Pathogenesis of the corneal destructive diseases

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Under normal circumstances the cornea is protected from infection and cellular infiltration by its environment and by its mechanical structure. The stroma of the cornea consists of lamellae of regularly arranged collagen fibrils, each of which is surrounded by and joined to each other, by hydrophilic proteoglycan.[1] This regular arrangement allows light to pass through without interruption or diffraction.[2] In order that the cornea shall remain transparent the proteoglycan must be provided with fluid. This is provided by the aqueous beneath, and the tears over the surface. The cornea then has to be dehydrated by the endothelial pump. The shape is maintained by Descemet's and Bowman's membrane and the slight irregularities of the epithelial surface are smoothed out by the mucous layer of the tear film. This smooth surface is washed by the tear film at regular intervals, trapping, destroying and removing all toxic foreign particles. Apart from the area adjacent to the limbus its nutrition comes from the tear film and through the endothelial surface.

This exquisite adaptation means that the cornea is very resistant to infection and inflammation, which can only occur if the surface protection is broken or the tight collagenous structure separated. Collagen separation occurs if the endothelial pump is damaged, or if toxic substances have access to the proteoglycans, or the corneal fibrocytes, (which are responsible for the normal maintenance of the proteoglycan and collagen structure), exhibit abnormal activity or die.

Because of the tight collagen structure, cellular infiltration or invasion by blood vessels is extremely difficult, so that the initiation or perpetuation of any inflammatory response has to be mediated by the presence and action of cytokines or soluble proteins, remote from the source of the reaction. The sequence of events which leads to corneal damage varies according to the nature of the initiating stimulus and the speed, the type and the intensity of the response to that stimulus. The response itself may be localized to a single area or be diffusely active through the whole corneal tissue. It is the variation in these responses that give rise to the clinical syndromes.

As the development of the clinical syndromes depends not only on the conditions within the cornea itself but on the environment in which the cornea is placed, very careful observation needs to be made of the tear film, the epithelium, the endothelium, the anterior chamber and the surrounding vascular networks of the conjunctiva, episclera and limbus. It is changes within these vascular networks which give the earliest indication of the type and severity of disease in many of the conditions in which the cornea is seriously damaged. It is therefore important to understand something of the nature of the blood supply of the anterior segment of the eye.

Normal circulation of the anterior segment of the eye

The nutrition of the peripheral cornea, anterior sclera and episclera is dependent on the blood from a combination of sources which are so arranged that at no time and whatever the position of the eye, there is always an inexhaustible supply. The blood is supplied by the long posterior ciliary arteries and the anterior ciliary arteries. In addition there is a supply from the conjunctival arteries which are the termination of vessels derived from the external carotid circulation. The number of arterioles and capillaries supplying this region is enormous, reflecting the very high metabolic rate of all the tissues supplied.[3] The anterior segment of eye is supplied by two arterial circles. (Figures 1 & 2) A saggital circle derived from the anterior ciliary arteries superficially and the long posterior ciliary arteries deep, and a coronal arterial circle consisting of the greater circle of the iris and superficially, the episcleral arterial circle. There is one unique feature of this blood supply which may well account for the site at which many of the inflammatory lesions commence. All the arterial circles end, not as is usual, through a diminishing size of blood vessels, a capillary bed and a venous drainage, but by arterial anastamoses.[4,5] This has the good effect of ensuring that no part of the capillary beds which arise from the arterioles is ever short of blood. It also has the possible adverse effect that

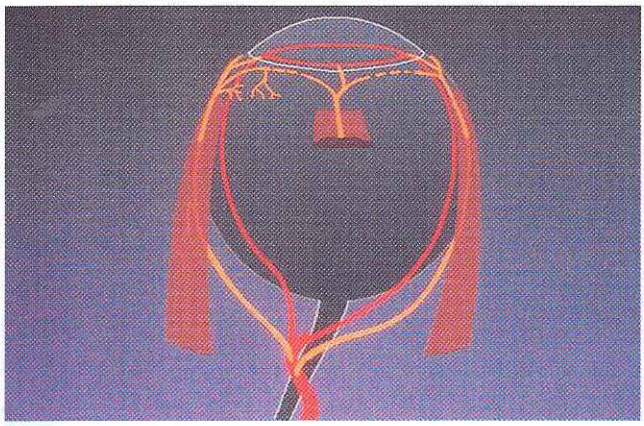


Figure 1. The blood supply of the anterior segment of the eye. There are two sagittal circulations from the long posterior ciliary artery and the anterior ciliary artery and two coronal circulations derived from these vessels; one forming the greater circle of the iris and the other the episcleral arterial circle (Figure 2).[4,5]

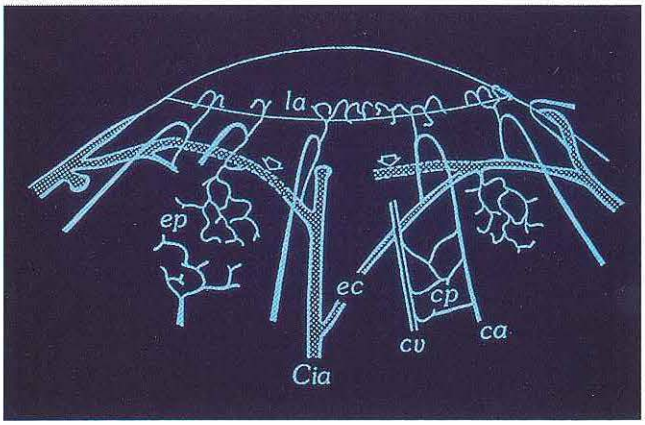


Figure 2. The blood supply of the anterior segment of the eye is derived from penetrating vessels from the long posterior artery circulation which meets with arterial blood from the anterior ciliary artery (cia)These together form the episcleral arterial circle in which blood may not flow but simply oscillate. From the episcleral arterial circle (ec) and the conjunctival vessels (cp) (cv) (ca) are derived the limbal arcades (la)[4,5] and the episcleral capillary plexus (ep).

at all times there are certain parts of the circulation in which there is no true blood flow, but rather oscillation of blood to and fro within the vessels. The consequence of this is that in inflammation toxic substances such as immune complexes are not flushed away and there is diminished movement of metabolites and cells to and from the vessels into the extravascular space. The majority of patients with both scleral disease and peripheral corneal disease present with the inflammation in these watershed zones.

Changes which lead to corneal damage

Whilst the majority of the factors which lead to corneal damage are due to infection or result from inflammatory mediators, there are a few conditions in which inflammation has no role.

Defects in the tear film

The tear film consists largely of the 'watery' secretion of the lacrimal gland which is prevented from evaporating by the oily secretion of the meibomian glands and is held stable by the mucous layer over the surface of the epithelium. If the tear film is prevented from covering the cornea as in Dellen or Pterygium, then (although the constitution of the tear film is entirely normal) desiccation of the cornea will occur; the cornea becomes extremely thin because of the over-dehydration of the proteoglycan and compaction of the collagen fibrils. Although this is almost always reversible if the shape of the cornea is restored to normal, some permanent changes can occur, particularly if there has been pooling of tears in a dellen, poor metabolic exchange, or infection.

In keratoconjunctivitis sicca and Sjoegren's syndrome, abnormal mucous is constantly present. This adheres to, and causes abnormalities within, the corneal epithelium, but it does not give rise to changes in the stroma deep to the epithelium. Whilst it is perfectly true that many patients with these conditions also have stromal corneal disease, there is no evidence to show that the abnormal tear secretion is causative. The stromal changes are due rather to infection arising from the lack of lysozyme, abnormal pH and constituents which change the maturation of the corneal epithelium and allow epithelial breaks and consequent deep infection. Sjoegren's syndrome is part of the symptom complex of other connective tissue disorders, many of which themselves induce stromal changes within the cornea.

Defects in the corneal epithelium[6]

Acute epithelial loss from superficial injury has no effect on the underlying stroma of the cornea and even if the stroma is damaged the cornea will undergo repair through activation of the stromal fibrocytes. However, if the epithelial loss becomes chronic, then permanent changes can occur. Chronic epithelial loss usually results from the loss of the limbal stem cells from which the corneal epithelium is derived. Although the corneal epithelium can be replaced from other areas of the cornea, area of the limbus is normally responsible for covering the area adjacent to it. If the stem cells are damaged by chemical injury or in the process of transplantation rejection, chronic epithelial loss will result and the stroma becomes exposed to inflammatory mediators or infective agents in the tears, which initiate the process of tissue destruction.

Bacterial and viral infection

Damage to the stroma from bacterial infection is relatively common, but irreversible damage from viral infections is rare. Defects in the corneal epithelium can allow access to the corneal stroma to any of these agents, but only on the rare occasions that the organisms themselves are introduced into the cornea that damage can occur. If the organism is of sufficient virulence and capable of producing proteoglycanases or collagenases, destructive changes occur. The proteolytic enzymes released from these organisms separate the tightly bound lamellae of the collagen bundles and not only damage the structure, causing an abscess to form, but also allow the organism to penetrate deeper into the tissue

where it can reproduce, delivering an even higher concentration of destructive enzymes. The body's immediate defense mechanisms are inhibited by the remoteness of vascular network through which the response is driven, allowing an infection to become firmly established. The neutrophil response is, in consequence, very intense. They themselves release proteolytic enzymes which not only destroy the invading organism but also damage the surrounding tissue.

Viral infections, even if they enter the corneal stroma, do not excite such an intense initial reaction, but rather set up a chronic immune response which is largely lymphocytic. Whilst this chronic response will alter the arrangement of the collagen fibrils and lead to clouding of the cornea, tissue destruction is very unusual.

Chemical injuries to the cornea

Much work has been directed to the understanding of the destruction of the cornea which follows severe chemical burns to the eye. The destruction of the cornea does not depend on the type of chemical which caused the injury, nor does it happen immediately. Penetration of the chemical into the cornea depends on how quickly the epithelial barrier can be overcome; thereafter the damage caused depends on the concentration and the change in pH which the chemical induces. Alkalis react with fats to form soaps and break down intracellular boundaries. They also dehydrate cells, being hydroscopic and, if in high enough concentration, kill corneal fibrocytes. The alkali binds temporarily to the proteoglycans, destroying them, thus exposing the collagen and any remaining corneal fibroblasts to the action of the collagenases from the damaged epithelium. The collagenases come from polymorphonuclear leukocytes which enter the cornea from the conjunctival sac, through the corneal surface into the widely spaced oedematous collagen structure. In a severely damaged cornea the stromal tissue can be lost at this point, but in others there follows an extensive period in which the cornea becomes invaded by blood vessels, disintegrates, and then perforates, suggesting that an immune process has become responsible for the final catastrophe.

Corneal tissue loss without inflammation

There are a number of conditions in which corneal tissue is lost without there being any evidence of infection, inflammation, epithelial loss or abnormalities in the tears. These changes can arise as a result of degeneration of corneal tissue, abnormalities of the metabolism or turnover of the connective tissue components or as the result of limbal capillary vaso-occlusion.

Whether keratoconus, either anterior or posterior, or keratoglobus, are truly degenerations or whether they are caused by a failure in the reconstitution of corneal constituents is uncertain but in these conditions[7] and pellucid peripheral corneal degeneration the substance of the stroma of the cornea gradually disappears allowing the tissues to stretch and become distorted. In Marfan's syndrome the limbus can sometimes be similarly affected.

Expansion of the peripheral cornea also occurs in Terrien's disease and in patients who have long-standing rheumatoid arthritis, who develop what is known as the contact lens cornea. In Terrien's disease the limbal vasculature is disrupted with new vessel formation and lipid deposits appear at the inner margin of the thin area which excite a macrophage response. The corneal fibrocytes in the region of the furrow are unhealthy but not absent and there is no loss of epithelial cover.

If the limbal capillary net becomes occluded in chronic rheumatoid arthritis, there is a similar loss of corneal stroma but no lipid deposition. The contact lens cornea is thick and normal centrally, but thins off peripherally. The cause is unknown but the capillary occlusion appears to be the result of a mild continuous vaso occlusion, so it is possible that the reconstruction of the collagen bundles through normal wear and tear is inhibited because of the poor blood supply and consequent lack of metabolic ingredients. Obstructing the anterior segment blood supply alone does not however lead to tissue loss, so the metabolism of the corneal fibrocyte in contact lens cornea must be slightly altered by a persistent vasculitis.

Corneal destruction with inflammation

Loss of corneal tissue in an inflamed eye is a potentially blinding problem requiring urgent and effective treatment. a cause can often be found so it is essential to investigate the patient fully. Careful enquiries must therefore be made to determine whether the patient has any associated systemic conditions, particularly the chronic granulomatous diseases such as tuberculosis or syphilis, any of the connective tissue diseases, or a systemic vasculitis.

Destructive changes in the cornea accompanied by inflammation of the surrounding tissues but without any evidence of infection may reasonably be assumed to be immunologically induced. Many terms have been used to describe the changes seen under these conditions. None of them is entirely satisfactory or particularly helpful in determining the cause [Table 1].

Table 1. Terms used in corneal destructive changes with inflammation

Corneal furrow
Corneal guttering
Peripheral ulcerative keratitis
Corneal melting

They are unsatisfactory because, for example, there is not necessarily any epithelial loss, hence no ulceration, or the tissue may not be guttered or lysed, only generally edematous and unhealthy. The mechanism which leads to the destruction varies from patient to patient and is sometimes completely obscure. However, there are several easily

recognizable and distinct clinical entities which can be distinguished one from another and form the basis of specific therapy. Apart from vaso-occlusive changes caused by irradiation such as β-irradiation and local application of cytotoxic agents such as 5 F.U. and mitomycin, there are three main groups: those who have developed the vasculitis of the late stages of the connective tissue disorders, such as rheumatoid arthritis, systemic lupus erythematosis, those who have a systemic vasculitis like relapsing polychondritis, polyarteritis nodosa and Wegener's granulomatosis and the third being Mooren's ulcer. Whereas the connective tissue diseases and systemic vasculitides are often acompanied by scleral disease, Mooren's ulceration never is.

In all these conditions observation of the limbal circulation will give a clue as to the nature and severity of both the ocular and the underlying systemic disease.

Vascular changes

Careful observation, aided by low concentration fluorescein angiography, will detect changes within the vessels of the episclera, conjunctiva and limbal vessels, which will not only aid diagnosis but change decisions about the correct form of treatment.

Limbal vessels

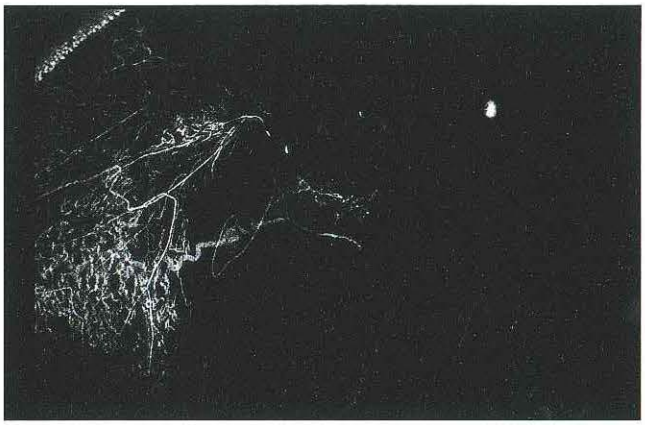
The normal limbal vessels leave the episcleral arterial circle and join with each other and with the conjunctival circulation in the regularly arranged limbal arcade (Figure 2). In response to severe inflammation within the cornea or in the episclera, changes occur within this arcade. The vessels, particularly the veins, dilate and leakage is observed at the tip of the arteriolar loop at the corneal edge. This is seen on the slit lamp as a fine grey exudate within the corneal tissue alongside the loop. If the inflammation persists then new vessels begin to appear. In the cornea these form straight new vessels arising from the tips of the loops into the cornea towards the source of the stimulus. These loops can arise from the superficial or deep vessels at the limbus.

Episcleral vessels

In the vessels adjacent to the limbus, although the vessels are dilated, the circulation is slow, again on the venous side of the circulation. If the inflammation persists some vessels become non-perfused and eventually totally occluded (Figure 3). In this case new vessels arise from adjacent perfused vessels to revascularize this tissue or to by-pass the damaged area. The anatomical structure of these new vessels is never normal so that they can always be distinguished by examination with the red-free light on the slit lamp. Arteriolar occlusion is a late and unusual event associated with infarction or necrosis of the surrounding tissue. In the patients who develop a granulomatous reaction these changes rapidly become obscured by the formation of the raised granulomatous tissue. However, observation of the advancing edge or the tissue adjacent to it, will often reveal the telltale signs within the vessels.

Corneal changes

Changes within the cornea can occur alone or together with



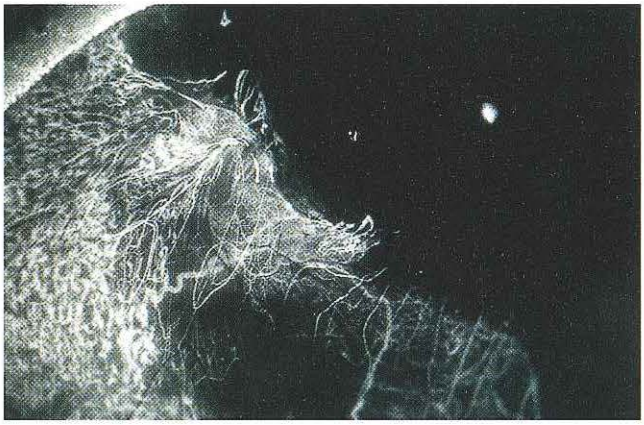


Figure 3(a & b). Low dosage anterior segment fluorescein angiography from a patient with corneo/scleral disease. Venous phase. An area of the episcleral vascular network from 3 - 5 o'clock in both the superficial and deep part of the circulation is non-perfused. This persists throughout the angiogram. The limbal arcade is disrupted. The vessels are straight and not looped to their neighbour. They are also leaking slightly at the top indicating continued activity of the disease.

similar abnormalities, within the neighbouring sclera. In some patients the changes are transient, recovering without any trace of the previous insult; in others permanent changes occur within the stroma of the cornea without tissue loss and in others there is tissue destruction. The type and the intensity of the reaction depends on the severity of the inflammation and the nature of any systemic disease with which it is associated.

Diffuse deep stromal and sclerosing keratitis

These changes usually start at the limbus but can occur suddenly or gradually at any point in the cornea. Stromal keratitis is characterized by single or multiple mid or superficial opacities which expand slowly, often with a "precipitin ring" surrounding them. If inadequately treated the opacities coalesce leaving a swollen and opaque cornea. At this stage the collagen structure becomes permanently altered and when the inflammation regresses, a permanent sclerosing keratitis has resulted. Sclerosing keratitis can also arise from a persistent transudate from incompetent new vessels which have developed in corneal tissue as a response to inflammation in the cornea or in the sclera. Sometimes these vessels will continue to grow and leak even when the causative disorder is suppressed or inactive.

If the leakage occurs from vessels derived from the deep limbal plexuses then a deep stromal keratitis - such as that seen in Cogan's syndrome, results.

Peripheral corneal guttering and melting

Destruction of the peripheral corneal tissue which can occur with or without scleral changes, is always associated with changes in the limbal and episcleral vasculature. These changes are of dilatation, non perfusion, leakage and new vessel formation in varying degrees.

Whilst the changes in the vasculitis seen in the later stages of the connective tissue disease differ clinically from those seen in the systemic vasculitis, they are not mutually exclusive so that terms such as "rheumatoid corneal melt" should be avoided because exactly similar changes are seen in many other conditions or even on occasion without any detectable systemic disease.

Peripheral corneal gutters start as grey, soft, swollen areas within an area 2 mm from the limbus. If there is a scleritis it will usually start in this area but may rapidly extend, the advancing tip of the gutter progressing around the limbus. (Figures 4 & 5) Rarely, several gutters can occur at the same time and coalesce. The thickness of the cornea may diminish very rapidly if untreated until it is all removed leaving a descemetocele which will perforate with the most minor trauma. The limbal vasculature shows venular non-perfusion and disruption of the limbal arcades, fine new vessels entering the base of the gutter. Epithelial loss is a rarity and if ulceration occurs it indicates a very severe necrotic reaction. This type of guttering is most frequently seen in patients in the vasculitic phase of rheumatoid arthritis.

In patients with the systemic vasculitides the guttering often develops in a different way. Characteristically, there is an immediate and intense leakage from the tips of the limbal arcades, which develop small new vessels loops which also leak. (Figure 6) Granulomata develop both in the scleral and corneal side of these changes, destroying the tissue of the limbal area (this does not happen in any other situation). As the disease advances into the cornea the area in front of the advancing edge is grey, infiltrated but not grossly swollen. The new vessels advance to the edge of the guttered area.

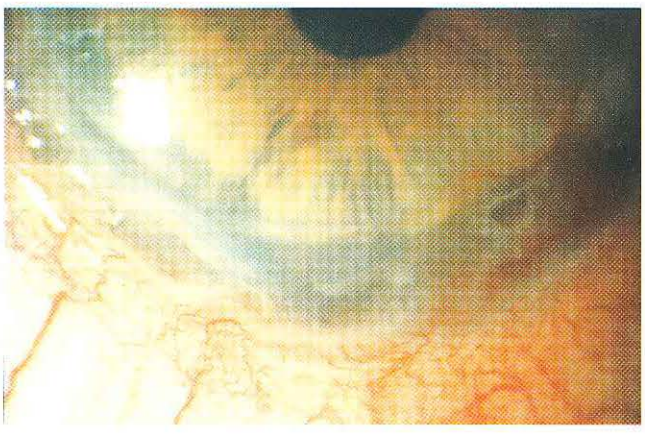


Figure 4. A patient with longstanding, but quiescent, rheumatoid arthritis, presented with a corneal infiltrate 3 mm from the limbus in a previously slightly vascularized, but clear, peripheral cornea.

Keratolysis

This is a term given to a rapid change, often in the center of the cornea in which the stroma disintegrates. The cornea in the area becomes swollen, the epithelium becomes irregular and may shed. Fine keratitic precipitates often develop beneath the area affected. Left untreated the damaged area expands, often with alarming rapidity to include the surrounding areas, until the whole of the stroma is resorbed, leaving only Descemet's membrane which can easily rupture. These changes are often painless and most often seen in patients with long standing rheumatoid arthritis.

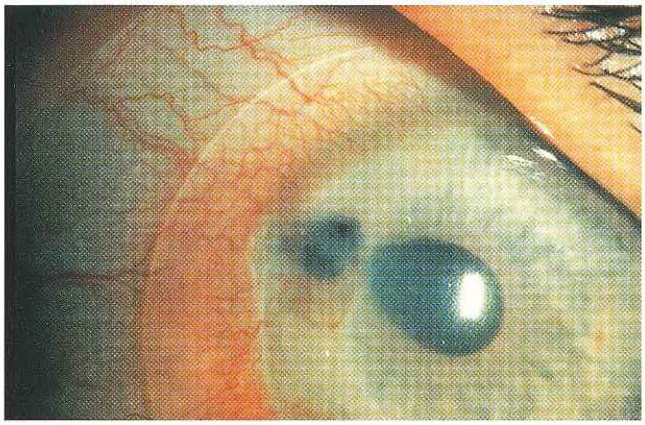


Figure 5. The same patient as Figure 4, 3 days later. The infiltrated area has extended in both directions and an area at 2 o'clock has thinned to become a descemetocoele. The limbal vessels have dilated and have advanced towards the ulcer.

Mooren's ulceration

The changes seen in limbal guttering associated with a primary or secondary systemic vasculitis need to be distinguished from Mooren's ulceration, which is a uniquely corneal disease. This differentiation is often extremely difficult, especially in the early stages when the peripheral corneal changes have a very similar appearance to that seen in other types of guttering disorders.

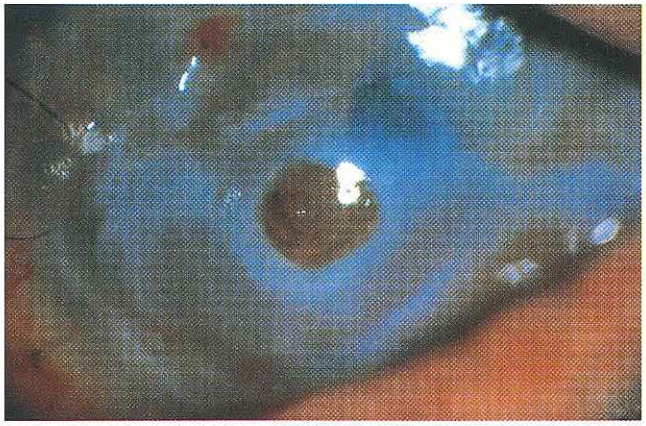


Figure 6. Granulomatous corneo-scleral destructive disease as seen in Wegener's granulomatosis. The granuloma of the sclera extended to 11.00 o'clock and the peripheral corneal destruction was circumferential. Infiltrates can be seen into the cornea at 5.30 o'clock.

Based on the evidence of fluorescein angiography there are three, apparently distinct types of Mooren's ulcers. One is unilateral, occurs in middle aged or elderly patients, is exceptionally painful, is inexorably progressive and very resistant to treatment. This is associated with non-perfusion of the superficial vascular plexuses of the anterior segment - all the vessels entering the cornea do so from the deep vascular plexuses derived directly from the long posterior ciliary vessels. Another variety occurs in younger people, is bilateral, less painful, but rapidly progressive. This is commonly found in African and Asian populations. Angiography shows marked vascular leakage (as opposed to occlusion) together with new vessels derived from the deep vascular plexuses. A third variety is a bilateral indolent form of the disease which is often self-limiting. There is no change in the vascular architecture except that new vessels enter the base of the ulcer from the deep vascular plexuses. The patients never have an associated systemic disease, and apart from congestion of the vessels and slight edema of the sclera at the limbus, there is no scleral involvement.

Even from the start of the disease the ulcer has a characteristic appearance. (Figure 7) The onset of the disease is marked by pain localized to the eye with slight limbal congestion. The peripheral cornea becomes infiltrated in one place about 2 mm from the corneo-scleral limbus. This area rapidly becomes grey and swollen but the epithelium remains intact. The stromal tissue rapidly becomes absorbed and the gutter extends both peripherally and centrally in the cornea.

The cornea central to the advancing ulcer is grossly swollen. This is accompanied by and grey and yellow infiltrates and the central limit of the ulcer becomes undermined. In contrast to other necrotic peripheral ulcers the scleral margin may also become undermined. Untreated the ulcer will extend into the center of the cornea until all the stromal tissue is removed. At this stage all that is left is a thin atrophic scar over Descemet's membrane, the inflammation at the limbus disappears and the eye becomes pain free. If a corneal graft is attempted the same process occurs in the graft which is rapidly removed by the method identical to that seen in the initial disease. The vascular changes at the limbus are variable. Sometimes in the unilateral disease the changes of vaso-obliteration of the limbal and episcleral vasculature are identical to that seen in the guttering of vasculitis and in others no changes of any type can be detected.

Pathogenesis

The sequence of events which lead to tissue degradation and eventual removal of corneal tissue in those who have no infection or injury varies according to multiple factors which are modified in each individual to give a unique clinical presentation. Many fall into well recognized patterns because the sequences are very similar but if only one part of the sequence is varied the pattern may change, or even reverse. The presentation is altered by the nature of the initiating stimulus and the speed type and intensity of the response and the reaction to it. This in turn is modified by the presence or absence of any other systemic disorder, the genetic makeup of the individual or whether there have been similar episodes in the cornea or adjacent tissues in the past.

All these factors put together give rise to the clinically recognizable syndromes of corneal destructive disease.

Case report

The fortuitous presentation of a patient with necrotizing sclero-keratitis who needed immediate surgery because he was unable to take either local or systemic non-steroidal anti-inflammatory drugs or steroid, has led to a considerable amount being known about the changes which occur up to the time the tissue is destroyed. It is the application of this knowledge which gives the opportunity to develop logical treatments. Pre-operative angiography revealed capillary

Histologically the center of the necrotic area was acellular. Adjacent to this the lamellae were separated and infiltrated with inflammatory cells and giant cells. At the limbus there was epithelial cover but deep to it the fibrocytes of the cornea were sparse and abnormal. E.M. reveals lymphocytes and a multitude of other inflammatory cells. There was evidence of a vasculitis and the endothelial cells of the vessels were necrotic in part and filled with platelet thrombus. These are the changes expected in a necrotic ulcer and were not helpful in deciding the etiology and pathology. Attention was therefore directed to the apparently normal sclera and cornea where it was known that there were angiographic abnormalities.

Vessel changes

The dominant finding in the region of capillary hypoperfusion was the prominence of the endothelium particularly of the venules which had led to rouleaux formation in the blood vessels and in one or two places complete occlusion of the vessel with thrombus. There was expression of HLA Class II antigens on fibroblasts, vessels and epithelium. There was a marked increase in the level of 'T' helper lymphocytes (CD4) and the normal helper/suppressor ratio was reversed.

Immune complexes

Another feature detected in the regions of apparently normal tissue was the presence of immune complexes in between the corneal and scleral lamellae.

Collagen changes

The corneal fibrocytes were activated remote from the presence of any cellular activity in apparently normal tissue. Where the fibrocytes were active the collagen could be seen to be unraveled and the fibrils separated from each other. This unraveling became very severe and the normal corneal architecture became completely disrupted close to the areas of active cellular infiltration.

This case was remarkable because it showed several very important pathological features, none of which had been modified by therapy. Firstly, the changes in the fibrocytes and their surrounding collagen are remote from the site of any cellular activity, indicating that the changes are lymphokine induced. Secondly there is a highly activated T cell response. Thirdly the endothelial cells in adjacent

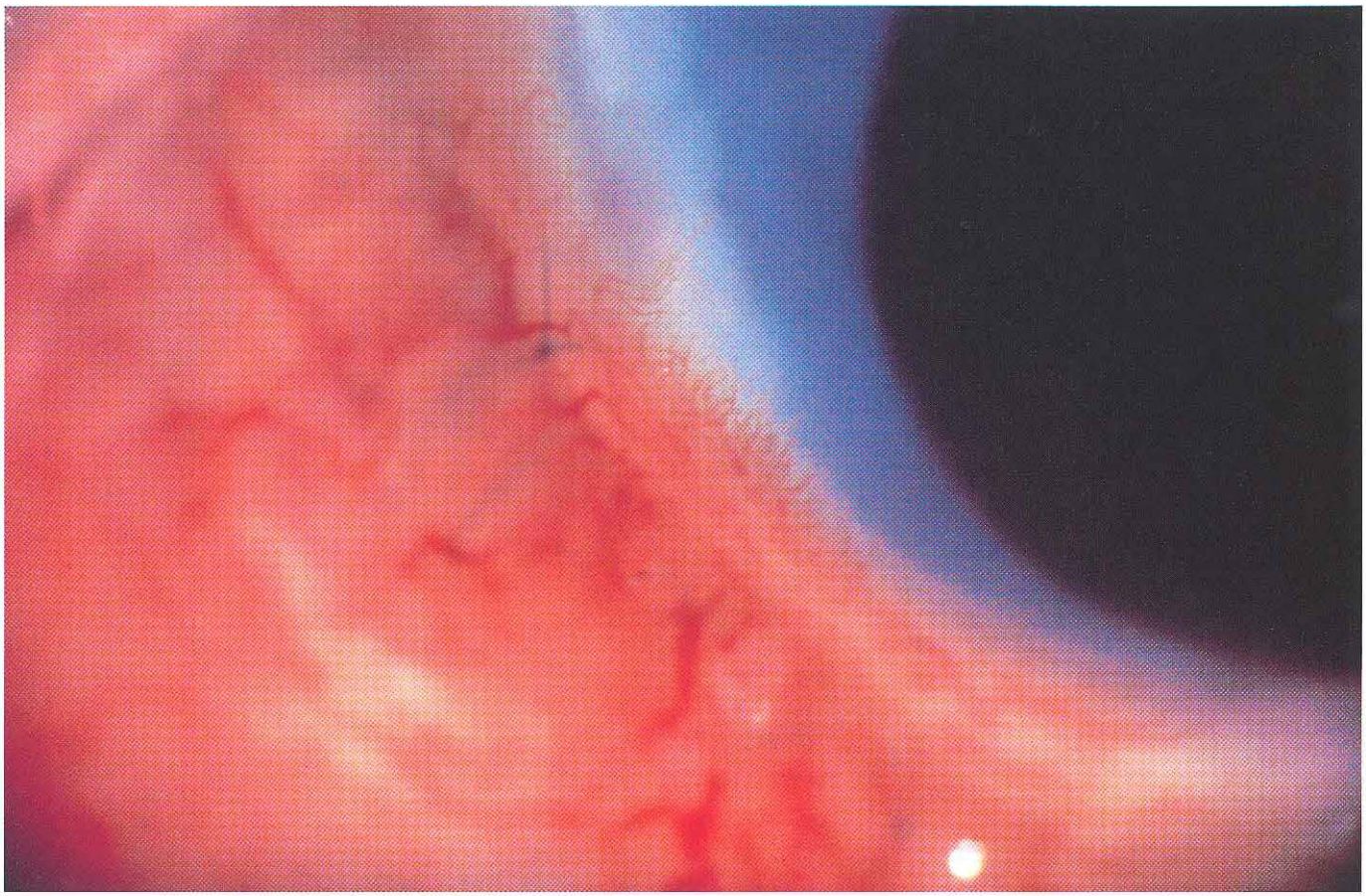


Figure 7. The typical appearances of a Moonren's ulcer. The ulcer, which has started at 8.30 o'clock has extended both peripherally and centrally in the cornea. The advancing edge is infiltrated and undermined and the apparently unaffected cornea is also swollen. The limbal arcades are all disrupted and new vessels have advanced to the edge of the ulcer from both superficial and mid-stromal vessels. There is a limbitis but no scleritis and no other systemic disorder.

vessels were swollen, and fourthly the immune complexes were present in the tissue. This was also a feature of the only successful animal model of scleral necrosis in which the disease was induced by local challenge in an animal chronically immunized with ovalbumen. These animals also showed angiographic and vascular changes similar to that seen in man. The presence of immune complexes in the peripheral tissue does not seem to excite any inflammatory response, but when they occur within and around the vessel wall, then the complement cascade is activated leading to vaso dilatation and the passage of inflammatory cells through the vessel wall into the extra vascular space. Under circumstances of high blood flow it is difficult for this to occur but in anastomotic circulations of the type found in the anterior segment of the eye, immune complexes can accumulate with ease.

Cellular changes

Non-infective inflammatory corneal destructive diseases are the result of an immune process which in most instances become auto-immune. The innate immune system depends on a cellular component consisting of neutrophils, macrophage and leukocytes and a soluble component containing such factors as complement. This response is not antigen specific. The adaptive immune system responds to specific antigens through the action of the 'T' and 'B' lymphocytes and the substances which they produce. There are three phases:- the afferent arc in which the cells recognize and become sensitized to an antigen through the mediation of the macrophage and Langerhans cells - a central processing phase in which the response is amplified and specific antibody and mature effector cells arise and finally the afferent arc where specific antigens become targeted and attacked by the specific antibody and the mature effector cells. At all of these phases the systems interact to ensure an amplified and rapid response with activation of complement, which in turn stimulates macrophages and neutrophils to release enzymes and other products.

Morphological changes in corneal collagen

The normal corneal collagen fibril is surrounded by proteoglycan consisting of the proteoglycans dermatan sulphate, keratan sulphate and chondroitin sulphate. These proteoglycans protect the collagen from attack and ensure the correct interval is maintained between the fibrils. They also surround the fibril in regular sequence and connect one fibril to another. Under the influence of a specific proteoglyconase these interconnecting bands separate. This apparently happens in sequence; the interconnecting bands breaking first to be followed by those which surround the fibril. The result of this is that the fibrils separate from each other, the proteoglycan falls from the surface exposing the underlying collagen. Once this happens the collagen fibril is susceptible to the action of the collagenase, allowing the collagen fibril to

unravel and be removed either by proteolytic destruction or by macrophage activity.

The corneal fibrocyte is responsible under normal circumstances for the maintenance and repair of the collagen and its coats. It derives the nutrients it requires for this process by diffusion from the limbus or from the anterior chamber of the eye. The fibrocyte can be influenced to create or destroy the collagen by the production of intra-cellular enzymes which in turn are influenced by messenger molecules which adhere to it's surface. It was particularly noticeable that in the situation where changes were first seen in the fibrocyte of the cornea and in the corneal collagen matrix there were no inflammatory cells of any sort. Indeed because of the very tight collagen structure it would be difficult for them to get there. This means that the changes must have been induced by soluble cytokines derived from these inflammatory cells, which have activated the fibrocyte. It is known that within the cornea all the fibrocytes are in contact with each other through their processes so that changes can easily occur remote from the original source of the stimulus. Indeed the source of this stimulus does not have to be from tissues adjacent to the limbus but could be induced via the epithelium which shows activation by cells away from the site of the lesion.

The influence of associated systemic disease

We have seen that different clinical syndromes occur in different patients, depending on the presence or absence of other systemic disease. Patients with a sero-positive arthritis such as rheumatoid arthritis develop vasculitis in the late stages of the disease. This is thought to be caused by the deposition of circulating antigen/antibody complexes within and adjacent to the vessel wall and is associated with vaso-occlusion of venules. It is this group of patients most liable to develop peripheral corneal disease. In patients with a systemic vasculitis such as Wegener's granulomatosis and polyarteritis nodosa, the prominent response is of vascular leakage (with eventual vascular obliteration) and destructive granuloma formation. The systemic vasculitis is associated with circulating antineutrophil cytoplasmic antibodies (pANCA and cANCA). The disease can be localized to the eye and orbit, but is usually systemic, causing in particular granulomata of the sinuses, nose, kidney and upper respiratory tract. Untreated it is a fatal disease.

Patients with relapsing polychondritis also develop a systemic vasculitis and sclero-keratitis. They are known to develop a specific reaction to collagen Type VI which eventually destroys the cartilage of the nose, ear and trachea. Thus different antigenic stimuli can lead to very similar clinical patterns.

Surprisingly there is very little association with any HLA type to any form of corneal destructive disorder apart from the HLADR4 and HLADW4 association found for rheumatoid arthritis.

The afferent arc of the immune response

All these highly complex interrelated reactions make it very difficult to determine which are the most important factors in the development of any specific pathological reaction and which are the factors which modify that response to induce particular syndromes. There are, however, some clues which can show the way at least some of the conditions develop. We have seen that in certain situations the reaction to an abnormal stimulus might be predictable, e.g. in rheumatoid arthritis where the joints are also involved in a destructive process very similar to that seen in the sclera and cornea. In many ways the eyes, which can be regarded as a modified ball and socket joint, might thus be expected to react in the same way to a similar stimulus. However, something has to happen which will cause the cornea or cornea and sclera to become involved and not some other tissue, i.e. there has to be a trigger which will set the train of events in motion; there has to be a specific antigen, antigen presentation and there has to be a central processing mechanism to induce the responses already discussed. Careful history taking about events near the start of the disease will often elicit the cause.

Trigger mechanisms

Viral and Bacterial Many patients with corneal destructive disease will give a history of a systemic or local infection at the time of, or just before, the onset of the disease. The most common is herpes zoster, but it can follow staphylococcal infections, herpes simplex and systemic infection with the Epstein Barr Virus and proteus[8] which have been implicated as a trigger in rheumatoid arthritis. Although not proven the bilateral Mooren's disease seen in young Africans has been associated with active helminthic infection.[9] Following these infections there is an abnormal response which develops into an auto-immune self perpetuating process e.g. in herpes zoster the initial viral stage of the disease passes and any localized blister heals. After an interval the eye becomes painful and inflamed and a typical progressive sclerokeratitis ensues.

Source of Antigen It is still unclear what makes any substance antigenic. Antigens are usually of large molecular weight, but small molecular weight substances can be made antigenic by binding to protein (hapten). A substance will normally only produce a response if it is foreign to that organism but an indigenous substance can become antigenic if it has been altered physically or if it becomes conjugated with another substance. Corneal collagen is normally protected from the immune system by its proteoglycan cover and is almost totally isolated from the immune system. If the proteoglycan is removed or damaged by infection or the action of cytokines or proteoglycanase, then the exposed collagen can combine, be attacked by native or foreign collagenase and also become antigenic. It is probably that this is the source of the antigenic response in these patients. The precise nature will depend on the trigger and/or the presence of foreign substances within the cornea itself.

In the case of Mooren's ulcer a corneal antigen (Co Ag) c DNA has been shown to be homologous with Calgranulin C (CAAF 1) which has been isolated from neutrophils exposed to the surface of the nematode orchocerca volvulus. A protein derived from the CAAF 1 and the carrier parasite molecule may be recognized by Co Ag in the cornea and this may initiate the immune response in this disease.[10,11]

Trauma A similar process occurs in S.I.N.S. (surgically induced necrotizing scleritis) where a necrotizing change

occurs at the site of surgery or where previous surgery has been performed. In this condition a scleritis or destructive sclero keratitis appears at a varying interval after an operation on the eye. There is usually a history of mild post-operative infection, an infected suture or the operation may have been performed in someone with a systemic disease. Importantly, however, the scleritis can occur at the site of an operation performed up to 20 years previously (as in a previous strabismus operation) and not at the site of the current procedure. This implies that the products of damaged cornea/scleral collagen are being recognized at a site remote from the site of trauma.

Antigen presentation Langerhan's cells and macrophages are both capable of presenting antigen to the immune system. In S.I.N.S. it would appear to be the resident tissue macrophage which has recognized foreign antigen. In the cornea Langerhan's cells are prolific at, and adjacent to, the limbus and are capable of presenting antigenic products from the cornea to the immune system. The response is modified according to whether the stimulus is from a specific protein, as in Mooren's ulceration,[9] or whether the immune system is already primed, such as in those with rheumatoid arthritis, Wegener's granulomatosis or relapsing polychondritis.

Mechanism of destruction in non-infectious corneal destruction

As we have seen corneal destruction can occur without any infection as a result of an intense inflammatory response due to an immune or autoimmune response. The trigger which precipitates this immune response can be a virus, bacteria or simple trauma in a patient whose immune system is already primed, as in systemic disease, or locally as with Co Ag or in some instances by the deposition of systemically derived immune complexes which cannot be removed because of the sluggish circulation.

These triggers also damage corneal collagen by depriving the collagen fibrils of their proteoglycan cover through the activation of MMP 1 leading to reduction of inhibitors (TIMP 1).[12] This leads to cleavage of the structure, the stimulation of the fibrocytes, production of collagenolytic enzymes and abnormal protein combinations. These substances, being antigenic, are presented to the immune system by macrophages (some of which may be resident tissue macrophages able to recognize the abnormal protein complexes) and the resident peripheral corneal Langerhans cells which are present in large numbers at the limbus.

Antigen is presented to the 'T' cells and circulating macrophages which are centrally processed to produce an intense 'T' cell response. At the site of this response the venules show "high endothelium" which allows lymphocytes to leave the circulation and also causes the slowing and obstruction of the circulation seen in fluorescein angiography. In the presence of other systemic disease there may be an active vasculitis, immune complex deposition, granuloma formation, antibody production and immune complex deposition. All of this leads to a massive cytokine release, which activates the fibrocytes of the cornea and actively destroys tissue, causing perpetuation of the cycle.

Treatment

Considering the great complexity of the interactions between inflammatory cells, the mediators and the target cells, it is not surprising that there should be differences between the various conditions and that the changes are often not confined to a single specialized tissue but spill over into other similar tissues around it.

Disorders which lead to tissue destruction are potentially blinding and must be treated intensively with local and systemic treatment aimed, if possible, at the cause rather than the final effects. Most, if not all, the non infective destructive diseases which have been discussed are associated with a cell mediated (Type IV) reaction in which there is macrophage and lymphocyte interaction or a Type III response where there is an immune complex reaction and a microangiopathy, so treatment is directed at inhibiting the immune response by lowering or eliminating the 'T' cell response by the use of immunosuppressive regimes of systemic steroid, immunosuppressives such as cyclophosphamide, specific 'T' cell inhibition with cyclosporin A and similar agents, or using monoclonal antibodies directed against the CD4 lymphocyte. In the presence of such an intensive immune response, local therapy has little effect and the membrane stabilising properties of the non-steroid agents are of little value. There is some evidence that specific anticollagenases can be of value if tissue destruction is continuing in spite of immunosuppression.

We have had very limited value from limbal conjunctival excision. In Mooren's ulcer the changes described above only occur in the superficial and mid-stroma. The removal of cornea to the level of Descemet's membrane will often stop the pain and lead to healing. However, these corneas cannot be grafted as the disease will recur in the grafted tissue even with immuno-suppression. Faced with an individual problem of corneal destruction we have adopted the following regime:-

Investigation

1. A very careful history is taken of the present and past ocular conditions in order to determine (a) the trigger and (b) any suggestion of other systemic disorder. 2. A full ocular history with accurate diagrams and drawings of corneal lesions and limbal activity is noted. 3. The patient is given a full medical examination. 4. Hematological studies of immunological function, including autoantibodies, Rheumatoid factor and C.R.P. 5. Chest X-Ray.

Treatment

Some peripheral corneal destructive lesions do respond to local steroid therapy so all are given hourly dexamethasone during the day. If an intercurrent disease is present this is treated appropriately. Systemic therapy depends on the underlying disease and the severity of the ocular disease.

In general, if there is leakage from corneal vessels, in spite of adequate local treatment or active destructive disease, systemic steroids are usually indicated. This is often more effective and has less systemic side effects if given as pulsed

methylprednisolone 500 mg i/v and then continued in a maintenance dose of oral prednisolone 10mg - 15 mg a day. Systemic vasculitis requires treatment with immunosuppressives, particularly cyclophosphamide which is given as a pulse of 500 mg i/v and washed out by i/v infusion with Hartmann's solution to prevent haemorrhagic cystitis. Oral therapy is continued, the dosage dependent on the lymphocyte count which requires to be reduced to 1.0/1,000. cyclosporin A may be used in 'T' cell induced disease and if there is not an immediate response to other immunosuppressives it should be used. cyclosporin A is not as effective in external disease as it is in uveitis. The individual requirements of these patients are best illustrated by reference to some specific examples:

Patient 1 This 59-year-old lady presented with a painful eye with a small avascular patch near the limbus. She was treated, whilst investigations were proceeding, with a non steroid anti-inflammatory agent. Five days later she presented with a large necrotic area and was therefore admitted to hospital and treated with 80 mg oral prednisolone. The pain disappeared within a few hours and although the area of avascularity increased over the next few days, new vessels could be seen entering the area. Within one month the whole area had returned to normal.

Patient 2 This 68-year-old man presented with a severe sclero keratitis in both eyes and an opaque keratolytic cornea with epithelial loss in the other. Fluorescein angiography revealed total non perfusion of the limbal region in both eyes. He was admitted to hospital and treated with pulsed I/V methylprednisolone 500 mg. As there was no immediate clinical response plasma exchange was performed and a further pulse of steroids and 500 mg of cyclophosphamide was given. At this stage fluorescein angiography showed reperfusion of the affected area, so a deep lamellar keratoplasty was performed and the patient continued on reducing dosages of systemic steroid and cyclophosphamide. After eventual cataract extraction and intra-ocular lens implantation the patient sees well and the steroids have now been completely withdrawn.

Patient 3 This 56-year-old man who had rheumatoid arthritis for 30 years but no longer required treatment, presented with a para-limbal corneal gutter and a descemetocoele. (Figures 4, 5) He was given a similar regime to patient 2, but in spite of this the grafts became opaque and were destroyed, resulting in further perforations. Eight grafts have been performed, the last with fresh tissue and limbal conjunctivae. At this stage he was given Campath 1, A humanised CD52, an anti-lymphocyte monoclonal antibody, which has eliminated his lymphocytes from the circulation. The graft has now been clear for 18 months.[8]

Conclusion

With a greater understanding of the pathogenesis it should be possible to develop specific therapies. As polyclonal antibody therapy has been shown to be effective in treating patients with destructive corneal changes, a further understanding of the responses could well lead to the development of specific monoclonal therapies, thus ending the horror of the progress to blindness that these conditions so often produce.

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