


Fuch's heterochromic iridocyclitis: an electron microscopic study of the iris. S. MELAMED, M. LAHAV, U. SANDBANK, Y. YASSUR, AND I. BEN-SIRA.

The irides of two patients with Fuch's heterochromic iridocyclitis were investigated by electron microscopy. The main findings were abnormal melanocytes with relatively few, small, and at times immature melanin granules, abundance of plasma cells, and membranous degeneration of nerve fibers. The defective melanin production may be due to abnormal adrenergic innervation, either primary or secondary to the inflammatory process. The cause for this inflammatory reaction was not evident in this study.

Fuch's iridocyclitis is a chronic disease manifested by unilateral low-grade uveitis, iris heterochromia, cataract, and occasional glaucoma. Up to now, the etiology of this syndrome has remained obscure. Several histopathological studies of the iris in this disease by conventional light microscopy have been reported. The findings were in most cases those of iris atrophy, hyalinization, narrowing of blood vessels, and degeneration of the iris pigment epithelium. In addition, abundance of plasma cells and histiocytes were found in the iris stroma. To our knowledge, no ultrastructural studies of the iris changes in this disease have been reported in the literature. In this report, we present an electron microscopic study of the iridectomy specimens taken from two patients with Fuch's heterochromic uveitis.

Materials. Two patients with classic history and signs of Fuch's heterochromic iridocyclitis were admitted to the Beilinson Medical Center for cataract extraction.

The first patient, a 54-year-old man, had visual acuity of 2/60 in the right eye and 6/6 in the left eye. External examination of the eyes showed heterochromia of the irides. The left iris was light brown in color, and the right was brown-green. Slit-lamp examination revealed several keratic
Fig. 2. Large melanocyte (M), which contains melanin granules of neuroepithelial origin, is probably related to iris epithelial cell. Few other cells which contain small irregular melanin granules are seen (arrows). A cell with scarce intracytoplasmic organelles suggestive of lymphocytes is noted (L), as well as plasma cells (P). (×3300.)

precipitates (KPs) with minimal flare and occasional cell in the anterior chamber of the right eye. The intraocular pressure was 17 mm Hg in both eyes. There was a mature cataract in the right eye, and details of the fundus could not be seen. The anterior and posterior segments of the left eye were normal.

The second patient, a 48-year-old woman, was admitted because of progressively decreased vision in her right eye, down to counting fingers at 1 meter. External examination showed heterochromia of the lightly brown irides, the right eye being green-brown in color. Slit-lamp examination revealed low-grade uveitis manifested by several white KPs and minimal flare in the anterior chamber. There was a mature cataract in that eye, and no fundus details could be seen. The anterior and posterior segments of the left eye were normal.

The two patients underwent a successful rightsided intracapsular lens extraction with sector iridectomy. The iris specimens were immediately fixed in 2% phosphate-buffered glutaraldehyde, post-fixed on 1% OsO₄, and embedded in Epon. Ultrathin sections were cut and stained with lead citrate and uranyl acetate. Later, an electron microscopic examination of the irides was done.
Results. Similar electron microscopic changes were seen in both specimens. The main findings were those of chronic inflammatory reaction, along with abnormal structure of the iris cells. Each of the histopathological findings will be described in detail.

Melanocytes. Relatively few melanocytes with abnormal structure were seen. All the melanocytes were abnormally rounded, with no dendritic processes seen. Occasional root filaments and membrane-associated cilia were present in these cells. The melanocytes contained relatively few melanin granules, which were smaller than normal and of irregular size and shape. Few immature melanosomes were identified in the cytoplasm (Figs. 1 to 3). A surrounding basement membrane material could be identified at times around cells which contained small melanin granules. Since these did not show composite phagocytized granules, it is possible that these represent either a melanocyte or a neuroepithelial cell which had migrated into the stroma (Fig. 4).

Other pigment-laden cells. At times, cells which contained large melanin granules of neuroepithelial origin were seen. These cells are probably related to the iris pigment epithelium which had migrated toward the iris stroma (Figs. 1 and 2).

Nerves. In a few areas, nonmyelinated nerves, which may represent adrenergic nerve fibers, were present. Most of these fibers showed signs of degeneration as manifested by the change in size and shape of the individual fibers, increased electron density, and disintegration of membranes (Fig. 5).

Plasma cells. Abundance of plasma cells and occasional lymphocytes were noted in the iris stroma.
Fig. 4. Pigmented cell (left) which demonstrates basement membrane-like material (arrowheads), melanin granules (M), and lobulated nucleus. Note plasma cell at right and a cell which resembles a lymphocyte (L). (x3300.)

(Fig. 2). These cells were seen in clusters, which were at times closely related to abnormal melanocytes (Figs. 2 and 4). Most of the plasma cells showed the normal configuration, with well-developed Golgi apparatus and rough endoplasmic reticulum. However, the presence of electron-dense mitochondria and lamellar bodies are suggestive of an early degenerative process within these cells (Fig. 4).

Fibroblasts. Many collagen-producing fibroblasts were seen. The periodicity of the collagen fibers was within normal range. In the fibroblasts occasional large lysosomes, microfilaments, and many pinocytotic vesicles were identified. A few root filaments and cilia were noted as well. This finding may indicate that these cells are related to the anterior border layer of the iris.

Smooth muscle. The smooth muscle cells of the iris sphincter could not be clearly identified. Few cells with electron-dense cytoplasm, scanty cytoplasmic organelles, and elongated nucleus were seen in areas contained extracellular debris. Basement membrane-like material was seen in areas around these cells. The overall appearance was suggestive of smooth muscle cells, which had undergone early degeneration in a necrotic area, and may probably represent the dilator region of the iris (Fig. 6).

Blood vessels. The capillary wall showed basement membrane with normal endothelial cells and pericytes.

Discussion. The overall histopathological appearance of Fuch’s heterochromic iridocyclitis is that of chronic mononuclear inflammation. Secondary damage to blood vessels and pigment epithelium along with iris atrophy and rubeosis iridis have been described.

The present report confirms the presence of
chronic inflammatory reaction, as manifested by lymphocytes, plasma cells, macrophages, and clump cells. In view of the scanty information which is available concerning the pathogenesis of this disease, the electron microscopic findings warrant additional consideration. The over-all histopathological appearance is that of chronic inflammatory reaction. Few other findings do stand out, namely, the structural changes in the nerve endings and melanocytes. Although degeneration of these nerve fibers may be secondary to the inflammatory process, there was no clear-cut association of these structures with the inflammatory cells. Therefore it is possible that the neural changes are due to a primary disturbance. The same may apply to the changes found in the melanocytes. The change in the cell configuration and the loss of dendritic processes may be due to the inflammatory process; however, the small immature pigment granules point toward defective production of melanin. This phenomenon may be attributed either to the direct effect of the inflammatory process or, alternatively, to the abnormal structure and function of the adrenergic innervation of the iris. There is a well-known association between adrenergic nerves and melanocytes. Laties elaborates in detail on the importance of the connection between the adrenergic nerve and melanin synthesis in the iris melanocyte. For instance, in long-standing Horner's syndrome, a clinical disease with defective adrenergic fibers, heterochromia is frequently seen. This most probably happens as a result of decreased tyrosinase activity in the melanocyte. Even though no inflammatory reaction is seen in Horner's syndrome, it is possible that the iris hypopigmentation in both Fuch's heterochromic uveitis and Horner's syndrome is caused by a
Fig. 6. Area of necrotic tissue with disintegrated membranes and vesicles (V). Cells with elongated nucleus and scant electron-dense cytoplasm are seen in this area (M). These cells resemble smooth muscle cells and may represent degenerative areas in the dilator region. (×5600.)

common end result—a defective production of melanin granules due to inadequate function of the adrenergic nerves.7 Whether this phenomenon is due to primary adrenergic defect or to an inflammatory reaction which affects these nerves cannot be determined from the present findings. The stimulus and nature of the inflammatory reaction which was detected in the irides of the two patients with Fuch's heterochromic iridocyclitis deserves further investigation.

From the Department of Ophthalmology, Beilinson Medical Center—Tel Aviv University, Petah Tikvah, Israel, and *Eye Pathology Laboratory, Hadassah Medical Center—Hebrew University of Jerusalem, Jerusalem, Israel. This work was supported in part by a grant from the Israel Ministry of Health (Dr. Lahav). Submitted for publication Feb. 13, 1978. Reprint requests: I. Ben-Sira, Department of Ophthalmology, Beilinson Medical Center, Petah Tikvah, Israel.

Key words: Fuch's heterochromic iridocyclitis, abnormal melanocytes, degenerated nerve fibers, plasma cells

REFERENCES

The effects of transcorneal freezing on protein content of aqueous humor and intraocular temperature at the posterior surface of the cornea, the angle, the iris, and the ciliary processes were determined in rabbits and cats. Normal aqueous protein concentration was 40 ± 2 mg/dl in rabbits and 43 ± 4 mg/dl in cats. In rabbits, total aqueous protein content reached its highest level (2790 ± 302 mg/dl) 3 hr after transcorneal freezing, decreased by 50% after 4 hr, and was not significantly different from normal at 7 days. In cats, total aqueous protein content also reached its highest level (1610 ± 290 mg/dl) 3 hr after corneal freezing. Fluctuations occurred thereafter, but protein content was not significantly different from normal after 7 days. The temperature at the corneal endothelium always decreased to below 0° C with a 10 to 25 sec application of the cryoprobe to the cornea in rabbit and cat. Intraocular temperature did not decrease below 24° C at the angle or ciliary processes during application of the cryoprobe for up to 25 sec, whereas the temperature at the pupillary margin of the iris sometimes decreased to near 0° C with a 15 to 25 sec application.

Transcorneal freezing has frequently been used as a noninvasive method for destroying portions of the corneal endothelium in studies of endothelial regeneration and wound healing. In rabbit, extensive cellular division occurs at the margin of the wound, and damaged cells are completely replaced by new cells. In contrast, little cellular division occurs in cat corneas, and the new endothelial layer is composed of enlarged, flattened cells that migrate from the margin of the wound onto the area of Descemet's membrane that had been denuded of cells. The regenerated endothelium in cat appears to be similar to stressed endothelium in the human and has been proposed as a model for evaluating intraocular solutions, drugs, or devices that might have an adverse effect on stressed endothelial cells.

Various forms of ocular injury (e.g., paracentesis) are known to produce a breakdown of the blood-aqueous barrier as reflected by an increase in protein concentration in the aqueous humor. The purpose of this study was to determine if transcorneal freezing causes a breakdown of the blood-aqueous barrier of rabbits and cats and to measure to what extent intraocular temperatures are lowered during freezing. A difference in response of the blood-aqueous barrier might explain the difference in regenerative capacity of the corneal endothelium in rabbit and cat.

Methods

Transcorneal freezing. Brass cryoprobes were machined to fit the radius of corneal curvature with diameters suitable for freezing approximately 50% of the corneal endothelium (8 mm for rabbits and 9 mm for cats). New Zealand white rabbits (2.6 to 4.3 kg) and cats (2.4 to 5.9 kg) were given an intramuscular injection of ketamine hydrochloride (10 to 15 mg/kg), and a topical anesthetic (benoxinate hydrochloride, 0.4%) was applied to the corneas prior to injury. Rabbit eyes were propotised to facilitate probe placement, whereas a speculum was used in cat eyes. The probes were cooled in liquid nitrogen (−196° C) and placed on the central corneal surface for 5, 10, 15, 20, or 25 sec.

Intraocular temperature. Ketamine hydrochloride, 30 to 50 mg/kg, and sodium pentobarbital, 10 to 30 mg/kg, were administered intramuscularly in separate syringes to provide anesthesia. Nasal congestion, when it occurred, was relieved by 0.2 mg of atropine sulfate intramuscularly.

Following propotosis of the eye in rabbits, the anterior chamber was entered at the limbus with a No. 64 Beaver blade. In cats, a lid speculum was inserted and the nictitating membrane excised before the anterior chamber was entered. A copper constantan (Type T) thermocouple (Honeywell Co.) was inserted through the wound. A mattress suture (5-0 proline or silk) was placed across the wound and tied to reform the anterior chamber. The thermocouple tip was then positioned at the posterior surface of the cornea, the pupillary margin of the iris, and the periphery of the posterior chamber (as close to the ciliary processes as possible without direct visualization). Bleeding did not occur in any eye. Control values for temperature were obtained, and the cryoprobe was then applied to the cornea for 5, 10, 15, 20, or 25 sec while temperature changes were monitored. Nine rabbit and nine cat eyes were used for the temperature measurements.

Protein content in aqueous humor. Rabbit and cat corneas were frozen for 15 sec with an 8 or 9 mm diameter probe cooled in liquid nitrogen. Each eye was paracentised once at specified times.