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Editorial

THE EYE AND LEPROSY

All those who study or work with leprosy are aware of the major problems that ocular complications present in the long-term management of the disease. Over a hundred years ago Bull and Hansen drew attention to the very high incidence of ocular involvement, commenting that 'there is no disease which so frequently gives rise to disorders of the eye, as leprosy does',[1] and the disturbing consequences of these complications were re-emphasized by Margaret Brand in her pamphlet on the care of the eye: 'Blindness in the individual who has normal skin sensitivity is enough of a handicap, but in one who has lost that faculty it is disastrous. Few have the resources, material, mental or spiritual, to live with it'.[2]

Despite this long awareness of the large variety of ocular changes that can occur in the disease there is still considerable ignorance of the underlying pathological processes and their consequences, and this ignorance stems mainly from two causes. First it derives from poor coordination of research into the clinical and pathological changes that affect the eye in all stages of leprosy, and secondly it relates more particularly to the lack, until recently, of an experimental animal that could be used to study the evolution and pathogenesis of the disease in the ocular tissues.

The problems of communication and coordinated research are mainly logistic and will always remain. The leprologist, working often in difficult circumstances with limited facilities and equipment, may not have the opportunity and ophthalmic experience to make detailed assessments of ocular disease and may not have the time to carry out the important longitudinal studies that are required to understand the natural history of the ocular changes. Evidence from the world literature on ocular complications of leprosy over the last 40 years shows how fragmented the knowledge of this important subject really is. There are many survey reports on groups of patients in scattered parts of the world, but little in the way of long-term follow-up studies which are so essential for the understanding of the disease process. Where these examinations have been carried out by ophthalmologists with specialized knowledge and sophisticated techniques and equipment, the information has proved more valuable but, with few exceptions, such colony surveys

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and case reports serve merely to build up a general picture of the immense problems of ocular damage throughout the world and provide only isolated glimpses of the pathology of a condition that has to be considered equally in terms of its evolution and duration.

The development of an experimental animal model ought to prove a turning point in the understanding of ocular pathology in leprosy, and evidence from animal and clinical studies may make it necessary to rethink some of the traditional ideas of the disease process and its therapy – particularly in lepromatous leprosy. The purpose of this paper is to draw together some of the clinical and experimental data that is now emerging in order to indicate lines of clinical and pathological research that could be followed, with the intention not only of solving some of the many unanswered questions about ocular complications and methods of preventive therapy, but also to remind leprologists that they have in the eye an organ that lends itself above all others to the clinical, pharmacological and pathological study of the neural involvement of the disease.

Some of the statements to be made will be hypothetical, some will be provocative, but all are intended to stimulate renewed interest into the effect of leprosy on the eye – an interest that has, with a few exceptions, remained sadly fallow over the past decade.

Incidence of blindness in leprosy

It is possible that there are between 500,000 and 750,000 patients in the world who are blind due to leprosy, but estimates are difficult because the information on which they are based is so variable and erratic. These estimates rely heavily on isolated reports from scattered leprosy communities, with differing ethnic populations, taken at different times, so that the extrapolated global figures are almost meaningless, except that they reveal the magnitude of the ocular problems. Certain general conclusions can be drawn from a closer analysis of the available data from these reports – that the ocular complications have a much higher incidence in the lepromatous form of leprosy, and therefore certain races, particularly Asiatics, are more susceptible to ocular disorders, and that ocular involvement is more prevalent in leprosy in temperate climates; thus the major ocular complications are to be expected in the more northerly parts of the Far East rather than in Africa. In the latter continent leprosy may just be one of a variety of endemic conditions that can cause blindness – these include trachoma and onchocerciasis – and the shorter life expectancy of the African patient means that many succumb before the inevitable late ocular complications have had time to develop. In addition most of the reports from leprologists working in the field stem from Africa where the ocular complications are relatively lower, and this therefore tends to understate the global significance of eye disease.

Ocular complications

It is not the purpose of this article to classify all the ocular complications of leprosy, many of which develop as manifestations of facial nerve paralysis and secondary infection causing a variety of degenerative corneal conditions. Primary involvement of the eye is demonstrated in Table 1 in a simplified form with the clear distinction being made between tuberculoid and lepromatous leprosy. Borderline leprosy has variable features depending on the stage and state of the patient's immunity.

Table 1

Tuberculoid	Lepromatous
V neuropathy	V neuropathy
VII neuropathy	VII neuropathy
	Episclera – nodules
	Cornea – 'beading' → keratitis
	– leproma
Iris – acute iritis	Iris – acute iritis
	– iris pearls → *chronic iritis*
	– iris leproma
	Ciliary body – ? phthisis
	Lens – ? cataract
	Choroid – ? peripheral lesions

The importance of paralysis of the facial nerve cannot be overstressed as a major cause of blindness. It occurs in all forms of leprosy and may result in a chronic exposure keratitis and subsequent corneal scarring and degeneration. The role of trigeminal neuropathy is less established; certainly corneal sensation is often badly affected in leprosy with an accompanying diminution in the normal protective responses, but several studies have shown that complete corneal anaesthesia is rare,[1–6] and it is probable that the effect of Vth nerve paralysis on metabolism and nutrition of the cornea is equally important.

All forms of leprosy may give rise to an acute iritis which, if left untreated, may lead to a profound and permanent loss of vision. In lepromatous leprosy the inflammation may be spontaneous and is believed to represent a reaction to the deposition of circulating immune complexes within the eye.[7–8] This reaction, also known as erythema nodosum leprosum, involves many tissues including the skin, eyes, peripheral nerves and sometimes the kidneys.[9] The iritis does not differ in its clinical presentation from any other form of acute iritis and requires intensive therapy with local mydriatics and steroids.

The blinding conditions produced by facial nerve palsies and by acute iritis are common to all forms of leprosy and are potentially preventable. Training of leprologists and paramedical workers in the management of these

two conditions is already being undertaken in several centres in the world, notably Carville in the United States, and timely tarsorrhaphies or even more extensive plastic surgery, together with encouragement of patients to report for treatment if an acute painful red eye develops, are already contributing significantly towards preventing the late corneal and intra ocular complications of these disorders.

Primary corneal involvement in lepromatous leprosy takes the form of infiltration and later destruction of corneal nerves followed by a chronic superficial stromal keratitis to which may be added pannus formation or corneal degeneration. These corneal changes are usually not serious for the vision unless corneal deposits are substantial,[2,10] and may take many years to evolve. A true leproma of the cornea or iris may occur but is rare. It is the so called *chronic iritis* of lepromatous leprosy that is responsible for the major visual impairment in the disease, a condition aptly described by Weekeroon[11] as 'the cause par excellence of blindness', and considered by most authors to be the prime ocular complication of leprosy, and the remaining part of this article will be directed towards an examination of existing knowledge of the pathogenesis of this interesting condition and its significance in the disease process.

Chronic iritis

The condition was described by Bull and Hansen[1] as 'iritis without violent symptoms with exudations around the borders of the pupils and adhesions to the capsule of the lens in patients who have not complained of pain or derangement of sight'. The iritis has many features that sets it apart from other forms of chronic inflammatory disease and it shows several characteristics of a basically degenerative process of slow evolution. An interpretation of the clinical signs, and of the few pharmacological and pathological studies that have been carried out, strongly suggests that the chronic iritis of lepromatous leprosy is *neuroparalytic* in origin, and the evidence for this and its diagnostic and therapeutic significance will be discussed.

Clinically the condition develops quietly a few years after the onset of the disease. It causes no symptoms and very few signs initially, the eye is quiet, without discomfort and with little overt evidence of inflammation. The iritis is usually bilateral and iris pearls are frequently seen in the early stages as a transient phenomenon. Many authors have reported that conventional mydriatics have little effect on pupil dilatation despite the fact that synechiae are uncommon,[12–13] although these may form if an acute iritis supervenes. The changes in the anterior chamber are described as showing a faint flare and fine atypical keratic precipitates often pigmented and the condition may drag on for years, and does not respond to local steroid therapy. Eventually the

iris shows progressive signs of atrophy and disintegration accompanied by increasing miosis, and it is this miosis associated with corneal or lenticular changes that is responsible for the severe visual impairment that inevitably ensues. The advanced iris atrophy has been noted for long by surgeons who have attempted to undertake cataract operations or optical iridectomies in these patients and have found the tissue extremely friable.[14–18]

This clinical pattern does not suggest a typical inflammatory disease, and some other underlying pathological mechanisms must be sought. The preference of the leprosy bacillus for areas of low body temperature has been noted by clinicians for many years,[19] and the involvement of superficial nerves in the generalized bacteraemia that occurs in lepromatous leprosy is responsible for the major neurological complications through its destruction of fine nerve endings in the cooler parts of the body. Temperature measurements in animals have demonstrated that the anterior segment of the eye is three degrees cooler than the general body temperature,[20] and this suggests that the nerves in the cornea and iris are some of the coldest nerves in the body. In the experimental animal bacilli were found to be concentrated at the front of the eye,[8] and clinical evidence reveals that it is rare for the posterior segment of the eye to be involved in the disease. Of additional interest is the fact that anterior segment temperatures are related to environmental conditions,[21] and this might explain the higher incidence of ocular complications in temperate areas.

The assumption can certainly be made that iris and corneal nerves are susceptible to attack from leprosy bacilli during the bacteraemia that occurs in lepromatous leprosy and there is ample evidence to support this supposition.

The sequence following corneal nerve involvement is well-established clinically and histologically. Leprous infiltration of the corneal nerves produces the typical transient beading followed by disintegration that leads to stromal disease and is associated with irregular loss of corneal sensation. Histology shows round cell infiltration of the Schwann cells with bacilli contained within characteristic foam cells. A parallel clinical situation seems to exist in the iris with the early transient appearance of iris pearls which are pathognomonic for lepromatous leprosy followed by progressive iris atrophy, and the resemblance to corneal beading has already been commented on by Choyce.[16] Histology of these iris pearls also shows tightly-packed bacilli inside mononuclear cells with no accompanying inflammation or foreign body reaction.[22] The distribution of the iris pearls conforms to the anatomical distribution of the autonomic nerves plexuses in the iris, these nerves contain small non-myelinated sympathetic and parasympathetic fibres supplying the sphincter and dilator muscles of the pupil – nerves that by their position and size would be expected to be particularly susceptible to leprous infiltration. The evidence suggests that iris pearls are the visible manifestations of the breakdown of the iris nerves (cf. corneal beading) and that the autonomic nerves are primarily involved.

Further support for this hypothesis can be obtained from clinical and pharmacological observations. The non-reacting pupil of lepromatous leprosy has already been noted, paralysis of the autonomic nerves would certainly produce no dilatation of the pupil after Atropine or its derivatives, and it would require a direct sympathomimetic drug such as Phenylephrine to achieve this, provided the dilator muscle was functioning. An intriguing study by Swift and Bauschard[23] on patients with early lepromatous leprosy showed that the pupils of a significant proportion (55%) of cases dilated with 1% L-epinephrine whereas only 5% of normal controls showed a similar dilatation. The results were interpreted as a manifestation of denervation hypersensitivity and suggested that early iris involvement was more common than previously reported. The authors concluded that the leprous eye was a model of peripheral post-ganglionic denervation and further studies were recommended. Slem, reporting his studies in Turkey,[24] also concluded that the progressive iris atrophy of leprosy was likely to be neurotrophic in aetiology.

Deprivation of the autonomic and therefore the motor supply of the iris muscles would be expected to be followed by progressive tissue atrophy such as occurs elsewhere in the body. Disintegration of muscle fibres over a long period of time sets up local inflammatory changes consisting mainly of round cell infiltration and these have been observed in iris tissue examined pathologically,[13, 22, 25] and the chronic low-grade flare and pigmented cells noted by slit-lamp examination of the anterior chamber could well be manifestations of this destructive process and account for the lack of clinical signs and symptoms and the failure to respond to local steroids. Hashizuma and Shionuma examined the iris in lepromatous leprosy by electron microscopy and found lepra cells infiltrating the stroma and non-myelinated nerves although they considered the primary disturbance to be in the muscles, but no further specific electron microscopical examinations of the iris nerves have been reported. The later stages of this evolutionary process are characterized by increasing iris atrophy and miosis. Studies on the histology of the sphincter and dilator muscles in lepromatous leprosy has shown a differential atrophy with the dilator more affected than the sphincter and in 15 specimens recently examined, 11 showed signs either of degeneration or complete dilator atrophy whereas in only 7 out of 15 was the sphincter muscle degenerate.[13] This differential atrophy could be explained by a difference in the innervation and morphology of the two muscles with the dilator more thinly spread throughout the iris, and its consequent atrophy gives rise to the increased friability of the tissue and the persistent and troublesome miosis.

The question of the relationship between leprosy and cataract remains unanswered. No figures are available for the overall incidence of cataract in the disease as the condition is common in most parts of the world where leprosy is endemic. Many authors consider there to be no true leprosy cataract and that the lens changes that are observed are part of the changes that are

seen in a normal ageing population. Certainly there is a higher incidence of cataract after acute iritis and it may be a major complication in untreated patients, but its relationship to the chronic iritis of lepromatous leprosy has not yet been satisfactorily established. A study by Prabhakaran[26] considered the affinity that *Mycobacterium leprae* is known to have for DOPA, and it is of interest that this substance is found in large quantities in iris tissue. Some of the breakdown products of DOPA metabolism, notably the quinones, are known to be cataractogenic in animals, and a current study by Clayton *et al.*[27] suggests that the biochemical profiles of cataracts in leprosy differ from those of other senile lens opacities.

Conclusion

Cochrane[28] described leprosy as 'the most thrilling and exciting adventure on which any medical man can embark' and certainly the ocular problems posed by the so-called chronic iritis of lepromatous leprosy will provide the leprologist and the ophthalmologist with a fascinating and rewarding exercise in medical detection. If this condition is truly a neuroparalytic iritis then it is one of the few situations in which this occurs clinically – it may be present in Herpes zoster ophthalmicus and in heterochromic cyclitis – and the diagnostic and therapeutic repercussions are far-reaching. The use of pharmacological pupil tests in the early stages of ocular involvement will need to be evaluated, but more important is the possible role of pupil testing in the detection of the systemic neurological manifestations of the disease, to augment and perhaps even replace some of the existing clinical and laboratory tests. The therapeutic implications of contemporary ophthalmic management will also need to be reassessed. For example, whether the conventional use of steroid and mydriatic drops has any value in the early stages of chronic iritis, since the use of a paralysing agent such as Atropine in an already paralytic situation has little to commend it on pharmacological grounds. On the other hand it might be possible to preserve the function of a failing dilator muscle by the administration of direct sympathetic stimulants in the same way that physiotherapy preserves the function of denervated voluntary muscle. The role of DOPA and its breakdown products in relationship to cataract formation and perhaps chronic iritis also merits further study. All these aspects of the condition require investigation and clinical research on a coordinated and if possible international basis. Long-term longitudinal studies are essential in the understanding of the natural history of the ocular manifestations, and pathological material is needed particularly in the study of the iris nerves which should be examined by both light and electron microscopy. Furthermore, it is hoped that studies on experimental infection in animals will provide some of the answers to the questions posed by clinical leprologists and pharmacologists.

Finally a cautionary note must also be sounded – 'the history of leprosy is strewn with the wrecks of so-called cures',[29] and the literature is full of noble aspirations that have come to nothing. This should not, however, be allowed to impede the combined efforts of experimental and clinical research in the hope of at least advancing some way towards alleviating the intolerable situation that the blind leprosy patient must experience.

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T. J. ffytche
St Thomas' Hospital
London

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