ASYMMETRIC PIGMENT DISPERSION SYNDROME

BY *Muriel I. Kaiser-Kupfer,* MD, *Carl Kupfer,* MD,
AND (BY INVITATION) *Lessie McCain,* RN

INTRODUCTION

IN 1979 CAMPBELL[1] PUT FORWARD A HYPOTHESIS SUGGESTING THAT THE CAUSE OF the loss of pigment from the posterior iris pigment epithelium in the pigment dispersion syndrome (PDS) was ". . . due to mechanical rubbing between the peripheral, often concave iris and anterior zonular packets in predisposed individuals." The purpose of this paper is to examine this new hypothesis with regard to four cases of markedly asymmetric PDS and three selected cases of early development of PDS. In this manner, it may be possible to confirm this hypothesis or suggest that other additional factors may be contributing to the pigment loss in PDS.

MATERIALS AND METHODS

All PDS patients in the study underwent complete ophthalmologic examination including iris transillumination, gonioscopy, intraocular pressure, tonography, ultrasonography, anterior chamber depth and volume. Iris transillumination was photographed using a transscleral stroboscopic flash. Koeppe lens gonioscopy allowed for photographic documentation of the angle structures using a Kowa camera. With the use of a Haag-Streit pachymeter, the anterior chamber depth was measured in both eyes. Intraocular pressure was measured using the Goldmann applanation tonometer. An average of three consecutive readings was recorded on each eye. Conventional tonography was done with patients in a comfortable supine position fixating on an overhead ceiling target. Corrected ocular rigidity for total facility of outflow was determined with paired electronic Schiøtz tonometer readings, made with 5.5 and 10.0 gm weights, and a 4-minute tonogram tracing was made on each eye. The axial length of the eye was obtained by utilizing an ultrasonic digital biometric ruler (Son-

ometrics Systems, Inc). Anterior chamber volume was measured using the photogrammetric method of Johnson and co-workers.[2]

CASE REPORTS

CASE 1

A 26-year-old white man was referred to the National Eye Institute (NEI) in March 1981 with a diagnosis of PDS since December 1980. The father has been said to have "borderline glaucoma" but on examination showed no evidence of PDS. The ophthalmic examination revealed the best corrected visual acuity to be 20/20 in the right eye with a $-1.25\ -0.25 \times 110°$, and 20/20 in the left eye with a $-1.50\ -0.25 \times 75°$. The patient had been wearing glasses to correct his myopia since age 11. The irides were blue. The corneas were clear, and in the right eye there was an occasional pigment fleck on the posterior corneal surface and some pigment deposited on the anterior iris surface. No pigment was noted on the left anterior iris surface. The right eye showed advanced slit-like iris transillumination defects throughout the entire iris circumference (Fig 1A). The left eye showed only fine punctate transillumination defect (Fig 1B). Gonioscopy in the right eye showed a 4+ pigment band on the trabecular meshwork overlying Schlemm's canal (Fig 1C). In the left eye there was a trace of pigment seen on trabecular meshwork (Fig 1D). Prominent iridodonesis, and a concave iris root were noted and appeared equal bilaterally. Tonography indicated an applanation tension in the right eye of 15.3 mm Hg with an outflow facility of 0.07 μl/min/mm Hg, and in the left eye 13 mm Hg with a outflow facility of 0.17 μl/min/mm Hg. Goldmann fields were full to the I4e and I2e targets. The optic nerve head, macula, and vessels were normal. On A-Scan, the right eye measured 24.51 mm and the left eye 24.60 mm in length. The anterior chamber depth was 4.2 mm on the right and 4.0 on the left and the anterior chamber volumes were 214.7 μl and 203.0 μl, respectively.

CASE 2

A 42-year-old white man was referred to the NEI in February 1983. Although the patient had been followed by his ophthalmologist since 1975, a Krukenberg spindle was first noted in 1982 at which time a diagnosis of PDS was made. The family history was non-contributory. The ophthalmic examination revealed the best corrected visual acuity to be 20/15 in the right eye with a $-0.50\ -1.00 \times 165°$ and 20/15 in the left eye with a $-2.50\ -1.75 \times 180°$. The patient had worn glasses to correct his myopia since high school. In addition, he had been involved in an automobile accident following which he developed double vision. On external examination, there was some limitation of abduction and adduction of the right eye. Otherwise, the anterior segment of the right eye was normal. The irides were blue-green. No iris transillumination could be demonstrated in the right eye (Fig 2A). The left eye had some flecks of pigment deposited on the corneal endothelium and demonstrated several areas of slit-like iris transillumination in

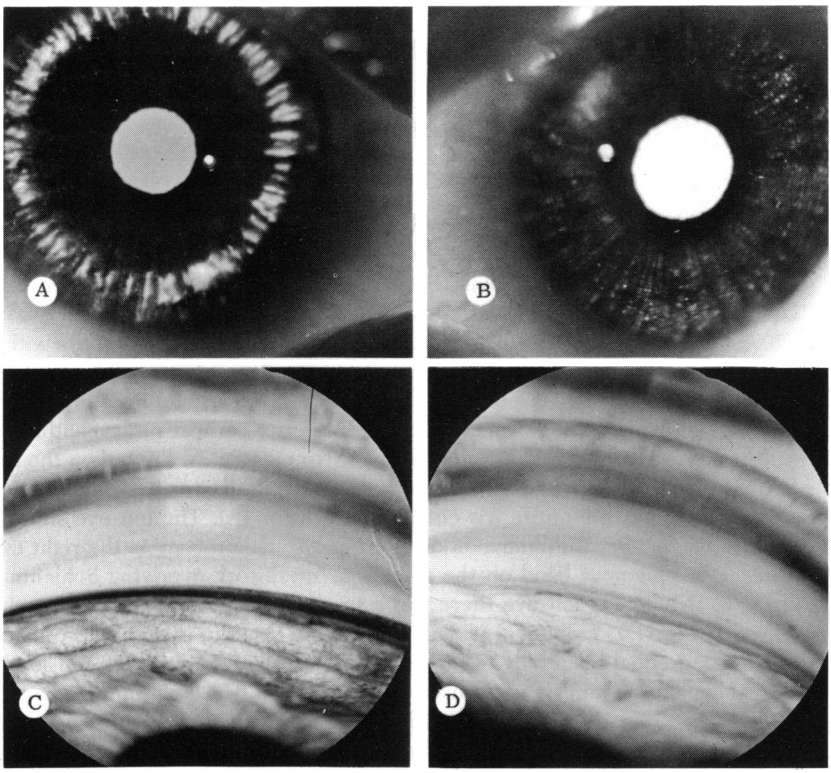


FIGURE 1
CASE 1. A: Advanced iris transillumination, right eye. B: Early punctate iris transillumination, left eye. C: Gonioscopy demonstrating heavy pigment on trabecular meshwork, right eye. D: Gonioscopy demonstrating only trace pigment, left eye.

the midperiphery arranged in scattered patches throughout the entire circumference of the iris (Fig 2B). Gonioscopy of the right eye showed an open angle with 1+ pigment on the trabecular meshwork (Fig 2C). In the left eye the angle was open 360° with a 4+ pigment band on the trabecular meshwork overlying Schlemm's canal, particularly heavy at 11 o'clock (Fig 2D). The patient did not have prominent iridodonesis or a concave iris root in either eye. Tonography indicated an applanation tension in the right eye of 11 mm Hg with an outflow facility of 0.22 μl/min/mm Hg, and in the left eye 13 mm Hg with an outflow facility of 0.14 μl/min/mm Hg. Goldmann fields were full to the I4e and I2e targets. The optic nerve head, macula and vessels were normal. On A-Scan, the right eye measured 25.10 mm and the left eye 24.74 mm in length. The anterior chamber depth was 4.3 mm on the right and 4.2 mm on the left and the anterior chamber volumes were 159.3 μl and 153.5 μl, respectively.

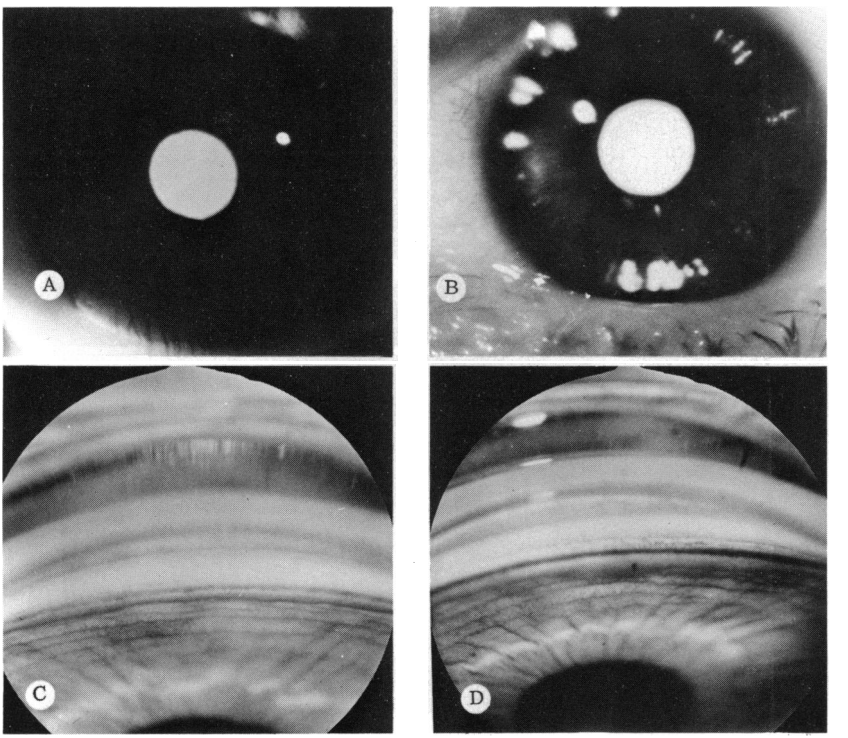


FIGURE 2
CASE 2. A: No iris transillumination, right eye. B: Moderately advanced iris transillumination, left eye. C: Gonioscopy demonstrating minimal pigment, right eye. D: Gonioscopy demonstrating heavy pigment on trabecular meshwork, left eye.

CASE 3

A 50-year-old white woman was referred to the NEI in March 1981 with a diagnosis of PDS since 1979. Family history was non-contributory. The patient noted that there had been some change in her irides from blue-green to more greenish in color. The ophthalmic examination revealed the best corrected visual acuity to be 20/20 in the right eye with a $-2.50\ -0.75 \times 130°$, and 20/20-2 in the left eye with a $-3.50\ -0.75 \times 30°$. The irides were green. The corneas were clear, and no pigment was noted on the posterior cornea or anterior iris surface. In the right eye, there was fine punctate iris transillumination (Fig 3A), while in the left eye there was some inferior areas of slit-like iris transillumination (Fig 3B). Gonioscopy in the right eye showed the angle open 360° without pigment on the trabecular meshwork (Fig 3C), while in the left eye the angle was open, and there was a 3+ pigment on the trabecular meshwork overlying Schlemm's canal (Fig 3D). Iridodonesis and a concave iris root were noted to be present and of equal

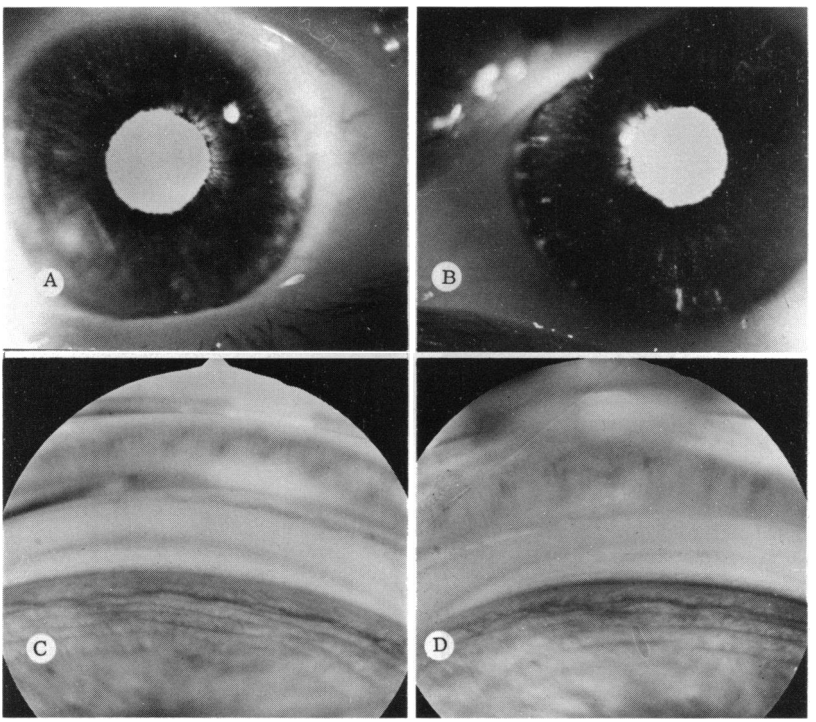


FIGURE 3
CASE 3. A: Early punctate iris transillumination, right eye. B: Iris transillumination inferiorly, left eye. C: Gonioscopy demonstrating absence of pigment, right eye. D: Gonioscopy demonstrating moderate pigment on trabecular meshwork, left eye.

magnitude bilaterally. Tonography indicated an applanation tension in the right eye of 9 mm Hg with an outflow facility of 0.35 μl/min/mm Hg and in the left eye 9 mm Hg with an outflow facility of 0.33 μl/min/mm Hg. Goldmann fields were full to the I4e and I2e targets. The optic nerve head, macula and vessels were normal. On A-Scan, the right eye measured 30.29 mm and the left eye 29.60 mm in length. The anterior chamber depth was 3.8 mm on the right and 4.0 mm on the left and the anterior chamber volumes were 136.4 μl and 138.7 μl, respectively.

CASE 4

A 66-year-old white man was referred to the NEI in May 1981 with a diagnosis of high myopia and incipient cataract. There was a family history of myopia. The ophthalmic examination revealed the best corrected visual acuity to be 20/40-1 in the right eye with a $-14.00\ -1.00 \times 75°$ and 20/40-3 in the left eye with a $-10.50\ -0.25 \times 90°$. The patient had worn glasses to correct his myopia for many years. The irides were blue. The corneas demonstrated bilateral Kruken-

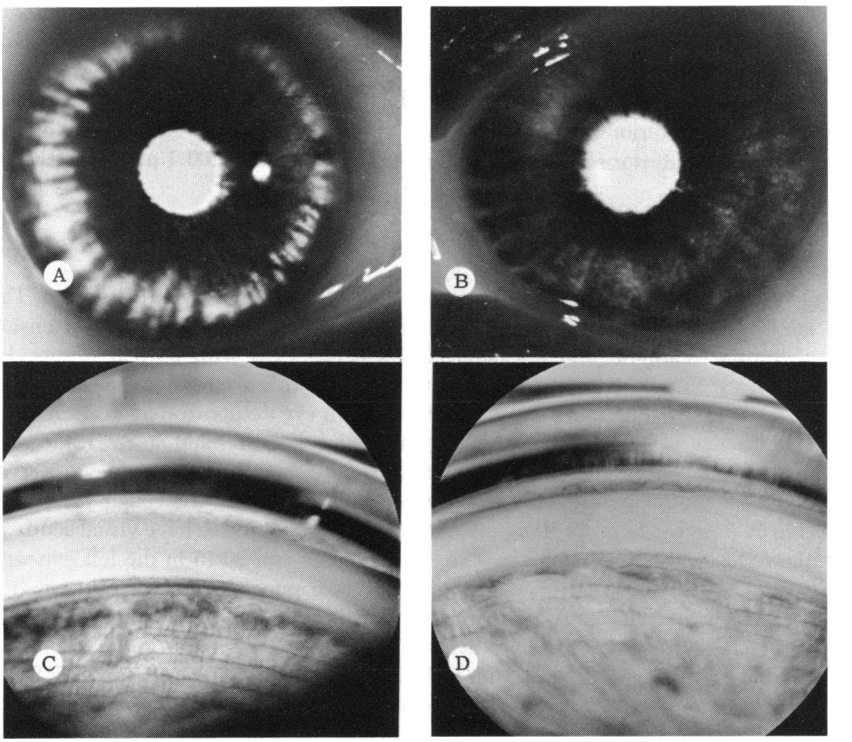


FIGURE 4
CASE 4. A: Advanced iris transillumination, right eye. B: No iris transillumination, left eye. C: Gonioscopy demonstrating heavy pigment on trabecular meshwork, right eye. D: Gonioscopy demonstrating trace pigment on trabecular meshwork, left eye.

berg spindles, marked on the right and minimal on the left. There was 4+ transillumination of the iris in the right eye (Fig 4A) and none in the left eye (Fig 4B). A significant amount of pigment was noted on the anterior iris surface of the right eye and none in the left eye. Gonioscopy in the right eye showed a 4+ pigment band on the trabecular meshwork which was so heavy that it partially filled the angle at 6 o'clock (Fig 4C). In the left eye there was a trace of pigment on the trabecular meshwork (Fig 4D). Prominent iridodonesis was noted bilaterally, perhaps slightly more on the right, but there was marked basal iris concavity bilaterally. Both lenses had early opacities, dense enough to explain the decrease in visual acuity. Tonography indicated an applanation tension in the right eye of 14 mm Hg and an outflow facility of 0.21 μl/min/mm Hg and in the left eye 15 mm Hg with an outflow facility of 0.15 μl/min/mm Hg. Goldmann visual fields were full to the I4e test object. However, on fundus examination, there was peripapillary atrophy surrounding the disc more evident on the right than the left, suggest-

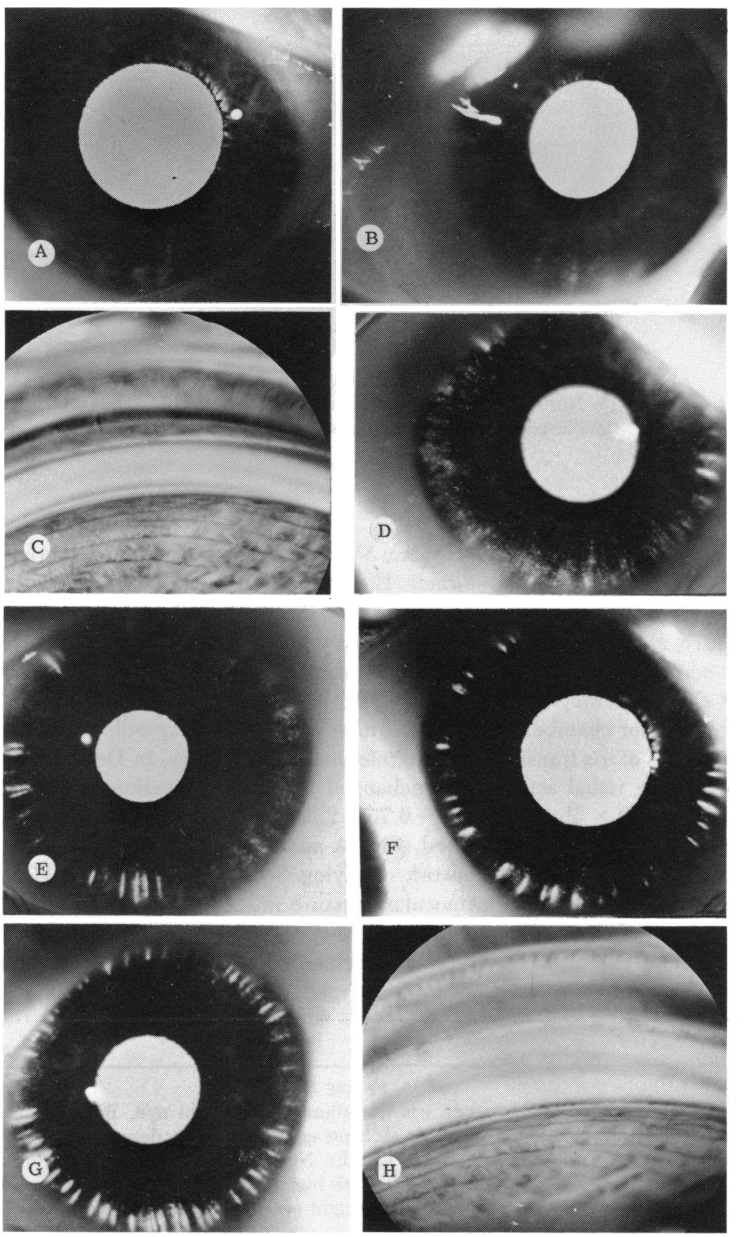
ing a posterior staphyloma secondary to the high myopia. There was a prominent choroidal pattern, and a foveal reflex was absent. A small horseshoe tear with a demarcation line of pigment around it was noted in the periphery of the right eye. On A-Scan, the right eye measured 30.04 mm and the left eye 28.80 mm in length. The anterior chamber depth was 3.8 mm on the right and 3.9 mm on the left and the anterior chamber volumes were 252.5 μl and 200.1 μl, respectively.

CASE 5

An 18-year-old white boy was referred to the NEI in February 1973 at age 8. The family history is significant in that his father has PDS and ocular hypertension requiring treatment and his paternal uncle has PDS with normal intraocular pressures. Visual acuity was 20/20 bilaterally. The irides were blue, and there was no iris transillumination. Gonioscopy of the right eye demonstrated an open angle and absence of pigment. The patient was followed yearly, and at age 12 definite areas of punctate iris transillumination were noted inferiorly in each eye (Fig 5A and B). Gonioscopy indicated absence of pigment on the trabecular meshwork (Fig 5C). At age 13 years 10 months, the patient was noted to have visual acuity in the right eye of 20/15 with a -0.75 $-0.25 \times 55°$ and 20/15 in the left eye with -1.00 $-0.25 \times 95°$. In addition to the diffuse punctate iris transillumination noted previously, some slit-like areas of transillumination were apparent (Fig 5D and E). Gonioscopy of the right eye still indicated no pigment on the trabecular meshwork. However, 2 years later in March 1982, the visual acuity was 20/20 with a correction of -1.50 sphere in the right eye and -1.75 to $0.25 \times 90°$ in the left eye. Punctate and slit-like iris transillumination were noted in the midperipheral iris bilaterally, more marked on the left (Fig 5F and G). Gonioscopy now demonstrated in both eyes a 3+ pigment band on the trabecular meshwork overlying Schlemm's canal (Fig 5H). Tonography indicated an intraocular pressure in the right eye of 18 mm Hg and outflow facility of 0.30 μl/min/mm Hg and 19 mm Hg in the left eye with an outflow facility of 0.29 μl/min/mm Hg in the right eye. Visual fields were full. The anterior chamber depth bilaterally was 4.2 mm.

CASE 6

A 16-year-old white boy and brother of case 5 was referred to the NEI in February 1973 at the age of 6. The visual acuity was 20/20 bilaterally, and no iris transillumination was noted. The irides were brown. At age 7, an atropine retinoscopy revealed a refractive error in the right eye of $+1.75$ $-0.50 \times 180°$, and in the left eye $+1.25$ sphere. Eight years later, the visual acuity was 20/20 bilaterally, and punctate iris transillumination was noted in the inferior portion of each iris (Fig 6A). Intraocular pressure was 14 mm Hg in the right eye and 13 mm Hg in the left eye. The anterior chamber depth was 3.7 mm in the right eye and 3.8 mm in the left eye. Gonioscopy showed no pigment deposited in the angle (Fig 6B).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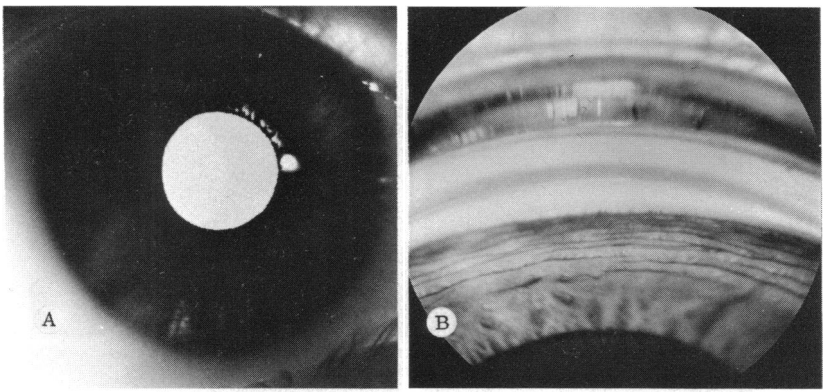

FIGURE 6

CASE 6. A: Age 15. Note punctate iris transillumination inferiorly, right eye. B: Same age. Gonioscopy demonstrating absence of pigment, right eye.

CASE 7

A 12-year-old boy and brother of case 5 was referred to the NEI in February 1973, at 2½ years of age and was normal. The patient returned in 1975 at age 4½ years, at which time the visual acuity was 20/20 in the right eye and 20/30 in the left eye. In 1977, at 7 years of age, the patient was examined again. At this time the vision was corrected to 20/20 in the right eye with $-0.50\ -1.50 \times 10°$ and in the left eye to 20/25 with $-0.50\ -1.50 \times 10°$. The iris was greyish-blue. There were deep anterior chambers bilaterally without Krukenberg spindle, and there were some areas of iris transillumination inferiorly in both eyes. In December 1982, at age 12, the visual acuity was unchanged with the correction in the right eye $+0.50\ -2.50 \times 5°$ and left eye $+0.75\ -2.00 \times 10°$. The iris transillumination in the midperiphery had increased (Fig 7A and B), and on gonioscopy there was pigment on trabecular meshwork overlying Schlemm's canal (Fig 7C and D). Tonography indicated an intraocular pressure in the right eye of 12 mm Hg and the left eye of 13 mm Hg and outflow facility of 0.35 μl/min/mm Hg and in the left eye 0.27 μl/min/mm Hg. The anterior chamber depth was 4.5 mm on the right and 4.7 mm on the left. On A-Scan, the right eye measured 24.5 mm and 24.7 mm on the left.

FIGURE 5

CASE 5. A: Age 12, early punctate iris transillumination, right eye. B: Same age. Early punctate iris transillumination, left eye. C: Same age. Gonioscopy demonstrating absence of pigment, right eye. D: Age 13 years 10 months. Note progression of iris transillumination, right eye. E: Same age. Note progression of iris transillumination, left eye. F: Age 15. Note further progression of iris transillumination, right eye. G: Same age. Note further progression of iris transillumination, left eye. H: Same age. Gonioscopy demonstrating moderate pigment on trabecular meshwork, right eye. Left eye was similar in appearance.

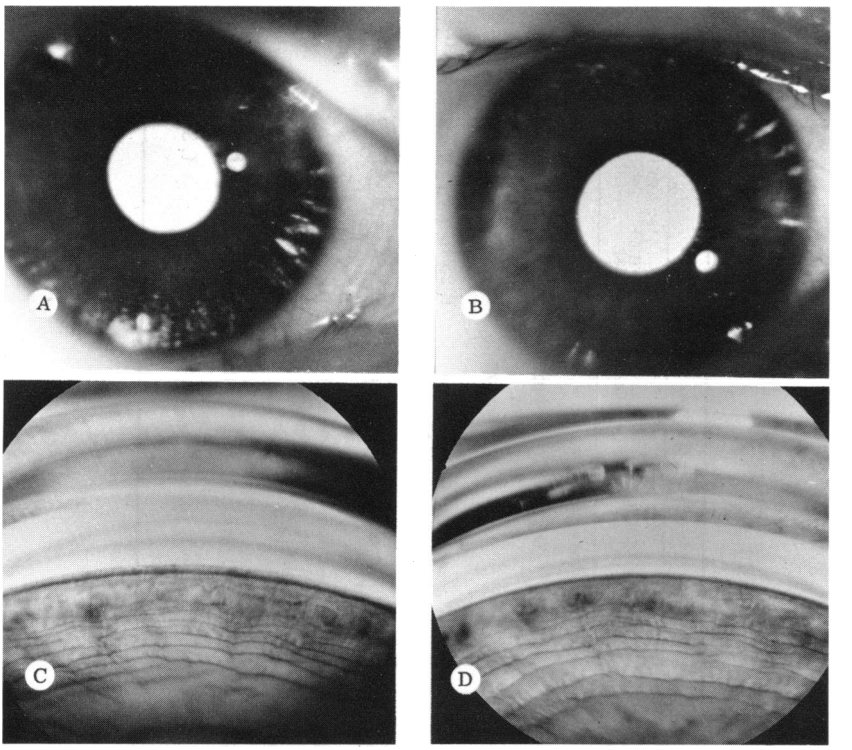

FIGURE 7
CASE 7. A: Age 12. Punctate and slit iris transillumination, right eye. B: Same age. Punctate and slit iris transillumination, left eye. C: Same age. Gonioscopy demonstrating pigment on trabecular meshwork, right eye. D: Same age. Gonioscopy demonstrating pigment on trabecular meshwork, left eye.

RESULTS

Table I summarizes the clinical findings of cases 1 to 4 which demonstrate an asymmetry between the two eyes with respect to the amount of iris transillumination as well as the quantity of pigment deposited on the trabecular meshwork. Except for case 4, there is a relative comparability between the two eyes with respect to the intraocular pressure and outflow facility, refractive error, length of globe and anterior chamber depth and volume. Cases 5 to 7 report the early appearance of iris transillumination which initially is punctate in appearance and can appear without myopia (case 6) or can precede the development of myopia and increase without

TABLE I:

CASE	AGE	AFFECTED EYE	REFRACTIVE ERROR	IRIS TRANS-ILLUMINATION	INTRAOCULAR PRESSURE	OUTFLOW FACILITY	GONIOSCOPY	LENGTH OF GLOBE	DEPTH OF ANTERIOR CHAMBER	VOLUME OF ANTERIOR CHAMBER
	YEARS				mm Hg	μl/min/mm Hg		mm	mm	μl
1	26	Right	R −1.25–0.35 × 110°	R advanced	15.3	0.07	R 4+ pigment	R 24.51	R 4.2	R 214.7
			L −1.50–0.25 × 75°	L early punctate	13	0.17	L trace pigment	L 24.60	L 4.0	L 203.0
2	42	Left	R −0.50–1.00 × 165°	R absent	11	0.22	R trace to 1+ pigment	R 25.10	R 4.3	R 159.3
			L −2.50–1.75 × 180°	L advanced	13	0.14	L 4+ pigment	L 24.74	L 4.2	L 153.5
3	50	Left	R −2.50–0.75 × 130°	R early punctate	9	0.35	R no pigment	R 30.29	R 3.8	R 136.4
			L −3.50–0.75 × 30°	L moderate	9	0.33	L 3+	R 29.60	L 4.0	L 138.7
4	66	Right	R −14.00–1.00 × 75°	R advanced	14	0.21	R 4+ pigment	R 30.04	R 3.8	R 252.5
			L −10.50–0.25 × 90°	L absent	15	0.15	L trace	L 28.80	L 3.9	L 200.1

any concomitant progression of significant refractive error (case 5). Noteworthy is that the earliest changes of iris transillumination appear inferiorly at 6 o'clock.

DISCUSSION

There is no doubt that the recent hypothesis concerning the mechanism for the loss of pigment from the posterior iris pigment epithelium in PDS has made a major contribution in focusing on the mechanical rubbing between peripheral iris, which is often concave, and the anterior zonular packets. This hypothesis explains the radial configuration of the iris transillumination, the high prevalence of myopia in patients with PDS, why the usual age at diagnosis is in the 20s or early 30s since the myopic eye reaches its full size, and finally, the greater prevalence of PDS among men because men tend to have larger eyes than women. Case 4 is a good demonstration of this hypothesis. Cases 1 to 3, although again confirming the frequent presence of myopia, a deep anterior chamber, and an iris root often concave, nevertheless raise some further questions concerning the cause of pigment loss in PDS. Despite the relative similarity between the two eyes in cases 1 to 3 with respect to intraocular pressure, outflow facility, anterior chamber depth, volume, presence of iridodonesis and iris concavity, length of the globe and refractive error, a marked asymmetry exists with respect to both the amount of iris transillumination and the quantity of pigment deposited on the trabecular meshwork. In addition, the earliest iris transillumination defects seen in cases 5 and 6 are punctate, usually beginning at 6 o'clock and do not appear to be closely correlated with the development of a myopic refractive error. Finally, the pigment loss that is often seen from the ciliary body[3] cannot easily be accounted for by a mechanism of mechanical rubbing. These findings would suggest that other risk factors may be playing an important role in pigment loss besides the mechanical rubbing. Campbell[1] does mention that the mechanical rubbing leads to loss of pigment in ". . . predisposed individuals." It may very well be that there is a basic abnormality of the pigment epithelium of the iris which makes some groups of cells especially vulnerable to the contact with the zonules and the subsequent mechanical rubbing. The fact that the epithelium of the iris displays focal hypopigmentation and atrophy with abnormal and immature melanosomes[4] as well as abnormalities in the dilator muscle and iris stroma,[4-6] would suggest that an underlying congenital or developmental defect in the pigmented epithelial cells of the iris (as well as the ciliary body) is the primary abnormality. The juxtaposition of normal and abnormal pigment

epithelial cells may explain the mosaic loss of pigment and the attendant punctate appearance of iris transillumination in early PDS. These changes within the iris may very well lead to the eventual characteristic configuration of the deep anterior chamber with a concave iris and the eye to have a myopic refractive error. The identification of these additional risk factors awaits further investigation.

SUMMARY

The hypothesis proposed by Campbell[1] goes a long way to clarify the loss of pigment from the posterior iris pigment epithelium in PDS. However, the present series of cases of either asymmetric PDS (cases 1 to 3) or early developing PDS (cases 5 to 7) suggest that other factors appear to play a role in addition to mechanical rubbing. These other factors await further identification.

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DISCUSSION

DR DOUGLAS R. ANDERSON. The authors report that they did not find compelling evidence in their own experience to confirm or deny the hypothesis of Campbell that pigmentary dispersion results when the anatomic relationships of certain myopic eyes permit the zonular fibers to rub against the posterior iris surface.

Their observations are of two types. The first, to examine cases of asymmetric pigmentary dispersion, is very clever. If any condition is asymmetric between the two eyes, there should be an asymmetry in the anatomic or physiologic factors that are relevant to the underlying pathogenesis. The authors were frustrated in their search and did not recognize an obvious anatomic asymmetry. On this half of their report, I would like to make two comments:

First, it seems that in three of the four cases presented, the anterior chamber was in fact 0.2 mm deeper in the more severely affected eye. The fourth case might be excused, because the eye with the greater pigmentary dispersion also had a shorter total axial length, and the anterior chamber might be deeper relative to the position of the zonule—one can't tell. It is after all not the absolute position of the iris, but its relationship to the position of the zonule, that is relevant to the mechanism suggested by Campbell. In any event, the rather small difference in anterior chamber depth, close to the limits of accuracy of the measurement, in only three of four cases is shaky evidence, so I agree with the authors that their observations do not confirm Campbell's hypothesis. However, the evidence is not sufficient to deny the theory either.

Secondly, the relevant asymmetry may be in the relationship between the iris insertion into the ciliary body and the attachment positions of the zonule to the lens and ciliary body. The difference between the two eyes that allows iris-zonule contact in one eye, but not the other, may be very small—perhaps not directly measurable clinically and not reflected in cornea-to-lens distance, that is the clinical measure of anterior chamber depth. Perhaps a biometric measure more complex than anterior chamber depth can be found that would relate more directly to the anatomic proximity of the zonule and peripheral iris that is presupposed by Campbell's theory.

The authors also report that a group of three brothers (whose father and uncle had pigmentary dispersion syndrome [PDS]) developed pigmentary dispersion rather early in life, even before they became myopic. It will take a couple of decades of waiting to determine whether or not the members of this family are typical representatives of PDS. If they are, these observations on the very early course of the disease will prove most interesting.

Meanwhile we can ask several questions that follow from these observations. Could the observations mean that the abnormal anatomic relationship between the ciliary body, zonule, and iris exists before the typical myopic shift in refraction that occurs during adolescence (perhaps due to an enlarging axial length resulting from an enlargement of the posterior portion of the globe)? Might an intraocular pressure higher than average during late childhood in eyes with dispersion facilitate the ocular lengthening process at this age, with myopia being in part a result of the dispersion occurring in the anterior segment? Might it be that in most or even all cases of pigmentary dispersion discovered in early middle age that the pigmentary dispersion actually began in childhood?

In summary, although the data are not conclusive, the careful observations of the authors and the ideas they suggest are most interesting, and I thank them for sharing their information with us today.

Dr George L. Spaeth. I would like to ask the authors if they considered a possible modification of Doctor Campbell's theory that the pigment dispersion syndrome is caused by the zonules rubbing on the posterior surface of the iris. I want to modify that theory by saying that it is the distribution of the pigment transillumi-

nation defects that is caused by the zonules rubbing on the iris, but that the basic problem is an abnormality of the pigment epithelium itself that allows it to be rubbed off by contact with the zonules. It is the abnormality of the iris that is the basic problem. Some years ago Doctor Rodrigues and I wrote a paper on the dispersion syndrome which showed that the pigment epithelial defects of the iris occurred in a mosaic type of pattern; there were normal cells immediately adjacent to pathological cells. This finding supports the hypothesis that the basic abnormality lies in the iris itself, and that it is only the distribution of the transillumination defects that is caused by their contact with the zonules.

DR W. RICHARD GREEN. The comment Doctor Spaeth made prompts me to make this remark. In our study of two cases of the pigment dispersion syndrome, one of which was followed for 23 years by Doctor Harold Pierce, there was a remarkable change in the cells adjacent to the areas of defects in the iris pigment epithelium. These cells had numerous microvillous processes in contrast to few or no microvillous processes in normal uninvolved areas.

DR CARL KUPFER. I want to thank Doctor Anderson for his very appropriate comments. I would like to say that I don't think the purpose of this paper is to deny the role that mechanical rubbing does play in production of the pigment dispersion syndrome (PDS). In the cases presented, there were deep anterior chambers, and some had marked iris concavity and much more iridodonesis than one would expect in a comparable myopic eye. Therefore, I do think that mechanical rubbing is a major factor, and we are in agreement with Campbell. The point is that one wonders whether there are other risk factors, and I think some of them have been brought up by both Doctor Anderson and in the comments of Doctor Spaeth and Doctor Green. There have been histopathologic reports of eyes with PDS indicating abnormalities in the iris stroma, pigment epithelium, and radial dilator muscle. This syndrome is probably a much more complex situation, and we thought that examination of the asymmetric cases might point to additional risk factors that would be involved. Doctor Anderson mentioned the desirability of additional measurements of the anterior chamber. Doctor Brubaker has shown that the greatest difference in the depth of anterior chambers in PDS as compared to controls is approximately 3.5 mm from the central corneal point. We did analyze those particular measurements, and they did not show any significant difference in the first three cases, but did show a difference in the fourth case. It is our expectation that as we collect more clinical material with histopathologic correlation, the cause will be further clarified.