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COMMUNICATIONS

DERANGEMENT OF THE CORNEAL NERVES

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IN former times there used to be many disputes with regard to the possible existence of trophic fibres in nerves, but to-day it is generally supposed that there is no need to assume the presence of special trophic elements. All nerve fibres may be regarded as trophic. They are intimately concerned with the activity and preservation of the cells to which they are distributed, so that a cell deprived of its nerve supply is heavily handicapped. Moreover, an injured nerve cell often discharges abnormal impulses along its fibres, whereby the tissues suffer further harm. In certain clinical conditions it is impossible to be certain whether changes observed in the affected part are due mainly to the loss of normal controlling nervous impulses, or whether the damage is caused chiefly by active deleterious stimuli conveyed along nerve fibres.

The epithelial cells of the cornea are extremely sensitive towards any interference with their nerve supply, but most of the clinical evidence suggests that abnormal impulses derived from unhealthy nerve cells or nerve fibres are chiefly responsible. Thus the corneal nutrition hardly ever suffers as a result of cataract extraction—an operation which must for a time cut off many of the cells from their customary nervous control, however much overlapping there may be on the part of nerve fibres entering

from different points on the circumference. Then in herpes zoster ophthalmicus, although there is almost always loss or impairment of the corneal sensation, yet only a minority of the cases proceed to develop keratitis. Furthermore, neuro-paralytic keratitis is not unknown in patients whose corneal sensation is retained. For these and similar reasons one must conclude that mere severance of normal nervous connections does not as a rule provoke serious corneal lesions, although it can predispose to such lesions by abolishing protective reactions.

The nervous communications of the cornea become disordered not only in conditions that are primarily neural, but also in any form of acute corneal infiltration. In most cases of hypopyon ulcer, for example, the whole surface of the cornea is insensitive to touch. Similar anaesthesia can be observed in acute glaucoma. Verderame has correctly pointed out that the corneal nerves are rendered more easily visible as a result of various pathological processes. Thus, in a typical case of keratoconus, it is well known that the nerves of the cornea become abnormally distinct. In early cases of interstitial keratitis I have often been able to see the nerves clearly without the aid of a loupe. Among normal corneæ, however, the degree of visibility of the nerves varies within wide limits. Often they can be seen by focal illumination and the use of a loupe. In other people they are comparatively difficult to see, even on slit-lamp examination. They occur in the middle and superficial layers of the substantia propria. Having entered at the limbus, they approach the centre of the cornea in a radial direction, fading from view before the end of their course. They branch into two or three sub-divisions at an acute angle, and they look like strands of fine thread. At the present stage of development in slit-lamp technique, direct observations on the inter-epithelial nerve-plexuses of the living eye are not feasible. Therefore many problems concerning neuropathic keratitis remain unsolved.

In herpes zoster ophthalmicus the association of ocular lesions with damage to the Gasserian ganglion is established by repeated pathological investigations and experiments. Neuro-paralytic keratitis following operative interference with the ganglion provides another example of this association. In addition to these two conditions, however, there are several corneal disorders in which the clinical evidence indicates derangement of the nerve supply as an important factor in causation. It is proposed in this paper to discuss some of these disorders after making brief mention of the main features of neuro-paralytic keratitis. Herpes zoster ophthalmicus will be considered in a later paper.

The main characteristic of neuro-paralytic keratitis is an epithelial oedema, most intense in the centre, but to some extent

involving the whole surface of the cornea, and greatly varying in severity among different patients. At one end of the scale are cases showing rapid exfoliation. At the opposite extreme are those in which the epithelium displays minute vesicles for months or years without any demonstrable breach of surface. In these mild cases the oedematous cells or cell-groups are, as a rule, inconstant in size, as contrasted with the condition of uniform epithelial bedewing commonly found, *e.g.*, in acute glaucoma. If a breach occurs on the surface, the corneal substance is liable to undergo rapid destruction, thus producing hypopyon ulcer. Lid-suture performed as a prophylactic measure, or else at the first sign of epithelial loss, usually succeeds in preventing this disaster. In order to protect the cornea from deep ulceration, it is not necessary for the lid-suture to be complete. Cases have been recorded in which rapid healing has resulted from partial suture. Sometimes there has been an immediate recurrence of ulceration after division of a small outer bridge of lid-tissue, not enough to have screened the eye from contact with the air. No satisfactory hypothesis has been devised as an explanation for all the phenomena in neuro-paralytic keratitis, although much speculative ingenuity has been employed in trying to account for them. It seems clear, however, that there must be a peripheral as well as a central factor in the causation of neuro-paralytic ulceration of the cornea.

I recently examined a 56-year-old woman who complained that her right eye, and the right side of her face had never been normal since a mastoid operation performed fifteen years previously. A right-sided facial nerve palsy was present. There was anaesthesia of the right cornea, and of the skin supplied by the first and second divisions of the right trigeminal nerve. In the centre of the affected cornea were numerous pin-point, calcareous-looking opacities situated in the epithelial layer. The peripheral epithelium presented a multitude of flat vesicles inconstant in shape and size. I feel sure that the original condition of this cornea was that of epithelial oedema over its whole surface, and that the white dots represent degenerative changes supervening on long-continued oedema. I have been able to watch similar opacities replace epithelial vesicles in a case of chronic uveitis. In this connection it is interesting to remember that epithelial oedema is a preliminary stage in band-shaped keratitis. Calcareous changes may also follow prolonged oedema in cases of epithelial dystrophy of the cornea.

In herpes febrilis of the cornea the most distinctive feature is the presence of epithelial blebs, often disposed in a dendritic design, and surrounded by more finely-vesiculated epithelium. Some of the blebs are likely to rupture, so that their position is conspicuously displayed by fluorescein; but it will often be found

that the dendritic figure stains faintly with fluorescein before any visible epithelial loss has occurred, or even after the repair of a denuded area by fresh epithelium. Since the rest of the cornea may appear normal, and may retain its sensation, it is probable that the nerves involved are the inter-epithelial plexuses in localised areas. Theobald, however, believes that the ciliary ganglion is the seat of damage. Lesions in the Gasserian ganglion itself have been blamed by others. Wherever the fundamental trouble may be, herpes febrilis shows a strong tendency to recur. I have seen cases in which attacks have arisen several times a year for many years; in others there have been periods of several years' immunity intervening between attacks. Herpes febrilis may begin insidiously, presenting the appearance of an ordinary small, irritable ulcer, not at first manifesting the dendritic figure. In fresh attacks any portion of the cornea may be implicated, but there is a predilection for those areas which have already suffered. After numerous relapses it is not uncommon to see new vessels developing on the surface of the cornea, or in its deeper layers. In the case of a recently-examined man, aged 72 years, who had had six previous dendritic ulcers, there were numerous large blood-vessels in the lower half of the left cornea. These vessels, occupying the superficial layers near the limbus, became deeper as they approached the centre, until they came to lie immediately in front of Descemet's membrane. The right eye was normal.

Recurrent abrasion of the cornea should probably be added to the list of neuropathic affections. At the time of a fresh bout of symptoms the site of the original abrasion may be demonstrably flat and completely healed, while portions of epithelium elsewhere are vacuolated. The following case illustrates this point: In January, 1932, a woman, aged 32 years, flicked her left eye with a newspaper, causing an abrasion on the upper nasal portion of the cornea. Healing was established in less than a week. During the next three months she had about five attacks of sharp pain in the same eye, usually arising in the early morning. She returned to hospital, whereupon it was found that the area occupied by the original abrasion was undisturbed. Along the inferior portion of the cornea, however, was a series of epithelial vesicles, variable in shape and in size, situated close to the limbus. Corneal sensation was normal above, diminished at the centre, and absent below.

A patient who has provided a train of symptoms and signs exactly like those of recurrent abrasion may find himself unable to remember a preceding abrasion to account for the disturbance. In some cases of this kind the original abrasion may have been too remote or trivial to be remembered; but it is more likely that

the so-called recurrent abrasion of the cornea is a neuropathic condition characterised by loosely-attached epithelium. Trauma may then be regarded as a precipitating factor, not the essential cause. From the above descriptions it would appear that there is a fairly close affinity between the behaviour of herpes febrilis and that of recurrent abrasion. They have a further feature in common. Both these conditions can produce deep keratitis as a sequel. Epithelial denudation may allow the access of infective agents to the substantia propria, leading to deep infiltration, folds in Descemet's membrane, precipitates, posterior synechiae, and the reduction of vision to finger-counting.

In the miscellaneous collection of diseases grouped under the name of superficial punctate keratitis it is highly probable that some nervous lesion is frequently responsible. The onset is not uncommonly heralded by sharp neuralgic pains in the vicinity of the orbit. Sometimes the skin of the eyelids on the affected side is defective in sensibility to light touch. During epidemic visitations some of the patients proceed to develop keratitis profunda comparable to that which may arise in severe cases of herpes febrilis or recurrent abrasion.

During convalescence from influenza the cornea is liable to be affected by a variety of lesions, including dendritic ulcer, multiple erosions with or without vascularisation, and deep keratitis. Now the influenza organisms or toxins are prone to attack either the nervous system as a whole, so as to produce general debility, or individual peripheral nerves, *e.g.*, those that supply the ocular muscles. It is, therefore, not unlikely that the corneal lesions frequently seen after an attack of this disease are produced through the medium of the corneal nerve supply. During the 1918-19 world-epidemic Monbrun saw, among patients recovering from influenza, a number of cases which he described as neuro-paralytic keratitis.

The corneal dystrophies are a group of rare, mysterious conditions, in which there is progressive interference with the nutrition of the cornea. Most of them are bilateral, and, with the exception of keratoconus, are associated with progressive diminution in the sensibility of the cornea, thereby suggesting the possibility of a neuropathic basis. Epithelial dystrophy of the cornea is a bilateral disease of elderly people, in which degenerative changes involving the corneal endothelium are the earliest sign. Progressive oedema of the epithelial cells marks the next stage, and is observed first in the centre, later in the periphery of the cornea. Sooner or later the substantia propria is affected. In the last stages the cornea becomes partially calcified. Admittedly the corneal anaesthesia associated with epithelial dystrophy may be due to degenerative changes spreading from

the cells of the epithelium to the fibres of the terminal nerveplexuses. The possibility that the nerves are primarily affected is, however, strengthened by the occurrence of a similar epithelial disorder in myotonia atrophica, as reported by Maillard and Birnbacher.

Nodular keratitis is another form of bilateral dystrophy of the cornea accompanied by diminished sensation, and often affecting several members of the same family. The diversity of clinical and pathological findings tends to show that nodular keratitis is a term applicable to a series of different obscure conditions, and that it is not one definite disease. Alphabet and reticular keratitis may be regarded as members of the same group, in which the opacities are usually superficial, but may occupy any of the corneal layers. In the course of a discussion on this subject (*Proc. Roy. Soc. Med., Sect. Ophthalm.*, Vol. XVI, p. 43, 1923) Neame mentioned a case which showed opacities in the middle layers of the substantia propria in both eyes: in the right eye they were of the linear type; in the left eye, nodular.

On the surface of eyes that have become blind from neglected glaucoma, a number of large epithelial bullae may be formed. Similar changes occasionally make their appearance in the corneae of people who have had no previous eye trouble, and show no evident cause for this degeneration. Attacks of irritability may arise from time to time after rupture of one or more bullae. Both eyes tend to be involved, and the largest of the bullae show a preference for the centre of the cornea, so that vision may be seriously impaired. Band-shaped keratitis resembles bullous keratitis in that it also exists in two main varieties. On the one hand there is the unilateral band-shaped opacity arising in a disorganised eye, *e.g.*, one that has long been blind from irido-cyclitis. The bilateral form, on the other hand, develops slowly and insidiously without any known cause. It is both preceded and accompanied by vesiculation of the epithelium, and may possibly be due to some derangement of the corneal nerve supply.

Marginal degeneration of the cornea is a slow destructive process which attacks the peripheral portion of the cornea around part or the whole of its circumference. This dystrophy attacks the middle-aged and elderly more often than the young, and is accompanied by progressive loss of sensation on the cornea. The affected regions show superficial vascularisation, and gradual diminution in the thickness of the substantia propria, leading first to gutter-formation, and later to localised ectasia. Rupture of the globe from the slightest of blows is a possible danger during the ectatic stage. Spontaneous rupture is not unknown. Both eyes are involved sooner or later.

Most of the disorders in which, for no evident reason, the

nutrition of the cornea declines, are associated with gradual diminution in the corneal sensation. To this rule keratoconus is an exception, for it is commonly accompanied by hyperaesthesia, which suggests that the increased visibility of the corneal nerves in this condition is an expression of their actual hypertrophy. Conical cornea is more often seen in women than in men. The last case I saw was that of a married woman, aged 36 years, who had been bedridden for several years, and was in a state of general weakness. I have, however, seen several examples of it in young, healthy, unmarried women, in whom the cause remained a mystery. Löwenstein believed that pregnancy accelerates the progress of this disorder. He also reported the interesting case of an elderly woman who developed keratoconus in her right eye six weeks after a right-sided partial thyroidectomy. Fourteen years later the condition remained unilateral, thereby leading him to believe that it was the result of injury to the cervical sympathetic nerve during the operation. On the other hand, I know of no case in which the ordinary form of birth-injury to this nerve has been associated with the development of a conical cornea. A different type of corneal lesion accompanying thyroid disorder was described by Treacher Collins. A woman, aged 58 years, suffering from myxoedema, gave a history of six months' haloes and failing vision in the left eye. On examination he found a number of small, superficial, discrete grey dots in the centre of the left cornea. Vision was reduced to 6/36, but recovered to 6/6 when the opacities had been dispersed by a course of thyroid extract.

In conclusion I would suggest that, epithelial oedema being the most characteristic early sign of disordered corneal nerve supply, it is necessary to consider the possibility of a nervous lesion in cases which persistently show this sign without any rise of ocular tension, and in the absence of any obvious traumatic or inflammatory cause.

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