The Ageing Macula

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In 2000 the Cambridge Ophthalmological Symposium addressed age-related maculopathy (ARM) and several papers are published in this issue derived from the meeting. That the disorder represents a major burden on Western society is not in doubt, and with increased life expectancy the burden will grow. There is also evidence that it will become a major problem in East Asia. The symposium opened with a discussion of the general concepts and mechanisms of ageing, and its manipulation.[1] Although certain changes may occur throughout the organism with time, particular metabolic attributes of a cell system may make it more vulnerable to certain ageing processes than others. This may be particularly relevant to age-related macular disease since it is widely believed that it is associated with a normal (or even extended) life expectancy.

The tissues involved in ARM comprise the photoreceptor cells, retinal pigment epithelium, Bruch's membrane and choroid. These are metabolically interdependent, and changes in any one may precipitate reactive changes in the others. There is some loss of photoreceptors with age, increasing levels of autofluorescent residual bodies in the pigment epithelium, thickening and loss of hydraulic conductivity of Bruch's membrane, and loss of density of the choriocapillaris.[2,3] Progressively more is now known about the biochemical contents of Bruch's membrane in early ARM, and it is surprising to find high concentrations of agents usually associated with immune-mediated disease therein.[4] The significance of these to disease is as yet uncertain.

There is very good evidence that there is a major genetic component to the pathogenesis of ARM.[5] It generally considered that the genetic risk becomes evident in the presence of environmental pressures, although smoking is the only one that is clearly associated with increased risk of visual loss. It appears that smoking may not influence the age changes but rather modulates the likelihood of neovascularisation. These conclusions are derived from the lack of correlation between smoking and early changes, and increased risk of choroidal neovascularisation, both *de novo* and after photocoagulation, in current smokers but not in ex-smokers.

Many believe that identification of the genes responsible for conferring risk carries the best chances of identifying new therapeutic advances. ARM is a complex disorder in that many genes might be involved. This is biologically plausible given the complexity and metabolic inter-relationships between the tissues involved. The high prevalence of age changes known to signal risk of visual loss within Western society implies that the prevalence of pathogenic sequence changes is high and that it cannot be assumed that a single gene is involved in a family. Developing techniques for identifying the responsible genes has been a challenge for molecular geneticists, and the techniques have been used in the investigation of other complex disorders such as diabetes, multiple sclerosis and bipolar disorder.[6] One potential advantage in the study of ARM as opposed to some other complex disorders is the potential to distinguish different phenotypes of ARM. There is evidence that the form of disease, both early and late, may reflect particular genetic influences. It will be the responsibility of the clinician to collect DNA from cases with well-characterised phenotypes.

Once the causative gene has been identified, it will be crucial to identify the role of the protein product and the primary influence of the mutant protein on function. It is assumed that the primary abnormality would give rise to a cascade of events involving all the relevant tissues.

What management is currently available to patients? New forms of treatment have been developed for late-stage ARM whereby modest benefit may be conferred on a proportion of cases, but at best they reduce the magnitude of visual loss rather than causing improvement of vision.[7–9] In many countries rehabilitation has been largely neglected since the clinician does not perceive it as his or her responsibility, and yet ideally it should be initiated at the point of diagnosis. It is evident that a great deal can be done to help patients cope with their disability.[10]

Until recently there has been very little research into the pathogenesis of ARM, most research support having been devoted to treatment trials. Whilst it is encouraging that new forms of treatment are being developed, no one would claim that any of the current therapeutic approaches will have an impact on

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blindness due to ARM. In retrospect the lack of research is surprising and disappointing given the high prevalence of disability in Western society due to the disorder. Identification of the causative genes may lead to novel treatments that would differ from one patient to another depending upon the gene involved. On the other hand, if common intermediary mechanisms are identified, a single approach may be possible. At worst, knowledge of the genes involved would allow identification of those at risk. The relevance of environmental pressures has yet to be proven, although there is circumstantial evidence of its importance. This question needs to be addressed.

To ophthalmologists it is encouraging that workers from many disciplines contributed to the symposium, and it is evident that they all have the capability of advancing the work. Success will not be achieved without the support of epidemiologists, gerontologists, molecular geneticists, cell biologists and biochemists; representatives from all these disciplines were present and contributed to the meeting. In a short time a great deal has been achieved, and it is hoped that this work will bear fruit in the foreseeable future.

References

1. Bürkle A. Mechanisms of ageing. Eye 2001;15:371–5.
2. Boulton M, Dayhaw-Barker P. The role of the pigment epithelium: topographical variation and ageing changes. Eye 2001;15:384–9.
3. Curcio CA. Photoreceptor topography in ageing and age-related maculopathy. Eye 2001;15:376–83.
4. Mullins RF, Aptsiauri N, Hageman GS. Structure and composition of drusen associated with glomerulonephritis: implications for the role of complement activation in drusen biogenesis. Eye 2001;15:390–5.
5. De Jong PTVM, Bergen AAB, Klaver CCW, van Duijn CM, Assink JM. Age-related maculopathy: its genetic basis. Eye 2001;15:396–400.
6. Wright AF. Strategies for mapping susceptibility genes and age-related maculopathy. Eye 2001;15:401–6.
7. Votruba M, Gregor Z. Neovascular age-related macular degeneration: present and future treatment options. Eye 2001;15:424–9.
8. Harding S. Photodynamic therapy in the treatment of subfoveal choroidal neovascularisation. Eye 2001;15:407–12.
9. De Juan E Jr, Fujii GY. Limited macular translocation. Eye 2001;15:413–23.
10. Rubin G. Vision rehabilitation for patients with age-related macular degeneration. Eye 2001;15:430–5.