This provides useful information for planners of eye care programmes in leprosy management, and further similar studies elsewhere would provide additional helpful information.

Since the early 1990s, much has been done to reduce leprosy related eye pathology to current levels. The difficulty is often in maintaining the momentum of eye care strategies. There is a need for (1) adequate numbers of ophthalmologists trained in leprosy, with a teaching as well as a clinical remit; (2) adequate numbers of ophthalmic trained nursing and paramedical personnel; (3) adequate measures for continuing education of paramedical personnel, maintaining and increasing their ophthalmic clinical examination and diagnostic skills; (4) adequate ongoing health education of patients and the vulnerable public regarding the eye complications of leprosy and the need for early diagnosis. It is known that, at present, the main cause of blindness in leprosy is cataract.⁷ Although, in some instances, other ocular pathology coexists, most patients gain some improvement in visual acuity with cataract surgery (unless obvious

contraindications are present). Resources allocated to dealing with this backlog of patients, and to other blindness prevention strategies in leprosy, would reduce the need for longer term resource allocation to care of the visually handicapped or blind, as well as improving the quality of life and possibly restoring economic and social independence for many.

The World Health Organization's aim to eliminate leprosy as a public health problem, by bringing the prevalence down to less than one per 10 000 by the year 2000 was not achieved in a number of countries, where it has been extended to 2010.³ The focus is now, perhaps rightly, on AIDS which is numerically a larger problem, and one with a rapidly increasing prevalence and a high mortality rate. However, to prematurely consign leprosy to the history books guarantees unnecessary future morbidity, including blindness, with inadequate knowledge and resources to manage it effectively.

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Correspondence to: K J Thompson, Tennent Institute of Ophthalmology, Gartnavel General Hospital, Great Western Road, Glasgow G12 0YN, UK; kirsteenjt@doctors.org.uk

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Exfoliation syndrome

Exfoliation and carotid stiffness

M Irkec

Casual or causal?

Exfoliation syndrome (XFS) is an age related and a generalised disorder of the extracellular matrix, characterised by the production and progressive deposition of fibrillar extracellular material in many ocular and extraocular tissues. XFS represents the most common identifiable cause of open angle glaucoma and may even account for the majority of glaucoma cases in some countries.¹ The exact aetiology of this systemic condition remains unknown. Current literature suggests that prevalence of XFS increases as the mean age of the general population increases, and in some geographic regions 5–40% of the general population over the age of 70 years may show evidence of exfoliation material (XFM) on clinical examination.² In the generalised process of exfoliation, the skin, heart, lung, liver, kidney, cerebral meninges, and gall bladder are also involved. Microscopically, focal exfoliation deposits were shown to be present

in the interstitial connective tissue of these organs, often close to elastic and collagen fibres, fibroblasts, and blood vessel walls. Intraocular and extraocular XFM display similar ultrastructural and immunohistochemical features.³ The basis for vascular connections of XFS has been underscored by the studies that showed an association of vascular walls and elastosis with XFM.^{4–7}

In XFS, systemic vascular associations reported include angina, hypertension, myocardial infarction, stroke, and abdominal aortic aneurysm.^{8,9} However, no clearcut association of XFS with a systemic disease has yet been shown. Comorbidity with acute cerebrovascular disease and chronic cerebral diseases, such as senile dementia, cerebral atrophy, and chronic cerebral ischaemia, were more common in patients with exfoliation glaucoma (XFG) than in patients with primary open angle glaucoma.¹⁰ Conversely, no significant difference was demonstrated

in the 15 year cumulative mortality from cardiovascular and cerebrovascular diseases between patients with ocular exfoliation and the general population.¹¹

Interestingly, a number of studies have shown that elevated plasma homocysteine (Hcy) is more common in XFS and XFG patients than in healthy controls.^{12–15} Furthermore, XFS and hyperhomocysteinaemia (HHcy) share common associations with various disorders. Homocysteine is a sulphur containing amino acid that occurs in a number of forms in plasma. Homocysteine is formed during the metabolism of the essential amino acid methionine, and is largely catabolised by trans-sulphuration to cysteine. It may also be remethylated to methionine in a reaction catalysed by methionine synthetase, which uses methyltetrahydrofolate as a methyl donor and cobalamin as an essential cofactor.¹⁶ Regulation of homocysteine is dependent on nutrient intake, especially folate, vitamins B6, and B12. Thus, the increased dietary intake of methionine, when often combined with other dietary (vitamin deficiencies) and/or genetic (enzyme abnormalities) factors, is a general cause of HHcy in humans. Under normal physiological conditions, Hcy blood concentrations increase gradually with age. In the general population, HHcy has been confirmed to be much more common than originally believed, with an estimated prevalence of 1:70.¹⁷ Many factors have been identified as determinants of

the total Hcy (tHcy) level. In fact, men have higher tHcy than women, which is partly caused by vitamin status and the influence of oestrogens, and tHcy levels in women increase after menopause, and under oestrogen treatment.¹⁸ Approximately two thirds of hyperhomocysteinemic cases are ascribed to low vitamin B levels. Also, a point mutation (C677T) in the methylenetetrahydrofolate reductase (MTHFR) gene, encoding a key enzyme in the remethylation cycle, increases tHcy by approximately 25% in subjects with the TT genotype.¹⁹ However, in most cases, an abnormal homocysteine status is not caused by a single factor alone but often is the result of combined effects.

HHcy has been shown to be a major risk factor for vascular disease, neural tube defects, cognitive impairment, and Alzheimer's disease. The underlying molecular mechanisms that are activated during HHcy are rather too complex to be fully understood. Nevertheless, in relation to vascular biology, various studies imply that endothelial dysfunction contributes to the complex changes that occur within the vessel wall during HHcy. HHcy also affects other components and cell types within the vessel wall, and alters expression of structural proteins and increases activity of matrix metalloproteinases in vessels.²⁰ In this context, XFS, possibly in combination with HHcy, has been associated with various ocular and systemic vascular abnormalities. As well, XFS was found to correlate positively with a history of coronary disease or arterial hypertension, or a combined history of angina and acute myocardial infarction or stroke, reminiscent of vascular effects of the disease.^{8, 21}

With this background, in this issue of *BJO* (p 563) Visontai and colleagues present data from their study of carotid artery rigidity and baroreflex sensitivity (BRS) in XFS and XFG. Despite the small number of subjects, this study may still indicate the role of pathological systemic vasoregulation in a group of patients with XFS/XFG, which increases with age and with relatively higher Hcy concentration. Previously, the authors provided evidence that systemic vasoregulation might be altered in XFS/XFG.²² In the present study, using an automated ultrasound wall tracking system they show decreased distensibility and compliance, and increased stiffness of the common carotid and brachial arteries. Additionally, patients with XFS/XFG had decreased BRS compared with the controls. Unlike the controls, in the XFS/XFG group a significant positive correlation was found between age and plasma tHcy,

and a significant negative correlation between age and BRS, as well as between plasma tHcy and BRS. Visontai *et al* also suggested increased vascular deposition of XFM and concurrent HHcy in the pathophysiology of vascular changes detected in XFS/XFG.

Genotype-phenotype studies on matrix proteins, and research to identify and characterise genes differentially expressed in various tissues, are warranted to unveil the complex pathophysiology of exfoliation syndrome

Increased central arterial stiffening is a characteristic of the ageing process and the result of many disease states such as diabetes, atherosclerosis, and chronic renal disease. Arterial stiffening develops from a complex interaction between stable and dynamic changes in connection with structural and cellular elements of the vessel wall. Arterial stiffening is an indicator for increased cardiovascular disease risk, including myocardial infarction, heart failure, and total mortality, as well as stroke, dementia, and renal disease.²³ Likewise, a decreased BRS has been described in hypertension, heart failure, myocardial infarction, obesity, dyslipidaemia, diabetes, and metabolic syndrome.²⁴ Consequently, as shown by Visontai *et al* vascular comorbidity in XFS may be explained in part by increased arterial stiffening and decreased BRS.

Despite the possible causal role of HHcy in the development of arterial stiffening, more research is needed to reveal the exact place of XFM in this process. A common link between XFS and arterial stiffening may involve changes of the extracellular matrix in both conditions. The present study, from the clinical point of view, adds more to understand generalised metabolic and vascular associations of XFS/XFG. However, further clinical studies are needed to determine the clinical significance of systemic metabolic and vasoregulatory changes in XFS and XFG. Moreover, genotype-phenotype studies on matrix proteins, and research to identify and characterise genes differentially expressed in various tissues, are warranted to unveil the complex pathophysiology of XFS, a significant systemic disorder with diverse vascular associations.

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Correspondence to: Murat Irkeç, MD, Department of Ophthalmology, Hacettepe University Faculty of Medicine, Ankara 06100, Turkey; mirkeç@isnet.net.tr

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