DISCIFORM KERATITIS SECONDARY TO SMALLPOX.

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In the case here reported a slight injury to the cornea occurred about the time the patient contracted smallpox. The eye became inflamed shortly before the eruption appeared, and subsequently ran a chronic course assuming the form indicated. With comments on the case are given abstracts of similar cases and a review of the literature. Read before the Ophthalmological Section of the Baltimore City Medical Society, December, 1920.

Case—Miss E was referred to me Feb. 23, 1920 by her physician, who had taken a foreign body off of the lower outer quadrant of the cornea on the 13th. The patient said that she had become so comfortable, after the foreign body had been removed, that she had returned to work, and that later it had become perfectly comfortable, but on the 17th her eye began to get red, and on the 19th became painful.

Feb. 23. A number of white vesicle-like formations are seen on the margin of the upper lid of the left eye. Cutaneous surface of the lid not inflamed. Bulbar conjunctiva shows about a half dozen red elevations in the region of the insertion of the internal rectus. The elevations are about the size of the lead in an ordinary pencil, are grouped closely together, are quite red, and do not contain fluid. Each single elevation looks very much like a phlyctenule. Other portions of the conjunctiva are injected, but there are no elevations. Cornea clear, and no mark from foreign body. Pupil active. Eye painful, photophobia and lacrimation marked.

There are a number of hard, painless, nonvesicular elevations on the forehead, face, nose, lips, and hands. Right eye normal. (Later learned that while the patient had continued with her work she had complained of feeling badly generally, but there was no particular reference to the eye until noted.)

Feb. 24th. More comfortable, eye a little less red. A very small central area of the cornea stains with fluorescein. Stained area not seen without the loupe. No change in spots on the lids, face, or hands. (Diagnosis of impetigo contagiosa and chicken pox considered.)

Feb. 25th. More comfortable. No changes in the conjunctival elevations;

cornea clear. Referred her to a dermatologist, who made a diagnosis of smallpox. The Health Department confirmed the diagnosis, and the patient was sent to quarantine.

March 16th. Released from quarantine on the 13th. No marks on face, or hands; margins of lids normal; conjunctiva still slightly congested, altho elevations have entirely disappeared. In the center of the cornea there is a round uniformly gray opacity that is a little larger than the pupil; the opacity is not deeply situated, but apparently is in the substantia propria, and is definitely outlined. Epithelium over the cloudy area is intact; pupil active; eye not painful; some lacrimation, and photophobia, but not so marked as at the first examination.

March 20th. Lacrimation and photophobia more marked; eye very uncomfortable; pupil active. Ordered atropin 1% t.i.d. Dark glasses.

March 24th. Pupil well dilated; little change in lacrimation and photophobia; conjunctiva not markedly congested. Opacity appears to be no larger, but has extended deeper in the cornea. Patient still very uncomfortable.

March 30th. Pupil not well dilated. Atropin 2%, one drop every 3 hrs.

April 2nd. Pupil well dilated. Patient says vision is better. Central opacity is still rather sharply defined, and appears to be superficial. There is a second deeper and concentric zone of grayish opacity that is not so dense, is circular, and involves about two-thirds of the cornea. The central portion of the opacity is about three mm. in diameter, the total opacity being about seven mm. Cornea does not take stain. Wasserman negative. Hot applications and dionin.

April 9th. Patient more comfortable.

Hot applications have given much comfort. Central portion of the opacity becoming more dense; the more diffuse, deeper, outer zone has not increased in extent. Pupil not dilated. Patient reports using atropin regularly. Atropin 5% t.i.d.

April 14th. Pupil dilated, opacity becoming more sharply circumscribed. Still complains of much pain.

April 15th. Reports eye comfortable yesterday, uncomfortable last night, comfortable today. Continue hot applications and atropin.

April 17th. In the cornea between the superficial and the deeper portion of the opacity there is a clear area that suggests a separation of the tissue. It appears as tho there were a drop of clear fluid lying between the lamellae. Patient continues comfortable.

April 20th. The deeper portion of the opacity is clearing, and decreasing in size. Vesicle like formation in the cornea is unchanged. No definite wall to vesicle, contents clear.

April 26th. Patient comfortable. Vesicle decreased in size, contents clear.

April 30th. Patient continues comfortable. Vesicle practically absorbed without leaving any trace. Peripheral opacity decreasing in extent, and density.

May 10th. Cornea clearer, central opacity more dense than peripheral portion, there being a definite difference in the density of the two areas. Photophobia and lacrimation much less. Injection of the conjunctiva has passed off.

May 15th. Cornea clearer, central opacity a little smaller, outer zone smaller and fainter. Boundary line between central, and peripheral portion of opacity is pronounced; there is not a gradual transition from inner to outer zone.

May 24th. Cornea clearer, central opacity rather dense; is about the size of the pupil. Outer zone is gradually fading out.

May 28th. Central portion unchanged, peripheral portion fainter. Discontinue atropin. Dionin 1%, one drop at bed time.

June 3rd. Pupil about normal size; central opacity less dense; peripheral

opacity shows only a faint halo. Vision 20/200.

June 6th. Vision 20/120. No change in central opacity; no photophobia, lacrimation, or redness of the conjunctiva. Continue dionin. Return to work tomorrow.

June 24th. Pupil normal size, and active. A central round opacity covers the entire pupillary area; margin of opacity quite definite. Halo has disappeared. Vision 20/200. Continue dionin.

Nov. 16th. Opacity somewhat smaller than at last examination. Is $3\frac{1}{2}$ mm. in diameter, and somewhat irregularly circular; not sharply outlined, the outer margins gradually fading into the clear cornea. In the lower, inner quadrant there are numerous tiny yellowish-white pin point like spots, which are so numerous as to lie in contact with one another. By oblique illumination it is difficult to determine the position as to the depth of the opacity. Apparently the yellowish-white spots are more superficial than the general gray opacity. All irritation has passed off. Vision 20/120.

COMMENT WITH REVIEW OF LITERATURE

The case just reported presents a number of interesting aspects. The variety of keratitis is certainly a rare one. The relation which it bore to the foreign body, and to the variola, is a question that becomes all the more important because the patient was one whose case was brought before the State Accident Commission for decision as to compensation insurance.

Concerning the diagnosis, the appearance quite agrees with the description of disciform keratitis.

Disciform keratitis was first fully described by Fuchs¹ in 1901, altho, according to Weeks², it had been described by v. Arlt of Vienna as early as 1870, under the name of abscessus siccus corneae. Vossius described it in 1885, but mentioned it as an abortive interstitial keratitis.

Fuchs³ under the heading Keratitis Disciformis says, "This is a keratitis that is allied to ulcus serpens, and consists in the development in the middle layers of the cornea of a gray disc shaped opacity.

In the center of the disc a small more deeply clouded speck is commonly observed. The periphery of the disc is sharply delimited by a border of deeper gray which in many cases is made up of concentric lines. This disc-shaped infiltrate never becomes yellow, nor leads to disintegration of the cornea. Only exceptionally a small loss of substance develops over a certain circumscribed area. The irritation symptoms are mostly not pronounced and hypopyon is absent or scanty. The course is protracted, as it takes one or more months for the eye to become free from congestion, and for the infiltration to become transformed into an opacity that becomes permanent. The cause of the disease, just as *ulcus serpens*, is an infection of the cornea from without, the central grayer speck representing the point of entrance of the bacteria. The epithelial lesion that precedes the infection may often be attributed to a slight injury, and in some cases to an antecedent herpes corneae febrilis, but in many cases the cause remains unknown."

Opportunities for microscopic study of disciform keratitis have been infrequent. Such studies have been made by Verhoeff⁴, Meller⁵, Hadano⁶, Wagner⁷, and Kuboki⁸. In the report by Verhoeff, as well as in that by Meller and by Hadano, there is apparently some uncertainty as to whether it is a case of disciform keratitis, or keratitis profunda. Verhoeff and Meller examined the whole eye, while Hadano examined a piece of tissue removed from the cornea with a sharp spoon.

Wagner's case was of particular interest, and is related in full: "A man 77 years of age presented a large crescentic marginal ulcer that stained with fluorescein. The largest part of the corneal center looked dull, somewhat fatty, and did not stain with fluorescein. The center is yellowish-white, sharply limited; and the opacity seems to be in the corneal substance, while a much larger grayish opacity, still deeper, surrounds it. Only at the nasal side a connection between the larger marginal ulcer, and the deep central disc exists."

Because of lack of improvement and

pain, enucleation was done: four days after admission to the hospital.

In summing up his microscopic findings he says: "We see that the necrotic disc is limited forward by a fairly strong infiltrated tissue, with numerous killed lymphocytes; backward, partly by a similar infiltration tissue, partly by the membrane of Descemet, partly by an agglomeration of polynuclear leucocytes, and toward the sides by living corneal tissue, which shows a moderate increase of its normal nuclear elements. Descemet's membrane is absent for about the fourth part of the corneal center. For nearly its entire extent, a single layer of lymphocytes is found between it, and the corneal parenchyma. The endothelium is nowhere present in normal condition. It is entirely absent or it is much proliferated. Spots are found where the endothelial cells are irregularly dispersed on the membrane; polynuclear leucocytes and some lymphocytes lie between these.

In other places the endothelial cells are entirely free from the membrane and sometimes at a little distance away; they then have proliferated in the fibrinous hypopyon, strongly infiltrated with polynuclear leucocytes, which cover the posterior wall of the cornea. They show a strong inclination to proliferation, which goes sometimes so far that true giant cells are present."

Wagner concludes "that disciform keratitis is characterized by a disc like part of strongly altered corneal tissue, lying deep; caused by toxins, produced by microorganisms existing in the epithelium. These toxins have not yet been discovered, but their presence we can surmise with great probability."

In Kuboki's case the disease was in the inner and lower quadrant, and showed in the center two concentric, ring like opacities. Histologic examination of a freshly cut portion showed that the opacity was due to cell infiltration, which occurred in the outer and middle layers of the parenchyma. Bowman's membrane was partially defective. The epithelial cells of the inner basal layers were irregular. The more lightly affected portions between the rings

showed cell infiltration due to edema, necrosis, and fatty degeneration.

Altho some of the features of disciform keratitis, as described by Fuchs, are lacking in this case it seems to me there can be no doubt of the diagnosis. There are but two points of dissimilarity, the first being the absence of the clearly defined ring, and the second the vesicle in the deeper structure of the cornea. There are a number of points of confirmation: A definite circular opacity, below Bowman's membrane, equal to the size of the pupil, and an outer zone involving about one-half of the remaining corneal tissue; no loss of epithelium, or breaking down of the deeper tissue; a mild iritis, no hypopyon, a marked photophobia and lacrimation; moderate injection of the conjunctiva, a long convalescence, resulting in a permanent impairment of vision.

In this study of disciform keratitis I have been impressed with the apparent confusion of disciform keratitis, *ulcus serpens*, and annular keratitis.

In the disciform keratitis there is no loss of epithelium or corneal tissue, except on rare occasions, and then the loss is slight, the opacity is central, circular, and may involve the cornea to any depth; it runs a long course, and results in impaired vision.

The early stage of *ulcus serpens* produces changes that are similar to changes in advanced disciform keratitis, but in a short time, in the *ulcus serpens*, there is a breaking down of the corneal tissue, ulcer formation, intense iritis, turbid aqueous hypopyon, and soon perforation of the cornea.

Fuchs⁹ describes annular keratitis as a variation of parenchymatous keratitis, and says it is that form which begins with maculae in the central portion of the cornea; and that it not infrequently happens that the maculae at a certain distance from the center are particularly dense, thus forming a very opaque ring which in its subsequent course contracts more and more toward the center of the cornea.

According to Fuchs¹⁰ disciform keratitis is an infection of the cornea from without, the bacteria gaining entrance

thru some slight injury to the corneal epithelium, and some cases may be due to an antecedent herpes corneae febrilis, but in very many cases the cause remains unknown.

Verhoeff¹¹ contends that it is of neuropathic origin, and states that it also may be caused by nongonorrheal ophthalmia neonatorum, due to the streptococcus mycosus.

Weeks¹² thinks that tuberculosis at times may be a cause.

Zani¹³ regards it as an infection that gains entrance thru an injured epithelium.

Nishimura¹⁴ reports a case in which the hay bacillus was isolated. But I wish especially to mention that Roemer¹⁵ states that it has *repeatedly developed after vaccine infection of the cornea*, and that Schirmer¹⁶ has also observed it from an *infection from vaccine virus*.

In discussing the importance of vaccinia to the eye, Roemer says, "In many cases the cornea becomes involved, especially when a defect is present in the epithelium, and a keratitis develops which resembles, to a certain extent, disciform keratitis. A delicate gray disc is formed, its margins denser than the central portions, which is sometimes surrounded by parallel rings. At the same time symptoms of a serous iritis appear, with deposits on Descemet's membrane. Permanent opacity results."

Schirmer writing on "Keratitis Disciformis and Keratitis Postvacciniolosa," reports: "The mother of a child vaccinated successfully developed an inflammation of the right eye eleven days after vaccination. After fourteen days she was examined. A vaccine pustule was found on the lower lid, the cornea had a paracentral epithelial defect of the size of a lentil, and to the nasal side of this a distinct gray circular line of infiltration of the parenchyma, perhaps even of the posterior surface, and irregular striations. The iris was slightly muddy and swollen. The epithelial defects healed over, but a large central, cloudy plaque, with a larger gray circle around it developed."

He concludes his article stating, "The term keratitis postvacciniolosa should be

abandoned in favor of keratitis disciformis."

Zani¹³ reports three cases, one of which follows a vaccine pustule on the lid.

Baker¹⁷ in a paper under the title "Eye Complications of Smallpox," published in 1903 describes the ocular complications observed in 2,746 cases. There were various lid, conjunctival, and corneal complications. Of the corneal complications five were noted as having small ulcers when discharged from the hospital. Two of these five perforated and resulted in phthisis bulbi.

I feel that we are justified in believing that the other three which were diagnosed as small ulcers were cases of disciform keratitis. They evidently developed late in the course of the smallpox, and were not well when the patients were ready to be discharged from the hospital.

Chance¹⁸, in *American Medicine*, describes eye complications observed in 2,000 cases of smallpox in Cleveland, in 1901 and 1902. He states, "The corneal inflammation may only be a slight, superficial haze confined to the corneal conjunctiva, or Bowman's membrane, or it may extend rapidly, and involve the entire cornea."

Finlay¹⁹ (1897) under the title of *Keratitis Variolosa* describes 24 cases of an unusual form of keratitis following smallpox that he observed during an epidemic in Havana. He states, "The usual time for the appearance of this complication is between the end of the second and the end of the third week of the disease, after desiccation has commenced; occasionally it occurs earlier, at times not until after convalescence is fully established. At this, its earliest stage, one finds at a point in the cornea, somewhere between its center and the margin, an irregularly square shaped patch, from one to two mm. square (even when involving the center of the cornea its situation is apt to be excentric). The greater part of its area is transparent, tho distinctly differentiated from the remainder of the cornea by oblique illumination with accurate focusing, and gives one the impression of a more or less large drop of fluid contained in the substance of the cornea. The edge nearest the corneal

margin, however, stands out prominently, showing a deep milky-white infiltration. The epithelium over all this area is intact. At this stage one also finds moderate ciliary injection, marked photophobia, blepharospasm and lacrimation. * * * Gradually the margin of infiltration extends over the remainder of the patch till the whole presents a uniform milky-white or yellowish color; occasionally, however, the edges show deep infiltration thruout the whole course. Whilst this is going on a partial or total desquamation of the epithelium covering the infiltration area takes place. Ciliary injection is, of course, more marked. * * * Seldom is there an accompanying iritis. Hypopyon at times is present; in none did spontaneous perforation occur. After lasting for a longer or shorter time, the objective symptoms slowly commenced to recede, the infiltration areas gradually becoming vascularized. This vascularization in its turn diminishes, and finally a more or less dense leucoma results."

This description was written, by Finley, about four years before Fuchs' description; and while there are points of dissimilarity, I believe these cases should be classed as disciform keratitis, due to smallpox infection.

Councilman²⁰ in his experimental work in searching for the organism of smallpox showed that he could inoculate from eye to eye indefinitely without any change in the character of the lesions. He showed that no other injury to the cornea of the rabbit, or no other infection, produced lesions of the same character as those produced by inoculating the cornea with vaccine, or variola virus. He inoculated from the cornea of the rabbit to the calf in the fifteenth and twenty-fifth generation, and in each obtained perfectly typical vaccine pustules. Children were vaccinated from the cornea of the rabbit in the thirty-sixth generation and typical vaccinia resulted.

Schirmer vaccinated with the gray corneal epithelium of one of his patients upon the cornea of rabbits, and guinea pigs, and produced disciform keratitis. Subsequent vaccinations from them to other animals reproduced the disease.

Nishimura isolated the hay bacillus from his case of disciform keratitis. The same form of corneal lesion was reproduced experimentally in the rabbit.

Zani interprets one of his cases as the result of nutritional disturbances of the cornea, consequent upon intense chemosis, thru which the specific organism gained entrance.

It is quite apparent that disciform keratitis that originates from vaccinia or variola is an infection that gains entrance into the cornea thru a defect in the corneal epithelium, and that it comes on late in the course of the smallpox.

In the case under study the foreign body was removed from the cornea four days before the eye became inflamed. Eight days later when the patient was removed to quarantine, the conjunctiva showed elevations that were analogous to those on the lids and face that later developed into pustules. At this time the cornea was clear. It seems reasonable to suppose that had the cornea been infected thru the break in the epithelium caused by the removal of the foreign body, and with the original infection, there would have been corneal changes of the same stage of development as in the conjunctiva, and on the lids and face. Such changes were not present. It is likely that the infection of the cornea did not occur at the time of the primary infection, but that it occurred in the later stage of the disease; possibly thru the break in the corneal epithelium that was present seven days after the conjunctiva began to get red. At this time (of conjunctival inflammation) elevations that resulted in pustules had formed on the lids, forehead, and face, but the cornea showed no sign of involvement. When the cornea did become involved is uncertain. On this point the patient could give no information.

The onset of her smallpox was about the time that she got the foreign body in the eye. After the removal of the foreign body she returned to work, and in a few days began to feel very badly, (the eye in the meantime having become quite comfortable). During that time, the patient states, she had headache, and could hardly continue with her work.

According to Story²¹ and also to Chance, smallpox pustules do not form on the cornea. They may form on the conjunctiva near the limbus, when extension into the cornea may follow. Chance further states that corneal complications also may arise during the stage of desiccation, when the contagion is transmitted from the broken down pustules, as, for instance, those of the skin or the eyelid.

Parsons²² states that the cornea is never involved before the 10th day, and generally it is the 12th to the 14th day.

In the cases reported by Finlay and by Harlan²³ the opacity appeared near the end of the second week, or even as late as the beginning of desquamation.

It is quite likely that the infection in this case occurred from the pustules that had formed on the lid, and conjunctiva. On her return from quarantine, which was 28 days after the eye first began to get red, and 20 days after the last observation, the corneal disease was in its early stage. This is shown by the small central opacity, and by the later extension of the opacity, and still later by vesicle formation, and a prolonged convalescence.

In the inoculation experiments the virus was injected into the cornea of healthy guinea-pigs, rabbits, and calves, the animals not having undergone the reaction from vaccination or from smallpox, and the lesion of disciform keratitis was not produced. So too in the corneal lesions that are reported as following accidental vaccine infections, there was not produced the picture of disciform keratitis; but a much more severe reaction, and a much more serious breaking down and loss of corneal tissue. This was seen in Caillaud's²⁴ case in which there occurred an injury to the cornea in vaccination, and three days later a central ulcer with the deep and slowly healing abscess, leaving a large scar. Almost similar conditions have been observed by Snyderacker²⁵ and by Story²⁶.

In the type of keratitis under discussion the corneal infection appears to occur after the pustules are formed, sometimes as late as the period of desiccation, the blood in the meantime having had time to react against the toxin, so

that when the second infection occurs, which involves the cornea, the reaction is not so severe.

Because there had been a foreign body on the left cornea near the time of the onset of the smallpox, the patient believed that the loss of vision was due to the foreign body. She made such a claim before the State Industrial Accident Commission. The Commission accepted her opinion, and awarded her compensation for the loss of an eye.

I am of the opinion that the corneal changes that at times occur during the progress of a case of smallpox are the result of a secondary infection, and that the corneal reaction is less severe because of the previous systemic reaction to the same toxin.

The indications are that disciform keratitis secondary to smallpox is a specific inflammation, probably as specific as the pustule itself.

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