# A UNIFICATION HYPOTHESIS OF PIGMENT DISPERSION SYNDROME*

BY *Robert Ritch*, MD


## ABSTRACT

*Purpose:* To synthesize recent findings regarding pigment dispersion syndrome in order to arrive at a hypothesis concerning the nature of an underlying genetic predisposition.

*Methods:* The literature on the subject was reviewed and analyzed.

*Results:* Eyes with pigment dispersion syndrome differ from normal in that they have a larger iris, a midperipheral posterior iris concavity that increases with accommodation, a more posterior iris insertion, increased irido-lenticular contact that is reversed by inhibition of blinking, possibly an inherent weakness of the iris pigment epithelium, and an increased incidence of lattice degeneration of the retina.

*Conclusion:* A gene affecting some aspect of the development of the middle third of the eye early in the third trimester appears at the present time to be the most likely cause.


## INTRODUCTION

Pigment dispersion syndrome (PDS) is a unique and fascinating entity. Far more prevalent than previously suspected,[1] it is the first common disease leading to glaucoma for which we are on the verge of a coherent overall explanation of pathogenesis and pathophysiology. This paper is an attempt to tie together many interesting and sometimes disparate and/or apparently anomalous findings in order to synthesize a coherent portrait of the disease.

PDS and pigmentary glaucoma (PG) are characterized by disruption of the iris pigment epithelium (IPE) and deposition of the dispersed pigment granules throughout the anterior segment. The classic diagnostic

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triad consists of corneal pigmentation (Krukenberg spindle); slitlike, radial, midperipheral iris transillumination defects, and dense trabecular pigmentation. The iris insertion is typically posterior, and the peripheral iris tends to have a concave configuration. The basic abnormality in this hereditary disorder remains unknown.

## HISTORICAL BACKGROUND

In 1899, Krukenberg[2] described spindle-shaped pigment deposition on the cornea. In 1901, von Hippel[3] suggested that pigment obstructing the aqueous outflow system could lead to elevated intraocular pressure (IOP). Levinsohn[4] first suggested that pigment in the anterior chamber angle of patients with glaucoma originated from the IPE. A cause-and-effect relationship between pigment and glaucoma found both support[5,6] and opposition.[7-9]

In 1949, Sugar and Barbour[10] described 2 young, myopic men with Krukenberg spindles, trabecular hyperpigmentation, and open angles, whose IOP increased with mydriasis and decreased with pilocarpine. The investigators identified the disorder as a rare, distinct form of glaucoma, which they termed pigmentary glaucoma. More patients were subsequently reported, and in 1966 Sugar[11] reviewed 147 cases in the world literature, mentioning several additional features, including bilaterality, frequent association with myopia, greater incidence in men than in women, and a relatively young age at onset. These features were confirmed by Scheie and Cameron.[12]

In the 1950s, the discovery of iris transillumination defects led to the concept that the trabecular pigment originated from the IPE and perhaps the ciliary body.[13,14] Congenital atrophy or degeneration of the IPE was suggested as a cause of loss of iris pigment.[15,16]

In 1979, Campbell[17] proposed the pathogenesis to involve mechanical damage to the IPE during rubbing of the posterior iris against the anterior zonular bundles during physiologic pupillary movement. Subsequently, the autosomal dominant inheritance, natural history, reversibility, and more precise therapeutic approaches have become increasingly delineated. Ultrasound biomicroscopic studies are presently revealing new insights into the pathophysiology of PDS.

## CLINICAL FINDINGS

### ANTERIOR SEGMENT

Loss of iris pigment appears clinically as a midperipheral, radial, slitlike pattern of transillumination defects seen most commonly inferonasally and

more easily in blue eyes than in brown ones (Fig 1). Although the defects can sometimes be seen by retroillumination, they are more easily detected by a dark-adapted examiner using a fiberoptic transilluminator in a darkened room. Infrared videography provides the most sensitive method of detection.[18] Pigment particles deposited on the iris surface tend to aggregate in the furrows.[11,19] Rarely, this pigment can be dense enough to darken the iris or to cause heterochromia when involvement is asymmetric.[11,20] Iris vascular hypoperfusion on fluorescein angiography has been reported,[21] a finding which awaits verification.

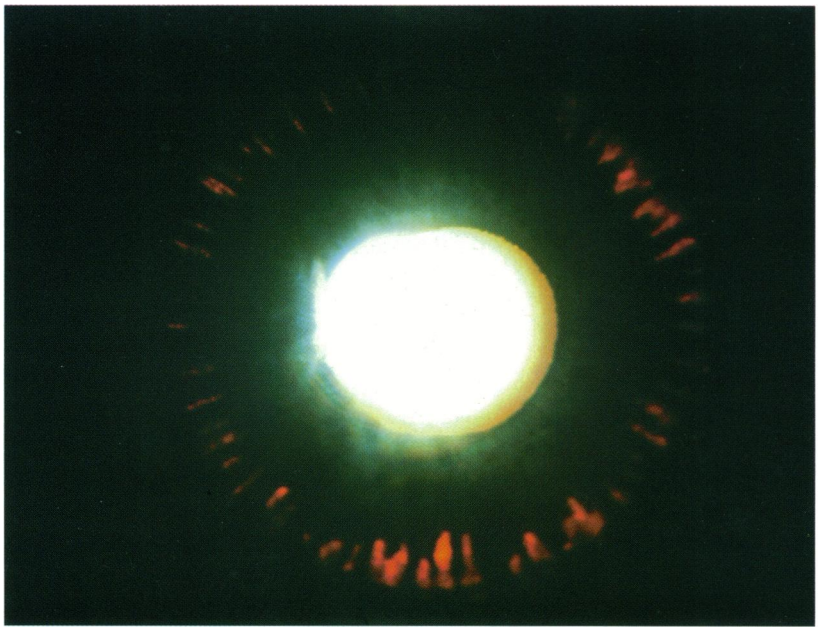

FIGURE 1
Iris transillumination defects. Typical defect is midperipheral, radial, and slit-like. Some defects, especially inferiorly, have peripheral clublike endings, giving them the appearance of an exclamation point. These peripheral transillumination dots might result from iridociliary contact.

Anisocoria may occur with asymmetric involvement, the larger pupil corresponding to the eye with greater pigment loss from the iris.[22-24] Alward and Haynes[22] suggested the presence of an efferent defect in the eye with the larger pupil. The pupil may be distorted in the direction of maximal iris transillumination.[23-25] This would be consistent with the presence of hyperplasia of the iris dilator muscle (see below).[26]

Corneal endothelial pigment generally appears as a central, vertical,

brown band (Krukenberg spindle), the shape being attributed to aqueous convection currents (Fig 2). The pigment is phagocytosed by endothelial cells,[27,28] but endothelial cell density and corneal thickness remain unchanged compared with controls.[19] Coincident PDS and megalocornea have been reported,[12,16,29,30] as have subluxated lenses.[12,31]

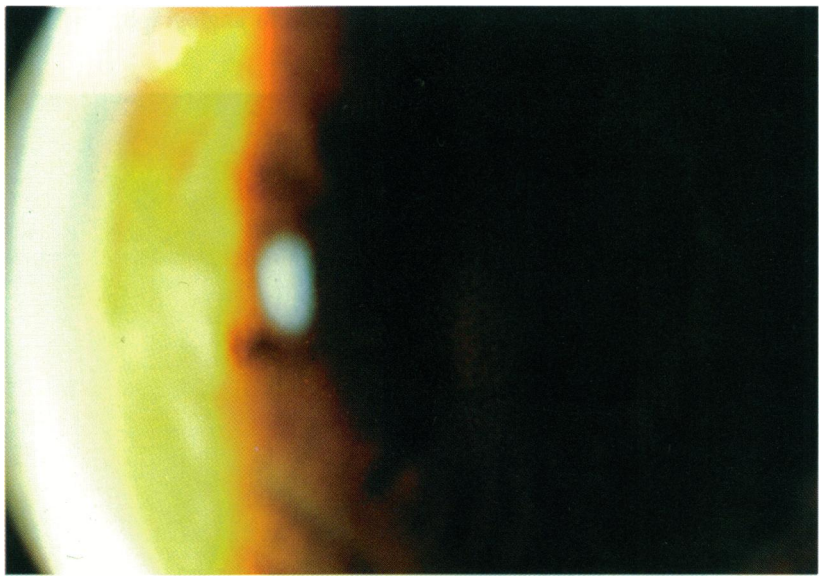

FIGURE 2
Krukenberg spindle.

The anterior chamber is deeper both centrally and peripherally than can be accounted for by sex, age, and refractive error. Davidson and associates[32] compared the central and peripheral anterior chamber depths of patients with PDS to statistical controls. The anterior chamber was significantly deeper, and the anterior chamber volume was significantly greater in the PDS group, the difference being greatest inferiorly.

The angle is characteristically widely open, with a homogeneous, dense hyperpigmented band on the trabecular meshwork (Fig 3). Pigment may also be deposited on Schwalbe's line. The iris insertion is posterior, and the peripheral iris approach is often concave. The iris is most concave in the midperiphery. In younger patients, the scleral spur may be poorly

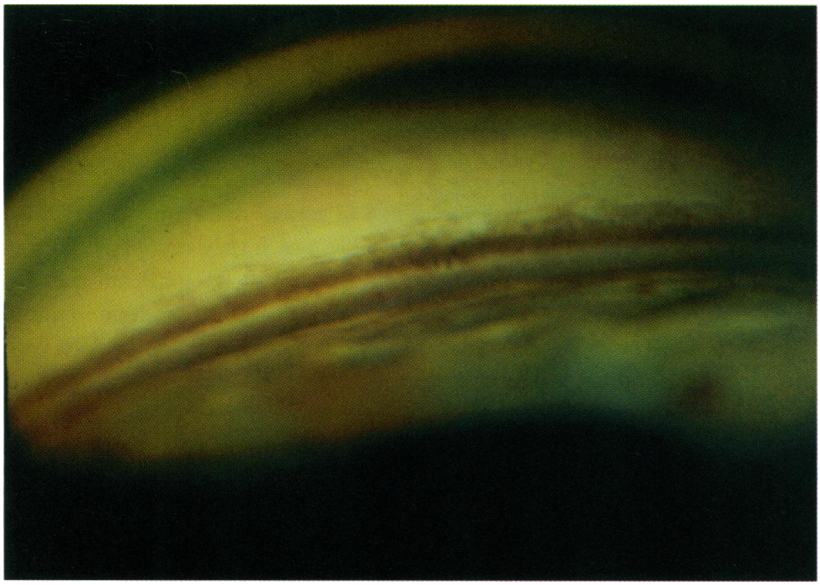

FIGURE 3A

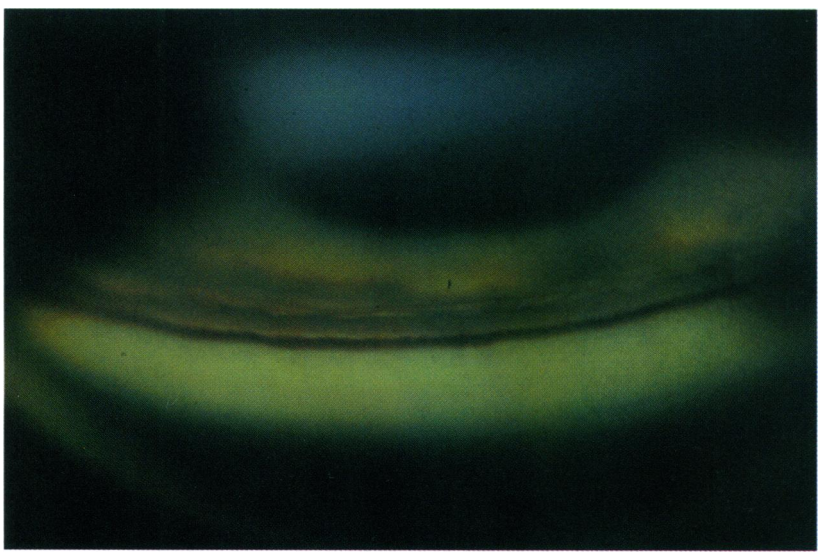

FIGURE 3B

FIGURE 3

Pigment reversal sign in 48-year-old man. A. Inferior angle. B. Superior angle. Pigment is denser in superior angle. Note that pigment band has sharp anterior and posterior margins and appears smooth, indicating that pigment was deposited in past and is now localized to region of filtering portion of trabecular meshwork. Iris is inserted posteriorly.

demarcated, blending with the ciliary face owing to pigment deposition on these structures. Pigment may be deposited on the zonules[14,20,33] and on the posterior capsule of the lens, where it is apposed to the anterior hyaloid face at the insertion of the posterior zonular fibers.[14,33-35]

**POSTERIOR SEGMENT**

PDS is associated with a high incidence of retinal detachment.[12,36,37] Most detachments occur in phakic men who are not highly myopic.[12] Miotics have been incriminated in precipitating these.[38-40] It is significant that the incidence of retinal detachment in PDS is 6% to 8% independent of miotic treatment, and when detachment is associated temporally with miotics, a preexisting lesion was most likely present. Lattice degeneration is commonly found in myopes[41,42] and may be hereditary.[43,44] Its incidence appears to be higher for all degrees of myopia in patients with PDS[45] than in the general population.[46] Despite the fact that comparable prevalences of lattice degeneration in blacks and whites have been demonstrated at autopsy,[47] PDS and retinal detachment are both uncommon in blacks. It may be preceded or caused by chronic, localized vitreoretinal traction,[48] which is exaggerated around the margins of the lesion.[49,50] The reason for the prominence of the vitreoretinal traction has not been explained.

In a small series of 5 patients with glaucoma and optic nerve head drusen, 4 had PG.[51] Additional such patients have not been reported, and the significance of this observation remains unknown.

**PATHOPHYSIOLOGY**

In 1958, Scheie and Fleischauer[14] described iris transillumination defects associated with PDS and attributed them to IPE atrophy. With no real evidence except a "somewhat waxy or pale" appearance of the ciliary body in a few patients, they extended the hypothesis of congenital atrophy to include this structure.

Fine and colleagues[52] examined the eyes of a 55-year-old man who had been found to have PDS without glaucoma at age 43. In the iris midperiphery, there was an abrupt transition from normal to abnormal IPE. In this region, IPE loss was accompanied by hyperplasia of the iris dilator muscle, and there was marked hyperplasia of the muscle spur of Grunert at the iris root. Pigment epithelial cells appeared to be migrating anteriorly and differentiating into smooth-muscle-containing cells. Rodrigues and coworkers,[16] on the other hand, reported a focally thickened dilator muscle with thinning in the areas of epithelial atrophy. They found an increased number of immature melanosomes in the IPE and suggested that a delay in melanogenesis occurred as part of a developmental defect.

Kupfer and coinvestigators[53] considered the primary lesion in PDS to be an epithelial abnormality. The dilator fibers of the inner IPE appeared to be hypertrophic and hyperplastic, resembling the sphincter muscle, and were associated with degenerated neural elements. They felt that the primary defect lay in the inner IPE and could represent a congenital or developmental abnormality, but could also be the result of interruption of sympathetic innervation.

The relevance of dilator muscle hyperplasia and nerve fiber degeneration to the disease process remain unknown. The possibility of an adrenergic hypersensitivity in patients with PDS and PG might explain comments made in passing that epinephrine compounds, alone or in combination with other agents, seem to be more effective in patients with PG than in those with POAG.[12,54]

Campbell[17,55] proposed that posterior bowing of the iris brings it into contact with the anterior zonular bundles. The location and number of the transillumination defects correlated with the position and number of the underlying zonular bundles. He noted that hyperplasia of the iris dilator muscle was localized to areas of iridozonular contact and hypothesized that iridozonular friction during pupillary movement disrupts the IPE, releasing pigment into the posterior chamber. Scanning electron microscopic observations supported this hypothesis.[56,57]

#### ULTRASOUND BIOMICROSCOPIC FINDINGS

The advent of high-frequency, high-resolution, anterior-segment ultrasound biomicroscopy has enabled us to elucidate a number of facets of the pathophysiology of PDS.[58-66] One overall impression obtained from imaging studies is that the size of the iris is overly large relative to that of the anterior segment (Fig 4). This may be the basic anatomic cause of the mid-peripheral iris concavity and predispose to iridozonular contact. Sokol and associates[65] compared patients with PDS to age-, sex-, and refraction-matched controls and found a greater mean iris-trabecular meshwork distance in the PDS group. Thus, iridozonular contact appears to be facilitated by a congenitally more posterior iris insertion.

Both iridozonular and iridociliary contact have been imaged (Fig 5). Although iridociliary contact does not appear to be much of a factor in pigment liberation, the occasional extension of transillumination defects into the periphery of the iris, creating an appearance similar to that of an exclamation point, suggests that contact between the 2 surfaces may damage the pigment epithelium of both and may account retrospectively for the observation of Scheie and Fleischauer[14] regarding the "pale and waxy" appearance of some ciliary processes (Fig 1).

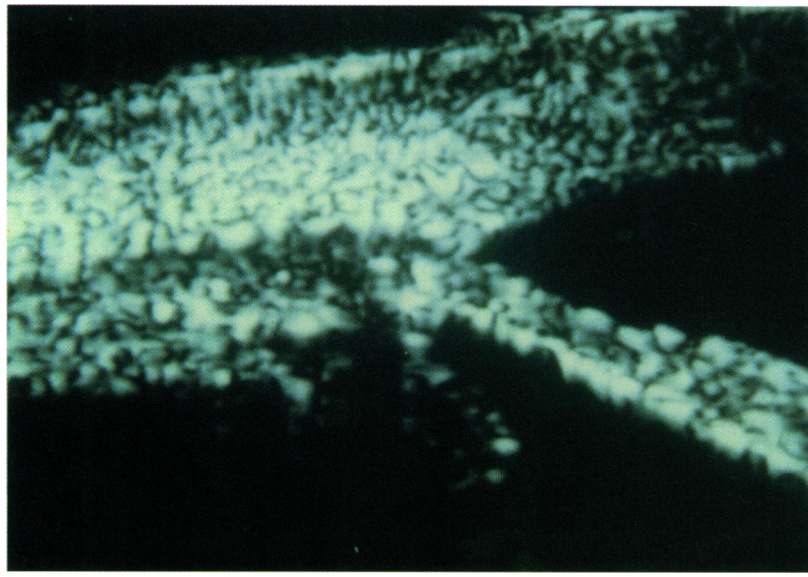

FIGURE 4A

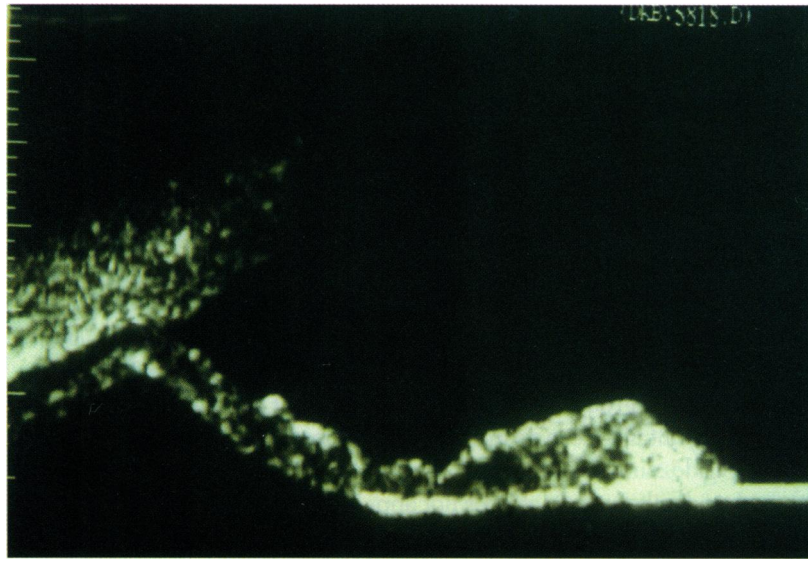

FIGURE 4B

FIGURE 4
Ultrasound biomicrograph of normal eye (A) and, eye with pigment dispersion syndrome (B). Iris is large relative to size of anterior segment, and midperipheral concavity is prominent. There is extensive iridolenticular contact.

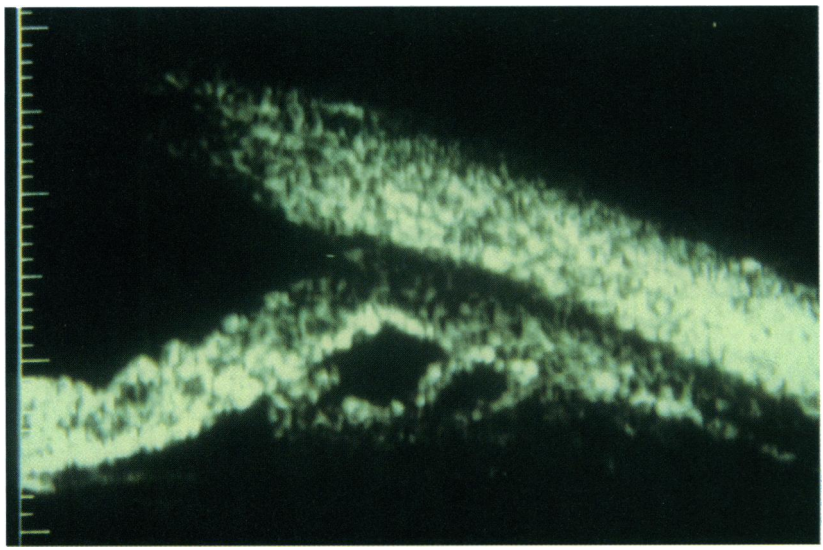

FIGURE 5
Anterior ciliary processes appear to be in contact with iris pigment epithelium. (Reproduced, with permission, from Potash SD, Tello C, Liebmann J, et al: Ultrasound biomicroscopy in pigment dispersion syndrome *Ophthalmology* 1994; 101:332-339.)

**BLINKING**

Lid blinking may be important in determining iris configuration. Campbell[67] noted and Liebmann and colleagues[62] confirmed that when blinking is prevented in PDS patients, aqueous humor builds up in the posterior chamber and the iris assumes a planar and even a convex configuration. As the volume of the posterior chamber increases relative to that of the anterior chamber, the iris gradually flattens, iridolenticular contact diminishes, and iridozonular and iridociliary process distances increase. In the most pronounced cases, iridolenticular contact disappears, the iris sphincter lifting completely off the surface of the lens without the posterior chamber losing its expanded volume (Fig 6). Eyes with PDS take longer to reach a steady-state position because their initial iris concavity is greater than that of control eyes.[62]

The mechanism by which blinking affects the anatomy of the anterior segment appears to be a mechanical one. Campbell[67] proposed that a blink initially deforms the cornea, transiently increasing IOP and pushing the iris posteriorly against the lens. When PDS patients are permitted to blink and rescanned, the concave iris configuration returns in all eyes.[62] Chew and coworkers[68] demonstrated that during blinking of the nictitating mem-

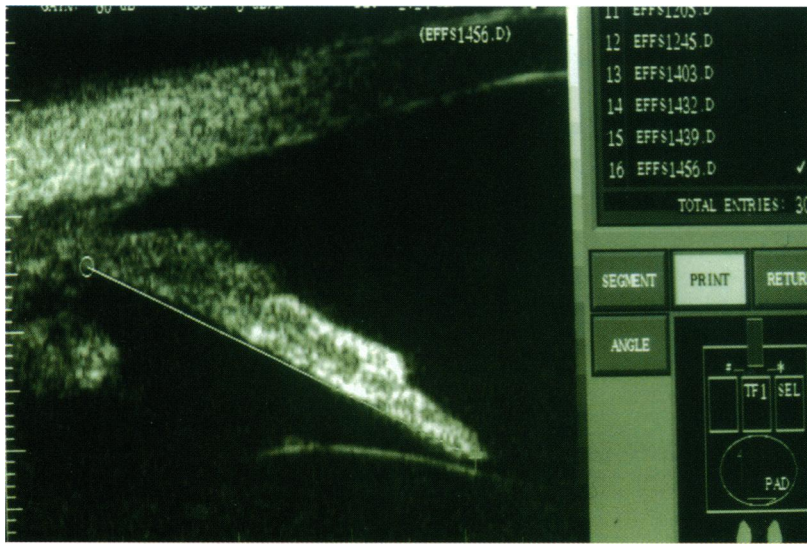


FIGURE 6
Inhibition of blinking for several minutes results in expansion of posterior chamber, a convex iris configuration, and loss of iridolenticular contact in this eye of patient with pigment dispersion syndrome. Despite lack of iridolenticular contact, aqueous pressure in posterior chamber is sufficient to maintain iris in convex position. (Reproduced, with permission, from Liebmann JM, Tello C, Chew SJ, et al: Prevention of blinking alters iris configuration in pigment dispersion syndrome and in normal eyes. *Ophthalmology* 1995; 102:446-455.)

brane in the chick eye, the cornea indents in a wave from the periphery to the center and that anterior chamber depth similarly decreases (Fig 7).

Extrapolating this to humans, we hypothesize that blinking acts as a mechanical pump to push aliquots of aqueous humor from the posterior chamber to the anterior chamber. A pressure wave is created, pushing the iris posteriorly toward the zonules. This wave begins at the iris periphery and moves centrally, pushing aqueous before it into the anterior chamber and emptying the posterior chamber. Abnormally extensive iridolenticular contact in eyes with PDS prevents equilibration of aqueous between the anterior and posterior chambers, a situation that has been termed reverse pupillary block.[67,69] At the same time, the iris reassumes its concave configuration. The now increased volume of aqueous in the anterior chamber helps to maintain the midperipheral iris concavity, although whether or not there is a pressure gradient accentuating the concavity remains to be shown. As aqueous leaves the eye through the meshwork and enters via ciliary secretion, the anterior chamber volume decreases and the posterior chamber volume increases, until the next blink starts the cycle all over

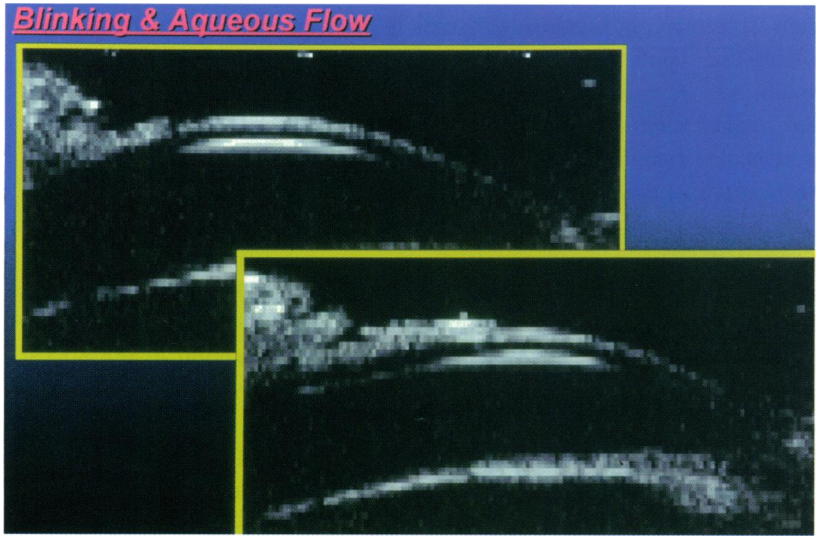


FIGURE 7A

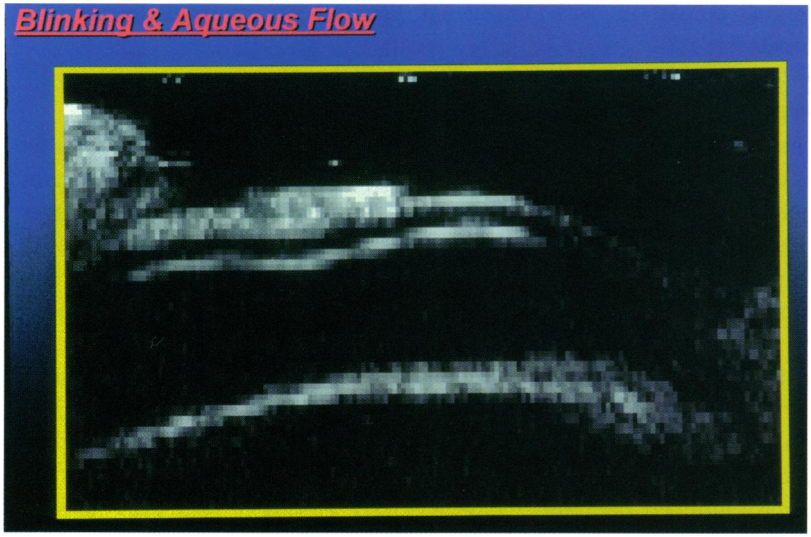


FIGURE 7B

FIGURE 7

A. Chick cornea prior to blinking of nictitating membrane. B. During blink, the cornea indents. (From reference 68)

again. Interestingly, increasing myopia is also a predictor of increasing iridolenticular contact, independent of the presence of PDS.[62] This may explain why myopia enhances the phenotypic expression of the genetic abnormality underlying PDS. It also raises the question as to whether decreased trabecular function and reduction of the aqueous outflow coefficient might serve to accentuate the iris concavity.

### ACCOMMODATION

Accommodation in normal, young individuals and PDS patients may also affect iris contour (Fig 8).[62,70] Accommodation in normal eyes causes an iris concavity indistinguishable from that in PDS. Contraction of the ciliary ring allows shallowing of the anterior chamber, anterior lens movement, and increased iridolenticular contact. Aqueous in the anterior chamber is forced into the angle recess, and the peripheral iris becomes more concave. As accommodation is relaxed, the iris resumes its initial configuration.

Accommodation might enhance pigment liberation in 2 ways. In addition to posterior iris bowing during accommodation, the pupil constricts. Relaxation of accommodation accompanied by pupillary dilation might result in additional iridozonular friction. Ultrasound biomicroscopy during accommodation in eyes with PDS shows iridozonular contact at the lens margin, consistent with the usual position of iris transillumination defects.[71]

### EFFECT OF MIOTICS AND LASER IRIDOTOMY

Scanning following administration of pilocarpine shows resolution of the iris concavity and iridozonular contact in all eyes (Fig 9). Pilocarpine produces a convex rather than a planar configuration. Laser iridotomy relieves reverse pupillary block by allowing aqueous to flow from the anterior to the posterior chamber and produces a planar iris configuration (Fig 10). Some eyes undergoing iridotomy may still retain a concave iris configuration.[72] Iridotomy does appear to prevent the accentuation of the iris concavity that accompanies accommodation.[71] In some PDS patients, rises in IOP may occur after shedding pigment with exercise or with pupillary dilation.[73-79] The exercise-induced release of pigment and elevation of IOP can be blocked by pilocarpine.[78,80,81] Whereas pilocarpine completely inhibits exercise-induced pigment release and IOP elevation, iridotomy does so incompletely.[63,81]

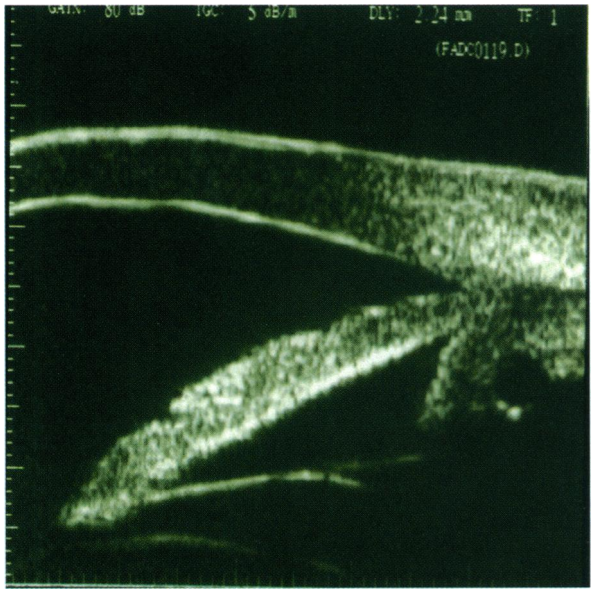

FIGURE 8A

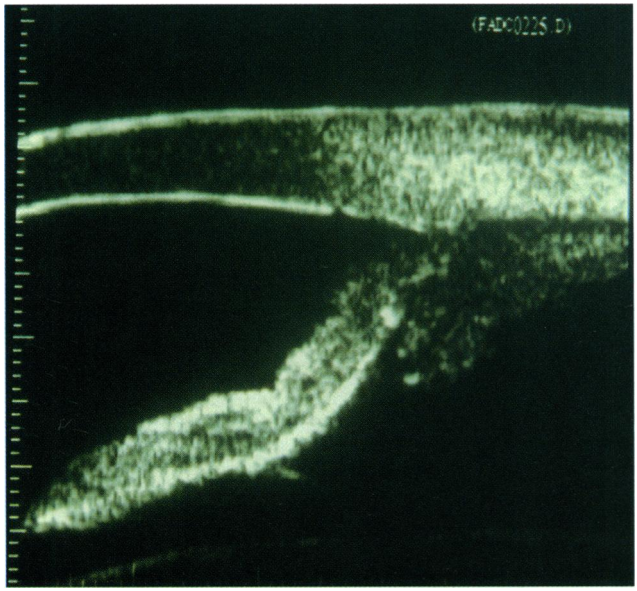


FIGURE 8B

FIGURE 8

A. Normal myopic eye prior to accommodation. B. Accommodation produces midperipheral iris concavity mimicking that seen in pigment dispersion syndrome. (Reproduced with permission, from Liebmann JM, Tello C, Chew SJ, et al: Prevention of blinking alters iris configuration in pigment dispersion syndrome and in normal eyes. *Ophthalmology* 1995; 102:446-455).

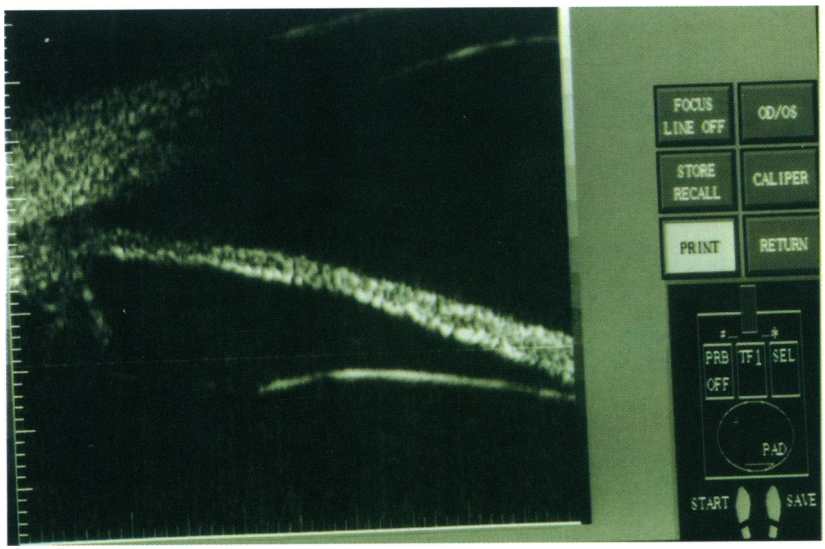


FIGURE 9

One drop of 2% pilocarpine produces convex iris configuration mimicking that produced by inhibition of blinking. (Reproduced, with permission, from Haynes WL, Alward WLM, Tello C, et al: Incomplete elimination of exercise-induced pigment dispersion by laser iridotomy in pigment dispersion syndrome. *Ophthalmic Surg Lasers* 1995; 26:484-486).

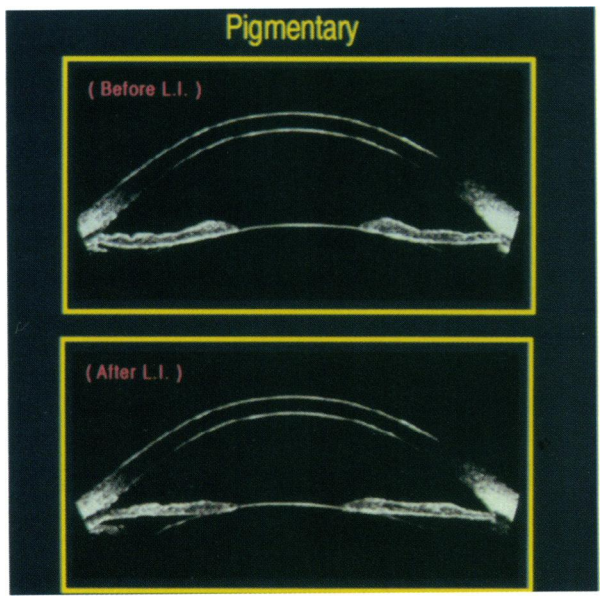


FIGURE 10

Laser iridotomy produces planar iris configuration, since aqueous can freely redistribute through iridotomy site.

## CLINICAL CORRELATIONS

### HEREDITY

The above concept of the pathophysiology of PDS helps us to better understand a number of clinical aspects of the disorder. Structural abnormalities are characteristic of autosomal dominant disorders. Only occasional families with Krukenberg spindles were reported prior to the 1980s.[9,12,82-86] Reports in the 1980s described familial PDS but were inconclusive regarding the mode of inheritance.[87-90] McDermott and colleagues[91] examined relatives of 21 probands and found involvement in 36% of parents and 50% of siblings, but none in children under the age of 21 years. This suggested a strong pattern of autosomal dominance, with phenotypic onset probably beginning in most persons in the mid 20s. That Caucasians are almost exclusively affected is also consistent with a genetic origin.

### GENDER

Men and women are equally affected by PDS, women having predominated in some series[12,92] and men in others.[93,94] However, men develop glaucoma about 3 times as often as women and at a younger mean age.[11,12,94-96] Berger and associates[97] found no difference in age at diagnosis of PDS between men and women, but men were significantly younger than women at the time of diagnosis of PG. No population-based study has yet been performed. If myopia is the major determinant of phenotypic expression, then one would expect an equal incidence of men and women, since the prevalence of myopia in the United States is similar between men and women.[98] Why, then, do more men develop glaucoma and do women appear to develop it at a somewhat older mean age? It is possible that female hormones exert a protective effect against the development of elevated IOP. A curious and unconfirmed finding reported by Duncan[99] was the development of Krukenberg spindles in 4 black women during pregnancy; these regressed after delivery. One report relating to hormonal treatment of PG has never received further attention in the literature.[100]

### REFRACTIVE ERROR

About 60% to 80% of patients with PDS and PG are myopes and 20% are emmetropes (-1.00 to +1.00 diopters).[11,12] In earlier series, which reported about 10% of patients to be hyperopes, there appears to have been some confusion between PDS and exfoliation syndrome, particularly as the hyperopes in these series tended to be older and to be women. Eyes with PG are significantly more myopic than those with PDS, and the higher the myopia, the earlier the age at onset of glaucoma.[97]

Campbell[17,55] suggested that enlargement of the myopic eye in young

patients allows the peripheral iris more space in which to bow posteriorly. Kaiser-Kupfer and coinvestigators[88] mentioned that transillumination defects can precede the development of myopia and increase without any concomitant progression of significant refractive error.

### ASYMMETRIC INVOLVEMENT

Since PDS is a bilateral disorder, asymmetric involvement requires explanation. A second disorder may make 1 eye worse. The most common cause in older patients appears to be the development of exfoliation syndrome in 1 eye in patients who had PDS or PG in earlier life.[101] Angle recession in 1 eye has also been reported.[102] It is also possible for one eye to have a second disorder that reduces the severity of PDS, such as unilateral traumatic cataract extraction in youth prior to the onset of pigment dispersion or development of unilateral cataract during the pigment dispersion phase, which decreases iridozonular contact by causing pupillary block.[103] Horner's syndrome may achieve the same effect.[104] We have also seen anisometropic patients with greater involvement in the more myopic eye (unpublished data).

In other cases, mild to marked asymmetry may exist without any other evident process. Kaiser-Kupfer and coinvestigators[88] reported 4 normotensive patients with markedly asymmetric involvement and no obvious cause for asymmetry. Three had anterior chamber depths 0.2 mm greater in the affected eye. Anderson[105] remarked that there should be asymmetry in the anatomic or physiologic factors relevant to the underlying pathogenesis. Liebmann and associates[64] examined 4 patients with markedly asymmetric PDS and no other ocular conditions to explain the asymmetry and found greater iridolenticular contact and a more posterior iris insertion in the more involved eye in all cases.

## NATURAL HISTORY

### ACTIVE PHASE

The mean age at onset of PDS remains unknown but is probably in the mid 20s. The youngest patients reported have been aged 12,[88] 14,[12,97] and 15.[16] Although it seems logical that PDS might develop in the mid teens, when myopia is commonly progressive, a screening of over 300 students at Stuyvesant High School, a school for especially intelligent children in New York City, did not reveal a single case (unpublished results). Moreover, McDermott and colleagues[91] found no children of probands positive up to age 21. Further studies are warranted. The development of PDS later in life is unlikely because of gradual lens enlargement and loss of accommo-

dation.

The phenotypic expression of PDS varies widely. Referral practices tend to have patients with more extensive involvement, although even in these patients, the diagnosis is often missed. More subtle manifestations may never be detected either because of a lack of suspicion on the part of the examiner, unawareness of the examiner of pathognomonic signs in patients with mild phenotypic involvement, failure to perform slit-lamp examination in patients presenting for refraction, and simply lack of an eye examination. Failure to perform gonioscopy may result in lack of diagnosis of patients with trabecular hyperpigmentation but without Krukenberg spindles, since transscleral transillumination is often the least likely test to be performed. It is not known whether the variability in phenotypic expression is hereditary, environmental, or a combination of both. For instance, the concavity due to iris position and size (genetic) could be affected by the cumulative amount of accommodation (environmental). Further studies are warranted.

**REGRESSION PHASE**

The timing of the onset of the regression phase of PDS is easier to explain. The severity of involvement of both PDS and PG decreases in middle age, when pigment liberation ceases, at least in the majority of patients. Lichter and Shaffer[93] observed decreased pigment in the trabecular meshwork in 10% of 102 cases, concluding that pigment could pass out of the meshwork with age. Transillumination defects may disappear,[17,106] most likely by migration of pigment epithelial cells adjacent to the defects. The IOP may return toward normal.[106-108] Some patients treated with long-term miotic therapy have been able to reduce or discontinue treatment for glaucoma.[80,107] Older patients presenting with glaucoma may have only very subtle manifestations of PDS, if any, and may be misdiagnosed as having primary open-angle glaucoma or low-tension glaucoma.[109] Remission of PG has also been reported following glaucoma surgery[12] and following lens subluxation.[31]

Trabecular pigmentation is initially dense and homogeneous for 360°. With age and clearance of pigment from the angle, it becomes lighter and more localized to the filtering portion of the meshwork, while it disappears from Schwalbe's line and the scleral spur. When the trabecular meshwork begins to recover, the normal pigment pattern reverses and the pigment band becomes darker superiorly than inferiorly. We have termed this the "pigment reversal sign," and in older patients, it may be the only finding suggestive of previous PDS (Fig 3). Although it cannot be regarded as diagnostic, examination of the patient's offspring in such a case may be

confirmatory. The pigment reversal sign may also be found in patients after long-term miotic therapy in patients with PDS or PG and also in patients with exfoliation syndrome, confirming that it occurs as a result of pigment clearing from the meshwork.

### LOGIC OF TREATMENT

The development of relative pupillary block secondary to an age-related increase in lens thickness and loss of accommodation with the onset of presbyopia are 2 processes that presumably lead to the cessation of pigment liberation in middle age. Older patients with PDS develop little or no accentuation of the iris concavity with accommodation.[71] By eliminating the iris concavity and iridozonular contact, miotic therapy may prevent progression of the disease and the development of glaucoma by immobilizing the pupil and may allow previously existing damage to reverse more readily. Since most PDS patients are young and cannot tolerate pilocarpine drops because of induced myopia and accommodative spasm, pilocarpine Ocuserts have proved to be the best available for of miotic therapy.

The success rate of argon laser trabeculoplasty (ALT) in PG is greater in younger patients than in older ones and decreases with age.[110-112] Pigment in younger patients is largely in the uveoscleral and corneoscleral meshworks, whereas in older patients, it is primarily localized to the juxtacanalicular meshwork and the back wall of Schlemm's canal.[111] A larger portion of patients fail within a shorter period of time compared with POAG patients.[110,111,113] Initially successful trabeculoplasty may be followed by a sudden, late rise in IOP, similar to that seen in exfoliative glaucoma. Patients in the pigment liberation stage who undergo ALT should be maintained on miotics or undergo laser iridotomy after ALT to prevent further contact between the iris and zonules. Although topical miotic drops or gel preparations are poorly tolerated by younger patients owing to induced myopia and accommodative spasm, pilocarpine Ocuserts are extremely well tolerated.

### THE BASIC LEGION

Any hypothesis concerning the basic defect in PDS must take into account the various anatomic findings noted above. Most difficult is explaining the relationship to lattice degeneration. A structural abnormality of the middle third of the eye causing an abnormally concave peripheral iris and the vitreous base/anterior retina to be drawn anteriorly could be consistent with previously proposed mechanisms.

During the formation of the secondary vitreous, a condensation of

fibers extends laterally between the lens and the iris to form the marginal bundle of Druault, which extends backward between the lens periphery and the equator, attaching strongly to the internal limiting membrane of the peripheral retina to form the vitreous base.[114] It also attaches to the posterior capsule of the lens around the primary vitreous, as a ring 8 to 10 mm in diameter, to form the hyaloideocapsular ligament of Wiegert. Developing zonular fibers (tertiary vitreous) pass through this bundle at right angles. As the ciliary processes and the iris develop, the marginal bundle loses its connection anteriorly but remains attached to the peripheral retina at the vitreous base.[114] A condensation of the anterior surface of the secondary vitreous finally separates the zonular fibers from the vitreous. An abnormal persistence of connections between the zonular apparatus and the marginal bundle of Druault might lead to tension on the peripheral retina.

During the seventh month, the apex of the angle moves posteriorly to become level with the middle portion of the meshwork. This is due not to cleavage, but to a differential growth rate of anterior neuroectoderm and anterior periocular mesenchyme, the latter growing more rapidly.[114] The ciliary processes move backward and become located behind the apex of the angle.

The responsible gene should also influence the size of the iris relative to the anterior segment and perhaps the susceptibility of the IPE to disruption by zonular friction. A gene affecting some aspect of the development of the middle third of the eye early in the third trimester appears reasonable at the present time.

## SUMMARY

PDS is an inherited disorder of abnormal iridozonular contact that is exaggerated by physiologic pupillary movement and accommodation. This contact results in disruption of the IPE cells and liberation of pigment, which is deposited on structures throughout the anterior segment. Pigment liberation can be triggered by exercise and by pupillary dilation Myopia predisposes to the phenotypic expression of the disorder, which affects men and women equally, but men develop glaucoma 2 to 3 times as often as women and at an earlier age. Pigment dispersion begins in the teens or 20s and continues until about the mid 40s in most people, at which time a combination of relative pupillary block and presbyopia leads to gradual cessation of pigment liberation. After this, the visible signs of pigment loss can reverse, and IOP control can improve. Older patients presenting for the first time with glaucomatous damage and normal IOP may be misdiagnosed as having normal-tension glaucoma.

Anatomically, the iris seems excessively large for the eye and is posteriorly inserted, resulting in a characteristic concave midperipheral configuration, iridozonular contact, and abnormally extensive iridolenticular contact. When blinking is inhibited, the iris assumes a convex configuration that is immediately reversed upon blinking, suggesting that the act of blinking acts as a mechanical pump to push aqueous humor from the posterior to the anterior chamber. Once in the anterior chamber, aqueous backflow is prevented by the abnormal iridolenticular contact, which produces a reverse pupillary block, further enhancing the iris concavity.

Treatment should begin early in order to prevent the development of glaucomatous damage and should be designed to prevent progression of the disease rather than merely lower IOP. Miotic treatment produces a convex iris configuration, completely inhibiting pigment liberation, while laser iridotomy produces a planar configuration and may not completely inhibit pigment liberation. Aqueous suppressants theoretically may negatively impact the course of the disease. Argon laser trabeculoplasty produces better results in younger patients than older ones because of the location of the pigment in the trabecular meshwork.

Persons with pigment dispersion also have an abnormally high incidence of lattice degeneration of the retina and retinal detachment. Any hypothesis regarding the origin of this disease must take this into account. It must also provide a reason why many myopes without PDS have an iris concavity that also increases with accommodation. An abnormal persistence of the marginal bundle of Druault might lead to an abnormality of zonular position. The responsible gene should also affect the size of the iris and perhaps susceptibility of the IPE cells to disruption. A gene affecting some aspect of the development of the middle third of the eye early in the third trimester appears at the present time to be the most likely cause.

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## DISCUSSION

DR MYRON YANOFF. Dr Ritch has presented a thoughtful analysis that tries to tie together the disparate findings in the pigment dispersion syndrome (PDS) into a unifying, genetic hypothesis. Many theories have been championed to explain the findings in PDS. Most of these theories, however, are less than satisfying because they explain findings after the fact without predictive value. Why does one myopic young man develop PDS and another does not? In fact, why are not all of the PDS patients myopic? Where does the glaucoma fit into the picture? From Krukenberg's original description in 1899 up until the present, many investigators have pondered the multitude of questions that Dr Ritch raises. I believe that his present analysis of PDS has elevated our understanding of this condition to a new level.

The ability to view in vivo a cross section of the peripheral irido-ciliary-zonular-lens structures by high-frequency, high-resolution, anterior-segment ultrasound biomicroscopy certainly has provided new information. The eyes with PDS have a more posterior insertion of the iris and a greater iridolenticular contact than normal eyes. Even in the 2 eyes of the same patient, 1 eye may be less involved than the other eye, leading to asymmetric findings. Simplistically, the iris appears to be too big for the eye. To explain this iris abnormality, Dr Ritch has postulated a genetic basis. As Dr Ritch points out in his paper, PDS families with an autosomal dominant inheritance pattern have been reported. Other investigators[1-4] have suggested a congenital origin to the iris abnormality, an abnormality that resides in the most posterior layer of the iris, namely, the iris pigment epithelium (IPE).

In 1974, my colleagues and I[2] described the light and electron microscopic changes in 2 autopsy eyes removed from a patient who had clinically documented PDS. One unexpected finding dealt with the IPE. We found, in the region of the posterior IPE defect, dysplastic changes in the

IPE. These changes consisted of transformation of the normally partially pigmented and partially smooth-muscularized anterior pigment epithelium into a complete smooth muscle cell, often in a hyperplastic form, and anteriorly migrated into the iris stroma. We felt that this type of dysplastic change could not have occurred secondarily but had to be a primary congenital abnormality of the iris. This finding of a congenital iris abnormality certainly fits in with Dr Ritch's hypothesis. Furthermore, one could propose that the anteriorly and centrally placed dilator muscle could account, perhaps in part, for the posterior bowing of the iris that is seen in PDS. A different degree of IPE congenital abnormality in each eye of a patient could account for the asymmetry often seen in a patient's eyes.

Dr Ritch's point about the high incidence of PDS, lattice degeneration of the retina, and retinal detachment is indeed interesting and also may be explained by Dr Ritch's overall genetic hypothesis. Greater numbers of patients with this association are needed for further meaningful analysis. Many other fascinating points are raised in this paper, too many to discuss in this brief time. I would like to ask Dr Ritch the following questions:

1. In light of his hypothesis, how does a peripheral iridectomy work to cause a flattening of the iris?
2. Does a laser peripheral iridectomy reduce the amount of pigment being shed? If so, how?
3. Does the development of a normal iris stroma depend on the prior development of a normal iris PE, or vice versa?
4. Is the genetic defect linked to myopia or only more likely to be expressed in myopia?
5. Although intuitively I agree with his statement that the diagnosis of PDS often is missed, does he have evidence to back this statement?

In closing, I congratulate the author on pulling together a wealth of material into a working hypothesis.

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PAUL LICHTER, M.D. The curiosity about pigmentary glaucoma has been that way for years and years. It is one of the more interesting entities that

we see in ophthalmology and it does give us curiosity as to why this pigment is there and what it does. But pigment dispersion syndrome, which Dr. Ritch indicated had an incidence of 2.54% in his screening of whites, is a fairly common finding. And so is glaucoma. The gene frequency for glaucoma is quite high. It is a widespread gene. One of the parts of the pigment dispersion syndrome that most interests us is that it can, if associated with glaucoma, lead to blindness. I want to ask Dr. Ritch why can't there simply be two genes, because pigment dispersion is by far, much more frequent than pigmentary glaucoma. So why can't individuals with pigment dispersion simply have the same incidence of glaucoma as the general population?

ROBERT RITCH, M.D. Dr. Yanoff asked four questions. First, how does an iridotomy work in pigment dispersion syndrome? Remember that pupillary block and reverse pupillary block are two sides of the same coin. Just as iridotomy eliminates relative pupillary block and allows aqueous to flow from the posterior to the anterior chamber in angle-closure glaucoma, it relieves the reverse pupillary block in pigment dispersion syndrome and allows aqueous to flow from the anterior to the posterior chamber. When the iris is penetrated, one can actually see the pigment flowing from the anterior into the posterior chamber, the same phenomenon but opposite direction of the "mushroom cloud" of aqueous and pigment which flow into the anterior chamber when the iris is penetrated in pupillary block. In addition to allowing equilibration of aqueous humor between the two chambers, the accentuation of the iris concavity with accommodation is significantly reduced if not totally eliminated.

Second, does laser iridotomy completely eliminate pigment dispersion? No, it does not. Drs. William Haynes and Lee Alward together with our group reported such a patient recently in *Ophthalmic Surgery and Lasers*. This patient had massive pigment liberation while playing basketball and this was completely eliminated by low-dose Pilocarpine pretreatment. Nevertheless, I have performed only about 20 iridotomies. My preferred treatment is pilocarpine in those patients who do not have peripheral retinal abnormalities, but of course the younger patients cannot tolerate miotic drops because they cause accommodative spasm and induced myopia. However, they do very well with Ocuserts. We have started hundreds of patients on these.

Third, does the development of the normal iris stroma depend on the normal development of the iris pigment epithelium? I just cannot answer that question. I am not a developmental biologist and I don't know if any

one has ever looked at this. It is possible that normal development of one is dependent on the other, or it is possible that both of them respond to the same transmitter during differentiation and that their differentiation occurs together as a parallel process.

Fourth, is the genetic defect linked to myopia or is myopia more likely to be expressed in glaucoma? It is possible that the two are linked, since it is very rare to see hyperopes with pigment dispersion. I have leaned toward the hypothesis that hyperopes can be carriers, but that myopia predisposes to the phenotypic expression. Accommodation may play a much greater role than we have previously thought and may account for why myopes manifest the phenotypic expression. There is a correlation between myopia and intelligence; pigment dispersion patients tend to be highly intelligent, and prolonged accommodation leads to myopia. There also seems to be a psychological profile which many patients with pigment dispersion fit. They are often highly goal oriented, more tense than average, and somewhat hypomanic. Surgeons and lawyers are more likely to have pigment dispersion than psychiatrists and accountants. There seems to be a generalized adrenergic hypersensitivity. Future studies may clarify this.

Dr. Lichter asked the "how-many-hits-does-it-take-to-make-glaucoma" question. I have always thought in terms of the three hit theory. You need something to affect the trabecular meshwork, such as pigment in pigmentary glaucoma or a gene causing decreased trabecular function in juvenile "primary" open-angle glaucoma (JPOAG). Dr. Lichter's question is no doubt prompted by the fact that not everyone with pigment dispersion, even when the pigment on the meshwork appears massive, develops elevated IOP. So the second hit is one which makes the meshwork susceptible to developing elevated IOP. I might add at this point, parenthetically, that people who have pigment dispersion who do not develop elevated IOP nevertheless may go on later to develop glaucoma at an earlier age than they would have, had they not had some trabecular damage by pigment earlier in life. We are presently looking at whether patients with pigment dispersion go on to have a higher incidence of normal-tension glaucoma later in life. The third hit would be susceptibility of the disc to damage, since not all patients with elevated pressure develop disc damage.

However, I think that we are dealing with two different primary hits, and it's not necessary to have two genes, at least not the genes we are thinking of in this discussion. Pigment dispersion is very common in the population but most of them remain undiagnosed. Most affected people go through life never knowing they have it; in fact, most people have never even heard of it. The juvenile glaucoma gene is common also, but proba-

bly less common than the one for pigment dispersion. Nevertheless, the only hard evidence we have are two studies presented at ARVO in 1995 by Drs. Zeev Stegman and Joseph Sokol, in which we looked at trabecular meshwork heights. Patients with pigmentary glaucoma had normal meshwork heights, while those with JPOAG had meshworks which were significantly smaller than normal.

I would like to take this opportunity to thank the Society for inviting me to speak today and to thank Dr. Yanoff for his excellent discussion.