CHOLESTEROL TURNOVER IN HEREDITARY CRYSTALLINE CORNEAL DYSTROPHY OF SCHNYDER*

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THE FIRST AMERICAN REPORT OF A FAMILY WITH HEREDITARY crystalline corneal dystrophy of Schnyder was presented to this Society in 1950 by W.E. Fry, the 70th President of the American Ophthalmologic Society and third editor of its Transactions.[1,2] A valuable study of the ocular manifestations of familial hypercholesterolemia was given to the Society by Blodi and Yarborough.[3] Their patients had elevated blood cholesterol but did not have corneal disease other than arcus lipidis. One of the patients in their series had retinal crystals which were felt to be cholesterol.

After the original report of hereditary crystalline dystrophy of the cornea by Van Went and Wibaut, in 1924,[4] the disease became recognized as a clinical entity through a series of publications by Schnyder from 1927 to 1939.[5] Since then approximately 51 cases have been described, 42 in family groups, and 9 isolated cases where a hereditary factor was not demonstrable.[6,7,8]

In 1950, when Fry and Pickett gave the first American report, only clinical description of the patients and their heredity was possible. The autosomal dominant transmission of the disorder had been proven, and the clinical pattern established. It had been suspected by Bonnet and associates[9] as early as 1934 that the crystals were cholesterol, since they were birefringent and soluble in ether. Sedan and Valles[10] carried out specific histochemical stain-

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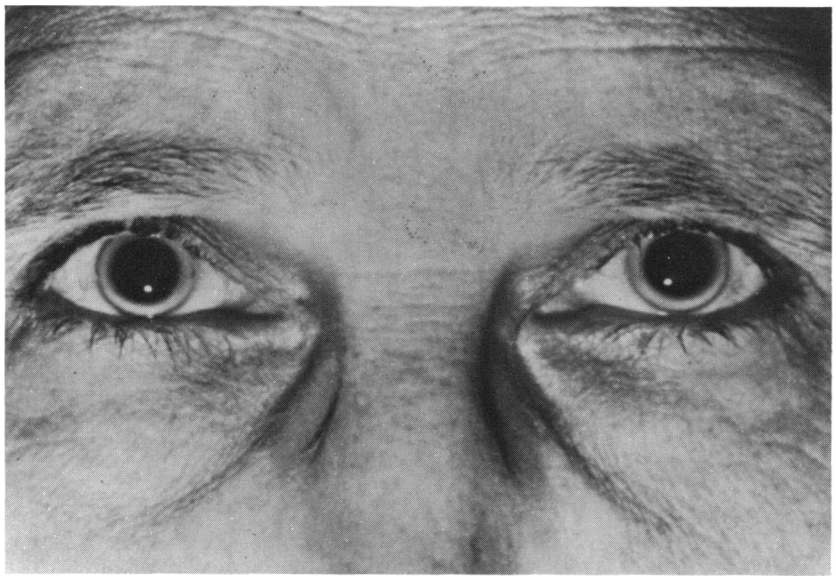

FIGURE 1
Proband (II-2) at the age of 52 (1973), showing heavy arcus lipidis and barely visible ovoid ring of crystals in central third of superficial cornea. Visual acuity OD 20/60- and OS 20/30-.

ing for cholesterol, but in neither of these reports was the hereditary nature of the lesion established.

The salient ocular features of Schnyder's crystalline corneal dystrophy known to Fry and Pickett are (a) autosomal dominant transmission, (b) bilateral affliction present since early age, (c) subepithelial corneal opacity, composed of many tiny glistening crystals, mainly in the anterior third of the stromal layers immediately posterior to Bowman's membrane, in the central portion of the cornea, (d) no signs of inflammation or irritation in the cornea, with preservation of good vision, (e) often a white limbal girdle of Vogt on the nasal and temporal sides of the cornea and a heavy arcus senilis, and (f) in a few cases, xanthelasmas of the eyelids.

Since 1950, other data have been collected about the genetic pattern of this disorder. Skeletal abnormalities, specifically genu valgum, are often present.[6] Luxenburg's extensive biochemical analysis of the lipids, proteins, and amino acids of the blood and urine, as well as chromosomal studies, were not revealing as to the etiology.[11] A clinical refinement in analysis of this disorder was

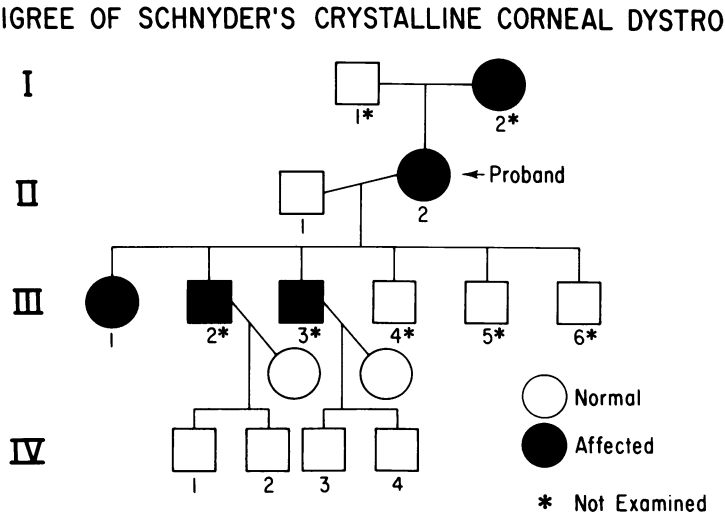

FIGURE 2
Pedigree of family with Schnyder's crystalline corneal dystrophy.

done by classifying the corneal appearance into five separate subtypes.[12] More than one phenotype may occur in the same family.[6,12] A rare and atypical feature is a cloudy appearance of the cornea outside the primary crystalline lesions.[6]

Histopathologic reports of crystalline dystrophy in which the hereditary pattern was established are scarce because the condition does not usually impair vision.[9,10,12,13,14,15] Apart from the case described by Offret,[16] in which cholesterol crystals were not demonstrated, there was no report of the ultrastructural appearances in this condition until Garner and Tripathi's report,[15] and the description of an isolated case by Ghosh and McCulloch.[8]

Hypercholesterolemia was present in 9, or possibly 11 of 26 patients in whom lipid studies have been done.[6] Hypercholesterolemia does not necessarily cause the corneal dystrophy.[3,17] However, Sysi felt that fluctuations in the blood cholesterol were reflected in changes in the severity of the corneal dystrophy.[18]

It is apparent that Schnyder's hereditary corneal dystrophy is one of nature's metabolic mistakes that lends itself to an analysis of an abnormal condition, thus allowing one to learn further about normal processes.

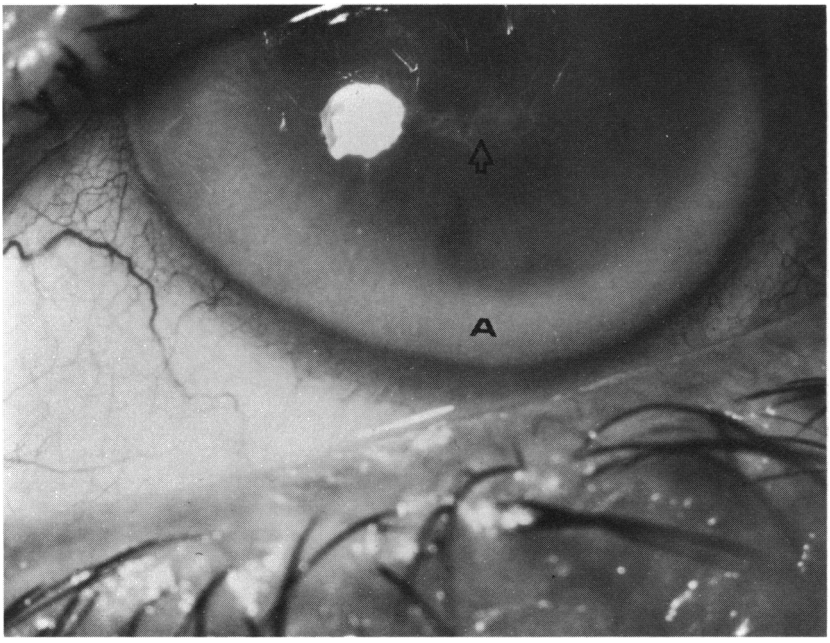

FIGURE 3
Proband's right eye in 1977. Visual acuity 20/100-. Note extremely heavy arcus lipidis (A) and central corneal ovoid ring of tiny multicolored crystals, with cloudy stroma between crystals (arrow).

CASE REPORT

The proband, a 56-year-old white female, was first examined in March, 1977 with the complaint of poor vision since 4 years of age. Ophthalmologic records were available since February, 1971 at which time she was found to have a moderately advanced crystalline corneal dystrophy in both eyes, with best corrected visual acuity of 20/60- in the right eye and 20/30- in the left eye. Over the next several years the corneal dystrophy had increased progressively to where her best corrected visual acuity was 20/80 in both eyes (Fig. 1).

Her mother had "bad eyes" but her father had good sight until age 89. Of her children, a daughter, age 20, had similar crystalline corneal dystrophy and two sons had "half moons" on their corneas. Three other sons were normal. Four grandchildren have been found to have normal eyes (Fig. 2).

The patient's best corrected visual acuity was 20/100 in the right eye and 20/70 in the left eye (Fig. 3). Both eyes had extensive arcus lipidis. There was an oval ring-shaped area of multicolored tiny crystals with a central

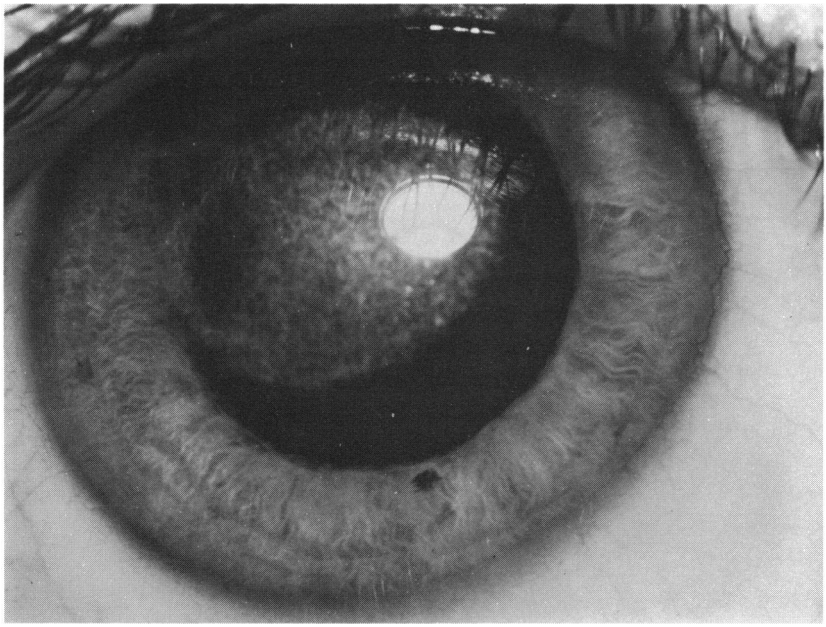

FIGURE 4

Daughter (III-1) of proband, whose central crystalline ovoid deposit is disk-like, without a clear center, but with clear corneal stroma, no arcus lipidis and visual acuity 20/40-.

clearer area in the cornea. The crystals were most marked towards the anterior part of the cornea, but extended deep to the level of Descemet's. The corneal stroma between the crystalline deposits had an overall haze which impaired the fundus view.

Her daughter had a central crystalline ovoid corneal deposit without a lighter area in the center (Fig. 4). The uncorrected visual acuity was 20/40 in both eyes, and she was functioning as a college student.

The patient had a complicated medical history. At age 25, she said that she was told after an exploratory operation for jaundice, that she had cirrhosis of the liver. She had a hysterectomy for cancer of the uterus, followed by X-ray therapy, at age 36. She was hypertensive and in 1974 had a cerebral vascular accident. General physical examination showed severe vascular disease and a loud bruit was heard over the left upper quadrant of the abdomen.

Laboratory studies showed unremarkable plasma lipid values with a cholesterol of 221 mg/dl and triglyceride of 221 mg/dl. Chemical screen was unremarkable. The daughter's blood lipids were cholesterol 150 mg/dl and triglycerides 52 mg/dl.

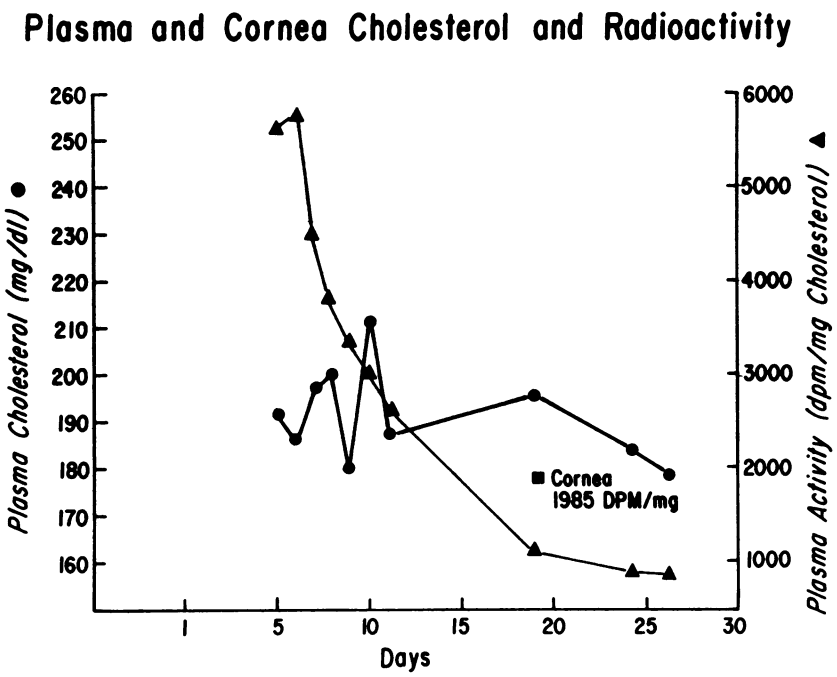

FIGURE 5

After labeling cholesterol, the expected fall off in plasma radio-activity was noted (triangles) while serum cholesterol (circles) fluctuated within normal limits. The single determination of corneal radioactivity in dpm/mg cholesterol is marked by a square.

Upon obtaining informed consent from the patient, she was hospitalized for blood lipid labeling, in the University of Oregon Health Sciences Center Clinical Research Center. She was given an intravenous injection of 100 μCi of 14C-labeled cholesterol.

Following labeling of the blood lipids, serial determination of blood cholesterol level and radioactivity in dpm per mgm of blood cholesterol were obtained. The usual falloff was noted (Fig. 5). Eleven days later the patient was hospitalized and a 7 mm penetrating keratoplasty was performed, using a running 9-0 nylon suture to secure the graft.

One week after the operation she had a transient ischemic attack, with right-sided weakness and difficulty talking. Her ocular postoperative course was otherwise uneventful, and she was treated with an atropine-prednisolone drop to prevent graft rejection. The visual acuity stabilized at 20/60 until the sutures were removed seven months postoperatively, and then improved to 20/40 (Fig. 6). She now reads and sews with the right eye, since the visual acuity is now 20/80 in the left eye. The graft remains clear

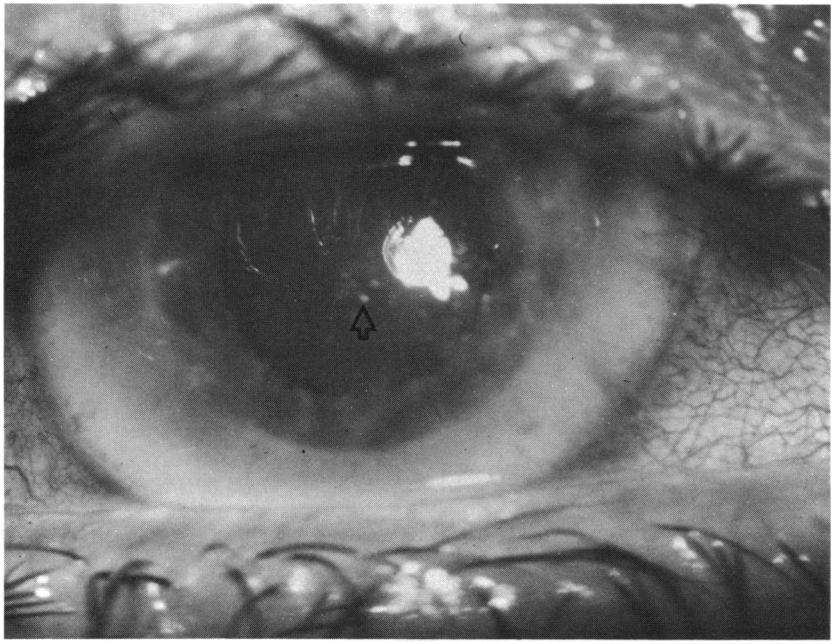

FIGURE 6
Right eye nine months after keratoplasty. Visual acuity 20/40-; graft thin and clear centrally without reaccumulation of crystals. Dots (arrows) represent punctate epithelial keratopathy, thought to be due to dry eye.

and thin, and there has been no recurrence of crystals in the transplanted cornea or in the suture marks. She has been hospitalized once for hepatitis, and is being treated for hypercholesterolemia and hypertension. She is using platelet inhibitors and sedatives.

LABORATORY STUDIES

The 7 mm corneal button removed at surgery was divided in half; one-half was examined by the Liebermann-Burchard test for cholesterol and was found to have 112 mg of cholesterol per gram of dry weight of cornea. Two control eyes from the Oregon Eye Bank examined at the same time had 8 mg per gram of cholesterol. There also was a tremendous amount of radioactivity present in the cornea, with a specific activity of 1985 dpm per mg (Fig. 5). On this day, the blood cholesterol levels were 55 mg free, 140 mg es-

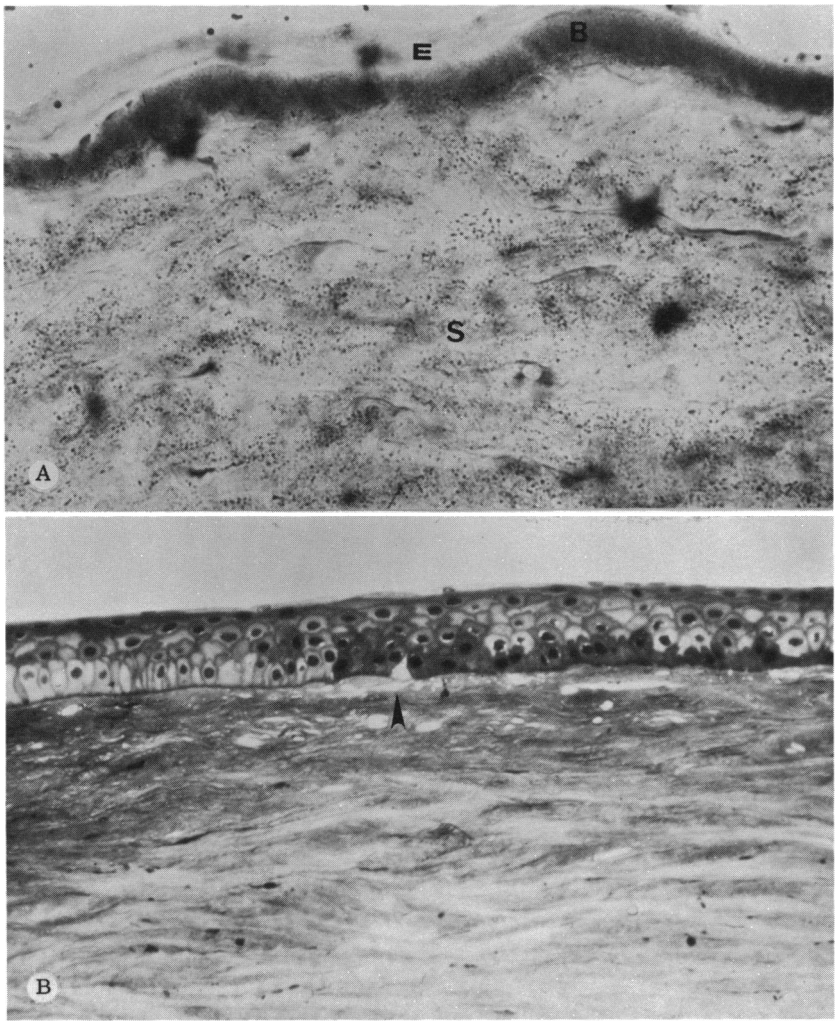

FIGURE 7

A: Frozen section of keratoplasty specimen of superficial cornea, oil red O stain. Epithelium (E) unstained, Bowman's layer (B) has very heavy deposit of stain, and stroma (S) has scattered granular stain (x 350). B: One-sixth of the corneal button removed at surgery was fixed in glutaraldehyde, embedded in plastic for light and electron microscopy. The thick section in this light micrograph was stained with toluidine blue. Numerous dark and light cells are seen in the epithelium; there are many optically empty spaces (arrow) in Bowman's zone (X 350).

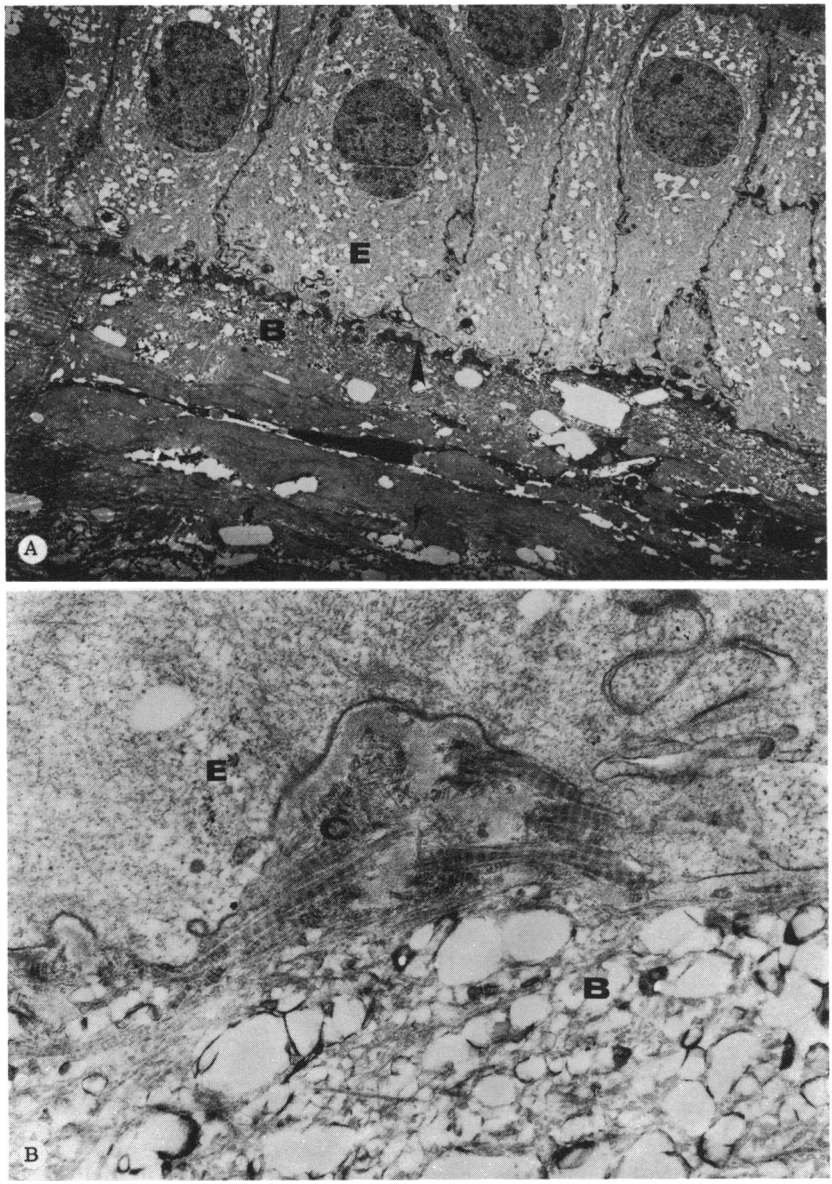

FIGURE 8

A: Electron micrograph of basal epithelium and Bowman's layer. Note vacuolated corneal epithelium (E), thickened basement membrane (arrow) and distorted, vacuolated Bowman's zone (B) (x 2,800). B: High magnification of area of basal epithelial cell cytoplasm (E); thickened basement membrane with long-spacing collagen (C) and almost unrecognizable Bowman's zone (B) with numerous vacuoles (X 62,000).

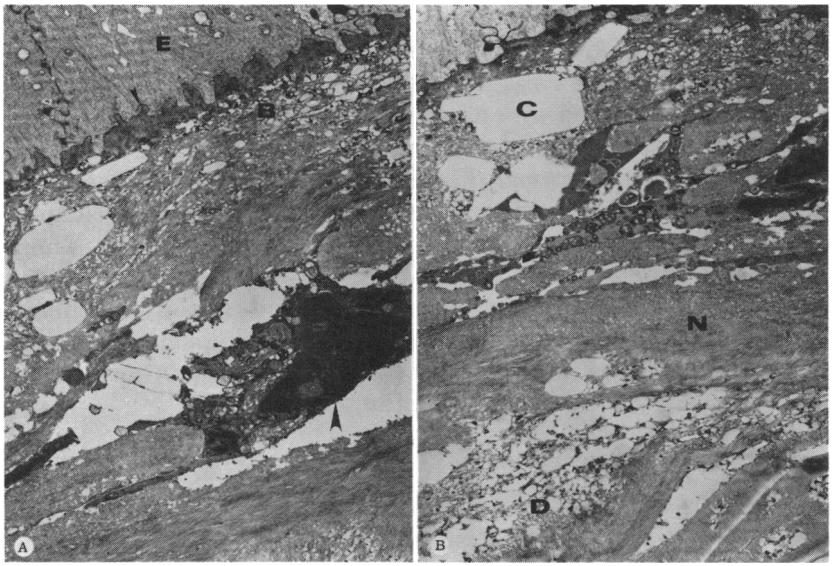

FIGURE 9

A: Region of cornea showing basal epithelium (E) with its thickened basement layer (small arrow), disorganized Bowman's zone (B) and vacuolated keratocyte (large arrow) (X 10,400). B: Electron micrograph of Bowman's layer. The notch at the end of the empty space (C) suggests that the structure is the ghost of a cholesterol crystal. Bundles of normal appearing collagen (N) alternated with disorganized collagen (D) are present (X10,000).

terified, for a total of 195, and the specific activity of the blood cholesterol was 1195 dpm per mg, or slightly more than half of the corneal level.

The remaining half of the corneal button was divided into three equal parts and examined by frozen section with fat stains, histochemical methods for lysosomal enzymes, and electron microscopy. The oil red O stain showed heavy stain in the area of Bowman's layer, with dust-like staining throughout the depths of the cornea (Fig. 7A). Light microscopic sections showed an essentially normal epithelium with numerous vacuoles in the area of Bowman's layer and the superficial stroma, which presumably represented crystals removed by the embedding (Fig. 7B). Histochemical examination for lysosomal enzymes, including acid phosphatase and aryl-sulfatase, was not revealing. Electron microscopy, which included only corneal epithelium and stroma, was in general confirmatory of the findings of Garner.[15] The epithelium appeared

essentially normal except for some vacuoles (Fig. 8A). However, the basement membrane had the nonspecific finding of thick deposition of long spacing collagen (Fig. 8B). Bowman's layer appeared to be totally destroyed with numerous clefts and vacuoles (Fig. 9A). Keratocytes examined by electron microscopy appeared disorganized and highly abnormal (Fig. 9B). The corneal stroma collagen bundles were interrupted and destroyed, with numerous vacuoles accounting for the stromal opacity seen between the crystals. There were many empty spaces in the stroma with a notch at one end suggestive of cholesterol crystals, which would confirm the chemical findings. Unfortunately, the endothelium did not appear on any of these specimens, and has not been mentioned in any of the previous pathologic reports in the literature.

DISCUSSION

Previous investigations into Schnyder's hereditary crystalline corneal dystrophy have emphasized its autosomal dominant pattern of transmission. A second aspect of importance is the effect of hyperlipidemia or hypercholesterolemia upon the cornea. It is well known that hyperlipidemia is associated with arcus lipidis.[3,17] However, the relationship to hereditary crystalline corneal dystrophy is less clear since hypercholesterolemia has been found in less than one-half of the cases.[6]

The theory of Cogan and Kuwabara that vascularization of the cornea is a prerequisite to lipid deposition, which appears first in intracellular dots and then in extracellular deposits, is not a factor in this nonvascularized corneal dystrophy.[19] The best theory advanced to fit the data is that there is an inherited abnormality of the keratocytes which under the influence of an abnormal burden of circulating lipid may result in the deposition of corneal crystals.[6]

Demonstration in this patient that there is a much higher level of cholesterol in the cornea than in the serum, 11 days after labeling, is important in that it shows that the cornea is an active uptake and storage site for cholesterol. It is probably less active in this respect than the liver, but more active than the skin. Additionally, it should be noted that the central crystalline dystrophy was the part that was removed surgically and analyzed, but not the peripheral arcus lipidis. The two are interrelated in this hereditary disorder.

Future studies are planned for this patient, if she remains in good enough health to request a second corneal transplant. Blood cholesterol could be labeled with a different radioactive label, such as tritium, then shortly after labeling, while monitoring the serum decay of tritiated cholesterol, a corneal transplant could be done. The corneal button would then be analyzed for both ^{14}C-labeled cholesterol to see if any still remains from the labeling prior to keratoplasty of May 1977, as well as ^{3}H-cholesterol to determine whether there is again a higher uptake of corneal compared to serum cholesterol. Additionally, it might be possible to look for lipid receptors on corneal stromal cells grown in tissue culture, paralleling the studies that have shown that endothelial cells from blood vessels have a specific affinity for uptake of lipids in atherosclerosis. This would be done by cell culture of keratocytes and studying ^{125}I lipid labeling of the cell membranes in Schnyder's dystrophy keratocytes compared to normal controls.

SUMMARY

A patient with hereditary crystalline corneal dystrophy of Schnyder required penetrating keratoplasty because of poor visual acuity. Blood cholesterol was labeled with ^{14}C-cholesterol and 11 days later a penetrating keratoplasty was done. At the time of surgery, corneal levels of cholesterol were much higher than serum levels, showing that the cornea is an active site for the uptake and storage of cholesterol in this disorder.

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