Generation of light-evoked electrical signals: The interaction of photons with photolabile pigments in the outer segments of our photoreceptors induces a cascade of intracellular changes, an opto-chemical-electrical process. The photoreceptor is a powerful natural amplifier by generating a signal from a single photon catch. The light flash induces hyperpolarization of the photoreceptor cell’s membrane, as a consequence of closure of cation channels. This process is intensity-, wavelength-, and adaptation-dependent. The hyperpolarization of vertebrate photoreceptors reduces their release of glutamate at the synapse to second order neurons in the outer plexiforme layer. This change in neurotransmitter release affects differentially the second order neurons: ON bipolar, OFF bipolar and horizontal cells. Changes in polarization, graded with the intensity of the light, characterize the responses of most retinal neurons (Figs.1, 2). Amacrine cells, interneurons in the inner nuclear layer, generate light-induced shifts in the membrane potential and abortive spikes. Third-order neurons, the ganglion cells, generate spontaneous and light-evoked trains of spikes, riding on the membrane potential (Figs. 1 and 2). These cells represent the end station of retinal information processing. The change in frequency of the spikes encodes all information of the sector of the visible world, which is imaged on the retina, to be propagated via the optic nerve to the higher visual centers. The optic nerve in primates consists of about $10^6$ insulated axons of the ganglion cells. - Anatomical convergence and also divergence, lateral inhibition, enormous amplification, receptive field organization, ON- and OFF-channels, temporal modulation as well as adaptation to a wide range (>12 log units) of light levels characterize information processing in the retinal circuits.

Electrical signals are propagated between cells by a number of excitatory as well as inhibitory chemical synapses, and by sign-preserving electrical synapses. The circuits are controlled by specific neurotransmitters and neuromodulators.

From responses of single cells to field potentials: a-, b- and c-waves of the electroretinogram (ERG)

The light-evoked retinal field potentials (mass potentials) arise from a concert of signals, generated by many different types of single cells. The summed extracellular events around neurons interacting with the surrounding glia generate field potentials. The field potential, inherently complex, is propagated passively through vitreous and anterior chamber as volume conductors to the cornea. These transient electrical changes form the electroretinogram, ERG, that we record non-invasively by using corneal or skin electrodes on the lower lid.
The **a-wave** (Figs. 2, 3), a cornea-negative mainly reflects the synchronized hyperpolarization of the photoreceptors in response to a flash of light. The a-wave is followed by the positive **b-wave**. The b-wave is understood to result from interaction of neurons in the inner nuclear layer, mainly ON-bipolars, with the radially oriented glial (Müller) cells (Figs. 2 and 3) via transient local changes in the concentration of extracellular potassium. The potassium (K) permeability of the Müller cell varies along its axis. Changes in extracellular currents along the Müller cell reflect activation of the retina by light. The ON-mechanism and the OFF-mechanism in the primate retina can be separated pharmacologically by blocking selectively post-photorceptor second order neurons. These pharmacological studies (Sieving et al) yielded evidence for contributions to the normal ERG from the depolarizing ON- as well as from the hyperpolarizing OFF- second order neurons.

The b-wave of the ERG, although relatively unspecific and probably not purely neural in origin, is the most accessible and widely used **objective** indicator of retinal function under normal, pathological, and also under experimental conditions. The major application of ERG testing includes early detection, differential diagnosis and follow-up of **inherited retinal degenerations**. The ERG is also useful to assess therapeutic, pharmacological or toxic effects in clinical and in experimental eye research. Typical changes in the ERG waveform are sketched in Fig.4.

The **amplitude vs. light intensity-function (stimulus-response relation)** of the b-wave describes a threshold range, a steep dynamic range, and saturation at high stimulus intensities, in a characteristic sigmoidal curve, that is similar in all vertebrates studied. Clinical ERG testing uses only few selected stimulus intensities according to an international I.S.C.E.V standard (see www/iscev.org, standards).

**Oscillatory potentials** (Ops, Fig.3) are wavelets superimposed on the b-wave at higher stimulus intensities in dark- as well as in light-adaptation. They are best observed and measured using a 60 to 200 Hz band pass filter for the ERG elicited by a bright flash. OPs are understood to arise from amacrine cells. OPs thus reflect aspects of the function of the inner retina.

The **pattern ERG** (pERG) is recorded in response to structured stimuli, typically checkerboard reversals with various check sizes. The response is sensitive to spatial frequency in the stimulus pattern and extracts activity from the central retina providing information of macular function.

**STR:** the **scotopic threshold response** is a signal of negative polarity generated in the inner retina that is recorded after full dark adaptation at intensities below the threshold of the b-wave (Fig.2). The purely rod-driven signal reflects inner retinal network adaptation and receives contributions from ganglion, amacrine and Müller glial cells.
The c-wave reflects the response of the retinal pigment epithelium (RPE) to light-induced decrease in the K⁺ concentration in the subretinal space, in algebraic summation with the slow P III component (similar time course, opposite polarity). The clinical recording of the c-wave is difficult due to the necessary DC-technique, interference from eye movements, and reported variability among healthy human subjects.

**Standing potential and electrooculogram EOG:** Across the retinal pigment epithelium (RPE), between the outer basolateral and inner apical membrane, exists an apical-positive standing potential (Fig.2). The potential difference, a dipole - like an imaginary battery - is based on an ionic equilibrium that differs between the apical and the baso-lateral side of the RPE. The standing potential reaches a dark trough during dark adaptation, and it increases in light (light peak). The light peak is a consequence of depolarization of the baso-lateral membrane of the RPE, induced by a postulated “light substance” that increases the conductance for Cl⁻.

Clinically the EOG is recorded non-invasively with skin electrodes near the inner and outer canthus during induced standardizes eye movements: the positively charged cornea influences the electrodes correspondingly. Light exposure increases the movement-induced amplitude. Reduction in magnitude or absence of the light peak are indicative of malfunction of the RPE. The electrooculogram and the c-wave thus provide opportunities to assess the functional state of the RPE in patients, important in the diagnosis of forms of Best’s disease.

**Focal ERG, Multifocal ERG:** Several instruments for focal stimulation on a stray light-reducing white background have been developed. Y. Miyake and colleagues obtained focal ERGs recorded from the macula, studying
responses to longer flashes and local oscillatory potentials. They observed an OFF-type with negative ERG in complete congenital stationary night blindness (CSNB), but an ON-type ERG in incomplete CSNB. Such observations help to understand underlying mechanisms in retinal degenerations.

Multifocal techniques: The approach, developed by E. Sutter, involves a matrix of 61 up to 124 M-sequence-controlled hexagonal stimuli scaled with eccentricity and projected on the central 30° of the fundus. The method, due to the nanovolt-range of the local ERG signals, requires substantial averaging and mathematical processing to derive local retinal sensitivity that can be presented as raw data or color-coded 2D or 3D maps. This approach is reported to help defining macular diseases and assessing paramacular loss of cone sensitivity. The stimulus matrix is also used to elicit, to study and to apply the multifocal VEP, that represents an analogue to the visual field.

In the last part I summarize major indications for ERG testing and “negative” ERGs.

<table>
<thead>
<tr>
<th>Meaningful Indications for ERG testing:</th>
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<tr>
<td>• Tapetoretinal degenerations, including all the variable phenotypes of <em>retinitis pigmentosa (RP)</em>, such as sine pigmento stage, sectorial, paravenous or unilateral manifestation</td>
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<td>• carriers in X-chromosomal-recessive RP</td>
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<tr>
<td>• Leber's congenital amaurosis (LCA)</td>
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<td>• choroideremia and respective female carriers</td>
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<td>• vitreoretinal degenerations Wagner and Goldmann Favre</td>
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<tr>
<td>• X-linked juvenile retinoschisis</td>
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<td>• progressive cone dystrophies</td>
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<tr>
<td>• flecked retina syndromes, in particular Stargardt's disease</td>
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<tr>
<td>• syndromic RP: Usher, Kearns, Bardet-Biedl, Refsum's disease, neurological degenerative and pediatric metabolic entities with retinal involvement</td>
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<tr>
<td>• non-progressive inherited conditions</td>
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<tr>
<td>achromatopsia (rod monochromatism, blue cone monochromatism)</td>
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<tr>
<td>congenital stationary night blindness</td>
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<td>• retinopathy of prematurity</td>
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<tr>
<td>• uveitis with retinal involvement and opacities of the media</td>
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<td>• cancer-associated retinopathies</td>
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<td>• toxic or drug-induced changes</td>
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<td>• metallic intraocular foreign bodies</td>
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<tr>
<td>• suspected retinal dysfunction in presence of opacities of the optical media</td>
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<tr>
<td>• abnormal visual function in presence of inconspicuous fundus</td>
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<tr>
<td>• non-organic visual impairment (visual conversion reaction)</td>
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If the ERG trace in response to intense flashes is mainly of *negative polarity* with a small or undetectable b-wave, it points towards the following diagnoses:

<table>
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<tr>
<th>Diseases presenting with negative ERG configuration</th>
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<tr>
<td>• central retinal artery occlusion</td>
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<tr>
<td>• X-linked congenital stationary night blindness</td>
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<tr>
<td>• X-linked retinoschisis</td>
</tr>
<tr>
<td>• cancer-associated retinopathy</td>
</tr>
<tr>
<td>• ceroid lipofuscinosis (Batten)</td>
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</tbody>
</table>
Birdshot retinopathy
methanol toxicity
quinine retinopathy
Duchenne muscular dystrophy

Diagnoses where ERG testing seems essential
- suspected retinal cause of visual handicap in infants
- abnormal function and normal fundus appearance
- non-organic visual impairment (visual conversion reaction)
- early retinitis pigmentosa, *sine pigmento* condition
- early stage of progressive cone dystrophy
- toxic retinal damage
- retinal involvement in uveitis with media opacities

Considerations concerning retinal degenerations are a very brief summary, referring in particular to refs. Berger et al. and Fishman et al. and to the large number of recent publications relating to specific mutations and their phenotype.

Night blindness

Stationary
- Complete CSNB
- Incomplete CSNB
- Fund. albipunctatus

Progressive
- Retinitis pigmentosa (RP)
- Cone-rod degeneration
- Gyrate atrophy
- Choroideremia

Major symptoms in retinitis pigmentosa
- Night blindness
- Constriction of the visual field, loss of sensitivity
- Decrease in visual acuity
- Reduced contrast sensitivity
- Associates symptoms, such as phosphenes in phases of RP

Tapetoretinal degenerations
- hereditary progressive retinal dysfunction
- can appear as nonorganic/dissociative visual problem
- require special counselling
- ERG needed as basis for counselling etc
- difficult to recognize early-on
- Atrophy of retina and RPE
- Visual field loss from unnoticed to tunnel vision
- often associated with loss of macular function
- Prevalence of ~ 1 in 5000 for isolated (typical) RP
- Syndromic forms, about 18%; Usher syndrome ~ 2-6 in 100 000

Fundus in retinal degenerations
- Attenuated retinal vessels
- Mottling or granular pigmentation, from RPE
- Bone spicule pigment
- Atrophy of RPE with large choroidal vessels visible
- Macular changes – cystic, edema, fibrosis
- Vitreal pigment dusting, from altered RPE cells
Cataract in RP:
at age 20 -39 years, varying with pattern of inheritance, autosomal dominant 52%, recessive 39%, X linked recessive 72%.

Inheritance of RP
• All patterns of inheritance, different age of onset, course and severity.
• Simplex cases: no other affected family member. Reported to be 15-63 % of the cases worldwide. Most are recessive RP.

Syndromic retinal degenerations
• Usher
• Neuronal Ceroidlipofuscinosis (NCL)
• late infantile (Bielschowsky-Jansky)
• juvenile (Spielmeier-Vogt)
• Refsum
• A-beta-Lipoproteinemia
• Hallervorden-Spatz spinopontocerebellar degeneration
• Zellweger Syndrom (peroxysomal disease)
• Mitochondrial Encephalomyopathy (Kearns-Sayre)
• Neurophathological R.P. (NARP)
• Leber’s congenital amaurosis with CNS malformations
• Joubert
• Laurence Moon Biedl
• Senior-Loken
• Friedreich’s Ataxia, spinocerebellar dystrophy
• Norrie-disease

Summary:
From single cell responses to complex field potentials: much like the EEG, the retinal field potential comprises several components of different origin arising in the distinct retinal layers. The ERG a- and b-waves reflect the overall functional state of the retina and detects primarily large widespread functional abnormalities.

Adaptation of the patient and stimulus conditions should follow the international standard, to enable comparison of ERG data across laboratories. The non-invasive recording of the ERG complements the standard psychophysical tests in clinical ophthalmology and retinal imaging in the entire diagnostic spectrum of “medical retina”. Selected diagnoses are documented preferably by ERG testing: including Leber’s congenital amaurosis, achromatopsia, CSNB, early retinitis pigmentosa, Usher’s syndrome and impaired visual function in presence of inconspicuous fundi upon ophthalmoscopy.

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