

## Lessons from the retinal diaspora

There are many rare and far flung retinal diseases which few of us will ever see in the office. One of these is Oguchi's disease, a night blinding disorder in which patients can recover their sensitivity to dim light over several hours in darkness, only to lose it to a brief light exposure that hardly bleaches any visual pigment. The report in this issue by Yamamoto *et al* (p 000) shows that the S cone electroretinogram (ERG) is normal in Oguchi's disease, which distinguishes it electrophysiologically from some other types of stationary night blindness. This paper shows the value of clinical electrophysiology as a unique window into the pathophysiology of the retina, although perceptive readers may ask why Yamamoto *et al* talk about cones in a night blinding disorder. The fact is that most night blinding disorders do involve cones, and it can be hazardous to interpret retinal symptoms without an awareness of retinal physiology. What also may not be immediately obvious is the relevance of this report for retinal function and retinal disease in general.

Consider three aspects of retinal physiology in which new knowledge is changing our interpretation of retinal disease. Laboratory studies have shown that cone photoreceptors feed into two different synaptic pathways in the retina, one in which the bipolar cells produce a positive response to the onset of light ('on' responses), and the other in which the bipolar cells produce a positive response when a light goes off ('off' responses).<sup>1</sup> Rods have only on responses, but cones have both on and off responses. Individuals with the most common form of congenital stationary night blindness (CSNB) have no measurable rod vision or rod ERG, and were thought for a long time to have a defect in the rod synaptic pathway. However, there are subtle cone ERG abnormalities in CSNB, and it turns out that this disease actually represents a selective defect of the on pathway that affects both rods and cones.<sup>2</sup> Night blindness is the most prominent symptom only because there is no off pathway for rod vision (whereas the cone off pathway still allows vision). Similar ERG findings are found in some patients with malignant melanoma who develop a cancer associated retinopathy with antibodies to the on bipolar cells.<sup>3</sup>

The transduction cascade is a sequence of events by which light is transformed into a neural signal within the photoreceptors.<sup>4</sup> In the dark, the sodium channels of the photoreceptor membrane are held open by cyclic GMP, and when light activates rhodopsin it begins a cascade of enzymatic activity that breaks down cGMP and closes the sodium channels to produce an electrical response. One molecule of activated rhodopsin can activate a million or more molecules of cyclic GMP. The activated rhodopsin is then turned off in part by phosphorylation and by binding to a protein called arrestin. The gene for Oguchi's disease was recently identified and found to code for arrestin<sup>5</sup>—which means that patients with Oguchi's disease (with

abnormal arrestin) cannot effectively turn off their transduction cascade. Thus, even a brief stimulation by light leads to a very prolonged period of rod desensitisation (and symptomatic night blindness). The transduction cascade is the site of pathology in many cases of retinitis pigmentosa. More than 50 different rhodopsin abnormalities have been identified in dominant RP pedigrees, and recessive families have been found with abnormalities in the phosphodiesterase gene. A protein called recoverin can block the phosphorylation of activated rhodopsin, and antibodies to recoverin are found in some cases of cancer associated retinopathy.<sup>6</sup> It remains to be determined why some of these genetic transduction abnormalities lead to retinal degeneration, and others to stationary functional disorders.

The human retina contains long (L), medium (M), and short (S) wavelength sensitive cones that are most sensitive to red, green, or blue light respectively. The L and M cones comprise more than 90% of our cones and account for our high visual acuity. S cones are absent from the centre of the fovea and also behave differently physiologically. S cone ERG responses are much slower than those of the L and M cones, and the S cones do not have a strong off pathway in the retina. In CSNB (which is an on pathway disease) S cone ERG responses are absent, while in Oguchi's disease (which is a defect in the rod transduction protein arrestin) Yamamoto *et al* found the S cone responses to be normal. S cones seem in general to be more susceptible to retinal disease than L or M cones and this explains why blue-yellow colour abnormalities are so common in retinal disorders as diverse as dystrophies, diabetes, and after retinal detachment.<sup>7</sup>

Through the melding of knowledge about retinal physiology and retinal pathology, mysterious disorders like Oguchi's disease—once in the diaspora of retinal understanding—are returning home.

MICHAEL F MARMOR

Department of Ophthalmology, A-157,  
Stanford University School of Medicine,  
Stanford, CA 94305-5308, USA

- 1 Sieving PA. Photopic ON- and OFF-pathway abnormalities in retinal dystrophies. *Trans Am Ophthalmol Soc* 1993;91:701-73.
- 2 Young RSL. Low-frequency component of the photopic ERG in patients with X-linked congenital stationary night blindness. *Clin Vis Sci* 1991;6:309-15.
- 3 Milam AH, Saari JC, Jacobson SG, Lubinski WP, Feun LG, Alexander KR. Autoantibodies against retinal bipolar cells in cutaneous melanoma-associated retinopathy. *Invest Ophthalmol Vis Sci* 1993;34:91-100.
- 4 Baylor D. How photons start vision. *Proc Natl Acad Sci* 1996;93:560-5.
- 5 Fuchs S, Nakazawa M, Maw M, Tamai M, Oguchi Y, Gal A. A homozygous 1-base pair deletion in the arrestin gene is a frequent cause of Oguchi disease in Japanese. *Nature Genetics* 1995;10:360-2.
- 6 Thirkill CE, Tait RC, Tyler NK, Roth AM, Keltner JL. The cancer-associated retinopathy antigen is a recoverin-like protein. *Invest Ophthalmol Vis Sci* 1992;33:2768-72.
- 7 Greenstein VC, Hood DC, Ritch R, Steinberger D, Carr RE. S (blue) cone pathway vulnerability in retinitis pigmentosa, diabetes and glaucoma. *Invest Ophthalmol Vis Sci* 1989;30:1732-7.



## Lessons from the retinal diaspora

MICHAEL F MARMOR

*Br J Ophthalmol* 1997 81: 1027  
doi: 10.1136/bjo.81.12.1027

---

Updated information and services can be found at:  
<http://bjo.bmj.com/content/81/12/1027.full.html>

---

*These include:*

### References

This article cites 6 articles, 4 of which can be accessed free at:  
<http://bjo.bmj.com/content/81/12/1027.full.html#ref-list-1>

### Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

### Topic Collections

Articles on similar topics can be found in the following collections

[Retina](#) (1217 articles)  
[Vision](#) (499 articles)  
[Neurology](#) (1042 articles)  
[Eye \(globe\)](#) (543 articles)

---

### Notes

---

To request permissions go to:  
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:  
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:  
<http://group.bmj.com/subscribe/>