A COMMON PATHWAY FOR DEVELOPMENTAL GLAUCOMAS*

BY *M. Bruce Shields*, MD

INTRODUCTION

AMONG THE MANY FORMS OF GLAUCOMA, ONE GROUP IS CHARACTERIZED BY DEvelopmental abnormalities of the anterior chamber angle. One condition in this group, primary congenital glaucoma, is not consistently associated with additional developmental defects, while other forms of developmental glaucoma have associated ocular or systemic anomalies. In each disorder, however, structural defects of the anterior chamber angle lead to aqueous outflow obstruction and, in most cases, intraocular pressure elevation. The glaucoma usually appears in infancy or early childhood, but may become manifest in late childhood or adulthood.

Studies of the normal development of the anterior chamber angle, as well as clinicopathologic evaluations of various developmental glaucomas, are expanding our understanding of the intraocular pressure-inducing mechanisms within this group of glaucomas. It is not surprising that these studies are disclosing certain common anterior chamber angle defects among the many forms of developmental glaucoma. The purpose of this paper is to review one of these common developmental pathways, based on a series of clinicopathologic studies and a survey of the literature.

MATERIALS AND METHODS

Ten patients with various forms of developmental or secondary glaucoma were included in this study. The details of these patients are summarized in Table I. In each case, the author examined the patient clinically and performed a modified trabeculectomy for uncontrolled glaucoma. No eye in this study had undergone previous surgery.

The modified trabeculectomy, which has been previously described,[1] was designed to allow en bloc resection of the trabecular tissue and

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adjacent peripheral iris for purposes of histologic study. After dissecting a partial-thickness scleral flap, the anterior margin and sides of the trabeculectomy block were cut, and the resulting 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, corresponding to the width of the trabecular block, and the two structures were excised together near the level of the scleral spur (Fig 1).

Immediately after removal from the eye, all specimens were placed in buffered 2% glutaraldehyde or 2.5% glutaraldehyde with 2% paraformaldehyde. After a minimum fixation time of 24 hours, the specimens were prepared for electron microscopic evaluation by washing them twice for 10 minutes in 0.1 mol/l cacodylate buffer with 5% sucrose, post-fixing them in 2% ozmium tetroxide for 45 minutes, washing them again in buffer, partially dehydrating them in 50% ethanol, and staining them 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%.

All specimens were studied by transmission or scanning electron microscopy, or both. For the former techniques, a portion of the specimen

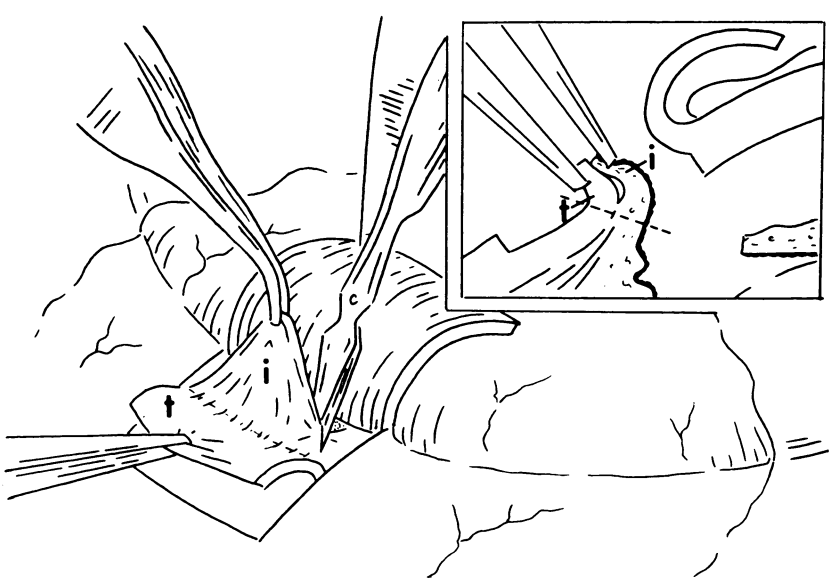

FIGURE 1
Modified trabeculectomy with en bloc resection of trabecular tissue (T) and adjacent iris (I), as used in all cases in present study. (Reprinted from Shields MB: *Trans Am Ophthalmol Soc* 1983; 81:736-784, with permission.)

was embedded in Spurr low viscosity medium and allowed to polymerize for 24 hours. Thick sections (1 μm) were stained with toluidine blue and basic fuchsin and examined by light microscopy, and thin sections (60 nm) were stained with uranyl acetate and lead citrate and studied with a Zeiss EM95 transmission electron microscope.

For scanning electron microscopy, either the entire specimen, or a portion thereof, was critical-point dried in a Tousimis Samdri PVT-3, mounted on aluminum stubs, coated with gold-palladium, and examined in a JEOL JSM 35-C scanning electron microscope at 18 kv accelerating voltage.

RESULTS

Table I summarizes the clinical and histopathologic findings of the ten patients in this study. By gonioscopic examination, all patients appeared to have a high insertion of peripheral iris into the posterior portion of the trabecular meshwork (Fig 2). In addition, five individuals with Axenfeld-Rieger syndrome had tissue strands of variable thickness bridging the anterior chamber from peripheral iris to a prominent, anteriorly displaced Schwalbe's line. The clinical and histopathologic details of these patients have been previously described.[1] One patient with aniridia had the characteristic feature of a rudimentary iris, while another patient with iridocorneal endothelial syndrome had the associated findings of pupillary distortion and iris atrophy. In the remaining cases, which included posterior polymorphous dystrophy, juvenile glaucoma, and Stickler's syndrome, the iris and anterior chamber angle were otherwise normal by clinical examination.

Histopathologic evaluation confirmed a high iris insertion in nine of the ten patients. In the tenth case, with Stickler's syndrome, the only apparent abnormality in the surgical specimen was a thickening of the juxtacanalicular tissue by an amorphous material. Of the nine cases in which the iris inserted into the trabecular meshwork, one had an apparent secondary mechanism for the anteriorly-displaced uveal tissue. In the eye with the iridocorneal endothelial syndrome, a Descement's-like membrane was noted in the area of high iris insertion, suggesting that contracture of an associated endothelial layer led to the synechial closure in this condition, as proposed by Campbell et al.[2]

In the remaining eight cases, several histologic findings supported the concept that the high iris insertion was due to a developmental arrest, rather than a secondary event. A membrane, as noted in cases of iridocorneal endothelial syndrome and some other secondary disorders, was not

TABLE I: CLINICAL AND HISTOPATHOLOGIC FEATURES OF PATIENTS IN PRESENT STUDY

CASE	AGE	RACE	SEX	DIAGNOSIS	HISTOLOGIC STUDIES* (No. OF EYES)	ANTERIOR CHAMBER ANGLE DEFECTS
1	16 yrs	White	Male	Axenfeld-Rieger syndrome	LM, TEM (1)	Iridocorneal tissue strands, high iris insertion, incomplete development of trabecular meshwork and Schlemm's canal
2	54 yrs	White	Male	Axenfeld-Rieger syndrome	LM, TEM (2)	Same as case 1
3	51 yrs	White	Male	Axenfeld-Rieger syndrome	LM, TEM, SEM (2)	Same as case 1
4	27 yrs	Black	Male	Axenfeld-Rieger syndrome	LM, TEM (1)	Same as case 1
5	3 mos	White	Male	Axenfeld-Rieger syndrome	LM, TEM, SEM (2)	Same as case 1
6	62 yrs	White	Male	Posterior polymorphous dystrophy	LM, TEM, SEM (1)	High iris insertion, compression of trabecular lamellae
7	18 yrs	White	Male	Juvenile glaucoma	LM, SEM (1)	Same as case 6
8	34 yrs	White	Male	Aniridia	LM, SEM (1)	Same as case 6, plus rudimentary iris
9	42 yrs	White	Female	Iridocorneal endothelial syndrome	LM, SEM (1)	Glassy membrane and secondary angle closure
10	27 yrs	White	Male	Stickler's syndrome	LM, SEM (1)	Thickening of juxtacanalicular tissue with amorphous material

*LM, light microscopy; TEM, transmission electron microscopy; SEM, scanning electron microscopy.

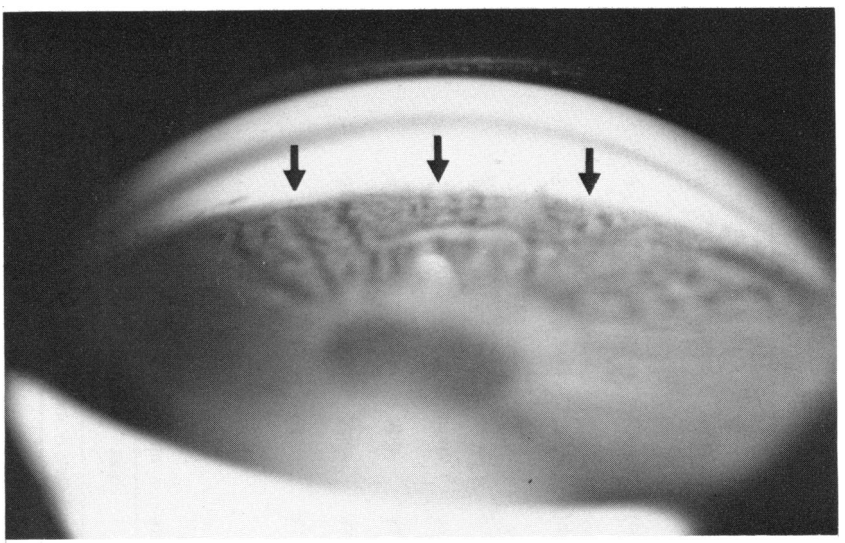

FIGURE 2
Gonioscopic view of high iris insertion into posterior trabecular meshwork (*arrows*) in patient with Axenfeld-Rieger syndrome.

associated with the high iris insertion in the eyes of these eight patients (Figs 3 and 4). While patients with the Axenfeld-Rieger syndrome frequently had a similar membrane on portions of the iris and the iridocorneal adhesions, this membrane was not consistently associated with the peripheral iris that inserted into the posterior portion of the trabecular meshwork.[1] The junction between iris and trabecular beams, as seen by light and transmission electron microscopic examination revealed no inflammatory cells or fibrous tissue, that might suggest a secondary synechial closure of the anterior chamber angle (Fig 5).

In the patients with Axenfeld-Rieger syndrome, there was also incomplete development of the trabecular meshwork and Schlemm's canal. No additional developmental abnormalities were noted in the aqueous outflow system in the remainder of the eyes studied, although apparent collapse of the trabecular meshwork was a common finding.

LITERATURE SURVEY

A high insertion of uveal tissue into the trabecular meshwork has been reported in several forms of developmental glaucoma on the basis of clinical and histopathologic observations (Table II). Barkan[3] noted this in

FIGURE 3
Scanning electron microscopic view of trabeculectomy/iridectomy specimen from patient with Axenfeld-Rieger syndrome showing high insertion (*arrows*) of iris (I) into trabecular meshwork (TM) (× 195).

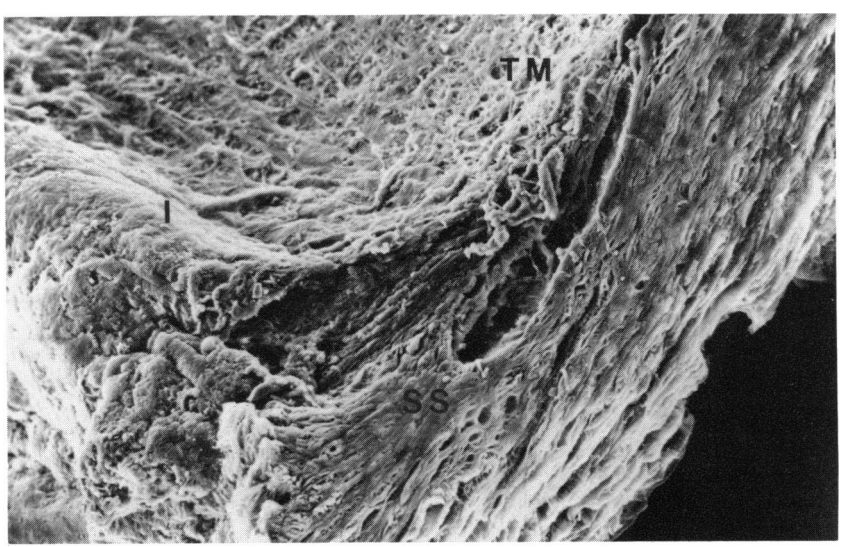

FIGURE 4
Scanning electron microscopic view of trabeculectomy/iridectomy specimen from patient with posterior polymorphous dystrophy showing iris (I) inserting into posterior aspect of trabecular meshwork (TM) well anterior to scleral spur (SS) (× 230). (Reprinted from Bourgeois J, Shields MB, Thresher R: *Ophthalmology* 1984; 91:420-423, with permission.)

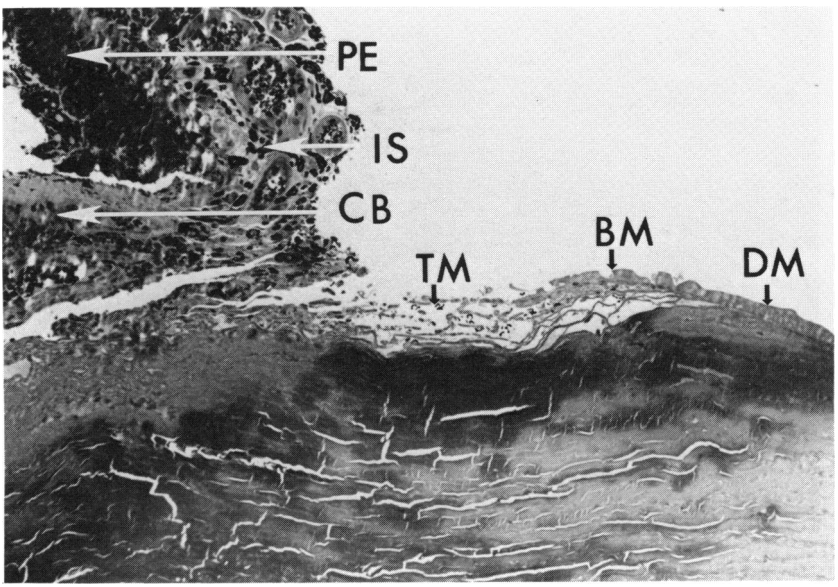

FIGURE 5
Light microscopic view of trabeculectomy/iridectomy specimen from patient with Axenfeld-Rieger syndrome showing high insertion of uveal tissue into posterior aspect of trabecular meshwork (TM). Basement membrane-like material (BM) also extends from Descemet's membrane (DM) over anterior trabecular lamellae. Uveal tissue includes iris stroma (IS) and pigment epithelium (PE) and ciliary body (CB) (toluidine blue-basic fuchsin, × 160). (Reprinted from Shields MB: *Trans Am Ophthalmol Soc* 1983; 81:736-784.)

TABLE II: DEVELOPMENTAL DISORDERS WITH HIGH IRIS INSERTION

CONDITION	SOURCE(S)
Primary congenital glaucoma	Barkan,[3] Worst,[4] Maumenee,[5] Anderson[6]
Axenfeld-Rieger syndrome	Shields,[1] Burian et al,[7] Alkemede,[8] present study
Neurofibromatosis	Grant and Walton[9]
Aniridia	Margo,[10] present study
Sturge-Weber syndrome	Barkan,[12] Weiss[13]
Posterior polymorphous dystrophy	Bourgeois et al,[14] present study
Juvenile glaucoma	Present study
Trisomy 18 (Edwards' syndrome)	Mayer et al[15]
Cockayne's syndrome	Levin et al[16]
Fetal alcohol syndrome	Miller et al[17]
Zellweger's syndrome	Cohen et al[18]
Oculodentodigital dysplasia syndrome	Sugar[19]

patients with primary congenital glaucoma, but felt that an associated endothelial membrane was responsible for aqueous outflow obstruction, a theory also held by Worst.[4] Maumenee[5] also noted a high insertion of uveal musculature into the trabecular meshwork in this disorder, and reasoned that contraction of the muscle might compress the scleral spur forward and externally, thereby narrowing Schlemm's canal. In a clinicopathologic study, Anderson[6] found the high insertion of anterior uvea into the trabecular meshwork, but no associated endothelial membrane. Anderson[6] also provided evidence that this abnormality is due to a developmental arrest in the normal migration of the uvea across the meshwork during the third trimester of gestation.

Burian et al,[7] and Alkemede[8] noted a similar high insertion of the iris in patients with the Axenfeld-Rieger syndrome, and Shields[1] demonstrated this in a clinicopathologic study, portions of which are included in the present report. Grant and Walton[9] described the clinical features of high iris insertion in patients with neurofibromatosis as one of several mechanisms for glaucoma among these patients. Margo[10] reported the histopathologic findings of seven eyes with aniridia, which included high iris insertion into the trabecular meshwork. Some of these aniridic cases appeared to have incomplete angle development, which was felt to be the situation in case eight of the present study, while others may have had secondary angle closure, as described by Grant and Walton.[11]

Some patients with the Sturge-Weber syndrome have been noted to have anterior chamber angle defects similar to those seen in primary congenital glaucoma, including the high iris insertion.[12,13] In one clinicopathologic study, a high iris insertion was found in a patient with posterior polymorphous dystrophy and secondary glaucoma.[14] This case is included in the present study. Several additional isolated case reports of high iris insertion in patients with development disorders are listed in Table II.[15-19] This is undoubtedly a partial list, and will continue to expand as additional developmental disorders are studied.

It is noteworthy that a high iris insertion was only one of several possible mechanisms for aqueous outflow obstruction in many of these developmental disorders. Furthermore, the presence of a high iris insertion was not invariably associated with glaucoma, especially among the younger patients. It is hard to know in many cases, therefore, to what degree, if any, the high insertion of the iris is contributing to the associated glaucoma.

DISCUSSION

The modified trabeculectomy, as used in the present study, which allows en bloc resection of trabecular meshwork and peripheral iris, has expanded our ability to study the connections between these structures in developmental and secondary glaucomas. With the exception of Anderson,[6] who used a similar surgical technique in his study of primary congenital glaucoma, most of the reports in the literature survey were based on clinical observations and/or histopathologic examinations of whole eyes.

Histologic study of intact blocks of peripheral iris and trabecular beams provides confirmation as to whether the iris is truly inserted abnormally into posterior trabecular meshwork, as well as evidence as to whether this is due to a developmental defect or a secondary event. Six disorders were evaluated in the present study. One patient with Stickler's syndrome, who appeared to have a high iris insertion by gonioscopy, did not have this feature confirmed by histologic study. Patients with the other five conditions did have a high iris insertion, but one (with the iridocorneal endothelial syndrome) had an associated membrane, contracture of which may have been the secondary event causing the angle closure, as suggested by Campbell et al.[2] In the remaining patients, with Axenfeld-Rieger syndrome, posterior polymorphous dystrophy, juvenile glaucoma, and aniridia, there was no apparent secondary cause for the high iris insertion. In the patients with Axenfeld-Rieger syndrome, additional developmental defects were noted in the trabecular meshwork and Schlemm's canal, which could have led to aqueous outflow obstruction, while the only additional finding in the other disorders was apparent collapse of trabecular meshwork.

The four disorders described in the present study, as well as those from the literature survey, in which the peripheral iris inserts into the posterior portion of the trabecular meshwork, are consistent with recent observations regarding development of the anterior chamber angle. Anderson[6] noted that the anterior iris surface at 5 months gestation inserts at the edge of the corneal endothelium, covering the cells that are destined to become the trabecular meshwork (Fig 6). He further noted a posterior repositioning of this uveal tissue during the third trimester. A developmental arrest during this period, therefore, could explain the high insertion of the iris in many developmental disorders. Recent study indicate that the tissues involved in this developmental process are derived from cranial neural crest cells.[20,21]

Although the developmental defect in this study has been referred to as a high iris insertion, it should be emphasized that it is actually both the

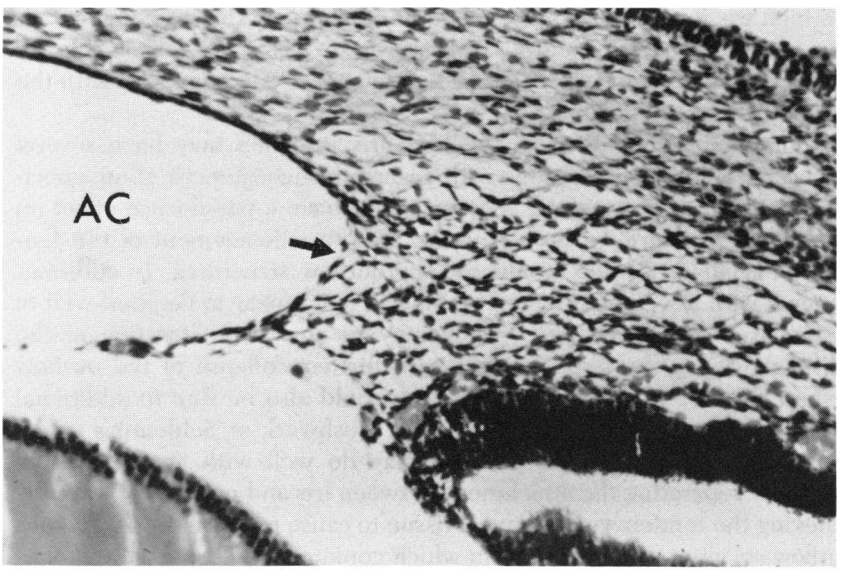

FIGURE 6
Light microscopic view of 11-week fetal eye in meridional section showing loosely arranged spindle-shaped cells (*arrow*) filling angle of anterior chamber (AC) and covering tissue destined to become trabecular meshwork. Failure of these cells to undergo normal posterior repositioning late in gestation results in high iris insertion (× 230). (Reprinted from Tripathi RC, Tripathi B: *Ocular Anatomy, Embryology, and Teratology*. Edited by FA Jakobiec. Philadelphia, Harper & Row, 1982, p 200, with permission.)

iris and ciliary body that are positioned abnormally forward. It is most likely the involvement of the ciliary body, which may have an indirect attachment to the trabecular meshwork through the iris, that is responsible for the obstruction to aqueous outflow. In the normal situation, the ciliary musculature attaches to the scleral spur in such a way that contraction of the muscle causes an inward, posterior rotation of the spur, which leads to a widening of the intertrabecular spaces and Schlemm's canal. With an insertion of the anterior uvea into the trabecular meshwork, however, contraction of the ciliary musculature, as proposed by Maumenee and others,[4-6] could cause a collapse of the meshwork and Schlemm's canal, with a reduction in facility of aqueous outflow.

It is not clear why the glaucoma, in some of these cases, does not appear until late childhood or adulthood. If collapse of the outflow structures does play a role in the glaucoma of these patients, it may be that time is required to build up structural changes that eventually result in significant obstruction to aqueous outflow. In other cases, it is likely that

the high iris insertion is a coincidental finding and that additional developmental defects in the outflow structures are primarily responsible for the glaucoma. This may be the situation in at least some patients with the Axenfeld-Rieger syndrome.

Gonioscopic recognition of the high iris insertion may have several important clinical implications with regard to management of an associated glaucoma. First, miotic therapy might have a paradoxical effect on intraocular pressure in these patients, due to enhancement of the tendency for ciliary muscle to collapse the outflow structures. In addition, patients with developmental glaucomas do not appear to respond well to argon laser trabeculoplasty, which may be due to contraction of the adjacent iris by the laser energy, with further collapse of the outflow system. Failure of laser trabeculoplasty could also be due to additional developmental defects in the trabecular meshwork or Schlemm's canal. On the other hand, these patients may do well with goniotomy, by surgically separating the attachment between iris and meshwork, thereby relieving the tendency of the uveal tissue to cause collapse of the aqueous outflow structures. Those cases in which goniotomy fails may be the ones with additional developmental defects in the trabecular meshwork or Schlemm's canal, in which case a trabeculotomy or filtering procedure may be more effective when surgery is required.

SUMMARY

In a clinicopathologic study of ten patients, utilizing a modified trabeculectomy technique for acquisition of histologic specimens, a high insertion of the iris was observed in four types of developmental glaucoma. A survey of the literature revealed additional developmental disorders with this abnormality of the anterior chamber angle. The common defect is believed to arise from a developmental arrest during the third trimester of gestation of tissues derived from cranial neural crest cells. The mechanism by which this developmental defect leads to aqueous outflow obstruction may, in some cases, be a paradoxical collapse of the trabecular meshwork and Schlemm's canal in response to contraction of the ciliary musculature, while other patients may have additional developmental abnormalities in the aqueous outflow system as the possible mechanism of glaucoma.

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DISCUSSION

Dr J. Brooks Crawford. Scientists of various disciplines search for unifying theories. In ophthalmology we like to group diseases not only to challenge our intellect, but also to recognize entities which share similar pathophysiologic processes in order to plan logical treatment. Doctor Shields has proposed a theory

of congenital and juvenile glaucoma that encompasses many diseases. His method of investigation, the ultrastructural evaluation of a modified trabeculectomy in eyes without previous surgery, is particularly commendable. A similar technique was used by Anderson in his studies of congenital glaucoma (his American Ophthalmologic Society thesis) and Alvarado in his studies of the iridocorneal endothelial syndrome. This technique eliminates many of the artifacts and erroneous appearances associated with standard histology.

It is not surprising that the high iris insertion in the patient with the iridocorneal endothelial syndrome appeared to be secondary to synechiae formation rather than a primary congenital defect. Campbell and colleagues showed that this syndrome results from proliferation of corneal endothelium. Alvarado and colleagues proved that this occurred after birth. I question whether the abnormality Doctor Shields describes in the other four developmental glaucoma entities is the common pathway for the glaucoma or is merely a structural abnormality, shared by various diseases, that may not directly or indirectly affect aqueous outflow. If indeed this defect in iris insertion is the common cause of the glaucoma associated with these diseases, then the treatment which is effective for one, namely goniotomy for congenital (isolated trabeculodysgenesis) glaucoma, should be effective for all. Numrous authorities have pointed out that goniotomy and trabeculotomy are less effective in treating the glaucoma associated with congenital abnormalities such as aniridia, neurofibromatosis, and the Axenfeld-Rieger syndrome.

Therefore I agree with Doctor Shields' statement that a high iris insertion may be only one of several possible mechanisms for aqueous outflow obstruction in many of these developmental disorders and that it is hard to know to what degree, if any, the high insertion of the iris is contributing to the associated glaucoma. To answer this challenging question, more cases should be studied with the excellent technique described by Doctor Shields.

Dr Ralph Levene. One occasionally sees a high iris insertion in primary open angle glaucoma. It is rarely seen in normal eyes. Thus, some cases of primary open angle glaucoma are delayed congenital glaucoma.

Dr Benjamin Sheppard. This is a great day in the morning, to hear what Doctor Shields has presented and Doctor Crawford has discussed. Doctor Shields today has presented us with up-to-date progressive findings in glaucoma with emphasis on congenital glaucoma. The causes of several of the glaucomas are many. Doctor Shields and Doctor Crawford have presented the up-to-date continued research of these by showing the developmental intraocular histopathological changes in the uveal tissues, particularly in the third trimester.

I have been quite interested in studying this disease since first in 1946 finding a bilateral buphthalmic rabbit at the Jackson Memorial Genetic Laboratory, Bar Harbor, Maine. We have kept statistics while studying these animals and found anomalies, for instance, spina bifida occurs in many of them. What we have found in these rabbits over the years, in many cases, is applicable to man.

A year or so ago we ran out of funds to maintain our rabbit colony and I am sure some of you have had the same thing happen. Fortunately Doctor Lam, University of Texas, Ophthalmological Department came to the rescue. I will try to give you some statistics on his findings. This morning a reference has been presented here on tonography. That is important in glaucoma.

First, we must know the normal. Everybody in this room remembers the great contributions of Doctors Georgiana Theobold, Jonas Friedenwald, and particularly, Karl Asher who gave us so much of the background in anatomy and histological (microanatomy) changes in the normal eye, especially in the aqueous veins. The ever present search for possible causes of disease continues. Heredity is the primary cause and there is little we can do about it. Doctor Shields suggested the increasing intraocular pressure is associated with a decrease in the normal outflow of fluid through the aqueous veins.

A recent finding of a high increase in the soluable fibrinogen in the ophthalmic anterior chamber aqueous fluids in early buphthalmia has led us to our present interest in the immunohistochemical demonstrations of an insoluable fibrin as to be found in the buphthalmic eye in the stroma tissues of the ciliary body, iris, trabecular meshwork, and particularly in the outflow aqueous channels, noted most in the aqueous veins. These are the findings by Doctor Kwok Wai Lam.

Ladies and gentlemen, this has been a significant paper this morning, particularly since it relates to the sight saving program.

DR A. EDWARD MAUMENEE. I too would like to congratulate Doctor Shields on this very excellent paper that he has just presented. I would like to make several observations. A number of years ago I went to the Armed Forces Institute of Pathology and looked at about 125 eyes with various stages of congenital glaucoma. In spite of the fact that the limbal area might migrate as much as 5 mm in front of Schwalbe's line, the trabecular meshwork and the insertion of the iris into the scleral spur or into the trabecular meshwork remains the same. In everyone of those patients there was an anterior insertion of the longitudinal muscle of the ciliary body. I then asked all of my friends in the Verhoeff Society if they had any eyes with congenital glaucoma in patients who died while they were undergoing operation or died immediately afterwards. I was able to collect about 24 cases of this type. Barkan's membrane is something observed with the gonioscope. He never saw it histologically. He did not look at children who had strabismus or who had retrolental fibroplasia with the gonioscope. They have the same picture of the trabecular meshwork as do those children with congenital glaucoma.

Next, one of the strongest evidence against a Barkan's membrane is that in all 24 cases of mine, the trabecular meshwork was filled with red blood cells even though one patient only had an iridectomy. If Barkan's membrane was porous enough to allow red blood cells to pass through the trabecular meshwork, certainly aqueous could get through. Doctor Crawford mentioned Alvarado's work. He has put in a request for grant funds on a committee I happen to be on, so I had a chance to review his entire work and it is true—he has found a couple of patients as you have mentioned that look like it might be a Barkan's membrane but the

majority of his patients didn't. He thinks some abnormal mucopolysaccharide in the trabecular meshwork causes the trouble in congenital glaucoma. How does goniotomy work? I do not know. The only thing I can suggest is, as Doctor Schaffer pointed out, if you make the incision near Schwalbe's line, it works quite efficiently. Thus it relaxes the trabecular meshwork so that it can open up a little bit better when the longitudinal muscle pulls on the meshwork.

Dr George L. Spaeth. Two questions for Doctor Shields. First, Doctor Crawford mentioned that he encouraged people to use this technique for obtaining specimens. Tripathi and I published a paper about 5 years ago on this particular method of obtaining specimens and I stopped doing it because in my hands it complicated the surgical technique. If you go further back, you get more bleeding and I think you jeopardize the results of the surgery. I would like to ask if you agree with that.

The second point has to do with the normal high frequency with which anterior iris insertion occur in black patients and in young brown-eyed patients. This seems to be routine. Is this your experience?

Dr Angelos Dellaporta. Is Doctor Maumenee here? Yes, Doctor Maumenee, 10 years ago when I wrote a paper on gonioscopy I questioned Doctor Ferguson, Jr, a close associate of Otto Barkan, about the trabecular membrane and what Barkan believed before he died. He told me that Barkan no longer believed there was a membrane over the trabecular meshwork. I mean, originally, he thought that it was there and then he retracted that and said no, he didn't believe there was a membrane there. I don't know whether Doctor Ferguson ever talked to you about that. According to Doctor Ferguson, Barkan never published this change of mind.

Doctor A. Edward Maumenee: Would you mind publishing that letter Doctor Dellaporta so that we may record this fact in the literature.

Doctor Angelos Dellaporta: I had mentioned this in a paper I once gave you about Historical Notes on Gonioscopy. It was published about 10 years ago in the *Survey of Ophthalmology* and the whole story is there.

Dr Bruce Shields. I would like to thank Doctor Crawford and all the others for their very pertinent and kind observations. I am especially humble and grateful for the kind comments of giants like Doctor Sheppard and Doctor Maumenee. As I have said before, I think this is one of the absolutely marvelous things about this society—to be able to hear the words of wisdom and the tremendous historical perspective of the men and the women who have led the changes in our profession.

Doctor Crawford certainly raises the most pertinent question about this study, and I can only agree with him. That is, what is the actual role of this high insertion of the anterior uveal tissue in the development of glaucoma? I am sure that it does not lead to the glaucoma in all cases. For one thing, we do know that there are cases in which one can find this gonioscopic appearance without the presence of

glaucoma. There are other cases, as has been pointed out, in which there is the high insertion but concomitant developmental abnormalities, such as failure of the trabecular meshwork or Schlemm's canal to develop. And yet there are still other cases in which there seems to be multiple secondary mechanisms, such as neurofibromatosis, the Sturge-Weber syndrome, and aniridia. So it is a very complex situation, and I am not suggesting that this particular common developmental anomaly is the mechanism of glaucoma in all cases. On the other hand, I think there is some clinical evidence that, at least in some cases, it does play a role, such as the response to miotic therapy and possibly to goniotomy. So I think we have to keep in mind that this is only one of many common developmental pathways and the pathogenesis of developmental glaucomas certainly needs more study.

Doctor Spaeth raised two questions. One is very pertinent to the question of ethics in medicine and research these days. It is true that the surgical technique used in this study is more difficult than standard trabeculectomy, and certainly when one enters the ciliary body, as you often do with this technique, the bleeding is almost invariably worse. The bipolar intraocular cautery unit has been very helpful in controlling this bleeding when it does occur. So far I have not felt that the outcome in these cases has been worse than might have been encountered otherwise. But it does raise the ethical point of how far does one go in the quest for scientific information; balancing that against the safety of the patient.

If I understood Doctor Spaeth's second question, he was asking about the racial influence, or the difference in the pigmentation of the iris in relation to the apparent level of insertion. I don't know the answer to that. Yet, as I was sitting there thinking about the question, it occurred to me that we do know that the uveal meshwork is contiguous from the iris stroma. We just simply don't see it normally because it is very thin and transparent. But in the eyes with heavy pigmentation in the stroma, it might tend to give the appearance of a high insertion or maybe these patients might have more iris process.

Again, I would like to thank very much the Society and all the discussants.