditions exist, however, where investigators and practitioners in the field of ophthalmology differ strongly in their opinions as to the efficacy of this therapeutic tool, and even to the advisability of its use, for example, chorioretinal malignant tumors.

Much overemphasis has been placed on the use of laser in clinical retinal photocoagulation over the already established “white light source,” a high pressure Xenon arc lamp, as employed in the Zeiss Photocoagulator. However, the latter is as useful today as it has been for over a decade prior to the invention of lasers. Of the many hundreds of laser sources now developed, only the solid state pulsed Ruby laser and the Argon gas laser—either with a continuous wave (CW) or in a pulsed operation—have, as of now, found wide utilization in clinical ophthalmology. Their use, sometimes in combination with the “white light” coagulator, add to our therapeutic armamentarium in certain clinical situations.

Figure 1 shows diagrammatically the spectral emission of the Xenon arc coagulator and the narrow band emissions within the visible, near ultraviolet (UV) and near infrared (IR) ranges of various lasers which are primarily of ophthalmological interest. Of those, the Ruby laser light is of a deep red color (λ 694.3 nm), and the Argon laser has several bands of spectral emission primarily in the blue-green region (λ 485-515 nm). Figure 2 presents the absorption characteristics of the retinal pigment epithelium and choroid for light of equal intensity and incident on the cornea.

The Ruby laser, usually operated in a single pulse mode in the microsecond range, and the variable retinal image diameter of the laser beam...
cause vessel obliteration. In cases where vessel proliferation into the vitreous has developed, as seen primarily in diabetic retinopathy (fig. 3) among other pathological conditions, the Ruby laser light is relatively ineffective and may even be hazardous if the light energy is increased to achieve coagulation of vascular structures within the vitreous itself (7). This is the area where the Argon laser has found its principal and dominant role in clinical ophthalmology. The bright bluish-green laser beam produces photophobia similar to white light and, thus, in most situations retrobulbar anesthesia is required. This spectral wavelength is strongly absorbed by the hemoglobin and achieves coagulation of the blood with vascular obliteration most easily and successfully (6, 9).

In early stages of diabetic retinopathy with retinal microaneurysms, hemorrhages, and exudates (figs. 4 and 5), and in more advanced stages where neovascularization has already developed (fig. 6), both white light and Argon laser light are equally effective. Only in conditions where the lesions are close to the macula is the Argon laser superior since its greater light intensity permits retinal coagulation of very small foci, thus creating a condition of less potential danger to the macula and fovea.

More recently, Blair and Gass (2) showed that “mild photocoagulation” in the area of the maculopapillary bundle did not produce large central scotomata due to destruction of nerve fibers passing over the coagulated site to the optic nerve. This observation had been described in animal experimentation using histological techniques at various time intervals following light exposure (7), and in human volunteers whose eyes had to be enucleated for other pathological reasons (8).

The effectiveness of photocoagulation in diabetic retinopathy has not been statistically established on a large scale. Its evaluation is difficult since the natural pathological condition may frequently undergo periods of arrested states or even improvement. It is, therefore, not astonishing that a number of ophthalmologists are not in favor of this relatively destructive form of therapy. Proponents for photocoagulation therapy can be largely separated into two groups, that is, 1) those who prefer to coagulate only those lesions which may potentially cause vitreous hemorrhages and areas of neovascularization; and 2) those who want to therapeutically produce large chorioretinal scars involving areas of diseased and ophthalmoscopically
normal-appearing retinal tissue as well. The latter concept is based on certain naturally occurring pathological processes involving the eye which have seemingly prevented the development of diabetic retinopathy or at least have retarded its progression to a significant degree.

Such conditions have been described in eyes with severe glaucomatous optic atrophy, severe myopia, conditions with decreased retinal arterial blood supply, retinitis pigmentosa, large chorioretinal scars following inflammatory reactions, and so forth. In many of the latter instances, the disease was present unilaterally with the fellow eye serving as a control. Hence, production of similar large chorioretinal scars with photocoagulation was expected to create a similar arrest of the progressing stages of diabetic retinopathy by way of reducing retinal blood supply as is common in all of the above mentioned disease entities.

However, regardless of whether one follows
Fig. 4—Retinal hemorrhages, few exudates, and microaneurysms.

Fig. 5—Hard exudates with some new vessel formation at the optic disc.

the more conservative and restricted application, as we do, or the more aggressive approach, photocoagulation therapy of diabetic retinopathy seems presently to be the most effective of all therapeutic attempts to bring this disease process under control. It is at the same time considered relatively safe as measured by experiences and data collected over the last 10 years with many hundreds of patients treated in this fashion. Also, in contrast to the surgical approach of pituitary ablation, the general state of the diabetic patient is not affected by photocoagulation. Pituitary ablation was amenable only to patients who had no other organs involved to any measurable extent, one eye having already become practically blind with the fellow eye still having useful visual acuity, and where the patients' background allowed for a continuous controlled medical substitute therapy throughout the remainder of their lives.

As to the prognosis of photocoagulation therapy, it is generally believed that its greatest beneficial results can be expected if treatment is provided in the early stages of the retinopathy before vasoproliferation takes place. In many cases of macular edema with reduced vision and in cases of extensive retinal exudates, fluorescein angiography allows visualization of vascular leakage which can then be effectively sealed off by coagulation treatment. However, this appears not to be the only mechanism involved in the further prevention of retinal edema. Peyman and Bok (12) have shown in peroxidase diffusion studies in the normal and laser-coagulated retina of primate retinae that the normal barrier at the site of tight junctions of the pigment epithelium broke down at the site of the coagulation. This allowed intercellular peroxidase diffusion to take place across the original junctional barrier in both directions, that is, from the choriocapillaries to the retina and vice versa. However, diffusion in the retina-to-choroid direction was more extensive than chorioretinal diffusion. The investigators concluded from these observations that the breakdown of the junctional complexes of the retinal pigment epithelium in addition to the alterations in the permeability of the choriocapillaries account for the disappearance of sub- and intraretinal fluid after photocoagulation treatment.

Severe vascular proliferation treated with the Argon laser is at present still experimental and its lasting effect is still questionable. However, in those conditions with extremely poor visual prognosis, photocoagulation as well as the more recent surgical attempts (1) seem to be warranted.

It should, again, be re-emphasized that light coagulation therapy in diabetic retinopathy is still debated as to its efficacy. If effective, it appears that treatment of early stages is more amenable and the response more successful. This possible success is somewhat interfered with by the delay in which the patient is referred for coagulation treatment. This understandable hesitation in subjecting the patient to a not firmly established certain form of therapy may lead on the other hand to more severe grades of the
retinopathy which are much more questionable in their response to photocoagulation.

Other therapeutic approaches using hormones, vitamins, anticoagulants, calcium, amino acids, lipotropic substances, antimetabolites, and so forth, have not provided a controlling effect on the progression of diabetic retinopathy. Recently, attention has again been focused on the possible beneficial action of salicylic acid on the development and progression of this retinal pathology. Carroll and Geeraets (3) reported clinical observations based on diabetic patients on long-term salicylic acid intake vs. those without or with only occasional intake of this medication. Their statistical evaluation seemed to prove a significantly lower grade of retinopathy in the former. Findings of Dobbie et al. (4) seem to support this. They advanced the theory by which salicylates interact with the progression of the retinopathy by the prevention of platelet coagulation due to an abnormal aggregation-enhancing plasma factor in diabetes. Such relatively simple chemotherapy should, therefore, be more closely examined as to its effectiveness under controlled conditions and in a relatively large patient population. In the apparently effective low dose in which salicylates would have to be prescribed, other side effects, that is, gastrointestinal hemorrhages, would not be expected. Caution would, however, be indicated in hepatic disease, hypoprothrombinemia, hemophilia, vitamin K deficiency, and other hemorrhagic diseases in association with diabetes. However, controlled studies of drugs in humans have been almost impossible because of the random occurrence, random progression, and irregular and unpredictable incidence of spontaneous remissions.

In recent years many authors have stressed that therapy in diabetic retinopathy cannot be successfully accomplished until adequate experimental animal models have been produced to study the various ramifications of the disease, including controlled drug studies. Although diabetic retinopathy in animals has been successfully produced (5), these
time consuming and very costly experiments have left the question unanswered as to the similarity of the pathogenesis of the retinopathy and, hence, whether it is comparable to human diabetic retinopathy. Heath (10) reported a literature review on this topic in 1970.

In previous efforts to study diabetic retinopathy in experimental animals, only two forms have been available: 1) animals with spontaneous diabetes which were kept alive and were bred for further observation, progression of the disease and its ocular complications, and its genetic implications in producing the disease in the offspring; 2) animals which were made artificially diabetic with alloxan or growth hormone, and their clinical status was followed under strict observation for possible development of diabetic retinopathy. The only variation in these two basic approaches has been to vary the degree of diabetic control.

Several important metabolic characteristics of retinas in human and animal diabetics have been ascertained in recent years:

1) increased lactate levels
2) increased CO₂ levels
3) increased glucose levels (higher than in the general circulation and insulin resistant)
4) increased lactic dehydrogenase activity

That the increased lactate level may be a direct stimulant to abnormal vascular changes was suggested by Imre's work (11) in which he produced intravitreal neovascularization in the eyes of kittens by injecting 0.1% lactic acid into the vitreous body.

In addition to the abnormal metabolic processes in diabetic retinas and the premise that these may produce the abnormal vascular changes, it is also now under consideration whether abnormal antigen-antibody reactions may be one of the etiologic factors in initiating the vascular changes. The insulin inhibitor may be the antigen in this abnormal immunological response, and increased capillary permeability caused by this reaction may be the initial process in the vascular changes. Abnormal metabolites might also act as antigens.

In addition to the present knowledge about the metabolic abnormalities in diabetic retinopathy, there is also some evidence about the changes occurring in retinitis pigmentosa which apparently prevent the development of diabetic retinopathy. In this disease, taurine is reduced in amount; β-aminoisobutyric acid is reduced in concentration; and there is a reduction in anaerobic glycolysis which can be reversed by giving pyruvate. One could speculate that by increasing these factors, diabetic retinopathy could be enhanced as well.

With this increasing knowledge of the pathological state of the retinal biochemistry, new chemotherapeutic agents may be developed and investigated.

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Glaucoma and the Optic Nerve

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In the past, emphasis in glaucoma has been placed on aqueous dynamics and the alterations in the anterior segment which have caused elevations in intraocular pressure. Although these are certainly important factors in the evaluation and treatment of glaucoma, there are many cases in which sustained elevations of pressure above the statistically normal range have not resulted in typical glaucomatous changes in the optic nerve or visual field. Similarly, there are cases where, in spite of normal intraocular pressure, damage to the nerve and defects in the field have occurred. Therefore, increasing emphasis has shifted to the posterior segment of the eye where changes in the optic disc may be the initial sign of glaucomatous damage or of progression of the disease.

A review of the anatomy is helpful in understanding the glaucomatous changes in the optic nerve head. The intraocular portion of the optic nerve is divided into two parts: laminar (scleral) and pre-laminar (choroidal and retinal). The pre-laminar portion is the most anterior extension of the nerve and is seen ophthalmoscopically as the optic disc. It is approximately 1.5 mm in diameter, being somewhat narrower in its horizontal dimension, and represents the point of convergence of the retinal nerve fibers where they leave the globe. The fibers pass posteriorly through the choroid to emerge from the eye via a scleral opening called the scleral ring. If this ring is small, as it often is in hyperopia (farsightedness), the nerve fibers will be compacted and the disc smaller, thus leaving little room for any empty space or "cupping" in the center of the disc. Conversely, in myopia (nearsightedness), the ring tends to be large and the ocular coats thinner, therefore allowing a larger though often quite shallow cup in the disc. It is this cup that is of interest to us in glaucoma.

The size of the optic disc cup has been shown to be congenitally determined (1) and does not normally change with the aging process. It is formed by atrophy of the embryonal Bergmeister's papilla which is a mesodermal structure arising from the center of the disc to support the hyaloid artery in the fetus. The amount of atrophy of this papilla and the size of the scleral ring seem to be the factors determining the size of the optic disc cup. There is an indication that these factors are hereditary in that optic disc morphology is often similar in close blood relations.

The depth of the cup is limited by the lamina cribrosa, a fenestrated grid work of scleral fibers through which fascicles of the nerve pass at the level of the sclera. It can be seen in the base of the cup as a whitish grid, and it divides the nerve into pre-laminar and laminar portions.

The laminar and pre-laminar portions of the nerve are affected by elevations in intraocular pressure. Although previous theories as to the mechanism causing this damage have dealt with actual pressure atrophy of the nerve fibers, more recent studies indicate that this damage results from ischemia. An elevation in intraocular pressure is transmitted directly to the intraocular blood vessels, compressing them and thus increasing their resistance to blood flow. This is most pronounced in the capillary circulation of the nerve head and the immediately adjacent retinal and choroidal tissues. It is thought that this reduction in blood flow causes a gradual ischemic atrophy of the cellular structures in the nerve head.

The pre-laminar portion of the nerve head is composed of two cell types: the nerve fibers which arise from the retinal ganglion cells and travel in an arcuate pattern from the periphery of the retina to convene at the disc and turn backward to pass out of the eye, and the astroglial cells which are

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the supporting elements of the nerve. Shaffer (3) has suggested that these glial cells are the first to succumb to the effects of chronic ischemia. This would explain the fact that loss of tissue from the nerve head resulting in an increase of the cup size often occurs prior to the development of field defects. This increase in the size of the cup may be the earliest indication that damage to the eye is occurring, and normalization of the pressure at this stage may prevent further structural and functional damage. Occasionally following such normalization, the cup size will decrease indicating regeneration of astroglial cells. Thus in the evaluation of the patient with elevated intraocular pressure, the appearance of the optic nerve head is particularly important.

There are three basic instruments available for examining the optic disc: the direct ophthalmoscope, the indirect ophthalmoscope, and the slit lamp. The direct ophthalmoscope provides an enlarged upright image and can be used with a relatively small pupil. Its disadvantage is that, unlike the other two instruments, it does not allow a stereoscopic evaluation of the disc. Therefore, one is forced to define a three-dimensional structure from interpretation of a two-dimensional image.

This two-dimensional image of the optic disc is composed of three parts: the excavation or cup, the surrounding rim of disc tissue, and the blood vessels that arise from the center of the disc. The cup is recognized as the paler central portion of the disc. Its nasal and superior walls are usually steep while the temporal and inferior walls tend to slope more gently. It may occupy the entire disc leaving no rim, as in end-stage glaucoma, or it may be virtually absent in which case the surface of the disc is flat and uniformly pink.

The size of the cup is estimated as a ratio of the overall horizontal diameter of the disc to the diameter of the cup expressed to the nearest tenth. A disc in which the horizontal diameter of the cup equals one half of the overall horizontal diameter of the disc would have a cup/disc (C/D) ratio of 0.5. The horizontal diameter of the cup is measured from the nasal wall, which is easily recognized because of its steepness, to the temporal wall which is less easily defined. As the temporal wall slopes upward from the bottom of the cup, there is a gradual intensification of the normal pink color of the rim, and the temporal edge of the cup is estimated to be in the middle of this area of color change. Another aid in locating the temporal edge is to mentally project the curve of the steeper superiör wall down and around the temporal side of the disc.

Evaluation of the rim of the disc can help in recognizing the glaucoma suspect. A rim of uniform thickness around the superior, inferior, and temporal aspects of the disc is less likely to be associated with glaucoma. If the rim is particularly thin in the inferior temporal area or, less often, the superior temporal area, then glaucomatous damage is more likely to be present.

The position of the blood vessels is of no particular help in this problem. However, the course they follow as they cross the rim can give one a clue as to the location of the edge of the cup. Sharp angulation of the vessel as it crosses the rim often occurs where the vessel turns downward over the edge of the cup. If the cup has undermined the rim of the disc, the vessel may seem to disappear as it turns over the rim to reappear in the bottom of the cup.

All these factors are useful in determining the extent of cupping of the optic disc expressed as the cup/disc ratio. Statistical studies have shown that a C/D ratio of 0.7 or greater occurs in only 3% of the normal population (2). Therefore, anyone with a C/D ratio of 0.7 or greater should be considered a glaucoma suspect and deserves further evaluation. Also, a difference in C/D ratios between the two eyes of 0.2 or greater occurs in less than 1% of the population and should be taken as evidence of glaucomatous damage until proven otherwise.

In summary, the anatomic characteristics of the optic nerve head have been described along with the ophthalmoscopic interpretation of these characteristics. One hopes that this information combined with a knowledge of what constitutes glaucomatous abnormality in the optic disc will encourage the ophthalmic as well as non-ophthalmic practitioner to evaluate the optic nerve head and recognize those which are suspicious of glaucoma.

REFERENCES
The Relationship of Motility Problems to Reading Problems

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Introduction. Normal reading incorporates two major criteria: speed and comprehension. Yet, it is soon apparent that the varying ability of human performance prevents rigid adherence to these criteria, and exceptions become common. We will grudgingly tolerate an inverse relationship between the two criteria as normal and quickly agree that a child faltering on both criteria is a reading problem suspect.

However, the majority of children learn to read with very little difficulty. Even the less than normal child is capable of mastering the task with adequate effort. Moreover, we are currently spending comparatively little time with the successful reader and devoting most attention to the small percentage of children who fail to learn during the prescribed time.

Lack of success in clarifying the mechanism of failure in these children has brought about the abuse of the diagnosis, dyslexia. The word is now applied to a number of other problems which interfere with the learning process including emotional problems, low intelligence quotient, disinterest, and even ophthalmological disorders. The abuse has received little recognition as the word continues to appear. Some of this may be due in part to only a vague understanding of the neurological mechanisms involved in reading failure, but the mechanism of failure is quite easily defined when the eye is involved as a cause of poor reading, permitting the ophthalmologist to perform a specific task in the care of reading problems.

Interpretation of the printed word, symbol, or letter is a function of the central nervous system. It can be logically argued that it makes little difference by what pathway the message gets to the brain; the process of reading by interpreting the printed word can occur as long as an impulse, properly coded, has a certain minimal clarity. For example, recent experiments (1) using a tactile stimulator strapped to the skin of a blind patient demonstrated beyond question that he was able to read printed matter without ever having used his eyes. That is not to say the eyes are not a very valuable part of the reading process, but it is to say that an important part of reading occurs in the central nervous system. The eye is unsurpassed as a convenient and valuable camera providing input for the central nervous system in the reading process. It is this distinction between input and interpretation that allows one to specify the ophthalmologist's tasks so clearly. The ophthalmologist is primarily concerned with the input system, obviously the eye, for the reading process. It then becomes only necessary for the ophthalmologist to discover any process interfering with minimal clarity in the visual input system so that he can proceed, when possible, with a remedy.

There are four categories of ocular disorders that can potentially interfere with the reading process. They are refractive errors, strabismus, nystagmus, and pathologic loss of vision.

Refractive Errors. Correctable interferences with minimal clarity are the routine refractive errors encountered in the every day practice of ophthalmology: hyperopia, myopia, and astigmatism. My-
opia, or nearsightedness, describes the child seeing very well within a few inches of his eyes and not seeing well at a distance. If the myopia is of a minor nature, the child can perform close work without lens correction but falters on tasks requiring clear vision at greater distances such as seeing a blackboard. With larger degrees of myopia, even a book held by the child at the usual reading distance is slightly blurred, and glasses are required.

Frequently with hyperopia and astigmatism, a young child has enough reserve accommodative strength in his eyes to clear the image for short periods of time. This introduces a fatigue factor. The child may perform well for short periods of time and soon become disinterested with the onset of fatigue. Therefore, hyperopia and astigmatism of a significant degree are strong indications for prescribing glasses in a school child.

It should be apparent that a child failing to perform the reading task because of an uncorrected refractive error should have lenses prescribed by the ophthalmologist. The cure rate is virtually 100%.

**Strabismus.** There is another quality of vision that must also be considered. Having two eyes (or two cameras) furnishing central nervous system input adds an additional burden on the visual system since it requires coordination, both motor and sensory. The advantages gained by this requirement are primarily in depth perception and increased peripheral range of vision. However, neither is a requisite to reading. Under normal circumstances, one has to see a single image in order to interpret visual information efficiently without confusion. Diplopia is an intolerable confusion to the central nervous system. Therefore, reading becomes virtually impossible when the lack of coordination between the two eyes is severe enough to result in double vision.

Reading is quite possible, frequently no more difficult than normal, if the absence of binocular coordination does not result in diplopia. For example, if there is failure to establish normal binocular coordination in the developing central nervous system of the child, compensatory sensory changes develop eliminating diplopia. With the onset of strabismus, the central nervous system soon ignores visual input from one eye as a response to an intolerable situation, diplopia. Suppression usually occurs intermittently at first as strabismus is frequently intermittent in the early stages. It later becomes a fixed pattern, and the child is no longer bothered with diplopia. Nature has thus provided a compensation for an intolerable situation. The visual input from the eye, though decompensated under these circumstances, is still adequate to perform with efficiency any visual task except refined depth perception and wide-angle viewing. Therefore, learning to read proceeds normally in the face of strabismus as long as the child has suppression, absence of diplopia, and adequate vision in the fixing eye.

Manifest strabismus is classified as a tropia state and latent strabismus as a phoria state. These suffixes identify whether the deviation is obvious, and we refer to exotropia, exophoria, and so forth, with diagnostic implication. There is another distinction that separates the two states even more solidly. The tropia, or manifest strabismus, implies suppression, and the phoria, or latent strabismus, implies absence of suppression. Practically, if the phoria becomes decompensated, as with fatigue, diplopia becomes the major symptom. Since diplopia is an intolerable confusion, it must be remedied to proceed with the learning task in reading.

Not all phoria states are symptomatic, and some children have built up considerable reserve strength allowing them to perform routine visual tasks without difficulty. Indeed, one of the goals of orthoptic or eye exercises is to build up the reserve strength and allow such a patient to perform without symptoms. It should be emphasized that this is the only time that eye exercises have any value in the treatment of reading problems. Even so, the eye exercises accomplish nothing more than a temporary goal and never cure anything permanently.

Small degree phoria states are also amenable to prismatic correction. A prism introduced in front of either one or both eyes can readily correct the entire deviation of a small degree strabismus and relieve fatigue symptoms. Prisms, like orthoptics, effect only a temporary relief of symptoms and are not curative.

Larger degrees of phoria state are beyond the reach of orthoptic exercises and prisms. Larger strabismus deviations require a constant exertion of large degrees of reserve strength, and there is comparatively little increase resulting from eye exercises. Prismatic correction is limited because the larger the prism, the greater the distortion in vision. The point is soon reached where vision is blurred below the passable level for reading.

It is also pertinent that a small amount of exophoria is normal, and any esophoria is abnormal.
The problem becomes increasingly complicated because many school systems are using diagnostic machinery with a built-in esophoria bias. Many of these have optical systems which induce a reflexive convergence of the eyes, which is then interpreted by the untrained observer as an esophoria. Such a false positive is usually discovered and remedied with an adequate examination in an ophthalmologist's office.

Phoria states are only permanently cured by surgery. One is justifiably reluctant to recommend surgery on small degree phorias. Conservative measures are more applicable. Conservative measures are also the proper choice for large degree phorias in the initial stages. If it becomes apparent that a large degree phoria causes chronic discomfort, then surgery is definitely indicated.

So far, the explanation of suppression has been elaborated only as it applied to visual infants. The child becomes a visual adult very early in life, or at approximately five years of age. After the visual apparatus has matured to its maximum level, it is no longer possible to learn to suppress vision as it is recognized in strabismus patients. Therefore, an adult acquiring strabismus (usually paretic) does not have the compensatory mechanism available to him as the young child, and diplopia becomes chronic. Then strabismus becomes a much more complicated and difficult problem. The best effort is usually surgical and directed towards the goal of getting the eyes straight in the primary position first and in the reading position second. Sometimes, with severely paretic states, even this is not possible. Some form of compensatory prism or head tilt becomes necessary for reading. A desperation treatment is simply to patch one eye while reading. Although effective, it is not the most desirable result.

**Nystagmus.** Nystagmus affects reading only insofar as it reduces visual acuity. There are many classifications of nystagmus, and they are based primarily on the physical characteristics rather than the effect on vision. Consequently, dealing with the classification of nystagmus as it relates to reading problems has little significance. Again the requirement for reading relates to a certain minimum of input, that is, adequate vision. Congenital jerk nystagmus not infrequently reduces the vision to 20/60 or better which is quite compatible with normal reading development. The pendular nystagmus, so frequently associated with albinism, is commonly associated with markedly subnormal vision, usually 20/200 or less, and this imposes a severe restriction to the learning process. It is not germane to discuss whether reduced vision causes nystagmus or vice versa; it is only important to emphasize that nystagmus, as it relates to reading problems, is significant only if the visual acuity loss is associated with it. Therefore, if nystagmus is to be treated with a view towards improving reading, a major effort should be directed at improvement in visual acuity. This usually amounts to correcting the subnormal vision and refractive errors frequently associated with nystagmus.

**Pathologic Loss of Vision.** Subnormal vision that cannot be corrected by optical devices to normal vision presents a different problem to the reader. The minimal clarity necessary to reading depends entirely on whether enough magnification can be placed in front of the eyes. The minimally clear message can be obtained by increasing the size of the print. Frequently some combination is utilized such as excessive magnification coupled with a large print book in order to improve vision to the extent that reading is possible.

In many instances, there are large refractive errors associated with the uncorrectable subnormal vision, and a corrective lens becomes necessary on that basis also. Limited optics, both in the affected eye and the corrective lenses, disallow the normal pace in reading or learning to read. Therefore, it does become necessary to make allowances for the anticipated reduction in speed of the learning process in affected children. Yet, these children still may not be classified as dyslectic, and they are quite capable of eventually learning to read as well as a normal child with the only deficit being speed. Comprehension of the printed material usually relates to intelligence and not to the basic ocular defect.

The pathologic subnormal vision that creates a reading problem has to be binocular because one-eyed children learn to read just as fast as two-eyed children. If there is one eye with normal vision and a second eye with subnormal vision, that is not a reading problem. The binocular subnormal vision children are those who present the major problem. Fortunately, binocular macular diseases are unusual. Congenital toxoplasmosis, albinism, and bilateral amblyopia associated with nystagmus are the more common entities.

In summary, the ophthalmologist's role in caring for dyslectic children is simply caring for ocular problems. It is rather easy to separate the ocular
defects from the nebulous concepts of dyslexia or learning disability. It is also easy to make the decision when and to what degree ophthalmological care is indicated with a clear and attainable goal in sight. Eye exercises or so-called visual training have virtually no value. Practically, the ophthalmologist's most valuable tool in caring for dyslexia is honesty about his results.

REFERENCES

Primary Position Deviation in Duane's Syndrome*

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Introduction. The diagnosis of an esotropic patient as having Duane's syndrome is not always clinically evident. There has been a paucity of attention directed to the size of the esodeviation in patients with this syndrome. The purpose of this paper is to point out the diagnostic significance of the size of the primary deviation in patients with, or suspected of having, Duane's syndrome.

Methods. Of the 93 patients with Duane's syndrome seen, 50 with an esodeviation were included in the study. Patients with orthophoria, exodeviation, bilateral involvement, and vertical misalignment were excluded. All patients were older than 18 months. Diagnosis was based on the presence of limitation of abduction-adduction, retraction, up or down shoots, and palpebral fissure changes on adduction (3, 1, 5). Electromyographic recordings were made in some cases.

The head is in the primary position when the head or sound eye is made to look at a distant object without a head turn. The deviation was measured by the prism cover test. When this was not possible, it was assessed by Krimsky or Hirschberg corneal reflex methods.

Results and Discussion. The results are summarized in Table 1. The size of the esodeviation was 30 prism dipters (\(30^\circ\)) or less in our entire population of 50 patients (fig. 1). The average size deviation was 16\(^\circ\) of esotropia in the primary position.

Dividing the patients arbitrarily into groups of 1-10\(^\circ\), 11-20\(^\circ\), and 21-30\(^\circ\), there were 17 patients

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TABLE 1.
PRIMARY POSITION ESODEVIATION IN DUANE’S SYNDROME
(50 PATIENTS)

<table>
<thead>
<tr>
<th>Size of deviation (prism diopters)</th>
<th>No. of patients</th>
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</thead>
<tbody>
<tr>
<td>1-10</td>
<td>17</td>
</tr>
<tr>
<td>11-20</td>
<td>21</td>
</tr>
<tr>
<td>21-30</td>
<td>12</td>
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Average esodeviation = 16 prism diopters

in the 1-10° group, 21 patients in the 11-20° group, and 12 in the 21-30° group.

A patient with an esodeviation of greater than 30°, on the basis of this study, would be excluded as having a possible Duane’s syndrome. One should be prompted to investigate other possible diagnoses, for example, the usual types of esotropia, iatrogenic or congenital structural anomalies, and sixth nerve palsy.

In the usual type of esotropia having greater than 30° of deviation, the feasible goals include alignment of the eyes in the primary position, provision of a normal range of rotation, and restoration of binocular function. Treatment should be started as soon as possible to enhance the possibility of bifoveal fusion. This is in contrast to the patient with Duane’s syndrome where fusion is generally accomplished by an abnormal head posture, and no urgency exists. Feasible goals are the alignment of the eyes in the primary position, abolishment of the head turn, reduction of the retraction, reduction of palpebral fissure narrowing, and shift of the horizontal rotation range to a more useful position. All can be improved by recession of the medial rectus muscle of the affected eye (4). Additional horizontal correction is possible by operating on other horizontal muscles (4, 2).

Summary. All of the 50 patients with Duane’s syndrome with esotropia had a primary position deviation of 30 prism diopters or less. Over half of the patients had a deviation of 15 prism diopters or less. A patient with an esodeviation of greater than 30 prism diopters is unlikely to have Duane’s syndrome, and efforts should more profitably be directed to establishing another diagnosis.

Authors’ note: We thank Fletcher Woodward for statistical help.

REFERENCES
Some Common and Less Common Aspects of Orthoptics

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Orthoptics (derived from the Greek "orthos"-straight and "ops"-vision) has been in use for centuries at various stages of sophistication and has been applied to the treatment of visual anomalies not amenable to other medical approaches. However, today’s orthoptic evaluation and treatment techniques date back only about 50 years, with continuous refinements in both knowledge and technical equipment. Orthoptic treatment is primarily directed towards restoring normal binocular vision; whereas, pleoptic treatment is aimed at regaining monocular vision. Thus, although the art of orthoptics is in the final analysis an ancient one (fig. 1), its scientific application has been greatly enhanced and placed on more solid scientific grounds, especially in the last decade.

An orthoptic examination consists of a complete muscle work-up, testing of visual acuity, and the diagnosis of the patient’s binocular function. Orthoptic treatment is essentially a process of mental training consisting of reeducative exercises. Thus, it must be diagnostic before it can be therapeutic. It is only possible to reeducate the binocular functions to a stage reached in their development before the onset of the eye deviation. Orthoptic treatment does not take the place of surgery, although some cases may be corrected by orthoptics alone. Other cases may require both pre- and postoperative treatment in order to attain a functional result. Cases without any potential for binocular vision may have surgery for a cosmetic result only, as orthoptic treatment could cause intractable diplopia where no fusion exists.

Most of the patients referred for an orthoptic evaluation are children. Thus, it is essential that both the examination and the treatment are made interesting and that the child enjoys the visits as much as possible. Adult cases include congenital and acquired muscle paresis, latent strabismus with symptoms, convergence insufficiency, and accommodative spasm and fatigue.
Pleoptic treatment presents a challenge when foveal fixation has been lost and the final outcome is speculative, even though treatment is based on scientific evaluations and predictions.

In this paper some daily orthoptic and pleoptic activities are discussed, and examples of more unusual and experimental approaches which have proved of benefit are presented.

Amblyopia (from the Greek “amblus”-blunt and “ops”-vision) represents a condition of reduced vision which is not traceable to a specific disease or injury and which cannot be corrected by optical means, that is, glasses or contact lenses. In suppression amblyopia the retinal function is normal, but because of “faulty alignment,” that is, visual representation on non-corresponding areas of the two eyes, double vision would be experienced. Although the morphology and function of the involved retina can be considered to be normal, the elicited experience activates a central, that is, cortical inhibition of the transferred stimuli, and suppression is the result (figs. 2 and 3).

The goal for orthoptic treatment is the reestablishment of single binocular vision, although retinal rivalry may persist without any form of spatial distortion. The objective for pleoptic treatment is improvement in visual acuity.

In summary, it should be understood that orthoptics and pleoptics represent non-surgical means by which the eyes are trained to function normally and to overcome previous disease entities which might have been instrumental in causing the existing condition. One of the more common problems encountered in orthoptic treatment is suppression amblyopia. A general approach to deal with this condition is demonstrated in a randomly selected case report. Though loss of vision due to suppression amblyopia is still too frequently found, the public is gradually becoming more aware of its existence, but until the urgency of strabismus is fully realized, vision will continue to be needlessly lost.

There are two kinds of suppression amblyopia: strabismic amblyopia and anisometropic amblyopia. In the former, the fovea of the deviating eye is suppressed to avoid confusion (that is, seeing a different image from that of the fixing eye), and a peripheral retinal point is suppressed to avoid diplopia. In the latter, there is suppression of the image seen by the eye with the greatest refractive error, but in this instance the foveal suppression is of the same image.

Over the years various methods of treatment have been tried and successes claimed for all of them. Treatment in every case is directed to the usage of the fovea, and it is designed to restore functional superiority of the fovea and to maintain the improved visual acuity once gained. The most frequently used method is occlusion of the eye with the better visual acuity. This method, combined with exercises which require visual skills such as dot drawings and jigsaw puzzles, often shows marked improvement in the vision of the amblyopic eye. An older child will, however, find it more difficult both to regain good visual acuity and to wear an occluder. Compromises have had to be made; for instance, part-time occlusion combined with an
hour per day spent doing some intricate close work, such as the Weiss exercise sheets (figs. 4, 5, and 6).

A different color is chosen for each symbol, and the child colors, for example, the “E” as far down the chart as it can be identified. Then another symbol is chosen, and the exercise is repeated. The Weiss sheets are also printed in red, and when combined with the use of a red filter over the dominant eye instead of total occlusion, even more effort is required of the amblyopic eye. Red filter occlusion can be used with any game or craft requiring acute vision where colors in the red/orange range predominate.

Occlusion of the fixing eye can be obtained by the use of atropine drops in that eye. This method has been chosen most often in the treatment of very young children when occlusion with an eye patch was not tolerated. Recently, this method of occlusion has been combined with the use of a miotic in the amblyopic eye. The miotic creates a pinhole effect, therefore, visual acuity is slightly im-

Fig. 4—Weiss exercise sheet containing eight different symbols.

proved. Unless the patient is myopic, the eye under the influence of the miotic is used in preference to the dilated eye for close work. A recent study in England reports successful results using this method, even in cases where foveal fixation had been lost. The miotic used was phospholine iodide 0.06%, and the cycloplegic was atropine 1%. Treatment was continued for as long as 20 months and included children up to 13 years of age. The advantage of this treatment is that the embarrassment of wearing a patch is avoided; consequently, both the parents and the child are happier.

Low vision optical aids can also be helpful in the treatment of amblyopia. There are two types of telescopes which may be used. For patients with very low visual acuity, there is a $6 \times$ magnifying monocular telescope; however, the field of vision is small, and much skill is required for its use. The $2\frac{1}{2} \times$ telescopic lens has the advantage of being able to be clipped on to glasses and also permits a
Fig. 6—Weiss labyrinth exercise.

larger field of vision. Part-time occlusion for one or two hours per day is necessary, and during that time active seeing is required for both near and distance. The treatment may sometimes be long and requires the effort and cooperation of both the child and the parents.

In 1953, Bangerter of St. Gallen, Switzerland, introduced pleoptic treatment of amblyopia, and Cuppers designed the visuscope for the diagnosis of amblyopia with eccentric fixation and the euthyscope for its treatment. Bangerter's method of treatment uses light to alternately dazzle the retina while sparing the fovea, followed by light stimulation of the fovea. It is very time consuming and requires above average cooperation of the patient. This is also true of Cuppers' treatment which utilizes after images and the Haidinger brush phenomenon.

Suppression is difficult to eradicate completely. For instance, a patient may demonstrate 20/20 vision in the previously amblyopic eye when tested monocularly, but when tested under binocular conditions with polaroid glasses and the vectograph slide, visual acuity may be considerably reduced in that eye. Ideally then, treatment should be continued until visual acuity is the same whether tested monocularly or binocularly (fig. 7).

Fig. 7—Vectograph slide, a test for monocular visual acuity under binocular conditions. (Courtesy of American Optical Corporation.)
Major amblyoscope measurements:

<table>
<thead>
<tr>
<th>Fixing Right Eye</th>
<th>Fixing Left Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>To patient’s right</strong></td>
<td><strong>To patient’s left</strong></td>
</tr>
<tr>
<td>+4 (LH1)</td>
<td>+2 (LH1)</td>
</tr>
<tr>
<td>+8 (LH8)</td>
<td>+6 (LH5)</td>
</tr>
<tr>
<td>+8 (LH16)</td>
<td>+10 (LH15)</td>
</tr>
</tbody>
</table>

Treatment of amblyopia should always be selected according to its severity and to the age and temperament of the patient. If one method does not prove to be satisfactory, others should be tried, as the improvement of visual acuity is a very worthwhile goal.

Some of the more unusual conditions requiring orthoptic evaluation are presented in the following case reports.

A 57-year-old secretary was referred to the Orthoptic Clinic in October, 1968, with a complaint of a gradual onset of diplopia. The patient presented a history of rheumatoid arthritis of long duration which had severely affected the hands and feet. No scleral or conjunctival involvement was noted. The orthoptic evaluation at that time revealed 12 prism dipters of left hypertropia by prism cover test. The chin was depressed, and the head was turned towards the right. Diplopia was present on level and on down gaze with the greatest vertical separation of images on dextro-depression, that is, with the eyes looking down and to the right.

The Hess screen test revealed a weakness of the left superior oblique and left inferior rectus muscles (fig. 8).

It was possible to join the diplopia on level gaze with a 6\(\Delta\) prism, and a clip-on prism was prescribed. The patient was comfortable with the
prismatic correction which was later incorporated into her refractive lenses. The prescription given was: O. D. = −2.75 − 0.50 × 150 ⊕ 3° base up; O. S. = 2.00 sphere ⊕ 3° base down with a +2.00 diopter spherical addition for near work. In September, 1972, the patient returned to the Orthoptic Clinic for reevaluation. She stated that the diplopia was quite variable and at times could be overcome with or without the glasses. The orthoptic findings were as follows: On level gaze there was a left hyperphoria for near and distance; on down gaze a left hypertropia and a left esotropia existed. The head posture was fairly straight, but the head was still held down at times. Diplopia was present on down gaze and most marked on laevo depression. The Hess screen test showed only a slight under action of the left superior oblique muscle (fig. 9).

Major amblyoscope measurements September, 1972:

<table>
<thead>
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<tr>
<td>+4Δ</td>
<td>+2LH1Δ</td>
</tr>
<tr>
<td>L. Ex 10°</td>
<td>L. Ex 10°</td>
</tr>
<tr>
<td>+8LH2Δ</td>
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<td>L. Ex 10°</td>
<td>L. Ex 10°</td>
</tr>
<tr>
<td>+24LH2Δ</td>
<td>+30LH2Δ</td>
</tr>
<tr>
<td>L. Ex 10°</td>
<td>L. Ex 10°</td>
</tr>
</tbody>
</table>

L. Ex = Left Excyclphoria
Fusion on level gaze at 0Δ and on down gaze at 18Δ.
Major amblyoscope measurements:

**Fixing Right Eye**

<table>
<thead>
<tr>
<th>To patient’s right</th>
<th>To patient’s left</th>
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</thead>
<tbody>
<tr>
<td>$-44^{\Delta L_{H8}}$</td>
<td>$-42^{\Delta L_{H6}}$</td>
</tr>
<tr>
<td>R. In $5^\circ$</td>
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<tr>
<td>$-44^{\Delta L_{H10}}$</td>
<td>$-44^{\Delta L_{H2}}$</td>
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<td>R. In $5^\circ$</td>
<td>R. In $5^\circ$</td>
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<td>$-46^{\Delta R_{H6}}$</td>
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<td>R. In $10^\circ$</td>
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R. In = Right Incyclotropia

Sandford-Smith (1969) and Sims (1971) have reported cases of patients suffering from rheumatoid arthritis who also had diplopia due to abnormalities of the superior oblique muscle. It appears possible that in this case there may also be a connection between the disease and the defective muscle or the tendon or muscle sheath. This possibility is supported by the frequent extensive pathology of the sclera which may occur in this disease entity.

Another patient, a 40-year-old timber merchant, suffered a III nerve paresis following a car accident in December, 1971. He had severe contusions and multiple injuries involving the right side of the body. The right eye showed a fixed dilated pupil, and there was retrograde amnesia of several months preceding the accident. In March, 1972, the patient was referred to the Orthoptic Clinic for evaluation. He was wearing an eye occluder over the injured eye to prevent diplopia. An orthoptic work-up in this case revealed the following findings: The prism cover test showed an exotropia of 45 prism diopters with a left hypertropia of 8 prism diopters. There was a marked weakness of the right internal rectus and a weakness of the right superior and right inferior recti muscles. Heteronymous and vertical diplopia were present with the greatest separation of images on dextro-depression (fig. 10). The Hess screen chart showed marked weakness of the right internal rectus and an overaction of the right external rectus, the smaller field belonging to the eye with the paretic muscle (fig. 11).

Fig. 10—A. shows limitation of right eye on dextro elevation; B. shows right exotropia on level gaze; C. shows right exotropia with right hypertropia on down gaze.
Fig. 11—Hess screen chart, March, 1972.

Fig. 12—Hess screen chart, August, 1972.
On the second visit a week later it was possible for the patient to fuse the two images on level gaze with the aid of a 40° prism base in over the right eye. Treatment was given on the major amblyoscope to improve fusional amplitudes, so that later it would be possible to reduce the amount of prism required to maintain single vision. The patient was given a prism bar with prism strength graduated from 1° to 40° for daily home exercises. He was asked to refrain from wearing the occluder as much as possible so that some attempt could be made to join the diplopia. The occluder, when worn, was transferred to the unaffected eye, as it was now possible to do so without causing proprioceptive difficulties. This enabled the right eye to be used instead of remaining in a divergent position behind the occluder.

At the end of that month it was possible to join the diplopia; however, this required an excess amount of accommodation, so that distance binocular visual acuity was reduced to 20/70. Treatment with the prism bar was then changed to base out exercises, with the result that prism convergence improved to 40°. Convergence exercises were given on the major amblyoscope, and control of the deviation was helped by teaching physiological diplopia exercises using stereograms. There was still some difficulty on up gaze and on down gaze due to weakness of the superior and inferior recti muscles. The field of binocular vision was increased by attempting to keep an object “one” in all cardinal fields. The patient’s difficulty in judging distance persisted, and he felt the loss of depth perception, although on testing it was present.

Treatment was continued, and by August, 1972, there was a marked improvement. At that time the Hess screen test showed only a slight weakness of the right inferior rectus muscle (fig. 12).

Major amblyoscope measurements showed an angle of deviation of 2° of exophoria with a left hyperphoria of 1°. Fusion existed at 0° with adduction to 30°, and depth perception was present.

Involuntary convergence was present to 6 cm, and the patient had the ability to converge voluntarily. Binocular visual acuity at that time measured 20/15. The only area where there was some difficulty was on extreme depression, but this was not sufficient to cause discomfort in everyday life (fig. 13).

The scope of orthoptics is wide, but it must be remembered that orthoptic treatment of eye devia-
tions is only part of the overall treatment. Medications and/or surgical treatment may be necessary, frequently in a combined effort with orthoptic treatment, for visual rehabilitation of the individual patient.

BIBLIOGRAPHY


Treatment of Hypertropia with Relaxing Conjugate Vertical Prisms

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Certain selected cases of hypertropia can be permanently corrected with identical prisms placed base up over each eye. A child was first successfully treated by this method more than 14 years ago, and the excellent long-term outcome in her case, as well as generally encouraging results in a series of over 100 subsequent patients, suggest that in suitable cases the double vertical prism may be a useful addition to the methods available for the treatment of hypertropia.

Traditionally, prism glasses are used in the management of strabismus to neutralize the sensory consequences of the turn, and they are therapeutic in somewhat the same sense as refractive corrections, which improve function without eliminating the underlying deficiency. While clinical results may be excellent, they are achieved within the framework of preexisting motor and sensory patterns; thus in this respect, the conventional prism may be considered as essentially a compensatory or “relieving” device. In contrast, conjugate vertical prisms, used as described in this paper, have no effect upon the sensory angle between the two eyes, but instead are intended to alter the long-term course of motor adaptations in certain types of hypertropia. Because these prisms decrease the use of the paretic muscle and thus reduce progressive contralateral spasm and inhibitional palsy, they may be logically called “relaxing” prisms as distinguished from the “relieving” (or neutralizing) prisms as defined by Duke-Elder (1).

It is generally accepted that in cases of elevator insufficiency, constant fixation with the paretic eye may eventually result in habitual spasm and even permanent contractures of the yoke muscle. Similarly, inhibitional palsy of the contralateral antagonist may exaggerate the effect of slight weakness in the fixing eye so much that the original paresis may be obscured by secondary changes on the opposite side. When these mechanisms confuse the diagnosis, they may be temporarily excluded by patching the fixing eye. If conditions are still reversible, occlusion may decrease or even temporarily eliminate the squint. In contrast to its diagnostic value, such occlusion is of little benefit as a therapeutic measure because as soon as binocular use is resumed the patient will revert to his preferred fixation, and the circumstances leading to the secondary motor adaptation will become reestablished. However, if prisms can sufficiently minimize the use of the fixing eye in the field of maximum action of the paretic muscle, the recurrence of the conditions that determined the progression of the deviation may be avoided.

To the best of my knowledge, a survey of the literature has shown no reports of the systematic clinical application of this idea. Conjugate vertical prisms (base up or base down over both eyes) have been used infrequently in A&V syndromes, bilateral inferior rectus contractures, or certain types of nystagmus (2), but in the conventional way as compensatory devices to place the eyes into an optimum position for fusion or postural comfort with improvement in function only so long as the prisms con-
tinue to be worn. In contradistinction, a similar correction prescribed as "relaxing" prisms has no immediate effect on measurements or symptoms, but over a prolonged course of time it exerts a cumulative influence on the underlying motor anomaly.

Prototype Case. The therapeutic rationale of relaxing conjugate vertical prisms is best explained in terms of the prototype case: the first and most successful clinical application of this method. The detailed history of this child can be considered as representative of the experience accumulated in the subsequent series of patients.

In August, 1957, a five-year-old girl was brought to the office because her left eye turned up and out to a conspicuous degree. Her mother also noticed that she closed the left eye in the bright sun and that the left eye became slightly "smaller" than the right when the child was especially tired. The initial examination showed an exotropia of 6 to 12 diopters and left hypertropia of 6 to 12 diopters. Both the horizontal and the vertical deviations varied markedly from day to day but were consistently greater for distance than for near. A slight ptosis on the left was also noted. The refractive error was insignificant, and visual acuity was 20/20 in each eye. The right hand and the right eye were strongly dominant. Ductions and versions at first seemed to be grossly normal in all directions of gaze. From the start it seemed that surgery would eventually be required, but the final decision was deferred until a series of repeated measurements could be collected over a period of time. Meanwhile, the child was referred to an orthoptist for further diagnostic studies and for antisuppression and fusion training. Conventional prism glasses with 2 diopters base up on the right and 2 diopters base down on the left were prescribed as a temporary measure.

After seven months, instrument fusion had improved considerably, but the amount of the deviation was essentially unchanged. A specific diagnosis of the muscles involved was still difficult. The left hypertropia was invariably greater with the right eye fixing than with the left eye fixing, and occasionally when the left eye fixed on a near object, a trace of right hyperphoria was observed. This would suggest that the deviation was primarily the result of a deficiency of an elevator on the right. However, the hypertropia was greatly increased on downward gaze, indicating paresis of a left depressor, and this possibility was supported by a positive Bielschowsky head tilt test. The Bielschowsky sign was absent when the child fixed on a near object with her left eye, and there was no habitual head tilt of the kind expected with true paresis of the left superior oblique in the presence of good vision and fusion. Furthermore, the left hypertropia was the same with eyes down and left as with eyes down and right, another finding that could not be explained on the basis of left superior oblique palsy alone. It was also puzzling that her conventional prism glasses were of no benefit but actually seemed to hinder fusion. With the glasses on, the child required an additional 3 or 4 diopters base up in the right cell of the stereoscope in order to fuse (the equivalent of 7 or 8 diopters of left hypertropia), but without the prism glasses she could fuse with only 1 to 3 diopters base up on the right. The visual acuity on the left had become very slightly subnormal, and even though objective and subjective angles seemed equal on the troposcope, the after image test indicated possible anomalous retinal correspondence both in the horizontal and vertical directions.

It appeared that secondary muscle spasm and inhibitional palsy might be important in this case. To clarify this situation, and also to correct the incipient amblyopia and the apparent tendency to abnormal correspondence, constant occlusion of the right eye was prescribed, and all binocular exercises were discontinued.

Several weeks later when the patch was removed, screen and parallax measurements showed: X4, LHO, X'O, and RH' trace. An increase of the hypertropia on downward gaze was no longer present. On the contrary, the turn was now greatest with the eyes elevated, and as expected with bilateral superior rectus palsy, there was left hypertropia on looking up and right and right hypertropia looking up and left. On the synoptophore the first measurement, immediately after removal of the patch, was X5, RH2. Within minutes the deviation changed into X5, LH2, and during the transition from the right to the left hyperphoria, the child spontaneously remarked that the picture tilted to one side and then righted itself at a different level. Occlusion was resumed and continued for a total of about six weeks until acuity had become bilaterally equal and all suggestion of anomalous correspondence had disappeared. At the end of this time no vertical deviation was detectable in the primary position, although there was 2 plus overaction of the left inferior oblique and 1 plus overaction of the right inferior oblique in their fields of maximum action. Nystagmoid movements were
seen in the fields of maximum action of both superior recti.

The patch was discontinued for one week, and left hypertropia of 10 diopters with XT6 for distance and left hypertropia of 8 diopters for near appeared again.

These findings seemed best explained on the basis of equal, or nearly equal, paresis of both superior recti. With the eyes relaxed, such equal weakness would result in no significant deviation, but the effort to fix would lead to spasm of the contralateral inferior oblique and inhibitional palsy of the contralateral superior oblique. With habitual preference of the right eye, the initially negligible deviation had become reinforced by the cumulative effects of continuous inhibition of the contralateral antagonist. Thus, the primary weakness of the superior recti had become masked by contralateral secondary changes, and the deviation had become dominated by the characteristics of the induced palsy of the left superior oblique including the positive Bielschowsky head tilt test and the accentuation of the hypertropia on downward gaze. The fact that the head tilt response was not always present, as well as the decrease or reversal of the left hypertropia when the child was forced to fix with her left eye, suggested that the weakness of the left superior oblique was the result of secondary changes. The nystagmoid movements on upward and outward gaze and the associated finding of slight ptosis on the left were also consistent with the diagnosis of superior rectus palsy. When prolonged fixation with the left eye was enforced by constant occlusion of the right eye, the inhibitional palsy of the left superior oblique and the secondary spasm of the left inferior oblique were relieved. A right hypertropia, resulting from underaction of the left superior rectus, was evident as long as left fixation was maintained. As soon as the child reverted to fixation with her right eye, the left hypertropia recurred almost immediately but, temporarily, to a lesser degree than before occlusion. It was now determined only by right superior rectus weakness, without the additional effect of the inhibitional palsy of the left superior oblique.

With the diagnosis reasonably clear, and acuity and retinal correspondence restored to normal, the child was considered ready for surgery which was planned for a convenient date several months later. Because of the strong preference of the right eye, it was decided to follow the usual procedure of correcting the secondary deviation with retroplacement of the left inferior obliques, more left than right.

While the child was being observed during the preoperative interval, the idea occurred that if bilateral base up prisms could decrease the use of the paretic superior rectus to a significant degree, the recurrence of the left hypertropia after removing occlusion might be prevented or at least delayed. Accordingly, the child's right eye was occluded again for three weeks until the vertical deviation in the primary position had again become negligible. Then, prisms of 4 diopters base up over each eye were prescribed to be used immediately and constantly after removal of the patch.

About one month later, the child returned quite remarkably improved. Screen and parallax measurements showed orthophoria for distance and near with or without the glasses. The Maddox rod showed right hyperphoria 3/4 diopter with the left eye fixing and left hyperphoria 3/4 diopter with the right eye fixing. In the primary position there was no exophoria, but with the eyes turned up or down 20 degrees at 6 meters there was an exophoria which averaged 10 diopters. Foveal fusion was present, although fusional amplitude was still rather low. The mother reported that the child's eyes always appeared straight with the prism glasses, but when she took them off, a slight inward turn of the left eye was occasionally noted, although spontaneous upward deviation was never seen again. There was still 2 plus overaction of the left inferior oblique and 1 plus overaction of the right inferior oblique on oblique upward gaze.

This was to have been the final preoperative visit, but even though the eyes were not absolutely perfect, the improvement was so striking that immediate surgery was no longer justified. The operation was deferred to permit a longer trial of the double vertical prisms. The child was to wear the prescription constantly, but no eye exercises were prescribed. When she was reexamined six months later, screen and parallax measurements showed no deviation either vertical or horizontal in the primary position at distance or near with or without the glasses. With the eyes turned up at 6 meters there was a 2 diopter exophoria, and with the eyes turned down at 6 meters there was a 4 diopter exophoria. Acuity was normal and equal. Fusional amplitude was considerably improved with prism convergence being 35 diopters at both distance and near. Not more than a
trace of overaction of the obliques was noted in their fields of maximum action.

In the attempt to be completely objective and honestly skeptical of this excellent result, an experienced orthoptist with no previous knowledge of the case was asked to verify these measurements with special attention to the vertical muscles. She also could find no vertical deviation either in the primary position or in the fields of maximum action of the obliques.

The prisms were continued for another five months, and in June, 1959, 11 months after the prism glasses were first prescribed, the child was examined and the following measurements were found: screen and parallax—X3 HO X'3 LH' 3/4; eyes down and right—no abnormalities; eyes up and right—left inferior oblique 1 plus; eyes up and left—right inferior oblique 2 plus; eyes down and left—no abnormalities. There was no detectable deviation with the cover and uncover test, and there was good fusion with stereopsis. Gradual decrease in the wearing time of the glasses was suggested.

The child has now been followed for over 11 years without recurrence of the original problem. From time to time a very small and well compensated exophoria has appeared and rarely some negligible hyperphoria in extreme upward and oblique direction of gaze. But vision, foveal fusion, and absence of symptoms have been consistently maintained. At this time it certainly seems fair to say the result of treatment with the conjugate vertical prisms was at least as good as the best we could hope to achieve by surgical means.

**Clinical Application.** Subsequent to the prototype case, about 100 children have been treated according to this method with encouraging results. It has not been possible to duplicate the complete success of the original patient because children so perfectly suitable for this therapeutic approach are rare. However, in properly selected cases, and combined with appropriate conventional measures, the double vertical prism has proved to be a valuable supplement to the traditional methods of treating hypertropia.

The total number of children so treated is relatively small because the double vertical prism is indicated only under certain limited and relatively infrequent conditions. It was found that this form of therapy can be expected to benefit only the one type of deviation defined by the following criteria:

1. The paretic eye must be the fixing eye.
   There must be reason to suspect a relatively slight paresis of a vertical muscle with all, or the clinically significant portion, of the deviation being due to cumulative secondary changes on the opposite side.

2. Occlusion of the paretic eye must either eliminate (temporarily) the hypertropia in the primary position or reduce it to so small an amount that it can easily be controlled by fusion. If the secondary, as well as the primary, deviation with the eyes straight ahead becomes negligible after several weeks of patching, success with the double vertical prism is highly probable, and 4 to 6 diopters base up (for elevator paresis) or each eye may be prescribed for constant use immediately after removing the patch. This most favorable situation is well illustrated by the prototype case.

3. If occlusion reduces the hypertropia but leaves a residual deviation of 2 or, at the most, 3 diopters in the primary position, success is possible, but it may be wise to prescribe a combination of compensatory and therapeutic prisms. For example, 5 diopters base up on the right and 3 diopters base up on the left (in effect the sum of 4 diopters base up over each eye with one diopter base up right and one diopter base down left) may be used for right superior rectus paresis with 2 diopters of residual hypertropia after patching.

4. Finally, if occlusion does not decrease the deviation, or more than 2 or 3 diopters of turn remain, the double prism will probably be of limited value. Sometimes it may have a palliative effect, particularly in reducing the deviation prior to surgery and in postoperative patients with an incomplete surgical correction. Here again, the functions of therapeutic and compensatory prisms may be combined by placing all, or at least 4 diopters, of the necessary compensatory prism over the paretic eye. If the postoperative deviation represents a secondary innervational response that is slow to resolve, the appropriate prism may reinforce the effect of surgery in promoting the reversal of those persistent motor adaptations which have not yet progressed to structural changes. Occasional instances of clinical improvement in this situation have been en-
countered from time to time in the past when vertical prisms were placed over the paretic eye without any deliberate application of the principle of relaxing prisms. Urist (3) includes in his paper on vertical deviations a case successfully treated in much this manner. A child with right superior oblique palsy was left with 14 to 17 diopters of right hypertropia after recession of the ipsilateral inferior oblique for a much larger initial deviation. With 8 diopters prism base down over the paretic eye, the deviation gradually decreased, and after one and one-half years, the eyes were straight in the primary position. Urist concludes that the use of the prism postoperatively may have helped in the gradual relaxation of the secondary vertically deviating muscles, as we would expect on the basis of experience with conjugate vertical prisms.

Postoperative relaxing prisms may also be effectively utilized in a slightly different way as illustrated by the following case:

Case #2. B. B. was first seen in December, 1957, at the age of nine with alternating accommodative esotropia and double hypertropia of 20 diopters in each eye. After preliminary treatment with glasses and orthoptics, retroplacement of both inferior obliques 9 mm was carried out by Dr. Conrad Berens in April, 1958.

The early postoperative result was fairly good with the right hypertropia eliminated and the left deviation reduced to about 8 diopters of hyperphoria. However, the vertical deviation increased with time until in April, 1963, there were about 14 diopters of right and left hypertropia. She was alternating spontaneously, and on casual observation there was a cosmetically unacceptable seesaw movement of the eyes. Conventional neutralizing prisms had been tried without success. Four diopter base up prisms over each eye were then prescribed, and examination three months later showed no hypertropia in the primary position. There was slight regression over a period of time, and on her last visit in August, 1965, there was again a left hypertropia of 8 diopters but only on upward gaze, the eyes being straight in the primary position. There were no symptoms, and her appearance was satisfactory. In retrospect, however, the results might have been better if a base up prism had been used over the right eye immediately after surgery.

In typical cases, preliminary patching is absolutely essential for the most effective use of relaxing prisms. In the strictest sense, these prisms are prophylactic rather than truly therapeutic because they prevent recurrence of cumulative secondary changes which have already been relieved by the occlusion of the fixing paretic eye. Such patching may be omitted only if the vertical deviation is limited to upward gaze and absent or only intermittently present in the primary position. This category of patients includes children with primarily horizontal deviations when a small and inconstant vertical component seems to interfere with stable fusion.

It is perhaps in this group that conjugate prisms seem to have their greatest practical value. A vertical deviation so slight as to require no therapy if present alone, may become significant when it complicates a horizontal problem, and yet be too small to justify surgery and too variable to treat with conventional compensatory prisms. Here equal base up prisms may have an excellent stabilizing effect when combined with appropriate measures for the control of the horizontal component of the deviation.

Case #3. K. K., a four-year-old girl first seen in October, 1958, was typical of such patients. Alternating esotropia had been noticed by her mother since early infancy and had been unsuccessfully treated elsewhere with glasses worn only irregularly and "drops." On the initial visits screen and parallax showed ET 25, ET'35, LH 4-5 without glasses. Visual acuity was 20/20 in each eye, although the right eye was dominant. The left superior oblique appeared to be paretic, with a positive Bielschowsky test, and there was overaction of both inferior obliques. With correction of her hyperopia and plus 2.50 segments, measurements were E1, ET'14 through the distance correction, and EP'2 through her add. Left hypertropia of up to 5 diopters was intermittently present in the primary position. After occlusion of the right eye for two weeks, intermittent hypertropia with spasm of the left inferior oblique was still apparent. But weakness of the left superior oblique could no longer be readily demonstrated, and the Bielschowsky test was now negative. These observations suggested that the apparent left superior oblique weakness might actually be inhibitional palsy derived from elevator paresis in the fixing right eye. The patch was removed, and three months later the Bielschowsky test was positive once more. Orthoptic therapy was prescribed, and glasses were continued. In October, 1959, her condition re-
mained essentially unchanged. The esotropia was partly controlled by the glasses, and fusion was somewhat improved but grossly apparent; vertical and horizontal deviation still occurred quite frequently, especially on upward gaze. At this time, 4 diopter prisms base up over each eye were incorporated in her glasses. On subsequent visits to the orthoptist, hypertropia in the primary position was never seen again although overaction of the left inferior oblique could still be demonstrated on looking up and right. Fusion and stereopsis continued to improve. She was last examined on August 29, 1967, after several months without any glasses, and measurements were as follows: acuity without correction 20/20 plus in each eye; screen and parallax O X'2; Maddox rod E2 O'. With maximum accommodation on fine print there was an esophoria of 10 diopters. No vertical deviation could be demonstrated even on oblique upward gaze. Glasses with plus 2.25 add were prescribed for prolonged study only.

One very small group of patients may possibly benefit from this method of treatment without occlusion and without regard to the foregoing principles of patient selection. We sometimes see a child with a large double hypertropia of 20 to 30 or more diopters in the primary position and spontaneous alternation so that under room conditions the eyes have a cosmetically disfiguring seesaw motion. These children are notoriously difficult to treat, and some may have repeated surgery to little avail. In four such cases, all of whom already had incompletely successful operations by various surgeons, equal prisms base up over each eye were empirically tried and seemed to have a marked stabilizing effect. The amount of measurable turn did not necessarily change significantly, and often alternate covering continued to elicit as large a deviation as before, but under normal room conditions the eyes remained much more quiet and grossly straight. Regardless of measurements, these patients and their parents were delighted with the result and described it with such words as “the difference between night and day.”

Unfortunately, in these cases the eventual complete removal of the prisms may not be possible. Two of these children, now young adults, have determined by trial and error that they can wear contact lenses (without prisms) up to about eight hours a day, but the base up prisms must apparently be used the rest of the time to prevent the recurrence of the seesaw phenomenon.

The theoretical considerations that indicate relaxing prisms in cases such as the prototype do not apply here, and it is admittedly most difficult to explain the action of the prisms in this special situation. However, from the practical standpoint, any evidence of improvement would seem to justify further clinical trial in these most difficult patients, especially since no adverse effects from conjugate vertical prisms have been observed. Even when such glasses prove ineffective, they are usually so well tolerated that there is no need to replace the lenses unless required for a change in refraction.

The useful role of double vertical prisms in the practical management of such complex deviation is shown by one of four patients mentioned above.

Case #4. C. R. was first seen in January, 1962, when she was 13 years old. She had a history of congenital nystagmus and myopia and esotropia first noted at the age of seven or eight months. Bilateral retroplacement of the medials had been done elsewhere in 1954, resulting in a very slight overcorrection which was being treated with orthoptics. On our initial visit she had 5 to 10 diopters of exotropia and a variable double hypertropia up to 30 diopters right and 40 diopters on the left. The right eye was dominant, and under ordinary room conditions the left hypertropia was prominent and cosmetically unacceptable. Four diopter prisms base up over each eye were incorporated in her refractive correction of $-8.50 = -1.50 \times 180$ right, and $-7.00 = -2.00 \times 175$ left, and orthoptic therapy was continued including fusion training as well as modified pleoptics for her slight amblyopia on the left. In May, 1962, the progress report from the orthoptist stated that the left hypertropia was seen less often, and the child's mother noticed marked improvement in her appearance at home. To a certain extent, this patient was her own control because subsequent attempts to remove the prisms resulted in recurrence of the left hypertropia, although the amount of the deviation was slowly decreasing over a prolonged period of time. In December, 1963, contact lenses were prescribed and worn eagerly, improving vision to about 20/25 right and 20/30 left. However, both the patient and her mother became aware that the left eye was again “floating” up with increasing frequency. She was, therefore, given glasses with a 5 diopter prism base up over each eye, but no refractive correction, to wear over her contacts as much as she found necessary to control the hypertropia. Use of these prisms for a few hours a day seemed to maintain the eyes in good position. When she was
In theoretical implications with respect to the pathogenesis of hypertropia, though the scope of this paper is admittedly confined to just one of the many well-known pathways the development of vertical deviation may take. In these special cases it appears that the habitual direction of gaze may play a leading role in the evolution of the squint. In such children the hypertropia may first become grossly evident or increase greatly at the age of two or three though it is thought to be the result of congenital anomaly. In early infancy, if the weakness of an elevator is very slight, and especially if it is balanced by a similar weakness on the other side, the eyes may be straight in the primary position and on downward gaze with deviation apparent only on looking up. Throughout most of a human life span, including early infancy, this condition would present little difficulty because of the relative unimportance of upward gaze. But when the child begins to crawl and walk, he suddenly discovers a world almost entirely above the level of his eyes, and he is encouraged to adopt an ocular posture which is unfavorable with respect to the field of action of the paretic muscle. These are the years of most intense challenge to upward gaze.

Although at first even the secondary deviation may be small enough to fall well within fusional range, if ocular dominance is established on the paretic side, chronic secondary motor adaptations may occur. With paresis of a superior rectus, the constant and prolonged overstimulation of the contralateral inferior oblique and under stimulation of the contralateral superior oblique may have cumulative and persistent effects that lead to ever increasing hypertropia of the non-fixing eye. Eventually the resulting chronic spasm of the yoke muscle and the persistent inhibitional palsy of its antagonist can dominate the clinical picture and be very difficult to distinguish from the originally negligible paresis of the opposite superior rectus, as in the prototype case. Initially the changes are reversible, and the hypertropia may decrease or entirely disappear for a short time after total occlusion of the fixing eye. Yet, as soon as binocular vision is again permitted, the secondary changes will occur as before.

Discussion. The success of relaxing prisms in even a limited number of patients has interesting theoretical implications with respect to the pathogenesis of hypertropia. As the child grows, his increasing height and periods spent in downward gaze on books, again ease the burden on the deficient elevators, and, occasionally, spontaneous improvement may occur. Yet, by this time the once reversible sensory and motor adaptations may have become firmly established. There may be permanent shortening and fibrosis of the contralateral inferior oblique and possibly foveal suppression with some degree of amblyopia. In this way an initially minor weakness of the superior rectus may in some cases develop into a substantial deviation that only surgery can correct, but if base up prisms can control the progress of these secondary changes and protect the normal development of stable fusion during the crucial years of upward gaze, the child might reach maturity with no clinically significant impairment of binocular vision.

Normal growth from kindergarten to the early teens raises a child's eyes by an amount roughly equivalent to the effect of 4 to 6 diopters at 20 feet. Thus if the prisms of this strength prove effective in controlling the hypertropia, we can reasonably hope that in due time the glasses can be removed with no recurrence of the vertical deviation. If a larger prism, that is, 10 to 15 diopters were required for the necessary effect, then normal growth would probably be insufficient to eliminate the need for this artificial method of lowering the eyes, and the patient would remain dependent on the prisms indefinitely. Such an outcome could hardly be considered as a complete cure. It was primarily for this reason that such larger prisms have not been tried, and the strength of the double base up correction was from the outset conservatively restricted to such a relatively small amount that at first it seemed improbable it could have any effect at all.

The same limitation applies to base down prisms which might logically be used for depressor paresis according to the same rationale as base up prisms are used for elevator paresis. It has been found that they may be effective to a certain extent, and improvement has been achieved this way in suitable cases, especially when the prisms are used as a supplement to other therapy. However, here normal growth intensifies the problem. The demands on the paretic depressor become greater rather than less with passage of time. Thus, the need for such prisms
is not outgrown, and no complete clinical cure can be expected by this method used alone.

Theoretically, it would be reasonable to weaken the base up prisms gradually as the child grows, but it has proved more practical to decrease the wearing time instead of reducing the strength of the glasses. The response to removing the correction is unpredictable, and if this step should prove premature, wearing time can be readjusted empirically without the additional time and expense of changing the lenses.

Perhaps the most interesting aspect of the successful outcome of this method of treatment is how very minimal a change in the habitual position of the eyes may be sufficient to alter the mechanisms leading to the progression of the secondary deviation. It may seem that if so small a change in the customary direction of gaze can forestall the development of the squint, a child could accomplish the same thing for himself simply by raising his chin. Doubtless this sometimes occurs, but postural adjustment is determined by conditions as they currently exist and not in anticipation of events yet to come. If elevator palsy is too slight to cause subjective difficulty on upward gaze, there may be no stimulus for postural adjustment until the contralateral secondary changes have become well established. The head tilt that may ultimately develop will then reflect the new configuration rather than the original paresis. Perhaps there may be a rather narrow range of elevator weakness that can lead to this particular type of motor adaptation: the paresis must be great enough to cause significant innervational imbalance but not so great as to provoke immediate compensatory reaction through postural means.

The comprehensive papers of Urist (3, 4) on vertical muscle paresis include a very lucid discussion of the various secondary changes that can aggravate the consequences of simple vertical muscle weakness, including this particular pattern of motor adaptations that is presumed to take place in cases amenable to treatment with double base up prisms. He classifies as “Type 1” those children with evident deviation only in the field of action of the specific paretic muscle but no hypertropia in the primary position and no secondary contractures. This is equivalent to the condition that exists in a child like the prototype case immediately after a period of occlusion of the paretic eye. Urist found it a matter of some concern that such patients might eventually progress to the development of secondary contractures not yet present on initial examination, with hypertropia in the primary position as the ultimate result. He says, however, that after following these cases over the years, he did not see this happen.

Urist’s experience in this matter is not necessarily incompatible with the less encouraging observations of this paper. In the susceptible child, secondary adaptations seem to appear quite rapidly, the recurrence of persistent inferior oblique spasm being a matter of weeks or days after occlusion of the paretic eye is stopped. Thus if the process is to take place at all, it is unlikely in the ordinary course of events that the child will be examined before the secondary changes are already well established. The elevator paresis in its original uncomplicated form may exist for so short a period in infancy that its presence as a minimal deviation limited to one particular direction of gaze would be impossible to evaluate with certainty in a child still too young for reliable fixation. Only by reversing the sequence of events by occlusion, say arranging an “instant replay” under direct observation, can the development of this type of heterotropia be witnessed as it takes place. The “Type 1” cases infrequently seen by Urist may represent those few children who are resistant for one reason or another to the cumulative and persistent secondary effects of fixation with the paretic eye.

The circumstances which determine whether a given patient will remain as “Type 1” or progress to another stage of strabismus are, as Urist also says, unknown. The degree of muscle weakness and whether fixation with the paretic eye is invariable or partly alternate may have some influence, and environmental factors must play at least some role. Although the relative importance of these conditions remains speculative, it seems sensible to try to limit the use of the eyes in the field of action of the paretic muscle and reasonable to advise the parents of such patients to discourage upward gaze when this can be done without undue disruption of the normal routines of life. Television viewing from the floor can be forbidden, easels and blackboards can be adjusted to eye level, and seating at the back of the classroom can be requested.

Evidence that minimal changes in habitual direction of gaze may have marked effects in certain cases of vertical muscle imbalance also has bearing on the general principles of prism use. It is necessary to reconsider the usual convention of dividing compensatory prisms into base up on one side and base down on the other. There are obvious practical advantages to splitting the prism, and frequently this
remains the procedure of choice. But if the paretic eye is preferred for fixation, and spasm of the yoke muscle is prominent, it may be best to use the entire prism on the paretic eye. Experience with conjugate base up prisms has definitely indicated that 4 prism diopters base up on the right, for example, is by no means always identical and interchangeable in effect with 2 diopters base up on the right and 2 diopters base down on the left. Obviously a given prism can move the eye or move the retinal image or move both, depending on how it is placed in relation to the dominant eye. If the prism is put over the fixing eye, the eye will follow the apparent displacement of the object of regard, and the shift of the contralateral retinal image will be brought about by a conjugate movement on that side. In contrast, if the prism is put over the deviating eye, it moves the retinal image on that side without a change in the position of the eyes, unless a small fusion movement takes place. Both reactions occur with the split prism. Thus, 2 prism diopters base up on a dominant right eye and 2 diopters base down on the left would neutralize a 4 diopter hypertropia but also lower both eyes by two diopters. Similarly, if the entire 4 diopter correction were used base up on the right, both eyes would be depressed to a corresponding degree. In contrast, 4 diopters of prism base down on the left would compensate for the deviation by moving the retinal image on that side with no direct effect on the position of the eyes and could thus be considered as having a neutral motor influence.

Although these differences seem negligible in amount, they cannot be overlooked when it has been found that even minor changes in the habitual direction of gaze may have significant long-term consequences in susceptible patients. It is not uncommon for an angle of vertical deviation to enlarge with the use of a compensatory prism correction. It is possible that in some of these cases secondary contractures and inhibitional palsy are truly increased by an inadvertently unfavorable arrangement of prisms which imposes additional innervating stress in the fields of the paretic muscles.

The immediate increase in hypertropia that occurred in the prototype patient described in this paper when a 4 diopter compensatory prism was equally split between the two eyes might possibly be explained as the result of lowering the right eye by 2 diopters while the marked inhibitional palsy of the contralateral superior oblique restrained adequate conjugate movement on the left.

Whenever a relieving prism is placed over the fixing eye, sensory neutralization of the deviation is complicated by a small shift in binocular posture which may be either advantageous or detrimental depending on the specific configuration of the motor imbalance. Thus it appears that in prescribing prisms for any purpose, not only the net strength of the combination but its distribution between the two eyes may be of great clinical importance.

Summary. Bilateral base up prisms can permanently correct hypertropia in selected patients. It appears that in such cases the deviation develops in consequence of chronic contralateral muscle changes induced by habitual use of the fixing eye in the field of maximum action of a paretic elevator. If hypertropia is temporarily relieved by occlusion of the fixing eye, appropriate prisms may sufficiently decrease the demands on the paretic muscle to prevent recurrent deviation when binocular vision is resumed. When occlusion only partly reduces hypertropia, prisms to limit gaze in the field of the paretic muscle may be advantageously combined with a neutralizing correction for the residual turn. The results obtained with double vertical prisms suggest that habitual direction of gaze may play an important part in the development of certain vertical deviations.

Author's note: The most important portions of this work were done while the author was privileged to be associated with the late Dr. Conrad Berens, whose indispensable encouragement and interest in this project are acknowledged with deepest gratitude. The original version of this paper was read and criticized by Dr. Berens not long before his untimely death in 1963. The present revision, incorporating more recent data, was presented in part to the meeting of the Eastern Section of the American Association of Certified Orthoptists at Nassau Hospital, Mineola, New York, April 29, 1969.

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Ophthalmic Teaching Problems: The Ayes Have It!*

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The problems associated with the teaching of ophthalmology to medical students in today's university setting are by no means unique to ophthalmology. However, these problems are more severe in small departments such as ophthalmology and are more disruptive to the teaching process than similar problems in larger departments. The purpose of this paper is to identify some of the more important teaching problems and propose solutions to them.

Problem: De-emphasis of Ophthalmic Curriculum. As curriculum changes have taken place in medical schools in recent years, ophthalmology along with other small specialties has had its teaching time reduced or entirely eliminated. This problem is universal and is important enough to have been the subject of the opening address of the Third Congress of the European Society of Ophthalmology. The speaker at this opening address was concerned with the deterioration of the status of ophthalmology as measured in the number of hours assigned to it in the curriculum of medical schools (2). The subject content and time spent in ophthalmic teaching cannot be left to the discretion of other departments who are concerned with their own specialty-oriented curriculum or a core-curriculum because comprehensive and complete instruction in the eye, its diseases, and their treatment will not be their primary objective. The problem can only be rectified by having representatives from all departments, large and small, on curriculum committees and by having medical school administrations committed to the concept of excellent medical education within all specialties and not at the expense of smaller specialties.

Problem: Efficient Presentation of Ophthalmic Curriculum. Assuming there are no severe organizational or administrative situations to restrain and disrupt ophthalmic teaching, ophthalmology is well suited to the efficient use of modern teaching concepts and techniques. Studies have been performed using the questionnaire format to gather information on what the curriculum content for medical school ophthalmology should be, and these can be used as a starting point to develop a useful curriculum or to change the present curriculum (4, 5).

Audio-visual resources are very useful since many ophthalmic diseases can be precisely recorded by photography. Programmed texts are available commercially on basic ophthalmology, and mannequins are becoming available for realistic teaching of ophthalmology (1). Ophthalmology departments should be the first to use and develop video taped lectures, surgery, and basic examining techniques. This emphasis on audio-visual materials allows understaffed and small departments to use their faculty more effectively (3). The solution to this problem is to develop an adequately funded curriculum that could utilize these developments.

Problem: Inadequate "Quality Control" of Medical Curriculum. The major fault of all medical education, in my opinion, appears to be the lack of "quality control" of the educational product. If techniques could be developed to monitor the medical curriculum in a direct fashion, a major benefit from such a program would be the elimination of redundant or irrelevant material from the curriculum. This would lead to more efficient use of teaching time. Figure 1 outlines the concept to be presented as one method of solving this problem.

* The views expressed by the author of this paper do not of necessity reflect those of the Department of Ophthalmology or the Institution. Reprint requests to Robert G. King, Jr., M.D.
Fig. 1—Schematic for medical curriculum evaluation. The department chairman initiates the teaching process which results in student evaluation. The dean's office processes the information and channels it back to each department and the appropriate committees.

All the parties directly involved in medical student teaching have a definite bias in evaluating their own specific medical curriculum. It appears a third party with the necessary information and authority to criticize each department's curriculum would have less bias and would add valuable perspective to curriculum evaluation. The logical unit to control this evaluation would be a division of the dean's office in the medical school administration.

The most important part of this type of curriculum "quality control" should be the student himself. This logically follows since the student knows what he thinks he needs to be taught, what he has been taught, and whether the subject rotation was effective in teaching that particular subject. I believe this type of "quality control" would work best by requiring each student to fill out a standard form after completion of each departmental rotation. This form should supply a list of faculty and house staff involved in his teaching and request an evaluation of the time each faculty and house staff member spent in didactic teaching and in the clinical setting. The student should be asked to list the most and least relevant parts of the material covered. Student ideas should be obtained as to how the course could be improved by changes in lecture time, patient care time, audio-visual techniques and so forth. In this fashion, each faculty member and the curriculum content would be evaluated by each student. Over a period of a few months, a student consensus and curriculum profile of that specific subject could be obtained.

These student evaluation forms would be the property of the dean's office. Periodically the digested material of the student evaluation would be sent to the respective department chairman for departmental analysis. Upon analysis of these forms within the dean's office, and with the input from each department and the curriculum committee, the following should result. Those departments which did not and could not use their block of student teaching time effectively would be identified, and the time would be made available for use by other specialties. The parts of the curriculum not felt relevant could be eliminated. Subjects considered less important by some departments but requested by the students as necessary, would have a greater chance for time allotment in the curriculum.

The digested information concerning the amount of time spent in teaching by each faculty member could also be recorded on each faculty member's activity and effort report as the student's evaluation of that teaching. This would give the administration an additional source of information concerning that specific faculty member's activity and could be used in the consideration of promotions, tenure, and so forth.

It appears the main disadvantage of the above concept for a "quality control" of the medical curriculum could be the additional paper work required to process the student evaluations. A properly designed computer program would undoubtedly decrease the paper shuffling and significantly increase the usefulness of information that has been gathered.

In general, the more constructive the discussion concerning the quality of a medical school curriculum, the better the curriculum should be. Students who are intimately involved in each department rotation should have a channel through which they can routinely express their collective view and know that it would be seriously considered. Almost without exception, in each ophthalmology rotation a student will ask why more classroom exposure or clinical time is not available for certain ophthalmic subjects. Departments such as ophthalmology frequently lack the size and influence needed to modify the general medical school curriculum to allow more teaching time for their specialty. By using the evaluation process outlined in this paper, all medical school departments would have to be more objective in evaluating their own specific curriculum. If an unfair distribution of teaching time was present, according to the students' evaluation, the problems could be identified and decisions made as to whether this problem should be corrected.

It is imperative that a continuing evaluation of the medical school curriculum be carried out to
insure a quality educational product. As the body of medical knowledge grows, the curriculum has to have less relevant parts eliminated and teaching efficiency increased. In addition to the more routine methods of curriculum evaluation used in the past, the student's opinion should be formally and routinely used to add additional information for curriculum evaluation and to add another important point of view. By providing a mechanism for this type of student "vote," the student can influence the educational process of which he is a part. Hopefully, medical students would then feel that their constructive evaluation would be important, and their "ayes" would produce a better medical educational system to give them the knowledge they will need to become better physicians.

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