THE ENDOTHELIUM OF THE CORNEA AND ITS CLINICAL IMPLICATIONS

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PREFATORY NOTE

IT MAY at first glance appear presumptuous to make a single layer of cells, the corneal endothelium, covering two areas of the human body of about one hundred square millimeters each, the subject of a monograph. Nevertheless this layer of cells is a very important one, almost as important to the satisfactory performance of the visual organ as is the highly differentiated retina. Its anatomical integrity and the preservation of its physiologic function are indispensable to the transparency of the cornea, without which the complicated system of refraction, accommodation, visual perception, and transmission becomes worthless.

The existence of the endothelium of the cornea has been known since the early days of human histology. Its function as a protective barrier between the aqueous humor and the stroma of the cornea was convincingly demonstrated as far back as 1873, when Leber reported his fundamental experiments on the role of the endothelium in the physiology of the cornea. Since, however, this layer of cells could be seen only in preparations of dead tissue under the microscope, its importance in various forms of corneal diseases was difficult to demonstrate clinically. Indeed, when in 1910 Fuchs described the clinical picture of what he called "Dystrophia corneae epithelialis," he had not grasped the fact that the very origin of this disease was in the endothelium. He even stated explicitly that there was no reason to believe that the endothelium was involved in this condition. The possibilities of clinical observation were dramatically improved when Vogt, in 1920, introduced the new technique of specular illumination in biomicroscopy. He discovered that the corneal endothelium could be seen

beautifully in the living eye when this method was used. Thereafter, numerous investigators contributed to the knowledge of the clinical implications of this layer of cells.

The perfection of the technique of corneal grafting, as well as certain conditions which led to failures in this field of ophthalmic surgery, emphasized the importance of the corneal endothelium. Having become interested in this subject a number of years ago, the author found that considerable research had been done and many clinical observations dealing with the endothelium of the cornea had been reported. The publications, spread over a considerable period of time, were written in many languages and were scattered throughout a number of books and periodicals. So that this information might be made easily available to researchers as well as to practitioners, a comprehensive report embracing all important aspects of the corneal endothelium appeared to be timely. In the field of research, the knowledge of what had already been done would contribute to the elimination of unnecessary repetition and duplication.

The literature was carefully reviewed. Great care was taken to read all publications in the original text whenever this was obtainable. Parallel to the study of the literature, experimental work of our own was done and a considerable number of our own clinical observations were accumulated. In this paper an attempt has been made to present not merely an objective report, but also a critical evaluation of the work done by others as well as of our own observations; as often as possible our own conclusions with regard to any particular problem have been stated.

Introductory paragraphs deal with questions of terminology, embryology, and anatomy. Next, the physiology of the corneal endothelium under normal and abnormal conditions is discussed. The clinical implications are then taken up, leading to the description of the various clinical pictures, concluding with therapeutic remarks. Abstracted case histories are collected in Appendix A and referred to in the text. In Appendix B are descriptions of the histologic technique used for flat preparations of the corneal endothelium.

Finally, we wish to express our gratitude to all those who gave us their valuable advice and passed on personal observations and

experience. We are particularly indebted to those who graciously permitted the reproduction of their original illustrations. Specific acknowledgment of this borrowed material is made in each case. The author and his collaborators have supplied all illustrations for which no specific acknowledgments are made.

In the experimental work we were assisted by Dr. Frank B. Cooper of the Department of Ophthalmology, in the development of staining techniques by Mr. Philip Pickett, chief technician of the Department of Pathology, and in the matter of drawings and photographs by the Department of Medical Illustration of the Duke University School of Medicine. The photomicrographs are by Mr. Carl M. Bishop, also of this institution. The clinical photographs were done by Mr. W. J. Crowder of McPherson Hospital. Most patients referred to in case histories were seen at McPherson Hospital; some were seen at Duke Hospital.

TERMINOLOGY AND EMBRYOLOGY

The layer of cells covering the posterior surface of the cornea has been given various names. Those most commonly used are "posterior epithelium of the cornea," "endothelium of the cornea," and "mesothelium of the cornea." Whether one chooses to accept one or the other of these terms depends on the viewpoint. Usually the term "epithelium" is used for the covering of the surface of the body, such as the skin, or for the lining of cavities of the body that open to the surface, such as the intestinal tract. The term "endothelium" is commonly applied to linings of enclosed cavities having no opening to the surface of the body, such as the pleural cavity or the anterior chamber of the eye. The term "mesothelium," on the other hand, definitely intends to specify from which embryonic tissue the cells derive. At this time, the most widely used term for the layer of cells with which we are concerned is "endothelium." For this reason, and others to be discussed later, "endothelium" will be used as a matter of convenience.

The development of the cornea and the anterior chamber was studied in detail by Seefelder and Wolfrum (93). These authors examined human embryos of the 53 mm., 65 mm., and 70 mm. stages (between the end of the second and the end of the third month). They did not find an anterior chamber in these specimens, but in

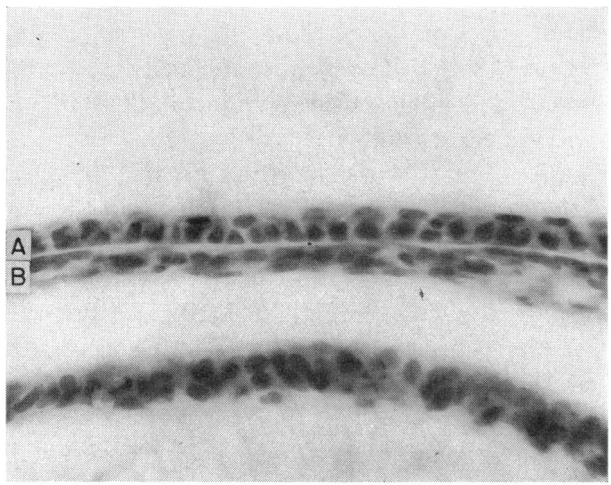


FIGURE 1. SECTION THROUGH THE CORNEA OF AN EMBRYO NINE WEEKS AND FIVE DAYS OLD

A. Corneal epithelium. B. Thin layer of mesodermal cells, one or two cells in thickness. (Original magnification x800.) From Streeter, *Developmental Horizons in Human Embryos.*

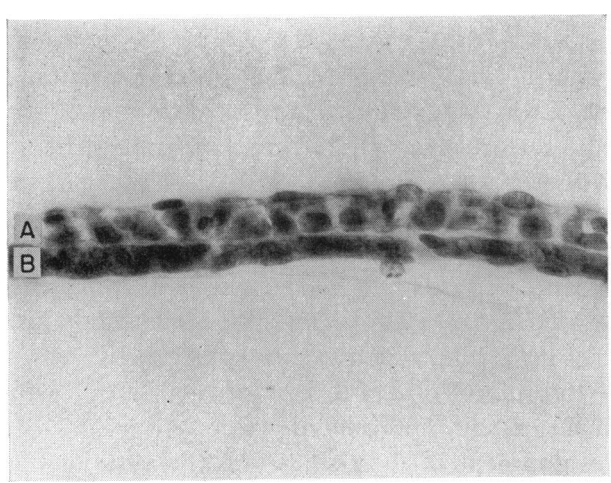


FIGURE 2. SECTION THROUGH THE CORNEA OF AN EMBRYO SEVEN WEEKS AND FOUR DAYS OLD (ESTIMATED)

A. Corneal epithelium. B. Layer of mesodermal cells slightly thicker than in Figure 1. (Original magnification x800.) From Streeter, *Developmental Horizons in Human Embryos.*

all stages a definite formation of the corneal endothelium was apparent, and in the oldest stage there already existed a thin Descemet's lamella. Ida Mann (66) accepts this date of appearance of the formation of Descemet's membrane. She states, however, that a narrow slit appears in the mesodermal lamina beneath the epithelium of the cornea as early as the 18 mm. stage, separating it into an anterior, slightly thicker portion (cornea) and a posterior, thin layer (pupillary membrane). She thinks that this is the beginning of the formation of the anterior chamber. She furthermore states that the corneal endothelium is formed by a slight rearrangement of the cells *in situ* and does not grow from the periphery. It is not important here to decide at exactly what stage the anterior chamber may be recognized, but it may be of considerable interest to know whether the endothelium is indeed of mesodermal origin or is derived from the ectoderm. Sondermann (97), unlike most other investigators, claims to prove that it really is of ectodermal origin. He contends that, after the lens vesicle has separated from the surface ectoderm, an accumulation of ectodermal cells is found in front of the vesicle. This group of cells is split into two layers by the advancing mesoderm, which becomes the stroma of the cornea. The inner layer develops into the endothelium, the outer into the epithelium. He produces photographs suggesting such a development. Very recently, however, Streeter (102) and his co-workers uphold the traditional theory of mesodermal derivation. They claim that the mesoderm invades the space between the epithelium of the lens and the surface ectoderm. They describe a thin layer of mesoderm, one to two cells in thickness, crossing the mid-point of the future corneal region. This layer becomes gradually thicker and the cells on the internal surface begin to arrange themselves in the form of a mesothelium. The mesothelium (this term is being used only while quoting) develops into a definite layer delimiting the cornea from the anterior chamber. The *substantia propria* gets thicker and thicker, gradually acquiring the properties of the corneal stroma. These developments during the stages of about 7 4/7 to 10 weeks are excellently illustrated by Figures 1 through 5. Streeter, *et al.*, (102) are so convinced of the mesodermal origin of the endothelium that they call it "mesothelium" outright. The fact, however, that their opinion, though well founded, is not uni-

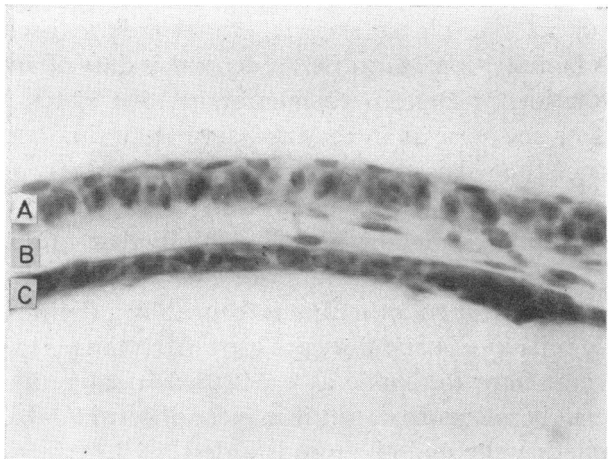


FIGURE 3. SECTION THROUGH THE CORNEA OF AN EMBRYO EIGHT WEEKS OLD (ESTIMATED)
A. Corneal epithelium. B. Mesodermal cells, undifferentiated. C. Mesodermal cells on the internal surface begin to arrange themselves in form of an endothelium (mesothelium). (Original magnification x800.) From Streeter, *Developmental Horizons in Human Embryos.*

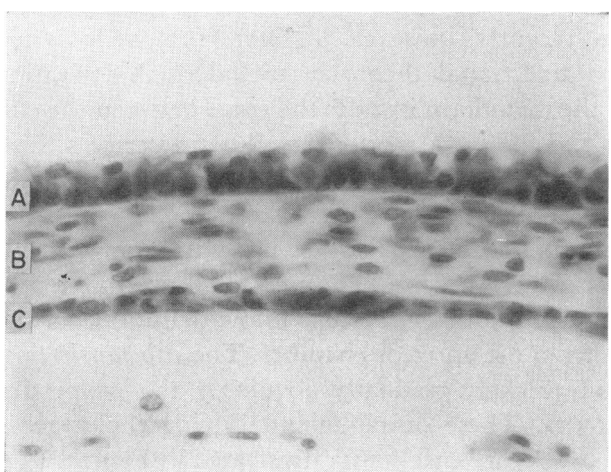


FIGURE 4. SECTION THROUGH THE CORNEA OF A NINE-WEEK-OLD EMBRYO
A. Corneal epithelium. B. Future stroma of the cornea. C. Endothelium has developed into a distinct single cell layer. From Streeter, *Developmental Horizons in Human Embryos.*

versally accepted, contributed to our decision to adhere to the more neutral term "endothelium." Verhoeff (105) also rejects the term endothelium and calls it a "mesenchymal epithelium." Nevertheless, he uses "endothelium" in his writing.

MORPHOLOGY OF THE NORMAL ENDOTHELIUM

The endothelium of the cornea may be described as a single layer of cells covering Descemet's membrane and separating the cornea proper from the anterior chamber. The cells that make up this layer are known to be of the most delicate type in the human body. Immediately after cessation of the circulation, changes in the structure of the cytoplasm take place. (This point will be discussed in detail in the section on keratoplasty.) Also, the endothelial cells are very easily altered by fixation and staining. It is, therefore, difficult to get an accurate picture of their normal and pathologic structure from the examination of fixed and stained microscopic slides.

Fortunately, we have now at our disposal a method of examining the endothelium of the cornea in vivo with slit lamp and binocular microscope. This method, however, is also limited in its possibilities, inasmuch as the magnification for accurate observation may not exceed 60 to 70 times. If extended to over 100 times linear magnification, which is possible with some of the instruments, the examination becomes technically difficult and the interpretation uncertain. It is, therefore, best to combine the two methods. During years of teaching slit-lamp examination and eye pathology, the parallel discussion of observations with both methods has proved very satisfactory. The excellent book by Busacca (9) which follows this line of thought is indeed to be welcomed.

We shall first describe the normal morphology of the endothelium as seen under the microscope and then compare the findings with the picture as seen with the slit lamp.

The cells composing the single layer of endothelium covering Descemet's membrane are of polygonal shape. This can be seen clearly in flat preparations in which the intercellular cement has been stained with silver nitrate. But even in flat preparations for which only hematoxylin stain has been used, the polygonal outline may be seen. Figure 6, showing a flat preparation of the rabbit

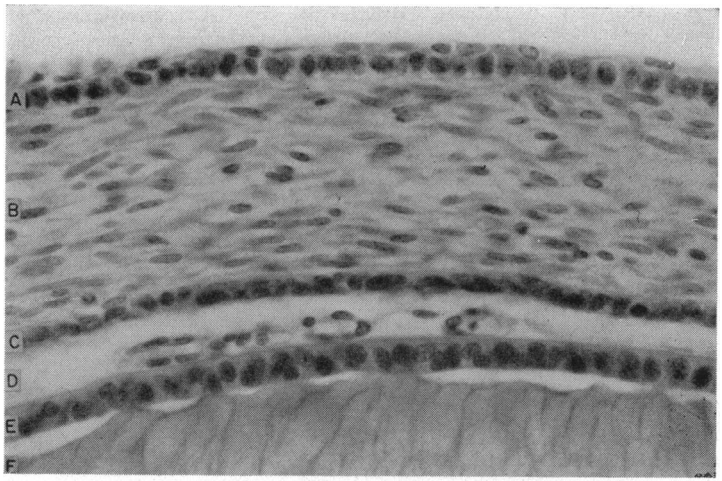


FIGURE 5. SECTION THROUGH THE CORNEA, ANTERIOR CHAMBER, AND ANTERIOR PART OF THE LENS OF A TEN-WEEK-OLD EMBRYO

A. Corneal epithelium showing several layers of cells. B. Layer of future stroma of the cornea. It has increased in thickness. The nuclei of its cells are elongated. C. Distinct single cell layer of endothelium. D. Parts of pupillary membrane. E. Epithelium of lens capsule. F. Lens substance. (Original magnification x800.) From Streeter, *Developmental Horizons in Human Embryos.*

endothelium, makes this clear. The technique of Nagano (74), slightly modified, was used in this case. The cells are mostly hexagonal, but cells with four, five, seven, and eight sides also occur. Lauber and Kolmer (59) state the height of one cell in the adult to be from 0.0050 to 0.0067 mm., and the diameter to be from 0.018 to 0.022 mm. In fetal life and in early childhood the cells are considerably higher and more cuboidal; in later life, flatter and larger. This agrees with the observations of Ballowitz (4,5) in animals. He found that mitoses were seen only in young cats, seven to fourteen days old. In animals two to three months old, he never could observe mitoses in endothelial cells. As the area to be covered by the endothelium increases during growth, the individual endothelial cells enlarge in width but get flatter. Thus the coverage of the enlarged area is accomplished by spreading rather than by the formation of additional cells. In Figure 7 are reproduced photographs of the endothelium in a seven-month-old child, a young adult sixteen years old, and a person sixty-two years old. Although in fixed preparations the cells undergo artificial changes, it can be seen

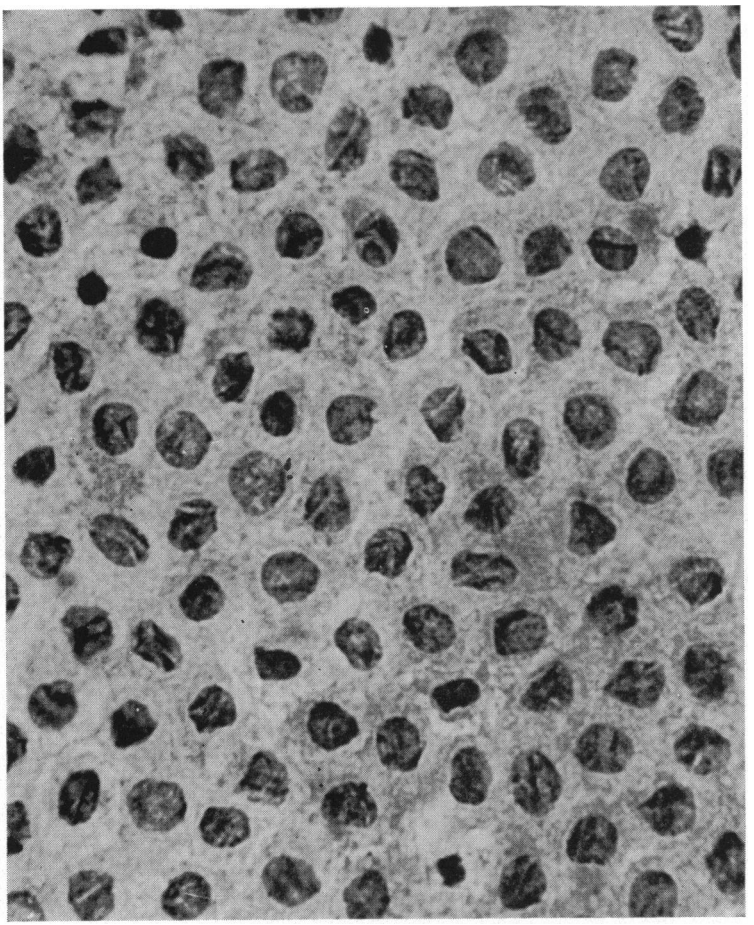


FIGURE 6. FLAT PREPARATION OF THE CORNEAL ENDOTHELIUM OF THE RABBIT, STAINED WITH HEMATOXYLIN

The regular arrangement of the endothelial cells is demonstrated. The cellular outlines are faintly visible, indicating the polygonal shape of the cells. (x764.)

that the cells in the young child are higher as compared with those of the adult. By counting the nuclei of the endothelial cells as per one high-power field in a histologic section, taking the average from a whole section, we could confirm that the cells are more closely packed in the younger individual than in the adult. We counted 14 nuclei in the average high-power field in the seven-month-old, 10 in the sixteen-year-old, and 11 in the sixty-two-year-

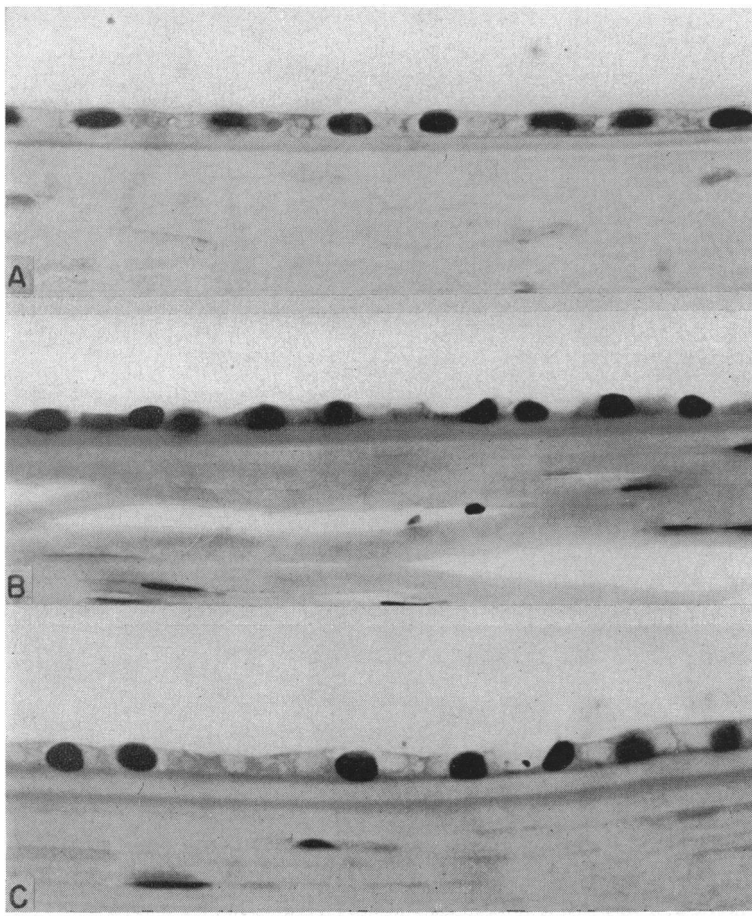


FIGURE 7. CROSS SECTIONS THROUGH THE POSTERIOR PARTS OF THREE CORNEAS

A. A child seven months old. B. A sixteen-year-old. C. A sixty-two-year-old individual. The endothelial cells appear flatter and stretched out in the adults as compared with the young child.

old. This feature is not clearly demonstrated in the photographs, since it is impossible to eliminate the error originating from superimposition of the nuclei from different layers.

It can be seen with the slit lamp that under certain conditions endothelial cells may be at least five times the normal size. Case 39 may serve as an example. This patient had suffered from interstitial keratitis when a child. It was assumed that some of the

endothelial cells had been expanded to cover the defects where diseased endothelia had perished. Evidently this process eventually had interfered with the normal physiology of the endothelial cells, since the patient in later life developed endothelial and epithelial dystrophy. The nuclei are well defined, oval shaped, and are usually located in about the center of the cells. In the presence of Henle's warts on Descemet's membrane, however, there is a flattening of the cells and the nuclei are displaced towards the

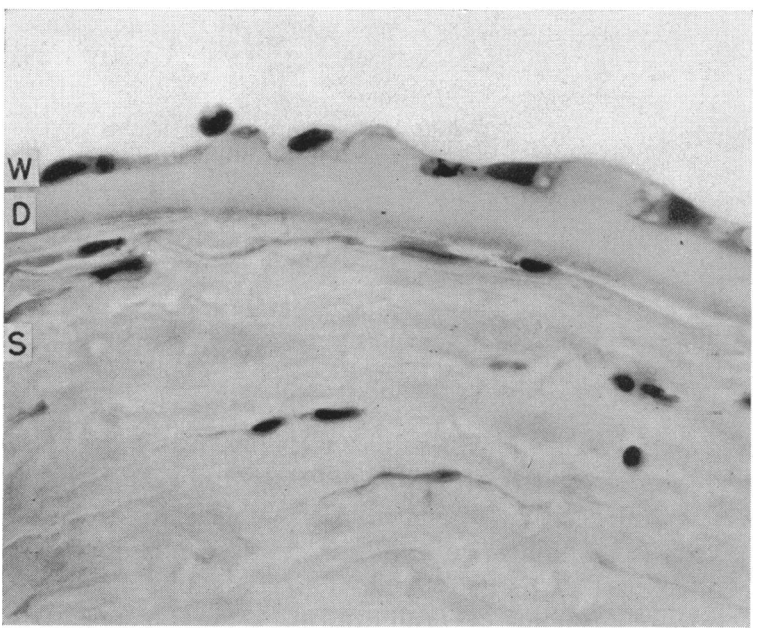


FIGURE 8. CROSS SECTION THROUGH THE PERIPHERAL PART OF THE CORNEA OF AN OLDER PERSON

S. Stroma of the cornea. D. Descemet's membrane. W. Henle's warts with endothelial cells stretched over their surface and the nuclei displaced into the valleys between the warts. Some of the endothelia contain pigment granules. (x593.)

periphery (Figure 8). The protoplasma is clear and contains fine granules. Towards the periphery the endothelial cells get flatter for a few cells, the nuclei bulging somewhat towards the anterior chamber, until finally they become continuous with the thin endothelium covering the chamber angle.

According to the most accepted theory, the endothelial cells

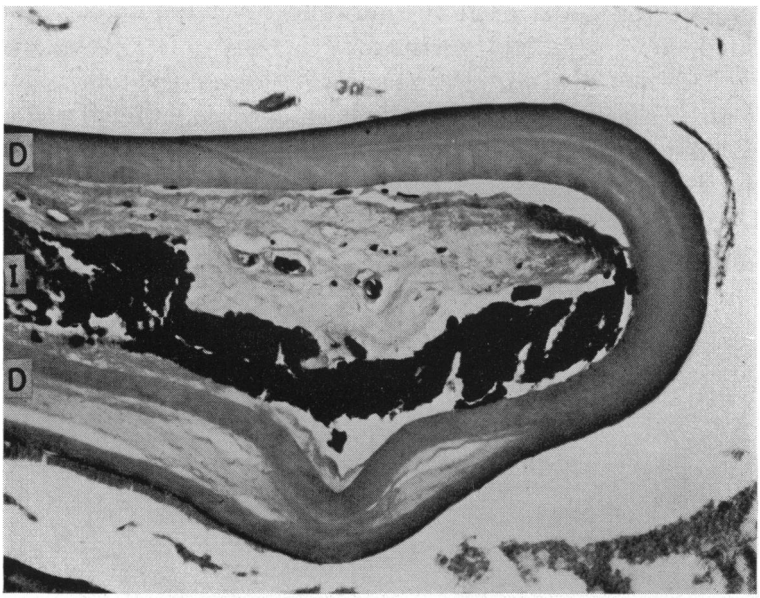


FIGURE 9. CROSS SECTION THROUGH A DESCEMET'S MEMBRANE PRODUCED BY CORNEAL ENDOTHELIUM WHICH HAD GROWN OVER THE IRIS
I. Iris. D. Descemet's membrane that is laminated. In the lower part the two lamellae are artificially separated. (x115.)

secrete the substance forming the amorphous membrane by which they are separated from the stroma of the cornea. This membrane is usually called after Descemet. Although lacking some of the properties in relation to stains possessed by true elastic tissue, it is in principle an elastic membrane. The elasticity diminishes with age. Its water content, according to Michel and Wagner (71), is about 5.5 percent higher than that of the corneal stroma. Although it is a homogenous structure, occasionally a faint lamellar appearance can be observed. It has been suggested that the outer layer might be a product of the stroma proper, whereas the inner layer would be secreted by the endothelium. There is, however, considerable evidence that the arrangement in layers might rather be the product of several episodes of secretion. Figure 9 shows a definite lamination of the membrane which resulted from overgrowth of the endothelium on the anterior surface of the iris. In this case there could certainly be no doubt that the whole membrane was produced by the endothelium. Towards the periphery the mem-

brane becomes thinner and finally splits into small bundles which in part engage with the sclerocorneal junction, and in part take a circular course forming the ring of Schwalbe (Eisler). Schwalbe's ring is difficult to visualize with the slit lamp. Schnyder (89) saw it only 5 times when looking for it in 200 eyes. It can be seen, however, with the gonioscope. At about the age of twenty or thereafter some peculiar excrescences, which according to Eisler had already been illustrated by Berres in 1837, appear on the posterior surface of Descemet's membrane. They now are generally called Hassal's, or Henle's, warts. Figure 8 shows their typical appearance, with the endothelial cells thinned out over the tops of the warts and the nuclei pushed towards the valleys between them. Pigment granules may be found on the surface of the warts and within the endothelial cells themselves. In a typical case, on one cross section we found 23 warts on one side and 3 on the other. In none of the cases reviewed did the area containing warts extend closer to the center than about one tenth of the total corneal diameter from the periphery. There is in this selective localization a fundamental difference from the degenerative form of warts, as seen in cornea guttata, which prefers the central area.

The individual endothelial cells are held together by an intercellular cement substance. Such a substance between endothelial cells had already been postulated by Cohnheim (in 1867) and Arnold (in 1887), and in 1893 Rable pointed to the fact that the silver nitrate staining of the cement was due to the formation of silver proteinate, cited by Chambers and Zweifach (15). Recently Vonwiller (113) used alizarin red for vital stain of the intercellular substance. In our own experiments we were able to stain the intercellular cement in the living or freshly excised rabbit cornea by using this technique. The intercellular lines stand out beautifully in yellow-red. Using the same stain, we were able to demonstrate these lines in a freshly excised human cornea as well. Having had difficulties in preserving the stain by fixation, we had the fresh, unfixed preparation photographed (Figure 10). Vonwiller, who worked with freshly excised beef corneas, also demonstrated that some of the endothelial cells are much larger than others and contain multiple nuclei. But he found no mitoses. He concludes that perhaps in embryonic life there had occurred incomplete mitosis,

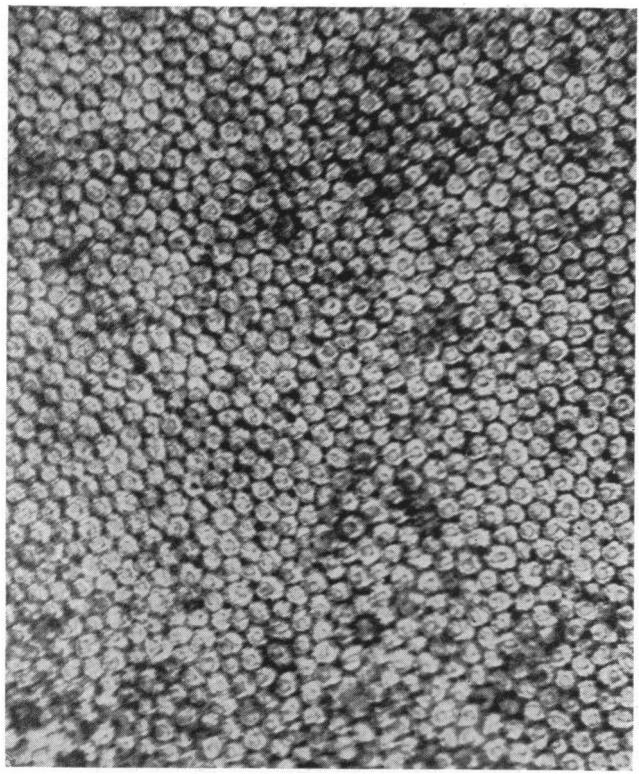


FIGURE 10. FLAT PREPARATION OF THE HUMAN CORNEAL ENDOTHELIUM The specimen was stained with alizarin red without fixation. The intercellular cement lines stand out clearly, emphasizing the polygonal shape of the cells. The nuclei are faintly stained. (x272.)

during which the division of the nuclei was not followed by a complete division of the cell itself. Waldeyer (115) denied the presence of an intercellular cement substance, but pointed out the existence of bridges between the cells. On the other hand, Schaffer (88) considers these bridges to be artefacts. We feel that considerable evidence of the existence of an intercellular cement has been produced by the use of staining methods as well as by experiments dealing with the permeability of the corneal endothelium. (The factor of permeability will be discussed in detail in the next section.)

As mentioned above, the corneal endothelium can be studied in vivo with the slit lamp and binocular microscope. This was first

described by Vogt (106). In order for the endothelium to be visualized, the examination has to be carried out in the light totally reflected from the optical plane of separation between endothelium and aqueous. With a magnification of from 68 to 80 times, the apparent size of an endothelial cell is 1.3 to 1.7 mm. (Vogt). However, the cells can be seen quite distinctly with a magnification of 40, which is more commonly used. They display a pattern which closely resembles a miniature honeycomb. Their polygonal shape can be recognized and a definite intercellular line seen. Under normal conditions the cells are of rather uniform size, although occasionally a single cell may appear somewhat larger. Now and then a cell shows a grayish dot, presumably the nucleus, in the

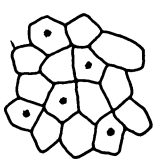


FIGURE 11. SCHEMATIC DRAWING OF THE APPEARANCE OF THE CORNEAL ENDOTHELIUM AS SEEN IN VIVO WITH THE BIOMICROSCOPE

The irregular polygonal shape and the slight variation in size of the cells are emphasized. The cellular outlines represent the intercellular cement, the gray dots the nuclei which are visible in some of the cells. (Much larger than actually seen.)

center. Figure 11 shows schematically the arrangement of the endothelium. Figure 12 is the artist's impression, reproduced from Vogt's atlas (110). Towards the periphery, beginning after the age of twenty years, the pattern usually becomes wavy; this increases with age. This effect is due to the appearance of Henle's warts on Descemet's membrane. When well developed the warts appear as dark spots in the mosaic pattern of cells. Occasionally, when the microscope is focused farther back, endothelial cells can be seen on the bottom of the bulge. This appearance is well in keeping with the findings in microscopic slides mentioned above. Schnyder (89), in his detailed description of the endothelium as seen with the slit lamp, reports persons of the ages of ten, fourteen, and twenty-two years as the youngest in whom he observed Henle's warts. He mentions that between warts larger endothelial cells than usual are often seen. In older people the endothelial pattern becomes more and more indistinct. This is partly due to the increased turbidity of the stroma. But it appears that the cells themselves also undergo changes which render the honeycomb pattern less distinct. Vacuolization and thinning of the cells occur, leading to

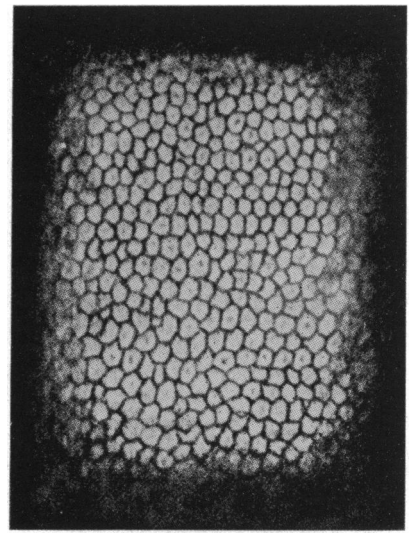


FIGURE 12. ARTIST'S CONCEPTION OF THE CORNEAL ENDOTHELIUM AS SEEN WITH THE BIOMICROSCOPE
Note the striking resemblance to the actual photograph taken after vital staining with alizarin red (Figure 10). From Vogt's *Atlas* (original in colors).

the final stage of atrophy which will give rise to the clinical picture of endothelial dystrophy. (This condition will be dealt with in a later section.)

PHYSIOLOGY OF THE CORNEAL ENDOTHELIUM

The fundamental facts concerning the function of the corneal endothelium were demonstrated by Leber as far back as 1873. Although valuable additional data were added by more recent investigators, it seems proper to refer to Leber's work in some detail. Whereas Demours, cited by Leber (61), one of the first to describe Descemet's membrane, had thought in 1865 that this membrane was the barrier preventing the cornea from becoming infiltrated by aqueous, Leber proved that it was actually the endothelium that possessed this property.

Leber used freshly excised corneas from cattle or horses. These were mounted on an ingeniously simple apparatus reproduced in Figure 13. A U-form glass tube was used, with the cornea (C) held tightly over one end, the space directly beneath the cornea filled with water, and the rest of the tube with mercury. The pressure the water exerted against the cornea could be altered and measured simply by varying and measuring the height of the column of mercury.

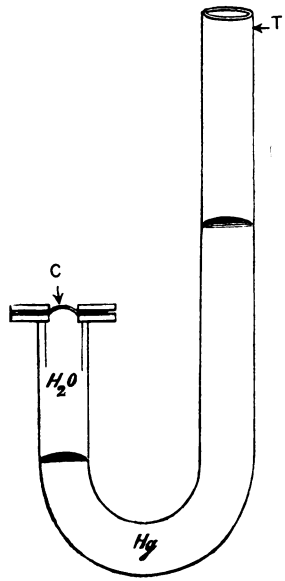


FIGURE 13. LEBER'S APPARATUS FOR TESTING THE PERMEABILITY OF THE CORNEAL ENDOTHELIUM

Over one opening of the glass tube (T) the cornea (C) is attached. Beneath the cornea is water (H_2O); in the bottom of the tube is mercury (Hg).

In the first place, it was found that more fluid would penetrate an isolated Descemet's membrane in a shorter period of time after the endothelium had been brushed off than with the endothelium intact. Whereas with the intact endothelium 30 to 40 mm. of mercury were necessary to produce droplets on the other side of the membrane, only 10 to 15 mm. were required after the membrane was denuded of the endothelium. Leber then examined the phenomenon of corneal opacification by absorption of fluid. He referred to the investigations of Coccius and His, reported in 1852; they had demonstrated that the excised cornea increases in weight and swells up when placed in fluid, even aqueous humor. Leber demonstrated that the cloudiness of the cornea from freshly killed rabbits was the same if either the endothelium alone or Descemet's membrane together with the endothelium was removed, whereas the nontreated cornea remained clear. In an experiment with living rabbits, Leber entered the anterior chamber with a blunt hook and destroyed the endothelium in places by moving the hook over the posterior surface of the cornea. Within fifteen minutes after this procedure the corneal stroma became cloudy in areas corresponding to the site of the injury. This cloudiness increased

for the next twenty-four hours, and the excised cornea was found to be three times as thick in these areas as in the clear parts. That the endothelium really was absent in these areas was proved by the failure of the silver impregnation stain to demonstrate the cellular outlines. Three days after the injury the cloudiness had almost disappeared, and after fourteen days the cornea became entirely clear. Since L. Meyer (70), cited by Leber (61), had previously mentioned that the cornea would become cloudy when pressure was exerted on the bulbus, Leber investigated the effect of pressure on eyes treated in the manner described above. During the first day after the operation, even slight pressure on the eyeball would momentarily increase the cloudiness. As soon as the pressure was removed, this additional cloudiness would disappear. One day later, much more pressure was necessary to produce the same effect. Further evidence for the protective function of the endothelium with regard to the cornea proper was established by Stokes's observations (101). In his experiments on the macrophages in the cornea he found that the response of the corneal tissues to the introduction of trypan blue into the anterior chamber was dependent upon the integrity of the endothelial lining of the posterior surface of the cornea. The dye was able to stimulate macrophagic activity in the cornea only after the endothelium had been injured.

There has been considerable speculation as to the mechanism by which the endothelium prevents the fluid from infiltrating the stroma of the cornea. In the first place, it was Leber who stated that this mechanism must be connected with the living properties of the cells, since he found that the endothelium loses its protective function gradually and progressively after death. The importance of this fact will be taken up again in the section on corneal grafting. Then the question arises: Is it the cell itself or the intercellular spaces that let the fluid pass under abnormal conditions? Taking the example of intraocular pressure, it is a known fact that experimentally it is possible to produce cloudiness of the cornea instantaneously by injecting normal saline solution under pressure into the anterior chamber. The three steps of this experiment are reproduced in Figure 14. If the pressure was relieved after a short while, the cornea became clear again immediately. If, however, the pressure was maintained for several minutes, we could

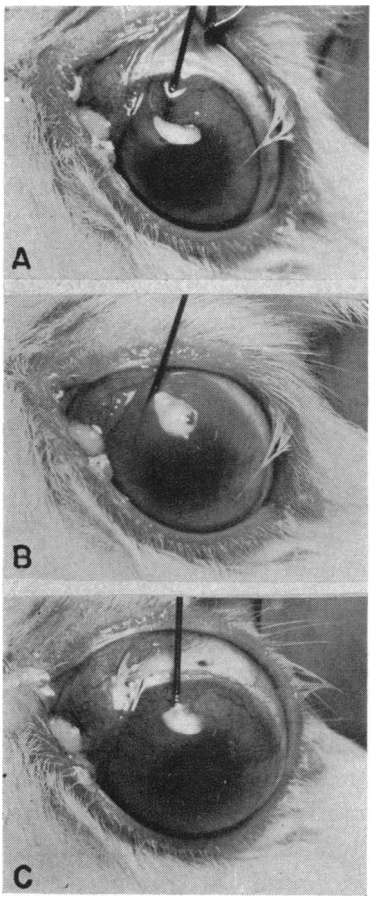


FIGURE 14. PRESSURE CREATED BY INJECTING NORMAL SALINE SOLUTION INTO THE ANTERIOR CHAMBER OF THE RABBIT PRODUCES CLOUDING OF THE CORNEA

A. Hypodermic needle attached to a syringe filled with normal saline solution is introduced into the anterior chamber. No pressure is exerted. The cornea is clear. B. Pressure is applied on the plunger. The cornea becomes cloudy instantaneously and remains cloudy as long as the pressure is maintained. C. The pressure is released. The cornea immediately becomes clear again.

observe a slight haze which remained in the cornea for several minutes after the pressure had been removed. These findings seem to be in keeping with Leber's statement that the sudden appearance and disappearance of corneal opacity in this experiment can hardly be due to infiltration with fluid. On the other hand, he admits that in glaucoma and pathologic changes of the endothelium, fluid might be forced into the stroma in spite of the presence of the endothelial layer. Probably, as in our own experiment described above, if the pressure has lasted a certain length of time, the endothelial layer becomes damaged and partly permeable to fluid. This would be in keeping with Redslob's (83) contention that

in glaucoma there are two sorts of corneal haziness. The first appears promptly when the intraocular pressure rises and disappears as soon as it falls again. This type of opacity might be caused by a displacement of the corneal lamellae. According to Cogan (25), temporary dislodgement of intramicellar fluid during stretching might be the reason for clouding. The second, more lasting, haziness would have to be considered a true edema. The question still remains whether the fluid passes through the cells themselves or through the intercellular spaces. Some interesting facts concerning capillary endothelia may be recalled in this connection, since it is not at all improbable that similar conditions may prevail with regard to the anterior chamber and its endothelium. Zweifach (118) states that thinness of a cell, as such, does not affect the selective nature of protoplasmic permeability; the tubular epithelium of the kidney maintains its selective permeability even when the cells are flattened by distension to a thinness approximating that of pavement epithelium. He thinks that the permeability of the endothelial membrane may be explained without taking into account the permeability of the individual cells. Although a selective permeability of the cells may coexist, the porosity of the intercellular cement, according to Zweifach, is a much more important factor in the permeability of the wall than are the cells themselves. The cells themselves, however, are not a simple osmotic system. Their permeability, according to Lucké (65), is influenced by various factors. In his experiments with arbacia eggs he found that the permeability to water was increased by factors such as injury, rise in temperature, absence of electrolytes, and the presence of anions. It was decreased by the presence of cations and certain narcotics. Contrary to what might be expected, a change in salt concentration of the natural medium (which in the case of arbacia eggs is sea water) did not affect permeability. According to Chambers and Zweifach (15), the intercellular substance is constantly secreted by the cells. In their experiments they found that if the cement substance is stained with silver nitrate in vivo, black globules begin to detach themselves after about 20 minutes and continue until finally no stain can be observed. Since no leakage of the capillary wall occurs during that period, the intercellular material must be continually replaced. They report that Ringer

(1890) had already observed that distilled water has a loosening effect on the intercellular cement substance; this effect may be reversed by sodium bicarbonate. In perfusion experiments, they found that if they perfused capillaries with normal Ringer solution, no visible abnormalities are observed. When a Ringer solution from which calcium has been omitted is used, a softening of the cement occurs when perfused. With the use of a solution containing double the amount of calcium contained in normal Ringer solution, the endothelial lines become intensified and later the entire surface of the cells seems to cover itself with secreted cement substance. Vitamin C has also been found an important factor in the production of intercellular cement. Wolbach and Howe (117) conclude from their experiments that scurvy, a vitamin C deficiency, may be characterized by the inability of the supporting tissues to produce and maintain intercellular substance. The ability to produce intercellular cement would return after an antiscorbutic diet was instituted. Buschke (11) examined intercellular cohesion in corneal epithelium. He found it decreased by trypsin, chymotrypsin, and papain. Lysosyme, hyaluronidase, ribonuclease, and crotoxinlecithinase did not decrease the intercellular cohesion. Calcium nullified the effect produced by proteolytic enzymes. The intercellular cohesion was also decreased at pH values of nine and above. These observations would support the assumption that the intercellular cement has a calcium salt of protein as its most important component. The intercellular cement has been discussed at some length, since there is some evidence that also in the corneal endothelium the passing of fluid through the endothelial layer into the stroma may be governed by the condition of the intercellular substance. In several cases we could observe with the slit lamp that during and immediately after an acute rise of intraocular pressure the intercellular lines between the endothelial cells appeared definitely enlarged as compared with the normal pattern. Figure 15 illustrates this schematically. The widening of the intercellular spaces might indicate a lessening of the intercellular cohesion which would allow fluid to pass between the cells. Indeed the picture reminded us strikingly of Buschke's illustration of the loosening of the intercellular cohesion in the corneal epithelium under the conditions mentioned above. Fuchs (44) had mentioned

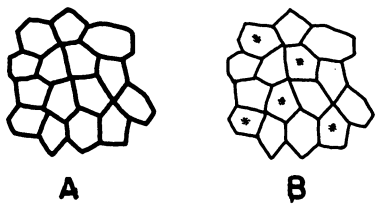


FIGURE 15. SCHEMATIC DRAWING DEMONSTRATING THE ENLARGEMENT OF THE INTERCELLULAR SPACES AFTER AN ACUTE RISE OF INTRAOCULAR PRESSURE
A. Enlarged intercellular lines in a case of acute glaucoma as seen with the biomicroscope after the cornea has been cleared with glycerine. B. Normal endothelial pattern for comparison.

the possibility of such an enlargement of the intercellular spaces, but did not demonstrate it. Schnyder (89) reports that he has seen such enlargements of the intercellular lines with the slit lamp, when he injected freshly enucleated animal eyes with normal and hypertonic saline solutions.

According to Fischer (35), the endothelium possesses a directed permeability for gases. There is transfer of oxygen through the corneal epithelium to the endothelium from the atmosphere. The endothelium uses up the oxygen. Carbon dioxide is transferred from the endothelium through the epithelium. This is the normal exchange. Coccius, cited by Leber (61), had already shown that evidently air does not injure the endothelium, for he could keep the anterior chamber of rabbits' eyes filled with air for three to four days without the cornea becoming opaque. This statement is confirmed by the everyday therapeutic practice of injecting air into the anterior chamber. If, according to Fischer, the cornea is left in saturated carbon dioxide instead of air, necrosis of the endothelium occurs and is followed by infiltration of the stroma with fluid and the development of cloudiness. In hydrogen the cornea remains clear. The passage of oxygen to the endothelium from the outside seems to be of vital importance, since the oxygen tension of the aqueous was found to be equal to that of the venous blood by DeHaan (cited by Fischer, 35); this is insufficient for the tissues.

Considerable work has been done to explain the biochemical mechanism governing corneal permeability and the development of corneal edema. Since most of the studies were done on the cornea as a whole or on the corneal epithelium, and very few definite facts concerning the endothelium were demonstrated, it is not proposed to go into this matter in detail here. Fischer (34) has reported fundamental experiments, later followed by Cogan (20),

Kinsey and Cogan (53), Cogan and Kinsey (21), Cogan, Hirsch and Kinsey (23), and others.[1] The subject is still quite controversial. From the clinical standpoint it may be said that, whatever the mechanism may be, the fact remains that the integrity of the endothelium alone is sufficient to maintain the cornea in a deturgesced state. If the endothelium is impaired, the importance of the epithelium to the elimination of water becomes evident. Water may be eliminated through the epithelial membrane both by osmotic action and by simple evaporation.

GENERAL PATHOLOGY AND REGENERATION OF THE CORNEAL ENDOTHELIUM

One of the outstanding characteristics of the corneal endothelium is its vulnerability. Extensive experimental work demonstrating this fact was done by Nagano (74). He studied the endothelial changes after external injuries such as lime burn, bee sting, the effect of ammonia vapors, silver nitrate, 5 percent methyl violet in the conjunctival sac, massage of the cornea, electric shock, steam, cautery, and abrasion of the cornea. After two days following even a trauma as slight as the abrasion of the corneal epithelium, he found changes in the arrangement of the nuclei of the endothelium; after five days, however, the endothelium had returned to normal. Various substances, such as scarlet oil, mercury bichloride 1:5000, and 10 percent sodium chloride solution, caused severe damage to the endothelium when injected into the anterior chamber. The relatively mild trauma produced by instillation of 10 percent sodium chloride resulted in vacuolization and shrinkage of the cells. A peculiar experimental finding was reported by von Hippel (51). After ligation of the venae vorticosae in a rabbit, the endothelium became heavily pigmented.

Clinically it is well known that the corneal endothelium may be damaged in many ways. In connection with the above-mentioned experimental observation of von Hippel, it may be mentioned that the endothelium is stained or pigmented in various ways. It may contain melanotic pigment, especially in cases of

[1] For review of literature in 1949, see V. E. Kinsey, *Arch. Ophth.* 44: 584-99, 1950. See also the complete summarizing report on corneal edema by G. Victor Simpson, *Tr. Am. Ophth. Soc.*, 85th meeting, 1949.

cornea guttata and endothelial dystrophy (see Figure 11). It may take up iron stain in siderosis, as we were able to demonstrate in some histologic sections, and recently we discovered with the slit lamp a yellowish tinge in the endothelial cells in two instances of severe argyrosis from prolonged use of argyrol locally. There is evidence that the endothelium may be damaged by severe or long-standing inflammatory processes such as serpiginous ulcer (Nagano, 74), interstitial keratitis (Stanculeano, 99), keratitis pustuliformis profunda (E. Fuchs, and Samuels and A. Fuchs, 87). Defects in the endothelium underlying keratitic precipitates have been demonstrated anatomically by Groenouw, cited by von Hippel (51). Harms, cited by von Hippel (51), found the endothelium intact beneath small precipitates, but missing under large ones. Seemer (95) demonstrated clinically the appearance of epithelial bullae exactly in front of large fatty precipitates. We made a similar observation in a patient with severe iridocyclitis due to sarcoidosis (Case 40). Edema and later a bandlike intraepithelial and subepithelial opacity developed over the site of long-standing fatty precipitates. Farther down towards the limbus, where a dense layer of whitish tissue had formed covering Descemet's membrane, the epithelium was intact. It is most probable that the endothelium was damaged beneath the precipitates, and fluid penetrated the cornea in those places. The dense scar tissue covering part of Descemet's membrane might have prevented the penetration of fluid and consequently the epithelium remained clear. It is not quite clear why in some instances of apparently the same pathologic process there is endothelial damage and in others none. It was demonstrated by DeHanssen, cited by Busacca (9), that in Krukenberg's spindle the endothelial cells are packed with pigment. Probably the course is influenced by the amount of toxic material present in a given case. Also, epithelium which has already degenerated, as in some older people, will fall victim to damaging causes more easily than will a healthy one. We have seen that the endothelium had degenerated in some of our own specimens of panophthalmitis. In such cases it can be noted that the leucocytic infiltration of the cornea is much more pronounced in areas where the endothelium has become deficient. It seems that the degeneration of the endothelial cells results from a direct con-

tact with leucocytes. In specimens with severe anterior chamber hemorrhage, we also have noticed degeneration of the endothelium.

In acute glaucoma a temporary disturbance of the corneal endothelium may be observed. In Case 50, the endothelial cells had acquired a droplet-like appearance as seen with the slit lamp after the epithelial edema had subsided. We interpreted the picture as edema of the endothelial cells.

Approaching the problem of regeneration of the corneal endothelium, one must differentiate between reformation of normal endothelial cells and those cells that will acquire different and abnormal morphologic and physiologic properties. In the latter case a defect may be covered and even a pseudo-Descemet's membrane secreted, but otherwise the cells would not be arranged in the same regular pattern characteristic of the original endothelium. E. Fuchs (43) expressed doubt as to whether a regular endothelial cover could ever be regenerated after the endothelial cells have been destroyed. The regenerated layer, he believed, would be more similar to connective tissue than to the original cells. This opinion appears to be in keeping with Wagenmann's idea of what he calls "endothelogenous connective tissue," cited by von Hippel (51). Since the endothelium is probably of mesodermal origin, it would not seem impossible that, under certain circumstances, it might acquire properties of connective tissue.

The mechanism and pattern of regeneration of the injured corneal endothelium are still poorly understood. In the first place, it appears that there are great differences in regeneration, depending on whether the endothelium has been injured by simple trauma or by toxic or chemical action (infection, chemical burns), or whether it is genuinely degenerated following an intrinsic disposition. Also some of the experimental injuries were produced with the use of such drastic means—blunt, sharp and chemical—that the results can hardly be interpreted as illustrating the healing process that might, for instance, follow a surgical wound. The discussion on wound healing in the endothelial layer after a corneal section, as in cataract surgery or keratoplasty, is deferred to the section on the role of the endothelium in corneal transplantation.

At this point some general aspects of endothelial regeneration

will be considered. The discussion might properly begin with a description of what happens in a tissue culture. Matsui (68) reported on this subject. He was able to grow corneal endothelium in culture when it was left in contact with Descemet's membrane, but failed when the endothelial layer was isolated. In the first case, after 24 hours of incubation the culture showed no signs of proliferation. After 48 hours many mitoses appeared and cells of polygonal or roundish shape grew into the culture medium. Some of the cells were long and spindle-shaped, with an elongated or oval nucleus. They often were in contact with each other through long protoplasmic pseudopodia. Sometimes these cells appeared to be very similar to fibroblasts. It seemed, however, that this probably was a transitional state, as later on the cells again acquired a more endotheloid appearance. Lippmann and Brueckner (7,63) found that after irritating substances had been introduced into the anterior chamber of rabbits' eyes, desquamation of endothelial cells occurred. They observed these cells to proliferate by amitotic division and assume the appearance of small round cells with round nuclei, closely resembling lymphocytes. Since these round cells appeared even after the animals had been made aleucocytic by intoxication with Thorium X, the investigators concluded that they cannot be derived from the blood but must originate from the endothelium.

The question of whether the endothelial cells may become macrophages is still undecided. Whereas authors like Hamburger (50) and Vonwiller (113) claimed they could demonstrate selective staining of the corneal endothelium by vital stain with methylene blue or trypan blue, others, for example Nemeth (75), found that the normal endothelium would not take up the dye and that a violent keratitis was necessary in order to produce vital staining. Stokes (101), after extensive experimental studies with trypan blue introduced into the anterior chamber, concluded that, unlike the case of corneal corpuscles, there was no evidence of transformation of the cells of the endothelium of the cornea into macrophages. We were unable to stain the endothelium in vivo with either a technique similar to that employed by Stokes or the one indicated by Vonwiller.

As to the healing of traumatic defects, Leber (61) stated that 14

days after injuring the endothelium by passing a blunt hook across the posterior surface of the cornea of rabbits, microscopic examination showed the endothelium to be continuous again except in one area, where its cells were arranged somewhat irregularly. Nagano (74), after scraping off the endothelium from behind, observed signs of regeneration at the borders of the defect after 12 hours, and mitoses after 16 hours. After five days, the defect was covered, the nuclei being of irregular shape. Two hours after lime burn from the epithelial side, the endothelial cells became necrotic. After 24 hours regeneration occurred, with mitoses and heaping up of new cells. Giant cells also appeared. More recently an interesting study on the regeneration of the corneal endothelium was done by Cogan (24). He succeeded in implanting magnetic foreign bodies into the anterior chambers of rabbits. Two weeks later these foreign bodies were raked over the internal surface of the cornea by a magnet moved across the outside of the cornea. Like previous experimentators, he observed cloudiness of the cornea due to the injury to the endothelium. The opacity was always greater in the axial portion of the cornea, even when the manipulation had been confined as much as possible to the limbal regions. After a day or two the opacity began to resolve, and at the end of one or two weeks it had almost or completely disappeared. After especially vigorous manipulations with the magnet a permanent opacity developed with the formation of a membrane on the posterior surface of the cornea. In animals that had been made deficient in vitamin C by a scorbutic diet, the clearing of the cornea and the regeneration of the endothelium did not seem to be delayed as compared with animals on a normal diet.

All these reports on the regeneration of the corneal endothelium after trauma, however valuable, were based on the effect of rather uncontrolled injuries and did not permit the study of cellular movements in detail. It therefore seemed desirable to supplement them by further studies. Stimulated by the work of Friedenwald and Buschke (39) and of Friedenwald, Buschke, and Morris (40) with the epithelium of the cornea, we studied the healing process of minute injuries to the endothelium in some detail. The authors just mentioned produced very small injuries to the corneal epithelium of rats with the point of a fine needle and observed the

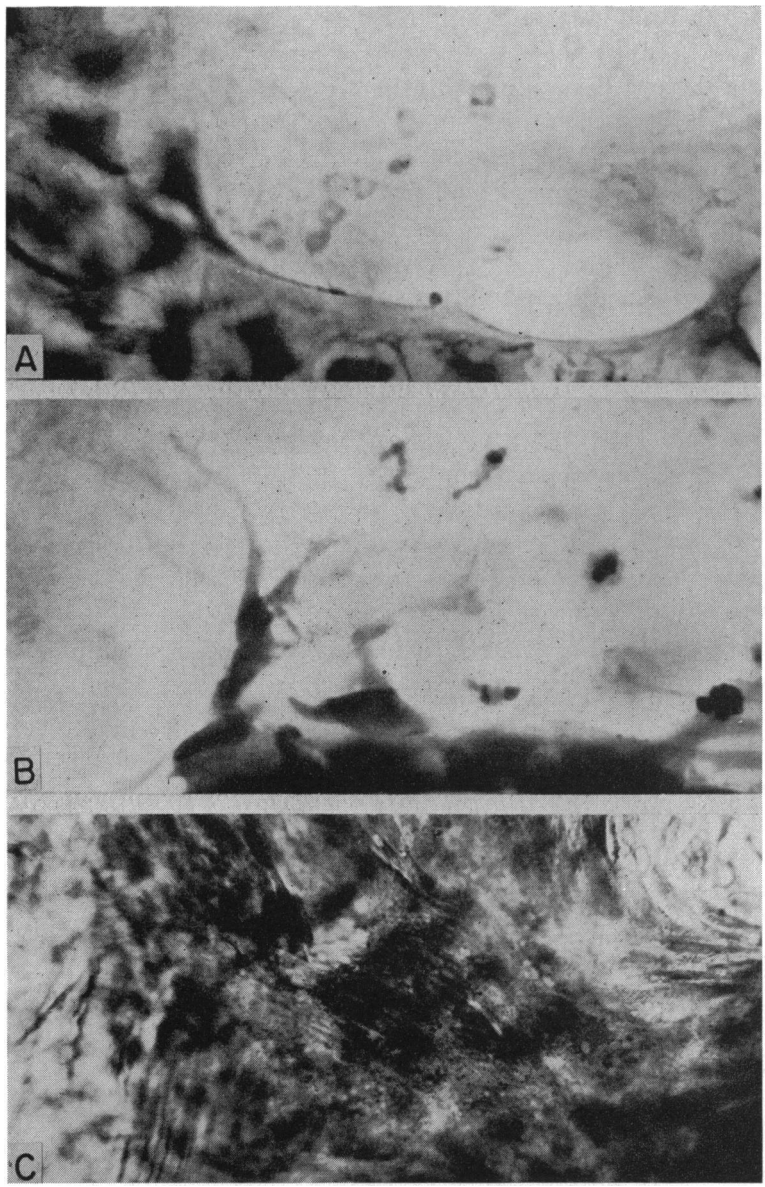


FIGURE 16. APPEARANCE OF CORNEAL ENDOTHELIUM IN FLAT PREPARATIONS AFTER MINUTE INJURIES (NEEDLE PRICKS)
A. After two hours. B. After twenty hours. C. After four days.

reaction after various times and under pathologic conditions. They could illustrate photographically how the defects were gradually covered by the migrating neighboring cells. In our case, the technique was somewhat more complicated, as the endothelium is less accessible. We managed, however, to introduce a small, sharp Grieshaber needle near the limbus and to prick the endothelium at numerous points without loosing the anterior chamber or causing damage to other structures. The animals were killed after various intervals and the endothelium examined, using our flat-section technique as outlined in Appendix B. One and two hours after the injury no cellular reaction was observed; there was, however, a sharp outline of the defect, suggesting that intercellular cement had been secreted to form a delimitation of the area where the endothelium was absent. After twenty hours, the cells bordering the defect appeared to be enlarged; some of them were elongated and were pushing long, ramified pseudopodia towards the defective area. After four days the defect appeared to be covered by an irregular mass of cells, poorly outlined, with mostly elongated nuclei. This coverage certainly did not resemble in the least the regular pattern of the endothelium (Figure 16). We have observed clinically that after a perforating injury the endothelium surrounding the site of the perforation remains damaged and does not regain its original pattern (Case 51).

It has long been known that in the case of rupture of Descemet's membrane the two ends do not heal together, but rather have a tendency to curl. The endothelium then covers the defect and reproduces a sort of pseudo-Descemet's membrane which usually, however, does not exactly resemble the original one. Figures 44 and 46 illustrate this process. Samuels and Fuchs (87) demonstrated that, when Descemet's membrane is detached over a wide area, the endothelium may even cover its anterior surface.

DYSTROPHIES AND DEGENERATIONS OF THE CORNEAL ENDOTHELIUM

Although the word "dystrophy" is defined as faulty or defective nourishment, in its common usage it has also the meaning of abnormal development or degeneration without definite reference to the factor of nourishment. In using the term in this wider sense,

we shall have to distinguish between endothelial dystrophies due to intrinsic factors such as constitution, heredity, and senility on one side, and degeneration as a sequela of some other condition on the other. We choose to call the first group primary dystrophies, the second group secondary dystrophies. It is not uncommon, even in cases belonging to the second group, that primarily there exists a constitutional tendency to degeneration which is not manifest, which will develop under the influence of some extrinsic factor, but which in itself would not have produced the disease. Sometimes, also, the end result is very much the same, whether the lesion developed originally as a primary or as a secondary dystrophy.

PRIMARY ENDOTHELIAL DYSTROPHIES

The primary dystrophies may be divided into two groups:

1) Congenital dystrophies or malformations;
2) Dystrophies developing later in life.

Congenital Dystrophies or Malformations

Histologic findings of congenital malformations of the corneal endothelium have been reported by von Hippel, cited by Seefelder (94), Mohr (72), Peters (82), and Seefelder (94). They observed defects in Descemet's membrane and irregularities in the endothelium, which in some instances was replaced by a layer of connective tissue. Clinically these cases presented the picture of congenital corneal opacities. More recently Theodore (103) described a clinical observation of a congenital type of endothelial dystrophy. He found the lesion present in three generations—a thirteen-year-old girl, her fifty-three-year-old father, and her seventy-seven-year-old grandmother. The cornea was clear in its anterior layers, but increasingly gray and relucent in a striated manner in its posterior layers. Descemet's membrane was studded with round and elliptic structures which appeared to be nodules with a convexity towards the examiner. Where a nodule was present, the endothelium was absent or very irregular. In contiguous areas it was normal. Theodore rightly differentiates this form of endothelial change from the progressive senile or presenile type and considers it as a separate clinical entity (Figure 17).

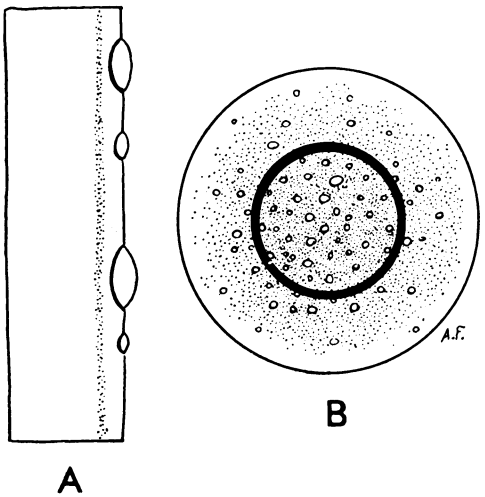


FIGURE 17. SCHEMATIC DRAWING SHOWING A CONGENITAL TYPE OF ENDOTHELIAL DYSTROPHY OF THE CORNEA

A. Endothelial vesicles as they appear in the narrow beam of the biomicroscope. B. Front view showing the distribution of the lesions. From Theodore, *Congenital Type of Endothelial Dystrophy.*

Dystrophy of Corneal Endothelium Developing Later in Life

From study of the literature and from personal observation it has become clear that there is in principle one course of events which leads in the end to the full picture of the combined endothelial and epithelial dystrophy of the cornea. Differences in detail exist and will be accounted for; but these differences do not seem to justify a division of the clinical entity which is characterized by deterioration of the endothelium, infiltration of the stroma with fluid, thickening and opacification of the cornea, edema of the corneal epithelium, and bullae formation. In connection with the term "endothelial and epithelial dystrophy," it should be understood that the epithelial dystrophy is a sequela of the endothelial disease and not a parallel occurrence. A classification separating the cases in which there are found only the endothelial changes, such as cornea guttata and degeneration of endothelial cells, from those in which edema of the corneal stroma and of the epithelium has developed, has been advocated by Franceschetti and Streiff (36), and was also adopted by Clark (16). This separation, however, does not appear to be justified. In too many instances the development of the full picture of the disease was observed where previously only cornea guttata or another form of endothelial degeneration had been present. Friedenwald and Friedenwald (38) already pointed out this fact. In our own series we observed the develop-

ment of endothelial and epithelial dystrophy in six cases which previously had been found to show only endothelial changes. Whether in a given case only endothelial changes, or also edema of the stroma and epithelium, are present depends only on the stage reached by the disease at the time observed. It is true that not all cases with cornea guttata will develop epithelial dystrophy. In many cases death intervenes before the dystrophy has reached its full development. It also should be made clear that this statement holds only for this particular clinical entity. There are other forms of corneal edema and bullous keratitis which develop from causes other than the diseased endothelium, as for instance in connection with inflammatory processes in the cornea proper. Case 35 demonstrates the occurrence as a complication in keratitis metaherpetica. For a summary of the various forms of corneal edema, see Simpson's paper (96).

Some phases of the clinical entity of endothelial and epithelial dystrophy, as we see it now, were observed and described many years ago. It was primarily the edema of the corneal epithelium similar to that occurring in glaucoma, if found in definitely nonglaucomatous eyes, that intrigued the clinician. Since the endothelium of the cornea could not be demonstrated clinically before Gullstrand's introduction of the slit lamp into the ophthalmologic armamentarium (1911), the paramount importance of the endothelium in the development of this condition was not demonstrable. Even in the more recent French literature one finds reports of cases with corneal edema without hypertension under the heading of "primary corneal edema" (Paufique *et al.*, 77) and "corneal edema without intraocular hypertension" (Marx, 67), either without any detailed reference to the condition of the corneal endothelium or without taking it into account as a causal factor.

Favaloro[2] and Scuderi,[3] in their recent monographs, differentiate clearly between "primary chronic edema of the cornea" and "Fuchs's dystrophy." We cannot help suspecting that, at least in some of the cases reported as primary chronic edema, an increased permeability of the endothelium might have been the cause for

[2] G. Favaloro, "Fisio-patologia del foglietto, Descemet-endotelio," *Relazione al XXXVIIIO Congresso della Società Italiana di Ottalmologia 1949,* Catania, 1949.

[3] Giuseppe Scuderi, *Fisiopatologia del ricambio idrico della cornea,* Editione Minerva Medica S.A., Torino, 1953.

the edema of the stroma and the epithelium of the cornea. As will be pointed out later, the endothelium may be diseased and its permeability increased without a typical cornea guttata being present. Also, the increase in permeability may be only transitory, as will be mentioned under "Miscellaneous and Atypical Lesions of the Corneal Endothelium," below.

However confusing the literature may be, it can be stated that the full clinical picture as an entity was first described by Fuchs in 1910 (42). In recognition of this fact, in the United States the term "Fuchs's dystrophy" is identical in meaning with "endothelial and epithelial dystrophy." In 1902 in his Bowman lecture (41), Fuchs made the remark that some ill-defined corneal disturbance might originally have been caused by a deficient endothelium. In 1910, in his definitive article on the subject, "Dystrophia epithelialis corneae" (42), he more or less abandoned the idea, stating "whether changes in the endothelium are present in the true dystrophy is unknown, no definite signs of this are present." The first report on the subject in the slit-lamp era was Koeppe's statement (56; 1916) that in cases of bullae of the corneal epithelium he found "dimples" (*Dellen*) in the endothelial layer. Staehli's report (98; 1920) of a "dewdrop endothelium" probably also described warts on Descemet's membrane, a pre-stage of the dystrophy. Kraupa (57; 1920) asserted that Fuchs's dystrophy was caused by a severe deterioration of the endothelium. Not unlike Fuchs himself, he later (58; 1932) stated that he had become more reluctant to relate the two and favored a general nutritional disturbance of the cornea as the cause of Fuchs's dystrophy. Neither Koeppe nor Kraupa had actually demonstrated the endothelium with the slit lamp. This was reserved for Vogt (106; 1920) after he had developed the technique of examination in the direct reflected or specular light of the slit lamp. Subsequent to this discovery the road was open to a clarification of the situation. The following authors, among others, contributed materially towards establishing the course of events and the clinical pattern of what is now known as the endothelial and epithelial dystrophy of the cornea: Vogt (107; 1921), Graves (48; 1924), Friedenwald and Friedenwald (38; 1925), Kirby (55; 1925), von Sallmann (86; 1925), Gifford (46; 1926), and Vogt (108; 1929). We shall not attempt to recapitulate in detail each contribu-

tion, but shall describe the clinical entity of endothelial and epithelial dystrophy of the cornea as it is seen today in the light of reports by previous investigators and from our own observations in 25 cases.

GENERALITIES. Much evidence points to the fact that the corneal endothelial and epithelial dystrophy is in principle a senile degeneration ruled by heredity. There is no point in differentiating between senility and heredity and choosing one or the other as the essential factor, since it has been demonstrated by Vogt and his co-workers that a number of senile occurrences in the eye are themselves subject to heredity (111, 112). Vogt found, among other instances, that senile cataract occurs in identical twins not only at about the same age but has in both the same morphologic appearance, which makes the hereditary factor quite clear. Furthermore, the fact that the disease has occasionally been observed in relatively young people does not disprove its senile character. Many senile characteristics, such as the premature graying of the hair, occasionally appear in young individuals. Yet isolated instances of this kind are not considered as disproving the general rule. Fuchs (42) stated the age of his 13 patients as from forty-three to seventy-two years, with an average of fifty-eight. In Doggart's series (29) of 47 cases, the youngest patient in which he observed the disease was thirty-six years old. All the others in the series were over fifty. In our series of 25 cases the ages ranged from forty-three to seventy-seven years, with an average of fifty-seven and a half years. These include only cases in which the disease had actually reached the point where corneal haziness had developed. The pre-stage cornea guttata, as will be discussed later, is much more common. In favor of a hereditary factor are the observations of several cases among siblings. Clegg (17) found the disease in two sisters of a family of three, the third one being reported to have it too. Juler, cited by Franceschetti and Streiff (36), reported it present in two sisters; Levitt and Lloyd (62) in a mother and one daughter; and in our series we found it in a mother and in three daughters among four siblings and in another instance of two sisters (Cases 1, 2, 3, and 4). It is reported almost unanimously that women are much more frequently affected than men. Fuchs's series of 13 cases comprises 4 men and 9 women. Of 47 cases reported by Doggart (29), 34 were

women and 13 men. Of our own 25 cases, 3 were men and 22 were women. Although a number of cases are seen every year in an eye clinic, endothelial and epithelial dystrophy of the cornea is a comparatively rare disease among the general population. Fuchs places its incidence at one in 2,000 eye patients.

For the sake of clarity, endothelial and epithelial corneal dystrophy may be discussed in the following stages:

1. Degeneration of endothelium without the stroma or the epithelium of the cornea being affected;
2. Permeation of corneal stroma with fluid, edema of epithelium, bullae formation;
3. Late stages with subepithelial connective tissue formation, vascularization, and scar formation;
4. Complications, as secondary infection and glaucoma.

1. Degeneration of endothelium without the stroma or the epithelium of the cornea being affected.—The degeneration of the corneal endothelium occurs mainly in two different ways: (a) endothelial degeneration accompanied by excrescences on Descemet's membrane (cornea guttata); (b) endothelial degeneration without the formation of excrescences on Descemet's membrane.

(a) Endothelial degeneration accompanied by excrescences on Descemet's membrane (cornea guttata). This stage is easily overlooked when only ordinary oblique illumination or the ophthalmoscope is used. In far advanced stages, a slight haziness is noted when the fundus of the eye is examined. In several cases we have observed a marked fuzziness of the ophthalmoscopic picture which could not be explained on other grounds, and yet the patient's vision was almost normal. We were inclined to attribute this discrepancy to an optical phenomenon due to the formation of warts on Descemet's membrane that would allow clear vision in one direction but not in the other. Using the slit lamp, the picture varies according to the mode of illumination. In the regredient or indirectly reflected light from the iris the cornea appears to be studded with numerous droplets. Hence, the term "cornea guttata" (Vogt). In spite of a certain similarity, these droplets should not be confused with what is called bedewing of the cornea. Bedewing may be produced either by edema of the endothelial cells or by

precipitation of small particles of inflammatory material on the posterior surface of the cornea. In the first case the droplets appear in a very regular way and are minute, corresponding to individual endothelial cells (Case 50); in the second case the droplets vary in size and are irregularly distributed, usually predominantly in the lower half of the cornea. Both are accompanied by inflammatory signs which are wholly absent in cornea guttata. When the posterior surface of the cornea is visualized directly in the beam of the slit lamp, it often has a grayish granular appearance suggesting corrugated glass. Sometimes golden glints appear as the beam is moved along, or the picture is that of "beaten silver." Not uncommon is the presence of pigment dust on the posterior surface of the cornea. Probably pigment originating from the iris and floating in the aqueous, a common senile occurrence, is caught by the excrescences on Descemet's membrane. Some of the pigment granules are found within endothelial cells (see Figure 8). There has been some difference of opinion as to whether the yellow-golden appearance was due to light reflex within Descemet's excrescences or to real pigmentation. It is quite clear that both exist. The most characteristic picture of cornea guttata is elicited when using the directly reflected or specular light of the slit lamp. Its appearance with this technique is best demonstrated by Vogt's original illustration (Figure 18). Within the regular pattern of the endothelium,

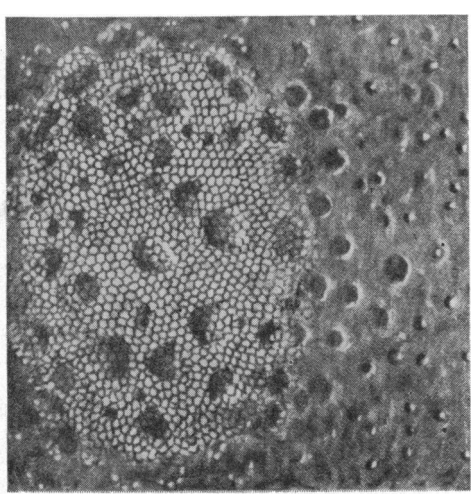


FIGURE 18. ARTIST'S CONCEPTION OF CORNEA GUTTATA AS SEEN IN THE SPECULAR LIGHT OF THE BIOMICROSCOPE
The dark spots represent warts on Descemet's membrane. In some instances it can be seen that the warts are still covered by endothelial cells. From Vogt's *Atlas* (original in colors).

black dots of various sizes are seen. In some instances the endothelial pattern can be followed to the bottom of the excrescences by focusing down with the microscope. Figure 18 shows only a moderate number of warts. In advanced cases Descemet's membrane is so studded with warts that practically no endothelial cells are seen between them. The characteristic difference between normally occurring Henle's warts, which are seen only in the peripheral parts, and the progressive cornea guttata is the latter's predilection for the central parts of the cornea. In some advanced cases, however, the cornea guttata spreads out to the periphery, covering the entire posterior surface of the cornea. In several instances we have seen cornea guttata occupying the central parts of the cornea and surrounded by a zone of almost normal endothelium which, out in the periphery, bordered on a zone of rather densely scattered Henle's warts. It appears that this occurrence would constitute another argument in favor of the fundamentally different clinical significance of cornea guttata and Henle's warts. There are several ways of differentiating defects in the endothelial pattern caused by cornea guttata from the simple degeneration of the endothelial cells without the formation of warts. In the first place, the presence of endothelial cells on the farther side of the optically empty space corresponding to the warts proves that the endothelium has been pushed backwards by the excrescences but still exists (Figure 18). Furthermore, if a very narrow beam of the slit lamp is used, minute glittering reflexes are seen inwards of the posterior surface of the cornea, giving proof of a protruding mass from which such reflexes must originate (Figure 19).

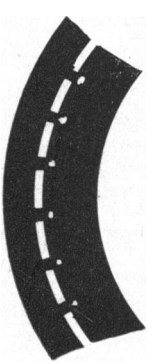


FIGURE 19. SCHEMATIC DRAWING OF THE APPEARANCE OF CORNEA GUTTATA AS SEEN WITH THE NARROW BEAM OF THE BIOMICROSCOPE

The small white dots indicate light reflexes originating from the top of the excrescences on Descemet's membrane.

As to the origin and significance of the excrescences on Descemet's membrane, it appears that they are the product of the endothelial cells undergoing senile or presenile degeneration. Verhoeff (quoted in 62) has mentioned that premature senility is often first associated with hyperplasia. He also points to the parallelism between senile excrescences on Bruch's membrane produced by the pigment epithelium and cornea guttata. We followed this interesting idea and attempted to find the degree of incidence of the coexistence of the two phenomena statistically. Table 1 sums up

TABLE 1. COINCIDENCE OF CORNEA GUTTATA WITH DRUSEN ON BRUCH'S MEMBRANE

	No. of Cases	*Percentage of Incidence*
With cornea guttata without drusen on Bruch's membrane	9	—
With drusen on Bruch's membrane without cornea guttata	11	—
With both cornea guttata and drusen on Bruch's membrane	4	16.6
Total	24	

our findings. It would appear that there is no striking coincidence of cornea guttata and drusen on Bruch's membrane. Because both are of senile nature, a certain coincidence is unavoidable, but each seems to follow its own law of occurrence. Cornea guttata, being the first stage of Fuchs's dystrophy, is much more frequently observed than the later stage which includes edema of the stroma and of the epithelium. Goar (47), in examining 800 eyes, found it to be present to some degree in 6 percent of all patients over thirty years of age.

The first histologic report of cornea guttata was made by Vogt (109), followed by Verhoeff (105), Goar (47), Calhoun (12), and others. We have reported on the cornea of a case that had already developed into the full Fuchs's dystrophy and was successfully grafted (100). Figure 20 represents the endothelial and epithelial part of the cornea of this case. It may be noted that Descemet's membrane, in contrast to the normal situation, is considerably

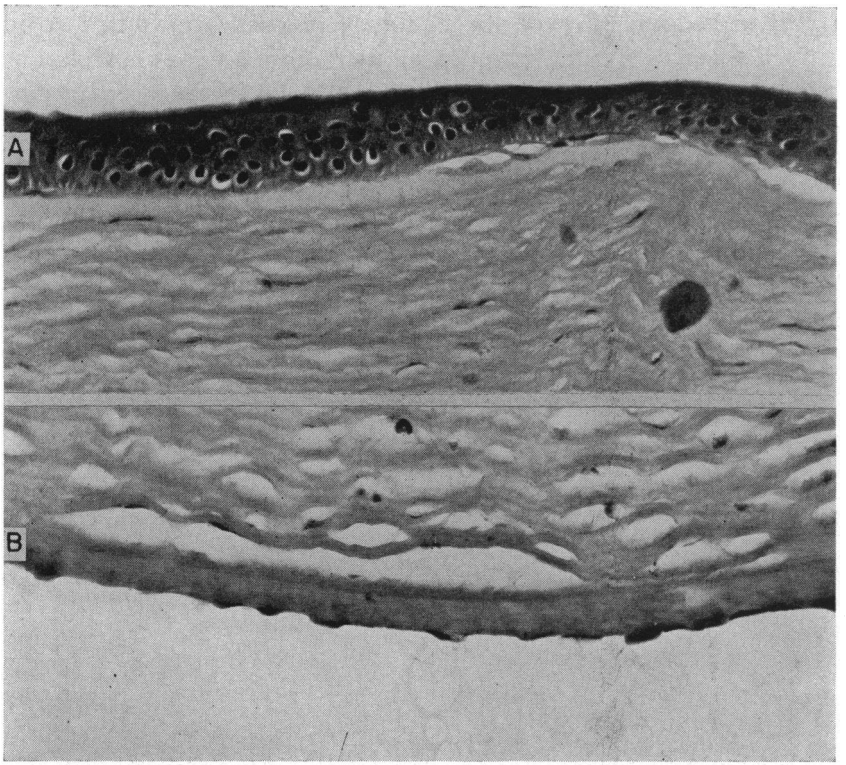


FIGURE 20. CROSS SECTIONS THROUGH THE ANTERIOR AND POSTERIOR PARTS OF THE CORNEA IN A CASE OF CORNEA GUTTATA AND FUCHS'S DYSTROPHY
The epithelium (A) is irregular, the individual cells partly edematous. Descemet's membrane (B) is thickened and studded with excrescences.

thicker than Bowman's membrane. This could be the result of increased secretion in general by the endothelial cells, or it could be caused by swelling following absorption of fluid. Since we did not find this thickening of Descemet's membrane in another case of cornea guttata which had not yet developed edema of the cornea, we are inclined to attribute it to swelling. If this is the case, it would then be a characteristic of Fuchs's dystrophy. The inner surface of Descemet's membrane is densely studded with warts. The endothelial cells seem to be stretched over the top of these warts, with the cell nuclei pushed to the sides of the excrescences. In places the cells seem to be reduced to a thin membrane, or to be completely absent.

Whereas some idea of the histology of cornea guttata can be gained by cross section, it appeared that a much better correlation with the slit-lamp findings would be obtained by flat preparation. We were able to put our new technique to good use in a case (Case 34) that had been found to have cornea guttata in vivo, and in which the eye was enucleated because of a melanoma of the choroid. Immediately after enucleation, the cornea was excised and part of it placed in 10 percent formalin. The other part was freshly stained with 1 percent alizarin red in normal saline, and immediately examined under the microscope. The intercellular cement lines were beautifully stained. In places, a regular pattern of the endothelium, as shown in Figure 10, could be observed. In other places, the individual cells were several times the size of the normal cells. Unfortunately the stain did not withstand fixation, and so no photograph of it is available. We did, however, succeed in

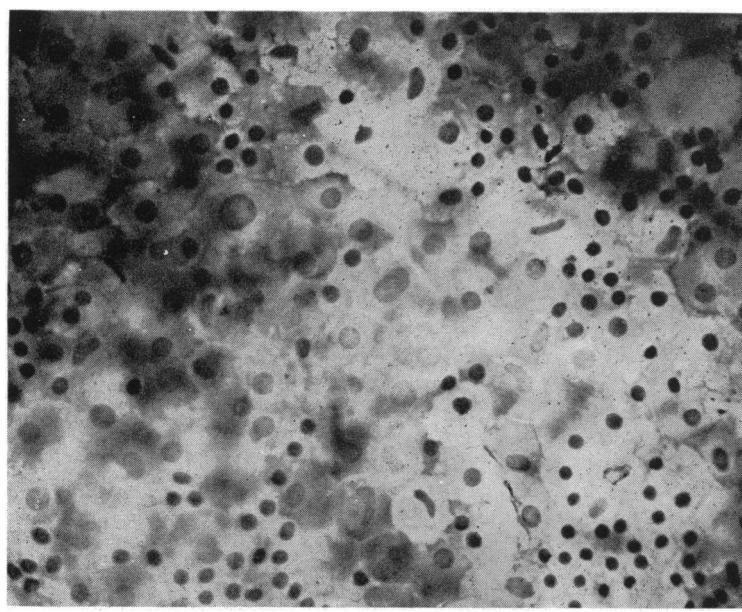


FIGURE 21. FLAT PREPARATION OF CORNEAL ENDOTHELIUM IN A CASE OF CLINICALLY OBSERVED CORNEA GUTTATA

The small cells with dark, round nuclei represent the normal endothelia. The large cells with round or sickle-shaped nuclei are the degenerated endothelial cells which probably produced the excrescences on Descemet's membrane. The light area in the upper right corner probably represents a wart without endothelial covering. (x236.)

staining a flat preparation from the fixed cornea with hematoxylin. The astounding picture which resulted is reproduced in Figure 21. Although the intercellular cement is not stained, the outlines of the cells can be recognized fairly well. The small cells with dark, round nuclei represent the normal endothelial cells. Between them there are numerous cells about five to eight times the normal size. They have much larger nuclei which stain faintly. These nuclei are either round, oval, or sickle shaped. It seems that these are probably the cells that secreted the warts and thus spread themselves out; this seems especially likely of the ones whose nuclei are sickle shaped, evidently from being pushed to the side of the wart. Some of these cells may have enlarged in order to cover the area of some completely degenerated endothelia. Such a sequence has been suggested by us from clinical observation. (Case 39, p. 774). There are also roundish areas, as in the upper right corner of Figure 21, in which no cellular cover seems to be present at all. These areas most probably represent large warts over which the endothelia have completely atrophied. They might well indicate the weak spots from which the infiltration of the stroma would begin.

(*b*) *Endothelial degeneration without the formation of excrescences on Descemet's membrane.* Contrary to common belief, we were able to demonstrate that endothelial and epithelial dystropy is not always preceded by cornea guttata. In some instances the endothelial cells seem to degenerate without first going through the stage of secreting excrescences on Descemet's membrane. The clinical picture, as seen with the slit lamp, is then that of dark areas within the pattern of the endothelium. Unlike the appearance in cornea guttata, those dark areas never show cells again

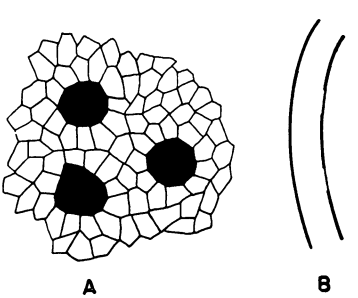


FIGURE 22. SCHEMATIC DRAWING OF DEGENERATION OF THE CORNEAL ENDOTHELIUM WITHOUT THE OCCURRENCE OF WARTS ON DESCEMET'S MEMBRANE, AS SEEN WITH THE BIOMICROSCOPE

A. In the specular light holes appear in the endothelial pattern. B. In the narrow beam no reflexes that would originate from warts are seen (see Figure 19).

when the microscope is focused farther back. Also, examination with the narrow beam shows that the glittering reflections on the inside of Descemet's membrane, which originate from the warts, are not present (Figure 22). Pre-stages to this condition seem to exist. In certain cases some of the endothelial cells are considerably larger than normal, with the intercellular cement lines more pronounced. From this condition an increased permeability might

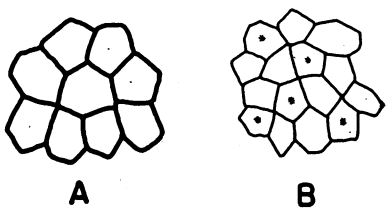
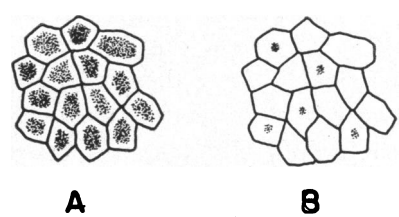


FIGURE 23. SCHEMATIC DRAWING DEMONSTRATING THE ENLARGEMENT OF THE ENDOTHELIAL CELLS AND THE INTERCELLULAR SPACES IN EARLY STAGES OF CORNEAL ENDOTHELIAL DYSTROPHY
A. Pattern in early stages. B. Normal pattern.

well originate (Figure 23). In other cases the endothelial cells show large grayish areas much exceeding the size of what we consider to be the nuclei. This most probably is vacuolization, a sign of degeneration, which we shall discuss in more detail in the section on keratoplasty (Figure 24).

FIGURE 24. SCHEMATIC DRAWING SHOWING VACUOLIZATION OF ENDOTHELIAL CELLS IN EARLY STAGES OF CORNEAL ENDOTHELIAL DYSTROPHY
A. Early stages. B. Normal endothelia.



It can be demonstrated histologically as well that cornea guttata is not a prerequisite to endothelial and epithelial dystrophy. Figure 25 represents a section of the internal surface of the cornea from a case of severe Fuchs's dystrophy (Case 1). It can be seen that there are no warts at all on Descemet's membrane in this section comprising the central part of the cornea. The endothelial cells are, however, absent over wide areas. In their place there is a fine membrane covering the posterior surface of Descemet's membrane. This could be a thin layer of secondary secretion on top of the original membrane, but it does not stain the same way, is clearer, and seems to be continuous with the remaining endo-

thelial cells. We are, therefore, more inclined to consider this membrane as the residue of the atrophied endothelial cells themselves. Farther toward the periphery there were a moderate number of Henle's warts, such as might be seen in any normal eye of a certain age. Here again we seem to have proof of our contention that Henle's warts in the periphery and the progressive condition of cornea guttata in the center of the cornea are two separate clinical entities.

In most instances of both types of endothelial degeneration just described, the subjective symptoms experienced by the patient are absent or very slight. Usually vision is unimpaired. Sometimes it is described as slightly blurred. Colored halos around lights may also be reported, as already mentioned by Staehli (98). These, no doubt, are produced by the droplet-like warts on Descemet's membrane. If they are very numerous, they may produce a visual effect similar to that of the edematous corneal epithelium in glaucoma. Only in quite advanced cases is the visual acuity found to be reduced to 20/25 or 20/30. The corneal sensitivity is usually normal. We have found it to be reduced in only one instance that had not yet reached the stage of corneal edema (Case 9).

2. *Edema of corneal stroma and epithelium, bullae formation.*—We were able to observe six cases (Cases 7, 13, 14, 20, 22, and 23) in which there was originally present a simple degeneration of the corneal endothelium, with or without cornea guttata, and which gradually developed edema of the stroma and epithelium, finally leading to the full picture of Fuchs's dystrophy. As the first sign of fluid infiltration, a grayish zone appears in front of Descemet's membrane. Sometimes, in very early stages, it can be observed that such turbidity is confined to areas where the endothelium is found to be particularly deficient (Case 24). The next step is the appearance in the stroma of dark lines, usually called fluid clefts. These seem to represent the channels through which the fluid exchange passes normally and which now have become enlarged. These also are seen first in the posterior part of the stroma. At this stage a slight thickening of the cornea may already be observed. At the same time, Descemet's membrane becomes wavy. Cogan (25) gave a plausible explanation for the

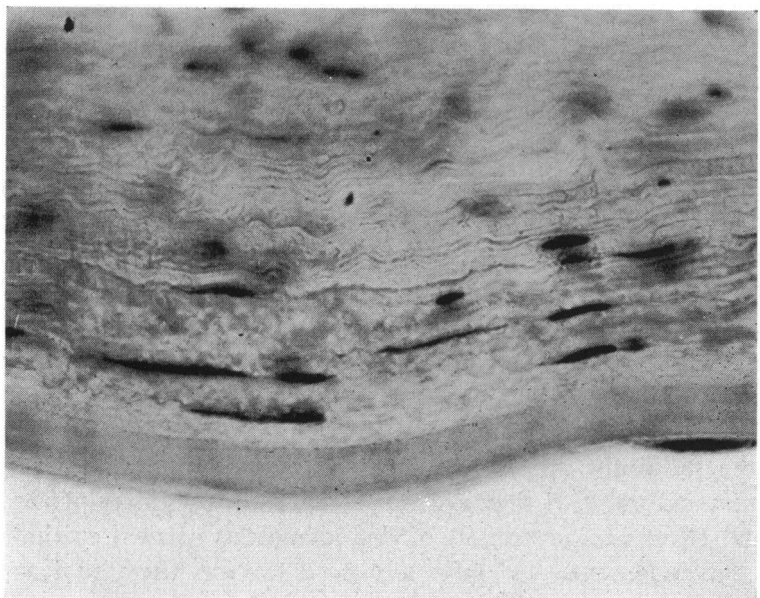


FIGURE 25. CROSS SECTION OF THE POSTERIOR PART OF THE CORNEA FROM A LATE STAGE OF ENDOTHELIAL AND EPITHELIAL DYSTROPHY
In contrast to Figure 20, there are no warts on Descemet's membrane which, however, is covered by a thin layer possibly representing the residue of the atrophied endothelia. To the right is a flattened and stretched endothelial cell. (x657.)

wrinkling of Descemet's membrane. Inasmuch as the convex surface of the cornea, Bowman's membrane and anterior layers of corneal lamellae are more rigid than the posterior layers and the concave posterior surface, the increase in volume caused by the intake of fluid is bound to push back Descemet's membrane. Since the lateral borders of the cornea are fixed, the distance between them to be spanned by Descemet's membrane becomes shorter and the membrane undergoes buckling (Figure 26). Later, while the middle stroma still remains fairly clear, a grayish layer appears beneath Bowman's membrane. This layer may appear as a diffuse, continuous opacity or may show numerous whitish dots. Figure 27, from Berliner (6), may serve as an approximate illustration for this description. Next the edema begins to involve the epithelial layer. With low-power magnification there is observed a cloudiness of the central part of the cornea, combined with a stippled appearance of the surface. Figure 28 shows the photograph

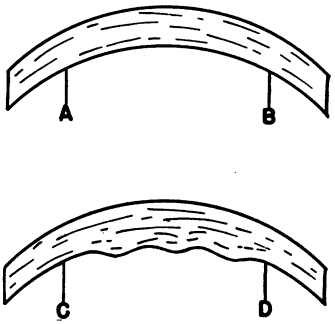


FIGURE 26. DIAGRAM REPRESENTING FOLDING OF THE POSTERIOR CORNEAL SURFACE SECONDARY TO SWELLING OF THE STROMA

The line C-D is actually of the same length as A-B, but with the displacement of the posterior surface backward there is a consequent buckling or "striate keratopathy," for the arc C-D is necessarily less than A-B. From Cogan, "Applied Anatomy and Physiology of the Cornea," from "Symposium on Corneal Diseases," *Tr. Am. Acad. Ophth.*, 1951.

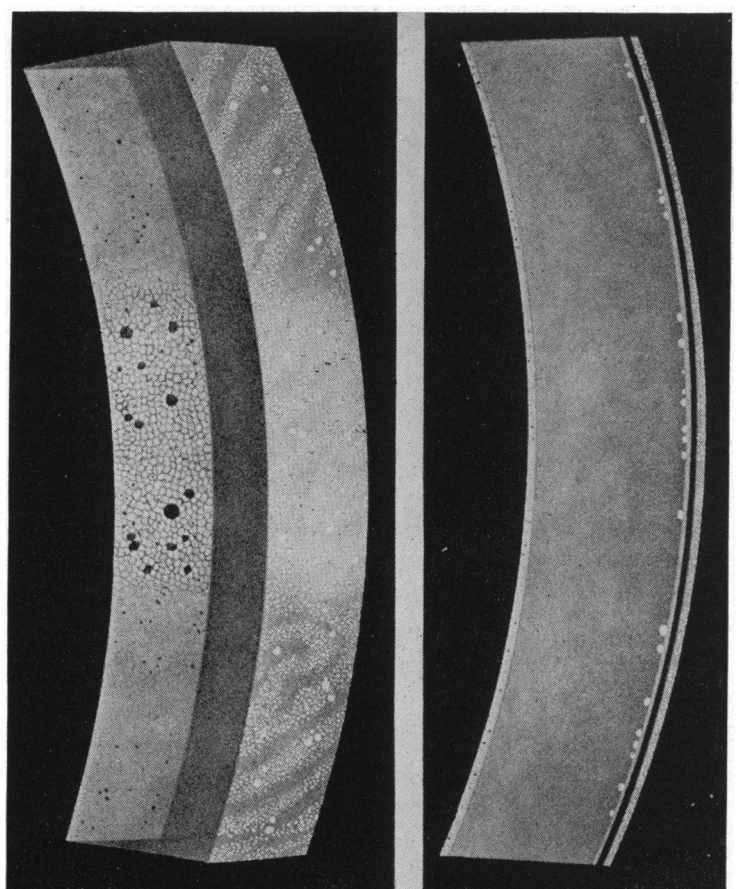


FIGURE 27. ARTIST'S DRAWINGS SHOWING EARLY ENDOTHELIAL AND EPITHELIAL CHANGES IN CORNEAL ENDOTHELIAL AND EPITHELIAL DYSTROPHY

From Berliner, *Biomicroscopy of the Eye.*

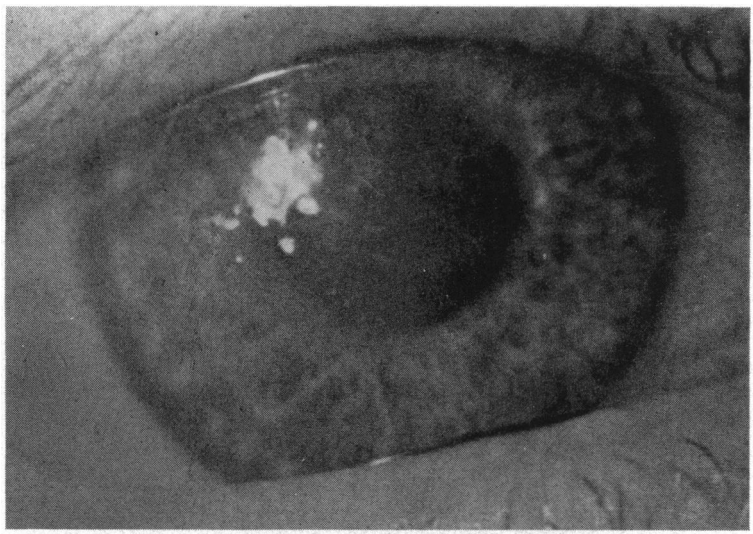


FIGURE 28. TYPICAL CLINICAL APPEARANCE OF A WELL-DEVELOPED CASE OF ENDOTHELIAL AND EPITHELIAL CORNEAL DYSTROPHY (FUCHS'S)
The cornea is cloudy, especially in the central parts. The light reflex on the cornea is indistinct and shows bubbles, indicating edema of the epithelium.

of a typical case in this stage. In the specular light, the characteristic picture of epithelial edema is present, giving the effect of "goose pimples." Finally, the epithelium becomes separated from Bowman's membrane in places, forming blisters or bullae. Figure 29, from Berliner (6), excellently illustrates this stage. It is of greatest importance to note that the changes just described are almost invariably confined to the central parts of the cornea for quite some time, and only gradually do they spread out towards the periphery and finally involve the entire cornea. For the practical application of the fact, the reader is referred to the section on keratoplasty.

The histologic substratum for the aforementioned clinical findings is illustrated in Figure 20. The corneal lamellae are loosened up into fine fuzzy fibrillae by the infiltration with fluid. The corneal epithelium is irregular, both as to the number of layers of epithelial cells and as to the shape and appearance of the individual cells. Some cells are vacuolized and enlarged, and in the superficial layer some are in a stage of complete disintegration. In

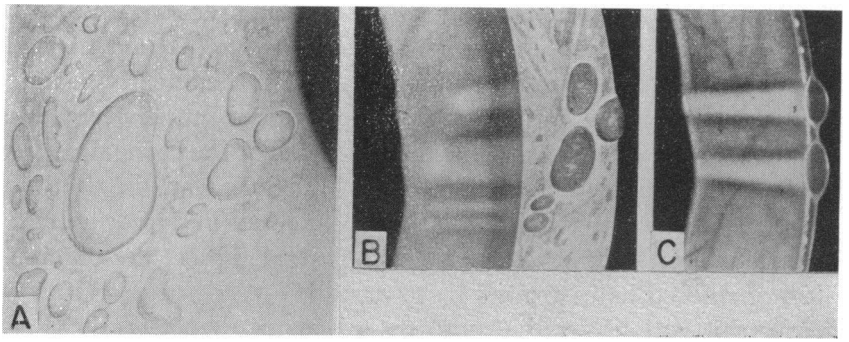


FIGURE 29. MARKED EPITHELIAL EDEMA AND FORMATION OF EPITHELIAL BULLAE IN ENDOTHELIAL AND EPITHELIAL DYSTROPHY AS SEEN WITH THE BIOMICROSCOPE

A, In the regredient; B, in the direct focal; C, in the light of the narrow beam. From Berliner, *Biomicroscopy of the Eye.*

places, the basal layer is separated from Bowman's membrane, with the interval partly occupied by pink staining fluid and cellular detritus. Bowman's membrane at this stage seems to be fairly well preserved.

As to the subjective symptoms, they naturally increase in number and severity as the process progresses from the back to the front of the cornea. In the beginning, the visual disturbance is slight. As pointed out by Cogan (25), the wrinkling of Descemet's membrane does not affect the vision much, because of the little differences in the refractive indices of cornea and aqueous. Irregularities on the anterior surface of the cornea necessarily entail considerably more marked visual disturbance, since the refractive index of air is quite different from that of the cornea. When the edema reaches the epithelium, the visual acuity is usually reduced to 20/200 or less, although the cloudiness of the cornea, when examined with the naked eye or low magnification, does not appear very intense. The patient's observation that the vision is much worse in the morning than in the afternoon is a frequent but by no means constant symptom. It is probably due to the accumulation of fluid in the cornea when the evaporation through the epithelium is rendered impossible during the closure of the eyes at night. This explanation is substantiated by the experimental facts previously mentioned as well as by some therapeutic experiences to

be discussed later. The corneal sensitivity is markedly reduced in most instances. It was found to be reduced in nine and normal in two of our eleven cases in which reports on the sensitivity were available. Fuchs (42,43) thinks that the reduced sensitivity is due to the pressure of edema on the fine branches of the corneal nerves as they pass through Bowman's membrane. Indeed, in the two cases with normal sensitivity, the edema had not reached the anterior segment of the cornea. Some patients report the observation of colored halos around lights at night. As in congestive glaucoma, this is doubtlessly due to the edema of the epithelium. As far as pain is concerned, the symptoms arise as soon as the epithelium becomes edematous and especially when bullae begin to develop. As long as the latter remain intact there is only slight irritation and foreign-body sensation. When the bullae burst, attacks of severe pain may occur.

3. *Late stages with subepithelial connective tissue formation and vascularization, leucoma.*—If no acute complications, such as infection or glaucoma, interfere with the course of the disease, a sclerosing process gradually sets in. The corneal stroma becomes more and more densely opaque. Epithelial bullae are replaced by scar tissue, which develops between the epithelium and Bowman's membrane. There remains an irregularity in the epithelium. However, examination by the specular light shows that the "goose-pimple" appearance which is characteristic of epithelial edema has disappeared. Blood vessels begin to invade the cornea from the limbus, mostly in the superficial and medial third of the stroma. Finally, a vascularized leucoma results. This represents a quiescent stage with little discomfort but with greatly reduced vision. Cases 1 and 23 are representative of this late stage. Peculiarly, as in Case 1, the corneal sensitivity may be only slightly reduced. This would fall in with Fuchs's theory (42,43) that the reduced corneal sensitivity is due to an injurious effect of the edema on the corneal nerves. Should the edema disappear, the sensitivity might return. Figure 30 shows a photograph of Case 1 presenting this stage. Microscopically it can be seen that the epithelium is very irregular. In places its thickness is ten or more cells; in others it is reduced to two or three cells. The cells vary greatly in size and shape. Some of them show a very light protoplasma or vacuoles. The nuclei are

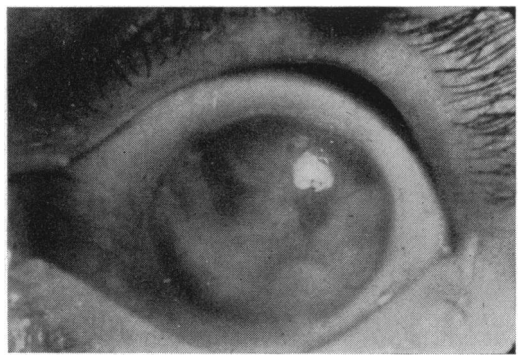


FIGURE 30. LATE STAGE OF ENDOTHELIAL AND EPITHELIAL CORNEAL DYSTROPHY
A sclerosed scar has developed. There is no marked epithelial edema, and therefore the light reflex on the cornea is less fuzzy than in Figure 28.

round, oval, or elongated. The surface of the epithelium is partly covered by a thin amorphous layer, possibly resulting from cellular detritus. The basal cell layer is very irregular. In most places it is not in contact with Bowman's membrane. The space between the two is filled mostly by a coagulated or fibrillar mass, evidently containing much fluid and a variable number of cells, some of which have the appearance of fibroblasts. Near the periphery there is vascularization in the space between epithelium and Bow-

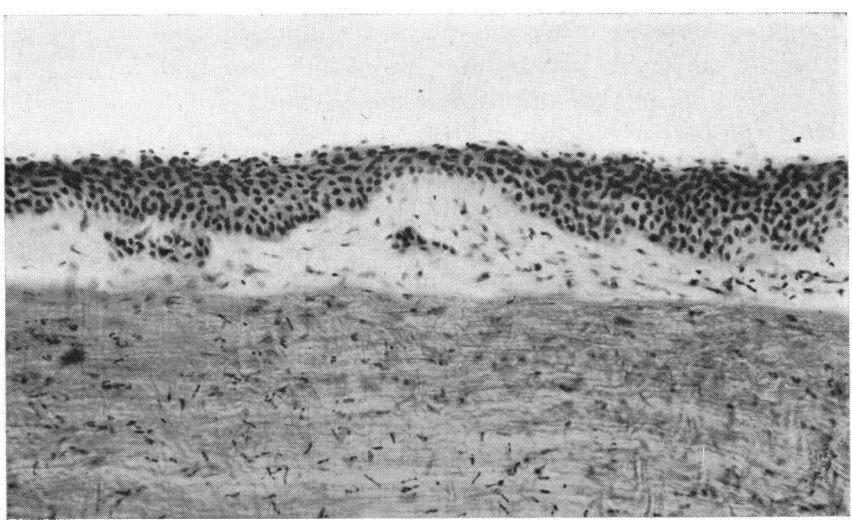


FIGURE 31. CROSS SECTION THROUGH THE ANTERIOR PART OF THE CORNEA IN LATE STAGE OF ENDOTHELIAL AND EPITHELIAL DYSTROPHY
A connective tissue layer has developed between epithelium and Bowman's membrane.

man's membrane, forming, together with connective tissue, a degenerative pannus. Bowman's membrane is present over most of the area; in places it may be absent. The stroma does not show as much edema as in the previous stage, but many cellular elements, varying from degenerated corneal corpuscles to fibroblasts, and round cells are present. The middle portion of the stroma is vascularized. The posterior part, containing Descemet's membrane and the endothelial layer, are as described in the previous stage. Figure 31 illustrates some of these features.

4. Complications: secondary glaucoma and infection.—The two main complications which may prevent the development of a quiescent stage, as just described, are: (a) glaucoma; (b) infection which ultimately may lead to the loss of the eye.

(*a*) *Glaucoma:* Since the clinical appearance of the epithelial edema of the cornea is very similar in both endothelial dystrophy and congestive glaucoma, the intraocular pressure in the dystrophies has always been watched with great interest. While in most cases the intraocular pressure was found to be within normal limits, in some cases it was elevated. From our study of 25 cases it became evident that very probably the glaucoma found in endothelial dystrophies is secondary and has nothing to do with the cause of the condition. In no case was the pressure found abnormally high in the beginning of the disease. On the other hand, the development of glaucoma in the course of the disease could be observed in two cases. In Case 10, in the beginning both eyes were found to have cornea guttata, the right eye the beginning of corneal edema. One year later, as more edema with thickening of the stroma had formed, the angle of the anterior chamber of the right eye was found to be very shallow. The anterior chamber of the left eye was also shallow, but to a lesser degree. The intraocular pressure was normal at that time. A year later the patient returned with an acute attack of glaucoma in the right eye, and intraocular pressure of 76 mm. Hg (Schiötz). The intraocular pressure of the left eye was 11 mm. Hg. After another year and four months, in spite of the use of pilocarpine as a precautionary measure, the left eye developed an acute attack of glaucoma, with intraocular pressure of 65 mm. Hg. It was quite evident that in this case the chamber angle became more and more obstructed

as the cornea became thicker and thicker from increasing edema. In Case 13 the anterior chamber was found to be moderately shallow in the right eye, which had cornea guttata without edema, but much shallower in the left eye, in which the cornea was permeated with fluid and considerably thickened. In spite of the shallowness of the anterior chamber the intraocular pressure was still 16 mm. Hg in each eye. This case also suggests that the chamber angle becomes obstructed by the swelling of the cornea. Another occurrence of acute glaucoma in both eyes simultaneously is documented by Case 20. Here cornea guttata in both eyes and beginning corneal edema in the left eye were noted at one time, with an intraocular pressure of 23 mm. Hg in both eyes. As a precautionary measure, 1 percent pilocarpine was prescribed for both eyes. Nevertheless, four months later the patient returned with a bilateral acute attack of glaucoma and moderate but definite increase of pressure in both eyes. These observations not only demonstrate the secondary character of the glaucoma in endothelial dystrophy, but also suggest a plausible explanation of the mechanism involved. It is possible that the pre-existence of a relatively shallow chamber angle facilitates the obstruction by the swollen cornea, which would account for the fact that glaucoma develops in some cases and not in others. As to the treatment of the secondary glaucoma in these cases, it appears that iridencleisis combined with Lagrange sclerectomy is the procedure of choice. It is of particuar interest that prophylactic treatment with miotics does not seem to prevent an acute attack of glaucoma in these conditions.

(*b*) *Infection:* It is quite understandable that in cases of epithelial bullae, ulceration and secondary infection may occur. Cases 1 and 10 represent this feature. Prior to the modern era of antibiotics this complication often led to the loss of the eye, as in Case 1. Nowadays the chances of saving such an eye are better, as in Case 10. In this instance it appeared that intensive scar formation following the ulceration consolidated the corneal process to some extent. As a result the epithelial edema was less marked than in the preceding stage. Nevertheless, secondary glaucoma developed later. In one case, belonging to the group of secondary dystrophies to be discussed, cortisone was used during the stage

of ulceration. This medication seemed to have had an adverse effect, since the ulcer perforated rapidly (Case 37).

SECONDARY ENDOTHELIAL DYSTROPHIES

In Appendix A we report twenty abridged case histories falling within this group. Although we made many more observations, we chose to select only a few examples illustrating the various aspects of this complication. Fuchs, in his original paper "Dystrophia epithelialis corneae" (42), mentioned the fact that sometimes, after cataract extraction and other intraocular operations, a condition develops that closely simulates the picture of his observations with spontaneously developing dystrophies. He also advanced the theory that damage to the endothelium during the operative manipulations was the cause of the disturbance. Since then most authors reporting corneal endothelial dystrophy have mentioned this fact. It has become such an everyday experience that it seems hardly necessary to quote these many comments. In view of the considerable practical importance of this complication, however, it may be worth-while to discuss in detail the circumstances in which it occurs.

The most important single cause of secondary endothelial and epithelial dystrophy is *cataract extraction*. Since it is agreed that probably damage to the endothelium during or after the operation is the most important factor in producing the condition, the pre-existence of an abnormal endothelium is regarded as a highly disposing factor. Consequently, the presence of cornea guttata in an eye to be subjected to a cataract extraction is a bad omen. Cases 26 and 27 bear supporting testimony to this statement. The first case also demonstrates that the condition does not necessarily occur immediately after the operation. In this case, everything went well for three months, with vision recorded as 20/40; it was only in the fifth month that corneal edema developed. The second case shows that the edema might be only transitory. Corneal edema developed about three weeks after operation, and had completely subsided one month after its appearance. Whereas the chances of postoperative corneal dystrophy increase if considerable manipulation has occurred, such as repeated discission, the two cases demonstrate that it may develop even after quite uneventful

intracapsular extractions, one done with a forceps, and the other with an erysiphake. On the other hand, we have done many cataract extractions on eyes with cornea guttata with good results. Several precautionary suggestions have been made for such cases. Certainly the least possible handling of the corneal flaps is highly desirable. Recently we seem to have had good results by using the Kirby method and sliding the lens out instead of tumbling and expressing it. We are unable to decide whether it is advantageous to make the section in the scleral part of the cornea, as has been suggested. Granting that the presence of cornea guttata is a disposing factor for postoperative dystrophy, its presence is by no means indispensable for the development of this complication. Cases 28, 29 and 30 were free of cornea guttata in both eyes, and nevertheless acquired the disease. The first case was an uneventful intracapsular extraction, but was followed by a severe anterior chamber hemorrhage. The second case was an extracapsular extraction, followed by striate keratitis of long duration, and the third one was a combined extracapsular extraction with loss of vitreous and recurrent anterior chamber hemorrhage. In none of these cases had there been more than one operative procedure. The presence of unduly marked striate keratitis, a considerable amount of cortical material, severe anterior chamber hemorrhage, or the persistent contact of a vitreous hernia with the posterior surface of the cornea may be regarded as unfavorable factors. This is illustrated by Case 31, in which a vitreous hernia was in contact with the cornea for more than two months. An air injection into the anterior chamber was followed by the complete disappearance of the corneal edema. On the other hand, as shown by Case 32, the endothelium sometimes withstands the contact with the herniated vitreous for a remarkably long time. Here a vitreous hernia had been in apposition with the cornea for one month. After six weeks, the hernia retracted spontaneously and the endothelium was found to be perfectly normal. In Case 33, a vitreous hernia which touched the posterior surface of the cornea had formed only six weeks after an uneventful intracapsular cataract extraction. One month later the vitreous was still in contact with the cornea, but the normal endothelial pattern was still visible and no corneal edema had developed.

In Case 36 the endothelial and epithelial dystrophy became manifest following a severe attack of malaria. This eye had been well for six months following an uneventful extracapsular cataract extraction. The relationship of the two events might be coincidence, but it seems well to consider the possibility that the process was touched off by an intercurrent illness.

Although the prognosis of endothelial and epithelial corneal dystrophy following cataract extraction is, in general, grave, a perfect recovery is possible. In Case 27, with moderate guttata, after an intracapsular extraction with the erysiphake a marked striate keratitis was first noted. Corneal edema then developed. On the 18th postoperative day, bullous keratitis was present. The patient was treated with atropine and warm compresses locally and sodium salicylate internally. Nine days later the epithelial bullae had disappeared. More than a year later the cornea was found to be clear. The cornea guttata was about as before the operation, and vision was 20/30 with correction. Such fortunate experiences are exceptional.

From Case 44 it would appear that the endothelial degeneration in the form of cornea guttata might become aggravated by an intercurrent inflammatory process of the eye, thus leading to secondary edema of stroma and epithelium. This patient had had several attacks of iritis in the right eye during a period of eleven years. In the temporal part of the cornea of this eye, epithelial edema and haziness of the stroma developed, corresponding to an area in which the endothelium was found to be deficient. Cornea guttata was present throughout the cornea. The left eye also showed cornea guttata, but to a lesser degree. In the area involved, there were no signs of keratitic precipitates, nor did the edema occupy the lower part of the cornea, which usually is most heavily covered with precipitates in iridocyclitis. Therefore, it seems reasonable to assume that the inflammatory process as such had a deleterious effect on the already degenerated endothelium, rather than that long-standing keratitic precipitates were the cause of this complication.

In the section on the general pathology of the corneal endothelium it has already been mentioned that the endothelium was found to be damaged in some cases of long-standing keratitic pre-

cipitates, and that localized corneal edema and bullous keratitis followed. Case 40, with Boeck's sarcoid, was mentioned as an example. Case 41, suffering from sympathetic ophthalmia, also clearly indicates that corneal edema and epithelial bullae may develop in the area where the endothelial pattern had become unrecognizable following long-standing keratitic precipitates. In the upper part of the cornea, where the endothelium could be seen distinctly, the cornea was clear and the epithelium normal. It can be observed, however, that sometimes the endothelium appears to be completely degenerated over the site of long-standing precipitates, and yet no corneal edema develops. Case 42 may serve as an example of this occurrence. Here, large areas in which the endothelial pattern was completely destroyed were present and corresponded to the site of long-standing precipitates, but during six years of observation no corneal edema developed. In order to explain the different behavior under apparently similar circumstances, one might think of the formation of some sort of amorphous membrane on the surface of Descemet's membrane that would render the latter impermeable to aqueous in some cases. But we still do not know why one course develops in one case and the other in another case.

In Cases 39 and 43 we could observe that corneas presenting the typical picture of healed interstitial keratitis may remain quiescent for many years before developing secondary endothelial and epithelial dystrophy. One patient was sixty and the other forty-eight years old when the condition was first observed. As previously mentioned (p. 709) it was found in one case that some of the endothelial cells were several times the size of the neighboring normal cells. The intercellular spaces were also much enlarged. It appears reasonable to assume that during the active process of interstitial keratitis some of the endothelial cells became degenerated. Since the disease usually develops at an age when endothelial cells still have the tendency to enlarge in order to cover the increased area of the posterior surface of the growing cornea, the remaining cells might have expanded to cover the places left by the destroyed cells. As the patient grows older, the aging process of the expanded endothelial cells might precociously increase the permeability of the endothelial layer.

MISCELLANEOUS AND ATYPICAL LESIONS OF THE CORNEAL ENDOTHELIUM

Within this category fall those cases of sudden and transitory corneal edema which presumably are associated with endothelial disturbance. Case 9 illustrates this group. In 1946 this sixty-nine-year-old woman was found to have macula degeneration in the left eye. Both corneas were clear at that time. In 1951 the patient reported recent pain and failure of vision in the right eye. She showed marked edema of epithelium and stroma, cornea guttata, and central degeneration of the endothelium. Vision was reduced to 20/80. After topical application of cortisone the condition cleared rapidly. Almost one year later there was no edema and vision was 20/30. Weekers and Barac (116) reported acute corneal edema which they considered part of the syndrome of Quincke. It seems possible that in Case 9 some changes in the permeability of the endothelium may have been brought about by similar allergic factors. D'Ermo (33) observed repeated attacks of unilateral corneal edema in a forty-eight-year-old woman. These attacks coincided with increased amounts of histamine in the blood. The administration of antihistaminic drugs reduced the frequency, severity, and duration of the attacks. Although the mechanism involved in these observations could not be demonstrated, the possibility of an increased permeability of the corneal endothelium should be kept in mind.

Under the name of "herpes corneae posterior," Schnyder (90) reported the appearance of vesicles in the corneal endothelium in a patient suffering from repeated herpetic eruptions around the mouth and nose, accompanied by general malaise. The eruptions on the cornea were usually preceded by a stinging pain in the eye and forehead. The blisters were surrounded by a grayish halo, and sometimes the endothelial pattern could be followed along their posterior concavity (Figure 32). Since the appearance of the corneal changes coincided with herpetic outbreaks of the skin, Schnyder concluded that they were actually herpetic lesions. Later, after he had observed somewhat similar endothelial vesicles in patients without herpes, he began to doubt the herpetic nature of these clinical manifestations (91). Vogt (110), who later reported

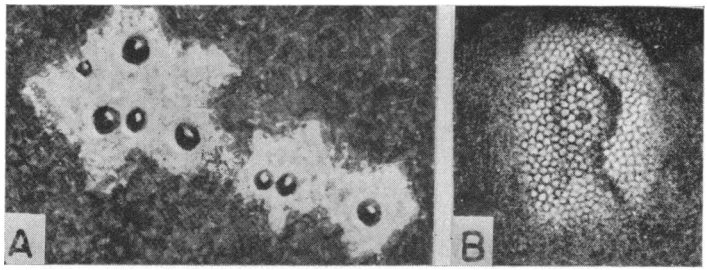


FIGURE 32. HERPES CORNEAE POSTERIOR AS SEEN WITH THE BIOMICROSCOPE
A, with direct focal illumination; B, in the specular light. From Schnyder, "Herpetiforme Erkrankung der Hornhaut Rückfläche (Herpes corneae posterior)," *Klin. Monatsbl. Augenh.*, 73: 1924.

similar observations, did not consider these vesicles as of herpetic origin. We had under observation a patient with endothelial vesiculosis which apparently had no connection with herpes (Case 38). Figures 33 and 34 illustrate schematically the arrangement of the vesicles found on the posterior surface of the cornea. Two different lesions seem to be involved. Schnyder's later cases and Vogt's cases are in line with our own observations. At present the

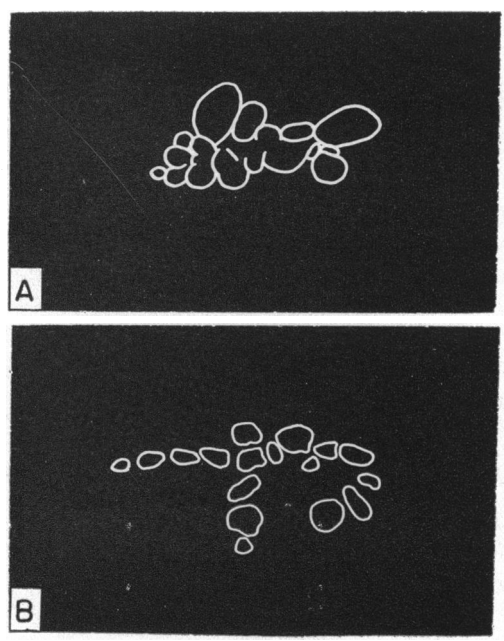


FIGURE 33. TWO STAGES IN THE DEVELOPMENT OF ENDOTHELIAL BULLAE, AS SEEN WITH DIRECT FOCAL ILLUMINATION (SCHEMATIC)

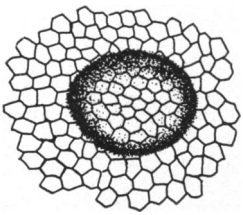


FIGURE 34. SCHEMATIC REPRESENTATION OF ENDOTHELIAL BULLAE AS SEEN IN THE SPECULAR LIGHT OF THE BIOMICROSCOPE

etiology of these vesicles is unknown. It still seems possible that Schnyder's first report was actually concerned with true herpetic lesions. An observation made by Freudenthal (37) should be mentioned in this connection. This author found the following condition in a father, forty-two years old, and a son, fourteen years old. There was no epithelial edema of the cornea, but there was a slight flecky cloudiness partly arranged in stripes in the deeper layers of the stroma. The endothelial cells were edematous and partly vacuolized. The condition was evenly distributed over the entire cornea and not particularly concentrated in the center. Corneal sensitivity was not reduced. Several members of this family showed signs of dysfunction of the thyroid and pituitary glands and congenital lues. The actual cause of the condition could not, however, be definitely determined.

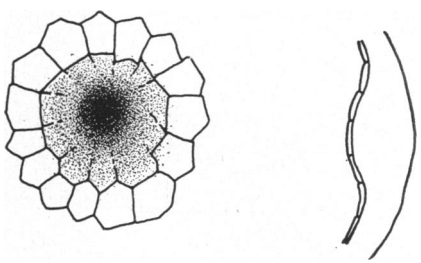


FIGURE 35. SCHEMATIC DRAWING SHOWING THE APPEARANCE OF A LARGE SOLITARY WART ON DESCEMET'S MEMBRANE
Left, in the specular light. Right, in the narrow beam of the biomicroscope.

Figures 35 and 36 illustrate unusually large isolated excrescences, covered by endothelium, on Descemet's membrane. We have found them clinically in a patient who presented peculiar glittery deposits of unknown origin in the conjunctiva and cornea. Blood chemistry was normal except for an unexplained reversed albumin-globulin ratio. No signs of sarcoidosis were present. The histologic picture of Figure 36 is taken from a specimen with an old retinal detachment in which this huge solitary excrescence on Descemet's membrane, covered by endothelial cells, was found

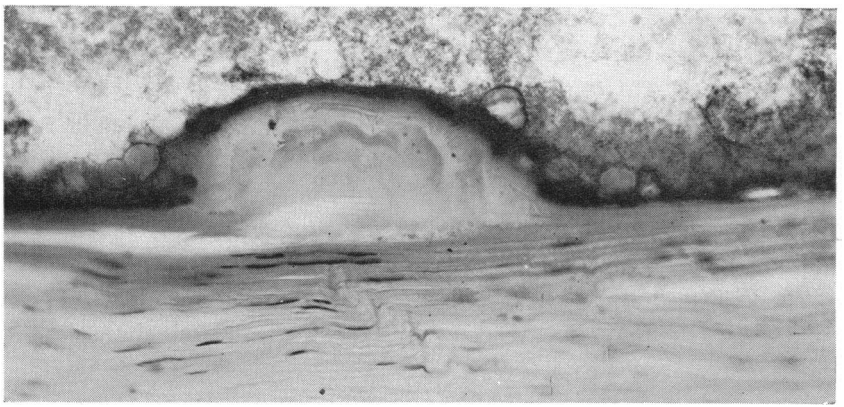


FIGURE 36. CROSS SECTION THROUGH AN UNUSUALLY LARGE SOLITARY WART ON DESCEMET'S MEMBRANE
The small dark dots to the right represent nuclei of individual endothelial cells.

accidentally. We are not able to give a plausible explanation for either case. Figure 36 resembles an illustration by Cogan (25) in which he demonstrates the tendency of the corneal endothelium to surround and cover foreign matter. Although in our cases no actual foreign bodies were demonstrated, it is possible that deposits of some undetermined matter, such as calcium or hyalin, might have provoked the proliferation. An observation, possibly belonging to this category of lesion, was reported by Busacca (8). In a case of band keratitis after iridocyclitis he saw with the slit lamp whitish glittery granules on the posterior surface of the cornea. In a flat preparation of Descemet's membrane and the endothelium, these granules proved to be hyalin deposits. They were surrounded by two kinds of cells; one kind had the appearance of histiocytes, while the others were lymphocytes.

MANAGEMENT OF ENDOTHELIAL AND EPITHELIAL CORNEAL DYSTROPHIES (FUCHS'S TYPE)

From what has been said in the preceding sections, it is clear that we consider primary endothelial dystrophies of Fuchs's type to be of degenerative nature, developing on the basis of senility and heredity. If this is true, results of any medical treatment will naturally be limited in scope. On the other hand, even hereditary lesions may be initiated primarily by disturbances of the metabolic,

endocrine, or nervous systems. These contributing factors might possibly be influenced by therapeutic measures. Also, a symptomatic treatment might be possible on the basis of our knowledge of the physiology of endothelia in general. Since in Fuchs's dystrophy we are confronted with increased permeability of the corneal endothelium as the cause of corneal edema, efforts may be directed towards reducing this permeability. An even more strictly symptomatic approach would simply tend to reduce the edema after it has already developed. Thus, a number of possibilities present themselves for ventures in the field of therapy, both by systemic and by local ways.

SYSTEMIC TREATMENT

Aubineau (3) reported increased blood cholesterol levels in some of his cases and obtained three cures and one improvement by a low-cholesterol diet. We examined blood cholesterol levels in twenty of our cases, and found it to be elevated in four. Since increased blood cholesterol levels are not infrequently found in older people with atherosclerosis, we determined whether the four cases were older than the others. This was not the case. On the contrary, the average age of the cases with normal blood cholesterol levels was sixty years, as compared with fifty-one years for the group with increased levels (Table 2). Thus, there seems to be some indication that increased blood cholesterol might be relatively more prevalent in people with endothelial dystrophy. Although Paufique, *et al.* (77) could not confirm the beneficial effect of a low-cholesterol diet, it might be well to consider this measure in patients that present the symptom. It would appear to be indicated anyway from a general medical standpoint. We have prescribed a low-cholesterol and low-fat diet to the four patients that showed increased cholesterol levels in the blood. No certain results have been observed so far, but our experience is not conclusive. We are not sure how strictly the diet was followed and whether the time during which it was used was long enough to produce results.

Francois, cited by Marx (67), advanced the theory that primary or chronic edema of the cornea (the terms used by most French authors for Fuchs's corneal dystrophy) might be caused by a neuro-

TABLE 2. BLOOD CALCIUM AND CHOLESTEROL LEVELS IN CASES OF ENDOTHELIAL AND EPITHELIAL DYSTROPHY

	Age of Patient	*Calcium (Normal 9–12 mg.)*	*Cholesterol (Normal 150–250 mg.)*	*Decreased Calcium*	*Increased Cholesterol*
	45	8.8	180	1	—
	62	9.5	—	—	—
	43	—	290	—	1
	22	10.4	166	—	—
	59	11.9	—	—	—
	75	13.4	—	—	—
	49	10.6	276	—	1
	47	10.7	233	—	—
	59	12.5	185	—	—
	64	8.8	152	1	—
	57	10.4	222	—	—
	72	12.5	252	—	1
	74	9.2	229	—	—
	50	9.7	—	—	—
	65	9.9	242	—	—
	52	11.5	—	—	—
	73	10.0	200	—	—
	47	—	266	—	1
	65	11.2	222	—	—
	79	11.0	235	—	—
	67	12.5	195	—	—
Total Cases	21	19	16	2	4
Percentage	—	—	—	10.5	20
Average Age	—	—	60	—	51

trophic disturbance of the cornea. Paufique, *et al.* (77) accept this theory and describe cases in which the corneal nerves are often found to be swollen. They also found general instability of the autonomic nervous system in several of their patients. On the other hand, in one case no result was obtained from irradiation of the superior cervical sympathetic ganglion. Whereas we have found the corneal nerves somewhat swollen in some cases, we are more inclined to attribute this fact to the presence of fluid related to the corneal edema rather than to a condition primary to the disease. The statements concerning the disorders of the nervous system are so vague that it seems impossible to take a definite stand

in this matter. When indicated, we have treated a number of our patients with sedatives. But we have never observed any change in the condition of the cornea.

Marx (67) reported an excellent result in a case of corneal edema without hypertension after systemic and local administration of vitamin A. The rationale for this treatment evidently was that vitamin A has been found to have a beneficial effect on disturbances of epithelia. Since in the condition under discussion the epithelium of the cornea is only secondarily affected, it seems doubtful whether the theory holds in this case. We have used vitamin A therapy in three cases. In one, Case 21, which received vitamin A systemically and vitamin A and D ointment locally, there seemed to be a slight temporary improvement. Case 37, which received only vitamin A and D ointment locally, did not show any changes after the treatment had been used for six weeks. The third, Case 29, was treated with vitamin A and D ointment locally and 100 mg. rutin three times a day systemically. After six weeks of treatment the affected cornea was much clearer. Because of the results observed with rutin in other cases, to be discussed later, we are more inclined to attribute the success to rutin rather than to vitamin A.

Our own plan for general medical treatment of corneal endothelial dystrophy is based on the fact that there is primarily an increased permeability of the endothelial layer to the aqueous humor; this causes corneal edema. The mechanism of cellular and intercellular permeability has been discussed at some length in the section on the physiology of the corneal endothelium. As one of the factors producing increased permeability, the lack of calcium was mentioned. We determined blood calcium levels in 19 of our cases and found them to be within normal limits except for two cases in which the level was only slightly reduced (see Table 2). In view of the negative result of this investigation we abandoned the idea of calcium therapy.

Another factor influencing permeability is ascorbic acid or vitamin C. It has been previously stated that vitamin C seems to play an important role in the production and regeneration of intercellular cement. It has also been pointed out that there is evidence that intercellular cohesion might become deficient in

some cases of diseased corneal endothelium. Consequently, adequate supply of ascorbic acid might be desirable.

Considerable interest has been concentrated on the compounds of the flavanol group since Szent-Gyorgyi and his co-workers extracted from lemon a substance which they called citrin or vitamin P. It was found that citrin, as well as related compounds like rutin and hesperidin, had a tightening effect on capillary walls (Griffith, *et al.*, 49). More recently Cella and Means (14), emphasizing the importance of the intercellular substance to the fragility of the capillary walls, pointed out that ascorbic acid, citrin and related substances such as rutin and hesperidin, and hyaluronic acid and its specific enzyme hyaluronidase were the most important substances affecting the capillary walls. They also explained the vitamin P effect in the following way: a deficiency in hyaluronic acid or an excess of hyaluronidase accentuates capillary

TABLE 3. EFFECT OF TREATMENT WITH RUTIN AND ASCORBIC ACID ON CORNEAL ENDOTHELIAL DYSTROPHY

Case No.	*Unimproved*	*Temporarily Improved (Number of Months)*	*Improved for More Than One Year*
26	—	6	—
45	—	1	—
30	1	—	—
28	—	2	—
26	—	—	1
18	1	—	—
17	—	1	—
11	—	8	—
10	1	—	—
8	—	—	1
7	—	5	—
6	—	7	—
3	—	2	—
21	—	4	—
Total Cases 14	3	9	2
Average Improvement (Months) —	—	4	—

fragility; hyaluronidase, however, is inactivated by vitamin P, hence it has a tightening influence on capillary walls.

We undertook to treat 14 cases of corneal endothelial dystrophy by systemic administration of rutin alone or rutin in combination with ascorbic acid (rutorbin). The results are summarized in Table 3. Details may be found in the individual case histories. Of the 14 cases, 11 responded to the treatment. Temporary improvement, for a period of from one to eight months, was seen in nine cases. Improvement for more than a year's duration resulted in two cases. Considering the precarious armamentarium at our disposal for the treatment of this disease, these results are quite encouraging. It may be said that in a number of cases the improvement might have been even more pronounced if the treatment had not been discontinued prematurely. Evidently it should be extended over many months and repeated as soon as a recurrence appears. We do not claim to produce a permanent cure with this treatment. We do believe that for variable periods of time the course of the disease may be favorably influenced. Its recommendation as a routine measure therefore seems to be justified.

LOCAL TREATMENT

Because of the resemblance of the epithelial edema in endothelial dystrophies to the appearance of the cornea in congestive glaucoma, interest had at first always been directed to the possibility of increased intraocular pressure. As previously noted, the pressure is usually found to be normal, at least in the beginning of the disease. Nevertheless, it was often assumed that there might be a temporarily elevated pressure at times, or that the pressure, although normal according to standards, might be too high for a particular eye. Therefore not only miotics but also filtering operations were advocated. Vogt (108,110) reported good results over a period of several years after the performance of Elliott trephine operations in some cases. He contended that after creation of a subnormal intraocular pressure there was less hydrostatic pressure exerted on the damaged endothelial layer by the aqueous, and therefore the cornea was less apt to become permeated. In one case (No. 21) in which we performed an Elliott trephine on an eye afflicted with primary endothelial and epithelial dystrophy

with normal intraocular pressure, we observed that the cornea became temporarily somewhat clearer. The effect, however, was of short duration. On the three eyes of our series (Cases 10 and 20) that had developed acute glaucoma, a combined iridencleisis-Lagrange sclerectomy was performed in two eyes, posterior sclerotomy and cyclodiathermy punctures in one. Although the glaucoma was controlled by these procedures, the course of the corneal disease was unaffected. In two cases with normal intraocular pressure in which we used miotics (Cases 6, 23), the pressure remained unchanged. The corneal haziness was temporarily improved in one case, not improved in the other. Paufique, *et al.* (77) and Marx (67) did not obtain any improvements from miotics. It would therefore appear that the results from conservative and surgical measures directed toward reducing the normal intraocular pressure are rather questionable, and are at most only of limited value and duration. On the other hand, in any case in which increased pressure might be suspected, a filtering operation is indicated because hypertension definitely seems to aggravate the condition. At this point, a warning against frequent instrumental tonometry issued by Doggart (29) should be wholeheartedly supported. The tonometer invariably produces smaller or larger injuries to the diseased epithelium; from these may result ulcers and infections, with disastrous consequences. We usually measure the pressure with the tonometer only on first examination, unless a later measurement is warranted by a strong suspicion of increased pressure arising from digital examination. Another point brought up by Lloyd (64) deserves consideration in this connection. In the presence of cornea guttata there is much danger of the development of endothelial and epithelial dystrophy after a cataract operation. If in such cases there is any evidence or suspicion of permanent or temporary increase of the intraocular pressure, a preliminary filtering operation is indicated.

The aim of local treatment, besides combatting increased intraocular pressure, is obviously to reduce corneal edema. This may be accomplished by purely physical means or by attempting to alter biologically the condition of the tissues involved.

Of the many possible means of increasing the osmotic pressure on the surface of the cornea and thus drawing water from it,

methyl cellulose, hypertonic solutions of glucose (Mueller, 73), sodium chloride (Cogan, 20), and glycerine (Cogan, 22) may be mentioned. Hypertonic salt solutions are probably most widely used. They usually are effective to some degree. In Case 29 the epithelial edema was found to have disappeared two hours after treatment with hypertonic salt solution. Glycerine is a very powerful clearing agent. In Case 30, vision improved temporarily from 20/200 to 20/40 after its application. But it does not seem to be well tolerated by most of the patients. Sometimes its use must be preceded by an anesthetic in order to avoid a very unpleasant stinging sensation. Also, its effect is of course temporary. It therefore cannot be recommended for prolonged use. Hypertonic saline solutions and concentrated glucose ointments are better tolerated and can be used for longer periods with some benefit. We usually employ a 2 percent to 5 percent sodium chloride solution to be instilled regularly every one to four hours throughout the day. A helpful adjuvant for the removal of edema is hot-air application. This can be done with a simple electric hair dryer.

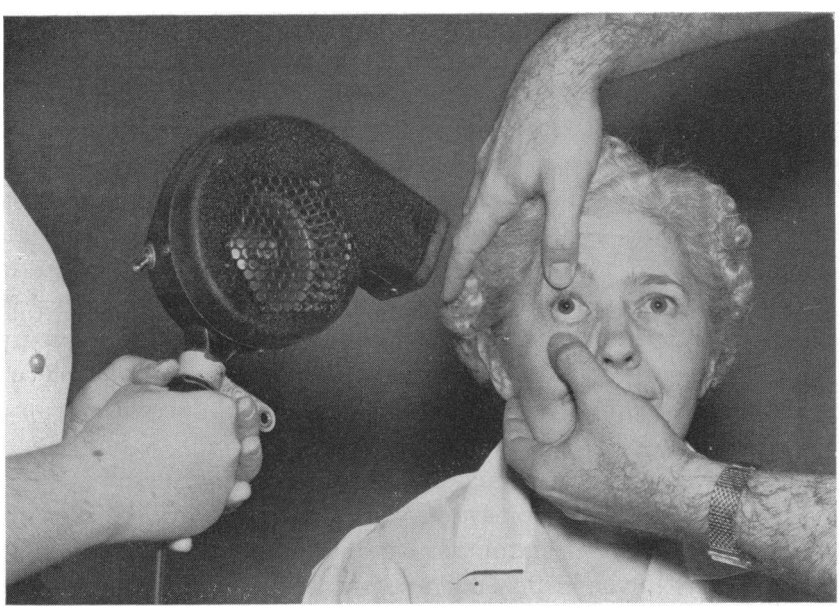


FIGURE 37. APPLICATION OF HOT AIR FOR REDUCING EPITHELIAL EDEMA OF THE CORNEA

As shown in Figure 37, the dryer is held at about 12 inches' distance and the air is blown directly onto the cornea, while an assistant keeps the lids apart and from time to time removes excessive tears with a cotton sponge. The distance has to be varied according to the heat of the air produced and to the sensitivity of the patient. There should be a definite sensation of heat without burning. The duration of the treatment is usually five minutes. In some cases, as in Cases 30 and 19, the result is quite spectacular; vision was improved from 10/400 to 20/40 in one case, and from 20/400 to 20/70 in the other, with bullae completely disappearing after five minutes of hot-air treatment. The vision remained quite clear for at least an hour and somewhat clearer throughout the day than it was before treatment. Figures 38 and 39 demonstrate the clear-

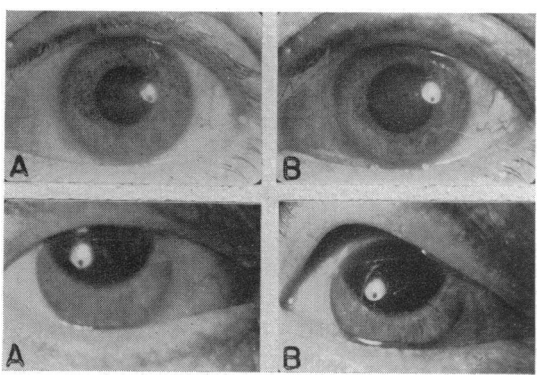


FIGURE 38 (ABOVE), FIGURE 39 (BELOW): CLEARING OF THE CORNEA BY HOT AIR TREATMENT
A. Before treatment. B. After treatment.

ing effect. In cases that respond we use hot-air treatment regularly in the morning to remove the edema accumulated during the night, and then follow with local cortisone. The effectiveness of this treatment supports the theory that the decreased vision in the morning observed in some cases is due to an accumulation of edema because of lack of evaporation during the night. All these measures are purely symptomatic; they combat the corneal edema but have no influence on the basic factor—the increased permeability of the posterior surface of the cornea.

Methods directed toward reducing the permeability of the endothelial layer by systemic treatment were outlined in the preceding paragraphs. For local treatment in this direction, cortisone

seemed to possess some possibilities. It is known not only to reduce permeability and edema, but also to reduce tissue reaction in general. Although Fulmer (45) did not observe any beneficial effect from parenteral administration of either adrenocorticotropic hormone (ACTH) or cortisone, we decided to test local treatment with cortisone extensively. The patients received from .5 percent to 2.5 percent cortisone in the form of drops, or 1.5 percent ointment. Usually in the beginning, the drops were given every two to three hours during the day, and the ointment at night. After an improvement was evident, the frequency of the application was reduced and a maintenance dose of four times a day was kept up indefinitely. Table 4 summarizes the results. Of the total of

TABLE 4. EFFECT OF LOCAL TREATMENT WITH CORTISONE ON ENDOTHELIAL AND EPITHELIAL DYSTROPHY

	Case No.	*Not Improved*	*Improved (Number of Months)*	*Improved for More Than One Year*
	11	—	—	1
	10	—	1	—
	7	1	—	—
	45	1	—	—
	12	—	7	—
	37	—	1	—
	9	—	10	—
	15	—	1	—
	16	1	—	—
	19	1	—	—
	20	—	3	—
	22	—	—	1
	25	1	—	—
	39	—	1	—
	41	—	3	—
	43	—	—	1
Total Cases	16	5	8	3

16 cases to which this treatment was given, no improvement was seen in five. Improvements of from one to ten months' duration occurred in eight cases, and three cases showed improvement for more than one year. Two cases, Numbers 19 and 25, which did not

respond to cortisone, were later successfully treated with corneal grafts, a point which will be taken up in detail in the next section. In Case 41 it could be demonstrated that an original improvement was followed by a recurrence after the drug was discontinued. But a favorable response was again obtained as soon as the treatment was resumed. Cortisone, therefore, seems to be the local treatment of choice in endothelial and epithelial dystrophy. It is more effective and the duration of its beneficial effect is longer than that of any other treatment we have used. Due to the degenerative nature of the disease a radical and lasting cure cannot be expected. But even temporary improvement which may postpone the unfortunate terminal stage of the disease should be gratefully welcomed.

CORNEAL ENDOTHELIUM AND KERATOPLASTY

The relationship between the endothelium of the cornea and corneal surgery is interesting from two viewpoints. First, it is important to know in what manner the results of corneal transplantation may be influenced by the condition of the endothelium of the graft at the time of the operation and afterward. Second, there is the question of how the condition of the recipient's corneal endothelium will influence the chances of success of a keratoplastic operation. The latter question will lead to the evaluation of the possibilities for corneal transplants in cases of endothelial and epithelial corneal dystrophy.

As to the first question, von Hippel, cited by Wagenmann (114), stated that a deficiency of the endothelium was a determining factor in the development of cloudiness of the graft. He also mentioned that the endothelium might be intact at the time of the operation but become detached later. In 1888, Wagenmann (114), taking up the subject, proved by his experiments that when he cut corneal flaps and sutured them into place again they would heal in promptly and remain clear. When he scraped off the endothelium, however, before reattaching the flap, it became cloudy and remained so. Maumenee[4] found that in cases of cloudiness of

[4] A. Edward Maumenee, "The Influence of Donor-Recipient Sensitization on Corneal Grafts," *Proceedings of the Association for Research in Ophthalmology,* 19th Meeting, June 24-25, 1950, pp. 142-52.

corneal grafts due to sensitization, the endothelium became detached from Descemet's membrane. In recent years other investigators have paid more attention to the other structures of the cornea. (Katzin [52], Laval [60], Dunnington and Region [31].

From our clinical observations and pathologic studies, it has become increasingly evident that the condition of the endothelium of both donor and host at the time of a corneal grafting is of paramount importance for the end result of a clear graft.

Before approaching the subject from the clinical angle, we should like to report some experimental work. First, we tried to evaluate the effect of cold storage for various lengths of time on the structure of the endothelial layer of the cornea. Human eyes kept under the usual refrigeration at about 4° C., either in the eye bank or in our own refrigerator, were used. The first eye received from the eye bank had been in cold storage for 24 hours at the time of examination. The cornea macroscopically appeared to be quite clear, no noticeable epithelial defect being present. With slit lamp and corneal microscope the stroma appeared to be slightly hazy. Descemet's membrane showed many wrinkles. The endothelial pattern could be identified, but the individual cells were indistinct and had a shriveled appearance. There was no cornea guttata. The picture resembled very much the illustration given by Schnyder (89), reproduced in Figure 40. Schnyder observed this condition in eyes after paracentesis, in some cases of iridocyclitis, and in eyes of animal cadavers. A flat section was

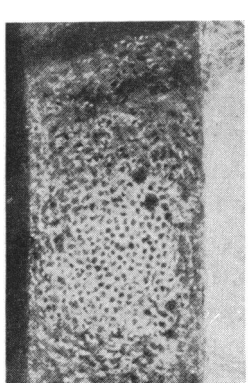


FIGURE 40. SHRIVELED APPEARANCE OF CORNEAL ENDOTHELIUM AS SEEN WITH THE BIOMICROSCOPE, AFTER COLD STORAGE

From Schnyder, "Untersuchungen des normalen und pathologischen Endothels der Hornhaut mittels Nernst Spaltlampe," *Klin. Monatsbl. Augenh.*, 65: 1920.

prepared with the modified Nagano technique (see Appendix B) and stained with hematoxylin. On the whole, the outline of the endothelial cells was still visible, the pattern was uninterrupted, and the nuclei were not disintegrated. Small vacuoles within the protoplasma were, however, present (Figure 41). A second eye was examined after 48 hours of cold storage, the section being made with our own technique (see Appendix B). The condition of the endothelium is shown in Figure 42. Here the endothelial layer had lost its continuity; in numerous places it had disappeared. The outlines of the cells were almost indistinguishable. The protoplasma was filled with vacuoles, and even the nuclei participated in this process. A third eye received from the eye bank after 71 hours of cold storage showed considerable cloudiness of the pos-

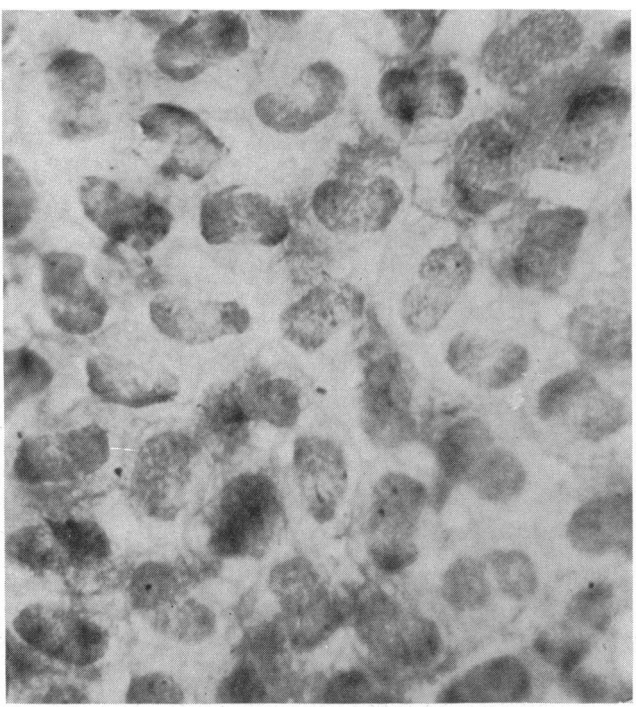


FIGURE 41. FLAT PREPARATION OF THE CORNEAL ENDOTHELIUM AFTER TWENTY-FOUR HOURS OF COLD STORAGE
There is beginning vacuolization of the cytoplasm.

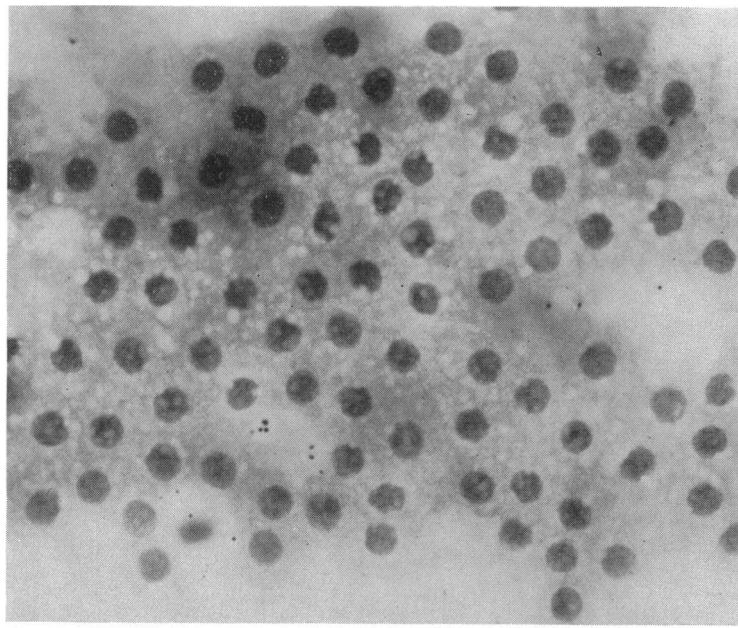


FIGURE 42. FLAT PREPARATION OF THE CORNEAL ENDOTHELIUM AFTER FORTY-EIGHT HOURS OF COLD STORAGE
The endothelial layer is not continuous any more. Extensive vacuolization of cytoplasm and nuclei is present. (x678.)

terior layers of the thickened corneal stroma. Many folds of Descemet's membrane were present. The endothelial pattern could not be discerned. There was no edema of the epithelium. The excised cornea was stained with 1 percent alizarin red without fixation. Under the microscope the endothelium could be seen. The intercellular cement, which is stained with this method, was clearly demonstrable. In places clumps of cement were present on the cells themselves. Some nuclei were stained faintly. Some of the cells were much larger than the others and stained lighter (edema, vacuolization?). The endothelial layer sloughed off very easily at the slightest manipulation. The stain did not withstand fixation, hence no photograph is available. A fourth eye was examined after 96 hours of cold storage and prepared like the second one. Under the microscope the endothelial layer was found to be absent over large areas. When it was present, as seen in Figure 43,

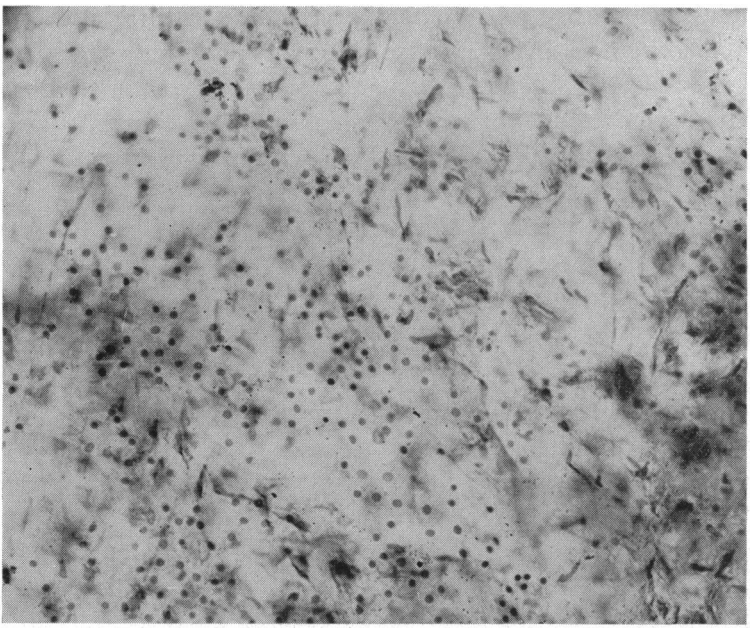


FIGURE 43. FLAT PREPARATION OF THE CORNEAL ENDOTHELIUM AFTER NINETY-SIX HOURS OF COLD STORAGE

In large areas the endothelium is absent. The remaining cells are of variable size and stain faintly. (x158.)

there was no continuous pattern. Clusters of loosely connected cells were separated from each other by denuded areas. They stained faintly, and in places there were holes of about the size of a cell suggesting that an individual cell had fallen out. It has been claimed by Sédan (92) and others that the corneal endothelium is affected by cold storage very rapidly; these findings are indeed evidence that this is true.

After having established the facts regarding the effect of cold storage, we investigated some aspects of how the endothelium reacts in the presence of a surgical wound or section in the cornea. This investigation was to supplement in a more specific manner the results obtained by the previous experiments with minute lesions set by needle pricks which were referred to in the section on regeneration. For this purpose, through the courtesy of Doctors John H. Dunnington and Ellen F. Regan, we were fortunate in

obtaining some sections of monkey eyes which these authors had used for their studies on ocular wound healing (30,31). Evidently for the reasons of convenience and economy, most of the experimental work on corneal grafting, including our own, so far has been done with rabbits. It must be said, however, that for studies of tissue regeneration the rabbit is not a very suitable animal. Its regenerative power is so much greater than that of the human that it is difficult to apply the results obtained with it to human pathology. It can easily be demonstrated that in rabbits porcelain-white leucomas or corneal grafts that have been perfectly opaque for weeks or months may eventually regain complete transparency. Furthermore, in our not yet published experiments on intravital

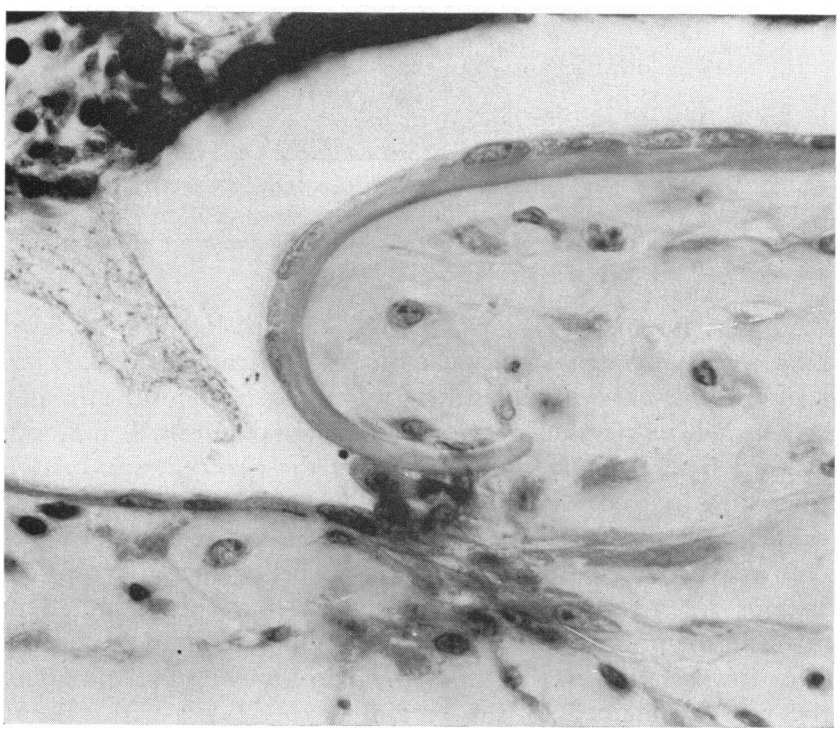


FIGURE 44. CROSS SECTION THROUGH THE POSTERIOR PART OF A MONKEY'S CORNEA FOUR DAYS AFTER A CORNEAL SECTION

The endothelium on Descemet's membrane (upper right) does not show any signs of proliferation. From the plug of fibroblasts (lower center) a layer of flat cells seems to originate and cover the gap. (Original magnification x893.)

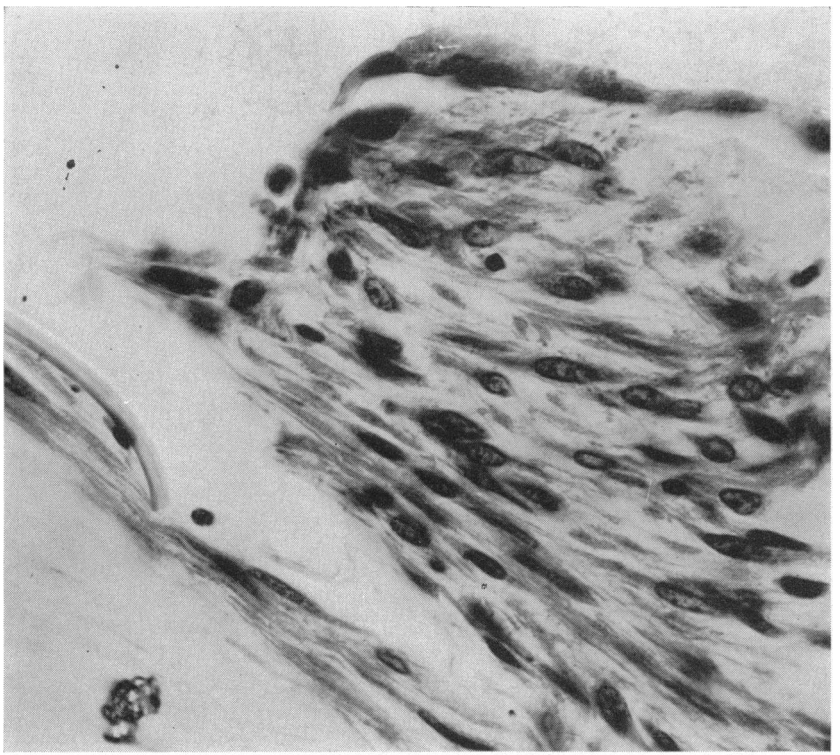


FIGURE 45. CROSS SECTION THROUGH THE POSTERIOR PART OF A MONKEY'S CORNEA TEN DAYS AFTER A CORNEAL SECTION

A flat layer of cells (upper right) extends from the plug of fibroblasts onto Descemet's membrane. These cells do not show any continuity with the original endothelia (not seen in the photograph). (Original magnification x893.)

dissolution of the lens by proteolytic ferments, we could observe that the lens, after it had been almost completely absorbed, would regenerate to a nearly normal lens again if the animal was left alone for several months. These phenomena are without parallel in human pathology and should make us cautious in drawing hard and fast conclusions from experiments with rabbits in this field.

Figures 44, 45, and 46 represent three stages corresponding to four days, ten days, and two weeks after a corneal section. In Figure 44 the original endothelial cells, which are seen to cover Descemet's membrane until it curls, do not show any signs of proliferation. The gap between the two ends of Descemet's membrane (only one

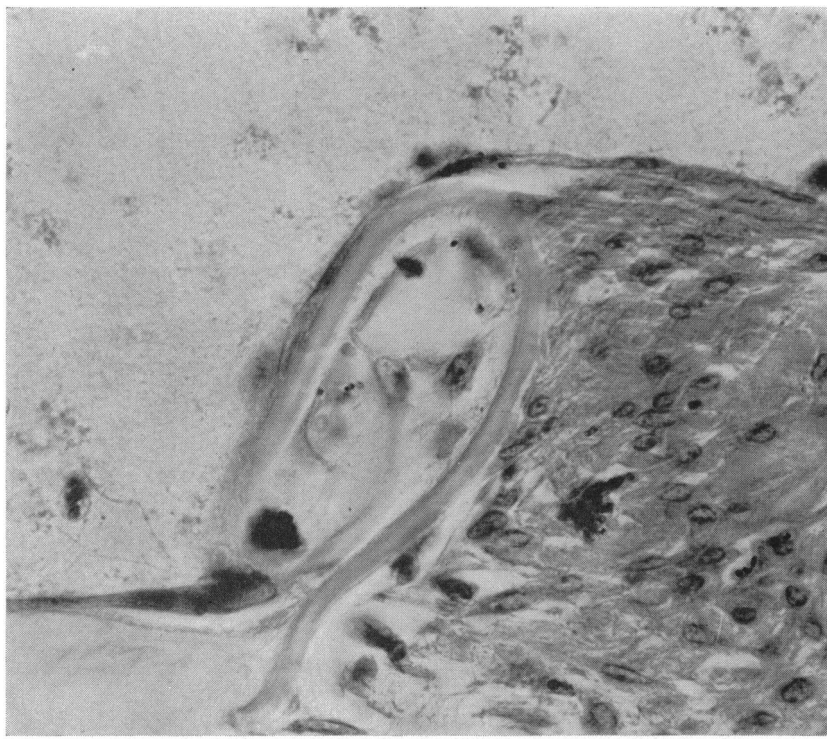


FIGURE 46. CROSS SECTION THROUGH THE POSTERIOR PART OF A MONKEY'S CORNEA TWO WEEKS AFTER A CORNEAL SECTION

The curled Descemet's membrane and the gap of the wound are almost completely covered by a layer of flat cells differentiated from the cells that form the fibroblastic plug and now produce connective tissue. (Original magnification x893.)

end is visible in the photograph) is lined by a single cell layer. Those cells are not quite similar to the original endothelial cells on Descemet's membrane. They are flat, stretched out, and in close contact with the fibroblasts forming the plug in the wound. The possibility may be considered that they do not originate from the adjacent endothelium but from the fibroblastic plug, and gradually develop into an endothelium-like layer without acquiring the exact properties of the original endothelia. An allusion to a secondary pseudo-Descemet's membrane, evidently produced by these cells, is visible in the section but not demonstrated by the photograph. The occurrence of such a membrane covering the gap between the two ends of a broken Descemet's membrane was pre-

viously reported by several investigators. In Figure 45 it can be seen that the fibroblastic plug is partly covered by a layer of cells arranged in line like an endothelium, but apparently in close contact with the cells of the plug. No definite connection with the original endothelium (not represented in the photograph) is established by these cells towards the right. Toward the left there is an artificial gap between the plug and the broken end of Descemet's membrane, but it can readily be seen that some cells from the plug extend their pseudopodia onto the membrane. Here again one gets the impression that the pseudo-endothelial covering of the gap originates from the fibroblastic plug rather than from each side of the interrupted endothelial layer. Figure 46 shows that after two weeks the gap and the curled Descemet's membrane are almost completely covered by a flat layer of cells. These cells, although differentiated from the fibroblasts of the plug which are in the process of transforming into connective tissue, are still far from having the morphologic properties of the normal corneal endothelium.

In order to establish the immediate influence of a graft with a partly deficient endothelium on the postoperative course, we did a 6 mm. corneal graft on a rabbit. Before the donor tissue was sutured into the host's cornea the endothelium was scraped from one half of the graft. After the completion of the operation a faint straight line through the middle of the implant could be seen.

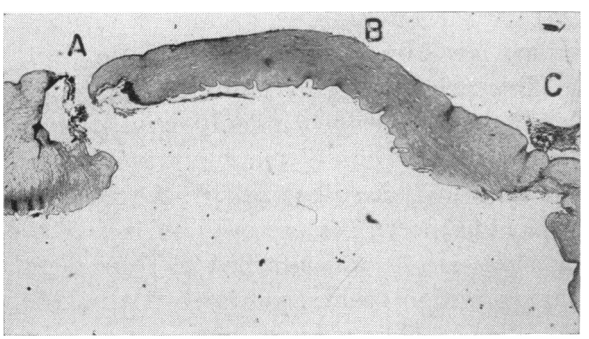


FIGURE 47. CROSS SECTION THROUGH THE CORNEA OF A RABBIT FOUR DAYS AFTER A PERFORATING GRAFT HAD BEEN PERFORMED

The endothelium had been scraped off from part B-C which is much thicker (edema) than part A-B where the endothelium was left intact.

After four days the animal was killed. Figure 47 shows the condition of the graft after fixation and staining with hematoxylin-eosin. The whole graft is edematous, but even in this low-power photograph it can be seen that the part to the right, B-C, from which the endothelium was scraped, is considerably more swollen than the untreated part, A-B. Under high-power magnification, the corneal lamellae are seen to be completely disintegrated into their fibrillae in part B-C, with fluid being accumulated between them. In the anterior segment of part A-B the lamellae are still recognizable and there is considerably less edema than in part B-C. This observation proves that the integrity or deficiency of the endothelium of the graft certainly must alter the immediate postoperative course considerably. As to the long-range effect, for the reasons previously stated it was not considered expedient to rely too much on the outcome of experiments with rabbits. An experience with a patient, Case 48, although it was an accidental and unfortunate occurrence, served almost as an experiment with a human eye. This patient suffered from bilateral granular corneal dystrophy (Groenouw). A square corneal transplant in the left eye had been done elsewhere several years ago, but the graft had become cloudy, with vision reduced to counting fingers at five feet. The cornea of the right eye showed a typical granular dystrophy comprising mostly the central part of the superficial and medium layers of the cornea. Vision of the right eye was counting fingers at two feet. The endothelium was perfectly normal throughout. A perforating partial corneal graft, 5.5 mm. in diameter, was done. During the first few days the graft stayed quite clear. There was no bulging, dislocation, or other postoperative complication. On the 13th day the graft became suddenly hazy. When examined at the slit lamp, the epithelium of the donor part of the cornea was edematous, the stroma succulent and thickened. A very delicate membrane extended from the posterior surface of the graft into the anterior chamber. It was attached to Descemet's membrane only by a narrow bridge; the rest was freely floating in the aqueous. The case was diagnosed as a detachment of the endothelial layer of the graft with corneal edema resulting from the infiltration of the aqueous into the unprotected cornea. After nine days the membrane had disappeared. The graft became more and more

cloudy and simulated exactly the picture of Fuchs's endothelial and epithelial dystrophy. The surrounding host's cornea remained unaltered by this process and the epithelial edema remained confined to the central part. Several months after the first graft, another partial penetrating graft, 7.5 mm. in diameter, was done. Thus the whole diseased part was removed. The microscopic examination of the removed disc revealed the typical picture of cornea guttata and endothelial dystrophy. The endothelial layer was absent, in keeping with the clinical picture, but numerous warts were present on Descemet's membrane. Pigment granules adhered to some of the excrescences. Descemet's membrane itself was thickened until it was slightly thicker than Bowman's membrane, one of the characteristic signs of permeation with fluid in the second stage of the disease. The lamellae of the stroma were edematous, especially in the posterior layers. The surface of the epithelial layer was slightly irregular, some of the endothelia edematous, and the nuclei degenerated in places. The partial loosening of the epithelium from Bowman's membrane suggests the beginning of bullae formation (Figure 48). In some sections parts of the host's cornea were seen. They did not show cornea guttata. There is little doubt that in this case a cornea guttata with endothelial dystrophy had been accidentally transplanted.

Two conclusions may be drawn from these observations:

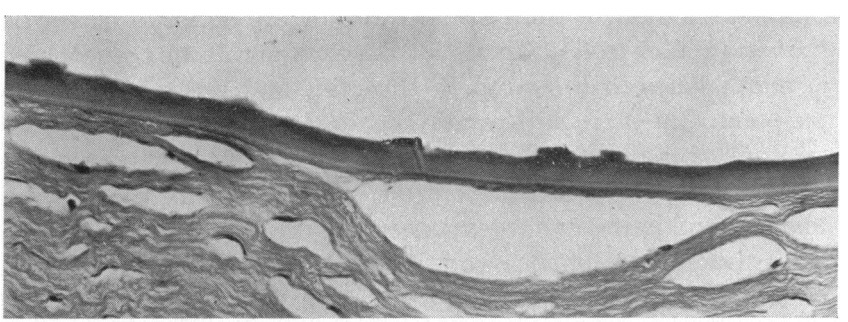


FIGURE 48. DESCEMET'S MEMBRANE OF A CORNEAL GRAFT THAT DEVELOPED A CONDITION CLOSELY SIMULATING FUCHS'S DYSTROPHY, ALTHOUGH THIS DISEASE WAS NOT PRESENT IN THE HOST

Note the absence of the endothelium and the numerous excrescences on Descemet's membrane. It was thought that cornea guttata was accidentally transplanted from the donor to the host. (Original magnification x365.)

First, since such detailed evidence has been brought forward to demonstrate how seriously injured the corneal endothelium becomes during cold storage, an early use of the graft after it has been removed from the donor is advocated. Since endothelial changes occur after 24 hours of cold storage, transplantations should, if possible, be performed within this period. As Paufique (79) rightly states, this is not so important for lamellar grafts, since in this case Descemet's membrane and the endothelium are not transplanted.

Second, in Case 48 a cornea guttata was accidentally transplanted. This was followed by a complete detachment of the endothelial layer. One cannot help speculating that the already pre-existent endothelial dystrophy was the cause of the graft's becoming diseased. Since it has been shown statistically (47) that about 6 percent of all older people have cornea guttata, it seems that an unduly high risk of transplanting cornea guttata is accepted when donor material from older people is used indiscriminately. Every older prospective donor should be searched for endothelial dystrophy with slit lamp and corneal microscope during life, before the cornea is considered for transplantation. Or, since this might be impractical in most instances, in order to avoid the accidental transplantation of cornea guttata, donor material from people under forty years of age should be preferred.

As mentioned above, we favor the theory that the gap between the endothelium of the host and that of the donor is closed by proliferation of cells originating from the fibroblastic tissue which develops between the edges of the graft and the cornea of the recipient. But there still remains the question whether the endothelium of the graft survives or whether it is gradually replaced by host cells proliferating from the periphery of the graft. Statements found in the literature concerning this important matter are rather vague. Maumenee and Kornblueth (69) conclude, "The endothelium is always damaged to some extent but part of it may remain on the graft" and "the endothelium may be repaired from the uninjured cells of the graft or a migration of cells from the recipient cornea." Katzin (52) states "We believe that the endothelium is replaced by the host in the same manner [as the epithelium]. Proof of this is, however, more difficult to obtain."

We attempted to obtain some information on the survival of the endothelium by tagging the cells with vital staining. The following experiment was done: After a similar amount of aqueous had been previously withdrawn, .2 c.c. of 2 percent trypan blue was injected into the anterior chamber of the right eye of an albino rabbit and .2 c.c. of 2 percent alizarin red into the anterior chamber of the left eye. Twelve days later the animal was killed. Macroscopically there was a bright blue hue in the cornea of the right eye, but practically no color in the left eye. On opening of the anterior chamber it was found that the aqueous of the right eye was quite blue and the iris definitely contained blue stain. The cornea, however, was colorless, and microscopically the endothelium contained no pigment granules. The red stain in the left eye had vanished. Evidently the trypan blue, the molecular weight of which is 960.808, was not able to pass through the chamber angle, whereas the alizarin red, with a molecular weight of 342.253, found its way through the drainage system. Since the endothelium would not retain the stain, or at least not for a sufficient length of time, the method of tagging with trypan blue seemed to be unsuitable for the identification of this layer of cells. Several other dyes were tested, but no satisfactory results were obtained for tagging the endothelial cells. Pending further experimental data one must rely on clinical observations which might afford information on the subject. The fact that corneal transplants in cases of endothelial dystrophy are usually unsuccessful when a small graft is placed within the diseased part of the cornea would indicate that the endothelium does not survive, and that the failure of the operation results from the inability of the diseased endothelium of the host to replace that of the donor. On the other hand, our observation in Case 48 would indicate that neither the perfectly normal endothelium of the host nor, according to our theory, the cells originating from the fibroblastic plug were able to cover Descemet's membrane of the graft after it had lost its endothelium. Consequently the picture of endothelial and epithelial dystrophy developed solely within the graft. We were also able to demonstrate that the endothelium of the graft does not become diseased and a clear graft may be obtained even in cases of endothelial dystrophy in which the peripheral parts of the

endothelium are partly diseased. In such cases a large graft has to be used and placed within the part of the cornea that is not yet damaged by the edema. (These cases will be discussed in detail in a subsequent paragraph.) We feel inclined to believe that if favorable conditions exist in the host's cornea the endothelium of the graft survives, and that the failure of transplantations within the diseased cornea in cases of Fuchs's dystrophy is due to the fact that the chances for survival of the endothelium of the graft are rendered extremely poor by the surrounding edematous cornea, rather than by the spreading of the disease of the host's endothelium unto the graft. The endothelium of the graft, however, seems to undergo a certain degree of degeneration even if the host had not been afflicted with endothelial dystrophy, as illustrated by Case 47. We have seen the most normal endothelial pattern on a corneal graft in a case that showed definite continuance of the host's corneal nerves into the graft. In this case (Case 46) the corneal sensitivity had returned in the graft.

From this discussion, the role of the endothelium in corneal transplantation appears to be an important one. In summary, the following conclusions may be drawn:

1) Since it was demonstrated that prolonged cold storage affects the corneal endothelium unfavorably, the early use of donor material, preferably within 24 hours after it has been obtained through death or surgery, is indicated in cases of perforating grafts.

2) When corneas from older individuals are used for transplantation they should be known to be free of endothelial dystrophy or cornea guttata. The possibility of transplanting this

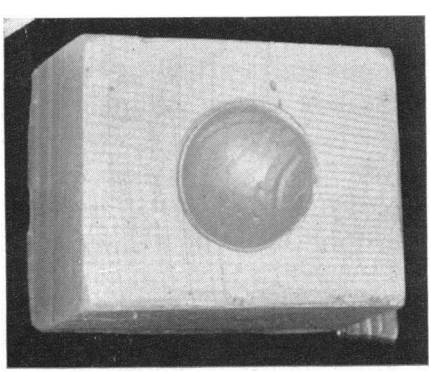


FIGURE 49. PARAFFIN BLOCK WITH EXCAVATION CORRESPONDING TO THE CORNEAL CURVATURE
Following Amsler's suggestion, the excised cornea of the donor is placed in the excavation and the graft trephined from the endothelial side.

condition, with subsequent development of Fuchs's dystrophy in the graft, should be kept in mind.

3) Extreme care should be taken not to injure the endothelium when removing the graft from the donor's cornea. Amsler's method (1) of cutting the cornea from behind might possibly be preferred to the usual way of trephining the donor's eye from the front, because it warrants a clear section through endothelium and Descemet's membrane (Figure 49). Since this method uses the excised cornea, it may easily be combined with routinely storing the cornea alone instead of the whole globe. This method has been reported by De Roeth (28) to be superior to the cold storage of the whole eye.

After having discussed the importance of the endothelium in corneal transplantation in general, we shall now examine the possibilities of treating endothelial dystrophies by corneal grafting. It is evident that only the most serious cases with severe loss of vision should be considered for surgery. The minor conditions mentioned under the heading "Miscellaneous and Atypical Lesions of the Corneal Endothelium" will not be reviewed in this connection. Only the advanced stages of primary and secondary endothelial dystrophy will be discussed. It is natural that these cases with vision reduced to 20/200 or less have always tempted the ophthalmic surgeon. Since the disease was purely corneal in nature, corneal transplantation seemed to be the treatment of choice. Unfortunately the results have been most discouraging. Owens, *et al.* (76) state that in none of the ten cases of Fuchs's dystrophy reported in the United States in which a corneal graft had been done had the graft remained clear for four months or longer. Castroviejo (13) lists Fuchs's dystrophy among the conditions that do not lend themselves to keratoplasty. Roberts (85), reporting 100 cases of corneal transplantation, states that the three cases of Fuchs's dystrophy included in his series were failures, and concludes that keratoplasty is contraindicated in this disease. Paufique, *et al.* (78,80) also consider the prognosis of corneal grafts as very grave in these instances. They saw a partial success in only two cases. In one of them a lamellar graft was done; in another a second graft of 4 mm. had been placed within a 5 mm. graft that had previously become diseased. We ourselves had been unsuccess-

ful in one case, Case 21, using a 4 mm. graft. It was generally accepted that the failures were due to the fact that the disease of the host's cornea invaded the graft. As mentioned above, we rather think that since the conditions for the survival of the endothelium of the graft within a swollen edematous recipient cornea are very unfavorable, the transplanted endothelium becomes necrotic, whereupon the graft assumes a disease similar to that of the host. We then decided to try transplantations in cases which had a markedly reduced vision, 20/200 or less, but in which the degeneration had been confined to the more central parts of the cornea. As previously mentioned, cornea guttata in the beginning in most of the cases is much more marked in the center of the cornea. The endothelium may be completely degenerated and marked corneal edema may be present in the central areas, whereas the periphery, although partly diseased, would still show patches of normal endothelium and be free of edema. It was concluded that the graft might remain clear if made large enough to replace all of the severely diseased central part and if brought in contact with a relatively normal cornea. Indeed, the first case operated on in such a manner was a perfect success. Vision was improved from 20/200 to 20/20 and the graft remained clear and is still clear after more than two years (Case 19). This represents the first entirely successful case of corneal transplantation in a case of endothelial and epithelial dystrophy reported in the literature

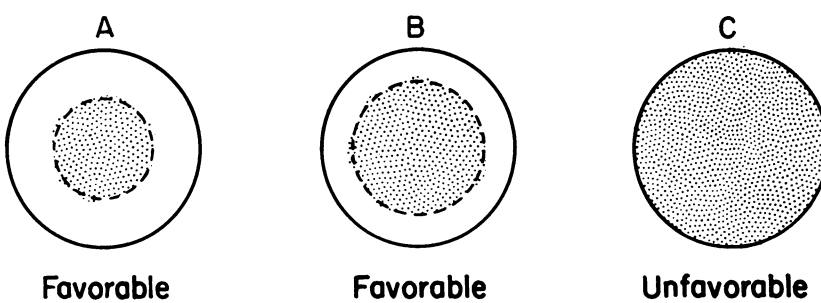


FIGURE 50. POSSIBILITIES OF SUCCESSFUL CORNEAL GRAFTS IN FUCHS'S DYSTROPHY

The shaded areas indicate the extent of corneal edema in endothelial and epithelial corneal dystrophy. For transplantations the size of the graft has to be chosen according to the size of the diseased area (A and B). When the whole cornea is involved (C), the prospects for a clear graft are reduced.

(100). Figure 50 demonstrates schematically the possibility of success of corneal grafts in the various stages of Fuchs's dystrophy. If the diseased part of the cornea is small and confined to the center, a relatively small graft will suffice; if the area of dystrophy is larger a larger graft is necessary. If the whole cornea is involved the chances of a clear graft are slight. In a second case of primary Fuchs's dystrophy, Case 25, the definitely diseased area was larger than in the first one. A 9 mm. perforating graft was done which replaced almost all of the host's cornea except for a small area adjacent to the limbus. This graft also remained clear and is still clear with vision 20/20—1 after more than a year. In this case, as mentioned above, the periphery of the host's cornea was more involved in the disease than in the previous one. Accordingly, the small area between the edge of the graft and the limbus began to show epithelial edema and bullous keratitis even after the graft had healed in and had remained free from disease. It may be that the endothelium has a better chance to survive on a relatively large graft than on a small one, even if surrounded by diseased cornea. In a third case of endothelial and epithelial dystrophy following an old interstitial keratitis (Case 39), a 9 mm. perforating graft was done. After an episode of transitory clouding during the second postoperative month the graft was still clear after seven months, and vision had improved from 5/200 to 20/30 (Figure 51).

Encouraged by a partial success with lamellar grafting reported by Paufique, as previously mentioned, we also considered this procedure. At first glance it seems strange that a lamellar graft which would not replace the diseased endothelium could possibly be of any use. One would expect that the fluid which had penetrated the endothelium and Descemet's membrane would also infiltrate the stroma of the lamellar graft and eventually cause edema of the epithelium and bullous keratitis. On the other hand, we have observed with the biomicroscope a fine line of separation between the recipient cornea and the graft in cases in which we had done lamellar grafts for conditions other than endothelial dystrophy. This line probably indicates the presence of a thin connective tissue membrane. Furthermore we know, as previously mentioned, that in cases of endothelial dystrophy after a connective tissue membrane has formed on Descemet's membrane the proc-

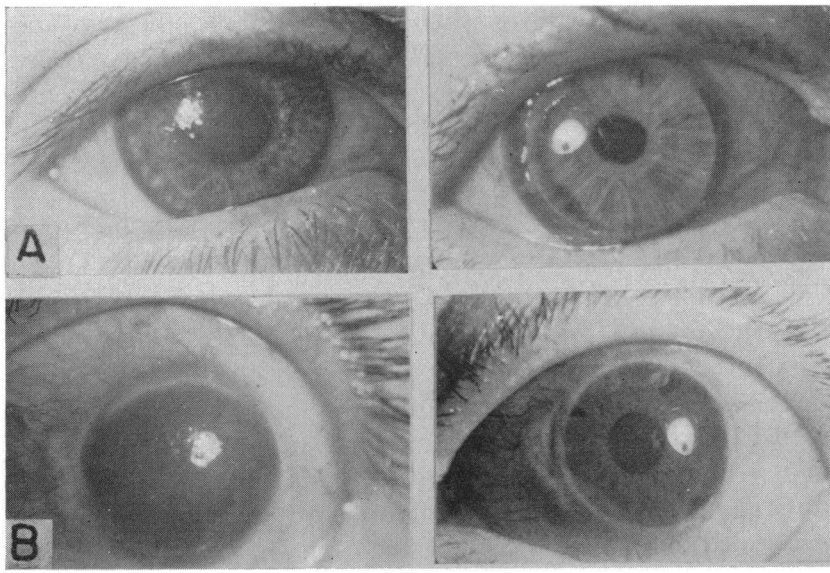


FIGURE 51. RESULTS OF LARGE PERFORATING GRAFTS IN PRIMARY AND SECONDARY ENDOTHELIAL AND EPITHELIAL DYSTROPHY

A. Left: primary dystrophy with cloudiness of the cornea and distorted light reflex (epithelial edema). Right: the same case after a 9 mm. perforating graft was done. Vision 20/20-1. B. Left: Secondary dystrophy many years after interstitial keratitis with cloudiness of the cornea and distorted light reflex (epithelial edema). Vision 5/200. Right: the same case after a 9 mm. perforating graft was done. Vision 20/30. Note the four peripheral iridectomies.

ess of infiltration of the corneal stroma with fluid may come to a standstill. It may be that a similar mechanism works in the case of a lamellar graft, inasmuch as the fluid which has infiltrated the posterior part of the cornea might be prevented by the connective tissue membrane from reaching the stroma and the epithelium of the graft. In one case (Case 49) with severe secondary endothelial and epithelial dystrophy after cataract extraction, we did a total lamellar graft, 10 mm. in diameter. The result may be termed a partial success. After an episode of severe irritation, possibly complicated by infection, the eye became quiescent and more comfortable. With biomicroscopy it could be observed that in some places the graft had firmly healed on the recipient cornea, forming the previously discussed connective tissue membrane. In other places there were clefts, apparently containing fluid, between

the graft and the host's cornea. The stroma of the graft seemed to be only slightly, if at all, edematous, and the epithelium seemed smooth and not edematous. Vision was slightly improved, from discerning finger movements to 10/400. In evaluation of the visual result it has to be taken into account that in addition to the corneal dystrophy secondary glaucoma had existed for some time.[5] The visual results of lamellar grafts hardly ever equal those of successful perforating grafts, but they seem to be especially indicated in cases of endothelial and epithelial dystrophies secondary to cataract extraction. It is well known that perforating corneal grafts in aphakic eyes are technically difficult to perform and represent a considerable operative risk. The lamellar corneal transplantation is less dangerous and easier to perform.

In summary, the following important points should be considered in corneal grafting operations in cases of endothelial and epithelial dystrophy.[6]

Perforating grafts:

(a) Keratoplasty should be performed as soon as the reduction of vision is marked, around 20/200, before the entire cornea is severely diseased.

(b) Large grafts, eliminating most of the diseased part of the patient's cornea, are indicated.

(c) For best possible adaptation, edge to edge corneal sutures should be used.

(d) Donor material should be particularly fresh, having been in cold storage for not longer than tweny-four hours.

(e) Donor should be known to be free of cornea guttata, and preferably be a person under forty years of age.

[5] In the meantime the total number of cases with endothelial and epithelial dystrophy in which keratoplasty was done mounted to nine. In five cases a perforating graft was done, in four cases a lamellar one. The three cases of perforating grafts that belonged to groups A and B (Figure 50) were entirely successful; the two belonging to group C, with almost all of the cornea being diseased, were only partly successful. All of the lamellar grafts showed a definite improvement in the clinical picture and the symptoms, but little improvement as far as vision is concerned.

[6] In June, 1953, at the 60th Congress of the French Ophthalmological Society, Paufique reported excellent results in three cases of endothelial and epithelial dystrophy from scraping off the endothelium first and, after scar tissue had formed in its place, adding a perforating corneal graft. (Not yet published; personal communication.) It may be remembered that Simpson (96) had previously suggested the radical removal of the endothelium. It appears, however, that he never performed this procedure.

(f) For the prevention of anterior synechiae of the iris and secondary glaucoma the following measures are recommended: four basal iridectomies, at 2:00, 4:00, 8:00 and 10:00 o'clock; air injection into the anterior chamber at the end of the operation; the use of miotics before the operation and during the postoperative course.

Lamellar grafts are indicated:

(a) In aphakic eyes.

(b) In non-aphakic eyes if the therapeutic effect on the bullous keratitis is mainly to be achieved rather than the restoration of vision.

SUMMARY

Based on a review of the literature and on our own experimental work and clinical experience in 51 cases, a comprehensive report on present-day knowledge concerning the endothelium of the cornea has been presented. The embryology and anatomy of this layer of cells has been described, its physiology discussed, and the importance of its integrity to the transparency of the cornea and consequently to the visual performance of the eye pointed out. Abnormalities and diseases affecting the corneal endothelium have been reviewed. General and local treatments for these conditions have been discussed. Finally, the importance of the corneal endothelium in keratoplasty has been stressed and principles have been laid down for successful corneal grafting in cases of Fuchs's corneal dystrophy.

APPENDIX A

CONDENSED CASE HISTORIES

CASE 1. SIXTY-FOUR-YEAR-OLD FEMALE. The right eye was enucleated by Dr. Banks Anderson in 1937 because of ulceration and intractable discomfort. At that time edema of the corneal epithelium, epithelial bullae, anesthesia of the cornea, and deep clouding were observed. The pathologic examination was done by Dr. A. B. Reese. The diagnosis was dystrophia epithelialis. The most important changes found were: corneal epithelium of irregular thickness separated in places from the underlying Bowman's membrane, in central parts fibrous tissue interposed between the epithelium and Bowman's membrane, in places edema of corneal lamellae. The endothelium was missing over wide areas, and a thin membrane seemed to be superimposed on the posterior

surface of Descemet's membrane. Endothelial cells showed phagocytosis of pigment granules. In the periphery and extending quite far centrally, very large Henle's warts were present. General medical examination was essentially negative. Blood cholesterol: 200 mg. per cent. Blood calcium: 10 mg. per cent.

5-22-43: When first seen by us, the left eye showed edema of corneal epithelium in central parts. The stroma was thickened and permeated with fluid. The endothelium was absent over large parts of the central area. Near the periphery, the texture of hexagonal cells was still present, but numerous smaller and larger holes interrupted the pattern. Diagnosis: endothelial and epithelial corneal dystrophy.

6-9-49: Corneal dystrophy had increased and epithelial bullae were present. Two percent saline solution, rutin (60 mg.) and ascorbic acid (250 mg.), three times a day, were prescribed.

7-9-49: Edema was less marked. No bullae were present.

9-11-49: Epithelial bullae were present again.

5-20-52: Vision 20/400. The cornea was almost opaque in lower part. There was moderate edema of epithelium; there were no bullae. The stroma was thickened, Descemet's membrane wavy. The endothelium could not be seen. The sensitivity of the cornea was only slightly reduced. Intraocular pressure was 22 mg. Hg (Schiötz).

(One sister, fourteen years younger, was found to have marked cornea guttata.)

CASE 2. FORTY-YEAR-OLD FEMALE.

6-11-52: Both eyes showed degeneration of the endothelium in the central part of the cornea. There were no warts on Descemet's membrane, but defects in the endothelial pattern of the size of one or several endothelial cells were present. Towards the periphery the endothelial pattern was almost normal. Corneal sensitivity was normal in both eyes. Vision: both eyes, 20/20 with correction.

(Mother, eighty years old, has advanced degeneration of endothelium without warts; one sister has advanced cornea guttata; one sister has endothelial dystrophy with beginning infiltration of the stroma.)

CASE 3. FIFTY-NINE-YEAR-OLD FEMALE.

1-28-52: Failing vision was reported for about three years, more in the right eye. Both eyes showed no edema of corneal epithelium, but the stroma was slightly cloudy in the posterior part. The endothelium was shriveled, almost completely degenerated in the central part, but the disease was not confined to the central area. No warts on Descemet's membrane were present. Vision: right eye, 20/70 with correction; left eye, 20/50 with correction. The patient did not notice any difference in vision between morning and afternoon. Rutorbin (50 mg. rutin and 100 mg. ascorbic acid) three times a day was prescribed.

2-26-52: The patient stated that vision began to improve after having taken rutorbin for one week. The stroma of the left eye was quite clear.

6-11-52: The corneal sensitivity was slightly reduced in both eyes. The patient stated that vision had become more cloudy. No objective change in condition was noted. Vision: right eye, 20/70; left eye, 20/50. Cortisone drops (.5 percent) in both eyes four times a day were prescribed.

(Mother, eighty years old, has advanced degeneration of endothelium without warts; one sister has advanced cornea guttata; one sister has endothelial degeneration without warts.)

CASE 4. FORTY-SEVEN-YEAR-OLD FEMALE.

6-18-52: Both eyes showed marked cornea guttata in the center, with endothelium deteriorated. Towards the periphery there were large patches of normal endothelium. Vision: both eyes, 20/20 with correction.

(Mother, eighty years old, has advanced degeneration of endothelium without warts; one sister has endothelial degeneration without warts; one sister has endothelial degeneration with beginning infiltration of the stroma.)

CASE 5. THIRTY-THREE-YEAR-OLD FEMALE.

1-9-35: Both eyes were normal with vision 20/20+.

1-12-51: In both eyes, the corneal epithelium was intact. There was a slight blurriness in the center of the cornea in the middle third of the stroma. The endothelium in this area appeared to be degenerated. There were no warts on Descemet's membrane.

CASE 6. SIXTY-ONE-YEAR-OLD FEMALE.

5-12-45: Right eye: the corneal epithelium was normal. There was advanced cornea guttata with endothelium almost completely destroyed. Vision: 20/20 with correction. Intraocular pressure: 17 mm. Hg (Schiötz). Left eye: the corneal epithelium was edematous. There was extreme cornea guttata with endothelium almost completely destroyed. Vision: 20/40 with correction. Intraocular pressure: 19 mm. Hg (Schiötz). One percent pilocarpine in left eye three times a day was prescribed.

6-9-45: Left eye: the corneal epithelium was somewhat less edematous. To continue pilocarpine.

11-9-45: Increased edema of epithelium and stroma was observed. Sixty mg. rutin three times a day were prescribed.

12-11-45: Left eye: condition was much improved and no edema of epithelium noticed.

6-11-46: Left eye: there was still no epithelial edema.

9-10-47: Patient had not taken rutin for one year. Left eye: the edema of the epithelium had recurred.

6-20-50: When last seen, the dystrophy of the left eye had become worse; more edema of epithelium and stroma was present. Vision: 20/70 with correction. Right eye: there was no edema of the cornea. Vision: 20/20 with correction. Rutorbin three times a day was prescribed again.

CASE 7. FORTY-SIX-YEAR-OLD FEMALE.

6-20-51: Both eyes showed marked cornea guttata with very few intact endothelial cells left in the center. Towards the periphery large patches of normal endothelium were present. The patient was not aware of a reduction in vision, but the eyes felt irritated. Vision: both eyes, 20/25 with correction. One and one-half percent cortisone drops locally four times a day were prescribed.

7-11-51: The patient felt much better. Objectively there was no change. Cortisone was discontinued.

11-6-51: Right eye: there was a slight blurriness in the posterior layers in the central part of the cornea, apparently due to permeation with fluid. Sixty mg. rutorbin three times a day was prescribed.

3-25-52: Right eye: the cornea was clearer. There were no signs of imbibition of water. Vision: 20/30. The corneal sensitivity was slightly decreased in both eyes.

CASE 8. FORTY-FIVE-YEAR-OLD FEMALE.

6-2-49: Bilateral endothelial and epithelial dystrophy with edema of the corneal epithelium and stroma and marked cornea guttata were present. Vision: 20/50. 50 mg. rutin and 100 mg. ascorbic acid three times a day were prescribed.

After six weeks of this treatment the condition was markedly improved.

After three months, vision was 20/30+ in both eyes.

1-5-52: When last seen, there was still marked cornea guttata, but no corneal edema and no bullae were present.

CASE 9. SIXTY-NINE-YEAR-OLD FEMALE.

5-8-46: Macula degeneration in the left eye was found. Both corneas were clear. Vision: right eye, 20/25; left eye, 20/400 with correction.

2-8-50: The condition was unchanged.

7-13-51: The patient gave a history of failing vision and pain in the right eye for the past few days, with vision more blurred in the morning than in the afternoon. Right eye: the corneal epithelium was edematous, the stroma permeated with water and somewhat opaque in the posterior third. Many folds in Descemet's membrane were present. There was considerable cornea guttata with alterations of endothelium in the central part, to a much lesser degree in the periphery. Corneal sensitivity was much reduced. Intraocular pressure: 21 mm. Hg (Schiötz). Vision: 20/80.

Impression: Acute corneal edema on the basis of endothelial dys-

trophy. Left eye: Few but rather large warts on Descemet's membrane, more in the center, were present. The corneal sensitivity was much reduced. One and one-half percent cortisone drops every three hours in the right eye were prescribed.

7-16-51: Right eye: the corneal epithelium was not edematous, the stroma was somewhat clearer, but still thickened and turbid in the posterior part.

7-30-51: The right cornea was clearer. Vision: 20/40. The patient had been using cortisone locally ever since it was prescribed. The condition had remained stationary.

5-29-52: When last seen, vision of the right eye was 20/30.

CASE 10. SIXTY-FOUR-YEAR-OLD FEMALE.

1-24-50: Right eye: there was marked cornea guttata in the center. Towards the periphery there were areas of normal endothelium. The epithelium was slightly stippled. A beginning nuclear cataract was present. Vision: 20/70 with correction. Left eye: there was moderate cornea guttata in the center and normal endothelium in the periphery. A beginning nuclear cataract was present. Vision: 20/50 with correction. Forty mg. rutin three times a day was prescribed.

6-6-50: The corneal lesion was the same, the cataracts had increased in both eyes. Five percent saline solution four times a day in the right eye was prescribed.

12-14-50: Right eye: in addition to epithelial edema, several small bullae were present, the stroma thickened, and Descemet's membrane in folds. Diagnosis: endothelial and epithelial dystrophy. One-half percent cortisone drops every three hours were prescribed.

12-18-50: Right eye: the stroma was clearer and fewer folds in Descemet's membrane were noted.

1-3-51: There was no change in the condition, but it was noted that the anterior chamber had become rather shallow, more so in the right eye, where most of the iris seemed to touch the posterior surface of the cornea. The intraocular pressure was found to be within normal limits to palpation in both eyes.

10-26-51: Right eye: a large ulcer had formed in the center of the cornea, with hypopyon being present. The culture taken from the ulcer showed *Staphylococcus albus.* The condition was treated with aureomycin, penicillin, and terramycin.

12-12-51: The ulcer had healed.

2-15-52: An attack of severe pain in the right eye and nausea for a few hours were reported. Right eye: the cornea was very cloudy, the epithelium stippled. The sensitivity was markedly reduced. The intraocular pressure was 76 mm. Hg (Schiötz). Left eye: intraocular pressure, 11 mm. Hg (Schiötz).

2-16-52: After intensive treatment with 10 percent furmethide, the

intraocular pressure of the right eye fell to 11 mm. Hg. The patient was discharged with 2 percent pilocarpine.

2-20-52: The patient reported the recurrence of severe pain in the right eye. The intraocular pressure was found to be +3.

2-21-52: Right eye: A combined iridencleisis and Lagrange sclerectomy was done.

3-5-52: Right eye: the cornea was still hazy, but no edema of the epithelium and no bullae were present. Vision: 20/400. Intraocular pressure: 17 mm. Hg. Two percent pilocarpine three times a day for the left eye was prescribed.

6-9-52: A severe attack of pain in the left eye was reported. The patient had been using pilocarpine regularly. Right eye: intraocular pressure 16. Left eye: the corneal epithelium was edematous, the stroma cloudy. The anterior chamber angle was completely obstructed. Intraocular pressure 65 mm. Hg.

6-10-52: Since miotics had no effect, a combined iridencleisis and Lagrange sclerectomy was done in the left eye.

CASE 11. SIXTY-FOUR-YEAR-OLD FEMALE.

5-9-46: Extreme cornea guttata in both eyes with endothelium almost completely destroyed in central parts was found. There was no cloudiness of the stroma. Some irregularities of epithelial cells were present in places (early edema?). Immature nuclear cataract was noted. The fundi were not remarkable. Vision: right eye, 20/200; left eye, 20/50 with correction.

6-3-50: The cornea of the right eye had become somewhat cloudy. Some edema of the epithelium was present in both eyes. Rutorbin, one tablet three times a day, was prescribed.

1-29-51: No edema of epithelium was noted. Local cortisone four times a day was prescribed.

2-12-51: Both corneas were clearer. There were still patches of endothelium present toward the periphery, whereas it seemed to be completely absent in the center.

2-26-51: The condition had remained unchanged. No edema of epithelium was noted.

5-12-51: Right eye: edema of epithelium was present again; also some small bullae were noted. Left eye: no edema of epithelium was found. A corneal transplant for the right eye was contemplated. The patient did not return.

CASE 12. SIXTY-NINE-YEAR-OLD FEMALE.

1-5-49: Beginning endothelial dystrophy and immature cataract were found in both eyes. Vision: right eye, counting fingers; left eye, 20/100 with correction.

1-20-49: After an uneventful intracapsular cataract extraction of the right eye, striate keratitis and later corneal edema developed.

3-9-49: Vision of the right eye was 20/200 with correction.

7-3-50: The corneal dystrophy had progressed in both eyes. Methyl cellulose three times a day in both eyes was prescribed.

11-9-50: Right eye: epithelial bullae were present.

11-8-51: The condition was unchanged. One-half percent cortisone drops in each eye three times a day were prescribed.

12-28-51: Right eye: epithelial bullae had disappeared.

6-18-52: When last seen the condition was unchanged.

CASE 13. SEVENTY-TWO-YEAR-OLD FEMALE.

6-11-52: The patient reported the vision of both eyes to be worse in the morning, usually better in the afternoon, especially in the left eye. Right eye: the cornea was clear. Few warts were present in the central area of Descemet's membrane. Corneal sensitivity was normal. There was a moderately shallow angle of the anterior chamber and beginning nuclear cataract. The fundus was normal. Intraocular pressure was 15 mm. Hg (Schiötz). Vision was 20/60 with correction. Left eye: the lids were edematous. The cornea was cloudy, throughout permeated with fluid, thickened. The epithelium was edematous and showed numerous bullae. Descemet's membrane was wavy. The endothelium could not be visualized. The anterior chamber was much shallower than in the right eye. The corneal sensitivity was greatly reduced. The intraocular pressure was 16 mm. Hg (Schiötz). Two and one-half percent cortisone drops in left eye every three hours during daytime, one and one-half percent cortisone ointment at bedtime, and 50 mg. pyribenzamine three times a day were prescribed.

CASE 14. SEVENTY-SEVEN-YEAR-OLD-FEMALE. The patient had been seen on several occasions after 1949, and the corneas were found to be clear every time.

6-25-52: When seen again, the status was as follows: Right eye: edema of the corneal epithelium was present. The central parts of the stroma were turbid. Descemet's membrane was wavy. Most of the endothelial cells were unusually large, with very distinct intercellular lines and probably vacuoles. Every now and then a dark area, several cells large, was seen. There were no warts on Descemet's membrane corresponding to these defects in the endothelial pattern. The corneal sensitivity was greatly reduced. Nuclear cataract was present. The intraocular pressure was normal to palpation. Vision was 20/200. Left eye: No edema of either corneal epithelium or stroma was seen. The endothelial disturbance was the same as in the right eye, but less pronounced. Nuclear cataract was present. The corneal sensitivity was slightly reduced. Vision was 20/100.

CASE 15. SIXTY-FIVE-YEAR-OLD FEMALE.

3-20-52: Both eyes showed well-developed endothelial dystrophy. The

epithelium of the cornea was edematous, the stroma permeated with fluid showing dark clefts. The endothelium was almost completely destroyed all the way out to the periphery. There seemed to be an extensive cornea guttata with very small warts on Descemet's membrane. The corneal sensitivity was markedly reduced. Moderate lenticular sclerosis was present. The intraocular pressure was normal to palpation. Vision: right eye, 20/50—; left eye, 20/40— with correction. One-half percent cortisone drops four times a day were prescribed.

5-1-52: Both eyes: no edema of corneal epithelium was seen. Otherwise the condition was unchanged.

CASE 16. SIXTY-NINE-YEAR-OLD FEMALE.

5-22-52: Gradual loss of vision for the past five years was reported. Both eyes: There was no edema of the corneal epithelium, but some fluid clefts were seen in the posterior part of the stroma. Extensive degeneration of the endothelium, with enlargement and vacuolization of the cells, was present, apparently with formation of innumerable warts on Descemet's membrane. The condition affected the entire area of the cornea almost uniformly. There was a considerable amount of pigment dust on the posterior surface of the cornea. The corneal sensitivity was normal. Beginning nuclear sclerosis was present. One-half percent cortisone drops three times a day were prescribed.

7-3-52: No change in condition was noted. Sixty mg. rutin and 100 mg. ascorbic acid (rutorbin) three times a day were prescribed.

CASE 17. FORTY-THREE-YEAR-OLD MALE. The patient had been seen several times since 1942 and no corneal disease had been noted.

7-5-49: There was edema of the corneal epithelium in both eyes, with marked cornea guttata extending towards the periphery. Fifty mg. rutin and 100 mg. ascorbic acid (rutorbin) three times a day were prescribed.

7-27-49: The corneal edema had completely disappeared.

6-13-52: Patient had not taken rutorbin for some time. There was some epithelial edema again.

CASE 18. FORTY-SEVEN-YEAR-OLD MALE.

5-20-51: The patient stated that a corneal lesion had been diagnosed in him as long as twelve to fourteen years ago. He complained of blurred vision in the morning. Both eyes: The corneal epithelium was clear, not edematous. The anterior part of the stroma was clear. There was some edema in the deep layers of the stroma, with dark water clefts. Descemet's membrane was recognizable as a grayish line. In the center the endothelial pattern was completely absent. Toward the periphery there were a few small patches of endothelium. The whole posterior surface of Descemet's membrane was studded with warts. The corneal sensitivity was normal. The intraocular pressure was normal to palpa-

tion. The fundus was seen very indistinctly, apparently due to the condition of extreme cornea guttata. Vision: right eye, 20/25; left eye, 20/20—1 with correction.

4-23-52: The condition was found to be unchanged. Fifty mg. rutin and 150 mg. ascorbic acid (rutorbin) three times a day were prescribed.

5-21-52: The patient stated that he had never seen as clearly as today. Vision and condition of cornea were unchanged.

CASE 19. SIXTY-YEAR-OLD MALE.

9-6-50: The patient complained of failing vision for the last two years, usually worse in the morning. Right eye: A faint haziness in central part of the cornea, not exceeding 5 mm. in diameter, was present. In that area, the epithelium was edematous, several small bullae were present, and the endothelium was almost completely deficient. There was cornea guttata less and less marked towards the periphery, where large patches of normal endothelium were still present. Vision: 20/200 with correction. Left eye: The same condition, slightly less developed, was present. Vision: 20/100 with correction.

10-26-50: Right eye: a round, penetrating corneal graft, 7.5 mm. in diameter, was done, using a cornea received by the eye bank from a forty-eight-year-old donor who died from uremia and diabetes mellitus. The graft was held in place with eight edge-to-edge sutures. There was an uneventful postoperative course. Cortisone was used topically from the fourteenth postoperative day on.

2-7-51: Right eye: the graft was perfectly clear. Vision: with +5.00 Sphere, —6.00 Cyl. Axis 155=20/20. Cortisone in both eyes was continued.

11-7-51: Right eye: the graft was clear. Vision 20/20 with correction. Left eye: The corneal dystrophy had increased. The epithelium was edematous, numerous bullae were present. Vision: 20/400 with correction. After hot-air application for five minutes, the cornea was much clearer and vision was 20/70 with correction.

5-12-52: Right eye: Nineteen months after keratoplasty, the graft was perfectly clear. The endothelial cells could be seen but they had a shriveled appearance, with several dark dots within the mosaic texture. These dots, however, did not seem to correspond to warts, but rather appeared to have been produced by the degeneration of some cells without wart formation. There were a few cortical opacities in the lens. Vision: 20/30 with correction. Left eye: the dystrophy had increased. Vision: 10/400 with correction. The patient stated that he used hot-air treatment regularly in the morning. This eliminated the blurring effect on the vision of the left eye for several hours. He also thought he saw better when using cortisone regularly in the left eye.

8-12-52: Twenty-two months after keratoplasty the graft of the right eye was still perfectly clear, vision 20/30 with correction.

CASE 20. SIXTY-FIVE-YEAR-OLD FEMALE:

6-29-44: Vision 20/20 with correction in each eye. No changes in either cornea were noted.

1-12-49: Right eye: cornea guttata and beginning nuclear cataract were present. Vision 20/30 with correction. Intraocular pressure 19 mm. Hg (Schiötz). Left eye: There was endothelial and epithelial dystrophy with edema of the corneal epithelium and beginning nuclear cataract. Vision 20/200; glasses did not improve. Intraocular pressure: 23 mm. Hg (Schiötz). One percent pilocarpine three times a day in each eye, 2 percent saline solution every three hours in each eye, and hesperidin-methyl-chalcone (50 mg.) three times a day, were prescribed.

5-7-49: The patient returned with a history of severe pain in both eyes and gradual loss of vision for the past three days. Diagnosis: bilateral subacute congestive glaucoma. The intraocular pressure was +2 to palpation.

5-19-49: Left eye: a posterior sclerotomy and 70 cyclodiathermy punctures were done.

5-24-49: Right eye: a posterior sclerotomy and combined Lagrange sclerectomy and iridencleisis were done.

6-3-49: Intraocular pressure: right eye, 11; left eye, 30 mm. Hg (Schiötz). Severe bullous keratitis gradually developed in both eyes. On 1 percent cortisone drops topically it improved temporarily for several months, but an almost complete opacification of both corneas had developed when seen last on 4-28-52.

CASE 21. FIFTY-FOUR-YEAR-OLD FEMALE.

9-26-45: Both eyes showed typical epithelial and endothelial dystrophy with edema of epithelium and stroma. The endothelium was not distinguishable. It was impossible to determine whether there was cornea guttata or not. Vision: right eye, 5/200; left eye, 2/200. Intraocular pressure: 14 mm. Hg (Schiötz) in both eyes. Vitamin A (50,000 units) orally and vitamin A and D ointment locally were prescribed.

10-17-45: The patient felt subjectively better. Vision: right eye, 10/100; left eye, 5/100.

11-13-45: An Elliott trephine was performed on the left eye.

12-7-45: The cornea of the left eye was definitely clearer; the intraocular pressure was lower than in the right eye to palpation.

2-21-46: The condition was worse in both eyes. Rutin, 50 mg. three times a day, was prescribed.

6-26-46: The patient stated she felt better since she took rutin. Both corneas showed less edema.

9-7-46: Corneal edema had increased. The patient was without rutin for three weeks and was advised to take rutin again.

11-23-46: No change in condition was noted.

11-26-46: Left eye: vision, counting fingers at two feet. A 4 mm. per-

forating corneal transplant was done. There was a partial displacement of the graft in the postoperative course which, however, adjusted itself gradually.

2-27-47: Left eye: the transplant was partly clear, but seemed to become cloudy from the nasal side, where originally it had been displaced. Vision: 5/100. Right eye: bullous keratitis had developed. Hesperidin-methyl-chalcone, 50 mg. three times a day, was prescribed.

9-4-48: The condition was unchanged. The patient thought she did better with rutin than with hesperidin. Two percent saline solution every three hours in each eye was prescribed.

10-4-49: The condition had become worse in both eyes. Five percent saline was prescribed.

9-5-50: When last seen, the corneal graft of the left eye was almost completely opaque; however, it did not show as much bullous keratitis as the right eye.

CASE 22. FORTY-SIX-YEAR-OLD FEMALE.

9-29-47: The patient complained of slightly hazy vision. Both eyes: vision 20/25+ with correction. Extreme cornea guttata was present in both eyes. The endothelium was almost completely absent in the central parts. Towards the periphery patches of endothelium were visible. The corneal stroma was slightly hazy; no edema of epithelium or bullae formation was present. Rutin, 50 mg. three times a day, was prescribed.

1-2-48: The corneal stroma was slightly clearer.

10-25-50: The full picture of endothelial and epithelial dystrophy had developed in both eyes. Edema of corneal epithelium and some bullae were present. Vision: right eye, 20/40; left eye, 20/30 with correction. The patient stated that vision was worse in the morning than in the afternoon. One percent cortisone every two hours in both eyes was prescribed.

10-27-50: The condition had greatly improved. No bullae were seen.

12-13-50: No epithelial edema and no bullae formation were present. The cornea guttata had extended far out towards the periphery; very few endothelial cells remained. Pigment dust was noted on the posterior surface of both corneas.

4-30-51: The condition was unchanged.

CASE 23. SIXTY-TWO-YEAR-OLD FEMALE.

5-30-44: Right eye: the corneal epithelium and stroma were edematous. The endothelium was almost completely degenerated in the central area. Vision: 20/70 with correction. Intraocular pressure, 17 mm. Hg (Schiötz). Left eye: the epithelium was normal. There was a beginning degeneration of the endothelium in the center. The fundus was normal. Intraocular pressure: 17 mm. Hg (Schiötz).

Diagnosis: Epithelial and endothelial dystrophy in the right eye and beginning in the left eye. Two percent pilocarpine three times a day in right eye was prescribed.

Gradually, severe bullous keratitis of the right eye developed, with ulceration and intractable pain, for which the right eye was enucleated on 7-2-46. The dystrophy progressed gradually in the left eye and had developed into a vascularized leucoma when last seen on 3-29-50.

CASE 24. FIFTY-EIGHT-YEAR-OLD FEMALE.

12-7-50: Both eyes: considerable cornea guttata was present, mostly in center, where the endothelium seemed to be completely degenerated. There were a few instances of slight cloudiness in front of Descemet's membrane. These areas corresponded to the places where the endothelium was absent (early penetration of fluid.)

CASE 25. FORTY-NINE-YEAR-OLD FEMALE.

11-22-48: Fully developed endothelial and epithelial dystrophy was noted in both eyes. There was edema of epithelium and stroma and extreme cornea guttata. Vision: 20/40 with correction in both eyes. Hesperidin-methyl-chalcone, 50 mg. three times a day, was prescribed.

12-29-48: No change in the condition of either eye was noted after one month of hesperidin. Blood pressure: 196/128.

4-6-49: Both corneas seemed slightly improved, less edematous. Vision: right eye, 20/40; left eye, 20/30 with correction.

6-29-49: Two percent saline drops locally every four hours, in addition to rutorbin three times a day, were prescribed.

7-29-50: The condition was worse in both eyes, with marked epithelial edema and bullae formation.

1-13-51: Vision: right eye, 20/100; left eye, 20/80 with correction.

10-26-51: In spite of rutorbin and cortisone locally the dystrophy had become worse in both eyes. Right eye: large epithelial bullae were present in the center. No endothelia were seen in the central area. Towards the periphery some indication of an endothelial pattern could be seen, together with marked cornea guttata. The corneal sensitivity was much reduced. The vision varied between 20/200 and 20/60 and was worse in the morning. Left eye: no bullae formation, but marked edema of epithelium and stroma in the central part of cornea was present. Marked cornea guttata in center, but large patches of normal endothelium could be seen towards the periphery. The corneal sensitivity was slightly reduced. Vision varied between 20/200 and 20/40.

12-5-51: Since it was noted that the really diseased part of the cornea did not exceed 7 mm. in diameter, a 9 mm. perforating graft was done in order to eliminate most of the actually diseased part. The graft was held in place by nine edge-to-edge sutures, using Grieshaber needles. The anterior chamber was filled with air. Pilocarpine and eserine

ointments were instilled. Postoperative course: the graft stayed clear until the seventh day, when a slight haziness appeared. One-half percent cortisone was applied every four hours, whereupon the graft cleared up rapidly. Three weeks after the operation, a slight bulge of the graft appeared in the lower outer quadrant. This was apparently due to swelling of the graft rather than to dislocation. The intraocular pressure was not elevated. On pressure bandage, cortisone, and miotics, the bulge gradually subsided.

1-14-52: The graft was perfectly clear, the endothelial pattern clearly visible. There were several small bullae on the small ring of the host's cornea surrounding the graft, no bullae and no epithelial edema on the graft. Vision: 20/20—1 with correction.

5-2-52: Right eye: the graft was clear, the pattern of the endothelium somewhat indistinct. There were numerous black dots in the endothelium, possibly indicating slight vacuolization. No signs of cornea guttata were present. Corneal sensitivity was absent. The intraocular pressure was rather low, but normal to palpation. Vision: 20/20—1 with correction.

11-7-52: Right eye: the graft was perfectly clear. The corneal sensitivity had returned to a low degree. Vision: 20/20—1 with correction.

CASE 26. SIXTY-THREE-YEAR-OLD FEMALE.

6-14-43: Both eyes showed cornea guttata in the central parts, beginning nuclear cataract, and gyrate atrophy of choroid. Vision: right eye, 20/50; left eye, 20/25 with correction.

8-22-45: The cataract in both eyes had increased. Vision: right eye, 20/80; left eye, 20/50 with correction. The patient could not read regular print with either eye. Cataract extraction of the right eye was advised with guarded prognosis.

9-18-45: An uneventful intracapsular cataract extraction with peripheral iridectomy was done on the right eye.

11-14-45: Right eye: well healed. Vision 20/40 with correction.

1-8-46: Right eye: edema of corneal epithelium and cloudiness of stroma had developed. Vision: 20/200 with correction. Vitamin A and D ointment was prescribed.

5-27-46: Right eye: the cornea was much clearer. Vision: 20/70 with correction.

4-30-47: The condition was unchanged. Rutin, 100 mg. three times a day, was prescribed.

12-7-48: The right cornea was much improved. No edema was present. Vision: 20/40 with correction.

6-16-49: The patient had not taken rutin recently. The cornea of the right eye showed marked edema again. Vision: 20/100 with correction. Left eye: cornea guttata, but no epithelial edema, was present. Rutorbin (rutin and ascorbic acid) was prescribed.

CASE 27. FIFTY-EIGHT-YEAR-OLD FEMALE.

10-31-49: Right eye: status after extracapsular cataract extraction, done elsewhere, was present. Left eye: a slightly hypermature cataract was found. Both eyes showed a moderate degree of cornea guttata.

11-8-49: An intracapsular extraction of the cataract, using the erysiphake, was done in the left eye. No complications occurred.

11-21-49: On discharge marked striate keratitis was present in the left eye.

11-26-49: The left eye was more irritated and bullous keratitis had developed in addition to the striate keratitis still present. Atropine and warm compresses locally and sodium salicylate internally were prescribed.

12-5-49: Left eye: no epithelial bullae were found, but there were still some folds in Descemet's membrane.

12-28-49: Left eye: the cornea was clear and the cornea guttata about as before the operation. Vision: 20/30 with correction.

CASE 28. FIFTY-NINE-YEAR-OLD FEMALE.

10-3-46: Advanced nuclear cataract of the right eye; beginning of the left eye was present. Both corneas were clear and did not show cornea guttata.

10-4-46: An uneventful intracapsular cataract extraction with peripheral iridectomy was done on the right eye. No vitreous was lost. On the third postoperative day a severe anterior chamber hemorrhage occurred. Later, secondary glaucoma developed; it was treated conservatively with miotics and finally was controlled.

10-15-47: Right eye: edema of the corneal epithelium and stroma had developed in the upper part.

4-13-49: Although the intraocular pressure had been kept between 17 and 30 mm. Hg, the edema gradually extended downwards toward the center. Sixty mg. rutin and 300 mg. ascorbic acid (rutorbin) three times a day were prescribed.

5-18-49: Left eye: the corneal edema had retracted upwards.

6-22-49: The condition was satisfactory.

8-8-49: Left eye: The corneal dystrophy had extended again. Intraocular pressure was 16 mm. Hg (Schiötz).

CASE 29. SIXTY-SEVEN-YEAR-OLD FEMALE.

2-6-45: Diagnosis: bilateral nuclear cataract. Both corneas were clear.

5-29-47: An extracapsular combined cataract extraction was done on the right eye. Considerable striate keratitis was present for several days.

11-5-47: Right eye: the lens material was mostly absorbed. Some cloudiness in the vitreous was present. Edema of the corneal epithelium had developed. Intraocular pressure was normal to palpation. Vision: 20/200 with correction. One hundred mg. rutin three times a day and vitamin A and D ointment were prescribed.

12-18-47: The right cornea was much clearer.

6-8-48: Right eye: no edema of corneal epithelium was present. Rutin was discontinued.

12-8-48: Right eye: there was considerable corneal edema again. Two percent saline solution every three hours was prescribed.

2-10-49: When seen before treatment there was corneal edema in the right eye. One hour after 2 percent saline the epithelial edema had disappeared.

1-17-51: Right eye: considerable edema of corneal epithelium and bullae were present. One and one-half percent cortisone locally every three hours was prescribed.

6-13-51: Right eye: no bullae, but some corneal edema was seen. Left eye: the corneal endothelium was normal. No cornea guttata, only an occasional Henle's wart toward the periphery was seen.

CASE 30. FIFTY-SIX-YEAR-OLD MALE.

3-17-50: Diagnosis: Right eye: mature cataract. Vision, hand movements and good light projection. Left eye: beginning cataract. Vision 20/30 with correction. Neither cornea showed cornea guttata.

5-4-50: Right eye: a combined extracapsular cataract extraction was done. A small amount of vitreous was lost. The patient had several anterior chamber hemorrhages during the first postoperative week.

9-7-50: Right eye: vision 20/20— with correction.

10-30-51: Right eye: the corneal epithelium and stroma was edematous. The endothelium could be seen only faintly. It showed an indistinct pattern, the outlines of the individual cells being hardly recognizable. There were no warts on Descemet's membrane. Vision: 20/200 with correction. After instillation of glycerine the epithelial edema cleared up and vision improved to 20/40 temporarily. Left eye: no cornea guttata was found. Intraocular pressure was 18 mm. Hg (Schiötz) in both eyes. Sixty mg. rutin and 200 mg. ascorbic acid (rutorbin) three times a day were prescribed.

11-14-51: Right eye: the condition had become worse. Vision 10/400. After hot-air treatment the cornea cleared up and vision was improved to 20/40. This treatment was continued. The vision stayed quite clear for about one hour and stayed somewhat clearer for the rest of the day. The next morning the condition was again as before.

4-2-52: The condition of the right eye had considerably improved. Vision: 20/70—1 with correction.

6-2-52: The patient had not used either heat or cortisone. Right eye: the cornea was very cloudy. Vision 20/400.

7-2-52: Right eye: epithelial bullae had formed.

11-21-52: Right eye: bullous keratitis was present. Vision 10/400. A total lamellar graft, 10 mm. in diameter, was done. The postoperative

course was uneventful, with the graft being fairly clear. The patient was still in the hospital when the record was closed.

CASE 31. SIXTY-NINE-YEAR-OLD FEMALE.

4-30-51: The patient was admitted with the diagnosis of bilateral nuclear cataract. Neither eye showed cornea guttata. Vision: right, 20/40; left, 20/200 with correction.

5-1-51: An intracapsular cataract extraction with round pupil was done on the left eye. No vitreous was lost. The postoperative course was uneventful except for a marked striate keratitis.

7-18-51: Left eye: a vitreous hernia was touching the upper part of the cornea. There was epithelial edema and cloudiness of the stroma in that area.

7-19-51: Left eye: air was injected into the anterior chamber and the vitreous hernia separated from the cornea.

4-9-52: Left eye: the cornea was clear. The endothelium in the upper part was partly of normal appearance, partly shriveled. No excrescences on Descemet's membrane were present. The intraocular pressure was normal to palpation, slightly lower than that of the right eye. There was a hole in the macula which accounted for the poor vision of 20/200.

CASE 32. FORTY-EIGHT-YEAR-OLD MALE.

1-24-52: Left eye: an intracapsular cataract extraction was performed.

2-5-52: A large vitreous hernia was touching the posterior surface of the cornea of the operated eye.

2-20-52: The vitreous hernia was still touching the cornea.

3-5-52: Left eye: the vitreous hernia no longer touched the cornea. The endothelium was perfectly normal. Vision 20/20 with correction.

CASE 33. SEVENTY-THREE-YEAR-OLD FEMALE.

9-27-51: Right eye: an intracapsular cataract extraction was done. The postoperative course was uneventful until 11-9-51.

11-9-51: Right eye:pain and pericorneal injection were noted. A huge vitreous hernia had invaded the anterior chamber and was in direct contact with the posterior surface of the cornea. The intraocular pressure was 19 mm. Hg (Schiötz).

11-13-51: Right eye: the intraocular pressure was 38 mm. Hg. One drop of DFP was instilled. Ever since the intraocular pressure has remained normal.

12-7-51: Right eye: the cornea was clear, the endothelium of normal appearance. The vitreous hernia still was touching the cornea. The intraocular pressure was 19 mm. Hg (Schiötz).

CASE 34. SEVENTY-THREE-YEAR-OLD FEMALE.

5-29-52: Diagnosis: choroidal melanoma of the right eye. Both eyes showed marked cornea guttata. The right eye was enucleated. The

cornea was immediately excised and treated in the following way:
1. Part of the cornea was put into 10 percent formalin. After fixation a flat section of Descemet's membrane and endothelium was prepared, stained with hematoxylin and photographed (Figure 21).
2. The other part of the cornea was freshly stained with 1 percent alizarin red and examined under the microscope without fixation (see p. 708).

CASE 35. SEVENTY-TWO-YEAR-OLD MALE.

10-30-46: The patient gave a history of herpetic eruptions on the lids and the cornea of the left eye years ago. The left eye had been painful for the last few days. There was ciliary irritation, edema of the corneal epithelium in the center, a slight cloudiness of the stroma in the center, and bedewing of the posterior surface of the cornea. Intraocular pressure was 16 mm. Hg (Schiötz). Under salicylate, atropine, and heat treatment, the infiltration of the cornea and the ciliary injection subsided.

1-27-50: Bullous keratitis of the left eye had developed with edema of the corneal stroma.

Impression: bullous keratitis on the basis of previous keratitis metaherpetica.

CASE 36. SIXTY-SIX-YEAR-OLD FEMALE.

2-17-45: Diagnosis: advanced nuclear cataract of right eye, beginning of left eye. Both corneas were clear.

5-6-47: Right eye: an extracapsular cataract extraction with peripheral iridectomy was done. The postoperative course was uneventful.

5-18-47: Right eye: without irritation but there was some striate keratitis.

6-23-47: Right eye: vision 20/30+ with correction.

11-22-47: The patient reported having had a severe attack of malaria, and that she had not seen so well since. Vision: right eye, 20/80 with correction.

9-7-48: Both eyes showed moderate amount of cornea guttata. Cataract of the left eye had matured. Vision of left eye reduced to 10/400.

10-20-49: A combined intracapsular extraction of the cataract of the left eye was done.

11-14-49: A slight postoperative anterior chamber hemorrhage was still present.

12-5-49: Left eye: the hemorrhage had absorbed. Vision 20/30 with correction.

2-24-51: Right eye: severe bullous keratitis with edema of the corneal stroma was present. The corneal endothelium was indistinguishable. The intraocular pressure was 15 mm. Hg (Schiötz). Vision: counting fingers at two feet. Left eye: normal except for moderate cornea guttata. Vision: 20/20 with correction.

3-13-52: There was no change in the condition of either eye. Hot-air application to the right eye made the epithelial bullae disappear, but the vision was not definitely improved.

CASE 37. SEVENTY-TWO-YEAR-OLD FEMALE.

8-2-45: An intracapsular cataract extraction with peripheral iridectomy was done on the right eye. There was no loss of vitreous, but its presence in the anterior chamber was suspected, as the chamber suddenly became very deep while the sutures were tied. An almost complete combined detachment of the choroid and retina with no fundus reflex was still present when the patient was discharged from the hospital on the nineteenth postoperative day.

9-8-45: Right eye: the choroid was completely reattached, but the optic disc appeared to be definitely paler than in the left eye. Vision 20/300 with correction. The intraocular pressure was 16 mm. Hg (Schiötz).

10-29-47: Right eye: the pupil seemed to be slightly displaced upward. No vitreous was noted in the anterior chamber. The intraocular pressure was 35 mm. Hg (Schiötz). Two percent pilocarpine drops three times a day were prescribed.

12-17-47: Right eye: the corneal epithelium was edematous and some epithelial bullae were present. The stroma was hazy. The endothelium could not be visualized. The intraocular pressure was 27 mm. Hg (Schiötz). Left eye: a very low degree of cornea guttata was present. During the further course of the secondary glaucoma the patient consistently refused any operation. The intraocular pressure was, however, fairly well controlled by 10 percent furmethide.

10-4-50: Right eye: the corneal dystrophy had further developed. An ulcer was present near the lower limbus. Vitamin A and D ointment was prescribed.

11-15-50: There was no change in the condition. The treatment was changed to 2.5 percent cortisone drops every two hours.

11-17-50: The patient felt much more comfortable. The cornea of the right eye was clearer.

12-6-50: The right eye had suddenly become very painful the day before. The ulcer had perforated. Iris, and possibly vitreous, was prolapsed.

12-8-50: The right eye was enucleated.

CASE 38. FIFTY-YEAR-OLD MALE.

7-11:51: This patient had been refracted several times since 1946. Never were any changes noted in either cornea. Recently he complained about blurriness of vision in the left eye. Right eye: normal. Vision 20/20 with correction. Left eye: vision 20/30 with correction. Slightly below the center the cornea showed a row of bullae protruding from the posterior surface towards the anterior chamber. The endo-

thelial pattern could be followed over the concavity of some of these vesicles.

8-1-51: Some of the vesicles had burst, leaving a hole in the endothelial pattern. There were no warts on Descemet's membrane.

3-27-52: The formerly noticed vesicles of the corneal endothelium of the left eye had enlarged and partly merged into larger bullae. In addition, a new row of smaller bullae could now be seen a little below the first lesion.

CASE 39. SIXTY-YEAR-OLD FEMALE.

6-14-50: This patient gave a history of severe inflammation of the right eye at the age of eight, and of the left eye at age of sixteen; probably interstitial keratitis. The Wassermann test of the blood was negative. Both eyes showed diffuse corneal opacities, mostly close to Descemet's membrane, with numerous ghost vessels. No edema of epithelium or stroma was present. The corneal endothelium was very irregular. In some places there was an almost normal pattern, in others the endothelial cells were several times the size of normal cells with large intercellular spaces. There were also areas in which the endothelial cells seemed to have completely degenerated. Vision: right eye 20/50, left eye 20/50—2 with correction.

1-20-51: Right eye: there was no edema of the epithelium, and the condition in general was as previously noted. Left eye: the corneal epithelium was edematous and there was bullae formation in the center. The stroma was permeated with fluid and thickened. The patient was unable to read even largest print with the left eye. Two and a half percent cortisone drops every three hours were prescribed.

1-24-51: The left eye was definitely improved, bullae were fewer and smaller, and the stroma clearer. Intraocular pressure was right eye 16, left eye 19 mm. Hg (Schiötz).

2-10-51: No epithelial bullae were present in either eye.

4-30-51: Left eye: bullae of the corneal epithelium had appeared again. Five percent saline solution every four hours was prescribed.

6-15-51: Left eye: vision 20/400. There was no improvement. One hundred mg. rutin and 200 mg. ascorbic acid (rutorbin) three times a day were prescribed.

7-13-51: There was no change in the condition.

12-10-51: Left eye: vision 5/200. After hot air had been applied for five minutes the epithelial bullae had disappeared, but vision remained unchanged.

3-10-52: The patient had considerable discomfort in the left eye. The corneal sensitivity was markedly reduced as compared with the right eye.

4-26-52: Left eye: under local novocaine anesthesia, a 9 mm. perforating corneal graft was done. Four peripheral iridectomies, at 1:30, 4:30,

7:30, and 10:30 o'clock, were done and the graft held in place by eight edge-to-edge sutures. A perfect adaptation was obtained. Beginning on the seventh postoperative day cortisone ointment was administered morning and night. On the twelfth day half of the sutures were removed, the rest on the fourteenth day.

5-12-52: The graft was clear except for some striate keratitis. The endothelium of the graft appeared to be in good condition.

5-16-52: Left eye: vision was 20/40+ with correction. The graft was perfectly clear. The endothelium had regained almost normal appearance.

6-9-52: Left eye: there was considerable irritation. The corneal graft was edematous in its lower part, Descemet's membrane was wavy. The intraocular pressure was not elevated to palpation. The patient was admitted to the hospital and treated with chloromycetin, cortisone, intravenous ACTH, and at last with fever (typhoid vaccine), but the whole cornea became cloudy and edematous.

7-8-52: After the second course of fever the left cornea began to clear.

7-10-52: The upper part of the left cornea was considerably clearer. Vision 20/100. Cortisone ointment four times a day was prescribed.

8-4-52: Left eye: the upper part of the cornea was quite clear and showed an almost normal endothelium pattern. The lower part was still somewhat edematous but less thick, and Descemet's membrane was less wavy. Vision: 20/30 with correction. The patient was advised to continue cortisone ointment.

10-17-52: Left eye: the edema of the lower part of the graft had disappeared. The whole graft was quite clear and vision 20/30 with correction.

CASE 40. FIFTY-SIX-YEAR-OLD FEMALE.

11-3-48: This patient presented the picture of a bilateral granulomatous iridocyclitis. A thorough physical examination and extensive laboratory studies were done in order to determine the etiology. Skin tests with tuberculin were negative up to 1:1000 dilution; Kahn negative; blood chemistry essentially normal, including normal albumin–globulin ratio. Because of the presence of large masses in the mediastinum and the course of the eye condition, Boeck's sarcoid was accepted as the most probable etiology.

In the long course of the disease following long-standing fatty keratic precipitates, a band keratitis of the left eye developed. Especially on the lower half of the posterior surface of the cornea, the endothelium appeared to be completely degenerated in some parts. Over these areas epithelial edema and later a whitish subepithelial opacity developed. In the lower part of the cornea dense vascularized scar tissue developed in front of Descemet's membrane. In that area there were no epithelial changes. This condition prevailed when last seen on 7-9-52.

CASE 41. SEVENTY-TWO-YEAR-OLD FEMALE.

10-5-50: Diagnosis: sympathetic ophthalmia of left eye after cataract extraction of right eye, done elsewhere. Left eye: no edema of epithelium, but cloudiness of stroma was present. Dense deposits were seen on the posterior surface of the cornea. Floating particles and increased flare of aqueous were present. The iris could be seen only faintly, but apparently there were several posterior synechiae. Atropine and warm compresses were administered.

10-10-50: In the lower part of the cornea epithelial bullae had developed. Local and systemic cortisone treatment was instituted.

10-21-50: Left eye: white and quiet. No corneal epithelial bullae could be seen any more.

1-19-51: Cortisone was discontinued.

4-3-51: Left eye: in the lower part of the cornea there was again edema of the epithelium with bullae formation. In that area extensive pigment deposits were seen on the posterior surface of the cornea, together with a layer of partly absorbed confluent precipitates. The endothelial pattern could not be visualized and the stroma was succulent in this part of the cornea. No warts on Descemet's membrane were present. In the upper part of the cornea there was no edema of the epithelium and the endothelial pattern was practically normal. Local cortisone treatment was resumed.

4-10-51: The left eye was much improved. The cornea was clearer.

5-11-51: There was no edema of the epithelium and no bullae could be seen.

CASE 42. SIXTY-TWO-YEAR-OLD FEMALE. This patient was followed since 9-6-45 for a recurrent iridocyclitis of the right eye.

6-29-51: The right eye was white and quiet. There were large patches, corresponding to the site of long-standing keratic precipitates, where the endothelium was completely degenerated and no pattern was recognizable. Yet there was no edema of either stroma or epithelium. No excrescences on Descemet's membrane were noted. Vision: 20/20 with correction.

CASE 43. FORTY-EIGHT-YEAR-OLD FEMALE.

8-21-46: The patient showed the picture of bilateral healed interstitial keratitis. There were some circumscribed intraepithelial and subepithelial opacities and diffuse cloudiness of the stroma (infiltration with fluid). A peculiar network of stripes was present in and in front of Descemet's membrane, probably representing old ghost vessels and defects in Descemet's membrane. The endothelium was irregular and diseased in the center, but fairly well preserved in the periphery. Treatment with local cortisone every three hours was instituted. The Wassermann test was weakly positive.

3-22-51: The patient felt subjectively better.

4-25-51: The corneal stroma was clearer.

7-19-51: Neither cornea appeared to be succulent. The treatment with cortisone was continued.

9-15-51: Right eye: a filamentous keratitis had developed. Cortisone was discontinued, and methyl cellulose drops four times a day were prescribed.

9-19-51: When last seen, no filaments were present on the cornea of the right eye.

CASE 44. SEVENTY-EIGHT-YEAR-OLD MALE. The patient had a history of recurrent iritis of the right eye since 1939.

10-30-50: The right eye was white and quiet. In the temporal part of the cornea, there was some epithelial edema and haziness of the stroma. In that place, there were several areas in which the endothelium was absent. All over, there was considerable cornea guttata. Left eye: the cornea was clear. Only moderate cornea guttata was present. Methyl cellulose drops were prescribed.

1-13-51: The right cornea was somewhat clearer.

5-2-52: The right cornea was without edema.

CASE 45. FORTY-YEAR-OLD FEMALE.

12-8-43: This patient has two brothers and one sister who are afflicted by the same condition. The mother was reported to have had it, too. Both eyes were white and quiet. There were numerous crumb-like whitish opacities scattered all over the cornea, but more thickly in the central parts. The superficial layers of the cornea were predominantly affected. In some places the lesions were bulging over the surface of the cornea. Vision was 20/200 with correction in both eyes. Diagnosis: bilateral granular corneal dystrophy (Groenouw).

2-16-46: Left eye: vision 20/400. A 5 mm. perforating corneal graft was done. During the first postoperative period the graft remained fairly clear.

5-8-46: The graft was slightly hazy due to edema of stroma and epithelium. The endothelium could not be visualized.

10-10-47: There was no change in the condition. One hundred mg. rutin three times a day was prescribed.

11-17-47: Left eye: the epithelium was much less edematous, the cornea clearer.

5-17-51: The condition was worse again. The graft of the left eye was edematous, thicker than the surrounding cornea. Local application of cortisone was prescribed.

8-2-52: The condition was unchanged.

CASE 46. TWENTY-SEVEN-YEAR-OLD FEMALE.

3-23-49: Diagnosis: bilateral keratoconus. Vision was 10/400 in both

eyes. Contact lenses improved vision in the right eye to 20/80, in the left eye to 20/70, but the patient was unable to wear them for any length of time. Even without them the eyes stayed irritated.

4-5-49: Left eye: a 5.5 mm. perforating corneal graft was done.

5-26-52: When last seen, the graft of the left eye was perfectly clear and vision 20/20 with correction. A definite continuity of corneal nerves of the host cornea with branches in the graft could be observed. The corneal sensitivity of the graft was present but somewhat reduced as compared with the right eye. The graft showed a perfectly normal endothelial pattern.

CASE 47. THIRTY-THREE-YEAR-OLD MALE.

9-19-51: This patient gave a history of corneal transplant for keratoconus one and a half years ago, done elsewhere, in the right eye. Right eye: a fairly clear 5.5 mm. corneal graft could be distinguished. There were some opacities in Descemet's membrane. The endothelium of the graft was irregular; some cells were much larger than others. In some places it was not recognizable. Some opacities in Descemet's membrane seemed to correspond to the areas of degeneration of the endothelium. No actual edema of stroma or epithelium was present. Vision: 20/40 with correction. Left eye: advanced keratoconus. Vision: counting fingers.

CASE 48. SIXTY-NINE-YEAR-OLD FEMALE.

6-5-50: Right eye: there was an advanced granular corneal dystrophy (Groenouw). The fundus could not be seen. Vision: counting fingers at two feet. Left eye: a square corneal graft had been done elsewhere five years ago. The graft was not clear but translucent. The surrounding cornea showed the same condition as the right eye (granular dystrophy). There was an anterior capsular cataract. Vision: counting fingers at five feet.

6-8-50: Right eye: a 5.5 mm. perforating circular corneal graft was done. The immediate postoperative course was uneventful.

6-21-50: Right eye: the corneal stitches were removed. The graft was well adapted but only fairly clear. With the slit lamp a delicate membrane was seen to protrude from the graft into the anterior chamber and to float therein. It was considered to be the detached endothelium.

9-30-50: The graft was edematous and thickened, and epithelial bullae were present. The endothelial membrane had disappeared. After local cortisone therapy was instituted the epithelial bullae disappeared, but the corneal edema persisted.

2-27-51: Right eye: a second corneal graft, 7.5 mm. in diameter, excising the diseased first graft within the host's tissue, was done. Fifteen edge-to-edge corneal sutures were inserted to hold the graft in place. The histologic examination of the first graft revealed complete absence

of endothelium and the presence of numerous warts on Descemet's membrane (cornea guttata). The postoperative course was uneventful, and the graft stayed perfectly clear until 3-12-51, the seventeenth postoperative day, when the patient fell in the bathroom and hit the right eye against the wash basin. The graft had been dislocated completely except for a small area below, and the lens was expelled through the corneal opening. After an iridectomy had been done, the graft was sutured into place and covered with a reversed conjunctival flap.

5-3-51: When last seen, the graft had healed in and was partly clear. A staphyloma developed, however, and the intraocular pressure was elevated. Vision was hand movements.

CASE 49. SIXTY-EIGHT-YEAR-OLD FEMALE.

8-23-50: The patient had had bilateral cataract extraction elsewhere. Right eye: marked cornea guttata with edema of the stroma and epithelium was present. Intraocular pressure was 38 mm. Hg (Schiötz). Left eye: cornea guttata, but no involvement of the stroma and epithelium, was present. Intraocular pressure was 16 mm. Hg (Schiötz).

Impression: Second stage of endothelial and epithelial dystrophy of the right eye, first stage of the same condition of the left eye. The patient was treated with miotics and cortisone for several months. After an initial improvement a severe bullous keratitis developed in the right eye.

8-28-52: Right eye: vision was counting fingers. There was considerable edema of the epithelium with formation of bullae. The patient was unable to open the eye. Vision was finger movements and good light projection.

8-29-52: Right eye: a total lamellar graft, 10 mm. in diameter, was done and the graft sutured into place with twelve edge-to-edge sutures. A cyclodialysis was done in the lower temporal quadrant.

9-11-52: Right eye: the intraocular pressure was found to be within normal limits to palpation. The epithelium of the graft was smooth. There were some clefts filled with fluid between the host's cornea and the graft. The patient was discharged with 1.5 percent cortisone ointment four times a day.

10-11-52: The patient showed considerable irritation and conjunctival discharge of the right eye. The culture showed gram positive cocci. Under combined local treatment with cortisone and chloromycetin, this condition cleared up within four days.

10-30-52: Right eye: white and quiet. The corneal epithelium was smooth. The clefts between the graft and the host's cornea were fewer and smaller. The vascularization had diminished. There was fairly good fundus reflex, but no details could be seen. The intraocular pressure was within normal limits to palpation. Vision was counting fingers at two feet, or 5/400.

11-26-52: When last seen, the corneal epithelium of the right eye was not edematous, and the graft was fairly clear. Vision: 10/400.

CASE 50. SIXTY-ONE-YEAR-OLD FEMALE.

7-3-44: The patient was seen for refraction review. No pathology was noted.

1-10-52: Left eye: acute glaucoma with intraocular pressure 36 mm. Hg (Schiötz) was diagnosed. After the edema of the corneal epithelium had cleared a peculiar pattern of the endothelium was seen. Each cell appeared as a small droplet approximating the appearance of cornea guttata, only that the individual droplet was much smaller. This was most probably edema of the endothelium.

CASE 51. TWENTY-SIX-YEAR-OLD MALE.

1-10-52: Both eyes were injured by a mine explosion in 1944, during the war. The left eye was lost. Right eye: several scars were present in the cornea, one perforating in center. In this central area the endothelium had a shriveled appearance, with black holes in the pattern. No excrescences on Descemet's membrane were seen with the narrow beam of the slit lamp.

APPENDIX B

HISTOLOGIC TECHNIQUES FOR FLAT PREPARATIONS OF CORNEAL ENDOTHELIUM

THE USE OF MERCURY-BICHLORIDE FIXATION. TECHNIQUE MODIFIED AFTER NAGANO

This technique is only applied to rabbit eyes, not to humans.

After the animal has been killed the eye is sectioned at the equator. A stripe about 3 or 4 mm. wide containing the site of interest is cut through the ciliary body of one side and cornea and ciliary body of the opposite side. The ciliary part of this stripe is grasped with a forceps such as is used for intracapsular cataract extraction, while the scleral part is held with any ordinary forceps. When the ciliary body is pulled from the sclera, Descemet's membrane, together with the endothelium, follows and is detached from the stroma of the cornea. After the whole stripe of Descemet's membrane has been separated a small piece, presumably containing the site of interest, is cut and treated in the following way:

1. Immersed in a solution of 3 percent mercury bichloride in normal saline solution for one minute
2. Washed in tap water
3. Placed in a solution of iodine in 70 percent alcohol of dark red color for 24 hours

4. Placed in water for 24 hours, or until no iodine color is noted
5. Immersed in regular hematoxylin solution for a few seconds
6. Washed in water
7. Immersed in xylol
8. Mounted in permount

This method has the advantage that the endothelium of the cornea is the only layer of cells present in the slide. The separation of Descemet's membrane from the stroma, however, is not always easy, and a tear might occur just at the place where something (e.g., an injury) had been done experimentally.

THE USE OF FORMALIN FIXATION. OUR TECHNIQUE

This technique is applicable to both human and animal corneal tissues.

After the animal has been killed or the human eye enucleated, the whole cornea is excised at the limbus. It is then placed in 10 percent neutral or slightly alkaline formalin solution for twenty-four hours or longer. Especially with the eye of rabbits, the results are better when the excised cornea is placed in the fixating solution than when the whole eye is submerged, because post mortem changes occur very rapidly in the rabbit's corneal endothelium. A stripe of cornea about 3 or 4 mm. wide containing the site of interest is then cut. Under the dissecting microscope Descemet's membrane is loosened from the stroma with a sharp knife. It is then grasped with a capsule forceps (such as is used in intracapsular cataract extraction) and dissected from the stroma. Great care is taken not to disturb the endothelium. In order to avoid the concave shape of the membrane as much as possible, small pieces, 4 or 5 mm. in diameter, are cut and treated in the following way:

1. Washed in tap water
2. Submerged in Harris's hematoxylin (stock solution) for 10 seconds
3. Washed in water
4. Dipped in acid alcohol
5. Washed in water
6. Placed in ammonium water until blue
7. Washed in water
8. Passed quickly through 80 percent, 95 percent, and absolute alcohol
9. Passed through xylol
10. Mounted in permount

Although a disadvantage of this method is the impossibility of separating Descemet's membrane from the stroma without taking with

it a thin layer of stromal tissue, it has been adopted as the method of choice. The staining technique outlined above tends to restrict the staining to the superficial endothelial layer as much as possible.

STAINING OF THE UNFIXED TISSUE, AFTER VONWILLER

A 1 percent solution of alizarin red in normal saline is used for staining intercellular cement. The cup of the excised cornea, endothelium up, is filled with this stain. After five to ten minutes, it is washed in normal saline and examined under the microscope. Fixation in 10 percent formalin after staining may be tried, but is not always successful.

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