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Editorials

Leprosy—a new look at an old disease

Leprosy is one of the oldest scourges of humankind. Accurate portrayals of the disease in Chinese medical treatises date from 400 BC, and classic descriptions in ancient Indian literature occur even earlier.[1] In our western tradition the fear and loathing directed towards the disease come directly from the bible. Leprosy was the "disease of the soul", the "punishment for sin". By the dawn of the Middle Ages the leper had become the universal symbol of persecution, the diseased and disenfranchised outcast of Western society.[2] Even though the prevalence of leprosy steadily declined in Western Europe after a peak in the 14th century, it became epidemic in other parts of the world, especially in Asia, Africa, and South America. Until the introduction of dapsone in the 1940s there was no effective treatment for leprosy, and infected individuals were routinely isolated and segregated from all contact with society. In some areas of the world this approach continued until well into the 1980s, even after a number of highly effective antileprosy drugs had been developed.

Today the prevalence of this ancient disease is rapidly declining in most countries around the world. This decline is a direct result of the widespread administration by public health workers of multidrug therapy (MDT), a combination of rifampin, dapsone, and clofazimine. The introduction of MDT by the World Health Organization in 1982 for the treatment of multibacillary leprosy has led to a shortened treatment time of 2 years and a high degree of bacterial eradication (99.9%). It is felt that MDT for 2 years in almost all cases is adequate for producing a complete bacteriological cure of the disease and for preventing the emergence of drug resistant strains of *Mycobacterium leprae*.[3] In spite of this optimistic assessment leprosy still affects 10–12 million people worldwide, the majority of whom are found in Africa and in the southern portion of the Indian subcontinent.[4] The disease invariably causes many visually disabling sequelae, and it is estimated that 3.2% of all leprosy patients are ultimately blinded by long term ocular complications.[5] Several recent studies have documented the main causes of blindness in leprosy.[4 5–12] These causes include iritis, posterior synechia, cataract, lagophthalmos, corneal ulceration, and all of the complications associated with corneal hypaesthesia and exposure. However, none of the studies has addressed the question of whether or not the sight threatening complications of leprosy continue to develop after the infectious component of the disease has been adequately treated.

We have had a highly effective treatment programme for leprosy for almost 20 years, and the treatment regimen, MDT, has been proved to be almost 100% effective in eliminating *M leprae* in infected patients. But the ocular complications of the disease remain a major cause of blindness worldwide, and we still do not understand how, why, or to what extent eye disease in "cured" leprosy patients continues to progress. Until we understand this phenomenon we will not be able to adequately address the eyecare needs of leprosy patients.

Lewallen *et al* (see p 817, this issue) have examined this question in an exhaustive study that spans an 11 year period from 1988 to 1999 and documents ocular changes in leprosy patients in eight resettlement villages in South Korea. Of 501 patients examined in 1988 the authors were able to find 270 for re-examination in 1999, a remarkable follow up effort. Eighty four of the patients had died. It is known that patients who are blind from leprosy have a 4.8-fold excess risk of death compared with their non-blind peers of the same age.[13] Lewallen and colleagues found that, over the 11 year period, of the patients with no sight threatening leprosy related ocular diseases (lagophthalmos, posterior synechia, keratitis, etc) in 1988, 14.7% had developed one or more of these conditions in 1999. Similarly, of those with no signs of cataract in 1988, 26.4% had developed a vision reducing cataract in at least one eye at the follow up examination. Overall, 14.3% of the patients developed visual impairment and 5.7% became blind in the intervening 11 years.

These findings are a sobering reminder that even though patients may be cured bacteriologically, leprosy related ocular lesions can slowly cause visual impairment that ultimately leads to blindness. Lewallen *et al* did not find any ocular lesions caused by active infection by *M leprae*. Instead, they found that progressive visual loss occurred as a result of chronic nerve damage that led to lagophthalmos, entropion, ectropion, corneal exposure, and keratitis. Small pupils, posterior synechia, and cataracts were frequently associated with a smouldering "chronic iritis". This phenomenon has been commonly described in "cured" leprosy patients and is felt to be caused by damage to the sympathetic nerves. Therefore, Lewallen *et al* concluded that all of the progressive long term blinding complications in these bacteriologically cured leprosy patients, with the exception of trichiasis, were the direct result of chronic nerve damage.

From a public health point of view this study documents for the first time the progressive nature of the blinding complications of leprosy long after a "cure" has been effected. This conclusive evidence should have a profound influence on the planning of future strategies for blindness prevention in leprosy treatment programmes. Improved methods for managing the ocular complications of leprosy are currently being proposed.[14] Any future recommendations for the worldwide eradication of leprosy and the treatment of the ocular complications of the disease should take into consideration the findings of this important study.

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Entry site neovascularisation after diabetic vitrectomy

When scleral entry sites over the pars plana were first used for vitrectomy access, concerns were raised that anterior vitreous complications might compromise surgical outcomes.[1 2] After all, it had long been recognised that, in chronic uveitis or in inflammation complicating a penetrating injury, the non-pigmented ciliary epithelium might undergo proliferation and fibrous metaplasia, accompanied by a stroma derived vascular component, to form a "cyclitic" membrane using the anterior surface of the vitreous as a scaffold; this could lead to traction on the ciliary processes and peripheral retina, hypotony, and phthisis.[3] The retrolental membrane might also include glial and retinal pigment epithelial cells in cases of concomitant rhegmatogenous retinal detachment or an "ingrowth" of episclera derived fibrovascular tissue at sites of penetration. Happily, such foreboding over pars plana vitrectomy has proved largely unfounded, presumably reflecting in part the dispersion of any inflammatory mediators involved. But vitrectomy for the ischaemic retinopathies, especially for proliferative diabetic retinopathy (PDR), has been a notable exception.

Following vitrectomy for PDR, any residual new vessels located posterior to the vitreous base usually undergo regression,[4] but some eyes develop florid basal neovascularisation as a supplement to the normal wound healing process at the sclerotomies.[2 5 6] Such entry site neovascularisation (ESNV) may arise as an isolated event after otherwise successful surgery when it represents one of a number of possible sources of "delayed" diabetic vitreous cavity haemorrhage (DVCH)—that is, bleeding after an initial haemorrhage-free period of 3 or more weeks post-vitrectomy. Other possible culprits for delayed DVCH include "secondary haemorrhage" from shedding of thrombus (for example, from a sclerotomy or from a retinal vein from which a neovascular outgrowth had been avulsed during vitrectomy) or detachment of residual attached post-basal cortex and avulsion of fibrovascular tissue contained therein. The mechanism of bleeding from ESNV (that is, whether through some mechanical event or simply as a manifestation of friability) is uncertain as is the nature of its spontaneous regression.[6] In other circumstances, however, ESNV forms part of a more widespread uveal proliferation involving both the iris and ciliary body and frequently associated with retinal detachment as a cause or consequence of the vascularised cyclitic membrane.[1 2 7 8]

The term "fibrovascular ingrowth" has been used inadvisedly[2 6] to denote the intraocular vascularised proliferation at sclerotomies for it implies an episcleral contribution to, or source of, ESNV[9] (which is seldom the case). There has also been a dearth of information regarding the incidence of ESNV post-vitrectomy. Michels[4] discovered only one example of ESNV within 18 months of successful vitrectomy in an early series of 107 eyes with PDR, most of which must be presumed to have been aphakic; many such aphakic vitrectomised eyes nevertheless developed rubeosis iridis, ostensibly though removal of the hyalolenticular barrier to anterior diffusion of cytokines and growth factors.[4 7] The source of DVCH in eyes kept phakic in later years was seldom identified,[10 11] albeit, many surgeons believed that ESNV was a major contributor to DVCH with consequential fears that any additional entry sites would increase the potential for rebleeding. However, two recent studies have provided new insights into the contribution of ESNV to DVCH. Firstly, Hotta and colleagues[12] found ESNV at one or more sclerotomies in six out of 13 eyes (46%) undergoing vitreous cavity washout (VCWO) for DVCH. Of the 12 affected sclerotomies, 11 had shown a "low reflective trapezoid image" on ultrasound biomicroscopy (though the overall predictive value of this ultrasonic feature for ESNV was only 50%). Secondly, West and Gregor, reporting in this issue of the *BJO* (p 822), found ESNV in 11 out of 19 eyes (58%) undergoing VCWO for DVCH. The presence or absence of an episcleral vessel at a sclerotomy (putatively a sentinel of ingrowth) was an unreliable predictor of ESNV and no instance of more widespread fibrovascular proliferation in the anterior vitreous, whether of cyclitic or retinal

origin, was discovered during VCWO. Vessels derived from the anterior retina are the distinctive and distinguishing feature of so called anterior hyaloid fibrovascular proliferation (AHFP) which complicated vitrectomy for PDR in a high proportion (13%) of a particular series of cases.[13 14] However, such rampant "retrolental neovascularisation" (RLNV),[15] apparently arising independently of ESNV,[14 15] was probably a consequence of concomitant scleral buckling (causing superimposed ischaemia).

Three factors appear to be important in the pathogenesis of ESNV (and indeed RLNV/AHFP). Firstly, continuing post-vitrectomy secretion of ischaemic retina derived angiogenic growth factors is essential since ESNV is not seen after vitrectomy for non-ischaemic pathologies. Secondly, the presence of an intact anterior hyaloid barrier to egress of these growth factors via the aqueous humour is postulated,[15] at least for RLNV/AHFP. Thirdly, a requirement for a vitreous scaffold for de novo growth of vessels is suggested by past experience of extension of iris neovascularisation onto the anterior hyaloid face in rubeotic, intracapsular aphakic eyes and by analogy with preretinal neovascularisation where the absence of a cortical vitreous substrate either precludes[16] or restricts[17] new vessel proliferation. Various preventative measures thus arise whereby the incidence of ESNV (and DVCH) might be reduced. The most obvious and currently applicable approach is to undertake scatter endophotocoagulation of all previously untreated ischaemic retina at the time of vitrectomy for PDR; this might logically be supplemented by post-oral cryotherapy behind the sclerotomies and wherever basal haemorrhagic residues or the danger of lens damage prevents fill-in laser up to the ora serrata through 360 degrees.[9 18 19] However, the evidence base for the effectiveness of such treatment is not substantial. Using surrogate measures for ESNV such as the incidence of DVCH, rubeosis, and VCWO historical comparisons of vitrectomy outcomes have been made before and after xenon arc[19] and later argon laser endophotocoagulation[18 20] became available. Liggett and colleagues[20] obtained a significant reduction in delayed DVCH and VCWO using an average of only 338 endolaser burns at the time of vitrectomy but, unless there is evidence of "burn out" or complete scatter laser of the retinopathy, much more extensive treatment is generally recommended as prophylaxis.[18]

A second preventative approach to the phakic or pseudophakic diabetic eye is to deliberately remove a small portion of the anterior hyaloid during vitrectomy. This creates the state of "pseudo-aphakia" whereby free exchange of cells and solutes takes place between the anterior chamber and vitreous cavity.[18] Just as aphakia accelerates the spontaneous clearance (via the trabecular meshwork) of both immediate[7 21] and delayed[7] DVCH, so does pseudo-aphakia, whether induced intentionally or arising incidentally (by surgical interference with the anterior hyaloid face at one or more entry sites). A full scatter photocoagulation (to prevent rubeosis) and thorough clearance of inferior basal gel haemorrhage (to prevent immediate DVCH and erythroclastic glaucoma[22]) are essential to this strategy. Chemical modulation or disruption of the anterior vitreous scaffold for vessel proliferation is a potential future extension of this approach.[23]

So far as management of established ESNV (and RLNV/AHFP) is concerned, further "indirect" treatment using additional scatter endolaser during VCWO[8 13 15 18] is the current mainstay is also promulgated by West and Gregor; an attempt to establish pseudo-aphakia should also be considered. Direct dissection of fibrovascular membranes (necessitating lensectomy) has previously been advocated for RLNV/AHFP complicated by peripheral traction retinal detachment,[9 13] and a similar method of managing extensive or persistent ESNV was employed by West and Gregor even in eyes without such detachment. Others have recommended "lens sparing surgery" for ESNV using silicone oil to obstruct access of growth factors to the sclerotomy sites,[8] but reparative epiretinal fibrosis and retro-silicone oil neovascularisation[15 24] are a danger. Such measures remain to be justified by longer term follow up of individual cases and formal comparison with more modest approaches to DVCH uncomplicated by cyclitic traction.

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It has become a truism that the internet revolution is bringing radical transformation to scientific and medical publications, and the demise of the traditional medical journal in the face of the web onslaught has been pronounced for some time now. However, the facts of readership patterns and preferences belie this, in the biomedical fields at least. The medical journal in its basic format fails to succumb, perhaps because the roles and standards of medical publication have, after all, remained the same whatever the modality employed for their transmission. The dissemination of research, the authority of peer review, the facilitation of literature review, and also the simple enjoyment of reading—these interests will drive the *eBJO* as it incorporates new features afforded by advances in internet technology. Or, to adopt "Silicon Valley" parlance, the *eBJO* will continue to evolve killer apps to capture eyeballs in our space.

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