HISTOPATHOLOGY OF THE ICE SYNDROME*

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INTRODUCTION

THE COGAN-REESE SYNDROME OF IRIS NODULES, ECTOPIC DESCEMET'S membrane, and unilateral glaucoma is now considered part of the spectrum of the iridocorneal endothelial (ICE) syndrome.[1] The primary pathology in this syndrome is thought to be an abnormality in the corneal endothelium. The sequence of events begins with proliferation of this endothelium, leading to corneal edema and extension over the trabecular meshwork onto the iris, which then can contract to produce broad peripheral anterior synechiae and iris atrophy.[2] Although this hypothesis can explain Chandler's syndrome and essential iris atrophy, it falls short of explaining the occurrence of multiple nevi on the iris surface and does not provide an explanation of the etiology of the endothelial cell proliferation and basement membrane production that covers the trabecular meshwork and anterior iris surface. The purpose of this report is to present two cases of the ICE syndrome, one of which is an iris nevus syndrome, and to present an alternative hypothesis, drawing upon the more recent evidence of involvement of abnormalities in neural crest cell migration and terminal differentiation.

CASE REPORTS

CASE 1

A 33-year-old physician first noted an asymmetric left pupil in 1981, when she was 28 years of age. Elevated intraocular pressure was diagnosed in the left eye in January 1985. The patient was first examined at the National Eye Institute (NEI) on September 15, 1986. At that time, vision in each eye was 20/15, with correction

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in the right eye of $-1.75+0.75\times35$ and in the left eye of $-2.50+1.25\times160$. Examination of the right eye showed no abnormalities. The left eye had an eccentric distorted pupil displaced nasally and superiorly. There was ectropion of the pupillary ruff nasally. Adhesions between iris and cornea were noted nasally. There was no iris transillumination. Multiple raised pigmented iris lesions were noted, especially nasally. On gonioscopy, the angle was closed almost three quarters of the circumference by broad iris-corneal adhesions, especially nasally, with intermittent small areas of angle structures visible. The diagnosis was ICE syndrome, Cogan-Reese variant. Despite treatment with timolol maleate, pilocarpine hydrochloride, dipivefrin Propine, and acetazolamide Diamox, the intraocular pressure in the left eye remained elevated at 29 mm Hg and the coefficient of facility of outflow was 0.08 μm/min/mm Hg. The visual fields and optic nerves were normal at that time.

In September 1988, there was constriction of the left visual field. The patient underwent a trabeculectomy with 5-FU, left eye, which was performed at another institution. In March 1989, intraocular pressure in the left eye had risen to the mid-30s and there was a visual field constriction. By October 1990, a superior Bjerrum scotoma had developed, intraocular pressure was in the mid-30s despite maximum medical therapy, and additional surgery was advised. On January 11, 1991, a left trabeculectomy and iridectomy was performed using 5-FU.

CASE 2

A 52-year-old woman was found to have elevated intraocular pressure (28 mm Hg) in the left eye on routine examination in 1989. Betaxolol hydrochloride (Betoptic) 0.5% was prescribed. The patient was first examined at the NEI on May 22, 1991. Visual acuity in the right eye was 20/16-1 with $+2.25+0.25$x150 and in the left eye was 20/20 with $+2.25+0.50+165$. The right eye was normal on examination. The left eye had a round pupil with three areas of iris stromal thinning but no transillumination. On gonioscopy, the left angle was closed about 300° by broad iridocorneal adhesions with the heaviest iris adhesions to cornea at the 1-o'clock position. The left visual field showed a superior Bjerrum scotoma and a relative inferior nasal step. Specular microscopy of the left endothelium revealed a beaten silver appearance with cellular pleomorphism and polymorphism. The diagnosis was a typical ICE syndrome. Because the patient could not tolerate maximum medical therapy, a trabeculectomy in the left eye was performed on June 12, 1991.

RESULTS

Sections of the iris tissue from case 1 revealed moderate stromal atrophy. The anterior surface of the iris was covered by a thick, basement membrane-like structure that was positive on periodic acid-Schiff (PAS) staining. On top of this membrane was a well-circumscribed nodule composed of heavily pigmented melanocytes (Fig 1A). These cells had abundant cytoplasm, round-to-oval nuclei, and numerous melanin granules, which were relatively uniform in size and shape. Transmission electron micros-

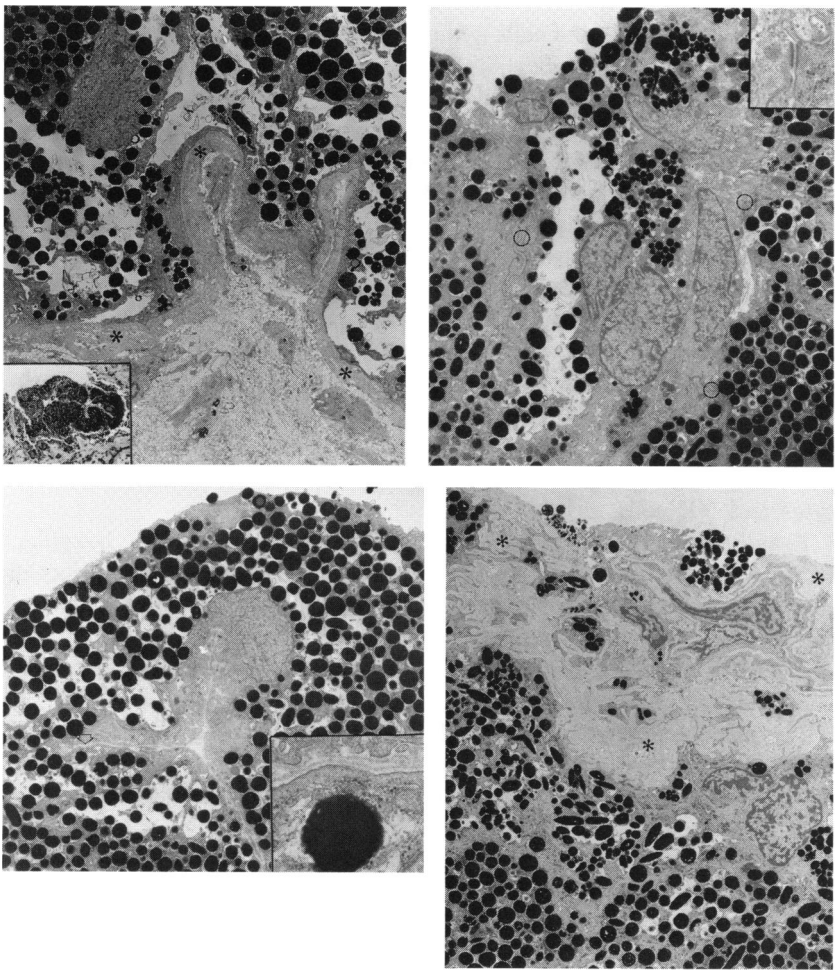

FIGURE 1

Case 1. Transmission electron micrograph of the left iris. A: Cells at base of iris nodule contain numerous round melanosomes measuring 0.4 to 1.3 μ in diameter resting on fibrillogranular basement membrane structure 0.5 to 1.5 μ thick (*asterisks*) (× 7500). INSET: Light microscopy shows large nodule consisting of deeply pigmented cells on surface of iris (toluidine blue, × 500). B: On anterior surface of iris nodule, numerous junctional complexes (*circles*) are present between adjoining cells with many round melanosomes and abundant ribosomes (× 7,500). INSET: Higher power view of single complex, which shows ultrastructural characteristics of tight junction (× 60,000). C: Basement membrane (*arrowhead*) is present along with basal surface of cells with numerous melanosomes (× 7500). INSET: Higher power view of well-defined basement membrane and two additional layers of reduplicated granular basement membrane material (× 60,000). D: On anterior surface of iris nodule, cells with elongated nuclei, fewer melanosomes, and abundant ribosomes and cytoplasmic processes are interspersed within multilayered fibrillogranular basement membrane material (*asterisks*) (× 7500).

copy showed two types of cells within the melanocytic nodule: the heavily pigmented plump melanocytes (Fig 1A) and some spindle-shaped cells with fewer melanosomes, abundant ribosomes, and cytoplasmic processes located on the anterior surface of the iris nodule (Fig 1B). Ultrastructural characteristics of basement membrane and tight junctions between adjoining cells are identified (Fig 1B and C). Irregular, thick basement membrane material is tightly adherent to the base of the iris nodule (Fig 1A) and interspersed between some cells on the anterior surface of the iris nodule (Fig 1D). An immunohistochemical study revealed that the melanocytes were positive for both S-100 protein and HMB-45. Immunostains for HLA-DQ showed positive staining in the melanocytes of the nodule but negative staining in the melanocytes of the iris stroma. Immunomarkers for lymphocytes and macrophages were negative. Immunomarkers of the trabecular meshwork sections showed positive stain for HLA-DR, HLA-DQ, and macrophages, and negative stain for both T and B lymphocytes and NK cells.

Examination of the iris specimen from case 2 revealed a thin, irregular, PAS-positive basement membrane covering most of the anterior surface of the iris (Fig 2A). Cells containing abundant ribosomes, many vacuoles, and some melanin granules were noted, as well as a partially degenerated cell (Fig 2B and C). Tight junctions were seen between cells, suggesting endothelial derivation (Fig 2D).

The membrane on the surface of the trabecular meshwork consisted of fibrillogranular basement membrane and bundles of banded collagen fibers. Degenerated cells were seen within the basement membrane (Fig 3).

No inflammatory cells or MHC class II antigens were identified by immunohistochemical staining.

DISCUSSION

The present hypothesis for the ICE syndrome focuses on a primary disorder of the corneal endothelium due to disease or injury that results in the proliferation of these corneal cells onto trabecular meshwork and iris, with secretion of an abnormal extracellular material by the disease or injured endothelial cells.[1-3] Although this explanation has been applied to patients such as described in case 2, it is more difficult to explain the clinical and pathologic findings in case 1. A number of questions concerning this hypothesis remain unanswered. Initially, corneal endothelial cell involvement may be localized to focal areas, with the remainder appearing normal on specular microscopy.[4] The trigger for the cells to migrate is

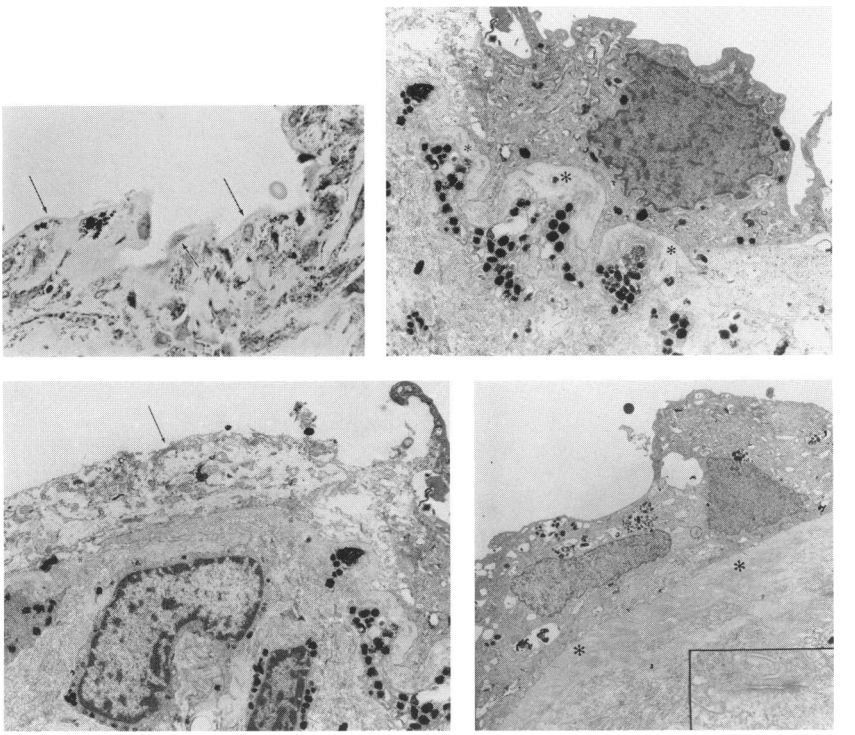

FIGURE 2

Case 2. Left iris. A: Thin PAS-positive membrane (*arrows*) covers most of anterior surface of iris (PAS, × 1000). B: fibrillogranular membrane, 1.0 to 1.5 μ thick (*asterisks*), is present beneath cell containing numerous ribosomes, a few melananin granules, and tight junction on surface of iris (× 15000). C: Fibrillogranular membrane, 0.5 to 1.0 μ thick (*asterisks*), is located beneath partially degenerated cell (*arrow*, × 15,000). D: Two elongated cells containing abundant ribosomes, many vacuoles, and some melanin granules are located above fibrillogranular membrane (*asterisks*) on surface of iris. Tight junction (*circle*) is identified between these two cells (× 60,000). INSET: Higher power shows detail of tight junction (× 7500).

unknown, as is the question of whether they actually proliferate by undergoing mitosis or merely migrate away from the cornea to cover a larger area including the trabeculum and iris. What is the mechanism for the iris nevi to be so prominent in some of these cases? Finally, what is the stimulus for the endothelial cells to proliferate or migrate? A viral etiology has been proposed without any supporting evidence other than the nonspecific appearance of occasional lymphocytes among the endothelial cells.

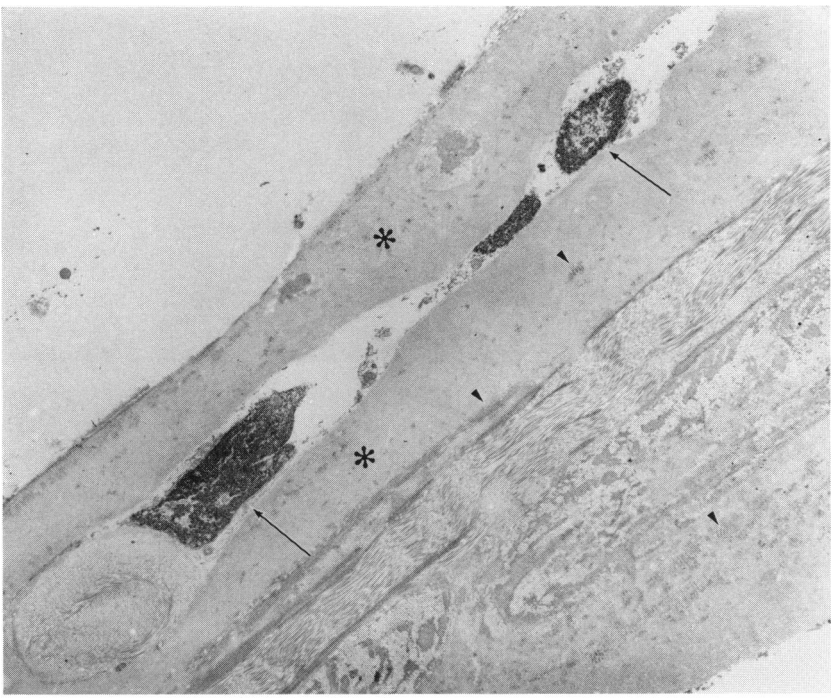

FIGURE 3
Membrane on surface of trabecular meshwork consists of fibrillogranular basement membrane (*asterisks*) and bundles of banded collagen fibers (*arrowheads*). Degenerated cells (*arrow*) are incorporated into basement membrane (× 7500).

In 1978, a new hypothesis was proposed to explain developmental anomalies of the anterior chamber associated with glaucoma.[5] Such developmental conditions included Axenfeld's anomaly, Rieger's anomaly or syndrome, and Peters' anomaly, as well as goniodysgenesis associated with hereditary juvenile glaucoma. A year later, this hypothesis was extended to the pathogenesis of some congenital glaucomas,[6] and in 1983 a discussion of the iridocorneal endothelial syndrome[7] was included in this unifying hypothesis.

The neural crest hypothesis is further supported by the two cases described here. Case 1 demonstrates the thick PAS-positive membrane-like structure on the iris surface on which sits the iris nodule. Transmission electron microscopy reveals two types of cells within the nodule: the heavily pigmented melanocytes and a spindle-shaped cell, consistent with an endothelial cell, that appears in intimate relationship to the basement

membrane. However, some of the melanoytes in the iris nodule demonstrate desmosomes (tight junctions) and basement membrane, which are characteristics of endothelial or mesenchymal cells. Also, the melanocytes of the nodule differ from those in the iris stroma in their HLA-DQ staining properties, the former staining positively, the latter negatively. This suggests that the iris nevus cells have class II antigen on their surface and thus differ from iris stromal melanocytes. In case 2 the abnormal cells associated with the membrane covering the iris surface also have desmosomes (tight junctions) between them and contain a few melanin granules. These cells probably represent endothelial cells, some of which are clearly undergoing degenerative changes.

How does one put these findings together? From laboratory studies, we know that "...all the connective tissues between the lens and the anterior corneal epithelium including those of the iris are of neural crest origin."[8] In addition, during embryogenesis, these neural crest-derived cells make up a continuous layer extending from the corneal endothelium to the trabecular meshwork endothelium and onto the anterior iris surface. Such a continuous layer of cells has been reported in both monkey and man.[9-11] It is also known that between the seventh and eighth month of human gestation, the layer of cells loses its continuity.[9] Some of these cells may persist as "nests" of relatively undifferentiated mesenchymal cells on the corneal endothelium, trabecular meshwork endothelium, or anterior iris melanocytes. Such mesenchymal cells could sit inactive for years until activated by some subclinical inflammatory event precipitated by trauma or some other insult. With such a stimulus, these "nests" could then become active, begin to proliferate and, laying down abnormal basement membrane, undergo variable growth on the one hand or degenerative changes on the other. Thus, activated "nests" on corneal endothelium may replace normal mature endothelium and produce variable specular microscopic changes and eventually corneal edema (Chandler's syndrome). If these "nests" are activated on the surface of the trabecular meshwork and the iris, glaucoma with or without iris hole formation and pupillary distortion may occur (essential iris atrophy). Finally, in addition to abnormal "nests" of mesenchymal cells on the back of the cornea cells, there may be "nests" of mesenchymal cells destined to become melanocytes in the anterior iris. These can develop into iris nevi when activated (iris-nevus syndrome). This mechanism could explain the findings observed in case 1. Such a hypothesis can account for the different clinical manifestations as well as the delayed onset, the preponderance of unilateral involvement, and the association of these syndromes with others of neural crest origin.[12] Better immunologic markers and more analytical clinical

measurements to determine the presence of abnormal cells and their progression in this group of cases are needed to delineate more clearly their pathogenesis.

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DISCUSSION

DR BARBARA W. STREETEN. The ICE syndrome is one of those baffling syndromes in ophthalmology where insight seems to progress in spurts, such as the recognition of the three classic ICE entities as a single syndrome by at least three different groups in 1978 and 1979, generally attributed to an abnormality of the corneal endothelium. In 1978, Doctor Kupfer and colleagues suggested linkage of this process with the neural crest origin of the involved cells. In the present paper, the authors pinpoint two problems with current theory: (1) a failure to explain the accumulation of nevus cells in the "iris nevus" variant and (2) lack of an etiology for spread of corneal endothelial cells over the trabeculum and iris. They now expand the neural crest hypothesis by postulating "nests" of relatively undifferentiated neural crest cells remaining on anterior chamber surfaces, later activated by trauma or inflammation, as the basis for this aberrant cellular behavior.

This hypothesis has many attractions although based on a number of unproven assumptions. There seems little doubt that corneal endothelium and iris melanocytes do originate from the neural crest. What is not proven is (1) that undifferen-

tiated rests of such cells persist postnatally and (2) that they can be stimulated to proliferate differentially, the iris nests to become nodules or diffuse areas of nevus cells and the endothelial nests to spread as a layer over the trabeculum and iris, producing abnormal basement membrane.

This pathologic study cannot be expected to answer such questions directly. The ultrastructure is consistent with other reports, though illustrating more fully in case 1 the morphology of an iris nodule. The large, rounded, hyperpigmented cells in this nodule seem unusual for the ICE syndrome, resembling somewhat melanocytoma cells or even pigment epithelial cells, which Doctor Kupfer could perhaps comment upon later. I could not with certainty identify endothelial cells or tight junctions in case 1, but rather desmosomes, a common intercellular feature. They were, however, well shown in the endothelial-like membrane of case 2. The positive HMB-4 staining of the nevous cells was most interesting. This melanoma antibody is known to bind to junctional and blue nevus cells, the latter thought to be related to uveal nevi, and possibly indicating a more active state of these cells.

The one unvarying feature in the ICE syndrome histologically is the posterior migration of the corneal endothelium with synthesis of abnormal thick basement membrane. Interestingly, this is a common phenomenon in end-stage ocular disease, noted by Colosi and Yanoff in 22% of 100 routine enucleated globes, usually growing over false angles in posttraumatic or inflamed eyes. This reactive endothelialization might be studied as a model for clues to the ICE syndrome. In the ICE syndrome its thickness varies, perhaps dependent upon the stage of the disease, and also the thickness of the complex matrix under it. This does not seem to be distinctive whether in ICE, reactive endothelialization, or hereditary posterior polymorphous dystrophy.

The most exciting finding in this paper was the positivity of the iris nodule nevus cells for class II HLA antigen (DQ) and unspecified cells in the trabeculum for HLA-DQ and HLA-DR. Normally, class II antigens are only expressed on immunocompetent cells, which raises the question of whether the iris and corneal cells have been transformed, such as by a virus infection. Class II antigens can also be induced on many nonimmunocompetent cells by interleukins during inflammation, which cannot be ruled out yet in ICE syndrome. This small finding offers new possibilities for investigation in ICE tissue cultures to look for evidence of transformation, further staining for abnormal expression of HLAs, a search for molecules related to the proliferative and migratory states of neural crest cells, and also for inherent defects in these cells.

I found this a stimulating paper and congratulate the authors for pointing out new directions in the attack on this difficult disease. We must see that all ICE syndrome tissue finds its way to the research laboratory for solution of this problem.

DR MYRON YANOFF. Mr President, members, and guests, I have a few comments and a few questions. I think the question of the origin of the iris nevi in the ICE syndrome has puzzled everybody from the beginning. I always have assumed that

at least two possibilities should be considered. One is that some of nevi are congenital, and the other possibility is that what appears to be nevi, may simply be islands on stroma pinched off by the advancing edge of the endothelium coming over the iris. In terms of mitotic figures in the corneal endothelium, we are dealing with a fine, very thin, tissue. Pathologists know that even in rapidly growing neoplasms mitotic figures may not be found. It is more important to find them than not to find them. How these corneal endothelial cells proliferate and slide and what is the stimulus are not known. One of the interesting things that I found in one case of the ICE syndrome, and I know that Ralph C. Eagle, Jr, MD has found in other cases, is an endothelial-covered, collagen bridge that extends from peripheral cornea to iris. It would appear that the corneal endothelial cells can travel from cornea to iris via the bridge. This bridge also can be seen in corneas from eyes that do not have the ICE syndrome. Somehow the "bridge" may be the "endothelial-stimulating factor," but this is quite speculative.

DR RALPH C. EAGLE, JR. I have a question about pigment granules. I was struck by the apparent large size and round morphology of the melanin granules in the iris nodule in your second case. They were somewhat reminiscent of the granules of neuroepithelial melanin that occur in the iris pigment epithelium. I wonder if that possibility was totally excluded; I assume that it was. Furthermore, I would like to ask if the diameter of the melanin granules was larger in the anterior border layer of the iris in your cases of ICE syndrome, or whether you noticed a difference in the size of the granules in the deep and superficial stroma. I have observed that the melanin granules were larger in the anterior border layer in several cases of ICE syndrome. This observation actually was a stimulus for my AOS thesis. In my thesis I performed transmission electron microscopy on a series of normal irises and found that there was no difference in the size of the granules in the deep and superficial stroma.

I found Doctor Streeten's comments about cellular activation very interesting because Doctor Alvarado has suggested that the transformation of corneal endothelial cells by herpes virus infection might be the stimulus for the corneal endothelial proliferation that occurs in the ICE syndrome. I personally have speculated whether the ICE syndrome might be some sort of benign neoplasm of the corneal endothelium, a relatively small population of cells that normally does not undergo mitosis in the adult. According to your theory the ICE syndrome results from an abnormal differentiation of cells derived embryologically from the neural crest. How does the resultant unbridled cellular proliferation differ from a neoplasm?

DR J. DONALD M. GASS. As I was listening to the presentation another interesting clinical syndrome came to mind and I wondered if it has anything to do with this syndrome. Probably it doesn't. But it goes by the name "bilateral diffuse uveal melanocytic proliferation." It is a very strange syndrome in which benign melanocytic cells of the uveal tract (cells of neural crest origin) are stimulated to grow, to become focally hyperpigmented and to undergo necrosis, presumably by a hor-

mone-producing, usually occult, carcinoma in older people. In females the carcinoma usually arises from their reproductive organs and in males it is usually a retroperitoneal carcinoma of uncertain source. In response to this hormone or hormones, multiple pigmented nevoid lesions appear in the uveal tract along with a secondary retinal detachment. As I say, I don't think it has anything to do with the subject under discussion, but I will mention it anyway.

DR ANDREW P. FERRY. A key point of Doctor Kupfer's presentation is his belief that the cells that produce the thick basement membrane found on the anterior surface of the iris and that constitute the nodular lesions on the iris are corneal endothelial cells. Doctor Kupfer and colleagues provide evidence to support that view.

During his presentation, Doctor Kupfer pointed out the presence of melanin granules in the cells he regards as being of endothelial origin, and Doctor Eagle subsequently commented on the curious size of those granules.

I believe that the presence of melanin granules in these cells offers at least some circumstantial evidence in support of Doctor Kupfer's view that the cells are of endothelial origin. The main function of the corneal endothelium (its role in maintaining corneal transparency) is well-known to all of us. But many ophthalmologists are unaware of another property of the endothelium: It has certain phagocytic properties, among which is a remarkable ability to ingest and store melanin. For example, in response to the question, "What is a Krukenberg spindle?", most ophthalmologists will respond that it is melanin arrayed in a vertical pattern on the posterior surface of the cornea.

Well, in a Krukenberg spindle, the uveal melanin that has been mobilized into the aqueous humor does initially come to rest on the back of the cornea. But it soon is ingested by the endothelium, where it remains. Thus, the melanin granules constituting a Krukenberg spindle are not *on* the cornea, they are *in* the cornea by virtue of their presence *in* the endothellum.

Returning to the iridocorneal endothelial syndrome and the melanin granules described by Doctor Kupfer, the melanin's presence in these cells can be explained by several developmental and pathogenetic mechanisms. Among the possibilities that may account for the presence of melanin in these cells that are presumed to be of endothelial origin is the hypothesis that as the iris becomes increasingly involved by the disease process, melanin granules are liberated into the aqueous humor and become ingested by the cells of corneal endothelial origin as the latter exercise their well-known ability to perform this function.

DR CARL KUPFER. I find that one of the most enjoyable aspects about presenting a paper at this meeting is the opportunity for extensive discussion. It is always a pleasure to receive comments. I guess there is no better way to provoke discussion from pathologists than to have a nonpathologist give a presentation.

I am glad that Doctor Streeten mentioned the immunohistochemical findings which I did not mention in the presentation because this was demonstrated in only one case, and it needs to be further substantiated. But the point is that the

cells in the nodule of the iris are HLA-DQ positive which meant that they expressed MHC class II antigens as opposed to the cells within the iris itself, the melanocytes, which were negative. Now if this is supported in other cases, then I think we have something very exciting. It does suggest that these cells have been stimulated either by trauma, inflammation or some other trigger mechanism. I would agree with Doctor Streeten that these cases are so rare that when they do come to surgery we really should preserve the trabecular material, corneal material, iris material for immunohistochemical and electron microscopic studies. Certainly there are enough pathologists in this room who would be very interested in receiving material and preparing it appropriately.

Doctor Yanoff mentioned the question of what is the stimulus for these cells to proliferate. We certainly don't know what that is, but it is known that neural crest cells often migrate to a site and then undergo terminal differentiation. Perhaps in these cases, terminal differentiation is delayed and later activated with proliferation of cells which are seen in these cases.

Doctor Eagle commented on the large pigment granules. They do range about 0.4 to 1.3 μ in comparison to the melanosome's size of 0.5 to 0.2 μ in the stromal melanocytes. The question of a benign neoplasm *vs* neural crest origin of these cells is beyond speculation. However, we should keep in mind that the corneal endothelium, trabecular endothelium, anterior iris stroma and iris melanocytes are neural crest in origin.

With respect to Doctor Gass, if the reference is to pigment epithelium, this would be neuroectodermal in origin rather than neural crest.

Doctor Ferry, I believe that the phagocytic activity of corneal endothelium should not be confused with endothelial-like cells containing melanosomes which may also be occurring in this condition.

Again, I find this a very stimulating opportunity to present in an area that we have many more questions than answers and I hope we will be able to clarify some of these issues over the next few years.