A Study of Iridectomy Histopathologic Features of Latanoprost- and Non–Latanoprost-Treated Patients

Daniel M. Albert, MD, MS; Ronald E. Gangnon, PhD; Michele L. Zimbric, BS; Christine M. Damico, BS; Marian R. Fisher, PhD; Joel Gleiser, MD; Hans E. Grossniklaus, MD; W. Richard Green, MD

Objectives: To examine the histopathologic features of iridectomy specimens from patients undergoing glaucoma surgery and to compare histologic abnormalities in a group of patients with a history of latanoprost therapy with those in a group of patients who had no history of prostaglandin therapy (controls).

Methods: Iridectomy specimens and patient history forms were submitted to the central Latanoprost Pathology Center. These were independently examined by 3 ophthalmic pathologists in a masked fashion. Specimens were evaluated for malignant, premalignant, and other changes including differences in levels of pigmentation, degrees of cellularity, inflammation, vascular abnormalities, and changes in the iris pigment epithelium.

Results: Specimens were received from 449 patients with a history of latanoprost treatment and 142 patients who had no history of treatment with latanoprost or other prostaglandin analogues. No evidence of malignant or premalignant changes was found. In latanoprost-treated irides, the prevalence of iris freckles was higher ($P=.001$) than in control irides, as was the combined number of stromal fibroblasts and melanocytes ($P<.001$). In a subgroup of specimens received through June 2002, there was no significant difference in mean melanocyte counts ($P=.35$) obtained by immunohistochemical staining techniques between the latanoprost-treated and control groups.

Conclusions: These findings support previous studies indicating that latanoprost-induced eye color changes are due to an increased amount of melanin within the iris stromal melanocytes. The increased numbers of freckles may be a focal manifestation of this effect.

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Author Affiliations:
Department of Ophthalmology and Visual Sciences (Drs Albert and Gleiser and Mss Zimbric and Damico) and Department of Biostatistics and Medical Informatics (Drs Gangnon and Fisher), University of Wisconsin Medical School, Madison; Department of Ophthalmology, Emory University, Atlanta, Ga (Dr Grossniklaus); and Department of Ophthalmology, The Johns Hopkins University, Baltimore, Md (Dr Green).
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NEW GLAUCOMA DRUGS including latanoprost, isopropyl unoprostone, travoprost, and bimatoprost are associated with increased pigmentation of the iris in some patients.[1] Our knowledge of this phenomenon is based primarily on clinical observations, with relatively limited histopathologic investigation.[2,3] This study was designed to evaluate, in a systematic manner, key histopathologic findings in iris specimens from patients undergoing glaucoma surgery and to compare the results in groups defined by a history of latanoprost therapy or no history of therapy with latanoprost or any prostaglandin analogues. Assessments of malignant or premalignant changes including the presence of melanoma, increased cell number, and mitotic figures were recorded. Other characteristics evaluated included the degree of pigmentation of the anterior border layer and stroma, inflammation, abnormalities of the stromal blood vessels, and pigment epithelial changes. This is the first large histopathologic study to address the effects of latanoprost on the human iris, including the safety aspects of latanoprost-induced iris pigmentation.

METHODS

Iris specimens, obtained at the time of iridectomy during glaucoma surgery, were received in 10% neutral-buffered formalin at the Latanoprost Pathology Center (LPC) and labeled by the LPC coordinator with a unique study accession number. The formalin-fixed tissue specimens were processed overnight on an automated tissue processor, embedded in paraffin, serially sectioned at 5 µm, and mounted onto treated slides. The first 3 slides were stained with hematoxylin-eosin, the next 3 slides were bleached with potassium permanganate prior to staining with hematoxylin-eosin, and the following 7 slides were left unstained. All slides were labeled with the unique study accession number assigned to the specimen. If any tissue remained after sectioning, the paraffin block was archived.

Sets of microscopic slides (1 hematoxylin-eosin slide, 1 bleached hematoxylin-eosin slide, and 1 unstained slide) were sent to 3 reviewing pathologists (D.M.A., H.E.G., and W.R.G.) who examined the set independently and with no knowledge of therapy history. They completed the accompanying pathology grading form, including an assessment of the quality of the specimens, their location, and their orientation. These forms were returned to the LPC coordinator, who completed a composite grading form using specific rules for combining data from the 3 grading forms.

An iris freckle (ephelis) was identified by the pathologists as a focal area of increased pigmentation in the anterior border layer melanocytes without an increased number of melanocytes.[4] This is consistent with the general definition of an iris freckle in the field of eye pathology. Using all specimens received by June 2002 and the techniques previously described,[5] 1 of the unstained slides was stained with S100a and fluorescein isothiocyanate. This stained slide was examined by a single reviewer (in the laboratory of D.M.A.) who was masked to treatment history and identified melanocytes and other cells (fibroblasts and clump cells) by their staining characteristics, counted them, and entered the counts into a spreadsheet. Specimens were adjudicated using a protocol formulated by the 3 pathologists prior to the beginning of the study.

The patient history form accompanying the specimen included iris color (blue, hazel, or brown); type of glaucoma; ocular history; type of surgery; treatment history, including the start of medical treatment; medication history, including specific medications used; duration of latanoprost therapy (<3 months, 3 months to 3 years, or >3 years); other glaucoma medications used; and presence or absence of increased pigmentation after glaucoma medication. The latanoprost group was defined by a history of latanoprost therapy, and the control group was defined by no history of therapy with latanoprost or any other prostaglandin analogue.

After review by the LPC coordinator, the patient history form and the composite grading form, each identified only by the unique accession number, were sent to the Statistical Data Analysis Center (Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison) for data entry (Oracle database; Oracle, Redwood Shores, Calif) and statistical analysis. The numbers of melanocytes and other cells from the subset of specimens were transferred separately from the laboratory for their inclusion in this article. This study received institutional review board approval from the University of Wisconsin Health Sciences Human Subjects Committee.

Comparisons of groups were based on the Wilcoxon rank sum test for continuous and ordinal variables and the Pearson χ^2 test for categorical variables. Analyses were performed using analysis of variance models for continuous and ordinal variables and logistic regression models for dichotomous variables, which included sex and iris color as covariates. Statistical significance was set at $P<.05$. No formal adjustment for multiple comparisons was used.

RESULTS

Between September 1998 and January 2003, 591 iris specimens were received at the LPC through the cooperation of 41 glaucoma surgeons and 22 centers, listed in **Table 1**. Specimens were received from 449 patients with a history of latanoprost treatment and 142 patients who had no history of treatment with latanoprost or other prostaglandin analogues. The duration of latanoprost treatment was recorded for 346 (77%) of the 449 patients in the latanoprost group; 57 used latanoprost for less than 3 months, 247 for 3 months to 3 years, and 42 for more than 3 years. **Table 2** summarizes, by treatment group, relevant information from the patient history form and

Table 1. Surgeons and Centers Contributing Iris Specimens

James C. Allen, MD	University of Wisconsin–Madison
James D. Brandt, MD	University of California–Davis
Carl B. Camras, MD	University of Nebraska Medical Center, Omaha
Joseph Caprioli, MD	Jules Stein Eye Institute, Los Angeles, Calif
George A. Cioffe, MD	Devers Eye Institute, Portland, Ore
John S. Cohen, MD	Cincinnati Eye Institute, Cincinnati, Ohio
Gordon R. Douglas, MD, FRSC	University of British Columbia, Vancouver
Donna J. Gagliuso, MD	Mount Sinai Medical Center, New York, NY
Gregg A. Heatley, MD	University of Wisconsin–Madison
Eve J. Higginbotham, MD	University of Maryland–Baltimore
Henry D. Jampel, MD, MHS	The Johns Hopkins University, Baltimore
Michael A. Kass, MD	Washington University, St Louis, Mo
L. Jay Katz, MD	Wills Eye Hospital, Philadelphia, Pa
Paul L. Kaufman, MD	University of Wisconsin–Madison
Allan E. Kolker, MD	Glaucoma Institute, Creve Coeur, Mo
Theodore Krupin, MD	University Eye Specialists, Chicago, Ill, and Northbrook, Ill; Northwestern University, Evanston, Ill
Jeffrey M. Liebmann, MD	The New York Eye and Ear Infirmary, New York, NY
Frederick S. Mikelberg, MD, FRSC	University of British Columbia
Donald S. Minckler, MD	Doheny Eye Institute, University of Southern California, Los Angeles
Marlene R. Moster, MD	Wills Eye Hospital
Jonathan S. Myers, MD	Wills Eye Hospital
Paul Palmberg, MD, PhD	Bascom Palmer Eye Institute, Miami, Fla
Richard K. Parrish II, MD	Bascom Palmer Eye Institute
Todd W. Perkins, MD	University of Wisconsin–Madison
Steven M. Podos, MD	Mount Sinai Medical Center
Harry A. Quigley, MD	The Wilmer Eye Institute at Johns Hopkins University
Robert Ritch, MD, FACS	New York Eye and Ear Infirmary
Alan L. Robin, MD	The Wilmer Eye Institute at Johns Hopkins University
Patricia C. Sabb, MD	University of Wisconsin–Madison
Thomas W. Samuelson, MD	University of Minnesota and Phillips Eye Institute, Minneapolis
Courtland M. Schmidt, Jr, MD	Wills Eye Hospital
Joel S. Schuman, MD	New England Eye Center, Boston, Mass
Janet B. Serle, MD	Mount Sinai Medical Center
M. Bruce Shields, MD	Yale University School of Medicine, New Haven, Conn
Dong Shin, MD, PhD*	Kresge Eye Institute, Detroit, Mich
George L. Spaeth, MD	Wills Eye Hospital
Annette K. Terebuh, MD	Mary Rutan Hospital, Bellefontaine, Ohio
E. Michael Van Buskirk, MD	Devers Eye Institute
Robert N. Weinreb, MD	University of California, San Diego
Richard P. Wilson, MD	Wills Eye Hospital
Michael E. Yablonski, MD, PhD	University of Nebraska Medical Center

*Deceased.

Table 2. Patient History Forms Summary*

	Controls	Latanoprost	*P* Value
Sex, F	94/139 (67.6)	246/441 (55.8)	.01
Race/ethnicity	(n = 135)	(n = 429)	.48
American Indian or Alaskan Native	0	2 (0.5)	
Asian or Pacific Islander	2 (1.5)	1 (0.2)	
Hispanic	2 (1.5)	6 (1.4)	
Black, not of Hispanic origin	17 (12.6)	42 (9.8)	
White, not of Hispanic origin	113 (83.7)	372 (86.7)	
Other	0	2 (0.5)	
Iris color	(n = 125)	(n = 416)	.22
Blue	36 (28.8)	155 (37.3)	
Hazel	24 (19.2)	69 (16.6)	
Brown	65 (52.0)	192 (46.2)	
Type of glaucoma	(n = 125)	(n = 416)	.07
POAG	81 (64.8)	294 (70.7)	
Angle closure	9 (7.2)	21 (5.1)	
Secondary	8 (6.4)	41 (9.9)	
Other	26 (20.8)	49 (11.8)	
POAG/angle closure	1 (0.8)	5 (1.2)	
POAG/secondary	0	6 (1.4)	
Ocular history	(n = 133)	(n = 432)	
Uveitis	8 (6.0)	17 (3.9)	.32
Diabetic retinopathy	4 (3.0)	11 (2.6)	.89
Eye trauma	2 (1.5)	7 (1.6)	.92
Hyphema	2 (1.5)	4 (0.9)	.58
Year of completion of pathology grading form	(n = 142)	(n = 449)	<.001
1998	39 (27.5)	61 (13.6)	
1999	53 (37.3)	128 (28.5)	
2000	18 (12.7)	82 (18.3)	
2001	15 (10.6)	59 (13.1)	
2002	10 (7.0)	89 (19.8)	
2003	7 (4.9)	30 (6.7)	

Abbreviation: POAG, primary open-angle glaucoma.
*Selected information from the patient history form along with year of completion of the pathology grading form by treatment group. Data are presented as number (percentage) of subjects within each group. Number of subjects with nonmissing data are indicated by the denominator in the fraction for dichotomous variables and by the sample size for other variables. *P* values are based on the Pearson χ^2 test.

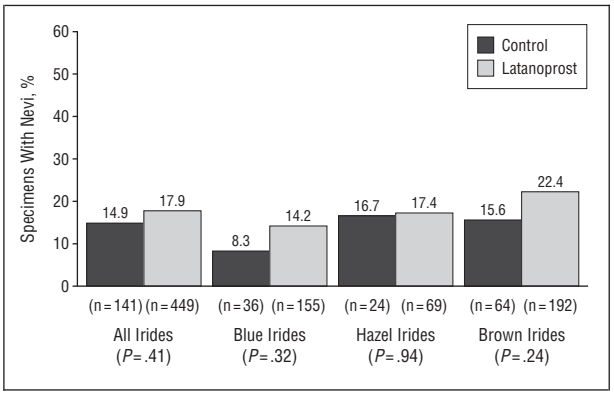

Figure 1. Proportion of specimens with nevi by treatment group for all irides and for subgroup based on iris color.

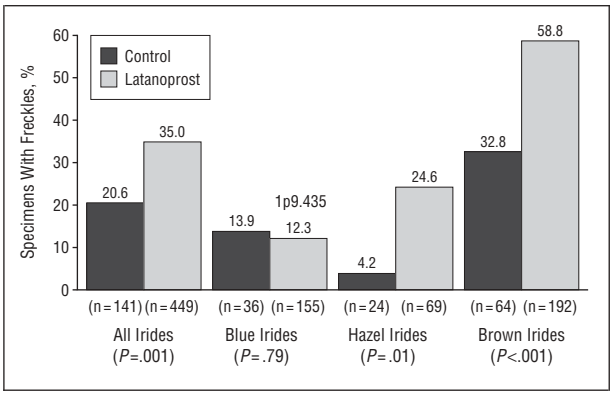

Figure 2. Proportion of specimens with freckles by treatment group for all irides and for subgroups based on iris color.

the year of completion of the pathology grading form. Race and ethnicity, iris color, type of glaucoma, and ocular history were statistically similar for the latanoprost and control groups; however, there were more women in the control group compared with the latanoprost group ($P=.01$). With regard to the year of completion of the pathology grading form, there was a statistically significant difference ($P<.001$) in the distribution of specimens by treatment group.

Evaluation of the composite pathology grading forms indicated that the latanoprost and control groups were comparable in terms of quality, location, and orientation of the iridectomy specimens (data not shown). All specimens were obtained from the peripheral iris.

No melanomas were reported on the pathology grading form in either the latanoprost or control group (data not shown). No statistically significant differences in the presence of nevi were noted either in all irides or in blue, hazel, or brown irides (**Figure 1**). There was, however, a statistically significant difference in the presence of freckles in the latanoprost group compared with the control group in all irides ($P=.001$) and in the hazel ($P=.01$) and brown ($P<.001$) irides (**Figure 2**). This difference remained statistically significant in multivariable logistic regression models, which included sex and iris color ($P=.009$).

There was a statistically significant difference between treatment groups in the number of combined stromal fibroblasts and melanocytes in all irides ($P<.001$) and in the brown irides ($P<.001$). In analyses by sex, there was no statistically significant difference between groups in the number of stromal fibroblasts and melanocytes in the irides of all men ($P=.24$) or in the irides of brown-eyed men ($P=.32$); there were statistically significant differences between groups in the irides of all women ($P<.001$) and in the irides of brown-eyed women ($P<.001$). (**Table 3**).

No statistically significant differences in the degree of pigmentation in the melanocytes of the anterior border layer or stroma, in the mean thickness, or in many stromal features were noted between the latanoprost and control groups (**Table 4**). Free pigment granules in the stroma ($P=.05$) were not statistically significantly different; rubeosis, although rare, was statistically significantly different ($P=.002$) (Table 4). The proportion of specimens determined to have a normal iris did not differ between the 2 groups (data not shown).

Table 3. Grading Form for Stromal Fibroblasts and Melanocytes in the Irides*

	Stromal Fibroblasts and Melanocytes				
	Controls		Latanoprost		
	No. of Patients	Mean (SD)	No. of Patients	Mean (SD)	*P* Value
All irides	141	85.9 (29.6)	447	98.1 (32.1)	<.001
Men	45	89.0 (34.3)	193	96.5 (31.8)	.24
Women	93	84.7 (27.5)	246	99.5 (32.5)	<.001
Blue irides	36	95.7 (27.8)	155	98.5 (29.9)	.74
Men	11	109.7 (29.6)	71	96.8 (27.5)	.10
Women	24	89.8 (25.7)	80	100.0 (32.3)	.19
Hazel irides	24	84.2 (21.4)	68	102.4 (39.6)	.05
Men	11	78.5 (19.6)	28	103.6 (49.4)	.13
Women	13	88.9 (22.4)	40	101.6 (31.6)	.23
Brown irides	64	81.1 (33.7)	191	96.1 (32.0)	<.001
Men	19	85.2 (41.8)	81	93.4 (27.7)	.32
Women	44	79.7 (30.3)	106	98.4 (35.1)	<.001

*Stromal fibroblasts and melanocytes as recorded on the composite pathology grading form by treatment group for all irides and for subgroups based on sex and iris color. Number of patients represents those with nonmissing data in each group. *P* values are based on the Wilcoxon rank sum test.

Table 4. Pathology Grading Form Summary*

	Controls	Latanoprost	*P* Value
Anterior border pigmentation	(n = 141)	(n = 443)	.72
None	1 (0.7)	4 (0.9)	
Minimal	64 (54.4)	180 (40.6)	
Moderate	52 (36.9)	168 (37.9)	
Heavy	24 (17.0)	91 (20.5)	
Stromal pigmentation	(n = 140)	(n = 446)	.53
None	4 (2.9)	7 (1.6)	
Minimal	91 (65.0)	284 (63.7)	
Moderate	28 (20.0)	109 (24.4)	
Heavy	17 (12.1)	46 (10.3)	
Free pigment granules (stroma)	(n = 141)	(n = 448)	.05
0-25	86 (61.0)	221 (49.3)	
26-100	40 (28.4)	167 (37.3)	
>100	15 (10.6)	60 (13.4)	
Inflammation (stroma)	(n = 140)	(n = 448)	.45
None to minimal	140 (100.0)	443 (98.9)	
Moderate	0	4 (0.9)	
Marked	0	1 (0.2)	
Abnormal stromal blood vessels	2/141 (1.4)	5/448 (1.1)	.77
Abnormal iris pigment epithelium	5/136 (3.7)	11/437 (2.5)	.47
Rubeosis	3/141 (2.1)	0/449	.002
Suggestions of pseudoexfoliation	0/141	0/449	>.99
Evidence of synechiae	0/141	3/449 (0.7)	.33
Attached Descemet membrane	0/141	2/449 (0.4)	.43
Attached lens capsule	0/141	1/449 (0.2)	.57
Hemorrhage in anterior border layer or iris pigment epithelium	2/141 (1.4)	3/449 (0.7)	.40
Endothelialization	0/141	1/449 (0.2)	.57
Descemetization	0/141	0/449	>.99
Mean thickness (anterior border layer), No. of cells†	2.0 (0.7), (n = 141)	2.0 (0.7), (n = 445)	.95
Macrophages (stroma), No.†	1.3 (1.9), (n = 141)	1.5 (2.4), (n = 448)	.30

*Selected information from the composite pathology grading form by treatment group. Data are presented as number (percentage) of subjects within each group unless otherwise indicated. Number of subjects with nonmissing data is indicated by the denominator in fractions for dichotomous variables and by the sample size for other variables.
†Data are presented as mean (SD).

Prior to iridectomy, 21 patients were reported to have darkening of the iris. All of these patients had received latanoprost treatment. In 6 cases, there was photographic documentation of the darkening. Data from patients with clinically observed darkening of the iris were included with data from other latanoprost-treated patients without darkening. No histopathologic abnormalities were seen in these specimens. It is presumed that subclinical or unnoticed eye color changes occurred in additional patients.

Using the subset of specimens received by June 2002, no statistically significant differences in melanocyte counts were noted. However, there was a statistically significant difference in other cell counts (fibroblasts and clump cells) between the latanoprost and control groups for all irides ($P=.005$; n=371), brown irides ($P=.02$; n=182), and men with blue irides ($P=.03$; n=56) (**Table 5**).

COMMENT

Differences in the iris color of normal eyes are the result of variable amounts of melanin granules within a constant number of melanocytes in the superficial stroma of the iris.[5-8] Iris melanocytes seem to reach their genetically determined amount of melanin in early childhood, and their melanin content usually remains constant in adulthood. Iris color, however, can be affected by a variety of ocular disorders.[9]

Latanoprost, a phenyl-substituted analogue of prostaglandin $F_{2\alpha}$, is effective for lowering intraocular pressure. In early trials in the United States, United Kingdom, and Scandinavia, it was associated with increased melanogenesis in the irides of patients treated in clinical trials.[10] Typically this change was manifested by a concentric increase in iris pigmentation appearing after about 6 months of treatment.[10] The incidence of increased pigmentation is apparently related to the color of the iris and has been reported to range from 5% to 70%.[11,12] More recently, other prostaglandin analogues introduced for the treatment of glaucoma have been associated with increased pigmentation of the iris in some individuals.[1] Most of the data regarding this phenomenon involve latanoprost, which was the first prostaglandin analogue available for the treatment of glaucoma.

In vitro studies in which human iris tissue or melanocyte cultures were incubated with latanoprost indicate that the iris darkening associated with latanoprost treatment is caused by the induction of tyrosinase expression.[13-16] In an additional in vitro study, Dutkiewicz et al[17] demon-

Table 5. Melanocyte and Other Cell Counts for Irides*

	Controls		Latanoprost		
	No. of Patients	Mean (SD)	No. of Patients	Mean (SD)	*P* Value
Melanocyte count					
All irides	102	70.7 (39.4)	269	76.5 (44.3)	.35
Men	37	74.6 (47.8)	122	78.2 (45.8)	.58
Women	65	68.5 (34.0)	147	75.1 (43.1)	.44
Blue irides	27	85.1 (41.9)	93	78.1 (44.2)	.27
Men	10	70.6 (60.4)	46	74.7 (81.2)	.58
Women	17	93.6 (24.9)	47	81.5 (42.2)	.14
Hazel irides	20	65.7 (26.6)	49	80.8 (56.0)	.62
Men	10	72.3 (26.6)	17	69.6 (51.6)	.44
Women	10	59.1 (26.2)	32	86.7 (58.1)	.24
Brown irides	55	65.4 (40.9)	127	73.7 (39.1)	.08
Men	17	78.2 (51.9)	59	83.4 (43.8)	.60
Women	38	59.7 (34.3)	68	65.3 (32.6)	.23
Other cell counts†					
All irides	102	143.2 (73.6)	269	168.0 (79.3)	.005
Men	37	153.8 (80.2)	122	179.9 (79.1)	.09
Women	65	137.2 (69.5)	147	158.2 (78.3)	.06
Blue irides	27	164.7 (69.8)	93	192.4 (79.5)	.12
Men	10	132.0 (83.2)	46	192.3 (81.2)	.03
Women	17	184.0 (57.8)	47	192.4 (77.8)	.76
Hazel irides	20	161.3 (58.9)	49	180.4 (83.6)	.48
Men	10	151.2 (68.4)	17	170.7 (86.2)	.74
Women	10	171.5 (49.2)	32	185.5 (83.1)	.54
Brown irides	55	126.0 (76.8)	127	145.4 (71.3)	.02
Men	17	168.1 (88.2)	59	172.8 (74.7)	.97
Women	38	107.2 (63.8)	68	121.6 (59.0)	.12

*Information on melanocyte and other cell counts from an immunohistochemical study of specimens received by June 2002 by treatment group for all irides and for subgroups based on sex and iris color. *P* values are based on the Wilcoxon rank sum test.
†Includes fibroblasts and clump cells.

strated that latanoprost induced tyrosinase activity but did not increase the mitotic index in a panel of human uveal and cutaneous melanoma cell lines. That study also suggested that the adverse effect of latanoprost on in vivo iris pigmentation did not result from increased cell division but from elevated tyrosinase activity.

The cynomolgus monkey has been described as an effective animal model for studying the increased pigmentation of the iris with latanoprost treatment.[10,18,19] Darkening of the iris was noted after about 2 months of treatment, with latanoprost inducing increased pigmentation in sympathectomized eyes. Nevi and freckles on the iris conjunctiva or eyelids were not affected. The authors concluded that latanoprost treatment increased the normal low melanin synthesis in the iridial melanocytes of the cynomolgus monkey. In latanoprost-treated eyes, the amount of eumelanin increased from 3- to 7-fold, whereas the variation of pheomelanin did not exceed 25%.[20]

Zhan et al[21] used Dutch-belted rabbits following unilateral superior cervical ganglionectomy as an experimental model for studying prostaglandin-induced iris color darkening. These investigators demonstrated that sympathetic innervation is required for age-related physiologic darkening of iris color and that prostoglandins may compensate for sympathetic denervation to produce the darkening.

Individual case reports and small series of iris specimens studied histopathologically following darkening from latanoprost treatment have been reported.[2,3,22-24] These light and electron microscopic studies indicate that latanoprost-induced eye color change is due to an increased amount of melanin within the iris stromal melanocytes rather than any increase in melanocyte number.

In our study, no evidence of malignant or premalignant changes was observed in either group based on the absence of melanomas, atypical nevi, cells with an atypical appearance, or increased numbers of mitotic figures. There was an increased prevalence of freckles in the latanoprost-treated group. We suggest that the increased number of freckles is a manifestation of focal increased tyrosinase expression and that the same pathogenesis exists for the more diffuse darkening. An extreme of this change may be the latanoprost-associated, diffuse, uniform dark velvet-brown appearance simulating a diffuse iris melanoma, as described by Tsai et al.[2] We do not believe that the increase in iris freckles has malignant potential or can lead to any adverse clinical effect on the eye.

There was a statistically significant increase in the number of combined stromal melanocytes and fibroblasts, most strongly evident in brown-eyed women. It should be noted that with the hematoxylin-eosin staining used for this study, stromal melanocytes and fibroblasts cannot be reliably differentiated. Because of this, immunohistochemical staining was performed for the subset of specimens received by June 2002, and no statistically significant dif-

ference in melanocyte count was seen in all irides or any subgroup. The combined stromal and fibroblast increase noted in the hematoxylin-eosin–stained slides appears to be due to an excess of fibroblasts and/or clump cells but not melanocytes.

Prostaglandin $F_{2\alpha}$ as well as prostaglandins E_1 and E_2 has been shown to act as an extracellular factor to regulate cell proliferation.[25] Prostaglandin $F_{2\alpha}$ stimulated DNA synthesis and cell proliferation in quiescent Swiss mouse 3T3 cell cultures[25,26] and in 1 of 2 clones of 3T3 cells from the National Institutes of Health (Bethesda, Md).[26] In addition, prostaglandin $F_{2\alpha}$ can modulate the growth and differentiation of corneal epithelial cells cultured in vitro. Consequently, it is not surprising that an increase in the number of iris fibroblasts and/or clump cells occurs in some latanoprost-treated eyes.[27]

In summary, our results are consistent with previous findings that latanoprost-induced eye color change is due to an increased amount of melanin within the iris stromal melanocytes and does not involve an increase in melanocyte number. Further examination of several histopathologic characteristics, as noted previously, shows no adverse histopathologic effects in latanoprost-treated irides as compared with controls.

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Correspondence: Daniel M. Albert, MD, MS, Department of Ophthalmology and Visual Sciences, F4/344 Clinical Science Center, 600 Highland Ave, Madison WI 53792-3284 (dalbert@wisc.edu).
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