DYSTROPHIA ADIPOSA CORNEAE*

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INTRODUCTION

This article is intentionally detailed in respect to the review and critical consideration of the previously reported cases of dystrophia adiposa corneae, in the hope that it may serve as a reference to those who may in the future encounter and report this clinical entity. In this article we have tried to separate the doubtful from the acceptable cases. In general we are of the opinion that the incidence of dystrophia adiposa corneae is much greater than the cases reported to date would indicate; and we believe that many of these cases have not been recognized or have been diagnosed incorrectly because the picture obtained by examination with the loupe or the slit-lamp is not generally known, few pieces from pathologic areas have been excised for chemical and microscopic study, and no previous report of the subject has appeared in the English literature.

Dystrophia adiposa corneae must not be confused with secondary fatty degeneration of the cornea, a well-known and frequently described pathologic process which sometimes

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follows an inflammation of the cornea, sclera, or uveal tract. Such cases were reported by Baumgartner following sclerosing keratitis; by Engelking following keratitis parenchymatosa; by Jaensch in cases of ulcerative keratitis and herpes corneae; and by Landman following tuberculous iridocyclitis.

Dystrophia adiposa corneae is not to be confused with xanthomatosis bulbi, the term applied by von Szily to those cases in which fatty degeneration occurs in various parts of the bulb, especially in the anterior segment, following injury.

A most careful search of the literature reveals only eight undoubted cases of dystrophia adiposa corneae. These are, in chronological order, the case reports of Kamocki (Warsaw, 1893), Tertsch (Vienna, 1911), Bachstez (Vienna, 1921), Kusama (Tokio, 1921), Verderame (Turin, 1922), H. H. Elschnig (Prague, 1923), Denti (Milan, 1925), and Meyer (Freiburg, 1928).

HISTORICAL REVIEW

In 1893 W. Kamocki reported the first case of dystrophia adiposa corneae. His article was entitled "A Case of Fatty Degeneration of the Cornea with Intermittent Irritative Phenomena." The patient, a female, aged forty-two years, had had periodic attacks of smarting, burning, redness, photophobia, and lacrimation of either or both eyes. These signs and symptoms would be present for several days, and would be followed by periods of several weeks during which the eyes were apparently normal. One year previous to the examination by Kamocki the patient had noticed the appearance of white spots in the periphery of each cornea, together with a reduction in the visual acuity of each eye. Kamocki's examination revealed superficial, vascularized, chalky-white plaques which lay from 1.5 to 2 mm. from the limbus and which simulated calcium incrustations. The plaques formed an incomplete ring, and extended axially, but did not involve an area of from 4 to 5 mm. in the center of the cornea. On

examination with the loupe these plaques dissolved into many thickly crowded, dot-like opacities.

A portion of the pathologically changed cornea was removed, and the whole specimen was examined with the microscope. The white areas were seen to consist of accumulations of irregular, highly refractile granules, which, when embedded in paraffin, were dissolved by xylol. Two additional pieces from the affected area were removed subsequently and placed in Flemming's fixative. The highly refractile granules were blackened immediately. This reaction, together with the change produced by xylol, proved the fatty nature of the substance. When stained, the tissue so fixed showed an occasional mitotic figure in the epithelium; an absence of Bowman's membrane in the pathologic area; a pannus degenerativus; and markedly dilated interlamellar spaces which contained many large, vacuolated, swollen cells having a net-like structure in the protoplasm. It was Kamocki's belief that these were degenerated fat cells, and that their origin might have been the fixed corneal corpuscles.

Tertsch considered that Kamocki's case was one of keratitis neuroparalytica. It is difficult to understand how he reached this conclusion. Kamocki should receive credit not only for having reported the first case of dystrophia adiposa corneae, in which the diagnosis was verified by histologic examination, but also for the description of the distended, vacuolated—"foamy"—cells which he believed resembled the "Schlummerzellen"—latent cells—of Grawitz. Cells having these characteristics are now most frequently referred to as histiocytes, and were recognized as such by some of the authors of the subsequently reported cases. In our case they were present in large numbers and they play an important rôle in the defensive mechanism of the tissue. Kamocki is responsible for another statement of great importance, namely: "It is possible that a part of the various

chronic conjunctival diseases complicated by what is called calcium deposition is to be conceived as fatty degeneration of the cornea." Those who have subsequently reported such cases, including the authors of this paper, have stated that, macroscopically, some of the corneal pathologic changes present resembled calcareous deposits. Microscopic examinations of the corneas of the various cases have not, however, revealed the presence of calcium.

In 1911 R. Tertsch, under the title of "A Case of Primary Fatty Degeneration of Both Corneas," reported the second case of dystrophia adiposa corneae. The patient, a farmer, aged thirty-two years, had had recurrent attacks of ocular redness of from two to three months' duration. The interval between the attacks was approximately three months. The left eye had been affected for five years and the right eye for two years. The patient had noticed a gradual reduction in visual acuity, which became more marked after each attack of redness.

Examination of the right eyeball showed the cornea to be of normal size and curvature. The surface of the central zone was slightly uneven. An elliptic opacity, 8 mm. in size horizontally and 5 mm. vertically, was present temporally and below, but involved in large part the central portion of the cornea. The opacity was differentiated into a 2 mm. wide, dense white peripheral ring, and a less dense, but yellower, center. The opacity appeared to involve the entire thickness of the cornea, and, except for some fine gray stripes which extended toward the limbus from the peripheral edge, was sharply demarcated from the transparent cornea. When examined with a loupe, the opacity was seen to contain many somewhat large, coarse bodies. Its density prevented a view of the underlying structures. The periphery of the cornea, with the exception of many superficial and deep blood-vessels, was normal. The visible portion of the iris was normal. The anterior chamber contained apparently

normal aqueous and was of normal depth. The corneal sensitivity was reduced. The tension of the eye was normal. The left cornea showed a smaller but a similar change. This opacity in the left cornea was displaced somewhat temporally and contained a number of chalky-white dots which resembled calcium deposits.

Tertsch removed a portion of the opaque right cornea. Microscopic examination of Sudan-stained sections showed reddish-brown granules of varying sizes between and within the epithelial cells. There was an increase in the number of wandering cells in this layer; some of these contained fat-staining substances. There were no mitotic figures. Bowman's membrane was normal for short stretches only; elsewhere it was markedly altered in that it was swollen or separated into lamellae, or entirely absent; no fatty changes were seen. The spaces between the stroma lamellae, as well as the lamellae themselves, contained small and large fat globules. In some areas the stroma lamellae were swollen and in others they were markedly shrunken. Some were finely granular and others were broken up into large fragments. There was an increase in the number of nuclear elements, fixed cells, and wandering cells, in island-like areas. Some of the fixed cells contained fat-staining substances; others showed degenerative phenomena. Some of the wandering cells contained fat. Blood-vessels, surrounded by a few leukocytes, were present. There was no evidence of a round-cell infiltration. Neither hyaline nor calcium deposits were found. No mention was made of the large foamy cells (histiocytes) described by Kamocki in his case. Examination of cut sections with the polarizing microscope revealed many doubly refracting bodies in the epithelium and corneal stroma.

Tertsch stated that the disease was a dystrophy. The slow, progressive course of the disease process, the tissue destruction without evidence of old or of recent inflammation

in the form of round-cell infiltration, and the absence of young or old newly formed tissue, even though the process was of several years' duration, all favored this view. Inflammatory phenomena, consisting of circumcorneal injection, newly formed blood-vessels, and a slight increase of cellular elements in the spaces between the lamellae, were present, but these are found in other degenerative or dystrophic conditions of the cornea and frequently in a much more marked degree. Tertsch believed that the pathologic change present was a primary fatty degeneration of the cornea, the fat forming from the destruction of corneal fibrillae following intoxication of the fixed corneal cells. Supporting his belief that the process was due to local decomposition was the fact that the disease occurred in the center of each cornea of a fairly young individual whose medical history and general examination, especially that of the vascular system, were negative. Tertsch assumed that if the process were an infiltration, the fat carried through the lymph would remain deposited in the periphery of the cornea. He concluded that the pathologic process was a fatty decomposition of the corneal lamellae, the precipitating cause of which lay in some primary interference with the vital function of the cell itself.

In 1921 E. Bachstez described the third case of dystrophia adiposa corneae. His article was entitled "Fatty Degeneration of the Cornea." The patient, a male, aged thirty-six years, in 1917 had had photophobia, circumcorneal injection, and a decrease of left visual acuity. In 1919 the right eye was similarly afflicted. About six months after the onset of symptoms in the left eye and one year after their onset in the right eye the patient became aware of a small white opacity in each cornea. These opacities gradually increased in size.

In December, 1920, an ophthalmologic examination revealed an apparent bilateral exophthalmos and a bilateral circumcorneal injection. The right cornea was of normal

size and curvature, and appeared to have a normal anterior surface. There was a thick, vascularized opacity in the cornea, extending horizontally from a point about 1.5 mm. from the temporal limbus to a point beyond the center of the cornea nasally. Vertically, the opacity extended to within 2 to 3 mm. of the superior and inferior limbus. The central portion of the opacity was yellow in color, whereas the peripheral portion was gray. The affected area appeared to be located in the anterior two-thirds of the cornea. The anterior chamber, iris, and pupil were normal. The pathologic changes in the left cornea were similar but more extensive. The entire central zone was occupied by a somewhat irregularly round, yellow disc. In each eye the corneal sensitivity, even in the transparent portions, was reduced, and it was absent in that part of each cornea which contained the yellow opacity. Examination with the slit-lamp revealed many glistening crystalline dots and plates in the yellow portion of the opacities.

Medical examination revealed a goiter—probably an early manifestation of Basedow's disease. No basal metabolic rate is recorded. In other respects the examination, including all the laboratory findings, was negative. The blood cholesterol figure was a high normal. The examination was not repeated.

A corneal transplantation was performed. The disc-like portion removed measured 3 mm. and was studied thoroughly. The polarizing microscope revealed a large number of doubly refracting crystals in the form of plates and needles. The cut sections were stained with a number of fat dyes. In general, the sections contained many vacuolated cells in the middle and deep layers of the epithelium. Fat droplets were present in some of the vacuolated cells and in the protoplasm of some of the normal appearing cells. Bowman's membrane was present throughout and was not separated into lamellae. In some of the preparations small fat-staining

bodies were visible, under high magnification, in Bowman's membrane. The corneal lamellae in the anterior one-third of the stroma were well preserved, distinctly separated from one another, and of normal thickness. In these lamellae and in the spaces between them there were many fat-stained droplets. Some of these were extremely small and were visible only with the high-power magnification, whereas others were readily visible with the low power. Although the droplets were sparse in the superficial layers, in the deeper layers they became numerous. There were no leukocytes in this portion of the cornea, although there was an increase in nuclear elements. Bachstez did not state whether or not these were nuclei of histiocytes.

Because of the almost complete absence of nuclei, the middle portion, approximately the middle one-third, of the cornea, was designated as the necrotic stratum. In this area the lamellae were thick and, except for the outer and inner edges (in cross-section), completely filled with fat-stained droplets. In hemalum-eosin-stained sections these lamellae were paler than those of the anterior one-third of the stroma.

A striking change was present in the stratum beneath the "necrotic portion." Because of the marked increase of nuclear elements Bachstez referred to this layer as the nuclear zone. The cells present were lymphocytes, leukocytes, and cells laden with fat. The lamellae in this zone had degenerated to a marked degree. The fat bodies consisted mainly of large droplets which were present between the stroma tissue. The innermost stratum of the removed cornea contained a few blood-vessels.

The microchemical tests showed that the fat present consisted mainly of cholesterol-fatty-acid mixtures and very little glycerol-fat. Bachstez was of the opinion that the pathologic process was one of primary fatty degeneration and not a fatty degeneration which developed in the course of an

inflammation. This opinion was based on the slow progress of the disease, its bilateral character, and the almost complete clinical and microscopic absence of inflammatory phenomena. He also called attention to the fact that slight irritative manifestations had been described in Groenouw's nodular corneal dystrophy, lattice-shaped keratitis, and other corneal dystrophies. Bachstez believed that in the cases of primary fatty degeneration of the cornea the inflammatory manifestations might be mechanical, due to injury of the epithelium or the corneal nerves; or chemical, due to the formation of transitory chemical changes. He also believed that the tissue of the cornea, as a result of some injury, was not able to digest the fat brought to it in normal amount in the nutrient material (lymph), so that there was a storage of this substance, and finally a tissue necrosis. Bachstez stated that in his patient the hyperthyroidism might be the cause of the primary injury.

Kusama, in 1921, under the heading, "A Contribution Concerning Primary Fatty Degeneration of the Cornea," reported the fourth case of dystrophia adiposa corneae.

The patient, a female, aged fifty-five years, developed phlyctenulae at the limbus of the left eye. This attack occurred in the spring of 1918, and was associated with photophobia and lacrimation. A round, yellowish-white opacity was first noted in the spring of 1919. When examined in 1920, the pathologic change was confined to the cornea of the left eye, and consisted macroscopically of a dense, discoid, yellowish-white opacity situated in the central zone of the cornea. The opacity was vascularized, and somewhat sharply delimited from a 2 mm. transparent peripheral zone. The central portion of the opacity was yellow, whereas the peripheral portion presented the appearance of mother of pearl. With the aid of the loupe many brilliant, yellowish-white dots were seen in the opacity.

A piece of the affected area was removed, fixed in 10 per

cent. formol, and cut with the freezing microtome. A number of fat stains were used. In general, the epithelium was normal except for fat-staining substances present in some of the basal cells, which were elongated. Bowman's membrane was absent in some areas, was swollen in others, frequently was separated into lamellae, and did not contain fat-staining substances. The corneal lamellae were swollen or fragmented. Fat-staining droplets varying markedly in size were present within the lamellae, but not in the interlamellar spaces. The fixed corneal cells and the wandering cells were somewhat increased in number in the corneal stroma. Neither calcium nor hyalin was present.

When examined with the polarizing microscope, the crystalline bodies were doubly refracting. They dissolved readily in ether, xylol, and chloroform, but with difficulty in alcohol. From the various examinations Kusama concluded that the fat substance consisted predominantly of cholesterol, cholesterol esters, and cholesterol-fatty-acid mixtures. Glycerol esters were not present. Kusama was of the opinion that the pathologic process was a fatty decomposition of the corneal lamellae due to a primary injury to the metabolism in these lamellae.

The dystrophy involved the left cornea only. In Bachstez' case the right cornea became involved two years after the left. In Kusama's case this length of time had not elapsed between the appearance of the opacity in the left cornea and the report of his case. We believe that this case, clinically and microscopically, is one of dystrophia adiposa corneae, and we do not exclude it on the basis of unilaterality.

"Anatomical and Histochemical Investigation of a Case of Symmetrical, Bilateral, Fatty Degeneration of the Cornea and Arcus Senilis" was the title of a report by Verderame in 1922. The original article was not available to us. The résumé of the case which follows, as well as our opinion that this belongs to the group of dystrophia adiposa corneae,

was derived from the abstract of the article which appeared in the Zentralblatt für die gesamte Ophthalmologie.

The patient, a female, aged thirty-eight years, developed, in the course of four years, without noteworthy inflammatory phenomena, an opacity in the lower outer quadrant of each cornea. The opacity extended inward to the middle of the pupillary area, was disc-like in form, gray-white in color, and contained a few vessels. An arcus lipoides was present in each cornea, and was separated sharply from the opacity. The other ocular structures were normal. The patient was emaciated, had acne rosacea, and suffered from a chronic gastro-intestinal disturbance.

Histopathologic examination of sections from an excised portion of the cornea showed a disintegration of the fibrillae, with the formation of lacunae-like spaces; fat was present in various forms, deposited in the basal cell layer of the epithelium, in the lamellae, and in the interlamellar spaces, and there was a slight increase in the number of leukocytes and fixed cells. The various findings led to the conclusion that the fat present was of the cholesterol ester variety. Verderame believed that the arcus and the opacity were expressions of one and the same process, a process that was influenced by the chronic gastro-intestinal disturbance.

We believe that Verderame recorded the fifth case of dystrophia adiposa corneae, but we do not agree with the opinion that the gastro-intestinal disturbance was necessarily the causal factor.

In 1923 H. H. Elschnig reported a case which we believe was one of dystrophia adiposa corneae. His article was entitled "Concerning a Remarkable Case of Fat Dystrophy of the Periphery of Both Corneas." His patient, a male, aged fifty-eight years, had never experienced any ocular inflammatory phenomena. A reduction of visual acuity had occurred early in 1922. When examined in October, 1922, a richly vascularized, opaque, yellowish-gray zone,

unequal in width, was present in each cornea. This opacity was sharply demarcated from the cornea centrally, and became continuous with the sclera peripherally. The surface of the cornea and sclera over the opacity was uneven. The other structures of the eyes were apparently normal, except for cortical opacities in each lens. Arteriosclerosis was the only abnormality found by the internist.

Elschnig excised a portion of the affected tissue, examined it chemically, and stated that it consisted chiefly of fat. The type of fat was not determined. Calcium was not present. The blood cholesterol of the only specimen examined was normal. The patient was seen again in December, 1923, at which time it was noted that the corneal opacities had not progressed.

This case report was incomplete in that it lacked many essential statements which would allow a differential diagnosis. It has been suggested that the disease was one of peripheral furrowing keratitis, but the characteristic changes of this disease were not present—at least, they were not described by the author. Furthermore, the illustration which accompanies the article does not suggest this condition. We believe that this case was one of dystrophia adiposa corneae, and that the apparent lack of progress over a period of one year is quite possible in this disease.

The seventh case of dystrophia adiposa corneae was reported by A. V. Denti in 1925. Our résumé was secured from an abstract of his paper which appeared in the Zentralblatt für die gesamte Ophthalmologie. This abstract was captioned "Primary Bilateral Fatty Degeneration of the Cornea."

The patient, a female, aged forty years, had had periodic attacks of redness, photophobia, and lacrimation, associated with a gradual but progressive reduction in vision. Both eyes were affected, the right before the left. The findings in each eye were analogous; namely, a slight pericorneal

injection and a corneal opacity. The latter was not dense enough to preclude a view of the iris, was situated in the deep layers of the cornea, and contained fine yellow, rod-like bodies. The pathologic process underwent no change during the course of a year. The cholesterol content of the blood was not determined.

Microscopic examination of an excised piece of one cornea showed that in some areas Bowman's membrane was missing or lamellated, and that some of the corneal lamellae were fragmented. There was an increase of lymphocytes in the corneal stroma. Sections stained with fat dyes revealed intracellular and extracellular fat droplets, which, when examined with the polarizing microscope, were anisotropic. The lipoidal substance consisted mainly of cholesterol esters.

Denti believed that the pathologic change in the corneas was due to a disturbed ovarian function, for menstruation had ceased when the patient was forty years of age, to reappear after the administration of ovarian preparations. This treatment, however, did not have any influence on the corneal disease.

In an article entitled "Contribution to the Clinical Picture of Dystrophia Adiposa Corneae (Primäre Xanthomatosis Corneae)," H. Meyer, in 1928, reported the eighth case of this type. A general examination of his patient—a female, aged sixty-five years—revealed a moderate degree of arteriosclerosis and cardiac insufficiency. There was no evidence of an endocrine disturbance, diabetic condition, or kidney dysfunction. About 1905 the patient noticed the development of an opacity in her right cornea, and soon thereafter an opacity appeared in her left cornea. The appearance and development of these opacities were not attended by inflammatory phenomena. In 1920 ophthalmologic examination of the right eye revealed a central corneal opacity which was large enough to cover the pupil. The central portion of the opacity was gray, whereas the

periphery was yellow. A somewhat similar but less marked opacity was present in the left cornea.

The patient was not seen again until 1928, when she returned because of a progressive reduction in the visual acuity of the left eye. Examination at this time revealed a marked difference in the appearance of the pathologic areas in the corneas as compared with that of 1920. The pathologic process in the right cornea had receded to a considerable degree. The lesion consisted of a rounded, diffuse, faint opacity, 5 mm. in diameter, which extended from the center of the cornea to the inner edge of the arcus senilis below and nasally, but nowhere touching the limbus. The surface was apparently even, but the keratoscopic reflex images were slightly distorted. The opacity was present in the superficial corneal lamellae and apparently extended into the deep layers. It was surrounded by an area which was light yellow in color. In this zone there were deposited light-reflecting yellowish masses which, under high magnification, were recognized as brilliant, shining crystalline bodies. Superficially lying blood-vessels crossed the limbus in the lower nasal quadrant and extended into the opacity. In this region the previous dense opacity had regressed markedly.

In the intervening eight years the opacity in the left cornea had increased considerably in size. Macroscopically it consisted of a vascularized, yellowish-white, sheet-like structure, 6 by 7 mm. in size, which completely covered the pupil and extended nasally. The peripheral zone of the opacity was white, and this was surrounded by a fine, gray-white zone which, when examined with the binocular loupe, was seen to contain many radially directed fine crystalline points. The keratoscope showed a relatively even reflex figure. Examination with the slit-lamp revealed shining refractile stripes and plaques, which, on the movement of the slit-lamp beam, gave an ever-changing brightness and luster to the opacity. The anterior chamber and iris appeared to be normal.

A bit of the opacity of the left cornea was excised for microscopic study. One half of the excised piece was embedded by the Greeff method (gelatin embedding), and the cut sections were stained with a number of fat stains. The other half of the specimen was studied with the polarizing microscope. Microscopic examinations revealed fine, fat-stained globules in the middle layers of the epithelium. These globules increased in number as the basal cell layer was approached. Bowman's membrane was absent in some areas and lamellated in others. Fatty changes, in large measure in the form of coarse droplets, were present in this membrane. The corneal lamellae, many of which were laden with fat, were placed irregularly. Between some of the separated lamellae the fat droplets became confluent and formed large accumulations. There were scattered areas of necrosis of the corneal stroma. An increased number of nuclear elements were deposited about the blood-vessels. Some were the nuclei of lymphocytes and some were the nuclei of large, round, fat-containing histiocytes. With Nile blue almost all the fat substance stained blue. Only a small number of fine droplets in the lamellae stained red. With the polarizing microscope small anisotropic needles and large anisotropic needles with cross formation were seen. The combined studies, therefore, revealed the presence in the cornea of cholesterol, cholesterol esters, and a small amount of neutral fat.

The remarkable feature of this case was the regression of the pathologic process in the right cornea. Meyer stated that this might have been due to the removal of the lipoids by the newly formed vessels. He believed that the lymphocytes and the newly formed vessels were secondary reactive phenomena. The author concluded that the process was endogenous in nature, and was due either to pathologic changes in the life of the corneal tissue or to a defect in the total metabolism of the body—probably a combination

of both. A statement by Bachstez as to the possible cause for the regression is pertinent. He wrote that one should not always assume that such processes (dystrophic) must continue to progress, for occasionally a disturbance of the metabolism of the cells can be transitory and the degenerated corneal tissue may again return to normal.

Seven other cases have been reported under the heading of "Primary Fatty Infiltration of the Cornea" or "Primary Fatty Degeneration of the Cornea." A critical analysis of these cases, however, has revealed various features which, in our opinion, place them in the group of fatty changes in the cornea secondary to an ocular inflammation. They are the case reports of Takajasu (Japan), Dor (France), Meesmann (Berlin), Spanlang (Vienna), and Gilbert (Hamburg).

The findings in the two cases described by Takajasu in 1912 were present when the patients were sixteen years of age. Both patients had suffered from trachoma. In the first case the opacities were central, grayish-white, vascularized, and consisted of dot-like and rod-like elements. The histologic findings were similar to those seen in the above described cases. The microscopic study of a piece of the pathologic tissue removed from a cornea in the second case was not conclusive in that he mounted and stained the entire specimen.

Takajasu did not believe that the corneal changes were secondary to the trachoma, because of the fact that there are many cases of trachoma in Japan and these two cases were the only ones with fat changes in the cornea reported from that country. He called attention to the fact that both patients were poor, anemic, and showed evidence of poor nutrition. Takajasu was of the opinion that the corneal degeneration might have been associated with deficient nutrition. If the latter were a factor, we do not understand why this characteristic corneal change has not been seen more frequently in Japan and elsewhere.

SUMMARY OF THE CASES OF DYSTROPHIA ADIPOSA CORNEAE

Author	*City or Country*	*Year of Report*	*Sex*	*Age*	*Pre-irritative Phenomena*	*Eyes Involved*	*Direction of Extension of Opacity*	*Corneal Sensitivity*	*Blood-Cholesterol Content*	*Path. Sections*	*Possible Etiologic Factor*
Kamocki	Warsaw	1893	F.	42	Yes	Both	Periphery to center	..	..	Yes	..
Tertsch	Vienna	1911	M.	32	Yes	Both	Center to periphery	Reduced	..	Yes	A fatty degeneration of the corneal lamellae following a primary injury to the metabolism of the corneal cell
Bachstez	Vienna	1921	M.	36	Yes	Both	Center to periphery	Reduced to absent	Upper limit of normal	Yes	Hyperthyroidism could be the cause of the primary injury to the corneal cells
Kusama	Tokio	1921	F.	55	Yes	Left	Center to periphery	..	..	Yes	Believes in Tertsch's hypothesis
Verderame	Turin	1922	F.	38	Yes	Both	Lower outer quadrant to center	..	..	Yes	Chronic gastro-intestinal disturbance
Elschnig	Prague	1923	M.	58	No	Both	Periphery to center	..	Normal	Chemical examination only	..
Denti	Milan	1925	F.	40	Yes	Both	Center to periphery	..	..	Yes	Disturbed ovarian function
Meyer	Freiburg	1928	F.	65	No	Both	Center to periphery	..	266 mg. %	Yes	? Pathologic state of the total metabolism of the body

It is difficult to evaluate the rôle played by trachoma in these two cases. We are of the same opinion as Bachstez, who said: "Both patients had passed through trachoma, so that the findings are not to be acknowledged with certainty as a primary degeneration, although the history and the clinical appearance in the cornea in both cases point to a corneal process of a peculiar type."

Dor's case report was entitled "Fatty Infiltration of the Cornea." Our knowledge of this case is derived solely from an abstract in the Jahresbericht für Ophthalmologie, as we were unable to gain access to the original article. In each cornea there was a yellow-gray opacity which "resembled a xanthelasma." We have placed the case in the group of doubtful cases of dystrophia adiposa corneae because there was no progress of the pathologic lesion in the course of three years, there was no mention in the abstract of crystalline substances, and there were no microscopic studies.

Meesmann, in 1924, demonstrated before the Berlin Ophthalmological Society two patients who had opacities in the cornea which he designated "Primary Fatty Degeneration of the Cornea." The first case was that of a female, aged fifty-four years, who had a severe degree of diabetes. Five years previously she had had an acute iridocyclitis in the left eye, during the course of which disease there developed a dense corneal opacity which subsequently partially receded. The opacity was located in the middle layers of the central portion of the cornea, was definitely yellow in color, and contained areas of cholesterol-like crystals. Later the patient developed an acute iritis of the right eye, and soon thereafter—within a few days' time—there appeared an opacity of the entire right cornea, except for a narrow peripheral zone. Subsequently the extent of this opacity decreased, and the condition then remained unaltered for two and one-half years. There was

an increased blood-cholesterol content (360 mg. per cent.). Microscopic examination of the trephined cornea supported the diagnosis of fatty degeneration of the cornea.

The second case was that of a female, aged twenty-nine years, who developed a vascularized, tongue-shaped, finely punctate opacity of the middle layers of the left cornea, which extended from the temporal limbus nasally over the pupillary area. There was no evidence of iritis. In the course of two and one-half years the opacity extended centrally and simultaneously receded from the temporal edge of the cornea. Anatomic examination supported the diagnosis of fatty degeneration of the cornea. Meesmann stated that the blood-cholesterol content was elevated but no figure was given.

We do not believe that the term "primary" should have been applied to the first case, for the corneal opacities developed acutely and followed closely upon the attacks of iridocyclitis. It was not a case of dystrophia adiposa corneae. In the second case, simultaneous progression and recession of the opacity in one cornea, together with its unilaterality for a period of two and one-half years, would argue against the inclusion of this case in the category of dystrophia adiposa corneae.

H. Spanlang (Vienna), in 1927, under the title "Dystrophia Adiposa Corneae," reported a case which we believe cannot without some doubt be placed in this category. His patient, a female, aged fifty-three years, had an advanced osteomalacia and a blood sugar of 141 mg. (one specimen). She first noticed a reduction of vision in 1920. When examined in 1927, both eyes showed similar changes. Each cornea, with the exception of a 1.5 mm. broad transparent peripheral zone, was studded with dense, round or irregularly shaped, white areas, which were about 2 mm. in diameter. These were sharply demarcated, and the majority were located in the middle and deep layers. The remainder of

the involved area showed a fine, gray, vascularized opacity. The underlying structures which were visible were normal.

Histologic examination revealed a degeneration of Bowman's membrane and of the corneal stroma. The latter was more marked in the anterior than in the posterior layers, and was associated with an extensive deposition of calcium and a less extensive deposition of fat-staining substances.

In our opinion these findings, although they resemble in some respects those present in the undoubted cases of dystrophia adiposa corneae, are also quite similar to the case of dystrophia calcarea described by Axenfeld. In the macroscopic description of some of the cases of dystrophia adiposa corneae, including our own, areas within the pathologic process seemed to present a calcareous appearance, but calcium was never seen microscopically. Spanlang's case is unique in that it combined the characteristics of dystrophia adiposa and dystrophia calcarea.

Another doubtful case of dystrophia adiposa corneae was reported by Gilbert in 1929 in an article entitled "Concerning Xanthomatosis of the Cornea and the Sclera." The patient, a female, aged fifty-three years, was examined in 1926 by an internist because of symptoms referable to the heart. The cardiac diagnosis was angina pectoris and aortic insufficiency. Ocular pathologic changes had been present in the left eye for five years and in the right eye for one year. The patient was first seen by Gilbert in 1928. He found that the left eye was slightly shrunken in its anterior segment. There were rather large yellow masses deposited in the lower sclera. The cornea was vascularized, slightly flattened, and opaque throughout. In general the opacity was gray, except for a somewhat irregularly shaped, yellowish area in the central zone. Vessels extended into this area. Examination of the deeper parts of the eye was impossible. Gilbert did not state whether or not light perception was present. This fact would have given us an indication as to the status of the posterior portion of the globe.

The sclera adjoining the right cornea was yellow in color. The upper half of the cornea was transparent, and devoid even of an arcus senilis. A kidney-shaped vascularized opacity, yellow in color, involved the lower half of the cornea. This opacity was dense at the sclera and became less so as it extended toward and into the lower portion of the pupillary area. The visible portion of the anterior chamber was normal, and the aqueous was clear and free from deposit. Posterior synechiae were present above and nasally. The visible portion of the iris did not contain any yellow masses. On repeated examinations the cholesterol-blood content varied from 194 to 200 mg. per cent. The patient was under Gilbert's observation for nine months, during which time the pathologic area in the right cornea did not increase in size. Tissue for microscopic study was not secured from either cornea.

Gilbert concluded that, because of the elevated blood-cholesterol content, the scleral and corneal pathologic changes were the result of an increased offering to, and subsequent storage of fat by, the cornea. In the opinion of some authors this mechanism serves for the production of arcus senilis.

Two hundred milligram per cent. is within normal limits for the cholesterol content of the blood when the determination is made by the Bloor method. We therefore do not believe that the cholesterol-blood content was an important factor in the production of the fatty changes in the fibrous coat of both eyes.

We are of the opinion that this case was not one of dystrophia adiposa corneae, since evidence of previous intra-ocular inflammation was present in each eye; namely, squaring of the anterior segment of the left eye and posterior synechiae in the right eye. In the discussion of his case, Gilbert stated that he believed one could assume that a preceding disease had prepared the ground for the fatty

deposit, but the complete transparency of the uninvolved part of the right cornea hardly permitted of such an assumption. That this theory of Gilbert's is possible, however, is shown by the fact that these were also the findings in Landman's case.

CASE REPORT

History

A. F. (No. 37716), male, aged fifty-three years, a painter for seven years, was admitted to Billings Hospital of the University of Chicago on May 5, 1931, for study, through the courtesy of Drs. G. G. Dowdall and Hiram Smith, of the Illinois Central Hospital. On admission the patient stated that in December, 1926, he had visited a physician in Iowa because of bilateral ocular injection of short duration. At that time there were lacrimation, photophobia, and moderate redness, but no reduction of vision or ocular pain. There was no history of ocular injury, and no cause for the signs and symptoms was found. Mydriatics and hot applications were prescribed. The symptoms grew more severe, and in March, 1927, the patient was sent to the Illinois Central Hospital, Chicago.

The following statements are from a résumé of the case furnished to the authors by Drs. Dowdall and Smith:

On March 12, 1927, unaided vision right eye = 0.2 + 1 and unaided vision left eye = 0.1. With correcting glasses V.R.E. = 0.4 + 1; and L.E. = 0.4. The cause of the poor vision was not known definitely. There was present a "low-grade inflammation of the conjunctiva of the right eye and the margin of the cornea." Although no cause for the symptoms was apparent, the patient was advised to be careful in regard to the handling of paints containing lead. No intra-ocular pathologic changes were noted. On July 25, 1927, the patient was readmitted to the Illinois Central Hospital and assigned to the medical service because of symptoms which suggested lead-poisoning or pernicious anemia. The diagnosis of neither one of these conditions, however, was supported by any of the findings. Ophthalmologic examination at this time revealed bilateral pericorneal injection and "marginal keratitis" involving the entire peripheral circumference. The centers of the corneas were clear. The cause of the marginal keratitis was not known. Dr. Smith stated at this time that: "This condition

resembles arcus senilis, but is not quite the same. I am unable to explain the lowered vision inasmuch as the central portions of the corneas are clear." On January 19, 1928, the patient was again admitted to the hospital because of the increased intensity of his general symptoms. On this date V.R.E. corrected = 0.4; L.E. corrected = 0.3; pericorneal injection was still present. On June 8, 1930, two and one-half years later, re-examination by Dr. Smith revealed "both corneas to be quite opaque except for a small area in the right through which the patient has a very limited amount of vision."

In a conversation with Dr. Smith we were informed that he was under the impression that the opacification of the cornea progressed somewhat concentrically from the periphery toward the center, and that the progression appeared to occur in waves, that is, a millimeter or two of apparently normal corneal tissue would become involved within a relatively short period of time and then progression appeared to be at a standstill for a period of time.

On admission to Billings Hospital the patient's vision was R.E. = finger counting at 2½ feet; L.E. = quick and accurate light perception, but light projection was quick and accurate in the temporal and upper quadrants only. The lid margins and cilia were normal. The palpebral fissures were 6.5 mm. wide. The upper and lower palpebral conjunctivae of the lids of both eyes were normal, and the meibomian glands were readily visible. The lower fornix conjunctivae were somewhat redder than normal and contained dilated tortuous vessels. There was a marked mixed injection of the bulbar conjunctiva. When seen through this injection, the scleras presented a definite yellow-white color. Abduction of each eyeball was somewhat limited, otherwise the ocular movements were normal. The eyeballs appeared to be of normal size and curvature, and the tactile tension of each globe was normal.

The right cornea was of normal size and curvature. Blood-vessels were seen to cross the limbus and extend for varying distances into the superficial layers of the cornea. The cornea was opaque throughout, except for a kidney-shaped area in the upper nasal quadrant, which measured 5 mm. in the vertical oblique direction and 3 mm. horizontally. When examined with the Coddington loupe, even this area was seen to have a fine gray stippling. Solid, plaque-like, yellowish-white areas, 3 to 4 mm. in diameter and simulating calcareous deposits, were located in the superficial

layers of the cornea near the limbus. In the central third the color of the opacity changed from white to yellow-white. The portion of the anterior chamber and of the iris seen through the transparent area was normal. The iris reacted to light. Atropin, 1 per cent., was instilled in the culdesac and the pupil was dilated. With the ophthalmoscope a faint red reflex was secured, but no fundus details were seen. Transillumination gave a red reflex only through the transparent area of the cornea. The corneal sensitivity was normal.

The left cornea was of normal size and curvature, but it was opaque throughout (Plate I). Superficial blood-vessels crossed the limbus and passed into the cornea for varying distances. By oblique illumination and the loupe some deep vessels were seen. Yellow-white plaques, less numerous than in the right cornea, were present and similarly located. There was a yellowish tinge to the central 5 mm. area of the cornea. No red reflex was secured on transillumination. The corneal sensitivity was normal.

Slit-lamp examination of the right cornea showed that although the majority of the blood-vessels which extended into the cornea were superficial, there were a moderate number of deep vessels, especially in the lower nasal quadrant. As they passed into the dense opacity in the innermost layers of the cornea these vessels were frequently lost to view. The opacities near the limbus, which macroscopically had the appearance of calcium deposits, lay in the superficial layers of the cornea and did not cause an elevation of the overlying cornea. These opacities were dense in appearance, and the fine layer of corneal stroma which covered them contained glistening, needle-shaped crystals. The entire thickness of the lower one-fourth of the cornea, as well as a peripheral zone 2 to 3 mm. wide, appeared to be opaque throughout. The rest of the opacity involved mainly the middle and the deep layers of the cornea. As the slit-lamp beam was passed from the lower limbus upward to the kidney-shaped transparent area, it was noted that, whereas the posterior layers of the cornea remained opaque, the superficial layers became transparent. This conveyed the impression that the posterior layers of the cornea were the first to become involved in the pathologic process. The epithelial layer of the cornea contained a crystalline-like substance. The pathologic elements in the corneal stroma varied throughout, for in some areas needle-like elements were seen, and nearby glistening, rainbow-colored dots were present. No nerve fibers were seen.

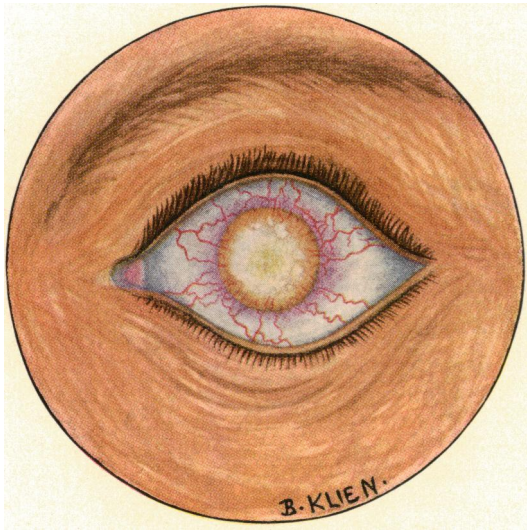

Plate I

The transparent portion of the cornea was seen to contain some crystalline needles and rainbow-colored dots. There were no precipitates on the posterior surface of the kidney-shaped transparent area of the cornea. The visible portions of the iris and of the anterior chamber were normal. The visible pupillary crypts were well defined.

Slit-lamp examination of the left cornea revealed about the same findings, except that the opacity appeared to be solid in the posterior one-half of the entire cornea, whereas the anterior half contained innumerable small, glistening, needle-shaped and rounded, highly refractile crystalline elements in lamellae which were as yet transparent. No nerve fibers were seen.

Examinations in various departments of the hospital showed a red cell count of 4,990,000; hemoglobin, 84 per cent.; white cell count, 13,100. A differential count revealed polymorphonuclears, 78 per cent.; large lymphocytes, 10 per cent.; small lymphocytes, 10 per cent.; and basophiles, 2 per cent. A smear did not disclose any of the blood changes characteristic of lead-poisoning. The blood non-protein nitrogen was 26.3 mg. per cent.; blood urea, 12.3 mg. per cent.; blood glucose, 82 mg. per cent.; blood calcium, 11.2 mg. per cent.; and blood phosphorus, 3 mg. per cent. A glucose tolerance test, urinalysis, and blood Wassermann test were negative. The blood-pressure was 130/90. A number of blood-cholesterol determinations were made. On May 6th the cholesterol content of the blood removed before breakfast was 243.5 mg. per cent. The high normal by the quantitative method used (Bloor) is considered to be 200 mg. per cent. On May 7th the cholesterol content of the blood removed after breakfast showed 209.5 mg. per cent. On May 13th it was 189.3 mg. per cent. On May 28th blood was removed one hour before and one hour after breakfast and one hour before and one hour after the noon meal. The specimens were examined for total cholesterol, cholesterol esters, and free cholesterol. The results of these examinations were:

Specimen	*1* mg. %	*2* mg. %	*3* mg. %	*4* mg. %	*Normal* mg. %
Total cholesterol..	199	180	196	179	150–200
Cholesterol esters.	103	131	167	150	..
Free cholesterol..	96 (48%)	49 (29%)	29 (15%)	29 (16%)	30–60% of the total cholesterol

On July 8th the patient was placed on a low fat to fat-free diet in order to note the effect of the diet on the lipoid deposit in the right cornea. The cornea showed no improvement under the dietary régime and it was discontinued on August 1st. On this date the cholesterol content of the blood was 119 mg. per cent. This period of time—twenty-three days—was inadequate properly to evaluate this type of therapy. Dermatologic examination did not reveal cutaneous xanthoma. Neurologic examination showed a peripheral (toxic?) neuronitis. The etiology for this was not established beyond a reasonable doubt, although lead-poisoning was strongly suspected. Ear, nose, and throat examinations were negative. The prostate was normal. Dental examination showed dental infection from pyorrhea, but no periapical lesions were present. Roentgenologic examinations were made of the sinuses, orbits, feet, hands, and chest. The sinuses were pneumatic. The pathologic change in the cornea did not cast a shadow, and no abnormality was seen in either orbit. Generalized osteoporosis was present in the bones of the hands and the feet. There was nothing to suggest deposits of uric acid crystals (gout) in the bones of the hands or feet. The chest pictures were most peculiar. A report stated: "Right lung: There is an advanced pathologic process in the right lung, which is scattered evenly throughout from apex to base. The appearance almost resembles snowflakes. Small soft tissue densities, 2 to 3 mm. in diameter, are scattered radially along the bronchovascular markings. Left lung: An almost similar appearance, resembling that of snowflakes, scattered diffusely and evenly throughout the entire left lung field. Have to consider: (*a*) a miliary distribution of tubercles throughout both lung fields. (*b*) If patient is a coal miner or has worked in a very dusty trade, such as granite, pottery, or cement, then would have to consider pneumoconiosis." The impression of another member of the *X*-Ray Department was: "Moderately advanced to advanced pulmonary tuberculosis located posteriorly in both upper lung fields but not involving the apices, with a good deal of fibrosis." The patient gave a history of a loss of from 50 to 60 pounds in weight three years ago, unassociated with fever or pulmonary symptoms. About eight months before admission to the hospital he regained his former weight. There was impaired percussion over the apices of both lungs, more marked over the right, but no abnormality in the breath sounds. No râles were heard. From chest and *x*-ray examination the opinion was:

"Tuberculosis of the lungs, far advanced, active?" During the one hundred and fifteen days the patient was in the hospital no abnormal temperature was recorded. During this period the patient neither coughed nor expectorated, therefore sputum was not available for examination.

Later the patient submitted samples of two compounds which were used by him in his occupation. One was a grayish-white granular substance consisting mainly of calcium hydroxid and carbonate; the other was a black paint in which there were present lead, zinc, manganese, iron, calcium, and aluminum, with lead in the largest amount.

CHEMICAL AND MICROSCOPIC STUDIES OF THE REMOVED CORNEA

On May 26, 1931, a total and complete corneal transplantation with attached conjunctival flap was performed on the left eye. The aqueous, which escaped following the incision through the limbus, presented a normal appearance. No crystalline substances were seen. When the cornea was removed, the iris and lens were seen to be normal. There was no evidence of a previous inflammation. The removed cornea was cut into several pieces. Chemical examination, by the Windaus technique, of a piece weighing 2.6 mg., showed extremely large amounts of both free cholesterol and cholesterol esters; in fact, the latter were present in an amount only infrequently seen in pathologic tissue. It was roughly estimated that about two-thirds of the whole amount of cholesterol was present in the form of esters.

One portion of the cornea was fixed in formol-Zenker solution; from a second portion frozen sections were prepared; and a third part was fixed in A. O. B. (acetic acid, osmic acid, potassium bichromate) solution.

In the hematoxylin and eosin stained preparations of the formol-Zenker fixed tissue the epithelial layer varied in thickness. This was due not only to a variation in the number of cell layers (from three to five), but also to a change in the form of the cells in the basal layer; i. e., from columnar to cuboidal. The superficial flat cells were slightly keratinized. An occasional mitotic figure was seen in the basal cell layer and much less frequently in the middle cell layers. Wandering cells, leukocytes, and lymphocytes were increased to approximately eight to ten times the number normally seen. The majority lay on Bowman's membrane, be-

tween the basal cells, but a number were present between the cells in the middle layers. Collagenous connective tissue rich in spindle-shaped nuclei was present in localized areas between the basal cell layer and Bowman's membrane. The amount, thickness, and extent of this tissue, which stained similarly to the lamellae of the corneal stroma, varied in certain areas.

Where Bowman's membrane was present and intact, it was usually of normal thickness. It was frequently split into lamellae, and the spaces between the lamellae were occupied by nucleated tissue. In all sections of the specimen there were areas in which the membrane was completely absent. The spaces between the free ends were filled with tissue passing from the stroma to end between the epithelium and Bowman's membrane. The rami perforantes were numerous and clearly seen.

The lamellae of the corneal stroma varied considerably in thickness. Many of the lamellae showed degenerative changes, including vacuolization; many contained cholesterol crystal clefts. A conspicuous increase of nuclear elements was present, due to a large number of neutrophilic leukocytes and a lesser number of lymphocytes and pyknotic nuclei. It was impossible to decide definitely whether the pyknotic nuclei were nuclei of lymphocytes, leukocytes, or of the fixed corneal cells, although the last was most probable. In a formol-Zenker-fixed Giemsa-stained section, large, oval-shaped, pale-staining nuclei resembling endothelial cells were frequently present in the widened interlamellar spaces bordering the lamellae. In this material many various-sized histiocytes with well-stained nuclei and nucleoli, vacuolated cytoplasm, and fairly well-outlined margins were seen in the interlamellar spaces. Although the leukocytes and lymphocytes were diffusely distributed through all the layers of the stroma, they were more numerous in the posterior half, they were more densely accumulated in some areas than in others, and they had no definite relationship to the blood-vessels, many of which were present in the middle and deep layers. The majority of the blood-vessels consisted of an endothelial wall which lay in stroma no different from that of the rest of the stroma, whereas other vessels were surrounded by richly nucleated tissue. In cross-section the small vessels contained two or three blood-cells; the large vessels, 20 or more blood-cells.

Descemet's membrane was homogeneous and of normal thickness. The underlying endothelium was normal.

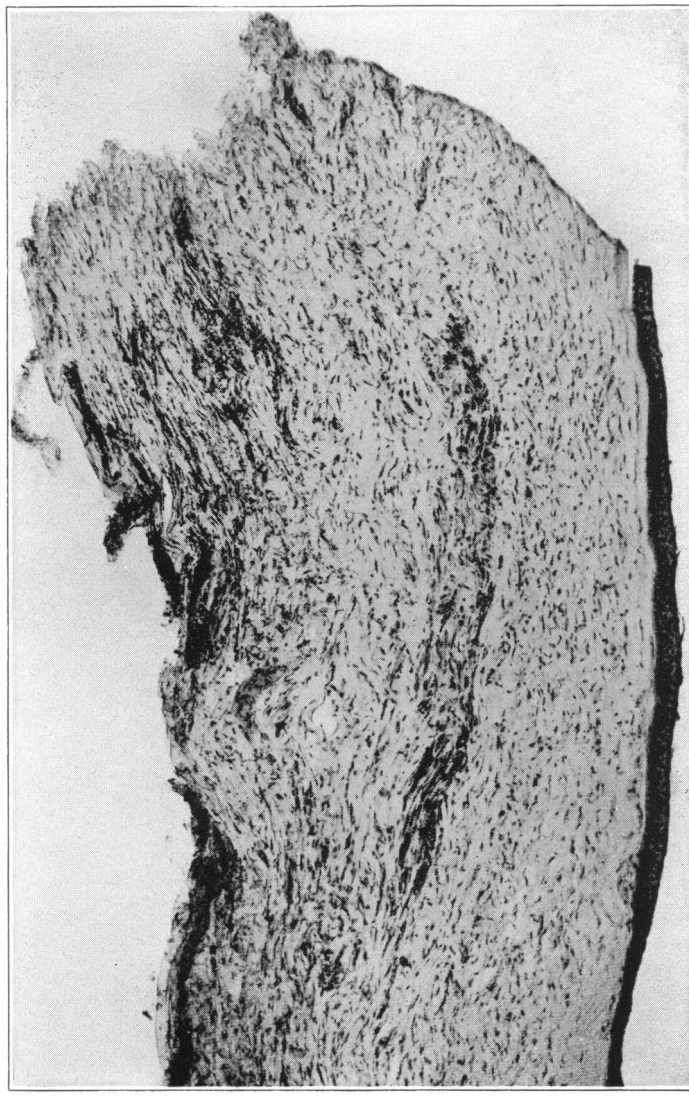

Plate II.—This plate was developed about four months after the section was stained. There was some fading of the stain in the meantime. The many small, red-staining areas in the epithelial layer and Bowman's membrane, readily visible when the slide was first stained, were seen best with high magnification when the plate was developed.

Frozen sections stained with hematoxylin and Scharlach R showed red-staining granules or masses, or both, in all layers of the cornea except Descemet's membrane and the endothelium (Plate II). In the epithelium and Bowman's membrane there was a diffuse, extremely fine, granular fatty deposit. In the epithelium this deposit was present in all layers, within and between the cells, and in Bowman's membrane it frequently involved the entire thickness of the membrane. This fine fat deposit was also present in some areas in the pannus degenerativus. In the corneal stroma the diffuse fatty distribution varied considerably in intensity. In many places the fat droplets had coalesced to form irregularly shaped fat bodies of varying sizes. These bodies were isolated in some areas, and in others they had accumulated in large numbers. The amount of fat that was stained by Scharlach R varied in different sections and in the different parts of the same section. Taken as a whole, the greatest deposition of fat took place in the middle and posterior layers of the corneal stroma. In some sections, however, the fatty deposition was marked in the anterior portion of the stroma. The greater part of the Sudan-stained fat content was apparently extracellular, although red-stained fat-laden histiocytes were readily identified.

The sections of the tissue fixed in A. O. B. were stained in a variety of ways. Several were stained with anilin acid fuchsin and counterstained with yellow metanil, in order to demonstrate the amount and distribution of fatty material capable of reducing osmic acid (Plate III). The sections from this material did not show any fat in the epithelium or in Bowman's membrane. Immediately beneath Bowman's membrane there were restricted areas of concentrated, fine, black-stained, fatty granules in lamellae which had degenerated. The deep layers of the cornea contained the same type of granules in and between the lamellae. Fat so distributed accounted for only a small portion of the osmicated fat present. The major part was present in the form of large, round, black, dot-like granules within histiocytes. These cells were scattered throughout the cornea, but were most numerous in the posterior half, between the lamellae, occasionally within the lamellae (Plate IV). In some areas the histiocytes were so numerous that they were incompletely separated into rows by strands of corneal lamellae. There was a characteristic tendency of the fat-laden histiocytes to group themselves about blood-vessels and to extend over comparatively wide fields. This dark, osmic-acid-

stained fat substance presented an interesting change,—apparently a bleaching process,—beginning soon after the application of the cover-glass and almost complete twenty-four hours after the cover-glass was applied. Examination at this time revealed the fact that the osmic-acid-stained fat had almost entirely disappeared, evidently a reaction due to the exclusion of air (oxygen). The histiocytes, formerly fat laden, were then seen to be large cells, well outlined, containing oval-shaped nuclei with well-defined nucleoli, cytoplasm with numerous large empty vacuoles, and a scanty mitochondria content. The size and shape of the histiocytes varied with the space within which they were located. Experimentation disclosed that, by removing the cover-glass, this fat decolorization could be inhibited at any point. The reaction was of special interest because it illustrated that the fatty combination present was decidedly less stable than and different from that of ordinary neutral fat. After decolorization the osmic oxid color could not be restored by removing the cover-glass and subjecting the sections to air or to oxidizing agents, nor could it be refixed in osmic acid.

The cellular contents of the lumen of many blood-vessels were examined, but no histiocytes were seen, although these were present immediately outside the endothelial walls. Here the histiocytes were frequently arranged in concentric rows, and were smaller in size than those observed in the interlamellar spaces. The rows were separated by thin strands of collagenous connective tissue. In the case of arterioles the histiocytes were seen in the walls of the vessels (Plate V). Many of the histiocytes had phagocytosed polymorphonuclear and red blood-cells. The latter were also found free in some of the tissue spaces. Intermixed with the fat-containing histiocytes were many leukocytes, largely neutrophiles, and some smaller mononuclears. The infiltration of neutrophiles between lamellae was present over a larger area than that occupied by the histiocytes.

In many lamellae the normal fibrillar appearance was almost entirely absent. There was definite vacuolization, due to degeneration. The degenerative process frequently affected the extracellular structure without visible microscopic change to the nucleus.

Descemet's membrane and the endothelium did not contain fat granules.

The elements stained by Sudan stain were far more numerous

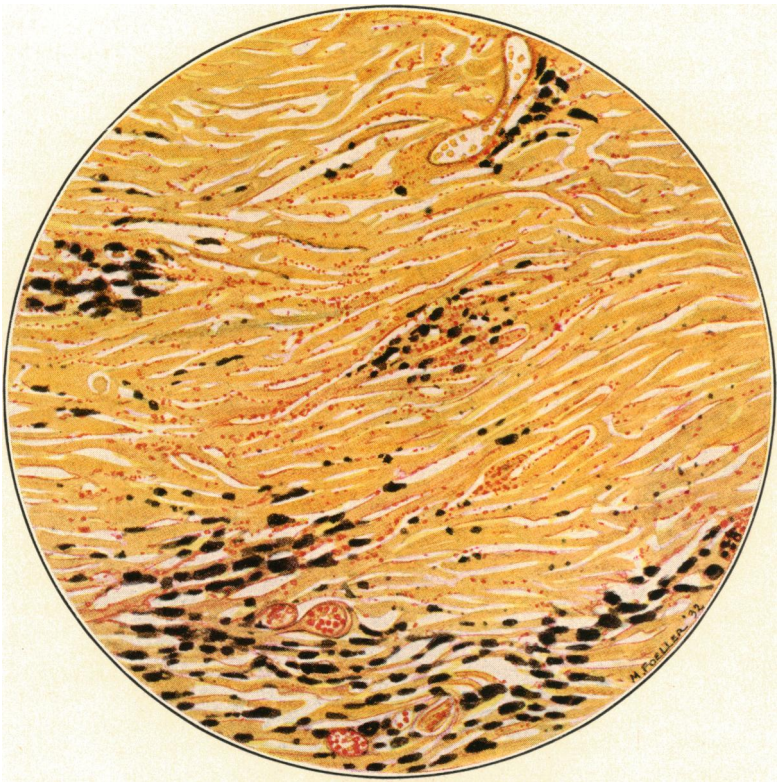

Plate III.—The fat-laden histiocytes are grouped about blood-vessels.

than those which were osmicated. This proved that, although neutral fat was present, the fat substance in the pathologically changed cornea consisted mainly of the cholesterol-fatty-acid group.

DISCUSSION

The ophthalmologic value of the case reported would be insignificant if we did not discuss some of the fundamental pathologic and biochemical problems involved. Among these are: (1) What is the nature of the fat process and how is it brought about? (2) What rôle does cholesterol play in the pathologic process? (3) What is the origin of the histiocytes present in the cornea?

FATTY METAMORPHOSIS

The authors of the various reports of dystrophia adiposa corneae differ in their opinion as to whether the fat changes present were in the nature of an infiltration or of a degeneration. Many pathologists have ceased to speak of "fatty infiltration" and "fatty degeneration" because of the frequent impossibility of differentiating the one from the other. They use the term "fatty change" to describe all fatty processes; the other terms, however, are still in common use.

Virchow's definition of fatty infiltration—an excessive accumulation of fat in the cells in the form of large droplets without destruction of the nucleus or irreparable damage to the cell—was postulated in 1847 and is still uniformly accepted. In this condition the fat enters the cell from without; the fat, in the form of fat droplets, fuses under the pressure of the cytoplasm; the cell remains structurally normal or nearly so; it is not functionally damaged, and is capable of returning to its normal condition whenever the fat is removed.

Under normal conditions there is little free visible fat in the cells of the parenchymatous organs, because it is

largely used up through oxidation by the action of the intracellular oxidase. When, for any reason, the oxidative power of the parenchymatous organ is reduced, fat accumulates in it and we find an excess of fat in the parenchymatous cells. When oxidation in a cell is checked by toxins, loss of nutrition, or through other means, the accumulation of fat brought to it will go on uncontrolled. Added to this is the fact that every cell contains lipins—fats and lipoids—the amount of which varies with the different organs. The lipins are so combined that they are not stained with the usual fat stains, nor can they be extracted with ether. They are referred to as "invisible fat." The lipins, however, are liberated during an autolytic process and become "visible," that is, identified as lipins by certain of the fat stains or by polarized light. Thus, when we have the accumulation of fat in a disintegrating cell, we have fatty degeneration. In this process the fat may enter the cell from without or may be derived from within, usually the accumulation occurs in both ways; the cell is functionally damaged and incapable of returning to its normal condition if the fat were removed.

In tissue disintegration cholesterol and its esters accumulate because these substances are not readily soluble and are not destroyed during autolysis. The characteristic plates of cholesterol may be seen in any tissue in which cells are undergoing slow destruction. Cholesterol and its esters may be slowly removed by the histiocytes which phagocytose these substances. Histiocytes are often found surrounding cholesterol and its esters.

EXPERIMENTAL PRODUCTION OF ARCUS LIPOIDES CORNEAE

Chuma, Versé, Rohrschneider, and others have produced in animals corneal opacities which resembled in color, form, and location the arcus lipoides corneae of man. Versé and others used mixtures of cholesterol and oil—usually a 5 per

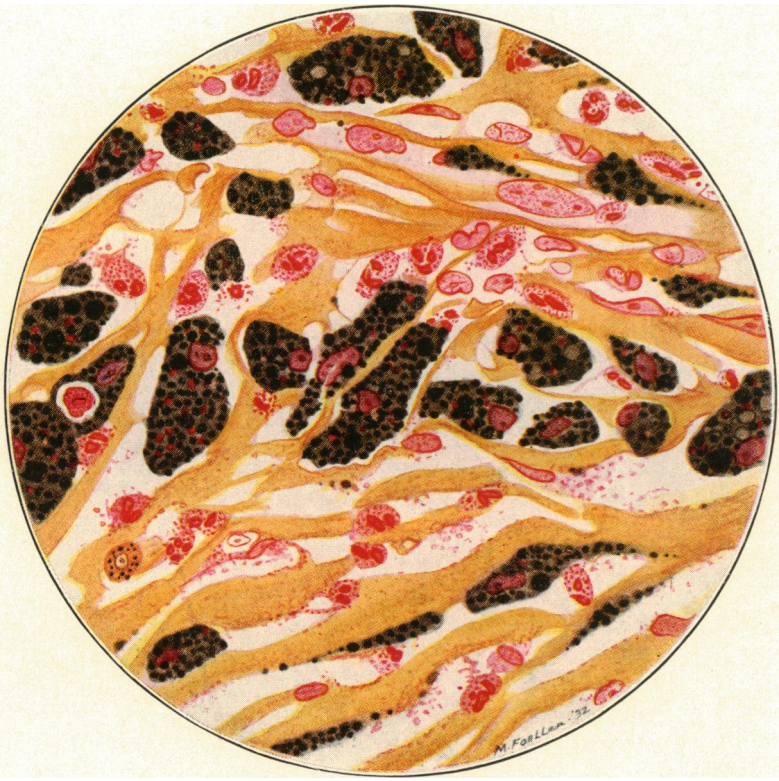

Plate IV.—Interlamellar and intralamellar fat-laden histiocytes with scanty mitochondria content, neutrophilic leukocytes, and swollen, vacuolated corneal lamellae are present.

cent. mixture of cholesterol in linseed oil. Four to 16 c.c. of this mixture was introduced almost daily into the stomachs of the animals — usually rabbits — by means of a tube. In the process of development the opacities encircled the cornea and frequently increased in width, in some cases passing over to the sclera and occasionally extending centrally into the pupillary area. Versé stated that the degree of development of the arcus lipoides depended not only upon the feeding time and upon the kind and amount of cholesterol-oil mixtures, but also upon accessory and constitutional conditions. He did not state what these constitutional conditions might be. As for accessory conditions, it may be mentioned that in his series the widest arcus developed in the left eye of a rabbit and the development was associated with a marked conjunctival redness. In our opinion the conjunctival redness could have been the effect, rather than the cause, of the marked corneal involvement. Animals fed the cholesterol-oil mixtures showed comparatively large fluctuations in the time of the appearance of the arcus lipoides, not only in the different animals, but also in both eyes of the same animal. In general, microscopic evidence of fat was present after eight days and a macroscopic opacity was present after twenty to twenty-four days. The developed arcus was relatively permanent, disappearing slowly and incompletely after the suspension of the cholesterol-oil feeding. When the animals were fed pure cholesterol, an arcus lipoides developed very late, and it was noteworthy that, notwithstanding the feeding of pure cholesterol, the greatest part of the deposited lipoid in the cornea was not doubly refracting.

Microscopic examination of Sudan-stained sections of the cases of well-developed arcus lipoides corneae experimentally produced showed a fatty change, especially in the outer layers of the cornea. With high magnification the fat substance was separated into extremely small droplets.

These droplets were present in the intercellular spaces in the epithelium, in Bowman's membrane, within and between the corneal lamellae, in the wandering and the fixed stroma cells, and in the endothelium. Descemet's membrane in the region of the arcus took the Sudan stain, but no fat droplets were visible. In some instances large foamy cells—histiocytes—flattened in rows between the lamellae were observed. A mantle-like proliferation of these cells laden with fat was frequently seen about the vessels. It is of interest to note that, following the intravital staining of his animals, Chuma found that the depositions of staining granules and of fat were almost identical in location.

It is believed that when the blood contains an excessive amount of fat the latter passes, in larger amount than normally, into the blood lymph, and from the lymph over into the tissue. The rôle played by the cholesterol is not clearly understood. It is probable that it serves as a vehicle for the transportation of fat. It may also favor the precipitation of neutral fat out of the tissue fluids into places where deposition of neutral fat alone does not usually occur.

That another factor or factors besides a high blood-cholesterol content is essential in the production of arcus lipoides corneae or dystrophia adiposa corneae in man is shown by the fact that in lipoid nephrosis the corneas remain uninvolved, even though the blood-cholesterol content is two or more times that of the high normal. One of us (D. K.) has seen two such cases. In the first case (No. 26376) the blood-cholesterol content was frequently determined by the Bloor method, and over a period of nine months varied from 287 to 608 mg. per cent. In the second case (No. 44080) the blood-cholesterol content was found to vary from 503 to 1025 mg. per cent. The corneas of these two patients were examined with the slit-lamp and no evidence of a fatty change was present.

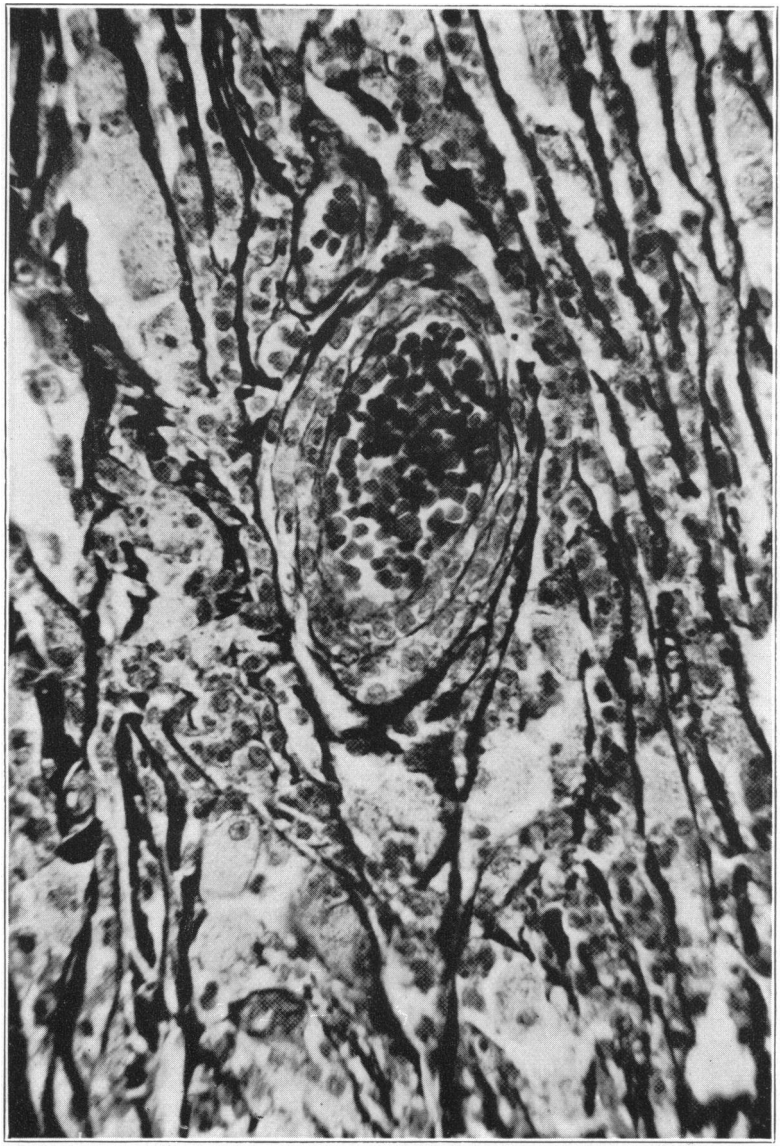

Plate V.—Cross-section of arteriole. Small cells (small histiocytes) are within the wall of an arteriole. Typical histiocytes are present in the immediate neighborhood.

ORIGIN OF THE HISTIOCYTES

One cannot be too dogmatic in answering the question of the origin of the histiocytes in the cornea, since they are not found there normally. Four possible sources from which these cells might originate must be considered. These are: (1) The structures encircling the cornea; namely, the sclera and its overlying conjunctival tissue; (2) the cellular elements of the corneal stroma; (3) the blood stream; and (4) the blood-vessel walls, especially the adventitia. A discussion of these possibilities follows:

(1) If we were to assume that the histiocytes originated from the structures encircling the cornea, it would be necessary to explain the presence of these cells in the sclera, no part of which was removed in our case; normally, the sclera is devoid of histiocytes, except for those present in the perivascular sheaths of the scleral blood-vessels. The overlying conjunctival tissue normally contains histiocytes. In the cornea of our case these cells were located between lamellae, mainly in the posterior half; the movement of these cells appeared to be confined to the interlamellar spaces, and there were no rows of histiocytes apparently continuous from the periphery to the center of the cornea. From all this it appears improbable that the histiocytes in the cornea were derived from the surrounding structures. On the other hand, it has been shown that particulate storing cells (histiocytes) are present in all layers of the arcus lipoides corneae experimentally produced.

(2) Most cytologists are of the opinion that histiocytes can be transformed into fibroblasts, but that the reverse does not occur. If this is true, the stroma fibroblasts could not be the progenitors of the histiocytes.

(3) It is known that histiocytes are present in the blood stream in a few infectious diseases (subacute bacterial endocarditis) only. In our case, blood smears did not reveal any histiocytes, neither were they seen among the

blood cells in the lumen of the many corneal blood-vessels which were studied. It is therefore highly improbable that the histiocytes as such were derived from the blood stream. The advocates of the "unitarian theory" of hemopoiesis believe that lymphocytes can be transformed into monocytes and that in inflammation the lymphocytes and monocytes which migrate out of the blood-vessels into the tissues are rapidly transformed into larger ameboid phagocytic elements, the polyblasts or histiocytes.

(4) In our sections the majority of the histiocytes present were found grouped about blood-vessels. Histiocytes, smaller than the average histiocytes seen, were present in the tissue of some of the blood-vessel walls. It is quite probable that the histiocytes in the cornea were derived from the cells of the perivascular sheaths which accompanied the newly formed corneal blood-vessels. A similar theory as to the origin of the histiocytes from the adventitia was postulated by Marchand, and he called the large phagocytic, particulate storing cells having this origin adventitial cells.

We do not desire to make a definite statement as to the origin of the histiocytes present in the cornea of our case, but we believe that histologic evidence points to their origin from perivascular sheaths.

CONCLUSION

It is our belief that dystrophia adiposa corneae is brought about by an impairment of the physiologic processes of the corneal cells. This leads to changes in the fixed cells, which are seen microscopically in the form of pyknosis and vacuolization. The fat brought to the cornea is not completely utilized and becomes deposited there. Impaired cell metabolism leads to the disintegration of the lamellae and the liberation of the "invisible fat," a component of which is cholesterol and its esters. To these changes may be added

cholesterol and cholesterol esters from the blood stream, especially if they are present in abnormal amounts. The presence of substances foreign to the cornea results in a chemical irritation which produces a circumcorneal redness and corneal vascularization. The latter may be for the dual purpose of furnishing direct nourishment to the afflicted tissue, as well as for transporting phagocytic elements, especially histiocytes, into the pathologic area. We have no theory to offer as to whether toxins, loss of nutrition, or abiotrophy produce the impairment of the physiologic cell function.

We gratefully acknowledge the aid given us by Dr. Rudolph Schonheimer and by Dr. Patrick A. Delaney—the former for the chemical analysis of the portion of the cornea, and the latter for his aid in the preparation and study of the histopathologic sections.

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DISCUSSION

DR. F. H. VERHOEFF, Boston: It seems to me that in the light of our present knowledge the essayists have investigated this case as completely as possible.

Clinically, I have seen only one or two cases of what I believed was fatty degeneration of the cornea. I did not have an opportunity, however, to substantiate the diagnosis by microscopic examination. Such fatty changes and the formation of cholesterin occur wherever there is lack of oxygen. You find all these present in the subretinal fluid after old separation of the retina. You find macrophages here, too—I insist on calling these cells macrophages because this was the first name given to them, and no one certainly knows their origin or very much about them. I was not surprised that Dr. Katz was unable to discover their origin in the tissue he studied. He would have been fortunate, indeed, if he had been able to do so.

A unique case like this does not mean much at this time, but it is worthy of the full report given it, since in the future it will, no doubt, have considerable significance. At the present time we have no idea as to what the corneal process means or what its origin is. It is so rare that, obviously, it cannot be due to any ordinary conditions. Moreover, it has not been found associated with conditions such as cholesteremia or diabetes, which, on *a priori* grounds, we might assume could cause it.

DR. WILLIAM H. WILDER, Chicago: I had the opportunity of seeing the case that Dr. Katz has so ably presented, and he demonstrated to me the condition that he has described to you. I was particularly interested because at that time I had a very similar case, which is still under observation and may at a later time be reported in detail.

The patient is a lady in middle life, large, fleshy, and an abundant eater, whose left cornea presents an appearance similar to that of the case Dr. Katz has described. The vision of the left eye is reduced to hand movements. In the right eye, around the periphery of the cornea, an apparently similar condition is developing, which resembles a very much broadened and irregular arcus senilis. The central portion of the right cornea is clear, allowing good vision. The slit-lamp appearance in the case seems to be similar to that described by Dr. Katz, but the opacity has a distinctly yellowish color, as if it were a deposit of fat.

To call a corneal opacity a dystrophy is merely to conceal our ignorance behind a fine-sounding word. It may be true, as the word implies, that there is faulty nutrition of the cornea, but the gross appearance would suggest that there may also be some disturbance of fat metabolism and that the deposits in the cornea may be lipoid in character.

DR. DEWEY KATZ, closing: In the short time allotted for the presentation of this paper I have purposely stated the bare essentials of the case in order that I might have sufficient time to discuss the fundamental problems involved. To us, these problems were of prime importance.

There is no ground for disagreement with Dr. Verhoeff in regard to the term which should be used for the cells under discussion, since various names are used by different histologic schools. However, I believe it would be desirable to define exactly the meaning of the two terms—macrophage and histiocyte. Macrophage was the term introduced by Metchnikoff; literally translated it means "large eater." This name indicates a function of the cell. Histiocyte was introduced by Aschoff; literally translated this means "tissue cell." This term indicates the possible origin of the cell.

We have found 16 cases reported under the caption "Primary Fatty Infiltration of the Cornea," or "Primary Fatty Degeneration of the Cornea." A critical review of the reports reveals the fact that only eight cases fulfil the requirements of a dystrophy of the cornea. The other eight cases were without doubt secondary to some ocular inflammation. Greater discrimination must be exercised in the future in determining whether or not an existing or a pre-existing inflammation of the cornea, sclera, or uveal tract is or has been present before a diagnosis of dystrophia adiposa corneae can be made.