Pterygium as an early indicator of ultraviolet insolation: a hypothesis

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'Among the many obscure points which puzzle the ophthalmic surgeon the condition of pterygium presents special difficulties; its origin, development, and its tendency to relapse and recurrence, all offer problems which are still to solve.' Little has changed since these observations were made in 1918. The role of climate had been surmised, but in recent years quickening depletion of the ozone layer has focused attention on the biological consequences of increased ultraviolet insolation. There is now firm evidence that exposure to broad band ultraviolet radiation (290–400 nm) is associated with the development of pterygium. It has been predicted that a 1% increase in ultraviolet radiation would increase the incidence of pterygium by 2.5–14% in the Australian population. There are compelling reasons for re-examining these consequences in the eye.

Pterygium is perhaps the most obvious of the ophthalmohelioses (sun-related eye conditions) and can blunt sight in several different ways. In essence, it represents conjunctivalisation (and therefore loss of transparency) of the cornea, usually commencing at the nasal limbus. In one study, however, 15% of pterygia were located only temporally and in 11% of cases, pterygia were located nasally and temporally.

There are several reviews dealing with the aetiology of this condition yet a satisfactory explanation has remained elusive. As Rosenthal concluded 'It has been analyzed statistically, geographically, etiologically, microscopically and chemically – yet it grows onward primarily and secondarily.'

Fuchs' involved inclement weather, smoke, and dust and suggested that the location was related to the degree of exposure of the bulbar conjunctiva which occurs when one 'squints' under these conditions. However, it has been noted in patients with divergent strabismus and pterygium, that pterygium does not affect the divergent eye in which the nasal bulbar conjunctiva is more exposed.

In this review, the various theories of aetiology are re-examined. An attempt will be made to explain the location and shape of pterygia as well as factors involved in an individual's susceptibility to pterygium in the light of a new hypothesis.

Ultraviolet light

There is strong circumstantial evidence that exposure to ultraviolet light is important in the aetiopathogenesis of pterygium but this is not accepted universally. Cameron pointed out that pterygium was most common between latitudes 40 degrees N and 40 degrees S and for island populations. Hence a relative 'pterygium belt' straddles the equator, paralleling local atmospheric ultraviolet energy intensity.

Ultraviolet radiation was tentatively suggested as the causative agent. However, later reports of high pterygium prevalence at high latitudes (8.6% at 65 degrees N) in eskimos provided exceptions to the general rule. Before this, Nicholls found the most common ocular abnormality among Cree Indians at Norway House, Manitoba, Canada to be pterygium and considered glare as an aetiological factor.

Labrador has less than one third of the global (incident) ultraviolet B light reported for regions such as the Dakahl Islands (16 degrees N) and North Cameroon (5–10 degrees N). However, ultraviolet radiation exposures may be similar in these locations if terrain reflectivity is taken into account. It is thus of interest that the two cases of pterygium blindness were reported in an Australian aborigine and an eskimo.

Confirmatory evidence for the involvement of ultraviolet radiation has been gained by examining three at risk groups: those known to be exposed to high levels of ultraviolet radiation (either outdoors or occupational); those with other diseases known to be induced by ultraviolet radiation; and subjects who may be hypersensitive to the effects of ultraviolet radiation.

The ultraviolet theory of pterygium causation is supported by studies on rural Australians and Japanese welders. In the Australian study, a strong positive correlation between climatic ultraviolet radiation and pterygium prevalence was demonstrated. Furthermore, there was a comparable prevalence in male and female aborigines and the rates were higher than for non-aboriginals. This was thought to be due to the fact that non-aboriginal women in rural Australia generally spend less time out of doors than men and are well housed and able to escape from solar radiation, either direct or scattered. A case-control study of pterygium in Japanese workers demonstrated that pterygium was more common in welders than in other factory workers in the same industrial city. This was associated with a high exposure to ultraviolet radiation and length of employment as a welder. However, the possibility that ocular irritation was part of the aetiology could not be excluded.

Other groups in whom a high prevalence of pterygium has been reported include surfers and sailors. Such individuals are exposed to high levels of ultraviolet albedo (reflected, scattered light) and adequate ocular protection is problematic. Interestingly, Lord Nelson was troubled by bilateral pterygia and a green eyeshade was added to his admiral's cocked hat.

Recently the case for the involvement of ultraviolet radiation in the aetiology of the anterior ophthalmohelioses has been strengthened by the work of Taylor et al who investigated the watermen of Chesapeake Bay, Maryland, USA. It is relevant that they found a clear association between high personal exposure to broad band ultraviolet radiation (290–400 nm) as well as to visible light and increased risk of developing pterygium. They, however, found a weaker association between these factors for pinguecula and sug-
gested that the aetiologies of pterygium and pinguecula are likely to be different.4

Further evidence for the involvement of ultraviolet light in the aetiology of pterygium comes from the systemic associations of pterygium. These include basal cell carcinoma (BCC),5 porphyria cutanea tarda (PCT),6 polymorphous light eruption,7 and xeroderma pigmentosum.8 Ker- kemezov9 was of the opinion that ultraviolet light was of importance and was also the first to observe that patients with pterygia more frequently had hyperkeratosis and/or rodent ulcers on their faces, ears, hands, and forearms (that is, sun-exposed areas). Furthermore, pterygia developed about a decade before the skin conditions.

There has been renewed interest10 in the association between polymorphous light eruption (actinic prurigo) and pterygium. This common chronic photodermatitis is thought to be caused by ultraviolet A radiation11 — the association with pterygium is thus consistent with the involvement of broad band ultraviolet light in pterygium aetiology. Polymorphous light eruption is said to be uncommon in Australia. A postulated reason is that this is because of the higher ratio of ultraviolet B to ultraviolet A in that country. In PCT, uroporphyrin accumulates in the tissues, is photoactivated (absorption spectrum peaks at about 400 nm and 500–600 nm), and causes tissue damage by a number of mechanisms including free radical generation.12

Further evidence for the ultraviolet theory comes from studies of ultrastructure.13 A large component of pingueculae and pterygia is the result of newly synthesised elastic fibre precursors and abnormal maturation forms of elastic fibre (elastodysplasia) that undergo secondary degeneration (elastodystrophy). These structures are presumed to be elaborated by actinally damaged fibroblasts of the substantia propria and are morphologically similar to solar degeneration of the skin. However, elastotic degeneration is reportedly uncommon in pterygia in India.14 Several authors (see Cameron15), however, have found changes in the basal limbal epithelial cells. These changes may occur consistently16 and may take on a new significance in that the cornal epithelial stem cells17 are located here. Some of the more recent reports on morphology of pterygium ignore this issue as the specimens examined are surgical, not post mortem. There is thus little, if any, possibility to examine limbal structures in such surgical specimens.

On the other hand, Johnson et al18 and Norn19 have found that while the geographic distribution of spheroidal degeneration in Labrador and Newfoundland is best explained by chronic exposure to reflected ultraviolet light; this was not so for pterygium.

Much has been made of the observation that pterygium has a high prevalence in sawmill workers in British Columbia, northern India, Taiwan, and Thailand compared with control groups in the same areas.1 This observation has been used to strengthen the importance of ocular irritation as a causative agent in pterygium formation and to play down the case for ultraviolet light (as the sawmill workers presumably work indoors). It is, however, possible that even when working indoors, these workers are exposed to albedo. It was known in Kenya16 (using the northern European complexion as an indicator) that hats should be worn indoors in houses with corrugated iron roofs and no ceilings as ‘galvanised sheets did not repel all the sun’s rays’, or more likely resulted in high albedo exposure ‘indoors’.

Although the evidence for involvement of ultraviolet light is strong, a precise mechanism by which a predominantly nasal location for pterygium occurs is lacking.

Tear film and heat

In some geographic areas where pterygia are prevalent, dust, wind, and excessive desiccation often coexist with solar glare, but these are not constant features of the external milieu in areas where pterygia are common. Tear function abnormalities have been proposed as an aetiological factor. It has been observed that a pterygium is further exacerbated by elevation of the pterygium head, dryness, and deline formation. No abnormalities of Schirmer’s test,20 tear break up time,21 or rose bengal staining of the cornea were found in eyes with pterygia compared with those without. Taylor,22 however, found that aborigines with pterygium (or climatic keratopathy) had a significant discontinuity of the marginal tear strip when compared with aborigines without these conditions. However, all the other tests of tear function in these eyes were normal and it was concluded that this disruption was secondary to a mechanical disruption of the tear film. Europeans with pterygium did not show this abnormality (however, pterygia in Europeans were smaller). This is hardly surprising, as pterygia interfere with and may destroy the nasal conjunctival fornix, the integrity of which is necessary for the maintenance of the normal tear film. Pterygium incidence is high in some areas of high humidity,23–25 where desiccation is less likely. Elliott,26 however, provided evidence that drying of the tear film by wind devitalises tissue, this being the thermal effect of the mesial third of the palpebral aperture and that this allows actinic radiation to damage the conjunctival and corneal epithelium and Bowman’s membrane. He also pointed out that tear drying can occur in areas of high humidity if the individual is exposed to constant wind, as in the trade wind belts.

Anderson1 postulated a causal relation between temperature and pterygium. Other workers27–30 have implicated infrared radiation, but the evidence for this is weak. One study31 points out that in mountainous areas which receive more ultraviolet radiation, there is no greater prevalence of pterygium and therefore infrared radiation is more likely to play a role. However, in Lima, Peru (150 metres above sea level), a pterygium prevalence rate of 31·1% has been reported.32 While Cameron33 states that no specific biological effects have been produced by infrared radiation, it has recently been shown34 that low level heating (even 39°C for 1 hour) induced scleral hyperplasia with activated fibroblasts in a rabbit model.

Microtrauma

Mechanical irritation by dust particles, enhanced by the tear flow from lateral to nasal35 has been proposed as a mechanism; however, pterygia occur in dust-free areas — for example, at sea in sailors,24 surfers,36 and in the Chesapeake Bay watermen.37

Angiogenesis factor

It has been suggested that a pterygium angiogenesis factor may exist which develops following repeated irritation at the limbus.38 The presence of this factor produces vessel ingrowth and the formation of pterygium. It may be that prolonged ultraviolet exposure causes the biological changes in Bowman’s membrane39 and that altered proteins so formed could then act as an angiogenic or ‘pterygiogenic’ factor. It may be significant that corneal epithelial cells and not keratocytes are able to release a heat stable factor, which, in a dose dependent manner increases the proliferation of vascular endothelial cells.40

Immunology

IgE and IgG deposits in pterygium connective tissue stroma have been described.41 Plasma cell and lymphocyte infiltration were seen in the same areas as IgE and IgG. However, it
is unclear whether chronic inflammation is a cause of pterygium or a secondary finding. Certainly, chronic conjunctivitis features prominently in the early reports on this subject. Interestingly these authors speculated that cell bound IgE irritant complexes may initiate the release of active pharmacological mediators from mast cells, which may in turn release stimulatory factors leading to the development of pterygium. Suggested mediators were platelet activation factor and platelet derived growth factor. The latter regulates the effects of epidermal growth factor which has epithelial regulatory actions.

Also in the early literature is the idea that ascribes pterygium to small limbal corneal ulcers to which the conjunctiva becomes adherent - these ulcers may have been due to phyctenulosis or herpes virus. Convincing proof for this theory is lacking.

Heredity
An inherited predisposition to pterygia seems to exist. Some pedigrees have shown an apparent transmission through several generations suggesting an autosomal dominant mode of inheritance. However, this may simply reflect common environmental factors or occupations or an inherited anterior segment shape factor.

Miscellaneous
It has recently been proposed that a factor in adult forehead perspiration, perhaps lactic acid, commences a chain of events in pterygium formation. Sweat flows along the brow, down the side of the nose and is deposited on the nasal bulbar conjunctiva (as demonstrated by applying rose bengal to the forehead). This theory, however, would not explain the occurrence of pterygium in situations where sweat would evaporate rapidly (as in sailors), or in cold environments where 'blinding sweat' would be unusual. Although this theory could easily be examined in experimental animals it remains untested.

Other theories which have not gained ready acceptance include:
(1) the notion that pterygium is due to a chronic infection;
(2) that pterygium is due to thrombosis of conjunctival veins;
(3) that contraction of the horizontal recti results in stasis in blood vessels and looseness of the conjunctiva which folds itself over the cornea forming a pterygium;
(4) that light is reflected from the skin of the nose back on to the nasal limbus.

These various theories do not provide a convincing explanation of pterygium pathogenesis, shape, or location. There is no explanation (other than inheritance) as to why only certain individuals develop pterygium in a particular environment. Unlike skin malignancy, skin pigmentation does not appear to play a role. Pterygium location has been explained by noting that the longer temporal eyelashes of the upper eyelid and the greater downward 'bowing' of the outer two thirds of the upper eyelid, shade and filter light falling on the temporal (compared with the nasal) conjunctiva and cornea. This does not explain why temporal pterygia occur. It is not consistent with the observation that pterygium is found in the fixing eye of patients with exotropia where it is expected that the nasal region of the exotropic eye is more exposed. It has also been observed that pterygium develops in the dominant eye, probably because in intense
sunlight the non-dominant eye is closed. These theories do not consider that the corneal epithelial stem cells, located in the basal limbal epithelium, play a role in maintaining the junction between corneal and conjunctival epithelia. Although it has recently been proposed that pterygium may be due to limbal stem cell dysfunction why this should be focal in nature remained unexplained.

**Hypothesis**

The ectoderm reaches sophisticated specialisation in the transparent cornea and crystalline lens. As these are the only refracting optical surfaces in the body and as indirect insolation (mostly albedo) is responsible for most of the ocular ultraviolet exposure, it might be expected that the ophthalmohelioses provide early human biological warning of increased ultraviolet insolation. This indeed appears to be the case. Kerkenzev was the first to observe that white people with pterygia suffered from hyperkeratoses and/or rodent ulcers. Further, pterygia developed about a decade before the dermatohelioses. Subsequent prevalence data confirm this observation.

**Shape and location**

An explanation for these findings has recently been proposed. The anterior eye acts as side on lens, focusing light from the side to the pattern of some ocular conditions thought to be caused by insolation. Thus foci are seen at the nasal limbus (Fig 1), the usual site of pterygium (Fig 2) and pinguecula, and in the nasal aspect of the crystalline lens (Fig 3), an initial site of cortical cataract (Fig 4). Light proceeds across the anterior eye via transcameral pathways (Figs 5 and 6). The degree of limbal focusing is determined by corneal shape and anterior chamber depth. and this may explain why particular individuals in a common environment are afflicted by these conditions. As these factors are quantifiable, it may be possible to identify at risk individuals.

Using computer assisted optical ray tracing techniques, we have calculated that the peak light intensity at the distal limbus is approximately 20 times that of the incident light intensity. Although these focusing phenomena are easily seen with visible light, they also occur at 308 nm. This is not unexpected as the cornea transmits significant amounts of these energetic and biologically active wavelengths (60% of radiation at 320 nm and 80% at 400 nm). The association of exposure to broad band ultraviolet radiation and visible light with pterygium is therefore not surprising.

Focal limbal irradiation may be particularly injurious as the corneal epithelial stem cells are struck from behind and are not protected by the more superficial layers of the epithelium. Evidence that basal limbal cells may be altered in pterygium formation was presented a century ago. The vertical axes of the basal cells become oblique and their regular order is lost. The cells become round, oblong, or distorted and there is more intense nuclear staining with haematoxylin and eosin. Such pyknotic nuclei have been seen in lenticular epithelium which has been exposed to ultraviolet radiation. Recent studies, utilising surgical specimens (in which the limbus would rarely be preserved), have concentrated on changes in the stroma of the pterygium. Such changes may well be secondary, and as Cameron pointed out, these studies 'concentrated on the wrong end of the pterygium'. He observed 'active' fibroblasts at the head of pterygia surrounding Bowman's membrane and hypothesised that these originated in the limbal connective tissue. Recently, however, cell surface markers have been used to identify altered limbal stem cells at the edge of Bowman's layer disruption.

Pigmentary patterns in the corneal epithelium suggest that areas of limbus contribute 'piece-of-pie' shaped areas of corneal epithelium. Chronic focal irradiation of the limbus may reduce the ability of that zone to renew corneal epithelium and to maintain the junction with vascularised conjunctiva. Alternatively, ultraviolet radiation may induce hyperplasia in limbal cells as has been described for epidermal and hair follicle cells. These altered cells invade the cornea and the limbal barrier moves centripetally with them. This is consistent with evidence of abnormal proliferation of epithelium in primary pterygium.

In either case this may explain the characteristic wing shape of pterygium (from which it derives its name). With these assumptions and by using a population balance model of corneal and limbal epithelial production, we have been able to confirm that a wing shape would be expected.

Focal modulation of the ocular surface immune system may also play a role in pterygium formation (see Coroneo). Langerhans' cells are numerous at the limbus, are depleted by ultraviolet irradiation and this is associated with immune tolerance. Two other peculiarities of pterygia may be explained by this phenomenon. Free radical generation is a prominent feature of photochemical injury. Free radicals stimulate mucus secretion in certain epithelia which may explain the intriguing observation of numerous goblet cells in pterygium epithelium. Secondly, tears contain lactoferrin, an iron binding protein known to inhibit free radical formation. If free radicals are being generated at the site of pterygium formation and lactoferrin plays an inhibitory role, then it is conceivable that iron is being delivered to this site and perhaps deposited there. This would account for Stocker's line of iron seen at the advancing edge of many pterygia.

Finally, it has long been recognised that cortical cataract often begins in the nasal aspect of the crystalline lens. These opacities may accompany pterygium but their presence not noted before surgery. Focal irradiation of lenticular stem cells, located at the equator of the crystalline lens, may cause localised lenticular opacification. The oblique nature of the insolation would circumvent the protection of the iris which ordinarily shields the crystalline lens equator. Furthermore, the pupil response is most sensitive to visible light (and insensitive to ultraviolet radiation) and is less sensitive to peripheral retinal illumination. Although there has been support for the ultraviolet theory of cataractogenesis, it...
appears that the risk of cortical cataract alone is increased with exposure to ultraviolet B. The effect of wearing sunglasses on ocular insulation is controversial. Most sunglasses do not offer side protection from albedo, as much of the lateral conjunctiva and cornea remain exposed. Such glasses reduce glare from direct, visible light and might allow wearers to increase their exposure to ultraviolet albedo. Wearing sunglasses under extreme albedo (such as in Antarctica), can be associated with the development of photokeratitis ("snowblindness"). As the pupil response is most sensitive to visible light, conventional sunglasses may allow increased intraocular as well as ocular surface insolation. As suggested, wearing a hat may help but the degree of protection would be as variable as the style of hat.

These observations, while not proving that peripheral refraction phenomena cause the anterior opthalmohelioses, provide strong circumstantial evidence for their involvement in the pathogenesis of these conditions. This conjunction of focused light (including ultraviolet) and vulnerable cells might be expected to cause accelerated pathology compared with exposure to the same levels of unfocused radiation on more resilient epidermal cells. This hypothesis provides an explanation for pterygium shape and location and may explain individual susceptibility.

Thus, increased prevalence of pterygium, a disease of the ocular surface associated with exposure to broad ultraviolet and visible light, may provide an early indicator of increased ultraviolet insolation. In some ways the solution to the riddle of pterygium may have come to light.1

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