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EOS 2019

27-29 March, 2019 | Hilton Cairo Heliopolis

We still need visual electrophysiology!
(Imaging and gene sequencing don't give all the answers)

Richard Smith
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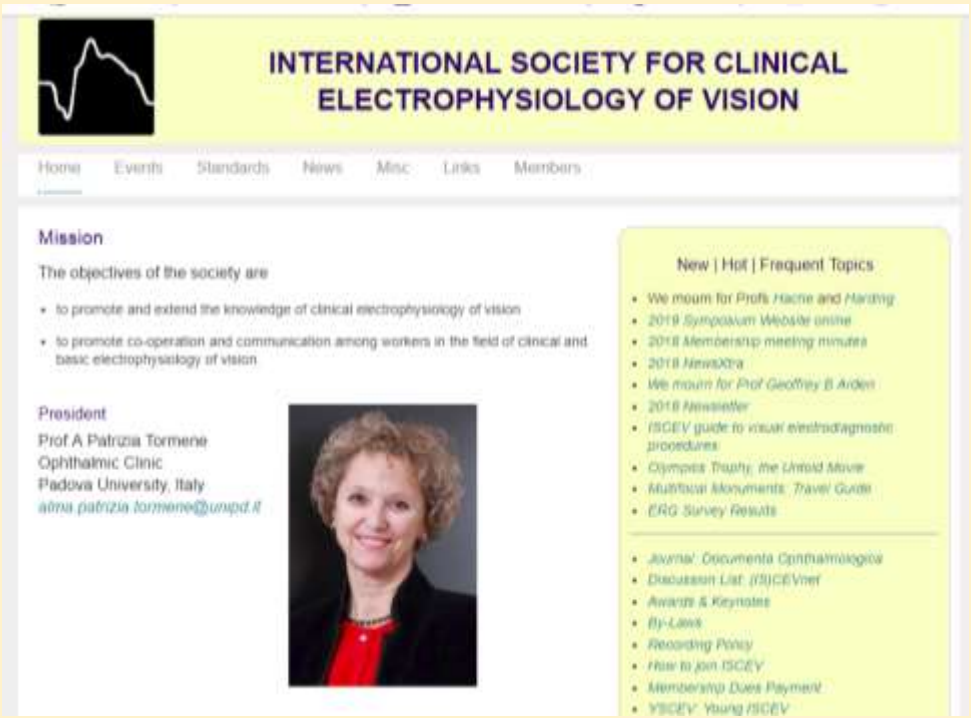

A quantum leap forward – for its time

Adoption of technology

- Utility (What will it do for me / my patients?)
- Practicality (How easy is it to use / perform?)
- Availability
- Size / portability
- Cost
- Marketing
- Fashion

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A brief timeline of visual electrophysiology

- 1848 – Dubois-Reymond: Discovery of electrical activity in in enucleated fish eyes
- 1865 – Holmgren: Discovery of an action potential in response to light in frog eye
- 1908 – Einthoven and Jolly: Recorded a- b-and c- waves of the electroretinogram
- 1933 – Granit: detailed analysis of the cat ERG
- 1934 – Adrian and Matthews: Cortical visual evoked potential recorded
- 1940s – Karpe: recording of ERG in conscious human subjects
- 1962 - Arden et al: Electro oculogram
- 1993 – Sutter: Multifocal ERG
- ….and much more (supporting many other areas of vision research)

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From the lab to the clinic

- Solid state electronics
- Fast computer processing: digital filtering, real-time averaging, Fourier analysis, kernel analysis
- Light-emitting diode technology
- Screen / monitor technology
- International standards (ISCEV)

- We now have a portfolio of standardized tests which can be performed relatively easily and inexpensively

Does visual electrophysiology have an image problem? The charges levelled against it by clinicians include:

- The knowledge-base is hard to acquire
- Tests only give definitive answers in rare conditions
- Reports can be hard to understand
- Tests are time-consuming
- We prefer pictures to wiggly lines
- Other technologies give us the answers more easily

Does it have a future?

Parallel advances in imaging

- 1851 – von Helmholz: Ophthalmoscopy
- 1926 – Nordenson (Zeiss): fundus photography
- 1956 – Mundt and Hughes: ocular ultrasonography
- 1959 – Alvis & Novotny: fluorescein angiography
- 1980 – Edelstein etc al: Magnetic resonance imaging
- 1980's onwards – scanning laser ophthalmoscopy, with adaptive optics
- 1980's – Delori: fundus autofluorescence imaging
- 1990 onwards – ocular coherence tomography (time domain, spectral domain)

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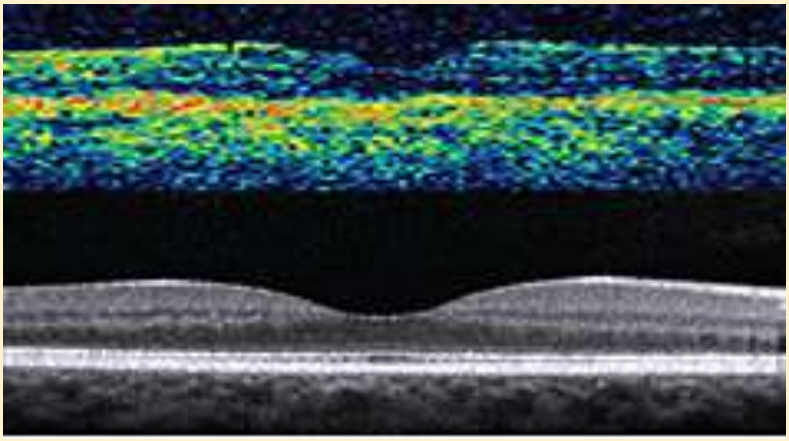
The difference a few years can make…..

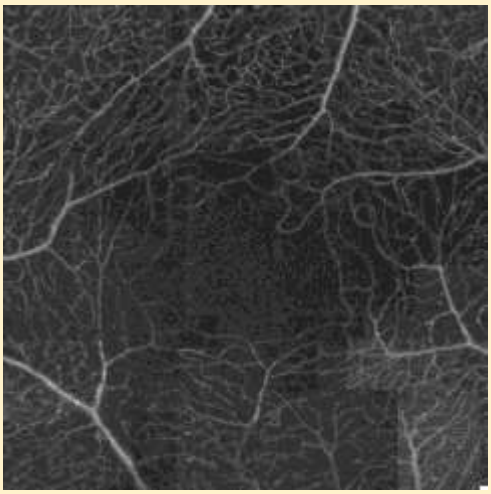


Zeiss Stratus

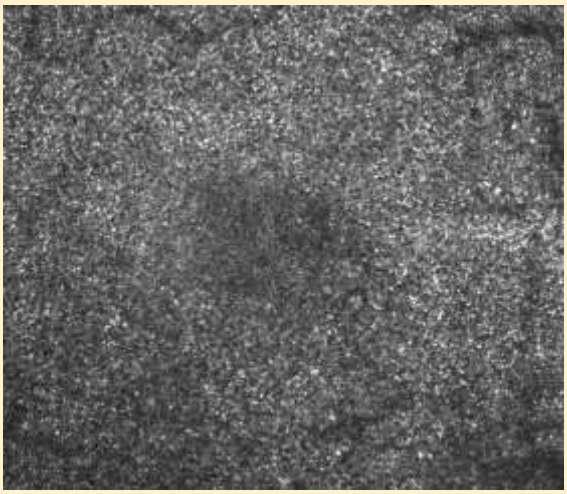
Heidelberg Spectralis

Karampelas et al 2014.

Ever-increasing levels of resolution

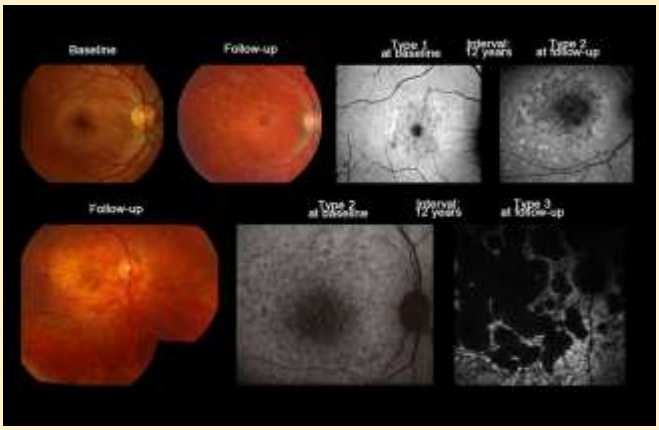


University of Indiana (www.opt.Indiana.edu)



Chui et al: J Optical Soc America (2008) 25:3021-3029

Fundus autofluorescence – imaging structure and function



Fujinami et al: Invest. Ophthalmol. Vis. Sci.. 2013;54(13):8181-8190. doi:10.1167/iovs.13-12104

Limitations of ophthalmic imaging

- It tells you what has happened, rather than what is happening
- Abnormalities of structure can be the end-result of a number of disease processes (eg cell death)
- Structure may not correlate closely with function (eg epiretinal membrane, rod monochromatism)
- Opportunity for treatment may precede any structural change

Parallel advances in genetics

- 1953- Franklin, Watson and Crick: structure of DNA
- 1955- Sanger: sequencing of amino acids of insulin
- 1977- Sanger: DNA sequencing with chain-terminating inhibitors
- 2001 – First human whole-genome sequencing (cost $100,000,000)
- 2000s- High-throughput (“next generation”) sequencing (cost approx. $1500)
- Applications:
- DNA micro-arrays (Chips): Rapid detection of disease-causing mutations in specific genes
- Single nucleotide polymorphism (SNP) arrays: detection of markers for genetic disease, susceptibility to disease, predicting behaviour of cancers.

Applications in eye disease

- Identification of causative genes in diseases with Mendelian inheritance (eg Rhodopsin mutation in AD retinitis pigmentosa)
- Correlation of type of mutation with pathology at a sub-cellular level (eg ABCA4 mutations in Stargardt disease)
- Understanding of susceptibility to complex disease (eg complement factor H polymorphisms in predicting risk of n-AMD)

Limitations of genomics

- Whole genome sequencing is impractical as a diagnostic tool (slow, expensive, volume of information)
- Selective gene testing may miss genes of possible interest
- It is not always clear whether a mutation or polymorphism is disease-causing
- Incidental findings are common and may present significant ethical dilemmas
- Some diseases show considerable phenotypic variation
- Non-mendelian (epigenetic) inheritance

What patients want to know (solving day-to-day clinical problems):

- What is wrong with me / Am I healthy?
- How will this condition behave with time?
- Will I lose my sight?
- Can it be treated?
- Is there anything I can do to stop it getting worse?
- Will I pass the condition on to the next generation?

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The ERG: “the sound of the retinal orchestra”

Electroretinography: “the sound of the retinal orchestra”

- Structurally and functionally elegant
- Naturally good “acoustics” (retinal elements oriented towards the pupil plane)
- Can listen to different instruments (cell types) or sections (pathways) by controlling the stimulus conditions
- The conductor (active electrode) can detect when something is silent, out of tune (amplitude) or out of time (latency)

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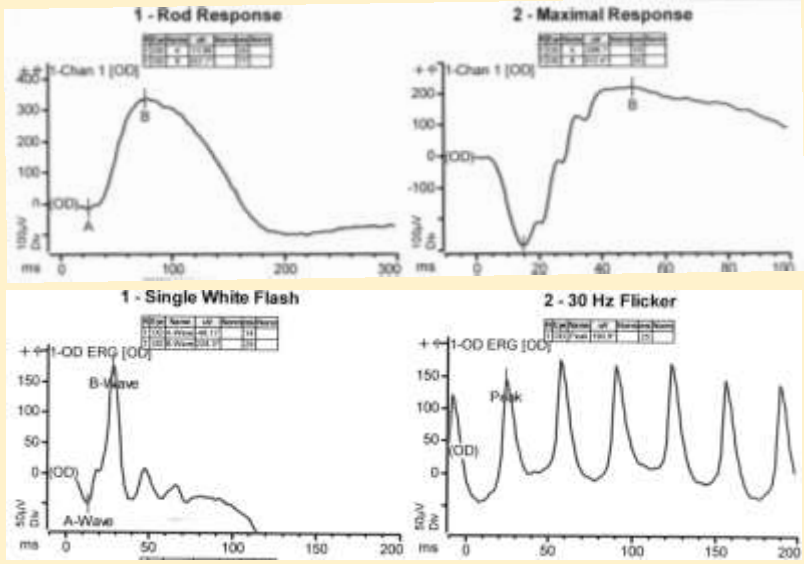
The signature-tune (ISCEV standard ERG)



Case 1:

- Amaar, aged 7 referred because he is not making progress with reading and holds things close to see them.
- Parents are first cousins and say that he has always held things close to see them. General health good.
- O/E: VA 1.0, 1.0. Seems genuine. R +4.50DS L +5.00/-0.50x75. Fine irregular jerky nystagmus.
- Fundi entirely normal, OCT foveas normal.
- Could this be a cone dystrophy, oculocutaneous albinism, or rod monochromatism?

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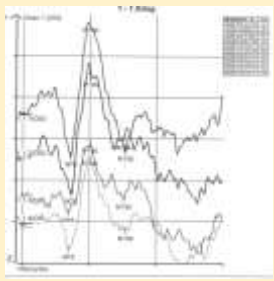
Pattern reversal VEP 60' check

Right eye

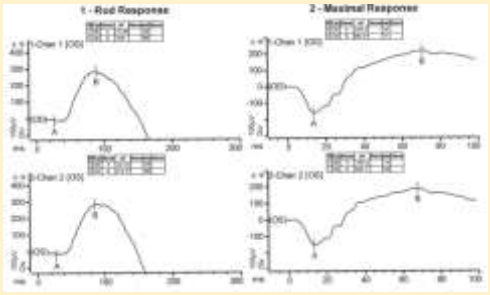
Left eye

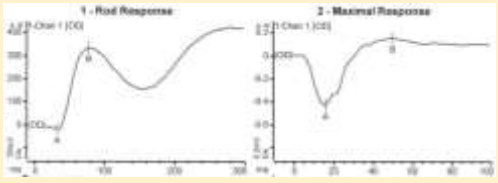


Normal

Full-field ERG

DA 0.01 DA 3.0



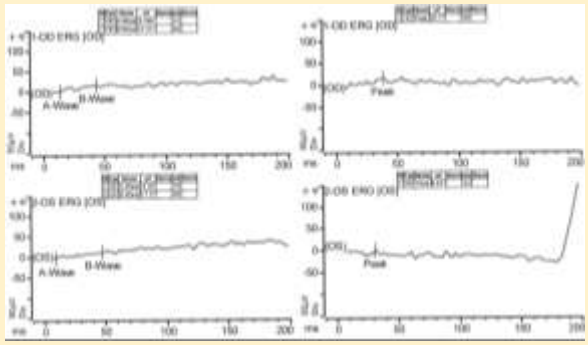


Light adapted full field ERG

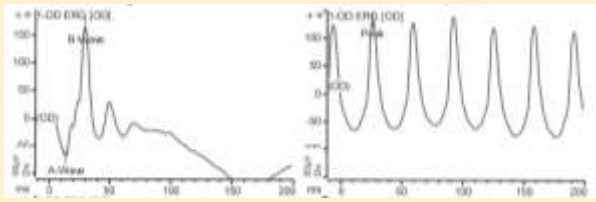
LA 3.0 30Hz flicker

Right eye

Left eye



Normal



Advice to Amaar's Mother

- Younger siblings could be affected (AR inheritance, consanguinity)
- Amaar will need additional help with his schooling, but his vision is unlikely to deteriorate
- Amaar does not need scans or other invasive tests to rule out other causes of his reduced vision
- We could test for mutations on CNGA3 gene, but this can wait until Amaar is happy to have a blood test

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Case 2 – James, aged 7

- Very fair hair and light blue eyes
- BCVA 0.2 logMAR both eyes
- No significant symptoms
- No family history of eye problems

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But....

- No nystagmus
- No evidence of chiasmal misrouting on 3-channel VEP
- OCT foveas normal

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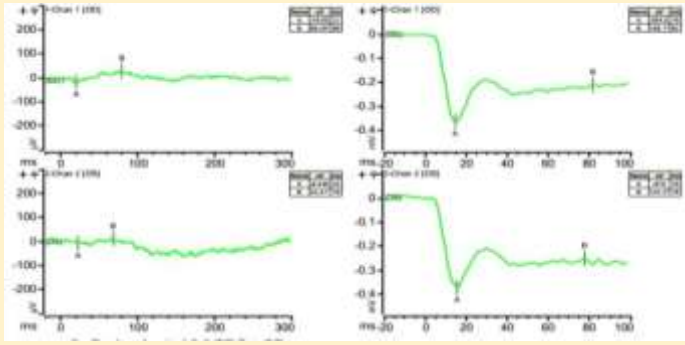
Dark adapted ERG

Right Eye

Left eye



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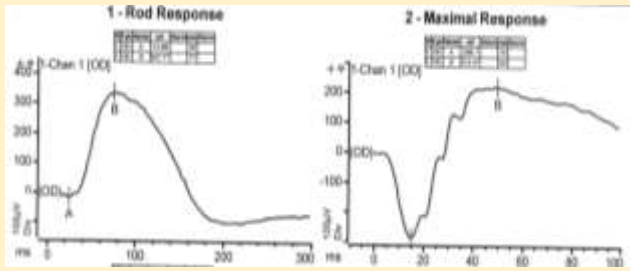
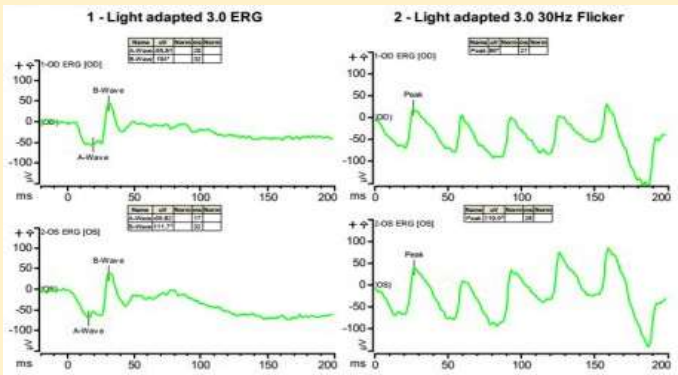


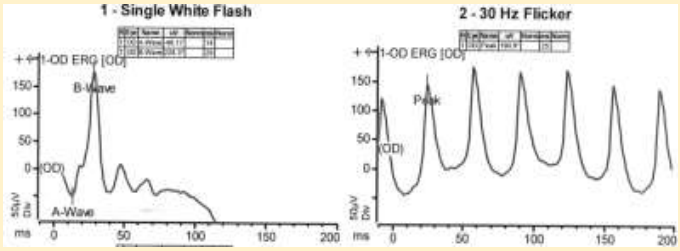
Light adapted ERG

Right Eye

Left Eye



Normal



- Complete form of congenital stationary night blindness
- ON-bipolar channel selectively affected
- Likely to be non-progressive
- People who are night-blind in western societies often don't notice it (or may not volunteer it unless asked)

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Dear colleague……

- Please see this 62 year old man who is on 2 medications for open angle glaucoma. His right eye has significant field loss but his pressures seem well controlled at 16mm right and left. He is complaining of declining vision in the right eye. His visual acuity is worse than I would expect for his visual field defects and optic disc appearances. Foveal OCTs are normal. Disc OCTs are unchanged. MRI scan of the brain and visual pathways are normal. Does he have a retinal problem, or do I just need to lower his pressures further?
- Please do some electrophysiology tests…

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Let's do an ERG to rule out unsuspected retinal disease, but it won't detect glaucomatous optic neuropathy, will it?

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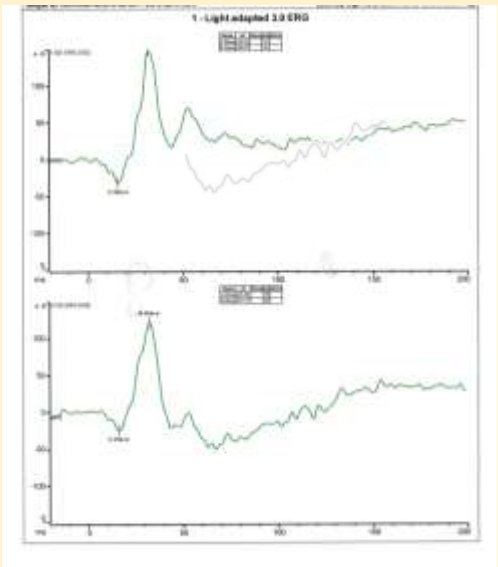
Right eye has advanced glaucoma

Normal left eye



What patients want to know:

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- How will this condition behave with time?
- Will I lose my sight?
- Can it be treated?
- Is there anything I can do to stop it getting worse?
- Will I pass the condition on to the next generation?

The electroretinogram

- Non-invasive
- Inexpensive – not just a “first world” test
- Versatile – can provide information quickly to answer a wide variety of clinical questions

- And there is still much more to discover in it!