

## Age-related macular disease

Over the past few years there has been an apparent steady increase in the prevalence of age-related macular disease which now accounts for approximately 50% of registered blindness in England and Wales.<sup>1</sup> In this issue of the *BJO* (p 9) Evans and Wormald examined the proposal that the increase cannot be explained by the increasing age of the population alone by analysing the published figures on blind and partially sighted registration. Despite the acknowledged deficits in the data and possible confounding variables, they make a strong case in support of this view. This is clearly important since age-related macular disease is a major contributor to handicap in the community, and there is every indication that this will increase. The lack of effective treatment for the vast majority of cases highlights the need for increasing research into the aetiology of the disorder in the hope that new forms of therapy or prevention may be identified.

In retrospect, it is unfortunate that clinical research and research funding have been devoted largely to defining the role of laser photocoagulation in the treatment of choroidal neovascularisation, and disappointing that it is now evident that this form of therapy will have little impact on blindness in age-related macular disease.<sup>2</sup> Other forms of treatment have been tried but none has yet proved effective.<sup>3-7</sup> Until recently, research into the pathogenetic mechanisms of age-related macular disease has been limited to a small number of centres despite the importance of the disease in numerical terms. It was as if there were few research ideas, and yet more than 20 years ago Hogan had created a good basis upon which hypotheses could be formulated.<sup>8,9</sup> This was reinforced by Sarks and colleagues who painstakingly documented the fundus changes in a group of subjects and correlated these with histological studies.<sup>10,11</sup> Recently, there has been renewed research activity which has involved workers in many disciplines. It is widely believed that visual loss is due to the influence of the changes which occur in Bruch's membrane with age.<sup>12</sup> A considerable body of information concerning the nature of these changes now exists. The sequence of events that lead to detachment of the retinal pigment epithelium and geographic atrophy can be reconstructed with the confirmation of the proposal made on clinical grounds that the conductivity of Bruch's membrane declines with age.<sup>13-15</sup> It is known that the retinal pigment epithelium moves fluid outwards and impedance of flow towards the choroid would result in detachment of the pigment epithelium. Reduction of metabolic exchange between choroid and pigment epithelium may eventually cause geographic atrophy. However, the mechanisms that regulate choroidal neovascularisation are still elusive. There is good evidence that the material in Bruch's membrane is derived from the retinal pigment epithelium,<sup>16-18</sup> and the aging changes in the pigment epithelium have been well summarised by Boulton.<sup>19</sup> That it is now possible to image the autofluorescence in vivo provides an additional indicator by which the disease can be monitored.<sup>20,21</sup>

In addition, the circumstances which determine that some will lose vision and others will not have also been addressed. It is now evident that there is genetic predisposition to disease. One or more genes may be involved.<sup>22-25</sup> The current strength of molecular biology allows this aspect of age-related macular disease to be investigated further, and highlights the need for good candidate genes. Recently, mutations in the TIMP-3 gene<sup>26,27</sup> have been shown to be responsible for Sorsby's fundus dystrophy

although the homology between this disease and aging does not appear to be very close. Discovery of the genetic mutations causing Doyme's honeycomb dystrophy and mallatia levantinese will add greatly to the power of this research.

Genetic predisposition alone cannot be responsible for the disorder if the conclusions of Evans and Wormald are correct. This view is reinforced by the impression from Japan that visual loss from age-related macular disease, which was virtually unknown 30 years ago, is now common.<sup>28,29</sup> The conclusion that environmental factors are important is inescapable, and that a change over the past decades accounts for the increasing prevalence of visual loss from macular degeneration in the elderly. Several studies have reported that factors such as diet and smoking may be important,<sup>30-33</sup> although they do not appear to account fully for the increased prevalence of disease. At present it seems most likely that individuals inherit a predisposition to age-related macular disease which becomes manifest only if those at risk are exposed to the appropriate environmental factors.

It is evident that age-related macular disease is amenable to investigation, and that researchers in many scientific disciplines have a role to play in this work. The advances in our understanding of inherited retinal diseases consequent upon multidisciplinary research provides a good example of the potential success which may be expected from such an approach. Those clinical features which identify people at high risk of losing vision from age-related macular disease may become known as a consequence of the longitudinal studies which are now in progress. The information from these studies will be complemented by further information of age-related changes in Bruch's membrane and retinal pigment epithelium in eye bank eyes. It is likely that there are environmental factors important in precipitating disease which have yet to be identified and these should be sought. Molecular genetic approaches may define the genes that modulate risk, which would give clues as to the aetiology of the disease, and would reinforce the definition of those at high risk of visual loss to whom new therapeutic approaches may be directed. The increasing prevalence of blindness from age-related macular disease underlines the importance and urgency of this work.

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