AXENFELD-RIEGER SYNDROME: A THEORY OF MECHANISM AND DISTINCTIONS FROM THE IRIDOCORNEAL ENDOTHELIAL SYNDROME*

BY *M. Bruce Shields,* MD

INTRODUCTION

AXENFELD[1] DESCRIBED, IN 1920, A PATIENT WHOSE OCULAR ABNORMALITY WAS A white line in the posterior aspect of the cornea, near the limbus, with tissue strands extending from peripheral iris to this prominent line. Beginning in the mid-1930s, Rieger[2-4] reported cases with similar anterior segment anomalies, but with additional changes in the iris, including corectopia, atrophy, and hole formation. It was also discovered that some of these patients had associated nonocular developmental defects, especially of the teeth and facial bones.[5,6] Axenfeld[1] referred to his case as posterior embryotoxon of the cornea, while Rieger[4] used the term mesodermal dysgenesis of the cornea and iris. In current nomenclature, these conditions are commonly designated by three eponyms: (1) Axenfeld's anomaly (limited to peripheral anterior segment defects); (2) Rieger's anomaly (peripheral abnormalities with additional changes in the iris); and (3) Rieger's syndrome (ocular anomalies plus nonocular developmental defects). Within each category, glaucoma occurs in approximately half the cases.

Although Axenfeld's anomaly and Rieger's anomaly and syndrome have been the subjects of numerous reported studies, the relatively rare incidence of the conditions and the sparse amount of histopathologic material has left many important questions unanswered. For example, are these clinical entities in fact simply different manifestations of the same developmental disorder, as many investigators have suggested?[7-9] If this is the case, what are the common embryologic disturbances underlying the spectrum of disease, and what is the mechanism of the glaucoma? Are

*From the Duke University Eye Center, Duke University Medical Center, Durham, North Carolina.

TR. AM. OPHTH. SOC. vol. LXXXI, 1983

some cases progressive, as has been reported,[10-13] and, if so, how is it that a developmental disorder might progress further after birth? Finally, are these conditions in any way related to another spectrum of disease, the iridocorneal endothelial syndrome, as some investigators have suggested on the basis of certain clinical and histopathologic similarities?[14-17]

The purpose of this thesis is to report a series of clinical and histopathologic studies concerning patients with Axenfeld's anomaly or Rieger's anomaly or syndrome, and to propose a theory based on these observations which is believed to answer the questions noted above.

MATERIALS AND METHODS

Twenty-four patients with a diagnosis of Axenfeld's anomaly or Rieger's anomaly or syndrome were examined by the author during a 7-year period. The criterion for inclusion in the study was the gonioscopic appearance of an abnormally prominent, usually anteriorly displaced Schwalbe's line, with strands of tissue extending from peripheral iris to the prominent ridge. Some patients also had atrophy of the iris and corectopia, as well as dental, facial, and other nonocular developmental defects. Individuals whose only finding was a prominent Schwalbe's line were not included in the study.

All patients were evaluated clinically either on a continued-care basis or during one or more referral visits. Close relatives of these patients were also examined whenever possible. In addition, the author performed trabeculectomies on nine eyes of seven patients in the study, and the surgical specimens were examined by light and electron microscopy. An enucleated eye from another patient in the study was provided by a referring physician and was studied by light microscopy.

The clinical examinations were performed either in the office or, when required by age, with the patient under anesthesia in the operating room. A history was obtained for all patients, with special emphasis on ocular and systemic abnormalities and family history. The basic examination included, as age would permit, visual acuity, applanation tonometry, external and slitlamp examinations, gonioscopy, dilated fundus evaluation, and visual field studies. Photographic documentation was obtained when possible of the slit lamp, gonioscopic, and funduscopic appearances. In addition, specular microscopic evaluation of the corneal endothelium was obtained in 16 patients, and fluorescein angiography of the iris was performed on 5 patients.

Specular microscopy was performed by means of a contact specular microscope and video recorder (Product Research Organization, Inc).

After the cornea had been anesthetized with one drop of proparacaine hydrochloride 0.5%, video images of the corneal endothelial cells in the central portion were recorded for approximately 15 seconds in each eye. Polaroid prints were then made of random areas, selected for optimum quality, using the freeze-frame features of the video recorder and a Polaroid CU-5 black-and-white CRT camera. The results were interpreted by three independent observers (the author and two specialists in external disease).

In patients who were to undergo fluorescein angiography of the iris, pre-injection color photographs of the entire iris of each eye were obtained using a Zeiss photo slitlamp and Ektachrome 200 film at 16× magnification. Control pictures of the primary eye were then taken with Kodak Tri-X 400 black-and-white film with excitor and barrier filters in place. After intravenous injection of 5 ml of 10% sodium fluorescein, 15 to 20 rapid sequence exposures of the primary eye were made at 16× magnification followed by two exposures at a magnification of 25×. Two exposures of the fellow eye were then made at the same magnifications. Five minutes after the injection, each eye was photographed at 16× and 25× magnifications. The black-and-white film was developed with Kodak D-19 developer at 21°C for 7 minutes.

Of the nine trabeculectomies, the first two (cases 1 and 3) were performed in a standard manner. Preliminary examination of the histologic specimens, however, revealed that most of the trabecular meshwork had been torn from the scleral sulcus, presumably at the time of surgery. This observation, as well as the gonioscopic appearance in all cases (to be described later), suggested that the artifact might have been caused by a high insertion of the peripheral iris into a posterior portion of the trabecular meshwork. For this reason, the following modification was used in the subsequent trabeculectomies. Dissection of the scleral flap was carried into clear cornea for 0.5 to 1 mm, or until it was anterior to Schwalbe's line. The anterior margin and sides of the trabeculectomy block were then cut, and the resultant flap of deep limbal tissue was reflected to expose the anterior chamber angle and peripheral iris. A semicircular incision was then made in the peripheral iris in such a way that the sides corresponded to those of the trabecular flap. While both trabecular tissue and iris were held in the same forceps, the two structures were excised en bloc at a level corresponding to the scleral scar (Fig 1). The operation was then completed in a standard manner.

The modified trabeculectomy was performed in the subsequent seven cases (one eye of patients 8, 20, and 24, and both eyes of 14 and 15). The age of each patient at the time of surgery is shown in Table I. In case 24, a

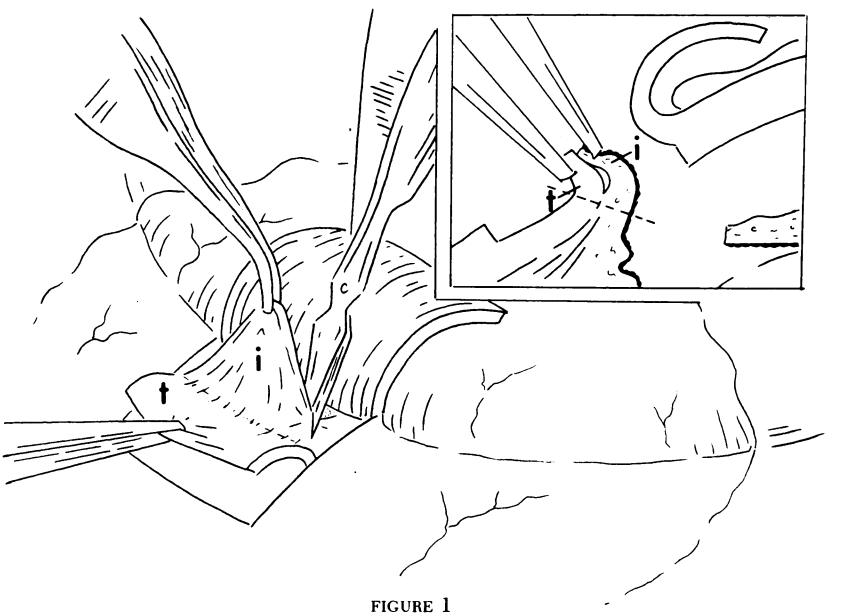


FIGURE 1
Schematic of modified trabeculectomy used in present study to obtain intact specimens of trabecular tissue and peripheral iris. After dissecting anterior margin and sides of deep limbal tissue (t), a semicircular incision was made in adjacent peripheral iris (i). The trabecular tissue and iris were then held in same forceps and excised near scleral spur (broken line), which was posterior to abnormally high insertion of iris (inset).

3-month-old infant, a trabeculotomy was first attempted, but Schlemm's canal could not be identified, and the modified trabeculectomy was then performed.

All trabeculectomy specimens were placed in a fixative immediately after removal from the eye. For the first seven eyes (cases 1, 3, 8, and 20, both eyes of 14, and the first eye of 15), the fixative was 2% glutaraldehyde in 0.1 mol/L cacodylate buffer. Because there were cellular artifacts apparent in these specimens, the last two (from case 24 and the second eye of 15) were fixed in 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 mol/L cacodylate buffer for 1 hour and then transferred to 3% glutaraldehyde and 2% tannic acid in 0.1 mol/L cacodylate buffer. After a minimum fixation time of 24 hours, all specimens were washed twice for 10 minutes in 0.1 mol/L cacodylate buffer with 5% sucrose, post-fixed in 2% ozmium tetroxide for 45 minutes, and washed again in buffer. The tissue blocks were next partially dehydrated in 50% ethanol and stained overnight with 3.5% uranyl acetate in 50% alcohol at 4°C. The specimens were then dehydrated through a series of ethanol up to 100%.

TABLE I: GENERAL FEATURES OF PATIENTS STUDIED

CASE	AGE (WHEN DIAGNOSED)	AGE (WHEN FIRST SEEN IN STUDY)	AGE (WHEN SURGICAL SPECIMEN OBTAINED)	LENGTH OF FOLLOW-UP IN STUDY	RACE	SEX	NONOCULAR DISORDERS	FAMILY HISTORY OF A-R SYNDROME
1	At birth	6 weeks	4 years	6 years	White	Female	Dental, facial, and umbilical	. . .
2	At birth	3 months	. . .	4.5 years	White	Male	. . .	. . .
3	At birth	10 years	12 years	4.5 years	White	Female	Dental, facial, and umbilical	Yes
4	6 years	37 years	. . .	4.5 years	White	Female	Dental, facial, and umbilical	Yes
5	10 years	10 years	12 years	1.3 years	Black	Male	Facial	. . .
6	71 years	71 years	. . .	4 years	White	Male	. . .	. . .
7	At birth	29 years	. . .	1.5 years	Black	Female	Angioma	. . .
8	10 days	16 years	16 years	1 year	White	Male	. . .	. . .
9	At birth	15 years	. . .	5 years	White	Female	Primary empty sella	Yes
10	At birth	21 years	. . .	1 visit	White	Male	. . .	Yes
11	At birth	20 years	. . .	1 year	White	Female	. . .	. . .
12	13 years	25 years	. . .	1 year	White	Female	Dental	Yes
13	21 years	32 years	. . .	1 visit	White	Male	Dental	Yes
14	Early 20's	54 years	54 years	1 year	White	Male	. . .	Yes
15	24 years	50 years	51 years	2 years	White	Male	Parasellar cyst	. . .
16	54 years	54 years	. . .	1 year	White	Male	. . .	. . .
17	At birth	14 years	. . .	1 visit	White	Male	. . .	. . .
18	32 years	35 years	. . .	5 years	White	Male	. . .	. . .
19	At birth	40 years	. . .	1 visit	White	Male	. . .	. . .
20	Early 20's	27 years	27 years	3 months	Black	Male	Dental and umbilical	. . .
21	10 years	10 years	. . .	1 visit	White	Male	. . .	Yes
22	15 years	15 years	. . .	3 years	White	Male	. . .	Yes
23	41 years	43 years	. . .	1 visit	White	Male	. . .	. . .
24	3 months	3 months	3 months	4 months	White	Male	Pectus excavatum	. . .

Portions of each specimen were embedded in Spurr low viscosity medium and allowed to polymerize for 24 hours. By means of an LKB Ultratome III, thick sections (1 μm) were cut, stained with toluidine blue and basic fuchsin, and examined by light microscopy. Thin sections (60 nm) were then taken from selected areas, stained with uranyl acetate and lead citrate, and studied with a Zeiss EM95 transmission electron microscope.

Tissue from cases 3, 15, and 24 were also examined by scanning electron microscopy. A thin slice was cut from one end of each block after the specimens had been post-fixed and washed in buffer. The tissues were then brought up to 100% ethanol and critical point dried in a Tousimis Samdri PVT-3. Dried specimens were mounted on aluminum stubs, coated with gold-palladium, and examined in a JEOL JSM 35-C scanning electron microscope at 18 kv accelerating voltage.

The enucleated eye from case 5 was received in formalin. It was then embedded in Paraplast and serial sections were cut in an anterior-posterior plane through the entire globe. These were mounted in the usual manner, stained with hematoxylin and eosin or periodic acid-Schiff, and studied by light microscopy.

RESULTS

GENERAL FEATURES OF PATIENTS

The general features of the 24 patients in this study are summarized in Table I. The ages at which the patients were first seen by the author ranged from 6 weeks to 71 years, with a mean of 26.2 years. Eighteen of these patients have been followed for periods ranging from 3 months to 6 years, with a mean follow-up of 2.6 years. The other six patients were seen on a single referral visit. Twenty-one patients were white and 3 were black, and there were 17 men and 7 women in the study.

The ages at which the disorder was recognized ranged from birth to 71 years. The diagnosis was made at birth or during infancy in 11 patients, and circumstances leading to this observation included abnormalities of the iris, signs of congenital glaucoma, suspicion of poor vision, a positive family history, or associated ocular defects. Of the other 13 patients, visual disturbances caused 4 to seek medical attention, leading to discovery of their condition, while the others were diagnosed during routine examinations.

A review of the past medical history revealed nonocular developmental defects in 11 patients. These included dental anomalies in six patients and hypoplasia of the maxilla in four individuals. Umbilical hernias were

present in four cases, and additional defects in one patient each included a facial angioma (case 7), an empty sella syndrome (case 9), a congenital parasellar arachnoid cyst (case 15), and pectus excavatum (case 24).

Nine patients in the study had one or more close relatives with Axenfeld's anomaly or Rieger's anomaly or syndrome (Fig 2). The diagnosis in each family member was confirmed by the author or by correspondence with the patient's ophthalmologist. One patient (case 7) had a twin sister who was found to have no ocular defects. In another family, the mother of two affected children (cases 9 and 10) had a normal ocular examination except for unusually numerous iris processes.

OCULAR FINDINGS

The ocular features of the 24 patients studied are summarized in Table II. The corneas were clear in all but three patients: case 1 had diffuse stromal haze during the first 2 months of life despite normal intraocular pressures, case 5 had a slight corneal haze in the blind eye that was enucleated, and

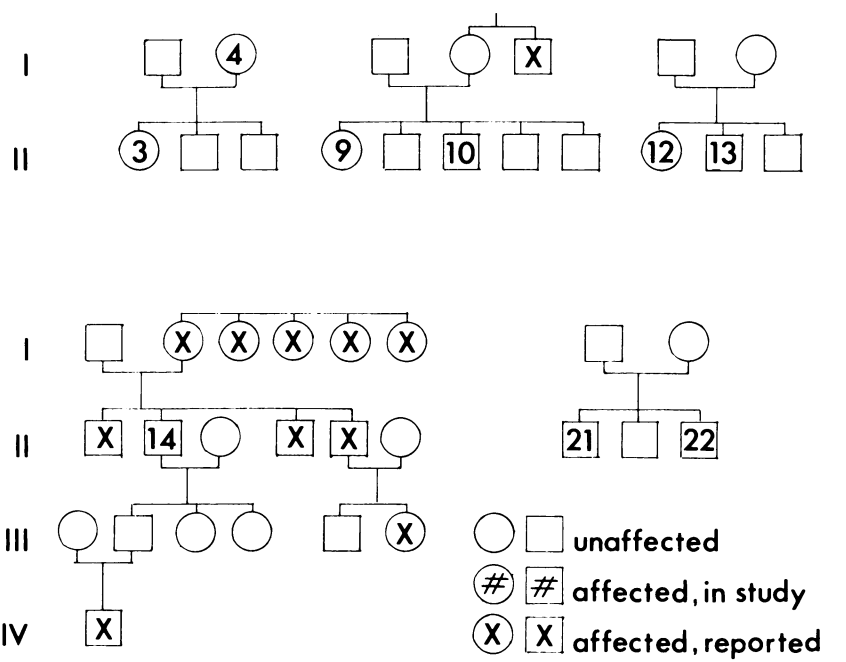


FIGURE 2
Pedigrees of nine patients from five families in present study with Axenfeld's anomaly or Rieger's anomaly or syndrome in more than one member. Numbers (#) correspond to case numbers of patients in study, and each X indicates a relative reported to be affected.

TABLE II: OCULAR FEATURES OF PATIENTS STUDIED

CASE	CORNEA	SCHWALBE'S LINE*	PERIPHERAL TISSUE STRANDS†	CENTRAL IRIS	OTHER OCULAR DISORDERS	GLAUCOMA TREATMENT	VISUAL ACUITY		CAUSE OF REDUCED VISION
							OD	OS	
1	Enlarged and hazy at birth	2+	2+	Holes and corectopia (progression noted)	Exotropia	Trabeculectomy OD and medical OS	20/30	20/30	. . .
2	Normal	3+	3+	Atrophy and corectopia (progression noted)	. . .	No glaucoma	20/20	20/20	. . .
3	Normal	1+	2+	Holes and corectopia (progression noted)	. . .	Trabeculectomy OD and medical OS	CF	20/20	Glaucoma
4	Few guttata	1+	2+	Holes and corectopia	Exotropia	Medical OU	20/100	LP	Glaucoma
5	Slight haze OD	2+	3+	Holes and corectopia	. . .	Enucleation OD and trabeculectomy OS	. . .	20/200	Glaucoma
6	Guttata	2+	1+	Normal	Macular degeneration	Medical OU	CF	20/40	Macular degeneration
7	Limbal dermoids	2+	2+	Corectopia	Staphylomas	No glaucoma	20/80	20/50	Staphylomas
8	Normal	3+	3+	Atrophy and corectopia	. . .	Trabeculectomy OS no glaucoma OD	20/15	20/80	Glaucoma
9	Normal	2+	2+	Normal	. . .	Medical OU	20/20	20/20	. . .
10	Normal	2+	3+	Normal	. . .	No glaucoma	20/20	20/20	. . .
11	Band keratopathy and microcornea	1+	3+	Atrophy and corectopia	. . .	Multiple operations OU	5/200	20/250	Glaucoma
12	Normal	3+	3+	Atrophy and corectopia	. . .	Multiple operations OU	20/20	20/20	. . .
13	Normal	1+	2+	Normal	Exotropia	Trabeculectomy OU	20/100	20/30	Glaucoma

TABLE II: OCULAR FEATURES OF PATIENTS STUDIED (CONTINUED)

CASE	CORNEA	SCHWALBE'S LINE*	PERIPHERAL TISSUE STRANDS†	CENTRAL IRIS	OTHER OCULAR DISORDERS	GLAUCOMA TREATMENT	VISUAL ACUITY		CAUSE OF REDUCED VISION
							OD	OS	
14	Guttata	1+	3+	Atrophy and corectopia	. . .	Trabeculectomy OU	20/300	3/200	Glaucoma
15	Enlarged	2+	2+	Corectopia	. . .	Trabeculectomy OU	20/70	20/50	Glaucoma
16	Normal	2+	3+	Normal	Horner's syndrome	No glaucoma	20/20	20/20	. . .
17	Pigment dispersion on endothelium	2+	3+	Atrophy, corectopia, and spoke-like transillumination	High myopia, cataract, and retinal detachment	No glaucoma	CF	20/200	Retinal detachment and myopic degeneration
18	Normal	2+	1+	Normal	. . .	No glaucoma	20/20	20/20	. . .
19	Normal	2+	2+	Atrophy	Disc hypoplasia, esotropia, and nystagmus	No glaucoma	20/400	20/200	Disc hypoplasia
20	Normal	2+	2+	Normal	Exotropia	Multiple operations OD medical OS	20/70	20/20	Glaucoma
21	Normal	2+	1+	Normal	. . .	No glaucoma	20/20	20/20	. . .
22	Normal	2+	1+	Normal	. . .	No glaucoma	20/20	20/20	. . .
23	Normal	2+	2+	Minimal atrophy	. . .	No glaucoma	20/20	20/20	. . .
24	Buphthalmos OS	3+	1+	Corectopia	. . .	Trabeculectomy OS	?	?	. . .

*Schwalbe's line: 3+ (visible by slitlamp in more than two quadrants); 2+ (visible in one or two quadrants); 1+ (prominent by gonioscopy only).
†Peripheral tissue strands: 3+ (in all quadrants); 2+ (two or three quadrants); 1+ (one quadrant); all cases were bilateral except case 8, which had only a prominent Schwalbe's line in one eye, and case 16, which had one entirely normal eye.

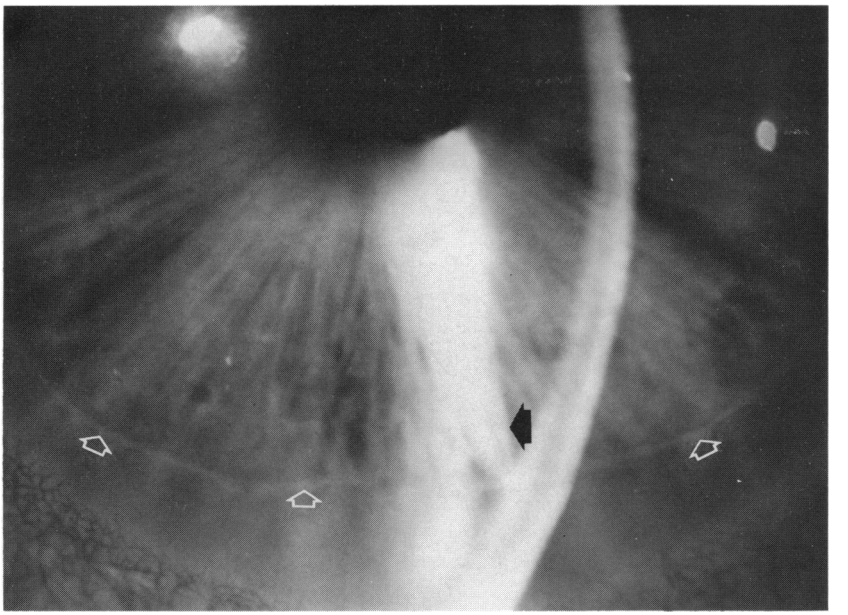


FIGURE 3
(Case 15) Slitlamp biomicroscopic appearance of prominent, anteriorly displaced Schwalbe's line (white arrows). Tissue strand (black arrow) extends from peripheral iris to prominent ridge.

case 11 had band keratopathy following long-standing glaucoma and multiple surgical procedures. The corneal diameters were normal except for one patient (case 11) with microcornea and three (cases 1, 15, and 24) with enlarged corneas. By slit lamp examination, the corneal endothelium was normal except in three adult patients (cases 4, 6, and 14) who had central cornea guttata. A prominent, anteriorly displaced Schwalbe's line was visible by slit lamp biomicroscopy (Fig 3) in all but five patients. In some cases, the line was continuous for 360°, although in most eyes it was limited to the temporal and, less frequently, to the nasal quadrants.

Gonioscopy revealed a prominent Schwalbe's line in all cases, with tissue strands bridging the anterior chamber angle from peripheral iris to the ridge, as required for inclusion in the study (Fig 4). There was considerable variation among the patients in the extent to which Schwalbe's line was enlarged and anteriorly displaced. In one individual (case 13), the line appeared to be suspended from the cornea in some areas by thin tissue. In all cases, the iridocorneal adhesions were similar in color and texture to the adjacent iris. The strands ranged in size from

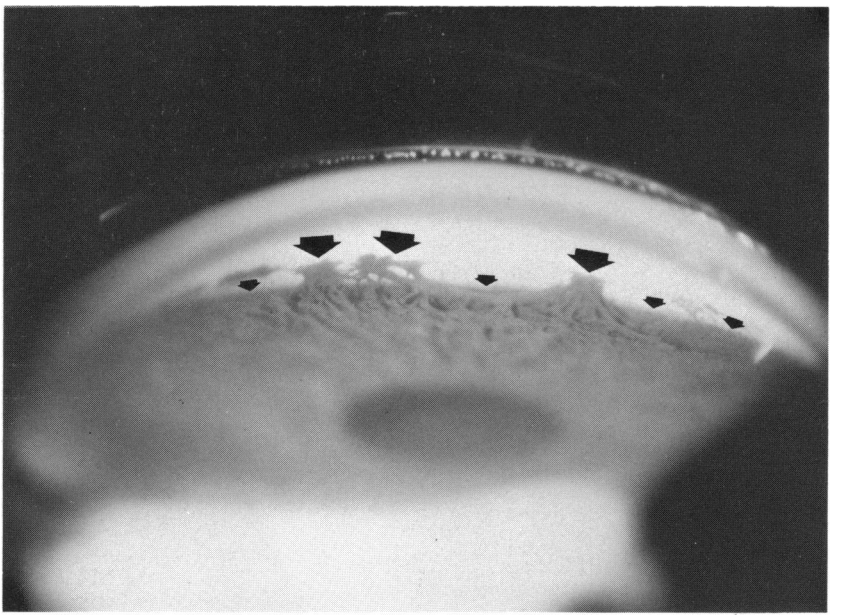


FIGURE 4
(Case 20) Gonioscopic appearance of tissue strands extending from peripheral iris to prominent Schwalbe's line (large arrows). Trabecular meshwork is visible (small arrows), but high insertion of iris obstructs visualization of scleral spur.

threadlike structures to broad bands extending for nearly 15° of the circumference. In some eyes, only one or two tissue strands could be seen, while others had several per quadrant. One patient (case 23) had tags of uveal tissue in some areas, suspended from Schwalbe's line with no attachment to the iris. The finding of a prominent Schwalbe's line and associated tissue strands was bilateral in all cases, with the exception of one patient (case 8) who had only a prominent Schwalbe's line in one eye, and another individual (case 16) who had one apparently normal eye.

In addition to the above characteristic gonioscopic features of Axenfeld's and Rieger's anomalies, a more subtle abnormality was also noted in the anterior chamber angle of all patients. Beyond the tissue strands, the anterior chamber angle was open and the trabecular meshwork was visible, but the scleral spur was obscured by the peripheral iris which inserted into the posterior portion of the meshwork (Fig 4). This alteration was distinctly different from the coarser strands of tissue that bridged the angle. In some eyes, this abnormality was continuous for 360°, while in others it involved only one or more quadrants.

In nine patients, aside from the peripheral abnormalities, the iris was normal in each eye. The other 15 cases had defects of the iris ranging from mild stromal thinning to marked atrophy with hole formation and corectopia. When corectopia was present, the pupil was most often displaced in the direction of a prominent peripheral tissue strand, usually visible by slit lamp biomicroscopy, while the atrophy and hole formation typically occurred in a quadrant away from the direction of the corectopia (Figs 5 and 6). Nine patients with iridic changes and two with normal central irides had nonocular developmental defects.

Abnormalities of the iris were observed to progress in three patients, two of whom were followed from infancy. In one (case 1), diffuse stromal atrophy with dilated, slightly irregular pupils were the only changes noted at birth. During the first few months of life, the pupils began gradually to shift nasally toward prominent tissue strands, and thinning of the iris with hole formation was observed in the temporal quadrants. These changes continued for the first 2 years of life, until the pupils were

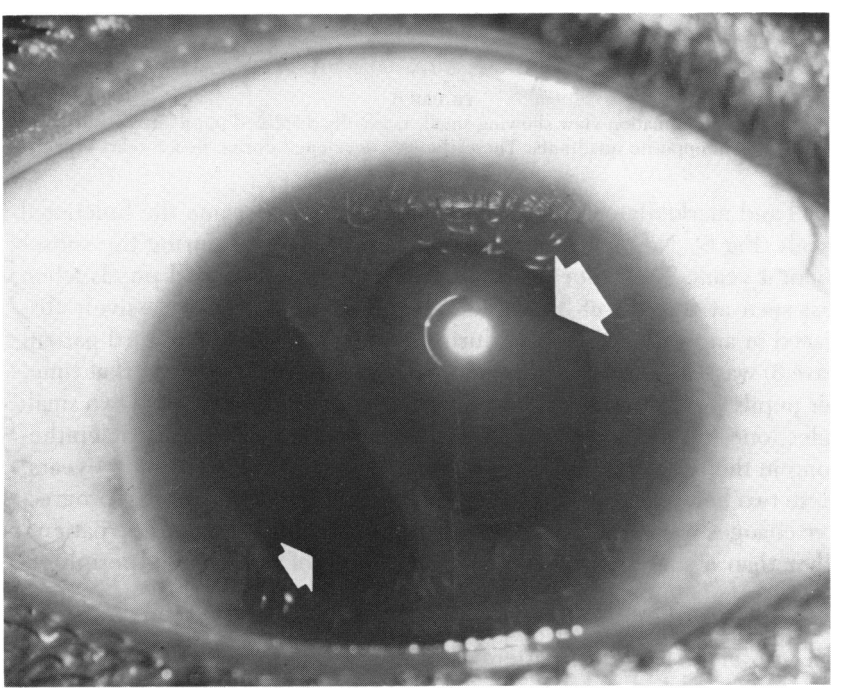


FIGURE 5
(Case 5) External view demonstrating corectopia (large arrow) and full-thickness hole (small arrow) in quadrant away from direction of pupillary displacement.

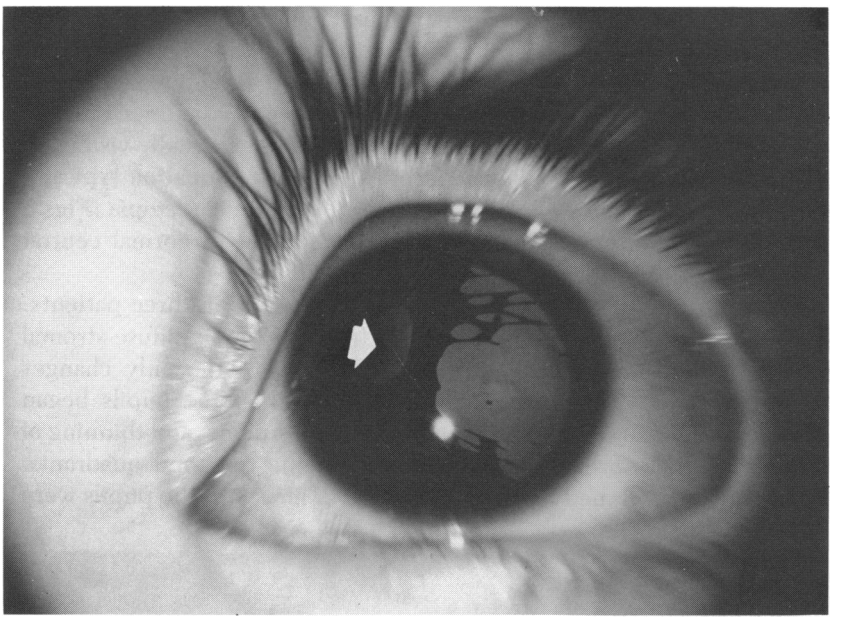


FIGURE 6
(Case 1) Transillumination view showing small, markedly displaced pupil (arrow) and large iridic hole in opposite quadrants. These changes developed during first 2 years of life.

small and markedly ectopic, and large iridic holes became the functional pupils (Fig 6). No further progression has been noted during the subsequent 4 years. The other infant (case 2) had spindle-shaped pupils when first seen at the age of 3 months, and these became progressively displaced in an upward direction during the next 4 years. The third patient (case 3) was 10 years old when first examined in this study. At that time, her pupils were round and centrally positioned, but there were two small holes (one full-thickness and the other exposing intact pigment epithelium) in the temporal quadrant of the left iris. In the subsequent 4 years, these two holes coalesced into one large, full-thickness hole. No progressive changes were observed in the anterior chamber angle of any patient, other than a slight thickening and shortening of pre-existing peripheral tissue strands in cases 1 and 2.

Additional ocular abnormalities, possibly of developmental origin, were observed in seven patients. Strabismus was present in five cases, with exotropia in four of these and esotropia in the other one. Four of these patients had significant visual impairment, however, and no conclusion could be established as to whether the muscle imbalance preceded

the reduced acuity. Other ocular anomalies included large limbal dermoids and peripapillary staphylomata in case 7; congenital cataracts, peripheral spoke-like transillumination defects of the iris, and retinal detachment in a 14-year-old boy (case 17); and hypoplasia of the optic nerve heads in case 19.

Fourteen patients in this study had glaucoma. In all cases, the glaucoma was discovered in childhood or young adulthood, except for one patient (case 6) with mild anterior chamber angle changes, whose condition was not diagnosed until the age of 71 years. Ten of the 14 patients with glaucoma had central iridic changes, although the extent of the defects did not correlate precisely with the presence or severity of the glaucoma. For example, in the patient with progressive hole formation in the left iris (case 3), the glaucoma was more severe in the right eye, which had minimal stromal atrophy of the iris. Nor did the abundance or paucity of peripheral tissue strands correlate in all cases with the presence or absence of glaucoma. As an example, of two siblings (cases 9 and 10), the brother had considerably more strands than his sister, yet she alone had glaucoma. On the other hand, the high insertion of peripheral iris into the trabecular meshwork, present to some degree in all cases, was pronounced in those eyes with glaucoma.

The glaucoma in the patients in this study was typically difficult to control, often leading to significant optic nerve head damage and visual loss. Of the 14 patients with glaucoma, the intraocular pressure could be controlled medically in only 3 cases, and each of these required more than one antiglaucoma medication. Filtering surgery was performed in one or both eyes of the other 11 patients, and repeated surgical attempts were required in 3 of these. As was previously noted, a trabeculotomy was attempted in one infant (case 24), but Schlemm's canal could not be located. One eye was enucleated because of absolute glaucoma (case 5).

SPECULAR MICROSCOPY

The interpretations of the corneal endothelial appearance by specular microscopy in 16 patients is summarized in Table III, and representative cases are shown in Fig 7. The cell margins were distinct in all areas studied. Mild to moderate variation in the size and shape of the endothelial cells was commonly observed. These changes were more prominent in the older patients and in those with long-standing glaucoma or previous intraocular surgery. Three adult patients (cases 6, 14, and 23) had dark spots that crossed cell boundaries and were interpreted as cornea guttata. Occasional intracellular dark spots were also present in some eyes. The one purely unilateral case in this study (case 16) had slightly more varia-

TABLE III: SPECULAR MICROSCOPY OF CORNEAL ENDOTHELIUM

CASE	SIZE VARIATION		SHAPE VARIATION		GUTTATA	
	OD	OS	OD	OS	OD	OS
3	2	2	2	2	0	0
4	2	2	2	2	0	0
6	2	1	1	1	2	1
7	1	1	1	1	0	0
8	1	1	1	1	0	0
9	0	0	0	1	0	0
10	0	1	0	1	0	0
12	1	2	1	2	0	0
13	1	1	0	0	0	0
14	1	3	2	3	1	2
15	1	0	1	1	0	0
16	0	1	0	1	0	0
17	0	0	0	0	0	0
18	0	1	0	1	0	0
20	1	1	0	1	0	0
23	1	2	1	2	1	1

Key: 0 = normal, 1 = mild, 2 = moderate, 3 = severe.

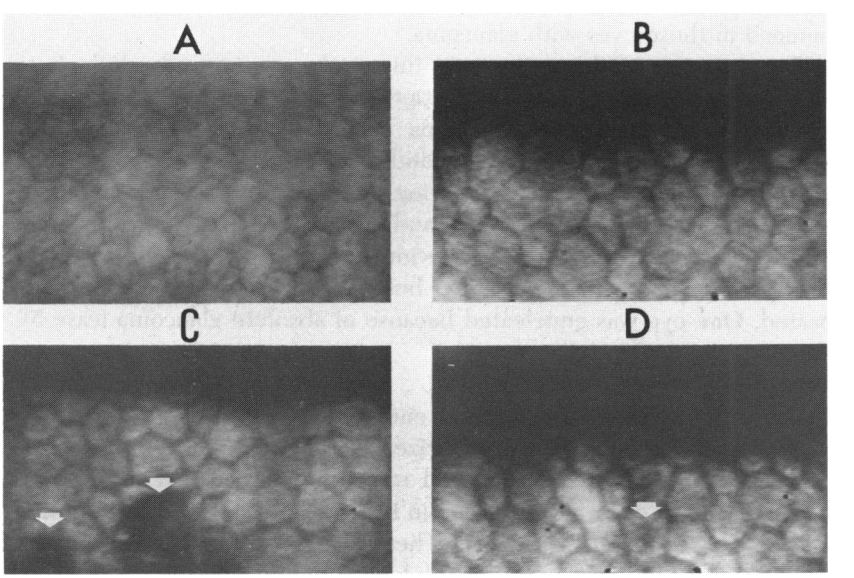


FIGURE 7

Specular microscopy of corneal endothelium showing representative findings from the 16 patients studied. A: (Case 18) Normal hexagonal pattern. B: (Case 16) Mild pleomorphism in size and shape of cells. C: (Case 6) Cornea guttata (arrows) in adult patient. D: (Case 12) Occasional intracellular dark spot (arrow).

tion in the size and shape of the corneal endothelial cells in the affected eye as compared to the fellow eye.

FLUORESCEIN ANGIOGRAPHY OF THE IRIS

Of five patients studied by fluorescein angiography of the iris, two had diffuse stromal atrophy with corectopia (cases 12 and 14), while the others had minimal corectopia (case 15), mild segmental stromal atrophy in one eye (case 23), or normal irides (case 16). The former two cases had fine, tortuous peripupillary vessels with leakage (Fig 8) and segmental delayed filling, especially in the quadrants away from the direction of pupillary distortion. In the left eye of case 12, which had marked corectopia, the peripupillary leakage appeared first and was most prominent on the side toward which the pupil was displaced. In the remaining three patients, no abnormalities were observed in the fluorescein studies, other than a trace of peripupillary leakage in both eyes of case 16.

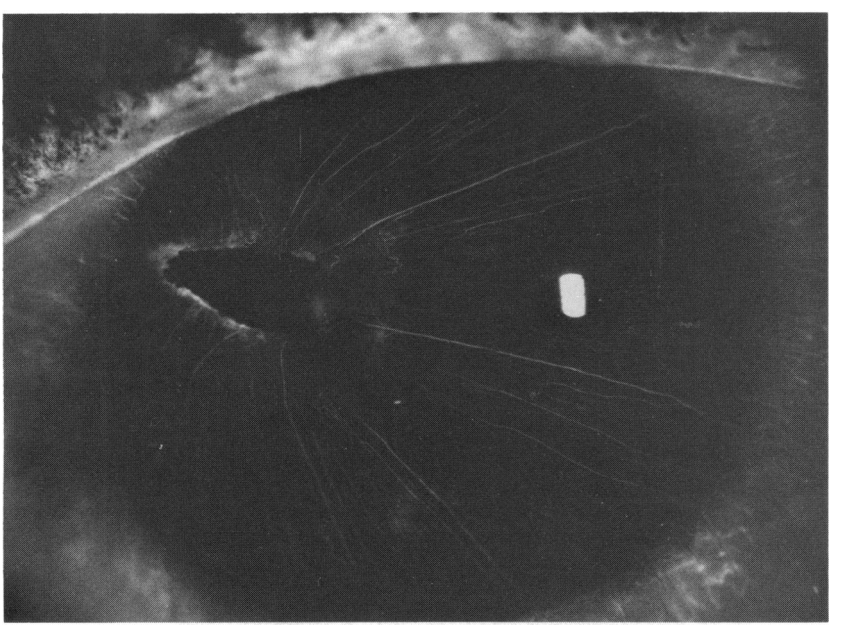
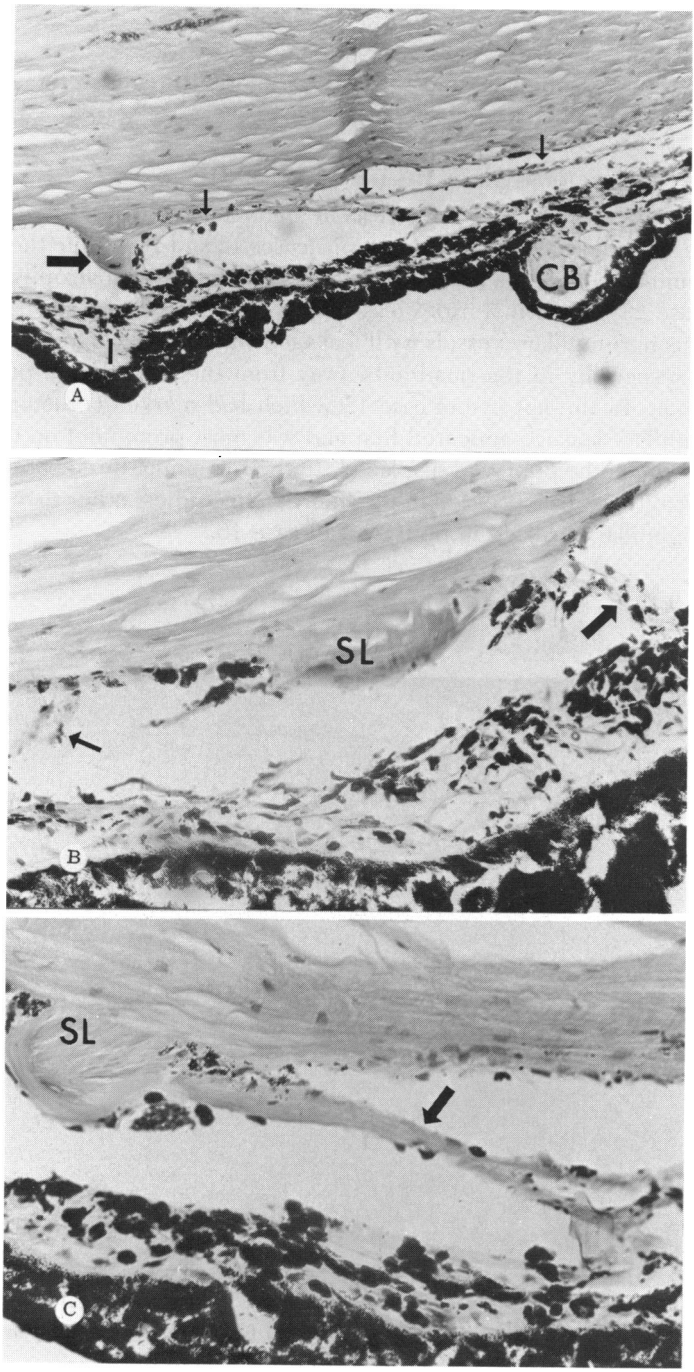


FIGURE 8
(Case 12) Fluorescein angiography of iris in early filling phase showing peripupillary leakage.


CB
A
SL
B
SL
C

HISTOPATHOLOGY

Light microscopic examination of the enucleated eye (case 5) revealed advanced atrophy and excavation of the optic nerve head, with extensive loss of retinal nerve fibers and ganglion cells. The central cornea appeared normal, but the periphery was characterized by a prominent, anteriorly displaced Schwalbe's line. The latter structure was composed of dense collagen and ground substance covered by a layer which resembled Descemet's membrane (Fig 9A).

In many sections, peripheral iris was attached to the corneolimbal junction by tissue strands, which usually connected with the prominent Schwalbe's line (Fig 9A). In some areas, however, the adhesions inserted either anterior or posterior to Schwalbe's line or on both sides of the ridge (Fig 9B). These strands were usually composed of tissue resembling stroma of the iris, although in some sections a basement membrane-like structure bridged the gap from Schwalbe's line to peripheral iris (Fig 9C).

The iris was covered in some areas by a monolayer of spindle-shaped cells, often accompanied by a thin basement membrane (Fig 10A). In other regions, a basement membrane with no overlying cellular layer covered portions of the iris. The tissue layer was seen most often on the portions of iris toward which the pupil was distorted, and was frequently connected to ectropion uveae (Fig 10B) or associated with the iridocorneal adhesions. In the quadrants away from the direction of pupillary displacement, the stroma of the iris was thin or absent, exposing pigment epithelium which contained one large hole.

The iris peripheral to the iridocorneal adhesions inserted into the posterior aspect of the trabecular meshwork. The meshwork was composed of a scant number of attenuated lamellae, which extended from beneath peripheral iris to the prominent Schwalbe's line. Schlemm's canal could not be identified.

Of the seven trabeculectomy specimens obtained by the modified surgical technique, the iris and trabecular meshwork remained intact in four eyes (cases 8, 14, 20, and 24). Light microscopic evaluation of all four

FIGURE 9

(Case 5) A: Histologic appearance of prominent, anteriorly displaced Schwalbe's line (large arrow) attached to iris (I) by strand composed of tissue resembling iridic stroma. Scant, attenuated trabecular lamellae (small arrows) extend to Schwalbe's line and attach to peripheral iris and ciliary body (CB) (hematoxylin-eosin, ×150). B: Histologic appearance of a tissue strand (large arrow) extending from iris to cornea just anterior to Schwalbe's line (SL). Smaller strand (small arrow) also connects iris and trabecular tissue posterior to Schwalbe's line (hematoxylin-eosin, ×400). C: Histologic appearance of tissue strand (arrow) from iris to prominent Schwalbe's line (SL) composed primarily of a basement membrane-like material similar to that covering Schwalbe's line. Incomplete cellular layer covers these structures (hematoxylin-eosin, ×385).

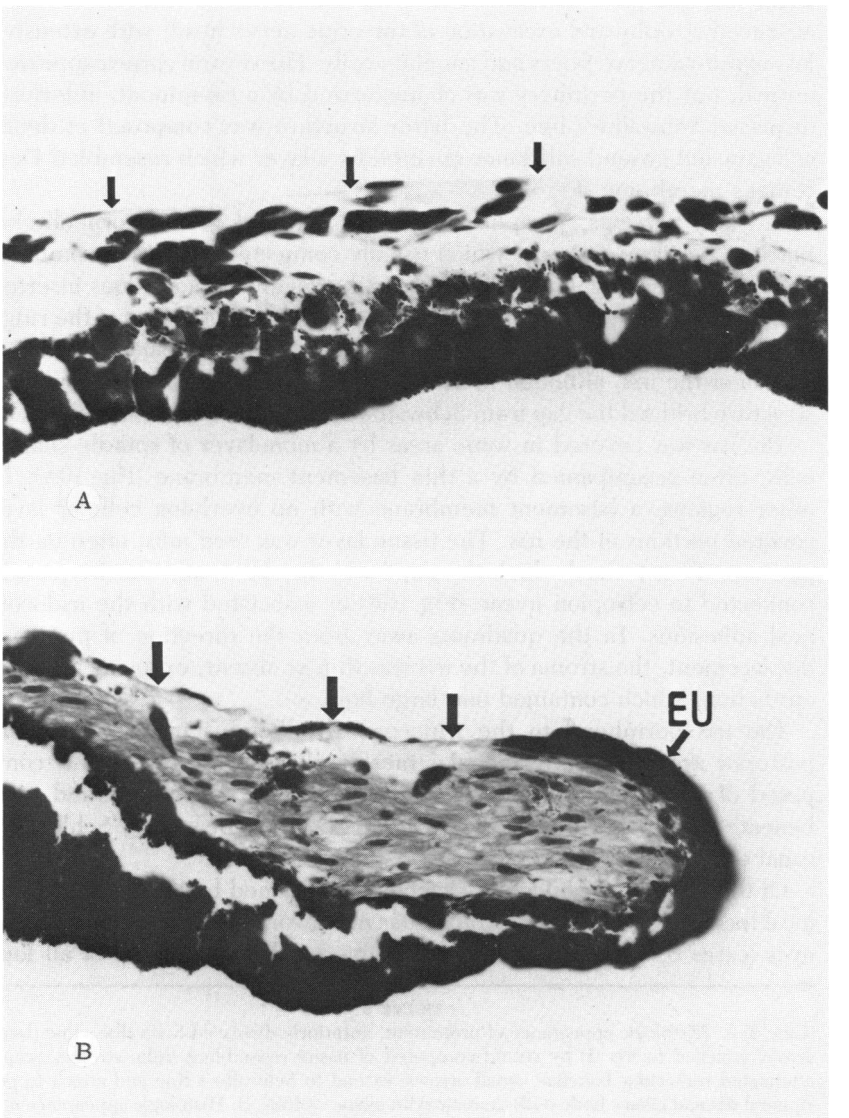


FIGURE 10
(Case 5) A: Histologic appearance of monolayer of spindle-shaped cells (arrows) covering a portion of iris (hematoxylin-eosin, ×400). B: Histologic appearance of monolayer of spindle-shaped cells (arrows) with thin basement membrane attached to ectropion uveae (EU) (hematoxylin-eosin, ×400).

specimens revealed peripheral iridic stroma inserting into the posterior one-third of the trabecular meshwork (Fig 11A). Transmission electron microscopic examination of the iris-meshwork junction revealed compacted trabecular lamellae beneath the iris with large amounts of loose collagen in the iridic stroma closest to the meshwork (Fig 11B). A basement membrane-like material covered this junction in case 20 and was seen in isolated sheets on the surface of the iris in case 8 (Fig 12). Blood vessels in some specimens of iris were characterized by an unusually large amount of basement membrane and in case 14 several vessels were surrounded by numerous poorly stained cells (Fig 13).

In all trabeculectomy specimens, the trabecular meshwork was compact, with marked thinning or absence of the intertrabecular spaces, especially in the anterior and outer portions. The lamellae were composed of a connective tissue core of typical collagen fibrils, with 64 nm periodicity, surrounded by a thick layer of ground substance, which frequently contained large amounts of broad-banded collagen of 128 nm periodicity (Fig 14A). Details of the trabecular endothelial cells were seen best in those specimens which were prepared by the modified fixation techniques. On scanning electron microscopy, the endothelial cells on the inner surface of the meshwork bridged the intertrabecular spaces in many areas and small holes were observed in these cells (Fig 14B). By transmission electron microscopic study, endothelial cells were often seen connecting adjacent lamellae with partial separation of the cells in

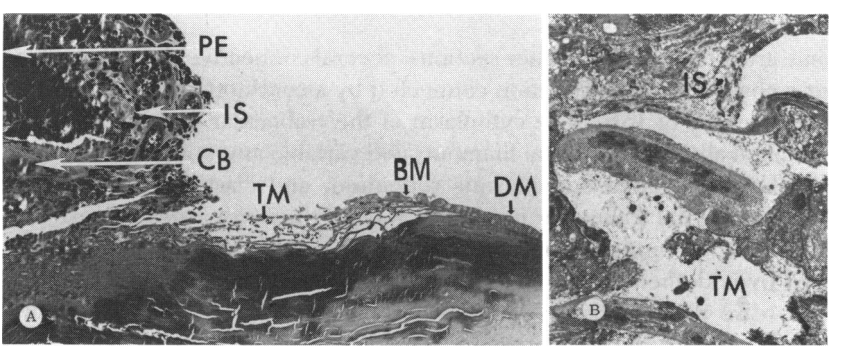


FIGURE 11

(Case 20) A: Histologic appearance of iris-trabecular meshwork specimen obtained by modified trabeculectomy. Uveal tissue inserts into posterior aspect of meshwork (TM) and basement membrane-like material (BM) extends from thick Descemet's membrane (DM) across anterior trabecular lamellae. Uveal tissue includes iridic stroma (IS) and pigment epithelium (PE) and ciliary body (CB) (toluidine blue-basic fuchsin, × 160). B: Transmission electron micrograph of junction between peripheral iridic stroma (IS) and trabecular meshwork (TM) (× 4125).

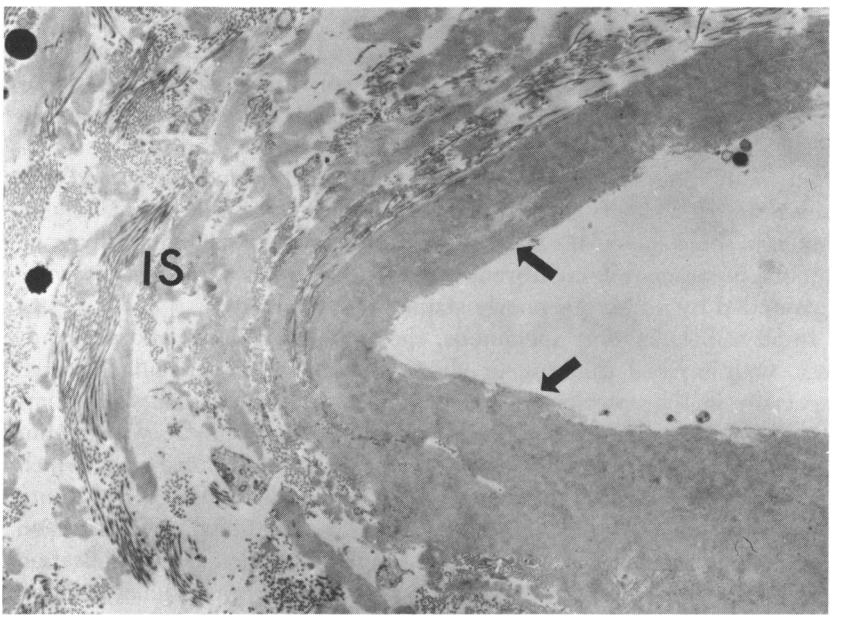


FIGURE 12
(Case 8) Transmission electron micrograph of basement membrane-like material (arrows) covering portion of iridic stroma (IS), which is composed predominantly of collagen and ground substance (×5450).

some areas (Fig 15A). In other sections, several connective tissue lamellae were observed in cross-section connected by a continuous sheet of endothelial cells (Fig 15B). The cytoplasm of the trabecular endothelial cells contained abundant 10.4 nm filaments and variable amounts of condensed mitochondria, rough endoplasmic reticulum, and elastin (Fig 16A). As one followed the trabecular meshwork toward the outer aspect, there was progressive compression until the intertrabecular spaces were completely filled by endothelial cells. In the outermost portion of the infant's meshwork (case 24), the tissue was almost entirely cellular, with only scant strands of collagen and ground substance (Fig 16B).

A normal Schlemm's canal was not found in any specimen in this study, including that of the 3-month-old infant (case 24). In several cases, however, one or more small endothelial-lined spaces, with few or no red blood cells, were observed just peripheral to the trabecular meshwork. The largest of these structures was seen in case 14, and thick, amorphous material separated this space from the adjacent meshwork (Fig 17).

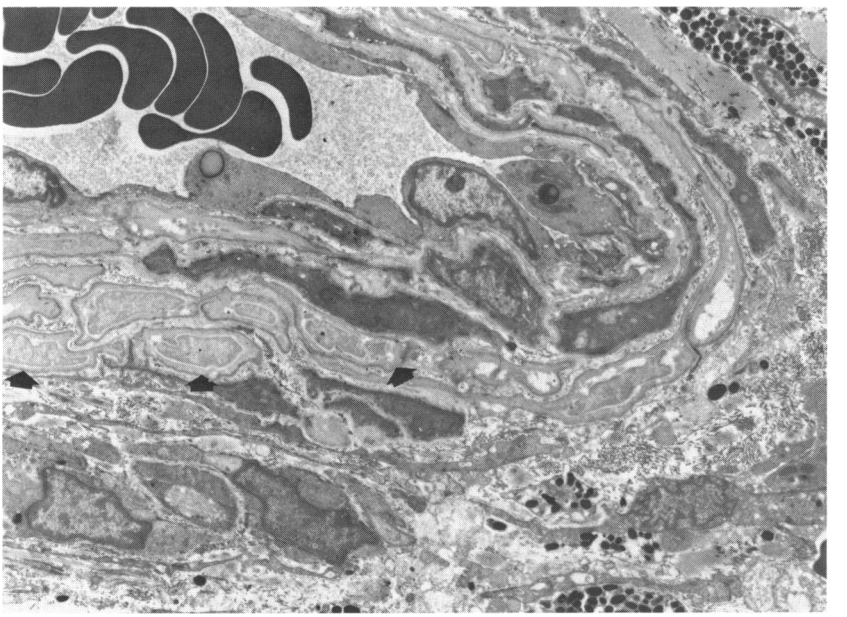


FIGURE 13
(Case 14) Transmission electron micrograph of iridic vessel surrounded by numerous pale staining cells (arrows) (×3850).

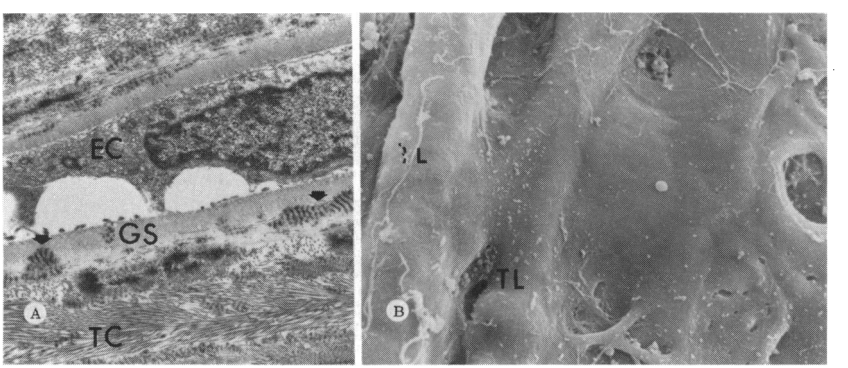


FIGURE 14
(Case 15) A: Transmission electron micrograph of compact trabecular lamellae composed of cores of typical collagen with 64 nm periodicity (TC), surrounded by ground substance (GS) containing islands of broad-banded collagen with 128 nm periodicity (arrows). Intervening endothelial cell (EC) fills most of intertrabecular space with partial separation from one trabecular beam (×15,150). B: Scanning electron micrograph of innermost trabecular lamellae (TL) in mid-portion of meshwork covered by cellular layer, which obliterates much of the intertrabecular spaces (×3400).

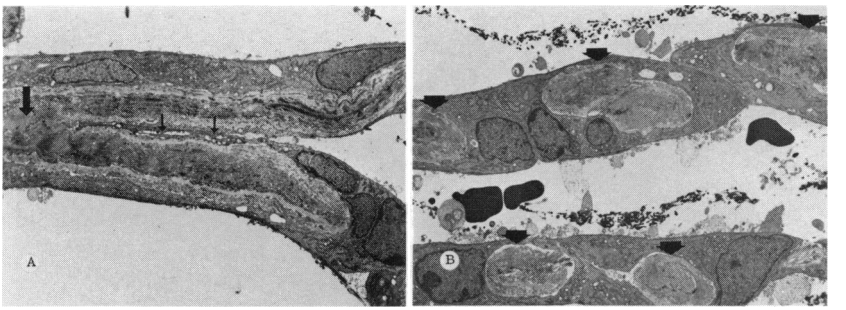


FIGURE 15
(Case 24) A: Transmission electron micrograph of two trabecular lamellae attached by fusion of connective tissue cores (large arrow) and incomplete separation of endothelial lining (small arrows) (×3800). B: Transmission electron micrograph showing cross-sections of several trabecular beams (arrows) attached by continuous endothelial linings (×3050). This view represents a portion of much longer sheets of uninterrupted trabecular tissue.

A prominent feature in all cases was a thick layer of collagen and ground substance, often arranged in whorl-like patterns, near the region of Schwalbe's line. In four specimens (cases 3, 8, 14, and 20), this tissue extended over the anterior trabecular meshwork and was continuous with

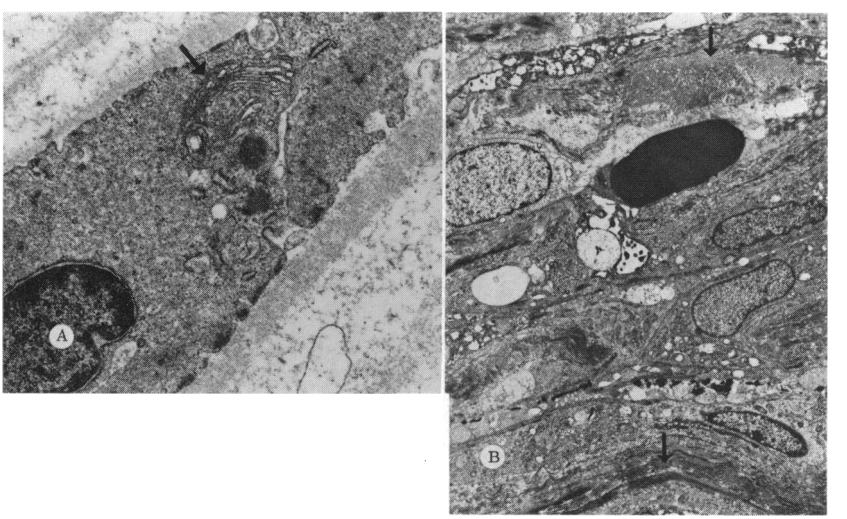


FIGURE 16
(Case 24) A: Transmission electron micrograph of trabecular endothelial cell between two connective tissue lamellae showing dense filaments of 10.4 nm diameter and a prominent Golgi apparatus (arrow) (×28,700). B: Transmission electron micrograph of outer portion of trabecular meshwork showing compact tissue composed predominantly of cells with scant collagen and ground substance (arrows) (×5400).

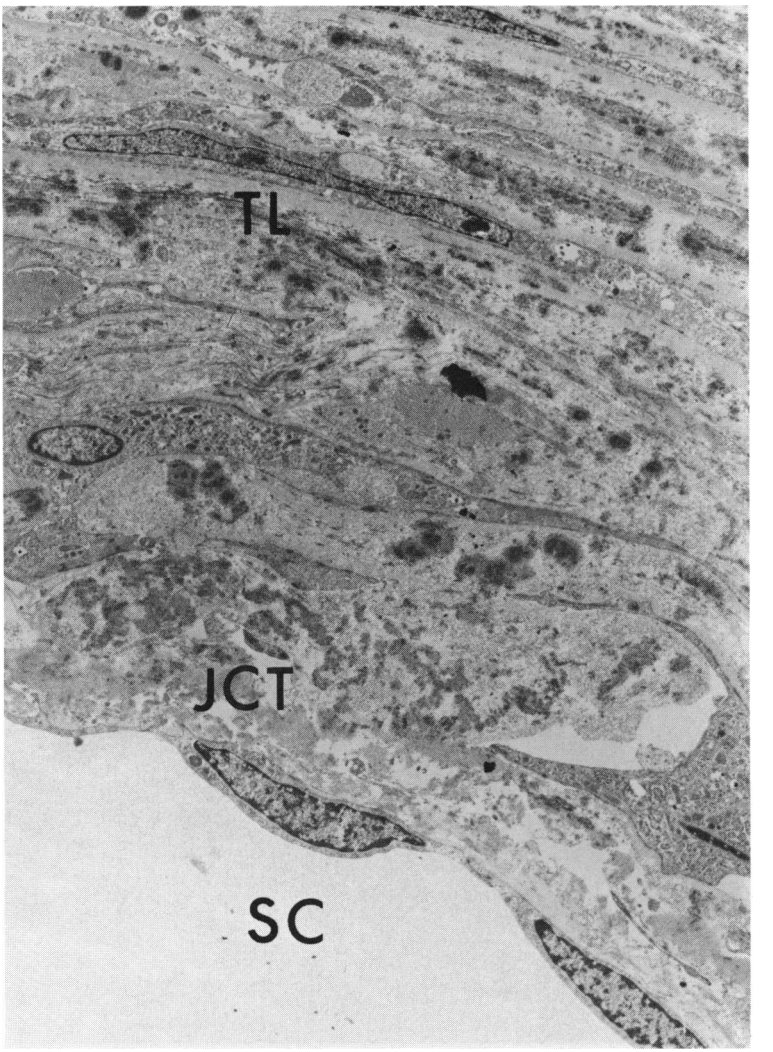


FIGURE 17
(Case 14) Transmission electron micrograph of outermost portion of trabecular meshwork showing compact trabecular lamellae (TL), amorphous material within the zone of juxtacanalicular tissue (JCT), and a portion of a rudimentary Schlemm's canal (SC) (×5500).

Descemet's membrane (Figs 11A and 18). Schwalbe's line was not apparent in any of these sections, although it was observed clinically in other quadrants of each of these eyes. A prominent, anteriorly displaced Schwalbe's line was present in the other trabeculectomy blocks. This

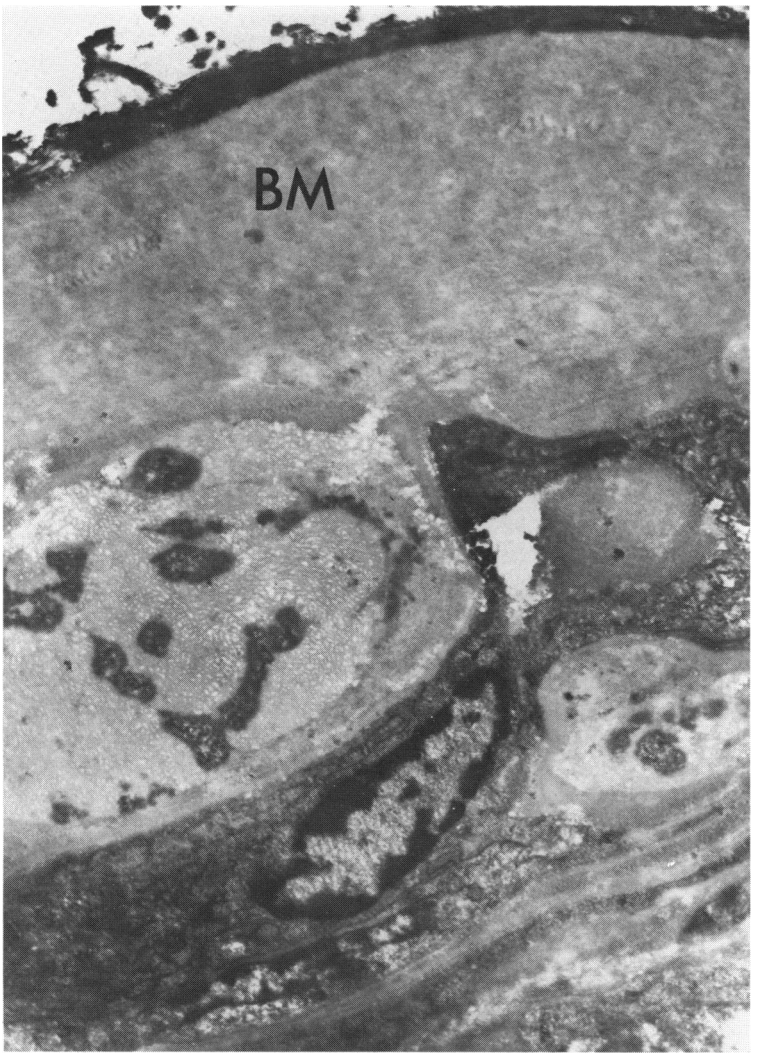


FIGURE 18
(Case 3) Transmission electron micrograph of innermost portion of trabecular meshwork near Schwalbe's line showing compact trabecular lamellae covered by basement membrane-like layer (BM). Dark material on surface of membrane is gold-palladium from processing for scanning electron microscopy prior to Transmission electron microscopy (× 15,000).

structure was composed of collagen and ground substance often in whorl-like patterns, similar to that described above, and was covered by a basement membrane-like material (Fig 19). Peripheral to Schwalbe's line,

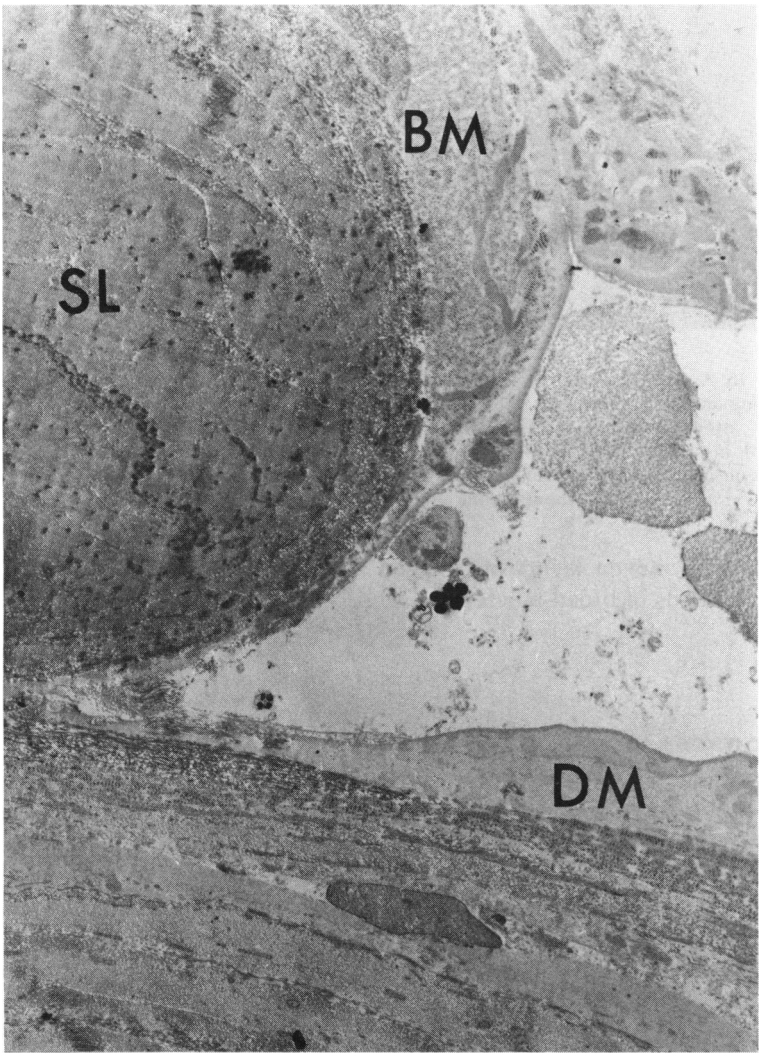


FIGURE 19
(Case 15) Transmission electron micrograph of anterior portion of prominent Schwalbe's line (SL) composed predominantly of collagen and covered by basement membrane-like material (BM). Descemet's membrane (DM) is attenuated and terminates just anterior to Schwalbe's line (×5400).

a scant number of attenuated trabecular lamellae extended from the prominent ridge to the main portion of the trabecular meshwork (Fig 20A and B). Descemet's membrane adjacent to Schwalbe's line contained

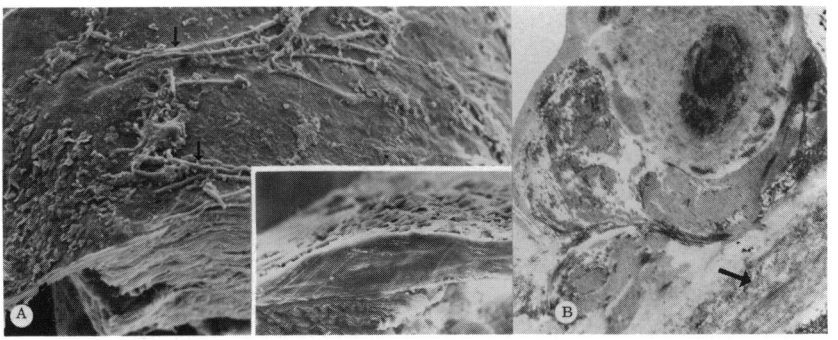


FIGURE 20
(Case 15) A: Scanning electron micrograph of anteriormost portion of trabecular meshwork showing anteriorly displaced Schwalbe's line (large arrow with enlargement in inset) and scant, attenuated trabecular lamellae (small arrows) extending toward prominent line (×310, inset, ×415). B: Transmission electron micrograph of cross-section of a trabecular beam on innermost surface of meshwork near Schwalbe's line (as seen in A) overlying a basement membrane-like layer (arrow) (×6950).

abnormal, uneven layers of collagen and ground substance with occasional islands of broad-banded collagen.

DISCUSSION

DEFINITIONS AND TERMINOLOGY

The similarity of anterior chamber angle abnormalities in Axenfeld's anomaly and Rieger's anomaly and syndrome, as previously defined, has led most investigators to agree that these three arbitrary categories represent the spectrum of a single developmental disorder.[7-9] The present investigation supports this concept on the basis of clinical and histopathologic similarities throughout the study group. Furthermore, the overlap of ocular and systemic anomalies is such that the traditional classification is difficult to apply in all cases. For example, the degree of iridic stromal atrophy is so slight in some patients that it is hard to know whether the term Axenfeld's anomaly or Rieger's anomaly should be used. Indeed, Axenfeld[1] described mild stromal atrophy of the iris in his patient, further compounding the difficulty of clearly separating this entity from Rieger's anomaly. In addition, the association between ocular and systemic anomalies is not always as clear-cut as the traditional classification scheme would imply. Although most of the patients with nonocular developmental defects in the present study had changes in the central iris, two individuals (cases 13 and 20) had systemic anomalies of Rieger's syn-

drome, but ocular findings consistent with a diagnosis of Axenfeld's anomaly. Furthermore, the sister of patient 13 (case 12) had typical ocular abnormalities of Rieger's anomaly or syndrome.

In view of the above observations, the author has found it useful to place all of these conditions under the single diagnostic term of Axenfeld-Rieger (A-R) syndrome. There seems to be no advantage in splitting this disease spectrum into subcategories, since the entire group of patients, irrespective of ocular manifestations, shares the same general features: (1) a bilateral, developmental disorder of the eyes; (2) a frequent family history (with an autosomal dominant mode of inheritance); (3) no sex predilection (although men outnumbered women 2-to-1 in the present study, Alkemade[7] found an equal sex distribution in reviewing 178 reported cases); (4) frequent nonocular developmental anomalies; and (5) a high incidence of secondary glaucoma. A single diagnostic category has the advantage not only of eliminating the difficulty of selecting an arbitrary subclassification, but also of reminding the physician to search for additional ocular and nonocular disorders in all cases.

There are certain conditions which specifically should not be included in the diagnosis of A-R syndrome. One of these is the isolated finding of a prominent, anteriorly displaced Schwalbe's line. This is often referred to as posterior embryotoxon, the term used by Axenfeld[1] in describing his original case. The prevalence of this minor anatomical variation has been variously estimated at 8%[7] and 15%.[18,19] Evidence will be considered later in this discussion to suggest that a prominent Schwalbe's line, as an isolated finding, may have the same underlying developmental defect as in the A-R syndrome and may indeed represent the mildest form of this disease spectrum. Nevertheless, considering the frequency of this condition and the fact that it does not carry an increased risk of glaucoma,[7] it is not thought that an isolated prominent Schwalbe's line should be included as a clinical variation of the A-R syndrome.

The developmental anomalies of the central anterior ocular segment, which have been referred to as Peters' anomaly, should also be kept separate from the A-R syndrome. It was once suggested that the peripheral and central developmental defects of the anterior ocular segment should be lumped together on the basis of common developmental abnormalities.[8] Although cases have been reported in which congenital corneal opacities were associated with dysgenesis of the anterior chamber angle,[20-26] the occurrence is not frequent enough to justify a common diagnostic category for all patients who have either Peters' anomaly or the A-R syndrome. Furthermore, previous studies suggest that the pathogenesis of these two conditions is distinctly different.[7,9,20] In the 24 cases

reported here, there was no evidence of central anterior segment anomalies, other than patient 17, who had congenital cataracts. The association of cataracts with developmental anomalies of the anterior chamber angles has been reported previously.[27] Indeed, the present study is consistent with numerous other reports (most of which appear in Alkemade's[7] extensive review) indicating that a variety of additional ocular anomalies may occasionally be found in patients with the A-R syndrome.

A third category of conditions that must be separated from the A-R syndrome is the iridocorneal endothelial (ICE) syndrome. Distinctions between the A-R and ICE syndromes will be considered in detail later in this discussion.

Most collective terms previously proposed for the A-R syndrome are based on presumed common developmental mechanisms, which in turn are dependent upon a particular concept of the related embryology. Those most frequently used are "anterior chamber cleavage syndrome"[8] and "mesodermal dysgenesis of the cornea and iris (dysgenesis mesodermalis corneae et iridis)"[4] or "primary dysgenesis mesodermalis of the iris."[7] As understanding of the related embryology has evolved, however, the concepts on which the above terms are based no longer appear to be entirely correct. The current concepts of the embryology related to the A-R syndrome, and how these may explain the clinical and histopathologic observations from the present study, will now be considered.

REVIEW OF RELATED EMBRYOLOGY

The lens vesicle begins to develop as an invagination of surface ectoderm during the third week of gestation and separates from the latter structure by the sixth week.[28] At this time, the optic cup, which arises from neural ectoderm, has reached the periphery of the lens, and a triangular mass of undifferentiated cells overrides the rim of the cup and surrounds the anterior periphery of the lens. From this tissue mass will arise portions of the cornea, iris, and the anterior chamber angle structures.

Although it has traditionally been taught that the undifferentiated cell mass referred to above is derived from mesoderm, more recent studies indicate that the tissue is of cranial neural crest cell origin. Johnston and co-workers[29,30] studied orofacial development in chick embryos by transplanting labeled neural crest or mesodermal cells into unlabeled host embryos. The donor tissue was either labeled with tritiated thymidine or was material from the Japanese quail. Cells from the latter bird are characterized by condensed chromatin in the center of the nucleus, in contrast to a more diffuse chromatin pattern in chick cells. Using these models, it was determined that corneal endothelium and stroma, iris,

ciliary body, and sclera are of neural crest origin, except for the associated vascular endothelium, which is derived from mesodermal mesenchyme.[30] It is of additional interest with regard to the A-R syndrome that the crest cells also give rise to most of the mesenchyme related to the forebrain and pituitary gland, bones and cartilage of the upper face, and dental papillae.[29,31,32]

From the mass of undifferentiated cells, three waves of tissue come forward between the surface ectoderm and lens. The first of these layers differentiates into the primordial corneal endothelium by the eighth week and subsequently produces Descemet's membrane, while the second wave grows between the corneal endothelium and epithelium to produce the stroma of the cornea.[33,34] The third wave insinuates between the primordia of the cornea and the lens and gives rise to the pupillary membrane and the stroma of the iris. In later months, the pigment epithelial layer of the iris develops from neural ectoderm.

The aqueous outflow structures in the anterior chamber angle appear to arise from the same mesenchymal mass, although the precise details of this development are not fully understood. Theories have included atrophy[35] or resorption[36] (progressive disappearance of portions of fetal tissue), cleavage[37] (separation of two pre-existing tissue layers due to differential growth rates), and rarefaction[38] (mechanical distention due to growth of the anterior ocular segment). None of these concepts appears to be completely satisfactory. Anderson[39] studied 40 normal fetal and infant eyes by light and electron microscopy and found that the anterior surface of the iris at 5 months' gestation inserts at the edge of the corneal endothelium, covering the cells that are destined to become trabecular meshwork. This appears to be what Worst[40] called the fetal pectinate ligament, separating the corneoscleral meshwork primordium from the anterior chamber angle. Anderson[39] noted a posterior sliding of the uveal tissue in relation to the cornea and sclera and a repositioning of the anterior uveal structures, presumably due to a differential growth rate. At birth, the insertion of the iris and ciliary body is near the level of the scleral spur, but the posterior migration of these structures continues for about the first year of life.

There is some difference of interpretation regarding the innermost layer of the trabecular meshwork primordium as it is uncovered by the posteriorly receding iris. Anderson[39] felt that the smooth surface represents multilayered mesenchymal tissue, which begins to cavitate by the seventh fetal month. Others have suggested, however, that a true endothelial layer covers the meshwork during gestation. Hansson and Jerndal[41] studied human fetal eyes by scanning electron microscopy and

described a single layer of endothelium, continuous with that of the cornea, extending over the primitive anterior chamber angle and iridopupillary structures, creating a closed cavity at the beginning of the fifth fetal month. Worst[40] observed a similar sheet of flat endothelial cells on the pupillary membrane and felt that the disappearance of this layer progresses centrifugally toward the chamber angle.

Hansson and Jerndal[41] noted that the anterior chamber angle portion of the endothelial layer begins to flatten, with loss of clear-cut cell borders, by the seventh fetal month. During the final weeks of gestation and the first weeks after birth, the endothelial layer undergoes fenestration with migration of cells into the underlying uveal meshwork. Van Buskirk[42] also observed intact endothelium completely lining the anterior chamber angle by the second gestational trimester in macaque monkey eyes studied by scanning electron microscopy. He noted that fenestration and gradual retraction of this tissue occurs in the third trimester and progresses in a posterior-to-anterior direction.

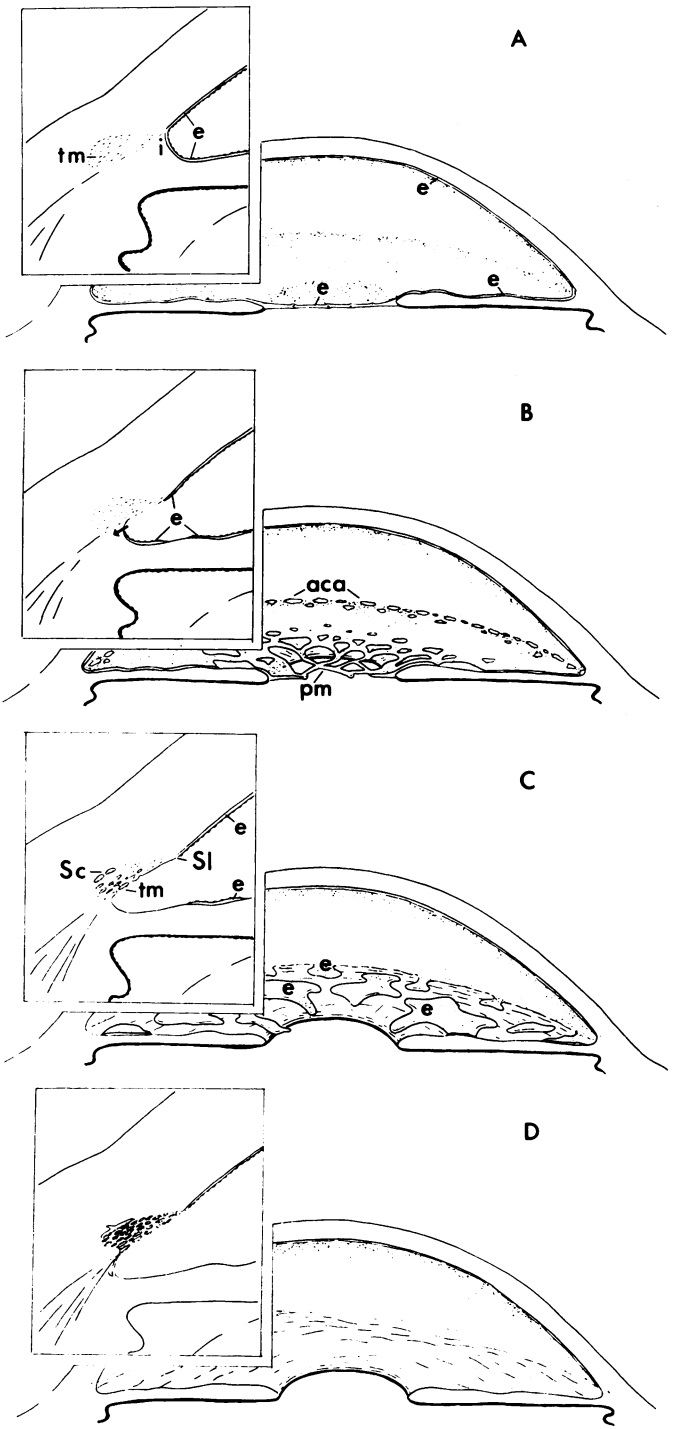
It has also been suggested, based on transmission electron microscopy of eyes from premature infants with gestational ages of 24 to 42 weeks, that formation of the trabecular meshwork begins on the anterior chamber side and progresses toward Schlemm's canal.[43] This is thought to be consistent with some cases of primary congenital glaucoma in which the site of obstruction to aqueous outflow appears to be a thickened tissue adjacent to the inner wall of Schlemm's canal.[43,44]

As the endothelium of the cornea and anterior chamber angle begins to differentiate, a distinct demarcation line develops at the primordium of Schwalbe's line.[41] Jerndal and co-workers[45] observed that the endothelial layer lining the anterior chamber angle had a close relationship to Schwalbe's line, which they thought might explain the abnormal tissue extending to this line in certain developmental anomalies of the angle, such as the A-R syndrome.

In Fig 21A to D, the aforementioned histologic observations have been combined into a unified concept of anterior chamber angle development, which will be used as a model in explaining the mechanism of the A-R syndrome.

A THEORY OF MECHANISM

Since Rieger's[2-4] work in the 1930s, it has been generally accepted that the spectrum of disorders herein referred to as the A-R syndrome represents developmental malformations, often inherited by autosomal dominant transmission. Controversy regarding the mechanism of embryodysgenesis has dealt more with the origin of the abnormal tissue than with


A
tm
i
e
e
e
e
B
e
aca
pm
C
Sc
tm
Sl
e
e
e
e
e
D

the specific details of the maldevelopment. Rieger[4] proposed that the anomalies were associated with cells derived from mesoderm, and his term "mesodermal dysgenesis" is still commonly used as a collective term for this group of disorders. Many investigators have objected to this concept, however, chiefly because of the frequent association of dental anomalies, and have felt that a maldevelopment of ectoderm, particularly neural ectoderm, more adequately explains all the clinical findings.[46-53] The possibility that neural crest ectoderm is most likely the primordial tissue received strong support from the previously discussed studies of Johnston and co-workers,[29,30] indicating that the related ocular and orofacial structures do indeed arise from neural crest cells.

While the neural crest appears to be the source of tissues involved in the A-R syndrome, an explanation has yet to be formulated as to how specific defects in these cells lead to the spectrum of ocular abnormalities. This gap in our knowledge exists largely because the number of reported histopathologic studies is small and limited to light microscopy. As a result, previously proposed theories of mechanism suggest only vague developmental alterations, in accordance with a particular concept of the related embryology. For example, Reese and Ellsworth[8] postulated that the anomalies might result from incomplete cleavage of the anterior chamber angle, based on the theory of embryology proposed by Allen, Burian, and Braley.[37] However, as previously noted, this and other traditional concepts of anterior chamber angle embryology no longer appear to be fully accurate.

The theory of mechanism proposed in this paper for the ocular abnormalities of the A-R syndrome is based on clinical and histopathologic observations from the present study and current concepts of the related embryology, as reviewed. The theory postulates a developmental arrest, late in gestation, of certain anterior segment structures derived from neural crest cells, leading to the following structural defects. Abnormal retention of the primordial endothelial layer on portions of the iris and

FIGURE 21

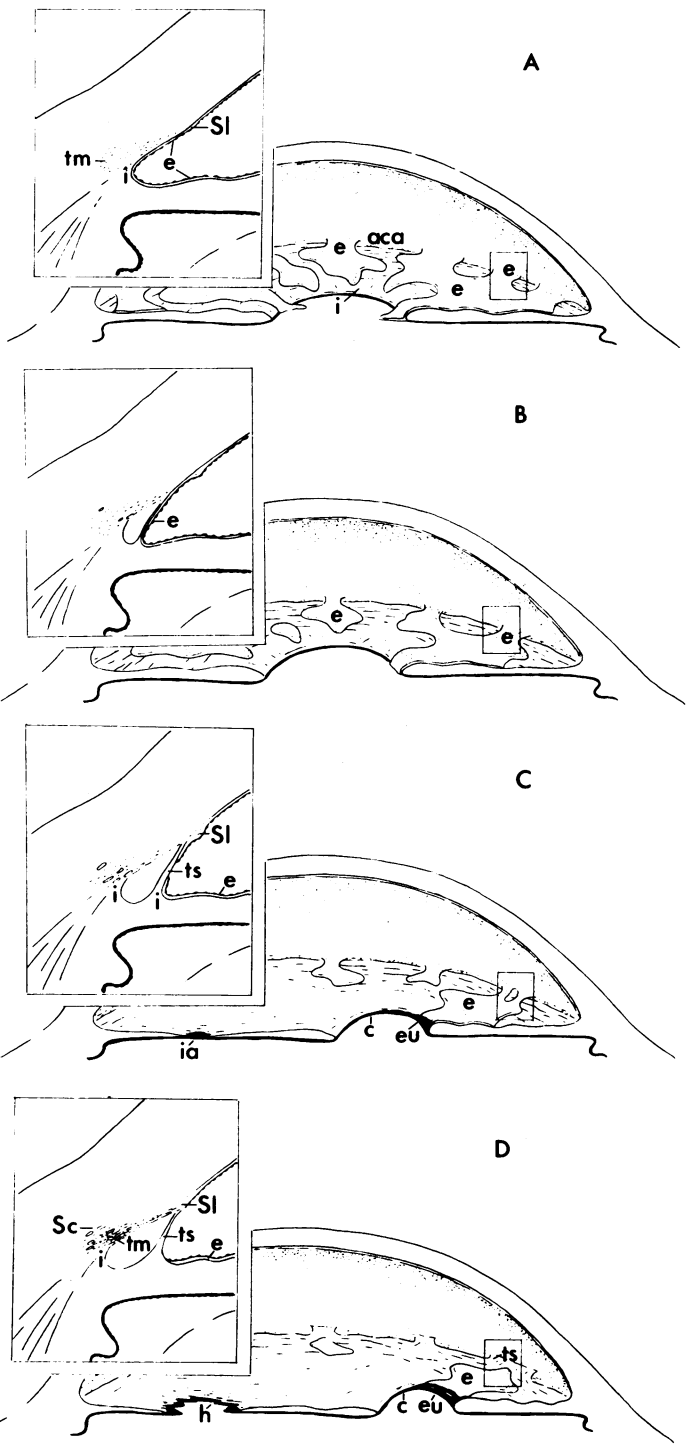
A concept of anterior segment embryogenesis based on reported studies (insets show representative cross-sectional views of chamber angle). A: At 5 months' gestation, continuous layer of endothelium (e) creates a closed cavity of the anterior chamber[41]; anterior surface of iris (i) inserts in front of primordial trabecular meshwork (tm).[39] B: During the third trimester, endothelial layer progressively disappears from pupillary membrane (pm) and iris[40,41] and cavitates over anterior chamber angle (aca), possibly becoming incorporated in trabecular meshwork.[41,42] Peripheral uveal tissue begins to slide posteriorly in relation to chamber angle structures (arrow).[39] C: Development of trabecular lamellae and intertrabecular spaces begins in inner and posterior aspects of primordial tissue and progresses toward Schlemm's canal (Sc)[43] and Schwalbe's line (Sl).[42] D: Normal anterior chamber angle is not fully developed until end of first year of life.[39]

anterior chamber angle, with subsequent contraction and/or deposition of basement membrane by these cells, is believed to account for the iridic changes, the tissue strands in the anterior chamber angle, and the abnormalities of Schwalbe's line. In addition, the developmental arrest leads to alterations in the aqueous outflow structures resembling those defects described in congenital and juvenile glaucomas.[39,54,55] The latter changes are thought to be responsible for the secondary glaucoma in the A-R syndrome. These aspects of the proposed theory, demonstrated schematically in Fig 22A to D, will now be considered in more detail.

One of the most consistent findings in the present histopathologic study was the presence of an abnormal membrane, an observation which has also been reported by others.[7,14-17,46,56] In the enucleated eye (case 5), examined by light microscopy, the membrane in some areas was composed of a monolayer of spindle-shaped cells with or without a basement membrane, while in other sections only basement membrane tissue was seen. In the specimens studied by transmission electron microscopy, the membrane consisted of collagen and ground substance of variable thickness often arranged in whorl-like patterns. A cellular layer was absent in most of the latter cases, although this most likely represents an artifact of preparation for histopathologic study. These membranes were observed in three areas in the eyes studied: (1) on the anterior surface of the iris, (2) in association with the tissue strands of the anterior chamber angle, and (3) on or near the abnormal Schwalbe's line. These three locations will now be considered individually.

Islands of the membrane were seen on the surface of the iris in cases 5 and 8. Only the enucleated eye (case 5) provided evidence, however, as to how this might relate to the clinically observed iridic changes. In this specimen, the membrane was primarily adjacent to ectropion uveae and in the quadrant toward which the pupil was displaced. It is postulated that contraction of the cellular membrane is responsible for the corectopia, ectropion uveae, atrophy of the iris, and hole formation seen in some cases of the A-R syndrome. These changes may occur late in gestation or after birth, as has been observed clinically by others[10-13] and was seen in three patients (cases 1 to 3) in the present study. Contraction of a pre-existing membrane may, therefore, explain how a developmental defect can undergo progressive change even years after birth.

It is likely that additional factors are involved in those cases with atrophy of the iris and hole formation. One such factor may be ischemia of the iris. In the specimens studied by transmission electron microscopy, iridic vessels were frequently abnormal, with an unusually large amount of basement membrane and occasional pale staining perivascular cells.


A
Sl
tm
i
e
aca
e
e
e
i
B
e
e
e
C
Sl
ts
e
i
i
e
c
eu
ia
D
Sc
Sl
tm
ts
e
i
ts
e
c
eu
h

The functional significance of these observations, however, is unclear. Fluorescein angiography of the iris in two patients with corectopia and diffuse stromal atrophy (cases 12 and 14) revealed fine, tortuous peripupillary vessels with leakage and segmental delayed filling especially in the quadrant away from the direction of pupillary distortion. No significant angiographic alternations were noted in three other patients (cases 15, 16, and 23) with minimal or no iridic changes. It may be, therefore, that vascular defects, whether primary or secondary to other tissue changes, contribute to the iridic atrophy in some patients with the A-R syndrome.

The abnormal membrane was also seen in association with tissue strands bridging the anterior chamber angle in case 5. Furthermore, in some sections the membrane alone extended from peripheral iris to Schwalbe's line. Based on these observations, it is postulated that retained strands of the endothelial layer lining the anterior chamber angle during gestation are responsible for the characteristic iridocorneal adhesions. In normal fetal development, this layer presumably disappears during or before the posterior recession of the peripheral iris, as described by Anderson.[39] In the A-R syndrome strands of this tissue are retained, however, and extend from the edge of the corneal endothelium to peripheral iris. These strands may pull away from the underlying trabecular meshwork during embryologic development through contraction of the cellular layer and/or failure of this tissue to keep pace with the growth rate of the surrounding structures. A portion of uveal tissue apparently remains in contact with the membrane, giving the strands their typical appearance. The membrane may subsequently disappear,

FIGURE 22

Theory of mechanism for ocular abnormalities of Axenfeld-Rieger syndrome (insets show cross-sectional views of anterior chamber angle corresponding to area within rectangle). A: Late in gestation, a developmental arrest leads to retention of primordial endothelium (e) over portions of iris (i) and anterior chamber angle (aca). Incomplete posterior recession of peripheral uvea produces high insertion of iris into posterior trabecular meshwork (tm). Zone of differentiation between corneal and chamber angle endothelium is abnormally forward and associated with excessive basement membrane deposition, causing prominence and anterior displacement of Schwalbe's line (Sl). B: Portions of retained endothelial layer crossing the anterior chamber angle, usually with few strands of iridic tissue, are displaced centrally from the trabecular meshwork, presumably by contraction of cellular layer or differential growth rate of adjacent structures. C: In most areas, endothelial layer disappears partially or completely, leaving uveal tissue strands (ts) of variable size extending from peripheral iris to prominent Schwalbe's line. Contraction of retained endothelium on iris, in some cases, leads to progressive development of corectopia (c) and ectropion uveae (eu) toward the contracting tissue and iridic thinning and atrophy (ia) in the opposite quadrants, which may continue after birth. D: Further endothelial contraction leads to hole formation (h) of iris in some eyes. Other factors, including secondary ischemia, are probably also involved in atrophic changes of the iris. Incomplete development of the trabecular meshwork and Schlemm's canal (Sc) is believed to be mechanism of the glaucoma.

although remnants or intact sheets of this layer were commonly found in association with the iridocorneal adhesions in case 5. Contraction of the cellular membrane portion of one or more of the tissue strands may continue after birth in some cases, causing further shortening and thickening of these structures, as observed clinically in cases 1 and 2.

The prominent, usually anteriorly displaced Schwalbe's line is also believed to be produced by abnormal activity of the primordial endothelial layer lining the anterior chamber angle. The normal Schwalbe's line is a discontinuous ridge formed by the oblique insertion of uveal meshwork into the anterior wall of the scleral sulcus just peripheral to the tapered termination of Descemet's membrane.[37] This is also the zone of transition from corneal to trabecular endothelium. In the A-R syndrome, the primordial endothelial layer in the corneolimbal region exhibits abnormal behavior with regard to the boundaries and maturation of these two cell populations. As a result, the junction is displaced centrally, pulling attenuated trabecular lamellae with it. The endothelium on both sides of the demarcation line exhibits unusual metabolic activity, leading to abnormal peripheral Descemet's membrane and in some cases, a Descemet's membrane-like structure over anterior portions of the trabecular meshwork. The greatest amount of this cellular activity appears to occur at the transition zone, accounting for the prominent Schwalbe's line. Previous histopathologic reports of unusually prominent Schwalbe's lines have described a dense granular or collagen core covered by a monolayer of spindle-shaped cells with a basement membrane.[18,19,38,39] In the present study, the ultrastructure of the core consisted of collagen and ground substance often in whorl-like patterns similar to that seen in the abnormal membranes of these specimens. It appears, therefore, that the prominent Schwalbe's line results from exceptionally active basement membrane production by the endothelial cells at the abnormally positioned transition zone between corneal and trabecular endothelium, a conclusion which is similar to the theory postulated by Burian, Braley, and Allen.[18,19]

The relatively common finding of a prominent, anteriorly displaced Schwalbe's line in an otherwise normal eye may represent a forme fruste of the A-R syndrome, in which the developmental defect occurs later in gestation and involves only this portion of the peripheral anterior ocular segment. Such an event would be consistent with the observation that normal development of the trabecular meshwork progresses in a posterior-to-anterior direction and that the portion near the corneotrabecular junction is the last to develop.[42]

The mechanism of the glaucoma in the A-R syndrome has been a

matter of controversy. Sugar[60] described the clinical and histopathologic ocular features of a 13-year-old boy, in whom the extent of the tissue strands in the anterior chamber angle was greater in the eye with the more severe glaucoma, suggesting a cause-and-effect relationship between these two conditions. Alkemade[7] did not feel that such a correlation existed, however, and reasoned that defective development of the trabecular meshwork and Schlemm's canal was more likely responsible for the obstruction to aqueous outflow. While there may be more than one mechanism of glaucoma in the A-R syndrome, observations from the present study are more consistent with Alkemade's theory. The extent of gonioscopically visible tissue strands in these patients did not correlate with the presence or severity of glaucoma. On the other hand, the gonioscopic appearance of peripheral iris inserting into the posterior portion of the trabecular meshwork, present to some degree in all patients, was pronounced in those with glaucoma, an observation which has also been made by others.[7,18,19]

Histopathologic examination of all specimens with an intact block of iris and trabecular tissue (cases 5, 8, 14, 20, and 24) revealed a high insertion of the iris into the posterior aspect of the trabecular meshwork, which explains the gonioscopic findings noted above. This is believed to represent a developmental arrest in the posterior recession of the peripheral iris, as described by Anderson.[39]

Structural alterations in the trabecular meshwork and Schlemm's canal were also observed and have been reported by others from light microscopic studies.[7,56,59] In normal embryogenesis, the trabecular meshwork and Schlemm's canal presumably begin as a compact mass of cells, which produce the connective tissue cores of the trabecular lamellae and eventually separate to create the intertrabecular spaces. In the A-R syndrome, there appears to be variable degrees of developmental arrest in this sequence. Light and electron microscopic examination of the trabecular meshwork in the present study consistently revealed compact lamellae and a rudimentary or absent Schlemm's canal. By transmission electron microscopy, the trabecular endothelial cells were frequently seen to join adjacent connective tissue cores, obliterating the intertrabecular space. In some cases, the cells were partially detached from one or both connective tissue cores, as though they had been arrested during the development of the intertrabecular spaces. These features were more marked in the outer meshwork, consistent with the concept that maturation may progress in an inner-to-outer direction. In the 3-month-old infant (case 24), the outer meshwork was a compact cellular mass, with a scant amount of collagen and extracellular ground substance. A normal Schlemm's canal

was not found in any specimen in this study, although one or more small endothelial-lined spaces with few or no red blood cells were observed in some cases, possibly representing a rudimentary Schlemm's canal.

These alterations in the aqueous outflow system are similar, but not identical, to those described for congenital and juvenile glaucomas.[39,40,54,55,61-63] It has been suggested that obstruction to aqueous outflow in the latter disorders is due to the compactness of the trabecular lamellae which may result from the high insertion of uveal tissue into the meshwork.[39,54,62] Ultrastructural observations in the present study suggest that the compactness of the trabecular meshwork in the A-R syndrome may be due to failure of the intertrabecular spaces to develop, rather than to subsequent mechanical compression. Furthermore, the extent of the developmental anomaly appears to be greater in the A-R syndrome than in congenital glaucoma, since Schlemm's canal is consistently rudimentary or absent in the former condition and usually present in the latter. Nevertheless, similarities in the histopathologic findings suggest that congenital glaucoma and the A-R syndrome may be parts of the same broad spectrum of developmental anomalies of the anterior ocular segment. Indeed, a prominent Schwalbe's line has been described in several cases of congenital glaucoma,[54,62] lending further support to this concept.

The age at which glaucoma is detected in patients with the A-R syndrome varies considerably, as demonstrated in the present study, although most cases appear in childhood or early adulthood. Data from this study do not provide an explanation as to why more cases of glaucoma are not seen in infants. The fact that the developmental alterations leading to the iridic changes, peripheral tissue strands, and prominent Schwalbe's line are not precisely the same as those conditions which cause the obstruction to aqueous outflow may explain why secondary glaucoma does not occur in all patients with the A-R syndrome and why the former anomalies do not fully correlate with the presence or severity of the glaucoma.

Glaucoma in the A-R syndrome is typically difficult to manage and frequently requires surgical intervention. The absence of a normal Schlemm's canal in all histopathologic specimens examined suggests that a standard goniotomy or trabeculotomy would not usually be successul. Indeed, Luntz[64] reported that a trabeculotomy controlled the intraocular pressure in only two of six eyes with this form of glaucoma. A trabeculectomy was used in all cases in the present study, and the results were comparable to those achieved in other forms of glaucoma involving patients in a similar age range.

All aspects of the theory of mechanism for the ocular anomalies in the A-R syndrome described above have a common basis in a maldevelopment of tissues derived from neural crest cells. As others have pointed out, this is consistent with the cause of the nonocular developmental abnormalities in this spectrum of disease.[31,53] The first systemic anomalies to be described, and those still most commonly associated with the A-R syndrome, are developmental defects of the teeth and facial bones. Dental defects were reported by Mathis[5] in 1936 and subsequently noted by Rieger[6] and many others.[11,48,52,65-72] These abnormalities include a reduction in crown size (microdontia), a decreased number of teeth (hypodontia), and a partial or total absence of teeth (oligodontia or anodontia). The teeth most commonly missing are anterior maxillary primary and permanent central incisors. In the present study, dental anomalies were documented in six patients. Traditionally, these cases would be classified as Rieger's syndrome. However, two of the patients had ocular findings consistent with Axenfeld's anomaly, ie, no iridic changes other than peripheral tissue strands. As previously discussed, this overlapping of ocular and nonocular abnormalities makes it difficult to subdivide the disease spectrum and is one reason for suggesting the single, collective term, Axenfeld-Rieger syndrome.

Rieger[6] also described facial anomalies in some of his patients, and these are now recognized as a frequent feature of the disease. The anomalies may include maxillary hypoplasia with flattening of the midface and a receding upper lip and prominent lower lip, especially in association with dental hypoplasia. Hypertelorism and a broad flat nose have also been described.[11,71-73] Similar findings were observed in four patients in the present study.

An especially noteworthy clinical observation in this study was that two patients from different families had anomalies in the region of the pituitary gland. A primary empty sella syndrome was documented in case 9, and a congenital parasellar arachnoid cyst was diagnosed and surgically corrected in case 15. Primary empty sella has been reported in seven members from three successive generations of a family with the A-R syndrome,[74] and two reports have described growth hormone deficiency and short stature in association with the disease spectrum.[53,75] It is not surprising that developmental anomalies related to the pituitary gland might be found in some patients with the A-R syndrome, since the connective tissue supporting the pituitary gland is of neural crest origin.[29]

Other features that have been reported in association with the A-R syndrome include redundant periumbilical skin and hypospadias.[11,76] Four patients in the present study underwent surgery for umbilical her-

nias. This defect is more difficult to correlate with the other anomalies in the A-R syndrome although the primitive umbilical ring, which gives rise to the umbilicus, does develop from the lateral portion of the ectodermal plate, which also contains the neural crest.[77]

Oculocutaneous albinism has been reported in two members of a family with the A-R syndrome.[78] This too is consistent with the theory of widespread developmental defects of tissue originating from neural crest cells, as the pigment cells of the iridic stroma, choroid, skin, and hair all develop in melanocytes derived from the neural crest.[79] Many other nonocular conditions have been reported in association with the A-R syndrome, most of which are listed in the extensive review by Alkemade.[7] It is likely that additional developmental anomalies will be discovered in various pedigrees, considering the apparently widespread manifestations of this disease spectrum.

DISTINCTIONS FROM THE IRIDOCORNEAL ENDOTHELIAL SYNDROME

The condition most frequently confused with the A-R syndrome is another spectrum of disease that has been referred to as the iridocorneal endothelial (ICE) syndrome.[80] Indeed, certain clinical and histopathologic features of the two disorders are so similar that some investigators have suggested a common mechanism.[14-17] However, the theory proposed in the present thesis offers an alternative concept, and distinctions between the two disease spectra will now be considered (Table IV).

TABLE IV: DISTINCTIONS BETWEEN A-R AND ICE SYNDROMES

CHARACTERISTICS	A-R SYNDROME	ICE SYNDROME
Laterality	Bilateral	Unilateral
Age of presentation	Birth	Young adulthood
Sex predilection	None*	Women
Familial	Frequently	Rarely
Associated nonocular disorders	Frequently	No
Corneal edema	No	Frequently
Corneal endothelium:		
Slitlamp	Normal	Abnormal
Specular microscopy	Normal	Abnormal
Origin of abnormal membrane	Retention of primordial tissue	Proliferation from abnormal corneal endothelium
Mechanism of secondary glaucoma	Maldevelopment of aqueous outflow system	Outflow obstruction by membrane or peripheral synechia

*Although men outnumbered women 2-to-1 in the present study, Alkemade[7] found an equal sex distribution in a review of 178 reported cases.

The ICE syndrome is composed of three major clinical variations: (1) Chandler's syndrome,[81] (2) progressive "essential" iris atrophy,[82] and (3) the Cogan-Reese[83] (or iris nevus[84]) syndrome. In each subdivision, the condition is typically unilateral, usually becomes manifest in young adulthood, and has a predilection for women. There is rarely a positive family history, and no additional ocular or systemic abnormalities are associated with the disease.[85,86] In all variations, there is an abnormality of the corneal endothelium which frequently leads to edema of the cornea.[87] The specular microscopic appearance of the endothelial cells is virtually pathognomonic in the ICE syndrome, with pleomorphism in shape and size, dark areas within the cells, and loss of clear hexagonal margins.[88] Ultrastructural studies of corneas with advanced edema revealed grossly abnormal cells lining a thickened, multilayered Descemet's membrane.[87]

A second characteristic feature common to all forms of the ICE syndrome is peripheral anterior synechiae, which often extend to or beyond Schwalbe's line. Progressive closure of the anterior chamber angle leads to secondary glaucoma in a high percentage of cases. This appearance of the angle and the associated glaucoma are features that may be confused with the A-R syndrome, although a prominent Schwalbe's line is rarely seen in the ICE syndrome.[85] An even more striking clinical similarity between the two diseases is the changes in the iris. In Chandler's syndrome, the iris may appear normal or have mild stromal atrophy and corectopia.[81] Progressive iris atrophy is characterized by marked corectopia and atrophy of the iris with hole formation, as in the more advanced cases of the A-R syndrome. Patients with the Cogan-Reese syndrome may have any degree of iridic change, as well as fine nodules[83,84,89] or diffuse nevi[84] on the stromal surface. Such nodules are not a typical feature of the A-R syndrome, although the association has been described.[90]

Histopathologic studies of the ICE syndrome have demonstrated a membrane, composed of a single layer of endothelial cells and a basement membrane, extending down from the cornea, across the anterior chamber angle, and onto the surface of the iris.[91-94] The similarity between this membrane and that seen in the A-R syndrome is the main feature leading some investigators to suspect a common mechanism for these two spectra of disease.[14-17] The difference, however, lies in the origin of the two membranes. According to the theory proposed by Campbell and co-workers[91] for the ICE syndrome, the fundamental defect is an abnormality of the corneal endothelium which leads to proliferation of the endothelial layer across the anterior chamber angle and over the iris. Subsequent contraction of the membrane pulls peripheral iris into the angle, forming peripheral anterior synechiae with frequent secondary glaucoma, and is

also the principal cause of the iridic changes, including nodule formation.[91,95,96]

The theory of pathogenesis for the A-R syndrome proposed in this thesis differs from the mechanism described above, in that the membrane is derived, not from abnormal corneal endothelium, but from retention of the primordial endothelial layer lining the anterior chamber during gestation. Several observations are believed to support this concept. The specular microscopic appearance of the corneal endothelium in the present study was within normal limits, allowing for age, chronic intraocular pressure elevation, and surgical intervention, in striking contrast to that previously noted for the ICE syndrome.[88] In addition, continuity in the membrane between the iris and the peripheral cornea was rarely observed in histopathologic specimens from patients with the A-R syndrome. This is in contrast to the ICE syndrome, in which the membrane is typically continuous from peripheral cornea, across the anterior chamber angle, and onto the iris.[91]

The two theories of mechanism are similar to the extent that contraction of the membrane is believed to be the principal cause of the iridic changes in both diseases. The situation in the anterior chamber angle is not the same, however, since the tissue strands in the ICE syndrome are believed to develop at some point after birth, as the membrane pulls peripheral iris into the angle, while those in the A-R syndrome are congenital but may become thicker and shorter by contraction of the associated membrane. Furthermore, the mechanism of the glaucoma differs in the two conditions, in that the membrane over the trabecular meshwork or the peripheral anterior synechiae are believed to cause the secondary glaucoma in the ICE syndrome, whereas maldevelopment of the trabecular meshwork and Schlemm's canal, and not the associated tissue strands, causes the secondary glaucoma in the A-R syndrome.

SUMMARY

Twenty-four patients with the diagnosis of Axenfeld's anomaly or Rieger's anomaly or syndrome were the subjects of a clinical study, which included specular microscopy of the corneal endothelium in 16 cases and fluorescein angiography of the iris in 5. Histopathologic material was obtained from ten eyes of eight of these patients (one enucleated eye and nine trabeculectomy specimens) and was studied by light and electron microscopy.

The overlapping of ocular and nonocular defects in these patients prevented subclassification according to traditional criteria. Any attempted

subdivision appears to have minimal clinical value, and a single classification for the disease spectrum is believed to be more practical. The collective term Axenfeld-Rieger (A-R) syndrome is proposed.

A theory of mechanism for the ocular features of the A-R syndrome is postulated which involves a developmental arrest, late in gestation, of tissues derived from neural crest cells. This leads to retention of primordial endothelial tissue on the iris and across the anterior chamber angle, which produces the iridic changes and the peripheral tissue strands. Continued contraction of these membranes after birth explains the progressive changes noted in some patients. This primordial endothelium also produces excessive and atypical basement membrane, especially near the corneolimbal junction, which accounts for the prominent Schwalbe's line. The secondary glaucoma results from arrested development of the anterior chamber angle structures, characterized by incomplete maturation of the trabecular meshwork and Schlemm's canal and a high insertion of the iris.

The ICE syndrome may be confused with the A-R syndrome on the basis of certain clinical and histopathologic similarities. Based on available evidence, however, it is postulated that the two entities are distinctly separate, in that the fundamental defect in the ICE syndrome is believed to be an abnormality of the corneal endothelium with secondary proliferation of a tissue layer over the anterior chamber angle and iris, while the A-R syndrome is thought to represent a developmental arrest with retention of a primordial membrane and other developmental defects.

ACKNOWLEDGMENTS

I am indebted to a large number of thoughtful and talented people who contributed in many ways to this study. To each of these I extend my most sincere thanks.

Patients in the study were referred by the following ophthalmologists: Charles L. Baltimore, Jr, R. Jeffery Board, William J. Burchfield, Arthur C. Chandler, Jr, Alfred N. Costner, Julian C. Culton, Andrew Davidson, C. Richard Epes, Albin W. Johnson, Martin J. Kreshon, Joseph Majstoravich, Jr, Brooks W. McCuen II, Samuel D. McPherson, Jr, Luther C. Sappenfield, Jr, J. Lawrence Sippe, Charles F. Sydnor, and Joe H. Woody. The enucleated eye was submitted by Dr Baltimore.

Randy Thresher assisted in preparation of the histologic specimens. Drs Edward Buckley and Gordon K. Klintworth assisted in interpreting the histopathologic findings. David Chandler and Bill Brock assisted in the specular microscopic studies of the corneal endothelium. Drs Michael

Cobo and Gary N. Foulks assisted in interpreting the results of the specular microscopy. Haig Garabedian and Ned Hinshaw assisted with the fluorescein angiographic studies of the iris and other photographic documentation.

Daphyne Boswell and Carolyn Lee typed the manuscript. Robin Goodwin provided secretarial assistance. Betsy White reviewed the manuscript.

I especially wish to thank Dr Joseph A. C. Wadsworth and Dr Samuel D. McPherson, Jr, without whose thoughtfulness and support this thesis would not have been possible.

REFERENCES

1. Axenfeld TH: Embryotoxon corneae posterius. *Ber Deutsch Ophthalmol Ges* 1920; 42:301-302.
2. Rieger H: Demonstration von zwei: Fällen von Verlagerung und Schlitzform der Pupille mit Hypoplasie des Irisvorderblattes an beiden Augen einer 10- und 25-jährigen Patientin. *Z Augenheilk* 1934; 84:98-99.
3. ———: Beiträge zur Kenntnis seltener Missbildungen der Iris. II. Über Hypoplasie des Irisvorderblattes mit Verlagerung und Entrundung der Pupille. *Albrecht von Graefes Arch Klin Exp Ophthalmol* 1935; 133:602-635.
4. ———: Dysgenesis mesodermalis corneae et iridis. *Z Augenheilk* 1935; 86:333.
5. Mathis H: Zahnunterzahl und Missbildungen der Iris. *Z Stomatol* 1936; 34:895-909.
6. Rieger H: Erbfragen in der Augenheilkunde. *Albrecht von Graefes Arch Klin Exp Ophthalmol* 1941; 143:277-299.
7. Alkemade PPH: *Dysgenesis Mesodermalis of the Iris and Cornea: A Study of Rieger's Syndrome and Peters' Anomaly*. Assen, The Netherlands, Van Gorcum and Comp NV, 1969.
8. Reese AB, Ellsworth RM: The anterior chamber cleavage syndrome. *Arch Ophthalmol* 1966; 75:307-318.
9. Waring GO III, Rodrigues MM, Laibson PR: Anterior chamber cleavage syndrome: a stepladder classification. *Surv Ophthalmol* 1975; 20:3-27.
10. Cross HE, Maumenee AE: Progressive spontaneous dissolution of the iris. *Surv Ophthalmol* 1973; 18:186-199.
11. Cross HE, Jorgenson RJ, Levin LS, et al: The Rieger syndrome: an autosomal dominant disorder with ocular, dental and systemic abnormalities. *Perspect Ophthalmol* 1979; 3:3-16.
12. Judisch GF, Phelps CD, Hanson J: Rieger's syndrome: a case report with a 15-year follow-up. *Arch Ophthalmol* 1979; 97:2120-2122.
13. Gregor Z, Hitchings RA: Rieger's anomaly: a 42-year follow-up. *Br J Ophthalmol* 1980; 64:56-58.
14. Pau H: Histologische Befunde bei "fortschreitender Atrophie des Irisstromas mit Lochbildung und Proliferation des Hornhautendothels." *Albrecht von Graefes Arch Klin Exp Ophthalmol* 1962; 164:351-361.
15. Pau H, Graeber W, Holtermann W: Die "Fortschreitende Atrophie des Irisstromas mit Lochbildung und Proliferation des Hornhautendothels." *Klin Monatsbl Augenheilkd* 1962; 141:568-582.
16. Pau H: Fortschreitende Atrophie des Irisstromas mit Lochbildung und Proliferation des Hornhautendothels. *Klin Monatsbl Augenheilkd* 1965; 147:894-899.
17. Troeber R, Rochels R: Histologische Befunde bei Dysgenesis mesodermalis iridis et corneae Rieger. *Albrecht von Graefes Arch Klin Exp Ophthalmol* 1980; 213:169-174.

18. Burian HM, Braley AE, Allen L: External and gonioscopic visibility of the ring of Schwalbe and the trabecular zone: an interpretation of the posterior corneal embryotoxon and the so-called congenital hyaline membranes on the posterior corneal surface. *Trans Am Ophthalmol Soc* 1954; 51:389-428.
19. ———: Visibility of the ring of Schwalbe and the trabecular zone: an interpretation of the posterior corneal embryotoxon and the so-called congenital hyaline membranes on the posterior corneal surface. *Arch Ophthalmol* 1955; 53:767-782.
20. Townsend WM, Font RL, Zimmerman LE: Congenital corneal leukomas. 2. Histopathologic findings in 19 eyes with central defect in Descemet's membrane. *Am J Ophthalmol* 1974; 77:192-206.
21. Stone DL, Kenyon KR, Green WR, et al: Congenital central corneal leukoma (Peters' anomaly). *Am J Ophthalmol* 1976; 81:173-193.
22. Nakanishi I, Brown SI: The histopathology and ultrastructure of congenital, central corneal opacity (Peters' anomaly). *Am J Ophthalmol* 1971; 72:801-812.
23. Scheie HG, Yanoff M: Peters' anomaly and total posterior coloboma of retinal pigment epithelium and choroid. *Arch Ophthalmol* 1972; 87:525-530.
24. Dark AJ, Kirkham TH: Congenital corneal opacities in a patient with Rieger's anomaly and Down's syndrome. *Br J Ophthalmol* 1968; 52:631-635.
25. Howard RO, Abrahams IW: Sclerocornea. *Am J Ophthalmol* 1971; 71:1254-1260.
26. Awan KJ: Peters-Rieger's syndrome. *J Pediatr Ophthalmol* 1977; 14:112-116.
27. Henkind P, Friedman AH: Iridogoniodysgenesis with cataract. *Am J Ophthalmol* 1971; 72:949-954.
28. Mann I: *The Development of the Human Eye*. ed 3, New York, Grune and Stratton Inc, 1964.
29. Johnston MC, Bhakdinaronk A, Reid YC: An expanded role of the neural crest in oral and pharyngeal development. In Bosma JF (ed): *Fourth Symposium on Oral Sensation and Perception*. US Govt Printing Office, 1973, pp 37-52.
30. Johnston MC, Noden DM, Hazelton RD, et al: Origins of avian ocular and periocular tissues. *Exp Eye Res* 1979; 29:27-43.
31. Kupfer C, Kaiser-Kupfer MI: Observations on the development of the anterior chamber angle with reference to the pathogenesis of congenital glaucomas. *Am J Ophthalmol* 1979; 88:424-426.
32. Edwards WC, Torczynski E: Neural crest cell behavior and facial anomalies. *Perspect Ophthalmol* 1981; 5:47-50.
33. Wulle KG: Electron microscopy of the fetal development of the corneal endothelium and Descemet's membrane of the human eye. *Invest Ophthalmol* 1972; 11:897-904.
34. Hay ED: Development of the vertebrate cornea. *Int Rev Cytol* 1980; 63:263-322.
35. Mann I: *Development of the Human Eye*. Cambridge, England, Cambridge University Press, 1928.
36. Barkan O: Pathogenesis of congenital glaucoma, gonioscopic and anatomic observations of the angle of the anterior chamber in the normal eye and in congenital glaucoma. *Am J Ophthalmol* 1955; 40:1-11.
37. Allen L, Burian HM, Braley AE: A new concept of the development of the anterior chamber angle: its relationship to developmental glaucoma and other structural anomalies. *Arch Ophthalmol* 1955; 53:783-798.
38. Smelser GK, Ozanics MS: The development of the trabecular meshwork in primate eyes. *Am J Ophthalmol* 1971; 70:366-385.
39. Anderson DR: The development of the trabecular meshwork and its abnormality in primary infantile glaucoma. *Trans Am Ophthalmol Soc* 1981; 79:458-485.
40. Worst JGF: *The Pathogenesis of Congenital Glaucoma. An Embryological and Goniosurgical Study*. Assen, The Netherlands, Royal Van Gorcum, 1966, pp 38-65.
41. Hansson HA, Jerndal T: Scanning electron microscopic studies on the development of the irido-corneal angle in human eyes. *Invest Ophthalmol* 1971; 10:252-265.
42. Van Buskirk EM: Clinical implications of iridocorneal angle development. *Ophthalmology* 1981; 88:361-367.

43. Tawara A, Inomata H: Developmental immaturity of the trabecular meshwork in congenital glaucoma. *Am J Ophthalmol* 1981; 92:508-525.
44. Maul E, Strozzi L, Munoz C, et al: The outflow pathway in congenital glaucoma. *Am J Ophthalmol* 1980; 89:667-675.
45. Jerndal T, Hansson HA, Bill A: *Goniodysgenesis. A New Perspective on Glaucoma*. Copenhagen, Scriptor, 1978.
46. Hagedoorn A: Congenital anomalies of the anterior segment of the eye. *Arch Ophthalmol* 1937; 17:223-227.
47. Unger VL: Beitrag zur sogen. Dysgenesis mesodermalis corneae et iridis (Rieger). *Ophthalmologica* 1956; 132:27-35.
48. Riethe VP, Lemmingson W: Zur Kombination von Oligodontie mit Dysgenesis mesodermalis corneae at iridis. *Stoma* 1962; 15:11-25.
49. Henkind P, Siegel IM, Carr RE: Mesodermal dysgenesis of the anterior segment: Rieger's anomaly. *Arch Ophthalmol* 1965;.73:810-817.
50. Klien BA: Dysgenesis mesodermalis der Hornhaut und iris mit gleichzeitigem Vorkommen von neuroektodermalen Entwicklungsstorungen. *Albrecht von Graefes Arch Klin Exp Ophthalmol* 1961; 164:12-23.
51. Falls HF: A gene producing various defects of the anterior segment of the eye: with a pedigree of a family. *Am J Ophthalmol* 1949; 32(pt 2):41-52.
52. Langdon JD: Rieger's syndrome. *Oral Surgery* 1970; 30:789-795.
53. Sadeghi-Nejad A, Senior B: Autosomal dominant transmission of isolated growth hormone deficiency in iris-dental dysplasia (Rieger's syndrome). *J Pediatr* 1974; 85:644-648.
54. Broughton WL, Fine BS, Zimmerman LE: Congenital glaucoma associated with a chromosomal defect: a histologic study. *Arch Ophthalmol* 1981; 99:481-486.
55. Swan KC: Developmental glaucomas in juveniles. *Perspect Ophthalmol* 1981; 5:21-25.
56. Delmarcelle MMY, De Clerck P, Pivont A: Glaucome congénital associé à des malformations oculaires et somatiques dans deux générations successives. *Bull Soc Belge Ophthalmol* 1958; 120:638-655.
57. Spencer WH, Alvarado J, Hayes TL: Scanning electron microscopy of human ocular tissues: trabecular meshwork. *Invest Ophthalmol* 1968; 7:651-662.
58. Loewenstein A: "Knob" at the periphery of Descemet's membrane. *Br J Ophthalmol* 1950; 34:246-250.
59. Wolter JR, Sandall GS, Fralick FB: Mesodermal dysgenesis of anterior eye: with a partially separated posterior embryotoxon. *J Pediatr Ophthalmol* 1967; 4:41-46.
60. Sugar HS: Juvenile glaucoma with Axenfeld's syndrome: a histologic report. *Am J Ophthalmol* 1965; 59:1012-1019.
61. Worst J: The causes and treatment of congenital glaucoma. *Trans Am Acad Ophthalmol Otolaryngol* 1964; 68:766-788.
62. Maumenee AE: Further observations on the pathogenesis of congenital glaucoma. *Am J Ophthalmol* 1963; 55:1163-1176.
63. Anderson DR: Pathology of the glaucomas. *Br J Ophthalmol* 1972; 56:146-157.
64. Luntz MH: Congenital, infantile, and juvenile glaucomas. *Ophthalmology* 1979; 86:793-802.
65. Rejchrt B, Miksa J: Dysgenesis mesodermalis corneae et iridis. *Cesk Oftalmol* 1952; 8:315-320.
66. Lemmingson W, Riethe P: Beobachtungen bei Dysgenesis mesodermalis corneae et iridis in Kombination mit Oligodontie. *Klin Monatsbl Augenheilkd* 1958; 133:877-891.
67. Busch VG, Weiskopf J, Busch K-Th: Dysgenesis mesodermalis et ectodermalis Rieger oder Rieger'sche Krankheit. *Klin Monatsbl Augenheilkd* 1960; 136:512-523.
68. Marx P: Malformations oculaires et malformations dentaires. *Doc Ophthalmol* 1966; 20:669-674.
69. Chosack A, Rosenzweig KA: Oligodontia associated with defects of the eyes. *Oral Surgery* 1966; 21:354-357.

70. Tabbara KF, Khouri FP, Der Kaloustian VM: Rieger's syndrome with chromosomal anomaly (report of a case). *Can J Ophthalmol* 1973; 8:488-491.
71. De Hauwere RC, Leroy JG, Adriaenssens K, Van Heule R: Iris dysplasia, orbital hypertelorism, and psychomotor retardation: a dominantly inherited developmental syndrome. *J Pediatr* 1973; 82:679-681.
72. Wesley RK, Baker JD, Golnick AL: Rieger's syndrome (oligodontia and primary mesodermal dysgenesis of the iris): clinical features and report of an isolated case. *J Pediatr Ophthalmol Strab* 1978; 15:67-70.
73. Rossano R: Absence presque complete du feuillet mesodermique de l'iris dans deux générations: hypertension oculaire et polycarie dans un cas. *Bull Soc Ophthalmol* Paris, pp 8-17, Jan 1, 1934.
74. Kleinman RE, Kazarian EL, Raptopoulos V, et al: Primary empty sella and Rieger's anomaly of the anterior chamber of the eye: a familial syndrome. *N Engl J Med* 1981; 304:90-93.
75. Feingold M, Shiere F, Fogels HR, et al: Rieger's syndrome. *Pediatrics* 1969; 44:564-569.
76. Jorgenson RJ, Levin LS, Cross HE, et al: The Rieger syndrome. *Am J Med Genet* 1978; 2:307-381.
77. Langman J: *Medical Embryology*, ed 4, Baltimore, Williams & Wilkins, 1981, p 93.
78. Lubin JR: Oculocutaneous albinism associated with corneal mesodermal dysgenesis. *Am J Ophthalmol* 1981; 91:347-350.
79. Taylor WOG: Visual disabilities of oculocutaneous albinism and their alleviation. *Trans Ophthalmol Soc UK* 1978; 98:423-445.
80. Yanoff M: In discussion of Shields MB, McCracken JS, Klintworth GK, Campbell DG: Corenal edema in essential iris atrophy. *Ophthalmology* 1979; 86:1549-1550.
81. Chandler PA: Atrophy of the stroma of the iris: endothelial dystrophy, corneal edema, and glaucoma. *Am J Ophthalmol* 1956; 41:607-615.
82. Harms C: Einseitige spontane Luckenbildung der Iris durch Atrophie ohne mechanische Zerrung. *Klin Monatsbl Augenheilkd* 1903; 41:522-528.
83. Cogan DG, Reese AB: A syndrome of iris nodules, ectopic Descemet's membrane, and unilateral glaucoma. *Doc Ophthalmol* 1969; 26:424-433.
84. Scheie HG, Yanoff M: Iris nevus (Cogan-Reese) syndrome: a cause of unilateral glaucoma. *Arch Ophthalmol* 1975; 93:963-970.
85. Shields MB, Campbell DG, Simmons RJ: The essential iris atrophies. *Am J Ophthalmol* 1978; 85:749-759.
86. Shields MB: Progressive essential iris atrophy, Chandler's syndrome, and the iris nevus (Cogan-Reese) syndrome: a spectrum of disease. *Surv Ophthalmol* 1979; 24:3-20.
87. Shields MB, McCracken JS, Klintworth GK, et al: Corneal edema in essential iris atrophy. *Ophthalmology* 1979; 86:1533-1548.
88. Hirst LW, Quigley HA, Stark WJ, et al: Specular microscopy of iridocorneal endothelia syndrome. *Am J Ophthalmol* 1980; 89:11-21.
89. Shields MB, Campbell DG, Simmons RJ, et al: Iris nodules in essential iris atrophy. *Arch Ophthalmol* 1976; 94:406-410.
90. Theil R: *Atlas of Disease of the Eye*. New York, Elsevier Publ Co, 1963, vol 1, pp 222-223.
91. Campbell DG, Shields MB, Smith TR: The corneal endothelium and the spectrum of essential iris atrophy. *Am J Ophthalmol* 1978; 86:317-324.
92. Rodrigues MM, Streeten BW, Spaeth GL: Chandler's syndrome as a variant of essential iris atrophy: a clinicopathological study. *Arch Ophthalmol* 1978; 96:643-652.
93. Eagle RC Jr, Font RL, Yanoff M, et al: Proliferative endotheliopathy with iris abnormalities: the iridocorneal endothelial syndrome. *Arch Ophthalmol* 1979; 97:2104-2111.
94. Rodrigues MM, Phelps CD, Krachmer JH, et al: Glaucoma due to endothelialization of the anterior chamber angle: a comparison of posterior polymorphous dystrophy of the cornea and Chandler's syndrome. *Arch Ophthalmol* 1980; 98:688-696.

95. Campbell DG: Formation of iris nodules in primary proliferative endothelial degeneration. Presented at meeting of the Association for Research in Vision and Ophthalmology, Sarasota, FL, April 30-May 4, 1979.
96. Eagle RC Jr, Font RL, Yanoff M, et al: The iris naevus (Cogan-Reese) syndrome: light and electron microscopic observations. *Br J Ophthalmol* 1980; 64:446-452.