1. CHROMATIC PUPILLOMETER-BASED PERIMETRY IN PATIENTS WITH BEST MACULAR DYSTROPHY

2. CHROMATIC PUPILLOMETER-BASED PERIMETRY IN RETINITIS PIGMENTOSA PATIENTS

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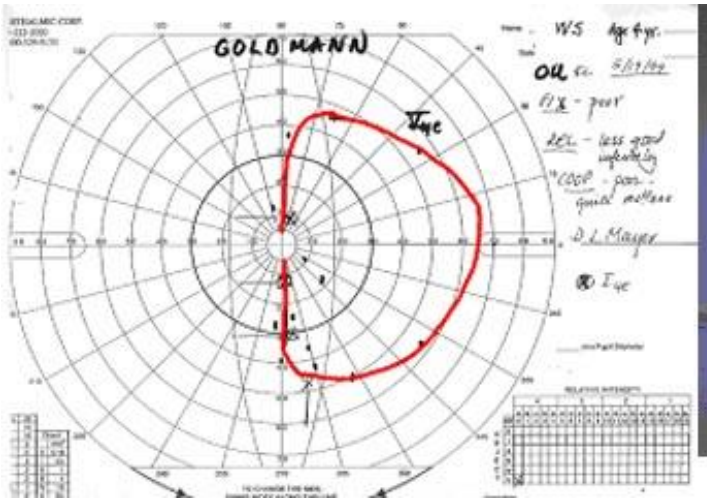
Static automated perimetry



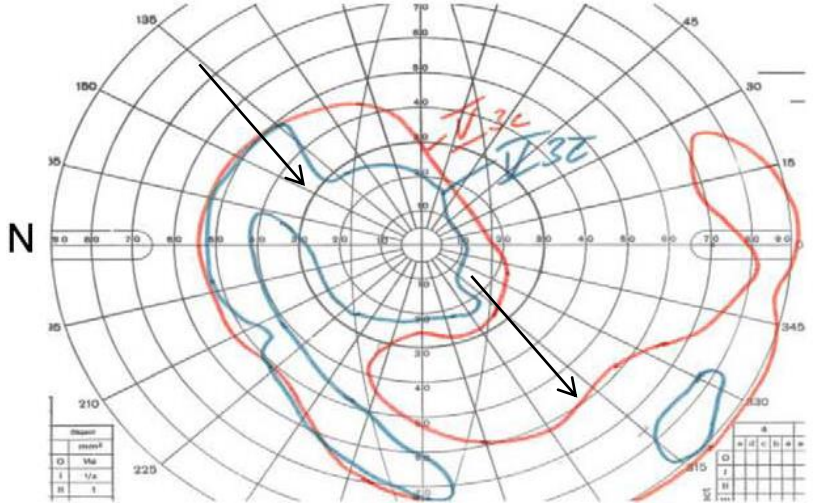
Computerized Perimetry (www.laguna.net)

Indications: to detect visual field loss in:

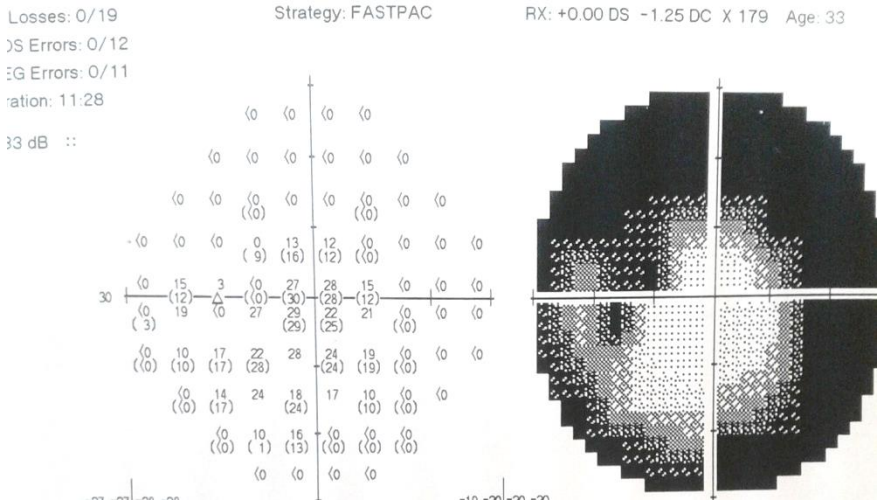
1. **Glaucoma (1%)**
2. **Neurological diseases**
3. **Retinal diseases**

Subjective Perimetry

Goldman



Humphrey



Perimetry and its Limitations

Goldman

- Patients' cooperation is essential
- Can't distinguish between damaged cells
- Qualified personnel
- Subjective

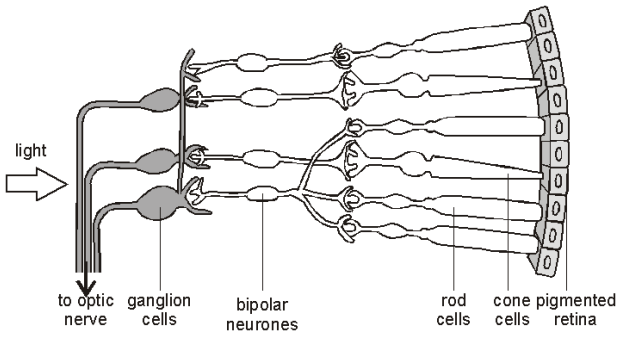
Humphery

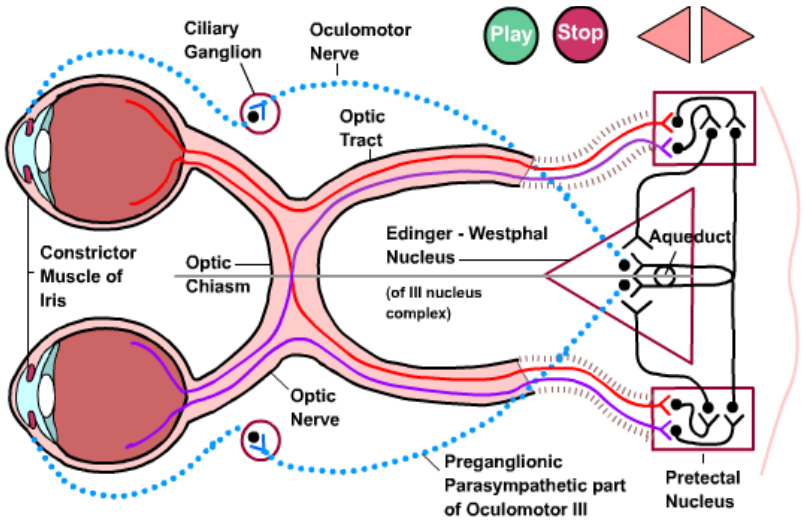
- It is easy to simulate neurologic field defects

  *(D*eepta at el. *Ophthalmology* 2014)

Because of all those limitations there is a need to develop an **objective test** that requires a less cooperation from the patient

Pupillary Light Reflex

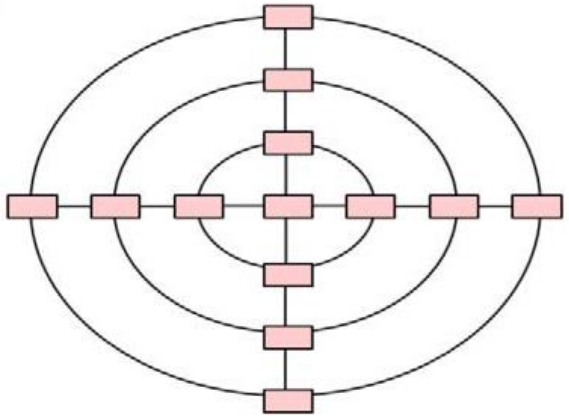


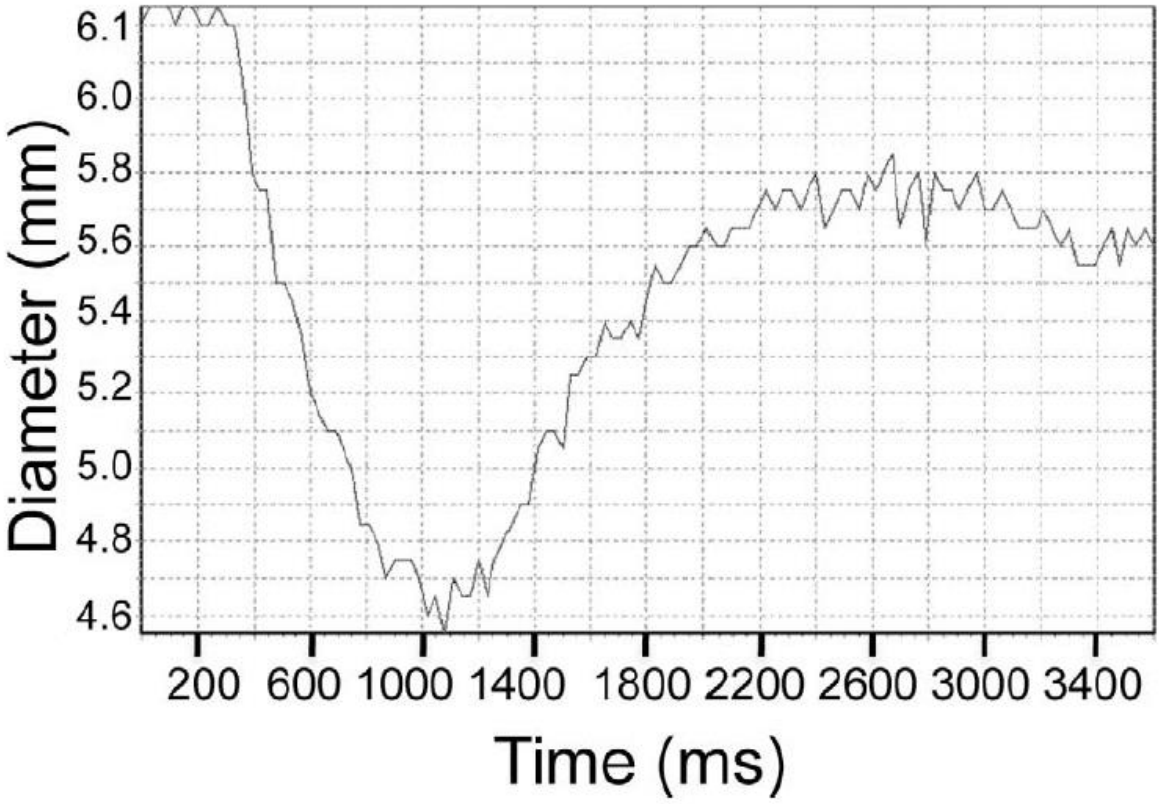


The pupillary light reflex controls the diameter of the pupil in response to the intensity (luminance) of light that stimulates the retina

- The light stimulus activates the retina
- The retina activates the optic nerve
- The optic nerve activates the brain
- The brain constricts the pupil

The first chromatic multifocal pupillometer system





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First prototype limitations:

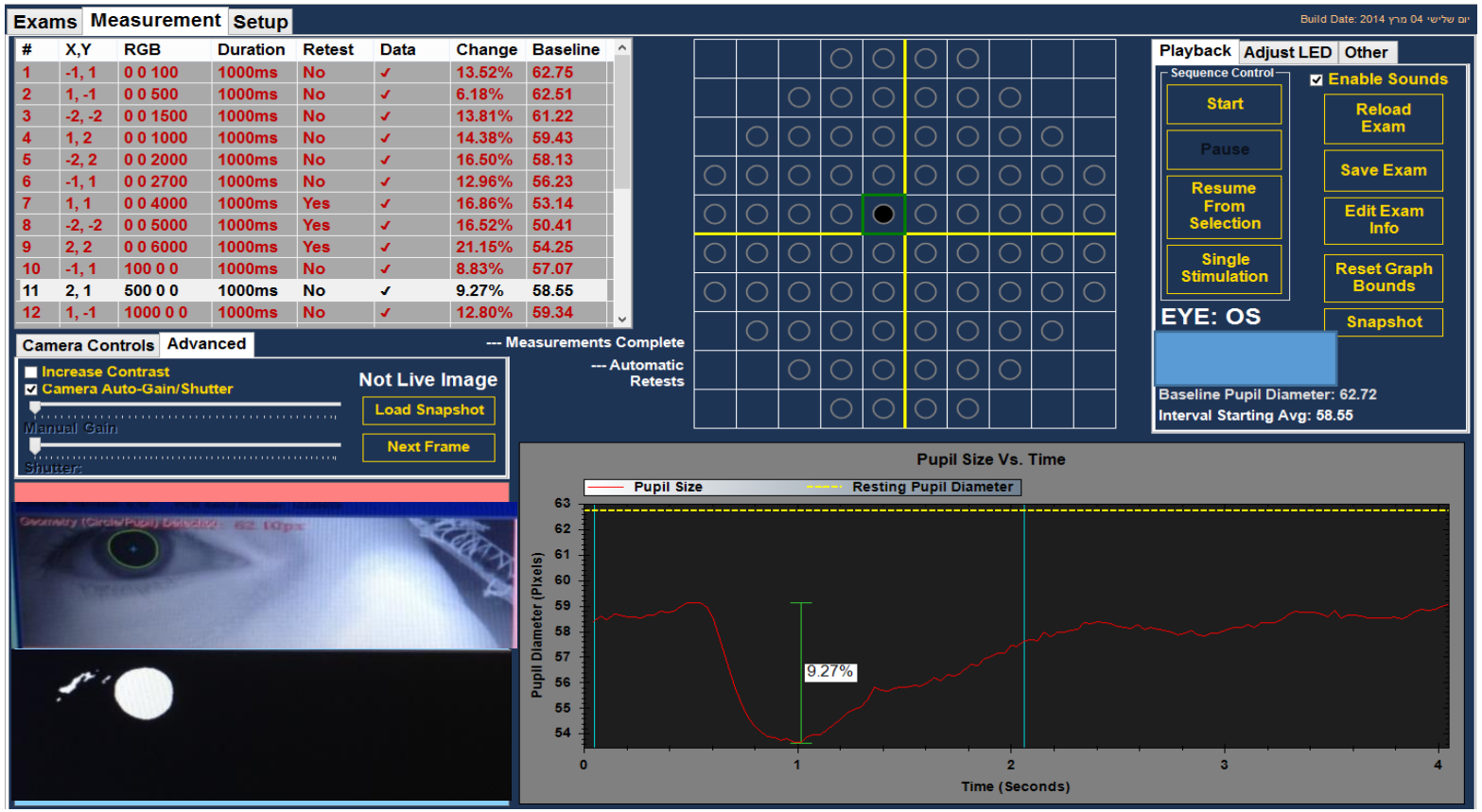
1. Only 13 locations
2. Some patient cooperation was required
3. Software

The second generation:

- The subjects look forward and stimuli are individually introduced at different VF locations.
- A smaller spot size is used with the aim of achieving better perimetric resolution.

The Chromatic multifocal pupillumeter:

- objective perimetry
- 76 locations for blue and red stimulus



The retina

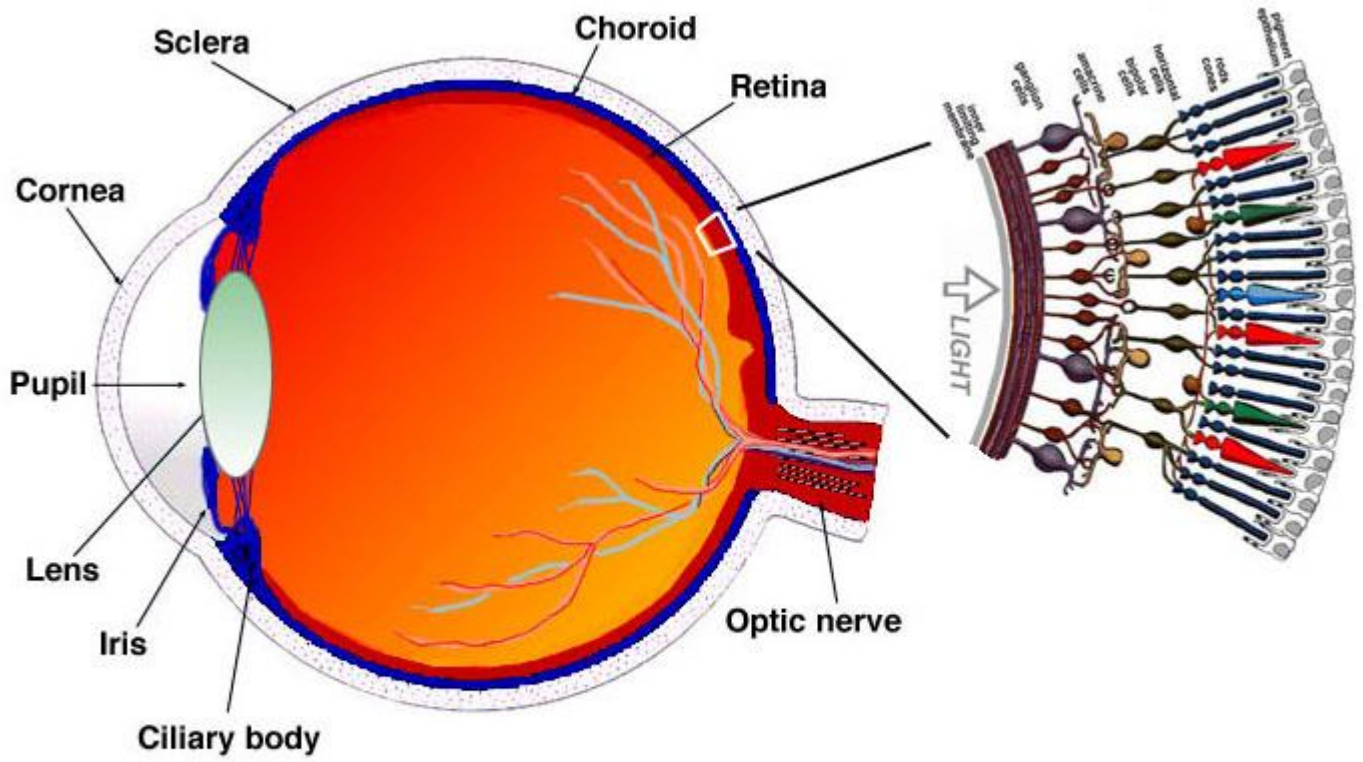


Fig. 1.1. A drawing of a section through the human eye with a schematic enlargement of the retina.

3 main groups compose the retina:

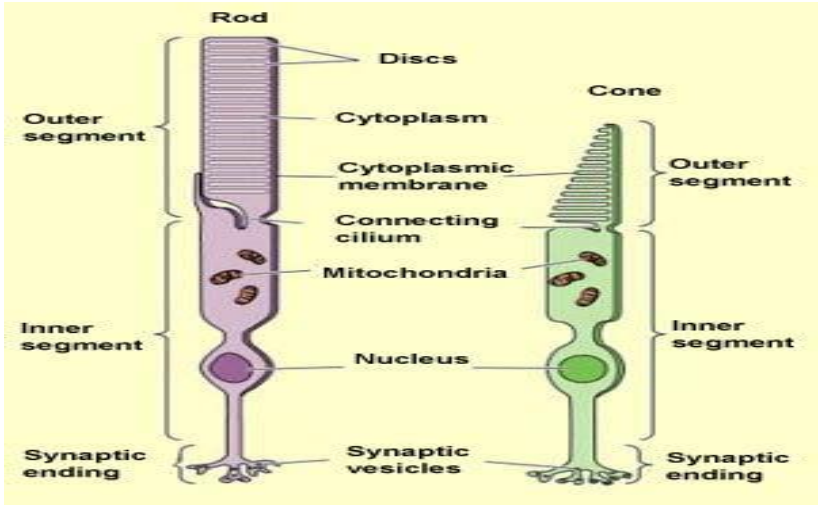
1. Photoreceptors
2. Bi-polar cells
3.Ganglion cells

The fovea is located in the center of the macula region of the retina. And responsible for sharp central vision.

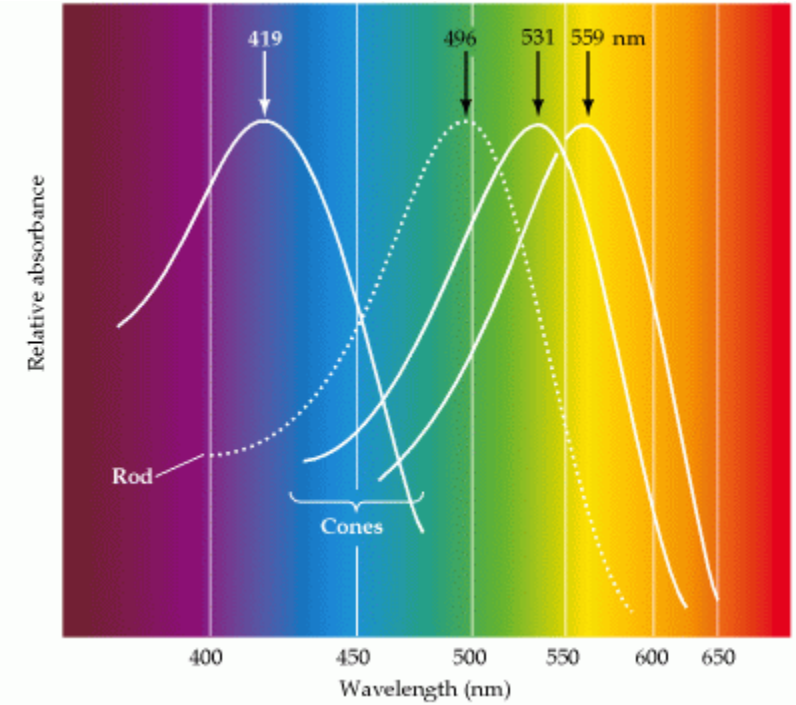
Photoreceptors

Within the retina 60-125 million rods and 3.2-6.5 million cones are distributed.

- No rods are present in the fovea.
- The cones are mainly concentrated in the fovea.



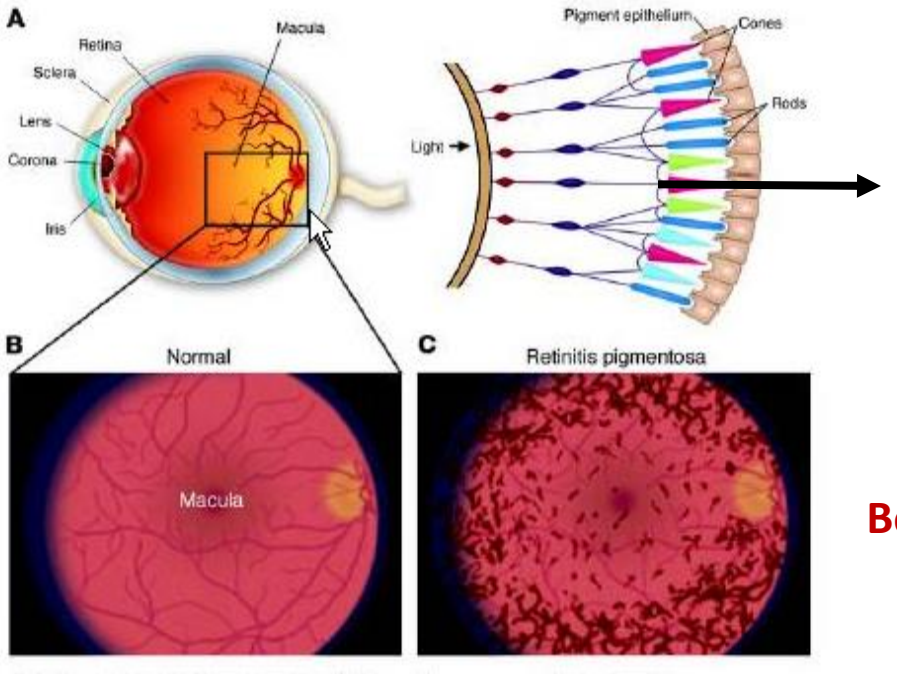
Perimetry based on Pupillary Light Reflex to multifocal chromatic stimuli



Cell Type	Stimulus
Cones	low-intensity red (640nm)
Rods	low-intensity blue (482 nm)
Ganglion	**High intensity blue (482 nm)**

Retinitis pigmentosa (RP)

- The most common cause of inherited blindness
- Progressive degeneration of the retina
- The rods are affected first leading to peripheral and night vision lost.

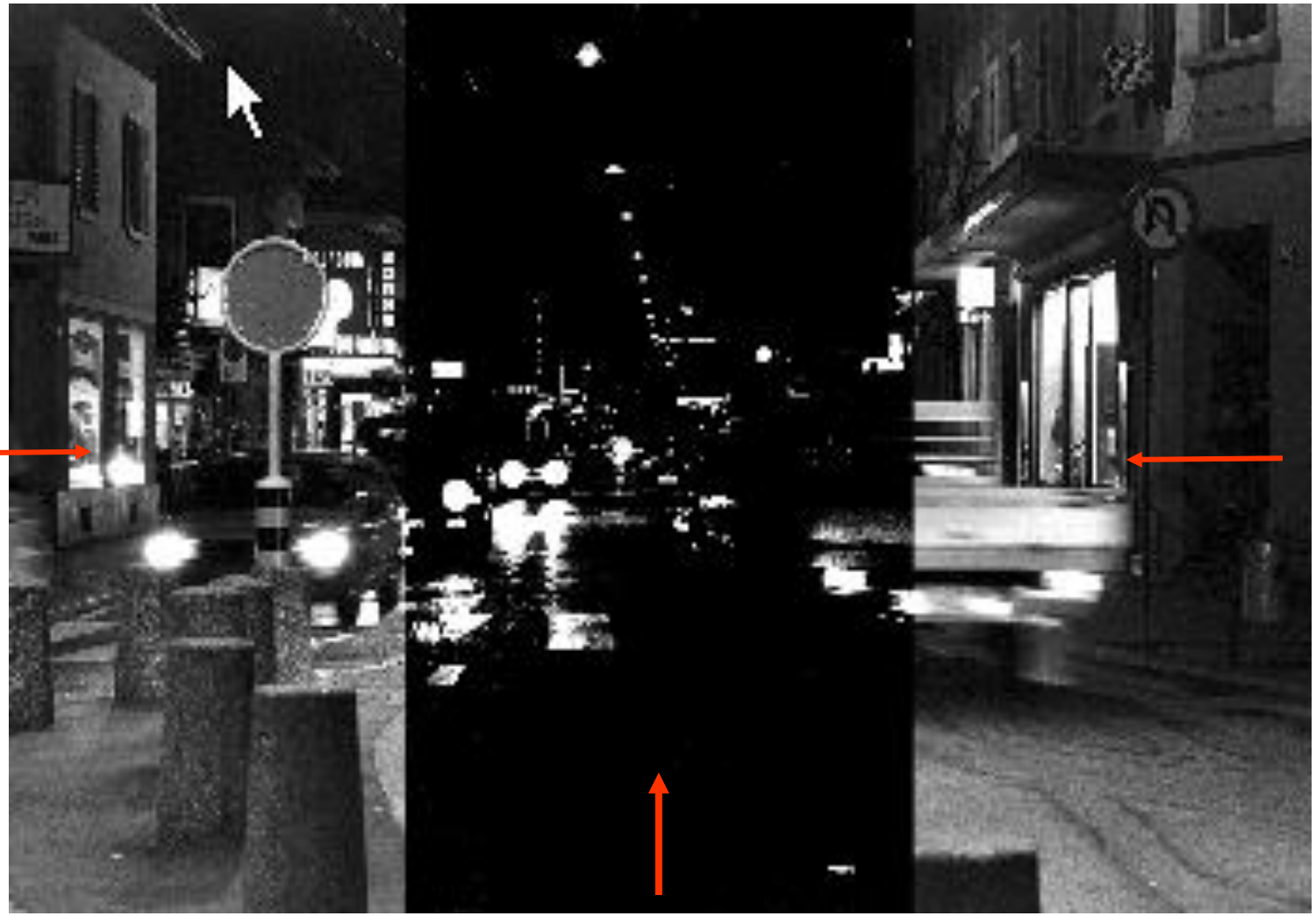


Retinal photoreceptors:

Bone spicule-shaped pigment deposits

RP – visual functions effects

Normal night vision



Normal night vision

Night blindness

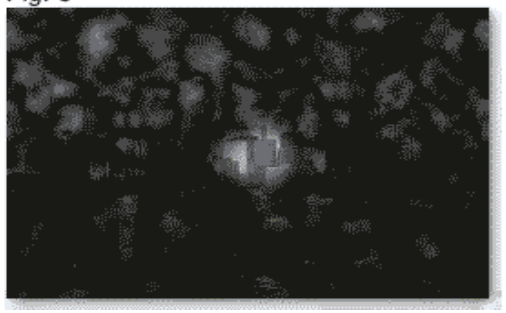
RP – visual functions effects

- Reduction in the peripheral visual field up to tunnel vision
- Central (day) vision is subsequently lost leading to total blindness

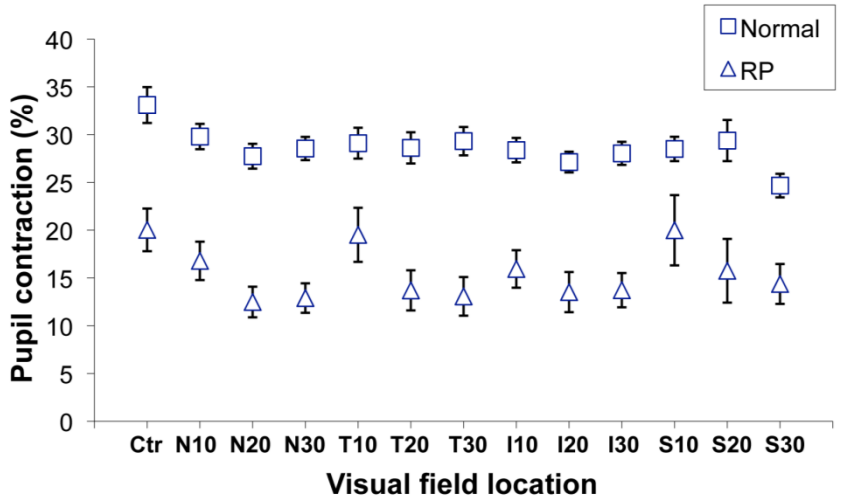
Fig. 1

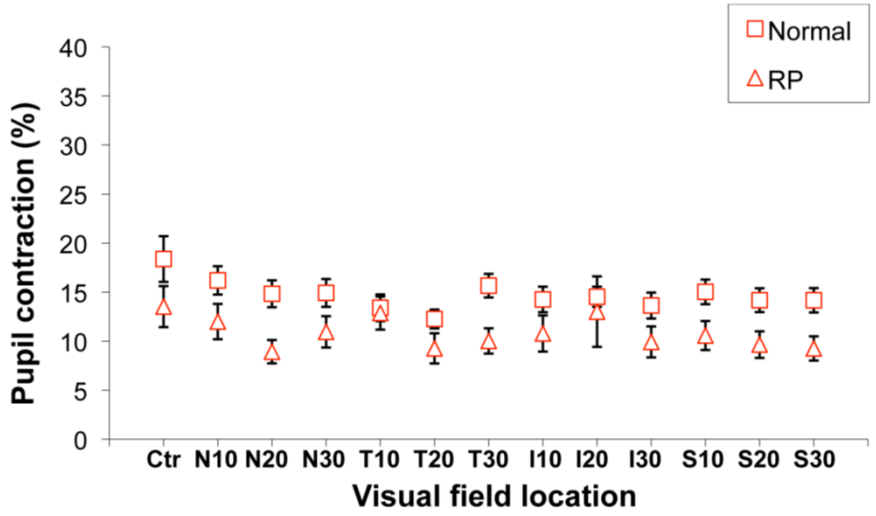
Fig. 2

Fig. 3



RP patients - significantly reduced pupillary responses in nearly all perimetric locations in response to blue stimulus





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Study design :

- 9 retinitis pigmentosa patients
- 9 healthy age-matched volunteers
- Comparison between patients and healthy controls for all perimetry locations was performed using One-Way Analysis of Variance
- In RP patients, the chromatic pupillometer recordings were compared with their dark-adapted chromatic Goldmann

Average- long-wavelength stimulus (622cd/m^2)

Healthy

		10	11	10	14			
	8	14	11	12	12	14		
13	11	15	15	16	12	14	15	
11	11	14	15	17	17	17	13	12	15
13	14	10	13	13	15	17	11	12	10
17	19	17	20	18	20	16	11	14	17
15	17	13	16	15	17	16	15	13	10
	15	12	13	17	14	13	15	11	
		16	13	14	13	11	12		
			13	16	10	10			

RP

		5	6	4	8			
	7	6	6	9	6	8		
6	6	9	11	9	9	7	4	
7	7	12	13	11	10	11	7	7	8
10	16	11	12	18	17	13	11	7	5
11	11	13	13	18	16	14	10	9	5
10	9	9	12	11	7	8	11	6	4
	9	10	13	11	10	8	8	7	
		7	8	9	10	7	4		
			10	9	5	6			

18 degrees

Average- short-wavelength stimulus (88 cd/m²)

Healthy

			23	24	17	17		
		22	21	10	18	21	14	
	18	14	25	25	22	22	19	15
8	38	12	13	18	16	17	17	18	27
19	28	19	18	11	18	21	20	21	19
13	27	22	20	20	24	21	26	23	21
20	29	34	23	16	21	21	23	22	27
	23	21	22	25	26	22	21	20	
		23	22	23	6	21	22		
			22	21	24	29			

RP

			12	11	8	10		
		7	10	9	9	7	8	
	7	11	11	12	9	11	10	5	
11	11	13	15	13	15	13	13	11	9
11	11	12	19	20	20	12	7	12	12
12	13	15	18	14	15	17	12	9	9
11	13	15	10	12	15	10	9	6	9
	13	12	11	11	12	13	14	9	
		13	12	7	12	12	9		
			8	15	13	10			

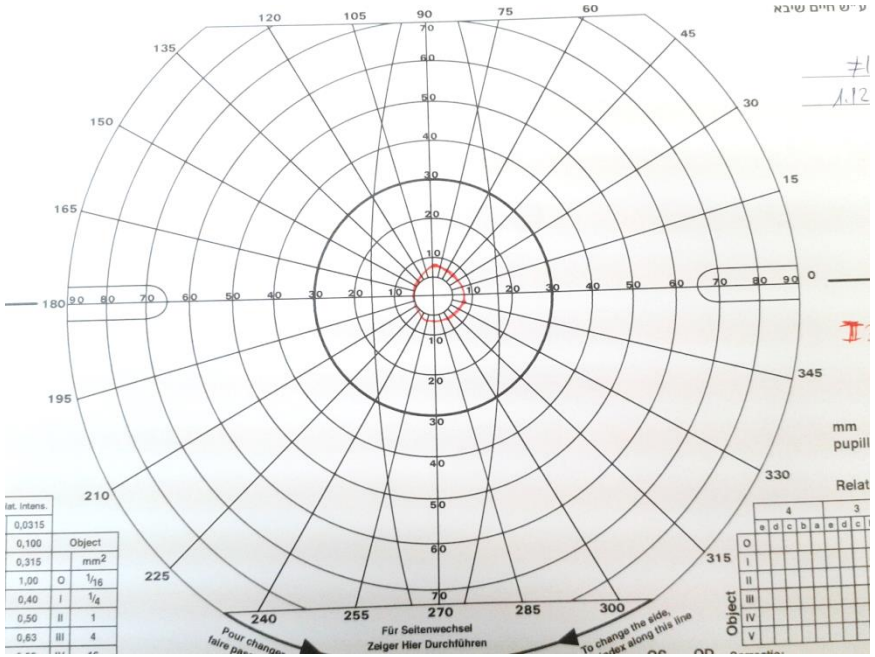
18 degrees

Patient #1 - long wavelength

Pupil Response (% of Normal Value)

		0.1	0.3	0.1	0.1			
	0.5	0.2	0.1	0.3	0.2	0.2		
	0.1	0.5	0.3	0.6	0.2	0.5	0.2	0.1	
0.3	0.7	0.4	0.7	0.9	0.5	0.4	0.6	0.5	0.1
0.1	0.2	0.6	0.5	1.3	0.9	0.5	0.4	0.2	0.2
0.1	0.2	0.3	0.4	0.7	0.5	0.4	1.3	0.3	0.1
0.1	0.1	0.3	0.6	0.4	0.2	0.2	0.1	0.2	0.4
	0	0.1	0.2	0.4	0.2	0.1	0.1	0.1	
		0.2	0.1	0.3	0.1	0.3	0.2		
			0.1	0.1	0.2	0.2			

Chromatic Goldman



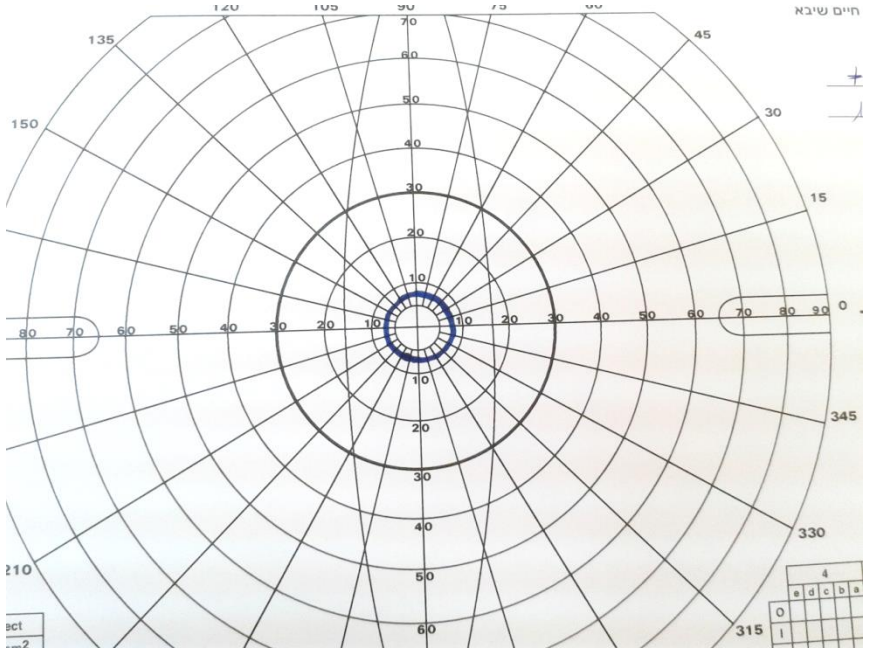
18 degrees

Patient #1 - short wavelength

Pupil Response (% of Normal Value)

		0.1	0.3	0.3	0.3			
		0.2	0.3	0.6	0.4	0.2	0.5	
	0	0.3	0.1	0.3	0.5	0.3	0.3	0.3	
0.3	0.1	0.3	0.5	0.4	0.3	0.4	0.6	0.3	0.1
0.3	0.1	0.2	0.5	1.2	0.7	0.3	0.2	0.2	0.1
0.4	0.1	0.2	0.4	0.6	0.6	0.3	0.3	0.2	0
0.2	0.2	0.3	0.4	0.8	0.5	0.3	0.2	0.2	0.1
	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.2	
		0.1	0.1	0.1	0.8	0.2	0.3		
			0.2	0	0.1	0.2			

Chromatic Goldman



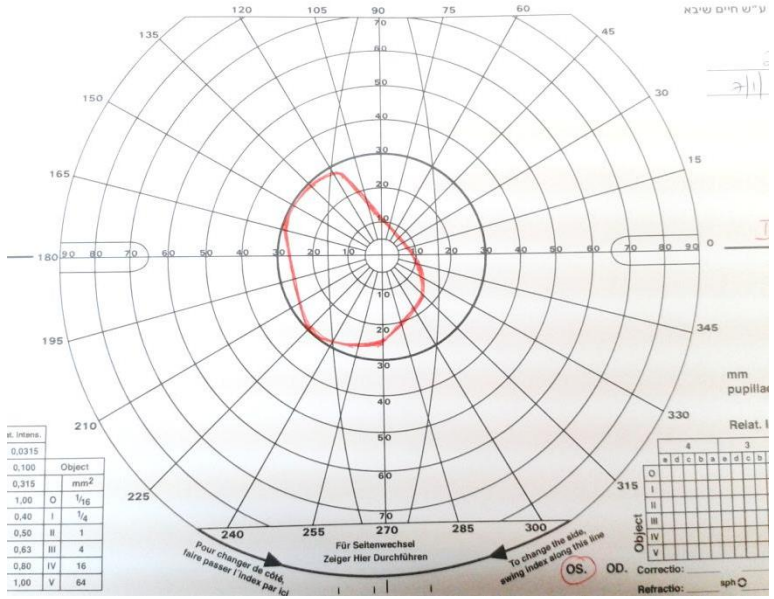
18 degrees

Patient #2 - long wavelength

Pupil Response (% of Normal Value)

			1.9	1.2	0.3	0.7			
			1.8	0.6	1.4	1.4	0.8	0.7	
		0.9	1.6	1.7	1.6	1.5	1.5	0.9	0.3
2.3	1.6	1.9	1.8	1.4	1.7	1.5	1.8	0.8	0.4
1.9	1.9	2.8	2	2.3	1.5	1.6	2.3	1.6	0.2
1.4	1.4	1.5	1.3	1.6	1.4	1.6	1.9	1.2	0.5
1.6	1.7	2	1.7	1.6	1.3	1.2	1.2	1.2	0.8
	1.6	2.1	2.1	1.6	1.4	1.7	1.1	1.4	
		1.2	1.5	1.6	1.7	1.8	1.2		
			1.6	1.1	2.2	1.4			

Chromatic Goldman



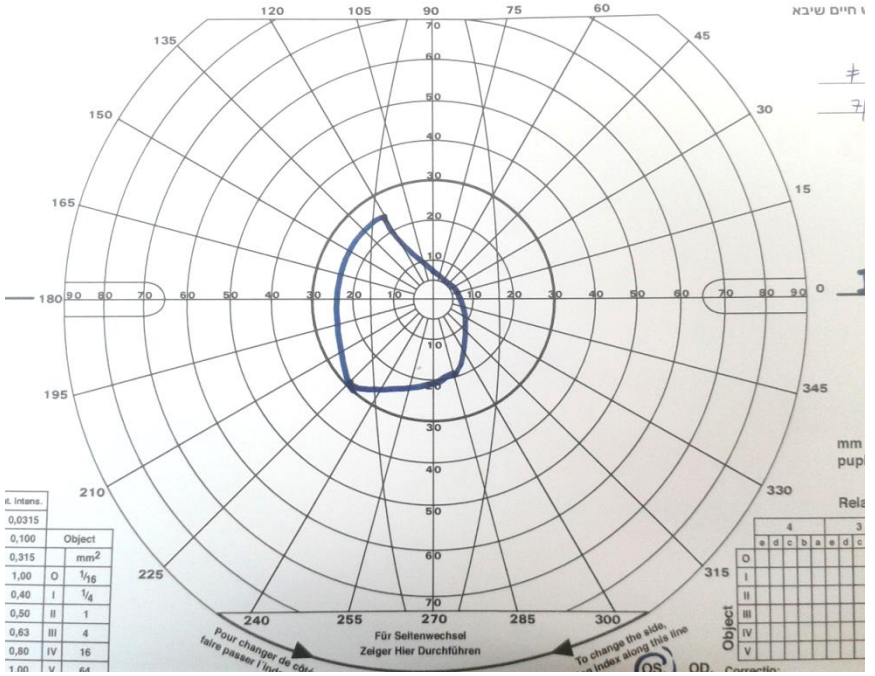
18 degrees

Patient #2 - short wavelength

Pupil Response (% of Normal Value)

			1.1	1	0.6	1.3			
		0.9	1.2	2.3	1.1	0.7	0.7		
	1.1	1.7	1	1.1	1.2	1.1	0.9	0.6	
3.8	0.6	2.1	2.6	1.5	1.8	1.6	1.5	1.3	0.7
1.4	1.1	1.5	1.7	3	1.7	1.4	1.3	0.8	1.2
2.3	0.8	1.2	1.7	1.2	1.3	1.5	1	0.8	0.9
1.3	1.1	0.8	1.1	1.3	1.6	1.1	1.2	0.4	0.7
	1.3	1.1	1.1	1	1	1.2	1.2	1	
		1.3	1.1	0.8	4.3	1.4	1		
			1.3	1.2	1	1			

Chromatic Goldman



18 degrees

Conclusions

- RP patients demonstrated reduced pupillary responses to short wavelength stimuli
- Good correlation with Chromatic Goldman
- The new device will enable objective VF patient diagnosis and objective

  evaluation of treatment benefit

Hereditary dystrophies

- Hereditary dystrophies affecting the central retina
- represent a heterogeneous group of diseases.

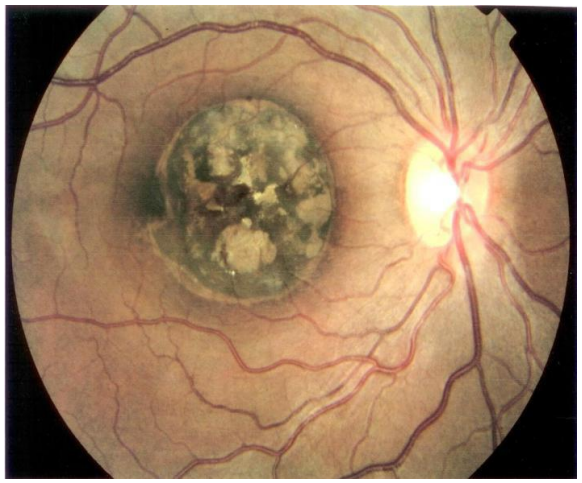
- Genetic alterations may be responsible for:
  - changes of the choroid
  - **changes of the retinal pigment epithelium [RPE] (Best's disease)**
  - changes of the photoreceptor outer segments (Stargardt's disease)
  - Changes of the bipolar and Mueller cells (x-linked retinoschisis).

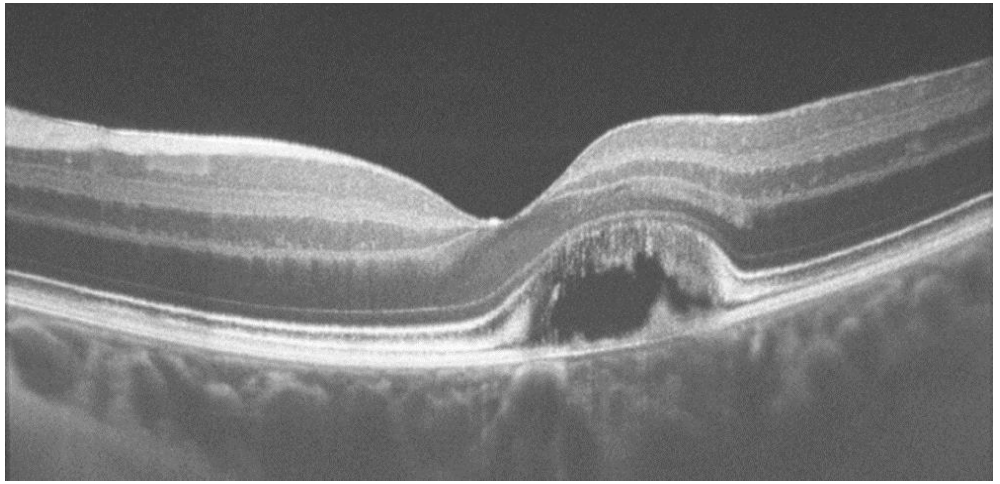
Best disease

- Autosomal dominant disease that affects the retinal pigment epithelium

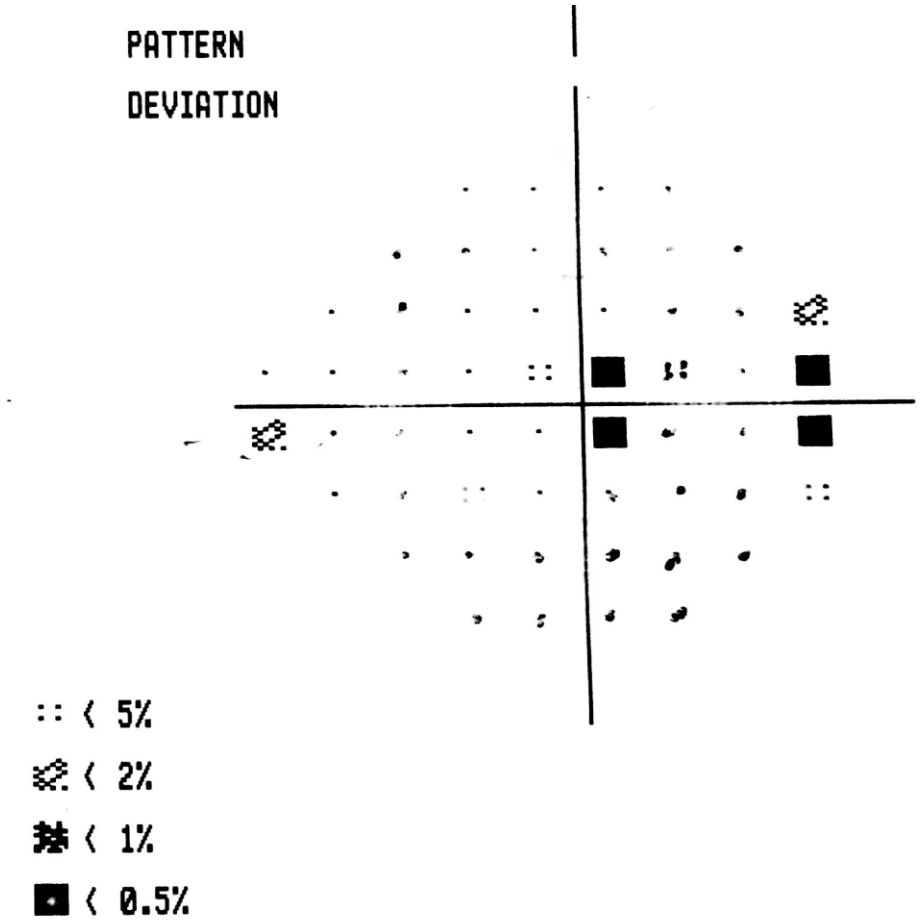
(RPE) at a very young age.

- Characterized by lipofuscin accumulation in the RPE.
- Atrophic changes of the RPE or scarring secondary to subretinal neovascular membranes with hemorrhage causes loss of central visual acuity.





- Typically, patients will present with an early central scotoma
- More dense scotomas will likely develop as the disease progresses



Best stages:

- Stage 1 is known as the pre-vitelliform stage, the macula looks normal, and there are only subtle RPE changes. Normally 20/20 vision is expected.

- Stage 2, the vitelliform stage, shows a yellow or orange elevated lesion which looks like an egg-yolk, Vision at this stage can range from 20/20 to 20/50.

- Stage 3, pseudohypopyon stage is when the yellow material breaks through the RPE and accumulates in the subretinal space forming a cyst of fluid. Vision remains stable at 20/20 to 20/50.

- Stage 4, vitelliruptive stage is known by its “scrambled egg” appearance. This is due to the vitelliform lesion breaking up. Vision may decrease to the range of 20/20 to 20/100.

- Stage 5 is the atrophic stage where the yellow material disappears and an area of RPE atrophy remains.

- Stage 6 follows the atrophic stage and presents with choroidal neovascular/cicatricial lesions. These lesions lead to subretinal fibrotic scars.

Vision at Stage 5 and 6 may deteriorate to less than 20/200.

Study design :

- 13 participants were recruited (4 BEST patients and 9 healthy individuals).
- A computerized infrared video pupillometer was used to record changes in pupil diameter in response to short- and long-wavelength stimuli (peak 485 nm and 620 nm, respectively).
- Target diameter was 2 mm, duration of stimulus was 1 sec.
- Stimuli were presented by 76 LEDs in a 18-degree visual field.
- Percentage change in pupil diameter was calculated.
- The pupillary responses of patients were compared with their findings on Humphrey's 24-2 perimetry and with the pupillary responses obtained from normal control subjects.

Average- short-wavelength stimulus (200 cd/m^2)

Normal

		18	24	19	24			
	18	21	20	23	22	23		
20	21	21	21	21	24	25	22	
22	20	21	25	27	24	25	27	26	27
22	21	22	23	25	29	24	19	22	21
15	19	22	20	25	24	21	19	18	21
20	23	16	24	22	17	18	21	22	19
	17	14	17	23	22	21	19	21	
		13	17	16	19	22	22		
			19	20	23	26			

BEST

		18	17	18	26			
	20	21	16	18	21	20		
18	17	20	14	22	23	26	20	
18	16	23	21	15	22	22	22	21	23
16	16	18	22	22	12	17	14	18	21
18	19	20	19	18	19	26	25	22	20
20	23	20	22	17	19	17	24	19	20
	20	18	16	17	20	15	21	17	
		20	18	13	16	23	19		
			20	14	18	23			

18 Degrees

Average- long-wavelength stimulus (622cd/m^2)

Normal

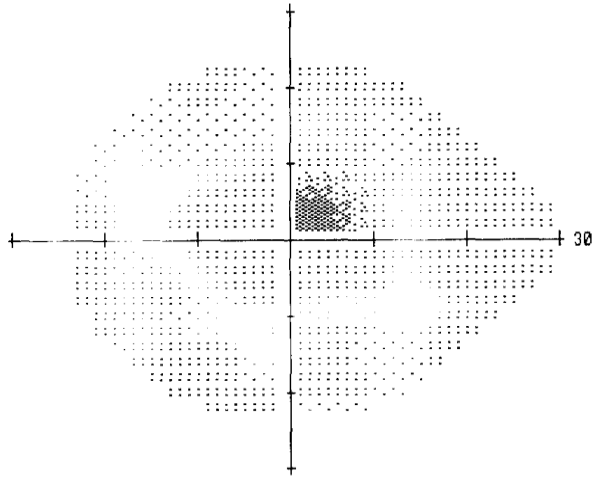
		10	11	10	14			
	8	14	11	12	12	14		
13	11	15	15	16	12	14	15	
11	11	14	15	17	17	17	13	12	15
13	14	10	13	13	15	17	11	12	10
17	19	17	20	18	20	16	11	14	17
15	17	13	16	15	17	16	15	13	10
	15	12	13	17	14	13	15	11	
		16	13	14	13	11	12		
			13	16	10	10			

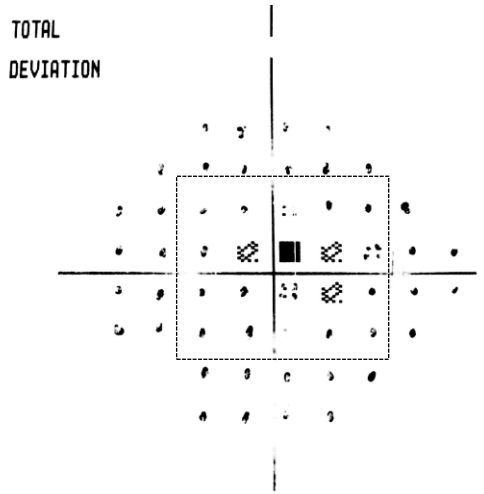
BEST

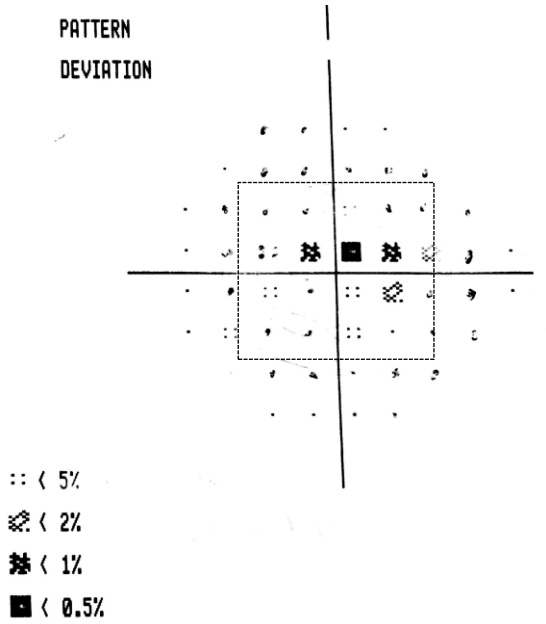
		6	9	6	8			
	6	9	10	7	11	13		
7	6	12	9	9	5	10	7	
9	10	9	15	9	8	8	10	8	7
9	10	7	10	16	5	13	9	9	7
10	8	9	9	10	13	9	10	8	10
6	8	4	5	8	5	9	9	9	13
	5	6	7	8	10	11	7	12	
		9	8	11	9	6	10		
			12	7	9	8			

18 Degrees

BEST patient # 1







			0.82	0.00	0.89	0.62			
		1.08	1.19	0.22	1.07	1.09	1.43		
	1.09	0.91	1.06	0.36	0.96	0.80	0.98	0.66	
0.84	1.25	0.78	1.15	0.50	0.70	1.03	1.19	1.04	
0.55	0.34	0.65	0.74	0.40	0.46	0.56	0.51	0.71	0.62
0.97	1.26	1.01	1.05	0.58	0.87	0.77	1.22	1.02	0.81
1.21	1.27	1.09	0.80	0.70	0.79	0.90	0.76	0.89	0.92
	1.58	0.70	1.48	0.51	0.50	1.06	1.15	0.91	
		1.14	1.33	0.00	0.89	1.18	1.06		
			1.58	0.67	0.95				

			0.69	0.52	0.00	0.00			
		1.43	0.80	0.80	0.99	0.98	0.00		
		1.55	0.90	0.42	0.61	0.00	0.35	1.43	
0.69	0.74	0.60	0.68	0.49	0.47	0.15	1.08	0.57	0.81
0.51	1.15	0.00	0.44	0.94	0.00	0.00	1.53	0.88	1.18
0.43	0.00	0.88	1.03	0.78	0.96	0.00	2.12	1.12	0.59
0.65	1.17	0.00	0.81	0.55	0.32	0.22	0.80	0.00	
	0.94	0.00	1.00	0.60	0.95	0.48	0.52	0.62	
		0.74	0.74	0.97	0.53	0.69	0.89		
			0.80	0.77	1.03	0.57			

Conclusions

- A good agreement was observed between the Humphrey's perimetry and the perimetry obtained by pupillary responses to short wave length stimuli.

- This study demonstrates the potential feasibility of using pupillometer-based chromatic perimetry for objective assessment of visual field defects and retinal function in patients with BEST vitelliform macular dystrophy.

- Perimetry testing based on pupillary responses to long wave length stimuli is more sensitive and may enable earlier detection of visual field defects in patients with central macular lesions.

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Thank you