PROGRESSIVE CHANGES IN THE ANGLE IN CONGENITAL ANIRIDIA, WITH DEVELOPMENT OF GLAUCOMA

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INTRODUCTION

WE HAVE EXAMINED 60 CHILDREN AND A SMALL NUMBER OF ADULTS WITH CONGENital aniridia during the last 18 years. Glaucoma occurred in 31. In 14 of the children whom we repeatedly examined gonioscopically during this period we observed an increasing abnormality of the anatomy of their irido-corneal angles. In 9 of these patients, increasing abnormality of the angles and worsening of glaucoma were clearly correlated. In most eyes the peripheral stump of iris gradually extended anteriorly to cover the filtration portion of the trabecular meshwork. Typically, later in childhood as the filtration area of the trabecular meshwork became covered by extension of abnormal iris tissue forward on to the trabecular meshwork the intraocular pressures became significantly elevated. In the serially studied aniridic patients, as well as in others who have not been examined so repeatedly, the severity of the glaucoma as a rule has been related to the condition of the angle. We have summarized the findings relative to glaucoma in these patients, and their responses to ordinary medical and surgical treatment. We have also begun to explore the possibility that prophylactic surgery in infancy may prevent the progression of changes in the angles which lead to glaucoma.

In the past it has been well recognized that there are gonioscopic differences between non-glaucomatous aniridic eyes (with open angles) and glaucomatous aniridic eyes (with angles obstructed or abnormally lined by tissue). These differences have been well described in small numbers of cases by Barkan[1] (1953), Blanck[2] (1971), Higgitt[3] (1956), Lewallen[4] (1958), and Shaffer and Weiss[5] (1970), but it was not noted that the configuration of these angles could be seen to change with time. A

comprehensive search of the literature indicates that the first documentation of progressive change in the angles associated with development of glaucoma after infancy in congenital aniridia was published in Chandler and Grant's[6] book on glaucoma in 1965. Sampaolesi[7] corroborated the fundamental aspects of these findings in 1968. The present report extends the observations recorded by Chandler and Grant.

It seems surprising to us that so little attention has been given to trying to account for the fact that glaucoma is unusual and buphthalmos rare in infants with congenital aniridia, and that glaucoma is commonly encountered later in childhood. Only occasional specific attention has been given to this delayed onset, although it has been long recognized clinically. In 1898, Foster[8] commented that in several of the 158 cases of aniridia (or "irideremia") that had been reported from 1766 to 1898 there was good reason to believe that when glaucoma developed it appeared several years after birth, although the aniridia was undoubtedly congenital. The late onset of glaucoma was first accurately established through systematic periodic observations by Hirschberg[9] in 1888 in a boy whom he periodically examined from age 4 months to 10 years, utilizing the limited clinical methods available at that time (no slit-lamp biomicroscopy, no gonioscopy, no tonometry), noting that at age 10 years the nerveheads were excavated and the ocular tensions were elevated for the first time.

Reports on pathology of fixed and sectioned eyes that have had glaucoma in association with congenital aniridia have satisfactorily accounted for the glaucoma on the basis of obstruction of portions of the angle by the iris stump, but so far they have provided no recognized clues relating to progression of changes in the angle or delayed onset of glaucoma. Some pathologists have raised questions about this. For instance, Lembeck in 1890, after reporting on the histopathology of an eye removed from an 8 year old boy with congenital aniridia because the eye had been made blind and painful by glaucoma, indicated that it was clear to him that the glaucoma was caused by the stump of iris closing the angle in the whole circumference, and obstructing aqueous outflow, but he was puzzled that the eye had gone some years before showing symptoms of glaucoma. He wondered whether intervening inflammation might have had an influence, but made no suggestion that the anatomic findings were other than congenitally established. In 1949, in discussing a report by Callahan[10] on histopathology in congenital aniridia with glaucoma, D. G. Cogan again raised the question why glaucoma should develop late in childhood in aniridia, when presumably it was based on a congenital defect, and he asked specifically whether in an enucleated specimen there was any evidence of a progressive lesion which had occurred

postnatally. This searching question received a negative reply, and apparently failed to stimulate further inquiry into the problem by histopathologists.

SUMMARY OF CLINICAL FINDINGS

All of the patients considered in this study had congenital aniridia which would be considered complete by ordinary slit-lamp biomicroscopy, but by gonioscopy in all eyes a stump of iris was identified in the periphery. Gonioscopy was performed by means of a Koeppe gonioscopy lens, a binocular microscope with 12 times magnification, and usually a Barkan gonio-illuminator, but in a few instances with Zeiss slit-lamp illumination. In this study there were no cases of so-called partial aniridia or coloboma of the iris.

Before recording the findings in the 31 glaucomatous patients who were repeatedly examined, we can record that in a separate group of 25 congenitally aniridic patients in whom there was no evidence of glaucoma the gonioscopic findings were different from those in the glaucomatous patients. In this group there were 10 patients whom we believed to be nonglaucomatous and not likely to develop glaucoma, including two adults, ages 39 and 56 years, and three adolescents, ages 10, 13, and 13 years. The angles in the non-glaucomatous adults and adolescents were notably free from attachments of iris stroma to trabecular meshwork in all or nearly all of the circumference. The iris stump in these patients was in the normal plane of the iris, perpendicular to the axis of the eye, with no tilting, no forward migration of the periphery of the iris, and little or no ectropion of the "pupillary" border of the stump. In 11 other patients with congenital aniridia without glaucoma gonioscopy revealed only beginning blockage of the trabecular meshwork. This group was made up of young children who had not yet developed a trabecular meshwork blockage, and adolescents with only minimal blockage and a greater than usual amount of iris leaf present, suggesting a possible milder and less progressive disease.

In general, both glaucomatous and nonglaucomatous eyes had the familiar characteristics associated with congential aniridia. The corneas were not enlarged. The iris stump, which was always present, was found in infancy in the same plane as a normal iris, perpendicular to the axis of the eye, and the ciliary processes were regularly visible posterior to the stump, with trabecular meshwork anterior to it. The pupillary edge of the stump commonly showed separation of the anterior stromal and posterior pigment layers.

In the glaucomatous eyes there were varied forms and stages of change in the angles that were distinctive gonioscopically. Most commonly the angle wall appeared to have become covered by an abnormal extension anteriorly from the anterior surface of the iris stump. The stroma of the iris seemed to extend forward, initially as synechia-like attachments to the trabecular meshwork, to be followed by a more homogeneous sheet extending from the stump forward against the trabecular meshwork, or by the forward movement of the periphery of the stump itself. Less commonly, the angle appeared to remain relatively open until adolescence, but then to become closed by anterior rotation or folding forward of the full thickness of the iris leaf.

The most common course of progression which we have observed has been as follows. The eyes of aniridic infants or very young children who were destined to develop glaucoma most often had irregular fine attachments of the iris stroma to varying distance onto the angle wall, somewhat resembling synechias, in the form of saw-teeth or ridges stretching from the periphery of the stromal stump across the ciliary band and scleral spur to the trabecular meshwork. These scattered attachments of iris stroma to angle wall commonly contained loops of radially disposed iris blood vessels clearly visible by gonioscopy. In eyes in which the iris stroma remained unpigmented later in childhood, the tissue attached to the angle wall also remained unpigmented, whereas in those eyes in which the iris stroma became pigmented, the attachments onto the angle walls also became pigmented. The blood vessels in the iris attachments to the trabecular meshwork, which could be seen early when the stroma was unpigmented, became hidden when the iris stroma became pigmented. In some eyes, even without pigmentation, these blood vessels later were gradually lost from view. Portions of the ciliary band and scleral spur commonly became hidden. The attachments to the angle wall, in addition to becoming either more dense or pigmented, broadened or migrated forward so that they increasingly obscured greater portions of the ciliary band, scleral spur, and posterior trabecular meshwork work that had previously been visible. This apparent forward migration of the iris stroma frequently resulted in a tilting of the plane of the anterior surface of the iris progressively from the normal iris plane perpendicular to the axis of the eye gradually to a new and abnormal plane at right angles to the original. There appeared by gonioscopy to be a vertical wall of iris stroma parallel to the axis of the eye, in place of its original horizontal surface. The pupillary edge of the stump commonly also began to curl forward. The whole thickness of the iris, including the posterior pigment layer and stroma in some cases folded forward to close portions of the angle. In

some severe cases this left essentially nothing visible but a vertical wall of posterior pigment layer of the iris turned forward, and the ciliary processes just posterior to it. Often one portion of the circumference was found at a different stage of progression than other portions, the superior angle tending to be more advanced than the inferior angle. One eye of a patient frequently underwent these changes at a different rate than the other eye.

In a small proportion of congenitally aniridic children who developed glaucoma the iris stump remained until a late stage as a small shelf in the normal plane of the iris and the angle appeared to remain grossly open with a peripheral sulcus, but a thin layer of amorphous, homogeneous and seemingly avascular tissue covered the angle wall, overlying and closely applied to the trabecular meshwork to varying distances. This layer was variably pigmented. The homogeneous tissue in the angle simply appeared to increase in density and to become more closely applied to the trabecular meshwork as the glaucoma worsened. The stroma of the stump of iris in these eyes appeared to change little as glaucoma became worse, but frequently separated and exposed the posterior pigment epithelium at its inner pupillary border.

To give an idea of the relative frequency of these varied changes, in eleven eyes that had the characteristic early findings of iris stump in the normal plane with early sawtooth or ridged attachments of stroma to angle wall, we have observed the following changes as the angle worsened and the glaucoma became more severe. The density of the tissue on the trabecular meshwork was noted to increase in 4 of the 11 eyes. The iris stump was noted to gradually tilt as the periphery of the stromal attachment moved forward in 7 of the 11 eyes. The pupillary border, both stroma and pigment layer, curled or rolled forward in 5 of the 11 eyes.

It is very rare to find all these changes in the angle already developed to their end stage at birth. In only one of 63 patients with congenital aniridia have we seen early in infancy the full thickness of iris stump turned forward, completely flat against the angle wall, accompanied by severe glaucoma.

RESULTS OF MEDICAL TREATMENT

Among the 31 patients with congenital aniridia complicated by glaucoma, medical treatment proved to be helpful in 12. Miotic eyedrops were effective in reducing intraocular pressure in all of these. Epinephrine eyedrops were also shown to be effective in 2 of these patients and might have been effective in more, but epinephrine was specifically evaluated only in the two mentioned. For adequate control of the glaucoma, car-

bonic anhydrase inhibitors were necessary in 6 of 12 patients who were responsive to medical treatment. In each instance in which carbonic anhydrase inhibitors were utilized, they clearly had a beneficial effect on the pressure.

RESULTS OF SURGICAL TREATMENT

Surgery was employed in 22 patients with congenital aniridia. Goniosurgery was performed in 15 patients (18 eyes), from one to three times on each eye. In 6 of these patients (6 eyes) goniotomy was done for prophylaxis of glaucoma. In all instances the goniotomies were performed internally, except in one eye in which trabeculotomy *ab externo* was done. Goniotomy consisted of dissecting or stripping back the tissues of the iris stump from their abnormal forward attachments overlying the trabecular meshwork.

Goniotomy was undertaken using the standard Barkan operating lens and contemporary Barkan knife. Light was supplied by a head light or hand-held focused bulb. Entry into the anterior chamber was through paralimbal clear cornea. In each instance the tip of the operating knife was used as a paddle to strip the abnormal iris tissue off its position on the trabecular meshwork. In each instance this iris tissue was found to strip off easily as the tip of the knife was used to pull the tissue posteriorly. Usually the knife was removed after producing a cleft of 2 to 4 hours in length. Due consideration was given to the exposed anterior lens surface, and in no instance was a lens damaged. Following removal of the knife, blood appeared in the anterior chamber in moderate amount. Irrigation of the anterior chamber was often necessary. In most instances a corneal suture was not required to obtain formation of the anteror chamber. In a few instances the goniotomies were followed by goniopuncture.

No cure could be claimed for any of these goniosurgical procedures, but nine eyes seemed to show greater responsiveness to medical treatment after the goniosurgery. There was a persistent cleared area of angle visible gonioscopically. Only one serious complication resulted from the goniosurgery; this was an instance of severe corneal edema, apparently resulting from inadvertent stripping of Descemet's membrane from the cornea by the one trabeculotomy *ab externo*.

In spite of disappointing results in the use of goniotomy to correct an elevation of the intraocular pressure in aniridia, this operation has been the one performed most frequently on our patients. The use of this operation for aniridia glaucoma was reported by Callahan,[10] who noted poor results in two teen-aged patients and speculated that this lack of

better results might be due to obliteration of Schlemm's Canal secondary to chronic glaucoma. Blake reviewed the combined experience of 87 ophthalmic surgeons with aniridia glaucoma.[11] Goniotomy was reported to have aided control in 10 of 11 cases but no convincing evidence was included to support this favorable experience with goniotomy for aniridia glaucoma. Barkan also reported the use of goniotomy in aniridia glaucoma, describing favorable initial results in one patient.[1] He attributed his success to the stripping of iris tissue off the blocked trabecular meshwork at a time in the course of the disease when the underlying normal angle structures were still capable of function. Favorable results have been reported in approximately one-third of the eyes treated by more extensive goniotomy procedures by Bietti,[12] and Paufique has reported one successful result from trabeculotomy *ab externo*.[13]

In recognition of the importance of avoiding chronic glaucoma and its secondary effects on ocular structures, the lack of success of surgery in established aniridia glaucoma, and the stages of the evolution of the blockage of the trabecular meshwork in aniridia by the extension of the iris anteriorly, it was suggested by one of us (WMG) that early "prophylactic" surgery be done in congenital aniridia.[6] Over the last seven years nine prophylactic goniotomy operations have been done on one eye of each of six children. In each patient the operative sites have remained open, with unobstructed view of the trabecular meshwork. Each operative procedure was performed in the same fashion as described for therapeutic goniotomy surgery. None of the eyes have developed glaucoma, but the follow-up for most of these cases is too short to be conclusive. Glaucoma has occurred in the unoperated eye in only one of these patients.

Eleven filtering operations were performed on seven patients (nine eyes) with aniridia and glaucoma, and were unsuccessful. Other surgical treatments that were considered unsuccessful included cyclodialysis in four patients (four eyes), and penetrating cyclodiathermy in three patients (three eyes). Cyclodiathermy was followed by phthisis in one eye. Cyclocryotreatment in two patients (two eyes) appeared helpful to one eye, but caused hypotony in the other. No cure could be claimed for any of these surgical treatments. Some slight or transient benefit could be attributed only to the goniotomies and in one instance to cyclocryotreatment. Operations on cataracts in six of the patients (eight eyes), including intracapsular extractions, extracapsular extractions, aspirations, and discissions, clearly had no beneficial effect on the glaucoma, although they improved the vision.

ILLUSTRATIVE CASES

CASE 1

A boy with congenital aniridia at age 2 months had applanation tensions of 20 in both eyes. Each iris stump was in a normal plane except for areas nasally in the right eye and both nasally and temporally in the left eye where its anterior surface sloped forward peripherally and attached to the angle wall just anterior to the scleral spur. The scleral spur could be identified in at least half of the circumference in each eye.

By age 8 months, applanation tensions were 22 in both eyes, but the anterior surface of both iris stumps had changed, presenting in the right eye nasally a surface nearly parallel to the visual axis, with the peripheral border of the stump attached irregularly to mid-portion of the filtration area, and temporally a moderately tilted tissue surface, still permitting glimpses of scleral spur. Nasally, in the left eye the anterior surface of the iris stump had become tilted less than in the right eye, mostly sparing the filtration area.

By 19 months, applanation tensions were in the mid-twenties. Iris stromal tissue appeared to have advanced further on the trabecular meshwork with finger-like processes extended further forward overlying and partially obscuring pre-existing uveal meshwork, which was distinguished by darker pigmentation.

By age 3 years, applanation tensions were 27 in both eyes. The stromal tissue on the surface of the stump in the right eye had advanced on the angle wall so that the surface of the stump was parallel to the axis nasally, at 45 degrees temporally. In the left eye the changes were similar but less marked. There was still very little ectropion uveae at the pupillary margin in either eye.

By age 39 months, applanation tensions were 40 in the right and 28 in the left eye. In the right eye the iris stroma swept forward covering nearly the whole wall of the angle nasally, and irregularly overlying the filtration area temporally. In the left eye the forward attachments of stromal tissue varied from a third to a half the distance from scleral spur to Schwalbe's line, tending to be less advanced temporally. The posterior pigment layer of the stump remained visible only as a narrow line of blackish brown at the pupillary margin in each eye, easily distinguished from the iris stroma, which was distinctively lighter brown. The pupillary margin of the stroma showed irregular forward curling.

At age 4 years, on echothiophate iodide 0.06% twice a day in the right eye and epinephrine twice a day in the both eyes, applanation tensions were 21 in both eyes.

Comment — When this child with aniridia was first examined in infancy the angles were impressively uncompromised except for small areas of early change in each eye. Progressively over his first 4 years of life the trabecular meshwork of each eye became more obscured from view by extension of iris stroma forward and by simultaneous circumferential extension. By his third year, significant elevation of intraocular pressure

occurred which was responsive to medical therapy. The character of the angle change, consisting of the tilting of the iris stroma anteriorly, was typical of what may be expected with progressive angle changes during early childhood. In this case there were no specific findings to suggest a "sliding" of the iris forward but rather one of extension of stroma on to the filtering areas to produce blockage and glaucoma without separation from its posterior pigment epithelium.

CASE 2

A girl with congenital aniridia but no family history of aniridia, had tensions of 22 on the right and 20 on the left when first seen at age 5 months. The iris stump in each eye was in a normal plane, but the iris stroma extended forward across the ciliary band and scleral spur in delicate tents and fine networks that, particularly on the temporal side, were interspersed with openings through which could be seen scleral spur, ciliary band, and occasionally blood in Schlemm's canal.

At age 2½ years, under no treatment, applanation tensions were 16 and 15, and the iris stump in each eye was still in its normal plane. However, brown iris stromal tissue on the angle wall of each eye formed a face parallel to the axis of the eye, and this tissue seemed more dense and more closely applied to the trabecular meshwork than it did earlier. Prophylactic goniotomy was performed on the left eye, detaching the iris stromal tissue from the trabecular meshwork nasally, causing it to drop back and expose the full width of trabecular meshwork and a little ciliary band in about 2 hours of the circumference.

At age 4 years, tensions were approximately 20 in both eyes, but the angles showed additional change. Whereas previously the iris stump in each eye formed a shelf perpendicular to the axis of the eye, now only the posterior pigment layer of the iris and the ciliary processes remained in this plane. The stroma of the iris appeared to have moved anteriorly parallel to the axis of the eye, attached irregularly above Schlemm's canal. However, it still appeared to have holes in it, and temporally the forward attachments were still finger-like and tenuous with small spaces in between. Further prophylactic goniotomy was performed in the left eye, in the lower nasal quadrant, pulling iris stromal tissue off the trabecular meshwork with the tip of the goniotomy knife over an additional 2 hours of the circumference.

At 8½ years, without medication, applanation tensions were 33 in the unoperated right eye, 24 in the left, and tonographic C values were 0.07 and 0.12. In the right eye, homogeneous dense brown iris stromal tissue covered approximately three-quarters of the width of the trabecular meshwork nasally, while temporally the porous-appearing stroma extended irregularly to about the mid-portion of the trabecular meshwork. In the left eye the findings were similar except that in the lower nasal quadrant at the site of previous goniosurgery, there were intervals of angle relatively free of iris stroma, and temporally the stroma extended on the trabecular meshwork more irregularly and delicately than in the right eye. Treatment with pilocarpine was started in both eyes.

By age 9 years, the tension of the right eye had increased to 40 despite treatment with echothiophate, epinephrine, and acetazaolamide. In the left eye the tension remained near normal. The angle in the right eye had changed further. The iris stromal tissue in this eye appeared dense, brown, and homogeneous, and now flattened against the angle wall, covering the filtration area of the trabecular meshwork in the whole circumference, In the left eye, in the lower nasal quadrant at the site of previous prophylactic goniosurgery, a sulcus remained between the iris stump and the angle wall. Here the trabecular meshwork was not grossly covered by iris stroma, though the untouched upper nasal angle was covered by tissue like that in the right eye. Temporally the iris stroma attached irregularly to trabecular meshwork anterior to the scleral spur, forming a surface tilted at about 45 degrees.

Comment — The progression of the angle abnormality from infancy through childhood, with the eventual development of glaucoma exemplifies the dynamic aspect of aniridia glaucoma. Initially in infancy the patient's angle featured only delicate stromal tenting across the scleral spur. By age 2 years, definite evidence of an extension of stroma anteriorly was present. At 4 years of age the iris stroma appeared to have moved over its posterior pigment epithelium towards the iris root and up on the face of the trabecular meshwork. By age 8 years, glaucoma was present in the right eye with the development of a more consolidated trabecular block. At 9 years of age this abnormal tissue appeared to have flattened against the angle, as is typical of the later stage of this process. The changes in the angles of this child's eyes were noted to have occurred asymmetrically and to be variable around the circumference of each eye. The effect of prophylactic goniotomy on the left eye has been one of angle-sparing and possible benefit in control of the intraocular pressure.

CASE 3

A boy with aniridia and a history of tensions of 30 on the right and 20 on the left at age 5 months, was receiving 1% pilocarpine once a day when first seen in consultation at age 10 months. Under this treatment his tensions were normal. The iris stump was in normal position in each eye, but in the right eye irregular extensions of thin lightly pigmented iris stroma, including visible normal-appearing vessels, irregularly covered the filtration portion of the trabecular meshwork, with gaps between the extensions. In these gaps could be seen normal scleral spur, ciliary band, and blood in Schlemm's canal. In the left eye there were similar extensions of iris stroma onto the angle wall in most of the circumference, but most reached just to the scleral spur and appeared to leave most of the filtration portion of the trabecular meshwork uncovered.

By age 4 years the pressure had increased to 40 in the right eye in spite of treatment with acetazolamide in addition to pilocarpine. The angle had changed

in appearance. The extensions of iris stroma over the trabecular meshwork had become pigmented and more homogeneous, obscuring all underlying structures and reaching nearly to Schwalbe's line. In a small fraction of the circumference the stump of the iris had rotated forward and grossly closed the angle. Between the age of 5 and 6 years, goniotomy was performed twice on the right eye, clearing iris stromal tissue from the angle wall in a portion of the circumference. At age 9 years the tension in the right eye was maintained between 25 and 30 under treatment with epinephrine and methazolamide. In the areas where goniosurgery had been performed the angle remained grossly opened.

The boy's left eye at age 4 years still had normal pressure. The angle showed changes that were not as marked as in the right eye at that age. The extensions of iris stromal tissue on the angle wall were pigmented and hid most of the angle structures nasally, but temporally the tissue overlying trabecular meshwork appeared porous, intermittently providing views of trabecular meshwork, scleral spur, and ciliary band. Except for slight curling forward of the pupillary margin, the iris stump in the left eye was still in its normal plane.

By age 9 years, the tension in the left eye had increased to 40 inspite of treatment with pilocarpine, epinephrine and methazolamide, and most of the angle had become closed by complete circumferential blockage of the trabecular meshwork by the anterior extension of the iris which was now homogeneous and well pigmented. The iris leaf itself was turned forward moderately with these other changes.

Comment — This boy's clinical history is typical of many aniridia patients. A mild pressure elevation was found early in life and yielded easily to medical therapy. At that time the angles showed early changes, characterized by only discrete extensions of iris stroma anteriorly. The angle abnormality progressed and a confluent, pigmented, and dense layer covered the previously visible angle structures, concomitant with worsening of his glaucoma. The rate of progression was different in the two eyes, which is common. Goniotomies performed on one eye resulted in preservation of the angle at the operated sites, and there was better control of the glaucoma in this eye, probably as a result of the surgery.

CASE 4

A girl with congenital aniridia, already under treatment with echothiophate drops in both eyes when seen in consultation at age 8 years, had tension of 13 on the right and 52 on the left. The right disc was normal, but the left was totally cupped and atrophic. In the angle of the right eye the stroma of the iris stump, including its vessels, extended on to the trabecular meshwork nearly up to Schwalbe's line nasally, but in the temporal half of the circumference the stromal tissue appeared only to bridge the angle irregularly, and there were many apertures through which ciliary band and scleral spur could be seen. In the left eye the entire iris stump was turned forward and covered the trabecular meshwork nearly to

Schwalbe's line in the whole circumference. During the next three years the left eye underwent several operations.

During the next 3 years the tension in the right eye rose from the teens to 50 and 60, despite intensive medical treatment. This increase of severity of the glaucoma in the left eye was associated with a striking change in the appearance of the angle. Whereas previously only the iris stroma had extended unevenly onto the trabecular meshwork, now both layers of the stump folded forward, completely closing the angle nasally and most of the angle temporally. Several operations were performed, but did not relieve the glaucoma.

Comment — In this adolescent aniridia patient a significant elevation of intraocular pressure occurred in the right eye at least three years after its development in the left eye. Initially when examined, the temporal half of the angle of the right was still unobstructed except for the presence of fine stromal processes extending up on the trabecular meshwork. Glaucoma then occurred in this eye with progression of the angle abnormality. The temporal iris leaf was pulled anteriorly, parallel to the visual axis and into a position to obstruct the angle. This type of angle obstruction is usually seen late in childhood, and we suspect is caused by the action of the abnormal iris stromal attachments bridging between the iris leaf and the trabecular meshwork.

CASE 5

A boy with congenital aniridia at age 3 years had tensions of 29 on the right and 26 on the left. In his angles dark brown iris stromal tissue extended from the iris stump on to the trabecular meshwork, hiding the scleral spur and irregularly covering the filtration area in both eyes. From age 3 years to 9.5 years tensions were maintained in the low 30's in both eyes, but this required progressively more intensive medical treatment, including pilocarpine, demecarium, epinephrine, and acetazolamide. During these years the tissue overlying the filtration portion of the trabecular meshwork appeared to have become progressively more thick and dense, more so in the left eye than the right, and with more extensive covering of the angle in the left. This tissue was not lacy like uveal meshwork, but was brown and homogeneous without visible blood vessels, and resembled the stroma of iris stump, with which it was continuous. The stump itself remained in approximately the normal plane, except for a slight forward rolling or ectropion of the pigmented layer at the pupillary margin. A small peripheral sulcus remained in most of the circumference.

Goniosurgery was performed on the left eye, peeling the pigmented tissue back from the trabecular meshwork in approximately one-third of the circumference. After this the tension was lower but not normal. Further stripping of brown tissue from the angle wall of the left eye, combined with trabeculotomy into Schlemm's canal in about one hour of the circumference, was also done but was of no lasting benefit in the control of the glaucoma. On one occasion at age 10 years, when

medical treatment was interrupted, the tensions rose to 27 on the right and 55 on the left.

By age 21 years, the left eye had become phthisical after more than ten years of medical treatment and antiglaucoma operations, including trephining, penetrating cyclodiathermies, and cyclocryo treatments in addition to the goniosurgery already described. In portions of the angle where goniosurgery had been performed the brown iris stromal tissue had remained reflected away from the trabecular wall, but what was exposed was cobwebby, grayish tissue unlike normal trabecular meshwork. Trephine sites were plugged by vitreous, and the ciliary processes had nearly disappeared following the cyclodiathermy and cyclocryo treatments.

The right eye continued to have tensions in the 20's under treatment with echothiophate, epinephrine and acetazolamide or methazolamide. In this eye the iris stump had curled forward on itself so that only the posterior pigment layer of the stump was visible, but the angle wall could still be seen through a narrow space separating the curled stump from the wall. Brown homogeneous tissue covered much of the trabecular meshwork temporally, but only irregularly covered the nasal angle.

Comment — When first examined at age 3 years the angle of each eye appeared already covered by an abnormal tissue that seemed to be continuous with stroma of the iris stump. The difference in involvement of the filtration portion of the trabecular meshwork with a more extensive and a thicker denser layer in the left eye seems to have been associated with considerable difference in the severity of the glaucoma. This child's clinical problem illustrates again a correlation between the angle anomaly and the severity of the glaucoma, as well as significant asymmetry of involvement. In this case it was a qualitative change in the character of the tissue blocking the angle rather than the extent of its involvement that was correlated with the progression of the glaucoma.

Medical therapy for the glaucoma initially proved to be of value in both eyes but by 10 years of age the more severely affected left eye could no longer be controlled in this way. Goniosurgery at that time exposed an angle wall that appeared abnormal and it did not reduce the intraocular pressure. This disappointing result of therapeutic goniosurgery appears to us to be common after the development of the advanced angle abnormality. Other anti-glaucoma procedures also proved of no value, which has been our experience with conventional glaucoma operations in aniridia glaucoma. Admittedly we have not tried all the types of operations that are mentioned in the literature.

It has been this inability to maintain control of aniridia glaucoma medically, reinforced by the frustration of surgical failures once the angle

abnormality has become a visible reality, that has encouraged us to attempt to prevent worsening of the angle anomaly and blockage of the trabecular meshwork by prophylactic surgery.

DISCUSSION

We would like to understand the fundamental mechanism that is responsible for the progressive changes in the angle in aniridia that we have recognized clinically as the cause of the development of glaucoma in aniridia. We have found few clues in what has been published on the histopathology of aniridia. In 1871 Pagenstecher published one paragraph describing his findings in one eye in which he observed a small amount of iris tissue extending forward over the trabecular meshwork.[14] The tissue contained pigment and vessels. It was thinner toward its anterior end, and this extended between layers of Descemet's membrane and was firmly united with the cornea. Where Descemet's membrane enveloped the iris stump the membrane split like two tines of a fork. The portion of Descemet's membrane that was nearest the anterior chamber extended back to the ciliary body, and had corneal endothelium on it surface. The other portion of Descemet's membrane, that was on the corneal side of the tongue of iris tissue, disappeared into the tissues of the trabecular meshwork. Pagenstecher did not speculate on the significance of these findings, or whether they were related to glaucoma. In 1886 DeBenedetti[15] also described an iris stump apparently grown in between lamellae of Descemet's membrane in a congenitally aniridic glaucomatous eye, and in 1890 Lembeck[16] reported in detail on the histopathology of the eye of an 8-year-old boy that had been enucleated because it was blind and painful from glaucoma associated with bilateral congenital aniridia. In this eye the iris stump appeared to occlude the angle in the whole circumference and to be united with the cornea in essentially the same manner as in DeBenedetti's and Pagenstecher's cases, with Descemet's membrane peripherally appearing split into two sheets, one inserting in fine lamellae into a compressed trabecular meshwork and into the attached stromal portion of the iris stump, while the other sheet extended onto the posterior pigment layer of the stump of iris, in places as far as ciliary body. The surface toward the anterior chamber was covered by endothelium like that of the cornea. Despite these abnormalities of the angle, Schlemm's canal was still present in some areas. Lembeck assumed that these abnormalities had been congenitally established, though glaucoma had not appeared until the patient was several years old. Hogan and Zimmerman in 1962 published a picture of a similar angle obliterated by

the iris stump, showing also a forked extension of Descemet's membrane.[17]

In 1891 Rindfleisch described the eye of a 57 year old woman in which the optic nervehead was normal, and therefore presumably not glaucomatous.[18] He pointed out that the angle differed from the angles of glaucomatous aniridic eyes. Though the iris stump lay close to the periphery of the cornea in this non-glaucomatous eye, and the trabecular meshwork appeared flattened, there was a space between the stump and the periphery of the cornea, and there was no extension of corneal endothelium or Descemet's membrane onto the stump. The iris was not enveloped by an extension of Descemet's membrane as in the previously reported glaucomatous eyes.

In 1891 Treacher Collins described briefly the pathology of aniridia complicated by glaucoma, and called attention to blockage of the angle by the iris.[19] Further observations by Collins on histopathology of aniridia were recorded in 1893 describing the eyes of a 3-year-old child who had died from a severe burn, but believed not to have had glaucoma.[20] Collins stated that in some sections "a delicate adhesion passes between the extreme root of the iris and the ligamentum pectinatum," but he concluded "this by no means blocks the filtration area." At one meridian a more pronounced band of adhesion from the root of the iris to the trabecular meshwork was present. Collins postulated with regard to the possible basis for glaucoma in congenital aniridia, that in the normal development of the human eye in embryo the lens and cornea were together except for an anterior fibrovascular sheet between them, and that the iris in congenital aniridia was prevented from growing due to some mechanical interference between the embryonic cornea and lens. The adhesions which he had seen between the root of the iris stump and the trabecular meshwork he postulated were due to imperfect separation of the anterior fibrovascular sheet from the cornea, and he speculated that congenitally aniridic eyes were predisposed to potential glaucoma through blockage of the surface of the trabecular meshwork by a sufficient rudimentary iris stump if rotated anteriorly, and the presence of adhesions between the iris and trabecular meshwork.

In 1907 Van Duyse[21] reported on the postmortem microscopic pathology of the eyes of a 9-month-old non-glaucomatous aniridic infant, showing persistent continuity between the iris and angle wall in portions of the circumference. Other reports on the histopathology of congenitally aniridic eyes from children and adults, with and without glaucoma, by Hopf[22] in 1900, Bergmeister[23] in 1904, Seefelder[24] in 1909, Holm[25] in 1921, and Sanders (as quoted by Callahan)[10] in 1949, have added more

static details, but have provided no notable perception of the dynamic processes that we recognize clinically. Parsons in 1904 did speculate on the possibility of progressive changes in the angles that might explain the glaucoma, postulating without evidence, that some sort of inflammatory process might be to blame for blocking the filtration meshwork.[26]

The concept of progressive change in the angles in aniridia such as we have recognized and established through our repeated examination of patients was in part anticipated by Barkan in 1953.[1] He thought that a mechanism for closing the angle would explain development of glaucoma. He did not say when in the life of a patient he thought this might occur, and did not record having actually witnessed the process, but he concluded that uveal meshwork between trabecular meshwork and iris stump pulled the latter forward to close the angle. Similar thoughts of a progressive process in the angle seem to be implied in a report by Higgitt[3] in 1956 describing 3 cases and giving the opinion that "the iris root appeared to have retracted onto the outer wall of the angle where it would obstruct the exit channels."

Putting together what we have observed clinically with what has been reported of the histopathology in congenital aniridia with and without glaucoma, it has seemed to us that Collins'[20] description in 1893 of delicate congenital adhesions between the extreme root of the iris and the trabecular meshwork in parts of the circumference in the non-glaucomatous eye of a three-year-old child may correspond to what we have seen by gonioscopy early before development of glaucoma, appearing as small translucent or pigmented sawteeth fingers or ridges of iris stroma irregularly extending forward across the ciliary band and scleral spur to varying distances on the trabecular meshwork at a time when the plane of the stump of iris is still normal, perpendicular to the axis of the eye. We have observed these delicate scattered sawtooth attachments to precede in some eyes a general forward migration of the peripheral iris stroma over the trabecular meshwork, and we have postulated that there is an active process of traction or growth based upon these early delicate bridges of tissue which can ultimately result in pulling the whole stump of iris forward to cover the trabecular meshwork. Apparently at some stage of this process the endothelium may migrate from the cornea over both anterior and posterior surfaces of the iris stump and at a late stage may lay down a new Descemet's membrane on both aspects, resulting in a histopathologic picture such as described by Pagenstecher[14] and Lembeck.[16] At what stage the endothelium of the cornea may take part in the process we have no information, but in view of the reported findings of Descemet's membrane between trabecular meshwork and iris stump, it

would seem to occur prior to complete folding forward of the stump. We note also the common tendency for the pupillary margin of the stump to curl forward at the same time that the forward migration or traction of the periphery of the stroma is occurring.

The ectropion uveae and the closing of the angle that is believed to be produced by contraction of a membrane between the angle wall and the iris in neovascular glaucoma and in other conditions which have become complicated by endothelialisation and an associated glass membrane may have some etiologic similarity to what we have observed to occur in aniridia. This suggests that also in aniridia there is an active degeneration of the corneo-scleral angle that leads to the development of a contractile membrane between the surface of the iris and the angle wall which is responsible for the progressive closing of the angle.

Our exploratory observation on the effects of cutting the early sawtooth attachments between the iris stroma and trabecular meshwork, done in the hope of eliminating this bridge, seems to lend support to these speculations, since this has apparently prevented or at least delayed the process of forward migration or traction in the portions of the circumference in which these bridges have been cut.

We have been asked whether we recommend prophylactic goniosurgery in aniridia, and if so, under what conditions. In answer to this, we believe that our studies have provided a rationale for proposing and performing prophylactic procedures in eyes in which threatening changes are developing in the angles, but clearly we do not yet have results from a sufficiently long period of observation to prove that glaucoma can be prevented in this way. Therefore, at the present time, we propose goniosurgery only as part of a careful process of evaluation in which systematic comparisons can be made of prophylactically operated eyes and contralateral uunoperated eyes to establish whether there is sufficient long-term benefit to the operated eyes to outweigh the risk of the surgical procedure itself. Furthermore, we would propose prophylactic surgery only if upon repeated examination of the angle we saw changes occurring that have lead to glaucoma in other cases. If the parents comprehended our reasoning, and agreed, we would plan to perform the goniosurgery in one eye in at least half the circumference. To do this we have found it best to do approximately a third of the circumference on one occasion, and another third on a second occasion. The technique is that described earlier under surgical results, aiming solely to detach the anomalous attachments of iris stroma from the trabecular meshwork, without incising the trabecular meshwork itself.

In patients in whom abnormality of the angle was greater in one eye

than in the other, as is often the case in aniridia, we would do the prophylactic procedure on the more abnormal or rapidly worsening eye. It will of course by more difficult to evaluate the effectiveness of prophylactic procedures in cases of asymmetrical involvement.

We anticipate that it may take 10 years or longer for preliminary assessment of effectiveness, but in the meantime we think it is worthwhile trying in this way to prevent or delay the onset of glaucoma, because according to our own experience and that reported by others, more than half of all children with aniridia otherwise can be expected to develop glaucoma, and as we have said, this glaucoma tends to become increasingly difficult to control either medically or surgically. We would greatly prefer a biochemical or medical approach to preventing the changes in the angles and the development of the glaucoma, but we will have to obtain a much better understanding of what occurs in the angle before we can hope to evolve a biochemically based prophylaxis.

If a major advance can be made in treating the glaucoma of aniridia once it has developed, assuring reasonable success without undue risk, we would of course not need to consider prevention so strongly. One of us (DSW) has begun evaluating a new surgical gonioprocedure which in advanced and desperate cases seems to offer more hope than the older procedures, but we foresee a considerable period before this too can be adequately evaluated.

SUMMARY AND CONCLUSIONS

During the last 18 years we have examined 60 children with congenital aniridia, 31 of whom had glaucoma, and by repeated gonioscopic examinations have documented an increasing abnormality of the anatomy of the iridocorneal angle in 14, clearly correlated with worsening of the glaucoma in 9.

It has been well recognized in the past that there are gonioscopic and histologic differences between non-glaucomatous and glaucomatous aniridic eyes, and it has been recognized clinically in aniridia in the past that buphthalmos is rare and glaucoma in infancy is unusual, but that glaucoma commonly develops later in childhood. The question of why glaucoma develops late in childhood in aniridia, though the initial defect is congenital, has been answered by our systematic documentation of progressive changes in the iridocorneal angles, extending observations that were first published by Chandler and Grant in 1965.

In all congenitally aniridic patients in this series a peripheral stump of iris was present. The eyes of aniridic infants who were destined to

develop glaucoma were found early in life to have irregular fine attachments of the iris stroma to varying distances onto the angle wall. In most of the children who developed glaucoma the anterior stromal layer of the stump gradually extended further anteriorly over the trabecular meshwork, and the intraocular pressure became elevated as the filtration area became covered by the extension of abnormal iris tissue.

We believe that in congenital aniridia there is a progressive degeneration of the corneo-scleral angle, with the development of a contractile membrane between the surface of the iris and the angle wall playing a role in the gradual obstruction or closing of the angle.

Medical treatment with miotics, epinephrine, and carbonic anhydrase inhibitors was often helpful, at least for a time, in controlling the glaucoma, but in a majority of patients medical treatment eventually proved inadequate, and antiglaucoma surgery was performed. In some patients goniotomy seemed to improve the response to medical treatment for a while, but produced no cures. Results of other standard antiglaucoma operations were unsatisfactory.

Because of the progressive nature of the changes in the angle and the worsening of the glaucoma that we have documented, and the difficulties of both medical and surgical treatment in advanced stages of the glaucoma, we have been investigating the possibility of preventing the glaucoma by prophylactic goniosurgery performed early, before progressive changes in the angle have seriously obstructed filtration. In one eye of each of several patients we have detached the abnormal extension of iris stroma from angle wall, and during several years of observation have seen the trabecular meshwork in these areas to have remained unobstructed. A longer time of observation will be needed to determine conclusively whether this will prevent or delay the onset of glaucoma.

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DISCUSSION

DR DAVID D. DONALDSON. I feel a little like Dr Hollenhorst in reference to Dr Kearn's paper which he discussed, because I work within a few feet of Dr Grant and have for many years. Also, I know Dr Walton very well and am familiar with this work. I must say I am therefore prejudiced, and I want to warn you about that.

There are 45 pages or more in this paper, and there is a great deal of interesting detail that Dr Grant was unable to present because of the limitation in time. The only thing I could really take exception to was two typographical errors. I will point them out to him later. [Laughter]

Aniridia is a rare disease; but even so, this paper is a very important contribution, because certainly some of you will in time or already may have had

occasion to treat such patients. Dr Grant and Dr Walton have offered us something that has never been offered before in this disease. They have shown with a great deal of time-consuming and meticulous observation over a period of eighteen years, that they have actually been able to document these changes as you have just heard, and they have developed a pathogenesis which is very important to the understanding of what is actually happening. And then, as you have just heard, they went on to develop a prophylactic approach which was successful when the standard approaches that you use in glaucoma in infants and children are unsuccessful.

I would like to ask a couple of questions that are of considerable interest to me, and might be to you also. In his paper Dr Grant mentioned that neovascular glaucoma has some similarities in the way the angle closes to the aniridic eye, and they also say in other conditions. I wonder if Dr Grant would say something about the interesting condition I have been very interested in and that he also has been interested in, namely, essential iris atrophy, particularly the Chandler type that Dr Chandler described a number of years ago, in which there is also angle closure. This is quite a different condition. I am not trying to say that aniridia and essential iris atrophy are similar, except possibly in the progressive changes that occur slowly over a period of years, producing the closure of the angle.

Dr Grant was one of the first, as far as I know, to point out in progressive essential iris atrophy of the classical type that there is bridging of the trabecular meshwork with these synechias, and I assume that this type of synechia has never been seen in angle closure with the aniridia. I would like him to mention something about that.

I also wonder if it might be appropriate at least to mention briefly the treatment that Dr Walton is using in advanced cases. Or does he think it is premature to say anything about this procedure?

Dr Harold F. Falls. I should like to report a clinical observation which in some respects is pertinent to this subject.

Early in my career I was contacted by a lawyer who was in touch with a family presenting "interstitial keratitis." Naturally I was excited because I knew of no cause of "hereditary interstitial keratitis."

To make a long story short the family was afflicted with congenital aniridia — in fact five generations are now known. An important observation that was made in the older affected members of the family was a metaplasia of the epithelium over the limbus which slowly extended and was eventually vascularized (a degenerative pannus?).

Individuals who did not develop glaucoma seldom if ever demonstrated the above complication.

In our hands goniotomy has been the only surgical procedure to successfully control the intraocular pressure in glaucomatous aniridia.

Drs Fralick, Barkan, and Scheie have previously advocated early goniotomy in glaucomatous aniridia.

DR W. MORTON GRANT. I thank both of the discussers. In the case of Dr. Donaldson it is good to have a friend as one's first discusser.

Dr Donaldson's question relative to neovascular glaucoma and essential iris atrophy refers back to observations made in the 1880's when aniridic eyes that had very severe glaucoma were enucleated, and one of the characteristic things found when the iris stump was up against the angle was a glass membrane which came from the cornea, enveloped the little stump, and sometimes even went back on the ciliary processes. There was endothelialization and glass membrane formation.

When we see a sort of pulling forward of the periphery and later a curling forward of the pupillary portion, it makes us think of some kind of a membrane pulling in the periphery. We have never seen what goes on histologically during this process, but we can speculate that there is some resemblance to what goes on in neovascular glaucoma and maybe in essential iris atrophy.

I have not seen the bridging of the angle in aniridia that we have seen in essential iris atrophy. On the angle wall in aniridia you may see little sheets of tissue making microbridges, but I have never seen them to Schwalbe's line or to the cornea.

Dr Falls' observation of the limbal metaplasia is very interesting. We have seen these changes going on externally, but haven't correlated them with the absence or presence of glaucoma. That is a very intriguing observation. We will have to review this.

Dr Falls experience favors early rather than late goniotomy. I think Dr Barkan was the first to report a successful result and to suggest that goniotomy was a logical procedure in aniridia glaucoma. In fact, Dr Barkan probably anticipated this whole idea of a progressive disease. He speculated that there was something in the angle that made the angle close. He never recorded having witnessed it, and never said when he thought it might occur, but he was certainly thinking about it.