The evolving role of visual electrodiagnostics

It has been 48 years since Professor Gösta Karpe introduced the diagnostic use of electroretinography and 35 years since a group of vision scientists banded together to form ISCERG to study and develop the field of clinical electrophysiology of vision. Tremendous strides have been made in the ability to diagnose numerous retinal and visual pathway disorders and to evaluate visual function through non-invasive electrodiagnostic testing.

Most of the tests use the principle of evoking a response by presenting a stimulus, such as a flash of light or alternating checkboards, under conditions that set off a signal from the targeted cellular layer which is measured by appropriately placed electrodes. Because analysis of visual information involves complex neuronal processing, an understanding of the relationship of responses is necessary in order to interpret the results, but the concepts are not difficult. For instance, if the photoreceptor layer is non-functional, signals derived from the normal middle retina or even the visual cortex will be absent or abnormal. It is therefore important to direct testing towards the visual level where the disease is likely to be having the primary effect.

The most commonly used tests to differentiate ocular diseases are: the electro-oculogram (EOG) which measures the standing potential of the retinal pigment epithelial layer, and the electroretinogram (ERG) where, by standardising the testing conditions, it is possible to measure the cone and rod component systems. The pattern electroretinogram measures ganglion cell activity, and the visual evoked cortical potential which, in the presence of a normal ERG, measures optic nerve to occipital cortex function.

The field of electrophysiology of vision has become more than just functional studies measuring how well certain layers of the visual system perform. The ability to separate the cone and rod systems on the ERG has provided the basis for a number of major diagnostic classification schemes, as well as allowing for a clear differentiation of diseases that affect one system or the other. This ability has been particularly valuable in looking at the category of cone dystrophy since these patients frequently have a paucity of retinal findings and the diagnosis can be difficult to make on a clinical examination alone and must be confirmed by electroretinographic testing. Additionally, there are a number of hereditary eye diseases which have electrophysiologically specific patterns and, when correlated with the clinical manifestations, result in clear clinical diagnoses. Examples are the cone dystrophies (as noted above and discussed in this issue in the article by Kellner and Foerster), retinoschisis, congenital stationary night blindness, Best's disease, and albinism, to name a few.

In the past year, there have been several examples of the use of electrophysiological testing which have expanded the understanding of gene mutations in retinal dystrophies. At the 1992 ARVO meeting Professor Paul Sieving reported a family with a dominantly inherited rhodopsin codon 90, glycine to asparagine mutation which, instead of having a typical form of retinitis pigmentosa, had electroretinographic and clinical findings of congenital stationary night blindness. An electroretinographic and psychophysical examination of X-linked RP2, one of the more common forms of retinitis pigmentosa in the United Kingdom, by Dr Sam Jacobson at the Bascom Palmer Institute in Miami, found that cone dysfunction preceded rod changes in hemizygous and heterozygous patients. In more advanced cases the rod and cone systems showed comparable degrees of dysfunction. He suggests that the reason that variable electroretinographic patterns are seen in RP2 families results from regional retinal variations of the disease studied at different stages of progression.

The most interesting recent use of electrophysiological testing to help characterise the phenotypes of mutational events appeared in the March issue of Nature Genetics in which three articles on retinal degeneration slow gene (RDS)/peripherin mutations were reported. Peripherin is a photoreceptor-specific glycoprotein which has been localised to outer segment disc membranes of both rods and cones. Depending on the location of the mutation in the gene, the clinical effect ranges from families with a localised atrophic macular degeneration with normal ERG, a pattern (butterfly) macular dystrophy with subnormal ERG, a fleck retina appearance similar to retinitis punctata albinescens with abnormal ERG, and families with a pigmented retinopathy and extinguished ERGs. This series of RDS/peripherin families demonstrates that different mutations within the same gene may lead to dissimilar clinical diseases. The simple concept of ‘one gene for one disease’ no longer appears to be always the case.

Molecular genetic identification of diseases by specific mutational site is rapidly expanding our understanding of hereditary sight-threatening diseases. The field of clinical electrophysiology is benefiting from studies that correlate the phenotype to genotype which sharpens the diagnostic understanding of these tests. The field of molecular genetics benefits by having functional evaluations of the gene effect. Within families with the same mutation, this will allow for study of other factors which affect the expression of the disease.

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Blindness in the developing world

The reasons for the continuing increase in the number of blind people worldwide and the efforts being taken to address this important problem are the issues discussed in this editorial.

The estimates of worldwide blindness are disturbing in their simplicity.

– in 1975, 28 million blind; in 1984, 31 million; today, probably 35 million
– at least 17 million blind with surgically curable cataract
– 6 million blind with treatable infections (trachoma, onchocerciasis, and supplicative keratitis)
– 1·5 million children blind; the major cause being vitamin A deficiency associated with malnutrition

Cataract, childhood blindness, and ocular infections – all potentially avoidable – remain the priorities in blindness control programmes, accounting for 70% of all blind people in the world, and more than 200 million years of blind life. The paper in this issue by Schwab and Kagame highlights the importance of corneal disease from vitamin A deficiency and measles as the major cause of childhood blindness in Zimbabwe.

The prevention of blindness programme of the World Health Organisation has been instrumental in developing strategies for the control of these blinding diseases in non-industrialised countries.1–5 For example, the control of cataract blindness will remain surgical until ways of slowing down the process of lens opacification are known. Intraocular lens (IOL) implantation is becoming routine in Latin American countries and in urban centres of Asia. The benefits and hazards of intracapsular cataract extraction or extracapsular cataract extraction, aphakic spectacles, anterior chamber IOLs, and posterior chamber IOLs have been clearly presented in the report of the WHO working group.4 Clinical trials are underway to answer questions concerning the safety and visual outcome of different cataract procedures in the context of the developing world.

In the control of ocular infections, risk factors and public health interventions have been defined for trachoma. A new antibiotic azithromycin offers the hope of a systemic long acting chemotherapeutic agent to control chlamydial infection; and the correction of trichiasis within affected communities by paramedical workers has been reported to give successful results.6–8 In parts of west Africa onchocerciasis has been prevented by putting larvicides in rivers to control the Simulium fly vector. Ivermectin, a microfilaricide, given orally on an annual basis, reduces the community microfilaria load with a consequent decrease in the incidence of ocular disease,9 and macrofilaricides which eliminate the adult worm, Onchocerca volvulus, are being field tested. There is therefore justified optimism that blindness from this disease can be prevented in the next decade.

Vitamin A deficiency, as well as being the main cause of childhood blindness, has been found to be an important cause of infant mortality.10 Major nutrition and vitamin A supplementation programmes are being developed as part of child survival programmes which should also lead to a reduction in nutritional blindness.

If the causes of blindness are known, and the knowledge and technology to control blinding diseases have been developed, what are the reasons for the continuing rise in the number of people becoming blind? An increasing world population and improved life expectancy in developing countries are obvious factors, but there are other important reasons to be considered, particularly when one realises that at least 80% of all blindness is potentially avoidable.

Awareness
The first reason is lack of awareness. Many blind people with cataract living in poor areas of the developing world are not aware that they can be helped. Similarly, health care professionals may not be aware of the size of the problem and the need to mobilise resources to deal with avoidable blindness as a priority.

Accessibility
The second reason is the problem of accessibility. Blind patients may have limited or no access to the available specialised services because of geographic or social isolation. The majority of blind people live in Asia (20 million) or Africa (6 million). They are usually elderly people who will not travel more than 20 miles to see a specialist at a hospital. In parts of Asia and, particularly, Africa there are few