THE BRITISH JOURNAL
OF
OPHTHALMOLOGY
JANUARY, 1919

COMMUNICATIONS

ON THE FORMATION OF CLEAR SPACES IN CORNEAL NEBULAE*

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THE changes in the cornea that follow inflammation are often striking in appearance and interest. No visible sign of inflammation may be left, as is not uncommonly seen after perforation of ulcers in ophthalmia neonatorum, or after mild attacks of interstitial keratitis; on the other hand, such factors as the persistence of vascular channels, the contraction of scars, changes in nutrition, and stagnation of lymph circulation, may bring about slowly advancing changes after all inflammatory appearances have long subsided.

Many of the changes are obscure, and the method of their production is unknown; but even such knowledge as we already possess is of use in the diagnosis, not only of ocular but of general pathological states.

The presence of clear lines in old corneal scars has been described by very few observers, although such lines have been long known, and were seen even before the *loupe* came into general use.

The earliest observation I have of them is a drawing given me

* Presidential address of the Section of Ophthalmology of the Royal Society of Medicine, read on November 6, 1918.

by Nettleship when he dispersed his collection in 1901; it is a pencil sketch of the two eyes of an old lady of 72, made in 1878, and was headed "Linear paths of clear corneal tissue in large diffuse leukomata, the leukomata probably caused by ulcers after small-pox in infancy." One of the drawings represents the branching form of clear lines in the body of a nebula, the other suggests a geometrical arrangement of lines. The drawing was apparently a single observation and not thought worthy of publication.

In 1893, in the *Beiträge zur Augenheilkunde*, Fuchs published a paper on these lines. He discussed at length the various linear formations which may exist in the cornea, Recklinghausen's canals, Bowman's tubes, and striated keratitis, and suggested that the lines were due to changes in the lymph streams in the nebulous area. He gave a number of sketches which well suggest the main forms of the lines.

W. Adams Frost showed a case of annular opacity of the cornea in 1896 (*Trans. Ophthal. Soc. U.K.*, Vol. XVI, p. 53) which is clearly a secondary opacity round the head of a tuft of vessels.

The best and most recent description of these lines is that of Sydney Stephenson (*Trans. Ophthal. Soc. U.K.*, Vols. XXXIII and XXXV). He gives a very good drawing of a case of clear branching lines running into a corneal nebula from the lower part of the limbus in an old case of interstitial keratitis; his other case is one of lines traversing a nebula with a well-developed secondary opacity. This case had been the subject of repeated attacks of corneal inflammation in early life.

In his remarks Stephenson says: "The clear lines remind one of blood-vessels, and it is probable that such were present when the opacity was recent. The present condition has likely followed resorption of the vessels, and inasmuch as many of the striae are wider than any corneal vessel there has almost certainly been some clearing of the opacity in the neighbourhood of the vascular streams."

In the discussion which followed, J. B. Story said he had seen such lines in cases of interstitial keratitis, and thought they were due to degenerate blood-vessels, or to a clearing round the course of shrivelled vessels. At the same meeting I showed some drawings of such lines.

My own attention was first directed to this subject about 1894 in a case of Marcus Gunn's, in which there was a crosshatch of clear lines in a central nebula; my first attempt at a careful drawing was in a case of Silcock's in 1896. Since then I have recorded cases as they have come, and have often made rough sketches of them; these sketches amount to scores: they have made me familiar with all forms of clear lines and of their surrounding opacity, and I have learned to recognize their essential features.

The advantage of a good drawing is that it is precise, it conveys to the mind the exact appearance so far as that can be done, and it remains a trustworthy record. I owe a great deal to some pen sketches, by an unknown hand, on a Moorfields case sheet of Adams, made eighteen years before I saw the case; it gave information as to the previous state of the cornea, and as to the changes which had taken place such as no description could possibly have given.

As the changes are dependent on the presence of blood-vessels, it will be best to describe the various types of vessels which are seen in the cornea; the types vary mainly according to their depth. Surface vessels pass over the edge of the cornea from the conjunctiva, run beneath the epithelium on the surface of Bowman's membrane, divide and twist freely much like the branching of an oak tree, the *arborescent form:* Fig. 1 A. These occur in superficial inflammations, ulcers or trachoma, and represent free branching uncontrolled by the pressure of surrounding tissues.

Besides this surface invasion of trunk vessels with their branches, the terminal capillary loops of the limbus advance over the cornea in a series of arches or loops not arising from any main trunk; Fig. 1 B. This *terminal loop* form is common in marginal inflammations and ulcers and trachoma; it is also seen in acute or vascular forms of interstitial keratitis in which vessels invade the cornea at almost all depths: it persists as fine silky lines on the surface.

Brush or Besom Form: Fig. 1 C. Vessels entering the substance of the cornea can often be traced from a trunk vessel running on the surface of the sclerotic to a few millimetres' distance from the limbus, then dipping down into the sclerotic and reappearing in the substance of the cornea. These deeply placed vessels are constrained by the layers of the cornea through which they run, to a less free distribution than that of the surface vessels; the course of their branches is more parallel and is more like the branching of a birch tree than that of an oak. This is the type which occurs in interstitial keratitis and other forms of deep inflammation. The leash of vessels which accompanies the fascicular or leash ulcer, although it is on the surface, approaches the brush formation, as it lies in the groove hollowed out by the march of the ulcer, which limits its free development.

Umbel Form: Fig. 1 D. There is another form which occurs in local inflammations of the deeper layers of the cornea, such as chronic abscesses or mild attacks of interstitial keratitis, not severe enough to promote a general vascular invasion, in which a single vessel grows into the cornea from the margin, and remains unbranched till it divides into a number of short straight radiating vessels like the head of a parsley flower.

Generally, arteries cannot be distinguished from veins by the naked eye, but with the *loupe* each vein can be seen single and accom-

panied by one or two small arteries; the veins are larger and darker than the arteries, and the transition from one to the other can be seen to take place without the intervention of capillaries: all these small vessels are to be regarded as capillaries in which the distinction of artery and vein is retained to the final transition.

It is uncommon for vessels to disappear and leave no trace; even though they contain no blood they may generally be seen as fine silky threads lying on or near the surface or as clear lines beneath the surface.

Vessels keep to their own level or layer of the cornea, their branches do not commonly anastomose with those of a different layer; it is possible to see tufts of deep vessels coming from different parts of the cornea crossing and breaking up into their finest branches without joining those coming from another direction, provided that they are at different levels; the layers of corneal tissue are thick and resistent enough to prevent the union of vessels of different layers. In severe cases of interstitial inflammation, the corneal lamellae are softened and may become masses of granulation tissue only; vessels may then penetrate them and communicate with those lying in other layers.

After this has occurred we sometimes find during the subsiding stage of severe interstitial keratitis, large trunks in the substance of the cornea ending in a fine network of vessels on the surface at one end, and at the other end disappearing beneath the limbus after having broken up into small vessels (Fig. 2).

The clear lines divide themselves into two kinds, the geometrical group, and the formation which I have for years called the mushroom cap or coral reef.

Geometrical Lines

These are clear lines in which no trace of haze, opacity, or structure can be seen; they lie in the midst of nebulae. The nebulae are of varying density, sometimes faint clouds, only visible with careful arrangement of illumination, and sometimes densely white and calcareous looking, so that they have been mistaken for lead deposits. The clear lines are perfectly straight or run in large smooth curves; they are sometimes parallel, sometimes diverging or converging, or crossed by other lines, and sometimes radiating from a centre. They are often so perfectly straight and sharply cut that they appear like machine-ruled geometrical figures, such as are seen in the Second Book of Euclid; they are often very much broader than any possible vessels. They can sometimes be traced to the limbus, but are often seen only in the centre of the cornea, and disappear outside it. As they have no visible structure they can only be made visible by the opacity in which they lie; where there is no opacity there are no visible lines.

Generally the opacities can only be seen against the pupil as a background, and require the use of a mydriatic, as well as of properly adjusted oblique illumination. They interfere little with transmission of light, they are less well seen by the ophthalmoscope than by the *loupe;* and they do not interfere greatly with vision: they are extremely thin layers which reflect light at certain angles, and except under such favourable conditions, many of them are not visible.

The explanation of the existence of these lines has been that they are lines of clearance or disappearance of nebulae due to the development of lymph tracks in already formed nebulae.

It is difficult to understand how perfectly straight tracks sometimes equal in length to one-third or one-half the corneal diameter could make their way across existing nebulae—they have no resemblance at all to Recklinghausen's canals or to Bowman's tubes, and if they had we should have to show how a lymph channel could be formed in the substance and at the expense of the nebulous material.

They have as their basis the tracks of old vessels; there can be little or no doubt about this, the process has been watched. In one case of interstitial keratitis I had made a sketch note of the presence of a large tuft of vessels invading the cornea (Fig. 7). I saw the patient some years later during a recurrence in the other eye. Some of the old blood tracks previously noted had become perfectly straight, as if stretched longitudinally, and had lost all their irregularities; others had disappeared. The geometrical formation was present (Fig. 8). In one or two cases I have detected a faint ruby tinge in the geometrical lines; they evidently still contained some blood colouring matter.

I believe the explanation to be the following:

At a certain depth within the layers of the cornea a tuft of brush vessels makes its way; at the end of the attack, the vessels shrink and lose their blood, but remain as potential channels. These channels become greatly flattened from compression in the layers of the cornea, during and after subsidence of inflammation, and owing to this they have a much greater width than when they contained blood.

The contractile process which follows all attacks of inflammation produces a stretching along the course of the newly-formed vessels confined to the coat of the vessel and its immediate neighbourhood; it is so limited that it does not interfere with the same process going on in neighbouring vessels. The result of the stretching is to straighten the course of the vessel, to remove inequalities and deviations, and to give it the geometrical quality of a straight line, the shortest distance between two points.

When vessels invade the cornea they go in response to some irritating cause which may be quite small and local, the rest of the

cornea may be little involved, and may be capable of complete restoration except for the presence of the vascular channels. The effect of vessels running through healthy cornea is an interference with the lymph circulation, i.e., with the flow of nutritional elements; where this interference is continuous and prolonged the cornea becomes opaque. It is this secondary opacification which makes the old vascular channels visible, and is more likely to occur at the centre of the cornea than at the periphery which is nearer the sources of supply.

The conditions most likely to result in these lines are acute vascular cases of interstitial keratitis which run a rapid course and result in little or no change of a permanent kind in the endothelium; if there is much change in the posterior part of the cornea the lines are masked or invisible. Insterstitial keratitis is not a necessity; any cause which produces a brush of deep vessels may have as a result geometrical lines.

Of 25 cases of geometrical lines investigated as to cause, in 6 there had been interstitial keratitis; in 2 cases ulcers and interstitial keratitis, and in 2 others probably interstitial keratitis. In 2 there had been an injury with perforation of the cornea; in 11 there had been ulcerations of various kinds penetrating deeply into the cornea, and in 4 no history could be obtained and no evidence of the nature of the case could be found.

Mushroom Cap

The second group of cases, to which I have given the name mushroom cap, forms quite a striking and beautiful object with the *loupe*, and is easily seen as to its main features by the naked eye. It has the appearance that a section of a mushroom would have if carried through the side of the stalk and head, showing the stalk in section, the crescent shaped head with the gills on its concave edge. The stalk is of a delicate blue-grey colour, and can often be followed to the edge of the cornea; sometimes it can only be traced for a short distance or made out as a nebulous spot within the concavity of the crescent. Vestiges of vessels can often be made out on the stalk, not extending as far as the head of the mushroom: between the head and the stalk there is an interval of clear cornea. The head of the mushroom is crescentic in shape, densest on its concave edge, fading away to nothing on its convex edge. The concave edge is almost always fringed with prolongations of the opacity towards the geometrical centre of the crescent; these are like the gills of the mushroom. The crescentic head of the mushroom contains neither blood-vessels nor remains of them, except when crossed by vessels belonging to another system. The head is of a different colour from the stalk, having a dirty white or buff colour in contrast with the cool grey of the stalk. It is very thin,

as may be easily seen if looked at from one side, and appears confined to one layer of the cornea. Sometimes the crescentic head becomes a complete circle, surrounding a central spot, the coral reef; but generally the stalk can be seen passing out to the edge of the cornea. Where this happens the complete circle dips behind the stalk; the stalk appears to be always superficial to the head of the mushroom.

Besides this simple arrangement of a single mushroom, there may be two or more systems, each with its head and stalk, crossing one another so that we get clear lines running across the head; or coalescing with each other so that we may have an opacity with gills on both sides; all such complications will be understood if one gets to recognize the characteristic forms of stalk with its terminal vessels, having fringes of opacity coalescing into a mass.

There can be little doubt as to the nature of these mushroom heads. They are not the scars of ulcers themselves, they are too large, too smooth, and too much like each other; they are different in colour from primary nebulae. They have also been seen to form; they appear a certain time after an ulcer has come to an end, the shortest time I have noticed is 9 months, but I have had notes of a case from Mr. Foster Moore of an officer who got a corneal ulcer in Gallipoli, was watched during treatment and convalescence from August to December, 1915. There was no secondary opacity then, but he was warned by Foster Moore that a secondary opacity might come. Four months later a fine mushroom cap had appeared.

They are secondary to ulcerations which have been attended by invasion of the cornea by blood-vessels; they appear specially to follow the fascicular or leash ulcer, but remain isolated from it by a space of clear cornea; the fringes of opacity seem to dip down between between the areas supplied by each terminal loop of capillary vessel.

A form of mushroom head is also seen after attacks of scleritis in which the cornea has not taken part; they are often the same in appearance as the mushroom head, that is, crescents of opacity lying in perfectly clear cornea with the concavity directed towards the scleral focus of inflammation. Successive attacks of scleritis may each have its secondary opaque crescent in the cornea, which may interlace or may form a continuous wavy band resembling an irregular arcus senilis. The opacities secondary to scleritis are not so generally gilled on their concavity as the purely corneal ones.

Similarly dermoid tumours at the edge of the cornea, pigmented moles or naevi of the same region may have secondary opacities.

The first necessity for the formation of all these secondary opacities is destruction of tissue attended by ingrowth of blood-vessels; the contraction which follows either interferes with nutrition, or interrupts the flow of lymph through the cornea in

their neighbourhood leading to stagnation, concentration, and deposit of salts.

There is some resemblance beween these opacities and the arcus senilis; the arcus is more likely to occur in eyes which have had corneal ulceration, that is, where nutrition has been interfered with; the clear space between the outer edge of the arcus and the scleral edge is analogous to the clear space between the concave edge of the cap and the end of the leash of vessels.

In one or two cases, round clear holes, like those found in the calcareous bands, have been seen; but no evidence of calcareous deposit, such as roughening of the surface, has been seen even where the mushroom has existed for seventy years.

AN UNUSUAL CASE OF IDIOSYNCRASY TO QUININE

BY

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MR. A. G., a dispensing chemist, understanding that the writer was interested in quinine poisoning, consulted him as to the nature of certain unpleasant symptoms, which he experienced when he took low doses of ammoniated quinine or of any other form of the drug for influenzal colds. He stated that within a quarter of an hour of taking the drug, he suffered from headache, deafness, a difficulty in seeing clearly, and a contraction of his field of vision. At the same time, he found a difficulty in reading, the letters appearing doubled. He consented to take a low dose for the purpose of observation. That actually taken was 2 grains of powdered sulphate of quinine in a cachet. Being a very busy man, the time he could give was limited.

On examination beforehand, it was found that the edges of his disc were slightly blurred and surrounded by faint haloes; the appearances suggested that he might at some time have had a very mild optic neuritis; the colour of the discs was normal. He stated that some years previously, he had had a severe attack of influenza, and had noticed that his sight had been worse ever since. The R.E.V.=6/6 nearly, not improved by spheres; L.E.V.=6/6 slowly but correctly; the diameter of each pupil=3·5 mm.; he read No. 1 type easily with his own glass at 41 cm.

Twenty minutes after swallowing the quinine, he had a headache, and was deaf and rather slow in manner. R.E.V.=6/12 partly; L.E.V.=6/6 partly; the optic discs were decidedly paler than before, and the arteries were slightly but distinctly lessened in