The hereditary dystrophies of the posterior pole of the eye

THE HEREDITARY DYSTROPHIES OF THE POSTERIOR POLE OF THE EYE

PROEFSCHRIFT

ter verkrijging van de graad van doctor in de geneeskunde
aan de Medische Faculteit te Rotterdam,
op gezag van de decaan Prof. D. C. den Haan,
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Aan mijn ouders, vrouw en kinderen

"So there he stands, our vertical, hunting, weapon-toting, territorial, neotenous, brainy, Naked Ape, a primate by ancestry and a carnivore by adoption, ready to conquer the world. But he is a very new and experimental departure, and new models frequently have imperfections. For him the main troubles will stem from the fact that his culturally operated advances will race ahead of any further genetic ones. His genes will lag behind, and he will be constantly reminded that, for all his environment-moulding achievements, he is still at heart a very naked ape".

DESMOND MORRIS: "THE NAKED APE"

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The hereditary dystrophies of the central retina and choroid

1. INTRODUCTION

Diminished vision as a result of macular degeneration or changes of the posterior pole of the eye constitutes an important ophthalmological problem. Kornzweig (1957) studied more than 1000 eyes and found diminished vision as a result of an affection of the posterior pole in 24.1% of patients under 80 and 38.6% of patients over 80. Only cataract was found to be a more frequent cause of diminished vision. However, whereas the therapeutic possibilities are ample in the case of cataract, they are usually very limited in the many macular affections. Yet a too defeatist attitude towards affections of the posterior pole is undesirable. A better understanding and improved knowledge of macular anomalies and degenerations may well lead to a more effective approach. Precisely in familial dystrophies of the posterior pole, more perceptive interpretation of the clinical features and a knowledge of the mode of transmission can make a meaningful contribution to prophylaxis by responsible genetic counselling. In this context it must be borne in mind that several dystrophies of the posterior pole cause so little loss of function that prophylaxis need not at all be considered. Since the clinical course and prognosis of the various macular degenerations are dependent on the type of affection, improved differentiation is of great importance also.

Because a substantial proportion of the macular affections are inherited, the hereditary dystrophies of the posterior pole have attracted increasing attention in the past few years; for these dystrophies prove to be considerably more common than they were initially thought to be. Many posterior pole changes previously regarded as consequences of an infectious process, are revealed at closer study and after genetic investigation to be of hereditary origin.

The confusion in the classification and differential diagnosis of hereditary dystrophies of the central retina and choroid – often referred to as "hereditary macular degenerations" – has been great, and still is.

Since Sorsby's study on "The dystrophies of the macula" (1940), there have been

no major publications especially devoted to this subject. Although the hereditary dystrophies of the posterior pole are discussed in detail in the manuals of Waardenburg, Franceschetti and Klein (1963), and Franceschetti, François and Babel (1963), which we frequently consulted, new points of view have since been advanced, and new findings obtained, which have made it desirable to write this monograph.

The purpose of our study was to attain a clear insight into the hereditary dystrophies of the posterior pole on the basis of an extensive clinical and genetic investigation of many personal patients and their relatives, and as comprehensive a study of the literature as it was possible to make. An effort was made to ensure better differentiation by giving as exact a description of the various entities as possible. Our additional intention was to use the material available for a classification which can be useful in actual practice.

For this purpose, a detailed ophthalmological study was made not only of the patients but also of their relatives. The patients as well as the ophthalmoscopically normal carriers were submitted to an exhaustive examination of the retinal functions.

The practical usefulness of our study soon became apparent in that it revealed several patients whose posterior pole changes proved to be of hereditary origin, although an infectious aetiology had been accepted. In some of these cases, in fact, an of course superfluous, intensive and by no means harmless medication had been prescribed. Occasionally, the patient or the parents had been informed that the condition would ultimately lead to blindness; if the correct pathogenesis had been understood, the prognosis could have been much more favourable because no dystrophy confined to the posterior pole can lead to true blindness.

We also encountered a few patients with a recessive posterior pole dystrophy, whose ophthalmologist had informed them that their children were bound to develop the same affection. These examples may serve to illustrate that a better and more comprehensive understanding of hereditary dystrophies of the central retina and choroid is desirable.

In principle, we decided to treat only such hereditary processes as involved exclusively the posterior pole of the eye. In actual practice, however, it was exceedingly difficult to apply this principle because we found that few dystrophies confined themselves exclusively to the central retina and/or choroid. It was frequently found also that an affection ophthalmoscopically confined to the fovea affected a much more extensive area of the retina in functional terms. A strict delimitation of central dystrophies can therefore not be made, and is therefore undesirable.

Our study encompasses only those hereditary conditions in which the foveal involvement dominates the disease picture.

An exception to this rule are the senile foveal dystrophies, which are known to be sometimes hereditary; these were not included in the study. Genetic investigations in these age groups poses almost unsolvable problems. However, the familial occurrence of this condition can be demonstrated, and has been demonstrated in a few

instances (Waardenburg, Franceschetti and Klein 1963; Franceschetti, François and Babel 1963).

Until recently it was maintained by many authors that the "hereditary macular degenerations" are different manifestations of a single entity. It was even believed that a single gene could cause all the different manifestations observed in posterior pole dystrophies. Even though one genotype can produce several phenotypes, it is too far-fetched in our opinion to regard the many different ophthalmoscopic features encountered in hereditary dystrophies of the posterior pole, as pleiotropic manifestations of the same gene.

There is certainly a great variability in the expressivity of the various genes, giving rise to polymorphous manifestations, but *it is our decided opinion that there are several hereditary dystrophies of the central retina and choroid, determined by several different genes.* This conviction is based on an exhaustive study of patients and survey of the literature. Without our large case material, it would have been difficult to reach this definite conclusion.

In many cases the various entities are clearly distinguishable, not only ophthalmoscopically but also on the basis of retinal function and mode of transmission. Waardenburg (1968) already pointed out the peculiarity of concluding on the one hand that the many retinal posterior pole dystrophies are homogenetically determined, while on the other hand accepting a polygenic theory in the classification of various corneal dystrophies. Since the retina (and certainly the fovea) represents an exceedingly complex functional structure, it is very likely determined by several genes.

We find it impossible to include in this study a detailed survey of the entire literature on hereditary posterior pole dystrophies, from 1875 on. In the early publications the data are often incomplete, and the nature of the conditions described can therefore not always be established with certainty. In many instances this is due to the impossibility of publishing photographs and the lack of reliable methods of determining retinal function. However, efforts have been made to refer to the existing pertinent literature whenever possible.

2. MATERIAL

The majority of the patients were traced in the case material available at the Oogziekenhuis, Rotterdam.

As the study progressed, patients from other ophthalmological clinics and ophthalmological practices throughout the country were also included. However, no attempt has been made at a complete inventory of all patients available in The Netherlands. All together over 240 patients with foveal dystrophics were examined.

3. METHODS

In all cases an extensive history was taken, and the usual routine examinations were made (slit-lamp, indirect and direct ophthalmoscopy and applanation tonometry).

In many cases, moreover, patients were submitted to binocular slit-lamp examination with the Hruby lens and with the three-mirror contact glass of Goldmann. In addition, the following retinal function tests were carried out.

a. visual acuity

b. visual fields

Visual fields were determined with the Goldmann perimeter, in white light and under photopic conditions after adaptation to the illuminated perimeter for 2-3 minutes. The perimeter was standardized with a light meter and with a photometer device, so that the largest test object measured 1000 apostilb (asb) at its brightest, and the eyeball illumination 31,5 asb. Next, the sensitivity of the retina was mapped with the test object, a light spot of varying size and intensity, while the patients were using their optimal correction.

We used only the kinetic (quantitative), not the static (qualitative) method of perimetry.

In many cases, use was made also of the double-projection campimeter (Hagedoorn and Van den Bosch 1955) in order to determine the exact size of the central scotomas.

In a few cases we used the Friedmann visual field analyser (Friedmann 1966) for qualitative (static) determination of the function of the central visual field.

c. colour vision

Colour vision was tested with the American Optical Hardy-Rand-Rittler (HRR) pseudo-isochromatic plates, with the Nagel anomaloscope model I, and with the Farnsworth dichotomous test (D-15) panel. In many cases the Farnsworth tritan plate was also used, and in a few cases the Farnsworth 100 hue test was employed to test colour vision.

d. dark adaptation

Dark adaptation was effected with the Goldmann-Weekers adaptometer. The patients were left in a room with moderate artificial illumination for 5-10 minutes, and then placed in complete darkness for 2 minutes. Next, they were adapted to a bright light of 2000-3000 lux for 5 minutes. The desired initial illumination for the field of stimulation was adjusted with the aid of a light meter.

The investigation was continued for 30 minutes, the patients using their optimal correction. Since loss of visual acuity is of course quite common in foveal dystrophies, the integral method of investigation with pulsating light was generally used. For it is our impression that the streak figure with 100% contrast is not or poorly perceived when visual acuity is diminished.

Using the integral method, we investigated the degree to which retinal sensitivity increased in the course of dark adaptation. We plotted no dark adaptation curves of local retinal sites because fixation was difficult or impossible in a large number of cases.

e. electro-retinography

Light stimulation and adaptive state. The source of stimulation for the electro-retinogram (ERG) and oscillatory potentials (OP) was a Van Gogh photostimulator type SV 1 E, of which the energy could be varied in 4 steps of about 0.5 log units each. Colour or neutral density filters (in steps of 1 log unit) could be placed in front of the lamphouse, subtending a visual angle of 30° and always fitted with a white opaque diffuser. The scotopic ERG was elicited in the dark-adapted state with a blue stimulus (flash energy 1 Joule, neutral filter with density 2 or 1, flash frequency 1 per second), and the photopic ERG in the light-adapted state with a red stimulus (flash energy 1 Joule, no neutral density filter, flash frequency 4 per second). For the OP, examined in the dark-adapted state, the energy of the photostimulator could be increased to 64 Joules.

The foveal ERG (F-ERG), always recorded together with the visually evoked responses (VER), was elicited in the light adapted state with a white stimulus of 3°, 5° or 8° visual angle. The stimulus, with a luminance of 1.5 log cd/m^2 and a duration of 20 msec, was presented at a frequency of 4 cps (Van Lith and Henkes 1967).

Adaptive state. The preliminary dark adaptation consisted of 20 minutes' adaptation to a deep red light of low luminance, during which period the subject's pupils were dilated and the electrodes and contact lenses (Henkes-Worst low-vacuum type) fitted. This period was followed by 5 minutes of absolute darkness. Dilatation was achieved with a mydriatic (Roche, Chibret). For light adaptation, a big lamphouse of 90° visual angle was placed behind the photostimulator. It consisted of 9 fluorescent tubes (Philips 34), a milky glass diffuser and a blue filter. The illumination, measured at the corneal plane, amounted to 1000 lumen/m^2 without and 250 lumen/m^2 with the blue filter.

Amplification and recording. All potentials were amplified with a Van Gogh six-channel EEG ink-writer with band pass filters of 0.2-75 cps for the scotopic and 2.0-75 cps for the photopic ERG. As a rule, scotopic and photopic ERGs were recorded with this apparatus, too. In some special cases the responses were averaged on a computer of average transients (CAT Mnemotron type no. 400) and plotted with an X-Y plotter (20 counts for the scotopic and 200 counts for the photopic ERG). The foveal ERG and VER could be obtained only with the aid of the CAT (both 500 counts).

The fast wavelets of the OP had to be recorded photographically from the screen of an oscilloscope, with a polaroid camera.

Normal values. Of the scotopic ERG, we measured the maximum height of the scotopic b-wave, i.e. the maximum positive wave without a preceding negative a-wave. In the circumstances described, the lower limit of the normal value is 180 μV. In our arrangement, the maximum height of the photopic b-wave, measured

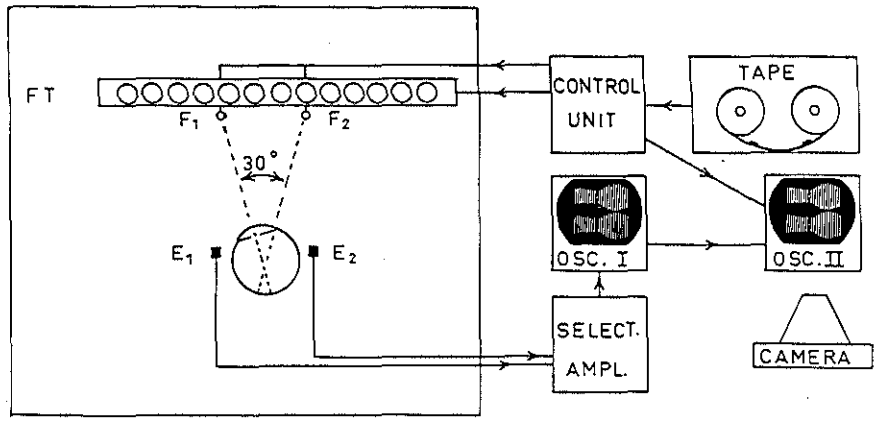


Fig. 1. Block-diagram of semi-automatic recording procedure.
F_1, F_2: fixation lights subtending 30°.
E_1, E_2: skin electrodes attached to each side of the eye.
FT: 13 fluorescent light tubes, providing background illumination during light adaptation.
OSC I: monitor CRO.
OSC II: recording CRO provided with camera (after Henkes et al. 1968).

from the trough of the a-wave, had to be 80 μV to be normal. The a-wave, measured from the base line, is normally 30 μV.

The lower limit of normal for the F-ERG had to be 3 μV for the 5° test field.

The OP and VER could not be measured quantitatively; they were merely rated normal, subnormal or absent.

f. electro-oculography

The electro-oculogram (EOG) was initially recorded as described by Arden et al. (1962), but nearly all patients were examined with the semi-automatic system described by Henkes et al. (1968) (figure 1). A great advantage of this method over the initial procedure is that it takes less of the investigator's time.

At electro-oculography, the ratio between the largest amplitude of the corneo-retinal potential (cornea positive in relation to retina) in the light, and the smallest amplitude of this potential in darkness is measured (light peak/dark trough-ratio: LP/DT-ratio). The LP/DT-ratio of the standing potential is measured because the absolute value of the indirectly measured standing potential is very highly variable, and therefore of little value as a clinical test.

The changes in the standing potential of the eye can be recorded only indirectly, via the patient's eye movements (figure 2), because it is impossible to insert an electrode behind the eye.

The indirectly measured absolute value of the standing potential can vary widely due to anatomical changes in and around the eyeball and due to differences in

electrode position. For example, higher values can be expected in the case of exophthalmos than in a patient with sunken eyes. An absolute measuring of the standing potential was therefore not attempted, although we fully realize that the absolute value of the standing potential and its L/D-ratio can give information on various retinal functions and/or structures.

Two electrodes were placed next to the temporal and nasal canthi of each eye. The patients viewed the light-adapting screen (measuring 140 × 150 cm) from a distance of 130 cm. The two fixation lights were placed 85 cm apart, subtending a (visual) angle of 30°. The screen was an opaque surface transilluminated by 13 bluish-white fluorescent tubes (Philips 65 W/33). The testing included 12 minutes of complete darkness and a final 12-13 minutes of light adaptation during which the patient was continuously exposed to a luminance of 2000 lux eq.

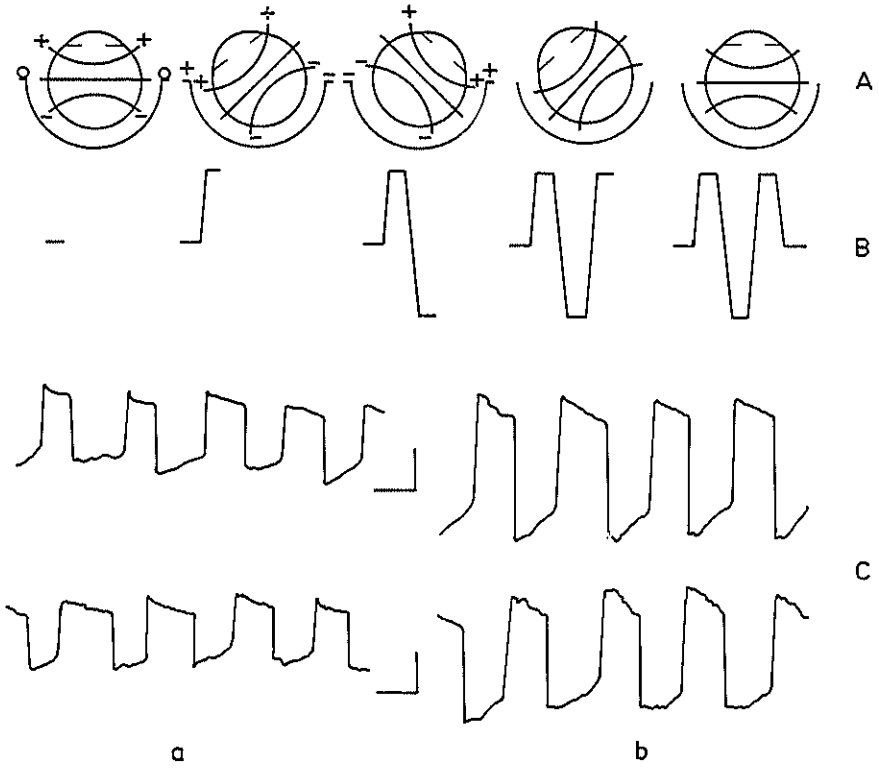


Fig. 2 (A) Principle of recording of standing potential based upon alterations in the electric field resulting from eye movements.
(B) Resulting changes in potential between the electrodes.
(C) The upper trace of the original graphs shows movements of the right eye; the lower one of the left eye. The amplitude of the initial vertical excursions is a measure of the height of the standing potential.
(*a*) after 12 minutes dark adaptation; (*b*) 8 minutes after re-illuminating the retina.
Calibration bars: 500 microvolts, 500 msec. (after Arden and Kelsey, 1962).

A magnetic tape was used to instruct the subject and operate the two fixation lights, only one of which was lit at a time. They alternated at a rate of 0.5/sec, and the eyes moved once per second from one fixation light to the other. This alternation was carried out for 15 seconds every minute. The eye movements caused a potential change between the electrodes, and this EOG signal was amplified and fed to a frequency-selective filter (quality filter Q 2), tuned to 0.5 cps.

As a result, only the fundamental frequency components of the eye movements passed through, and irregularities were greatly reduced. Since transients were preponderant during the first seconds of the period during which the fixation lights were followed, only the final 5 seconds of each 15-second fixation period were used. Due to the slow time base, only one vertical bar became visible on the screen and was photographed during this period. The bars recorded every minute for 25 minutes, formed composite figures like the ones shown in figure 3.

Normal values. The mean value of the L/D-ratio of the EOG was found to be 2.15,

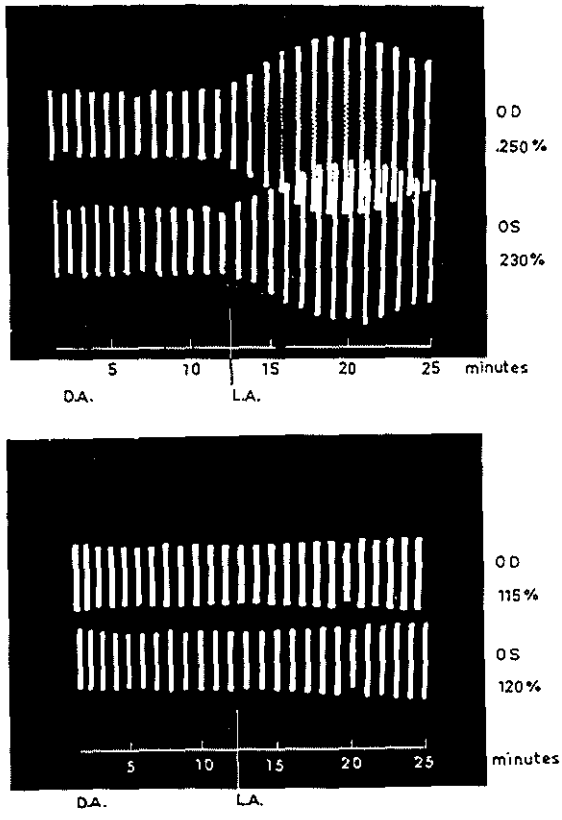


Fig. 3. EOG bar figure in a normal individual (top) and in a patient with vitelliform dystrophy (bottom).

with a standard deviation of 0.25 (Van Lith and Balik, to be published). An L/D-ratio < 1.65 (2.15 minus twice the standard deviation) was interpreted as probably abnormal; a ratio of 1.40 (2.15 minus thrice the standard deviation) was accepted as definitely abnormal. Values between 1.65 and 1.90 were regarded as borderline cases.

g. photography

Colour photography was carried out with a modified Zeiss fundus camera. We used a Nikon motor transport camera, which was loaded with Kodachrome-II film.

Black-and-white photography was likewise carried out with a modified Zeiss camera. The films used were Agfa Copex Orthochromatic and Agfa Copex Panchromatic graphic films. The orthochromatic film has its maximum spectral sensitivity at a wavelength of 580 mμ, while the panchromatic film has it at 595 mμ (fig. 4). Both films were processed in normal developer (Promicrol).

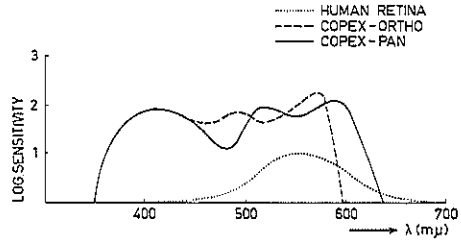


Fig. 4. Spectral sensitivity curves of human retina, Copex orthochromatic and Copex panchromatic graphic films.

Generally, orthochromatic films give better details of the disc and retinal vessels. But in the presence of pigmentations, especially those localized in deeper retinal layers, better results are obtained with panchromatic films (Craandijk and Aan de Kerk 1969).

h. fluorescein angiography

The technique of fluorescein angiography which Novotny and Alvis developed in 1961, is essentially the same as that described by Oosterhuis and Lammens in 1965. It calls for rapid injection (in 1-2 seconds) of 5 ml of a 10% fluorescein solution, whereupon serial photographs are made every 2 seconds with a modified Zeiss fundus camera. A separate input (Van Gogh, 840 Joules) and a separate time plotter were used.

We used a Schott GG 14 3.0 filter and a Baird Atomic B 4 interference filter. The Nikon motor transport camera was loaded with Ilford FP 3 film (Craandijk 1968).

i. general physical examination and laboratory study

This was carried out by Drs. A. J. Houtsmuller and G. van der Kamp, internists. As routine screening of patients with affections of the posterior pole, the following examinations are generally made at the Oogziekenhuis, Rotterdam.

General physical examination; electrocardiogram; X-rays of the chest, paranasal sinuses and teeth; complete haemogram; Hb determination and ESR; complete urinanalysis; protein pattern (agar method); 50 g. glucose tolerance test and lipid pattern (comprising cholesterol and cholesterol-esters, total lipid, triglycerides, phospholipids, α- and β-lipoproteins; agarose-gel-electrophoresis); renal function tests (creatinine, urea, concentration test); liver function tests (alkaline phosphatase, TTT, prothrombin time); capillary resistance (Houtsmuller 1963); serology (AST, Rose, Mantoux, Wassermann and Sabin-Feldmann tests and complement fixation test for toxoplasmosis; in a few cases a histoplasmin skin test).

Neurological examination was carried out in a few cases (EEG, cranial X-rays, etc.) but always failed to disclose any neurological changes.

4. NOMENCLATURE

Before we broach the subject proper, it may be useful to elucidate a number of terms and concepts. Some of the terms used in this study might otherwise give rise to confusion.

a. fovea

As we mentioned in the introduction, the hereditary dystrophies of the central retina and choroid are frequently referred to in general as macular degenerations. This designation is open to some criticism.

In ophthalmological usage, the word macula refers to the macula lutea – an area in the retina which is characterized by the presence of a yellow pigment in the inner (cerebral) retinal layer (inner nuclear layer, inner plexiform layer, ganglion cell layer and nerve fibre layer).

This yellow pigment was discovered by Buzzi (1782), later corroborated by Soemmerring (1795). In live subjects it is clearly visible only in red-free light; and it is visible postmortem. It is of a lemon-yellow colour, most pronounced in highly pigmented eyes and absent from albinotic eyes. The yellow pigment is totally absent at the site of the foveola, where the inner retinal layer is absent.

Little is known as yet of the exact nature of this pigment. Wald (1945) suggested that it is xanthophyll: a carotenoid.

There is no agreement as to the distribution of the macular yellow, and the size of the area called macula is highly variable, dependent as it is on interindividual differences and the views held by different authors.

Many authors (Rochon Duvigneaud 1903, 1907; Fuchs 1926; Eisler 1930; Redslob 1939; Thiel 1948; Baillart 1961; Waardenburg 1963; and others) maintain that the

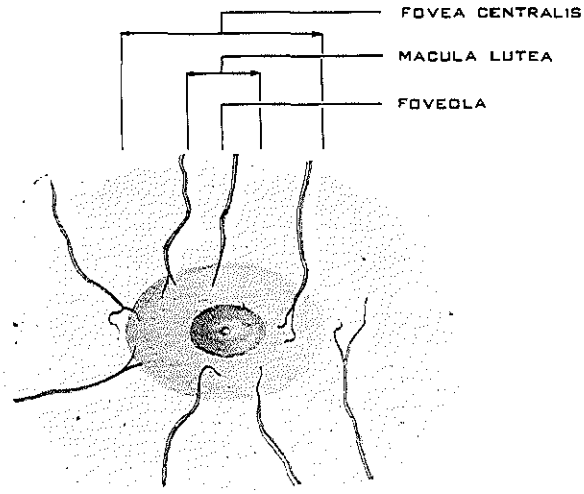


Fig. 5. The fovea, macula and foveola seen in red-free light (after Vogt and Waardenburg).

macula lutea encompasses the central one-third of the central fovea, where the yellow pigmentation is most intensive and most pronounced in red-free light (Vogt 1921) (figure 5,6). Eisler (1930) referred to the central area which comprises the fovea and of which the macula in its turn forms a part. Baillart (1961) wrote: "La zone déprimée au centre de la fovea est la macula".

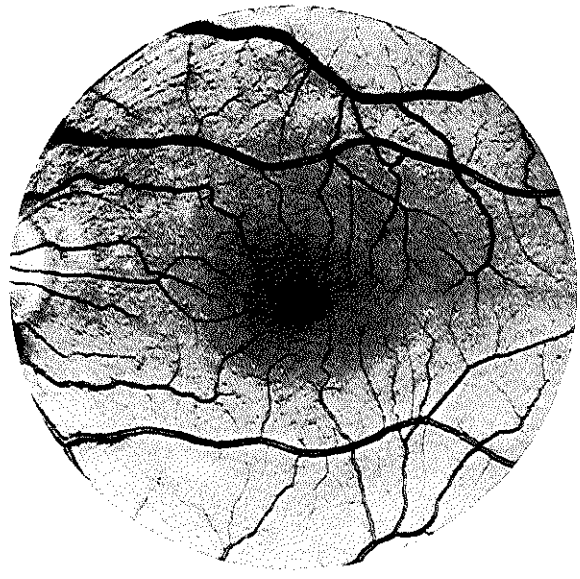


Fig. 6. Photography of a normal fovea. Note the dark region, corresponding with the macula in fig. 5.

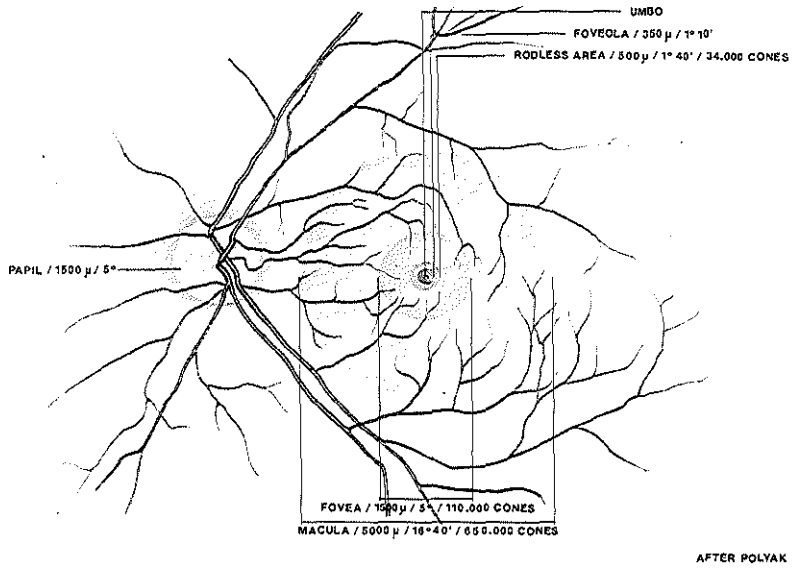


Fig. 7. The central retinal area, after Polyak (1941).

However, Polyak (1941) reported that the yellow pigment extends far beyond the central fovea (although in diminishing intensity) and is vaguely perceptible even at the temporal margin of the disc. He reported: "The diameter of the yellow pigmented macula exceeds that of the foveal depression, being in fact three or more times the diameter of the latter". He held that the transverse diameter of the intensively pigmented central part is 3 mm, the surrounding zone of faded yellow measuring 1 mm so that the diameter of the entire macular area is 5 mm (fig. 7).

This means that the macula should encompass about 16° of the centre of the visual field, and possess some 650,000 of the 7 million retinal cones. We agree with Polyak's statement (1941) that: "The only correct principle in determining the size of the yellow spot is to measure the extent of the yellow pigmented area seen in the fresh retina, when freed from the dark pigment, irrespective of structure". This makes it clear that an adequate demarcation of the macula can never be achieved on clinical grounds. And this is why we prefer the term fovea to the word macula.

The term fovea is much more precise and defines a well-demarcated region which, unlike the macula, is clearly visible under normal conditions. The central fovea is the fairly dark, oval-shaped retinal area localized some 3.5 papilla diameters (pd) temporal to the disc, and 0.8 mm below the horizontal meridian, and the outline of which is visible at ophthalmoscopy as a bright oval-shaped reflex: the foveal margin reflex (figures 5 and 8). The foveal depression is caused by virtual absence of the inner retinal layer at this site, although this is in part compensated by the increased

local thickness of the photoreceptor layer. The slope of the fovea is called the clivus, its angle usually being some 20°. The depth of the fovea is 240 μ, so that at the level of the foveola the thickness of the retina diminishes to 130 μ.

The central fovea measures 2 mm in horizontal and 1.5 mm in vertical diameter, that is about 1 disc diameter. According to Polyak (1941), the foveal diameter is about 1.5 mm (1500 μ), which corresponds to about 5° in the visual field; and the fovea encompasses some 110,000 cones.

Within the fovea we find a rod-less area which measures 0.5 mm (500 μ) in diameter and comprises some 34,000 cones but none of the total of 130 million rods

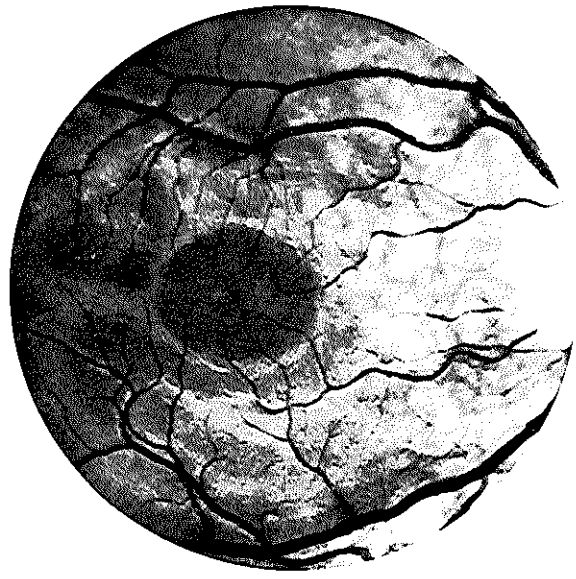


Fig. 8. Normal foveal reflex, indicating the borders of the fovea centralis.

present in the retina (Polyak 1941). This area is about as large as the avascular central retinal area, and corresponds to 1°40′ of the visual field.

The foveola is the deepest point of the fovea and can be observed as a small dark-red spot in which a sickle-shaped or punctiform reflex is visible. The diameter of the foveola is 350 μ; it encompasses about 1°10′ of the visual field and subtends a visual angle of 20′. The deepest point of the foveola is called umbo.

From this multitude of terms, we choose the terms fovea and foveola for clinical usage, rather than macula; for the human fovea and foveola are readily visible under nearly all conditions, and represent a well-defined region. However, no too serious objections can be made to the clinical use of the term macula, in part also because many macular processes, like the macular yellow proper, encompass an ill-defined retinal area.

In imitation of Müller (1852), Chievitz (1887) and Eisler (1930) we shall frequently refer to the central area or central retina. This area is characterized by the presence of more than one row of ganglion cells. Polyak (1941) subdivided this central area into three regions: 1) central fovea; 2) parafoveal zone (ganglion cells in 5-8 rows); 3) perifoveal zone (ganglion cells in 1-4 rows). The parafoveal zone is 2.1 mm wide and surrounds the fovea; in its turn it is surrounded by the perifoveal zone of 1.5 mm width (Duke-Elder 1961).

Yamada (1969) published a beautiful photograph (fig. 9) of a section through the centre of the fovea. He did not find a structural organization comparable to the given diameter of the so called foveola (350 μ; Polyak 1941). He found a central area of the fovea, about 200 μ in diameter, which lacked in cone pedicles as well as in the inner nuclear layer, the inner plexiform layer, the ganglion cell layer and the nerve fibre layer. This area is largely composed of foveal cone cells and Müller cells and may correspond to the so called "Bouquet des cônes centraux" of Rochon Duvigneaud (1907). Probably this area corresponds to the foveola, which may have a smaller diameter than is usually accepted.

We shall frequently use the term central retina besides fovea, because so far as we know at this time there is no dystrophy that is ultimately confined to the central fovea (in initial stages, however, some dystrophies can be confined to the foveal region).

It has been established, however, that ophthalmoscopically and psychophysically purely central dystrophies are often already associated with diffuse retinal electrophysiological changes; solely on the basis of ophthalmoscopic findings, therefore, it cannot always be established with certainty that a purely foveal dystrophy is in fact present.

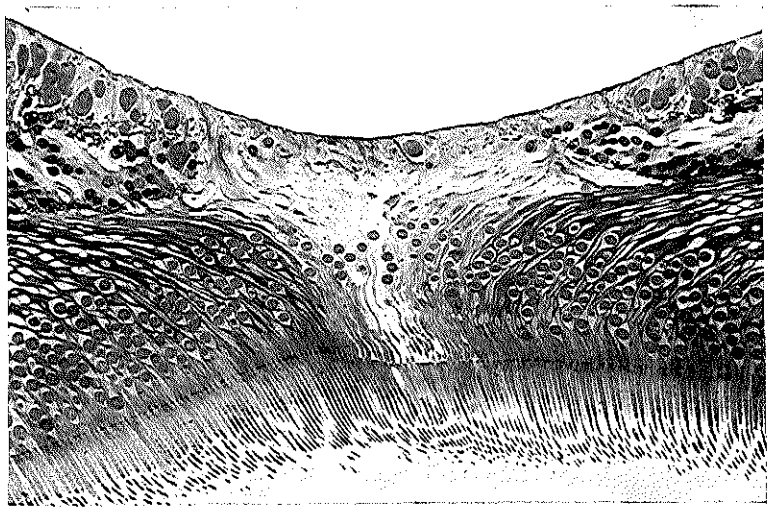
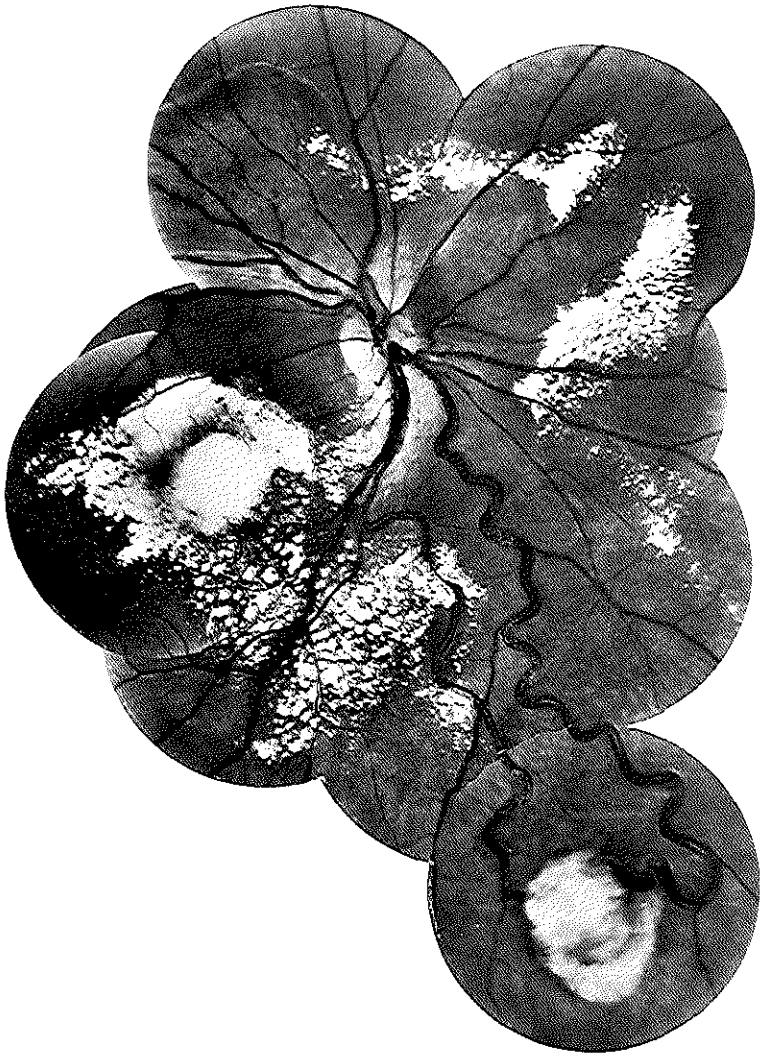


Fig. 9. Section through centre of the fovea (after Yamada).



Angiomatosis retinae (von Hippel-Lindau disease) in a 16-year-old girl. There are extensive degenerative changes in the posterior pole. The phacomatoses, which are dominantly inherited, rather often present alterations in the posterior pole of the eye.*

* Addendum to the affections not included in this study, in which foveal dystrophies may occur (see page 17).

b. dystrophy

Another term which requires some elucidation is dystrophy. We prefer the word dystrophy to degeneration. Degeneration is a pathological anatomical concept covering certain conditions or processes which involve cell death. The underlying mechanisms are very diverse, and no hereditary origin need be involved.

Originally, the term abiotrophy was used with reference to these hereditary conditions. Gowers (1902) introduced the term for the premature disintegration of highly differentiated tissues as a result of defective vitality. Treacher Collins (1919) was the first to use the term abiotrophy in connection with hereditary retinal anomalies. Abiotrophy is regarded as a general concept in pathology, whereas dystrophy is rather its localized manifestation (Sorsby 1934).

Subsequently the concept of heredo-degeneration, introduced in neurology by Jendrassik (1911), was used in ophthalmology with reference to posterior pole dystrophies (Behr 1920). Jendrassik originally used the term to indicate the close interrelations between all degenerative and familial anomalies of the nervous system. He wrote: "Die hereditären Krankheiten bieten in ihren höchst mannigfaltigen Erscheinungen solche Uebergänge zwischen den einzelnen Formen dar, dasz man kaum oder gar nicht von beständigen Symptomgruppen sprechen kann. Während man in der internen Pathologie die ätiologisch identischen Leiden als einheitlichen Prozess auffasst, hat man in der Neurologie den einzelnen Symptomen viel zu grosse Wichtigkeit beigelegt und hierdurch sind uns oft imponierend benannte Krankheiten künstlich geschaffen worden".

Behr (1920) held the same view of posterior pole dystrophies, and it is therefore not surprising that he adopted the term heredo-degeneration. In its original significance, this concept is decidedly misplaced in the present study, in which it is demonstrated that the posterior pole dystrophies include distinctly different entities, determined by several independent pathological genes.

With Waardenburg (1963), Blodi (1966), Braley (1966), Falls (1966), Duke-Elder (1967) and others, therefore, we prefer the designation dystrophy for those hereditary affections that lead to early and premature cell changes and cell death and of which no clearly demonstrable cause is known.

These affections become manifest at a certain age as a result of a genetically determined disorder in the function of the enzymes and the metabolism.

According to Waardenburg (1963), dystrophies can occur on the basis of a dysplastic primordial stage, after which seemingly normal cells or tissues gradually deteriorate towards an early death.

c. carrier

The carrier concept will be regularly referred to in this study. Carriers are individuals capable of transmitting hereditary diseases of which they themselves show no or hardly any symptoms. Individuals who show the changes of the disease in a more pronounced form are known as patients. Evidently, a strict distinction between

carrier and patient may be difficult in certain cases. In many cases, the carier state is not demonstrable: in such cases the pathological gene is recessive in relation to its normal allele. However, there are eye diseases caused by autosomal "recessive" genes, in which in occasional heterozygotes the pathological gene is not totally recessive in relation to its allele, so that the heterozygotic state is expressed in one way or another (Falls 1968). Consequently the phenotype resulting from this heterozygote is affected. This means that the terms recessive and dominant are very relative terms. As soon as a recessive gene is only slightly dominant over its allele, as happens occasionally, it might be described as a dominant gene with incomplete penetrance.

Carriers have been demonstrated not only in sex-linked hereditary diseases but also in affections involving recessive and dominant autosomal transmission. Well-known examples of sex-linked eye disease of which carriers are demonstrable, are choroideremia (progressive tapetochoroidal dystrophy), sex-linked retinopathia pigmentosa and ocular albinism.

The carriers of autosomal recessive affections (i.e. the heterozygotes) can be recognized, for example, on the basis of diminished enzyme activities. Examples include galactosaemia and Wilson's disease.

In autosomal dominant syndromes such as Waardenburg's syndrome and Marfan's syndrome, the expressivity of the pathological gene in a given individual can be so low that the term patient hardly applies from a clinical point of view. In these cases the designation carrier is often preferred (Falls 1968). In this context it is important to note that one of several pleiotropic characteristics can be dominant (and thus have a distinct expression), while another is recessive or intermediary. This too is found in Waardenburg's syndrome, among other conditions.

In this study the carrier concept will be used in the above indicated manner. That is to say: as carrier we regard every individual who carries a pathological gene on a given locus of a given chromosome, and who shows no or hardly any symptoms of disease.

5. AFFECTIONS NOT INCLUDED IN THIS STUDY, IN WHICH FOVEAL DYSTROPHIES MAY OCCUR

In an attempt to present a useful survey of the dystrophies not included in this study, we give the following brief review. It concerns mainly those dystrophies in which the posterior pole changes play no dominant role in the clinical picture but are merely part of a more extensive eye disease or general affection. It should be borne in mind that it is difficult to make a strict distinction between what does and what does not belong to the subject matter of this study.

a. the lipidoses

Foveal changes are quite common in lipidoses. Duke-Elder (1967) divided the lipidoses into three categories:

1. systematic lipidoses as Gaucher's disease and Fabry's disease;
2. cerebroretinal lipidoses (amaurotic familial idiocy);
3. systemic as well as cerebroretinal lipidoses (Niemann-Pick disease and Farber's disease).

In addition he mentioned complex syndromes such as the Refsum syndrome and the-Bassen-Kornzweig syndrome.

Foveal changes can occur both in Gaucher's disease (Gaucher 1882) and in Fabry's disease (Fabry 1898: angiokeratoma corporis diffusum or hereditary dystopic lipidosis). In the former disease there is annular perimacular degeneration and a cherry-red spot at the site of the macula according to some reports. Perimacular oedema has occasionally been observed in the latter disease.

Duke-Elder (1967) subdivided the cerebroretinal lipidoses into:

a. congenital forms (Norman and Wood 1941);
b. infantile forms (Tay-Sachs 1881, 1887);
c. late infantile forms (Jansky-Bielschowsky 1910, 1914);
d. juvenile forms (Batten-Mayou-Spielmeyer-Vogt-Stock-Oatman 1903, 1904, 1905, 1908, 1911);
e. adult forms (Kufs 1925).

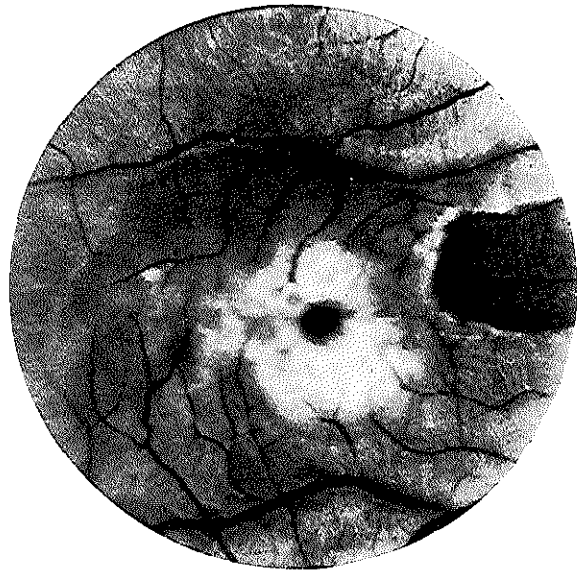


Fig. 10. The fovea in occlusion of the central retinal artery. Note the presence of an unoccluded cilioretinal artery.

The conditions under the last heading are also known as cerebromacular degenerations. This is a group of enzymatic disorders in which the ganglion cells of the retina are affected. There are many ganglion cells around the fovea, whereas the foveola itself contains no ganglion cells. In the neurolipidoses, the latter fact results

Fig. 11a. The posterior pole of an 18-year-old individual suffering from Bassen-Kornzweig syndrome.

Fig. 11b. Fluorescence photograph of the fundus of fig. 11a, indicating extensive atrophy of the retinal pigment epithelium and atrophy of some sharply defined circular areas in the choriocapillaris and choroid (after Craandijk).

in the wellknown cherry-red spot surrounded by a greyish-white retina – a picture encountered also in the case of recent occlusion of the central retinal artery (figure 10). A cherry-red spot at the site of the foveola can be found both in Niemann-Pick's disease (essential lipid histiocytosis: Niemann 1914; Pick 1922) and in Farber's disease (disseminated lipogranulomatosis: Farber et al. 1957), as reported by Cogan et al. (1966).

In the Refsum syndrome (heredopathia atactica polyneuritiformis: Refsum 1945, 1946) it is chiefly peripheral retinal changes that are found, but perifoveal pigment displacements have also been reported in these cases. Likewise, the Bassen-Kornzweig syndrome (Bassen and Kornzweig 1950; Craandijk and Houtsmuller 1970) can involve a diffuse tapetoretinal dystrophy which does not leave the posterior pole unaffected (figure 11). In the Refsum as well as in the Bassen-Kornzweig syndrome, extensive cerebellar changes are found besides the retinal abnormalities.

In addition to these two syndromes, other hereditary "cerebello-retinal degenerations" have been described which cannot be readily classified. In many of these cases, foveal dystrophy has been found as part of the disease process (Froment et al. 1937, 1938; Sjögren 1943; Louis Bar and Pirot 1945; Walsh 1947, 1957; Stadlin and Van Bogaert 1949; Havener 1951; Arnould et al. 1955; Van Bogaert 1957; Ledic and Van Bogaert 1960; Foster and Ingram 1962; Bergstedt et al. 1962; Bessière et al. 1962; Carpenter and Schumacher 1966; Weiner et al. 1967; Halsey et al. 1967; De Marco 1968).

The available data on these foveal dystrophies are still insufficient to establish

Fig. 12. The posterior pole of an 8-year-old girl with Spielmeyer-Vogt disease.

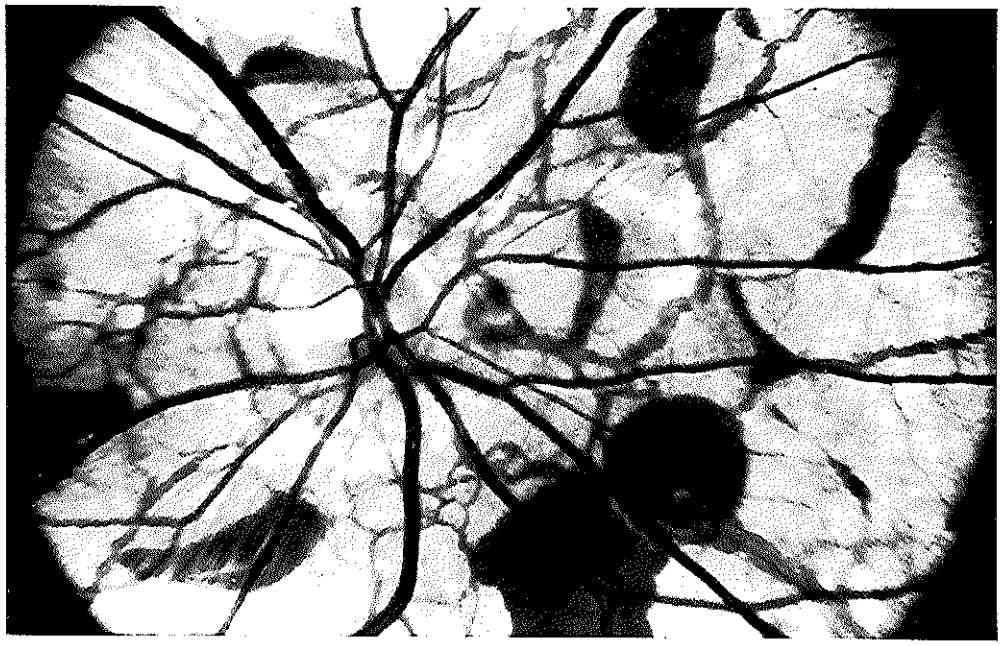


Fig. 13*a-b.* Bilateral and almost symmetrical angioid streaks with profuse haemorrhages.

whether they resemble one of the hereditary foveal dystrophies which usually occur without neurological disorders, e.g. Stargardt's disease. Ledic and Van Bogaert (1960) and Bessière et al. (1962) did use the designation Stargardt's disease with reference to the families with spinocerebellofoveal dystrophies they described. However, these disorders are not necessarily lipidoses.

In the near future, the abovementioned lipidoses will undoubtedly be classified on the basis of the absent or deficient enzyme.

In general, however, the lipidoses can be readily distinguished from hereditary posterior pole dystrophies not associated with other disturbances. Transitions between these two totally different groups of diseases have not been observed. It may be mentioned, however, that Alkio (1923) saw a 5-year-old boy with presumably Tay-Sachs disease or Spielmeyer-Vogt disease who had three paternal uncles and one paternal aunt with Stargardt's disaese.

Differential diagnosis can be difficult only in the case of incipient Spielmeyer-Vogt disease (figure 12), when neurological symptoms are still absent. In that case it is difficult to differentiate this disease from an early stage of Stargardt's disease because Spielmeyer-Vogt disease involves not only an affection of the ganglion cells but also a peripheral and central tapetoretinal dystrophy; and the latter occurs in Stargardt's disease also.

b. angioid streaks (figure 13)

These streaks are found in several different conditions, e.g. pseudoxanthoma elasticum (Grönblad-Strandberg syndrome), fibrodysplasia hyperelastica (Ehlers-Danlos syndrome), osteitis deformans (Paget's disease) and sickle-cell anaemia; and sometimes they are observed also in patients with senile elastosis of the skin and in hypertensive cardiovascular disorders. A foveal affection is often found after some time. Yellowish, round disciform structures are seen in the posterior pole in such cases, often amidst extensive pigment changes. The pathology underlying the angioid streaks is localized in the lamina elastica which is the mesodermal component of Bruch's membrane (Böck 1938; Hagedoorn 1939; Klien 1947; Winkelman 1948). The mode of transmission depends on the primary affection.

c. dystrophia myotonica

In dystrophia myotonica or Steinert's disease (Steinert 1909), there may be signs indicative of a foveal dystrophy (Verrey 1947; Bégaux, DeCock and Van Bogaert 1955; Magistretti 1955; Bégaux and DeCock 1957; Junge 1966; Burian and Burns 1966). However, this foveal affection hardly influences vision, and no specific morphological changes are found. The mode of transmission is autosomal dominant.

d. Sjögren-Larsson syndrome

This syndrome consists of congenital ichthyosis, spastic diplegia and mental retardation. In some 25% of patients there may be a foveal affection of a very variable

type. The majority of authors assume that there is a primary disturbance in the pigment epithelium, resulting in atrophy of the pigment layer at the site of the fovea (Sjögren 1956; Sjögren and Larsson 1957; Gilbert et al. 1968). The mode of transmission is autosomal recessive.

e. myopia gravior

This condition is known sometimes to be associated with extensive chorioretinal changes in the posterior pole. These changes are frequently preceded or accompanied by the occurrence of a dark spot at the site of the fovea (Fuchs' spot) (figure 14). The mode of transmission is autosomal recessive as well as autosomal dominant.

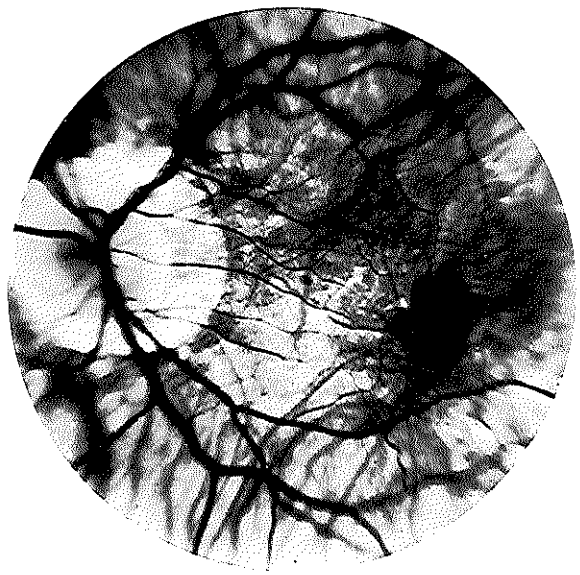


Fig. 14. Foveal degeneration (Fuchs' spot) in degenerative myopia.

f. vitreotapetoretinal degeneration of Goldmann-Favre

This condition involves peripheral and central retinoschisis, combined with tapetoretinal degeneration and vitreous degeneration (Favre 1958, 1960, 1961; Ricci 1961). The foveal retinoschisis which can occur, can cause difficulty in differential diagnosis from sex-linked juvenile retinoschisis, which will be discussed in the next chapter. The mode of transmission is autosomal recessive.

g. senile foveal processes

This is undoubtedly a condition in which posterior pole dystrophy is often the only demonstrable abnormality. Senile foveal processes have not been included in this

study because family studies often pose considerable difficulties in the case of elderly patients. Hereditary factors have been demonstrated in these conditions (Behr 1921, 1931; Vogt 1935; Waardenburg 1936, 1950, 1958; Sandoz 1939; Fleischer 1944; François and DeWeer 1952; Streiff and Babel 1963; Klien 1964, François, 1969). In some cases dystrophies which have started much earlier can become manifest later in life. Before a foveal dystrophy can be called senile, therefore, it must be ascertained that it did occur later in life instead of being latent for some considerable time.

The question remains whether the designation senile foveal dystrophy is at all tenable, and in particular whether there are indeed hereditary foveal dystrophies which specifically occur as senile manifestation. This question arises because, for hereditary foveal dystrophies in general, the classification on the basis of the age of manifestation proves to be unsatisfactory.

After a detailed study, Klien (1964) formulated the following conclusions, which we can accept without reservation. "Senile macular degeneration is neither a clinical nor a histopathologic, nor a genetic entity. It comprises:

1. The true heredodegenerative diseases:
   a. Some primarily and selectively affecting the percipient retinal elements.
   b. Some the probably genetic unit of choriocapillaris, pigment epithelium and neuroepithelium (central areolar choroidal atrophy).
   c. And some representing the end stages of the vitelliform degeneration, the initial site of which has so far remained in the realm of speculation.
2. Degeneration of the percipient retinal elements secondary to:
   a. Diffuse and pronounced thickening and degeneration of the intercapillary connective tissue, representing an intensification of the physiologic aging process at a critical place, such as the regulating barrier between choriocapillaris and retina, resulting in altered diffusion of nutritive substances in this region and thus leading to the only true senile form of macular degeneration.
   b. Damage to Bruch's membrane (disciform degeneration, with or without associated systemic disease). Disturbances in the vascular supply of the choroid, more specifically the choriocapillaris, which may be a rare incidental segmental degeneration, and not invariably a macular involvement.

In none of the secondary degenerations, excepting perhaps those from damage to the vascular supply, can genetic influences in a wider sense be ruled out completely."

h. foveal dystrophy associated with deafmutism

In 1960, Amalric described a syndrome characterized by foveal dystrophy and congenital deafmutism (Amalric 1960; Albouy 1960; Amalric and Bessou 1962, 1964; Amalric et al. 1963). He found this combination in 15 out of 200 deafmutes. However, the hereditary nature of this syndrome has not been demonstrated with certainty. Many investigators believe that it may represent the sequelae of rubeola or some other virus infection during the mother's pregnancy (François et al. 1967).

Fig. 15. The posterior pole of a 10-year-old boy with congenital rubeolar retinopathy.

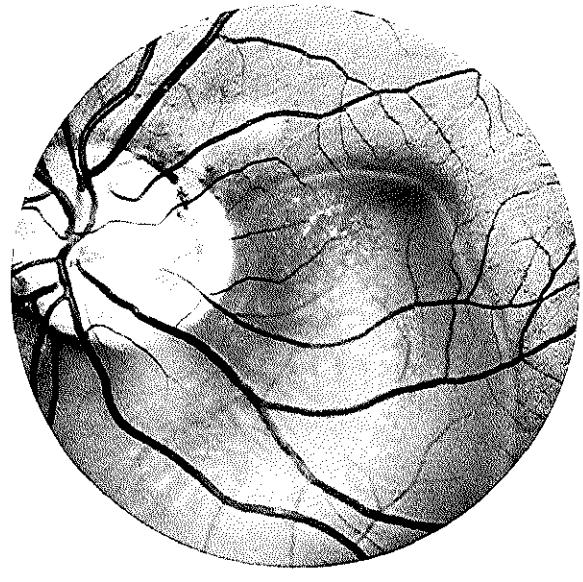


Fig. 16. Fundus with crater-like hole in the optic disc and central serous chorioretinopathy (after Oosterhuis).

The small loss of vision and the ophthalmoscopic features of the foveae remind us very vividly of a rubeolar retinopathy (figure 15).

i. crater-like holes in the optic disc (fig. 16)

This condition often involves a foveal affection reminiscent of central serous choroidopathy (Kranenburg 1959). The craters can occasionally show a dominant pattern of transmission, as a result of which an apparently dominant foveal dystrophy may be observed (Verduin 1965; Babel and Farpour 1967).

j. foveal dystrophy as part of a more diffuse retinal or choroidal dystrophy

Foveal changes can be encountered as part of diffuse retinal dystrophies such as the tapetoretinal and tapetochoroidal dystrophies (retinopathia pigmentosa, choroideremia, general choroidal atrophy etc.). They can be found also as part of a diffuse tapetoretinal degeneration in the Laurence-Moon-Biedl-Bardet syndrome. (fig. 17) Very often these foveal changes do not occur until in a late stage.

Also, foveal changes are sometimes found in diffuse disturbances of the retinal primordium, e.g. Leber's congenital amaurosis, achromatopsia and monochromatism (Falls 1966).

k. foveal hypoplasia

This is no dystrophy but might easily be confused with it. This hypoplasia is characterized by total or nearly total absence of the macular yellow, absence or irregularity of the foveal and perifoveal reflexes, and an irregular distribution of perifoveal capillary endings (Waardenburg 1948); moreover, the number of perifoveal capillaries is smaller than usual. This foveal hypoplasia is found in many hereditary anomalies such as aniridia, achromatopsia, sex-linked hemeralopia, ocular and general complete and incomplete albinism, and microphthalmos.

Waardenburg (1963) described an X-chromosomal foveal hypoplasia in three individuals who later developed features of foveal dystrophy. In addition, Waardenburg (1963) described – like Koyanagi (quoted by Waardenburg) – a probably recessive "simple foveal hypoplasia".

l. foveal dysplasia

This condition is also known as macular coloboma; literally, the latter term is incorrect because the abnormality cannot have arisen from incomplete closure of the optic cleft. This is why the designation foveal dysplasia or macular pseudo-coloboma is used. Hereditary foveal dysplasias have been described by Clausen (1921, 1928), Schott (1921), Davenport (1927), Evans (1937) and Waardenburg (1938).

Sorsby (1935) and Phillips and Griffiths (1969) described families in which foveal

dysplasia occurred in combination with abnormalities of the extremities. The mode of transmission is autosomal, dominant as well as recessive.

A very unusual form of foveal dysplasia was recently described as "progressive bifocal chorioretinal abiotrophy" (Douglas et al. 1968). In these cases there is a

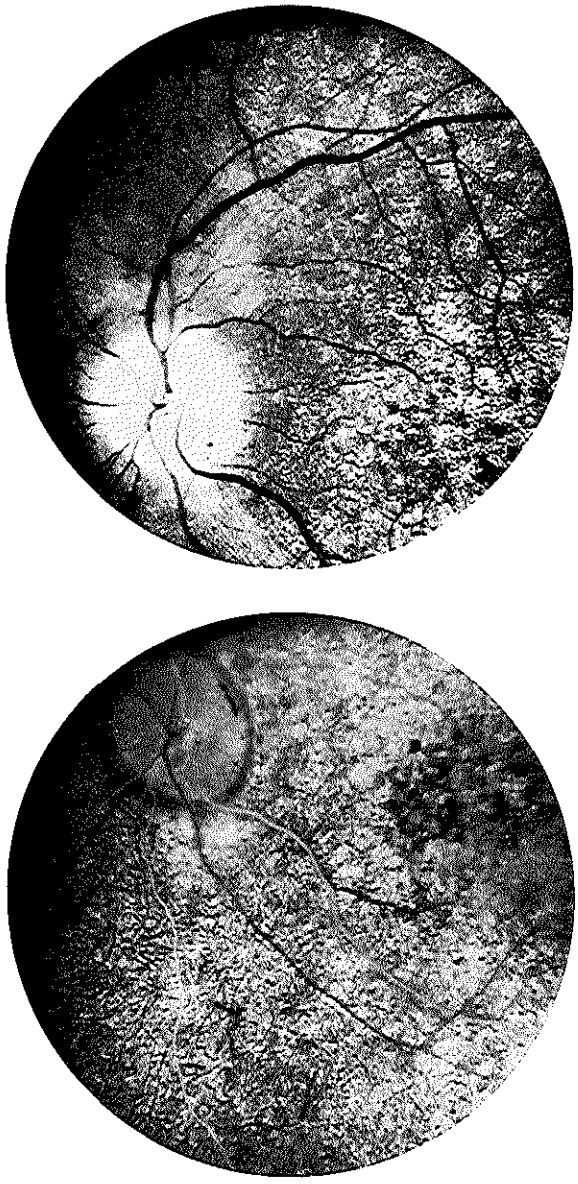


Fig. 17ab. Conventional photograph and fluorescein angiogram of a patient with the Laurence-Moon-Biedl-Bardet syndrome. Note the foveal dystrophy (after Amalric).

connatal white atrophic focus at the site of the fovea. In the early years of life, an atrophic focus develops at a site nasal to the disc, and finally a progressive chorioretinal dystrophy occurs without total loss of vision. The mode of transmission is dominant.

6. GENERAL HISTORICAL REVIEW

During the 19th century the hereditary dystrophies of the posterior pole of the eye were still regarded generally as results of inflammatory processes. It is therefore not surprising that the condition was frequently described as choroiditis. Later, in the early years of this century, there were still authors who regarded these familial abnormalities of the posterior pole as results of inflammations (Morax; Tillé et al. 1929, 1936). Very often, therapy against syphilis or tuberculosis was instituted in these cases. Even today, these patients are still regularly being submitted to comprehensive medical and neurological examinations to verify a suspicion of an infectious disease, or of toxoplasmosis or histoplasmosis; and they are being treated with antibiotics and corticosteroids with no hope of success.

Hutchinson and Tay (1875) were the first to describe a familial abnormality of the posterior pole. Their patients were three sisters (aged 57, 48 and 40) suffering from a symmetrical affection characterized by numerous small round white spots marking an oval-shaped area around the fovea and disc. Today, we recognize this picture with certainty as dominant drusen of Bruch's membrane (hyaline dystrophies).

In 1885, Lang mentioned a 28-year-old brother and his sister aged 30, with greatly diminished vision and in the foveal region "considerable disturbance of the retinal pigment epithelium with increased pigmentation in one or two places"; he called this condition "central choroiditis". In the posterior pole he also found "numerous small round or oval yellowish-white patches scattered in every direction".

These features are most reminiscent of Stargardt's disease, which can also involve markedly diminished vision and perifoveal yellowish-white spots. The fact that vision in the parents was undisturbed supports this opinion. However, a fundus flavimaculatus with foveal dystrophy cannot be ruled out with certainty.

Another publication on this subject was devoted by Liebrecht (1895) to two sisters and two brothers in the same sibship, in whom he found numerous white spots in the posterior pole. The onset of this affection had been in the foveal region, and this is one reason why we doubt the correctness of his diagnosis: retinitis punctata albescens (especially since visual fields and dark adaptation were normal). In true retinitis punctata albescens, the posterior pole is usually unaffected, and dark adaptation is decidedly disturbed. This may be an example of dominant drusen of Bruch's membrane, although the patients' poor vision is more reminiscent of Stargardt's disease or a fundus flavimaculatus with foveal dystrophy.

R. D. Batten (1897) described two brothers aged 21 and 14, with a symmetrical affection of the posterior pole which in both had first occurred at age 14. Vision was 1/10 in both boys, but the fundal changes were much more pronounced in the elder

brother. These two cases are without doubt instances of the disease which was later to receive Stargardt's name. The parents were syphilitic but had no visual disorders.

Haas (1898) observed two brothers aged 21 and 14, with annular and stellate whitish lines forming a reticular pattern in the foveal region. Vision had been poor from early infancy. The drawing which illustrates the original article leaves no doubt in my mind that these were cases of sex-linked juvenile retinoschisis.

In 1899, Doyne published his famous paper on choroiditis in four sisters. He found a "honeycomb appearance of white spots affecting almost entirely the disc-macular region".

Magers mentioned in his thesis (1899, Jena) one of two brothers, who showed marked symmetrical pigmentations in the foveal region and sclerotic choroidal vessels. On the basis of his description, no definite diagnosis can now be made. An advanced stage of Stargardt's disease is among the possibilities.

It is remarkable that Lang, Magers and Doyne mentioned choroiditis with reference to their cases, whereas Batten and Haas did not. Haas in fact went so far as to state that a hereditary origin was a likelihood in his cases – a notable statement at that time.

The beginning of the 20th century marks an increase in the number of publications on dystrophies of the central retina and choroid. In this general review we can mention only the most important of these.

Dujardin (1904) described two out of five children of consanguineous parents, showing progressive foveal dystrophy of the type later to be described by Stargardt.

Particularly through the publications of Best (1905) and Stargardt (1909, 1913, 1916, 1917, 1925) it became apparent in the early years of this century that familial affections of the posterior pole are of a hereditary nature.

Best described eight cases in two generations, with a foveal dystrophy which he assumed but did not demonstrate to be of a congenital type. He regarded this dystrophy as a stationary affection. Today it is generally accepted that Best's disease is identical to vitelliform dystrophy of the fovea. It has also become clear that this abnormality is certainly not always demonstrable at birth.

Stargardt described a total of 13 cases of progressive posterior pole dystrophy, which became manifest without associated disturbances at the age of 8-12 years. He sharply differentiated this affection from juvenile maculocerebral dystrophies as described by F. E. Batten (1903), Mayou (1904), Spielmeyer (1905), Vogt (1905), Stock (1908) and Oatman (1911). Stargardt's patients certainly all showed the same entity, which today is known as Stargardt's disease.

The mode of transmission was recessive in all these cases. It should be emphasized at this point that the cases described by Stargardt also included patients who showed not only degeneration of the central retina but also unmistakable peripheral retinal changes (family S, 1913).

Leber (1916) corroborated the findings of Doyne, Best and Stargardt by stating clearly that nearly all familial posterior pole affections are of a hereditary nature. He distinguished two major groups of hereditary retinal dystrophies:

1. central tapetoretinal degeneration;
2. peripheral tapetoretinal degeneration.

Stargardt (1917), however, was the first to suggest an adequate and clear classification of the dystrophies of the central retina. He distinguished unequivocally different entities among the central tapetoretinal degenerations, and he advanced a classification which was very valuable at the time and has retained this value, grossly speaking, to this very day:

1. presenile familial macular degeneration (Hutchinson-Tay);
2. honeycomb dystrophy of the macula (Doyne);
3. congenital macular degeneration (Best);
4. progressive familial macular degeneration:
   a. with dementia.
   b. without dementia.

It is group 4b that ultimately received the name Stargardt's disease, although Stargardt was by no means the first to describe this entity.

The only objection that could be raised to this classification today is the fact that the cases of Hutchinson and Tay (1875) and those of Doyne (1899) are not clearly distinguishable. This is why they are now classified under the heading of dominant drusen of Bruch's membrane or hyaline dystrophies (Duke-Elder 1967). Moreover, the group named after Best is more widely known today as vitelliform foveal dystrophy; this condition is by no means always congenital.

Behr's investigation (1920), although very exhaustive, was a step back in a sense because he followed Leber in advocating a monistic view of the central retinal dystrophies. As a disciple of Jendrassik (1911) he maintained: "Die bestehenden Unterschiede und Abweichungen der einzelnen Typen der Krankheiten des makularen Bezirkes sind im Grunde nur Spielarten eines und des gleichen erblichen Krankheitsprozesses". He regarded the many different clinical manifestations as variations of the same entity.

He suggested a classification on the basis of the age of manifestation of the dystrophies:

1. congenital form,
2. infantile form,
3. juvenile form,
4. adolescent form,
5. adult form,
6. presenile form,
7. senile form.

The condition was believed to become manifest during periods of life characterized by more pronounced physiological stress. According to Behr, these periods are: birth, secondary dentition (6-8 years), puberty (12-14 years), the end of skeletal growth and sexual maturity (20 years), full maturity, the climacteric and incipient involution (50 years) and senescence as the herald of approaching physiological death (Behr 1920).

Although it is useful in a way, Behr's classification is too artificial and forced. There is one major objection: the fact that certain entities can manifest themselves at different ages. Stargardt's disease, for example, usually begins between age 8 and age 14, but it is not uncommon to find an age of onset of 30-40 or even later.

The vitelliform foveal dystrophy has been diagnosed in a one-week-old infant (Barkman 1961), while we ourselves observed a true bilateral vitelliform foveal dystrophy in a man aged 44, who had normal foveae only a year before. Also, we saw dominant drusen of Bruch's membrane in two boys aged 12 and 14, although this condition is generally believed not to become manifest until age 30-40. There had been no previous report on this dystrophy prior to age 20.

Sorsby (1940) disagreed with Behr's classification and suggested in his study "The dystrophies of the macula" that there is an unbroken, continuous line of ages at which the dystrophies first manifest themselves. Behr (1920) described families which on the basis of his data can now be classified without hesitation as Stargardt's disease (families G and H) and vitelliform foveal dystrophy (family M). The former families showed a recessive mode of transmission, markedly progressive diminution of vision and the grey atrophic foci in the posterior pole which Stargardt described. The latter family, however, showed dominant transmission and a much less marked diminution of vision, while the fundi showed round yellowish structures at the site of the fovea. Inadvertently, Behr thus supplied strong arguments against his own monistic view.

The adult form of hereditary posterior pole dystrophy is often given Behr's name. We believe that this designation is meaningless because several different hereditary foveal dystrophies can occur at an adult age. – Moreover, Behr regarded the disorders of colour vision and the pallor of the temporal part of the disc that can occur in hereditary foveal dystrophies, as separate entities not resulting from foveal degeneration: "Die Optikusbeteiligung gehört nicht in das Gebiet der makularen Heredodegeneration, sie ist lediglich eine Komplikation, wie die Störungen des Farbensinnes, und demonstriert wiederum die Neigung der erblichen Erkrankungen zu Variationen und Kombinationen mit anderen hereditären Veränderungen".

This view has become quite obsolete now that a study of the literature and personal observations have shown that foveal dystrophy as such gives rise to these disturbances.

Clausen (1921) described a father and three of his children with "finely mottled macular tapetoretinal degeneration". Since in the past they had had good colour vision but now showed unmistakable dyschromatopsia, Clausen concluded that the disorders of colour vision were the result of foveal changes. Rieger (1925) described two brothers from consanguineous parents, who developed disturbances of colour vision parallel to a foveal dystrophy. Again evidence that the dyschromatopoia results from the posterior pole dystrophy. This certainly applies also to the slight pallor of the temporal part of the disc that occurs in Stargardt's foveal dystrophy.

Since Behr, many authors have concerned themselves with the difficult problem of the scientific classification of various dystrophies of the posterior pole. The

criteria most commonly used were: age of onset, ophthalmoscopic features, mode of transmission, and retinal layers primarily and/or mainly affected by the dystrophic process.

Only a few of these classifications will be discussed. Their authors, including some recognized authorities, generally follow Behr's monistic view. Also, his classification on the basis of the age of manifestation of the dystrophy is the one most frequently used.

Bietti (1937) agreed with Behr that no sharp distinction can be made between the many different hereditary abnormalities of the posterior pole.

Sorsby (1940) stated: "The numerous types of central macular dystrophy described by different observers constitute a single clinical entity with more than one mode of inheritance". He believed that only central areolar choroidal atrophy and angioid streaks could be distinguished from the "central retinal dystrophy entity", under which latter heading he arranged the cases described by Doyne, Best and Stargardt. The nosological entity of central retinal dystrophy, he maintained, shows "a great range of ophthalmoscopic appearances, extending from fine mottling of the maculae to exudative reaction, inverse retinitis pigmentosa, intense central pigmentary changes, hole formation, extensive perimacular involvement and the patterned reaction of "Doyne's choroiditis"." He rightly distinguished the lipidoses and congenital macular colobomas from central retinal dystrophy. He rejected the classification based on the age of manifestation: "The age of incidence extends, just as the ophthalmoscopic appearances do, over a continuous unbroken range". With this we agree; but we do not agree that the ophthalmoscopic features of the fovea constitute an unbroken line, and in this respect we differ from Sorsby's opinion in 1940.

In 1950, François supported the views of Behr and Sorsby: "All macular dystrophies fundamentally represent the same heredodegenerative lesion".

Elwyn (1955) was of the same opinion: "There is only one heredodegeneration of the macula, and only the time of life when the degeneration begins differentiates the manifestations of the disease".

In his book "Heredity in Ophthalmology", François (1961) presented the following classification of hereditary processes of the posterior pole of the eye:

I. Hereditary degeneration of the macula (central tapetoretinal degeneration)
   a. Congenital or infantile form (Best)
   b. Stargardt's juvenile form
   c. Behr's adult form
   d. Behr's presenile form
   e. Senile form (Waardenburg)

II. Sorsby's inflammatory hereditary degeneration of the macula.

III. Rare variants of macular degeneration
   a. Hyaline degeneration of the maculopapillary region
   b. Doyne's honeycomb degeneration
   c. Malattia leventinese

François nevertheless maintained: "An examination of all published material on hereditary degenerative disorders of the macula leaves the impression, in spite of the obvious polymorphism of the lesions, that we have been mistaken in trying to establish different terms and characteristics, because, alongside the so-called typical forms, there are at least as many intermediary forms. In effect, all forms of macular dystrophy represent the same fundamental hereditary degenerative lesion, the same central tapetoretinal degeneration which in different families and different age groups gives a different ophthalmoscopic appearance".

Waardenburg (1963) formulated several classifications, thereby clearly indicating just how difficult it is to find an adequate and satisfactory classification. His classifications were the following:

I. Based on ophthalmoscopic features:
   1. Dystrophia tapeto-retinalis centralis posterior (Hutchinson and Tay 1875)
   2. Dystrophia tapeto-retinalis centralis (Doyne 1899)
   3. Dystrophia tapeto-retinalis centralis with particular exudative phenomena (Sorsby 1940)
   4. Dystrophia tapeto-retinalis centralis with pronounced central pigment proliferation (Sorsby 1940)
   5. Dystrophia tapeto-retinalis centralis cystoidea (or retinitis centralis serosa)
   6. Dystrophia tapeto-retinalis centralis stellata polycystoidea (Brown 1928)
   7. Dystrophia tapeto-retinalis polaris pigmentosa inversa (Von Rötth 1930)

II. Based on the age of manifestation:
   1. Congenital or probably congenital type.
   2. Infantile type (0-8 years)
   3. Juvenile type (Stargardt) (8-25 years)
   4. Adult type (25-30 years)
   5. Middle age and presenile type (35-55 years)
   6. Senile type (55-70 years)

III. Based on the extent of retinal involvement:
   1. Fovea only
   2. Fovea and perifoveal area
   3. Fovea with peripheral tapetoretinal dystrophy

IV. Based on the mode of transmission:
   1. Autosomal recessive
   2. Autosomal dominant
   3. Sex-linked

Waardenburg emphasized that he had made only an "attempt at classification". The field was still too imperfectly explored to give a well-reasoned and practicable classification. The great value in Waardenburg's effort lies in the fact that, like Stargardt, he indicated that there are many different dystrophies of the posterior pole. In the

light of data now available, the classification based on ophthalmoscopic features now requires modification on a few points. The affections described by Hutchinson and Tay (1875) and by Doyne (1899, 1910) are very likely manifestations of the same entity: hyaline dystrophies (Duke-Elder 1967) or dominant drusen of Bruch's membrane (see page 367). In our opinion, moreover, dystrophia tapeto-retinalis centralis with particular exudative phenomena and dystrophia tapeto-retinalis centralis cystoidea should both come under the heading of vitelliform foveal dystrophy (see page 198). The retinitis centralis serosa (which Gass (1967) called central serous choroidopathy) is not a hereditary condition so far as we know, although Jonkers (1960) described its occurrence in monozygotic twins.

It is uncertain whether the dystrophia tapeto-retinalis stellata polycystoidea (Brown 1928) is a separate entity. The description of the foveal features is reminiscent of the fovea in sex-linked juvenile retinoschisis. The drawing shows a rosette pattern encompassing small, round "reddish deposits not unlike the color and setting of the seeds of a raspberry". The fact that a girl also had this abnormality virtually rules out a diagnosis of sex-linked juvenile retinoschisis. But we have been unable to find a distinct similarity to any other foveal dystrophy. A somewhat nonspecific form of Stargardt's disease is a possibility, but for the time being we regard Brown's case as unclassified.

Franceschetti, François and Babel (1963) are still following Behr's conception: "l'Hypothèse la plus probable est celle d'une seule et unique affection hérédo-dégénérative à manifestation variable"; and: "Malgré le polymorphisme des lésions, on a l'impression d'une même affection hérédo-dégénérative, localisée au pôle postérieur". In spite of this hypothesis, they nevertheless accepted the following classification of foveal dystrophies:

1. Infantile and juvenile form (Stargardt's disease).
2. Early forms (Best's disease).
3. Vitelliform macular degeneration.
4. Special forms, manifested in particular through changes in Bruch's membrane (Hutchinson-Tay, Holthouse-Batten, Doyne, malattia leventinese).

Velzeboer (1963), Braley (1966) and Blodi (1966) presented classifications based on the retinal structures primarily and mainly affected. Blodi's classification of central tapetoretinal dystrophies is clear and perspicuous, but not quite complete.

1. The choroid: central areolar choroidal sclerosis.
2. Bruch's membrane: Doyne's honeycomb choroiditis, Tay's guttate choroiditis, malattia leventinese.
3. The pigment epithelium: vitelliform macular degeneration (Best).
4. The retina: Stargardt's disease.

In 1966, Falls presented an extensive classification of the various hereditary posterior pole dystrophies, again on the basis of the age of manifestation; but unlike many earlier authors he clearly distinguished several different entities that can be readily differentiated on clinical grounds. Yet he did not totally reject Behr's concept of "heredodegeneration of the macula".

Finally, Duke-Elder (1967) presented the following classification of central tapetoretinal dystrophies:

1. Heredomacular dystrophies.
   a. infantile (Best)
   b. juvenile (Stargardt)
   c. adult (Behr)
   d. presenile and senile
2. Reticular pigmentary dystrophy of Sjögren.
3. Polymorphic macular dystrophy of Braley.
4. The hyaline dystrophies (Hutchinson, Tay, Doyne, malattia leventinese, and others).

It is remarkable that Duke-Elder still accepts Behr's monistic view: "The many different clinical pictures described probably represent phenotypical manifestations of a fundamentally single dystrophic process and not a number of autonomous lesions".

The "polymorphic macular dystrophy of Braley" which Duke-Elder (1967) mentions, is identical in our opinion to vitelliform foveal dystrophy, and certainly merits no separate place (see page 208). The fact that, in the same chapter, Stargardt's disease is discussed with reference to fundus pictures from a family with vitelliform dystrophy, is probably due to a typographic error.

7. CLASSIFICATION

After this historical review with the introductory remarks on some of the more prominent classifications, we come to the task of presenting our own classification. *Our findings have shown that the still persistent monistic theory advanced by Behr (1920) must be refuted. The many data we have collected from the literature and in personal observations clearly indicate the existence of several foveal dystrophies determined by different genes.* Any classification now formulated is bound to show imperfections, certainly as long as the basic biochemical processes underlying the dystrophies are still obscure.

In the final analysis, however, classification on the basis of various deficient or absent enzymes will be the most meaningful from a scientific point of view. A first step in this direction has been taken in the realm of the so-called "maculocerebral" dystrophies (lipidoses). O'Brien (1969) demonstrated that the enzyme hexosaminidase A is totally absent in Tay-Sachs disease. This results in storage of a specific ganglioside in many parts of the organism.

Working on these lines, O'Brien and his co-workers learned to differentiate five clinically different gangliosidoses on the basis of their enzymatic defects. There are more retinal dystrophies in which biochemical changes have been found that are probably based on enzymatic disturbances. For example, the Bassen-Kornzweig syndrome (figure 11) shows a reduced β-lipoprotein concentration and low cholesterol concentrations in the serum, while in the Refsum syndrome an abnormal

fatty acid (tetramethylhexadecanoic acid) occurs throughout the organism (Cogan 1965).

Future biochemical research is bound to yield results of importance, but a biochemical basis of classification is not likely to present itself soon. It will be more difficult to detect enzymatic defects in clinically only ophthalmological conditions than in more generalized affections such as Tay-Sachs disease.

At this time, the possible types of classification include:

I. That based on the mode of transmission of the dystrophy.
II. That based on the extent of the dystrophic process.
III. That based on the age of manifestation of the dystrophy.
IV. That based on the ophthalmoscopic features of the central retina.
V. That based on the results of various retinal function tests.
VI. That based on the primary localization in the retinal layers and/or the retinal layers mainly involved.

re I. The dystrophies of the posterior pole can be classified on the basis of the mode of transmission. The latter is important in clinical and differential diagnostic terms, but not entirely decisive for classification. The fact is that most dystrophies are autosomal recessive or autosomal dominant. Sex-linked recessive transmission prevails only in juvenile retinoschisis, which can in any case hardly be described as an affection of the central retina alone. In Halbertsma's family (1927, 1928) in which colour blindness occurred, an X-chromosomal foveal dystrophy was also reported to occur. The description of these cases is very incomplete, and the various posterior poles showed widely disparate changes; moreover, vision was 10/10 in three of the four individuals affected.

We are by no means convinced that the family described by Halbertsma can be accepted as representative for X-chromosomal foveal dystrophy. Falls (1952) described what may have been sex-linked vitelliform foveal dystrophy; however, the mode of transmission in his family was probably irregular dominant.

Waardenburg (1963) described an X-chromosomal foveal hypoplasia which later became a foveal dystrophy in three individuals.

The classification on the basis of the mode of transmission can be as follows:

Autosomal dominant
- dominant progressive foveal dystrophy
- progressive cone dystrophy
- vitelliform dystrophy
- butterfly-shaped pigment dystrophy
- drusen of Bruch's membrane
- Sorsby's "pseudo-inflammatory dystrophy"
- central areolar choroidal dystrophy

recessive
- Stargardt's disease
- central retinopathia pigmentosa
- fundus flavimaculatus
- reticular dystrophy of the pigment layer of the retina (Sjögren)

– grouped pigmentations of the central retina
– central areolar choroidal dystrophy

Sex-linked
X-chromosomal – juvenile retinoschisis

re II. It is not really possible to formulate a strict classification on the basis of the extent of the dystrophic process. Too many transitional forms between purely central and centroperipheral are encountered. Some dystrophies show an initial central localization but gradually extend beyond it; consequently they would have to be classified differently dependent on their stage of development. Also, a condition such as vitelliform dystrophy would come under several headings if it involved multiple perifoveal lesions (as in rare cases it does). On other grounds, too, this classification must be refuted, for it has been established that many processes ophthalmoscopically confined to the fovea, involve a much larger part of the retina in functional terms. Vitelliform dystrophy, for example, usually shows a lesion confined to the foveal region, but the highly pathological L/D-ratio of the EOG suggests a diffuse retinal disturbance. In many cases, sex-linked juvenile retinoschisis is ophthalmoscopically confined to the fovea, but the subnormal ERG indicates a diffuse retinal disturbance. Stargardt's disease often shows ophthalmoscopic as well as electrophysiological evidence of a very gradual transition from purely central tapetoretinal dystrophy to diffuse centroperipheral dystrophy. In the ophthalmoscopically purely central form, the EOG is sometimes already subnormal.

Additional examples could be given, but the above may be sufficient to show that a classification based on the extent of the dystrophic process can give no satisfaction.

re III. As pointed out earlier, classification based on the age of manifestation is hardly meaningful, as the following examples may illustrate. Stargardt's disease usually manifests itself at age 8-14, but it has been observed in younger subjects, and in some cases the onset has been much later in life. Vitelliform foveal dystrophy has been observed in a one-week-old infant (Barkman 1961), but we ourselves saw originate vitelliform changes in a man aged 44. Although most authors maintain that dominant drusen of Bruch's membrane occur at age 30-40, we observed them in a boy of 12 and another boy of 14. Also, it has been found that in many families various individuals develop the manifestations of foveal dystrophy in that family at widely different ages. This is a striking feature especially in the dominant forms.

Since a strict classification on the basis of the age of manifestation is practically impossible due to the wide range of the ages of onset, we prefer not to use this classification.

re IV. We believe that a meaningful classification could be based on ophthalmoscopic features. Unlike many authors (Blodi 1966; and others), we consider it possible to identify and differentiate the various entities ophthalmoscopically. Although we realize that in the various dystrophies of the posterior pole there is a

continuous evolution of the ophthalmoscopic picture, this does not usually prohibit identification of the specific entity. However, this evolution is indeed an obstacle to any attempt at classification on the basis of the foveal appearance. This obstacle might be overcome by selecting a characteristic fundus picture for each dystrophy, but this would make the classification rather artificial. It is relevant in this context to mention the great importance of a follow-up covering several years, which makes it possible to study the total dynamics of the evolution of the clinical picture. This has been illustrated by such studies as that of Rosehr (1954). In one of Stargardt's patients, the initial purely central dystrophy was found 50 years later to have become an extensive diffuse centroperipheral tapetoretinal dystrophy.

Besides such follow-up studies, an investigation of patients of all age groups is also an effective method to gain an impression of the evolution of the various dystrophies. Evidently our understanding of this subject will increase with an increasing number of patients observed.

re V. It might be possible to make a classification based on the results of the various retinal function tests used in the various dystrophies. Such a classification, however, would be too complicated to be very useful.

We intend to present a diagram in which the results of various tests in the various dystrophies are arranged for convenient reading (see page 428).

re VI. From a clinical point of view, a classification based on the retinal layers primary and mainly involved would seem to be the most practical and meaningful solution (Deutman 1970). Such a classification makes it possible to understand and predict in rough outline the clinical course of the various dystrophies. For example, a dystrophy primarily confined to the pigment epithelium (e.g. fundus flavimaculatus) is not likely to produce soon changes in the neuroepithelium or the choriocapillaris. Likewise, drusen of Bruch's membrane can be expected to have an unfavourable effect on the retinal neuroepithelium only in later stages.

A problem in formulating this type of classification is the fact that little is known of the histology of the posterior pole dystrophies. Exceedingly scanty histological data are available on young patients, in whom senile retinal and choroidal changes are of course not yet present. Histological specimens from older patients often show senile and autolytic postmortem changes, which impair assessment.

With the more sophisticated techniques of retinal electrophysiology and fluorescein angiography, however, localization of retinal changes has become less difficult. It is therefore that we have used these modern facilities in order to ensure a firm foundation for the classification we prefer: that on the basis of the localization of the changes in the various retinal layers.

The various components of the ERG and EOG have become more important in localization as our understanding of these techniques has improved (Gouras 1968). Moreover, fluorescein angiography affords excellent possibilities for the differentiation of changes of the pigment epithelium, Bruch's membrane, the choriocapillaris

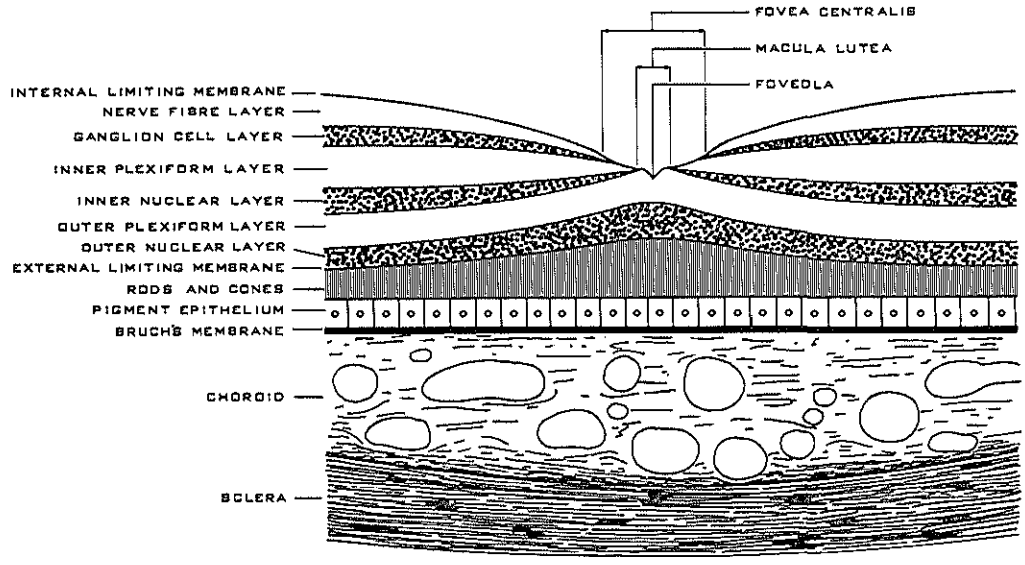


Fig. 18.

Nerve fibre layer	-	sex-linked juvenile retinoschisis
Neuroepithelium	-	Stargardt's disease
	-	dominant progressive foveal dystrophy
	-	progressive cone dystrophy
	-	central retinopathia pigmentosa
Pigment epithelium	-	vitelliform dystrophy of the fovea
	-	fundus flavimaculatus
	-	reticular dystrophy of the retinal pigment epithelium
	-	butterfly-shaped pigment dystrophy of the fovea
	-	grouped pigmentation of the foveal area
Bruch's membrane	-	dominant drusen of Bruch's membrane (hyaline dystrophies)
	-	pseudo-inflammatory foveal dystrophy (Sorsby)
Choroid	-	central areolar choroidal dystrophy

and the choroid in relatively early stages. In addition, information on the probable localization-in-depth of retinal lesions can be obtained with the aid of photographs made with monochromatic light (Krill et al. 1966) and photographs made on orthochromatic and panchromatic film (Craandijk and Aan de Kerk 1969).

Combination of these data with the other clinical findings facilitates classification in this manner. It should be borne in mind, however, that with increasing age the degenerative changes secondarily manifest themselves in the more superficial as well as in the deeper layers of the posterior pole. For example, the terminal stage of a condition of evidently tapetoretinal onset, such as Stargardt's disease, often shows extensive atrophy of the choriocapillaris and the choroid. In such a case, differential diagnosis from central areolar choroidal dystrophy is impossible unless the history of the case is known.

Our purpose in designing our own classification was not only to facilitate identifi-

cation and differentiation of the many clinical entities, but also to provide a frame in which newly discovered entities could be readily accommodated (figure 18). For we are convinced that several as yet unknown dystrophies will be discovered in future or will arise from new mutations.

Of course we are not sure that the primary enzymatic disturbances are indeed localized in the layers indicated in our diagram of structures primarily and mainly involved. It looks as if many of the enzymatic disturbances which give rise to dystrophies, will have to be localized in the pigment epithelium, the "heart and soul of the retina" (Krill 1969). Ophthalmoscopic, electrophysiological and fluorescein-angiographic findings seem to warrant this conclusion. It is highly probable that, apart from the dystrophies shown under the heading pigment epithelium in our classification, the dominant drusen of Bruch's membrane and the choroideremia or tapetochoroidal dystrophy (Goedbloed 1942; Pameyer et al. 1960; Kurstjens 1965), and possibly also central areolar choroidal dystrophy are likewise primarily dystrophies of the pigment epithelium in which the deeper retinal layers are quickly affected.

Stargardt's disease might be a primary dystrophy of the pigment epithelium in which the more superficial localized photoreceptors are involved after a short time. This is suggested by the pigment displacements and the perifoveal deep-seated white spots. The fact that the EOG becomes subnormal before the ERG does when the peripheral retina is affected, also points in this direction.

In initial stages of retinopathia pigmentosa, too, the EOG is often seen to become subnormal before the ERG does (Arden 1962; Arden and Fojas 1962; Arden and Kolb 1964; Imaizumi et al. 1965). However, Gouras and Carr (1964) found dark adaptation changes and scotopic ERG changes as the first pronounced abnormalities in the early stages of retinopathia pigmentosa. On this basis they localized the primary defect somewhere in the receptor system, affecting the rods more than the cones.

There may well be several forms of retinopathia pigmentosa, with different sites of primary involvement. The results obtained by De Haas (1970) also point in this direction. Arden and Kolb (1964) suggested that there are two ophthalmoscopically indistinguishable forms of this condition, one of which starts in the pigment epithelium while the other begins in the rods.

Discrepancies between results can also be caused by differences in techniques used and by differences in material studied.

Moreover, there are probably some dystrophies in which the photoreceptors are primarily affected, e.g. dominant progressive central tapetoretinal dystrophy (see page 172) and progressive cone dystrophy (see page 181). In these cases, there are no or only insignificant ophthalmoscopic changes in the presence of extensive abnormalities of the photoreceptors. Likewise sex-linked juvenile retinoschisis (see page 48) shows from the onset a subnormal ERG in combination with a normal EOG; and this suggests an intact pigment epithelium. This is confirmed by fluorescein angiography and histological examination.

It can be concluded that the primary defect is localized in the pigment epithelium in many, but certainly not in all, dystrophies of the central retina. In any case, we cannot agree with a statement made by Elwyn (1955) that: "The pigment epithelium of the retina is not subject to degenerations on a hereditary basis". Many arguments can be advanced against this statement. We need only point out that Klien and Krill (1967) found dystrophy of the pigment epithelium as the sole histological abnormality in a case of fundus flavimaculatus. The other dystrophies we have described as starting in the pigment epithelium, can hardly have any primary localization other than the pigment epithelium. This will be further discussed in the various pertinent chapters.

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II

Sex-linked juvenile retinoschisis

1. INTRODUCTION

Sex-linked juvenile retinoschisis belongs in the group of vitreoretinal dystrophies which also includes Wagner's vitreoretinal dystrophy and Goldmann-Favre vitreotapetoretinal dystrophy. Although initially it was considered to be a relatively rare abnormality, it has recently become apparent that it is a fairly common condition. In the course of our study we have been able to confirm this.

According to Franceschetti et al. (1963), only about 100 case reports could be found in the literature; but a study by Vainio-Mattila et al. (1969) in Finland revealed over 100 patients in one large family alone.

We ourselves found 48 individuals with this affection, although we made no specific effort to collect as many cases as we could.

In many cases the correct diagnosis is probably not made due to the very great differences in expression of this condition. Not infrequently it is diagnosed as "heredodegeneration of the macula" (Korchmáros et al. 1965) or Stargardt's disease (Peralta and Santori 1967); others (Barut 1955) have diagnosed it as periphlebitis. Falls (1966) emphasized the deceptive similarity between juvenile retinoschisis and Eales' disease. All these different diagnoses are not so surprising because, on the one hand a foveal retinoschisis is the only abnormality in some 50% of cases (Jager 1953; Ricci 1960, 1961), while on the other hand vascular sheaths and vitreous opacities are quite common in the more severe forms.

Haas (1898) was the first to describe cases of X-chromosomal juvenile retinoschisis. He observed two brothers with this condition, and his publication includes beautiful drawings of the foveal abnormality which characterizes juvenile retinoschisis and occurs in virtually all patients. The disease has been described in the literature under a wide variety of names.

Haas (1898) described it as "Veränderungen der Retina und Chorioidea", and Thomson (1932) reported on a "neuroretinal disease in males". Anderson (1932) described a 2-year-old boy who suffered from "anterior dialysis of the young", which

may have been juvenile retinoschisis. Pagenstecher (1913) described the first family with juvenile retinoschisis (in which an X-chromosomal pattern of transmission was demonstrable, as in the families described later) in a paper entitled: "Ueber eine unter dem Bilde der Netzhautablösung verlaufende, erbliche Erkrankung der Retina".

The term retinoschisis, introduced for this disorder by Jager (1953) is generally accepted to date in the designation sex-linked juvenile retinoschisis or idiopathic hereditary retinoschisis (in young men) (Jager, 1953; Kleinert 1953; Ricci 1960, 1961; Gieser and Falls 1961; Forsius et al. 1962, 1963; Sarin et al. 1964; Isbey and Beuerman 1964; Cibis 1965; Boudon and Sole 1965; Sabates 1966; Spencer 1966; Schepens 1966; Brockhurst 1966; Falls 1966; Bengtsson and Linder 1967; Goodman 1968; Yanoff et al. 1968; Donaldson 1968; Lisch 1968; Stepanik 1969; Guyot-Sionnest 1969; Vainnio-Mattila et al. 1969; Harris 1969; Pischel 1969; Yazawa and Nakajima 1969; Ewing and Ives 1969 and Hauschild et al. 1970).

A few authors use the term "congenital cystic retinal detachment" or "inherited retinal detachment" (Cibis 1940; Juler 1948; Magnus 1951; Sorsby 1951, 1955, 1967; Levy 1952).

"Vitreous veils" (Condon and Somerville-Large 1955; Goodman et al. 1965) and "congenital vascular veils (in the vitreous)" (Mann and McRay 1938; Sheehan 1952; McRay 1954; Scorciarini-Coppola et al. 1958; Balian and Falls 1960; Keith 1966) are likewise designations often used for this syndrome, and "cystic disease of the retina" (Juler 1951; Pischel 1963) is occasionally used also. Trevor Roper (1950) described a man aged 28 with a "congenital retinal fold in association with pseudo-papillitis", who is now generally accepted as having suffered from sex-linked juvenile retinoschisis.

We prefer the term sex-linked or X-linked juvenile retinoschisis, because this condition has an X-chromosomal pattern of transmission, occurs very early in life (probably it is ophthalmoscopically present at birth), and histological studies have disclosed cleavage of the retina at the level of the nerve fibre layer (Yanoff et al. 1968; Manschot 1969). Since vascular or avascular vitreous veils and cysts are by no means always seen in these cases, we reject designations which emphasize these phenomena.

Since true detachment of the retina is rare in this condition (Schepens 1966), we also reject the term "congenital retinal detachment" (Sorsby et al. 1951; Sorsby 1955, 1967).

Virtually all cases (98-100%) involve foveal retinoschisis, the characteristics of which have been described clearly and in detail by several authors (Haas 1898; Lisch 1937; Jager 1953; Kleinert 1953). This foveal retinoschisis is pathognomonic for the syndrome, and thus constitutes the principal symptom of this relatively common condition.

I have never observed peripheral retinoschisis without foveal retinoschisis; it is my impression that it is non-existent, although such authors as Sorsby et al. (1951), Condon and Somerville Large (1955) and Gieser and Falls (1961) have reported it.

In most cases, however, vision was greatly diminished, and this could hardly have any cause other than foveal changes. In elderly patients the characteristic foveal pattern disappears, and in some cases the foveal changes are not readily observable. This may explain the fact that some reports describe a normal fovea.

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

The syndrome is found virtually only in males. It is probably present since birth, and very young boys can be encountered as patients. They often do not visit an ophthalmologist until vision proves to be insufficient at school, and the condition is therefore frequently seen in age group 4-8.

We saw two boys with this condition as early as age 3, and juvenile retinoschisis has been observed even earlier in life. Pischel (1963, 1969) saw three brothers aged 2 years, 1 year and three months, respectively; Harris (1969) saw an infant aged 16 months.

Also, these patients are often first seen when vitreous haemorrhage has occurred as a result of rupture of a retinal vessel.

The condition takes a slowly progressive course and can therefore be interpreted as dystrophy on the basis of dysplasia. Complaints about poor vision can long remain absent, and some patients will therefore not be recognized as such until later in life.

Strabismus (8 patients) and nystagmus (4 patients) are frequently seen in this syndrome; they are best interpreted in the light of the foveal changes and the nearly always present hypermetropia with astigmatism.

Anterior segment and lens are usually quite normal, although occasional reports mention posterior cortical cataract and slight opacities of the posterior capsule (Balian and Falls 1960).

We observed an opacity of the posterior capsule in one eye, although generally the abnormalities are symmetrical. At times, there are marked interfamilial differences in clinical features, but on the other hand there are usually close intrafamiliar similarities of the manifestations.

3. FUNDUS (OPHTHALMOSCOPIC FEATURES)

In this condition in particular, the fundus is best assessed by means of contact lens and slit-lamp examination, for both the vitreous and the retina can show extensive changes which can be properly judged only by binocular examination. The syndrome of sex-linked juvenile retinoschisis comprises many symptoms, some of which are often absent. In the severe cases, however, the full multitude of symptoms may be encountered; but the expression of the gene is often so low, or the process so little advanced, that only foveal retinoschisis is present. However, this foveal retinoschisis is the characteristic symptom of sex-linked juvenile retinoschisis, and is

Fig. 1ab. Pathognomonic bilateral symmetrical picture of foveal retinoschisis in an 8-year-old boy with X-linked juvenile retinoschisis. Note the wheel-like configuration with the radiate spoke-like striation. In this case the discs, vessels and retinal peripheries are quite normal.

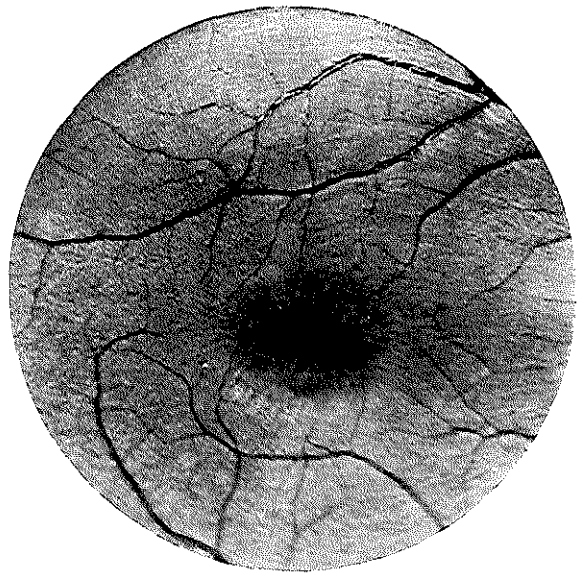


Fig. 2. Foveal retinoschisis in a 17-year-old boy. In this case the cystoid structure is well discernible (Fam. Pie).

present in virtually all cases (Falls (1966) mentioned 98% of cases; our impression is that 100% would be correct).

This symptom is the sole pathological finding in some 50% of cases. Only in Goldmann-Favre vitreotapetoretinal dystrophy has a similar foveal involvement been described (Franceschetti et al. 1963), but according to Ricci (1961) the fovea shows no true cystic degeneration in Goldmann-Favre disease. Dependent on the expressivity of the pathological gene and the evolution of the syndrome, we find the following characteristics:

1. *Foveal retinoschisis* (figures 1 and 2). This consists of an optically empty zone, delimited by two retinal layers of which the more superficial one is very thin. This layer shows a typical radial plication which, we believe, is not determined by the course of the nerve fibres in the foveal area (Lisch 1968) but by small plicae in the internal limiting membrane, resulting from the presence of a cystoid structure in the foveal centre (figure 3).

These sometimes subtle radial folds (figures 4 and 5) can be easily overlooked at ophthalmoscopy but, if seen, are unmistakable. They are always bilateral and nearly always symmetrical (figures 1, 5 and 6). They are more clearly visible at narrow-beam than at broad-beam ophthalmoscopy, and more readily identified in red-free than in ordinary white light. Round microcysts are often seen in the perifoveal area (figure 6 and 7).

With increasing age, the characteristic radial folds in the foveal area disappear, and a fovea of non-specific atrophic appearance remains. We observed this in 6

patients over 40 years of age. The remaining patients showed the characteristic radial plication, except in two eyes in which general retinoschisis had involved the foveal area.

2. *Silver-grey, glistening, spotty areas* scattered over the retina (figure 8 and 13). We found this likewise characteristic feature in all our cases, and we agree with Bengtsson and Linder (1967) that these areas are somewhat reminiscent of Berlin oedema. They probably represent the first visible pathological changes of the retinal periphery.

3. *Greyish-white arborescent and dendritiform structures* are fairly often observed on the anterior aspect of the retina (figure 9), usually in the lower temporal quadrant. They are assumed to be of vascular origin (Ewing and Ives 1969).

4. *Perivascular silver-grey cuffs* are also often visible in the fundus. They closely resemble vascular sheaths and not infrequently lead to a diagnosis of periphlebitis (figures 9 and 15).

5. *True retinoschisis in the retinal periphery* (figure 10 and 11) is usually found in the lower temporal quadrant; it is sometimes not observed well until an exhaustive examination is made of the extreme periphery. We found this in about 50% of

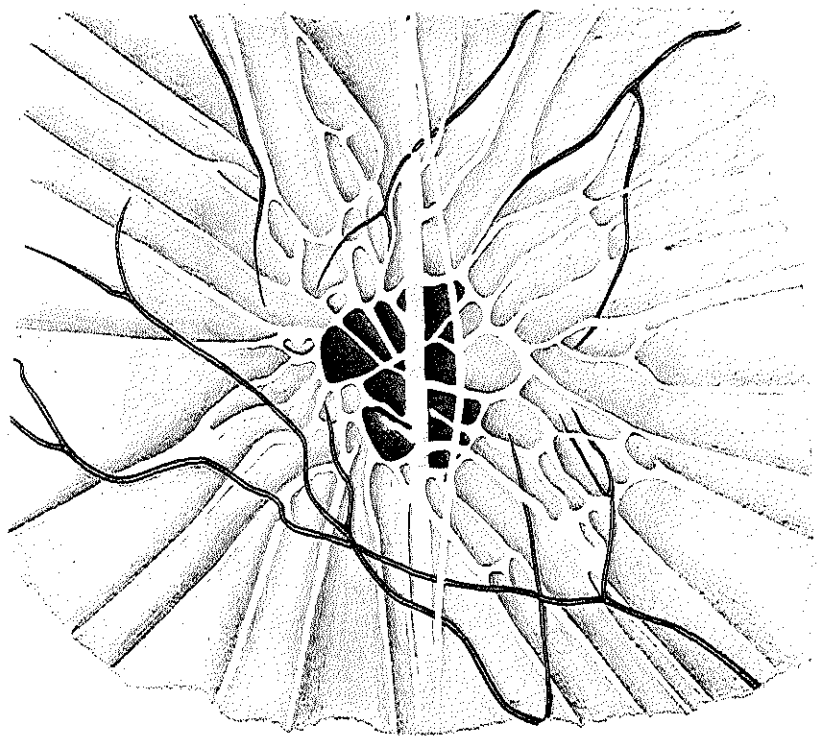


Fig. 3. The fovea in X-linked juvenile retinoschisis as seen in binocular slitlamp examination.

patients, and always bilaterally. The lower temporal quadrant may be predisposed to the more extensive changes because the optic cup closes in the lower temporal quadrant in the development of the eye. The superficial retinoschisis layer is very thin and may show round or oval-shaped defects.

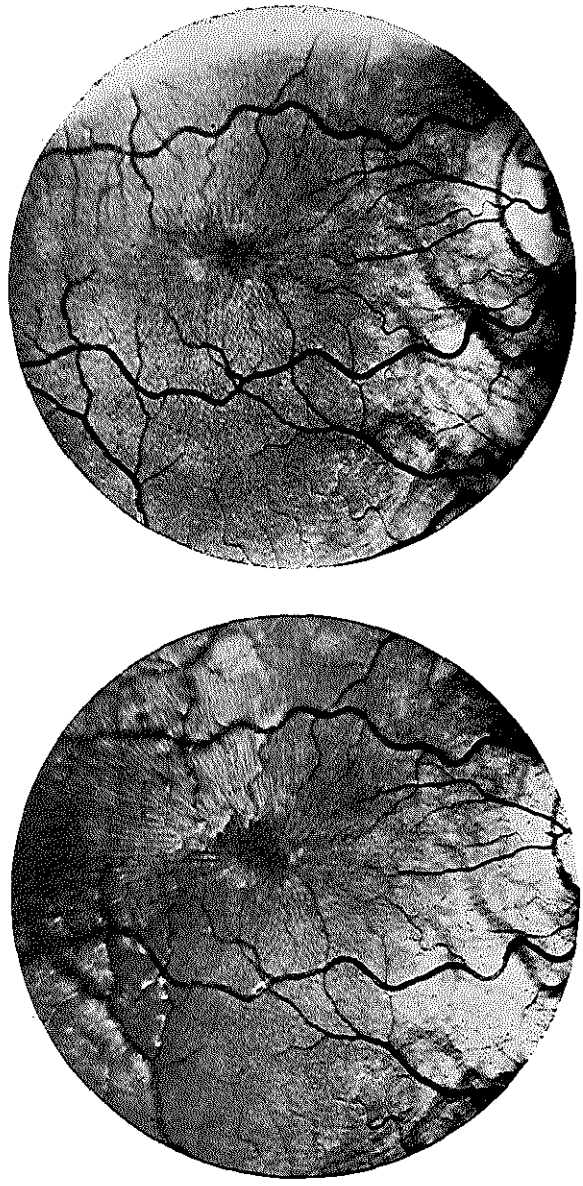


Fig. 4a-b. Delicate radiate folds in the right fovea of a 9-year-old boy with hardly discernible microcysts perifoveally.

6. *Veils in the vitreous, with or without retinal vessels enclosed* (figures 12, 13, 14) were found in less than 50% of our patients. The vessels in the veils were usually veins. However, like Balian and Falls (1960) we also observed some arterioles. The

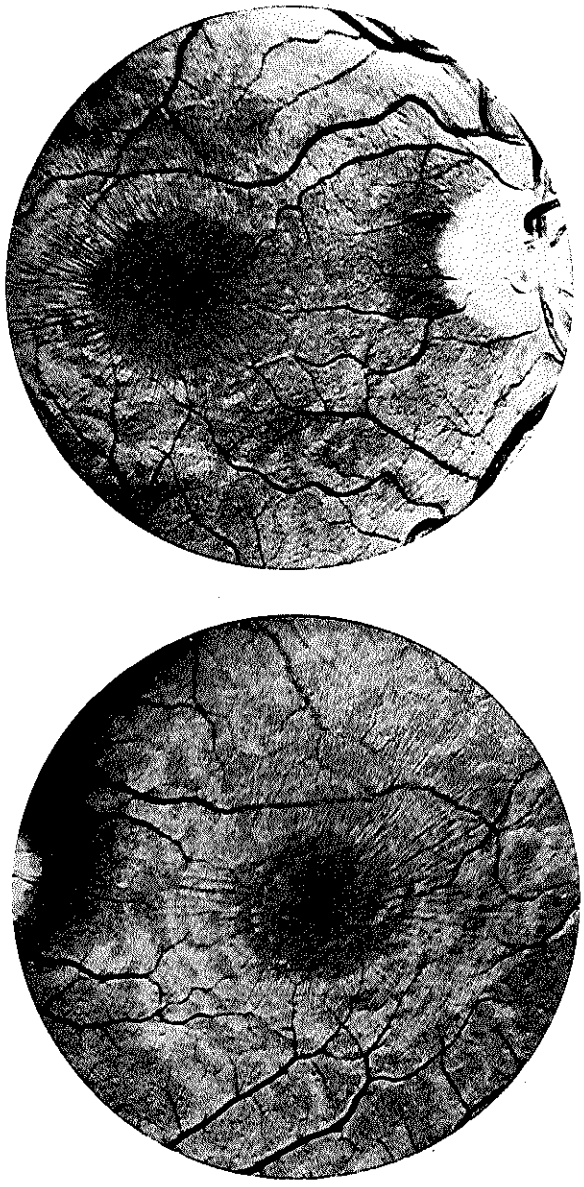


Fig. 5a-b. Tiny radiate folds and small microcysts perifoveally in another boy with X-linked juvenile retinoschisis. It is obvious that these changes may be missed in a superficial examination.

vessels enter the vitreous from the retinal vessels, while other branches of the retinal vessels continue in the retina.

The veils may be attached to the disc (Forsius et al. 1963), as we observed in several cases (figure 15). In some cases the vitreous veils are localized in front of

Fig. 6a-b. Clearly visible microcysts in foveal retinoschisis in an 18-year-old male.

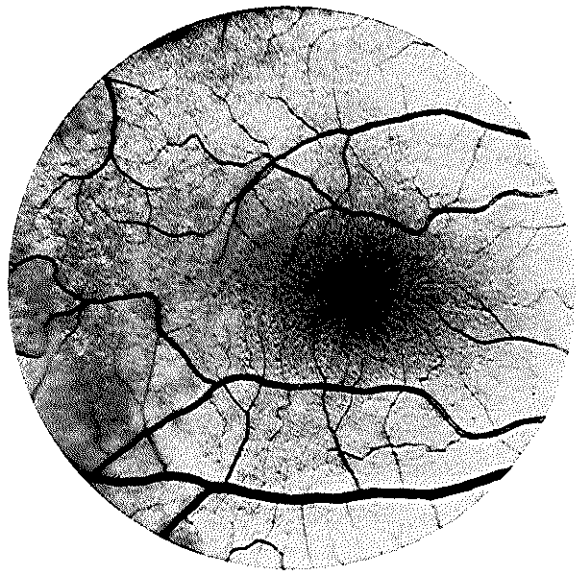


Fig. 7. Foveal retinoschisis surrounded by a silver greyish retina in a 32-year-old male. The glistening retina is somewhat reminiscent of Berlin oedema.

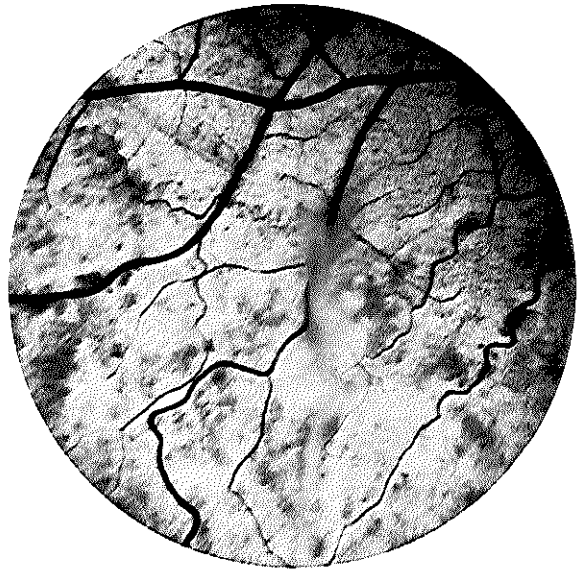


Fig. 8. Silvery gloss of the retina in X-linked juvenile retinoschisis. There is a small preretinal avascular veil. Some of the vessels have a corkscrew appearance.

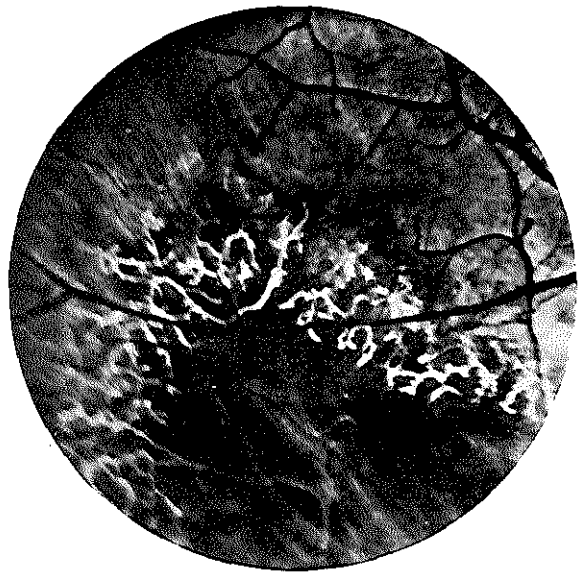


Fig. 9. Characteristic white lattice-like dendritic markings in the midperiphery of a 17-year-old boy (for foveal area see fig. 2) (Fam. Pie). Note the drumstick appearance of some of the retinal vessels and the vascular sheathing due to perivascular and intraretinal opalescence, suggesting gliosis.

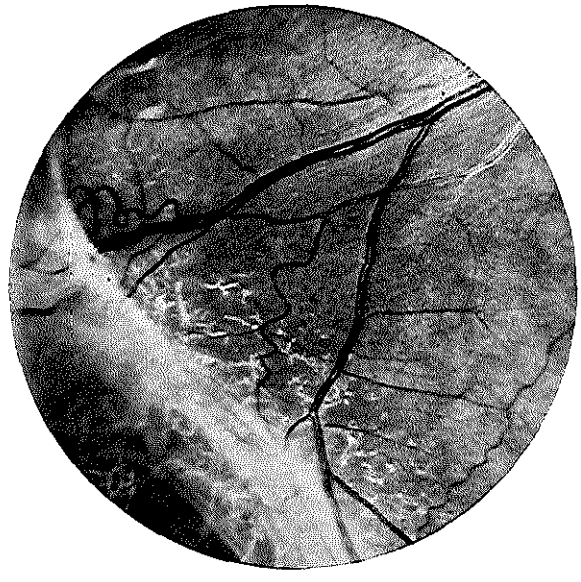


Fig. 10. Retinoschisis in the inferior temporal quadrant of a 20-year-old male, showing corkscrew arterioles, lattice-like arborescent markings and vascular sheathing. There is a denuded retinal area at the bottom left.

Fig. 11. Translucent veil-like membranes and a denuded retinal area, having an atrophic appearance.

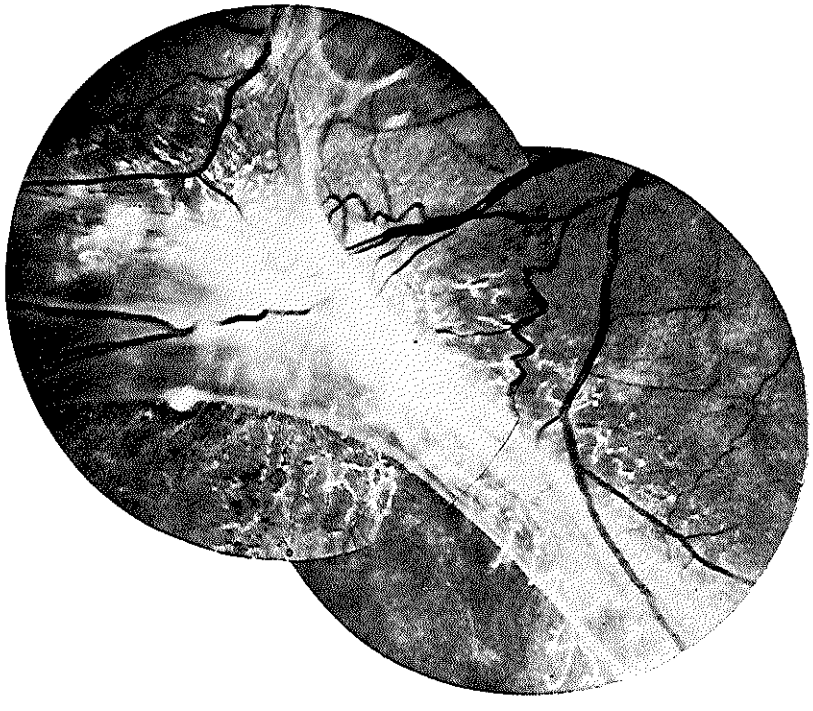


Fig. 12. Vascular veils and many other characteristics of X-linked juvenile retinoschisis in a 20-year-old male (Fam.Wil).

Fig. 13. Translucent preretinal veils in the surrounding of foveal retinoschisis with perifoveal microcysts.

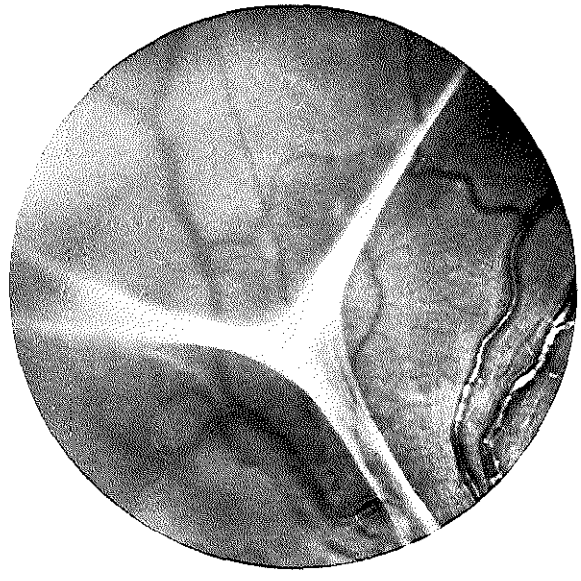


Fig. 14. Avascular veil in X-linked juvenile retinoschisis.

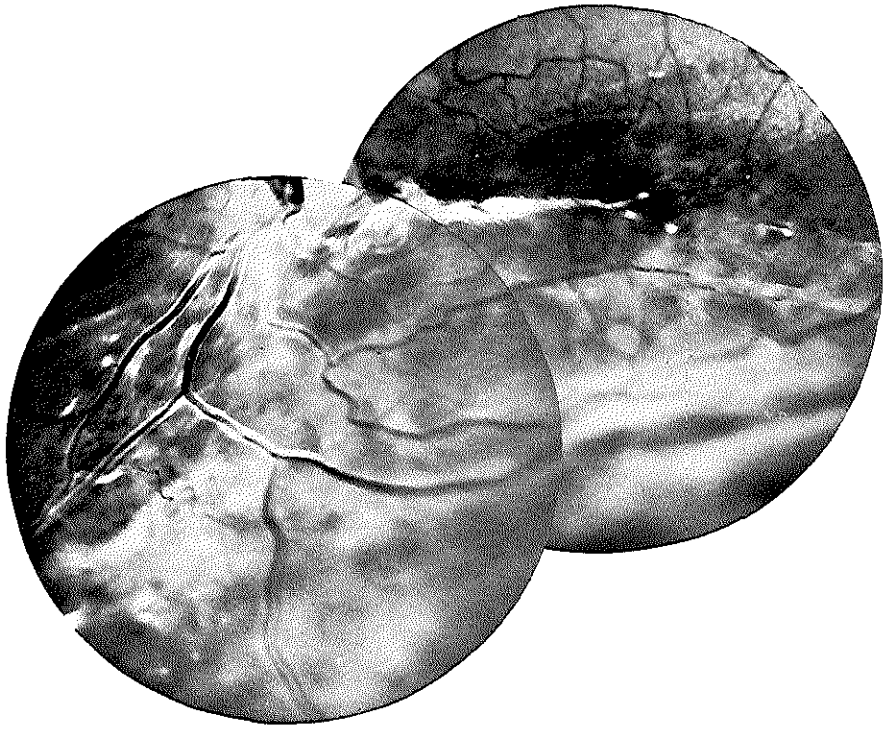


Fig. 15. Retinoschisis endangering the foveal area. There is marked vascular sheathing and the margins of the disc are blurred (Fam. Hel).

the posterior pole and conceal the characteristic foveal changes. As a rule, however, they are to be found in the periphery.

7. *A pseudopapillitis picture*, probably caused by glial tissue which spreads beyond the edges of the disc, has been observed in some cases (Trevor Roper 1950; Magnus 1951; Levy 1952). We observed this in, among other cases, patient VI-5, fam. Ra (figure 16). In advanced cases the disc is nearly always pale, especially on the temporal side, while the retinal vessels usually retain their normal calibre.

8. *Pigmentations and greyish-white spots suggestive of a healed chorioretinitis* can be observed throughout the retina (Levy 1952; Sabates 1966). In advanced cases, extensive (chorio)retinal atrophy becomes manifest in the areas of retinoschisis, where the retina has been stripped of part of the nerve fibre layer (figure 11). In three of our patients a pigment line traversed the foveal area obliquely. This line probably demarcates the boundary between the normal retina and the retinoschisis. In these eyes visual acuity was very low (light perception and 1/60) and there was strabismus or nystagmus.

9. *Anterior vitreous detachment* (Kleinert 1953; Balian and Falls 1960; Sarin et al.

1964; Sabates 1966; Lisch 1968; Boudon and Sole 1965; Guyot-Sionnest 1969) and *syneresis of the vitreous* can be found also. But this is not seen in cases in which only foveal retinoschisis is present; in my experience, it occurs only in cases in which pronounced retinoschisis exists.

The vitreous can also show vacuoles and punctiform opacities. We observed an apparently quite normal vitreous in 14 cases, while Bengtsson and Linder (1967) and Ricci (1960, 1961) described a normal vitreous in all their cases.

10. *A common complication is haemorrhage in the vitreous* due to rupture of retinal vessels in areas with retinoschisis. The reduced vision resulting from vitreous haemorrhage is often what prompts the patient to consult an ophthalmologist.

11. *True retinal detachment is rarely found* (Schepens 1966). Like Bengtsson and Linder (1967), we saw it in none of our patients. Ricci (1960, 1961) described retinal detachment in no fewer than 4 of his 12 personal observations. In dubious cases the presence of pigment in the vitreous can be an important aid in differential diagnosis between retinoschisis and true detachment of the retina (Eisner 1967). Furthermore differentiation may be made using the "white with pressure test". In retinoschisis scleral indentation results in blanching deep to the retinal vessels, whereas this phenomenon occurs at the vessel level in retinal detachment.

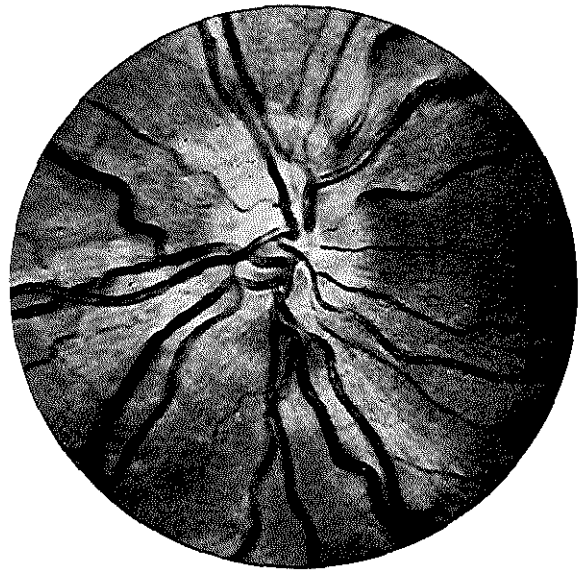


Fig. 16. Pseudo-papillitis picture in a 14-year-old boy with X-linked juvenile retinoschisis.

4. REFRACTION

Refraction of the eyes in patients with juvenile retinoschisis is usually emmetropic or hypermetropic, and astigmatism is common in these cases. Four of our patients were emmetropes, and myopia was found in only one of our cases (Fam. vdBr). Myopia is sporadically described; it was reported by Guyot-Sionnest (1969) and Harris (1969).

5. VISUAL ACUITY

Vision can be virtually normal, even in the presence of foveal retinoschisis; no prediction as to vision can therefore be made on the basis of the fundal features. We saw young patients with a vision of 5/60, but also one with 8/10, without any ophthalmoscopically demonstrable difference.

Visual acuity generally ranges between light perception and 9/10, and a vision of 2/10-4/10 is often found. Vision gradually diminishes with increasing age, and in nearly all cases is likely to end at something like 1/10. Complete blindness is an exception. We saw an 85-year-old man with this affection (III-2, fam. Kru), who could still move about his home with comparative ease. His vision was OD 2/60, OS 3/60.

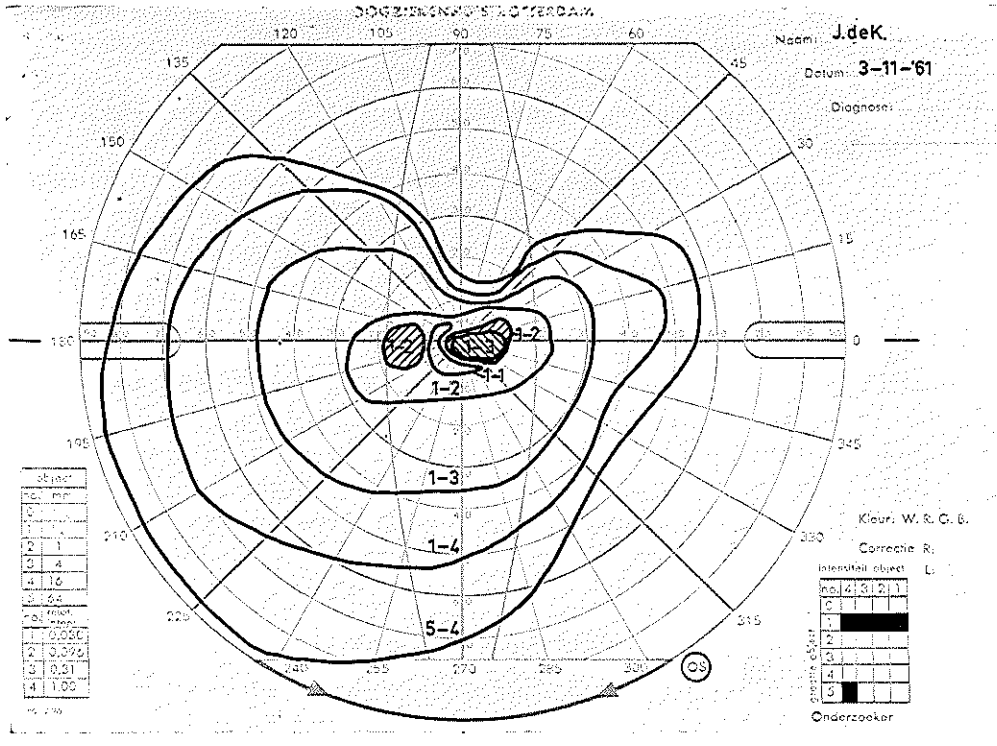


Fig. 17. Characteristic visual field defects in X-linked juvenile retinoschisis. Relative central scotoma and restriction in the superior nasal quadrant.

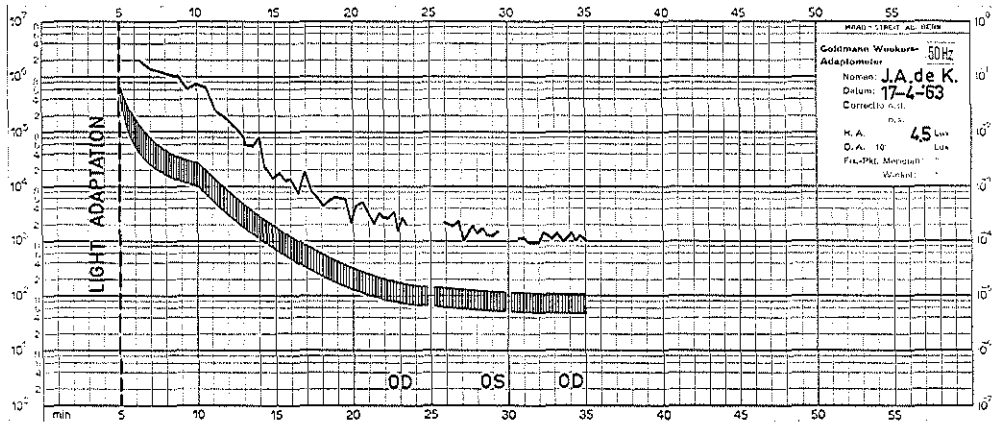


Fig. 18. Delayed dark adaptation in X-linked juvenile retinoschisis. Both the photopic and the scotopic components are disturbed.

6. VISUAL FIELDS

The visual fields in patients with juvenile retinoschisis nearly always show a relative central scotoma, and in severe cases there may even be absolute scotoma. Reduction of the peripheral visual field is frequently encountered. Since the retinoschisis usually involves the lower temporal quadrant, the visual field reduction is often observed in the upper nasal quadrant (figure 17); however, visual field reductions can be found in the other quadrants as well.

We found limitation of the visual field in 22 of 38 eyes examined under this heading. It largely corresponded to the ophthalmoscopically observed areas of retinoschisis. Furthermore there is often a concentric constriction of the isopters.

7. COLOUR VISION

Several authors reported intact colour vision in sex-linked juvenile retinoschisis (Lisch 1937, 1968; Levy 1952; Ricci 1961); but Forsius et al. (1963) and Gieser and Falls (1961) observed red-green dyschromatopsia in one of their cases, and Falls (1966) and Vainio-Mattila et al. (1969) likewise reported dyschromatopsias.

In 7 of our 12 patients examined for colour vision, we saw red-green dyschromatopsia with slightly reduced red sensitivity (more pronounced with diminishing visual acuity).

8. DARK ADAPTATION

Dark adaptation in juvenile retinoschisis has been described as normal by some authors (Ricci 1960; Bengtsson and Linder 1967; Ponte 1967), but slightly disturbed dark adaptation curves have been reported by Lisch (1937), Gieser and Falls (1961), Forsius et al. (1963) and Vainio-Mattila et al. (1969).

We obtained a normal dark adaptation curve in only 5 of the 14 subjects examined; in 9, the curve was evidently delayed for cones and rods and took a course which was 0.5-1 log unit above the normal (figure 18).

9. ELECTRORETINOGRAPHY

Such ERG records as were obtained were invariably disturbed (Ricci 1960; Forsius et al. 1963; Ponte 1967; Bengtsson and Linder 1967; Harris 1969; Vainio-Mattila et al. 1969); a subnormal b-wave was always seen.

In 26 patients we recorded a subnormal b-wave, which was more disturbed scotopically than photopically. In no case was a normal ERG recorded. The photopic a-waves were at the lower limit of normal (fig. 19); this indicates that the photoreceptors themselves were not primarily affected. In patients over 40 and also in more severe cases earlier in life, no scotopic ERG could be obtained. In this affection, therefore, the retinal dysfunction showed unmistakable progression.

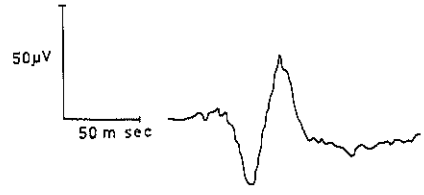


Fig. 19. ERG in a 60-year-old patient with X-linked juvenile retinoschisis. The scotopic b-waves are absent (not shown here). The photopic a-waves are normal and the photopic b-waves are definitely subnormal.

Disorders in the blood supply may be the cause of the ERG changes in the superficial retinal layers. The cleavage in the nerve fibre layer can severely obstruct the blood flow. In cases in which ophthalmoscopy shows only foveal involvement, while the visual fields are still intact, a subnormal ERG is already obtained. This can be assumed to mean that a circulatory disturbance already exists; but it is also conceivable that, independent of the schisis, there is dysfunction of the bipolar cells (where the ERG b-waves are produced). Another possibility is retrograde disturbance of the bipolar cells by the retinoschisis. In that case, however, a subnormal ERG could be expected also in Tay-Sachs disease, in which the ganglion cells are severely affected; but in this disease the ERG is entirely normal.

Local ERG and VER

The local ERG of the fovea was subnormal and, in patients with better vision (> 0.5) in whom it produced a response, it showed a typical broad wave (page 435). The VER largely parallelled the foveal ERG findings.

In the few cases in which they were elicited, the OP's were decidedly subnormal.

10. ELECTRO-OCULOGRAPHY

So far, no EOG data have been published on patients with juvenile retinoschisis. We studied the EOG in 21 patients with juvenile retinoschisis. In three patients who were over 40 and had a hardly recordable ERG, we found likewise a subnormal EOG in which not only the L/D-ratio but the standing potential itself was highly pathological. In 3 other patients there were slightly subnormal values.

In the remaining 15 patients the EOG was entirely normal. This is an unusual finding, because it gives us the rare combination of a normal EOG and a subnormal ERG b-wave. This is the opposite of what can be observed in vitelliform foveal dystrophy, in which a highly pathological EOG is accompanied by a normal ERG (a- and b-wave). The normal EOG is suggestive of intactness of the deeper retinal structures such as photoreceptors, pigment epithelium, Bruch's membrane and choriocapillaris. This has been corroborated by the histological findings which Yanoff et al. (1968) found in the eye of a 4-year-old boy.

Only in longstanding cases did we find a subnormal EOG, and Manschot (1969) indeed found marked disturbances of the pigment epithelium in the posterior pole in a 60-year-old man. As shown by the fact that ERG records can hardly be obtained in these longstanding cases, if at all, the photoreceptors probably have suffered badly; and this, too, can give rise to a pathological L/D-ratio.

11. PHOTOGRAPHY

Orthochromatic films give prints on which foveal retinoschisis is fairly well visible (figure 20ab). However, the foveal retinoschisis is of cystoid structure, and optimal reproduction therefore requires stereophotography.

Prints from panchromatic films show no changes, and this also suggests that the deeper retinal structures are intact (figure 20c).

12. FLUORESCEIN ANGIOGRAPHY

At fluorescein angiography of the posterior pole in an 18-year-old patient with juvenile retinoschisis (figure 21), the fovea showed no changes; this has been confirmed by others (Harris 1969; Vainio-Mattila et al. 1969). This warrants the conclusion that the pigment epithelium and the deeper layers such as Bruch's membrane and choriocapillaris are probably free from pathological changes.

Electrophysiological, photographic and fluorescein-angiographic as well as histological findings (Yanoff et al. 1968) show that this condition has its primary onset in superficial retinal layers, while the deeper retinal structures are still intact. Only in advanced stages there is indication of atrophic pigment epithelium in the central retinal area (Krause et al. 1970).

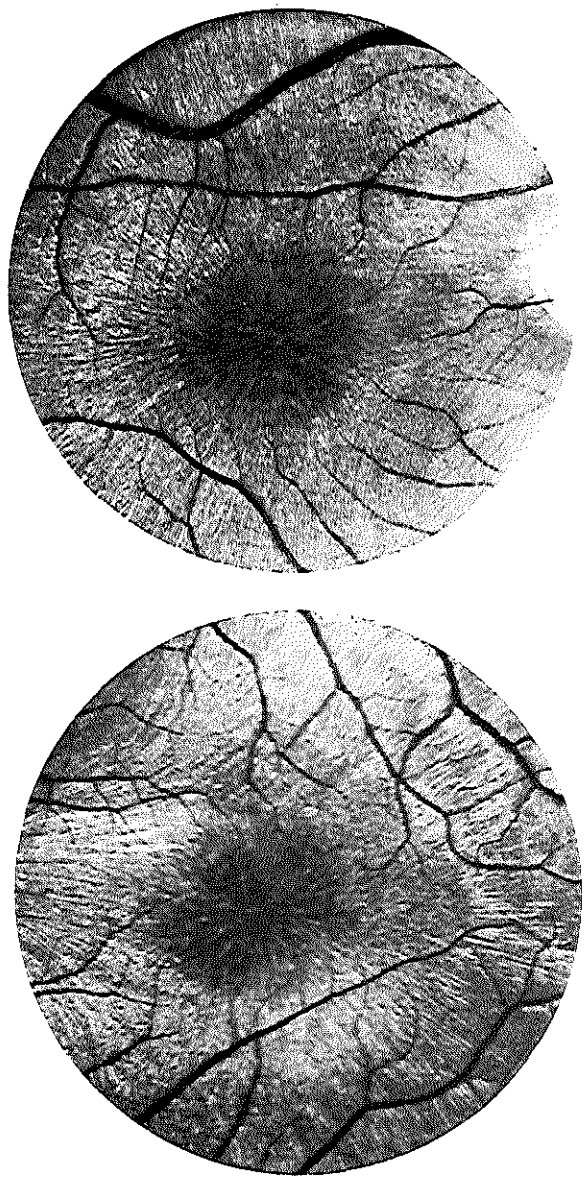


Fig. 20a-b. Superficial retinal striae in the fovea filmed on orthochromatic film. Right and left posterior pole of III-23, fam. Br.

13. CARRIERS

The carriers of the pathological gene of sex-linked juvenile retinoschisis are in any case the patients' mothers. I believe that these carriers cannot be distinguished from normal subjects either ophthalmoscopically or electrophysiologically, or in any

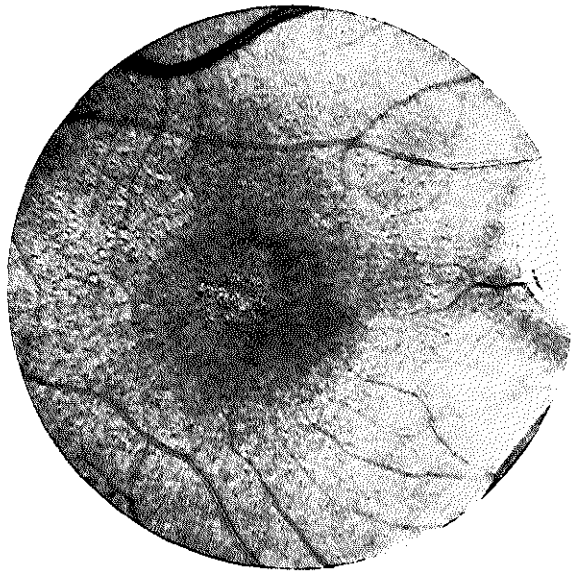


Fig. 20c. The same striae filmed on panchromatic film. The pathological striation is not visible on this material. Compare Fig. 20a-b.

other way. We have made an exhaustive study of several of these carriers (19 in total), without finding any abnormality. Retinal periphery, fovea, disc, retinal vessels and vitreous were quite normal, as were colour vision, visual fields, dark adaptation, ERG, local foveal ERG, OP and EOG.

Some authors, however, have reported slight abnormalities found in carriers.

Gieser and Falls (1961) found a unilateral macular cyst and a bilateral relative central scotoma in a carrier.

Sabates (1966) observed retinal changes of the type encountered in senile retinoschisis in two carriers, aged 41 and 42, respectively.

Stepanik (1969) found slight retinoschisis in the retinal periphery in one carrier, involving only one eye.

Vainio-Mattila et al. (1969) and Ewing and Ives (1969), like we ourselves, failed to find abnormalities in carriers they submitted to exhaustive ophthalmoscopic examination. In a few older carriers they did find macular degeneration or peripheral retinoschisis, but because these changes are quite common in elderly people in general, they need not necessarily indicate a special predisposition of the carriers.

At this time, therefore, there is unfortunately as yet no method to demonstrate carriers before they have produced a son with sex-linked juvenile retinoschisis.

The literature includes only one description of a woman with X-chromosomal juvenile retinoschisis (Forsius et al. 1962, 1963). This woman proved to be homozygotic for the pathological gene due to consanguineousness of her parents: father patient and mother carrier.

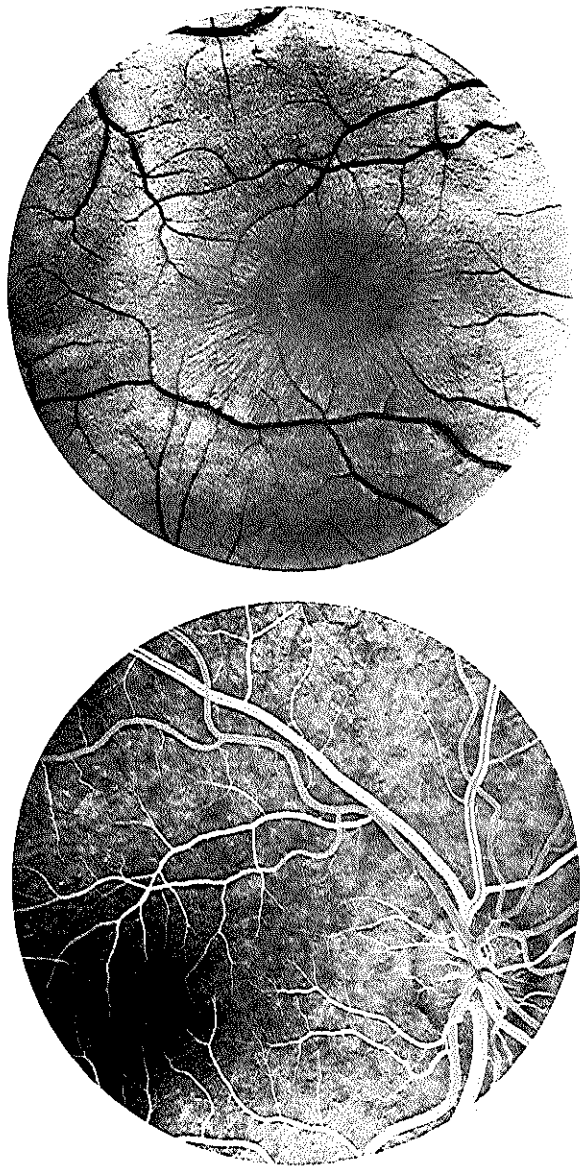


Fig. 21a-b. Conventional and fluorescence photograph of foveal retinoschisis in a 19-year-old boy (Fam. Wes.). The fluorescein pattern is normal.

14. HISTOLOGICAL FINDINGS

Yanoff et al. (1968) were the first to make a histological investigation in a well-documented case of sex-linked juvenile retinoschisis. The eye of a 4-year-old boy was enucleated on suspicion of retinoblastoma, although the contralateral eye

showed unequivocal signs of retinoschisis, which were also found in his brother.

The retina was found to show a cleavage at the level of the nerve fibre layer. The internal limiting membrane and part of the innermost retinal tissue were detached from the retina in large portions of the eye, but mainly in the lower temporal quadrant. "Special stains revealed no acid mucopolysaccharide within the areas of retinoschisis. A few of the sections showed a well-delineated hole in the outer layer of the split retina just posterior to the ora serrata. Erythrocytes and hemosiderin-laden macrophages were present in the subretinal space. Numerous tiny nodules of hyperplasia of the underlying retinal pigment epithelium and one large nodule associated with abundant PAS-positive material were present."

Thus we find that, in this affection, the cleavage is localized in much more superficial layers of the retina than in senile retinoschisis, where it affects the outer plexiform and adjacent nuclear layers.

Correctly in our opinion, Yanoff et al. (1968) prefer the term retinoschisis to the designation "congenital vascular veils" which Keith (1966) attempted to re-introduce. True retinoschisis is in fact involved, and our experience indicates that vascular veils are by no means always present in this condition.

Unlike juvenile retinoschisis, senile retinoschisis proves to be a slow-growing

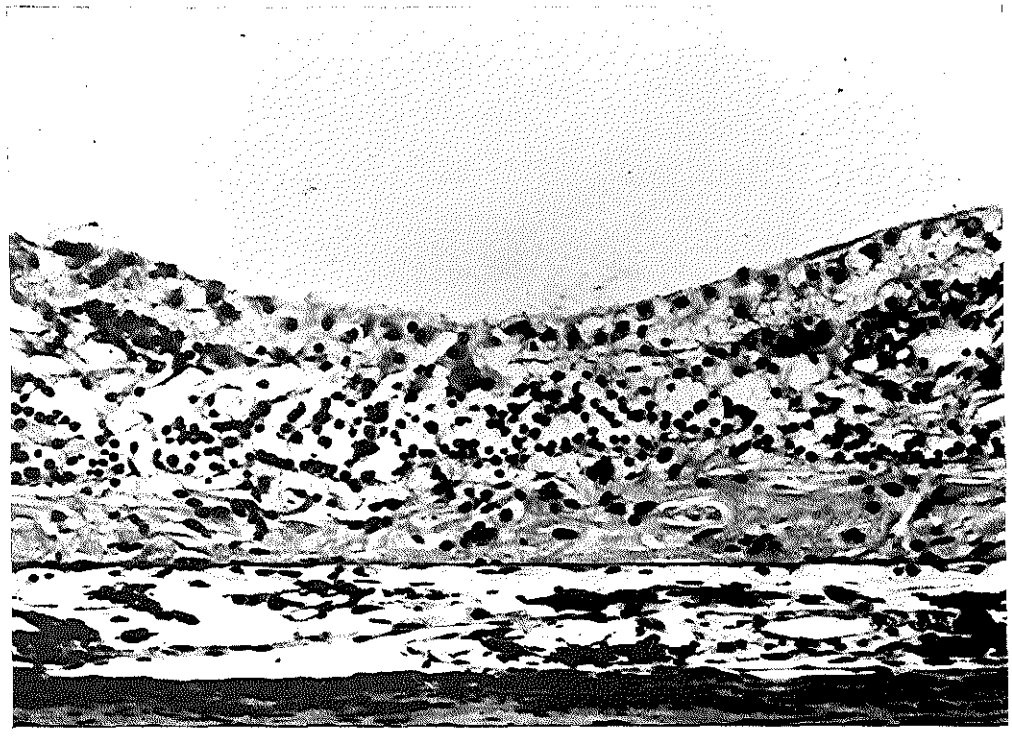


Fig. 22. Microscopic section of macular region showing atrophy of pigment epithelium.

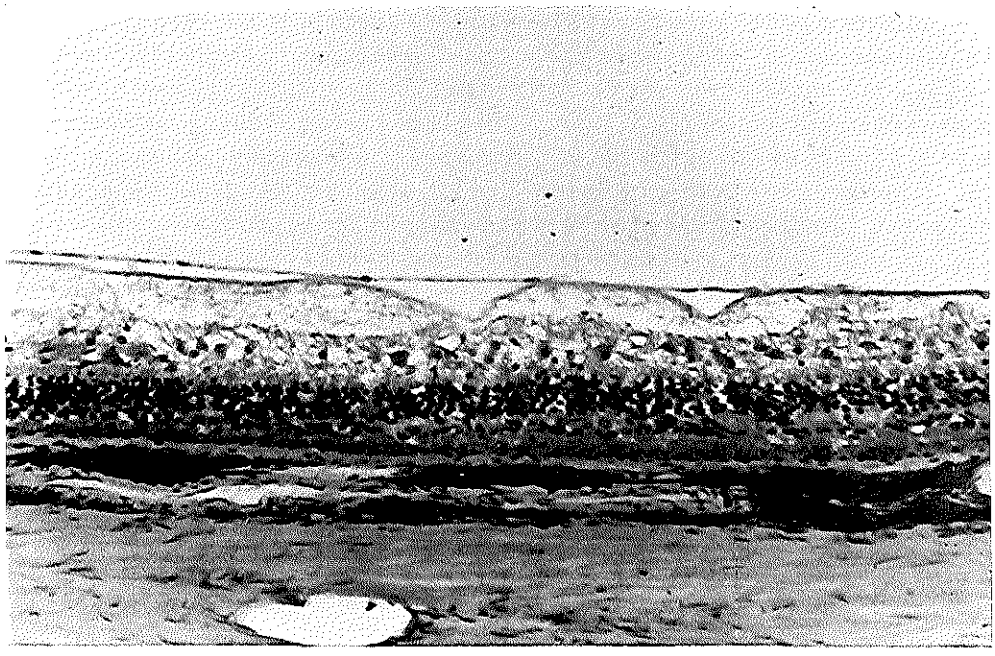


Fig. 23. Section of paramacular region showing folds in thickened internal limiting membrane covered by unfolded posterior hyaloid surface.

cyst which develops as a result of abnormal intraretinal secretion and accumulation of a hyaluronidase-susceptible acid mucopolysaccharide (Zimmerman and Spencer 1960; Hogan and Zimmerman 1962).

Yanoff et al. (1968) supposed that the basic pathology in juvenile retinoschisis consists of a hereditary disturbance of the innermost retinal layers.

The primary disorder might well be localized in the inner core of the cytoplasm of the Müller's cells. This defect would result in detachment of the internal limiting membrane with its adherent inner cores of the Müller's cells, from the remainder of the retina. The fact, that Yamada (1969) found many Müller's cells at the fovea combined with the phenomenon, that a foveal retinoschisis is always present supports this assumption.

Manschot (1969) had occasion to make a histological examination of the eyes of a man who died at age 60, who had been a member of the family investigated by Jager (1953), and who had had poor vision all his life. These eyes (unfortunately never submitted to ophthalmological examination) were enucleated 5 hours after death. Manschot's findings and conclusions were as follows:

"The sections through the macular (figure 22) and paramacular (figure 23, 24) region revealed a folded, thickened internal limiting membrane, degeneration of the nerve fibre layer – which seems to be the first stage of retinoschisis – and atrophy and proliferation of the pigment epithelium. The posterior hyaloid membrane

– recognizable by the presence of vitreous cells – had separated from the internal limiting membrane. More peripherally, the degeneration of the nerve fibre layer was more advanced; in fact the nerve fibres had almost completely disappeared over large areas. At some places, the almost detached internal limiting membrane was kept in position by only a few pillars composed of compressed axonal extensions of the photoreceptor cells together with the compressed cytoplasm of Müller's cells. (figure 25). Elsewhere an actual superficial splitting in a level above the retinal vessels had occurred. A rupture in the detached internal limiting membrane was met with in a series of consecutive serial sections. The external retinal layers and the pigment epithelium peripheral of the perimacular region and also the choroid showed no abnormalities. The histopathology of these two eyes confirms the finding by Yanoff, Rahn and Zimmerman (1968) that in hereditary sex-linked retinoschisis – as in non-familial infantile retinoschisis – the splitting of the retina occurs in the nerve fibre layer and not in the deeper retinal layers as is found in idiopathic and secondary retinoschisis in adults. It was believed by these authors that the superficial retinoschisis is probably due to an inherited defect in the innermost portion of the cytoplasm of Müller's cells by which the internal limiting membrane and attached parts of Müller's cells split away from the rest of the retina. The findings of severe degeneration and atrophy of nerve fibres in both the central and peripheral parts of the

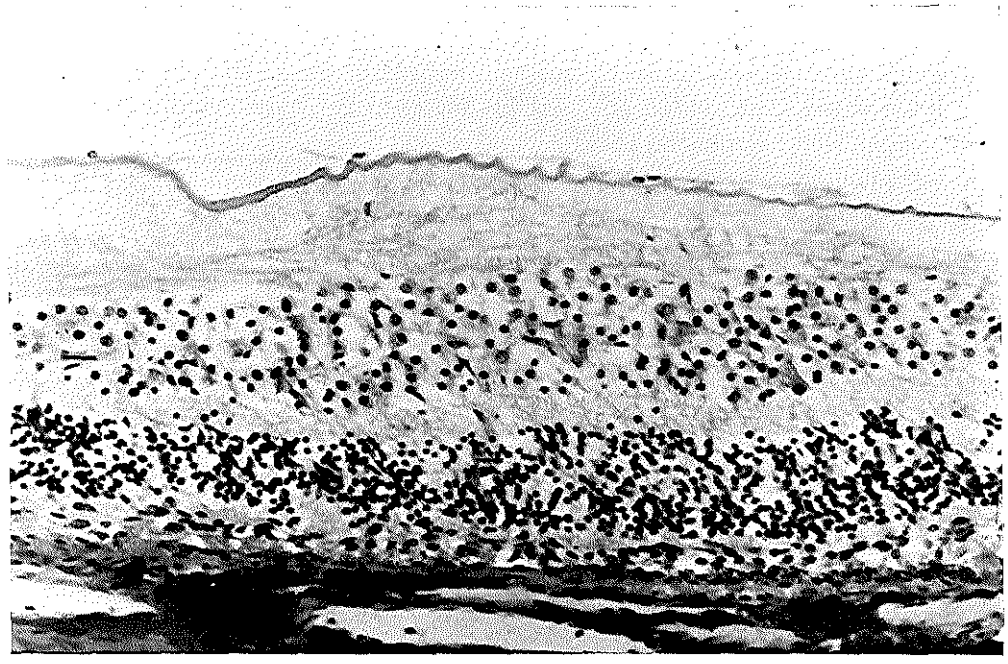


Fig. 24. Section of paramacular region showing a thickened internal limiting membrane with one large and numerous small folds. Beginning degeneration of nerve fibre layer. Irregular pigment epithelium.

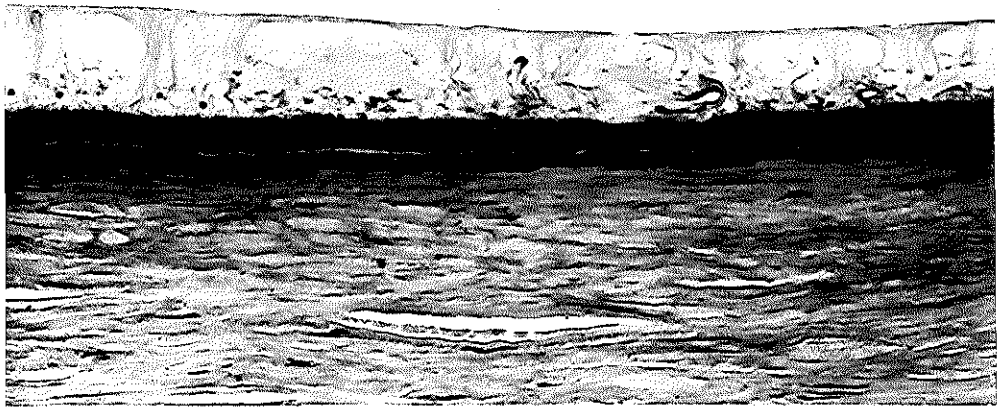


Fig. 25. Section of equatorial region: severe atrophy of nerve fibre layer.

retina in the present microscopic study seems to indicate that an inherited defect may also be located in the retinal nerve fibres. The optic atrophy which has been encountered in a large number of clinically studied cases seems in favour of this view."

However, it is possible that the nerve fibre and optic atrophy nearly always found in advanced cases, may be secondary to defects in Müller's cells.

15. PATHOGENESIS

The evolution of this condition is probably as follows. A primary defect in the nerve fibre layer or its supportive tissue results in retinoschisis. This retinoschisis causes posterior vitreous body detachment, and traction from the vitreous can gradually lead to ruptures and defects in the separated superficial retinal structures. Next, veils come to float in the vitreous which do or do not enclose retinal vessels (figures 12, 13 and 14). Ruptures of retinal vessels caused by traction from the vitreous, can give rise to vitreous haemorrhages. The denuded retinal areas begin to assume an atrophic appearance, and extensive retinal atrophy can occur. In some cases there may next be defects also in the outer retinal layer, and true retinal detachment can then result. The vitreous ultimately shows vacuolation, syneresis and fibrillar degeneration. This vitreous degeneration can be a primary development; but it can also result from the retinoschisis. An argument in favour of the latter possibility is the fact that we found a normal vitreous in cases with only foveal retinoschisis. It is still uncertain whether the ERG changes are a result of the retinoschisis or con-

stitute a primary disorder in the bipolar cells. We can fully agree with the views of Juler (1947), Jager (1953) and Bengtsson and Linder (1967), and others, that the primary pathological structures are to be found in the inner retinal layers. We disagree with the views of Mann and McRay (1938) and Keith (1966), who opt in favour of a primary vitreous defect and a secondary retinal disturbance. The suggestion offered by Scorciarini-Coppola et al. (1958) – that intraocular haemorrhages could cause proliferative retinitis – can be refuted, we believe, especially since histological findings are now available.

Juler (1951) suggested an inflammatory, possibly syphilitic cause for a few of his cases; Arruga and Weve (quoted by Juler 1951) likewise concluded that an early inflammation or vascular change rather than a developmental disorder may have been involved. Juler's hypothesis (in 1947) that there was a "cystic change in the layers of the retina, having a developmental basis, with thinning and ruptures of the inner linings of the cyst", was much more in accordance with current views.

16. MODE OF TRANSMISSION

Sex-linked juvenile retinoschisis shows an X-chromosomal recessive mode of transmission. Male patients transmit the pathological gene to all their apparently normal daughters, while their sons are entirely normal. The daughters, indistinguishable from normal subjects, produce sons who are affected in 50% of cases, and daughters who, in 50% of cases, carry the gene like their mothers.

Although carriers are generally not affected, it is possible that later in life they show a predisposition to macular degeneration and peripheral retinoschisis. In view of the Lyon hypothesis of random inactivation of one of the two X-chromosomes, one might expect mild abnormalities in the carriers (Krill 1969), but this proves so far not to be true.

Linkage

The locus of the retinoschisis is currently a candidate for measurable linkage to the locus of the Xg blood group. The six families that provide linkage information indicate that these loci are not lying very close together (Eriksson et al. 1967; Vainio-Mattila et al. 1969). In two retinoschisis families in which deuteranomalopia occurred, the loci likewise did not seem to be closely spaced (Vainio-Mattila et al. 1969).

Sex ratio

There are indications that the secondary sex ratio is high (Eriksson et al. 1967; Vainio-Mattila et al. 1969). Schepens (1966) had also noticed that children of retinoschisis carriers seemed to include more boys than girls. In the families we investigated, the carriers likewise showed a predilection for male children (69 males, 49 females).

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

General physical examination and laboratory studies disclosed no abnormalities in those of our patients in whom they were carried out.

Some authors have suggested shrinkage of the vitreous as a result of intraocular haemorrhage as a possible cause of this condition.

Scorciarini-Coppola (1958) found hypoprothrombinaemia and factor VII deficiency. Balian and Falls (1960) described a thrombocytopathy in one family. Hauschild et al. (1970) found in one of their 3 patients a mild thrombocytopenia and a slightly prolonged bleeding time. Gieser and Falls (1961) had exhaustive clotting studies made in five of their cases: "Capillary fragility, Ivy bleeding time, whole blood and silicone clotting times, clot retraction, platelet count, platelet thromboplastic activity, one-stage prothrombin time, serum prothrombin activity, thromboplastin generation test, factors V and VII estimation and thrombelastography. There were no consistent significant abnormalities present." Kahán et al. (1963) found symptoms of thalassaemia minor in a boy and those of acanthocytosis in his twin-brother. Falls (1966) described acanthocytosis in two patients with juvenile retinoschisis. In three patients examined in this respect, we found no abnormalities of the red corpuscles.

As can be expected in a condition which, so far as we know, involves only the eyes, the chromosome pattern was entirely normal (Korchmáros 1965; Bengtsson and Linder 1967).

18. ASSOCIATED CONDITIONS

In one of our patients (III-23, fam. Br) we diagnosed glaucoma at a very early age. Gonioscopy revealed that the iris was inserted too anteriorly.

Adequate regulation of the ocular pressure was ensured by means of filtering operations. A younger brother of this patient, likewise suffering from juvenile retinoschisis, showed a normal iridocorneal angle and a normal ocular pressure.

Sabates (1966) also described abnormalities of the irido-corneal angle, but no glaucoma. His most frequent finding was a delicate membrane extending from the iridal root to the line of Schwalbe, while fairly large dilated vessels were visible in the iridocorneal angle.

Otherwise I have been unable to find associated conditions either in the literature or in personal observations.

19. DIFFERENTIAL DIAGNOSIS

We believe that sex-linked juvenile retinoschisis is a common condition. It is probably the most common form of "juvenile macular degeneration". The fact that the condition is still often overlooked or misdiagnosed has led to the impression of rarity. We have noticed this in several of our patients and others have reported a similar experience (Bengtsson and Linder 1967; Vainio-Mattila 1969). The condition is often diagnosed as heredodegeneration of the macula or retinal periphlebitis; other

diagnoses given are bilateral amblyopia of unknown origin, and retinal dysfunction. The cases described by Barut (1955: périphlébite rétinienne), Oksala (1953: juvenile macular dystrophy), Korchmáros et al. (1965: heredodegeneration of the fovea centralis), Peralta and Santori (1967: Stargardt's disease), Sebestyén et al. (1967: juvenile degenerative ablatio retinae), Amalric (1968: nouveau type de plis rétiniens congénitaux) are reminiscent of juvenile retinoschisis; and Planche XX fig. 2 in the book "Les Lérédo-dégénérescences choriorétiniennes" (Franceschetti et al. 1963) is more reminiscent of sex-linked juvenile retinoschisis than of Stargardt's disease.

The cases described by Bartels (1933), Jancke (1935) and Goodside (1960) are sometimes classified as juvenile retinoschisis, but I doubt the correctness of this classification, partly because these patients showed no cystoid foveal affection and because no sex-linked transmission was demonstrated.

Since juvenile retinoschisis shows substantial differences in expressivity, the differential diagnosis should encompass a great many, sometimes widely disparate diseases. Differentiation should consider the following conditions, dependent on the expressivity of the pathological gene and the evolution of the clinical picture.

1. *Stargardt's disease.* This is likewise frequently found in several children in the same family; however, girls are affected as frequently as boys. The transmission is autosomal recessive, and the fovea does not show the characteristic radial and cystoid features of juvenile retinoschisis, but instead an atrophic aspect. Patients with Stargardt's disease have always had good vision prior to manifestation of the ocular abnormality, whereas patients with juvenile retinoschisis have diminished vision from birth.

2. *Eales' disease* (*retinal periphlebitis*). Vitreous haemorrhages and opacities as well as vascular sheaths and retinitis proliferans are seen in this disease. Since this disease if often found in young males and is bilateral, moreover, differential diagnosis is sometimes not easy. But foveal abnormalities are rare in the initial stages and, if present, they do not show the radial plication which characterizes foveal retinoschisis (Rosselet-Huguenin 1970).

3. *Cicatrices of chorioretinitis.* The pigmentations and greyish-white foci sometimes found in juvenile retinoschisis can be very reminiscent of a former chorioretinitis.

4. *Wagner's vitreoretinal dystrophy.* This condition, first described by Wagner in 1938, has an autosomal dominant mode of transmission. In these cases vision is often initially good, and the posterior pole normal at ophthalmoscopy. The vitreous shows marked syneresis and as a rule is optically empty, while non-vascularized preretinal white-grey bands are usually visible at the level of the equator. No vascular veils are seen. Finally, complicated cataract occurs. Dark adaptation is undisturbed and the ERG is subnormal.

5. *Vitreotapetoretinal dystrophy of Goldmann-Favre.* This condition, first described by Goldmann and Favre in 1957, has an autosomal recessive mode of transmission. The vitreous is degenerative, and no veils with vessels are observed in it. Central and peripheral retinoschisis occurs, and lattice-like degeneration as well as

preretinal glial strands are often present in the retinal periphery, which also shows trabecular pigmentations (MacVicar and Wilbrandt, 1970). All this is accompanied by progressive impairment of retinal function, resulting in severe night-blindness and an unrecordable ERG. Complicated cataract finally results, and the progression of the dystrophic process ultimately leads to blindness.

6. *Ablatio falciformis.* This condition, in which a retinal fold extends from the disc, usually in temporal direction, has an autosomal recessive mode of transmission. No vitreous veils are observed.

7. *Inferior dialysis of the young* (Sabates 1966; Schepens 1966) or juvenile retinal cyst (Falls 1966) usually entails bilateral retinal detachment in the lower temporal quadrant. According to Schepens (1966), many cases of so-called cysts which later produce dialysis are erroneous diagnoses of an early retinal detachment with a dialysis already present but initially overlooked.

8. *Senile retinoschisis.* This is a retinoschisis at the level of the outer plexiform retinal layer in elderly individuals, caused by intraretinal cystic degeneration of the peripheral retina. In none of these cases will the characteristic foveal retinoschisis with radial plication be encountered.

9. *Retinal detachment.* In the retinal detachment usually observed, none of the symptoms characteristic of juvenile retinoschisis is present.

10. In severe cases with extensive vitreous opacities, differentiation from *gliomas* and *pseudogliomas* is required (Pajtáš 1950; Yanoff et al. 1968).

11. *Autosomal juvenile retinoschisis.* In this rare disorder females are affected, too, and there is no pathognomonic foveal retinoschisis (Cibis 1965).

The "hereditary vitreoretinal degeneration and night-blindness" recently reported by Feiler-Ofry et al. (1966), and the "familial exudative vitreoretinopathy" which Criswick and Schepens (1969) described, somewhat resemble sex-linked juvenile retinoschisis, and adequate, clear differentiation of these syndromes is desirable. At the present time the syndromes, so recently described, are not readily classifiable.

The last differential diagnosis we mention concerns the *chorio-retinal folds* which can occur upon retrobulbar pressure on the eyeball and in association with thyroid dysfunction; radial plicae in the fovea also occur in many of these cases (figure 26). *Sickle cell ocular disease* (Goodman, 1968), too, can occasionally present symptoms and signs reminiscent of X-linked juvenile retinoschisis.

20. THERAPY

There is as yet no agreement about the treatment of choice in sex-linked juvenile retinoschisis. In fact no therapy seems be very successful. All the techniques employed against retinal detachment have been used in this condition, and photocoagulation in particular has been frequently resorted to (Pischel 1963, 1969; Utermann 1964; Törnquist 1964; Okun and Cibis 1964; Cibis 1965; Colyear 1965; Harris 1968, 1969; Johnson 1969; Brockhurst 1970).

These authors advocate photocoagulation, by which the retinoschisis is arrested

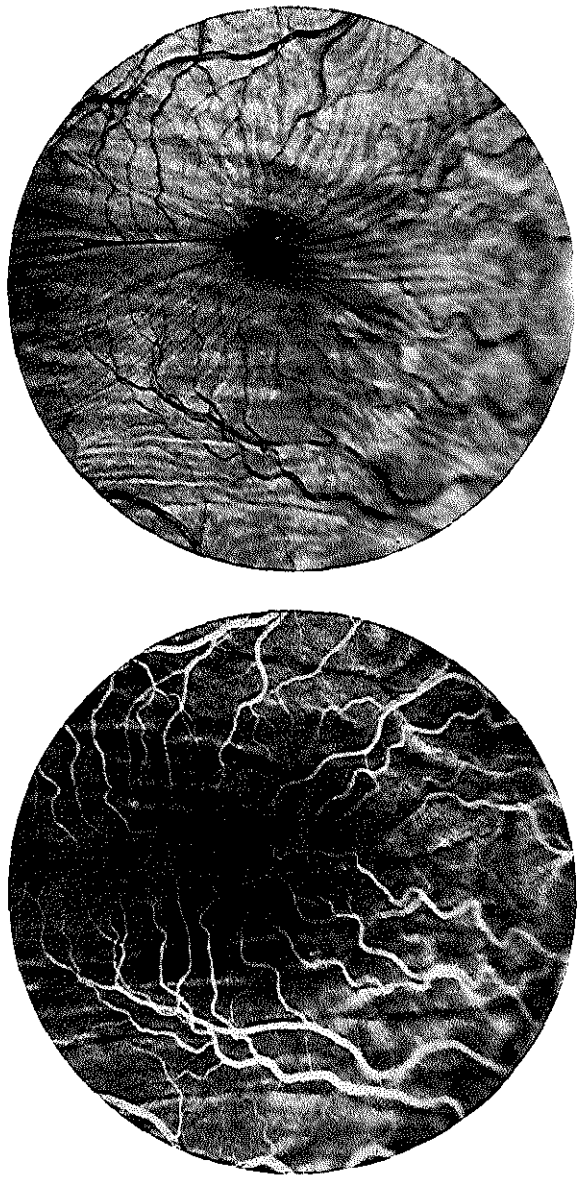


Fig. 26a-b. Conventional and fluorescence photograph of chorioretinal folds in a 55-year-old female, presumably suffering from an euthyroid form of Graves' disease.

with the aid of coagulates on the central side. The results of this therapy are described as very satisfactory. Okun and Cibis (1964) have advocated coagulation of the entire surface in the case of a cyst, because complete and permanent collapse of the retinal cyst usually followed.

Brockhurst (1966) is afraid that photocoagulation can in fact cause exacerbation of the retinoschisis; experience reported by Witmer (1965), Liesenhoff (1969) and Jungschaffer (1969) also points in this direction. Of course the luminance used and the duration of photocoagulation play an important role in this respect. Doses should be determined with prudence because overdosage is bound to produce disastrous results. Witmer (1965) has advocated diathermy, followed if necessary by puncture of the intraretinal cyst. Like sclerectomy and various buckling procedures, this method is used by various authors (Pischel 1963, 1969; Harris 1969).

Schepens (1966) advised that surgery be resorted to only if true retinal detachment has occurred, but Pischel (1969) had the impression after treating seven patients that early intervention offers the best chance of success. However, spontaneous improvement has also been observed (Schepens 1966). In only one of our patients (IV-3, fam. Hel) did we resort to surgery because the fovea was seriously endangered by retinoschisis (figure 15). Sclerectomy with pucture of the intraretinal cyst was performed. The success of this operation in regard to the visual field will have to become apparent in future. Vision was already poor due to the foveal retinoschisis. It should always be borne in mind that, in the vast majority of cases, the ever-present foveal retinoschisis will make it impossible to obtain an ultimate visual acuity much better than 1/10. In summary, we tend to advise surgical intervention in any case:

1. if true retinal detachment exists;
2. if the posterior pole is endangered by retinoschisis from the periphery;
3. if the retinoschisis shows so marked a progression that it exceeds the equator.

Regular ophthalmoscopic and perimetric examinations are consequently important in all these cases, especially since the condition takes a very slow, gradually progressive course. The frequently seen defects in the inner retinal layer constitute no therapeutic indication. Only defects in the outer layer of the retina (rarely observed in this condition) require surgical intervention lest retinal detachment results.

21. FUTURE

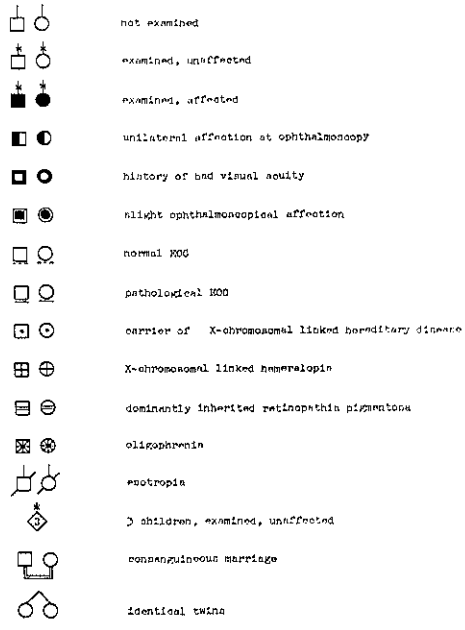
It will be of importance to develop methods for the detection of carriers, and efforts will have to be made to identify the exact cause of the developmental defect underlying this condition.

In addition, it will be interesting to establish the extent to which sex-linked juvenile retinoschisis and sex-linked hemeralopia are related. Both conditions have an X-chromosomal mode of transmission; both are already present at birth, and involve disturbances in the cone- as well as in the rod-systems. In both conditions retinal function tests disclose diminished visual acuity, photopic as well as scotopic disorders of dark adaptation, a photopically and scotopically subnormal ERG, and a normal EOG. Both are characterized by diminished sensitivity to red. Both conditions show changes which seem to be localized on the innerside of the pigment epithelium.

22. CASE HISTORIES

The description of the case histories is restricted as much as possible to pathological findings. Normal findings usually are not mentioned.

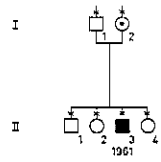
The letters and numbers in brackets refer to the names and the dates of birth. This facilitates follow-up examinations.
(for example: JJ-08.06.14 means: Jan Jansen, born 14th June 1908).



1. Fam. vBaa
PvB (65.05.18) Poor vision since early childhood. The maternal grandfather and a maternal uncle are reported to have bad visual acuity in both eyes since many years.
1969: VOD S+3.50 5/20; VOS S+4 1/30.
There is a concomitant convergent strabismus of OS.
Refracting media: Normal anterior segment of the eye. The vitreous body shows fine opacities and some fibrillary degeneration.
Fundi: Foveal retinoschisis. In OS is a pigmented line visible in the posterior pole. In the inferior quadrants vascular veils are present. Oval and round defects are in these vascularized veils.

Summary: A 4-year-old boy with X-linked juvenile retinoschisis. He has had a convergent strabismus since early childhood. In all probability the father and one of the brothers of this patient's mother are suffering from this condition too. The mother, being a carrier, has quite normal visual acuity, media and fundi.

2. Fam. Bak

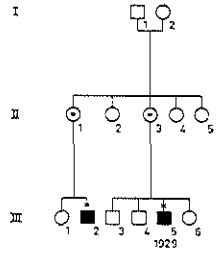


I-2 (BR) VODS 10/10, emmetropic.
Refracting media and fundi: Normal.

II-3 (NCB-61.09.27) Poor vision was noted in early childhood.
1967: VOD C+1×25° 1.5/10; VOS C+1×35° 1.5/10.
Vitreous body: Posterior vitreous detachment. Fibrillary degeneration and fine white opacities.
Fundi: Foveal retinoschisis. Peripheral retinoschisis infratemporally. Some retinal veils in which veins are visible.
Visual fields: Limitation in the superior nasal quadrant. Reduced central sensitivity.
Colour vision: Slight red-green dyschromatopsia (HRR).
Dark adaptation: Phot. curves almost normal. Scot. curves 0.5 log.U. too high.
ERG: 1967: Scot. b-waves OD 55μV; OS 65μV.
Phot. b-waves OD 75μV; OS 70μV.
1968: Scot. b-waves OD 85μV; OS 90μV.
Phot. b-waves OD 60μV; OS 65μV.
EOG: Unreliable because of bad fixation.

Summary: A 6-year-old boy, suffering from sex-linked juvenile retinoschisis. The mother, carrier of the pathological gene, has normal eyes.

3. Fam. dB



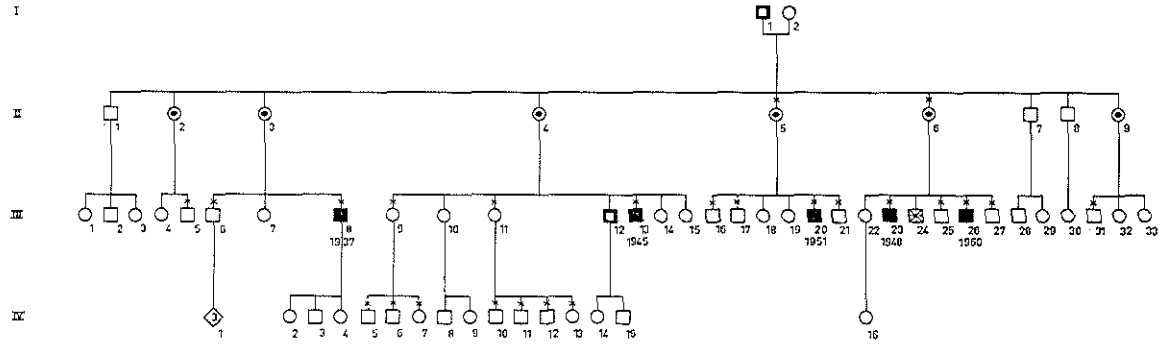
III-2 (WK) Poor vision was noted in early childhood. Visited many ophthalmologists. No definite diagnosis has been made so far:
1969: VOD C+4.25×185° 2/10; VOS C+3×175° 1/10.
Vitreous body: Posterior vitreous detachment. Fibrillary degeneration.
Fundi: Atrophic changes in the foveal area. No stellate folds and no cystoid structure in the fovea. Vascularized retinal veils in the inferior temporal periphery. These veils project into the vitreous and carry veins from the retinal vasculature. The retina as a whole has a silver-grey glistening appearance.

III-5 (WAdB-29.02.08) This man has always had poor visual acuity in both eyes. Asks, whether he will become blind. No definite diagnosis has been made.
1969: VOD S+3 1/60; VOS S+3.50 1/10.
Vitreous body: Fibrillary degeneration and posterior vitreous detachment.
Fundi: Atrophic changes in the foveal area. Absent foveal and foveolar reflexes. No stellate folds and no cystoid structure visible in the fovea. In the right eye is a pigmented line, extending from the disc across the foveal area towards the periphery. The temporal side of the disc shows some pallor. The periphery has a silver-grey glistening appearance. Vascular veils are present infratemporally.
Visual fields: Limitation in the superior nasal quadrant.
Colour vision: Red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: Phot. and scot. curves 2/3 log.U. too high.
ERG: Unrecordable.

F-ERG: Unrecordable.
VER: Absent.
EOG: Very low standing potential, which shows a very small rise during light adaptation.

Summary: Two cousins, who always had poor visual acuity in both eyes. No definite diagnosis had been made before the examination, although both individuals, being over 40 years of age, had visited many ophthalmologists. The diagnosis is X-linked juvenile retinoschisis. Vascular veils are present. The foveal retinoschisis has changed into foveal atrophy.

4. Fam. Br



I-1 (CMAEvE-90.05.25) This man has always had poor visual acuity in both eyes. Died 50 years ago.

II-5 (CZvE-23.02.07) VODS 10/10, emmetropic.
Refracting media and fundi: Normal.
ERG: Scot. b-waves OD 250μV; OS 235μV.
Phot. b-waves OD 110μV; OS 120μV.
EOG: OD 2.10; OS 2.15.

II-6 (JJBvE-27.12.19) VODS 10/10.
Refracting media and fundi: Normal.

III-8 (JCV-37.10.28) Poor vision since early childhood. Slight complaints about vision in dark. No complaints about colour vision.
1968: VOD S+0.50=C+1.50×30° 4/10; VOS S+0.50=C+1.50×150° 2/10.
Refracting media: Slight opacities in the lens of the left eye.
Vitreous body: Fibrillary degeneration and syneresis.
Fundi: Foveal retinoschisis, consisting of a cystoid structure with a typical radiate folding of the superficial layer (fig. 7). Retinoschisis in the inferior part of the retina (fig. 8, 13).
Refuses further examination.

III-12 (LDG-42.12.04) Is reported to have poor vision since early childhood. Refuses to come for examination.

III-13 (CMAG-45.03.25.)
1964: VOD 4/60, emmetropic; VOS 2/10, emmetropic.
Old vitreous haemorrhage in the right eye.
Vitreous body: Posterior vitreous detachment.
Fundi: Foveal retinoschisis. Discs, vessels and retinal periphery are normal.
1970: VOD 4/60, emmetropic; VOS S+0.50=C−0.75×60° 5/10.

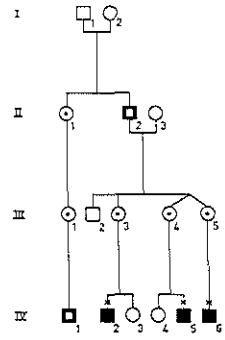
III-20 (CFZ-51.01.27) This boy had never visual complaints.
1969: VOD S+0.50=C+0.50×180° 7/10; VOS S+0.50=C+0.50×180° 7/10.
Vitreous body: Normal.
Fundi: Foveal retinoschisis (fig. 6). Silver-grey glistening retina.
Colour vision: Slight red-green dyschromatopsia (HRR). Slightly decreased sensitivity to red (anomaloscope).
Visual fields: Decreased central sensitivity. Normal peripheral limitations.
Dark adaptation: Phot. and scot. curve about 1 log. U. too high.
ERG: Scot. b-waves OD 115 μV; OS 120 μV.
Phot. a-waves OD 35 μV; OS 40 μV.
Phot. b-waves OD 60 μV; OS 55 μV.
F-ERG: Subnormal. Curve broader than normal.
VER: Present.
EOG: ODS 2.10.

III-23 (ABr-48.02.10) Poor vision since early childhood.
1956: VOD S+0.50=C+1×180° 1/10; VOS C+1×180° 1/10.
Refracting media and vitreous body: Normal.
Fundi: "Absent foveal reflexes. No distinct abnormalities".
1958: VODS 1/10.
Visual fields: Concentric limitation of sensitivity. No peripheral suppression.
Colour vision: Red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: Curve slightly too high.
ERG: Scot. b-waves subnormal.
Phot. b-waves slightly subnormal.
1966: VODS 5/60. The tension of both eyes is elevated. An Elliot trephining is performed on the right eye. After the operation the eye pressure of OD is normalized.
1968: VODS 5/60. The tension of OD is normal, the tension of OS is still too high.
Gonioscopy: Narrow angle, which is closed on some spots. The irisroots are inserted too far forward. The ciliary band is not visible.
Vitreous body: Normal.
Colour vision: Unchanged.
Visual fields: Unchanged.
Dark adaptation: The curve is 1.5 – 2 log.U. too high.
ERG: Scot. b-waves ODS unrecordable.
Phot. b-waves OD 70 μV; OS 75 μV.
F-ERG: Subnormal.
EOG: OD 2.56; OS 2.54.
Photography: Orthochromatic films give far better results than do panchromatic graphic films. This suggests a superficial localization of the main abnormalities in X-linked juvenile retinoschisis (fig. 20).
1969: A filtering procedure according to Scheie is performed in the left eye. Postoperatively the tension is normalized.

III-26 (FBr-60.04.13) This boy resembles his brother, III-23 strikingly. Both individuals are blond and have blue eyes, and they have the same character and physique.
1968: VOD 2/10, emmetropic; VOS 2/10, emmetropic.
Refracting media and vitreous body: Normal.
Fundi: Foveal retinoschisis (fig. 4). The foveal and foveolar reflexes are absent. The disc of the right eye has a strange recess. Vessels and retinal periphery are normal.
Visual fields: Decreased central sensitivity. Normal peripheral limitations.
Colour vision: Slight red-green dyschromatopsia (HRR). Decreased sensitivity to red.
Dark adaptation: Phot. almost normal, scot. 0.5 log. U. too high.
ERG: Scot. b-waves OD 65 μV; OS 75 μV.
Phot. b-waves OD 70 μV; OS 70 μV.
EOG: OD 2.15; OS 2.30.
Photography: Orthochromatic films give good details of the fine stellate folds radiating from the foveola toward the perifoveal area. Panchromatic films give far fewer details, often suggesting a normal posterior pole.
Gonioscopy: Normal.

Summary: X-linked juvenile retinoschisis in at least 5 individuals belonging to one family. Foveal retinoschisis is present in all these 5 patients. Although the foveal alterations differ hardly at all ophthalmoscopically, the differences in visual acuity are remarkable (compare III-20 and III-23). Peripheral retinoschisis was found in only one of these 5 cases.

5. Fam. vdBr



II-2 (HP) Poor visual acuity since early childhood.

IV-1 (vB) Reported to have had poor visual acuity since early childhood.

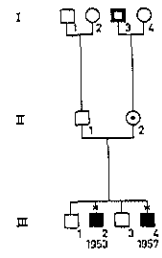
IV-2 (HD-46.12.15) Poor visual acuity since early childhood. Foveal and peripheral retinoschisis in fundo.

IV-5 (DvdB-53.03.07)
1966: VOD S−3.50 10/10; VOS S−0.50 2/10.
1968: VOD S−5 8/10; VOS S−0.50 2/10.
1970: VOD S−5 2/10; VOS S−1 2/10.
Media: Fibrillary degeneration of the vitreous body. Syneresis and some optically empty structures.
Fundi: Foveal retinoschisis on both sides. Peripheral retinoschisis and greyish reflexes in the inferior part of both fundi.
Visual fields: Decreased central sensitivity. Restriction on the upper side of both fields.

IV-6 (WvR-52.03.11) Has long been known as a patient with retinal detachment or retinoschisis and macular degeneration.
Fundi: Foveal and peripheral retinoschisis.

Summary: Pedigree with 5 affected individuals, suffering from X-linked juvenile retinoschisis. It is of interest to note that IV-5 is myopic in contrast to the hypermetropia which is nearly always found in this syndrome.

6. Fam. E-E



I-3 (AE-80.04.15) Was the only child. Has always had poor visual acuity in both eyes.

II-2 (CAvdE-20.05.08) VODS S−0.25 10/10.
Refracting media and fundi: Normal.

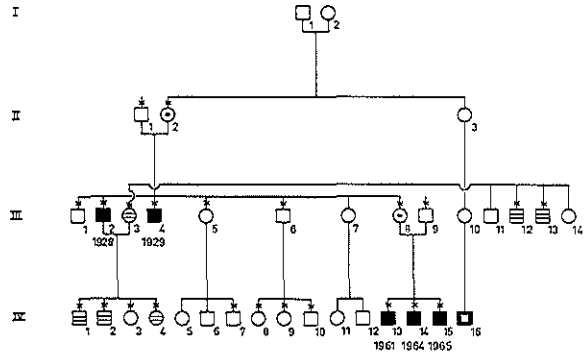
ERG: Scot. b-waves OD 290μV; OS 315μV.
Phot. b-waves OD 105μV; OS 125μV.

III-2 (WHvdE-53.04.13)
1960: VOD S+3=C+1.50×180° 3/10; VOS S+2=C+0.50×180° 4/10.
Vitreous body: Normal.
Fundi: Foveal retinoschisis. Silver-greyish glistening retina.
Visual fields: Decreased central sensitivity.
Colour vision: Normal.
Dark adaptation: Curve 0.5 log.U. too high.
ERG: Scot. b-waves OD 60μV; OS 70μV.
Phot. b-waves OD 55μV; OS 70μV.
Systemic examination: Normal.
1967: VOD S+3.50=C+1×175° 2/10; VOS S+2=C+0.50×180° 4/10.
Media, fundi, visual fields and colour vision: Unchanged.
Dark adaptation: Curve 0.5 log.U. too high.
ERG: Scot. b-waves OD 115μV.; OS 100μV.
Phot. b-waves OD 70μV.; OS 65μV.
EOG: OD 3.45; OS 2.60.

III-4 (AvdE-57.07.27)
1960: Skiascopy: ODS +6.
Refracting media: Normal.
Fundi: Foveal retinoschisis. Parafoveally there are some white-greyish areas with pigmentary changes. There is no retinoschisis present.
ERG: Scot. b-waves OD 72μV; OS 55μV.
Phot. b-waves OD 69μV; OS 54μV.
Systematic examination: Normal.
1967: VODS S+6 5/60.
Refracting media and fundi: Unchanged.
Visual fields: Decreased central sensitivity. Normal peripheral limitations.
Dark adaptation: Curve ends 1 log.U. too high.
ERG: Scot. b-waves OD 65μV; OS 70μV.
Phot. b-waves OD 50μV; OS 40μV.
EOG: OD 1.95; OS 2.00.

Summary: Two brothers with X-linked juvenile retinoschisis. The younger of the brothers shows greyish retinal scars, resembling scars of a choroiditis.

7. Fam. Go



II-2 (NGV-02....) VODS 10/10, emmetropic.
Refracting media and fundi: Normal.

III-2 (WCG-28.03.11) Poor vision since early childhood. Many times operated on the left eye. In both eyes nystagmus with horizontal and rotatory components.
VOD 1/300; VOS 2/60.
Refracting media: OD normal. OS some after-cataract.
Fundi: In the posterior pole of OD a white-greyish patch, resembling the scar of a choroiditis. The right disc is too pale. In the midpheriphery distinct retinoschisis. The fundus of the left eye is not very well to judge because of the after-cataract.

III-3 (MGvH-31.02.11) This patient is suffering from a dominantly inherited retinopathia pigmentosa. Her father has been affected, while two of her brothers (III-12, 13) and three of her children (IV-1,2,4) are affected too. She met her husband in an institute for visually handicapped individuals. All affected individuals have discs with wax-like yellowish appearance, while the retinal vessels are extremely attenuated.

III-4 (JFG-29.07.09) Bad visual acuity since early childhood.
Refracting media: Normal.
Fundi: Atrophic changes in the foveal area. The discs are slightly too pale.

III-8 (JAvdHG-41.11.01) VODS 10/10.
Media and fundi: Normal.
ERG: Scot. b-waves OD 445μV; OS 370μV.
Phot. b-waves OD 110μV; OS 115μV.
EOG: ODS 1.80.

IV-13 (JvdH-61.11.12) VOD 5/30; VOS C+1×100° 5/30.
Vitreous body: Fibrillary degeneration and fine white opacities. Posterior vitreous detachment.
Fundi: Foveal retinoschisis. Vascular veils in the inferior part of the vitreous body. Some white preretinal strands and dendritic structures.
Colour vision: Slight red-green dyschromatopsia (HRR).
ERG: Scot. and Phot. b-waves definitely subnormal.

IV-14 (MvdH-64.02.20) Nystagmus of the left eye.
1968: VOD 5/15; VOS searching movements.
Vitreous body: Posterior vitreous detachment.
Fundi: Foveal retinoschisis in OD. A darkly pigmented line runs over the fovea of the left eye. Greyish preretinal strands and vascularized veils are visible in the inferior part of both fundi.
ERG: Scot. b-waves OD 60μV; OS 50μV.
Phot. b-waves OD 80μV; OS 65μV.

IV-15 (BvdH-65.11.11) First examination on 18-12-1967.
Fundi: Foveal retinoschisis in both eyes. Discs, vessels and retinal periphery are normal ophthalmoscopically.

IV-18 (GCvD-62.11.07) Is reported to have bad visual acuity since early childhood.

Summary: X-linked juvenile retinoschisis in 5 individuals, belonging to one family. Three brothers (IV-13, 14 and 15) show the pathognomonic foveal retinoschisis, while the abnormalities in III-2 and 4 are more difficult to interpret. This illustrates the importance of family examination, whenever the diagnosis renders difficulties. A sad circumstance, worthy of mention, is the marriage between an affected man and a wife, suffering from a primary pigmentary retinopathy. IV-3 is the only child out of this marriage with normal eyes. However, since her father is suffering from X-linked juvenile retinoschisis, she is a carrier of this disease.

8. Fam. Hel.
II-2 (R-91) Has always had poor visual acuity in both eyes.
Refracting media: Senile cataract.
Fundi: Vascular sheathing and vascularized veils. Coarse pigmentations in the retinal periphery. Discs pale temporally. Vessels slightly attenuated.

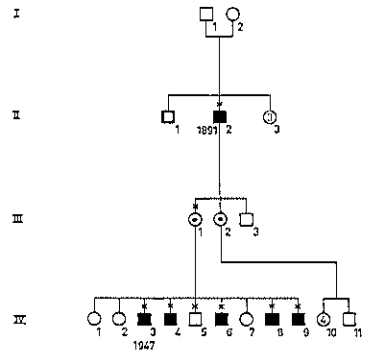
III-1 (AHR) VODS 10/10.
Media and fundi: Normal.

IV-3 (JH-47.08.27)
1966: Operated elsewhere because of "retinal detachment".
1969: VOD C−1.50×5° 3/10; VOS S+2.50 0.5/60.
Vitreous body: Posterior vitreous detachment and syneresis. Fine white opacities and fibrillary degeneration.
Fundi: OD: Foveal retinoschisis. Supratemporally old pigmented coagulations. In the inferior part a large cystoid structure of retinoschisis with two superficial defects. This cystlike structure extends as far as the fovea. (fig. 15).

OS: Extensive areas of retinoschisis with arcade-like dehiscences and vascularized veils.
Visual fields: OD: Strong defects in the superior part, particularly supranasally.

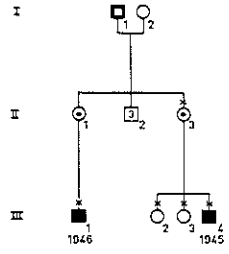
OS: A small remnant temporally.
Dark adaptation: Curve 1 log.U. too high.
ERG: Unreliable.
F-ERG: OD subnormal. OS: no fixation possible.
VER: Subnormal.
EOG: OD 2.00; OS 2.40.
Therapy: An encircling procedure with sclera-donor-tissue is done in the right eye. The retina around the area of retinoschisis is treated with photocoagulations.

II-4 (HH); *II-6 (JH)*; *II-8 (BH)* and *II-9 (SH)* all suffer from a serious type of sex-linked juvenile retinoschisis, characterized by large areas of retinoschisis and large visual field defects.



Summary: Five brothers showing a serious type of X-linked juvenile retinoschisis. The right eye of one of these brothers was operated upon, because the posterior pole was endangered by a large area of retinoschisis.

9. Fam. Jac



I-1 Reported to have had poor visual acuity all his life.

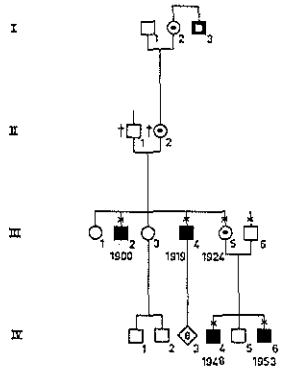
II-3 (NAJO) VODS 10/10, emmetropic.
Refracting media and fundi: Normal.

III-1 (WJ-46.10.15) Bad visual acuity since early childhood.
1954: Diagnosis elsewhere "Periphlebitis retinae with retinitis proliferans". Concomitant convergent squint of the right eye.
VOD S+5=C+2×180° 2/60; VOS S+7.50=C+1.50×180° 2/10.
Refracting media: White opacities in the anterior and posterior cortex.
Fundi: Pre-retinal whitish strands before the posterior pole of OD. Pigment-clumping in the inferior retinal periphery. In the left eye remnants of a vitreous haemorrhage and white strands in the inferior part of the retina. Vascular sheathing infratemporally.

III-4 (WJ-45-04.18) Poor visual acuity since early childhood.
1957: VOD S+6=C+0.75×40° 3/10; VOS S+3=C+1×130° 3/10.
Refracting media: Normal.
Fundi: Foveal retinoschisis. Silver-greyish reflexes in the retinal periphery.
Visual fields: Decreased central sensitivity.
Dark adaptation: Curve 0.5 log.U. too high.
ERG: Scot. b-waves OD 115 μV; OS 135 μV.
Phot. b-waves OD 105 μV; OS 105 μV.
EOG: ODS 2.00.
1969: VOD S+3.25=C+0.50×40° 3/10; VOS S+3=C+1×130° 3/10.
Refracting media: Normal. Normal vitreous body.
Fundi: Foveal retinoschisis consisting of a cystoid structure with a fine radiate folding of the superficial layer. Silver-greyish glistening areas in the retinal periphery. No peripheral retinoschisis visible.
Visual fields: Unchanged.
Colour vision: Decreased sensitivity to red (anomaloscope). Slight red-green dyschromatopsia (HRR).
Dark adaptation: Phot. and scot. part of the curve 1 log.U. too high.
ERG: Scot. b-waves OD 105 μV; OS 115 μV.
Phot. b-waves OD 65 μV; OS 85 μV.
F-ERG: Subnormal.
VER: Slightly subnormal.
EOG: OD 1.82; OS 1.86.
1970: Condition unchanged.
ERG: Scot. b-waves OD 137 μV; OS 164 μV.
Phot. b-waves OD 40 μV; OS 67 μV.
Phot. a-waves OD 21 μV; OS 36 μV.

Summary: X-linked juvenile retinoschisis in two cousins. There is a remarkable difference in expression in these two cases. III-4 demonstrates a foveal retinoschisis and some silver-greyish glistening retinal areas, while III-1 shows an extensive type of this complex syndrome. In III-1 differential diagnosis has to be made with periphlebitis retinae.

10. Fam. dKn.



I-3 Reported to have had bad visual acuity all his life.

III-2 (JAB-00.08.06) Bad visual acuity since early childhood.
1969: VOD S+1.50 5/60; VOS S+1=C+0.50×180° 1/10.
Reads D=0.80 with addition S+5.
Refracting media: OD senile cataract; OS incipient senile cataract.
Vitreous body: Fibrillary degeneration, syneresis and posterior vitreous detachment.
Fundi: Atrophic changes in the posterior pole. Drusen of Bruch's membrane are present. The discs are pale and the vessels are slightly attenuated. The foveae show some stellate folds. Infratemporally retinoschisis and vascular veils.
Colour vision: Medium red-green dyschromatopsia and medium blue-yellow dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
ERG: Scot. b-waves ODS unrecordable.
Phot. a-waves OD 22μV; OS 30μV.
Phot. b-waves OD 30μV; OS 50μV.
EOG: ODS 1.40 (not quite reliable). The standing potential itself is lower than normal.

III-4 (GB-19.04.29) Has always had poor visual acuity in both eyes.
1969: OS: Concomitant divergent squint.
VOD S+5=C+3.50×180° 2/10; VOS S+5=C+3×180° 1/300.
Reads D=0.80 with addition S+4.
Refracting media: Some lental opacities. Fibrillary degeneration and posterior detachment of the vitreous body.
Fundi: Atrophic changes in the posterior pole. Particularly infratemporally vascular veils. Discs are too pale on the temporal side, while the vessels are slightly attenuated.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
ERG: Scot. b-waves ODS unrecordable.
Phot. a-waves OD 14μV; OS 30μV.
Phot. b-waves OD 36μV; OS 52μV.
EOG: ODS 1.40. The light-insensitive part of the standing potential is lower than normal.

III-5 (JHdKB-24) VODS 10/10, emmetropic.
Refracting media and fundi: Normal.

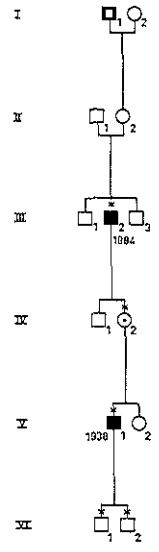
IV-4 (JAdK-48.01.03) Bad visual acuity since early childhood. Concomitant divergent squint of OS.
1961: VOD S−1=C−2×90° 3/10; VOS S−1=C−2×90° 4/60.
Fundi: Cystoid foveal structure. In the inferior temporal periphery retinoschisis and pigmentations.
Visual fields: Restriction in the superior nasal periphery. Relative central scotoma (fig. 17).
Dark adaptation: Curve 1 log.U. too high. (scot and phot.) (fig. 18).
ERG: Scot. b-waves ODS unrecordable.
Phot. b-waves ODS 40μV.
EOG: OD 1.80; OS 1.70.
1969: VOD C+1×110° 2/10; VOS S−0.50=C+1.50×105° 2/60.
Refracting media: Fibrillary degeneration of the vitreous body. Some parts of the vitreous are optically empty.
Fundi: Foveal retinoschisis with fine stellate folds. Some vascular sheathing around the disc. Infratemporally vascular veils with veins, originating in the retina (fig. 11).
Visual fields: On both sides restriction supranasally up to 30 degrees from the centre. Decreased central sensitivity and relative central scotomata.
Dark adaptation: The curve is 1 log.U. too high.
ERG: Scot. b-waves ODS unrecordable.
Phot. b-waves ODS 30μV.
F-ERG: Subnormal.
VER: Subnormal.
EOG: OD 2.26; OS 1.74.

IV-6 (LCdK-53.10.25) Bad visual acuity since early childhood. Had nystagmus, which disappeared spontaneously.
1961: VOD S+9.50 1.5/10; VOS S+8=C+1×90° 6/60.
Fundi: Cystoid foveal alterations with superficially located radial folds. In the inferior temporal periphery retinoschisis and pigment alterations.

Visual fields: Restriction of the upper halves up to 20 degrees from the centre.
Colour vision: Very mild red-green dyschromatopsia (HRR).
Dark adaptation: Phot. and scot. part of the curve 1 log.U. too high.
ERG: Scot. b-waves OD 70μV; OS 75μV.
Phot. b-waves OD 60μV; OS unreliable.
EOG: OD 1.50; OS 1.70.
1969: VOD S+6=C=0.50×90° 1/10; VOS S+6=C+2×90° 1/10.
Media: Degenerative vitreous body.
Fundi: Foveal retinoschisis. In the inferior part extensive retinoschisis, vascular veils and vascular sheathing. Furthermore dendritic markings.
Visual fields: Restriction of the superior parts to 20 degrees from the centre. General constriction of the isopters and decreased central sensitivity.
Dark adaptation: Curve 1 log.U. too high.
ERG: Scot. b-waves OD 45μV; OS 40μV.
Phot. b-waves ODS unrecordable.
F-ERG: Subnormal.
VER: Present, but subnormal.
EOG: ODS 1.50. Fixation doubtful. Light-insensitive part of the standing potential is lower than normal.

Summary: Four members of one family with X-linked juvenile retinoschisis. One carrier was examined and found to be normal. All 4 affected individuals have a rather severe form of this affection. One man (III-2) has still a useful vision despite his age of 69 years. The characteristic pattern of the foveal retinoschisis is disappeared in the 69- year-old and the 50-year-old man. (III-2 and III-4).

11. Fam. Kru.



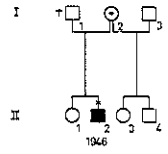
III-2 (HB-84.01.31) Bad visual acuity since early childhood. This man is now 85 years old.
1969: VOD S+4.25=C+2.50×55° 1-2/60; VOS S+4=C+1.50×80° 2-3/60.
Media: Incipient senile cataract. Fibrillary degeneration of the vitreous body. Vascular veils project into the vitreous.
Fundi: Atrophic changes in the foveal area. Discs pale. The retinal vessels are slightly attenuated. Pigment-clumping in the retinal periphery, while retinoschisis is present in the inferior part of the retina.

IV-2 (JMKB-20.08.20) VOD S+2 10/10; VOS S+1.50 10/10.
Refracting media and fundi: Normal.

V-1 (JK-38.11.23)
1962: VOD S−0.50=C+2×180° 4/10; VOS C+2×180° 3/10.
1969: VOD C+1.50×180° 2/10; VOS C+2×180° 5/60.
Is complaining of metamorphopsia. This is demonstrated with the help of the Amsler test.
Vitreous body: Syneresis and fibrillary degeneration. Fine white opacities throughout the vitreous. Vascular veils infratemporally.
Fundi: Normal reflexes are absent. Pathognomonic cystoid structure with superficial stellate folds in both foveae. The discs are slightly too pale on the temporal side. The retinal vessels have a normal calibre. In the inferior temporal periphery retinoschisis, vascular veils, vascular sheathing and dendritic markings are present.
Visual fields: Decreased central sensitivity. Restriction supranasally.
Colour vision: Very mild red-green and blue-yellow dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope). Tritan axis in the right eye (Farnsworth D-15). No specific axis in the left eye (Farnsworth D-15).
ERG: Scot. b-waves OD 55μV; OS 69μV.
Phot. b-waves OD 48μV; OS 63μV.
Phot. a-waves OD 18μV; OS 26μV.
EOG: OD 1.76; OS 1.71.
OP: Subnormal.

Summary: X-linked juvenile retinoschisis in a 85-year old man and his 31-year old grandson. The carrier of the pathological gene has normal eyes. The 85-year old man is able to move around in his house and has useful sight. This might be a consolation for other individuals suffering from this affection.

12. Fam. Ma.



III-2 (WJM-46.10.13) This patient got a bullet in his left eye in 1965. The traumatic cataract has been removed.
1968: VOD 8/10, emmetropic; VOS 1/60 S+12 3/10.
Refracting media: OD normal. OS corneal scar and aphakia.
Fundi: Foveal retinoschisis (fig. 5). Silver-greyish glistening patches in the retinal periphery.
Visual fields: Decreased central sensitivity. Normal peripheral limitations.
Dark adaptation: Curve 1 log.U. too high, phot. and scot.
ERG: Scot. b-waves OD 120μV; OS 135μV.
Phot. b-waves OD 55μV; OS 55μV.
EOG: ODS 2.00.

Summary: A patient with X-linked juvenile retinoschisis, showing the pathognomonic foveal alterations of this condition. The visual acuity of 8/10 of the right eye is remarkably good.

13. Fam. Pie
II-2 (PF) Born in Indonesia. Like her husband of Indonesian origin.
VODS 10/10.
Media and fundi: Normal.

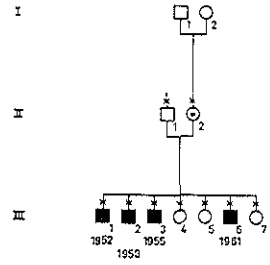
III-1 (JP-52.03.06) Bad visual acuity since early childhood.
VODS S+1 3/10.
Vitreous body: Posterior vitreous detachment. Fibrillary degeneration and optically empty structures. Tiny white opacities all over the vitreous.

Fundi: Foveal retinoschisis (fig. 2). The discs show a temporal crescent. The vessels are normal. Infratemporally preretinal whitish dendritic structures and vascular sheathing (fig. 9). Retinoschisis in the temporal inferior periphery.
Visual fields: Supranasally restriction to 20 degrees from the centre. Decreased central sensitivity.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 95 μV; OS 85 μV.
Phot. b-waves OD 80 μV; OS 60 μV.
EOG: OD 1.70; OS 1.75.
Blood: No acanthocytosis. Normal.

III-2 (FP-53.06.28)
VOD C+0.50×180° 2/10; VOS C+0.50×180° 5/10.
Vitreous body: Posterior vitreous detachment. Degenerative changes.
Fundi: Foveal retinoschisis. Discs and vessels are normal. In the far inferior temporal periphery preretinal whitish dendritic structures and some retinoschisis.
Colour vision: Normal (HRR).
Visual fields: Concentric constriction, more in the superior parts than in the inferior parts.
ERG: Scot. b-waves OD 120 μV; OS 100 μV.
Phot. b-waves OD 70 μV; OS 70 μV.
EOG: OD 2.00; OS 1.50.

III-3 (GP-55.01.17)
VOD C+1×165° 5/10; VOS S+1.50 2/10.
Vitreous body: Posterior vitreous detachment and degenerative changes.
Fundi: Foveal retinoschisis. Infratemporally vascular veils and dendritic markings.
Colour vision: Normal.
ERG: Scot. b-waves OD 170 μV; OS 130 μV.
Phot. b-waves OD 90 μV; OS 90 μV.

III-6 (MP-61.10.23)
VOD S+0.50=C+0.75×80° 10/10; VOS S+0.50=C+0.75×100° 3/10.
Vitreous body: Posterior vitreous detachment and degenerative changes.
Fundi: Foveal retinoschisis. In the far inferior temporal periphery dendritic structures and some retinoschisis.
Blood: Normal, no acanthocytosis.



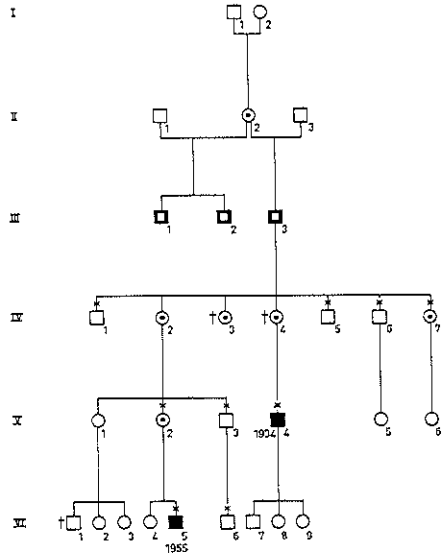
Summary: All 4 sons of an Indonesian married couple are suffering from X-linked juvenile retinoschisis. The 3 daughters are normal. The patients demonstrate the characteristic foveal retinoschisis, while infratemporally retinoschisis and white dendritic markings are present. The interindividual ophthalmoscopic patterns in the family-members are very much alike, indicating that there are only slight differences in expression in this family.

14. Fam. Ra.
III-1,2 en 3. Reported to have had bad visual acuity all their life.

IV-7 en V-2. Carriers. They have normal media and fundi.

V-4 (JdC-34.05.07) Bad visual acuity since early childhood. Concomitant convergent squint of OS.
1968: VOD S+2 2/10; VOS S+2.50 3/60.
Media: Normal.
Fundi: Foveal retinoschisis. Patchy silver-greyish glistening reflexes in some parts of the retina, particularly infratemporally.

VI-5 (RR-55.02.28) Has always had bad visual acuity.
1960: Diagnosis elsewhere: "persistent hyperplastic primary vitreous".
VOD 2/10; VOS 2/60.
1968: VOD S+5.25=C+1×90° 2/10; VOS S+5.25=C+1×90° 2/60.
Refracting media: Slight opacities in the posterior cortex of OD. Cataract of the posterior cortex of OS. Fibrillary degeneration and syneresis of the vitreous body, in which fine white opacities are present. Posterior vitreous detachment. In both eyes big vascularized veils with arcade-like dehiscences are present.
Fundi: Foveal retinoschisis. Extensive retinoschisis infratemporally. Retinal arteries and veins project from the retina into the vitreous in translucent veil-like membranes (fig. 14). Some of the veils insert on the disc. The disc of the left eye has a pseudopapillitis picture (fig. 16).
Visual fields: Both visual fields are confined to 25 degrees from the centre on the nasal side. There is a decreased central sensitivity.
Dark adaptation: The curve is 0.5 log.U. too high. Phot. and scot.
ERG: Scot. b-waves OD 90μV; OS 65μV. Phot. b-waves OD 65μV; OS 45μV.
EOG: OD 1.85; OS 1.70.
OP: Subnormal.
Systemic examination: Normal.
1969: Vitreous haemorrhage occurs suddenly in OS. This is cleared up in 3 weeks without any therapy.



Summary: Two members of a family with X-linked juvenile retinoschisis. There is a striking difference in expression between the two patients. Foveal retinoschisis is the only abnormality found in V-4, while VI-5 demonstrates the whole range of abnormalities, which may be found in this complex syndrome. Two carriers, examined ophthalmologically are fully normal.

15. Fam. Si
I-1 Reported to have had bad visual acuity all his life.

II-1 (JSvD-17.02....) VODS 10/10.
Refracting media and fundi: Normal.

II-6 (JWvD-23.10.23) VODS 10/10.
Refracting media and fundi: Normal.

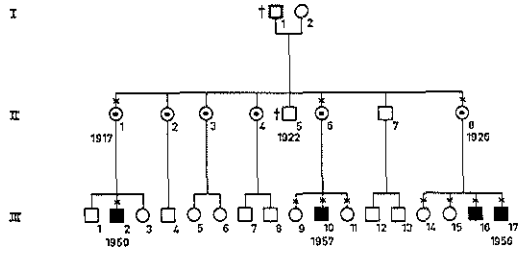
II-8 (EOvD-26.06.11) VODS 10/10.
Refracting media and fundi: Normal.

III-2 (FS-50.06.24) Bad visual acuity since early childhood.
1969: VOD 3/10, emmetropic; VOS 4/10, emmetropic.
Media: Normal.
Fundi: Foveal retinoschisis. No other abnormalities.
ERG: Scot. b-waves OD 50μV; OS 70μV.
Phot. b-waves OD 65μV; OS 50μV.
EOG: OD 2.40; OS 2.36.

III-10 (WW-57.07.01)
1967: VOD S+1=C+0.50×10° 4/10; VOS C+1.25×170° 4/10.
Media: Normal.
Fundi: Foveal retinoschisis.
Visual fields: Decreased central sensitivity.
ERG: Scot. b-waves and phot. b-waves subnormal.
EOG: OD 2.18; OS 2.23.

III-16 (RvO-55.02.09)
1967: VOD C+0.50×75° 4/10; VOS S+0.50=C+0.50×120° 6/10.
Media: Normal.
Fundi: Foveal retinoschisis. Preretinal strands in the inferior parts.
Visual fields: Restricted supranasally. Decreased central sensitivity.
ERG: Scot. b-waves and phot. b-waves: Subnormal.

III-17 (EvO-56.10.25) Concomitant convergent squint of OD.
1967: VOD S+2.50=C+1.50×100° 1/10; VOS S+1.50=C+0.50×90° 7/10.
Media: Normal.
Fundi: Foveal retinoschisis. Retinoschisis infratemporally.
Visual fields: Restriction supranasally. Decreased central sensitivity and concentric impairment.
ERG: Scot. b-waves and phot. b-waves: Subnormal.



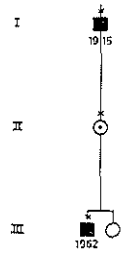
Summary: X-linked juvenile retinoschisis in four boys, belonging to the same family. All affected individuals have a foveal retinoschisis, while only one of them (III-17) has a peripheral retinoschisis too. Three carriers were examined and found to be normal.

16. Fam. v.Sol
I-1 (PR-15.01.11) Bad visual acuity since early childhood. Had a connatal cataract of the right eye.
1943: Discission of the cataract of OD.
1967: Complains of bad visual acuity, particularly in darkness.
VOD S+5 light perception; VOS S+5 1/60.

There is a concomitant divergent squint of OD and nystagmus of both eyes.
Media: OD: Aphakia with some after-cataract. OS: Immature cataract.
Fundi: OD: Pigmentations and depigmentations with preretinal glious alterations. Atrophic fovea. OS: Vascular sheathing and patches resembling an old chorioretinitis. Atrophic foveal alterations.
VER: OD: Absent. OS: Very slight responses.

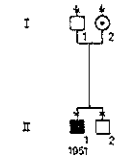
II-1 (vSR) VODS 10/10.
Media and fundi: Normal.

III-1 (RvS-62.07.11)
1969: VOD S+1.50 8/10; VOS S+1.50 4/10.
1970: VOD S+1.50 3/10; VOS S+1.50 3/10.
Media: Normal.
Fundi: Foveal retinoschisis (fig. 1ab). Silver-greyish glistening reflexes in some parts of the retinal periphery
Colour vision: Normal (HRR).



Summary: X-linked juvenile retinoschisis in a 54-year-old man and his grandson. The grandson has a foveal retinoschisis, the 54-year-old man, however, has severe lento-vitreo-retinal changes. The carrier has normal eyes.

17. Fam. Wes



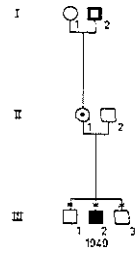
I-2 (HWB) VODS 10/10.
Media and fundi: Normal.

II-1 (HW-51.12.27) Since some years bad visual acuity with both eyes. No family-members with bad visual acuity are known.
1966: VODS S+0.50 4/10.
Diagnosis: "Heredodegeneration of the macula".
Systemic examination: Normal.
1967: VODS S+0.50 4/10.
Amsler test: Normal.
Media: Normal.
Fundi: Foveal retinoschisis (fig. 21). In the far inferior temporal periphery there are some greyish-white opalescent structures and pigmentations. The whole retina has patchy metallic glistening reflexes.
Visual fields: Slightly decreased central sensitivity. Normal peripheries.
Colour vision: Normal (HRR, anomaloscope, Farnsworth D 15).
Dark adaptation: The curve is 2/3 log.U. too high.
ERG: Scot. b-waves OD 100μV; OS 105μV.
Phot. b-waves OD 60μV; OS 50μV.
F-ERG: Subnormal.

EOG: OD 3.32; OS 2.91.
1968: VODS S+0.50 4/10.
No changes.
Fluorescein angiography: Normal angiogram (fig. 21).

Summary: A boy with X-linked juvenile retinoschisis. The pathognomonic foveal retinoschisis presents the diagnosis, although no history of bad vision is reported in this family.

18. Fam. Wil



I-2 (MvG-82.01.03) Is reported to have bad visual acuity since early childhood.

II-1 (WWvG-16.05.30)
VOD S+1.75=C+0.50×160° 10/10; VOS S+2=C+0.25×45° 10/10.
Media and fundi: Normal.

III-2 (JW-49.08.10) Bad visual acuity since early childhood. Concomitant divergent squint of the right eye.
VOD S+4=C+0.75×125° 1/10; VOS S+6.50=C+0.50×30° 2/10.
Media: Slight opacities in both posterior cortices. Posterior vitreous detachment and fibrillary degeneration of the vitreous body.
Fundi: Foveal retinoschisis. Temporally a distinct retinoschisis with vascular veils and preretinal strands. Furthermore white dendritic markings and vascular sheathing (fig. 10,12). The discs have a pseudopapillitis picture.
Visual fields: Restriction nasally. Supranasally there is more restriction than infranasally.
Dark adaptation: Almost normal curve.
ERG: Scot. b-waves OD 95μV; OS 155μV.
Phot. b-waves OD 90μV; OS 75μV.
EOG: OD 1.20; OS 1.85.
The value of OD is unreliable because of the squint.

Summary: A boy, suffering from a severe form of X-linked juvenile retinoschisis. Nearly all possible ophthalmoscopic alterations of X-linked juvenile retinoschisis are to be found in this patient.

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III

Stargardt's disease

1. INTRODUCTION

Stargardt's disease is a bilateral, symmetrical, progressive affection which, at least in the initial stage, is confined to the foveal area; its occurrence is familial and usually at an early age, and it ultimately leads to loss of central vision.

In 1909, Stargardt described two families (H and N) which, in age group 12-20, included seven individuals with progressive degeneration of the macular region. The patients' parents had good visual acuity and normal eyes, and were not consanguineous. The patients had had good vision in early childhood, but between age 8 and age 15 developed gradual, progressive loss of central vision. In the posterior pole there were slight pigment changes with yellow-grey spots, resulting in a fairly well-defined, grubby atrophic central focus of horizontal oval shape. In some patients a broad ring of numerous white-yellow spots developed around this focus (diameter 1-2 pd), while the retinal vessels and retinal periphery remained quite normal. The optic discs were somewhat too pale on the temporal side.

However, patients with conditions closely resembling that described by Stargardt in 1909, had been known earlier. Leber (1874) had described a 7-year-old girl with progressive degeneration of the retinal centre, to which slight changes in the retinal periphery were later added (Stargardt, 1909).

The brother and sister with central and pericentral changes described by Lang (1885) may also have suffered for some time from Stargardt's disease.

R. D. Batten (1897) described two brothers who at age 14 developed a symmetrical macular affection characterized by finely mottled pigment displacements. It was specifically mentioned that the elder brother (age 21) showed not only more marked central pigment disturbances than his younger brohter (age 14), but unlike the latter also showed pigment displacement in the retinal periphery.

The two brothers described by Magers (1899) were very probably patients with long-standing Stargardt's disease, because the posterior pole showed pronounced pigmentations and choroidal atrophy.

Dujardin (1904) described two brothers and Jackson (1905) reported on two sisters – all children of consanguineous parents.

The literature also comprises the solitary case described by Valude (1906) and two sisters described by Steindorff (1906). Baumgarten (1907) observed a 13-year-old girl with central and peripheral fundal changes, and Jennings (1909) made mention of three children with progressive posterior pole dystrophy in a consanguineous marriage.

After 1909 Stargardt continued to publish reports on this progressive posterior pole dystrophy in young patients. In 1913 he described two brothers aged 45 and 38, and their 43-year-old sister, whose vision had been poor for years. In these patients he found peripheral retinal changes besides a marked central affection. Stargardt himself described the picture as a retinitis pigmentosa taking an inversed course (retinopathia pigmentosa inversa): in classical retinopathia pigmentosa the equatorial retinal areas are first affected, in contrast to the course seen in his cases. In 1916 he added to his series the case of a 35-year-old man whose vision had been poor since age 12; and in 1917 and 1925 he again described patients with the same affection (Stargardt 1917, 1925).

In 1917, Stargardt published a classification of central tapetoretinal dystrophies in which he strictly differentiated between the progressive dystrophies of the central retina without dementia, and those with dementia: the so-called maculo-cerebral dystrophies (lipidoses) which several other authors have also described (F. E. Batten 1903; Mayou 1904; Stephenson 1904; Spielmeyer 1905; Vogt 1905; Stock 1908; Oatman 1911; Beach 1926, and others).

None of the families described included individuals with a purely retinal affection as well as patients with a maculo-cerebral condition. From this fact Stargardt rightly concluded that the progressive posterior pole dystrophy he had described, and the maculocerebral dystrophy, are totally different entities. Only Alkio (1923) found concomitance of Stargardt's disease and Tay-Sachs disease in the same family (an incidental finding, in our opinion). A boy with possibly Tay-Sachs disease or Spielmeyer-Vogt disease had a father with normal eyes, but this father had three brothers and one sister suffering from Stargardt's disease.

Since Stargardt's perspicuous studies, publications on this affection have continued to appear: Lutz (1911): 4 children in 1 family; Stirling (1912): 1 case; Darier (1914): 5 children in 2 families; Maewsky (1914): 1 case with suggestion of peripheral retinal changes; Pusey (1915): 5 children in 1 family; Feingold (1916): 3 children in a consanguineous marriage.

Many publications have followed in subsequent decades. The observations of the various authors are not always the same; purely central, but also centroperipheral affections as well as transitions between these two types have been described.

For the sake of simplicity we present in table I a survey of publications which, so far as we could establish, concern themselves with Stargardt's disease.

Table I

a. *1920-1930*

1920	Chance
1921	Becker; Oguchi and Yano
1922	Nakajima (quoted by Waardenburg et al. 1963)
1923	Alkio; Lewina; Takeuchi and Horiguchi
1924	Cavara; Firjukowa; Morelli
1925	Bollack; Rieger
1926	Lagrange and Peron; Steyn; Urbanek
1927	Vom Hofe
1928	Blank; Knapp; Morelli
1929	Tillé

b. *1930-1940*

1930	Pillat, Schiff-Wertheimer and Tillé
1931	Letchworth; Rossi; Von Rötth
1932	Accardi; Waardenburg
1933	Braun
1934	Danielson
1935	Borsellino; Caocci; Ibuki; Neame
1936	Burnier; Klien; Tillé
1937	Muromoto
1938	Alvaro; Ogata
1939	Wakayama

c. *1940-1950*

1940	Danis; MacRay; O'Rourke; Sorsby
1941	Franceschetti and Klien; Hallermann; Sorsby
1942	Crawford; O'Brien and Roper
1943	Lloyd
1944	Neame
1945	Missiroli
1946	Bonnet; Folk; Gartner; MacRay; Renard
1947	Feldman; Moffat; Ryerson; Sukumlyn
1948	Agatston
1949	Brognoli; Redslob

d. *1950-1960*

1950	Mortelmans; Peiker
1951	Biro; Di Prima; Scuderi and Siliato; Sun
1952	Danic; Klimková and Velický; Peterson; Szekler
1953	Kaplan; Perron et al.
1954	Anastasi and Bellavia; Bernheim et al.; Rosehr; Samuels
1955	Bonamour; Friemann; Landolt; Mylius
1956	François et al.; Gába; Schönfelder
1957	Bessière et al.; Van Bogaert; Hong; Ohrt
1958	Bessière and Chabot; Kozlowski; Spallino
1959	Bozzoni; Tiberi and Cuccagna

e. *1960-1970*

1960	Cox; Lux; Vancea and Tudor
1961	Cox; Etzine; Straub
1962	Bessière et al.; Calmettes et al.; Chen and Lin; François et al.; Gruetzner
1963	Biesheuvel; Dalgleish and Naylor

1964 Komzweig
1965 François and De Rouck; Norton et al.
1966 Blodi; Krill; Ruedemann
1967 Shershevskaya; Yasukura et al.
1968 Ersler and Jaczynowska; Bengisu et al.
1969 Bessière et al.; François and De Laey
1970 Soler Sala; Merin and Landau.

This survey lists those dystrophies that had or can be suspected to have had a recessive mode of transmission. Since the literature also comprises reports on dominant progressive foveal dystrophies, several authors have described these affections as the dominant form of Stargardt's disease (Franceschetti et al. 1963; Duke-Elder 1967); but because Stargardt himself described a recessive affection, we consider it desirable to confine the designation Stargardt's disease to the recessive form and to give the dominant foveal dystrophy which resembles it a separate place under the heading dominant progressive central tapetoretinal dystrophy or dominant progressive foveal dystrophy.

The disease must be strictly differentiated from dominant progressive cone dystrophy and dominant vitelliform dystrophy, which on occasion are mistakenly recorded as dominant form of Stargardt's disease (Bruna 1951; Franceschetti et al. 1963; Duke-Elder 1967). – The central tapetoretinal dystrophies in which peripheral retinal changes develop after some time, constitute a problem in a way. There is still considerable confusion in this respect as a result of the numerous different names by which these centroperipheral tapetoretinal dystrophies are known. As early as 1913, Stargardt himself described three individuals in one family who showed such a centroperipheral tapetoretinal dystrophy (fam. S). In our opinion there can be no convincing objection to the use of the term Stargardt's disease with reference to these diffuse retinal affections. Franceschetti, François and Babel (1963) described this form as Stargardt's disease with peripheral involvement ("maladie de Stargardt avec participation périphérique"), and we agree with this designation.

Other terms used are: centroperipheral tapetoretinal dystrophy (TRD) (Waardenburg et al. 1963); macular form of diffuse TRD (Gruetzner 1962); mixed TRD (Bessière et al. 1962); diffuse TRD (Duke-Elder 1967); and central retinitis pigmentosa (Lux 1960).

We believe that many cases described as "central (inverse) tapetoretinal dystrophy" (Franceschetti, François and Babel 1963; Duke-Elder 1967) should also be classified in this group. The "progressive rod-cone degeneration" described by Berson et al. (1968) is probably the same affection. This form – in which the fovea first becomes dystrophic, while peripheral changes occur later – might be called centrifugal TRD or centrally started TRD.

Occasionally, however, it may be impossible to establish whether the dystrophic process in fact started in the central retina. Perron et al. (1953), for example, described a patient in whom retinal centre and periphery were simultaneously involved; and our own case material includes patients of whom we do not know with certainty whether the dystrophy started centrally or was diffuse from the onset (fam. Bol and

Hu). Be this as it may, it is a fact that the literature and our own case material both include many examples in which an initially purely central TRD was later associated with peripheral retinal changes.

Rieger (1925) described two brothers with central and peripheral retinal changes, while a third brother showed a normal posterior pole and only peripheral changes. So far as we know, there have been no other observations of this kind.

Bonnet (1946), Gruetzner (1962) and Shapira (quoted by Perron et al. 1953) hold that a strict distinction must be made between Stargardt's disease, which remains purely central, and TRD which starts at the centre and extends towards the periphery. In our opinion this is impossible, because all transitions between purely central and diffuse TRD have been described. There are purely foveal forms besides affections which involve not only the fovea but also the pericentral or even the entire peripheral retina. If observations are limited to a single period in the patient's life, the impression may be gained that there are clearly distinct purely central and centroperipheral forms. Unfortunately, many reports cover only a single period of observation. But when long-term follow-ups have been made it is quite clear that in many cases an originally purely central TRD develops into a centroperipheral TRD (Leber 1874; Waardenburg 1932, 1963; Wakayama 1939; Brognoli 1949; Rosehr 1954; Gaba 1956, and others). It has also been frequently found that, in a given family, older brothres or sisters had already developed a centroperipheral TRD, while younger brothers or sisters still showed a purely central TRD (Batten 1897; Becker 1921; Oguchi and Yano 1921; Von Rötth 1931; Wakayama 1939; Etzine 1961, and others). The reverse situation has never been described. This means, we believe, that the eyes of older brothers or sisters generally indicate how the eyes of younger brothers or sisters will ultimately become. In only one family (fam. Me) we found the rare situation, that the youngest had Stargardt's disease with peripheral involvement, while 2 older siblings had a pure central form of Stargardt's disease.

A beautiful example of an unsuspected development has been given by Rosehr (1954). In 1953 – 50 years after Stargardt first examined Dorothea H – it was found that an affection initially confined to the fovea had led to diffuse retinal changes: pigment proliferations and drusen-like structures; and the posterior pole likewise showed marked changes. The younger sister, Marie H, did show posterior pole changes but the retinal periphery was still virtually normal. These findings would seem to contradict most other data in the literature and our own observations, which show that affected children in the same family are likely to show the same development.

Stargardt's own studies already yielded arguments against the widely accepted view that the affection which bears his name would be confined to the fovea. The S family in which in 1913 he described a centroperipheral TRD provides such an argument, and the fundal pattern in Paul H – one of his first patients – already showed numerous white sharkfin-shaped spots around the papillofoveal area. In cases in which many white spots are visible around the dystrophic fovea, differential diagnosis from fundus flavimaculatus is exceedingly difficult. Mylius (1955) also

pointed out that Stargardt's disease is not strictly limited to the foveal area. Today, many ophthalmologists confronted with the Paul H originally described by Stargardt, would diagnose a case of fundus flavimaculatus!

The same applies to the patients described by Hallermann (1941), Agatston (1948), Friemann (1955) and Mylius (1955). On the other hand, some of the cases of fundus flavimaculatus described by such authors as Franceschetti and François (1965), Carr (1965), Amalric et al. (1967) and Scialfa (1964) might well be classified as Stargardt's disease. Cases 2 and 5 in Carr's study (1965) in fact do not resemble a fundus flavimaculatus strikingly but are more suggestive in my opinion of a centrally started TRD.

In the terminal stage of Stargardt's disease, the posterior pole often shows the features of extensive choroidal atrophy with or without pigmentations, and the retinal periphery can show features ranging from a normal fundus through advanced retinopathia pigmentosa. It can be deduced from this that in advanced stages it is not always possible to establish a reliable diagnosis on the basis of the ophthalmoscopic findings if one is not familiar with the initial stages of the disease.

Unlike many authors, we agree with Stargardt and Tillé (1929) that Stargardt's disease is an ophthalmoscopically well-recognizable entity. Additional data on mode of transmission and retinal functions can verify the diagnosis. The progressive loss of vision is an important characteristic. The age of onset is much less characteristic and varies widely. The entity named after Stargardt might be roughly divided as follows:

1. purely central TRD;
2. central and pericentral TRD (sometimes indistinguishable from fundus flavimaculatus with foveal dystrophy);
3. centroperipheral TRD:
   a. with an intact visual field (pigmentations and depigmentations, virtually normal calibre of fundal vessels);
   b. with visual field defects (bone trabeculae and constricted fundal vessels).

In this respect we should bear in mind the evolutional character of this affection, which can cause the picture to change substantially in the course of the years and may present all forms and transitions of 1, 2 and 3 in succession. Ultimately a sharply defined focus of choroidal atrophy, indistinguishable from central choroidal atrophy, may develop in the posterior pole.

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

The two principal features of the clinical picture of Stargardt's disease are the changes in visual acuity and the fundal features.

The patients usually report between age 6 and age 20 with bilateral gradual diminution of vision, although previously visual acuity has been entirely normal. In some cases the first symptoms do not occur until age 30-40.

There is often mild myopia and patients complain of photophobia, vision usually being optimal in twilight. There is no male or female predominance, and several

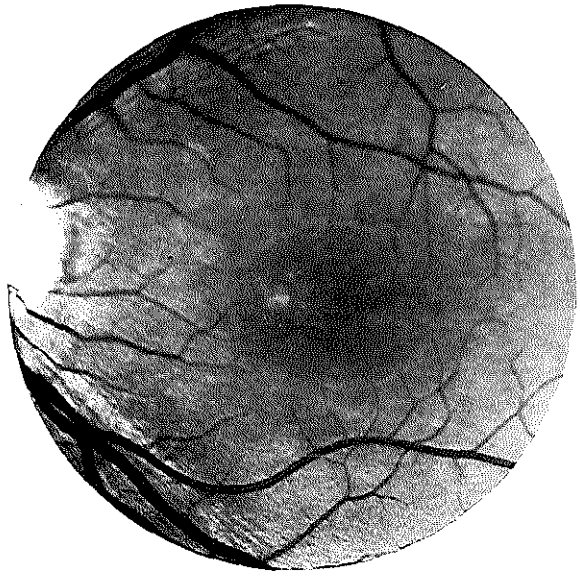


Fig. 1a. Initial stage of Stargardt's disease. Disturbed foveal and foveolar reflexes. Fovea looks as if covered with varnish (snail's slime). Some unobtrusive yellowish-white flecks in the foveal area. (Fam. Oe).

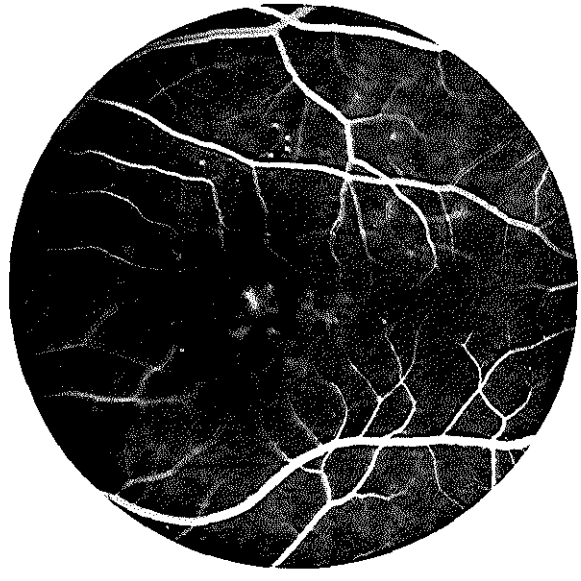


Fig. 1b. Fluorescein angiography reveals not only defects in the retinal pigment epithelium at the site of the fovea, but also small round defects in the pigment epithelium in the perifoveal area.

children in the same family are often affected. Consanguineousness of parents of patients with Stargardt's disease has a higher incidence than normal.

A familiar story is the one about the schoolchild who has always been seated at the back of the classroom but must move to the front because no spectacles are effective.

In some cases there is considerable diminution of vision although no ophthalmoscopic changes exist. Neurasthenia or even hysteria is often suggested in such cases, and some ophthalmologist may even so far forget themselves as to get angry with the patients (always a mistake). The reverse situation – still normal visual acuity in association with slight foveal changes – can also be encountered. An important point is that the loss of visual acuity is nearly always symmetrical, although there are exceptions to this rule. We have seen patients with vision 1/10 in one and vision 9/10 in the other eye (fam. Kat), but in these cases the ophthalmoscopic changes were already symmetrical. The fact that ophthalmoscopy discloses an almost photographically exact symmetry of the two eyes can suggest a hereditary origin at an early stage.

Vision gradually diminishes to 1/10; in many cases it takes many years to reach this low value, but occasionally one may see very rapid deterioration of vision (Lutz 1911). Peripheral retinal dystrophy comes on insidiously in many cases, and in these cases vision can be even worse, although true blindness is a rarity.

3. FUNDUS (OPHTHALMOSCOPIC FINDINGS)

In the initial stage there are no or hardly any ophthalmoscopic changes. The first signs are disappearance of the foveolar reflex (fig. 1), followed after some time by disappearance of the foveal margin reflex (fig. 2). Changes in the pigment epithelium become visible in the form of grey, yellowish and brown spots, and the fovea shows a granulated appearance (figs. 2, 3). The fovea also gives an impression of being covered by varnish or snail-slime (fig. 1-4). Sometimes there is an exceedingly delicate plication of the internal limiting membrane, radiating in all directions (fig. 5). This radial aspect entails a risk of confusion with sex-linked juvenile retinoschisis, in which the fovea shows a characteristic cystoid alteration with clearly visible superficially localized radial plicae (page 51). These striae, however, are usually less delicate than the very fine plicae seen in Stargardt's disease. As in Stargardt's original cases, one frequently observes the occurrence of whitish-yellow, ill-defined perifoveal spots, localized beneath the vessels and probably in the pigment epithelium of the retina (fig. 6). The pigmentations in the foveal area vary markedly; thick "soot-flakes" can appear at the site of what used to be the fovea (fig. 7).

Finally there appears a horizontal oval of atrophic pigment epithelium which usually measures 2 pd in width and 1.5 pd in height (fig. 8). As the process advances, the focus can increase to as much as 5 pd. This more or less sharply defined focus of atrophic pigment epithelium has a greyish, grubby appearance and shows glistening

metallic reflexes when illuminated. The American literature describes this as "beaten bronze atrophy", and this is a very precise description. The glistening reflexes might be caused by hyalinization of Bruch's membrane.

While the central focus is extending, new white spots often occur which ultimately

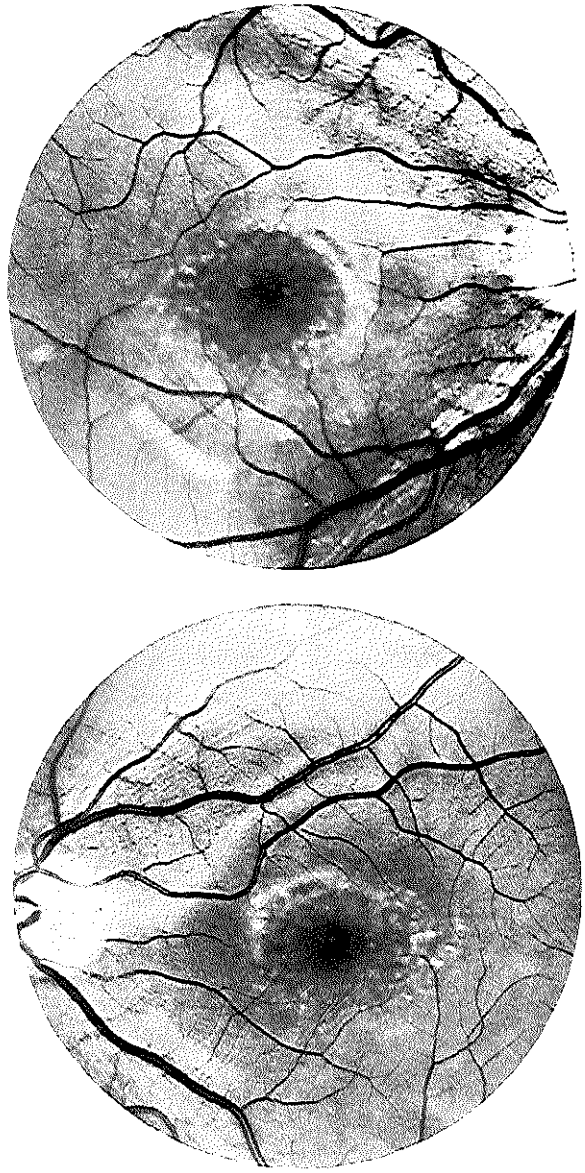


Fig. 2a-b. Stargardt's disease in a 24-year-old male. Visual complaints started six months previously. Tiny ill-defined whitish flecks at the exact site of the foveal margin. The normal foveal reflexes have disappeared. (Fam. Wu).

form a broad ring around the central retina or even around the disc and central retina (figs 6a, 9). In such cases differential diagnosis from fundus flavimaculatus constitutes a problem, but in view of Stargardt's original publications on this picture we prefer the designation Stargardt's disease.

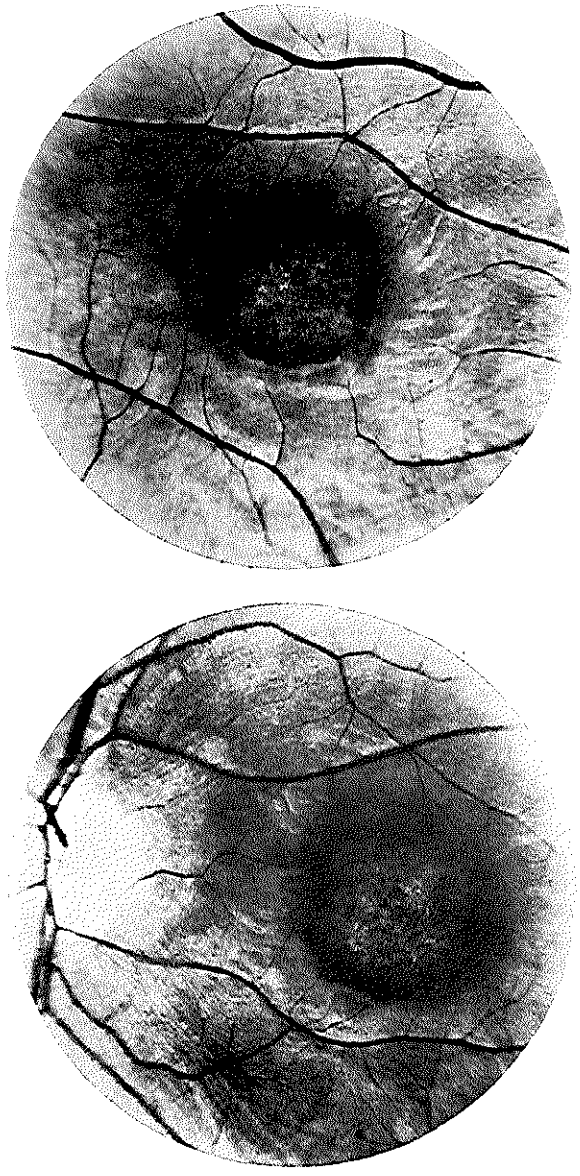


Fig. 3a-b. Another case of Stargardt's disease. Symmetrical atrophic patches, which measure approximately one disc diameter are the only abnormalities at ophthalmoscopy. There is a fine granular aspect in the foveal area. (Fam. Hor).

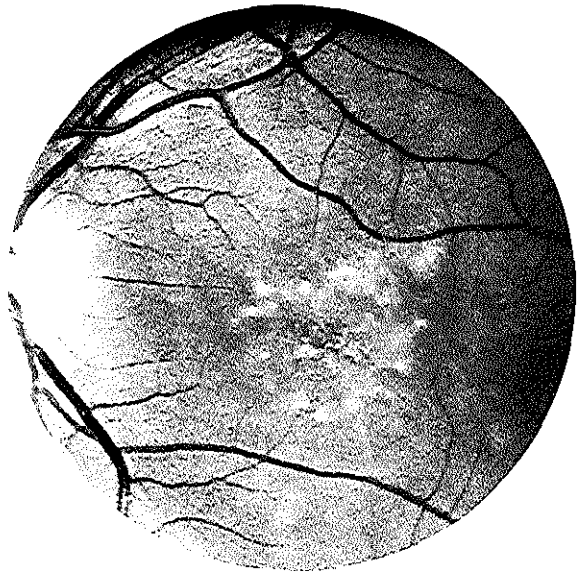


Fig. 4a. Whitish flecks in the foveal area, which has a slightly swollen aspect. (Fam. Oe).

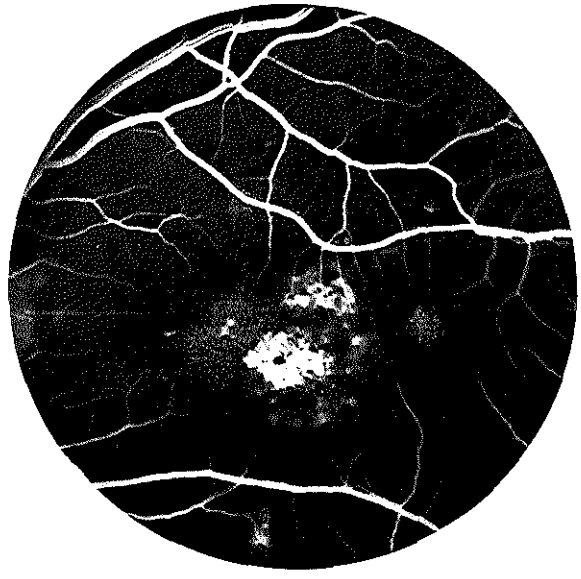


Fig. 4b. Fluorescein angiography reveals defects in the retinal pigment epithelium, mainly in the foveal area, but also in the perifoveal area.

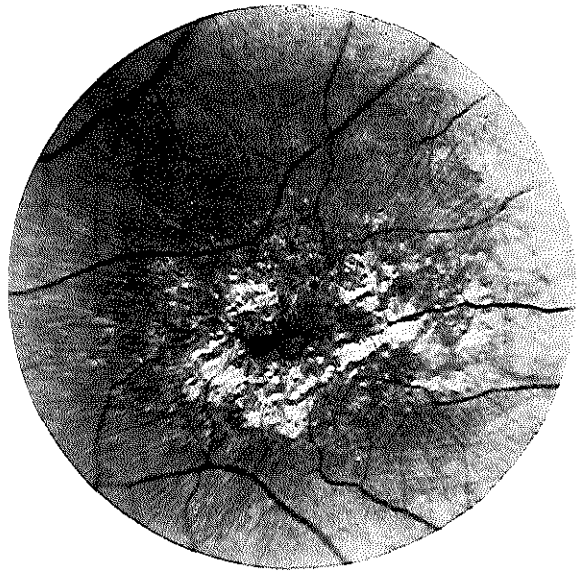


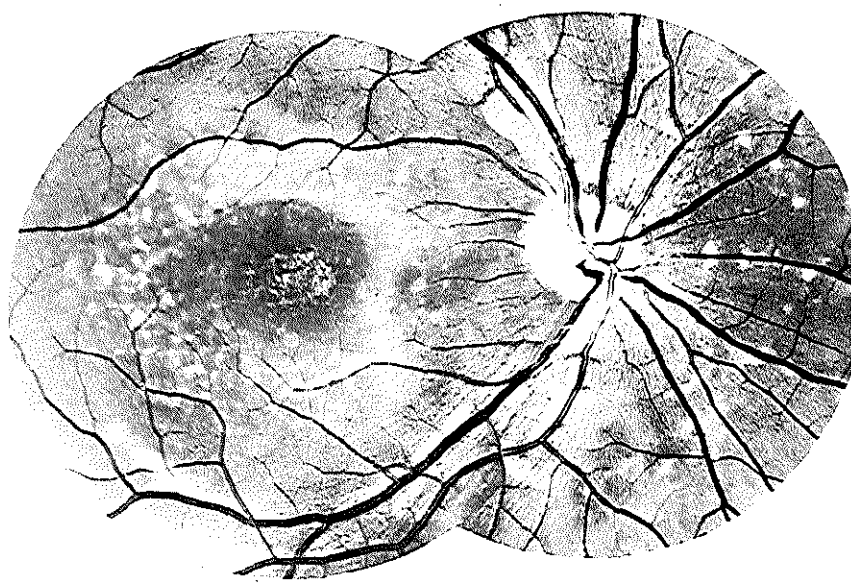
Fig. 5. Delicate radiate striation of the internal limiting membrane in Stargardt's disease with peripheral involvement (Fam. Bol). There is extensive atrophy of the pigment epithelium and the choriocapillaris. Some of the larger choroidal vessels are visible.

The atrophic process extends not only in width but often also in depth. In such cases the choroid becomes visible due to atrophy of the pigment layer, and after many years it assumes an atrophic appearance (figs. 9, 10). The ultimate result is an atrophic posterior pole, which can assume the features of central choroidal atrophy (fig. 11).

A striking feature is the symmetrical aspect of the posterior pole through all stages of development (figs. 2, 3, 6, 7, 8 and 12). Only very occasionally are the fundal features less symmetrical (fig. 13). It is questionable whether the cases described in the literature as unilateral Stargardt's disease can in fact be counted as such. Our material includes not a single case of unilateral Stargardt's disease. In recessive conditions the expression generally seems to be more constant than in dominant conditions, which often show marked differences in expression; this can be observed in such affections as Waardenburg's syndrome, Rieger's syndrome, vitelliform foveal dystrophy and dominant drusen of Bruch's membrane.

The disc, retinal vessels and peripheral retina are normal in the early stages, and remain normal if the dystrophic process is confined to the posterior pole.

Very often, however, an initially purely foveal dystrophy is followed by a perifoveal central affection, characterized by whitish-yellow round or sharkfin-shaped spots, or by true peripheral dystrophy. We observed this in many cases (fam. vB, fam. Boe, fam. Bol, fam. dBr, fam. dG, fam. Ha, fam. Hu, fam. Kni, fam. Ste, fam.



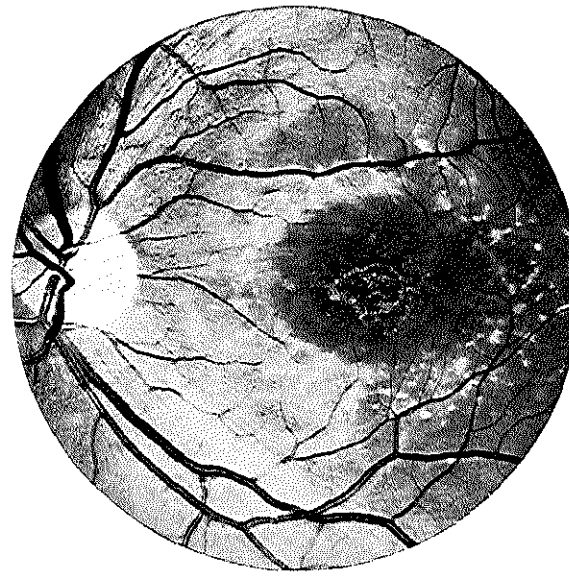


Fig. 6a-b. Symmetrical areas of beaten bronze atrophy surrounded by a crown of fuzzy whitish flecks (Fam. Krij). These flecks are also on the nasal side of the disc. Differential diagnosis with fundus flavimaculatus has to be made.

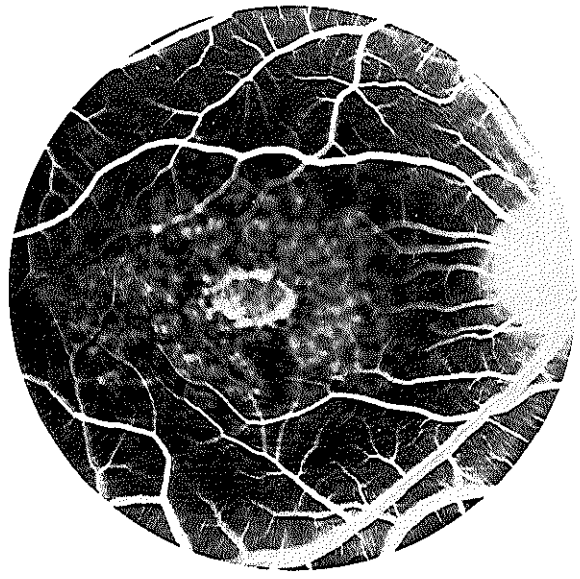


Fig. 6c. A horizontal oval of atrophic pigment epithelium surrounded by a broad band of ill-defined flecks. Fluorescence photograph of the fundus depicted in fig. 6a.

Sto, fam. vdZ). We found central TRD in the families Hor, Ja, Kat, KlW, Krij, Oe, Wil, Wu and Zo.

We are not sure, however, that some slight affection of the periphery has already occurred in some families. Fam. vW showed an unmistakable transition from a central to a centroperipheral dystrophy; transitional forms can be observed also in the families vB, Har, Krij and vdZ.

When affected, the retinal periphery shows round, granular black pigmentations, often surrounded by areas of depigmentation (figs. 14, 15, 16). In cases showing these centroperipheral dystrophies the horizontal oval central area of "beaten bronze atrophy" nearly always loses its well-defined features (figs. 7, 12, 17). In a few cases, bone trabeculae even appear in the retinal periphery (fig. 18a), while the disc assumes a wax-like pallor and the retinal arteries become very slender (fam. Kni) (fig. 18b). But the terminal stage of centroperipheral TRD can also be characterized by circumscribed areas of chorioretinal atrophy, which are most pronounced in the posterior pole (fig. 11, 19).

Examples in the literature are the cases reported by Leber (1874), Waardenburg (1932, 1963), Wakayama (1939), Brognoli (1949), Perron et al. (1953), Rosehr 1954) and Gaba (1956). These authors observed transitions from purely central to centroperipheral dystrophies. And many authors reported already developed centroperipheral dystrophies (Batten 1897; Baumgarten 1907; Stargardt 1913; Maewski 1914; Becker 1921; Oguchi and Yano 1921; Takeuchi and Horiguchi 1923; Firjukowa 1924; Rieger 1925; Urbanek 1926; Morelli 1928; Schiff-Wertheimer and

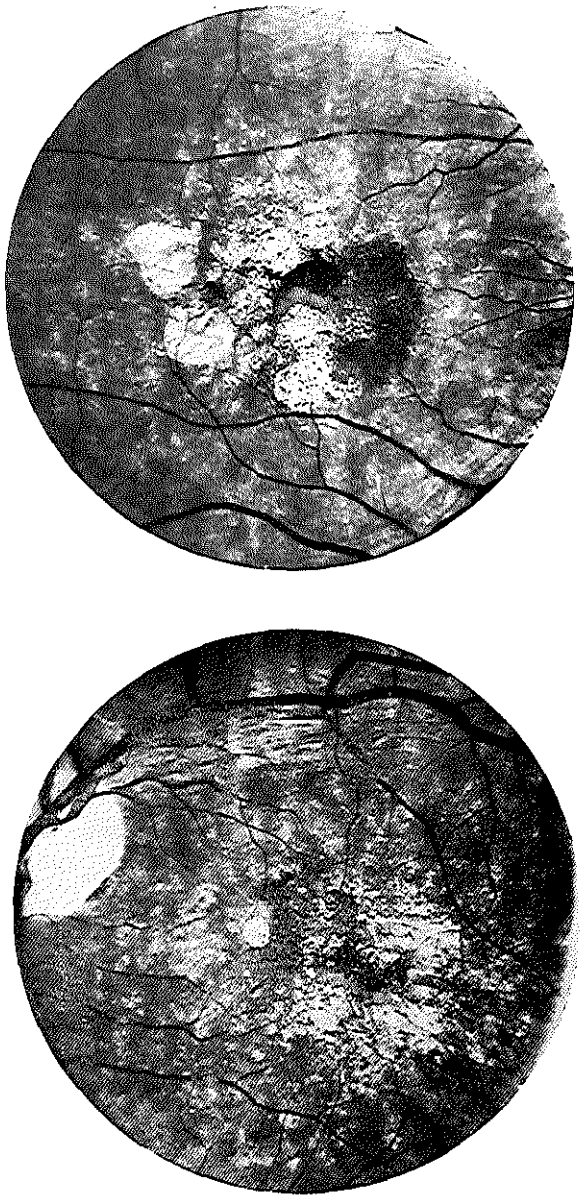


Fig. 7a-b. Atrophic pigment epithelium and choriocapillaris in the posterior poles of a patient with Stargardt's disease with peripheral involvement (centroperipheral tapeto-retinal dystrophy). Many ill-defined whitish flecks surround the heavily pigmented atrophic central zone (Fam. dBr).

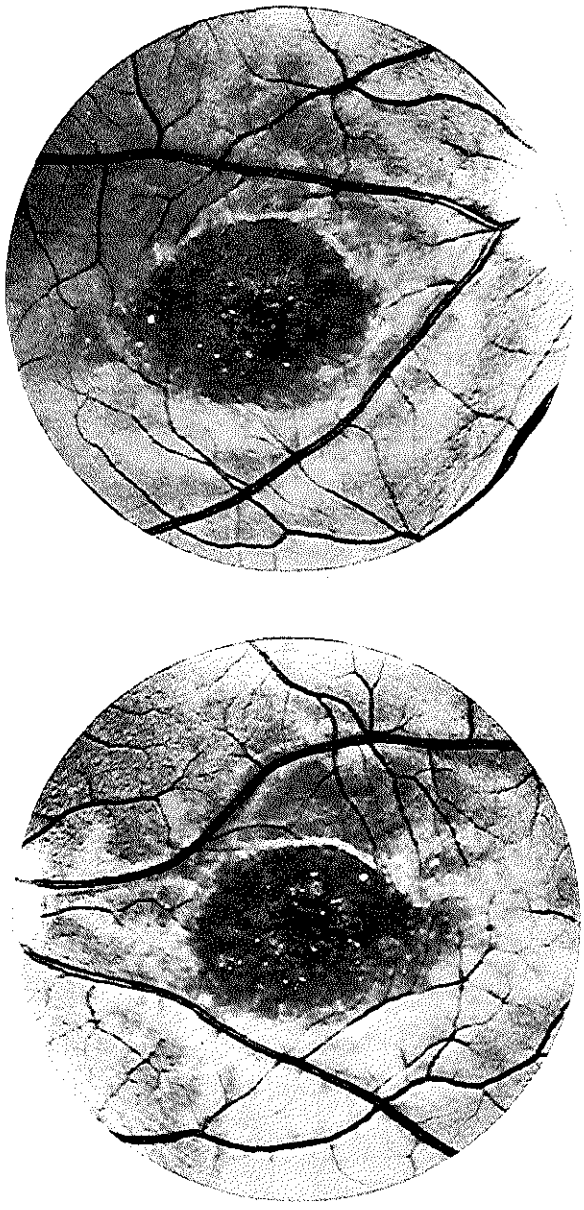


Fig. 8a-b. Symmetrical atrophic lesions with granular pigmentation restricted exactly to the area of the fovea centralis. Some whitish flecks are at the site of the foveal margin. (Fam. Ja).

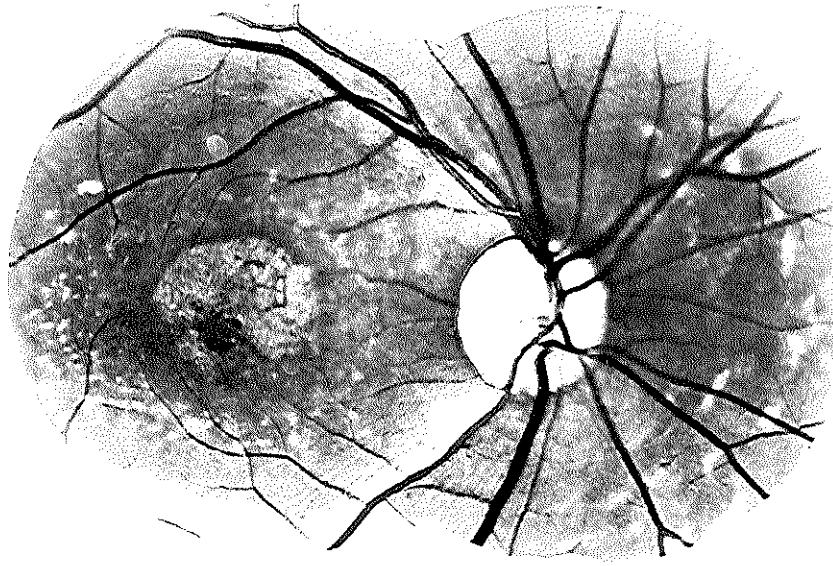


Fig. 9. A central patch of atrophic pigment epithelium and choriocapillaris surrounded by tiny flecks and larger fundus flavimaculatus-like lesions, also on the nasal side of the disc.

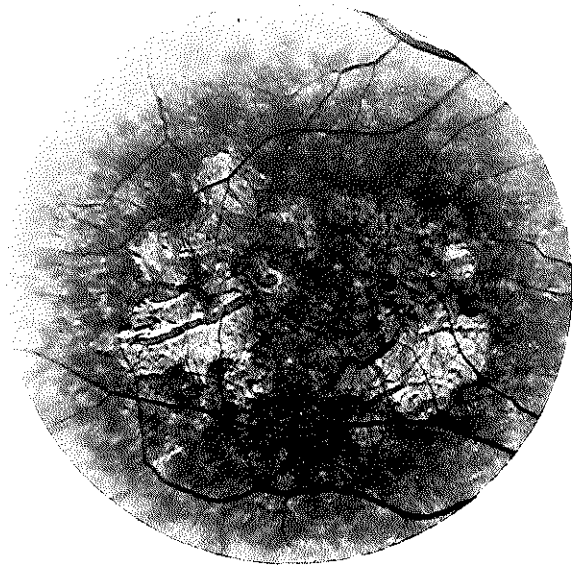


Fig. 10. There is distinct atrophy of the choroid, choriocapillaris and pigment epithelium in this individual with Stargardt's disease with peripheral involvement. Differential diagnosis with incipient areolar choroidal dystrophy is almost impossible (Fam. vB).

Fig. 11. Extensive chorioretinal atrophy of the posterior pole in a 56-year-old female with centroperipheral tapetoretinal dystrophy (Fam. Kni). This picture is undistinguishable from that of central areolar choroidal atrophy.

Tillé 1930; Von Rötth 1931; Rossi 1931; Danielson 1934; Ibuki 1935; Klien 1936; Tillé 1936; Borsotti 1937; Muromoto 1937; Ogata 1938; Sorsby 1940, 1941; Offret and Brégéat 1942; Feldman 1947; Ryerson 1947; Brognoli 1949; François 1949; Biro 1951; Danic 1952; Perron et al. 1953; L. Samuels 1954; Anastasi and Bellavia 1954; Bessière et al. 1957; Kozlowski 1958; Lux 1960; Etzine 1961; Bessière et al. 1962; Gruetzner 1962; Biesheuvel 1963; Shershevskaya 1967; Ersler and Jaczynowska 1968; Sicault 1968, and others).

4. REFRACTION

The majority of cases showed low myopia with or without astigmatism; this was in marked contrast to vitelliform dystrophy, in which hypermetropia with or without astigmatism was practically the only abnormality of refraction observed.

5. VISUAL ACUITY

Central vision is ultimately lost, although it may be many years before this happens. Some authors have described fairly rapid loss of central vision (Lutz 1911). Our own experience indicates that this is fairly rare. In two sisters, however, we saw visual acuity diminish in two years from 8/10 to 1/10 (fam. vW). In many cases vision diminishes gradually and symmetrically; in other cases vision may be as low

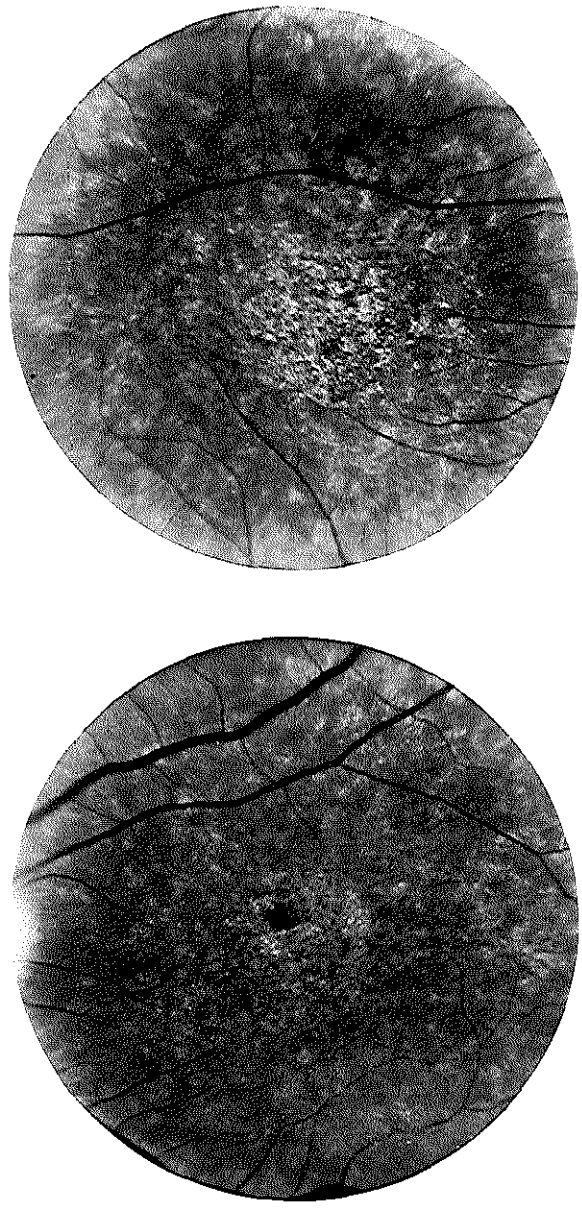


Fig. 12a-b. The posterior poles in Stargardt's disease with peripheral involvement showing centrally ill-defined atrophic lesions surrounded by whitish flecks (Fam. dBr).

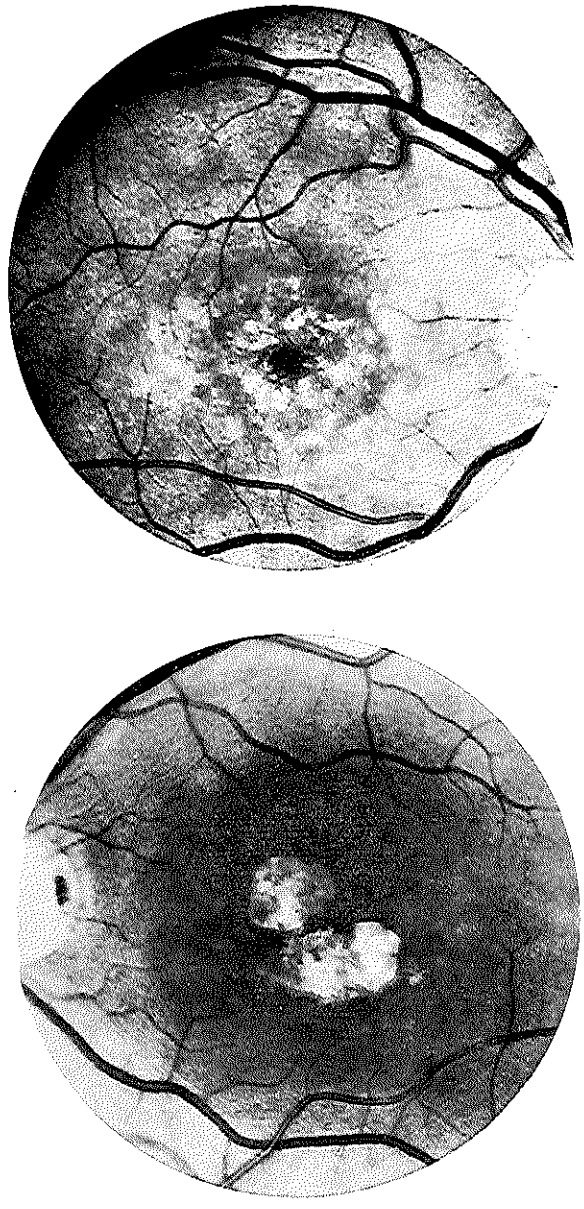


Fig. 13a-b. Asymmetrical lesions in Stargardt's disease. In both eyes perifoveal whitish spots are visible in this 33-year-old male (Fam. Zo).

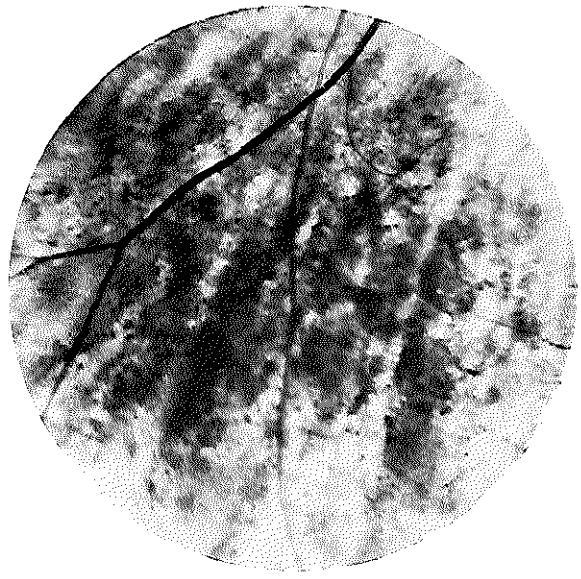


Fig. 14

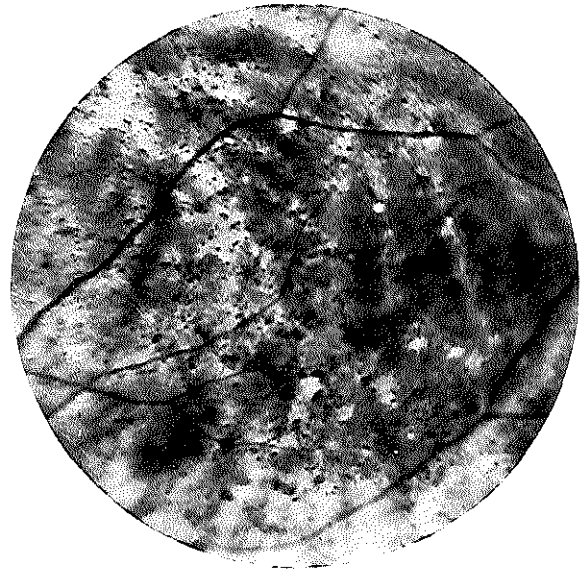


Fig. 15

Fig. 14-15-16. Pathognomonic lesions of the retinal periphery in 3 different individuals with Stargardt's disease with peripheral involvement (Fam. vB; dBr; Bol). Many small round pigmented spots often surrounded by whitish areas. The retinal vessels are only slightly attenuated.

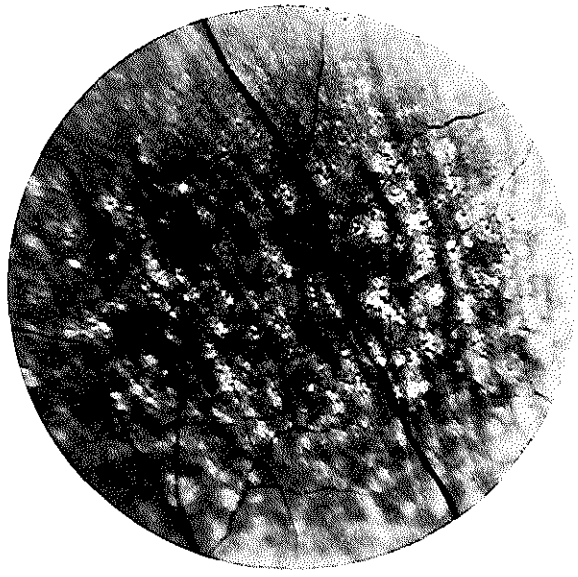


Fig. 16

Fig. 17a. Another patient with centroperipheral tapetoretinal dystrophy. The foveal lesions are rather ill-defined. For left eye see fig. 17b. (Fam. Sto).

Fig. 17b. Another patient with centroperipheral tapetoretinal dystrophy. The foveal lesions are rather ill-defined (Fam. Sto). For right eye see fig. 17a.

Fig. 17c. Fluorescein angiography reveals atrophy of the pigment epithelium, choriocapillaris and partly of the choroid. There is no leakage of fluorescein, indicating a normal Bruch's membrane.

Fig. 18a. Bone corpuscles in the perifoveal area, in the mid- and far periphery of a 22-year-old patient with centro-peripheral tapetoretinal dystrophy (Fam. Kni).

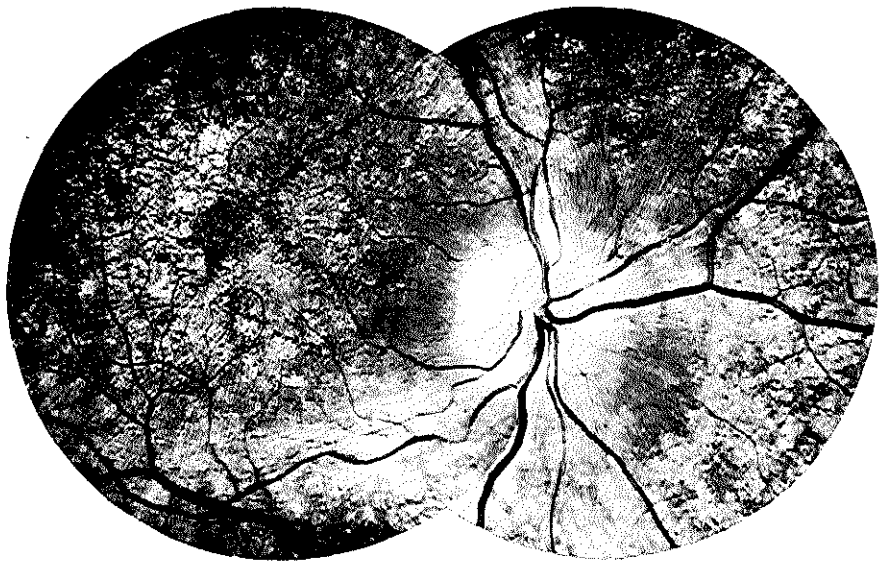


Fig. 18b. The same patient showing diffuse chorioretinal atrophy in the posterior pole. This dystrophy started with foveal changes in an otherwise normal retina. The discs are pale and the arterioles are attenuated.

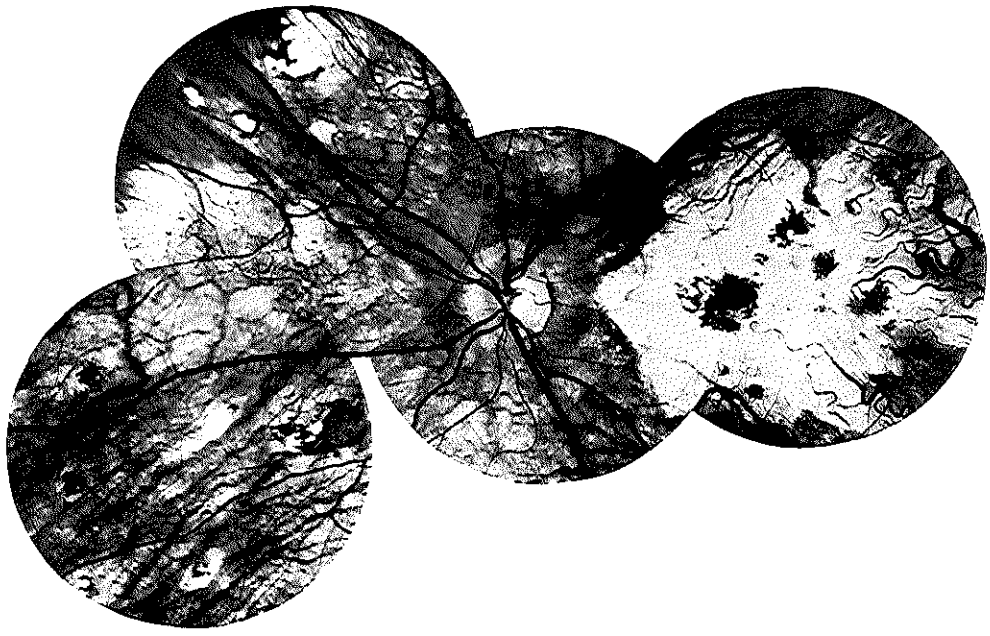


Fig. 19. Composite photograph of the fundus of a 56-year-old female (see fig. 11) with centroperipheral tapetoretinal dystrophy (Fam. Kni). Note the patches of choroidal atrophy.

as 5/60 in one eye while in the contralateral eye it is still 9/10 (families Kat, KlW and Oe).

In these cases, however, the ophthalmoscopic features are nevertheless virtually symmetrical. Vision finally diminishes to 1/10 or 5/60. Only if the retinal periphery becomes involved in the dystrophic process can vision diminish further to values between 1/60 and 5/60 (fam. Kni).

In dubious cases, when Stargardt's disease is suspected and the fovea shows no pronounced changes, vision can be determined with a neutral density filter. This amblyopia test indicates whether the loss of vision has a functional or an organic cause. True functional amblyopia (unlike organic abnormalities as for instance Stargardt's disease) is not associated with diminution of vision. Bessière et al. (1969) used a similar procedure in such cases. They determined the "acuité visuelle dynamique" (determining visual acuity at low luminances). In 5 patients this function test was the first to be disturbed.

6. VISUAL FIELDS

The peripheral limits of the visual fields remain normal as long as the retinal periphery is unaffected. Once it is affected, some slight concentric limitation of the isopters usually occurs. A relative central scotoma is soon found, although fixation problems may make it possible to record only a diminished central sensitivity. This

relative scotoma develops rapidly for red, and later for green. The central scotoma corresponds to the size of the central atrophic focus, and rarely exceeds 20 degrees. The ultimate result is an absolute central scotoma with sensitivity gradually increasing towards the periphery, and associated with eccentric fixation.

It is remarkable that the peripheral visual field is so little affected in most centroperipheral forms of Stargardt's disease. Ultimate visual field defects occur only in those forms which show the presence of true trabeculae, wax-like pallor of the disc and very constricted vessels.

Bessière et al. (1969) found static perimetry to be very valuable in the initial stages of Stargardt's disease in which a diagnosis has not yet been established with certainty. In more advanced stages, the curve obtained was usually a transitional form of the curves usually seen in purely retinal and purely opticoneural affections. In affections of the optic nerve there are often spiked curve-segments, whereas in retinal affections the curves have a more gradual course. In view of their findings, Bessière et al. (1969) maintained that in Stargardt's disease both the photoreceptors and the intraretinal nerve fibres are affected.

In our opinion the nerve fibres are affected only secondarily because in advances stages there is always temporal pallor of the disc, which is never observed in early stages.

7. COLOUR VISION

Detailed studies of colour vision have been made in Stargardt patients (Kahán and Sipós 1951; Hong 1957; Cox 1960, 1961; Gruetzner 1961, 1962; Verriest 1964). Our findings corroborate the results obtained by these authors. In all cases we found acquired red-green dyschromatopsia with diminished red sensitivity, of the type encountered in congenital protanomaly or protanopia (acquired red-green dyschromatopsia type I, Verriest 1964). In the centroperipheral dystrophies we also found a tritan disturbance.

Even earlier case reports described a central scotoma for red and green objects (Leber 1877; Batten 1897; Baumgarten 1907; Stargardt 1909, 1913, 1916, 1917; Behr 1920; Morelli 1924). It was initially thought that the dyschromatopsia occurred as a separate congenital anomaly linked to the foveal dystrophy, and not as a consequence of the dystrophy (Behr 1920). Clausen (1921) and Rieger (1925), however, demonstrated that the dyschromatopsia is acquired as a result of an affection of the photoreceptors in the posterior pole. They noticed that patients whose colour vision had been normal, developed dyschromatopsia with the progress of the foveal dystrophy. Nevertheless, congenital disorders of colour vision can indeed be incidental findings in individuals with foveal dystrophy, for about 8% of all males and 0.5% of all females suffer from congenital colour blindness (Krill 1968). In our opinion the cases of Halbertsma (1928) and possibly those of Landolt (1955) come under this heading.

According to Gruetzner (1961), the degree of acquired dyschromatopsia in Stargardt's disease is largely independent of the remaining visual acuity, the ophthal-

moscopic findings and the duration of the affection. Landolt (1955), Gruetzner (1961) and Verriest (1964) maintained that colour vision is affected very early, sometimes while visual acuity is still quite normal. But Cox (1960, 1961) believed that visual acuity is nearly always affected when an acquired dyschromatopsia is found. We never saw Stargardt patients with normal visual acuity, and can therefore form no opinion on this point. Bessière et al. (1969), however, found normal colour vision in patients with normal or slightly diminished visual acuity. Of course it is largely dependent on the sensitivity of the methods used whether diminished visual acuity or diminished colour vision is first demonstrated. It is my impression that, in hereditary dystrophies of the posterior pole in general, disorders of colour vision occur only when visual acuity is already diminished.

It has been demonstrated with the aid of the *anomaloscope* (Stargardt 1925; Rieger 1925; Franceschetti 1930; Franceschetti and Klein 1941, 1947; Kahán and Sipós 1951; Landolt 1955; François et al. 1956, 1957, 1961, 1962; Hong 1957; Cox 1960, 1961; Gruetzner 1961; Verriest 1964) that red sensitivity is so diminished as to produce results resembling those obtained in the case of protanomaly. Later, there are results such as those obtained in protanopia, and finally an acquired achromatopsia occurs in the central visual field (Gruetzner 1961).

Thus we find a gradual transition from the trichromatic stage (acquired protanomaly) through the dichromatic stage (acquired protanopia) to the monochromatic stage (acquired achromatopsia).

The dichromatic stage is often found in association with a visual acuity of 1/10, and the monochromatic stage corresponds with an acuity lower than 5/100 (Verriest 1964). Red-green dyschromatopsia is often found as far as 30 degrees from the retinal centre, and the retinal periphery usually retains normal colour vision. In all our patients we found an unmistakable diminution of red sensitivity with the anomaloscope.

The *HRR test* often demonstrates mild or medium red-green dyschromatopsia, which increases with diminishing visual acuity. In a few cases in which the retinal periphery was involved in the dystrophic process, we also found blue-yellow dyschromatopsia (families dBr, Bol, dG and Sto).

The *Farnsworth panel D-15* and the *Farnsworth 100 hue test* reveal no abnormality in the early stages; in more advanced stages of Stargardt's disease a red-green axis (and several times also a tritan axis) has been found. However, unclassifiable results have been reported also. Verriest (1964) maintained that a correlation exists between visual acuity and the total numeral index of the 100 hue test. None of the Stargardt patients adequately perceived the *Farnsworth tritan plate*. The blue square was never seen. However, the selective invisibility of the blue square is of no great diagnostic value because it is encountered in red-green as well as in blue-yellow dyschromatopsias (Franceschetti et al. 1963).

The maximum of the spectral luminosity curve shows a progressive displacement to the shorter wavelengths (Hong 1957; Cox 1960; Gruetzner 1961; François et al. 1962).

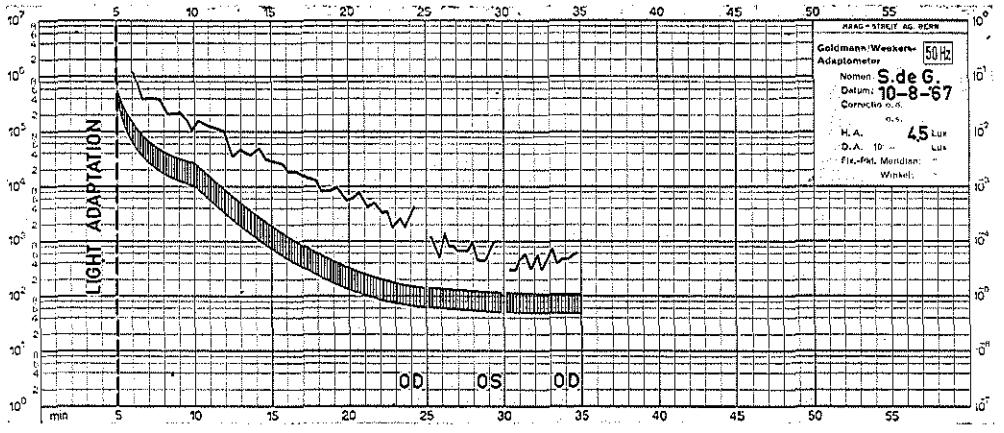


Fig. 20. Representative dark adaptation curve in a patient with Stargardt's disease with peripheral involvement (Fam. dG). Both photopic and scotopic components are delayed (approximately 1 log U).

In Stargardt's disease, the maximum hue discrimination is no longer at the orange hues, and in centroperipheral dystrophies the blue-green hues are likewise perceived less well (Gruetzner 1962).

The impression is that in this type I red-green dyschromatopsia there is a gradual diminution of sensitivity and then total destruction of all foveal cones; the function of the cones containing the fundamental red is affected first and most intensively (Gruetzner 1961, 1962; Verriest 1964). In early stages this could result from selective affection of the red-sensitive cones, but it is more likely due to the fact that the retinal centre largely consists of red-sensitive cones.

It is a conspicuous fact that the patients are often unaware of their disturbed colour vision, although in some cases the patients themselves had already noticed that they saw the colour red less well.

The findings warrant the conclusion that the most characteristic disturbance of colour vision in Stargardt's disease is a diminished red sensitivity which, via a protanomalous and a protanopic stage, can ultimately lead to achromatopsia in the centre of the visual field.

8. DARK ADAPTATION

Dark adaptation is quite normal in Stargardt's disease if the dystrophic process is confined to the fovea or the posterior pole. But when the retinal periphery is involved in the dystrophic process, there is gradually increasing delay in dark adaptation for both systems. Both the photopic and the scotopic segment of the dark adaptation curve are disturbed in such cases (fig. 20). This delay rarely exceeds 1.5 log. U. Only in cases in which true retinopathia pigmentosa features develop can dark adaptation diminish further.

The dark adaptation test is a sensitive indicator in demonstrating diffuse involvement of the retina in centroperipheral TRD; it usually indicates involvement of the retinal periphery in early stages.

9. ELECTRORETINOGRAPHY

The routine electroretinogram (ERG) is quite normal in the purely central form of Stargardt's disease; and this is understandable because the ERG shows the overall response of the entire retina. Jacobson et al. (1960) found a normal ERG in monkeys in which they had photocoagulated the maculae; and Ponte (1961) described a normal ERG in patients with a solar retinopathy.

Subnormal ERG features in central retinal affections warrant the conclusion that a larger part of the retina is involved than ophthalmoscopic findings suggest. In our patients with only central ophthalmoscopic changes, we found an entirely normal scotopic and photopic ERG (families vB, Dr, Har, Hor, Krij, Oe, Wil, Wu and Zo).

In the case of perifoveal and peripheral retinal involvement, however, gradually diminishing responses are obtained, both in the scotopic and the photopic system. The designation cone-rod dystrophy is justifiable in these cases (Berson et al. 1968).

It is our experience that the ERG findings generally parallel the ophthalmoscopic changes. When the retinal periphery was ophthalmoscopically entirely normal, we nearly always obtained a normal ERG. We were unable to corroborate the observation of Franceschetti et al. (1955), who obtained a highly pathological ERG in a patient in whom only foveal changes were seen. However, we did always obtain a decidedly subnormal ERG in association with only foveal ophthalmoscopic changes in cases of sex-linked juvenile retinoschisis. This raises the question whether the patient described by Franceschetti et al. (1955) – a 23-year-old man with a perifoveal reflexring showing delicate radial striation – was not in fact suffering from sex-linked juvenile retinoschisis.

Many other authors have described a normal scotopic ERG in the purely central form of Stargardt's disease (Karpe 1945, 1958; Dollfus et al. 1951; François 1952; Franceschetti et al. 1955; Wadensten 1956; Bessière et al. 1957; François et al. 1958, 1962, 1968; Straub 1961); and the photopic ERG is usually normal also (Franceschetti et al. 1963).

However, a subnormal ERG was obtained several times upon red light stimulation (Jacobson et al. 1956; Bessière and Chabot 1958; Jayle et al. 1959; Toufic 1959; Ruedemann and Noell 1961; Bessière et al. 1962, 1969; Krill 1966).

The CFF (critical frequency of flicker fusion) is generally normal also (Iser and Goodman 1956; François et al. 1956; Wadensten 1956; Heck 1957; Henkes 1958).

Jaeger et al. (1960) found with the help of the photopic ERG, that the spectral sensitivity curve may show displacement to the shorter wavelengths.

Noell (1960), Ruedemann and Noell (1961) and Ruedemann (1966) focused attention on the fact that, in many cases in which the central retina is involved, a

normal ERG is obtained because the technique used is not sufficiently sophisticated. In every patient with a circumscribed lesion of 1 disc diameter or more, Noell (1960) found several changes in the a-wave, in flicker response and in red light response.

We obtained photopically as well as scotopically subnormal, electro-negative or even unobtainable ERG's in the centroperipheral dystrophies (families Boe, Bol, dBr, dG, Hu, Kni, Ste and Sto), confirming the findings of Perron et al. (1953), François et al. (1956), Bessière et al. (1958), Biesheuvel (1963), Ruedemann (1966), Berson et al. (1968) and Sicault (1968).

Foveal electroretinogram and visually evoked responses

The foveal ERG (F-ERG) was distinctly subnormal in all cases, including those in which visual acuity was still fair (II-3, fam. Wu). The VER were likewise subnormal in all cases. Bankes (1967) also reported a subnormal local ERG of the fovea.

These techniques are very important for an early diagnosis, especially in cases in which ophthalmoscopy shows no or hardly any changes as yet, and in which optic nerve lesions or functional disorders must be ruled out.

Oscillatory potentials

The OP were normal in dystrophies which were ophthalmoscopically confined to the retinal centre. The OP showed changes at an early stage in cases of peripheral involvement.

10. ELECTRO-OCULOGRAPHY

Like the ERG, the LP/DT-ratio of the EOG was quite normal in the purely central forms of Stargardt's disease (families Dr, Hor, Ja, Krij and Oe); but when the retinal periphery was involved the EOG soon became subnormal; in our experience, the EOG is the most sensitive objective indicator of diffuse retinal dysfunction in this disease.

In fact the EOG was already slightly subnormal in a few cases in which hardly any ophthalmoscopic changes were seen as yet outside the foveal area (families vW, Wu, Zo and vdZ).

In centroperipheral dystrophies the EOG is very pathological, and the standing potential shows no rise whatever in light adaptation in cases characterized by trabeculae in the retinal periphery, wax-like pallor of the disc and constricted arteries.

In no patient did we find the combination of a normal EOG with a subnormal ERG. This confirms the findings of François et al. (1968, 1969), who obtained a subnormal EOG whenever the ERG was subnormal. In many cases, however, we did find a subnormal EOG in combination with a normal ERG (families vB, Har, Wu, vW, Zo and vdZ).

A subnormal EOG and subnormal ERG were always found in families with centroperipheral dystrophy (families Boe, Bol, dBr, dG, Hu, Kni, Ste and Sto).

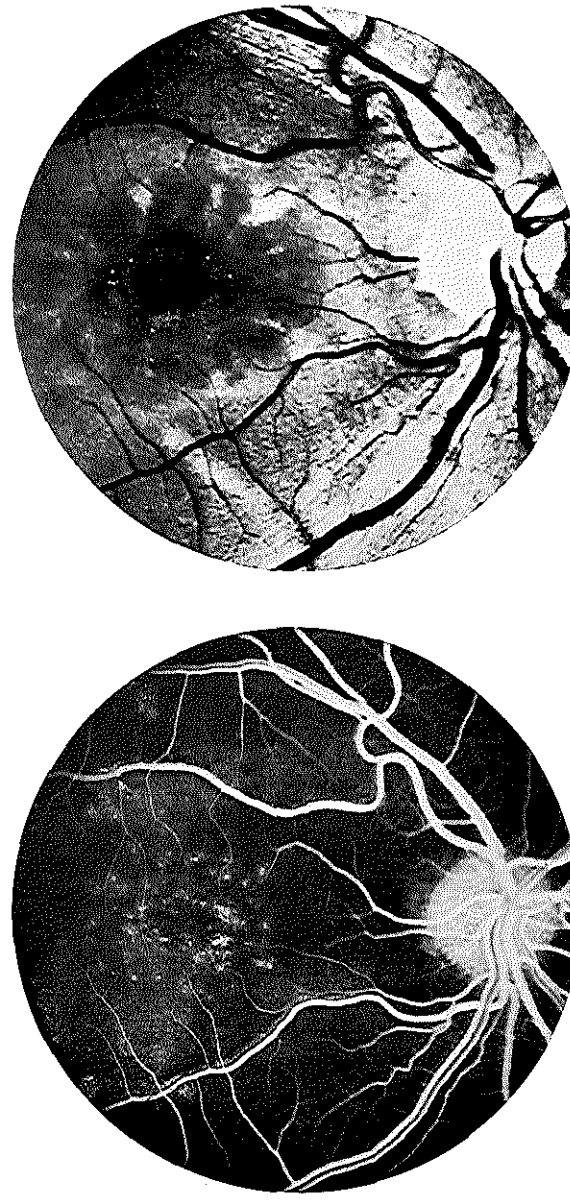


Fig. 21a-b. Conventional and fluorescence photograph of Stargardt's disease in a 41-year-old female, showing the pathognomonic central area of beaten bronze atrophy surrounded by whitish flecks. There are distinct defects in the retinal pigment epithelum at the site of the fovea.

In conclusion, it can be stated that the EOG is generally the first of the overall retinal function tests to become subnormal in cases of Stargardt's disease in which the retinal periphery becomes involved in the dystrophic process. This is suggestive of a primary affection of the pigment epithelium (see page 40).

For differential diagnosis from vitelliform dystrophy of the fovea it is important to know that the low EOG-ratios observed in vitelliform foveal dystrophy are seen only in the terminal stages of ophthalmoscopically centroperipheral dystrophies.

11. PHOTOGRAPHY

The areas of beaten bronze atrophy in the posterior pole are very clearly visible in photographs on orthochromatic graphic film (fig. 6). The photographs on panchromatic graphic film, however, show the changes at the level of the pigment epithelium, e.g. the peripheral pigmentations, in better detail (fig. 18a).

12. FLUORESCEIN ANGIOGRAPHY

Fluorescence in the centre of the central retinal focus is already visible in the arterial phase, and becomes more intensive in the venous phase (fig. 1, 4, 6c). The fluorescence persists for a fairly long time but no leakage of fluorescein occurs, and the fluorescence pattern therefore suggests defects of the pigment layer while Bruch's membrane is intact. The afterfluorescence is probably explained by the fact that the pigment epithelium defects give a view of the fluorescein normally oozing from the smaller vessels of the choriocapillaris. The size of the fluorescent area depends on the size of the defect in the pigment epithelium.

Very often there is an annular pattern of numerous fluorescent spots around the central fluorescent focus (fig. 6c, 21b, 22b). We do not share Amalric's view (1966) that Bruch's membrane has a hyperpermeability to fluorescein; for no sign of fluorescein leakage is observed.

Fluorescein angiograms of Stargardt's disease have been published by several authors (Norton et al. 1965; Amalric 1966, 1967; Keneyeres and Slezak 1967; Babel and Farpour 1967; Jütte and Lemke 1968; François and De Laey 1969; and others).

13. CARRIERS

The parents of patients with Stargardt's disease show quite normal ophthalmoscopic findings. The parents can be regarded as "sure heterozygotes" for the pathological gene, and are therefore carriers of this gene.

Several parents of patients with Stargardt's disease were submitted to comprehensive investigation, including various electrophysiological studies (families Hor, Sto and vW).

All carriers proved to yield entirely normal ophthalmoscopic and electrophysiological findings. EOG, ERG, F-ERG and OP were without abnormalities. This is

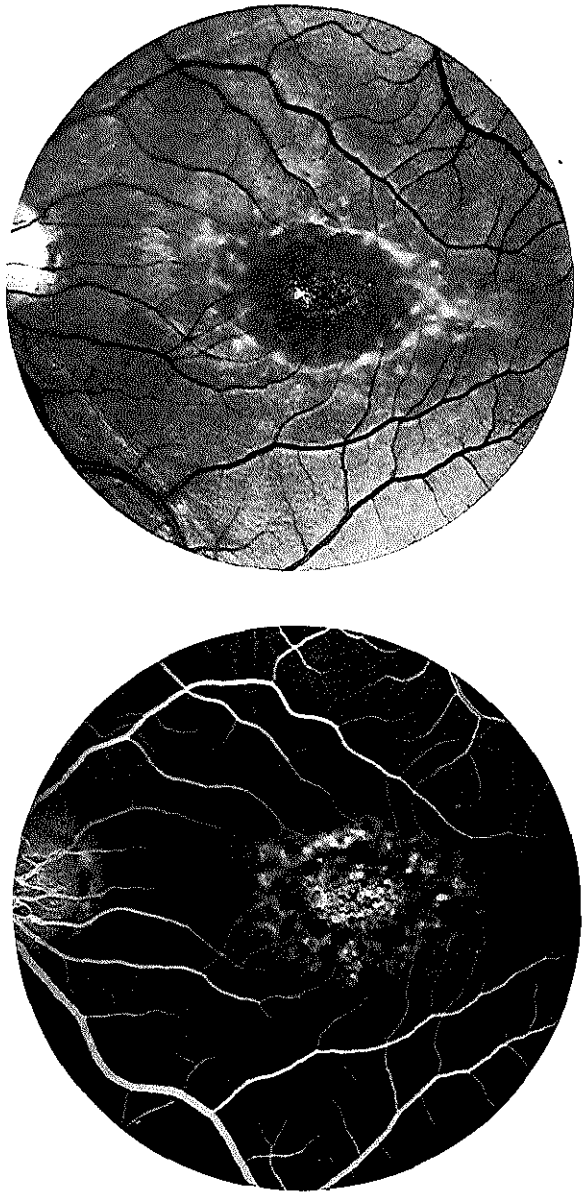


Fig. 22a-b. Conventional and fluorescence photograph of Stargardt's disease in another female showing the characteristic pattern of athrophic pigment epithelium in the foveal area.

not too surprising in view of the fact that in the patients themselves the F-ERG is initially the only evidently disturbed electrophysiological function test.

However, Merin and Landau (1970) shortly reported about abnormal findings in relatives of patients with Stargardt's disease.

14. HISTOLOGICAL FINDINGS

Histological studies on Stargardt's disease have been few and far between. The studies published by Harms (1904) and Behr (1921) may concern Stargardt patients, but this is by no means certain.

Klien (1950) had occasion to make a histological examination of a Stargardt eye which had been removed in an exenteration for infiltrative squamous-cell carcinoma; Paufique and Hervouet (1963) examined an eye enucleated from a 35-year-old Stargardt patient in view of a peripheral malignant melanoma of the choroid.

Vail and Shoch (1965) studied the eyes of a 78-year-old woman with dominant progressive foveal dystrophy; Brihaye-Van Geertruyden (1962) had occasion to make a histological study of an eye from a patient with spinocerebellar ataxia and progressive foveal dystrophy, who had died at age 31.

The histological findings reported are generally in agreement. Blodi (1966) has summarized them as follows. "The hallmark is a complete disappearance of the visual elements in the macular area. The macular cones are gone and so are the cones and rods in the perimacular region. The pigment epithelium has also disappeared in this area and only a few degenerated nuclei are visible between Bruch's membrane and the external limiting membrane. Farther out, towards the periphery, a layer of vascularized connective tissue may lie between Bruch's membrane and the atrophic external layers of the retina. The extent of the atrophy seems to increase with age, so that in old patients an area much larger than the macula is involved. Secondary degenerative or proliferative changes may occur. The inner layers of the retina may show a cystoid degeneration and there may be deposition of calcium. The proliferative changes occur mainly in the pigment epithelium. They are usually spotty, circumscribed and occasionally quite subtle and mild. Bruch's membrane and choroid, especially the choriocapillaris, show no pathologic changes of note."

In our opinion, atrophic changes of the choroid can certainly be found in terminal stages. At least this was clinically quite evident in some of our patients (families vB, Kni and vdZ).

15. PATHOGENESIS

The basic pathological process seems to be localized in the photoreceptors of the central retina. This is suggested by the fact that diminution of vision is frequently observed in the initial stages in the absence of pronounced ophthalmoscopic changes.

On the other hand, the often perifoveal yellow-white spots, the pathological fluorescein angiogram, and the often subnormal EOG in processes extending

towards the periphery, in combination with a normal ERG and normal dark adaptation, are suggestive of a localization of the primary pathological agent in the pigment epithelium.

For the time being, therefore, the designation central TRD would seem to be well-chosen. The question whether the cells of the pigment epithelium or the photoreceptors are first affected, must remain unanswered. These cases may immediately develop a combined dystrophy of both retinal structures on the basis of an enzymatic disorder.

16. MODE OF TRANSMISSION

The mode of transmission of Stargardt's disease is autosomal recessive. There have been reports on progressive foveal dystrophies with autosomal dominant transmission, and these have been interpreted as dominant forms of Stargardt's disease. These forms will be discussed in a separate chapter because no dominant transmission has been observed in Stargardt's original patients.

The autosomal recessive mode of transmission is plausible for the following reasons.

1. There are often several Stargardt siblings in one family.
2. The parents of patients are ophthalmologically quite normal and often consanguineous.
3. Males and females are about equally affected.
4. There are generally more normal subjects than patients in each sibship.

We found parental consanguineousness in five families (Bol, Har, Hor, Kni and Krij). In fam. Kni, with centroperipheral TRD, the mother and 7 of the 12 children are affected. This is probable an example of pseudo-dominance, for the mother married a relative. The mother is probably homozygote and the father heterozygote for the pathological gene.

The fam. vB, in which 3 brothers in one family married 3 sisters in another family, is likewise interesting. Two of the marriages produced Stargardt children. The four parents of these children would appear to be all heterozygotes for the pathological gene that causes Stargardt's disease.

In the literature we find numerous descriptions of families with parental consanguineousness (Dujardin 1904; Jackson 1905; Jennings 1909; Feingold 1916; Behr 1920; Oguchi and Yano 1921; Nakajima 1922 (quoted by Waardenburg et al. 1963); Maeda 1925 (quoted by Waardenburg et al. 1963); Rieger 1925; Togano 1930 (quoted by Waardenburg et al. 1963); Caocci 1935; Ibuki 1935; Neame 1935; Wagner 1935; Burnier 1936; Ishida 1936; Alvaro 1938; Ogata 1938; MacRay 1940, 1946; Sorsby 1940, 1941; Gartner 1946; Agatston 1948; Perron et al. 1953; Anastasi and Bellavia 1954; François and Verriest 1956; Tiberi and Cuccagna 1959; Etzine 1961; François et al. 1962; Yasukura et al. 1967).

A great many of the families described in the literature include more than one affected child, as do many of the families we studied. Nevertheless, sporadic cases

are encountered also, and this need not be surprising because, fortunately, only 25% of children of heterozygotes for the pathological gene are affected.

In the majority of our families we found more than one affected child (see Case histories). Affected twins have been described by Dujardin (1904), Nettleship (1908), Neame (1944), and others.

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

The literature reports no abnormalities regularly found in Stargardt's disease. In our patients, extensive physical and laboratory examinations disclosed no abnormalities. Neurological examination also produced negative results.

18. ASSOCIATED CONDITIONS

The literature has described many affections as associated with Stargardt's disease. It is exceedingly difficult to estimate the merits of all these publications; it is not certain that the term Stargardt's disease is always correctly used.

We therefore discuss the combination of progressive foveal dystrophies with affections elsewhere in the organism. Progressive foveal dystrophies accompanied by peripheral retinal changes have already been discussed in detail. The lipidoses (maculocerebral dystrophies) will be left undiscussed here because they are quite different conditions which can be clearly distinguished from Stargardt's disease.

We believe that Stargardt's disease is a purely retinal affection which normally occurs without any associated abnormality, and is only sporadically accompanied by an affection elsewhere in the organism.

No concomitant abnormality was found in any of our patients. In the literature, we found the following conditions mentioned in association with progressive foveal dystrophy.

1. *Neurological changes.* There are spinocerebellar and cerebellar spastic disorders in which foveal dystrophies or centroperipheral TRD occur (Froment et al. 1937, 1938; Sjögren 1943; Walsh 1947, 1957; Havener 1951; Arnould et al. 1955; Van Bogaert 1957; Ledic and Van Bogaert 1960; Foster and Ingram 1962; Bergstedt et al. 1962; Bessière et al. 1962; Carpenter and Schumacher 1966; Weiner et al. 1967; Halsey et al. 1967; De Marco 1968). In view of their progressive nature these foveal affections have been described as Stargardt's disease (Van Bogaert 1957; Ledic and Van Bogaert 1960; Bessière et al. 1962).

In other publications, however, the fovea shows none of the characteristic features of Stargardt's disease (Stadlin and Van Bogaert 1949; Weiner et al. 1967). The manifestations of the spino-cerebello-retinal dystrophies must probably be ascribed to one or several pleiotropic genes.

Franceschetti and Klein (1941, 1947) found 21 patients with Friedreich's ataxia and 4 with Stargardt's disease in one large family (Glaser). No individual showed

both conditions. These authors suggested that in this family there was a pleiotropy with a phenotype alternating between Friedreich's ataxia and Stargardt's disease. They interpreted Friedreich's ataxia and Stargardt's disease as equivalents. In my opinion it is highly probable that two different pathological genes prevailed in this family.

Louis-Bar and Pirot (1945) observed centroperipheral TRD in paraplegic patients, and Jéquier and Streiff (1947) described patients with foveal dystrophy in a family in which other members showed paraplegia.

Other conditions described in Stargardt patients are hyperkinesia (Friemann 1955), statokinetic tremors with increased reflexes (Vancea and Tudor 1960), absence of patellar reflexes (Dejean et al. 1942) and abnormalities of the sella turcica (Klimková-Deutschová and Velický 1952; Schönfelder 1956).

2. *Endocrine disorders.* There are reports on individuals with foveal dystrophy and abortive forms of the Laurence-Moon-Biedl-Bardet syndrome (Borsotti 1939; Klimková-Deutschová and Velický 1952; Albrectsen and Svendsen (1956).

Redslob (1940, 1946) and Rau (1947) described hypothyroidism in association with progressive foveal changes which cannot be identified with certainty as Stargardt's disease.

3. *Hearing defects.* Morelli (1928) described a family with hypacusis which started at the same time as progressive foveal changes. Cogan (1945, 1948) and Rau (1947) described progressive loss of hearing in association with progressive foveal dystrophy, and Scuderi and Siliato (1952) observed connatal hypacusis.

4. *Disturbed hairgrowth* has been described in association with progressive foveal dystrophy (Wagner 1935; Albrectsen and Svendsen 1956; Yasukura et al. 1967).

5. *Other ocular affections.* Stargardt-type progressive foveal dystrophy has been described in association with Fuchs' heterochromia (François and Mastilovic 1961; François et al. 1962), corneal dystrophy (Walsh 1962; Kornzweig 1964), and keratoconus (Bunge 1936; Malik et al. 1966).

De Rosa (1924) and Borsellino (1935) described foveal dystrophy in association with connatal microphthalmos.

6. *Other affections.* There are reports on progressive bilateral foveal dystrophies in association with ovalocytosis (Scuderi and Siliato 1951), Duhring-Brocq disease (Bonamour 1955), gangrenous manifestations (Bernheim et al. 1954), nephrocalcinosis (Calmettes et al. 1962), occlusion of the central retinal vein (Bonnet and Hugonnier 1947), melanoblastoma (Paufique and Hervouet 1963), and craniopharyngeoma (Paufique et al. 1955) and syndrome of the first branchial arch (Di Tizio and Melchionda 1965). François and De Rouck (1965) found slightly pathological EEG-changes in 11 of 26 examined individuals with Stargardt's disease.

19. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Stargardt's disease is not always easy, although after our study we are convinced that its ophthalmoscopic features are sufficiently characteristic to warrant a definite diagnosis. The bilaterality and symmetry of this condition of course play an important role in differential diagnosis, which should consider the following possibilities.

1. *Spielmeyer-Vogt disease.* In this condition, foveal degeneration can be the first conspicuous symptom. If the cerebral manifestations of this condition are absent, then differential diagnosis from Stargardt's disease can be difficult. In Spielmeyer-Vogt disease, too, one often observes peripheral retinal changes, constricted vessels and pale discs. The fovea (page 20) does not show the perifoveal yellow-white spots that more or less characterize the Stargardt patient.

The ERG and EOG in Spielmeyer-Vogt patients are disturbed earlier than in Stargardt patients, in whom the retinal periphery becomes dystrophic. The parents of children with Spielmeyer-Vogt disease show ophthalmoscopically normal retinae and quite normal retinal function tests (personal observations).

2. *Dominant progressive foveal dystrophy.* This dominant affection can closely resemble Stargardt's disease. However, it tends to occur at a later age and to progress less rapidly. The mode of transmission is so far the principal factor on the basis of which these conditions can be differentiated. The difference in mode of transmission, however, does not necessarily mean that these are two different entities.

3. *Progressive cone dystrophy.* So far as we know, this condition likewise has an autosomal dominant mode of transmission. Its diagnosis is established on the basis of the extreme photophobia, acquired total achromatopsia and a decidedly subnormal photopic ERG with virtually normal scotopic ERG. In the initial stages the slight foveal alterations may impede differential diagnosis from Stargardt's disease.

4. *Sex-linked juvenile retinoschisis.* This condition occurs only in males and shows a pathognomonic cystoid foveal alteration with radial plicae. The ERG is very subnormal even while the retinal periphery is apparently normal; in our experience, this is the principal distinction because Stargardt patients do not show a subnormal ERG until the retinal periphery starts to show ophthalmoscopic changes.

In its more extensive form, sex-linked juvenile retinoschisis is characterized by so many changes that differential diagnosis poses no problem.

5. *Vitelliform dystrophy of the fovea.* This condition is readily differentiated from Stargardt's disease on the basis of the ophthalmoscopic findings; moreover its mode of transmission is dominant. Occasionally, an atrophic stage of vitelliform foveal dystrophy might theoretically be confused with Stargardt's disease. But the diagnosis

can be established on the basis of the EOG, which is markedly pathological in all stages of vitelliform dystrophy, and if necessary by a family study.

6. *Chloroquine retinopathy.* In this condition the fovea develops a so-called bull's eye (fig. 23a) which somewhat resembles the foveal dystrophy in Stargardt's disease. The fluorescein angiograms in both conditions are also more or less alike (fig. 23b). History and family history are important in differential diagnosis. The ultimate picture in chloroquine retinopathy is one of delicate pigment changes in the retinal periphery, constricted vessels and pale discs, with subnormal EOG and ERG. However, dark adaptation often remains unaffected while EOG and ERG are already pathological (Gouras and Gunkel 1963; Potts 1966).

7. *Phenothiazine retinopathy.* In this condition the fovea shows no bull's-eye but delicate punctiform pigment changes; otherwise the features closely resemble those of chloroquine retinopathy.

8. *Affections of the optic nerve.* A wide variety of bilateral optic nerve affections can give difficulties of differential diagnosis from the early stage of Stargardt's disease, when the foveal features are still almost normal. Possibilities always to be taken into account are Leber's optic atrophy and the autosomal recessive and dominant atrophies of the optic nerve.

An important aid in differential diagnosis is the F-ERG with the simultaneously obtained VER. A subnormal F-ERG indicates a foveal involvement, but a normal F-ERG with subnormal VER is suggestive of an affection of the optic nerve.

In most cases, however, the ophthalmoscopic changes will establish the diagnosis.

20. THERAPY

There is no therapy, and this is why it is important to prevent consanguineous marriages whenever possible, especially in families in which Stargardt's disease is already present.

21. FUTURE

Like the other dystrophies of the central retina and choroid, Stargardt's disease would seem to be a congenital metabolic disorder. Histochemical studies will be required to demonstrate the primary disturbance in enzymatic function.

It would be a great advance if carriers could be identified before they can produce children with this disease. Stargardt patients are often quite capable of leading a happy life, but the visual handicap is nevertheless such that there are few occupations or professions in which the patients can hold their own.

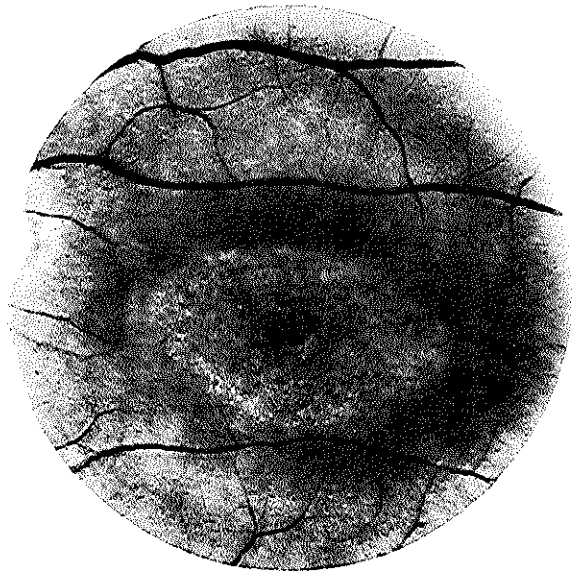


Fig. 23a. Chloroquine retinopathy in a man in his forties showing the bull's eye picture.

Fig. 23b. Fluorescein angiography shows a well defined horizontal oval of atrophic pigment epithelium. There are no whitish flecks perifoveally.

1. Fam. Boe

II-2 (JMAB-41.01.27) Bad visual acuity since 1950.
1959: VODS 5/60, emmetropic.
Refracting media: Normal.
Fundi: Sharply defined atrophic area in the posterior pole of both eyes. Discs slightly pale on the temporal side. Retinal periphery and retinal vessels normal.
Visual fields: Central scotomata.
Dark adaptation: Curve 0.5 log U. too high (phot. and scot.).
ERG: Scot. b-waves OD 200μV; OS 205μV.
Phot. b-waves OD 80μV; OS 75μV.
1964: Visual acuity is diminishing. VODS 1/60.
Fundi: Atrophic areas in the posterior pole with glistening reflexes. Retinal vessels slightly attenuated. Retinal periphery shows pigmentations and depigmentations. No real bone corpuscles are present.
Visual fields: Large central scotomata. Concentric impairment of sensitivity.
Colour vision: Red-green dyschromatopsia (HRR).
Dark adaptation: 0.5 log. U. delayed in the phot. and scot. part of the curve.
ERG: Scot. b-waves OD 130μV; OS 145μV.
Phot. b-waves OD 25μV; OS 35μV.
EOG: OD 1.44; OS 1.40.
1966: VODS 1/60.
Patient complains of decreasing vision in darkness.
Fundi: Centroperipheral dystrophy.

II-3 (HB-48.09.21) Bad visual acuity since the age of 9.
1959: VODS S+1 1/10.
Fundi: A horizontal-oval area of tapetoretinal atrophy in the centre of the retina. Glistening reflexes from this area of beaten bronze atrophy, which measures 1 disc diameter. Discs: Slightly too pale on the temporal side. Normal retinal vessels and retinal periphery.
Visual fields: Small central scotoma.
Dark adaptation: The curve is 1 log. U. too high for both systems.
ERG: Scot. b-waves OD 215μV; OS 235μV.
Phot. b-waves OD 60μV; OS 65μV.
1961: VODS 5/60, emmetropic.
Fundi: Posterior poles: Beaten bronze atrophy. Discs: Slightly too pale on the temporal side. Vessels: Normal. Retinal periphery: pigment-clumping along the retinal vessels.
Colour vision: Mild red-green dyschromatopsia.
ERG: Scot. b-waves OD 160μV; OS 120μV.
Phot. b-waves OD 80μV; OS 85μV.

Summary: Two children from a non-consanguineous marriage with a centroperipheral tapetoretinal dystrophy (Stargardt's disease with peripheral involvement). Initially the diagnosis was Stargardt's disease (the pure form being without peripheral involvement). Follow-up studies revealed the spreading of the dystrophic process to the retinal periphery. The sister (II-2) suffers from an advanced form of diffuse tapetoretinal dystrophy, while the brother in 1961 only had central tapetoretinal changes. There is no doubt, that the sister demonstrates the future development of the fundi of her brother (II-3).

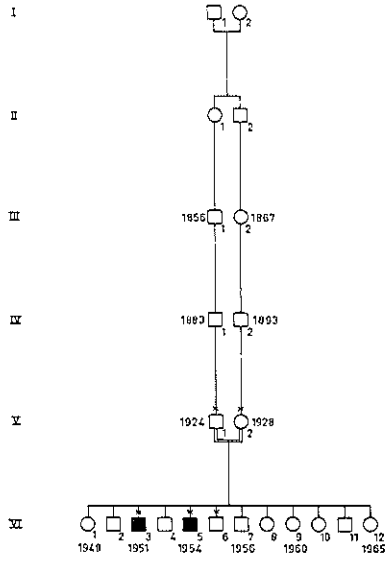
2. Fam. Bol

VI-3 (PB-51.01.13) Bad visual acuity since the age of 8.
1964: VOD 3/60, emmetropic. VOS 5/60, emmetropic.
Fundi: Central tapetoretinal dystrophy. Discs and vessels are normal. Pigmentary clumping and areas of depigmentation in the retinal periphery.
Visual fields: Central scotoma. (OD: 10 degrees. OS: 15 degrees.)
Dark adaptation: Curve 1 log. U. too high for both systems.

ERG: Scot. b-waves OD 50μV; OS 70μV.
Phot. b-waves OD 60μV; OS 65μV.
EOG: ODS 1.00.
1966: VOD 3/60; VOS 5/60.
Fundi: Ill-defined area of tapetoretinal atrophy in the centre of the posterior pole. Fine pigmentations, depigmentations and glistening reflexes in an area of 2 disc diameters. A delicate radiate folding of the internal limiting membrane. (fig. 5). Discs slightly too pale on the temporal side. Retinal vessels are normal. In the retinal mid-periphery greyish-black clumps of pigment, often surrounded by a white halo (fig. 16).
Visual fields: Central scotoma of 15 degrees. Concentric limitation of sensitivity.
Colour vision: Red-green dyschromatopsia and a very mild blue-yellow dyschromatopsia (HRR).
Dark adaptation: The curve is 1 log. U. too high (phot. and scot.).
ERG: Scot. b-waves OD 75μV; OS 84μV.
Phot. b-waves OD 17μV; OS 22μV.
EOG: ODS 1.00.

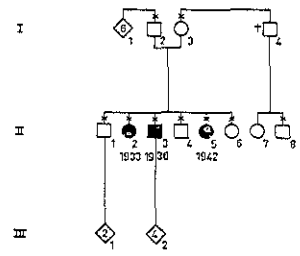
VI-5 (LB-54.01.19) Bad visual acuity since the age of 8.
VODS 5/60, emmetropic.
Fundi: Essentially the same pattern as demonstrated by his brother VI-3. Centroperipheral tapetoretinal dystrophy with uneven distribution of pigment throughout the fundus.
Visual fields, colour vision and dark adaptation: Similar to VI-3.
ERG: Scot. b-waves OD 80μV; OS 82μV.
Phot. b-waves ODS 10μV.
EOG: ODS 1.00.

VI-6 (AB-55.04.16) No visual complaints.
VODS 11/10.
Fundi: Normal.
Visual fields, colour vision and dark adaptation: Normal.
ERG: Scot. b-waves OD 260μV; OS 220μV.
Phot. b-waves OD 220μV; OS 95μV.
EOG: OD 1.88; OS 2.08.



Summary: Two children with an initially central started tapetoretinal dystrophy from a consanguineous marriage. Both boys had their first visual complaints at the age of 8.

3. Fam. dBr



II-2 (PHdB-33.04.20) Poor visual acuity since the age of 14.
1956: VODS 1/10, emmetropic.
Visual fields: Central scotoma. Concentric impairment of sensitivity.
Dark adaptation: The curve is 1 log U. too high for both systems.
ERG: Normal.
1958: VOD 5/60; VOS 6/60.
Fundi: Absent foveal and foveolar reflexes. Brownish pigmentary disturbances in the centre of the retina. Diffuse disturbance of the normal pigmentation. Numerous yellowish-white spots are present in the mid-periphery. The retinal vessels are normal and the discs are slightly too pale on the temporal side (fig. 7).
Visual fields: Central scotoma. Concentrically decreased sensitivity.
Colour vision: Red-green dyschromatopsia and decreased sensitivity to red (HRR and anomaloscope).
Dark adaptation: The curve is 1 log. U. too high for both systems.
1965: Concomitant divergent strabismus of OD. Fixation slightly temporal of the disc.
Fundi: No striking changes, as compared to 1958.
Colour vision: The HRR-test reveals also a mild blue-yellow dyschromatopsia.
1968: VODS 4/60.
Fundi: Clumping of pigment in the foveal area, which shows atrophy of the pigment epithelium. Yellowish-white dots throughout the fundus and some greyish pigmentations. Discs too pale on the temporal side. The retinal arteries are slightly attenuated.
Visual fields: Central scotoma. Concentric impairment of sensitivity. Normal peripheral limitations.
Colour vision: Mild red-green and very mild blue-yellow dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: Curve 1.5 log U. too high for both systems.
ERG: Scot. b-waves OD 150μV; OS 175μV.
Phot. b-waves OD 80μV; OS 125μV.
EOG: Unreliable results because of bad fixation.

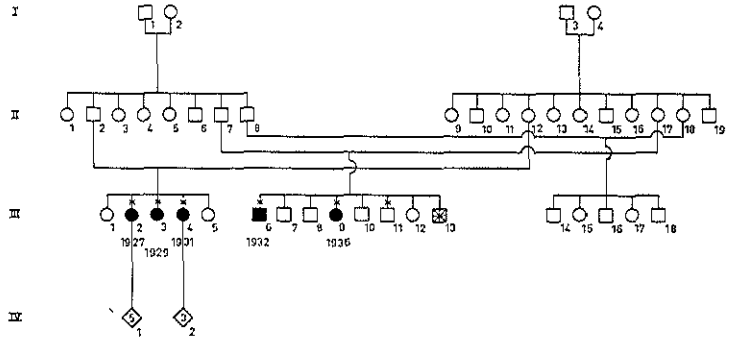
II-3 (PCdB-36.08.16) Poor visual acuity since the age of 12. Better vision at dusk than in daytime.
1959: VODS S−2.50 6/60.
Fundi: Atrophic foveal area. Normal periphery, vessels and discs.
Visual fields: Central scotoma of 15 degrees. Normal periphery.
Colour vision: Medium red-green dyschromatopsia and mild blue-yellow dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: Normal.
1967: VOD 3/60; VOS 4/60.
Fundi: Atrophic foveal areas of 3 disc diameters. Glistening reflexes and clumping of pigment in the posterior pole (fig. 12). Normal vessels and discs. Greyish pigmentations surrounded by a whitish halo in the mid-periphery (fig. 15).
Visual fields and colour vision: Unchanged.
Dark adaptation: Curve 0.5 log U. too high for both systems.
ERG: Scot. b-waves OD 85μV; OS 45μV.
Phot. b-waves OD 40μV; OS 70μV.
EOG: OD 1.38; OS 1.36.

II-5 (HdB-42.01.27)
1958: Poor visual acuity since some years.
VODS: S−4 1/10.

Fundi: Fine pigmentary changes in the foveal area. Normal disc, vessels and periphery.
Visual fields: Decreased central sensitivity.
Colour vision: Decreased sensitivity to red (anomaloscope).
Dark adaptation: Curve 0.5 log. U. too high for both systems.
ERG: Scot. b-waves OD 214μV; OS 332μV.
Phot. b-waves OD 92μV; OS 94μV.
1968: VOD 2/60; VOS 3/60.
Fundi: Atrophic changes with pigmentary disturbances and yellowish glistening reflexes in the foveal area. Disc slightly too pale on the temporal side. Vessels slightly attenuated. In the periphery greyish-black pigmentations surrounded by a white halo (fig. 15).
Visual fields: Central scotoma. Concentric impairment of sensitivity. Normal peripheral limitations.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: Curve 1 log. U. too high for both systems.
ERG: Scot. b-waves OD 95μV; OS 120μV.
Phot. b-waves OD 55μV; OS 60μV.
EOG: OD 1.50; OS 1.72.

Summary: One man and two of his sisters from a non-consanguineous marriage, suffering from an initially central diffuse tapetoretinal dystrophy. Bone corpuscle figures and pigmentation along the sheaths of the vessels are absent. The dark adaptation, ERG and EOG illustrate the peripheral involvement of the eyes in this centroperipheral tapetoretinal dystrophy.

4. Fam. vB



III-2 (ASvB-27.03.28) Poor visual acuity since the age of 18. Increased impairment of vision after the birth of her second child in 1949.
1949: VOD S+1 4/10; VOS S+1 4/10.
Fundi: Bilateral symmetrical pigment clumping and yellowish dots in a horizontally ovoid zone, slightly larger than 1 disc diameter. The pigment epithelium in the foveal area is atrophic. Discs, vessels and retinal periphery are normal.
Therapy: Vitamine B complex.
1956: A rather rapid loss of central visual acuity has occurred. She is told by an ophthalmologist that her children will have the same affection.
VODS 1/10.
1967: Gradually visual acuity diminishes.
VODS 3/60.
Fundi: Normal foveal reflexes are absent. "Beaten bronze" retinal atrophy in the foveal area. The choroid has an atrophic aspect too (fig. 10). Glistening reflexes and fine pigmentary disturbances are present in the posterior pole. The discs are slightly too pale temporally. The vessels are normal. Small greyish-black and yellowish-white dots are scattered throughout the retinal periphery (fig. 14).
Visual fields: Central scotoma of 10-15 degrees.

Dark adaptation: The curve is 1 log. U. too high for both systems.
ERG: Scot. b-waves OD 200μV; OS 220μV.
Phot. b-waves OD 130μV; OS 160μV.
EOG: Unreliable because of bad fixation. The L/D-ratio seems to be too low.

III-3 (JvB-29.08.07)
1967: Stargardt's disease with peripheral involvement.
ERG: Normal.
EOG: Subnormal (Made elsewhere).

III-4 (MJWCvdMvB-31.02.20) Poor visual acuity since the age of 18. Impairment of vision in pregnancy and shortly after deliveries.
1954: VOD 1/10; VOS 2/10, emmetropic.
1960: VOD 5/60; VOS 1/10.
1965: VOD 4/60; VOS 5/60.
Fundi: Atrophic foveal areas with fine pigmentary changes and many perifoveal yellowish-white dots. Spotty retinal periphery with pigmentations and depigmentations.
Visual fields: Relative central scotoma. Normal peripheral limitations.
ERG: Scot. and Phot. subnormal (made elsewhere).

III-6 (BvB-32.03.31) Poor visual acuity since the age of 17.
1960: VOD S$-$3.50 5/10; VOS S$-$5 4/10.
Fundi: Brownish atrophic foveal area, surrounded by many yellowish-white spots.
1968: VOD S$-$5 5/60; VOS S$-$4.50 5/60.
Refracting media: Cataracta coronaria.
Fundi: Horizontally ovoid zone of beaten bronze atrophy. Many perifoveal whitish spots. Discs slightly too pale on the temporal side. Retinal vessels and periphery are normal.
Visual fields: Absolute central scotoma of 5 degrees.
Colour vision: Red-green dyschromatopsia (HRR). Decreased red sensitivity (anomaloscope).
ERG: Scot. b-waves OD 195μV; OS 175μV.
Phot. b-waves OD 120μV; OS 125μV.
EOG: OD 1.29; OS 1.42.

III-9 (AEvGvB-36.04.26) Poor visual acuity since the age of 21.
1960: VOD 1/10; VOS 3/10. Emmetropic.
1967: VOD 1/10; VOS 5/60.
Fundi: Horizontally ovoid zone of beaten bronze atrophy, surrounded by many yellowish-white spots, localized perifoveally (fig. 9). The posterior pole resembles the picture described in fundus flavimaculatus. Disc slightly too pale temporally. Vessels and periphery normal.
Visual fields: Central scotoma of 20-30 degrees.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased red-sensitivity (anomaloscope). Red is seen as grey or black in low illumination.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 238μV; OS 311μV.
Phot. b-waves OD 85μV; OS 112μV.
EOG: OD 1.78; OS 2.18.

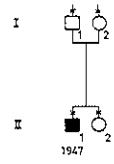
Summary: Three brothers married three sisters from another family. There is no consanguinity. The gene of Stargardt's disease occurs in both families (in II-2,7 and in II-12,17). The patients are suffering from Stargardt's disease with gradual involvement of the retinal periphery. In III-6 the EOG is already pathological, whereas the retinal periphery is still normal ophthalmoscopically. III-2,3 have peripheral retinal alterations, subnormal EOG's and still normal ERG's. The EOG appears to be more sensitive in this affection as regards detecting diffuse retinal abnormalities. The picture of the fundus of III-9 resembles closely the pictures described in fundus flavimaculatus.
This patient demonstrates, that strict separation of Stargardt's disease from fundus flavimaculatus with foveal involvement is often difficult, if not impossible.
This pedigree resembles the pedigree described by Gruetzner in 1962. Gruetzner described 2 brothers, who

married 2 sisters from another family. Four of the 9 children from these 2 marriages developed centroperipheral dystrophy (Stargardt's disease with peripheral involvement).

5. Fam. Dr.
FD- (59.01.05) Poor visual acuity since 1966. The parents are not consanguineous.
1967: VODS 2/10, emmetropic.
Fundi: A horizontally ovoid zone of retinal atrophy in the foveal area. Yellowish-white dots surround this area of beaten bronze atrophy. Disc, vessels and periphery are normal.
Visual fields: Central scotoma.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 240μV; OS 245μV.
Phot. b-waves OD 110μV; OS 115μV.
EOG: OD 2.36; OS 2.09.

Summary: An 8-year-old girl from a non-consanguineous marriage. She had normal visual acuity until the age of 7. Then visually acuity decreased gradually to 2/10. This is a classical example of Stargardt's disease.

6. Fam. dG



I-1 and *I-2* are not consanguineous.

II-1 (SdG-47.06.16) Poor visual acuity since the age of 8.
1957: VOD 5/60; VOS 1/10, emmetropic.
Fundi: Slight pigmentary disturbances in the foveal area. Disc too pale on the temporal side. Vessels and periphery are normal.
Visual fields: Decreased central sensitivity.
Colour vision: Decreased sensitivity to red (anomaloscope).
Dark adaptation: Curve slightly too high for both systems.
ERG: Scot. and phot. subnormal. Since the photopic ERG is affected more than the scotopic ERG one thinks of incomplete achromatopsia.
1958: VOD S−2 4/60; VOS S−3.25 1/10.
Fundi: Slight foveal alterations. No normal foveal reflexes.
Colour vision: Red-greed dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: Unchanged.
ERG: Scot. b-waves OD 142μV; OS 160μV.
Phot. b-waves OD 45μV; OS 40μV.
1959: VOD 4/60; VOS 1/10.
Fundi: Unchanged.
Visual fields and dark adaptation: Unchanged.
Colour vision: Strong red-green dyschromatopsia (HRR). Protan axis (Farnsworth D 15). Decreased sensitivity to red (anomaloscope).
ERG: Scot. b-waves OD 175μV; OS 205μV.
Phot. b-waves OD 40μV; OS 30μV.
CFF: 72 Hz.
1960: VOD 4/60; VOS 1/10.
Fundi: No essential changes. Some fine pigmentations throughout the periphery.
Visual fields: Central scotoma.
Colour vision: Marked red-green dyschromatopsia and mild blue-yellow dyschromatopsia (HRR). Protan and tritan axis (Farnsworth D 15).

Dark adaptation: Curve 1 log. U. too high for both systems.
ERG: Scot. b-waves OD 205μV; OS 160μV.
Phot. b-waves OD 40μV; OS 30μV.
CFF: 47 Hz.
1962: VOD 2/60; VOS 5/60.
Fundi: A horizontally ovoid zone, slightly larger than 2 disc diameter, of retinal atrophy, fine pigmentations and yellowish glistening reflexes. Disc slightly too pale temporally. Vessels normal. In the retinal periphery whitish and greyish-black dots.
ERG: Scot. b-waves OD 90μV; OS 105μV.
Phot. b-waves OD 60μV; OS 35μV.
EOG: Subnormal.
1965: VOD 2/60; VOS 3/60.
ERG: Scot. b-waves OD 80μV; OS 90μV; Phot. b-waves ODS unrecordable.
EOG: ODS 1.00.
1967: VOD S−7 3/60; VOS S−6 3/60.
Fundi: Atrophic posterior pole. Disc too pale temporally. Vessels slightly attenuated. Pigmentary disturbances throughout the retinal periphery.
Visual fields: Central scotoma. Concentric impairment of sensitivity. Normal peripheral limitations.
Dark adaptation: The curve is 1.5 log. U. too high.
ERG: Scot. b-waves OD 145μV; OS 135μV.
Phot. b-waves ODS unrecordable.
F-ERG: Subnormal.
VER: Subnormal.

II-2 (AdG-52.06.25) No visual complaints.
1967: VOD S−6 11/10; VOS S−7 11/10.
Fundi: Normal.
Visual fields, colour vision and dark adaptation: Normal.
ERG: Scot. b-waves OD 340μV; OS 270μV.
Phot. b-waves OD 80μV; OS 70μV.
F-ERG: Normal.
VER: Normal.
EOG: OD 2.00; OS 2.40.

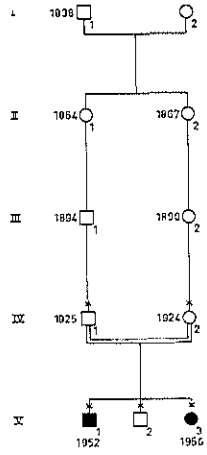
Summary: A boy with Stargardt's disease and peripheral involvement. The dystrophy started in the centre of the retina and spread gradually over the whole retina during the follow-up of 10 years. This is a good example of a centrally started diffuse tapetoretinal dystrophy. The sister of the patient has normal eyes ophthalmoscopically and normal retinal functions.

7. Fam. Har.
V-1 (BH-52.03.24) Born with a hare-lip.
January 1962: First ophthalmological consultation.
VOD S−2 2/10; VOS S−2 5/10.
May 1962: VOD 1/10; VOS 3/10.
December 1962: VOD 1/10; VOS 3/60.
Fundi: Fine pigmentary disturbances in the foveal area. Disc, vessels and periphery are normal.
Visual fields: Decreased central sensitivity.
Colour vision: Red-green dyschromatopsia (HRR).
Dark adaptation: Curve 0.5 log. U. too high for both systems.
ERG: Scot. b-waves OD 205μV; OS 200μV.
Phot. b-waves OD 60μV; OS 50μV.
EOG: OD 1.90; OS 1.70.
1966: VODS 3/10.
Fundi: Absent foveal reflexes. Glistening reflexes and pigmentary disturbances in the foveal area. Disc and vessels are normal. Pigmentations and depigmentations throughout the retinal periphery.
Visual fields: Central scotoma of 10 degrees.

Dark adaptation: The curve is 2/3 log U. too high for both systems.
ERG: Scot. b-waves ODS 155μV.
Phot. b-waves OD 45μV; OS 40μV.
EOG: OD 1.18; OS 1.13.

V-2 (JPH-54.04.17) Also has a hare-lip.
VODS 10/10.
Fundi: Normal.
Visual fields, colour vision, dark adaptation, ERG and EOG are normal.

V-3 (CMH-56.01.05) Also has a hare-lip.
1966: VODS 1.5/10.
Fundi: Pigmentary disturbances in the foveal area. Disc and vessels are normal. Some pigmentary disturbances in the retinal periphery.
Visual fields: Relative central scotoma of 8 degrees.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 255μV; OS 240μV.
Phot. b-waves OD 150μV; OS 95μV.
EOG: OD 1.50; OS 1.70.



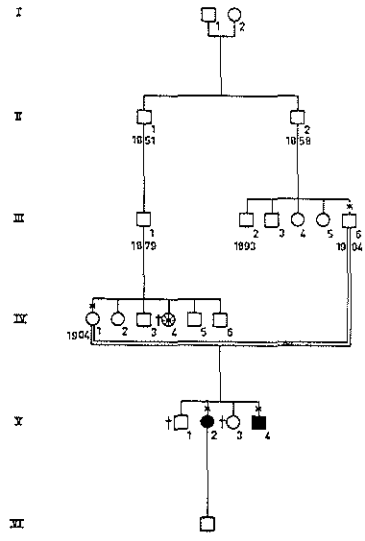
Summary: An initially central progressive diffuse tapetoretinal dystrophy in a boy and his sister from a consanguineous marriage. V-1 had only foveal alterations in 1962. In 1966, however, the retinal periphery was clearly involved in the dystrophic process. V-3 shows slight peripheral alterations and a mildly subnormal EOG, indicating the initial stages of the peripheral dystrophy.

8. Fam. Hor.
IV-1 (HH-04.08.19) Sure heterozygote for the pathological gene.
Fundi: Normal.
OP: Normal.

V-2 (NVH-35.05.19) Poor visual acuity since 1960.
1968: VODS S−1 5/60.
Fundi: Fine pigmentary disturbances, yellowish reflexes and retinal atrophy in an almost round area, localized at the site of the fovea. Disc, vessels and periphery are normal.
Colour vision: Red-green dyschromatopsia (HRR). Tritan axis (Farnsworth D 15).

V-4 (HH-40.06.30)
1964: Since 6 months visual complaints. Vision at dusk is better than in daytime.
VODS S−1.25 1/10.

Fundi: Essentially similar to the fundi of V-2 (fig. 3). No normal foveal reflexes. Disc slightly too pale temporally.
Visual fields: Decreased central sensitivity.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 280μV; OS 250μV.
Phot. b-waves OD 75μV; OS 70μV.
EOG: OD 2.00; OS 2.01.
1967: VODS 5/60.
Fundi: Atrophic foveal area of about 1 disc diameter. The atrophic area has been slightly enlarged since 1964. Fixation on the temporal side of the damaged fovea. Normal vessels and periphery. Disc slightly too pale temporally.
Colour vision: Red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
ERG: Scot. b-waves OD 245μV; OS 185μV.
Phot. b-waves OD 100μV; OS 55μV.



Summary: Two children from a consanguineous marriage with Stargardt's disease. The dystrophy is limited to the fovea in both individuals. There are no perifoveal yellowish dots. The retinal function tests indicate a normal retinal periphery. It is important to examine these individuals later to establish whether there is a tendency to develop a centroperipheral dystrophy.

9. Fam. Ja
(AMJE-44.03.03) Patient is an adopted child. Family-examination is not possible. Decreased visual acuity since the age of 16.
1965: VOD S−1=C−1×180° 1/10; VOS S−1=C−1×180° 1/10.
Fundi: Horizontally ovoid, sharply defined area of atrophic pigment epithelium in both foveae. Disc slightly too pale temporally.
Visual fields: Decreased central sensitivity.
Colour vision: Mild red-green dyschromatopsia (HRR).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 215μV; OS 305μV.
Phot. b-waves OD 95μV; OS 95μV.
EOG: OD 1.79; OS 1.86.
1968: VODS 4/60.
Fundi: The central atrophic area is surrounded by small yellowish flecks (fig. 8). The retinal periphery

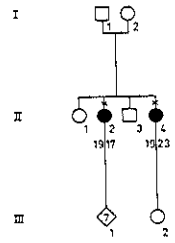
demonstrates a mild granular pigmentary disturbance. The disc is slightly too pale temporally. The retinal vessels are normal.
Visual fields: Central scotoma of 5-10 degrees.
Colour vision: Decreased sensitivity to red (anomaloscope). Mild red-green dyschromatopsia (HRR).
Dark adaptation: The curve is 0.5 log. U. too high for both systems.
ERG: Scot. b-waves OD 195μV; OS 275μV.
Phot. b-waves OD 80μV; OS 90μV.
EOG: OD 1.94; OS 2.32.

Summary: Stargardt's disease in a female patient with no known relatives. Ophthalmoscopically there are slight peripheral alterations, while ERG and EOG are still normal. The dark adaptation is mildly disturbed.

10. Fam. Hu
II-1 (PH-57.10.30)
1968: Poor visual acuity since one year. Elsewhere the diagnosis of braintumour or lipidosis has been mentioned.
VOD 1/60; VOS 5/60.
Both eyes have a nystagmus.
Fundi: Atrophic foveal area with glistening reflexes. Disc too pale temporally. The vessels are normal. The retinal periphery demonstrates pigmentary disturbances.
Visual fields: Large central scotoma of 26 degrees.
Dark adaptation: The curve is 1 log. U. too high for both systems.
ERG: Scot. b-waves OD 125μV; OS 100μV.
Phot. b-waves OD 60μV; OS no responses recorded.
EOG: OD 1.18; OS 1.08.
Systemic examination: Extensive general physical and laboratory examinations revealed no abnormalities. Neurological examination was normal, too.

Summary: An 11-year-old boy from a non-consanguineous marriage suffering from centroperipheral tapetoretinal dystrophy. The most severe abnormalities are found in the centre of the retina, indicating that this dystrophy has started in all probability in the foveal area.

11. Fam. Kat



II-2 (LJRK-17-02-03)
1946: VOD S−1 10/10; VOS S−1.25 10/10.
Refracting media and fundi: Normal.
1956: VOD S−1.25 7/10; VOS S−1.25 5/60.
Fundi: Pigmentary disturbances at the fovea. The disc of the left eye is slightly too pale.
1966: VODS S−1.25 1/10.
Fundi: Atrophic area of "beaten bronze atrophy" in the centre of the posterior pole. Some ill defined yellowish flecks around the zone of atrophy. Disc too pale on the temporal side. Vessels and periphery are normal.
Systemic examination: Normal.

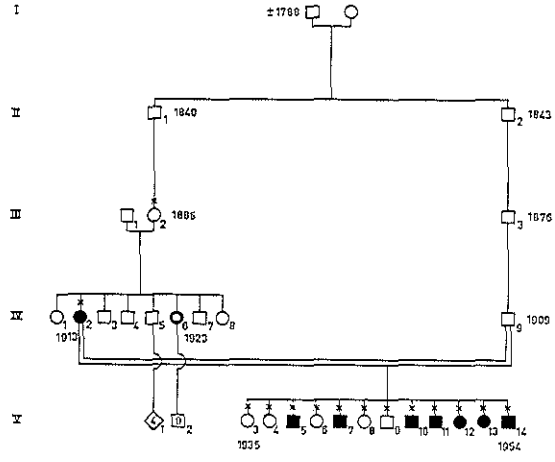
II-4 (BCWK-23.12.08) Has always had normal visual acuity.
1969: VOD S−0.50 9/10; VOS S−2 5/60.
Fundi: Essentially the same abnormalities as in II-2. It is remarkable that the ophthalmoscopic lesions are so symmetrical, despite the difference in visual acuity of both eyes.

Summary: Two sisters showing Stargardt's disease at a relatively late age. The parents of the patients are in all probability non-consanguineous. There are 3 interesting features:
1. In both patients decrease of visual acuity started at the age of 40.
2. The a-symmetrical impairment of visual acuity. (In both patients the left eye was the first to be affected).
3. Ophthalmoscopically there are no clear differences between both eyes at the stage in which the visual acuities differ widely.

12. Fam. KlW
(MKLWvP-28.02.09) Poor visual acuity in OD since one year. Family-history negative.
1969: VOD 3/60; VOS 7/10. ODS are emmetropic.
Fundi: Atrophic foveal area, surrounded by yellowish-white dots (fig. 21a). Striking symmetrical lesions.
Visual fields: OD central scotoma; OS decreased central sensitivity.
Colour vision: OD mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope). OS normal.
Dark adaptation: Normal.
ERG: Normal scotopic and photopic b-waves.
F-ERG: Rudimentary responses.
VER: Rudimentary responses.
EOG: OD 1.46; OS 1.34.
Fluorescein angiography: This reveals a flecked pattern of atrophic pigment epithelium. There is no leakage of fluorescein (fig. 21b).
Systemic examination: Normal.

Summary: A 41-year-old patient with Stargardt's disease. Before the age of 40 there were no visual complaints. Despite the symmetrical appearance of both fundi, the visual acuity differs considerably. Usually the impairment of visual acuity is rather similar in both eyes. The subnormal EOG indicates a diffuse disturbance of retinal function, despite the normal ophthalmoscopic picture of the retinal periphery.

13. Fam. Kni.



III-2 (JVK-85.01.08)
1954: VOD 5/5; VOS 5/10.
Refracting media and fundi: Normal.

IV-2 (JKV-13.01.23)
1943: VODS S−1 5/10.
Fundi: Fine pigmentary disturbances in the foveal area. The periphery shows a diffuse mottling of pigment.
Systemic examination: Normal.
1967: VOD S−1.50 1/20; VOS S−2 5/50.
Fundi: Large area of chorioretinal atrophy in the posterior pole (fig. 11). Severe pigmentary disturbances. In the retinal periphery there are round patches of chorioretinal atrophy with and without pigmentations (fig. 19). Disc too pale temporally. The vessels are close to normal.
Visual fields: Large central scotoma. Concentric impairment of sensitivity.
Dark adaptation: The curve is 1.5 log U. too high for both systems.
ERG: Unrecordable.
EOG: ODS 1.00.

IV-6 (JAV-23.12.11) Since childhood poor visual acuity in both eyes. Is reported to have the same affection as IV-2.

V-5 (HK-38.01.10) Poor visual acuity since the age of 5.
1943: VOD 5/10; VOS 5/15.
1948: VODS 5/50. Atrophic foveal area.
1951: VODS S−1 5/50.
1957: VODS 2-3/60.
1960: Fundi: Narrow arteries. Pale disc.
Visual fields: Central scotoma. Restricted in the periphery.
1964: Fundi: Narrow arteries. Pale disc. Atrophic foveal area and bone corpuscles in the retinal periphery.
1967: VOD 1/15; VOS 1/50.
1968: VOD: light perception; VOS 3/300.
Concomitant convergent strabismus of OS.
Fundi: The picture closely resembles the end-stage of retinopathia pigmentosa. In addition to this the posterior pole is showing marked chorioretinal atrophy.

V-7 (PK-41.03.01)
1952: VOD 5/30; VOS 5/20.
Fundi: Dystrophic changes in the foveal area.
1959: VODS 5/30.
Visual fields: Normal peripheral limitations.
1960: Fundi: Atrophic foveal area. Greyish-white and pigmented dots in the retinal periphery.
Visual fields: Decreased central sensitivity. Restriction temporally.
1965: VOD S−0.50 5/50; VOS S−1 5/30.
Fundi: Atrophic posterior pole. Some more albescens-like as well as pigmented flecks in the retinal periphery. Disc and retinal vessels are normal.

V-8 (JvdBK-42.10.31) Some visual complaints after the delivery of her first and second child.
VODS: 10/10, emmetropic.
Fundi: Normal.
ERG: Normal.

V-10 (HK-46.07.28) Poor visual acuity since the age of 6.
1952: VOD 5/10; VOS 5/20.
Fundi: The foveal reflexes are not normal.
8-8-1956: VOD 4/10; VOS 5/30.
Fundi: Fine pigmentary changes in the foveal area.
12-9-1956: VODS 5/50.
1959: Fundi: Atrophic foveal area. Fine pigmentary dots and whitish flecks in the retinal periphery.
Visual fields: Restricted.
Dark adaptation: Subjectively decreased.
1967: VOD 1/30; VOS 1/20.
1968: VOD 1/60; VOS 2/60.

Fundi: Atrophic foveal area with pigmentary changes and glistening reflexes. Disc too pale. The vessels are slightly attenuated, particularly the arteries. Bone corpuscles are visible in the retinal periphery.
Visual fields: Restricted, particularly on the nasal side.

V-11 (AJK-47.08.30) Visual acuity was normal at the age of 6. Poor visual acuity since the age of 8.
1954: VOD S+1=C+2×90° 5/15; VOS S+1=C+1×90° 5/10.
Fundi: Normal. The fovea is normal at ophthalmoscopy.
1955: VOD 5/50; VOS 5/20.
Fundi: Dystrophic changes in the foveal area.
1956: VODS 5/50.
1960: VODS 5/50. Concomitant divergent strabismus of OD.
Fundi: Atrophic foveal area. Normal periphery.
Visual fields: Normal.
Dark adaptation: Mild subjective hemeralopia.
1963: VODS 5/50.
Fundi: There are now clear pigmentary disturbances in the retinal periphery.
1968: VOD 1/60; VOS 4/60.
Fundi: A horizontally ovoid zone of chorioretinal atrophy in the posterior pole. This area is not sharply defined and about 3 disc diameter in size. Around this atrophic zone there are fine pigmentations and depigmentations (fig. 18b). The retinal periphery demonstrates bone corpuscles along the vessels (fig. 18a). The disc is pale and the vessels are attenuated.
Visual fields: Marked defects. The nasal part is absent.
Colour vision: Tritan axis (Farnsworth D 15).
Dark adaptation: The curve is 2 log. U. too high for both systems.
ERG: Scot. b-waves OD 35μV; OS 70μV.
Phot. b-waves OD 50μV; OS 65μV.
EOG: Impossible because of the poor fixation.

V-12 (JK-49.03.06) Poor visual acuity since the age of 10.
1958: VODS 5/5.
Fundi: Normal.
1963: VODS S−0.50 5/30.
1968: VODS S−0.50 6/60. Eccentric fixation.
Fundi: Fine pigmentary changes on a glistening background in the posterior pole. Small whitish and black spots in the periphery. The disc is too pale on the temporal side. The vessels are close to normal.

V-13 (AK-51.02.01) Poor visual acuity since the age of 12.
1958: VODS 5/5.
Fundi: Normal.
1963: VODS 5/20.
Fundi: Pigmentary changes and retinal atrophy in the fovea.
1968: VODS 2/10.
Fundi: Chorioretinal atrophy in the posterior pole. The disc is normal, while the retinal arteries are slightly attenuated. The retinal periphery shows whitish dots and small round greyish-black spots surrounded by a white halo. There are no bone corpuscles.

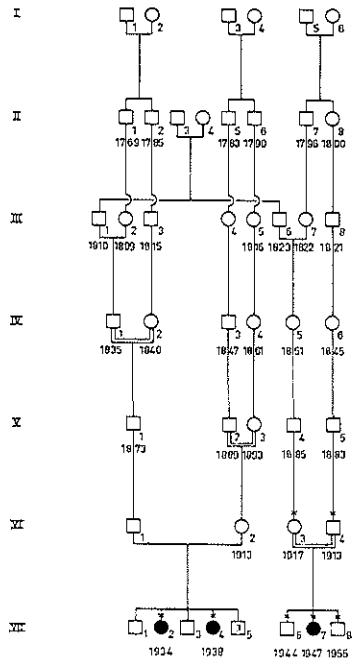
V-14 (FK-54.10.21)
1963: VODS S+2 5/10.
Fundi: The foveal reflexes are not clearly visible.
1965: VOD 1/20; VOS 1/15.
Fundi: Atrophic and pigmentary changes in the foveal area. This is a rather sharply defined area. The retinal periphery shows a flecked appearance with pigmentations and depigmentations. The disc is too pale temporally. The vessels have a normal calibre.
Visual fields: Central scotoma. Concentric impairment of sensitivity.

Summary: An interesting family, suffering from an initially central diffuse tapetoretinal dystrophy. The boys develop in the endstages a genuine retinopathia pigmentosa with pale discs, narrow vessels and bone

corpuscles in the retinal periphery. The visual fields tend to disappear completely. The female patients keep their visual fields and demonstrate pigmentary disturbances in the retinal periphery, but no bone corpuscles. The discs are slightly too pale temporally and the arteries are slightly attenuated. In this family, as in Stargardt's family S (1913) there is "sex limitation". The male patients are more severely affected than are the female patients. A dominant mode of inheritance is suggested by the fact, that the mother and 7 of the 12 children are affected. However, the mother (examined) and the father (anamnestic) of IV-2 were not affected. Furthermore, IV-2 and IV-3 have a consanguineous marriage, indicating the possibility, that IV-2 is homozygous and IV-3 is heterozygous for the same gene. In all probability, like in other families with a centroperipheral tapetoretinal dystrophy the mode of inheritance in this family is autosomally recessive. This is supported by the fact that IV-6, who is reported to have the same affection as has IV-2, has 9 children with a good visual acuity.

Consequently there is a pseudo-dominant mode of inheritance in this family. The follow-up of this family has been done carefully over many years and beautifully demonstrates the gradual development of an originally foveal dystrophy into a centroperipheral tapetoretinal dystrophy.

14. Fam. Krij



VII-2 (KDG-34.05.06)

1956: Hospitalized with diagnosis "central chorio-retinitis".

Fundi: Atrophic changes and pigmentary disturbances in the foveal area. In the retinal periphery there are pigmentary disturbances too.

Systemic examination: Normal.

1958: VODS S−0.50 2/10.

Diagnosis: "Juvenile macular degeneration".

1960: VODS 2/10.

Fundi: A horizontally ovoid zone of retinal atrophy in the foveal area. This area measures 2 disc diameters. The retinal periphery shows pigmentary disturbances and whitish spots.

VII-4 (CNG-38.03.25)

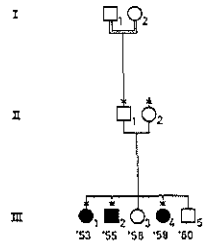
1970: VOD 2/10, emmetropic; VOS S+0.50 10/10.

Fundi: Symmetrical atrophic changes in the posterior pole of both eyes. Glistening reflexes and fine pigmentary disturbances. Perifoveally yellowish-white flecks. Normal retinal periphery, disc and vessels.

VII-7 (EMK-47.05.26)
1963: Since one year visual complaints.
VOD S−2.50 4/10; VOS S−3 1/10.
Fundi: Fine symmetrical pigmentary changes in the foveal area.
Visual fields: Central scotoma of 7 degrees.
Dark adaptation, ERG and EOG: Normal.
Systemic examination: Normal.
1964: VOD 3/10; VOS 1/10.
1965: VOD 1/10; VOS 1/10.
1967: VODS 5/60.
Fundi: Horizontally ovoid zone of "beaten bronze atrophy", surrounded by yellowish-white, ill-defined spots. These spots are also on the nasal side of the disc (fig. 6). The disc is slightly too pale temporally. The retinal periphery and the retinal vessels are normal.
Visual fields: Central scotoma of 12 degrees.
Colour vision: Decreased sensitivity to red (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves ODS 220μV; Phot. b-waves OD 150μV; OS 115μV.
EOG: OD 1.90; OS 1.78.
F-ERG: Subnormal.
VER: Subnormal.
Fluorescein angiography: Fluorescence in the arterial phase in the central atrophic area. This fluorescence increases slightly in the venous phase. There is a broad band of fluorescing areas aroung this central area of atrophic retinal pigment epithelium. No fluorescein-leakage is visible (fig. 6c).

Summary: A girl from a consanguineous marriage, with Stargardt's disease. The dystrophic process is limited to the posterior pole of the eye. Differential diagnosis from fundus flavimaculatus is difficult due to the many whitish flecks. In Stargardt's own cases (1909) there were patients with these flecks too, and therefore we make the diagnosis of Stargardt's disease.
VII-1 and VII-2 ,who have a distant relationship with VII-4 also suffer from Stargardt's disease. VII-1 has a centroperipheral tapetoretinal dystrophy, while VII-2 has so far had a pure central form of Stargardt's disease. This suggests, that the pure central type of Stargardt's disease and the centro-peripheral type (Stargardt's disease with peripheral involvement) are different expressions of one disease, caused by one gene.

15. Fam. Me



II-1,2 The parents of II-1 are reported to be consanguineous.
VODS 10/10.
Refracting media and fundi: Normal.

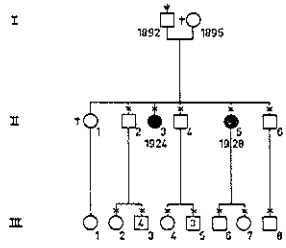
III-1 (LM-53.07.08)
1970: VOD S−0.50 8/10; VOS S−0.75 8/10.
Refracting media: Normal.
Fundi: Mild atrophic changes in the centre of the fovea. The fovea has a greyish aspect, not unlike oedema. Perifoveally there are many yellowish flecks, arranged in a garland-pattern. The disc, vessels and periphery are normal.

III-2 (JPM-55.07.22)
1970: VOD S−2 6/10; VOS S−.5 14/10.
Refracting media: Normal.
Fundi: The fovea has an aspect, not unlike oedema. It looks greyish and as if being varnished or covered with snail's slime. Perifoveally there are yellowish flecks, located beneath the vessels. The disc, vessels and retinal periphery are normal.

III-4 (MM-58.02.11) Impairment of visual acuity during the last 2 years.
8-10-1969: VODS 9/10.
2-7-1970: VOD 1/10; VOS 2/10.
17-7-1970: VODS 4/60.
Media: Normal.
Fundi: Absent foveal reflexes. Darkly pigmented flecks in the foveal area. The disc and vessels are normal. In the retinal periphery there are many pigmentary disturbances. Greyish-black spots, surrounded by whitish halo's are spread diffusely through the retina.

Summary: A very interesting family. Three children suffer from Stargardt's disease. The youngest has a centroperipheral tapetoretinal dystrophy (Stargardt's disease with peripheral involvement), while the other 2 children have a purely central tapetoretinal dystrophy. The finding of a pure central tapetoretinal dystrophy and a centroperipheral tapetoretinal dystrophy in one and the same sibship (particularly the fact, that the youngest affected has the centroperipheral form) suggests that central TRD and centroperipheral TRD are caused by the same genes and that consequently these different manifestations are due to difference in expression. This justifies the use of the term "Stargardt's disease" in the centroperipheral tapetoretinal dystrophies (centrally started diffuse TRD's).

16. Fam. Oe



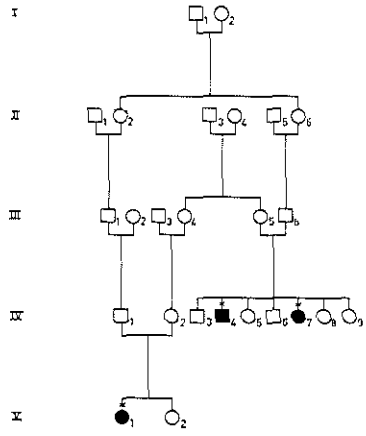
II-3 (GO-24.11.08) Poor visual acuity since the age of 15.
1956: VODS 5/10, emmetropic.
Fundi: Fine pigmentary changes in the foveal area.
1960: VODS 2/10.
1967: VODS 1/10.
Fundi: A symmetrical area measuring 1 disc diameter of fine pigmentary changes, glistening reflexes and mild atrophy of the retinal pigment epithelium. The disc is slightly too pale temporally, while the retinal vessels and retinal periphery are normal (fig. 1).
Visual fields: Relative central scotoma, increasing in intensity and size every year.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: The curve was obtained several times. The results were always normal.
ERG: Scot. b-waves OD 260μV; OS 325μV.
Phot. b-waves OD 135μV; OS 120μV.
Re-examination: Scot. b-waves OD 286μV; OS 316μV.
Phot. a-waves OD 40μV; OS 42μV.
Phot. b-waves OD 101μV; OS 116μV.
EOG: OD 2.83; OS 3.11.
OP: Normal.
Fluorescein angiography: Slightly pathological fluorescein pattern in the arterial phase in the centre of the

fovea. This fluorescence increases in the venous phase. After-fluorescence is visible during 2 minutes. Above the foveal area, there are some small defects in the retinal pigment epithelium as well.

II-5 (ASO-28.12.42) Poor visual acuity since the age of 12.
1960: VOD C+0.50×90° 7/10; VOS C+0.50×180° 4/60.
1963: VOD 2/10, decreasing to 3/60.
Refracting media: Small maculae, located centrally in the cornea.
Fundi: Symmetrical horizontally ovoid zone of atrophic pigment epithelium in the foveal area. The area measures 1.5 disc-diameter. The disc is slightly too pale temporally, while the retinal periphery and vessels are normal (fig. 4).
Visual fields: Relative central scotoma.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: Normal.
ERG: Normal.
EOG: OD 2.60; OS 2.40.
Systemic examination: Normal.
1967: VODS 4/60.
Fundi: Horizontally ovoid zone of "beaten bronze atrophy". The foveal reflexes have disappeared.
Visual fields: Central scotoma of 10-15 degrees.
Colour vision: Red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope),
Dark adaptation: Normal.
ERG: Scot. b-waves OD 385μV; OS 410μV.
Phot. b-waves ODS 105μV.
F-ERG: Subnormal.
VER: Subnormal.
OP: Normal.
EOG: Unreliable.
Fluorescein angiography: Fluorescein pattern indicating defects in the retinal pigment epithelium. Pathological fluorescence in the arterial phase, increasing in the venous phase in the foveal area. After-fluorescence is visible during 5 minutes. Under the fovea there is a very small fluorescent area, indicating a pigment epithelium defect (fig. 4b).

Summary: Two sisters from a non-consanguineous marriage, with Stargardt's disease. The dystrophy is limited to the foveal area in these 2 cases. This is reflected by the normal dark adaptation, ERG and EOG. No consanguinity was found, although the ancestors were traced back through 5 generations.

17. Fam. dRo



IV-4 (BvdL) Poor visual acuity since the age of 7. At the age of 7 gradual impairment of visual acuity started.
Media: Normal.

Fundi: Pale discs and attenuated vessels. Strong pigmentations in the posterior pole. Diffuse chorioretinal atrophy and some pigment dots in the retinal peripheries.

IV-7 (MvdL) Since the age of 7 gradually developing visual impairment. Approximately the same findings as in her brother.

V-1 (MFEdR-58.08.08)
1970: Visual impairment since some months.
March: VOD C−0.50×180° 5/10; VOS C−0.75×165° 7/10.
Diagnosis: Neuritis optica (?).
Treatment: Prednisone and Vitamine B preparations. No results.
April: VOD 3/10; VOS 7/10.
June: VOD 2/10; VOS 6/10.
July: VOD 1/10; VOS 5/10.
Media: Normal.
Fundi: Small atrophic area in the centre of a slightly swollen appearing fovea. Many yellowish flecks surround the foveal area in a garland pattern. The discs are slightly too pale on the temporal side. The vessels and retinal peripheries are normal.
Systemic examination: No abnormalities. The neurologist reported everything to be normal.

Summary: The proband is a 12 year-old-girl with Stargardt's disease. Visual impairment proceeds quickly. Because of the slight foveal alterations differential diagnosis from abnormalities of the optic nerve is necessary. The perifoveal yellow flecks strongly support the diagnosis of Stargardt's disease. The other affected members of this pedigree show Stargardt's disease with peripheral involvement (centroperipheral tapetoretinal dystrophy).

18. Fam. Ste
(JJHS-37.01.02) Poor visual acuity since 1950. Her parents have always had a normal visual acuity. Her brother has the same affection.
1952: VOD 2/10; VOS 4/60.
Fundi: Atrophic changes in the foveal area.
1962: VOD S−0.50=C−2×10° 1/60; VOS S−0.50=C−3×5° 4/60.
Refracting media: Normal.
Fundi: Symmetrical atrophic changes in the posterior pole. Many pigmentary disturbances. In the retinal periphery pigment clumping and whitish flecks. Disc too pale on the temporal side.
Visual fields: Central scotoma. Normal periphery.
Dark adaptation: The curve is 1 log. U. too high for both systems.
ERG: Scot. b-waves OD 70μV; OS 85μV.
Phot. b-waves unrecordable.

(JS)
1955: VODS 1/60.
Fundi: Centroperipheral tapetoretinal dystrophy (Stargardt's diseae with peripheral involvement).

Summary: A brother and sister with Stargardt's disease with peripheral involvement.

19. Fam. Sto
I-1 (SS-15.03.15)
VODS 10/10, emmetropic.
Fundi: Normal.
ERG: Scot. b-waves OD 220μV; OS 240μV.
Phot. b-waves OD 100μV; OS 110μV.
EOG: OD 1.78; OS 1.86.

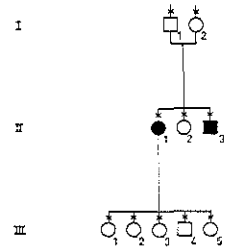
I-2 (AASM-14.03.21)
VODS S+2.50 11/10.
Fundi: Normal.

ERG: Scot. b-waves OD 240μV; OS 245μV.
Phot. b-waves OD 100μV; OS 90μV.
EOG: OD 2.00; OS 2.66.

II-1 (EvdHS-38.07.26) Poor visual acuity since the age of 12. Impairment of visual acuity particularly after deliveries.
1953: VOD S−1.50 2/10; VOS S−1.50 4/10.
Fundi: Fine pigmentary disturbances in the foveal area. Some whitish and greyish spots in the retinal periphery.
ERG: Scot. b-waves ODS 350μV.
Systemic examination: Normal.
1954: VODS 1.5/10.
ERG: Subnormal.
1962: VODS 4/60.
Fundi: A 1.5 disc diameter area of diffuse pigmentations and yellowish reflexes. Pigmentary dots and whitish flecks are scattered throughout the retinal periphery. The disc is too pale temporally whereas the retinal vessels are normal.
Visual fields: Relative scotoma of 30 degrees.
Absolute scotoma of 10 degrees.
Dark adaptation: The curve is 1 log. U. too high for both systems.
ERG: Scot. b-waves OD 125 μV; OS 135μV.
Phot. CFF-curve is subnormal.
EOG: ODS 1.70.
1967: VOD 3/60; VOS 2/60. At dusk, visual acuity is best. Gradual impairment of visual functions subjectively. Complains of nightblindness.
Fundi: An extensive area of atrophic pigment epithelium, pigmentations, and glistening reflexes in the posterior pole. Greyish-black and whitish flecks all over the retinal periphery. The disc is slightly too pale on the temporal side. The arteries are slightly attenuated. It was not possible to do a renewed retinal function study.

II-2 (RS-44.12.13)
VODS 11/10.
Fundi: Normal.
ERG: Scot. b-waves OD 230μV; OS 290μV.
Phot. b-waves OD 125μV; OS 125μV.
EOG: OD 2.24; OS 2.20.

II-3 (CJS-48.01.08) Poor visual acuity since the age of 6.
1961: VODS 1/10.
Fundi: A 1 disc-diameter area of atrophic changes in the foveal area. Fine pigmentations and glistening reflexes. Perifoveally many yellowish spots. Normal periphery. The disc is slightly too pale temporally.
Visual fields: Central scotoma of 5 degrees.
Colour vision: Red-green dyschromatopsia (HRR).
Dark adaptation: The curve is 1 log U. too high for both systems.
ERG: Scot. b-waves ODS 160μV.
CFF: Normal photopic activity.
EOG: ODS 1.53.
1968: VODS 3/60. Reads D=0.8 with hyperocular 4×.
Fundi: Centroperipheral tapetoretinal dystrophy. Atrophic changes in the foveal area (fig. 17). Many, whitish spots and some pigmentations in the retinal periphery. The disc is slightly too pale temporally, the vessels are normal.
Visual fields: Central scotoma of 20 degrees.
Colour vision: Medium red-green and mild blue-yellow dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope). Protan axis (Farnsworth D 15).
Dark adaptation: For both systems, the curve is 1.5 log U. too high.
ERG: Scot. b-waves OD 70μV; OS 50μV.
Phot. b-waves OD 50μV; OS 60μV.
EOG: Unreliable.



Summary: Initially central diffuse tapetoretinal dystrophy in a sister and brother from a non-consanguineous marriage. No consanguinity was found when the ancestors were searched as far back as 4 generations. The parents (I-1,2) had normal eyes and normal retinal function tests. The carriers of Stargardt's disease appear to be undetectable so far, unless their children have Stargardt's disease. The course of the retinal alterations in sister and brother runs parallel. The fundi of the sister indicate the future of the fundi of the brother. This family was described by Biesheuvel (1963) in an article entitled "Central tapetoretinal degeneration with peripheral involvement".

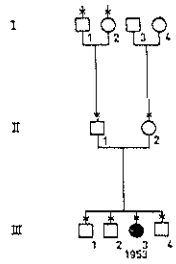
20. Fam. TS

(JMTS-46.11.05) The family history reveals no visual defects. Visual impairment since 4 years.
1970: VOD 1/10; VOS 1/10. Emmetropic.
Media: Normal.
Fundi: The fovea has the characteristic pattern of Stargardt's disease. Centrally in the fovea an area of atrophic retinal pigment epithelium. Around this atrophic zone a rather normal retina and around this almost normal zone a garland of whitish flecks in a horizontally ovoid pattern. The disc is slightly too pale on the temporal side. The vessels and periphery are normal (fig. 22a).
Visual fields: Central scotoma. Normal periphery.
Colour vision: Decreased red sensitivity (anomaloscope); Medium red-green dyschromatopsia (HRR); Protan and deutan defects (Farnsworth D-15).
Dark adaptation: Normal.
ERG: Normal.
EOG: Normal.
Fluorescein angiography: A target-shaped configuration, resembling the "bull's eye" of chloroquine retinopathy. There is pathological fluorescence due to defects in the pigment epithelium in the centre of the fovea and in an oval area around this centre. Between the fluorescing zones a normally appearing retinal area is found. There is no leakage of fluorescein. Without any doubt the fluorescing areas indicate defective pigment epithelium. In all probability Bruch's membrane is undamaged (fig. 22b).

Summary: A 24-year-old girl with foveae and visual acuities as characteristic for Stargardt's disease.

21. Fam. Wil

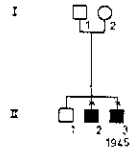
III-3 (JW-53.01.22)
1963: VODS C−0.50×180° 8/10.
1966: VODS 1.5/10.
1968: VODS 1/10.
Refracting media: Normal.
Fundi: A horizontally ovoid zone of atrophy with glistening reflexes and fine pigmentary disturbances in the posterior pole. This zone is surrounded by many yellowish-white spots. In the retinal periphery fine pigmentary disturbances are visible. The disc is slightly too pale temporally. The retinal vessels are normal.
Colour vision: Mild red-green dyschromatopsia (HRR).
Visual fields: Central scotoma.
Dark adaptation: Normal.
ERG: Normal.
EOG: Normal.



Summary: A girl, from a non-consanguineous marriage with Stargardt's disease. In 3 years' time the visual acuity decreased from 8/10 to 1.5/10. Since the retinal periphery is showing mild pigmentary changes we may expect the development of a diffuse centroperipheral dystrophy.

22. Fam. Wu
II-2 (JGW)
1969: VOD S−3.75=C−0.75×60° 6/10; VOS S−4.25 6/10.
Fundi: Atrophic changes in the foveal area.

II-3 (AJW-45.03.12)
1968: Decreasing visual acuity since 3-4 months. Difficulty in reading small print. Fixation-problems.
VOD S−2.50=C−1×175° 6/10; VOS S−2.50=C−1×5° 6/10.
Fundi: The foveal area has a somewhat greyish slightly swollen aspect, as if being varnished (fig. 2). Perifoveally there is a garland of yellowish-white fuzzy flecks, located beneath the vessels. Disc, vessels and retinal periphery are normal.
Visual fields: Relative central scotoma of 5-10 degrees.
Colour vision: Decreased sensitivity to red (anomaloscope). HRR and Farnsworth D15: Normal.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 315μV; OS 335μV.
Phot. a-waves ODS 60μV.
Phot. b-waves OD 125μV; OS 135μV.
EOG: ODS 1.73.
F-ERG: Subnormal.
VER: Subnormal.
1969: VODS 1/10.
Fundi: No important changes as compared to last year.



Summary: Two brothers from a non-consanguineous marriage, with Stargardt's disease. The impairment of visual acuity had a very rapid course. Ophthalmoscopically, the dystrophy is limited to the foveal area. Nevertheless the EOG of II-3 is already somewhat subnormal, indicating probably a more diffuse affection of the retina. In this family the age of onset of the manifestation of the dystrophy is over 20.

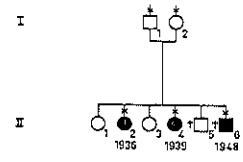
23. Fam. vW
I-1,2 VODS 10/10.
Fundi: Normal.
ERG and EOG: Normal.

II-2 (AvW-36.01.10) Poor visual acuity since the age of 24.
October 1959: VOD C−2.50×165° 8/10; VOS S+0.50=C−3×175° 8/10.
September 1960: VOD 3/10; VOS 2/10.
Juli 1961: VODS 1-2/10.
Fundi: Atrophic changes in the foveal area.
Systemic examination: Normal.
1963: VODS 1/10.
Fundi: Atrophic changes in the foveal area, surrounded by a garland of yellowish flecks.
Visual fields: Central scotoma of 8 degrees.
Colour vision: Mild red-green dyschromatopsia (HRR).
Dark adaptation: The curve is 0.5 log. U. too high for both systems.
ERG: Scot. b-waves OD 230μV; OS 201μV.
Phot. b-waves OD 81μV; OS 56μV.
1967: VODS 1/10.
Fundi: Atrophic fovea. Normal retinal periphery, disc and vessels.
Colour vision: Decreased sensitivity to red (anomaloscope).
Dark adaptation: The curve is 2/3 log. U. too high for both systems.
ERG: Scot. b-waves OD 320μV; OS 330μV.
Phot. b-waves OD 100μV; OS 95μV.
EOG: OD 1.64; OS 1.57.

II-4 (PMBvW-39.03.04) Poor visual acuity since 1961.
1963: VOD S−0.75 4/60; VOS S−1=C−0.50×150° 4/60.
Fundi: A horizontally ovoid zone of beaten bronze atrophy surrounded by many whitish flecks. Pigmentary disturbances centrally.
Visual fields: Central scotoma of 7 degrees.
Colour vision: Mild red-green dyschromatopsia (HRR).
Dark adaptation: 2/3 log. U. higher than normal for both systems.
ERG: Scot. b-waves OD 210μV; OS 215μV.
Phot. b-waves OD 85μV; OS 56μV.
EOG: ODS 1.50.
1967: VODS 4/60.
Fundi: Atrophic changes in the foveal area with severe pigmentary disturbances, particularly in OD.
Visual fields: Central scotoma of 10 degrees.
Colour vision: Decreased sensitivity to red (anomaloscope).
Dark adaptation: The curve is 1 log. U. too high for both systems.
ERG: Scot. b-waves OD 170μV; OS 210μV.
Phot. b-waves OD 115μV; OS 115μV.
EOG: OD 1.66; OS 1.44.

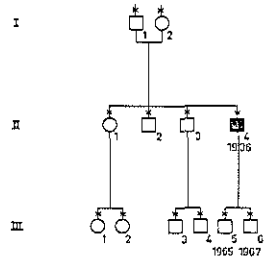
II-5 Died of leukaemia at the age of 4.

II-6 (HvW-48.11.01)
1961: VODS 5/10.
Fundi: The foveal reflexes are disturbed.
1963: VODS 2/10.
Fundi: Pigmentary changes in the foveal area.
1966: VODS 1-2/10.
Fundi: Atrophic glistening changes in the foveal area, surrounded by a garland of yellowish-white spots. Fine pigmentary disturbances in the centre of the atrophic foveal area.
June 1966: Died of encephalitis.



Summary: Stargardt's disease in 3 children, born out of a non-consanguineous marriage. No consanguinity was found as far back as 4 generations.
The retinal function tests indicate a disturbance of the diffuse (overall) retinal function. Nevertheless, ophthalmoscopically the retinal periphery is normal. In all probability the patients will develop a centroperipheral tapetoretinal dystrophy. We can regard this stage as a transitional stage between a pure central and a centroperipheral dystrophy.

24. Fam. Zo



II-3 (HZ-34.02.02) Myopia gravior with chorioretinal atrophy in the posterior pole of OS. The posterior pole of OD is normal.

II-4 (GZ-36.05.14)
1967: Poor visual acuity since 1 year. Treated some months ago for "toxoplasmosis" (Sabin-Feldman reaction 1:128 positive; CBR negative).
VOD 4/10; VOS 3/10. Emmetropic.
Fundi: OD: A 1 disc-diameter area of fine pigmentary alterations, surrounded by yellowish flecks in the posterior pole (fig. 13a). OS: Two round punched out areas of atrophic pigment epithelium in the foveal area (fig. 13b). Discs, vessels and retinal periphery are normal.
Visual fields: Central scotoma (20 degrees in OD; 10 degrees in OS).
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope). Tritan axis in OD (Farnsworth D15).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 355μV; OS 405μV.
Phot. b-waves OD 115μV; OS 115μV.
F-ERG: Subnormal.
VER: Subnormal.
EOG: OD 1.62; OS 1.57.
Fluorescein angiography: Patient collapses.
1968: VOD 2/10; VOS 3/10.

Summary: Stargardt's disease with first manifestations in a 30-year-old man. In this case the retinal lesions are not quite symmetrical, in contrast to most patients with Stargardt's disease. This man was treated elsewhere for toxoplasmosis despite a negative CBR. The subnormal EOG indicates a diffuse functional disturbance of the retina, although the retinal periphery is normal, ophthalmoscopically. It is quite possible that a diffuse centroperipheral dystrophy will be visible later.

25. Fam. vdZ
(IvdZS-24.12.24)
1958: VOD S$-$1=C+0.75$\times$90° 6/10; VOS S$-$0.50=C+0.75$\times$90° 6/10.
1960: VOD 6/10; VOS 2/10.
Fundi: Brownish pigmentary disturbances and atrophic changes in the foveal area. Normal retinal periphery.
ERG: Scot. b-waves OD 350μV; OS 380μV.
Phot. b-waves OD 105μV; OS 130μV.
Systemic examination: Normal.
1963: VOD 6/10; VOS 2/10.

Fundi: Atrophic changes in the posterior pole.
Colour vision: Mild red-green dyschromatopsia (HRR).
ERG: Scot. b-waves OD 295 μV; OS 195 μV.
Phot. b-waves OD 90 μV; OS 90 μV.
EOG: Normal.
1968: VOD 6/10; VOS 2/10.
Fundi: Sharply defined atrophic patches in the posterior pole of the eye. The choroid has an atrophic aspect, too. In the retinal periphery there are pigmentary disturbances and whitish flecks.
ERG: Scot. b-waves OD 205 μV; OS 215 μV.
Phot. b-waves OD 95 μV; OS 90 μV.
EOG: OD 1.50; OS 1.45.

Summary: A lady in her forties with atrophic dystrophy of both foveae. The differential diagnosis is between Stargardt's disease and incipient central areolar choroidal atrophy. The retinal periphery is affected, too. This is reflected by the subnormal EOG. The members of her family are reported to have normal eyes. In all probability, this is a case of Stargardt's disease with peripheral involvement.

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ADDENDUM

DI TIZIO, A. and MELCHIONDA, C.: Stargardt's central macular degeneration associated with the syndrome of the first branchial arch. Ann. Ottal. 91:1545-1557 (1965).
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IV

Dominant progressive foveal dystrophy

1. INTRODUCTION

Dominant progressive foveal dystrophy closely resembles Stargardt's disease, and in fact is described as dominant Stargardt disease by several authors (Franceschetti et al. 1963; Duke-Elder 1967). Sorsby and Davey (1955) and Sorsby (1957), however, differentiated this condition from recessive Stargardt's disease. We agree with this differentiation because all the cases described by Stargardt (1909, 1913, 1916, 1917, 1925) showed a recessive mode of transmission.

The clinical picture of this condition shows marked similarities to that of Stargardt's disease, and in this respect these affections can be compared with retinopathia pigmentosa, which shows as many as three modes of transmission. Dominant progressive foveal dystrophy is much less frequently seen than recessive Stargardt's disease; it tends less towards affection of the peripheral retina, occurs at a later age and generally takes a less progressive course (Sorsby and Davey 1955, Sorsby 1957).

We advocate strict differentiation of this dominant condition from recessive progressive foveal dystrophy, because it is only by sharp differentiation of the various forms that the singularly complicated group of the hereditary foveal dystrophies can to some extent be disentangled. Moreover, it is my impression that we may be dealing with two different entities, caused by different pathological genes.

Blue (1919) was the first to report on progressive foveal dystrophy occurring in more than one generation: a case involving a 43-year-old father and his 18-year-old daughter. Since a further family study was impossible, it is not certain that this dystrophy had an autosomal dominant mode of transmission.

Clausen (1921) described a "typische feinfleckige, auf die Makula beschränkte tapeto-retinale Degeneration" in a father and three of his children (the father's father being reported also to have had poor vision). Clausen also found acquired achromatopsia, and this means that a diagnosis of progressive cone dystrophy cannot be ruled out with certainty.

McQuarry (1935) reported on four generations of the "Jones family". The diag-

nosis had initially been hereditary optic nerve atrophy, and then retinitis pigmentosa, but was ultimately established as "macular degeneration with no affection of the cerebral region". Another report on dominant progressive foveal dystrophy was that by Gasteiger (1936), who in three generations found slight pigment irregularities in the fovea, which developed into a large, dirty yellow focus.

In his study "The dystrophies of the macula", Sorsby (1940) described the C family with progressive foveal dystrophy in two (anamnestically in three) generations.

Bonnet and Hugonnier (1943, 1947) observed progressive foveal dystrophy in four generations, and Dollfus (1948) described progressive foveal dystrophy in five patients in two generations of a family with a history of foveal dystrophy through six generations.

François (1949) saw a family with "central tapetoretinal degeneration" in three generations. Kodilinye (1952) found atrophic lesions in the central retina in a mother and three of her children. In addition there were slight peripheral changes in the mother and one of the daughters.

Dominant progressive foveal dystrophies were described in 1955 by Davis and Hollenhorst, Franceschetti et al., Goslich, and Sorsby and Davey. The 24 patients found by Davis and Hollenhorst in five generations, may have suffered from dominant progressive cone dystrophy.

Goslich (1955) and Franceschetti et al. (1955) reported on five affected individuals in four generations of the same family with "Stargardt-type hereditary familial juvenile macular degeneration". Sorsby and Davey (1955) described three families in which dominant progressive foveal dystrophy occurred.

Vail and Shoch (1958, 1965) presented a large family in which dominant progressive foveal dystrophy occurred, while Teterina (1970) described a progressive hereditary dystrophy of the fovea, which resembled Stargardt's disease and occurred in five generations.

The possibility of pseudo-dominance should always be borne in mind. The Kni family we present on page 150 includes an affected mother with seven affected children. The genealogical study disclosed that the father and mother were consanguineous, and the hereditary retinal affection is therefore probably autosomal recessive instead of dominant. The anamnestic data in this case also suggested a resessive condition.

Both Franceschetti et al. (1963) and Duke-Elder (1967) have listed other authors of case reports on dominant progressive foveal dystrophies. However, in my opinion the authors in question described not always progressive foveal dystrophies under this heading but also instances of vitelliform dystrophy of the fovea.

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

The clinical picture closely resembles that of Stargardt's disease. The condition generally occurs a little later in life and its progression is less rapid than in Stargardt patients. The patients report diminished vision and sometimes diminution of colour

discrimination. The bilaterality of the affection and otherwise unaffected health suggest a hereditary process.

3. FUNDUS (OPHTHALMOSCOPIC FEATURES)

In the early stages there is no or hardly any sign of foveal alteration, and even in later stages the fundal changes may be hardly perceptible (fam. Hoo). The most common finding is disappearance of the normal foveal and foveolar reflexes (figs. 1 and 2), and finely mottled pigment changes may be evident (Clausen 1921; Gasteiger 1936; Dollfus 1948; Goslich 1955; Sorsby and Davey 1955). In a few cases there is a focus of beaten bronze atrophy as often observed in Stargardt's disease (Gasteiger 1936; Dollfus 1948; Sorsby and Davey 1955). General atrophy of the central retina can ultimately occur (Goslich 1955; Vail and Shoch 1958).

Disc, retinal vessels and retinal periphery usually remain normal. Some temporal pallor of the disc can be observed in advanced cases, and slight peripheral retinal changes have been occasionally described (Kodilinye 1952; Ponte and Scialfa 1965). In our cases absent foveal and foveolar reflexes were the sole ophthalmoscopic changes (fig. 1, 2), even in a man aged 54 (I-1, fam. Hoo).

4. REFRACTION

Hypermetropia as well as myopia, with or without astigmatism, have been described. The number of reports is too small to warrant definite conclusions.

5. VISUAL ACUITY

As in Stargardt's disease, visual acuity finally diminishes to 1/10. The course of the loss of vision is slower, however, and it may take years before vision is so poor. Since the remainder of the retina is usually not involved, there is no further diminution of vision.

6. VISUAL FIELDS

There are no changes other than a central scotoma, which always increases in extent and depth with progression of the dystrophic process. The peripheral boundaries remain intact. The patients we examined showed a scotoma of 5 degrees.

7. COLOUR VISION

Colour vision seems to be subject to the same changes as those found in Stargardt's disease. In general, the few publications on this condition make very little mention of colour vision. In our three patients we found diminished red sensitivity. Sorsby and Davey (1955) also described red weakness as the most common abnormality. Vail and Shoch (1965) reported an early red-green dyschromatopsia followed ultimately by acquired achromatopsia. The families described as showing total acquired

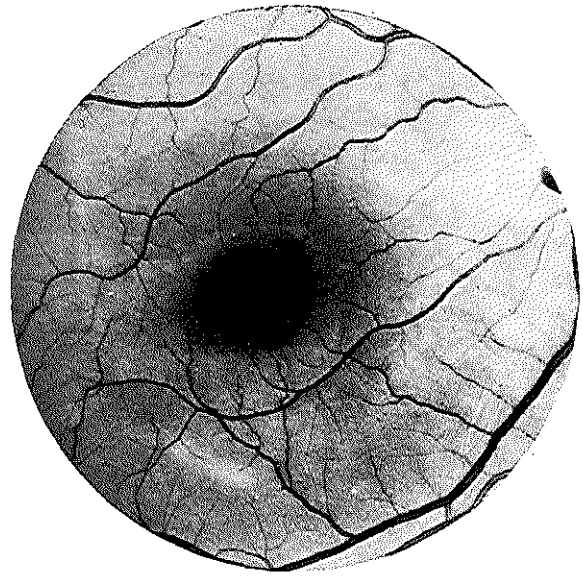


Fig. 1. Irregular foveal reflexes and a slightly swollen appearance of the foveal area in a 28-year-old male with dominantly inherited progressive foveal dystrophy.

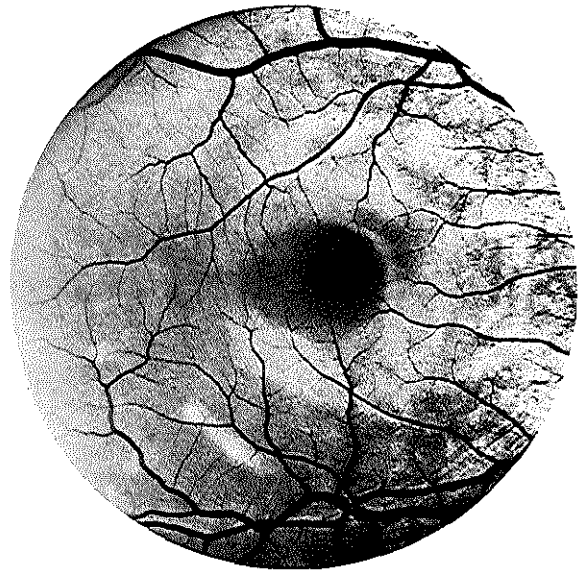


Fig. 2. Mild pathological changes in the posterior pole of a 22-year-old male with dominantly inherited progressive foveal dystrophy, consisting of irregular foveal reflexes and a slightly swollen appearance of the foveal area.

colour blindness (Clausen 1921: Davis and Hollenhorst 1955; Steinmetz et al. 1956) may have been suffering from dominant progressive cone dystrophy (page 181).

Vail and Shoch (1958) described an "almost complete absence of color sense" in their cases. It is difficult to conclude from the early publications whether the dominant foveal dystrophies described come under the heading of progressive cone dystrophy or under that of dominant progressive foveal dystrophy. The methods of examining colour vision are not always specified, and exact assessment of results is therefore impossible. Inability to read all the Ishihara test plates does not necessarily imply almost total colour blindness, as Vail and Shoch (1958) suggested.

8. DARK ADAPTATION

Dark adaptation is generally quite normal (Goslich 1955). Sorsby and Davey (1955) described normal as well as slightly disturbed curves, indicating slight diminution of cone and rod sensitivity. We ourselves obtained entirely normal dark adaptation curves.

9. ELECTRORETINOGRAPHY

Dominant progressive foveal dystrophy has an entirely normal photopic and scotopic ERG (Goslich 1955; Franceschetti et al. 1955). If indeed there are forms with involvement of the retinal periphery, as mentioned by Kodilinye (1952), then a subnormal photopic as well as scotopic ERG can be expected. The patients we examined had a normal ERG.

The F-ERG of the fovea was highly subnormal in the three patients we examined. Since the ophthalmoscopic foveal changes were very slight, this finding was conclusive of the foveal dystrophy we suspected on the basis of visual fields, colour vision and ophthalmoscopy. The VER were likewise diminished, but still present.

10. ELECTRO-OCULOGRAPHY

In two of the three patients we examined the EOG was subnormal; the values in the third patient were borderline values. There may already have been a diffuse disturbance in the function of the pigment epithelium.

11. PHOTOGRAPHY

Our photographs show hardly any changes. The foveal reflexes are not pronounced, and the foveolar reflex is absent. The entire foveal area is somewhat greyish, and rich in reflexes.

12. FLUORESCEIN ANGIOGRAPHY

We have obtained no fluorescein angiograms, nor do we know of any published in the literature.

13. CARRIERS

Since the mode of transmission was regularly dominant in the dominant progressive foveal dystrophies so far reported, the expression is probably already so strong that no real carriers occur.

14. HISTOLOGICAL FINDINGS

Vail and Shoch (1965) had occasion to have a histological study made of the eyes of one of their patients: a woman aged 78. The outer nuclear layer and the layer of rods and cones had disappeared completely, while the pigment epithelium showed pronounced pigment changes.

15. PATHOGENESIS

Like Stargardt's disease, dominant progressive foveal dystrophy is probably a primary dystrophy of the photoreceptors and pigment epithelium at the site of the fovea. The inconsiderable ophthalmoscopic changes are suggestive of a normal pigment epithelium, but the subnormal EOG (at least in our patients) in the presence of otherwise normal retinal function tests, indicates the possibility of a diffuse dysfunction of the pigment epithelium.

16. MODE OF TRANSMISSION

The mode of transmission of dominant progressive foveal dystrophy is regularly autosomal dominant (McQuarry 1935; Bonnet and Hugonnier 1943; Dollfus 1948; Charbonneau 1954 (quoted by Francheschetti et al. 1963); Davis and Hollenhorst 1955; Goslich 1955; Sorsby and Davey 1955; Vail and Shoch 1958, 1965).

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

No general abnormalities were found in any of the patients submitted to comprehensive examination.

18. ASSOCIATED CONDITIONS

There have been no reports on conditions found associated with dominant progressive foveal dystrophy, incidentally or otherwise.

19. DIFFERENTIAL DIAGNOSIS

The disease must be differentiated from the other dystrophies described in this study. In addition to the conditions listed in the differential diagnosis of Stargardt's disease, the following entities should receive special attention:

a. *Stargardt's disease* (recessive progressive foveal dystrophy, see page 100). Apart from the mode of transmission there are hardly any differences between the recessive and the dominant form of progressive foveal dystrophy (Sorsby and Davey 1955).

b. *Progressive cone dystrophy.* This likewise dominant condition can pose great difficulties of differentiation, especially in early stages when there are no or hardly any ophthalmoscopic foveal changes. Diagnostics of cone dystrophy are: extreme photophobia, rapidly developing achromatopsia, an unrecordable photopic and a normal scotopic ERG.

c. *Vitelliform dystrophy of the fovea.* Its mode of transmission is irregularly dominant; its ophthalmoscopic features nearly always distinguish it from dominant progressive foveal dystrophy. In dubious cases the family history and the very pathological EOG can confirm a diagnosis of vitelliform dystrophy.

d. *Acquired bilateral optic nerve atrophy* of any aetiology is the last condition to be differentiated. The fundal changes in dominant progressive foveal dystrophy can be so slight that an ophthalmoscopic diagnosis cannot be made with certainty. In such cases the F-ERG, recorded simultaneously with the VER, provide the solution. A normal F-ERG with absent VER indicates involvement of the optic nerve; a subnormal F-ERG, however, suggests foveal involvement. This is a very valuable aid in deciding between foveal and optic nerve involvement in dubious cases.

20. THERAPY

There is no therapy.

21. FUTURE

It will be of paramount importance to trace more families with dominant progressive foveal dystrophy. Whenever such a family is detected, the retinal function should be investigated as fully as possible so that any possible differences between dominant and recessive progressive foveal dystrophy (Stargardt's disease) can be established. Improved differentiation from the likewise dominant progressive cone dystrophy is also required. Too few cases have so far been described in the literature.

Also, it is not inconceivable that there are several different dominant progressive foveal dystrophies. Only careful examination and computation of new cases can improve our understanding of these conditions.

22. CASE HISTORIES

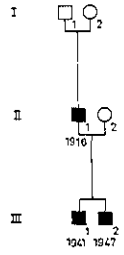
1. Fam. Hoo

I-1,2 Nothing is known about their visual acuity. Died a long time ago. There is no consanguinity.

II-1 (JH-16.03.08) Gradual impairment of visual acuity during the last years.
1969: VODS 1/10, emmetropic.
Media: Normal.
Fundi: Discs, vessels and retinal peripheries are normal. The foveal reflexes are disturbed. There are slight pigmentary alterations in the foveal area.
Visual fields: Central scotoma, approximately 5 degrees in size.
Colour vision: Decreased red sensitivity (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 202μV; OS 330μV.
Phot. b-waves OD 70μV; OS 110μV.
F-ERG: Subnormal.
VER: Subnormal, but present.
EOG: OD 1.76; OS 1.80.

III-1 (JH-41.06.27) Since some years and particularly in the last year visual impairment.
1969: VOD S−0.50 7/10; VOS S−0.75 2/10.
Media: Normal.
Fundi: Absent foveal reflexes and tiny pigmentary disturbances in the centre of the fovea (fig. 1). Normal discs, vessels and retinal peripheries.
Visual fields: Central scotoma of 5 degrees.
Colour vision: Decreased red sensitivity (anomaloscope). Mild red-green dyschromatopsia (HRR).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 260μV; OS 265μV.
Phot. b-waves OD 120μV; OS 120μV.
F-ERG: Subnormal.
VER: Subnormal, but present.
EOG: OD 1.34; OS 1.28.

III-2 (CH-47.08.22) Impairment of visual acuity during the last few years.
1969: VOD S−4.50 1/10; VOS S−5 1/10.
Fundi: Irregular, abnormal foveal reflexes. Slight pigmentary alterations in the foveal area (fig. 2).
Visual fields: Central scotoma of 5 degrees.
Colour vision: Decreased red sensitivity (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 280μV; OS 280μV. Phot. b-waves OD 115μV; OS 130μV.
F-ERG: Subnormal.
VER: Subnormal but present responses.
EOG: OD 1.70; OS 1.54.



Summary: A father and two of his sons with progressive loss of visual acuity, without distinct ophthalmoscopic alterations. The only visible abnormalities consist of irregular or absent foveal reflexes and tiny pigment disturbances at the site of the fovea. The results of the retinal function tests indicate foveal dystrophy. The subnormal EOG reflects a more diffuse affection of the retina than foveal dystrophy alone.

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ADDENDUM

PONTE, F. and SCIALFA, A.: Some uncommon symptoms of hereditary macular degeneration. Clinical investigation. G. ital. Oftal. 17:269-290 (1965).

V

Progressive cone dystrophy

I. INTRODUCTION

There are several known types of cone dysfunction, stationary as well as progressive. Goodman et al. (1963) distinguished the following so-called cone dysfunction syndromes.

A. *Congenital colour vision defects without amblyopia*
Deuteranopia and protanopia (sex-linked recessive transmission), tritanopia (probably autosomal dominant transmission).

B. *Complete colour blindness without amblyopia*
Cone monochromatism. The mode of transmission remains to be established.

C. *Congenital incomplete colour blindness with subnormal visual acuity*
Incomplete achromatopsia. Sex-linked recessive and possibly also autosomal recessive transmission.

D. *Congenital complete colour blindness with subnormal visual acuity*
Complete achromatopsia with amblyopia; rod monochromatism. Autosomal recessive transmission.

E. *Progressive cone degenerations*
Mode of transmission as yet unknown.

F. *Generalized cone-rod deficiencies, where symptoms relating to the cone dysfunctions dominate*
In our opinion this heading covers the cases of centroperipheral tapetoretinal dystrophy (Stargardt's disease with peripheral involvement) (see page 103).

G. *Generalized cone-rod deficiencies, where rod disorders dominate*
Retinopathia pigmentosa is a good example of this category.

To these conditions we made add sex-linked hemeralopia, which is often accompanied by myopia, as "congenital cone-rod deficiency where cones and rods seem equally affected".

The congenital forms are usually stationary, whereas the forms which become manifest at a later age, are progressive. The abovementioned "progressive cone degeneration", which we prefer to call progressive cone dystrophy, has so far been described in only a few reports. Steinmetz et al. (1956), using psychophysical test methods, demonstrated autosomal dominant progressive cone dystrophy in a family. Berson et al. (1968) described a father and son with progressive cone dystrophy, the paternal father and paternal grandmother having been affected also according to the history. ERG studies demonstrated a selective dysfunction of the cone system.

Other retinal dystrophies which seemed to involve selective cone dysfunction have been described by François et al. (1956), Sloan and Brown (1962) and Goodman et al. (1963, 1966).

François et al. (1956) presented the case of a 17-year-old male who showed all the clinical features of Stargardt's disease. Visual acuity and visual fields were more affected under photopic than under scotopic conditions, and the retinal centre totally lacked colour vision. It seems questionable whether this was indeed a case of progressive cone dystrophy, for colour vision was undisturbed in the retinal periphery.

Sloan and Brown (1962) described five cases, including two brothers, with progressive loss of vision and loss of colour vision. Three of the five patients had relatives with similar disturbances.

Goodman et al. (1963) described a man aged 35 with a two-year history of visual complaints. Visual acuity was diminished; additional findings were achromatopsia and absent photopic ERG in the presence of a normal scotopic ERG; these findings met the criteria of progressive cone dystrophy.

In 1966, Goodman et al. described a 40-year-old man with pronounced loss of visual acuity and colour vision in the right eye, and a similar but less pronounced disturbance in the left eye. The changes had come gradually. The photophobia was such that patient always used sunglasses outdoors, and avoided sunlight whenever possible.

The "typical finely mottled tapetoretinal degeneration of the macula" described by Clausen (1921) in a father and three of his children, might likewise represent cone dystrophy: the patients showed total colour blindness although colour vision had previously been normal.

Davis and Hollenhorst (1955) described a family with dominant progressive foveal dystrophy in which slight foveal changes were accompanied by extreme photophobia and marked loss of vision and colour vision; this family may also have suffered from progressive cone dystrophy.

Among our own patients with foveal dystrophies we have found none with selective cone dystrophy, although in all these patients colour vision and photopic

ERG were examined. Stationary congenital cone dysfunctions such as complete and incomplete achromatopsia, however, were observed fairly often; the diagnosis was verified on the basis of the ERG. This always showed normal scotopic and absent or decidedly subnormal photopic responses.

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

Patients report to the ophthalmologist because their previously normal vision has diminished. Photophobia is a common complaint, and colour vision is much diminished. The photophobia is exactly like that seen in achromatopsia, and suggests diffuse involvement of the cones. Visual acuity is experienced as much better in twilight than in bright light (dayblindness). A history disclosing several similarly affected relatives is not uncommon (Steinmetz et al. 1956; Sloan and Brown 1962; Berson et al. 1968). The age of manifestation in the cases so far described was between 6 and 50 years. A striking characteristic of the patients is that they nearly always wear sunglasses and avoid sunlight. They feel virtually blinded in bright sunlight.

3. FUNDUS (OPHTHALMOSCOPIC FEATURES)

In many cases the retina shows no abnormalities, and certainly not in initial stages. In some cases, however, there are slight foveal changes such as absent reflexes, slight depigmentations or slight granular pigmentations. The disc, retinal vessels and retinal periphery are usually normal, but the temporal part of the disc may show some pallor.

4. REFRACTION

The patients described by Berson et al. (1968) showed myopia and astigmatism. In the other publications, refraction is hardly mentioned.

5. VISUAL ACUITY

Visual acuity is initially normal but in the early stages of the affection soon shows a diminution which continues down to values below 1/10. The 45-year-old man described by Berson et al. (1968) had a vision of 2/300 ODS.

6. VISUAL FIELDS

Bilateral central scotomas develop, while the peripheral boundaries remain intact.

7. COLOUR VISION

Colour vision is totally lost after some time (Berson et al. 1968), so that the term acquired total achromatopsia applies. In early stages there may be a tritanomaly but also red-green dyschromatopsia (Steinmetz et al. 1956). The process as a rule develops gradually from normal colour vision to total achromatopsia.

8. DARK ADAPTATION

The dark adaptation test discloses monophasic curves with normal rod thresholds (Steinmetz et al. 1956; Berson et al. 1968). However, Sloan and Brown (1962) found a biphasic curve with abnormal cone and normal or virtually normal rod thresholds.

9. ELECTRORETINOGRAPHY

The ERG shows markedly diminished or absent cone responses, while the rod responses are normal (Sloan and Brown 1962; Goodman et al. 1963; Berson et al. 1968).

10. ELECTRO-OCULOGRAPHY

The EOG shows a normal Lp/Dt-ratio in progressive cone dystrophy. Both the standing potential itself and the L/D-ratio are normal (Berson et al. 1968).

11. PHOTOGRAPHY

Photographs of progressive cone dystrophy were published by Goodman et al. (1966). Hardly any changes are discernible.

12. FLUORESCEIN ANGIOGRAPHY

So far as we know, fluorescein angiography has not been used in this condition. The inconsiderable ophthalmoscopic changes and the normal EOG indicate that a normal angiogram might be expected.

13. CARRIERS

Little is known about the mode of transmission of this condition, and nothing about possible carriers.

14. HISTOLOGICAL FINDINGS

There are no reports on histological findings in this condition, but it is beyond doubt that the dystrophy primarily and selectively involves the cones.

15. PATHOGENESIS

The hypothesis of an enzymatic disorder in the cones proper seems attractive.

16. MODE OF TRANSMISSION

The mode of transmission of progressive cone dystrophy is probably autosomal dominant (Steinmetz et al. 1956; Berson et al. 1968; Schmidt 1970). However, it is

possible that there are several modes of transmission (Sloan and Brown 1962; Goodman et al. 1963).

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

General physical and laboratory findings have been reported as normal (Berson et al. 1968).

18. ASSOCIATED CONDITIONS

There is one report on association of progressive cone dystrophy with other affections. Björk et al. (1956) found several patients with hereditary cerebellar ataxia and an acquired cone dysfunction.

19. DIFFERENTIAL DIAGNOSIS

Progressive cone dystrophy must be differentiated from the following conditions.

a. *Complete or incomplete achromatopsia.* In these cases there is the same retinal dysfunction as in the terminal stages of progressive cone dystrophy, but the changes have been present since birth. Slight foveal changes may exist, but normal foveae have also been described. Complete achromatopsia has an autosomal recessive mode of transmission; the transmission of incomplete achromatopsia can be autosomal recessive as well as sex-linked recessive.

b. *Dominant progressive foveal dystrophy.* In this condition only the fovea and its immediate surroundings are generally affected. The remaining retina usually shows quite normal functions of cones as well as rods (page 172).

c. *Stargardt's disease.* If in this recessive disease only the central retina is involved, then the cone and rod functions of the remainder of the retina are quite intact. If both the central and the peripheral retina are involved, then there is an affection of the cones and rods which in our opinion is identical to the "generalized cone-rod deficiencies, where symptoms relating to the cone dysfunctions dominate" (Goodman et al. 1963), and to "progressive cone-rod degeneration" (Berson et al. 1968).

d. *Retinopathia pigmentosa.* This differential diagnosis generally offers no difficulty. When dealing with the "sine pigmento" variant, the ERG can decide the diagnosis, at least in the early stages. The scotopic ERG is soon affected while the photopic ERG remains normal a little longer. The ophthalmoscopic features differ from those of progressive cone dystrophy in that there are pale discs, attenuated arteries and trabecular pigmentations to some extent.

e. *Central retinopathia pigmentosa.* This condition is characterized by the presence of perifoveal pigmentation of trabecular shape, and the cone function tests are long quite normal (page 189).

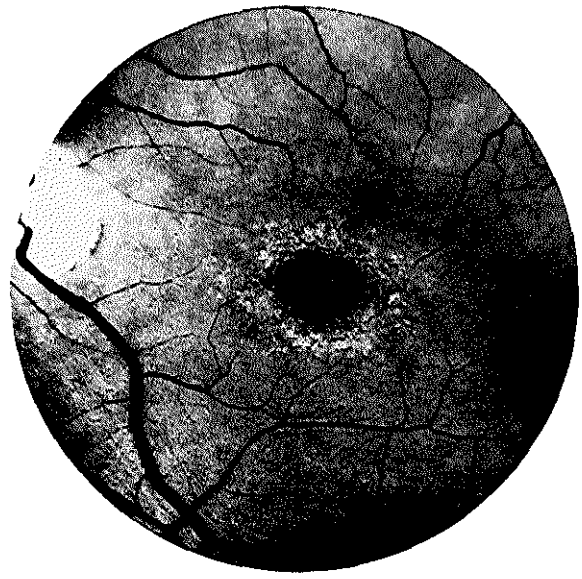

Fig. 1a. Chloroquine retinopathy in a 68-year-old female showing the pathognomonic bull's eye picture. This affection has to be differentiated from hereditary foveal affections.

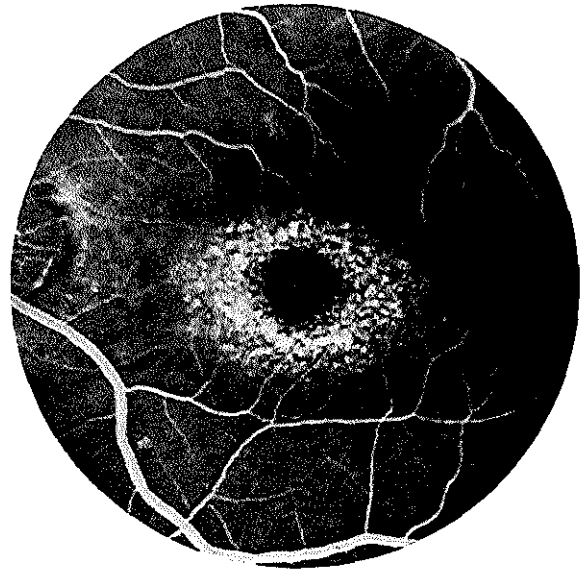

Fig. 1b. Fluorescein angiography reveals a horizontally ovoid zone of atrophic pigment epithelium, surrounding a centrally located pigmented circular structure.

f. *Drug-induced retinopathy.* Chloroquine and phenothiazine derivatives can give rise to an extensive retinopathy; one of its characteristics is the presence of delicate central and peripheral retinal pigment changes (fig. 1). In this retinopathy both the rod and the cone functions are affected after some time (Potts 1966). The scotopic and photopic ERG as well as the EOG are decidedly pathological in these cases. Dark adaptation, however, is generally normal until advanced stages.

g. *Acquired bilateral optic nerve atrophy.* Progressive loss of vision without distinct ophthalmoscopic changes can cause difficulties of differentiation. ERG and simultaneous recording of F-ERG and VER can ascertain the diagnosis. In optic nerve atrophy, both scotopic and photopic ERG's are generally normal. The F-ERG is likewise normal, but the VER are absent.

Zweifach and Wolf (1968) found, that patients with cone dysfunction regularly demonstrated improvement in acuity with reduction in illumination in contrast to normals and patients with optic nerve or macular disease.

h. *Non-hereditary acquired cone dysfunction.* This could be caused by drugs or toxins (Siegel and Smith 1967).

20. THERAPY

There is no therapy.

21. FUTURE

It is of importance that more families with this condition be described in the near future, so that the mode of transmission can be established and this condition, as a separate entity, can be more sharply differentiated from other, similar conditions.

22. CASE HISTORIES

We do not have own case histories.

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VI

Central (and pericentral) retinopathia pigmentosa

(*retinopathia pigmentosa inversa*)

1. INTRODUCTION

Duke-Elder (1940, 1967) has defined "central (inverse) pigmentary dystrophy" as: "A dystrophy in which the pigmentary disturbances, either as spiderlike clumps or scattered black dots, take the form of an island round the macula". Duke-Elder pointed out that these pigmentations are frequently accompanied by choroidal atrophy. No strict division into central and pericentral retinopathia pigmentosa can be made. Duke-Elder defined the latter as a condition "showing a picture between the true central and the classical equatorial lesions, wherein a pigmented zone occurs immediately around the macula, often having good central vision".

Franceschetti et al. (1963) presented a similar description of this condition. They noted that the degenerative process of retinopathia pigmentosa can be confined to one eye (unilateral retinopathia pigmentosa) or can be localized in a sector of the retina (sector retinopathy) or in the posterior pole of the eye, the macula remaining or not remaining intact. In the latter case they speak of central, pericentral, or inverse retinopathia pigmentosa.

The literature comprises many controversial views on this condition, and it is quite evident that authors are by no means always speaking of the same process when they use one of the three abovementioned designations.

In 1948, Sorsby described retinopathia pigmentosa inversa as an "ill-defined entity"; today, 22 years later, we are still unable to make a much more positive statement concerning this condition.

We intend to use this designation with reference to such cases as fulfil the ciriteria set by Duke-Elder (1940, 1967) and Franceschetti et al. (1963). Falls (1966) took a similar view of this affection.

It should be stressed that we do not use this designation for central tapetoretinal dystrophies in which centroperipheral involvement is observed after some time (Stargardt's disease with involvement of the periphery); some authors in fact do use

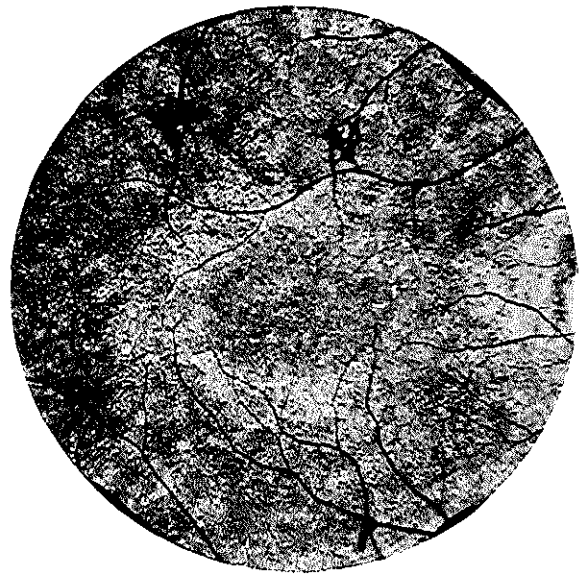


Fig. 1. Perifoveal bone corpuscles in the right eye of a 26-year-old male (Fam. Mel.).

these terms to refer to conditions which we call centroperipheral dystrophies (Von Rötth 1930; Lux 1961).

In Stargardt's disease, but also in vitelliform dystrophy of the fovea, extensive pigmentations can occur in the posterior pole; but in our opinion this does not warrant a description of these conditions as central retinopathia pigmentosa.

Central retinopathia pigmentosa means: changes like those of classical retinopathia pigmentosa, but confined to the centre of the retina. The fovea proper contains no vessels, and true trabeculae can therefore not occur at this site.

Retinopathia pigmentosa inversa means: retinopathia pigmentosa which takes a course that is the opposite of the course of classical peripheral retinopathia pigmentosa. Stargardt (1913) used this term, for example, to indicate the inverse course of a retinopathia pigmentosa-like condition in his S family. In this family there was foveal dystrophy and also dystrophy of the peripheral retina, which had probably occurred later. The affections with these features have been discussed in detail in the chapter on Stargardt's disease: Stargardt's disease with involvement of the periphery, or centroperipheral TRD. This affection is also known as mixed TRD or "rod-cone dystrophy". It is characterized by an initial involvement of the retinal centre, later followed by involvement of the retinal periphery. In view of this development, the word "inversa" is very appropriate, even though a centroperipheral TRD with classical trabeculae, wax-like pallor of the discs and stenosed arteries is seldom observed. We saw it only in one family (fam. Kni, page 150).

Since this picture has been discussed in detail in the Stargardt chapter, we need not dwell on it here.

In this chapter we confine ourselves to conditions in which trabecula-like pigmentations are observed around or near the fovea. There are several relevant publications (Kapuscinski 1908; Wittmer 1911; Lafon 1913; Pillat 1930; Cardello 1949; François et al. 1956; Franceschetti et al. 1963; Miglior et al. 1969).

The following publications are probably also dealing with this entity: Danis (1924); Hine (1928), Renard (1946), Ohrt (1957) and Hommer (1969).

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

Patients are often identified at routine ophthalmoscopic examination; in the early stages in particular, they are asymptomatic.

3. FUNDUS (OPHTHALMOSCOPIC FEATURES)

The fovea presents a normal appearance, with trabecula-like pigmentations surrounding it (fig. 1, 2). The retinal periphery, retinal vessels and disc are quite normal. The choroid may in some cases present an atrophic appearance, and pigmentations sometimes come very close to the foveal area (fig. 2ab).

4. REFRACTION

The exact data on this not very clearly defined entity are too scanty to warrant the conclusion that any abnormality of refraction can be described as characteristic of this condition.

5. VISUAL ACUITY

Visual acuity is generally normal in the initial stages, but can be markedly diminished in more advanced stages.

6. VISUAL FIELDS

The visual fields often show an annular scotoma around the foveal area, and the retinal periphery shows normal boundaries.

7. COLOUR VISION

Colour vision is normal in the initial stages, but after some time a blue-yellow dyschromatopsia develops which can be accompanied by diminished red sensitivity if the fovea proper becomes involved in the dystrophic process.

8. DARK ADAPTATION

Dark adaptation is either normal or shows a very slight delay.

The ERG is either normal or slightly subnormal (Falls 1966; Duke-Elder 1967; Miglior et al. 1969).

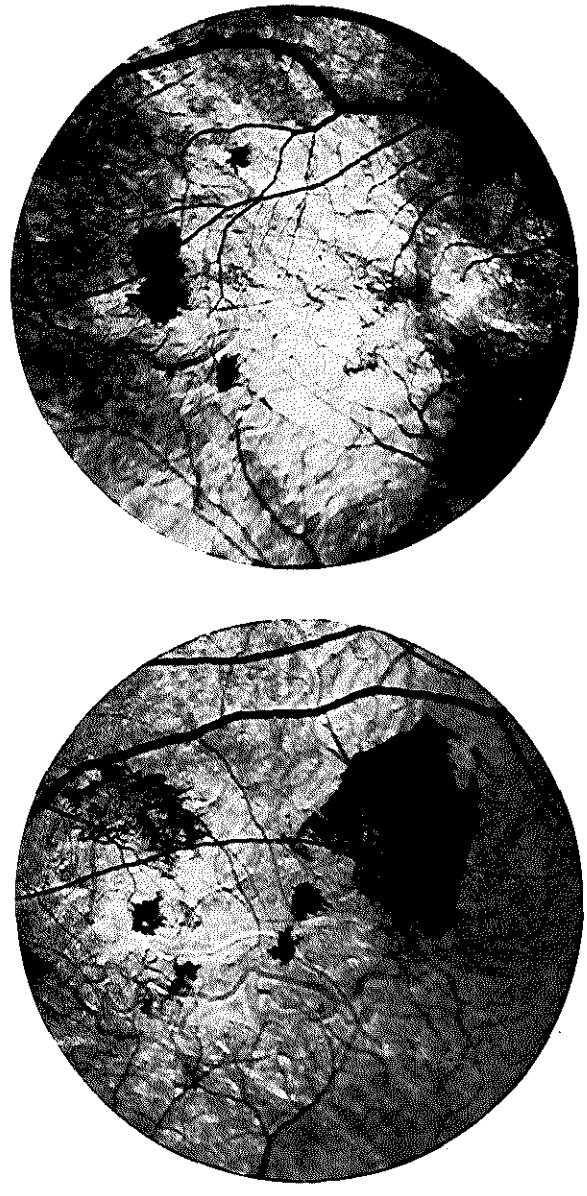


Fig. 2a-b. Retinopathia pigmentosa-like pigmentations and choroidal atrophy in the posterior poles of a 46-year-old man (Fam. Zijl).

The EOG is initially normal but after some times becomes subnormal (earlier than the ERG).

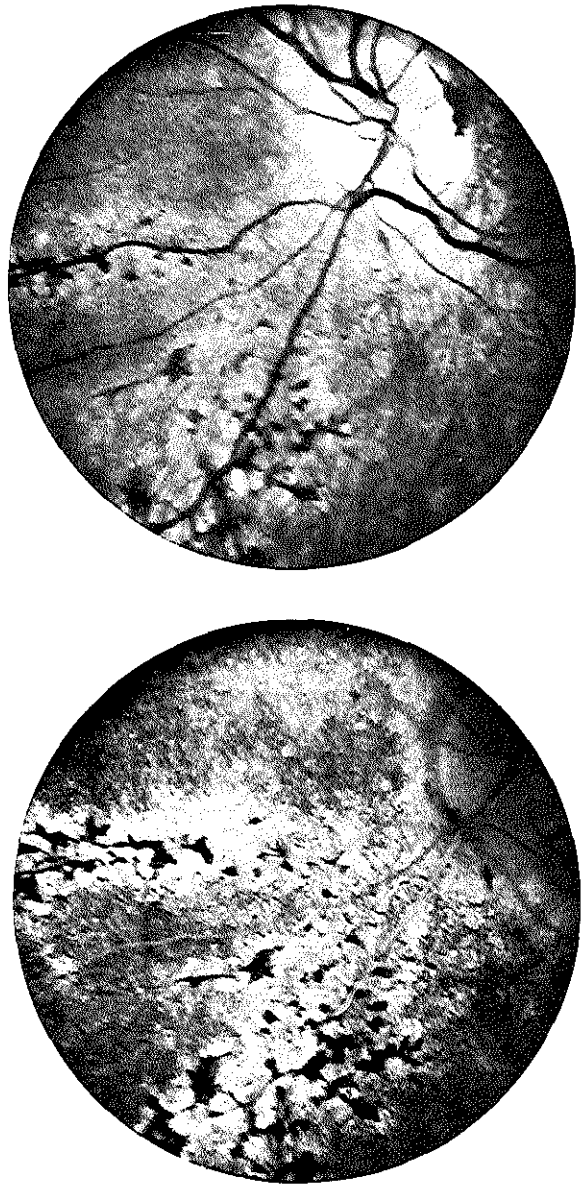


Fig. 3. Conventional and fluorescence photograph of a patient with pigmented paravenous retinal degeneration (after Amalric).

11. PHOTOGRAPHY

Orthochromatic and panchromatic graphic films produce no very different prints in this condition.

12. FLUORESCEIN ANGIOGRAPHY

Fluorescein angiography discloses an atrophic pigment epithelium, and shows black trabecular pigmentations clearly outlined in front of the fluorescent choroid.

13. CARRIERS

The carriers (the parents of the affected individuals) are quite normal.

14. HISTOLOGICAL FINDINGS

The histology is probably exactly the same as that of classical retinopathia pigmentosa (Duke-Elder 1967), but the process is more localized.

15. PATHOGENESIS

As in classical retinopathia pigmentosa, photoreceptors and pigment epithelium seem to be primarily affected.

16. MODE OF TRANSMISSION

The mode of transmission of central (pericentral) retinopathia pigmentosa is presumed to be autosomal recessive (Franceschetti et al. 1963).

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

There are no characteristic findings of general physical and laboratory studies.

18. ASSOCIATED CONDITIONS

There are no reports on conditions associated with this retinal abnormality.

19. DIFFERENTIAL DIAGNOSIS

Central (pericentral) retinopathia pigmentosa is to be differentiated from the following conditions.

a. *Classical retinopathia pigmentosa*, in which the posterior pole of the eye remains intact for a long time.

b. *Sector-shaped retinopathia pigmentosa*, in which only a sector of the retina shows trabecular pigmentations. (Franceschetti et al. 1963; Krill et al. 1970).

c. *Pigmented paravenous retinal degeneration*, in which pigmentations extend along the veins from the disc to the periphery (Brown, 1937; Weve, 1957; Amalric and Schum 1968; Baquis 1968; Bonamour and Ravault, 1968). (fig. 3).

d. *Stargardt's disease*, in which pigmentations may occur in the atrophic foveal focus in a minority of cases; no true trabecular pigmentations are found in the posterior pole.

e. *Other conditions in which marked pigmentations can occur in the posterior pole* (chorioretinitis, vitelliform dystrophy, rubeolar retinopathy, etc.).

20. THERAPY

There is no effective therapy. None of the medications tried (hormonal or vitamin preparations and vasodilators) has been successful. Nor have surgical interventions such as placenta implantations been effective. The futility of the abovementioned therapies is explained by the fact that the primary pathological process is localized in the photoreceptors and the pigment epithelium, but not in the choroidal and retinal vasculature.

21. FUTURE

A more unequivocal and better defined picture of this condition is desirable. To ensure this, reports on this condition should carefully define what is understood by central or pericentral or inverse retinopathia pigmentosa. The literature has so far comprised few cases described with precision.

Extensive family studies and photographic and retinal function studies can help us establish whether we are dealing with a variant of (peripheral) retinopathia pigmentosa or rather with a separate entity.

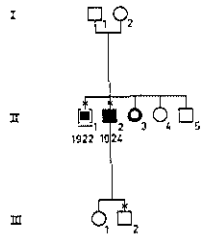
22. CASE HISTORIES

1. Fam. Mel
PAMM-43.07.10 Since some years poor visual acuity in the right eye. The family is reported to have normal eyes. The parents are not consanguineous.
1962: VOD 0.5/60; VOS 11/10.
Media: Normal.
Fundi: Bone corpuscles in the perifoveal area. The choroid has an atrophic appearance in the posterior pole (fig. 1).
Visual fields: OD central scotoma. OS normal.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 160μV; OS 210μV.
Phot. b-waves OD 65μV; OS 90μV.
1968: VOD 1/60; VOS 10/10.

Fundi: In the perifoveal area of OD some bone corpuscles and an atrophic choroid. In the retinal peripheries of both eyes some bone corpuscles.
Visual fields: OD central scotoma. OS annular scotoma around the fovea.
Colour vision: OD unrecordable. OS normal.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 150μV; OS 225μV.
Phot. a-waves OD 35μV; OS 55μV.
Phot. b-waves OD 50μV; OS 75μV.
EOG: OD 1.23; OS 1.98.

Summary: Pericentral retinopathia pigmentosa in a young man. Ophthalmoscopically there are distinct abnormalities in the right eye and slight abnormalities in the left eye. Particularly the visual fields indicate the bilateral affection, which seems to be unilateral on superficial examination.

2. Fam. Zijl



II-1 (ACZ-22.12.23)
VOD S+0.50=C−0.25×80° 11/10; VOS S+0.50 10/10.
Media: Normal.
Fundi: Rather coarse pigmentations scattered over the fundus. The posterior poles show the most widespread pigmentations.
Visual fields: Normal.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 272μV; OS 260μV.
Phot. a-waves OD 38μV; OS 32μV.
Phot. b-waves OD 82μV; OS 74μV.
EOG: OD 1.43; OS 1.44.

II-2 (CJZ-24.05.21) Poor visual acuity since 10 years. Concomitant divergent strabismus OD.
VOD C−1×90° 0.5/60; VOS C−1.50×110° 2/10.
Media: Normal.
Fundi: Large clumps of pigment in the perifoveal area. The choroid has an atrophic aspect (fig. 2ab).Discs and vessels are normal. The retinal peripheries show a granular pigmentation.
ERG: Scot. b-waves OD 124μV; OS 128μV.
Phot. a-waves OD 18μV; OS 17μV.
Phot. b-waves OD 44μV; OS 47μV.
EOG: OD 1.41; OS 1.17.

Summary: A patient (II-2) with a pericentral retinopathia pigmentosa. His brother had no complaints, however, diffuse pigmentation was seen throughout the fundus and he had a clearly subnormal EOG. This might be a patient with a low expression of the pathological gene.

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VII

Vitelliform dystrophy of the fovea

I. INTRODUCTION

It is only in recent years that vitelliform dystrophy of the fovea has been identified as a clearly separate entity. The many names given to this condition in the course of the years demonstrate this. In table I we present a review of the various designations used with reference to vitelliform dystrophy.

In 1883, Adams presented the first report on vitelliform dystrophy of the fovea in a paper entitled "Case showing peculiar changes in the macula". He found these peculiar changes in the eyes of a 37-year-old woman, who nevertheless had a vision of 1.0 OD and 0.4 OS.

The first familial cases were described by Best in 1905; in 8 of the 59 members of a family he examined, he found foveal changes which consisted of red, round, sharply defined foci that closely resembled the cicatrix of central chorioretinitis. In 6 individuals the condition was bilateral, and in the remaining 2 it was unilateral. None of the cases described by Best showed the classical, perfectly vitelliform stage which was later to become known from such publications as that of Zanen and Rausin (1950). This was possibly due to the fact that the youngest of his patients was 9 years old, while the majority were over 20.

Best found many other ocular abnormalities in this family (the J family in Klein Linden, near Giessen). Of the 59 family members examined, 31 showed one of the often hereditary abnormalities: marked hypermetropia, astigmatism, concomitant or convergent strabismus and amblyopia.

Further investigations of this family were later made by Vossius (1921), Weisel (1922) and Jung (1936), who identified 22 affected individuals among 300 members examined.

There are still authors who question the identity of the affection in this family (later also called Best's disease) with vitelliform dystrophy of the fovea (François 1967, 1968; Zanen and Balsacq 1968), but we have no doubt that the family described by Best was in fact suffering from vitelliform dystrophy. The fact that Best did not

observe the classical vitelliform stage later described by such authors as Zanen and Rausin (1950) does not alter our conviction. For it has been established that the vitelliform stage represents an early developmental phase of this dystrophy and, moreover, is by no means an obligate feature. We believe that many patients never show this stage.

In his exhaustive study on heredodegeneration of the macula, Behr (1920) likewise described a family with vitelliform dystrophy of the fovea. This family M was later re-investigated by Friemann (1953). Behr's description clearly warrants the conclusion that vitelliform dystrophy was involved. He observed yellow round structures in the central fundus, with still fairly intact vision, in several generations with the characteristics of dominant transmission.

Roll (1921) described a patient with a "circular plaque of what appears to be organized fibrous tissue in the macula of each eye"; this, too may have been a case of vitelliform dystrophy.

Table I

1883	Adams	Peculiar changes in the macula
1905	Best	A hereditary macular degeneration
1921	Vossius	Best's familial macular degeneration
1936	Jung	Congenital macular degeneration
1940	Huysmans	Exudative central detachment of the retina (macular pseudocysts)
1940	Rochat	Familial cystic macular degeneration
1946	Bonnet et al.	Central serous chorioretinitis
1949	Berkley and Bussey	Heredodegeneration of the macula
1950	Zanen and Rausin	Kyste vitelliforme de la macula
1951	Friedenwald and Maumenee	Peculiar macular lesions with unaccountably good vision
1953	Pameyer	Juvenile disciform macular degeneration
1956	Sorsby et al.	Macular cysts
1958	Gregory	Familial macular defects
1961	Zanen and Hermans	Vitelliform discs
1961	Barkman	Central tapetoretinal degeneration
1964	Braley and Spivey	Hereditary vitelline macular degeneration
1965	Remky et al.	Dominant autosomal macular degeneration with cystic and vitelliform stages
1966	Krill et al.	Hereditary vitelliruptive macular degeneration
1966	Falls	Best's disease

A selective review of various designations used with reference to vitelliform dystrophy of the fovea.

It is uncertain whether the 2 brothers with foveal dystrophy described by Steyn (1926) belong under this heading. The father and his sister had a history of poor vision; however, they may have suffered from Stargardt's disease.

So far as can be established, the first report from South America was that of Tiscornia (1926), who described a 61-year-old woman and 3 of her children with

greyish-yellow macular foci reminiscent of chorioretinitis. This family, later re-investigated by Damel (1948), is probably suffering from vitelliform dystrophy.

Argañaraz and Esteban Androgué (1927) described a family with 3 patients, one of whom had a disc-sized yellow focus in each fovea; these are probably also cases of vitelliform dystrophy.

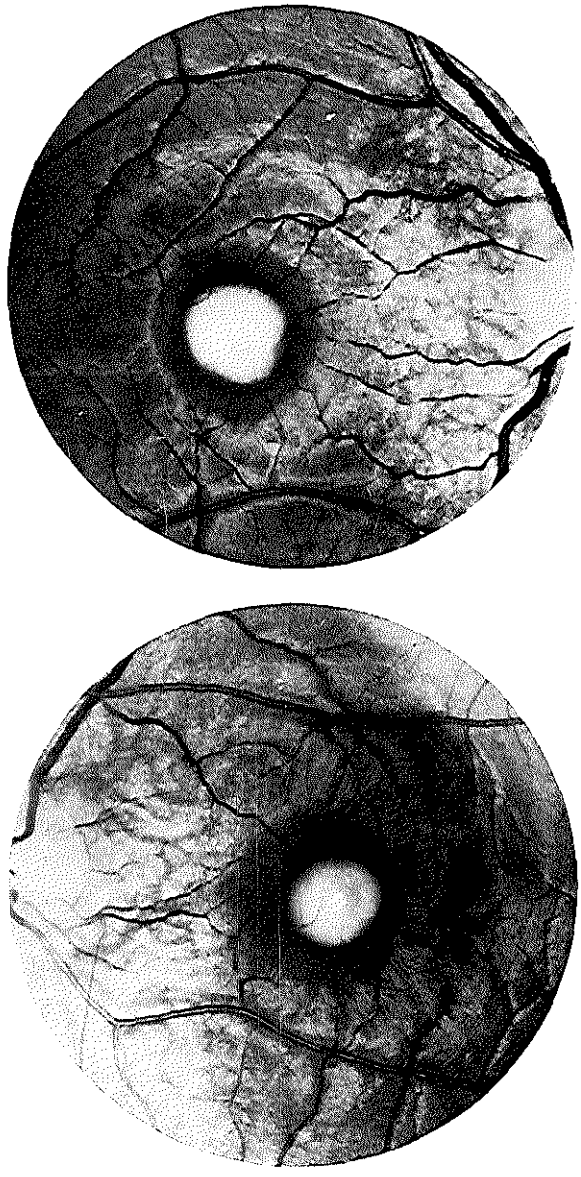


Fig. 1a-b. Right and left fovea of a boy with vitelliform dystrophy showing in both eyes the intact egg-yolk lesion (Fam. Ko-K).

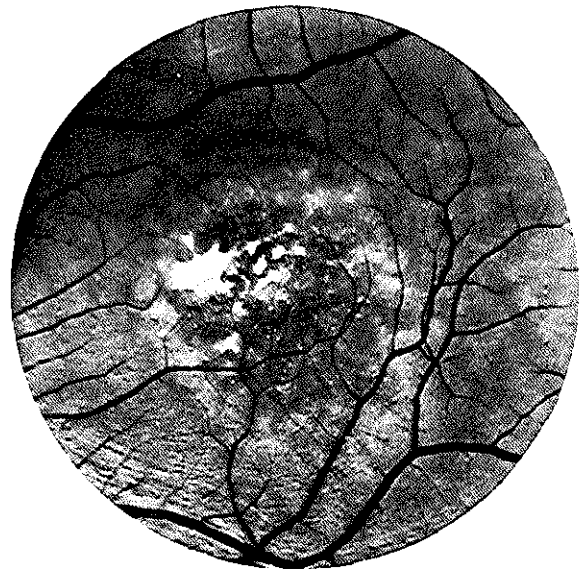


Fig. 2. Ruptured vitelliform disc with drusen-like deposits in a 43-year-old man (Fam. F1).

Rieger (1929) described a girl whose left eye contained a structure resembling a vitelliform lesion.

In 1934, Mazzi found a bilateral oval-shaped foveal chorioretinitis focus with haemorrhages in a 51-year-old man and his 25-year-old son. In view of the illustrations and because vision was not seriously affected, we conclude that these were cases of vitelliform dystrophy.

The characteristic yellow focus which can be observed in the fovea in vitelliform dystrophy (fig. 1) was described by Jess (1938) as "ein durch Nebel scheinender Sonnenball".

Niccol (1938) described a boy of 4 and his sister of 3 years with bilateral round yellow-white non-excavated "developmental defects at the macula". Vision was undisturbed. The mother's foveae showed light-yellow spots beneath the retinal vessels. Both children were hypermetropic, and the boy had a mild degree of convergent strabismus. Niccol himself and subsequent authors described this condition as macular coloboma. We believe that these were undoubtedly cases of vitelliform dystrophy: they presented the appearance, and vision was not markedly disturbed (which rules out macular coloboma).

The distinction between vitelliform foveal dystrophy and central serous choroidopathy (Gass 1967) was initially not at all clear, and the conditions were confused. For example, Streiff (1939) described "chorioretinitis centralis serosa" in a 27-year-old man with a bilateral vesiculiform foveal lesion which encompassed some sort of hypopyon. This was undoubtedly a case of vitelliform dystrophy.

Galeazzi (1939) observed a man and 4 of his children with a symmetrical paramacular lesion which, according to his data, may have been vitelliform dystrophy.

In 1940 three reports described vitelliform dystrophy by different names: "exudative foveal dystrophy" (Sorsby), "exudative central detachment of the retina (macular pseudocysts)" (Huysmans) and "cystic macular degeneration" (Rochat).

In his exhaustive study on "The dystrophies of the macula", Sorsby (1940) described two families (M and N) with "exudative foveal dystrophy". The M family included 14 affected members in 3 generations; in the N family a brother and sister were affected. These families almost certainly come under the heading of vitelliform dystrophy.

In The Netherlands Huysmans (1940) described 7 affected siblings as suffering from "exudative central detachment of the retina (macular pseudocysts)", while Rochat (1940) reported on 3 children of the same parents, who showed "cystic macular degeneration".

Renard (1946) in France observed 2 families (T and C) with vitelliform changes. The T family included 3 affected individuals in 2 generations, while the C family had 4 affected members in 3 generations.

Folk (1946) described 3 families, one of which might have shown the vitelliform entity. At the 1948 Chicago meeting of the American Academy of Ophthalmology and Otolaryngology, Riser et al. (1948) presented fundus photographs of several members of an American family with foveal changes which were described as "an egg with the sunny side up".

Fig. 3. Almost intact vitelliform disc in an 8-year-old boy, son of the man whose fundus is depicted in fig. 2.

Berkley and Bussey (1949) described a family with 8 patients in 3 generations; special feature: 3 cases of unilateral vitelliform foveal dystrophy.

The early fifties were characterized by a flood of reports, including the publication of Zanen and Rausin (1950), which introduced the designation "vitelliformis". The name vitelliform macular degeneration (better: vitelliform foveal dystrophy) has since been used for all stages of this evolutive condition. The classical egg-yolk appearance, however, need not be present or have been present in all patients or families in order to warrant a diagnosis of vitelliform foveal dystrophy. Krill et al. (1966) perfer the designation "vitelliruptive macular degeneration" to indicate the evolutive character of this dystrophy, and also because the name vitelliform refers to only one particular stage of this condition.

Table II

Argentina	Tiscornia (1926); Argañaraz and Androgué (1927); Damel (1948); Corrêa-Meyer (1953); Garcia Nocito et al. (1964); Urrets-Zavalia and Moyano (1969).
Austria	Rieger (1929); Hruby (1956, 1967); Rieger (1969, 1970).
Belgium	Michiels and Delfosse (1949); Hambresin (1950); Zanen and Rausin (1950, 1951); Zanen (1953); Zanen and Lempereur (1954); Zanen and Hermans (1961); de Walsche (1963); François et al. (1966, 1967, 1968); Zanen (1967); Zanen and Balsacq (1968); François and de Laey (1969).
Czechoslovakia	Pur (1964); Streicher (1967).
England	Adams (1883); Roll (1921); Niccol (1938); Sorsby (1940); Sorsby et al. (1956); Gregory (1958); Sorsby and Wren (1960); Graham et al. (1964); Sorsby (1967); Rosen (1969).
France	Bonnet (1938); Bonnet et al. (1946); Renard (1946); Belz (1948); Bischler (1952); Hermann (1952); Bérard (1953); Renard et al. (1960); Gallet (1961); Calmettes and Déodati (1962); Nordmann and Eberhardt (1962); P. François et al. (1963); Hermann and Vernin (1963); Moser (1963); Étienne et al. (1964); Pommier (1964); Bonamour and Pommier (1965); Bronner et al. (1965); Bérard (1966); Bonnet et al. (1966); Lefranc (1966); Bonamour (1967); Le Hunsec and Pierre (1967); Dorne (1970); P. François et al. (1970).
Germany	Best (1905); Behr (1920); Vossius (1921); Weisel (1922); Blank (1928); Jung (1936); Jess (1938); Jaeger (1951); Richm (1952); Friemann (1953); Weber (1960); Haimböck (1962); Littann (1965); Remky et al. (1965); Denden (1966).
Hungary	Varga (1967); Biró (1968).
Italy	Mazzi (1934); Galeazzi (1939); Bruna (1951); Capalbi (1954); Montaldi and Nicodemi (1961); Capalbi and Salvi (1962); Pansini and Ligorio (1962); Maggi (1963); Chinaglia and Perini (1964); Massimeo et al. (1964); Melodia and Tabacchi (1965); Spinelli and De Molfetta (1965); Belmonte (1966); Tota (1966); Gorgone (1967); Mazza et al. (1968); Palmieri and Mazza (1968).
Japan	Tsukahara (1968).
the Netherlands	Steyn (1926); Huysmans (1940); Rochat (1940, 1941); Weve 1944; Pameyer (1953, 1954); Dekking (1955); Velzeboer (1963); Deutman (1968, 1969).
Peru	Ego-Aguirre Benvenuto (1959).
Sweden	Barkman (1961).
Switzerland	Streiff (1939); Martenet (1967, 1968); Ricci et al. (1969).
United States of America	Riser et al. (1948); Berkley and Bussey (1949); Falls (1949); Bussey and Berkley (1950); Friedenwald and Maumenee (1951); Falls (1952); McFarland (1955); Grimm and Tedford (1963); Braley and Spivey (1964); Braconnier (1965); Cogan (1965); Braley (1966); Hermann (1966); Krill et al. (1966); Braley (1968); Curry and Moorman (1968); Krill et al. (1968); Morse and MacLean (1968).

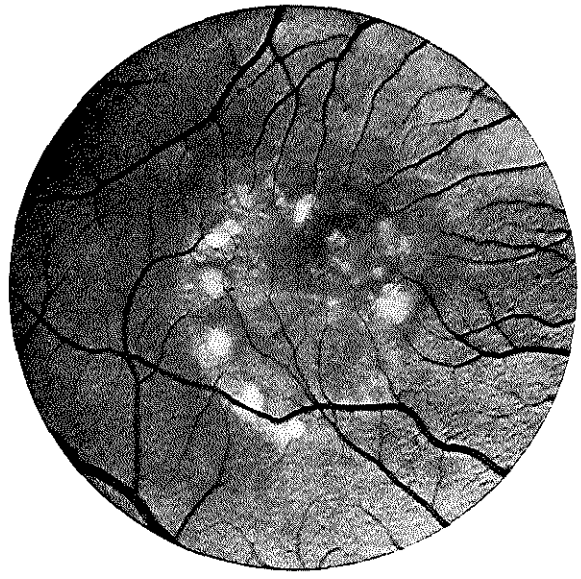


Fig. 4. Small multiple vitelliform lesions (deposits) near the margin of a large atrophic vitelliform lesion. This lesion resembles the figures shown by Braley and diagnosed as polymorphic foveal dystrophy.

The many publications which have appeared since 1950, will not be discussed in detail, but they will be mentioned at relevant places elsewhere in this chapter and tabulated with the earlier publications in table II.

Although we have long been convinced, with many others, that vitelliform foveal dystrophy is a separate entity, there is still a surprising amount of confusion about this condition. In the French literature in particular, the prevalent view is that retinopathia centralis serosa or chorioidopathia centralis serosa (Gass 1967) is closely related to vitelliform foveal dystrophy (Bonnet et al. 1938, 1946, 1966; Bischler 1952; Nordmann and Eberhardt 1962; Le Hunsec and Pierre 1967; Martenet 1967; Urrets-Zavalia and Moyano 1969). Vitelliform foveal dystrophy (VFD) is consequently often described as "atypical retinopathia centralis serosa". Streiff (1939) and Riehm (1952) likewise described VFD as atypical retinopathia centralis serosa. In our opinion, however the two conditions should be regarded as separate entities, as demonstrated by our EOG findings, which were quite different in the two conditions. A detailed discussion of these findings will be presented later.

There is also often confusion with Stargardt's disease, but this can also be differentitated in several ways. Bruna (1951) and Bérard (1966) reported VFD in families with Stargardt's disease. These were undoubtedly families with VFD. There are no transitional or mixed forms, and we believe that coincidence of these two entirely different entities in the same family has never been really observed. Nor is it under-

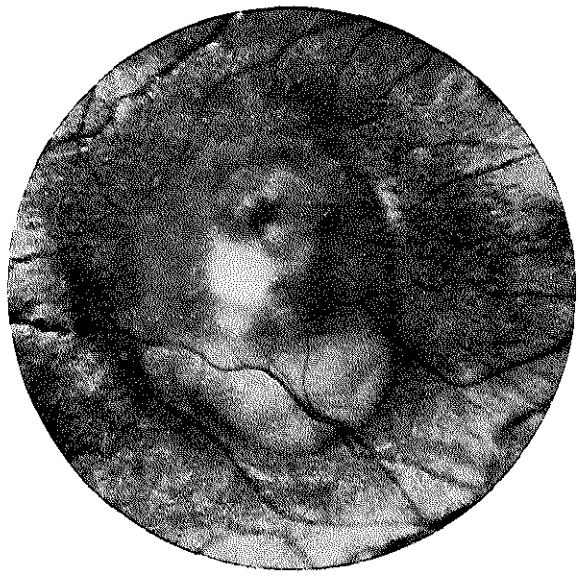


Fig. 5a. Vitelliform cyst with pseudohypopyon in a 27-year-old male (Fam. KlK) (after Pameyer).

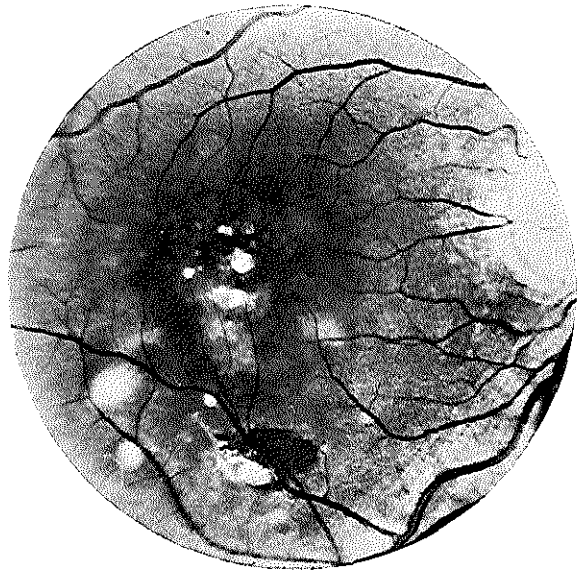


Fig. 5b. The same eye 15 years later, showing a ruptured cyst with atrophic pigment epithelium centrally and multiple vitelliform structures and deposits at the bottom.

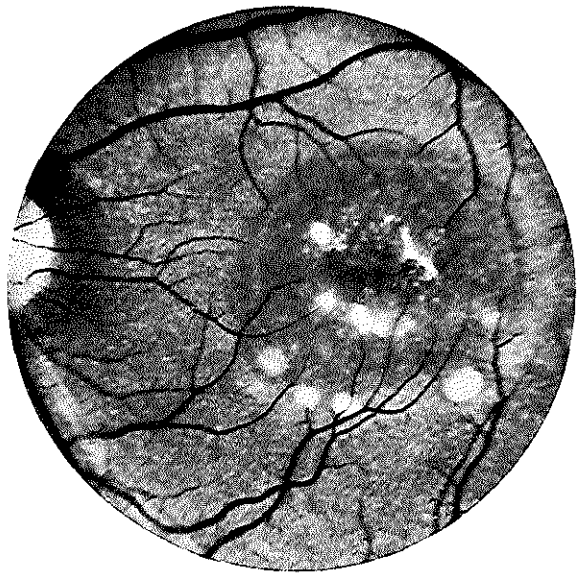


Fig. 6. Vitelliform cyst with deposits centrally and small multiple vitelliform lesions at the bottom.

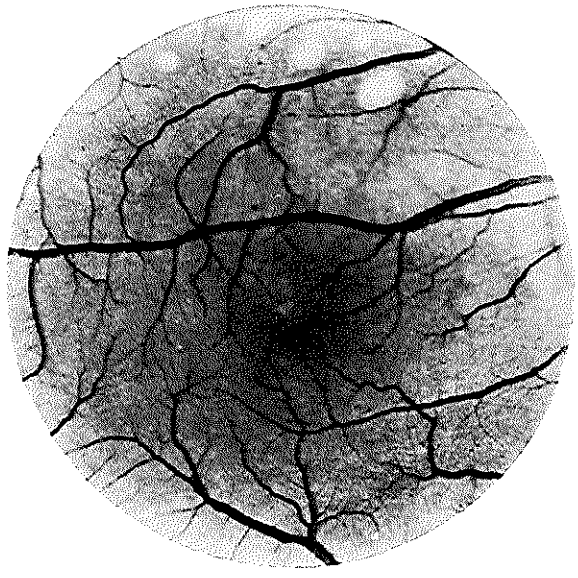


Fig. 7a. A tiny yellowish fleck near the foveola and some small multiple vitelliform lesions above the fovea in a 44-year-old man (Fam. Vr).

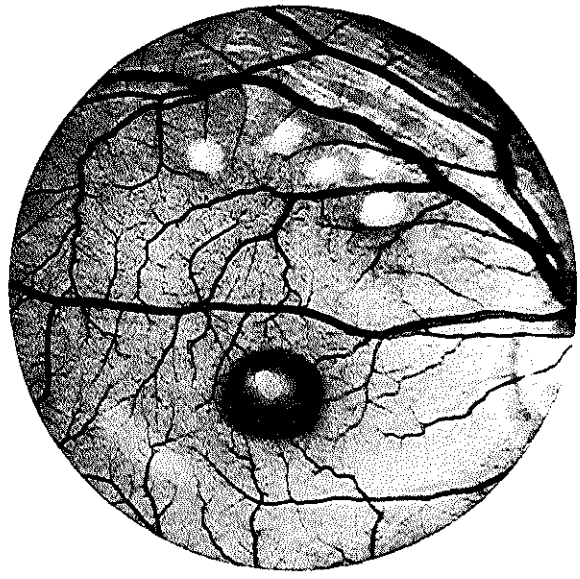


Fig. 7b. One year later a real vitelliform disc is visible in the foveal area.

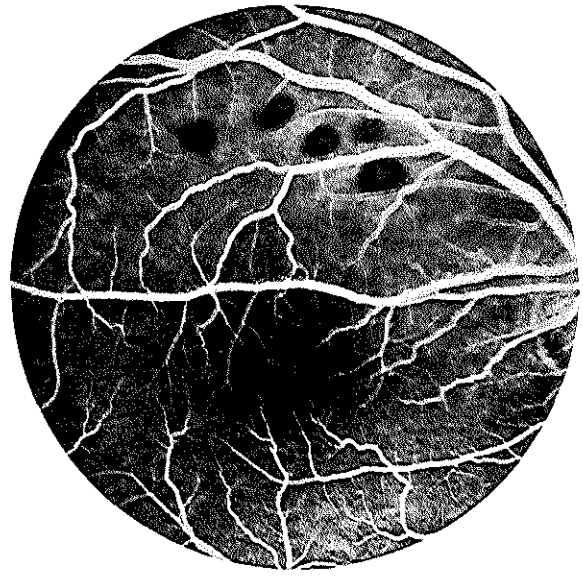


Fig. 7c. Fluorescein angiography reveals minimal fluorescence centrally and less fluorescence than normal at the site of the multiple vitelliform lesions.

standable that Duke-Elder (1967) described a family with VFD while the caption of the excellent colour photographs read "Stargardt's disease"; this must have been an error in printing.

Another condition which closely resembles VFD is central chorioretinitis. Patients with VFD are still being submitted to extensive examinations and treatments because an inflammation is believed to exist. In view of the ophthalmoscopic features this is understandable. But it is strange that even in evidently familial cases an inflammatory aetiology is often not ruled out, even after a negative general clinical examination (Ferrié 1946; Jaeger 1951; Riehm 1952; Pillat 1962).

It is also remarkable that J. François (1967, 1968) distinguished between VFD, "cystic macular degeneration" and "Best's macular heredodegeneration"; in our opinion there can be no doubt that all these designations refer to the same condition, and several other authors have reached the same conclusion (P. François et al. 1963; Braley and Spivey 1964; Remky et al. 1965; Krill et al. 1966; Deutman 1969).

In 1966 Braley introduced what he believed to be a new syndrome, which in our opinion is an evident representative of VFD. He called this condition "polymorphic macular degeneration" and Duke-Elder (1967) also described this "polymorphic macular degeneration" as a separate entity. We do not believe that this is in fact a new syndrome. The clinical features of VFD are known to be very variable. In one of our families (fam. Fl) we observed a father with fundus features (fig. 2) identical to the photographs which Braley published to illustrate his polymorphic macular degeneration; but one of this man's children showed a classical vitelliform disc ODS (fig. 3). We made a similar observation in another family (fam. Bl). The family described by Pameyer (1954) had likewise shown true vitelliform lesions in the past (fam. Kl K), but in 1968 there were extensive changes identical to what Braley introduced as a new entity (fig. 4-6).

The multiple vitelliform lesions (fig. 4-7) so beautifully described by Littann (1965), and later by Denden (1966) and Deutman (1969), are nothing but variants of VFD in our opinion. They support the theory (based on EOG findings) that VFD involves a diffuse disturbance in the deeper retinal layers, probably in the pigment epithelium.

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

A vitelliform lesion can be detected at ophthalmoscopic examination of a patient with quite normal visual acuity. It is a general fact that substantial ophthalmoscopic changes can be associated with normal vision, while on the other hand hardly discernible changes can accompany greatly diminished vision (e.g. in incipient Stargardt's disease).

Pronounced hypermetropia with or without astigmatism is a common finding, and convergent strabismus is also frequent; nystagmus, however, is rarely observed.

Some authors were convinced that the vitelliform lesion is always present at birth (Best 1905; Jung 1936; Falls, quoted by Grimm and Tedford 1963, and Braley 1966;

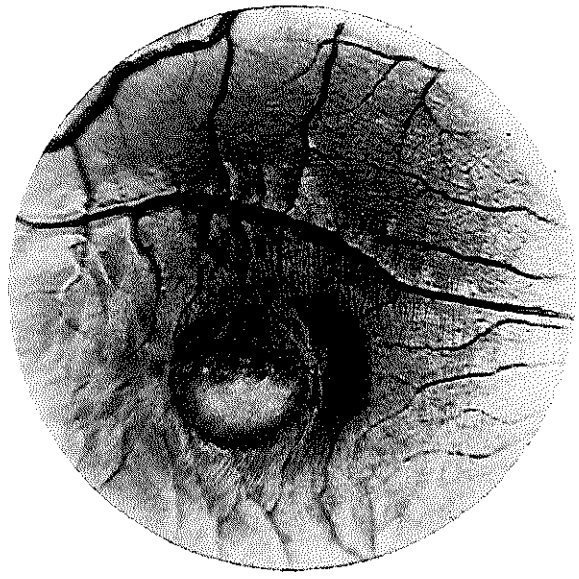


Fig. 8a. Vitelliform lesion shortly after the origin in an 8-year-old boy (Fam. T-T), filmed on orthochromatic film.

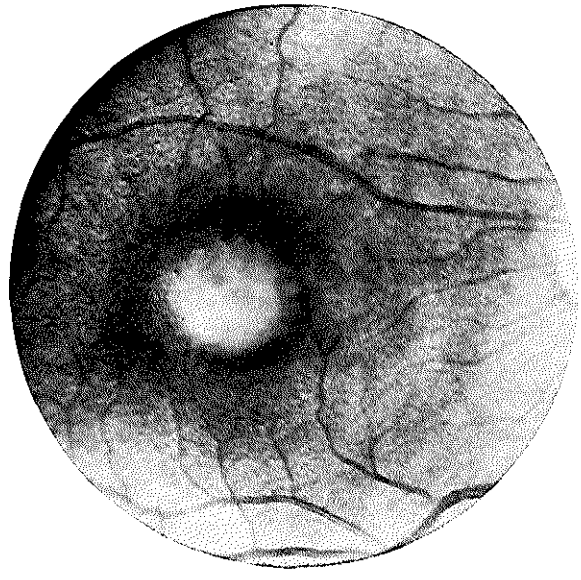


Fig. 8b. The same lesion photographed on panchromatic film. More abnormal structures are visible.

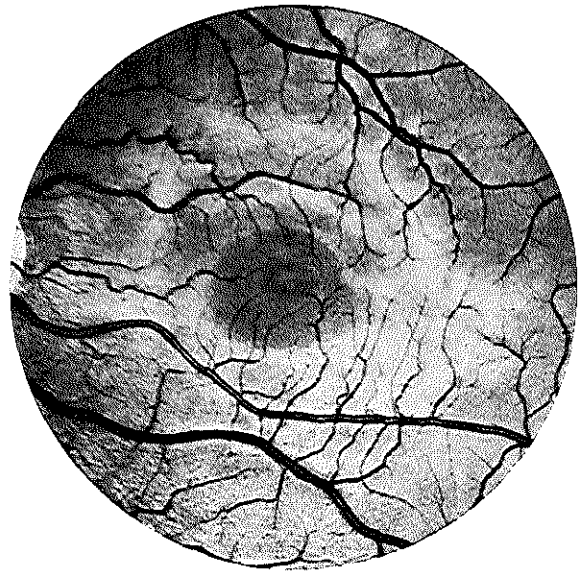


Fig. 9. Delicate alterations in the foveola of a 22-year-old female. Probably this is an initial stage of the vitelliform disc. Rather often we found these minimal lesions in family-members of patients suffering from vitelliform dystrophy. A pathological EOG L/D-ratio was always found in these cases.

Braley 1966), and this is why this condition is still often counted among the congenital macular heredodegenerations. Since Barkman (1961) observed this foveal abnormality in an infant aged 1 week, while Braley (1968) made the same observation in an infant aged 2 weeks, it is indeed likely that the vitelliform structure can be present already at birth. Falls (quoted by Grimm and Tedford 1963, and Braley 1966) even held that an individual with normal fundi cannot later develop VFD. We have found that this is a fallacy, because many investigators have observed normal foveae to develop pathological changes later in life (Huysmans 1940; Hermann and Vernin 1963; Friedenwald and Maumenee 1951; Zanen and Hermans 1961).

We personally observed a vitelliform disc in a 6-year-old boy (IV-15, fam. TT; fig. 8) and in a 44-year-old man (V-7, fam. Vr; fig. 7), in eyes which had been normal or virtually normal. One year earlier the boy's foveae were entirely normal; but the man had already shown a few small multiple vitelliform lesions over the right fovea and a small white-yellow spot at the site of the foveola when examined a year earlier (fig. 7). In two women aged 43 and 32, respectively, who were known as carriers on the basis of EOG findings, we saw normal foveae develop pathological changes in the course of a year (III-2; III-8, fam. EW). It should be pointed out that these

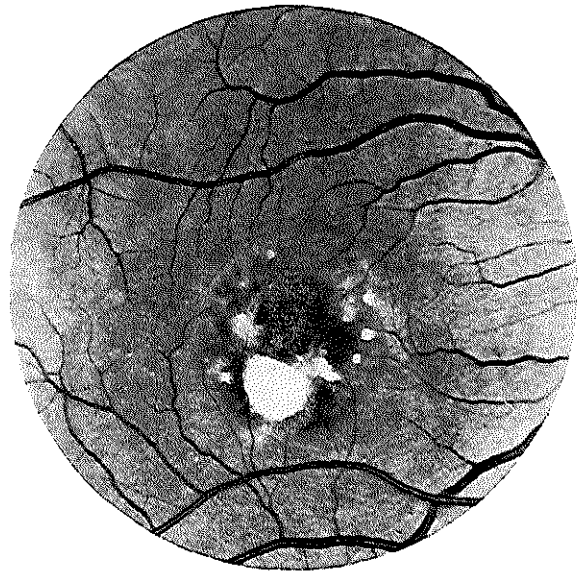
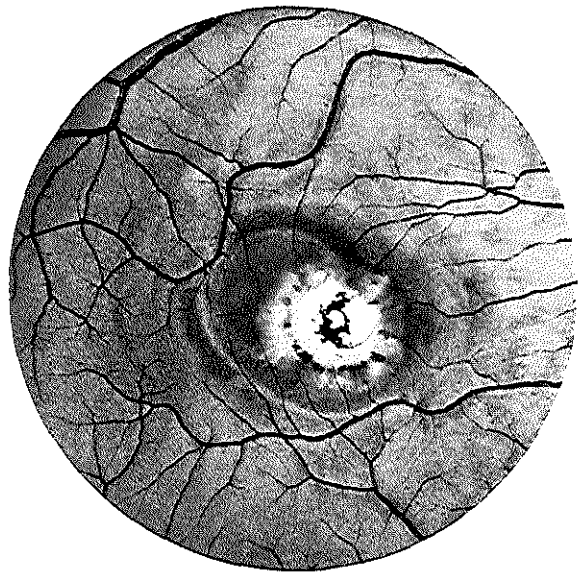


Fig. 10. Partly ruptured vitelliform disc in a 35-year-old male. (Fam. B-E).

Fig. 11. Intravitelline haemorrhage in one of our patients (Fam. Pl). In all probability these haemorrhages are based on ruptures in Bruch's membrane.



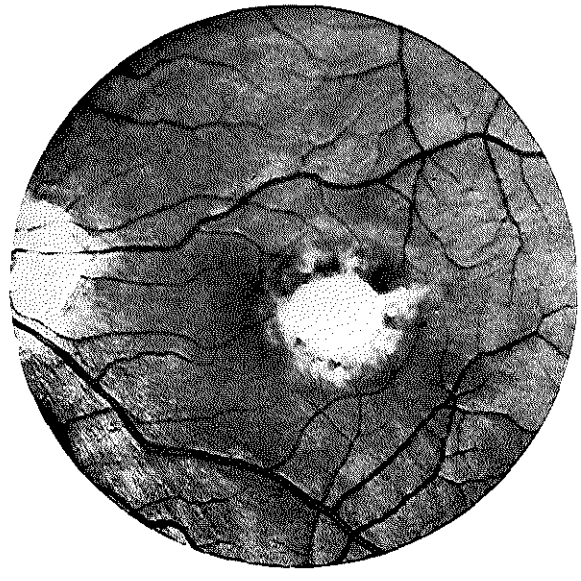


Fig. 12a-b. Vitelliform lesions resembling scars of central choroiditis (Fam. Vr). In this case a diagnosis of toxoplasmosis was initially made.

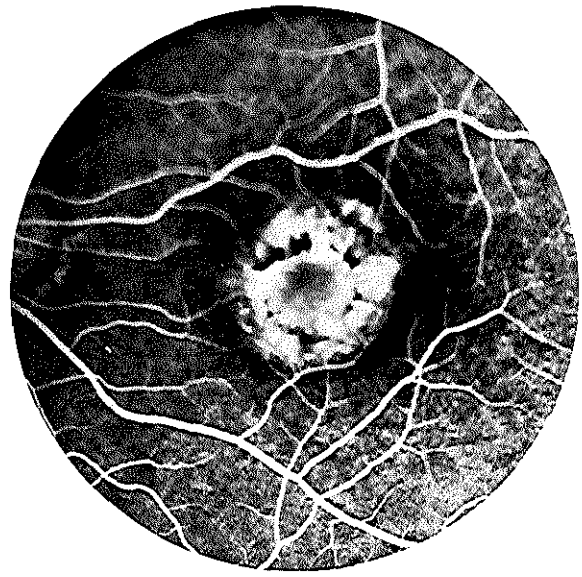


Fig. 12c. Fluorescein angiography of the left eye reveals a central defect of the pigment epithelium. This defect is not larger than is suggested by normal ophthalmoscopy.

Fig. 12d. There is after-fluorescence (after the clearance of the fluorescein from the retinal vessels) but not leakage of fluorescein. This suggests a normal Bruch's membrane.

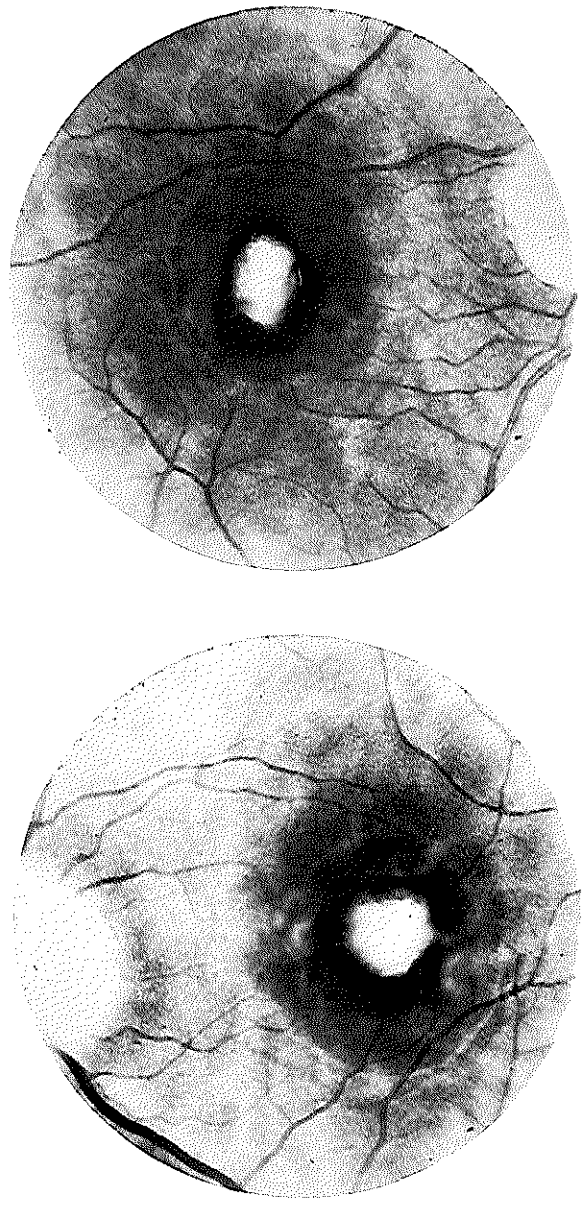


Fig. 15a-b. Vitelliform lesions in a 15-year-old boy. In this case also a diagnosis of toxoplasmosis was made despite normal serology (Fam. Vr).

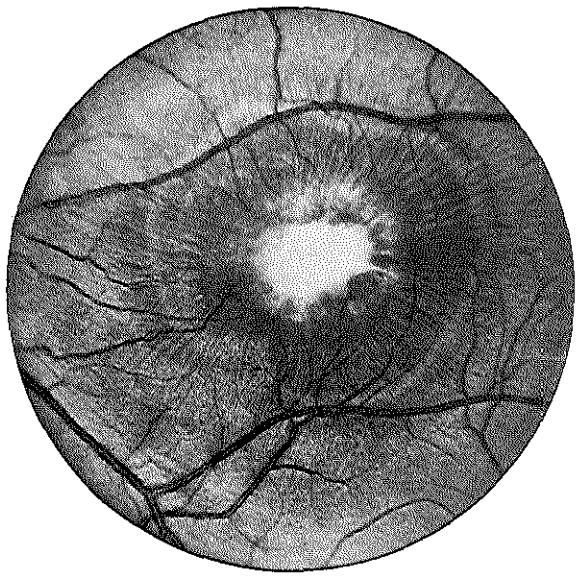


Fig. 14. Delicate folding of the internal limiting membrane around a slightly prominent vitelliform disc (Fam. WA).

pathological changes were very slight: both women showed only a small yellow-white spot at the site of the foveola (fig. 9).

The literature shows that the classical vitelliform lesion is most frequently observed between age 3 and age 15, with a maximum at about age 6. Since most children start attending kindergarten at age 4 (vision is usually examined periodically at schools), this fact need not be conclusive of the age of onset. Even in the presence of a vitelliform lesion, vision is initially good, and the time of onset can therefore not be determined on the basis of visual acuity.

The possibility that a vitelliform lesion occurs in senescence cannot be ruled out, theoretically. This is why a classification of posterior pole dystrophies on the basis of the age of onset is untenable. Apart from ophthalmoscopic examination at normal visual acuity, the foveal abnormality can be detected also in a patient with diminished vision. More or less acute diminution of vision in patients with VFD can occur in several different ways:

1. due to rupture of the vitelliform cyst, causing cyst contents to emerge and cause damage to the photoreceptors. The consequences of a rupture are clearly visible in patient IV-1, fam. B-E (fig. 10); part of the vitelliform structure is still intact, while another part has ruptured;
2. due to intravitelline haemorrhage (fig. 11) (III-2, fam. Pl);
3. without any ophthalmoscopically visible changes in the existing picture, e.g. in V-19 and V-20, fam. Vr (fig. 12, 13).

In these patients vision returned to the initial level after some time. At the out-

patient clinic we also saw several patients (e.g. V-3, fam. W.A.) with acute irreversible changes in vision, without any changes other than the already observed vitelliform structures.

In most cases, therefore, the ophthalmoscopic picture gives no information on vision. This is quite apparent in patient V-3 fam. W.A. This young man showed more or less identical structures in both foveae but vision was 10/10 OD and 1/10 OS.

Metamorphopsia can occur at the time of diminution of vision, but it is rarely as pronounced as that in chorioidiopathia centralis serosa. The same applies to hypermetropia.

It is worthy of note that one of our patients (V-7, fam. Vr) perceived light flashes in one of his eyes in the dark at the time of occurrence of the vitelliform disc. This patient was already known to show dubious changes in the posterior pole (fig. 7a), with a highly pathological EOG. About a year after the last examination at which no vitelliform structure had been visible in the fovea, the patient complained to me about light flashes in his left eye. To my surprise, I found a classical, intact vitelliform lesion in both foveae (fig. 7b).

3. FUNDUS (OPHTHALMOSCOPIC FEATURES)

In most cases VFD is a bilateral abnormality, but unilateral cases have been frequently described, both in young people and in middle-aged indiviuals (Best 1905; Huysmans 1940; Berkley and Bussey 1949; Bruna 1951; Zanen and Rausin 1951; Capalbi 1954; Zanen and Hermans 1961; De Walsche 1963; Braley and Spivey 1964; Remky et al. 1965; Krill et al. 1966; François 1968; Deutman 1969).

De Walsche (1963) described a 56-year-old woman and Zanen and Hermans (1961) an 11-year-old boy with unilateral VFD; this illustrates that unilateral changes can be found early as well as later in life.

There are many exact descriptions of the classical vitelliform structure. The fovea encompasses an egg-yellow (sometimes orange or pinkish red), round, slightly elevated structure surrounded by a somewhat darker border. The retinal vessels take an undisturbed course past the edge of this disc (the size of which is 0.5-3 optic disc diameters), which shows an unmistakable resemblance to the intact yolk of a fried egg or to a tinned peach half (fig. 1).

Very often this classical structure is not seen at the time of examination, and our impression is that in some cases this characteristic picture never occurs.

Our study of 98 ophthalmoscopically affected individuals shows that the pictures found range from an exceedingly slight change to a condition resembling the terminal stage of extensive chorioretinitis. Moreover, the carriers of the pathological gene can show a normal fovea, or a fovea with a not obviously pathological, more or less non-specific macrogranular appearance.

In several cases we found as the first sign of VFD a very small yellow-white spot (fig. 15), developing into a small yellowish disc, sometimes exactly in the foveola

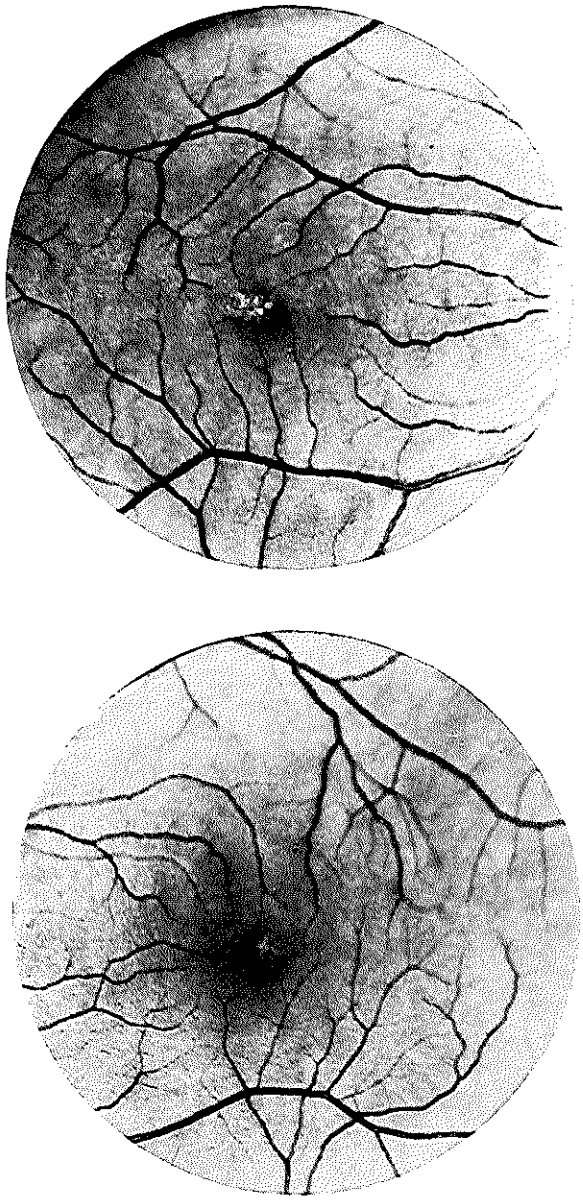


Fig. 1 a-b. Mild foveal alterations in a 48-year-old female suffering from vitelliform dystrophy (Fam. Ko-K). This individual is the mother of the boy whose fundi are depicted in fig. 1.

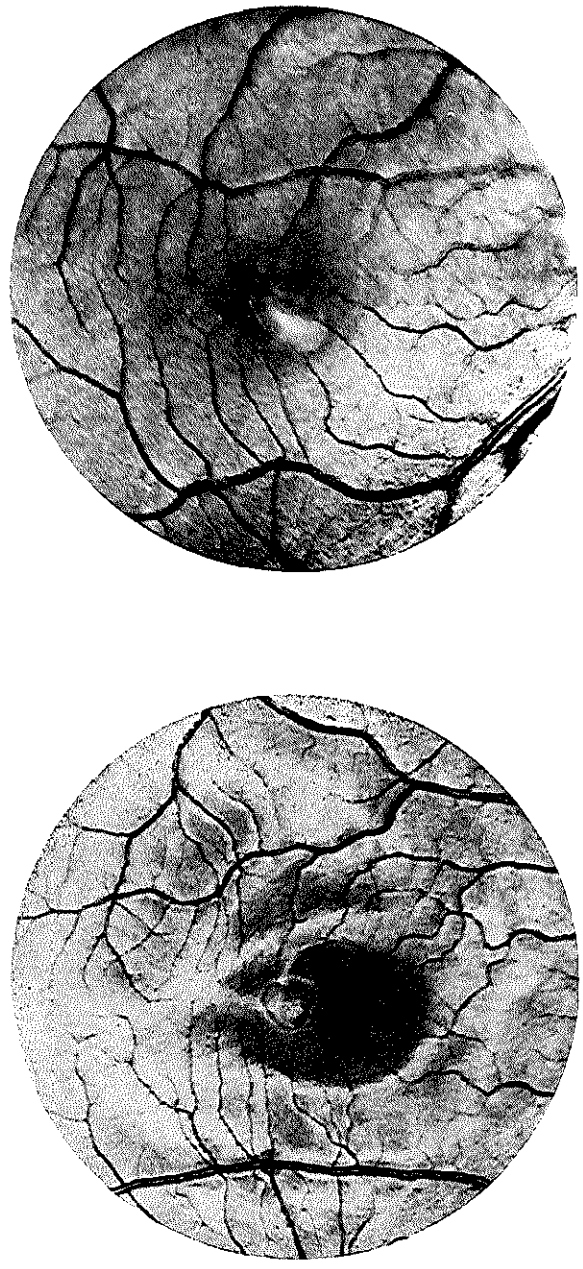
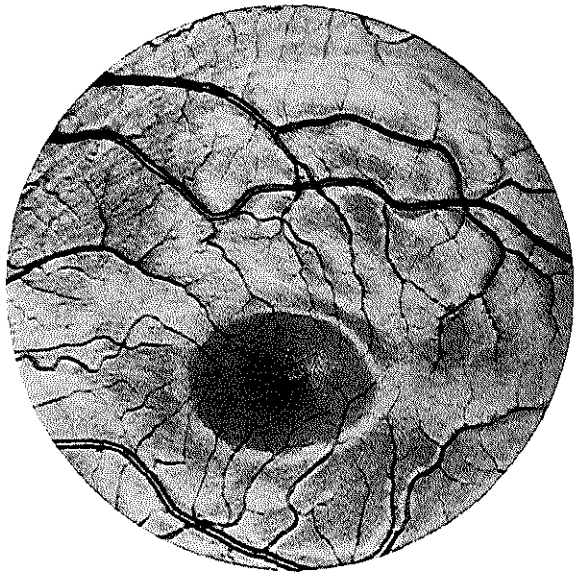


Fig. 16-17. Foveal changes in the "previtelliform stage". These lesions were found during examination of families of patients with true vitelliform lesions (Fam. WA; Fl and Ko-K).



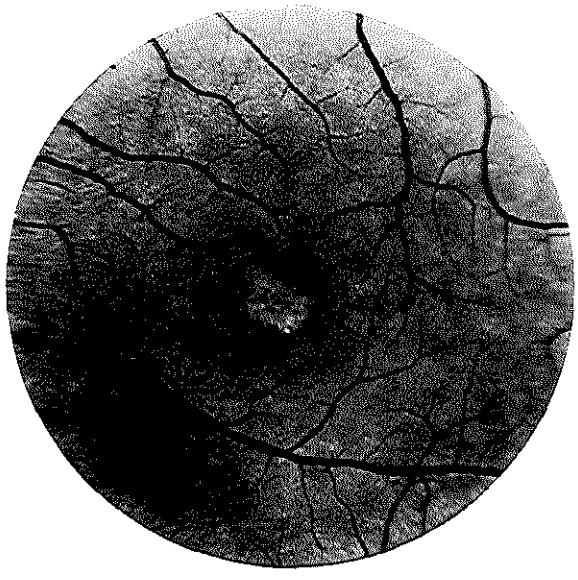


Fig. 18-19. Foveal changes in the "previtelliform stage". These lesions were found during examination of families of patients with true vitelliform lesions (Fam. WA; Fl and Ko-K).

but at other times eccentric (fig. 16, 17). This disc can become a vitelliform lesion, but in some cases several drusen-like or spotty configurations occur (fig. 18, 19). In many cases, however, the egg-yolk lesion does make its appearance.

The age of occurrence of this vitelliform stage is usually between age 3 and age 15, according to the literature and our personal observations. We observed the egg-yolk in 9 patients whose respective ages were 6, 6, 7, 7, 9, 44, 19, 13, and 9 years (V-13 fam. BE; IV-2 fam. WE; IV-15 fam. T-T; IV-17 fam. Fl; IX-6 fam. Ko-K; V-7 fam. Vr; III-2 fam. Bl; III-4 fam. Bl; III-6 fam. Bl).

Friedenwald and Maumenee (1951) observed the vitelliform stage in a woman aged 42 and in a middle-aged man.

The vitelliform lesion is not always found in the exact centre of the retina; this is quite apparent in the multiple vitelliform structures (Littann 1965; Denden 1966). Extrafoveally localized vitelliform structures were also described by Galeazzi (1939) and Calmettes and Deodati (1962). Our patients V-7 fam. Vr and II-7 fam. KZ likewise showed eccentric vitelliform changes (figs. 7 and 20).

The vitelliform lesion can be slightly more prominent than the surrounding pigment epithelium, but this causes only a slight prominence (rarely exceeding 1 dioptre) of the retina in front of it. As a result, a delicate radial pattern of streaks can occur around this structure (fig. 14, 21).

Binocular contact lens examination indicates the likelihood that the egg-yolk is localized in the pigment epithelium (fig. 22). The fact that the yellow of a fully developed, intact vitelliform disc is so clearly visible, indicates that the pigment epithelium cannot be entirely intact in front of it. The fact that vision is usually normal at this stage proves that het neuroepithelium is still intact. A dark border surrounds the disc and marks the boundary between egg-yolk and pigment epithelium. The yolk proper admits little light, but it is clearly visible that a yellowish, homogeneous substance, hardly prominent if at all, lies immediately beneath the retina, that is to say: probably in the pigment epithelium. No true cyst is visible at this stage, and this is why in the early stages of VFD we use the designation "vitelliform disc" (Zanen and Hermans 1961).

Optic disc, retinal vessels and retinal periphery are nearly always quite normal in patients with VFD. So far as can be established, the choroid shows no abnormality. Occasionally, several vitelliform structures can be found in the posterior pole (fig. 7, 20), and in a fair number of cases the fundal periphery shows a granular appearance which cannot be identified as a distinctly pathological change (fig. 23). In one patient (IV-19 fam. UT) we found peripheral areas of pigmentation and depigmentation (fig. 24). The classical vitelliform lesion is not irreversible but may persist more than a year before it begins to show distinct changes.

As a rule there is disintegration; the contents of the yolk show fragmentation, possibly as a result of syneresis of pigment epithelium cells that have become necrotic (fig. 25). The yolk may even disappear, whereupon the fovea resumes a virtually normal appearance (Zanen and Hermans 1961; Bischler 1952). We ourselves observed complete disappearance of a vitelliform structure in two cases (II-7 fam. KZ;

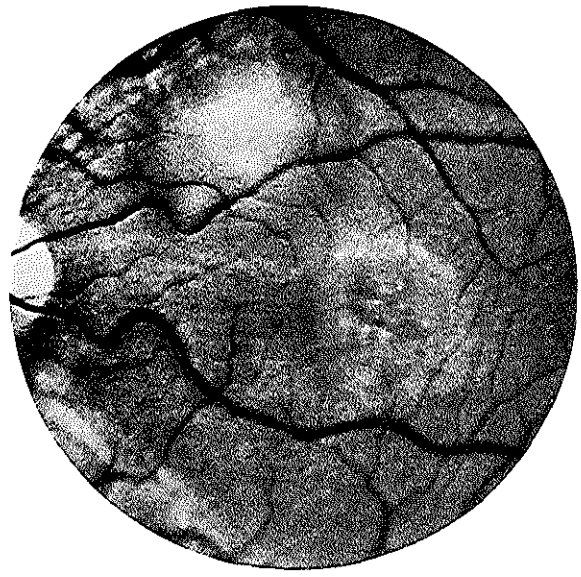


Fig. 20a. Two vitelliform lesions in the eye of a female in her thirties (Fam. K-Z). At the fovea an atrophic lesion. On the superior nasal side of this lesion an intact vitelliform disc.

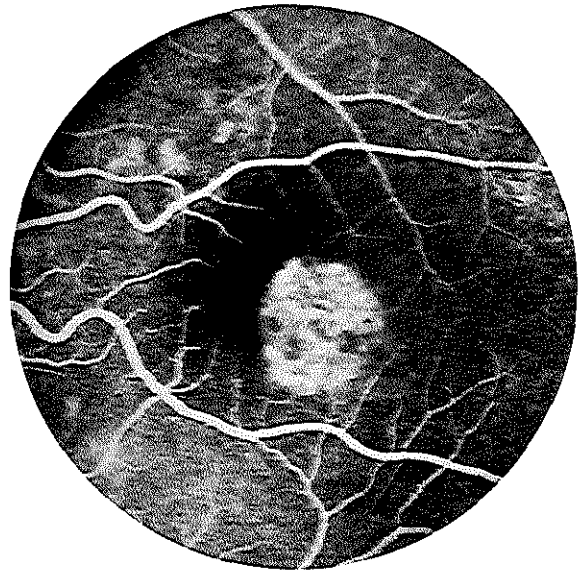


Fig. 20b. Fluorescein angiography shows pathological fluorescence mainly at the site of the fovea. Some spots of increased fluorescence are visible at the site of the intact vitelliform disc. This suggests slight defects in the retinal pigment epithelium.

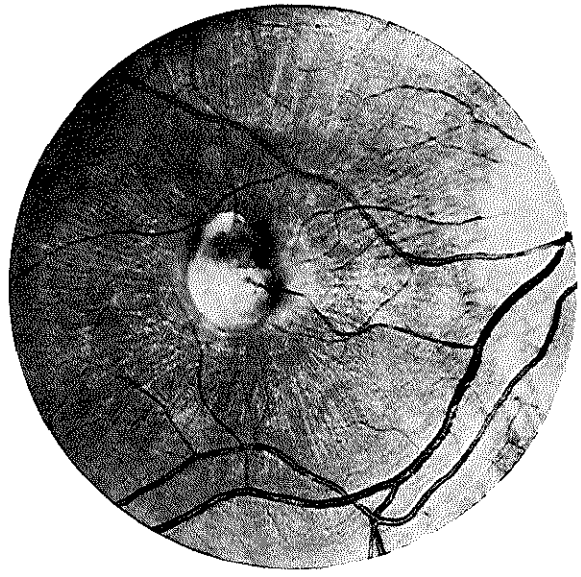


Fig. 21. Vitelliform lesion in an 18-year-old boy. Note the fine folding of the internal limiting membrane. In the other eye this boy developed an anterior disinsertion of the retina (Fam. UT).

V-13 fam. BE). The vitelliform abnormality can recur after such a regression (Zanen and Hermans 1961; Franceschetti et al. 1963).

Regression of the vitelliform lesion to an ophthalmoscopically normal fovea can be explained both by metabolic processes in the pigment epithelium and by absorption from the choriocapillaris. As a rule the vitelliform disc develops into a cyst, in which vitelliform remnants can still be observed (fig. 26). If the egg metaphor is to be continued, this stage can be described as "scrambled egg" stage. At the site of disappearance of the egg-yolk one often observes atrophic pigment epithelium with the choroid (redder than adjacent parts) shimmering through (fig. 27).

A different course is also possible. The contents of the yolk can become subject to syneresis, giving rise to a cyst with a fluid-level (fig. 28). Because of the striking resemblance to a hypopyon, this stage is sometimes called pseudo-hypopyon stage. There may also be pseudo-descemet mottling on the posterior aspect of the cyst's anterior wall, the retina (Pameyer 1954).

Remky et al. (1965) clearly demonstrated the liquid character of this pseudo-hypopyon by photographing a patient's fundus in different positions. This pseudo-hypopyon stage is most commonly encountered between age 30 and age 40 (Remky et al. 1965). The cyst can rupture, with proliferation of pigment epithelium as a result, which may produce marked pigmentations.

The resulting clinical picture (fig. 29) can be readily confused with a cicatrix of chorioretinitis centralis (fig. 30).

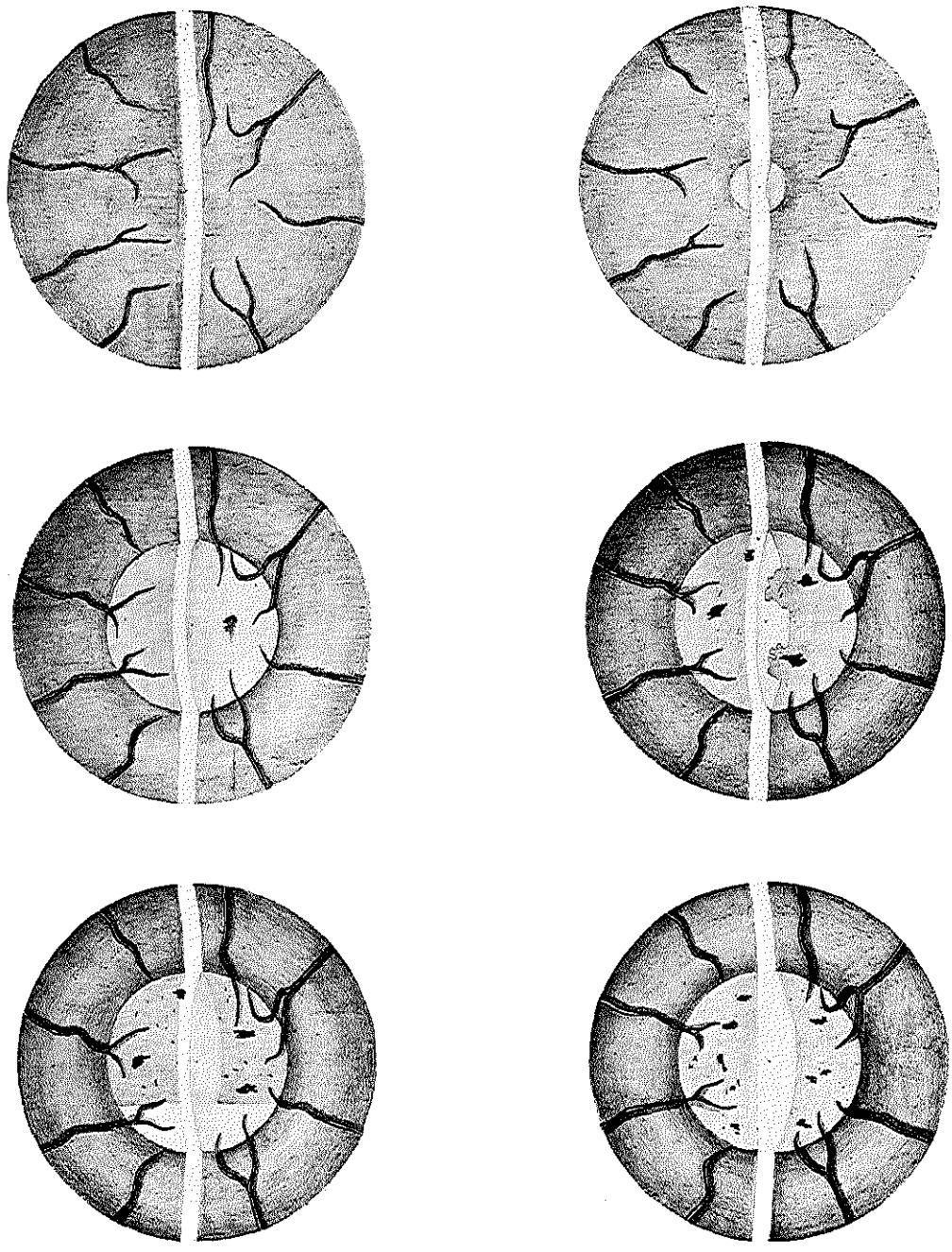


Fig. 22. Schematic drawing of six different stages of the rise and fall of the vitelliform disc (binocular slitlamp-examination).

a. normal fovea, pathological EOG
b. minimal foveal lesion
c. intact vitelliform disc
d. ruptured vitelliform disc
e. pseudo-hypopyon (vitelliform cyst)
f. atrophy of the centrəl retina.

Fig. 23. Fine mottling of pigment as is often seen in the retinal peripheries of patients with vitelliform dystrophy (Fam. WA) (panchromatic film).

Fig. 24. Area of pigmentation and depigmentation in the retinal periphery of a 21-year-old male with vitelliform dystrophy.

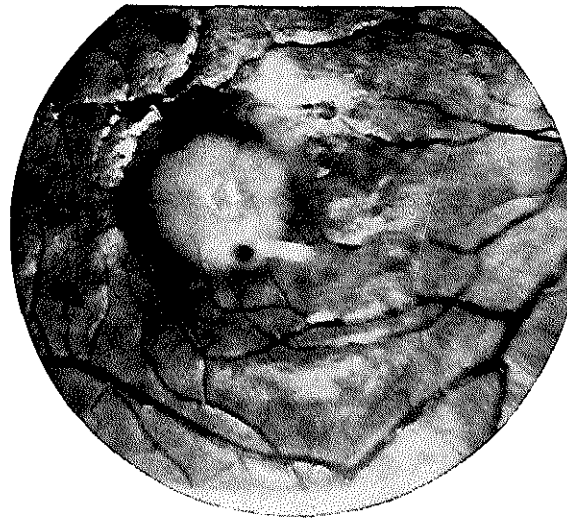


Fig. 25a. Intact vitelliform disc in a 6-year-old boy (Fam. E-W).

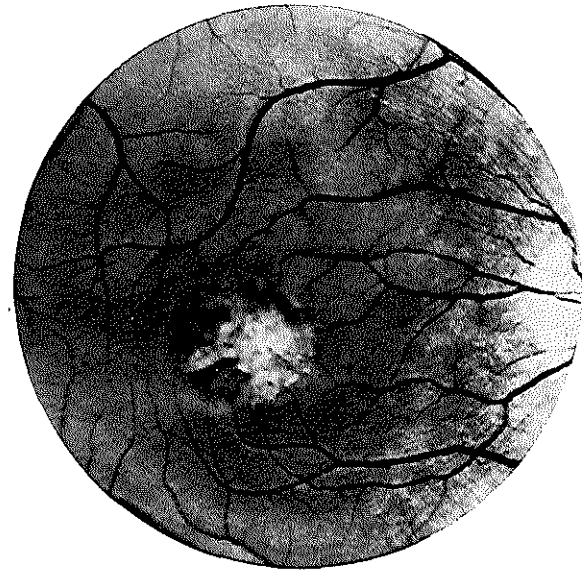


Fig. 25b. The same eye 6 years later. The disc is disintegrated (Fam. E-W).

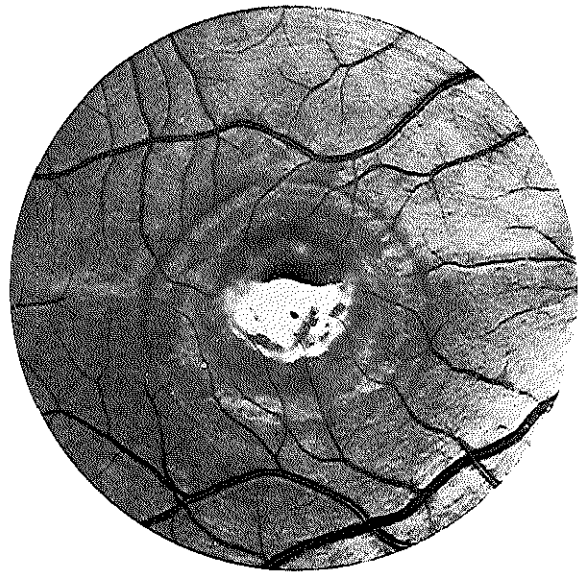


Fig. 26. Vitelliform cyst in a 24-year-old male (Fam. Ko-K).

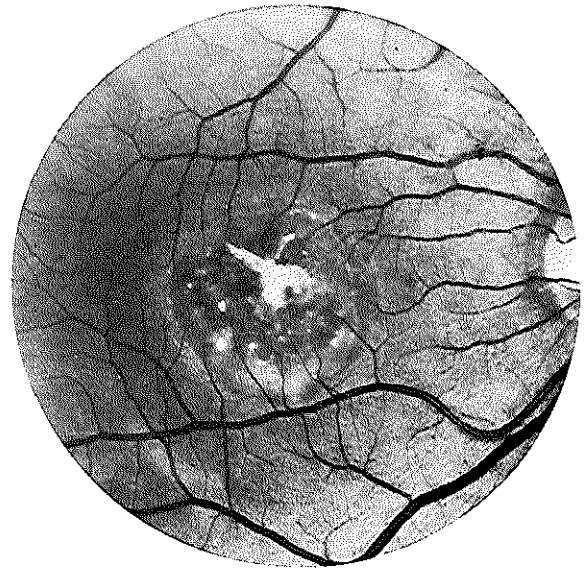


Fig. 27. Vitelliform cyst with yellowish-white deposits in a 52-year-old male (Fam. Fl).

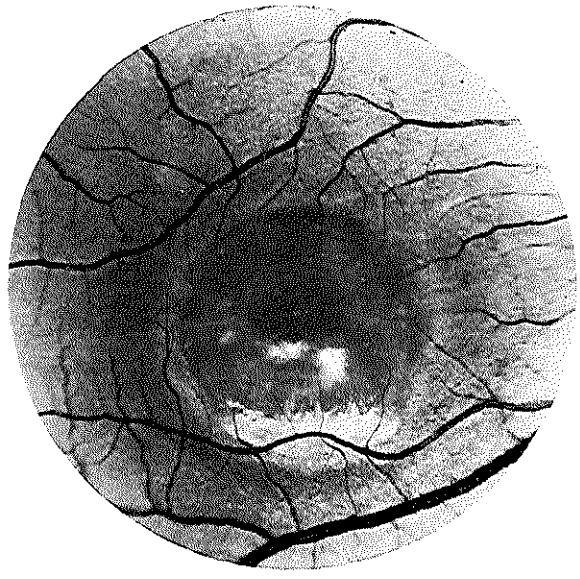


Fig. 28. Pseudohypopyon-structure in a vitelliform cyst in the eye of a 37-year-old female (Fam dB).

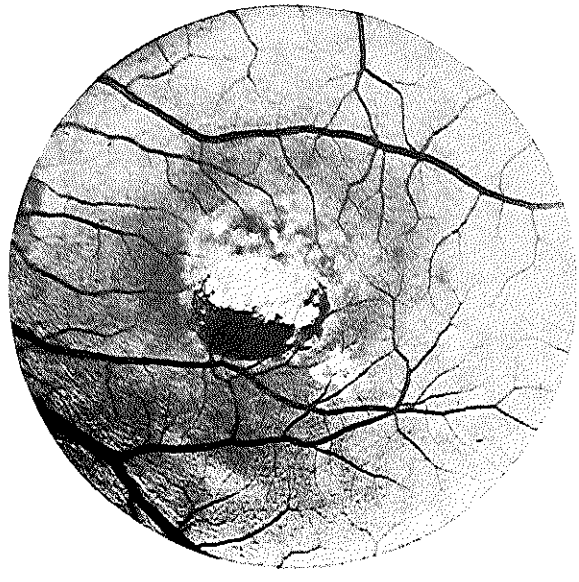


Fig. 29. Severe pigmentations at the bottom of a vitelliform lesion in a 52-year-old male (Fam. Fl).

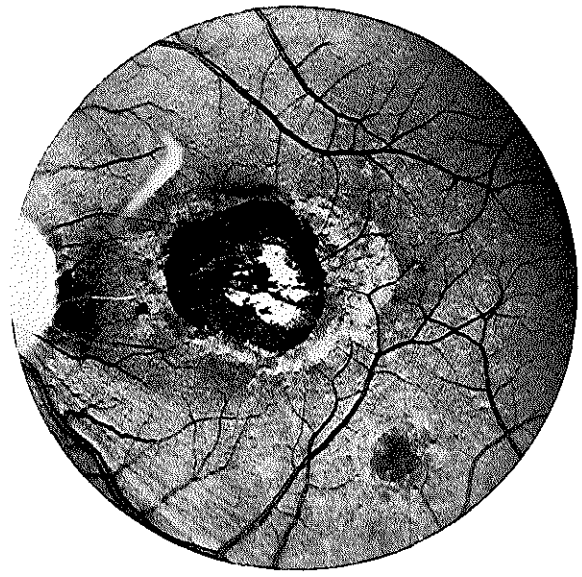


Fig. 30. Scar of central choroiditis in the foveal area. Note the small scar infratemporally from the fovea.

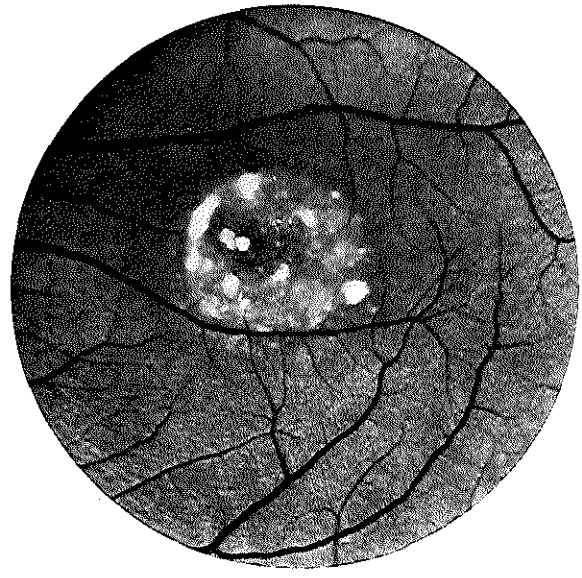


Fig. 31. Multiple deposits in a round area of atrophic pigment epithelium in a 41-year-old male suffering from vitelliform dystrophy (Fam. Vr).

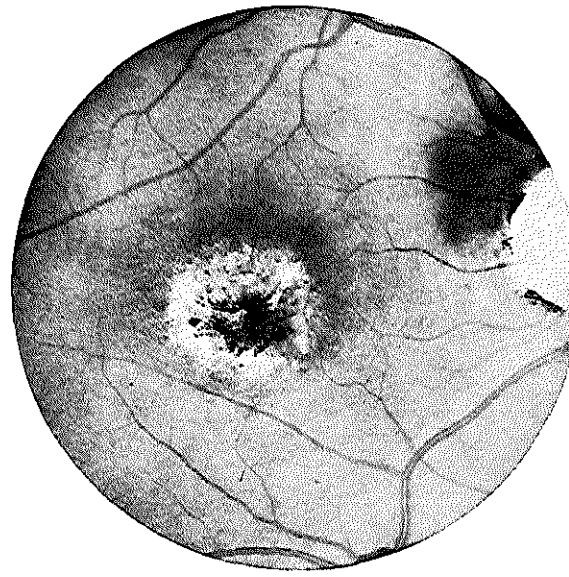


Fig. 32. Distinct pigmentations in a vitelliform lesion necessitating differential diagnosis with central choroiditis. There is also a pigment naevus near the disc (Fam. UT).

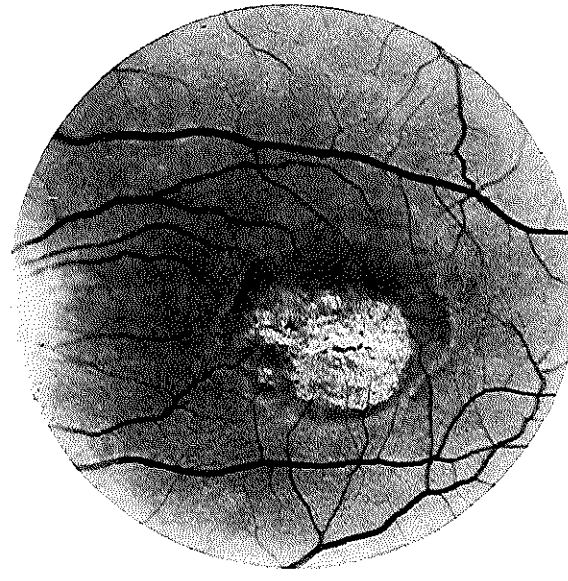


Fig. 33. Atrophic foveal area with a delicate honeycomb structure in a 54-year-old female with vitelliform dystrophy (Fam. Vr).

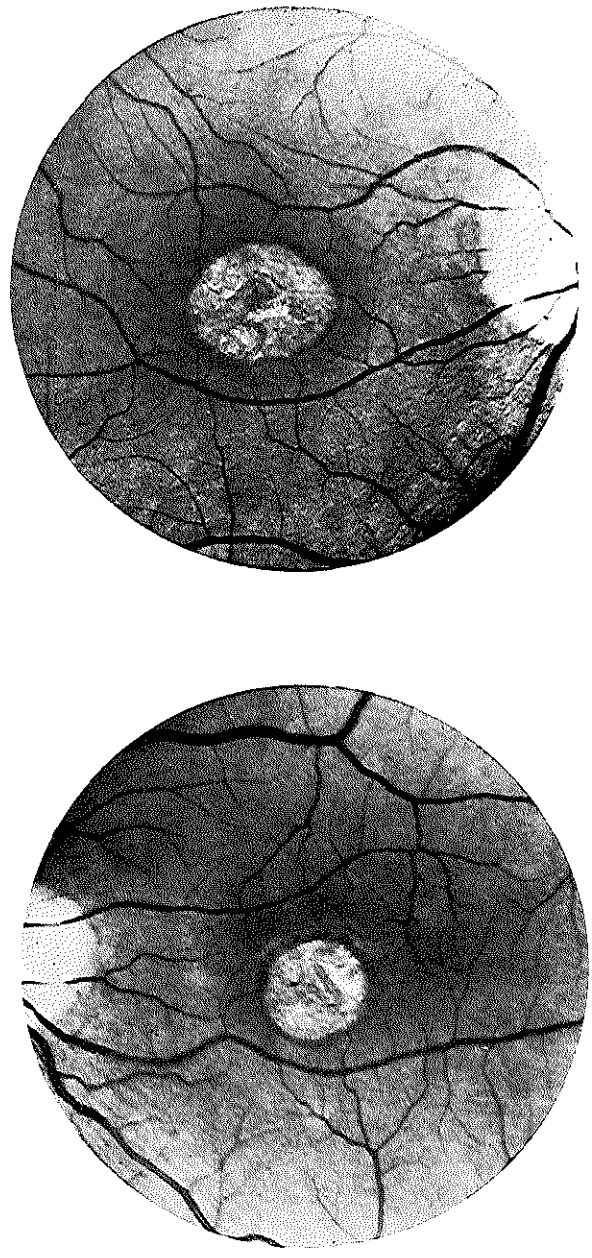


Fig. 34. Well defined area of retinal atrophy in both eyes of a 73-year-old male with vitelliform dystrophy (Fam. UT).

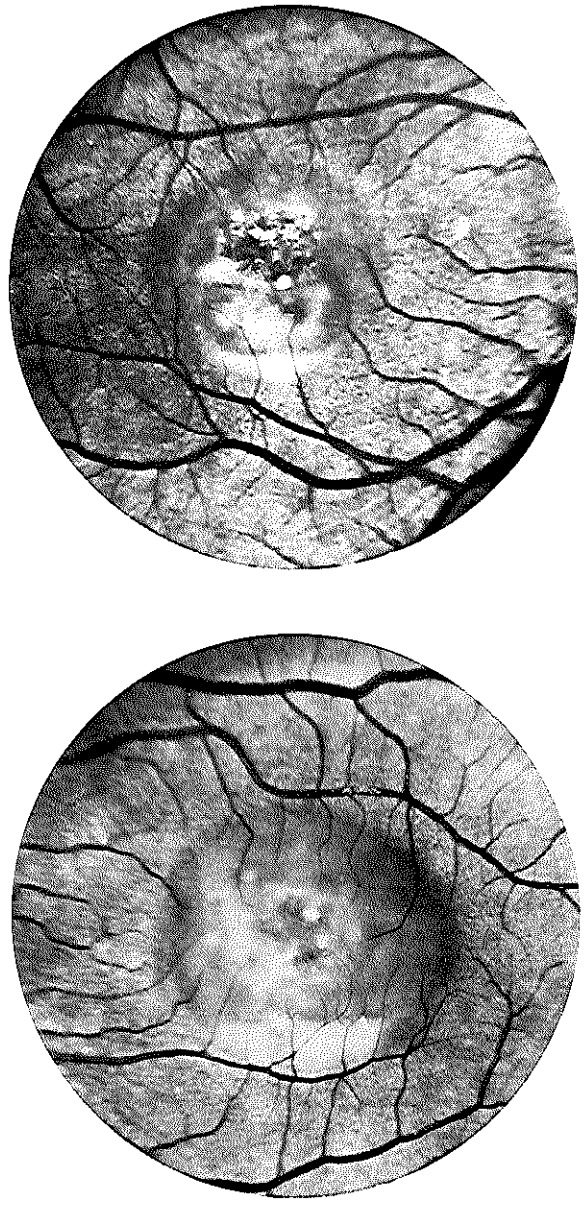


Fig. 31a-b. Vitelliform cysts with pseudo-hypopyon aspects. Note the differences in size of the vitelliform cysts in the right and left eye (Fam. UT).

In a few cases there may be haemorrhages deep in the retina at the site of the vitelliform lesion (Mazzi 1934; De Walsche 1963; Braley 1966). We ourselves observed this in only one case (III-2 fam. Pl; fig. 11). These haematomas are absorbed in the course of a few weeks. We believe that the occurrence of haemorrhages points in the direction of a no longer quite intact Bruch's membrane and/or choriocapillaris. But in initial stages these haemorrhages are never seen, and on this basis a primary affection of the choriocapillaris and/or Bruch's membrane can be practically ruled out.

The vitelliform lesion ultimately results in a circular area of atrophic pigment epithelium in which yellow lumps can become manifest (fig. 31). There are sometimes fairly pronounced pigmentations (fig. 32), although in many cases these are absent (fig. 33). One of the patients in whom we saw this was a 74-year-old man (II-6 fam. UT), who showed a circumscribed area of pigmental epithelium atrophy and an atrophic choroid (fig. 34).

Many authors, including François (1967) and Krill et al. (1966) maintain that, after disintegration, the foveal features are indistinguishable from those in other affections. Although we could confirm this in incidental cases, our study has convinced us that in most cases the foveal abnormality retains its typical characteristics in which the basic vitelliform process can still be clearly recognized up to a very advanced age. We observed this in several patients (II-6 fam. UT; III-8, IV-5,V-6 and V-9, fam. Vr). The circular central atrophy of the pigment epithelium remains a characteristic feature of the vitelliform dystrophy until advanced age (fig. 34).

In summary, and in a strictly schematic way, the evolution of VFD can be described as follows:

1. normal fovea (but already a pathological EOG) (fig. 41);
2. previtelliform stage (fig. 15);
3. vitelliform stage (fig. 1, 42b);
4. "scrambled egg" stage (fig. 26, fig. 42a).
5. cyst stage (fig. 27);
6. pseudo-hypopyon stage (fig. 28, 35);
7. chorioretinal atrophy stage (fig. 33, 34).

The development of VFD can skip several of these stages, and various transitional forms of course occur.

Although VFD is usually bilateral, a perfectly symmetrical fundus picture is rarely seen. There may be substantial differences between OD and OS, both ophthalmoscopically and in terms of visual acuity (figs. 35, 36).

4. REFRACTION

Pronounced hypermetropia with astigmatism is often found in patients as well as their relatives; convergent concomitant strabismus with amblyopia is also often observed. Practically all authors mention hypermetropia (Best 1905; Behr 1920; Huysmans 1940; Sorsby 1940; Berkley and Bussey 1949; Falls 1949; Zanen and Rausin 1951; Capalbi 1954; Pameyer 1954; McFarland 1955; Sorsby et al. 1956;

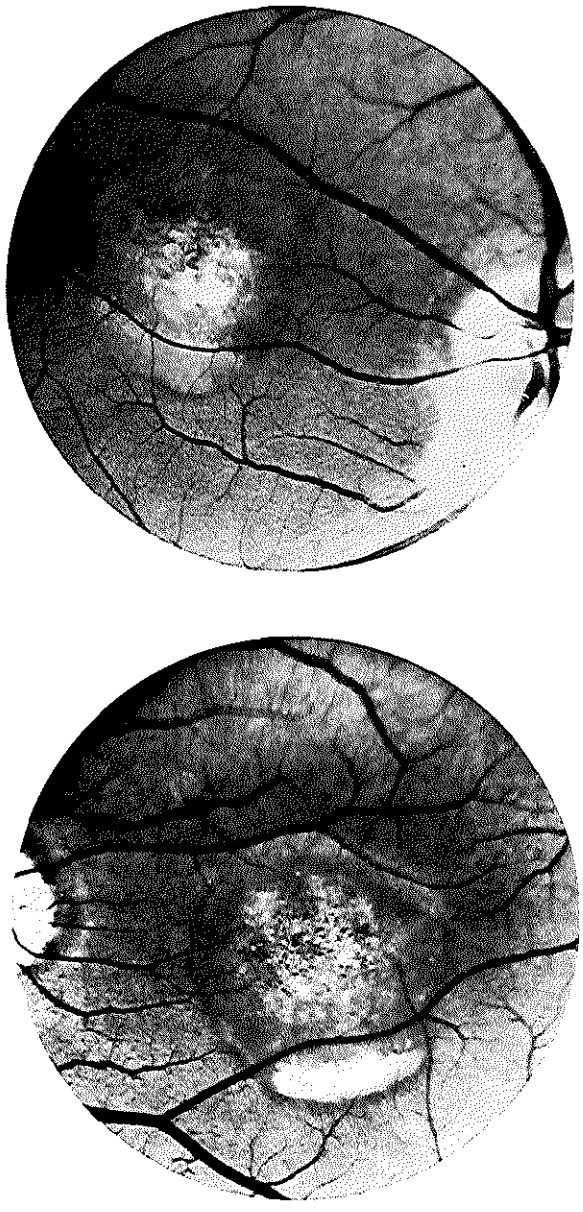


Fig. 36a-b. Vitelliform cysts with pseudo-hypopyon aspects. Note the differences in size of the vitelliform cysts in the right and left eye.

Gregory 1958; Chinaglia and Perini 1964; Braley and Spivey 1964; Melodia and Tabacchi 1965; Spinelli and De Molfetta 1965; Remky et al. 1965; Hermann 1966; Belmonte 1966; Krill et al. 1966; Gorgone 1967; Curry and Moorman 1968; and others).

Yet this hypermetropia is not an obligate finding. In one patient we found slight myopia (IV-2 fam. EW). Bonnet et al. (1966) saw a girl who developed slight myopia; and Gorgone (1967) saw a myopic girl with a hypermetropic mother, both showing VFD. The pronounced hypermetropia usually found cannot be ascribed to any prominence of the fovea because this is rarely more than 1 dioptre.

There are no marked abnormalities of refraction of the type found in central serous choroidopathy. The commonly observed hypermetropia with strabismus makes it desirable to point out to future parents in these families that their children will have to be examined by the ophthalmologist at a very early age.

5. VISUAL ACUITY

Vision is initially normal or only slightly subnormal, even in the presence of a fully developed vitelliform disc. This often causes surprise. This good vision can only be explained by assuming that the neuroepithelium (i.e. the cones) are initially not involved in the pathological process. Moreover, the functions usually required for good vision, usually show no fundamental disturbances. In spite of the vitelliform structure, therefore, the pigment epithelium which is its site will continue to function fairly well, even at the site of the fovea. A primary disturbance of Bruch's membrane is more likely to give rise to exudates and haemorrhagic processes, as in the case of angioid streaks, Sorsby's pseudo-inflammatory dystrophy and Junius-Kuhnt disciform posterior pole degeneration; in that case there is leakage of fluorescein in fluorescein angiography. But this is never observed in VFD.

If very sensitive methods are used to determine vision, it is probably always possible to demonstrate at least a very slight diminution of vision. Using a photometer and different light intensities with different wavelengths, Zanen and Balsacq (1968) found an unmistakable diminution of foveal sensitivity in a patient with VFD whose visual acuity was still virtually normal. We were able to demonstrate the same in our of our patients (IV-2 fam. EW) with the aid of the Friedman visual field analyser.

As determined by conventional routine methods now in use, visual acuity is in many cases still quite normal or only slightly subnormal in the initial stages; but when the contents of the vitelliform disc begin to disintegrate, vision is seen to diminish.

This diminution of vision can be abrupt (upon rupture of the vitelliform cyst). The contents of the vitelliform structure then emerge and damage the photoreceptors. The cause of diminished vision is sometimes quite apparent at ophthalmoscopy; on the other hand there are many cases without any change at the time of abrupt diminution of vision.

As we pointed out, haemorrhages in the vitelliform structure can also cause abrupt

diminution of vision. It is impossible to predict whether the loss of vision will be reversible or irreversible, but it is conspicuous that loss of vision occurs when general resistance is low, e.g. during illness, after operation or parturition, and also in response to traumatic mental influences.

In the atrophic terminal stage, vision is often as low as 5/60 to 2/10. Many authors report that substantial diminution of vision does not occur until a more advanced age, but we have seen considerably diminished vision at an earlier age (fam.Kl.K). We saw a patient under 20 whose vision was only 0.2 ODS (V-19 fam. V) and a boy of 10 with vision 1/10 ODS (IV-20 fam. UT). Patients with non-specific lesions (yellow drusen-like alterations in the posterior pole) can retain good vision to a very advanced age because the neuroepithelium remains intact.

When the foveal cones are involved, variable patterns of eccentric fixation develop. Hermann (1966) reported "eccentric viewing" but no genuine eccentric fixation in a 7-year-old girl in whom a vitelliform structure developed in the course of 5 years to a lesion with degeneration and pigmented changes. In the long run, however, genuine eccentric fixation does develop as damage of the photoreceptors increases (Graham et al. 1964; personal observations).

6. VISUAL FIELDS

The peripheral boundaries of the visual fields are quite normal throughout all stages of this condition. The central visual field of course shows a diminution of sensitivity, which roughly parallels the loss of vision.

Scotomas occur, initially for red and later for green, followed by relative scotomas for white light; in serious cases an absolute central scotoma can occur. The size of the scotoma is dependent on the size of the vitelliform structure.

A paracentral scotoma is occasionally found in association with paracentral vitelliform structures of the kind sometimes seen in multiple vitelliform lesions.

7. COLOUR VISION

Diminution of visual acuity in VFD is generally accompanied by an acquired disturbance of colour vision. The patient is usually unaware of this, but some patients complain that the colour red is less well perceptible. There are no characteristic disturbances of colour vision. The findings obtained in this respect prove to be largely dependent on the methods used to determine colour vision. Central colour vision shows marked deterioration with increasingly disturbed vision. Krill et al. (1966) demonstrated this quite clearly with the Farnsworth-Munsell 100-hue test.

A wide range of various disturbances of colour vision have been described, but undisturbed colour vision has likewise been reported fairly often (Falls 1949; Zanen and Rausin 1951; Capalbi 1954; Sorsby and Wren 1960; Hermann and Vernin 1963; Franceschetti, François and Babel 1963; Etienne et al. 1964; Hermann 1966; Belmonte 1966; Le Hunsec and Pierre 1967; Tsukahara et al. 1968).

Others have reported a slightly diminished general colour sense without specific axis (anomalous trichromasia) (Falls 1949; Zanen and Lempereur 1954; Zanen and Hermans 1961; Verriest 1964).

Mild red-green dyschromatopsia has been described also (Zanen and Hermans 1961; Grimm and Tedford 1963; Velzeboer 1963; Braley and Spivey 1964; Remky et al. 1965; François et al. 1966; Krill et al. 1966).

Many authors reported anomaloscopic evidence of reduced red sensitivity (Bischler 1952; Sorsby et al. 1956; Zanen and Hermans 1961; Velzeboer 1963; Krill et al. 1966). This corresponds to type II of acquired red-green dyschromatopsia (Verriest 1964). But Braley and Spivey (1964) described type I acquired red-green dyschromatopsia, and Melodia and Tabacchi (1965) established mild deuteranomaly with the 100-hue test. Blue-yellow dyschromatopsia was found in a few cases (Spinelli and De Molfetta 1965; Krill et al. 1966), and blue-green dyschromatopsia was reported by others (Zanen and Rausin 1951; Velzeboer 1963; Melodia and Tabacchi 1965; Krill et al. 1966).

This enumeration shows that a wide variety of disturbances of colour vision can be found. In 23 of the 30 affected subjects we examined for colour vision, we found a more or less markedly reduced red sensitivity (anomaloscope). The HRR test disclosed mild-to-moderate red-green dyschromatopsia in 20 of the 30 individuals examined, and slight blue-yellow dyschromatopsia was observed in only one case. The decrease in red sensitivity was quite apparent at a vision of 0.5 or less. The Farnsworth panel D-15 test revealed a tritan disorder in 8 patients, while a red-green disorder was found in only 2 cases. All the patients with a tritan disorder had a vision of 0.2 or less. Some slight disturbance of colour vision without specific axis (anomalous trichromasia) was observed in 5 patients.

The effect of the vitelliform abnormality on colour vision is perfectly illustrated by the data on our patient IV-19 fam. UT, with a vitelliform lesion and loss of vision to 1/10 OD, and a normal posterior pole, and vision 10/10 OS (table III).

Table III

	Vision	Anomaloscope	HRR test	Farnsworth D-15
OD	1/10	diminished red sensitivity	mild R-G dyschromatopsia	tritan axis
OS	10/10	normal	normal	normal

This case confirms the incorrectness of Behr's original view that the colour vision disorders do not result from the VFD but occur as a concurrent hereditary abnormality.

Our conclusion is that with increasing loss of vision colour vision diminishes on the whole, and that the red receptors in particular are affected. With increasing loss of vision, a subsequent tritan disorder is not uncommon.

8. DARK ADAPTATION

Sorsby et al. (1956) found a slight disturbance of dark adaptation in 2 members of the CNS family, but good dark adaptation in another member of this family. In their HN family – also with VFD – they found good dark adaptation. Braley and Spivey (1964) also described a slightly disturbed dark adaptation curve: "The rod or final phase of dark adaptation was normal in all our instances, both afflicted and normal. However, although the early mesopic plateau was not grossly abnormal, there was certainly a general prolongation of the Kohlrausch kink in those affected".

Unlike these authors, we found an entirely normal dark adaptation curve in 21 of 22 cases studied. In cases of repeated examination, too, we found no anomalies. When vision is poor the streak figure of the Goldmann-Weekers apparatus can be perceived too late, without dark adaptation being pathological.

This possibility should always be borne in mind; in dubious cases the curve should be plotted again by the integral method.

Other authors have also described normal dark adaptation curves (Remky et al. 1965; François et al. 1966, 1967; Krill et al. 1966; Tsukahara et al. 1968).

9. ELECTRORETINOGRAPHY

The ERG is usually normal in VFD (Gallet 1961; Franceschetti, François and Babel 1963; Braley and Spivey 1964; Chinaglia and Perini 1964; Krill et al. 1966; Bonnet et al. 1966; Denden 1966; François 1967, 1968; Tsukahara et al. 1968; Deutman 1969). The critical flicker fusion (CFF) is likewise normal (Braley and Spivey 1964; François et al. 1967, 1968).

François et al. (1967, 1968) did point out that the ERG values of the a- and b-waves were lower than normal, but they defined these values as decidedly within the limits of normal. Braley and Spivey (1964) likewise reported normal ERG's. The a-waves were normal, and failed to show the anomalous slope reported by Ruedemann and Noell (1961). The following features were found to deviate from the normal. "By plotting the amplitude of the b-wave in microvolts against time of increasing dark adaptation at a constant stimulus intensity, it was found that most affected individuals exhibit a slow rise during the first 12 minutes of dark adaptation. At 20 minutes the b-wave amplitude exhibits a very sharp elevation to a level equal to that of the normals. By contrast in the unaffected, the progress is rather rapid to the 12 minute period. They then show proportionally very little increase in the 20 minute stimulus."

We ourselves found normal scotopic and photopic ERG values in 23 individuals (page 432). The photopic a- and b-wave were both normal. In only one man of 77 years (III-8, fam. V) did we find a subnormal scotopic b-wave of the ERG, probably due to senile retinal changes.

Local ERG of the fovea and visually evoked responses

The F-ERG was recorded in 7 individuals. It was normal in association with good

vision, and subnormal when vision was poor (as was to be expected). There was no distinct correlation between vision and F-ERG response, which was probably in part determined by the poor fixation in diminishing vision.

We generally found normal responses at a vision exceeding 4/10, and subnormal responses at lower values. The VER largely parallelled the F-ERG responses. They were normal at a vision exceeding 4/10, and subnormal at lower values.

Biersdorf and Diller (1969), who used a different technique of local foveal stimulation, found a normal foveal response ODS in a patient with VFD whose vision was 20/40 OD and 20/20 OS.

Oscillatory potentials

The literature comprises no reports on the OP in VFD. In 2 patients examined (IV-2 fam. EW; fam. Vr) we found quite normal OP's and we consequently believe that the OP as well as the ERG a- and b-waves are generally normal in VFD.

10. ELECTRO-OCULOGRAPHY

Krill et al. (1966) and François et al. (1966, 1967, 1968) obtained a distinctly abnormal EOG as the sole sign of disturbed retinal function.

The standing potential proper is somewhat low, or normal (François 1966, 1967), but the Lp/Dt-ratio is clearly pathological. We have confirmed this in 40 cases from 12 different families. In none of the patients did the Lp/Dt-ratio exceed 1.50, and 1.65 can be regarded as the extreme lower limit of normal.* Although the EOG can show marked variations in normal subjects (Kelsey 1967), it can be categorically stated that our cases of VFD showed a highly pathological EOG, with in many cases complete absence of a light rise, causing the EOG to take a more or less flat course (fig. 37).

This flat course of the EOG record is characteristic of VFD.

The foveal changes were not very pronounced in 5 of the 40 patients examined.

Like a patient described by François et al. (1967), our own patient with a unilateral vitelliform abnormality (IV-19 fam. UT) also proved to show a highly pathological EOG in both eyes.

A new finding was that carriers of the pathological gene with ophthalmoscopically normal foveae proved to show a highly pathological EOG, like the patients (Deutman 1969). This means that the EOG is a useful aid in the diagnosis of carriers, and is therefore an indispensable method of investigation in genetic counselling. We detected 16 ophthalmoscopically normal carriers of the gene in 5 different families (families TT, K-Z, EW, dB and Vr); in 2 of these 16, slight ophthalmoscopic changes were later observed. If a patient were examined for it at birth it is highly probable that a pathological Lp/Dt-ratio of the EOG would be found.

* The other day we examined a new family with VFD. In this family, there were two affected individuals who showed the comparatively high L/D-ratio of 1.60.

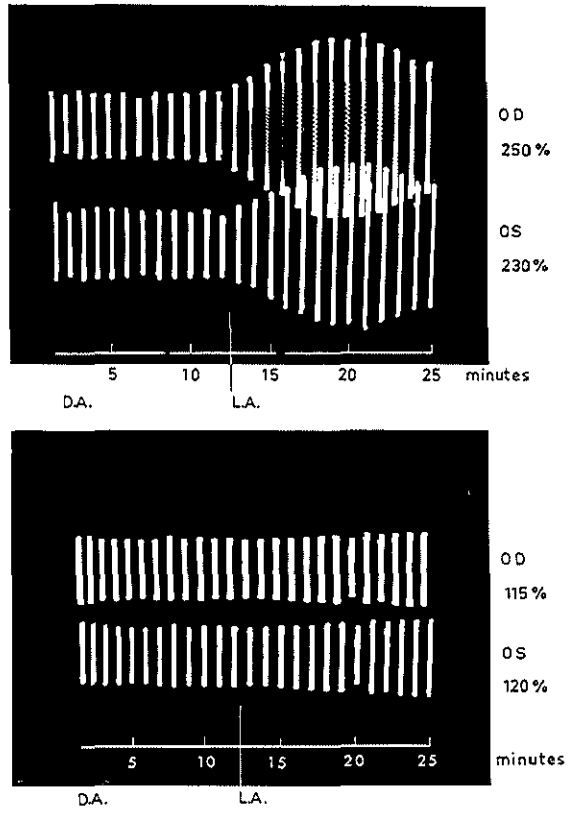


Fig. 37a. EOG bar figure in a normal individual (top) and in a patient with vitelliform dystrophy (bottom).

The cause of this pathological EOG is probably a metabolic dysfunction resulting from a disorder of absence of an enzyme in the retinal pigment epithelium.

The EOG should be regarded as a function test for the entire retina, and a pathological EOG therefore indicates an overall retinal dysfunction.

This means that it is an interesting and unexpected finding to encounter a highly pathological EOG in a condition in which as a rule only the central retina shows any ophthalmoscopic change. The occurrence of multiple vitelliform structures already suggested a diffuse retinal disorder (Littann 1965; Denden 1966). The fact that it is usually only the fovea which shows changes, can be explained by the fact that the fovea has a quite special and highly differentiated anatomical and functional position in the retina. Apart from this, the fovea centralis is a locus minoris resistentiae also in many other affections, e.g. chloroquine retinopathy (Hobbs et al. 1959; Gouras and Gunkel 1963; Butler 1966), phenothiazine retinopathy (Verrey 1956; Rintelen et al. 1957; Alkemade 1968; Henkes 1698; Boet 1970) and senile changes. The fact that the metabolism is probably higher at the site of the fovea centralis than else-

where in the retina may explain the frequent occurrence of foveal changes in an apparently normal retina. Potts (1966) explained the predisposition of the fovea to certain pathological changes on the basis of the vascular conditions in the choroid. This hypothesis is very attractive for cases in which defects in Bruchs' membrane occur, e.g. in central serous choroidopathy, but we believe that it is untenable for the hereditary dystrophies.

In our opinion, the pathological EOG in VFD cannot be explained solely by an affection of the central retina – a possibility considered by François et al. (1967) as well as by Morse and MacLean (1968). An important argument against this view arose from our own study which, among other things, disclosed that the EOG is normal in many other affections of the posterior pole of the eye.

In central serous choroidopathy, central choroiditis and cases of foveal changes on the basis of angioid streaks, we obtained a quite normal EOG (fig. 37b). The EOG is repeatedly quite normal also in many senile foveal degenerations as well as in exudative disciform and dry atrophic processes. However, senile degenerative changes may also give subnormal EOG's.

Another argument against the view that a pathological EOG might be due to the localization of the vitelliform abnormality in the central retina, lies in the fact that ophthalmoscopically normal carriers with no posterior pole affection, likewise show a highly pathological EOG.

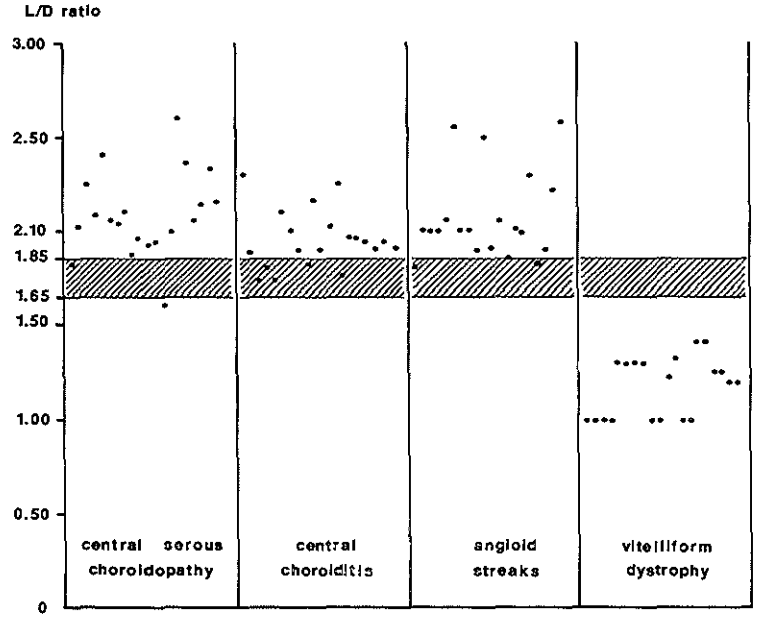


Fig. 37b. EOG-L/D-ratio in individuals with central serous choroidophathy, central choroiditis, angioid straks and vitelliform dystrophy. The results in 10 unselected patients (20 eyes) per entity are presented (every black point means one eye).

The fact that initially the visual acuity, visual fields and colour vision, and ultimately the dark adaptation and ERG remain normal warrants the conclusion that the retinal neuro-epithelium in VFD must be entirely intact, initially and later, except at the site of the fovea. The additional fact that the EOG is highly pathological from the onset in cases of VFD warrants the conclusion that this condition involves a diffuse dysfunction of the pigment epithelium or deeper layers. Since fluorescein angiography shows that the choroid and Bruch's membrane are quite normal, at least in initial stages, we can conclude that diffuse dysfunction of the pigment epithelium exists. This is consistent with the suggestion, based on many exhaustive investigations, that the vitelliform disc must be localized in the pigment epithelium.

II. PHOTOGRAPHY

Interesting findings were reported by Krill et al. (1966), who used a fundus camera modified for monochromatic light. They used wavelengths of 450 mμ (blue), 533 mμ (green) and 675 mμ (red) as light sources. "The blue revealed mainly retinal details not beyond the level of the receptors (where most of the light was probably absorbed); the green light revealed details at a more external retinal level, probably back to the pigment epithelium. The red light penetrated receptors and pigment epithelium and allowed visualization of the choroid. Large deposits of melanin at any level absorbed the red light and appeared black in the photographs."

The red light photographs disclosed the most extensive lesions, and with red light a more homogeneous affection was seen than with white light.

In our photographic study we used orthochromatic and panchromatic graphic films, which have maximum spectral sensitivity at 580 mμ and 595 mμ, respectively (Craandijk and Aan de Kerk 1969).

As expected, panchromatic film showed the changes of pigment epithelium much better than orthochromatic film, not only because of higher sensitivity for the long wavelengths which penetrate deeper into the retina, but mainly as a result of better contrast:

1. The choroidal vessels are best visualized on orthochromatic film, but the choroidal pigment is more clearly visible on panchromatic film (fig. 38).
2. Photographs made of a colour slide with orthochromatic and panchromatic film, show exactly the same differences as do photographs made directly of the posterior pole of the eye.

By using this method, therefore, we were able to detect more indications of the localization of retinal changes in depth.

On panchromatic film the vitelliform structures are visible much more extensively than on orthochromatic film (fig. 38, 39), and the results obtained with this film are therefore comparable with those obtained with monochromatic light. Using panchromatic film, we obtained a result in VFD which was about the same as that obtained by Krill et al. (1966) with red monochromatic light: visualization of the area

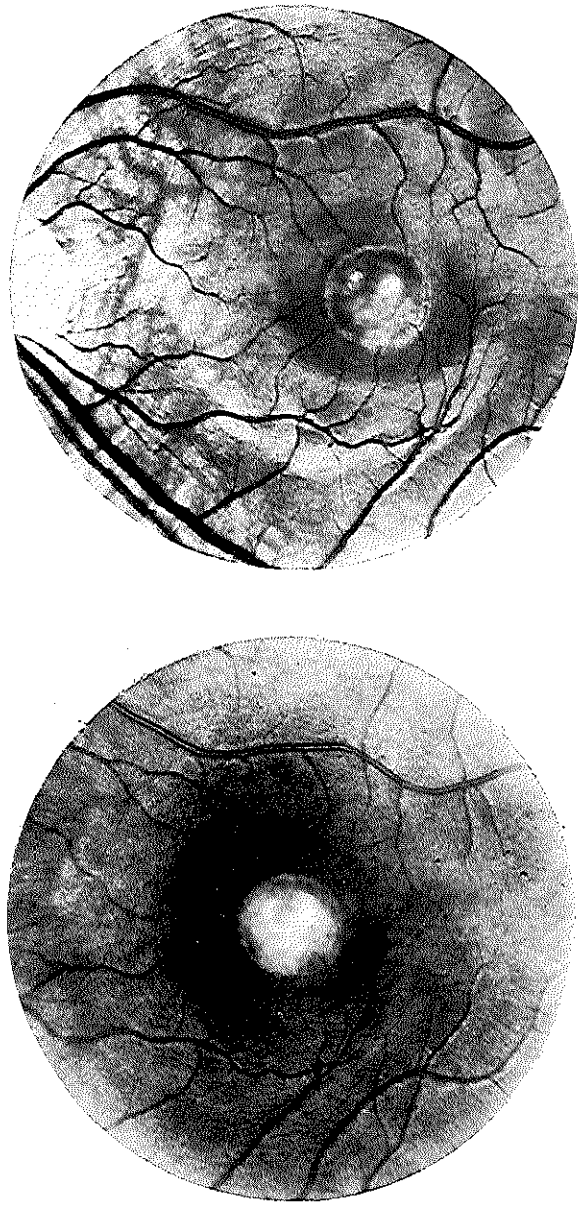


Fig. 38a-b. Intact vitelliform disc, on orthochromatic and panchromatic film respectively (Fam. Ko-K).

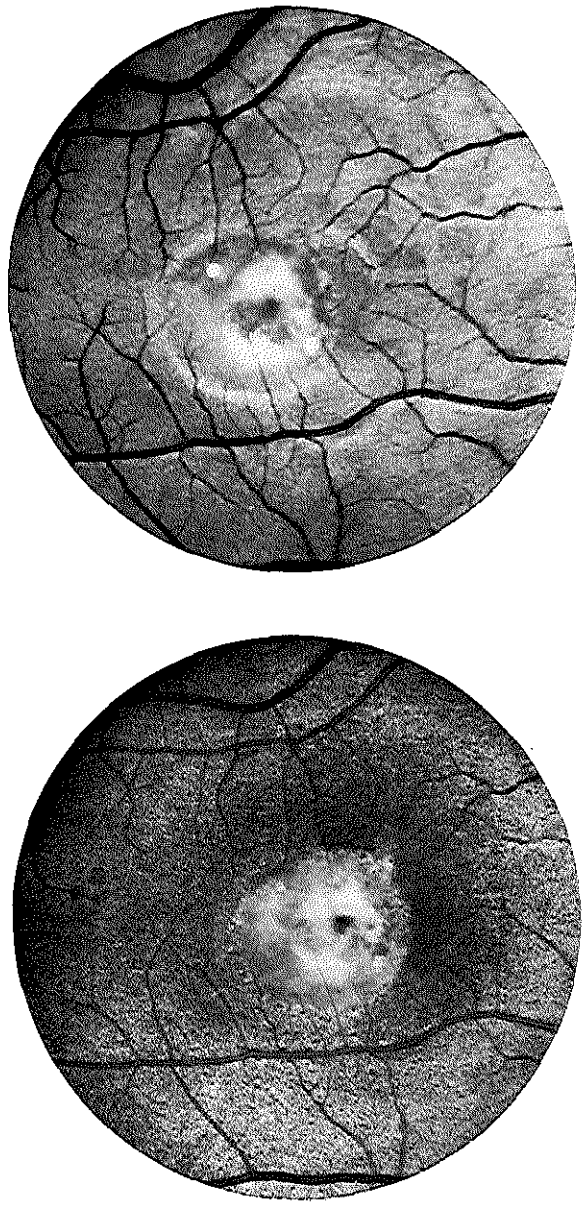


Fig. 39a-b. Vitelliform lesion, on orthochromatic and panchromatic film respectively. The latter gives more details about the pathological structure (Fam. WA).

with the most extensive involvement. These findings argue in favour of a localization of the vitelliform disc in or next to the pigment epithelium.

12. FLUORESCEIN ANGIOGRAPHY

Several fluorescein-angiographic studies have been made of VFD. Martenet (1967) published an excellent photograph of an advanced stage of VFD in a 10-year-old boy, and a fluorescein angiogram of what we believe was a central serous choroidopathy, which she described as VFD.

She observed:

1. marked fluorescence at the time of maximum filling, suggestive of an extensive defect in the pigment layer;
2. increased permeability to fluorescein at the site of the abnormality, possibly due to increased permeability of the choroidal vessels.

The fluorescein pattern was characteristic of that of an old chorioretinitis focus, or that often seen some times after photocoagulation.

Tsukahara et al (1968) assumed on the basis of their fluorescein study that VFD must primarily be a congenital lesion of Bruch's membrane. We cannot accept this, for in fresh vitelliform lesions the fluorescein pattern is quite normal, as shown by Curry and Moorman (1968) and others. They made a fluorescein study of a classical intact vitelliform lesion. Their photographs showed a normal fluorescein pattern. A patient with a vitelliform disc of somewhat longer standing and with ophthalmoscopic features suggestive of pigment layer atrophy, showed slightly pathological fluorescence. These authors maintained that the normal fluorescein pattern in intact vitelliform lesions indicates structural intactness of Bruch's membrane and the pigment epithelium; and we agree with them. Only a very slight defect in Bruch's membrane, with intact pigment epithelium, might possibly escape observation at fluorescein angiography; although it is likely that in that case, as in central serous choroidopathy, fluorescein leakage would occur.

Morse and MacLean (1968) as well as Krill et al. (1968) and François and De Laey (1969) described a fluorescein pattern in VFD which was characteristic of pigment layer defects, without fluorescein leakage being observed. Fluorescein leakage would indicate defects in Bruch's membrane and/or disturbances in the permeability of the choroid. Urrets-Zavalia and Moyano (1969) emphasized a finding which we obtained also: that the fluorescence of the central lesion is intensified (but not increased) after disappearance of the fluorescein from the retinal vessels.

They ascribed this to "increased choriocapillary and pigmentary epithelium permeability", from which they concluded that VFD must be a specific form of central serous choroidopathy. We must reject this conclusion because central serous choroidopathy is a quite different entity (as demonstrated by the EOG), with an entirely different fluorescein pattern. In central serous choroidopathy the fluorescein angiogram shows very localized leakage of fluorescein in the subretinal space, probably as a result of increased permeability of the chorio-capillaris (Gass

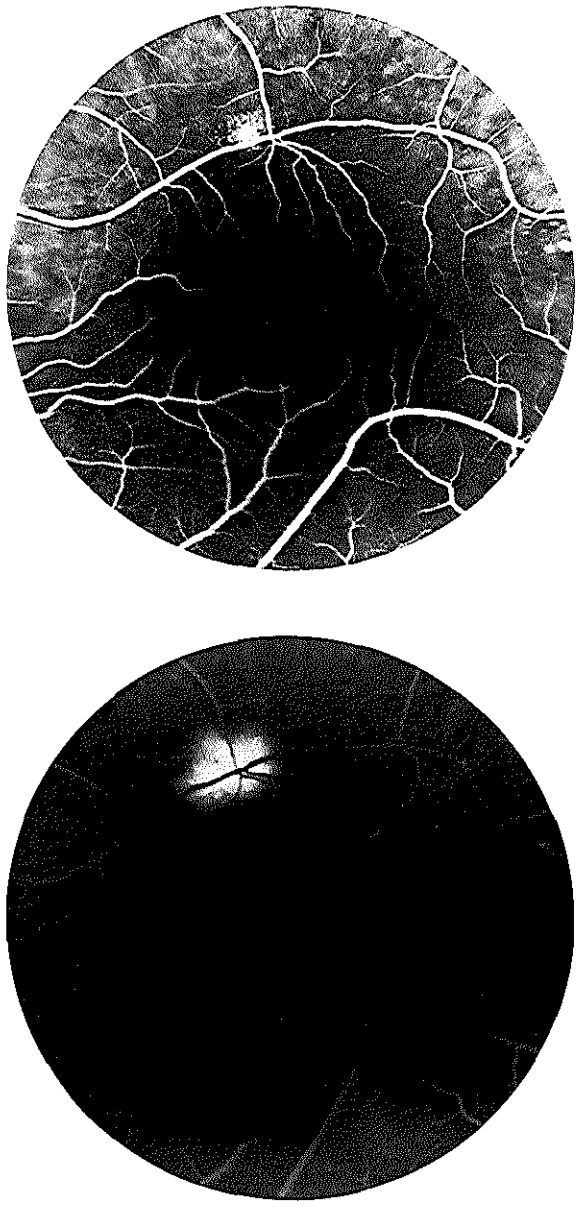


Fig. 40a-b. Fluorescein angiography in central serous choroidopathy, showing leakage of fluorescein through Bruch's membrane.

1967) and/or possibly due to a defect in Bruch's membrane (fig. 40). This leakage of fluorescein can be identified by a fluorescent area which increases in size and intensity and persists after the normal background fluorescence disappears. However, no fluorescein leakage has ever been demonstrated in VFD. Rosen (1969) ascribed the after-fluorescence in VFD to fluorescein absorption by the cyst contents.

In our carriers and patients with VFD we carried out an extensive fluorescein-angiographic investigation, the findings of which can be summarized as follows.

In one carrier (IV-15 fam. Vr) we observed a quite normal fluorescein pattern, and this pattern is also normal or virtually normal in the presence of a fresh vitelliform disc (fig. 41). In one patient with a recently formed vitelliform disc (V-7 fam. Vr), a hardly discernible fluorescence was observed only in the centre of the disc (fig. 7). In another man with an intact vitelliform lesion there was no pathological fluorescence either (Fam. Can.) (fig. 42). In VFD of some longer standing (V-19 fam. Vr) the pigment layer had in part disappeared so that pathological fluorescence was observed (fig. 12). This started in the arterial phase and increased in the venous phase. After disappearance of fluorescein from the choroidal and retinal vessels, a small central fluorescent area remained which gradually diminished in size.

However, the intensity of fluorescence initially increased (fig. 12d). There was no increase in the size of the fluorescent zone, and consequently there was no leakage of fluorescein. Perhaps the contents of the vitelliform cyst absorbed some fluorescein through Bruch's membrane (with or without pathological changes), whereupon the fluorescein spread forward through the "egg-yolk". The yellow-white cyst contents adjacent to Bruch's membrane could absorb fluorescein much as drusen may do (Rubinstein and Paton 1966). It is probable, however, that after-fluorescence is visible because one looks through the pigment layer at the fluorescein normally escaping from the smaller vessels in the choriocapillaris. An increase of contrast might explain the apparently increasing fluorescence of the centre of the vitelliform lesion.

We also obtained fluorescein photographs in another interesting case. A woman (II-7 fam. K-Z) with two vitelliform lesions in the posterior pole (fig. 20) was submitted to fluorescein angiography in 1967. The extrafoveally localized, virtually intact vitelliform lesion which had recently appeared, showed some slight pathological fluorescence, unlike the older atrophic foveal focus which showed the fluorescence that characterizes extensive central pigment epithelium atrophy (fig. 20).

13. CARRIERS

Ophthalmoscopically normal individuals who carry the pathological gene, are regarded as carriers. These individuals are encountered in some families with irregular dominant transmission of VFD. When skipping of a generation occurs, one may assume that a carrier is involved. Sorsby (1967) thought that these carriers differ from normal subjects in that they show microgranular pigmentation of the fovea and its surroundings.

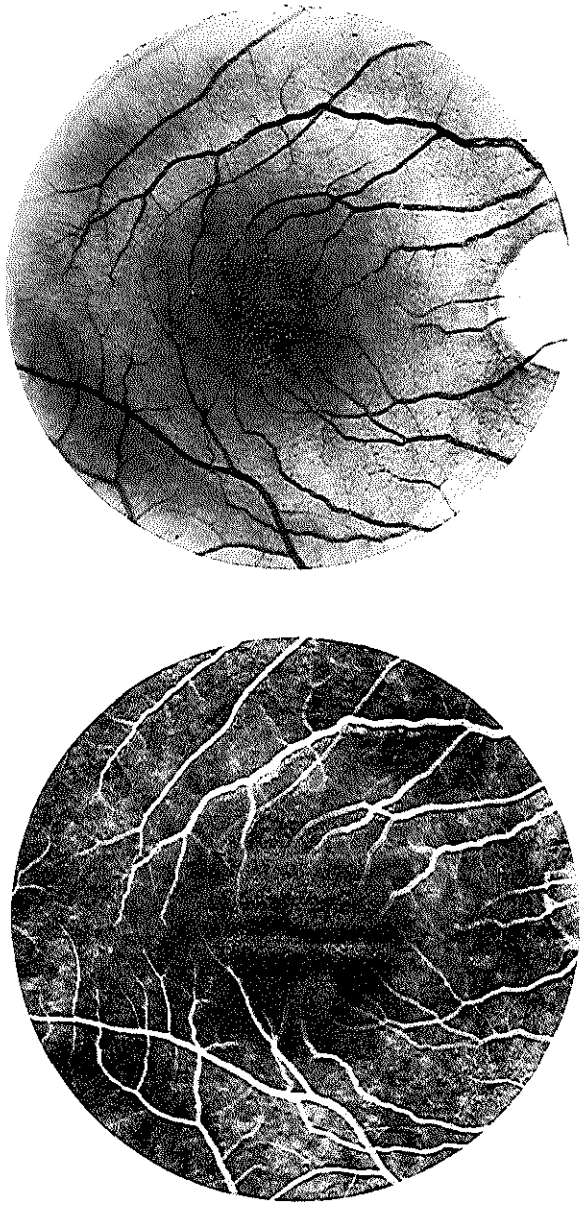


Fig. 41a-b. Conventional and fluorescence photograph of the posterior pole of a carrier of vitelliform dystrophy (Fam. Vr).

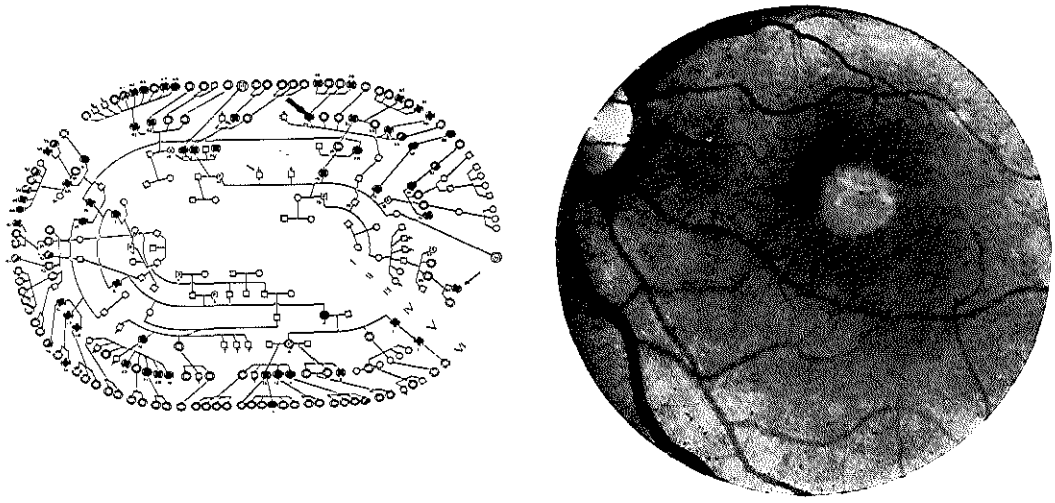


Fig. 41c.

Photograph of section through the centre of the fovea of the left eye of the 59-year-old female proband (V-49) of the pedigree (see top left) with 69 affected individuals, presented by Barkman (1961). The photograph had to be composed of two pieces because of an artificial detachment of the retina. The fundus photograph is from the left eye of this woman and was taken in June, 1958 (see top right). Deterioration of vision started at the age of 28 and she visited an ophthalmologist for the first time at the age of 46. Vision right eye 0.4; left eye 0.8. In both foveae "cystic degeneration", measuring one disc-diameter was noticed. She died in 1969, at the age of 59, from coronary thrombosis.

Ry Andersen performed the histopathological examination: „Histopathological examination shows that the choriocapillaris is fairly well preserved and Bruch's membrane too, apart from some PAS-positive flat masses of cuticular substance from the inner cuticular part of Bruch's membrane and a couple of larger drusen one of which containing a small capillary from the choriocapillaris in the macular area. Serial sections of the eye show, a spotty thinning and degeneration of the retinal pigment epithelium with few or no melanin granules in an area a little less than one dd*. The inner retinal layer which is artificially detached from the pigment epithelium shows a severe defect of the sensory cells which are lacking in the same area as the degeneration of the retinal pigment epithelium. The outer intermediary layer in an area about three dd in and around the macula shows a proteinaceous eosinophilic oedema in hematoxylin and eosin stain.

Special stains show that this oedema does not contain acid or neutral mucopolysaccharides or phospholipids. Oxydized tannin azo and mercury bromphenol blue stain are positive suggesting protein. It cannot be excluded that this oedema could be a remnant of the vitelliform yellow cyst-like material seen in the early stage of the disease. But most likely it is not specific."

Ry Andersen and Barkman concluded from their findings: „It is impossible from this old material to state the primary site or pathogenesis. But we find it most likely that the pigment epithelium in some way plays a very important part in the pathogenesis of the disease being responsible for the drusen and particular masses in the inner part of Bruch's membrane and for the increasing damage of the neuro-epithelium". (After Ry Andersen and Barkman, to be published by Ry Andersen, S. and Barkman Y. in Acta Ophthalmologica).

* dd = disc diameter

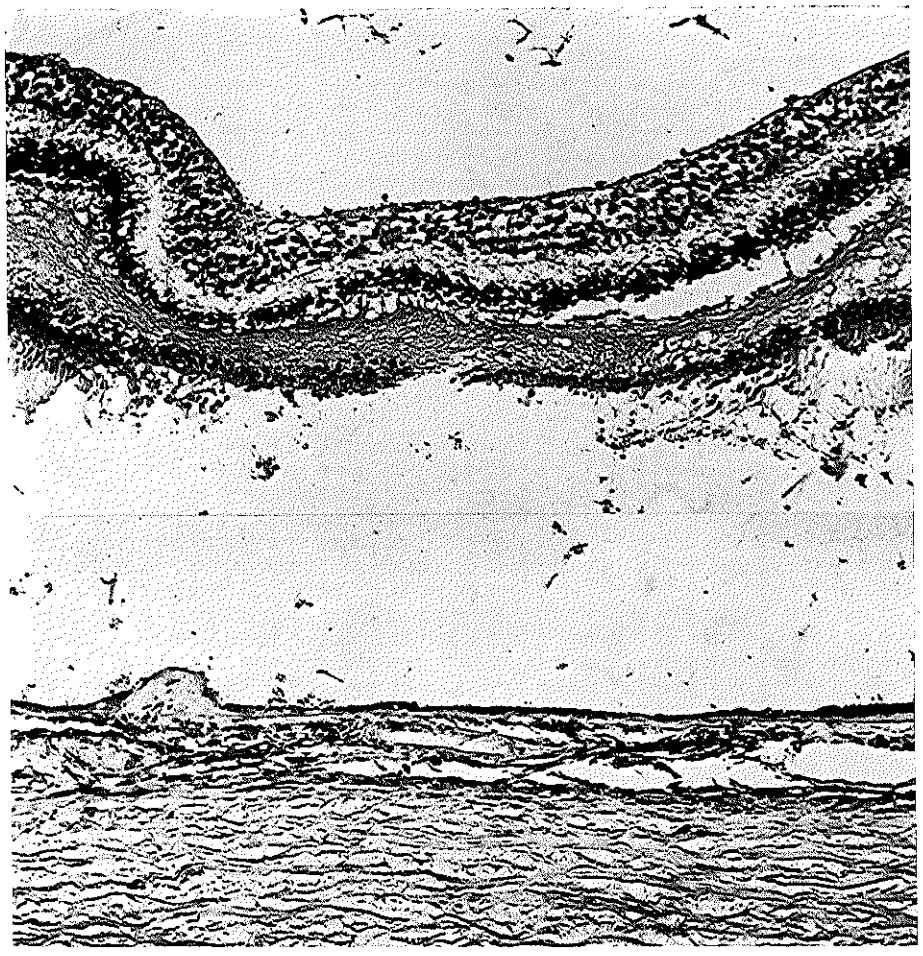


Fig. 41c

We have indeed observed this, but this cannot be described as a really abnormal condition. As soon as the fovea begins to show distinct alterations, one is dealing with a patient and not with a carrier.

We were able to identify our first carrier in fam. Vr (IV-16 fam. Vr): his father, his sister and two of his sons were suffering from VFD, while the two different mothers of his affected sons had quite normal eyes. The carrier showed no ophthalmoscopic peculiarities (fig. 41ab) and his visual acuity was normal. But the EOG study revealed that his EOG was as pathological as that in the patients. After this surprising finding, we used the EOG for large-scale screening in this family and other families with VFD. This enabled us to identify 16 carriers with certainty in 5 of these families.

Because the Lp/Dt ratio of the EOG is particularly low in carriers of the pathological gene of VFD, we can be sure of the value of this study.

Fig. 42a. Slightly disintegrated vitelliform disc (Fam. Can).

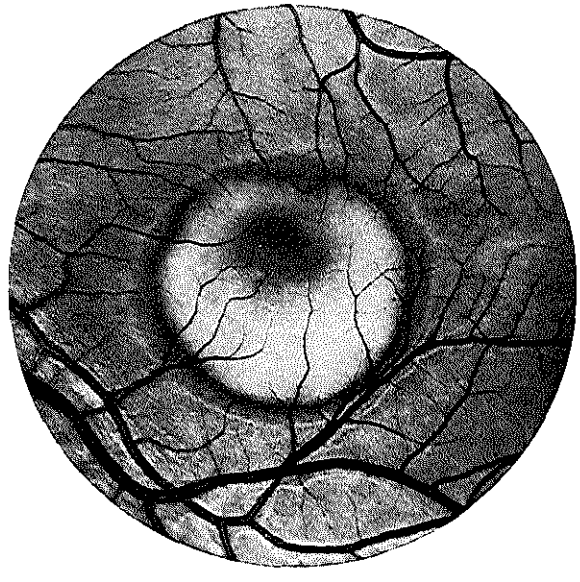


Fig. 42b. Intact vitelliform disc. Note the tiny yellowish-whitish spots in the egg-yolk.

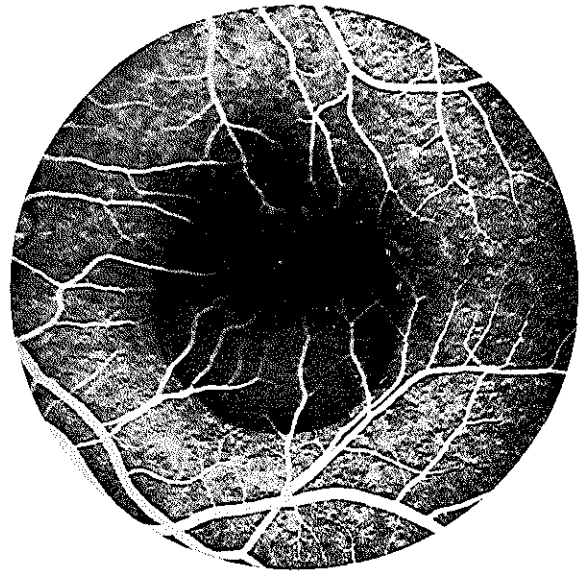


Fig. 42c. Fluorescein angiography demonstrates an almost normal fluorescence pattern in the intact vitelliform disc. The choroidal fluorescence pattern is less well visible at the site of the egg-yolk.

An even more extensive investigation of the families known to us, would undoubtedly have identified many more carriers. We found carriers in the families dB, EW, KZ, TT and Vr.

Of the 16 identified carriers, we were able to follow 6 through 2 years; 2 of these developed an unmistakable foveal abnormality which had not been previously present (III-2 and III-8 fam. EW). Both women had quite normal foveae to begin with, but already a pathological EOG. At follow-up, both showed a small yellow-white spot at the site of one of the foveolae (fig. 9, 15).

Moreover, one patient with very slight perifoveal changes and a white-yellow spot in the right foveola which could have been easily overlooked, showed bilateral fresh vitelliform structures one year after an EOG study which gave evidently pathological results (V-7 fam. Vr) (fig. 7).

Our findings emphasize not only the value but also the necessity of EOG examination of ophthalmoscopically normal relatives of patients with VFD. With the exception of the EOG, all functions tests we carried out in carriers of VFD were normal. In carrier IV-16 fam. Vr, the F-ERG, VER and OP were normal, as were colour vision, visual fields and dark adaptation.

Fluorescein angiography was likewise normal in this carrier, as was to be expected in view of the fact that even in fresh vitelliform abnormalities a normal fluorescein pattern is still found (Curry and Moorman 1968) (fig. 41).

14. HISTOLOGICAL FINDINGS

The histological features of the classical vitelliform stage or of VFD in young patients are unknown. McFarland (1955) did report on the histology (assessed by Klien) of the fovea in an 87-year-old man with a late stage of VFD. At age 85, ophthalmoscopic examination of this man disclosed "generalized retinal atrophy in the macular area and extensive choroidal sclerosis. Interspersed among the sclerotic choroidal vessels, was an occasional round area resembling a moderate size druse". Vision was 5/200 ODS without correction.

The histological report reads as follows. "The anterior segment is normal, the ciliary muscle is of the hyperopic type, the ciliary processes show senile hyalinization. The main pathologic changes are found in the macular retina. There is an extensive defect of the first neuron, its nuclei are absent over an area of 2 disc diameters temporal to the nerve head. The pigment epithelium is missing over a less extensive area. In the foveal and adjacent region a glial membrane replaces the pigment and neuroephitelium. The pigment epithelium is present for about 1/2 dd temporal to the disc but its cells are flat and irregular. They appear of similar shape on the other side of the macular defect before they assume normal appearance again.

Bruch's membrane is very obvious due to a bluish cast, which is deepest at the posterior pole region and becomes uneven towards the periphery. In the circumpapillary and macular zones there are numerous breaks in it. V. Kossa stain was faintly positive, indicating some calcification of Bruch's membrane. The choriocapillaris is completely absent in the posterior polar region and here the large choroidal vessels show marked sclerosis of the senile involutionary type, viz.: thickening of the media and adventitia but no hyalinization.

In the macula there are several bleb-like spaces between external limiting and Bruch's membrane which contains finely granular debris of a bluish color (calcium?). There is a partial atrophy of the temporal half of the optic nerve with some glial proliferation. The marked choroidal sclerosis, fragility and calcification of Bruch's membrane and the atrophy of the chorio-capillaris are senile changes and are coexisting with the primary macular retinal degeneration. Diagnosis: heredodegeneration of the macula lutea, infantile type, at age 87."*

15. PATHOGENESIS

The primary localization of the vitelliform disc is as yet uncertain because there are no known histological studies of the initial stages of VFD. There are indications, however, that a localization in the pigment epithelium is probable.

There are the following possibilities concerning the primary localization of the vitelliform structure.

1. *In the neuroepithelium.* This was initially assumed by Klien (1950), but the good

* Addendum: For the newest histological findings, see fig. 41c, page 248-249.

vision in many cases argues against it. The fact that, at least in the initial stages, colour vision and F-ERG are normal also suggests intactness of the photoreceptors at the site of the fovea.

Binocular contact lens examination likewise suggests a localization past the photoreceptors (fig. 22); and the normal ERG indicates that the neuroepithelium in its totality functions well.

2. *Between neuroepithelium and pigment epithelium.* The appearance of the yellow disc is so clear that it may well be believed to lie in front of the pigment epithelium. However, the margin of the vitelliform structure merges so gradually into the surrounding apparently normal pigment epithelium that a localization in front of the pigment epithelium seems unlikely. Moreover, such a localization could also more quickly lead to involvement of the photoreceptors. The fact that fluorescein angiography discloses defects of the pigment epithelium after some time, indicates that the vitelliform structure is probably localized more to the back.

3. *In the pigment epithelium.* The following factors argue in favour of localization of the vitelliform lesion in the pigment epithelium.

a. The clear visibility of the yellow of the disc shows that no normal pigment epithelium can lie in front of it. We observed a recently formed vitelliform structure in a 44-year-old patient (V-7 fam. Vr), in whom the colour of the disc was yellow at the centre but increasingly reddish-brown towards the periphery, as if a yellowish substance were advancing in the cells of the pigment epithelium, with maximum prominence at the centre.

b. The virtually normal fluorescein pattern in the fresh vitelliform stage (fig. 7, 42) indicates an intact structure of Bruch's membrane and an almost intact pigment epithelium. The fact that no pathological fluorescence is observed in the initial stages does not rule out a localization in the pigment epithelium. For Klien and Krill (1967) demonstrated that some recently formed fundus flavimaculatus lesions localized in the pigment epithelium cells produced a normal fluorescein pattern. Only in advanced stages did pathological fluorescence appear.

Abnormalities of Bruch's membrane cause leakage of fluorescein from the choriocapillaris to the subretinal spaces, as is frequently observed in central serous choroidopathy, disciform macular degeneration and angioid streaks.

The yellow intracellular mass will ultimately cause pigment layer atrophy, giving rise to the characteristic fluorescence of defects in the pigment epithelium.

c. In the presence of a normal ERG and dark adaptation curve, the pathological Lp/Dt-ratio of the EOG suggests dysfunction of the pigment epithelium, particularly since fluorescein angiography demonstrates that the Bruch membrane and choriocapillaris are probably intact.

d. Histological examination of an eye with fundus flavimaculatus disclosed that the yellowish spots which characterize this condition consist of acid mucopolysaccharides lying on the anterior side of the cells of the pigment epithelium (Klien

and Krill 1967). Apart from the pigment epithelium, no structure of the eye showed pathological changes. Fluorescein angiography and retinal function tests produce virtually identical results in fundus flavimaculatus and VFD. In fundus flavimaculatus, too, fluorescein angiography has disclosed defects of the pigment epithelium; and in this condition the EOG is the only retinal function test which shows unmistakable pathological changes.

e. Panchromatic graphic film shows a much more extensive lesion in VFD than orthochromatic graphic film (fig. 38, 39). Our experience shows that panchromatic film gives a much more faithful picture of changes in the pigment epithelium than orthochromatic film (Craandijk and Aan de Kerk 1969).

f. Photography with monochromatic light discloses much more extensive changes in VFD at the longer wavelengths, which penetrate deeper into the deeper retinal layers (red light) than at the shorter wavelengths (blue light) (Krill et al. 1966).

In view of the above arguments I have formed the opinion that the substance which causes visualization of the vitelliform structure is localized in the cells of the pigment epithelium, mainly on the anterior side, immediately next to the photoreceptors. This localization has also been suggested by other authors (McFarland 1955; Velzeboer 1963; Blodi 1966; Braley 1968; Curry and Moorman 1968; Krill et al. 1968; Morse and MacLean 1968).

4. *Between pigment epithelium and Bruch's membrane.* The appearance of the fully developed vitelliform disc shows that this localization is highly improbable. The vitelliform structure would never be so clearly visible and yellow if it were localized behind an intact pigment layer. If the pigment epithelium were pushed aside by the structure, then a pathological fluorescein pattern could be expected because the egg-yolk is not likely to screen the fluorescent choriocapillaris. However, this localization cannot be ruled out with certainty (Krill et al. 1966; Falls 1966; Morse and MacLean 1968).

5. *In Bruch's membrane.* This localization is exceedingly improbable in view of the anatomy of Bruch's membrane. It might be the site of the primary defect that gives rise to the formation of the vitelliform disc, but in that case one would certainly expect a pathological fluorescein angiogram in the initial stages.

The round lesion which occurs in VFD is reminiscent of central serous chroidopathy and disciform macular degeneration, and on the basis of this round structure a small primary defect in Bruch's membrane seems an attractive hypothesis. However, fluorescein findings have not so far lent support to it. Several authors have suggested a primary defect in Bruch's membrane (Grimm and Tedford 1963; Braley and Spivey 1964; Krill et al. 1966; Tsukahara et al. 1968; Urrets-Zavalia and Moyano 1969; and others).

6. *In the choriocapillaris or between choriocapillaris and Bruch's membrane.* Falls (1949) suggested that: "Slow acting mild sub-oxidation and deficient nutrition were presumed to produce the hyaline and colloid-like changes and glial infiltration". But

he added: "That the hypothesis of primary retinal transudation may be wrong, however, is suggested by the very early and severe visual loss seen in senile disciform degenerations".

As we pointed out, we regard a localization in the pigment epithelium as most plausible. It seems that the cells of the pigment epithelium secrete a viscous yellowish substance which accumulates in the cells and becomes visible on the anterior side. The nature of this substance has been the subject of many speculations. Renard et al. (1960) and Remky et al. (1965) thought of lipids, and studied the lipid pattern (without much success). Since an acid mucopolysaccharide has been found in the lesions in fundus flavimaculatus (Klien and Krill 1967), the presence of a similar substance in VFD is an attractive hypothesis. Both conditions show a normal fluorescein pattern in the initial stages and a subnormal EOG as the only pathological function test.

Through the metabolism in the cells of the pigment epithelium the yellow substance can be transformed and disappear; another possibility is that the yellow substance destroys the cells in the long run so that they become necrotic, rupture or show syneresis; the result is a cyst with a "scrambled egg" appearance. Liquefaction of the yellowish contents of the cyst then produces the pseudo-hypopyon appearance, and proliferation of pigment epithelium can produce pigmentations when the "vitelliruptive" process has damaged the adjacent pigment epithelium. The fact that this process is nearly always confined to the fovea may well be ascribed to the higher metabolism at this site in the retina, although anatomical factors cannot be ruled out.

16. MODE OF TRANSMISSION

It is generally accepted that VFD has an autosomal dominant mode of transmission with diminished penetrance and highly variable expression. Our findings confirm this.

We found a regular autosomal dominant transmission in 3 or more generations in 5 families (families BE, Fl, vM, UT and WA).

In 4 families there was irregular dominance in 3 generations as judged by the fundus picture (families EW, KZ, TT and Vr). If a pathological EOG were accepted as indicating penetrance of the pathological gene, then the mode of transmission in these families might be described as regular.

In 2 families we saw 2 affected generations (families Bl and Ko-K). In the dB family a second affected generation was demonstrable with the aid of the EOG; in 2 families (KlK and Pl) the family study (incomplete as it was) supplied ophthalmoscopic evidence on only one affected generation. EOG examination was unfortunately impossible in these families.

The figures for affected and unaffected members roughly corresponded. The 98 (initially 96) ophthalmoscopically affected individuals included 43 (initially 41) women and 55 men; and 5 (initially 7) women and 9 men were identified as carriers

with the aid of the EOG. As could be expected in an autosomal dominant condition, the affected individuals showed no marked male or female predominance.

The literature comprises many reports on regular dominant transmission in 3 or more generations (Behr 1920; Sorsby 1940: fam. M; Renard 1946: fam. F; Friemann 1953; McFarland 1955; Sorsby et al. 1956; Sorsby and Wren 1960; Gallet 1961; Grimm and Tedford 1963; Hermann and Vernin 1963; Velzeboer 1963; Braley and Spivey 1964; Graham et al. 1964; Remky et al. 1965: fam. H, fam. F; Belmonte 1966; Streicher 1967).

There are also publications on irregular dominant transmission (Best 1905; Vossius 1921; Weisel 1922; Jung 1936; Berkley and Bussey 1949; Barkman 1961).

Several authors have described VFD in 2 generations (Tiscornia 1926; Argañaraz and Androgué 1927; Galeazzi 1939; Renard 1964: fam. C; Bruna 1951; Corrêa Meyer 1953; Dekking 1955; Sorsby et al. 1956; Gregory 1958; Chinaglia and Perini 1964; Melodia and Tabacchi 1965; Remky et al. 1965: fam. KDH; Krill et al. 1966; François et al. 1967; Gorgone 1967; Le Hunsec and Pierre 1967; Martenet 1967; Zanen and Balsacq 1968).

X-chromosomal transmission was suggested by Falls (1952) in one family. However, the mode of transmission in this family might also be irregular dominant. In our patients we could find no indications of sex-linked transmission.

Autosomal recessive transmission was not considered ruled out until recently. Sorsby (1940: fam. N) and Zanen and Hermans (1961) described consanguineousness of ophthalmoscopically normal parents of patients with VFD. Many others (e.g. Hambresin 1950; Gallet 1961; P. François et al. 1963) likewise found normal parents of ophthalmoscopically affected children.

In all our families in which skipping of a generation occurred, or in which parents of patients had ophthalmoscopically normal eyes, the carrier state could be demonstrated with the aid of the EOG (if we had occasion to record it). This EOG examination will probably demonstrate in future that the mode of transmission of VFD is always dominant.

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

Patients with VFD are generally healthy individuals with a normal intelligence and no demonstrable abnormality. Such of our patients as were hospitalized because the nature of their condition was not yet known, were submitted to an extensive physical examination (cf. Methods). None of them showed any significant abnormality.

A few authors, however, have described slight abnormalities. Renard et al. (1960) reported relatively increased serum cholesterol values in a 5-year-old girl. Braley and Spivey (1964) found that the serum cholesterol values in their patients were rather high. Their comment on this finding was: "It is most likely due to a well-supplied Iowa dietary intake".

Zanen and Hermans (1961), Remky et al. (1965) and ourselves found normal serum cholesterol values and a normal serum lipid pattern.

In the abovementioned girl, Renard et al. (1960) found slight changes in the protein pattern: increased α_2-globulin and decreased γ-globulin fraction. Braley and Spivey (1964), however, found a significantly increased β_2-globulin fraction in 3 patients with VFD. Hermann and Vernin (1963) found a normal protein and lipid pattern in 3 female patients; Belmonte (1966) and Denden (1966) found a normal protein pattern. We found normal values in all cases in which serum electrophoresis was carried out.

Koulischer (quoted by Zanen and Balsacq 1968) made karyotype studies in 3 patients in one family and found abnormal satellites at chromosomes 17 and 18. We considered it very unlikely that chromosome abnormalities should be demonstrable as constant findings in VFD. It seems very improbable that so localized an abnormality as VFD could be based on a visible chromosomal anomaly; for in the case of such gross abnormalities of the chromosomes one usually finds extensive symptom complexes and syndromes but, so far as we know, never very localized disorders.

18. ASSOCIATED CONDITIONS

VFD generally occurs as an isolated abnormality. Some authors have described occurrence of Stargardt's disease and VFD in the same family (Bruna 1951; Graham et al. 1964; Bérard 1966; Duke-Elder 1967). Others found central serous choroidopathy in a family in which VFD occurred (Bonnet 1938; Le Hunsec and Pierre 1967).

We believe that these reports are based on misinterpretations of findings in families in which only VFD occurred. None of the families we studied showed foveal changes inconsistent with the picture of VFD. However, these misinterpretations are understandable because the very variable features of VFD have long been insufficiently known.

Maggi (1963) described a child in whom he observed Leber's congenital amaurosis with a unilateral round yellow foveal lesion of 1 disc diameter, which he diagnosed as VFD. We doubt this diagnosis because: the family history was negative, the lesion was unilateral and showed an atrophic aspect.

Similar yellow round foveal changes with atrophy of the pigment layer have been observed in the Sjögren-Larsson syndrome (Gilbert et al. 1968).

Hambresin (1950) observed VFD in a brother and sister, of whom the former had a harelip.

In 2 of our patients (IV-20 fam. UT; V-10 fam. WA), detachment of the retina occurred for no apparent reason at age 10 and age 30, respectively. Diffuse dysfunction of the pigment epithelium may have played a role in this respect.

We also found what we believed to be an incidental association of sex-linked hemeralopia, often accompanied by myopia, and VFD in one family (fam. EW). Two women (II-5 and III-7), carriers of both pathological genes, each had 2 sons with sex-linked hemeralopia without VFD, while these women themselves showed un-

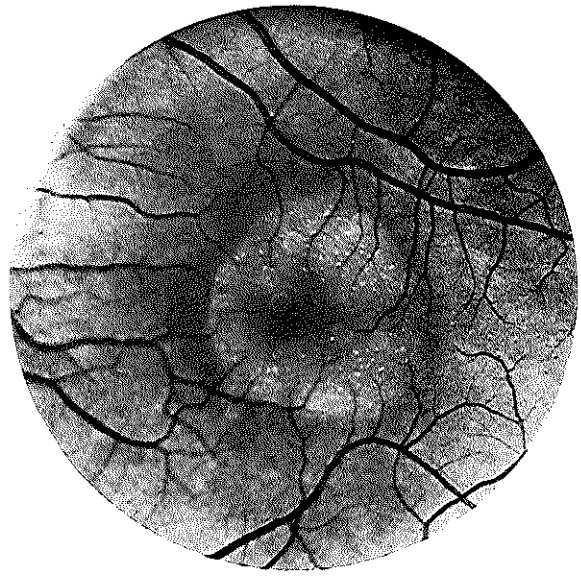


Fig. 43. Central serous choroidopathy in the left eye of a 41-year-old male. Note the characteristic small white flecks in the serous cyst.

mistakable foveal changes of a vitelliform type. At examination of the patients with sex-linked hemeralopia we noticed that differential diagnosis from the so-called Åland syndrome (Forsius and Eriksson 1964) was impossible. This is why we believe that the Åland syndrome is not a separate entity at all, but merely sex-linked hemeralopia ("hemeralopia-myopia syndrome") (see page 293). (Franceschetti et al. 1963).

In fam. KK, with pronounced parental consanguineousness, a child with Leber's congenital amaurosis was born. When examined this child showed no vitelliform changes.

19. DIFFERENTIAL DIAGNOSIS

The ophthalmoscopic features of VFD are characteristic in many cases, but they are not always pathognomonic. There are pictures which closely resemble that of VFD and may make it difficult to differentiate, especially if family study and EOG examination are impossible. VFD must be differentiated from the following conditions.

a. *All other dystrophies of the central retina and choroid* mentioned in this study. Of these conditions, Stargardt's disease (page 112) with its horizontal-oval focus of beaten bronze atrophy shows the closest similarity to an atrophic stage of VFD (fig. 33, 34). When the vitelliform lesion disintegrates, honeycomb patterns of

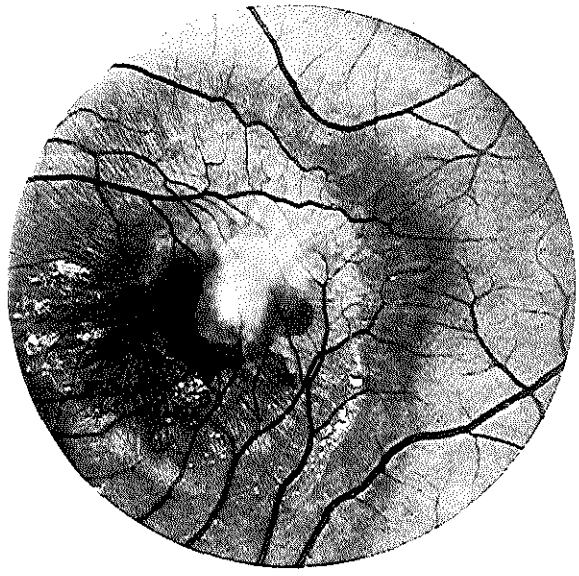


Fig. 44. "Juvenile disciform degeneration" of the posterior pole in the left eye of a 15-year-old boy. This could be a case of histoplasmosis.

drusen-like structures can result (fig. 2) which necessitate differentiation from dominant drusen of Bruch's membrane (page 372). In the case of multiple vitelliform structures, differentiation must be made also from fundus flavimaculatus and fundus albipunctatus.

b. *Central serous choroidopathy* (retinitis or retinopathia centralis serosa) (fig.43). This condition is usually unilateral and most commonly seen in males aged 20-40. No familial factors are generally demonstrable. Marked metamorphopsia, micropsia and hypermetropia can occur in this condition, and circumscribed detachment of the neuroepithelium is observed. The EOG is normal (fig. 37b), unlike that in VFD, and colour vision usually shows a blue-yellow defect.

Fluorescein angiography often discloses one or several small foci where fluorescein leakage is observed (fig. 40). This is probably due to increased capillary permeability and/or a defect in Bruch's membrane, through which serous fluid escapes.

c. *Serous detachment of the retinal pigment epithelium.* This presents itself as an elevated, oval-shaped or round, sharply defined, convex yellow-grey lesion which looks solid and is localized at the site of the fovea. This condition shows marked subjective and objective similarity to central serous choroidopathy. The most characteristic difference from the latter is found at fluorescein angiography. The entire area of detachment becomes fluorescent soon after occurrence of the choroidal fluorescence.

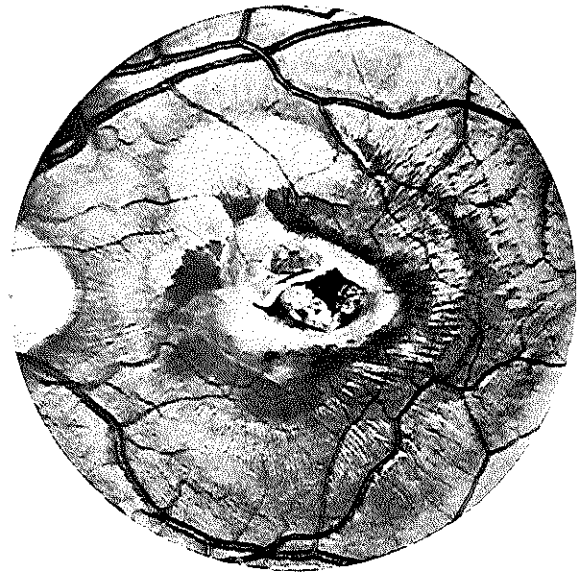


Fig. 45. Strange acquired unilateral foveal affection in an 8-year-old boy. Despite negative systemic reactions toxocara canis is suspected.

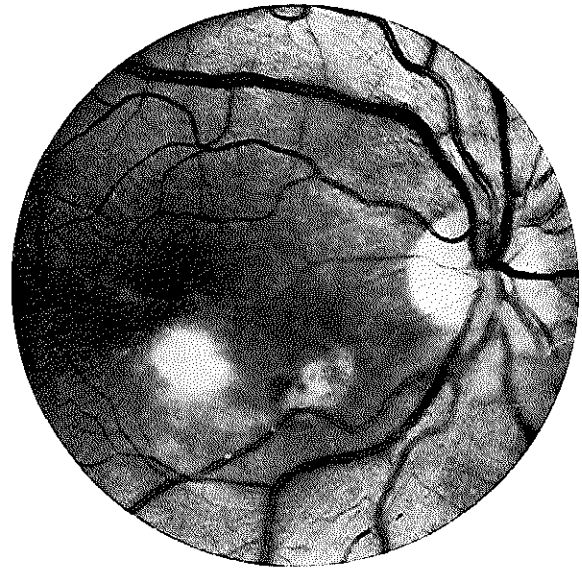


Fig. 46. Fresh paracentral choroiditis on the temporal side of a small scar. Toxoplasmosis serology was positive in this case.

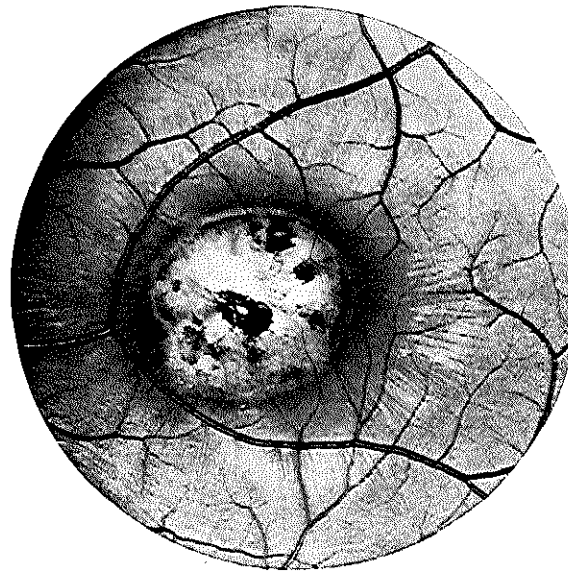


Fig. 47. Scar of central choroiditis resembling a ruptured vitelliform disc.

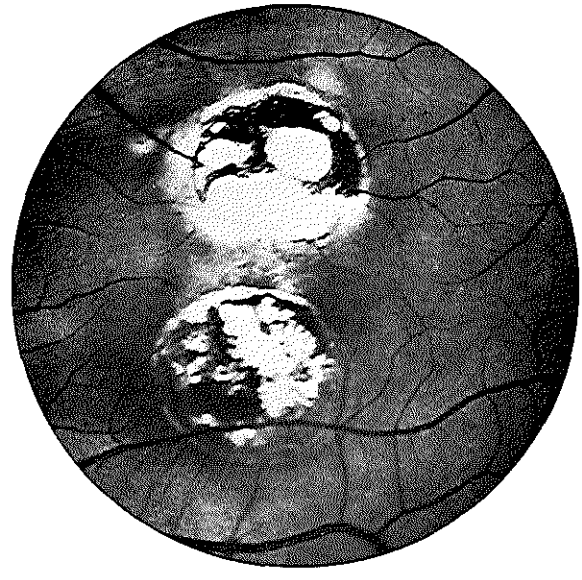


Fig. 48. Two patches of connatal toxoplasmosis in the posterior polar area.

Fluorescein leaks into this area and remains present 10-30 minutes or longer (Gass et al. 1966; Maumenee 1967).

d. *Juvenile disciform macular degeneration.* This condition, described by Verhoeff and Grosmann (1937) and others, has been given several different names and its clinical picture is ill-defined. It is known also as haemorrhagic disciform macular degeneration (Watzke and Snyder 1968) and multifocal inner choroiditis (Krill et al. 1969). A positive histoplasmin skin test is often found, and the picture is therefore often ascribed to histoplasmosis-choroiditis (Woods and Wahlen 1960). The clinical picture shows diminished visual acuity in a patient aged 15-50, due to a parafoveal dark-grey or yellow swelling of the choroid and pigment epithelium, often with subretinal haemorrhage (fig. 44). The retinal periphery frequently shows small cicatrices of chorioretinitis, while the vitreous is clear.

Most of these cases probably involve a reaction to focal inflammatory infiltrates of choroidal cells (Gass 1967). In view of the fair variability of clinical pictures, Gass (1967) suspected that several aetiological factors determine the focal choroiditis (fig. 45).

e. *Central chorioretinitis.* This condition is characterized by an ill-defined yellow (para)foveal focus (fig. 46), while inflammatory cells are often seen in the vitreous. The patient experiences an abrupt diminution of visual acuity. Differentiation between this entity and juvenile disciform macular degeneration can be difficult. The cause has been described as toxoplasmosis (Friedmann and Knox 1969), onchocerciasis (Budden 1962), infection with toxocara canis (Wilder 1950; Duguid 1961) and many other infectious diseases (cf. Duke-Elder 1966).

f. *A cicatrix of central chorioretinitis.* The cicatrix of a central chorioretinitis (fig. 47), regardless of its cause, can closely resemble VFD in a stage following disintegration of the egg-yolk (fig. 27). Congenital toxoplasmosis cicatrices, nearly always of central localization, are usually characterized by a horizontal oval of intensive pigmentations surrounding a central area of lighter colour (fig. 48) (François 1956). That differential diagnosis can be difficult is demonstrated by François (1956), who in his paper on "Toxoplasmose oculaire" presents a drawing of congenital toxoplasmosis (p. 126, fig. 30), while the same drawing is presented in "Les hérédodégénérescences choriorétiniennes" (Franceschetti et al. 1963) as illustration of a vitelliform disc (Vol. I, p. 481, fig. 311).

g. *Colobomas of the central retina* may occasional resemble vitelliform lesions. Differentiation offers no difficulty in view of poor vision since birth, usually extensive changes and white appearance of the colobomas.

h. *Disciform macular degeneration* (Junius Kuhnt). This rarely occurs before age 60, but in some cases it may exactly copy the features of the vitelliform disc (fig. 49)

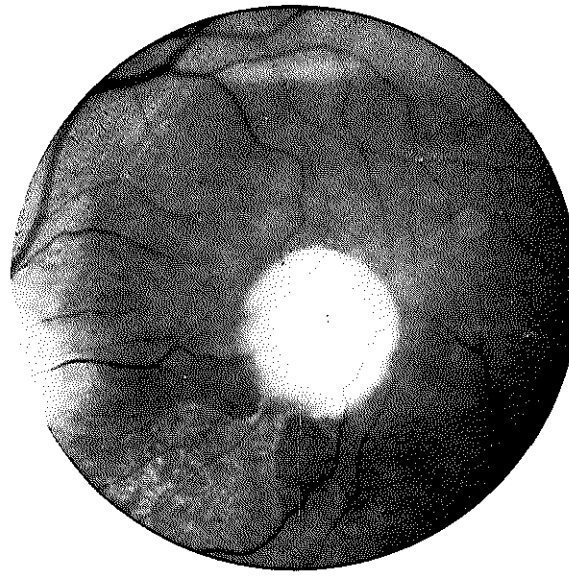


Fig. 49. Disciform macular degeneration resembling vitelliform dystrophy in a 85-year-old female (after Oosterhuis).

Fig. 50. Angioid streaks causing exudative reactions in the posterior pole.

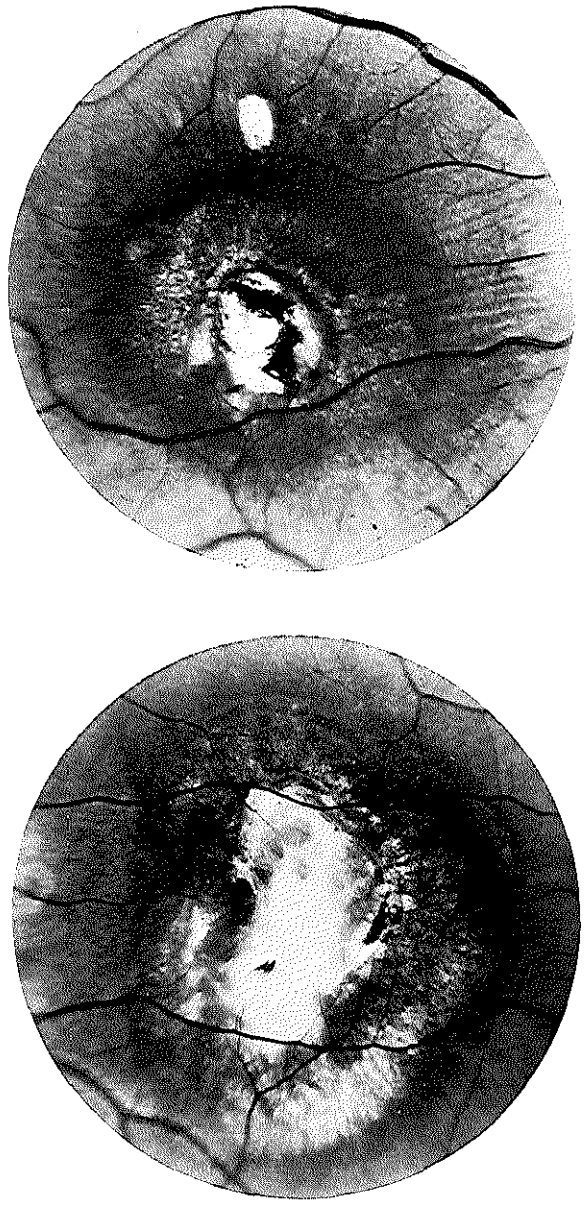


Fig. 51ab. Undefined bilateral lesions in the foveae of a man in his forties (histoplasmosis?). Systemic examination was negative. EOG was normal.

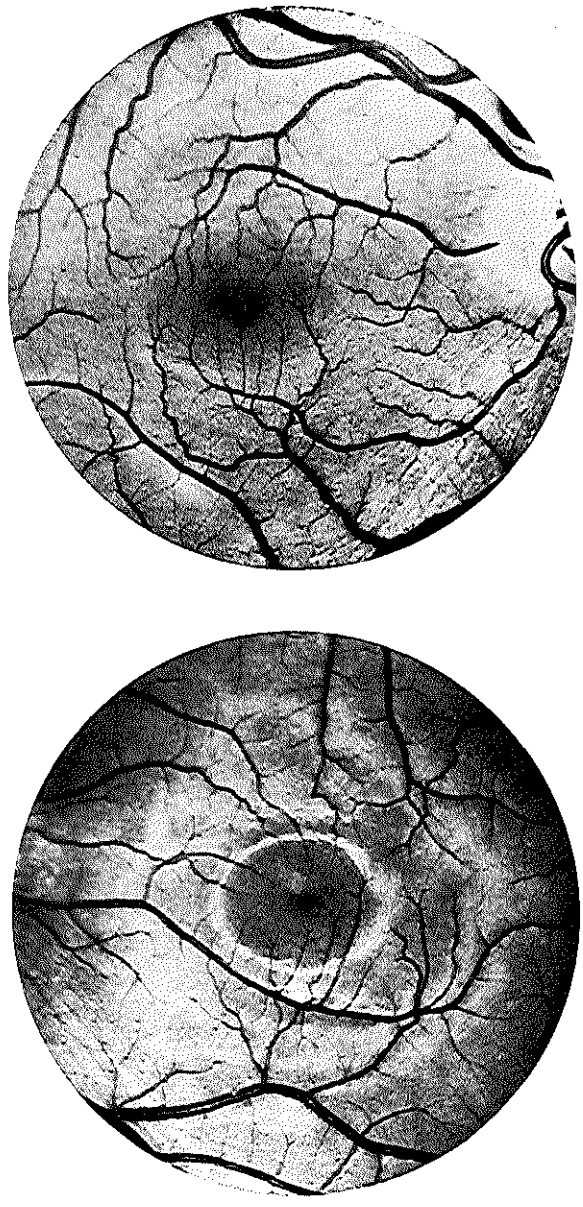


Fig. 52a-b. Pathognomonic lesions of solar retinopathy showing small defects at the site of the foveola. Fluorescein angiography is normal in this condition.

(Tota 1966). Differentiation generally offers little difficulty. Fluorescein angiography discloses leakage of fluorescein, and the EOG is often normal; both findings argue against VFD.

i. *Foveal changes in angioid streaks.* Angioid streaks often involve disciform degenerations (fig. 50) of the posterior pole which, if round and yellowish, can somewhat resemble vitelliform changes. The EOG is generally normal in angioid streaks (Van Balen and Houtsmuller 1965) (fig. 37b).

j. *Foveal haemorrhage.* In a few patients we observed a unilateral pre- or intraretinal haemorrhage of unknown origin, at the exact site of the fovea. The ophthalmoscopic features seemed to suggest that a drop of blood had fallen on the fovea. After a few weeks only a round yellowish focus remained, which necessitated differentiation from VFD.

k. *The Sjögren-Larsson syndrome* can be associated with foveal changes reminiscent of VFD (Gilbert et al. 1968).

Unidentified changes. In the course of our study we found a few patients with more or less round yellowish bilateral foveal changes which we could not identify as any of the conditions listed here (fig. 51). The EOG was always normal and family studies failed to supply any clues.

Further investigations are being made in an attempt to identify these processes. ("Multifocal inner choroiditis"?).

Last, but not least *solar retinopathy* has to be differentiated particularly when there is a negative history. The bilateral foveal alterations could lead to the diagnosis hereditary dystrophy (fig. 52). Except for the visual acuity, retinal function tests and fluorescein angiography are normal in this affection.

20. THERAPY

In our opinion there is no rational therapy against VFD. Many attempts to ensure improvement by general cortisone medication have failed to produce unmistakable success. Visual loss is so often followed by spontaneous improvement that it is exceedingly difficult to assess the value of any therapy. Cortisone was used by Barkman (1961), Braley and Spivey (1964) and others. Barkman (1961) reported visual improvement following steroid medication, and Braley and Spivey (1964) reported that: "Steroid therapy may have beneficial effects". It is possible that, at the time of gross changes in the vitelliform structure (vitelliruptive stage), cortisone can delay the formation of cicatrizing processes. But it is questionable whether a lasting effect can be expected without continued medication; and long-term corticosteroid medication can hardly be resorted to in view of the many side effects of steroids.

Braley (1966) mentioned that Watzke treated 3 patients by photocoagulation. His conclusions were: "Photocoagulation may be a hopeful procedure in certain cases, but it is dangerous when applied directly to the fovea. Care must be exercised, in any event, to avoid excessive treatment. When the area around the fovea is to be burned, it is better to treat too little than too much".

It is impossible to compare any therapeutic results whatever with cases left untreated, because spontaneous improvement is very common.

The value of any therapy seems singularly questionable at this time, and especially the value of photocoagulation, which entails a grave risk for the fovea.

In a few of our patients in whom cortisone medication was or was not combined with pyrimethamine (Daraprim), because central chorioretinitis was thought possible, no distinct therapeutic effect was demonstrable.

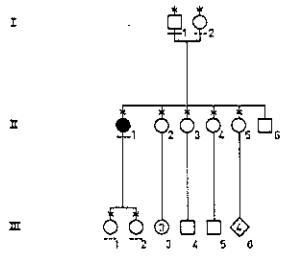
21. FUTURE

Biochemical and histochemical research will have to determine the causative factor of this intriguing condition. The underlying affection is probably an enzymatic disorder or a defect in the cells of the pigment epithelium.

It will be of importance to make a search for micro-changes elsewhere in the body in the hope of lifting at least part of the veil which obscures vitelliform dystrophy of the fovea.

22. CASE HISTORIES

1. Fam. dB



I-1 (FdB-04.07.24) VODS 10/10.
Fundi: Normal.
EOG: ODS 1.50.

I-2 (MdB) VOD 10/10; OS prosthesis (after trauma).
Fundus: Normal.
EOG: OD 2.57.

II-1 (CMCvEdB-32.03.19)
1965: Impairment of visual acuity. Hospitalized.
VOD 3/10; VOS 2/10.
Fundi: "Atypical central serous choroidopathy with pseudohypopyon".
Treatment: Prednisone orally and Complamin. No improvement.
1967: VOD S+0.75 3/10; VOS S+0.75 4/60.
Reads D=0.8 without glasses.

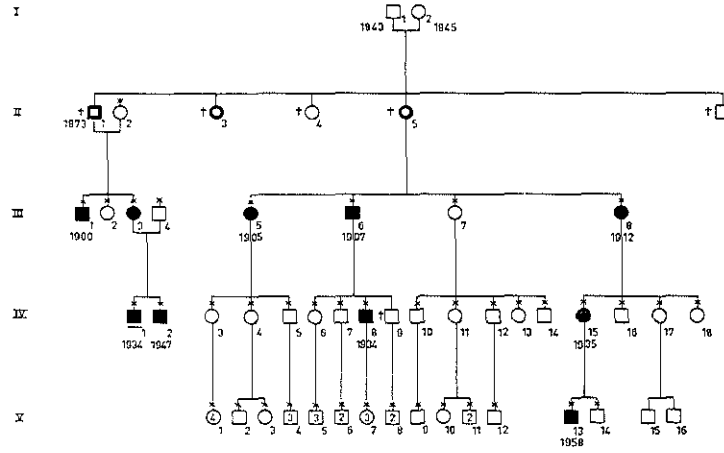
Fundi: OD: Perfectly circular cystoid structure in the posterior pole. There is a pseudohypopyon. The structure is approximately 2 disc diameter in size (fig. 28). OS: Circular cystoid structure of 3 disc diameter in the foveal area. Particularly at the bottom of this structure there are whitish deposits.
Visual fields: Central scotoma of 5 degrees.
Colour vision: Decreased sensitivity to red (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 395μV; OS 360μV.
Phot. b-waves OD 135μV; OS 140μV.
EOG: ODS 1.50.

III-1 (AvE) VODS 10/10.
Fundi: Normal.
EOG: OD 1.86; OS 1.99.

III-2 (WvE) VODS 10/10.
Fundi: Normal.
EOG: OD 1.92; OS 2.04.

Summary: In this family we detected a carrier (I-1) with the help of the EOG. This carrier is quite normal ophthalmoscopically, but his EOG L/D-ratio is definitely subnormal.
The patient (II-1) shows the characteristic cystoid structure with the pseudohypopyon picture. The children do not possess the gene of vitelliform dystrophy, as indicated by the normal EOG. The EOG of the patient and the carrier in this family are slightly higher than we are used to in other families.

2. Fam. B-E



This family was examined near Deventer in April, 1968. Only one patient (IV-1) was willing to come to Rotterdam for photographic and electrophysiologic examination.

III-1 (JWE-00.10.28) Poor visual acuity since childhood. His father is reported to have had poor vision too during most of his life.
VOD S+10=C+2×30° 2/10; VOS S+10=C+2×150° 3/10.
Fundi: The foveae show small yellow deposits, surrounded by round pigmentations. The whole pattern has a honeycomb appearance, approximately 1 disc diameter in size.

III-3 (EBE-05.07.22)
1943: VOD S+5 7/10; VOS S+4=C+1×110° 7/10.
1959: VOD S+7.50 7/10; VOS S+6.50 7/10.

Fundi: Round yellowish spots in a circular area of atrophic pigment epithelium. This area is somewhat redder than the surrounding retina.

III-5 (JHJS-05.04.10)
Fundi: OD: Circular area of atrophic pigment epithelium surrounded by yellowish deposits.
OS: Yellow deposits deep in the foveal area.

III-6 (JWS-07.07.24) Poor visual acuity since the age of 10. Has glasses ODS +8.
Fundi: Round area of 1.5 disc diameter in size in the foveal region with pigmentary disruption and yellowish bodies.

III-8 (HPS-12.12.30)
VOD S+6.50 4/60; VOS S+6 4/60.
Fundi: A circular atrophic area of approximately 1 disc diameter in size in the fovea. This area is surrounded by deep yellowish deposits. The left eye demonstrates also a dense pigment reaction, resembling the scar of chorioretinitis.

IV-1 (JHB-34.03.31)
1943: VOD S+5 7/10; VOS S+5 3/10.
Fundi: A picture in both foveae resembling a central serous choroidophathy.
1952: VOD 5/10; VOS 3/10.
Fundi: Cystoid structure in both foveae with a pseudohypopyon aspect.
1956: Pseudohypopyon has disappeared.
1968: VOD S+5 3/10; VOS S+4.50 3/10.
Fixation: With the centre of the vitelliform lesion.
Fundi: OD: A partly ruptured vitelliform disc (fig. 10).
OS: An orange-yellow circular area of atrophic pigment epithelium in the fovea. In this area there are many deposits of a yellowish material.
Visual fields: Decreased central sensitivity in both eyes.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 305μV; OS 225μV.
Phot. b-waves OD 140μV; OS 120μV.
EOG: OD 1.40; OS 1.45.

IV-2 (GWB-47.12.25)
1955: VODS S+0.50 8/10.
Fundi: Ruptured vitelliform disc with a scrambled-egg appearance.
1967: Fundi: Circular area of atrophic pigment epithelium at the site of the fovea. Small round yellowish deposits, approximately 0.1 disc diameter in size, are spread diffusely in this area.

IV-8 (JS-34.03.09)
Has glasses S+3.50. Complains of decreased colour vision.
Fundi: In the foveal area a scrambled egg appearance with some pigmentary disruption. As in all other members of this family, the disc, retinal periphery and retinal vessels are perfectly normal.

IV-15 (HJWP-35.03.10)
VOD S+2 8/10; VOS S+2 1/60. Concomitant divergent strabismus of OS.
Fundi: Delicate drusen-like yellowish bodies in the foveal area.

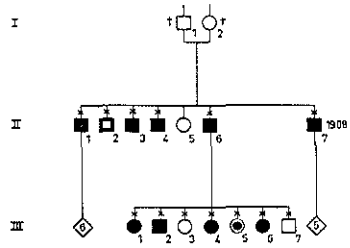
V-6 (HJ-64.12.05)
Fundi: The foveae are normal. The left eye shows a grouped pigmentation in the upper half of the fundus.

V-13 (BGW-58.07.24)
1964: OD has an iris bicolor.
VOD S+1 9/10; VOS S+1 9/10.

Fundi: A sharply demarcated homogeneous circular lesion about 1 disc diameter in size, located in the region of the fovea. The disc has a yellowish-orange colour.
1967: The vitelliform disc has "dried up" and has partly disappeared.
1968: VOD 6/10; VOS 9/10.
Fundi: In both foveae a mild pigmentary disruption and slightly abnormal reflexes. The vitelliform structure has disappeared completely. The appearance of the fovea is slightly swollen, but otherwise there are no distinct pathological abnormalities.

Summary: A pedigree in which vitelliform dystrophy of the fovea occurs. In this family the dystrophy is transmitted following a regular dominant inheritance pattern. A subnormal EOG was found in the only member of this family to be tested electrophysiologically (IV-1).
V-13 is a very interesting case. At the age of 6 he showed a vitelliform structure in both foveae, but, at the age of 10 the vitelliform lesion had disappeared completely. This illustrates the polymorphic appearance of vitelliform dystrophy and stresses the importance of family-studies whenever an uncommon foveal picture is encountered.

3. Fam. Bl



II-6 (JBl)
1953: VOD 10/10; VOS 1/60.
1956: VOD 3/10; VOS 1/60.
Fundi: Large round yellowish structures in the foveal area. Atrophic pigment epithelium centrally. The affected area measures 2.5 disc diameters.

II-7 (ABl-08.03.25)
1970: VOD S+1.50=C+0.50×50° 1.5/10; VOS S+1.50=C+0.50×45° 1.5/10.
Reads D=0.80 with addition S+2.50 and a magnifying glass.
Fundi: Round atrophic structure in the posterior pole. Yellowish clots surround the 3 disc diameter atrophic area. In the centre of this area is a fine yellowish-white honeycomb pattern. The disc is slightly too pale temporally.

III-1 (ABl-33.10.15)
1956: VOD 10/10; VOS 2/10.
Fundi: A yellow disc of 2.5 disc diameter in the foveal area of OD. The disc demonstrates a honeycomb pattern. The left eye shows a round yellow vitelliform structure of 1 disc diameter.

III-2 (JBl-37.11.15)
1956: VODS 10/10.
Fundi: Intact vitelliform disc in the foveal area. The disc measures 1.5 disc diameter.

III-4 (RBl-43.07.20)
1956: VOD 10/10; VOS 1/60.
Fundi: Intact vitelliform disc of 1.5 disc diameter in both foveae.

III-5 (CBl)
1956: VODS 10/10.
Fundi: A very small round yellow spot exactly at the site of the foveola in both eyes.

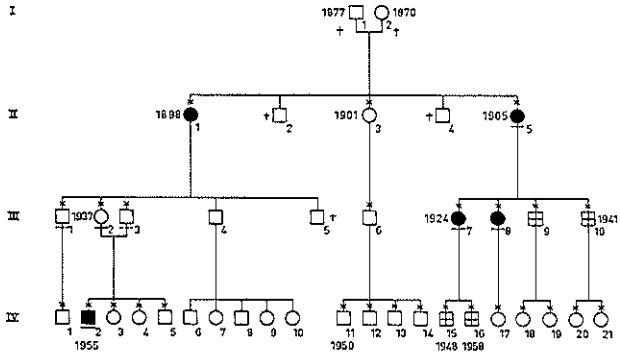
III-6 (MBl-47.12.02)
1956: VOD 4/60; VOS 10/10.
Fundi: Classic, perfectly intact vitelliform disc in both eyes. In OD 2/3 disc diameter, in OS 1 disc diameter.

Summary: A family with vitelliform dystrophy of the fovea. The pathological gene demonstrates high penetrance and high expressivity. In this family the inheritance pattern is that of an autosomally regular dominant.
II-6 and II-7 show posterior pole lesions, such as they were described by Braley (1966) in a family with "polymorphic macular degeneration". III-2,4 and III-6 demonstrate the intact vitelliform lesion. From this observation it is concluded that Braley's polymorphic degeneration and vitelliform dystrophy are identical.

4. Fam. Can
(CG-43.08.11)
1970: Navigator of an Italian ship. Is coming from the vicinity of Genoa. Visual complaints about the right eye since 3 months. There is no strabismus.
VOD S+1.25=C−2×180° 2/10; VOS S+2.50=C−2×10° 10/10.
Fundi: A 2 disc diameter vitelliform disc in the foveal area of OD. The disc is somewhat desintegrated. This is probably the cause of the decreased visual acuity (fig. 42a). The left eye demonstrates a beautiful 3 disc diameter vitelliform disc. It is perfectly intact (fig. 42b).
Fluorescein angiography: OS: There is hardly any fluorescence visible in the foveal area, indicating that there are no large defects in the pigment epithelium. There is no leakage of fluorescein subretinally. This indicates a normal membrane of Bruch (fig. 42c).

Summary: Pathognomonic vitelliform lesions in an Italian navigating officer who visited Rotterdam by ship. The 27-year-old man had had visual complaints since 3 months.
The opportunity to do fluorescein angiography in an intact vitelliform disc was gratefully accepted. The results suggest a primary localization of the vitelliform lesion in the retinal pigment epithelium.

5. Fam. E-W



II-1 (HCKvtH-98.05.11) Normal visual acuity until the age of 50. Is capable of reading papers. Refuses to come to the Eye Hospital.
Fundi: A 0.5 disc diameter area of atrophic pigment epithelium in the centre of the fovea.

II-5 (MPvtH-05.02.25)
1958: VOD S+3 3/10; VOS S+4.50 4/10.
Fundi: Pigmentary disruption in the foveal area.
Visual fields: Decreased central sensitivity.
Colour vision: Normal.
Dark adaptation: Normal.

ERG: Scot. b-waves OD 210μV; OS 205μV.
Phot. b-waves OD 100μV; OS 110μV.
1967: VOD S+5 3/10; VOS S+5.25 4/10.
Fundi: In the centre of the fovea a deposit of pigment, surrounded by a circular area of atrophic pigment epithelium.
Visual fields: Decreased sensitivity centrally.
Colour vision: Decreased sensitivity to red (anomaloscope). OD tritan axis; OS without characteristic axis (Farnsworth D-15).
Dark adaptation: Normal.
ERG: Unsuccesful.
EOG: OD 1.07; OS 1.34.

III-2 (EK-37.04.24)
1967: VODS 11/10.
Fundi: Mild pigment mottling in the posterior pole. The foveal reflexes are present but not quite normal.
EOG: ODS 1.00.
1969: VODS 11/10.
Fundi: A small yellowish-white deposit at the site of the foveola of the right eye. The left eye shows no pathological changes.

III-3 (JBJE-34.08.21)
1967: VODS 11/10.
Fundi: Normal.
EOG: OD 2.30; OS 2.10.

III-7 (RMKW-24.10.30)
1958: VOD 7/10; VOS 8/10.
Fundi: In the centre of the foveal area an atrophic area with fine pigmentary alterations.
Visual fields: Normal.
Colour vision: OD normal; OS Decreased sensitivity to red (anomaloscope).
Dark adaptation: Normal.
ERG: Normal.
1967: VOD 9/10; VOS 9/10. Emmetropic.
Fundi: A yellowish cystoid structure of 0.5 disc diameter. There is some pigmentary disturbance in this lesion.
Visual fields: Slightly decreased central sensitivity. Normal periphery.
Colour vision: Decreased red sensitivity (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 230μV; OS 195μV.
Phot. b-waves OD 100μV; OS 85μV.
EOG: ODS 1.00.

III-8 (KBW-26.04.28)
1960 en 1967: Fundi normal.
1969: VOD S+2 7/10; VOS S+1.50 8/10.
Fundi: Small round yellowish deposit in the centre of the fovea. Around the yellow foveola there are fine punctiform yellowish lesions.
EOG: ODS 1.00.

III-9 (AW-30.06.30) Brown hair, blue eyes. Poor visual acuity since early childhood. Nystagmoid movements with horizontal and rotatory components.
1951: VOD C+1.50×90° 6/10; VOS C+2×90° 6/10.
1957: VOD 4/10; VOS 3/10.
Fundi: No clear abnormalities. The fundi are quite blond, particularly around the disc. The vessels have a normal calibre. The foveae do not have normal reflexes and look hypoplastic.
Visual fields: Concentric decreased sensitivity.
Dark adaptation: The photopic part of the curve is 1 log. U. too high. The scotopic part of the curve is 2 log. U. too high.

1968: VOD 2/10; VOS 3/10.
The iris demonstrates some atrophic spots in the infero-nasal parts.
Fundi: Unchanged as compared to 1957.
Visual fields: Normal peripheral limitations. Decreased sensitivity concentrically and particularly centrally.
Colour vision: Mild red-green dyschromatopsia.
Dark adaptation: The curve starts 1 log. U. too high and ends 2.5 log. U. too high.
ERG: Scot. b-waves OD 61μV; OS 70μV.
Phot. b-waves ODS unrecordable.
EOG: OD 1.35; OS 1.31. Unreliable because of the nystagmus.

III-10 (JW-41.04.03) Blond hair, blue eyes.
1950: VOD S−2=C−2×5° 5/10; VOS S+1=C−3×165° 5/10.
1958: VOD 3/10; VOS 2/10.
Fundi: Blond fundi. No distinct abnormalities. Disc slightly pale temporally. The foveae have no normal reflexes and look hypoplastic.
Visual fields: Decreased sensitivity concentrically.
Dark adaptation: The photopic part of the curve is 1 log. U. too high. The scotopic part ends 2.5 log. U. too high.
ERG: Scot. b-waves 34μV; OS 52μV.
Phot. b-waves unrecordable.
1967: A delicate nystagmus latens. Slightly diaphanous irides.
VOD 3/10; VOS 2/10.
Fundi: The foveal reflexes are irregular and broader than normal.
Visual fields: Constriction of the isopters.
Colour vision: Decreased sensitivity to red (anomaloscope).
Dark adaptation: Phot. and scot. systems are disturbed. The curve ends 2.5-3 log U. too high.
ERG: Scot. b-waves OD 60μV; OS 45μV.
Phot. b-waves OD 45μV; OS unrecordable.
EOG: OD 1.40; OS 1.69. Fixation unreliable.

IV-2 (RBAE-55.06.06)
1961: VOD 5/5; VOS 5/15.
Fundi: In OD, a classic yellow vitelliform disc is visible (fig. 25a). In OS there is a red and yellowish coloured area of 1 disc diameter at the site of the fovea. There is no protrusion.
Visual fields: Normal.
Colour vision: Normal.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 305μV; OS 285μV.
Phot. b-waves OD 120μV; OS 125μV.
Systematic examination: Normal.
1967: VOD S−1.25 10/10; VOS S−1.25 10/10.
Fundi: Sharply defined circular structure at the fovea. There is no distinct protrusion. There are in this circular area yellow deposits, surrounded by an atrophic pigment epithelium. This atrophic pigment epithelium is redder than the surrounding normal retina. The yellow deposits protrude slightly from the atrophic pigment epithelium (fig. 25b).
Visual fields: Slightly decreased central sensitivity.
Colour vision: Decreased sensitivity to red (anomaloscope).
ERG: Scot. b-waves OD 265μV; OS 260μV.
Phot. b-waves OD 120μV; OS 115μV.
OP: Normal.
EOG: OD 1.22; OS 1.21.
1968: VOD S−1.50 8/10; VOS S−1.50 9/10.

IV-15 (RK-48.08.23)
1956: VODS 5/20.
1959: VOD S−1.50=C−1.50×180° 3/10; VOS S−0.50=C−0.50×180° 3/10.
1962: VODS 4/10.

Fundi: The foveal reflexes are irregular. The retina around the disc looks thin and very blond. The disc, vessels and retinal periphery show no distinct abnormalities.
Visual fields: Decreased sensitivity centrally and concentrically. Normal peripheral limitations.
Colour vision: Slightly decreased sensitivity to red (anomaloscope).
Dark adaptation: The curve is 1 log. U. too high for both systems.
ERG: Scotopic b-waves: rudimentary responses.
Photopic b-waves: unrecordable.
EOG: ODS 2.00.
1968: VODS 4/10. No diaphanous irides. No metamorphopsia.
Retinal functions: Unchanged as compared to 1962.
OP: Subnormal.
F-ERG and VER: Subnormal.
The subnormal F-ERG indicates a foveal hypoplasia and at least a foveal dysfunction.
EOG: ODS 1.75.

IV-16 (EK-58.02.03) Blond hair. Blue eyes.
1958: Photophobia since birth. Also nystagmoid movements with horizontal and rotatory components.
1964: VOD S+1=C+0.50×180° 5/60; VOS S+1.50 5/60.
Fundi: Irregular foveal reflexes. There is some macular yellow present. The disc is slightly pale temporally. The vessels and periphery are normal. The peripapillary area is very blond.
1967: VODS 5/60. The irides are slightly diaphanous in the periphery.
Fundi: No changes as compared to 1964.
Visual fields: Normal periphery. Decreased sensitivity centrally and concentrically.
Colour vision: Mild red-green dyschromatopsia (HRR).
Dark adaptation: The curve ends 2 log U. too high. Both systems are disturbed.
ERG: Scot. b-waves OD 95μV; OS 100μV.
Phot. b-waves ODS unrecordable.
EOG: Unreliable because of nystagmus.

Summary: An interesting pedigree, in which 2 hereditary retinal diseases occur: a. vitelliform dystrophy of the fovea and b. X-linked hemeralopia. The following individuals are affected by vitelliform dystrophy: II-1,5; III-7,8 and IV-2. Affected by X-linked hemeralopia are III-9,10 and IV-15,16.
IV-2 demonstrates a fundus picture pathognomonic for vitelliform dystrophy. His mother (III-2) had normal foveae in 1967, however her EOG was definitely subnormal. As her husband (III-3) had a normal EOG, III-2 was detected as a carrier. In 1969 she showed a mild ophthalmoscopic abnormality in the right eye, indicating that the EOG is a valuable detector for carriers of the gene causing vitelliform dystrophy. II-5 and III-7 are in all probability having 2 pathological genes. The only ophthalmoscopic abnormalities visible are mild vitelliform changes in the foveal area. X-linked hemeralopia is not giving any detectable abnormality in the carriers, as we saw in fam. SKn and Ver. It is interesting to note that the children of II-5 and III-7 only have X-linked hemeralopia and no vitelliform dystrophy.

6. Fam. Fl
II-2 (CFvD-82.07.20)
Fundi: Circular areas of atrophic pigment epithelium in the fovea. Some pigmentary disruption. The areas are approximately 2 disc diameter in size.

III-1 (MBF-13.05.30)
1955: VODS S+1 3/10.
Diagnosis: "retinitis centralis serosa".
1962: VOD S+1.50 3/10; VOS S+1.50 2/10.
1966: VODS 1-2/10.
1968: Fundi: The fovea has a scrambled egg appearance. Yellow deposits in a circular area of atrophic pigment epithelium.

III-3 (GF-17.08.06)
1968: VOD S+2 4/10; VOS S+2 5/60. Reads D=0.50 with S+5.50.

Fundi: OD: A circular cystoid structure of 1.5 disc diameter in the foveal area. There is a small pseudo-hypopyon and yellowish-white deposits are also found (fig. 27).
OS: A flat cystoid structure at the site of the fovea, approximately 1 disc diameter in size. There are severe pigmentations in the shape of a sickle at the bottom (fig. 29).
EOG: ODS 1.25.

III-5 (WvBF-24.05.05)
1964: VOD 2/10, emmetropic; VOS S−0.50 5/10.
Diagnosis: "Familial cystoid macular degeneration".
1968: Fundi: Vitelliform structure in the scrambled egg stage. The foveal and foveolar reflexes are normal in spite of the atrophic pigment epithelium at the site of the fovea.

III-6 (JF-26.02.08)
1968: Army sergeant. Complains of impairment of visual acuity and colour vision. The visual complaints started 12 years ago with metamorphopsia and decreased visual acuity.
VODS: S−0.50=C+0.50×90° 2/10; Reads D=0.8 with addition.
There is metamorphopsia (Amsler test).
Fundi: A vertical oval of yellow deposits in a honeycomb pattern, approximately 3 disc diameter in size (fig. 2). The right disc shows a pit, while there is a pigmented spot at the bottom of the retinal periphery.
Visual fields: Central scotoma.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
EOG: ODS 1.25.

IV-1 (KB-36.01.25) Has been in the military service.
1967: VOD S+1=C−0.75×130° 5/10; VOS S+1=C−0.75×90° 5/10.
Fundi: Yellow deposits in a circular area at the site of the fovea.

IV-2 (GB-42.04.18) Has some problems in distinguishing colours, particularly red.
1967: Fundi: OD shows a cystoid structure of 1 disc diameter in the foveal area. There is some pseudo-hypopyon.
OS demonstrates a somewhat larger cystoid structure. At the bottom there is a small pigmentation, resembling the scar of choroiditis.

IV-3 (KB-46.03.11) Truck driver. Not present, when the family was examined.

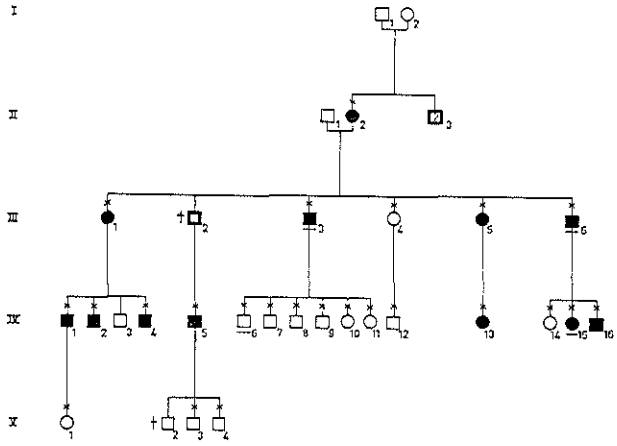
IV-4 (HB-57.10.24)
1967: VOD S+2 6/10; VOS S+2=C−1×120° 4/10.
Fundi: The fovea shows a symmetrical intact vitelliform disc of 1 disc diameter.

IV-5 (GF-38.02.13) Has a licence for driving a car.
1967: Fundi: Circular areas of atrophic pigment epithelium in the centre of the posterior pole. There are some yellow deposits and pigmentations in these areas.

IV-13 (HvB-48.10.18)
1964: VOD S+0.25 3/10; VOS S+0.25 9/10.
1968: No visual complaints.
Fundi: OD: A circular cystoid structure in the foveal area, approximately 1.5 disc diameter in size. Yellow deposits and red atrophic areas are visible.
OS: A circular cystoid structure in the foveal area, 2/3 disc diameter in size.

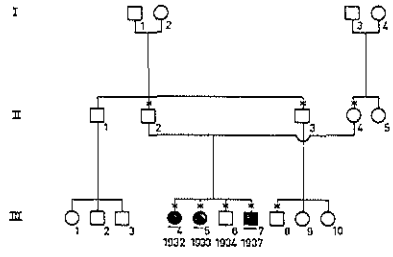
IV-15 (AF-59.03.21)
1968: VODS S+0.50 11/10. No metamorphopsia.
Fundi: OD: Small yellowish cyst on the temporal side of the foveola (fig. 17). The disc has an "optic pit".
OS: Fine yellowish spots on the temporal side of the foveola (fig. 18). The retinal periphery of both eyes shows a rather coarse granular pigmentation.
Visual fields: Normal.
Colour vision: Normal.
Dark adaptation: Normal.
EOG: OD 1.42; OS 1.43.
1970: VODS 11/10. The fundi are quite unchanged.

IV-16 (GF-61.01.04)
1968: VOD S+0.50; VOS S+0.50 10/10.
Fundi: Perfectly intact vitelliform disc, 1 disc diameter in size. Some fine whitish punctiform structures are visible in the disc. There is no prominence of the vitelliform structure.
Colour vision: Normal.
EOG and photography do not succeed because of crying.
1970: VODS 8/10, emmetropic.
Fundi: The vitelliform structures are slightly disintegrated (ruptured) (fig. 3).



Summary: A pedigree, in which a regular dominant inheritance pattern is present. The penetrance of the vitelliform dystrophy is high. The foveae of III-6 closely resemble the lesions described and photographed by Braley (1966). Braley suggested the term "polymorphic macular degeneration" for this picture and he doubted the relationship of vitelliform dystrophy and "polymorphic macular degeneration". In our opinion there is no such entity as "polymorphic macular degeneration". The son of III-6 (IV-16) had perfectly intact vitelliform discs in 1968 and slightly desintegrated lesions in 1970 (fig. 3). The polymorphic pattern of vitelliform dystrophy is beautifully demonstrated when we compare the fovea-pictures of III-6 and IV-16.

7. Fam. KlK



II-2 (HCKK-01.01.06) Strong hypermetropia. This could indicate the carrier state.
Spectacles: OD S+4=C+2×10°; OS S+5=2×180°.
Fundi: Normal foveae. Some small haemorrhages perifoveally.

II-4 (JKKT-99.04.15)
Fundi: Normal foveae.

III-4 (WGMKK-32.01.11) Complains of photophobia. Likes best to be in dusk.
1938: VOD S+4.50=C+1.50×95° 1/10; VOS S+5=C+1.50×95° 5/10.
1939: Impairment of visual acuity.

Fundi: Vesicle-like yellow structure in both foveae.
1948: VOD 2/10; VOS 3/10.
Fundi: Yellowish deposits in cystoid structures.
1960: VOD 1/10; VOS 2/10.
1967: VOD 5/60; VOS 1/10. Concomitant divergent strabismus. Eccentric fixation.
Fundi: Circular structures in the fovea, approximately 2-3 disc diameters in size. Disintegrated vitelliform disc, "scrambled egg appearance". Yellow deposits surround the central area of atrophic pigment epithelium (fig. 6).
Visual fields: Decreased central sensitivity.
Colour vision: Red-green and blue-yellow dyschromatopsia (HRR). Decreased red-sensitivity (anomaloscope). Tritan axis in OS (Farnsworth D-15).
Dark adaptation: Normal.
ERG: Scot. OD 290μV; OS 370μV. Phot. b-waves OD 100μV; OS 120μV.
EOG: ODS 1.20.

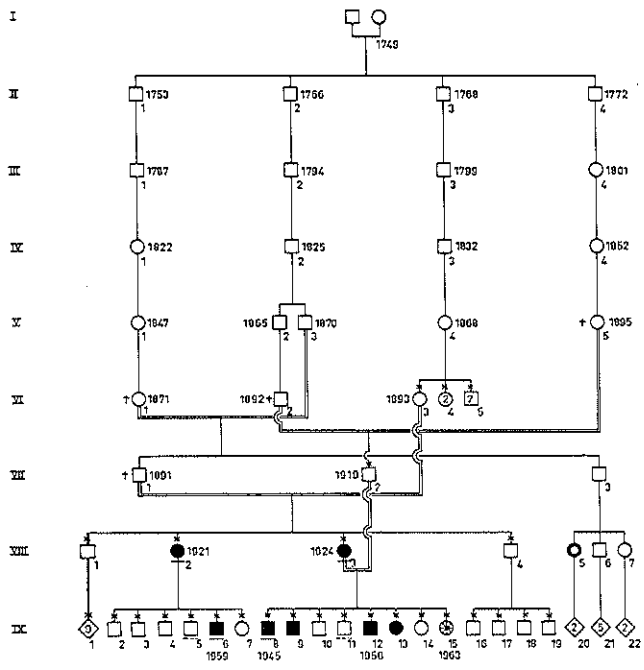
III-5 (MKK-33.05.28) Poor visual acuity since the age of 10.
1947: VOD S+2 2/10; VOS S+2 3/10.
Fundi: Picture resembling disciform foveal degeneration.
1967: VOD S+4 2/10; VOS S+4.50 2/10.
Fundi: Circular area of atrophic pigment epithelium, which measures approximately 5 disc diameters in the right posterior pole. This area is surrounded by a garland of yellow deposits (fig. 4). The left fovea shows a ruptured vitelliform cyst, approximately 1 disc diameter in size. In the centre of this cyst there are strong pigmentations.
Visual fields: Decreased central sensitivity.
Colour vision: Red-green and blue-yellow dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope). Tritan axis in ODS (Farnworth D-15).
Dark adaptation: The curve is slightly too high. No significant pathology.
ERG: Scot. b-waves OD 370μV; OS 345μV; Phot. b-waves OD 165μV; OS 155μV.
EOG: OD 1.18; OS 1.15.

III-7 (AWMKK-37.04.05)
1945: Fundi: Vitelliform disc in the foveal area.
1952: VOD 4/10; VOS 2/60.
Fundi: Cystoid structure in the right fovea. The horizontal diameter measures 2 disc diameters, while the vertical diameter measures 3 disc diameters. There is a large pseudohypopyon with pseudo-Descemet-deposits (fig. 5a). The left fovea shows a circular area of atrophic pigment epithelium with pigmentations and yellowish deposits.
1967: VOD S+1.50 3/10; VOS S+1.50 2/10.
Fundi: OD: Yellow deposits at the bottom of a vertical oval structure. The cystoid structure is disintegrated. Severe pigmentations at the site of the former pseudohypopyon (fig. 5b).
OS: Disintegrated vitelliform lesion. At the bottom yellow deposits and pigmentary disruption.
Visual fields: Decreased central sensitivity.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased red sensitivity.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 222μV; OS 240μV. Phot. b-waves OD 155μV; OS 190μV.
EOG: ODS 1.00.

Summary: One man and his two sisters have suffered from vitelliform dystrophy sinc early childhood. The evolution of the vitelliform disc has a rapid course in this family. The visual acuities are severely disturbed at a relatively young age, in contrast to what is usually described in literature.
It was not possible to perform electro-oculography in the parents (II-2,4). The father might be the carrier of the pathological gene since he has a high hypermetropia, as have his 3 affected children. This family was reported by Pameyer in 1952 at a meeting of the Netherlands Ophthalmological Society (Pameyer, 1954). Pameyer reported on the different stages of development of the vitelliform disc. He distinguished the following stages: 1. macular vesicle without contents. 2. appearance of liquid contents with fluid level "hypopyon". 3. appearance of "precipitates" against the posterior pole of the retina. 4. picture of the disciform degeneration. 5. total degeneration of the affected region.

The stages in which we examined the patients resemble the pictures found in "polymorphic macular degeneration", described by Braley (1966). The development of the foveal picture in this family indicates that vitelliform dystrophy and polymorphic macular degeneration are identical.

8. Fam. Ko-K



VIII-2 (JdJK-21.03.06)
1968: VOD S+1.50 6/10; VOS S+2 7/10.
Fundi: In the foveae a very small honeycomb pattern of yellowish-white deposits. Around these deposits some fine pimentations (fig. 15).
Colour vision: Normal.
EOG: OD 1.15; OS 1.30.

VIII-3 (GKK-24.02.02)
1968: VOD S−1=C+1.50×30° 4/10; VOS S−1.25=C+1.75×155° 11/10.
Fundi: In the right fovea a circular vitelliform disc, approximately 0.5 disc diameter in size. This structure is much better visible on panchromatic than on orthochromatic film. In the left eye a small horizontally ovoid defect in the pigment epithelium. There are whitish deposits in this atrophic area (fig. 19).
EOG: OD 1.20; OS 1.22.

IX-6 (TdJ-59.05.08)
1968: VODS 8/10, emmetropic.
Fundi: A classic vitelliform disc, approximately two-thirds of a disc diameter in size in both foveae. The disc has a yellowish-orange colour and is surrounded by a brown-red circle (fig. 1). The disc and vessels are normal. The retinal periphery shows a fine granular pigmentation.
Colour vision: Decreased sensitivity to red (anomaloscope).
EOG: OD 1.28; OS 1.31.

IX-8 (AK-45.07.04) This boy is the proband of the family.
1961: Hospitalized. Impairment of visual acuity after furunculosis.
VOD C−0.50×180° 7/10; VOS S−0.75 4/10.

Fundi: The right fovea shows a yellowish-white "scar of a choroiditis" surrounded by pigmentations. The left eye demonstrates a cystoid structure with in the centre a small haemorrhage.
Diagnosis: Possibly toxoplasmosis.
Therapy: Prednisone, achromycin, vitamine B complex.
Systemic examination: Normal.
1962: Ten months after hospitalization the visual acuity of both eyes is 10/10.
1968: VOD S+0.50 5/10; VOS 11/10, emmetropic.
Fundi: A circular yellowish-white structure approximately 1 disc diameter in size with severe pigmentations at the bottom in the right fovea (fig. 26). The left fovea shows a cystoid structure with a pseudohypopyon at the bottom.
Visual fields: Central scotoma in the right eye. Normal in the left eye.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 320μV; OS 280μV.
Phot. b-waves OD 80μV; OS 101μV.
EOG: OD 1.24; OS 1.17.
F-ERG and VER: OD subnormal.

IX-9 (AK-46.11.10)
1968: VOD 10/10; VOS 6/10; emmetropic.
Fundi: Delicate pigmentations and whitish flecks in the foveal area. The abnormal area is approximately 0.25 disc diameter in size. The lesions are better discernible on panchromatic than on orthochromatic film.

IX-12 (AK-56.04.18)
1968: VOD C−0.50×180° 10/10; VOS S−0.50=C−0.50×180° 10/10.
Fundi: A perfectly circular vitelliform disc, approximately two-thirds of a disc diameter in size in both foveae. The lesions are strikingly symmetrical. The panchromatic films demonstrate more abnormalities than do the orthochromatic films (fig. 38).

IX-13 (TK-58.06.14)
1968: VODS C−0.50×180° 10/10.
Fundi: Vitelliform disc in the foveal area. The disc measures one disc diameter.

IX-15 (GK-63.05.21)
Blind since early childhood and probably since birth. There is ologophrenia and generalized epilepsy. The pupillary reactions are absent and the discs are pale. No electrophysiological examinations have been performed.

An EOG was made of IX-5 (AdJ-55.05.12) and IX-11 (TK-52.04.25) in order to establish whether they were carriers or not. Both individuals had a normal EOG. The former OD 1.98; OS 2.15 and the latter OD 2.20; OS 2.10.

Summary: A pedigree in which vitelliform dystrophy is inherited in a regular dominant manner. Genealogical examination revealed a striking number of consanguineous marriages in this pedigree. The proband is in 5 ways related to the couple who married in 1749, 3 times on the side of the father and 2 times on the side of the mother. This pedigree demonstrates the extreme degree in which in-breeding may be present in some parts of The Netherlands. Since vitelliform dystrophy is inherited in a dominant manner the consanguineousness is not so important as in recessively inherited diseases. The genealogical examination was done in order to establish whether there were any relationships with other pedigrees in which vitelliform dystrophy occurs.

9. Fam. K-Z
I-1 (PZ-89.06.06)
VOD S+1.50 10/10; VOS S+2 10/10.
Fundi: Normal foveae.
EOG: OD 2.37; OS 2.90.

I-2 (JAZS-92.02.15)
VOD S+6.50=C+0.75×180° 10/10; VOS S+5.75=C+1×180° 4/10.
Fundi: Small yellowish deposits in the centre of the foveal area.
EOG: ODS 1.00.

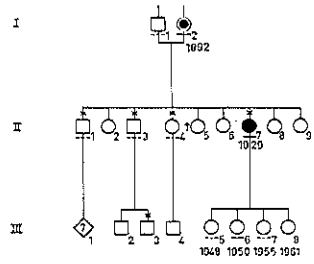
II-7 (MKZ-29.02.23) Visual complaints since the age of 8. Further decrease in visual acuity at the age of 30. Particularly visual impairment after deliveries. The family-history was negative and the definite diagnosis could only be made with the help of the EOG.
1962: VOD S+4.50=C+1×180° 4/10; VOS S+4.50=C+1.50×180° 1/10.
There is concomitant divergent strabismus of OS.
Fundi: The foveal areas show a disciform pathological process. The disc and vessels are normal. The retinal periphery demonstrates a fine granular pigmentation.
Visual fields: OD: central sensitivity decreased. OS: central scotoma.
Colour vision: Red-green dyschromatopsia (HRR).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 305μV; OS 275μV; Phot. b-waves OD 90μV; OS 120μV.
EOG: OD 1.10; OS 1.16.
Systemic examination: Normal.
1963: No important changes as compared to 1962.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 390μV; OS 465μV.
Phot. b-waves OD 65μV; OS 70μV.
EOG: OD 1.13; OS 1.14.
1964: VOD 3/10; VOS 2/10.
Colour vision: Tritan axis (Farnsworth D-15).
1965: Dark adaptation: Normal.
ERG: Scot. b-waves OD 250μV; OS 210μV. Phot. b-waves OD 65μV; OS 70μV.
EOG: ODS 1.00.
1967: VOD S+5.50=C+1×180° 2/10; VOS S+5.50=C+1.50×180° 2/10.
Better subjective vision with dark glasses.
Fundi: OD: Circular area of atrophic pigment epithelium, approximately 0.5 disc diameter in size. Yellow deposits are present in this area, which is situated at the site of the fovea.
OS: Rather ill-defined circular area of atrophic pigment epithelium in the fovea. This area measures approximately 1 disc diameter. Between the disc and the foveal lesion and slightly upward is an intact vitelliform disc, which measures one disc diameter (fig. 20a).
Visual fields, dark adaptation, ERG and EOG are unchanged, as compared to 1965.
Colour vision: Red-green dyschromatopsia (HRR). Decreased red sensitivity (anomaloscope).
Fluorescein angiography: Slightly pathological fluorescein pattern indicating defects in the retinal pigment epithelium at the fovea and at the site of the extra-foveal vitelliform lesion (fig. 20b).
1969: Visual acuity: Unchanged.
Fundi: The second vitelliform lesion in the left eye, which was localized extra-foveally, has disappeared without leaving any trace. The foveal lesions in both eyes are unchanged.
ERG: Scot. b-waves OD 220μV; OS 238μV.
Phot. a-waves OD 51μV; OS 50μV.
Phot. b-waves OD 128μV; OS 142μV.
F-ERG: Normal.
VER: Normal.

III-5 (KK-48.06.14)
VODS S+0.50 11/10.
Fundi: Normal foveae.
EOG: OD 2.26; OS 2.36.

III-6 (JK-50.09.09)
VODS 11/10.
Fundi: Normal. The foveae show a delicate granular pigmentation.
EOG: OD 1.10; OS 1.00.

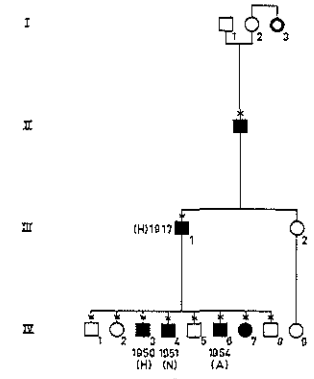
III-7 (MK-55.02.08)
VODS 11/10.
Fundi: Normal.
EOG: OD 2.00; OS 1.93.

III-8 (AK-61.08.13)
VODS 10/10.
EOG: Unreliable because of bad fixation.



Summary: A pedigree in which vitelliform dystrophy occurs. There is only one individual who is ophthalmoscopically clearly affected. The EOG renders the diagnosis. I-2, who has slight ophthalmoscopic alterations and III-6, who has ophthalmoscopically normal foveae, were detected as carriers with the help of the EOG. Of great interest is the finding of a second, extrafoveally localized, vitelliform lesion in the left eye of II-7. This lesion disappeared without leaving any visible trace.

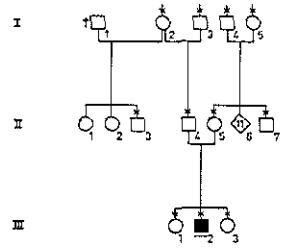
10. Fam. Me



This pedigree has been examined at home. It is well known in this family, that poor visual acuity occurs in every generation. The inheritance has a regular dominant pattern. All affected individuals show disintegrated vitelliform lesions with a circular area of atrophic pigment epithelium as the predominant sign. Pigmentations occur in a lesser degree, while yellowish deposits are present in all examined affected individuals (II-1; III-1; IV-3,4,6,7). The most extensive dystrophic changes were found in the elder patients.

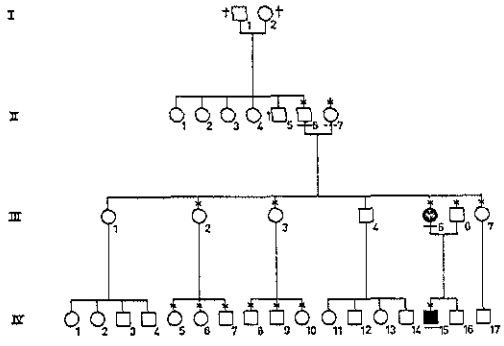
11. Fam. Pl
III-2 (LP-50.10.14)
1959: Diminishing visual acuity. Hospitalized.
VOD S+5=C+0.50×95° 4/60; VOS S+4=C+1×90° 2/10.
After 2 weeks: VOD 2/10; VOS 3/10.
Fundi: Intact vitelliform disc in the foveal area.
Visual fields: Decreased central sensitivity.

Colour vision: Decreased red-sensitivity (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 255μV; OS 325μV. Phot. b-waves OD 90μV; OS 95μV.
Systemic examination: Normal.
Therapy: Prednisone.
1963: VODS 3/10.
Fundi: A haemorrhage has occurred in the vitelliform cyst of the left eye (fig. 11).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 300μV; OS 205μV.
Phot. b-waves OD 75μV; OS 90μV.
EOG: ODS 1.40.
After 1 month the haemorrhage disappeared. VOS 6/10.
1967: VOD S+4.50=C=1×90° 2/10; VOS S+3.50=C+1×90° 9/10.
Fundi: Circular areas of atrophic pigment epithelium in the foveal area. These areas are redder than the surrounding apparently normal retina. Some pigmentations and yellowish deposits are spread in the atrophic areas.



Summary: Vitelliform dystrophy in a 9-year-old boy. At the age of 13 he developed a haemorrhage in one of the vitelliform lesions. This haemorrhage disappeared in 1 month time and visual acuity returned from 3/10 to 9/10. The parents being ophthalmoscopically normal, refused electro-oculographic examination.

12. Fam. T-T



II-6 (LvdT-05.02.10) Family history negative.
VODS S+3 10/10.
Fundi: Normal foveae. Perifoveally in OD some drusen-like yellowish deposits.
EOG: ODS 1.20.

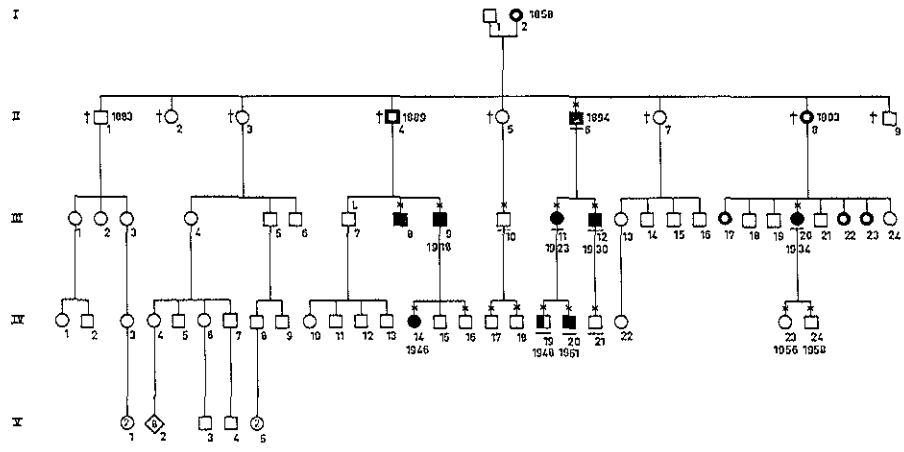
II-7 (LvdTH-08.12.27)
VOD S−3 8/10; VOS S−0.50=C−0.50×90° 10/10.
Fundi: Normal foveae. The retinal periphery shows large areas of chorio-retinal atrophy with many so-called "dyshorische Herdchen".
Visual fields: Normal peripheries. Concentrically slightly decreased sensitivity.
EOG: OD 1.92; OS 1.93.

III-5 (ACTvdT-41.03.16) Concomitant divergent strabismus of OD.
VOD S+3.50 0.5/60; VOS S+3.25=C+0.50×180° 10/10.
Fundi: Fine granular pigmentations in both foveae. In the foveal area of OS there are also some yellowish flecks.
Visual fields: Central scotoma OD. Normal in OS.
Colour vision: OD impossible to record. OS normal.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 235 μV; OS 245 μV.
Phot. b-waves OD 105 μV; OS 115 μV.
EOG: OD 1.00; OS 1.37.

IV-15 (GAT-61.05.20)
1966: Decreased visual acuity. Slight strabismus of OD.
VOD S+4.50 5/15; VOS S+3 5/5.
Fundi: Normal foveae.
1968: VOD S+3.50 8/10; VOS S+2 9/10.
Fundi: Intact vitelliform disc at the site of the fovea. These discs measure approximately 1 disc diameter. The upper half of the lesions is reddish, while the lower half is yellowish (fig. 8).
Colour vision: Normal.
EOG: ODS 1.20.

Summary: A pedigree in which vitelliform dystrophy occurs with increasing expression in the younger generations. II-6 has normal foveae ophthalmoscopically, but his EOG is definitely subnormal. Consequently he is a carrier. III-5 has slight foveal alterations and a subnormal EOG. IV-15 has the classic vitelliform lesions and also a subnormal EOG. The penetrance of the gene of vitelliform dystrophy seems to be low in this family. We could not examine the whole family because many family members had emigrated.

13. Fam. U-T



II-6 (LT-94.11.16)
1968: VOD S+2.50 1/10; VOS S+2.50 3/10.
Fundi: Sharply defined horizontal oval of atrophic pigment epithelium and choroid, in which glistening reflexes are present, in the foveal area of OD (fig. 34a). Sharply defined circular zone of chorioretinal atrophy in the foveal area of OS (fig. 34b). The peripheries of both eyes show a fine granular pigmentation.
EOG: ODS 1.30.

III-8 (PT-15.04.05)
1963: Circular areas of atrophic pigment epithelium in both foveal areas. Pigmentations and yellowish deposits are present in these areas.

III-9 (JT-18.01.07)
1962: VOD 2/10; VOS 5/10. Emmetropic.
Diagnosis: "Central chorioretinitis caused by tuberculosis".
1966: VOD 1/10; VOS 3/10.
Fundi: Circular areas of chorioretinal atrophy in the foveal areas.

III-11 (EUT-23.03.08) Visual complaints for the first time at the age of 10.
1962: VOD S+2 2/10; VOS S+3 1/10.
1968: VOD S+4 2/10; VOS S+3.50 1/10.
Fundi: Circular area of atrophic retinal pigment epithelium, approximately 3 disc diameters in size. "Scrambled egg" appearance.
Visual fields: Central scotoma of 8 degrees.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased red sensitivity (anomaloscope). OS protan axis (Farnsworth D-15).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 320μV; OS 378μV. Phot. b-waves OD 89μV; OS 135μV.
EOG: ODS 1.00.

III-12 (ERT-30.05.24) First visual complaints at the age of 6. Was hospitalized at that time.
1968: VOD S+9 2/10; VOS S+10.50 5/10.
Fundi: OD: Cystoid structure approximately 1.5 disc diameter in size in the foveal area. There is a pseudo-hypopyon and there are pseudo-Descemet precipitates (fig. 35a).
OS: A structure resembling the foveal lesion of OD. In this case the cystoid structure measures approximately 2.5 disc diameters (fig. 35b).
The retinal peripheries show a fine granular pigmentation.
Visual fields: Decreased central sensitivity.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased red sensitivity (anomaloscope).
EOG: ODS 1.00.

III-20 (OKIESH-34.10.30) Reports, that her mother has had bad visual acuity from childhood. Three of her sisters are reported to have poor vision, too. Her parents and brothers and sisters had emigrated to Australia. OD has poor vision since many years.
1969: VOD 6/60; VOS 11/10. Emmetropic.
Fundi: OD: Circular foveal structure of 1 disc diameter. Severe pigmentations suggest a scar of chorioretinitis. On the upper temporal side of the disc a naevus pigmentosus (fig. 32).
OS: Circular area of atrophic pigment epithelium, 1 disc diameter in size. Yellowish deposits are found at the bottom of this structure.
EOG: ODS 1.00.

IV-14 (SET-46.07.08) No visual complaints.
1968: "Scrambled egg appearance" in both foveae. A circular ruptured vitelliform lesion, approximately 1 disc diameter in size.

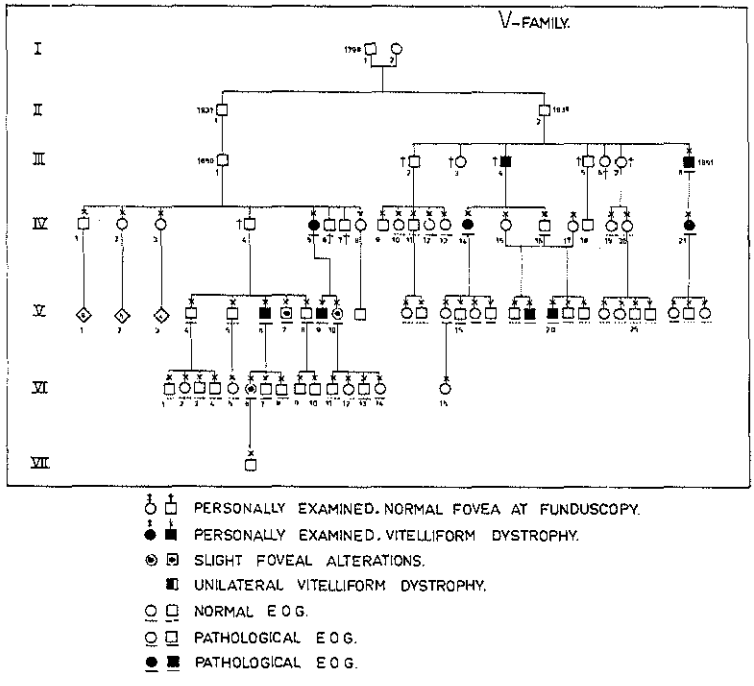
IV-19 (BLU-48.01.06)
1962: VOD 2/10; VOS 10/10 emmetropic. "Scar of toxoplasmosis-chorioretinitis OD".
1968: VOD 1/10; VOS 10/10 emmetropic.
Fundi: OD: Vitelliform disc in the right fovea. Approximately 1 disc diameter in size. Fine radial folds surround this lesion.
OS: Normal. The fovea is perfectly normal. The retinal peripheries are showing a fine granular pigmentation and some areas with pigmentations and depigmentations (fig. 24).
Colour vision: Mild red-green dyschromatopsia (HRR)
Decreased red sensitivity (anomaloscope)
Tritan axis (Farnsworth D-15)
} OD
OS: Normal
EOG: ODS 1.30.

IV-20 (LJU-51.06.06) Poor visual acuity since 1964. The vision of OD decreased during the last months.
1966: VOD 1/10; VOS 2/60 emmetropic.

Fundi: Vitelliform dystrophy in both foveae. The retinal periphery shows in the inferior temporal quadrant a disinsertion from 4-6 hours. The disinsertion was treated operatively with good result.
1968: VODS 1/10, emmetropic.
Fundi: Vitelliform disc in the right fovea (fig. 21). The left fovea shows a circular area of atrophic pigment epithelium. Yellowish deposits are visible in this area. The surroundings of the atrophic foveal area have a swollen aspect. The vitelliform disc, present before the operation, has disappeared. The retinal periphery of the left eye shows pigmentations in the infero-temporal quadrant.
Visual fields: Central scotoma. Restriction of the periphery supranasally in the left eye.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased red sensitivity (anomaloscope). Tritan axis (Farnsworth D-15).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 330μV; OS 380μV.; Phot. b-waves OD 145μV; OS 110μV.
EOG: OD 1.26; OS 1.30.

Summary: A rather large pedigree with vitelliform dystrophy, with a regular dominant inheritance pattern. The following points are of interest:
1. We had the opportunity to make photographs of the vitelliform lesion in a 74-year-old man (II-6) (fig. 34).
2. One individual had a unilateral vitelliform lesion. The right eye was affected and had a visual acuity of 1/10. The left eye had ophthalmoscopically normal foveae and had a visual acuity of 10/10. This is a good case to compare the acquired dyschromatopsia of the right eye with the (normal) colour vision of the ophthalmoscopically unaffected left eye (IV-19).
   The EOG is definitely subnormal in both eyes, indicating that the EOG is completely independent of the ophthalmoscopic aspect.
3. IV-20 spontaneously developed an anterior dialysis in the infero-temporal quadrant of his left eye at the age of 15.

14. Fam. Vr



III-4 (GV-84) Decreased visual acuity in 1933.
1959: Seventy-five years of age.
VODS S+4=1/10.
Fundi: Atrophic areas in the posterior pole. This man died some years ago.

III-8 (AV-91.02.17) Visited Prof. van der Hoeve in Leiden in 1927 because of visual complaints. His daughter had the same foveal affection at that time. Nothing is known about the visual functions of the parents.
1968: VOD S+1=C+1.50×100° 1/10; VOS S+0.50=C+1.50×85° 1.5/10.
Media: Incipient senile cataract.
Fundi: A circular area of chorioretinal atrophy at the site of the fovea. This area measures approximately 1.5-2 disc diameters in size.
Visual fields: Central scotoma. Normal periphery.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 120μV; OS 135μV.
Phot. b-waves OD 95μV; OS 105μV.
EOG: OD 1.14; OS 1.14.

IV-5 (JKV)
1968: VOD S+2=C+1×180° 3/10; VOS S+2.50=C+1×180° 5/10.
Fundi: Circular areas of pigment epithelium atrophy at the site of the fovea. These areas are approximately 1.5 disc diameter in size.
EOG: OD 1.20; OS 1.15.

IV-14 (JMVV-14.02.01)
1957: Decreased visual acuity after a delivery.
VOD 3/10; VOS 5/10.
Fundi: Round lesions in the foveal area.
1967: VOD S+0.50 4/10; VOS S+0.50 5/60.
Fundi: Horizontally ovoid foveal structures, approximately 1 disc diameter in size. The structures demonstrate an atrophic pigment epithelium (fig. 35).
Visual fields: Central scotoma.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased red sensitivity (anomaloscope).
OS: tritan axis (Farnsworth D-15).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 250μV; OS 235μV. Phot. b-waves OD 110μV; OS 80 μV.
EOG: OD 1.15; OS 1.15.

IV-16 (AV-18.02.24) The father, the sister, and 2 of the sons of this individual are ophthalmoscopically affected by vitelliform dystrophy of the fovea. The 2 sons have 2 different mothers, who both have normal eyes. Since this man has normal foveae he has to be a carrier of the gene of vitelliform dystrophy.
1968: VOD S+0.50 11/10; VOS S+1 11/10.
Fundi: Completely normal (fig. 41a).
Visual fields: Normal.
Colour vision: Normal.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 295μV; OS 255μV. Phot. b-waves OD 125μV; OS 110μV.
EOG: ODS 1.20. Fluorescein angiography: normal. (fig. 41b).

IV-21 (JMWV-19.12.14)
1949: VOD S+2=C+5×95° 3/10; VOS S+2=C+4×80° 5/10.
Fundi: Disciform foveal lesions.
1967: VOD S+3=C+5×95° 4/60; VOS S+3=4×80° 2/10.
Fundi: A circular area of atrophic pigment epithelium in both foveae. At the bottom yellowish deposits. The lesion in the right eye is larger than in the left eye.
Visual fields: Central scotoma of 10 degrees in the right eye and 5 degrees in the left eye.
Colour vision: Decreased sensitivity to red (anomaloscope).

Dark adaptation: Normal.
ERG: Scot. b-waves OD 255μV; OS 190μV.
Phot. b-waves OD 115μV; OS 110μV.
EOG: OD 1.14; OS 1.11.
Systemic examination: Normal.
1969: Fundi: Unchanged.
ERG: Scot. b-waves OD 315μV; OS 300μV.
Phot. a-waves OD 40μV; OS 49μV.
Phot. b-waves OD 120μV; OS 126μV.

V-6 (WV-23.08.23) Visual impairment at the age of 27. At the age of 35 further impairment.
1949: VOD 9/10; VOS 1/60. Concomitant divergent strabismus of OS.
Fundi: "Scar of central chorioretinitis" in both eyes. The left eye has a retina leporina.
1956: VOD 7/10; VOS 1/60.
1959: VOD 3/10; VOS 1/60.
1961: VOD S+2 1/10; VOS 1/60. Hospitalized and treated with prednisone.
Fundi: Yellowish-black cystoid lesions in the foveal area.
Visual fields: Central scotoma of 8 degrees.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope). Tritan axis (Farnsworth D-15).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 220μV; OS 245μV. Phot. b-waves OD 70μV; OS 80 μV.
EOG: ODS 1.00.
Systemic examination: Normal.
1968: VOD S+2 5/60; VOS S+2 1/60.
Fundi: OD: Circular area of atrophic pigment epithelium at the site of the fovea. At the bottom of this area a pseudohypopyon. The area is approximately 1.5 disc diameter in size (fig. 36a)
OS: A flat cystoid structure approximately 2 disc diameters in size in the foveal area (fig. 36b).
Retinal function tests: Unchanged.

V-7 (EV-24.07.26) Patient has low intelligence.
15-11-1967: VOD S+3 10/10; VOS S+3.50=C+0.50×180° 4/10.
Concomitant divergent strabismus of OS.
Fundi: OD: A tiny yellowish spot at the site of the foveola. Above the fovea and the disc 7 small round orangish-yellow structures are visible (fig. 7a).
OS: Normal.
Visual fields: Normal.
Colour vision: Normal.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 325μV; OS 290μV.
Phot. b-waves OD 135μV; OS 125μV.
EOG: OD 1.30; OS 1.30.
26-11-1968: Since 2 weeks light flashes in the left eye.
VOD S+3 8/10; VOS S+3.50=C+0.5°=×180° 4/10.
Fundi: A symmetrical intact yellowish-orange vitelliform disc in both foveal areas. The more central, the yellower is the disc. Binocular slitlamp examination suggests a localization in the retinal pigment epithelium (fig. 7b).
ERG: Scot. b-waves OD 345μV; OS 300μV.
Phot. a-waves OD 65μV; OS 60μV.
Phot. b-waves OD 145μV; OS 135μV.
F-ERG: Subnormal in both eyes. Poor fixation?
VER: Subnormal in both eyes.
EOG: ODS 1.10.
Fluorescein angiography: The fluorescein pattern is close to normal. There is a slightly fluorescing area in the centre of the fovea, but this is hardly discernible (fig. 7c).

V-9 (EGK-19.06.28)
1961: VODS 3/10.

Visual fields: Central scotoma.
Dark adaptation: Normal.
ERG: Normal.
1968: VOD S+4=C+1×90° 2/10; VOS S+4.50=C+1.50×90° 2/10.
Fundi: A circular, rather flat cystoid structure, approximately 1 disc diameter in size, at the foveal area. The retinal pigment epithelium at the site of the fovea is atrophic. Some yellowish deposits are present in the foveal structure (fig. 31).
Visual fields: Central scotoma of 5 degrees.
Colour vision: Decreased red-sensitivity (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 290μV; OS 285μV.
Phot. b-waves OD 85μV.; OS 95μV.
EOG: OD 1.35; OS 1.15.

V-10 (PVK-42.01.09) No visual complaints.
1968: VODS S+4 10/10.
Fundi: OD: A small circular yellow structure at the site of the foveola. This structure is approximately 0.15 disc diameter in size. Above the changed foveola there is another yellowish spot at a distance of 2 disc diameters.
OS: Normal.
Colour vision: Normal.
EOG: OD 1.12; OS 1.14.

V-19 (AGV-49.07.27)
1962: Suddenly visual complaints about OS.
1963: Rather suddenly impairment of visual acuity OD. Hospitalized with diagnosis "Chorioretinitis centralis duplex", possibly caused by toxoplasmosis.
VOD S+1.50 2/10; VOS S+2 1/10.
Fundi: Yellowish-white circular lesions surrounded by halos of pigment in the foveal area. There is a slight prominence of the lesions.
Visual fields: Central scotoma.
Colour vision: Decreased red-sensitivity (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 310μV; OS 330μV.
Phot. b-waves OD 115μV; OS 125μV.
Systemic examination: Normal. Patient is treated with prednisone and Tripyron.
1968: VOD 3/10; VOS 2/10.
Fundi: OD: The fovea demonstrates a vitelliform disc, approximately 1 disc diameter in size and surrounded by a halo of pigment. There are severe pigmentations in the centre of the disc (fig. 12a).
OS: A vitelliform disc, which measures 1 disc diameter in the foveal area. The superior part of the disc is yellower than is the inferior part (fig. 12b).
Visual fields: Central scotoma.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 275μV; OS 235μV.
Phot. a-waves OD 30μV; OS 30μV.
Phot. b-waves OD 75μV; OS 72μV.
F-ERG: Subnormal.
VER: Subnormal.
OP: Normal.
EOG: ODS 1.00.
Fluorescein angiography: Pathological fluorescence at the site of the fovea. This fluorescence is present in the arterial phase and increases in the venous phase. There is after-fluorescence for 30 minutes after the fluorescein has left the retinal vessels. No leakage of fluorescein is visible. The fluorescence decreases gradually, but the centre of the lesion, which was initially rather dark, shows increasing fluorescence until this decreases again. Possibly there is some staining of the contents of the vitelliform disc through a more or less pathologically changed Bruch's membrane. The main fluorescence pattern, however, indicates defects in the retinal pigment epithelium at the site of the fovea (fig. 12cd).

V-20 (EV-54.03.25)
1962: Hospitalized because of increasing loss of vision. The diagnosis was central chorioretinitis, possibly caused by toxoplasmosis.
VOD 3/10; VOS 2/60.
Fundi: OD: A cystoid foveal structure with a yellowish-white colour. Some small haemorrhages are visible in this structure.
OS: A circular yellowish lesion at the centre of the fovea. No haemorrhages.
Systemic examination: Normal. Was treated with dosulfine.
1967: VOD 3/10; VOS 9/10, emmetropic.
The visual acuity of OS has increased considerably!
Fundi: A yellowish-white cystoid structure in the foveal area. This lesion measures approximately 0.5 disc diameter (fig. 13).
Visual fields: OD: central scotoma. OS: Decreased central sensitivity.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: Normal.
ERG: Refused by the patient's father.
EOG: ODS 1.15.
12-6-1968: Metamorphopsia in both eyes. Visual impairment.
VOD 2/10; VOS 4/10.
Fundi: No distinct alterations. Therapy: oxyphenbutazone, 3 tablets/die.
24-6-1968: VOD 3/10; VOS 9/10!
The metamorphopsia is disappeared.
Fundi: The foveal structures are unchanged.

VI-6 (TvdWV-47.09.22)
1969: VODS 10/10, emmetropic.
Fundi: OD normal. OS demonstrates a tiny round yellow deposit at the site of the foveola (fig. 9). No other changes.
EOG: OD 1.30; OS 1.23.

IV-16, V-8, V-14, V-15, V-16, V-17, V-27, VI-7, VI-8, VI-13 and VI-14 all have a definitely pathological EOG and normal fundi:

V-8 EOG OD 1.20; OS 1.20	V-27 EOG OD 1.19; OS 1.12
V-14 EOG OD 1.13; OS 1.23	VI-7 EOG OD 1.00; OS 1.00
V-15 EOG OD 1.25; OS 1.16	VI-8 EOG OD 1.00; OS 1.00
V-16 EOG OD 1.06; OS 1.07	VI-13 EOG OD 1.36; OS 1.30
V-17 EOG OD 1.00; OS 1.00	VI-14 EOG OD 1.00; OS 1.00

Summary: A large pedigree in which there is a very low expression of the gene of vitelliform dystrophy of the fovea. Since many members of the family are ophthalmoscopically normal carriers of the gene, the faulty diagnosis of central chorioretinitis was made in some ophthalmoscopically affected individuals (IV-21, V-19, V-20). None of these individuals had abnormalities when examined systematically. Nevertheless a thorough anti-toxoplasmotic therapy was given.
The value of electro-oculographic examinations is fully demonstrated in this interesting pedigree.
Without the help of the EOG we detected our first carrier in this pedigree (IV-16). This man proved to be a carrier since his father, his sister and 2 of his sons (from 2 different women) were ophthalmoscopically affected, while he himself had normal foveae. This man had a severely pathological EOG and so we found the possibility to detect carriers by means of the EOG. We found 11 carriers in this pedigree with the help of electro-oculography.
The descendants of individuals with a normal EOG, always had a normal EOG in contrast to the descendants of individuals with a pathological EOG, who had a pathological EOG in approximately 50% of cases. This pedigree has taught us much about vitelliform dystrophy of the fovea.

15. Fam. WA
The proband of this large pedigree is V-3. He visited the Eye Hospital because of a rather sudden loss of central vision of the left eye. Examination of the family revealed, that this individual is related to the

family described by Huysmans in 1940 ("Exudative central detachment of the retina" or "Macular pseudocysts").

III-6 (PvAdJ-85) Never had serious visual complaints. The last few years there are reading problems.
Media: Incipient senile cataract OS. Mature cataract OD.
Fundi: OD invisible. OS demonstrates pigmentations in a circular area of atrophic pigment epithelium at the site of the fovea.

III-9 (DKdJ-95) Never had serious visual complaints.
Fundi: In both foveal areas a circular area, approximately 0.5 disc diameter in size. This area shows atrophic pigment epithelium and pigmentary disturbances.

III-10 (ABdJ) Uses pilocarpine eye drops because of a glaucoma simplex.
Fundi: Both foveae display a circular area, approximately 1 disc diameter in size with yellowish deposits and pigmentary disturbances. The picture resembles the scar of a chorioretinitis.

III-11 (JWW-81.10.15)
1938: Examined by Huysmans. VODS S+2 10/10.
Fundi: Normal. According to the pedigree this man has to be carrier of the gene of vitelliform dystrophy.

III-12 (HG-78.06.02)
1938: Examined by Huysmans. VODS S+1.75 10/10.
Fundi: Abnormal pigmentation in both foveae. Irregular perifoveal reflexes. This woman was suspected of being the carrier by Huysmans. The pedigree indicates that her husband (III-11) is the carrier.

IV-7 (AANvA-18.11.17) Poor visual acuity with OD since early childhood. Concomitant convergent strabismus of OD (10 degrees). Latent nystagmus ODS.
1969: VOD S+5=C+1×20° 5/60; VOS S+4.50=C+2.50×135° 11/10.
Fundi: OD: A small yellowish cystoid structure, approximately 0.25 disc diameter in size. Extending from the foveola to infranasally (fig. 16).
OS: Very small yellow flecks with pigment alterations in the centre of the fovea.
The retinal peripheries of both eyes demonstrate a diffuse granular pigmentation, which is not clearly pathological.
EOG: OD 1.24; OS 1.36.

IV-10 Father of an affected boy (V-5). This man has a concomitant convergent strabismus of his right eye. Furthermore there is latent nystagmus ODS.
Fundi: Normal.
Consequently this man is a carrier of vitelliform dystrophy of the fovea.

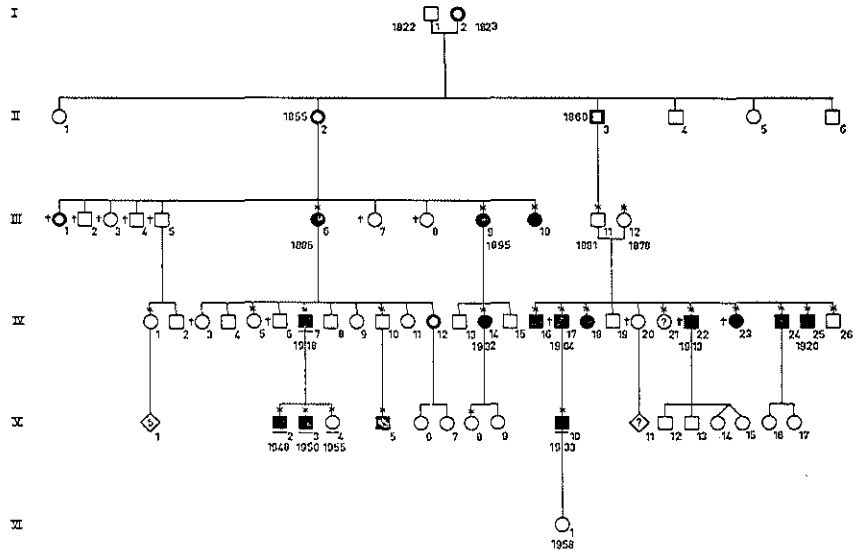
IV-14 (JSK-32.02.24) First visual complaints at the age of 24. At that time metamorphopsia. During pregnancies and after deliveries increasing visual complaints. Is treated with prednisone orally.
Fundi: OD: A darkly pigmented zone around a horizontal oval of atrophic pigment epithelium, which measures approximately 1 disc diameter.
OS: A circular yellowish cystoid structure, 1 disc diameter in size. Pseudohypopyon. No pigmentations.

IV-16, 17, 18, 21, 22, 23, 24, 25, 26 were described already by Huysmans in 1940.

IV-19 (ThBW-*08.05.01*) and IV-20 (BMHW-09.07.20) were not described in the pedigree published by Huysmans (1940).

IV-16 (HJW-00.02.10)
1939: VOD S+2=C+0.50×180° 5/10; VOS S+2=C+0.50×180° 8/10.
Fundi: Vitelliform discs in the foveal areas.
1958: VOD S+2.50=C+0.50×180° 7/10; VOS S+2=C+1.50×180° 7/10.
Fundi: Ruptured vitelliform discs. Circular areas of atrophic pigment epithelium.

IV-23 (HW-15.08.12)
1939: Vitelliform structures in the foveal areas.



1947: Vitelliform structures have disappeared. Irregular foveal reflexes.
1949: Fundi: No distinct alterations.

IV-25 (PAW-20.06.22)
1938: Fundi: Pigmentary disturbance in the foveal area.
1943: Fundi: Vitelliform discs in the foveal area.
1949: VOD S+5=C+2×65°; VOS S+5=C+1.50×15° 5/10.
Fundi: ODS:
Yellowish deposits in a honeycomb pattern at the site of the fovea.

V-2 (PvA-48.09.20) Photophobia.
1969: VOD S+2 8/10; VOS S+1.50 11/10.
Fundi: OD: Vitelliform disc, approximately 1 disc diameter in size at the site of the fovea. Pigmentations in the yellowish disc (fig. 39).
OS: Around the foveola some small yellowish deposits and fine pigmentations in a honeycomb pattern approximately 0.2 disc diameter in size.
EOG: OD 1.17; OS 1.10.

V-3 (JMvA-50.06.21) Many years ago the parents were told by an ophthalmologist that this boy was going to be blind.
1968: Suddenly visual impairment in OS. Prior to the visual impairment there has been metamorphopsia. Patient thought at first that the decrease in visual acuity was due to fatigue.
VOD S+6 10/10; VOS S+6 1/10.
Fundi: Vitelliform discs in the foveal area. Fine radiating folds around the vitelliform lesion in the left eye (fig. 14).
Visual fields: OD normal. OS Central scotoma of 15 degrees.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 320μV; OS 280μV.
Phot. b-waves OD 120μV; OS 100μV.
EOG: OD 1.40; OS 1.32.
Systemic examination: Sabin-Feldmann: 1:256 positive. Complement fixation reaction: negative.
1969: VOD 10/10; VOS 3/60.
Complains of a dark spot in the centre of the visual field.
Fundi: No changes.

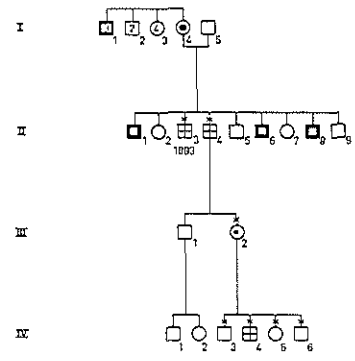
V-4 (MJvA-55.10.29)
VODS 10/10.
Fundi: Normal foveae. The retinal periphery displays a delicate granular pigmentation (fig. 23). The right foveola is more yellow than normal.
EOG: OD 1.22; OS 1.32. Re-examination ODS 1.00. Conclusion: carrier.

V-5 No visual complaints.
Fundi: In both foveae a circular area of atrophic pigment epithelium, yellowish deposits and pigmentations. Symmetrical lesions.

V-10 (JWW-33.05.18)
1963: VOD 9/10; VOS 11/10.
Fundi: Pigmentary disturbances arranged in a honeycomb pattern. The lesions are circular and located in the foveal area. The right eye had an anterior dialysis infratemporally. No trauma in the anamnesis. The disinsertion is succesfully operated.
1968: Dark adaptation: Normal.
ERG: Normal.
EOG: Definitely pathological.

Summary: A large pedigree with vitelliform dystrophy of the fovea. The mode of inheritance is not quite regularly dominant (IV-10 is a carrier). This pedigree was partly described by Huysmans (1940). It is clear by now that the family described by Huysmans suffers from vitelliform dystrophy. Huysmans choose the terms "Exudative central detachment of the retina" and "Macular pseudocysts".
As in fam. UT, there is a patient who also suffered from a disinsertion of the retina (V-10). Possibly there is a slight preponderance of anterior dialysis of the retina in individuals suffering from vitelliform dystrophy.

16. Fam. SKn



II-3 (AdK-93.09.20) Poor visual acuity since early childhood. Hospitalized for 8 weeks in 1929 because of his poor vision.
1968: Nystagmoid movements with horizontal and rotatory components. There is also a latent factor in the nystagmoid movements.
VOD S−13 3/60; VOS S−15 3/60. Reads D=0.80 with S−8.
Media: Senile cataract in both eyes.
Fundi: Blond fundi. Some isolated pigment spots in the periphery. The discs are slightly too pale. The vessels are normal.
Visual fields: Concentrically decreased sensitivity. There is also some peripheral constriction.
Colour vision: Mild red-green and blue-yellow dyschromatopsia.
Dark adaptation: Both systems are affected. The curve ends 2.5 log. U. too high.
ERG: Unrecordable.
EOG: OD 1.70; OS 1.34. Unreliable because of nystagmus.

II-4 (JdK-94.11.10) Poor visual acuity since early childhood. Fine nystagmoid movements with horizontal and rotatory components. There is also a latent factor. Concomitant convergent strabismus of OS.
1967: VOD S−8.50 2/10; VOS S−8 2/10.
Visual fields: Normal periphery. Concentrically decreased sensitivity.
Colour vision: Mild red-green dyschromatopsia (HRR).
Dark adaptation: Both systems are severely disturbed.
ERG: The scotopic and photopic components are severely disturbed.

III-2 (SdK-28.05.28) No visual complaints.
1968: VODS 10/10.
Fundi: Normal.
ERG: Scot. b-waves OD 220μV; OS 230μV.
Phot. b-waves OD 85μV; OS 80μV.
EOG: OD 1.92; OS 1.76.

IV-4 (ES-52.11.29) Poor visual acuity since early childhood.
1967: VOD 3/10; VOS 2/10; Emmetropic.
Fine horizontal nystagmoid movements.
Fundi: No distinct alterations. The foveal reflexes are not quite normal and have a somewhat irregular aspect. The vessels are normal. The discs are obliquely implanted (like in II-3).
Visual fields: Slight peripheral limitation. Concentrically decreased sensitivity.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope). Protan axis (Farnsworth D-15).
Dark adaptation: Both systems are disturbed. The curve ends 2.5 log. U. too high. No change as compared to 1958.
ERG: Scot. OD 80μV; OS 90μV. Phot. b-waves OD 40μV; OS 45μV.
EOG: Unreliable because of the nystagmoid movements.

Summary: In this pedigree there is a combined dysfunction of the scotopic and the photopic system of the retina. The mode of inheritance is sex-linked. This syndrome is usually called "sex-linked hemeralopia" (Franceschetti, François and Babel, 1963) or "hemeralopia-myopia syndrome". However, myopia does not have to be present in this syndrome (see for instance IV-4) and furthermore the scotopic system is not the only system affected. Therefore the designation of this syndrome is not yet satisfactory. The affection occurring in this pedigree closely resembles the affection described as "Åland syndrome" (Forsius and Eriksson, 1964; Waardenburg et al., 1967; Elenius et al, 1968). In our opinion it is doubtful whether the "Åland syndrome" constitutes a new distinct entity since there are no clear differences between this syndrome and the X-linked hemeralopia (perhaps connatal retinal dysfunction or X-linked retinal hypoplasia is a better name).
This pedigree is reported since in Fam. E-W vitelliform dystrophy occurred together with this X-linked syndrome. We questioned whether the carriers of X-linked hemeralopia are normal and this could not be established in Fam. E-W, as the carriers were also suffering from vitelliform dystrophy. The carrier examined in this pedigree (III-2) appeared to be completely normal, ophthalmoscopically as well as electrophysiologically.

17. Fam. Ver
In this family are 2 brothers possibly suffering from "X-linked hemeralopia", like the individuals in fam. E-W and fam. SKn.

II-2 (LV-42.05.04) Poor visual acuity since early childhood.
1969: VOD S−1.25=C−2.25×160° 4/10; VOS S−1=C−2×20° 2/10. Nystagmus latens.
Media: Normal.
Fundi: Blond fundi. The foveal reflexes are irregular. The discs are slightly pale on the temporal side. The vessels are normal.
Visual fields: Decreased central sensitivity. Concentrically impaired sensitivity. Normal peripheral limitations.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased red-sensitivity (anomaloscope). Protan axis (Farnsworth D-15) in OS.

Dark adaptation: Both systems are disturbed. The photopic part of the curve ends two-third log. U. too high, whereas the scotopic part of the curve ends 1.5 log U. too high.
ERG: Scot. b-waves OD 40μV; OS 55μV.
Phot. a-waves OD 17μV; OS 26μV.
Phot. b-waves OD 46μV; OS 48μV.
EOG: OD 1.68; OS 1.74.
F-ERG: Subnormal. Broad curve like that in X-linked juvenile retinoschisis.
VER: Subnormal.

II-4 (JL-43.05.11) Poor visual acuity since early childhood.
1969: Nystagmoid movements with horizontal and rotatory components.
Family history is not distinctly positive. There seems to be some occurrence of poor vision in the mother's family.
VOD S−1.50 C−1×180° 2/10; VOS S−2.25 C−1×180° 2/10.
Fundi: Blond fundi. Normal vessels and normal discs. The foveae have irregular reflexes.

Summary: Two brothers suffering from "X-linked hemeralopia", also called syndrome of congenital high myopia with nyctalopia (Merin et al., 1970).

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ADDENDUM

ELENIUS, V., ERIKSSON, A. W. and FORSIUS, H.: ERG in a case of X-chromosomal pigment deficiency of fundus in combination with myopia, dyschromatopsia and defective dark adaptation. In The clinical value of electroretinography, Proc. 5th ISCERG symp. Ghent, 1966, p. 369-377. Karger, Basel, 1968.
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VIII

Fundus flavimaculatus

I. INTRODUCTION

In 1953 Franceschetti noticed a degenerative retinal abnormality which he could not readily classify among the tapetoretinal dystrophies known at that time. This abnormality was frequently diagnosed as chorioretinitis disseminata or retinitis punctata albescens but, unlike these two conditions, the retinal abnormality detected by Franceschetti nearly always had a stationary course and a good prognosis (Franceschetti and François 1965).

At an ophthalmological refresher course held in Hamburg in 1962, Franceschetti (1963) introduced the term "fundus flavimaculatus" to describe the fundus picture in this still unclassified group of cases, which was characterized by the presence of ill-defined white-yellow spots in the deeper retinal layers of the posterior pole. He noted that this group of affections could not yet be sharply differentiated, so that the entity he called fundus flavimaculatus remained to be sharply defined.

Fundus flavimaculatus clearly differs from the diffuse TRD, in which retinal function tests such as dark adaptation, ERG and EOG are decidedly pathological. Jointly with François, Franceschetti (1965) then published 30 cases of fundus flavimaculatus – a number he later increased to a total of 36 cases. In a study of the literature Franceschetti and François (1965) found several reports which, they believed, described the entity they had introduced.

They identified the case described as drusen by Oeller (1898) and that described as retinitis punctata albescens by Renard (1946) as instances of fundus flavimaculatus. They also found publications on Stargardt's disease (Caocci 1935; Mylius 1955; Friemann 1955) in which many deep-seated white-yellow spots surrounded the central atrophic focus which characterizes this disease. These cases, they thought, likewise came under the heading of fundus flavimaculatus. We believe, however, that these cases can be described as Stargardt's disease with equal justification. Franceschetti himself in fact wrote (1965): "If the foci are localized at the posterior pole of the eye and accompanied by macular affection, the distinction from Star-

gardt's disease may be difficult or even impossible". This is true, for even in Stargardt's first publication are patients described with many perifoveally localized whitish spots (Paul H and Dorothy H) (Stargardt 1909; Rosehr 1954). Today, many ophthalmologists would diagnose fundus flavimaculatus particularly when confronted with the fundus in Paul H.

There are many descriptions of Stargardt's disease indicating an atrophic focus surrounded by numerous deep-seated white-yellow spots (Morelli 1924; Sorsby 1940: families F and B; Hallermann 1941; Agatston 1948; Mortelmans 1950; Kozlowski 1958; François et al. 1962; Ersler and Jaczynowska 1968; and others). We personally observed in many Stargardt patients numerous white perifoveal spots, also covering the nasal part of the disc (page 116). These fundus features warrant a diagnosis of Stargardt's disease as well as one of fundus flavimaculatus.

With an increasing number of yellow-white spots in the retina the term fundus flavimaculatus will gain favour as compared with the designation Stargardt's disease.

Some of the cases (fig. 32 and 33) described in Sorsby's "The Dystrophies of the macula" (1940) are resembling fundus flavimaculatus strikingly.

The "degeneración tapeto-retiniana de aspecto cristalino-luminiscente" described by Lijo Pavia (1952) and Lijo Pavia and Lachman (1953) also comes under the heading "fundus flavimaculatus with Stargardt's disease".

It will be understood from the above that foveal dystrophy is quite common in association with fundus flavimaculatus: it is observed in over 50% of cases. Franceschetti (1965) found more or less pronounced foveal dystrophy, closely resembling Stargardt's disease, in 28 of the 36 patients examined; Klien and Krill (1967) reported the same in 18 out of 27 patients examined.

Franceschetti and François (1965) presented the following classification of 30 cases of fundus flavimaculatus:

I. *Pure forms* (13), with yellow spots only at the posterior pole, and more or less intact retinal functions;
II. *Associated forms*: a. with foveal dystrophy (11),
b. with nightblindness (2);
III. *Atypical forms* (4).

Klien and Krill (1967) divided 27 patients as follows:

I. *Pure forms* (9), with only typical flavimaculatus lesions,
   a. with macular involvement (4);
   b. with varying encroachment of the foveal region by lesions formed by confluence of typical flavimaculatus flecks (5).
II. *Forms with foveal dystrophy* (18),
   a. with a flat atrophic foveal lesion type Stargardt (17);
   b. with an elevated foveal lesion (1).

This classification is practical and useful, even though it is our impression that an "elevated foveal lesion" is not likely to be frequently seen. In fact we regard this finding as incidental.

It is perhaps advisable to regard Stargardt patients with fundus flavimaculatus lesions as a category quite separate from the fundus flavimaculatus entity, under which heading only the pure forms should be arranged. In these pure forms, flavimaculatus spots can be visible in the foveal area, but vision is usually only slightly affected in these cases. The distinction between Stargardt's disease involving many perifoveal yellow-white spots, and fundus flavimaculatus with foveal dystrophy, probably lies in the fact that Stargardt's disease has a central onset, whereas in fundus flavimaculatus the yellow-white spots are often already present in the posterior pole before the fovea is affected.

Whenever an atrophic plaque of the type seen in Stargardt's disease is present at the site of the fovea, vision is rarely more than 1/10.

Other publications on fundus flavimaculatus concerned familial cases (Hollwich 1963: brother and sister; Ravault et al. 1966: 2 sisters; Amalric et al. 1967: 2 brothers in one and 5 sisters in another family; Brown and Hill 1968: 2 sisters; Karel 1968: mother and daughter, possibly with dominant drusen) and solitary cases (Scialfa 1964: 3 cases; Schenk 1964: 1 case; Carr 1965: 5 cases; Brini 1966: 1 case; Rouher et al. 1966: 2 cases; Babel and Farpour 1967: 2 cases; Hellner 1967: 1 case resembling drusen; Amalric et al. 1967: 5 cases; Buiuc and Buiuc 1967: 1 case; Yuri et al. 1969: 1 case; François 1970). The photographs published by Carr (1965) are in my opinion more suggestive of centroperipheral dystrophy (Stargardt's disease with involvement of the peripheral retina) than of fundus flavimaculatus, although it must be admitted that this differential diagnosis can be difficult.

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

Fundus flavimaculatus can be found at a very early age. Of the 36 cases described by Franceschetti (1965), 17 were less than 25 years old when first seen; the youngest was 10. Of the 27 patients examined by Klien and Krill (1967), 15 were 30 or younger, the youngest being 7 years old.

This posterior pole abnormality can be observed in patients with entirely normal visual acuity, who are unaware of the abnormality. In many cases, however, vision is diminished; this is especially the case when the fovea shows a dystrophy that may closely resemble that seen in Stargardt's disease. The evolution of the process is very slow, and retinal function need not be impaired; but in observations over many years new spots may be seen to occur in the retina (Klien and Krill 1967; Amalric et al. 1967). There is no male or female predominance. Franceschetti (1965) saw, jointly with François, 16 females and 20 males; Klien and Krill (1967) saw 13 females and 14 males. A fair number of familial cases have been described (Hollwich 1963; Ravault et al. 1966; Amalric et al. 1967; Brown and Hill 1968); it is therefore of importance always to examine the patient's relatives whenever a diagnosis of fundus flavimaculatus is not entirely certain.

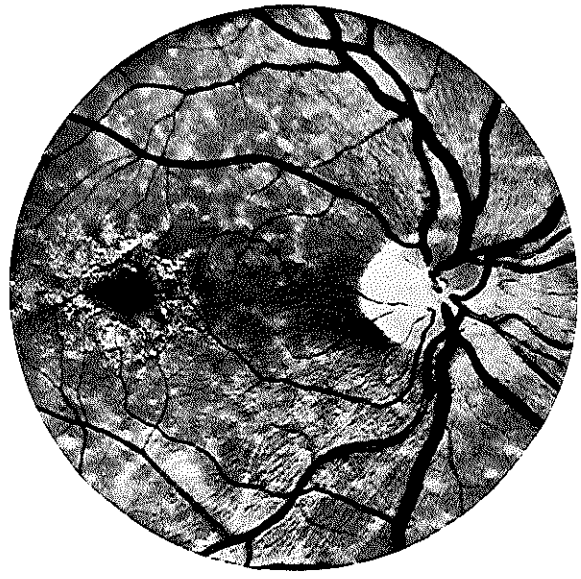


Fig. 1a. Fundus flavimaculatus in a 44-year-old man (Fam. dW). The fovea is atrophic and shows a pattern which does not completely resemble the foveal changes found in Stargardt's disease. The flecks have a soft contour and show a tendency to confluence.

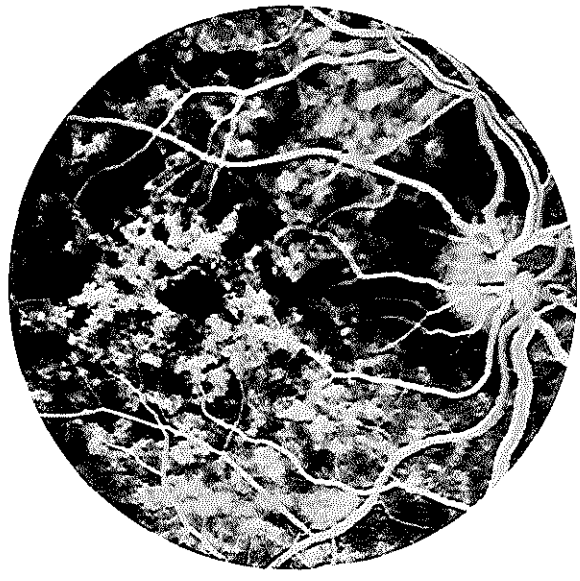


Fig. 1b. Fluorescein angiography shows multiple defects in the retinal pigment epithelium and confluence of most of the lesions. There is no leakage of fluorescein, indicating a normal Bruch's membrane.

3. FUNDUS (OPHTHALMOSCOPIC FEATURES)

The posterior poles of both eyes show a virtually symmetrical fundus picture: yellowish spots below the level of the retinal vessels, often ill-defined and shaped like a crescent, a sharkfin, a fishtail or a fish (figs. 1-4). There may also be circular or linear forms. One often observes confluence of the spots, which are never seen peripheral to the equator but always central to it, and frequently form garlands surrounding the foveal area (fig. 2).

Genuine unilateral fundus flavimaculatus is probably exceedingly rare, for symmetrical involvement is among the chief characteristics of hereditary retinal affections in general, and of the recessive abnormalities in particular. Franceschetti himself (1965) described a unilateral case in a patient with bilateral lenticonus.

A Stargardt-type atrophic lesion of the foveal area (fig. 3) is seen in some 50% of cases, and in some cases typical fundus flavimaculatus spots may infiltrate an otherwise normal fovea. In such cases the fovea often begins to show areas of atrophy or pigment changes after some time (fig. 1, 2, 4).

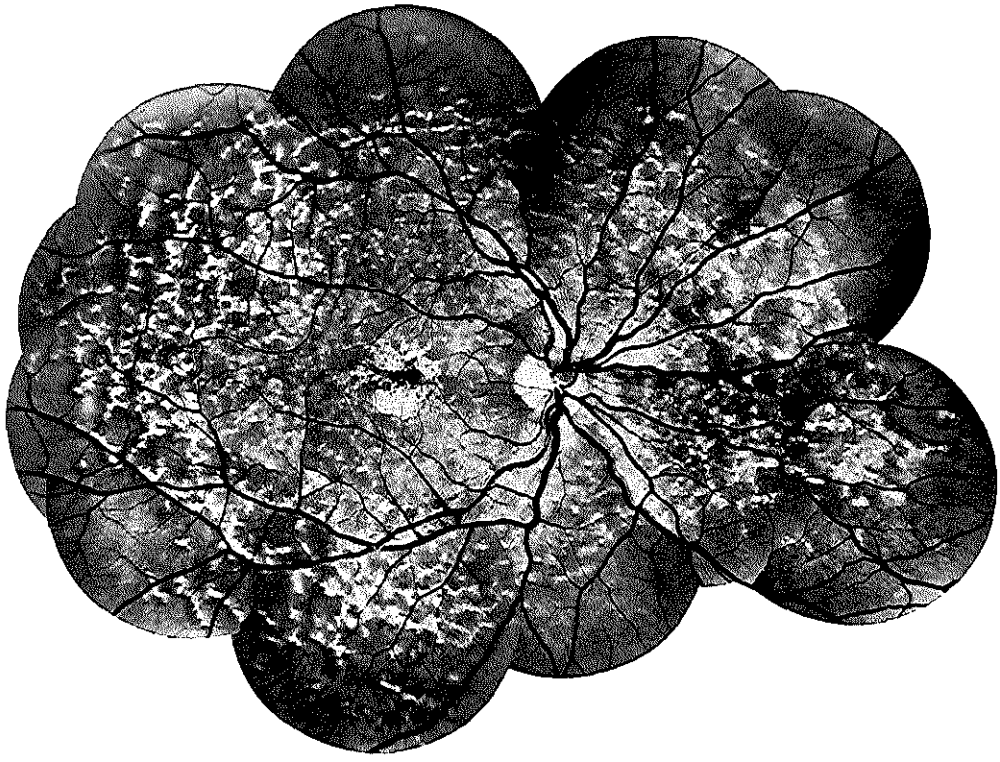


Fig. 2. Composite photograph of the posterior pole and part of the midperiphery in a case with fundus flavimaculatus (Fam. dW). Note the many "fish tail" lesions with fuzzy borders. There is a garland arrangement of pisciform flecks in the posterior polar region.

We have observed in Stargardt's disease that the foveal dystrophy is the primary affection, followed later by the occurrence of perifoveal yellow-white spots. In a patient with fundus flavimaculatus (II-3, fam. dW), yellow-white spots had long been present throughout the posterior pole before the fovea became dystrophic.

One occasionally sees delicate pigment changes interspersed between the spots; disc, retinal vessels and extreme retinal periphery are always normal.

4. REFRACTION

Few exact data are available on refraction. In our cases we observed emmetropia and hypermetropia (see case histories). Nordmann (1966; discussion Brini 1966) observed a patient with a fundus flavimaculatus picture and a hypermetropia of 18 dioptres.

5. VISUAL ACUITY

Visual acuity is quite normal in the pure form of fundus flavimaculatus, not involving the fovea. Since the condition has a very stationary course, vision can always remain intact in the pure form without foveal involvement. Once the typical fundus flavimaculatus spots also occur in the fovea, vision can gradually diminish; we observed this in our patients II-3 fam. dW and II-1 fam. Kro (figs. 1, 2, 4).

In the many cases which show a Stargardt-type atrophic foveal lesion (fig. 3), there is considerable loss of vision, down to 1/10. In many cases, however, there is no distinct correlation between ophthalmoscopic findings and visual acuity (II-1 fam. Kro) (fig. 4).

6. VISUAL FIELDS

The visual fields retain their normal peripheral boundaries; in those cases in which the fovea is involved, there may be initially a relative and later an absolute central scotoma.

7. COLOUR VISION

Only in cases with foveal involvement is acquired dyschromatopsia to be found. As in Stargardt's disease, this usually consists of acquired red-green dyschromatopsia and diminished red sensitivity; in the presence of more extensive lesions acquired blue-yellow dyschromatopsia may be found also (Franceschetti and François 1963, 1965; Hollwich 1963; Schenk 1964; Krill and Klien 1965; Ravault et al. 1966).

8. DARK ADAPTATION

In many cases dark adaptation is described as quite normal (Franceschetti and François 1963; Schenk 1964; Brini 1966; Rouher et al. 1966); however, there are also reports on slightly pathological dark adaptation curves (Franceschetti and

Fig. 3a. Fundus flavimaculatus with Stargardt-type foveal dystrophy (the bird's head) in one of two affected brothers (Fam. tH). There is a very fine radial folding of the superficial retinal layer.

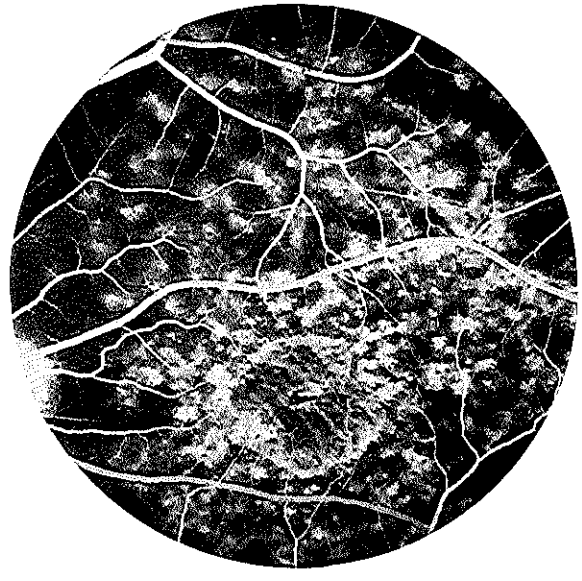


Fig. 3b. Fluorescein angiography shows multiple pigment epithelium defects surrounding a centrally located area of atrophic pigment epithelium and choriocapillaris.

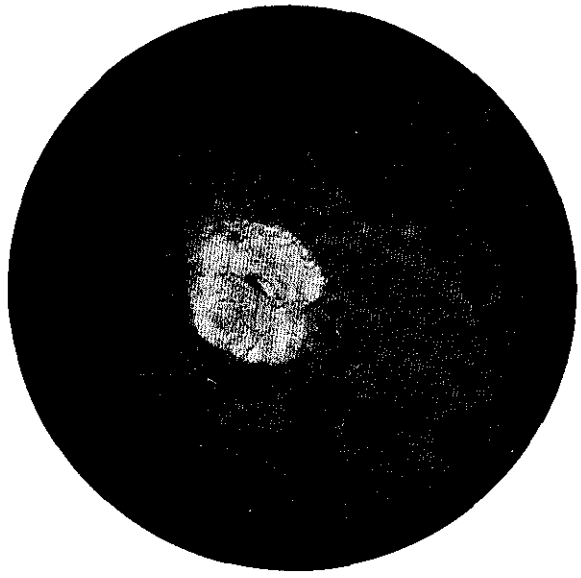


Fig. 3c. After-fluorescence of the central atrophic zone, probably due to fluorescein, which has oozed out of the choroidal vessels.

François 1963, 1965; Scialfa 1964; Carr 1965; Krill and Klien 1965; Ravault et al. 1966; Klien and Krill 1967; Yuri et al. 1969).

Franceschetti and François (1965) obtained a slightly disturbed curve in 7 of the 30 patients they examined; Scialfa (1964) observed slight changes in 2 out of 3, and Carr (1965) in 1 out of 5 patients examined.

Klien and Krill (1965, 1967) reported a slightly disturbed dark adaptation curve in 22 of 23 patients examined, in whom they observed a delay at the transition from cone to rod adaptation and a delay when the ultimately normal cone and rod threshold was attained.

In 2 brothers (V-5 and V-8 fam. tH), we observed a normally terminating dark adaptation curve which initially had been slightly delayed for both systems. One patient (II-3 fam. dW) showed a slightly delayed curve with the streak figure, but at integral registration the curve proved to be normal. A fourth patient (II-1 fam. Kro) also had an entirely normal dark adaptation curve.

9. ELECTRORETINOGRAPHY

The ERG is either normal or slightly subnormal. Several authors have reported normal ERG's (Franceschetti and François 1963, 1965; Hollwich 1963; Schenk 1964; Scialfa 1964; Carr 1965; Ravault et al. 1966; Hellner 1967; Yuri et al. 1969).

Franceschetti and François (1965) found a subnormal ERG in only 1 of the 30 patients they examined; Carr (1965) found a normal scotopic ERG in 5 patients and

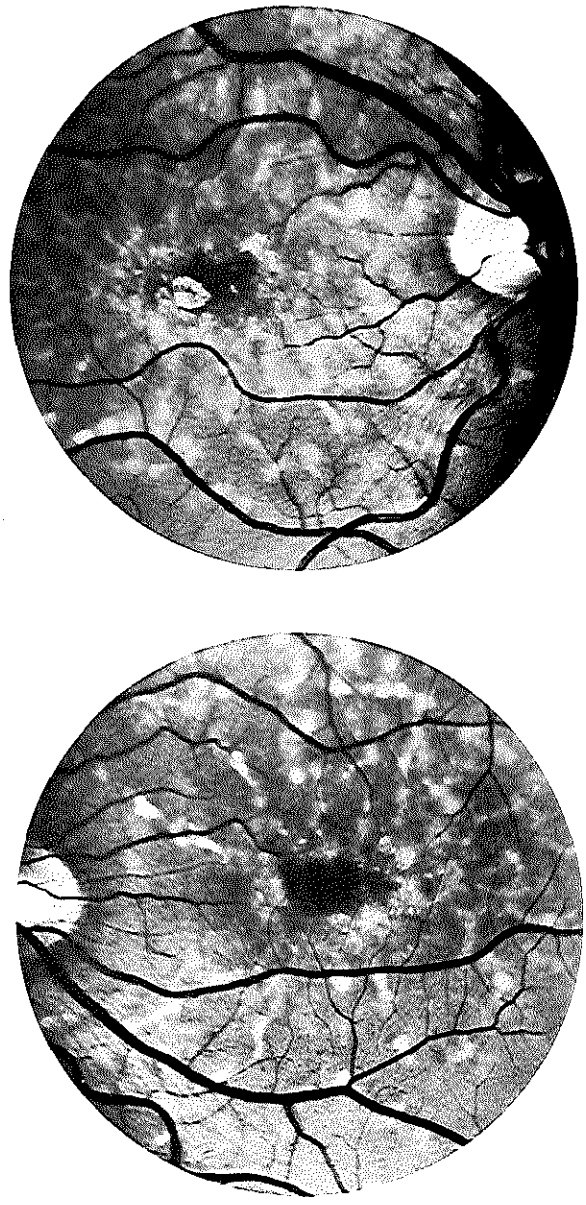


Fig. 4a-b. Fundus flavimaculatus in a 49-year-old man (Fam. Kr). Despite the symmetrical appearance of both fundi, there is a visual acuity of OD 4/60 and OS 10/10. The centre of the fovea is pigmented. The pisciform lesions show no pigmentation at all.

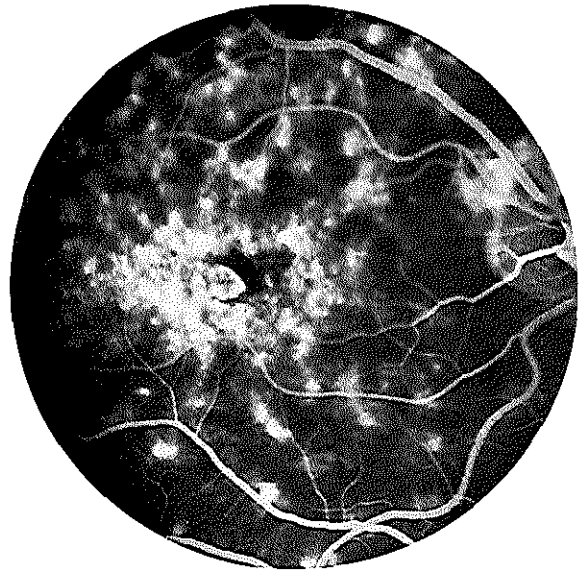


Fig. 4c. The fluorescence photograph of OD shows multiple defects in the retinal pigment epithelium around a centrally located pigmented spot.

a slightly subnormal photopic ERG in 2 patients. Slightly subnormal ERG's were also reported by Krill (1966, 1968), Klien and Krill (1967), Brini (1966) and Rouher et al. (1966).

Klien and Krill (1967) found an ERG subnormal at all intensities in only 2 of 24 individuals examined; 17 showed a slight delay when the otherwise normal maximum b-wave amplitude was attained.

We found a subnormal ERG in 2 of our patients (V-5 and V-8 fam. tH); our method of registration produced an entirely normal ERG in 2 other patients (II-3 fam. dW and II-1 fam. Kro).

Unlike Krill and Klien (1965, 1967), we did not record the increase of the b-wave at increasing dark adaptation, nor the time at which the maximum b-wave amplitude occurred.

In conclusion we find that the ERG is never unrecordable in fundus flavimaculatus, and that such abnormalities as do occur are not very severe. In this respect, therefore, fundus flavimaculatus clearly differs from the diffuse tapetoretinal dystrophies, in which the ERG is often unrecordable.

10. ELECTRO-OCULOGRAPHY

The EOG is subnormal in many cases, although the Lp/Dt-ratio is rarely as low as that in vitelliform dystrophy of the fovea.

Klien and Krill (1967) found a subnormal EOG in 14 of 18 patients examined.

We found a distinctly subnormal EOG in 3 of 4 patients examined; in the presence of normal visual fields and very slight changes in dark adaptation and the ERG, this suggests a disturbance in the pigment epithelium. Since histological studies (Klien and Krill 1967) have shown that fundus flavimaculatus lesions are found exclusively in the pigment epithelium, the indication that the EOG Lp/Dt-ratio is an important index of the function of the pigment epithelium, is strengthened to a substantial degree.

11. PHOTOGRAPHY

Panchromatic graphic film discloses some more pathological structures in fundus flavimaculatus than does orthochromatic film; this, too, indicates that fundus flavimaculatus lesions should be localized near or in the pigment epithelium.

12. FLUORESCEIN ANGIOGRAPHY

Fluorescein angiography has been frequently carried out in fundus flavimaculatus cases (Ernest and Krill 1966; Amalric 1967; Klien and Krill 1967; Babel and Farpour 1968; Brown and Hill 1968; François and De Laey 1969).

The fluorescein pattern of fundus flavimaculatus closely resembles that found in dominant drusen of Bruch's membrane, fundus albipunctatus and vitelliform dystrophy of the fovea, as well as that of angioid streaks. The arterial phase is characterized by the appearance of multiple ill-defined irregular fluorescent spots, with boundaries more or less like those that are visible at normal ophthalmoscopy. But there are evidently more defects visible in the pigment epithelium than in normal ophthalmoscopy, and many spots prove to be confluent (figs. 1, 3, 4). However, recent flavimaculatus lesions prove not to become fluorescent (Klien and Krill 1967; Amalric et al. 1968), and this is explained by the fact that the cells of the pigment epithelium are still intact and contain a yellow-white substance only at the surface. Once the fluorescein disappears from the choroid and the retinal vessels, after-fluorescence persists for some time in the fluorescent areas. The cause of this after-fluorescence is still obscure. Perhaps the fluorescein becomes attached to the acid mucopolysaccharides in the fundus flavimaculatus lesions (Klien and Krill 1967), if these lesions are of longer standing. It may also be bound to a no longer entirely intact Bruch membrane, or possibly to the sclera (Sollom and Brown 1967; Sollom and Adlakha 1968). There is no fluorescein leakage, and this suggests intactness of Bruch's membrane and the choroid. It seems most likely that the after-fluorescence is due to fluorescein which is normally still present in the extravascular choroidal spaces (Wessing 1968). Since fluorescein leaves the choroid even more rapidly than the retinal vessels, after-fluorescence cannot very well be ascribed to intravascular fluorescein.

13. CARRIERS

Parents of patients with fundus flavimaculatus are ophthalmoscopically normal, as

could be expected in an autosomal recessive process. The parents (who are therefore probably heterozygotic for the pathological gene) were not submitted to retinal function tests because, except in advanced stages, the patients themselves show virtually normal retinal function.

14. HISTOLOGICAL FINDINGS

A histological study has been made in one case of fundus flavimaculatus (Klien and Krill 1967); the findings have taught us much about the interpretation of function tests and fluorescein angiograms of the retina.

The histological findings showed that neuroepithelium, Bruch's membrane and choroid are quite normal. In the pigment epithelium the following changes were found.

a. Displacement of the nucleus from the base of the cell to the centre or inner surface.
b. A peculiar line of condensation of pigment granules in the centre or near the inner surface of the cell, frequently at the level of the displaced nucleus.
c. Accumulation of a pathological substance, largely within the inner half of the cells, in circumscribed areas.
d. Great variations in cell size, from much larger than normal to small, without pigment granules or discernible nuclei.

Most of the changes in the pigment epithelium were diffuse, and they were frequently accompanied by accumulation of a pathological substance mainly on the inside of the cells; this substance was identified as an acid mucopolysaccharide.

Recent fundus flavimaculatus lesions proved to be contained in still fully intact pigment epithelium cells. This explains why fresh flavimaculatus lesions show no pathological fluorescence, as Klien and Krill (1967) noticed.

15. PATHOGENESIS

The abovementioned histological findings confirm the suspicion (based on retinal function tests and fluorescein angiography) that fundus flavimaculatus is a primary dystrophy of the cells of the pigment epithelium.

16. MODE OF TRANSMISSION

Fundus flavimaculatus is probably a hereditary dystrophy of the retina with an autosomal recessive mode of transmission. Franceschetti (1965) found a familial incidence in only one of his 36 cases; parental consanguineousness existed in 2 cases.

Klien and Krill (1967) found a definite familial incidence in 10 out of 27 patients; this was consistent with autosomal recessive transmission because brothers or sisters of patients likewise showed this fundus picture. Hollwich (1963), Ravault et al. (1966), Amalric et al. (1967) and Brown and Hill (1968) observed brothers or sisters of patients who were also affected.

Some of the cases which Franceschetti diagnosed as fundus flavimaculatus in the literature prior to 1962, also showed a familial incidence (Caocci 1935: brother and sister with consanguineous parents; Friemann 1955: brother and sister).

Since Stargaidt's disease (which might as well be called fundus flavimaculatus if it is associated with many yellowish perifoveally localized spots) shows an autosomal recessive mode of transmission, it is of great importance to establish whether Stargardt-type fundus flavimaculatus without foveal dystrophy can also be a familial affection. Little pertinent information is available on this question.

We personally observed 2 brothers (V-5 and V-8 fam. tH) with fundus flavimaculatus, whose parents were not consanguineous. But in these cases there was unmistakable Stargardt-type foveal dystrophy as well. The patients with a pure form of fundus flavimaculatus (II-3 fam. dW and II-1 fam. Kro) had only normal relatives.

Karel (1968) described a mother and daughter with fundus flavimaculatus; so far as the photographs permit of interpretation, however, these were instances of dominant drusen of Bruch's membrane.

Amalric et al. (1967) believed "dasz Degeneratio vitelliformis multiplex and Fundus flavimaculatus ebenso wie Discus vitelliformis der Macula und Stargardtsche Degeneration Äquivalente darstellen können". We cannot agree with this, but maintain that the pure form of fundus flavimaculatus, vitelliform dystrophy of the fovea and Stargardt's disease are three quite different hereditary dystrophies of the central retina. In the families we investigated we never observed alternative occurrence of these entities; we did see different types of manifestation determined by differences in expression.

Krill (1968) assumed that the frequent concomitance of Stargardt-type atrophic foveal dystrophy and fundus flavimaculatus might indicate that the genetic loci of the two conditions are to be found close together on the same chromosome. In that case the differences between the pathological genes causing Stargardt's disease and fundus flavimaculatus, might be exceedingly small.

It is also conceivable that, dependent on the expressivity of the gene, Stargardt's disease can manifest itself either solely as foveal dystrophy or as foveal dystrophy with fundus flavimaculatus features, or as foveal dystrophy with peripheral tapetoretinal dystrophy, while the pure form of fundus flavimaculatus is caused by a separate gene. A final conclusion on these problems remains to be formed.

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

There are no indications that a constant general physical or laboratory abnormality can be found in all fundus flavimaculatus cases within the foreseeable future. In our patients (III-3 fam. dW and II-1 fam. Kro), a detailed physical examination failed to demonstrate any abnormality.

Fig. 5a. Irregularly shaped whitish flecks and pigmentations in one of the posterior poles of a 45-year-old female (Fam. Phi).

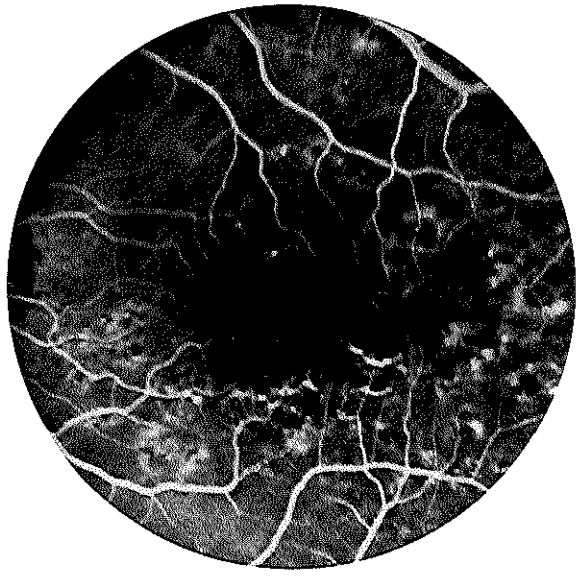


Fig. 5b. Fluorescein angiography shows defects in the retinal pigment epithelium and condensation of pigment.

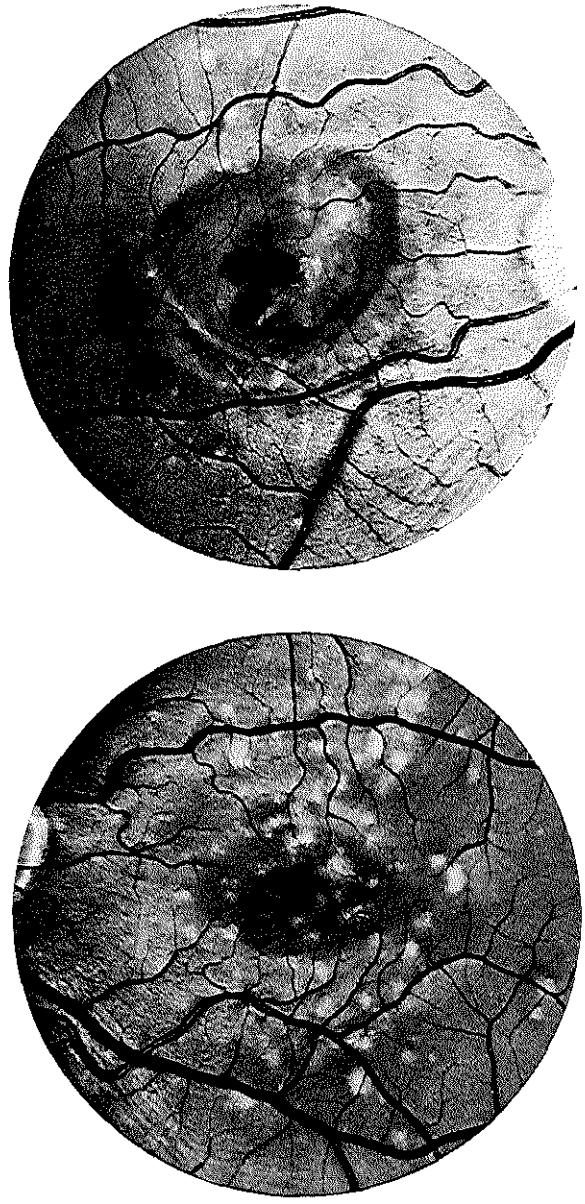


Fig. 6a-b. Whitish flecks with soft contour in the posterior poles of a 21-year-old female. The right fovea shows a subretinal haemorrhage.

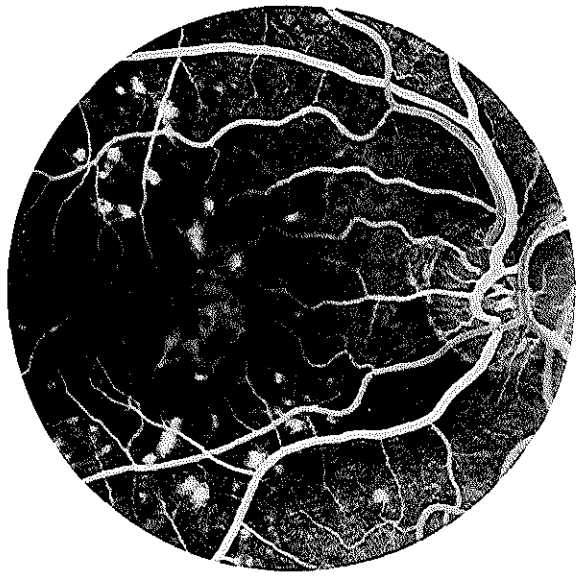


Fig. 6e. Fluorescence photograph of the fundus depicted in fig. 6a. There are isolated defects in the pigment epithelium. Centrally at the site of the haemorrhage there is a pattern indicative of leakage of fluorescein through Bruch's membrane.

18. ASSOCIATED CONDITIONS

As pointed out, Stargardt-type foveal dystrophy occurs in about 50% of the cases of fundus flavimaculatus. Since fundus flavimaculatus also occurred in a few of Stargardt's original patients (1909), the designation Stargardt's disease is as applicable to these cases as the term fundus flavimaculatus. The syndrome might be described as "Stargardt flavimaculatus". The exact relationship between these clinical pictures is still obscure.

Franceschetti and François (1965) described a woman with fundus flavimaculatus who had a cousin with retinopathia pigmentosa; Renard (1946) described a boy suffering from fundus flavimaculatus, whose father showed retinopathia pigmentosa. These sporadic observations warrant no conclusion at this time. One of our patients with a "Stargardt flavimaculatus" had a very distant relative with Stargardt's disease involving the periphery (fam. Krij; page 153). This might be regarded as a difference in expressivity of the same gene, but we cannot rule out the possibility that separate genes were involved.

Franceschetti (1965) discovered a bilateral lenticonus in one of his patients who showed the rarity of an unilateral fundus flavimaculatus.

19. DIFFERENTIAL DIAGNOSIS

Fundus flavimaculatus must be differentiated from all conditions involving white-yellow spots in the posterior pole of the eye. The differential diagnosis is therefore the same as that of dominant drusen of Bruch's membrane, to which the reader may be referred (page 388).

In this context I should like to present a few photographs of patients with a "flecked retina syndrome". We considered these cases not sufficiently characteristic to be identified outright as fundus flavimaculatus or fundus albipunctatus or drusen (figs. 5-7).

The first case (fam. Phi; fig. 5) showed odd-shaped white-yellow spots in both posterior poles, and structures resembling "dyshorische Herdchen".

The second case (fam. Ba; fig. 6) was that of a 21-year-old female with ill-defined spots in both eyes and a haemorrhage of obscure origin in the right fovea. We diagnosed this condition as an early stage of fundus flavimaculatus.

The third case (fam. Kos; fig. 7) showed many round white spots arranged in a coronary pattern around the fovea. Differentiation from drusen was the question here, but the ill-defined contours of many spots was evocative of a diagnosis of fundus flavimaculatus.

As last cases in this chapter I like to present a 21-year-old boy and a 20-year-old girl with bilateral symmetrical changes in their posterior poles. They were unrelated and their relatives had normal eyes. They had a cystoid foveal affection and many round rather large, ill-defined, yellowish-white flecks surrounding the foveal region. Visual acuity was approximately 5/10 in both eyes. The EOG was severely disturbed, the ERG was slightly subnormal. The dark adaptation curve was 1.5 log. U. too high. Fluorescein angiography showed a normal foveal fluorescence pattern and many large defects in the pigment epithelium around the foveal area. This seems to be a special type of flecked retina (fig. 8). Discs and vessels were normal.

20. THERAPY

There is no known therapy for fundus flavimaculatus.

21. FUTURE

It is our impression that several other entities with flecked retinae will be found or differentiated in future. For this reason also, it will be important to ensure an exact definition of the entity of fundus flavimaculatus. So far, this term has denoted a collection of too disparate conditions; this is quite apparent in the original publication of Franceschetti and François (1965), in which many different fundus pictures are shown. Some of these are very similar to those of drusen or "dyshorische Herdchen", whereas in our opinion the pisciform lesions that characterize fundus flavimaculatus are not always in evidence. I do believe, however, that the patients demonstrated

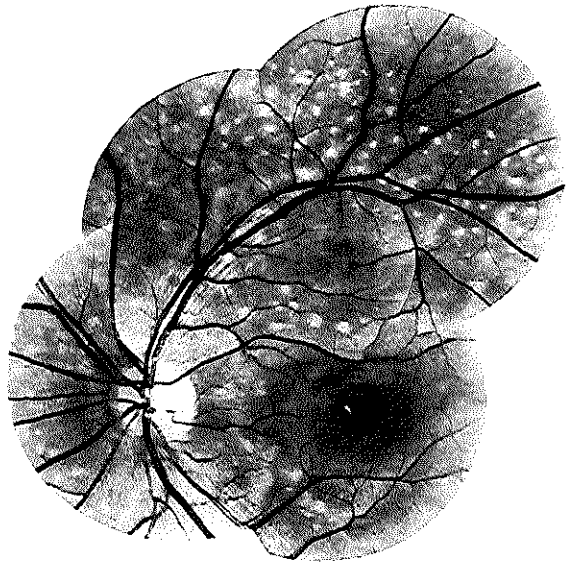


Fig. 7. Whitish flecks in a garland pattern around the papillo-foveal region (Fam. Kos). This picture is suggestive of fundus flavimaculatus.

Fig. 8. Ill-defined round flecks surrounding a fovea with cystoid alterations, somewhat resembling the foveal retinoschisis of X-linked juvenile retinoschisis. This pattern does not fit in one of the affections described so far.

here in figures 1-4 are characteristic examples of a fairly well-defined clinical entity, and that the term fundus flavimaculatus is best reserved for these pictures.

In future, any cases of flecked retinae encountered will have to be carefully investigated and documented, and this effort must include as extensive a family study as is possible.

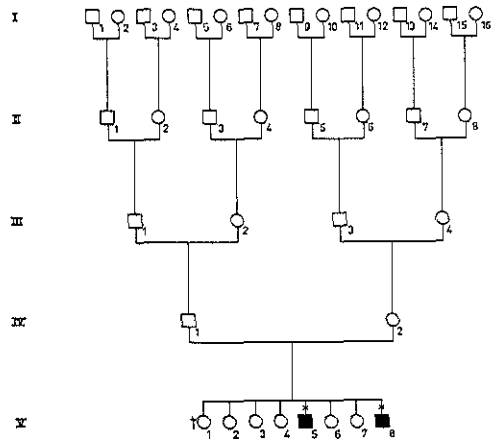
One of the questions which arise in this context is whether we should not learn to regard pure fundus flavimaculatus and Stargardt-type fundus flavimaculatus with foveal dystrophy as two separate entities.

It is quite possible, meanwhile, that a case originally regarded as a pure form of fundus flavimaculatus, will in the course of time develop an atrophic focus in the fovea which is indistinguishable from the foveal condition in Stargardt's disease. This only emphasizes the importance of follow-up studies.

Also, it is to be hoped that future histochemical and biochemical research will identify the deficient or absent enzyme underlying this primary dystrophy of the pigment epithelium.

22. CASE HISTORIES

1. Fam. tH



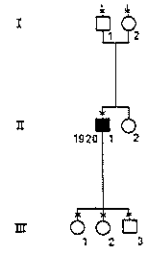
V-5 (DtH-19.10.03) Poor visual acuity since more than 30 years.
VOD S+2 5/60; VOS S+2 5/60.
1967: Fundi: An atrophic zone in each fovea, surrounded by numerous fishtail-like lesions. These flecks have a yellowish colour and extend as far as the equator of the eye. The discs, vessels and retinal peripheries are normal.
Visual fields: Absolute central scotoma. Normal peripheral limitations.
Dark adaptation: Initially some delay, normal at the end of the curve.
1965: ERG: Made elsewhere in 1965. The b-waves are normal (Scot. and phot.). The photopic a-waves are slightly subnormal.
EOG: OD 2.09; OS 2.00.

V-8 (FtH-30.02.02) Poor visual acuity since the age of 15. The last years there is no further visual impairment. No subjective nightblindness.
1967: VOD S+4 2/10; VOS S+4 2/10.
Fundi: A well defined atrophic area at the site of the foveae. Many yellowish flecks perifoveally. These

flecks are ill-defined and have a polymorphous appearance. They resemble the shape of fishes, fishtails and half moons (fig. 3a). The discs, retinal vessels and retinal peripheries are normal.
Visual fields: Central scotomata. Normal peripheries.
Dark adaptation: Initially delayed curve, which ends normal.
ERG: Scot. b-waves OD 170μV; OS 125μV.
Phot. b-waves OD 55μV; OS 45μV.
EOG: OD 1.50; OS 1.66.
Fluorescein angiography: OS: Pathological fluorescence in the arterial phase, increasing in the venous phase. There are visible more defects in the retinal pigment epithelium than normal ophthalmoscopy suggests. Furthermore there is more confluence of the lesions than with normal ophthalmoscopy. The fluorescence persists some time in the central atrophic zone after the disappearance of the fluorescein from the retinal vessels. This fluorescence pattern indicates a widespread affection of the retinal pigment epithelium (fig. 3bc). Furthermore there is marked atrophy of the choriocapillaris at the site of the fovea.

Summary: Two brothers from a non-consanguineous marriage. No consanguinity as far back as 4 generations. The brothers have the pathognomonic fundus picture of fundus flavimaculatus. The atrophic foveal dystrophy which is present in these two brothers is reminiscent of the foveal picture found in Stargardt's disease. The numerous fuzzy flecks in the posterior pole of both eyes, however, are characteristic of fundus flavimaculatus. The parents and sisters of the affected brothers have a history of normal vision.

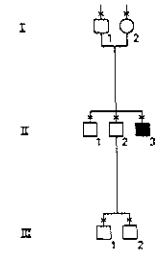
2. Fam. Kro



II-1 (HCK-20.02.12)
1969: Since 18 months visual impairment in OD.
VOD 4/60; VOS 10/10. Emmetropic.
Media: Normal.
Fundi: Many ill-defined yellowish flecks in the posterior pole of both eyes. These flecks are located beneath the retinal vessels. The fovea of the right eye demonstrates an atrophic aspect and resembles slightly the fovea of Stargardt's disease. The fovea of the left eye also shows atrophic and pigmentary changes, however, in a lesser degree (fig. 4ab).
Colour vision: OD red-green dyschromatopsia (HRR); OS normal.
Visual fields: OD absolute central scotoma. OS relative central scotoma. Normal peripheral limitations.
Dark adaptation: Normal.
ERG: Normal. Scot. b-waves OD 295μV; OS 280μV.
Phot. a-waves OD 34μV; OS 40μV.
Phot. b-waves OD 95μV; OS 105μV.
EOG: OD 1.42; OS 1.51.
Systemic examination: Normal.
Fluorescein angiography: OD: Pathological fluorescence in the arterial phase, still increasing in the venous phase. Most but not all visible flecks show pathological fluorescence. Furthermore there are visible defects in the retinal pigment epithelium in normally appearing areas (fig. 4c). There is a marked confluence of defects in the pigment epithelium. No fluorescein leakage is visible. There is some after-fluorescence after the disappearance of fluorescein from the retinal vessels.
1970: VOD 2/60; VOS S+0.50 9/10.

Summary: A 49-year-old man with the characteristic features of fundus flavimaculatus. There is a marked difference in visual acuity between the two eyes, whereas the ophthalmoscopic alterations are far less distinct. Examination of the family members was negative, suggesting an autosomally recessive inheritance of fundus flavimaculatus.

3. Fam. dW



II-3 (JdW-25.08.08) Problems when reading.
1969: VOD C+0.50×90° 9/10; VOS 10/10, emmetropic.
Fundi: Normal foveal reflexes. Slight pigment alterations in the foveal area. Many yellowish pisciform flecks arranged in a garland pattern extending from the perifoveal area to the equator. The flecks have fuzzy borders and are located beneath the retinal vessels. Discs, vessels and retinal peripheries are normal (fig. 1, 2).
Visual fields: Relative central scotoma of 10 degrees.
Colour vision: Decreased red-sensitivity (anomaloscope). Mild red-green dyschromatopsia (HRR).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 215 μV; OS 245 μV.
Phot. b-waves OD 115 μV; OS 119 μV.
EOG: OD 1.57; OS 1.71.
Fluorescein angiography: Pathological fluorescence in the arterial phase, increasing in the venous phase. There are areas in which confluence of the retinal defects is visible. Fluorescein angiography demonstrates more flecks than does normal ophthalmoscopy. There is some slight after-fluorescence. The fluorescein pattern is indicative of defects in the retinal pigment epithelium (fig. 1b).
1970: VOD 2/10; VOS 10/10.
Fundi: The right eye demonstrates further involvement of the foveal area. There are atrophic patches at the site of the fovea.

Summary: A patient with an originally pure form of fundus flavimaculatus. The fundus flavimaculatus lesions invade the foveal area. A Stargardt-type foveal dystrophy has not appeared so far. The EOG is the only pathological function test of the retina as a whole. Examination of the family suggests an autosomally recessive inheritance pattern of fundus flavimaculatus.

4. Fam. Ba
(MAB-48.11.24)
1969: Since some weeks blurred vision in OD.
VOD S+0.50 9/10; VOS 10/10.
Fundi: Ill-defined yellowish-white flecks in the deeper retinal layers of the posterior pole of both eyes. There is also a subretinal haemorrhage in OD (fig. 6ab).
Visual fields: Relative central scotoma OD. OS normal.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 345 μV; OS 328 μV.
Phot. a-waves OD 23 μV; OS 38 μV.
Phot. b-waves OD 53 μV; OS 81 μV.
OP: Normal.
F-ERG: OD subnormal; OS normal.
VER: OD absent; OS present.
EOG: OD 2.35; OS 2.02.
Fluorescein angiography: There are ill-defined defects in the retinal pigment epithelium. In the centre of the fovea there is leakage of fluorescein, indicating a defect in Bruch's membrane (fig. 6c).
Systemic examination: Normal.
Family: The parents have normal fundi.

Summary: A 21-year-old girl with lesions in the posterior pole which are not quite characteristic of fundus flavimaculatus. Nevertheless the diagnosis fundus flavimaculatus seems to be the most suitable in this case.

5. Fam. Kos
(ThAMK-02.05.31) No visual complaints.
VODS 10/10, emmetropic.
Fundi: A garland of yellowish-white flecks around both foveae (fig. 7).
Examination of the family was not possible.

6. Fam. Phi
II-1 (EPS-24.03.03) Complains of visual impairment.
1968: VOD S+6.50=C+0.75×90° 7/10; VOS S+6=C+0.50×90° 7/10.
Fundi: Polymorphous yellowish-white flecks, located beneath the retinal vessels. The flecks are concentrated in the posterior poles. Many flecks have pigmented borders. Discs, vessels and retinal peripheries are normal (fig. 5a).
Visual fields: Decreased central sensitivity.
Dark adaptation: The curve is slightly delayed initially, but it ends normal.
ERG: Scot. b-waves OD 265μV; OS 275μV.
Phot. a-waves OD 55μV; OS 50μV.
Phot. b-waves OD 140μV; OS 160μV.
EOG: OD 2.20; OS 3.04.
Fluorescein angiography: A fluorescein pattern suggestive of defects in the retinal pigment epithelium. There is no tendency to confluence (fig. 5b).

Summary: A 44-year-old woman with a fundus picture which is difficult to interpret. The yellowish flecks presented here resemble the "dyshorische Herdchen". These, however, are usually found in the retinal periphery. Franceschetti and François (1965) published cases with fundus pictures closely resembling those of this case and they diagnosed their cases as fundus flavimaculatus. I do not think that the ophthalmoscopic pattern is quite characteristic of fundus flavimaculatus. The definite diagnosis remains open to discussion. The parents of the proband were dead. The siblings and children had normal posterior poles.

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IX

Reticular dystrophy of the retinal pigment epithelium (Sjögren)

1. INTRODUCTION

An exceedingly rare affection of the pigment epithelium was observed by H. Sjögren (1950) in 5 children from a Swedish family. In view of the reticular character of the retinal pigmentations he named this condition "dystrophia reticularis laminae pigmentosae retinae". The foveae showed accumulations of dark pigment, surrounded by a finely meshed network of polygonally arranged pigment granules with densifications at the sites of the knots of the network. In view of the fact that these pigmentations and the network were localized below the retinal vessels and were not clearly visible in red-free light, it was concluded that the reticulum was localized in the pigment epithelium.

At this time there are data on only 7 patients from 2 families showing these features. The second family with this intriguing fundus picture was encountered in The Netherlands (Ten Doesschate 1965; Deutman and Rümke 1969).

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

Reticular dystrophy of the retinal pigment epithelium can be encountered at a very early age. Sjögren (1950) found this picture in an 8-year-old patient, and we ourselves observed it in a 5-year-old boy (Deutman and Rümke 1969). The condition is probably not yet discernible at birth. The 5-year-old boy we mentioned had ophthalmoscopically normal fundi at the age of 1 year.

Since visual acuity is intact, patients with this condition can be detected only by performing ophthalmoscopy despite the normal visual acuity. Metamorphopsia does not occur in these cases. The condition is progressive but takes a very slow course. In advanced cases the characteristic network tends to disappear, and visual acuity can show some slight diminution.

Strabismus occurred in 3 of the 7 patients. Nystagmus was not observed.

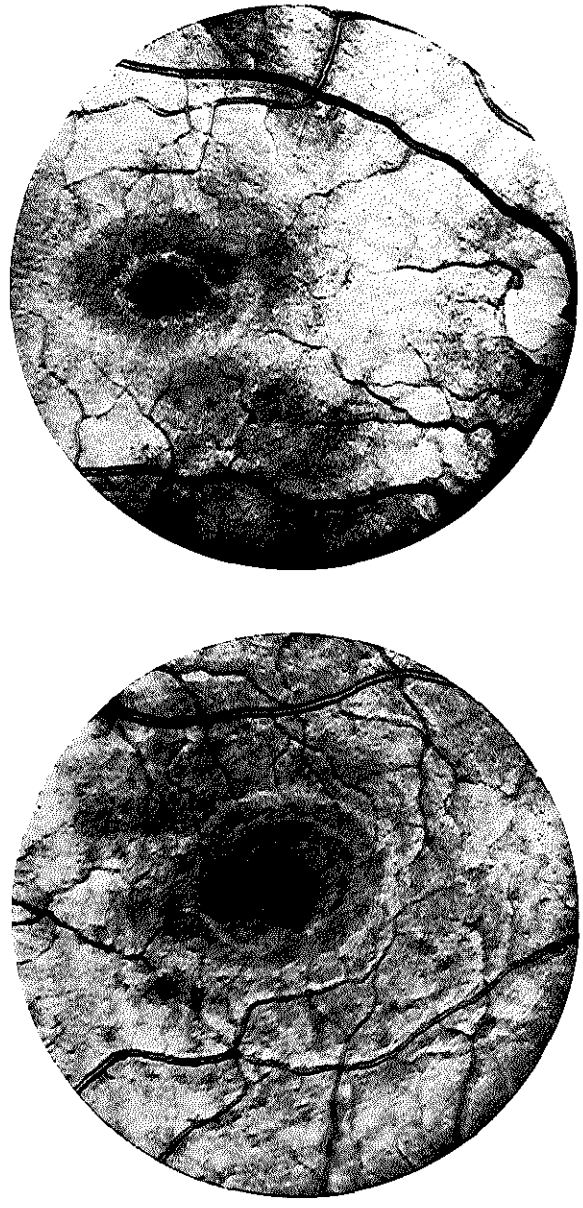


Fig. 1a-b. Initial stages of reticular dystrophy of the retinal pigment epithelium in a 5-year-old boy, who had normal fundi 4 years previously. Both foveae are darkly pigmented (Fam. dB). The left eye already shows thread-like pigmentations in the perifoveal area.

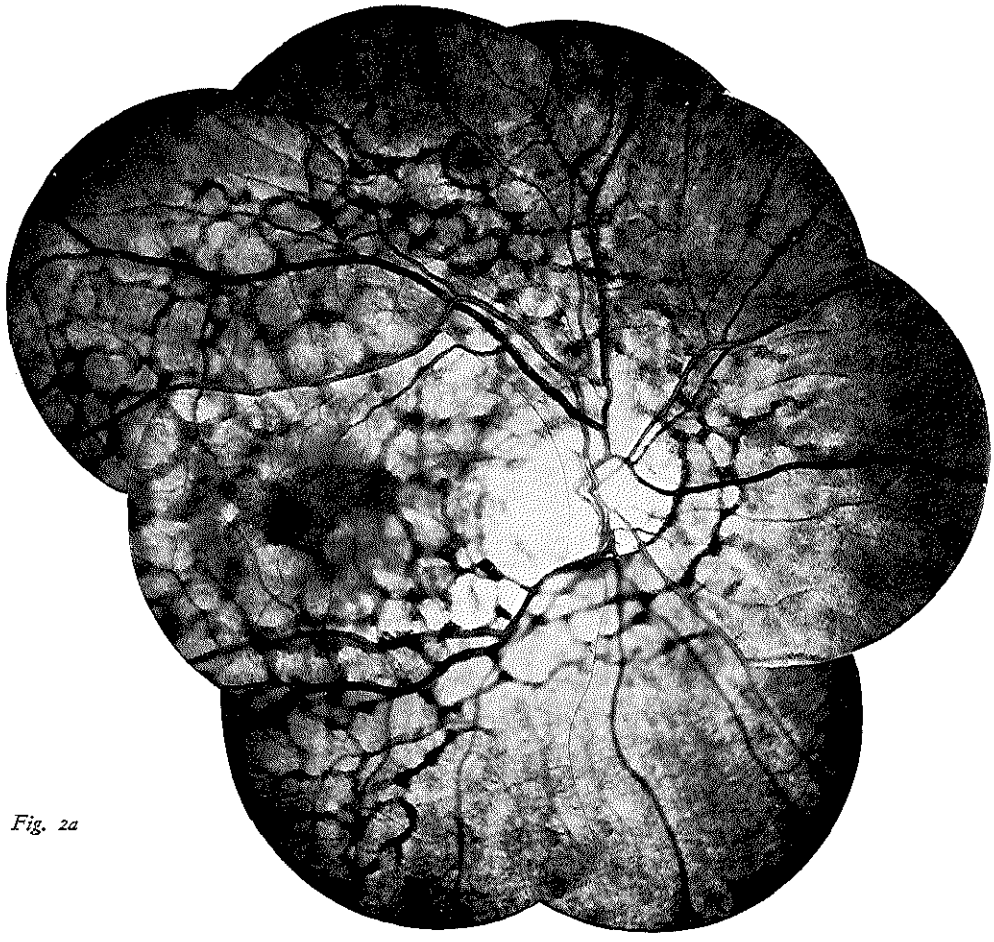


Fig. 2a

Fig. 2. The network of Sjögren's dystrophia reticularis laminae pigmentosae retinae in the posterior poles of a 14-year-old girl.
ab. filmed on panchromatic film.

3. FUNDUS (OPHTHALMOSCOPIC FEATURES)

In the initial stages (fig. 1) there is an accumulation of pigment granules at the site of the fovea. This possibly starts at about age 5. A network gradually forms around the central accumulation and extends towards the periphery, until finally it closely resembles a knotted fishing-net. In advanced stages (fig. 2) the network assumes an oval shape with a vertical diameter of about 5 disc diameters (dd) and a horizontal diameter of about 7 dd. This network is arranged about a dark pigment spot of about 1 dd, localized in the fovea (fig. 3). This stage is found at about age 15. In

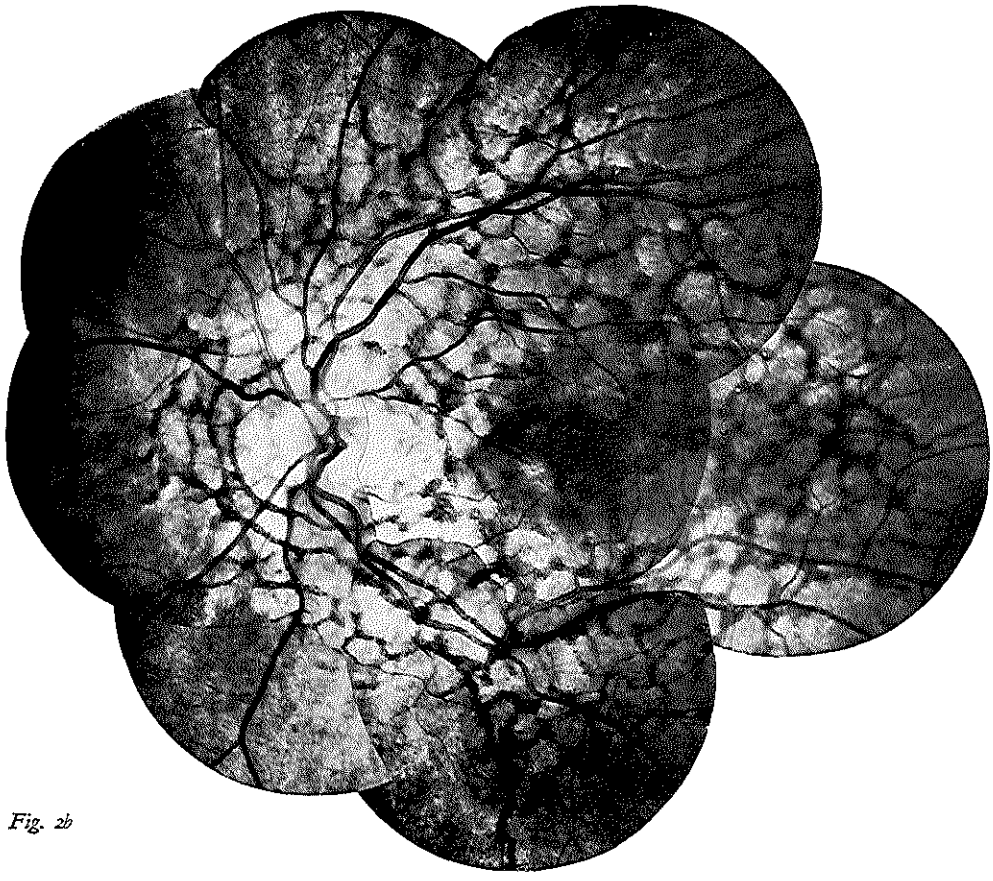


Fig. 2b

even more advanced stages (about age 30) the shape of the network becomes irregular and its appearance is bleached; white drusen-like spots occur at that time. In later stages the pigment gradually disappears.

The meshes of the net are less than 1 dd in size and of irregular shape (fig. 2-4). The ophthalmoscopically involved retinal area is of roughly the same size as the affected area in dominant drusen of Bruch's membrane and fundus flavimaculatus.

Binocular contact lens examination of the retina shows that the pigmentations are localized below the neuro-epithelium, that is to say: very likely in the pigment epithelium. Ophthalmoscopy in red-free light hardly discloses a discernible network. This, too, indicates that the pigmentations are not localized in the superficial retinal layers.

Foveolar, foveal and intimal reflexes are normal. The course of the retinal vessels is undisturbed, and anterior to the network; disc and retinal periphery are quite normal.

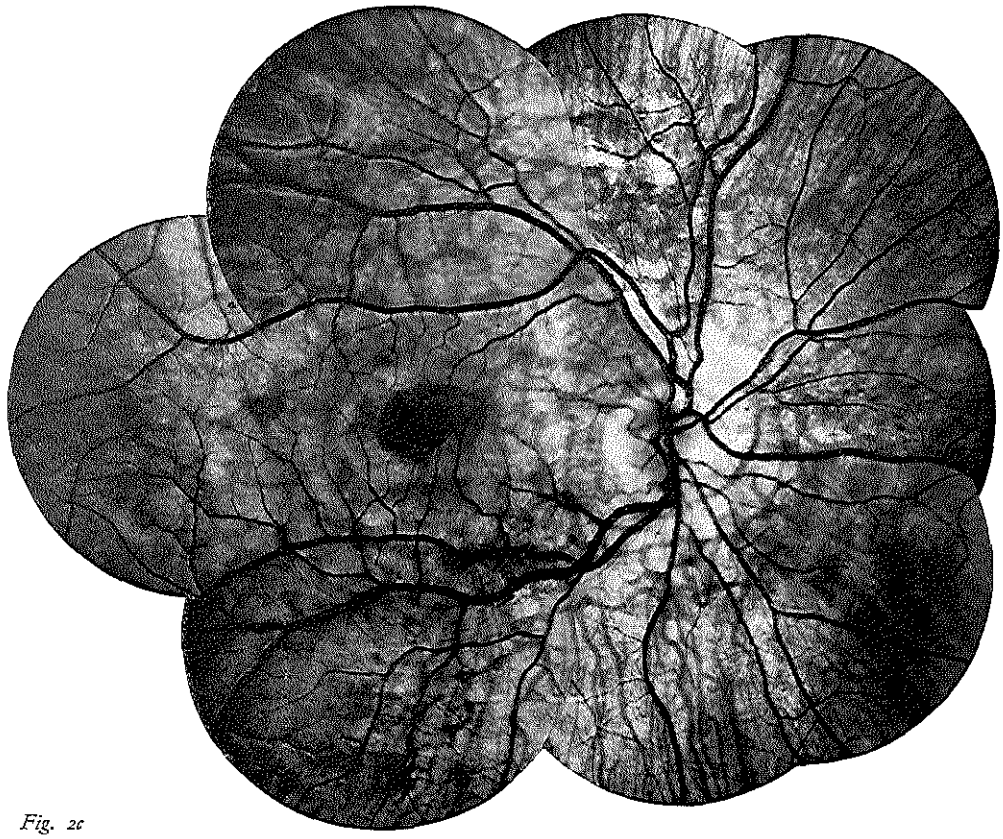


Fig. 2c

cd. filmed on orthochromatic film.

4. REFRACTION

Our two patients showed hypermetropia and astigmatism; Sjögren described one patient with high myopia and 4 with hypermetropia.

5. VISUAL ACUITY

Visual acuity is quite normal. Sjögren (quoted by Franceschetti, François and Babel 1963) did mention that visual acuity in 2 of his patients had slightly diminished 12 years after the original study.

Strabismus is not uncommon in this condition (3 of the 7 cases). The diminished visual acuity observed in a few cases must undoubtedly be ascribed to amblyopia.

6. VISUAL FIELDS

The visual fields are normal (III-1 fam. dB).

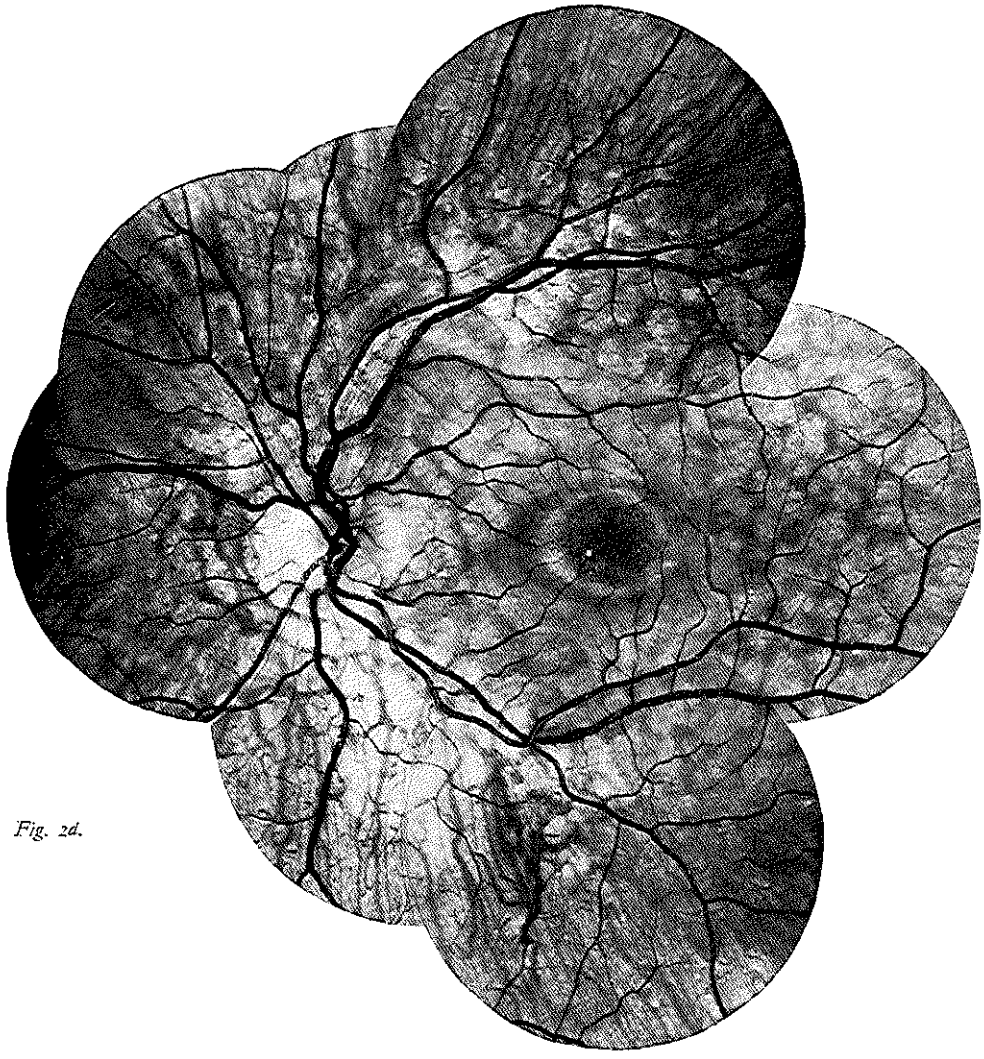


Fig. 2d.

7. COLOUR VISION

Colour vision is normal (III-1 and III-5 fam. dB).

8. DARK ADAPTION

Dark adaptation is normal (III-1 fam. dB).

9. ELECTRORETINOGRAPHY

The ERG is normal (III-1 fam. dB).

Fig. 3. Detail of the posterior polar area of the left eye of a 14-year-old girl. Note the dark foveal area.

10. ELECTRO-OCULOGRAPHY

The EOG is normal, at least at an early age (III-1 fam. dB).

These findings are suggestive of normal retinal functions and also, contrary to expectations, of a basically normal function of the pigment epithelium.

11. PHOTOGRAPHY

Orthochromatic graphic film gives photographs in which the pathognomonic fishing-net is hardly visible (figs. 2cd, 4b). Panchromatic graphic film, however, gives photographs in which the network is splendidly defined (figs. 2ab, 4a).

These findings argue in favour of a localization of the pigment changes in the pigment epithelium, for it is our experience that changes in the pigment epithelium are very clearly visible on panchromatic film.

12. FLUORESCEIN ANGIOGRAPHY

As soon as the choroid is filled by fluorescein, the network stands out as if held in front of a light box (fig. 5a). No defects are demonstrable in the pigment epithelium, but the meshes of the network seem to contain exceedingly pigment-poor pigment epithelium cells. There is no fluorescein leakage, and this suggests an intact Bruch's membrane (fig. 5b). No after-fluorescence is observed, and this warrants the assumption that there are no defects in the pigment epithelium.

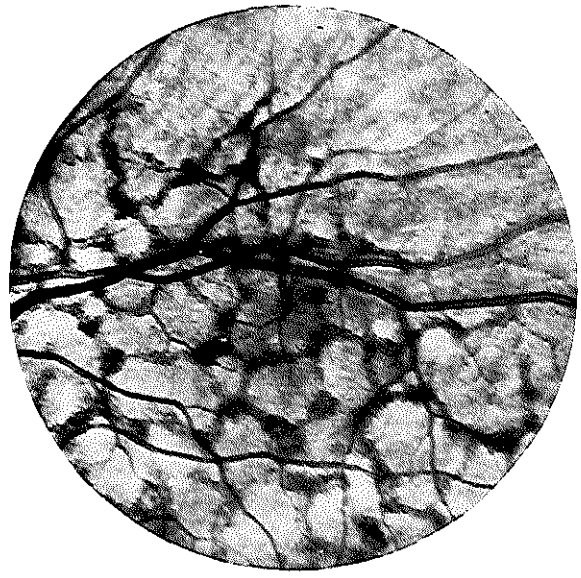


Fig. 4a. The mosaic-like pattern of polygons is very well visible in the retinal midperiphery, in the periphery of the network (panchromatic film).

Fig. 4b. Orthochromatic film shows slight abnormalities.

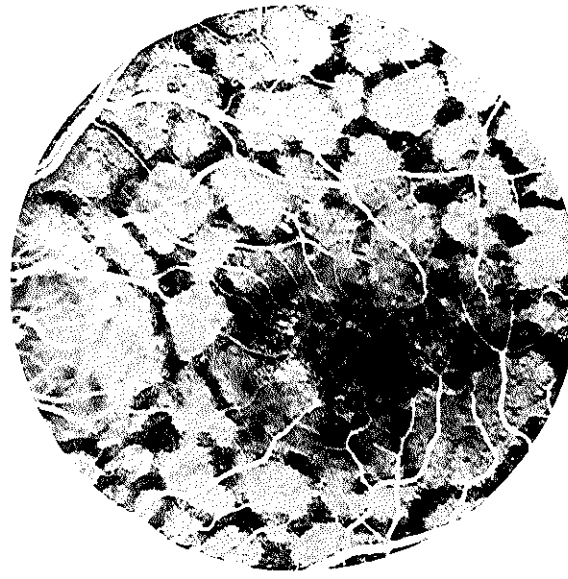


Fig. 5a. Fluorescein angiography shows a network of pigment condensation in front of a brightly fluorescent choroid. The meshes of the network seem to be deprived of pigment (19 seconds after fluorescein injection).

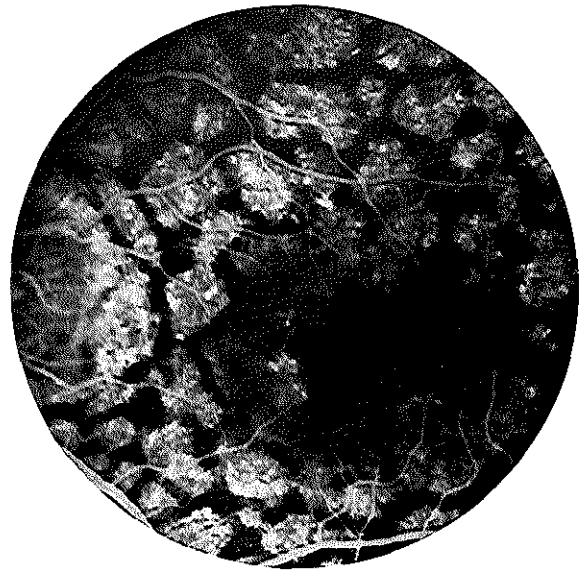


Fig. 5b. There is no leakage of fluorescein. The choroidal fluorescence is still visible 39 seconds after fluorescein injection.

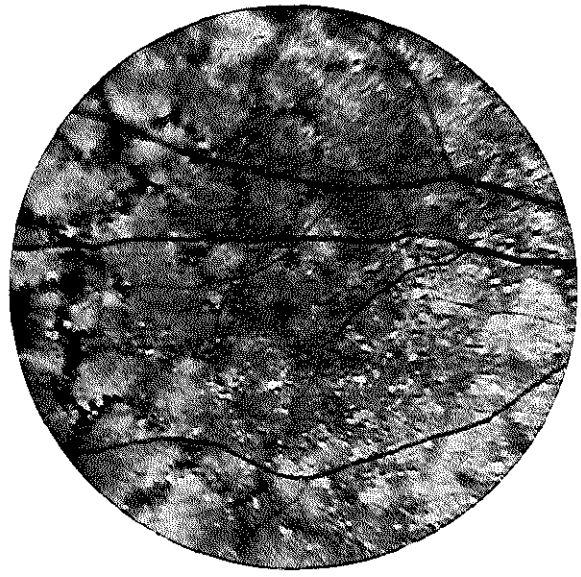


Fig. 6. A network of pigment resembling Sjögren's reticular dystrophy in the retinal periphery of a 60-year-old female. These structures are found rather frequently in the retinal peripheries of patients over 60 years of age.

13. CARRIERS

The parents of patients with reticular dystrophy of the retinal pigment epithelium are ophthalmoscopically quite normal. Since the patients themselves have quite normal retinal function tests, we carried out no retinal function tests in the parents.

14. HISTOLOGICAL FINDINGS

No histological study has so far been made of reticular dystrophy of the retinal pigment epithelium.

15. PATHOGENESIS

This condition would seem to be a primary dystrophy of the cells of the pigment epithelium, which leaves these cells functionnaly intact. Both the photoreceptors and the Bruch membrane are normal at least until middle age. It is surprising that the pigment granules form such a mosaic-like pattern, and that the boundaries of the network meshes resemble the shape of the boundaries of the pigment epithelium cells. It might well be that each mesh of the reticulum constitutes a functional or anatomical unit.

It is a remarkable fact that such polygonal shapes are more frequently encountered in ophthalmology. Mosaic-like patterns are encountered in the cornea in "anterior

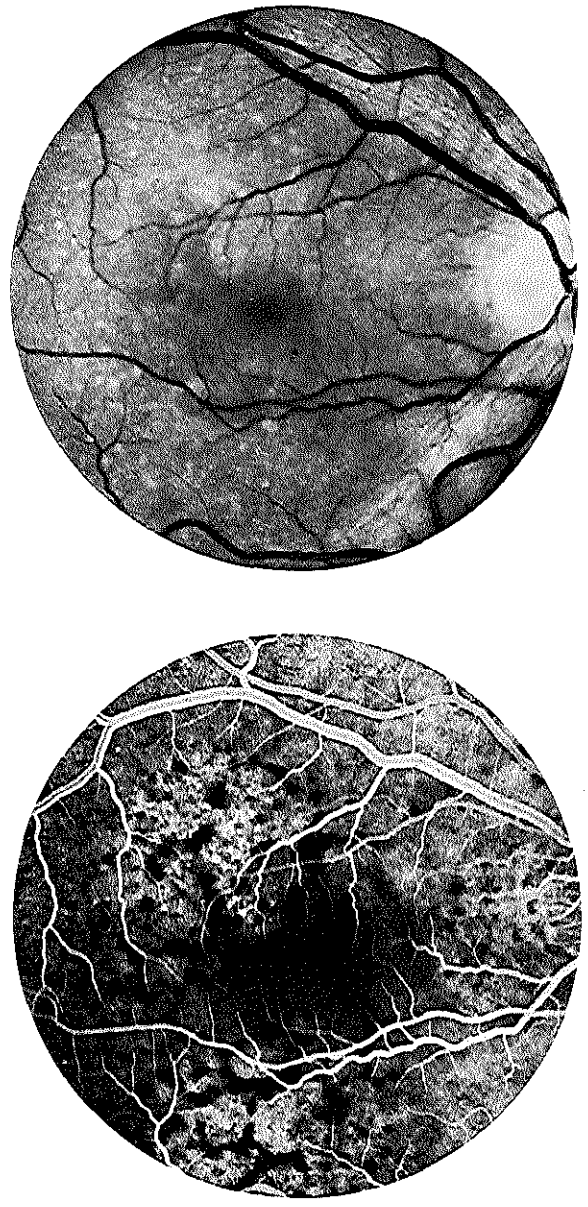


Fig. 7a-b. Small and rather vague drusen in the eye of a man in his forties. Fluorescein angiography reveals the surprising pattern of a reticular pigmented network (after Oosterhuis).

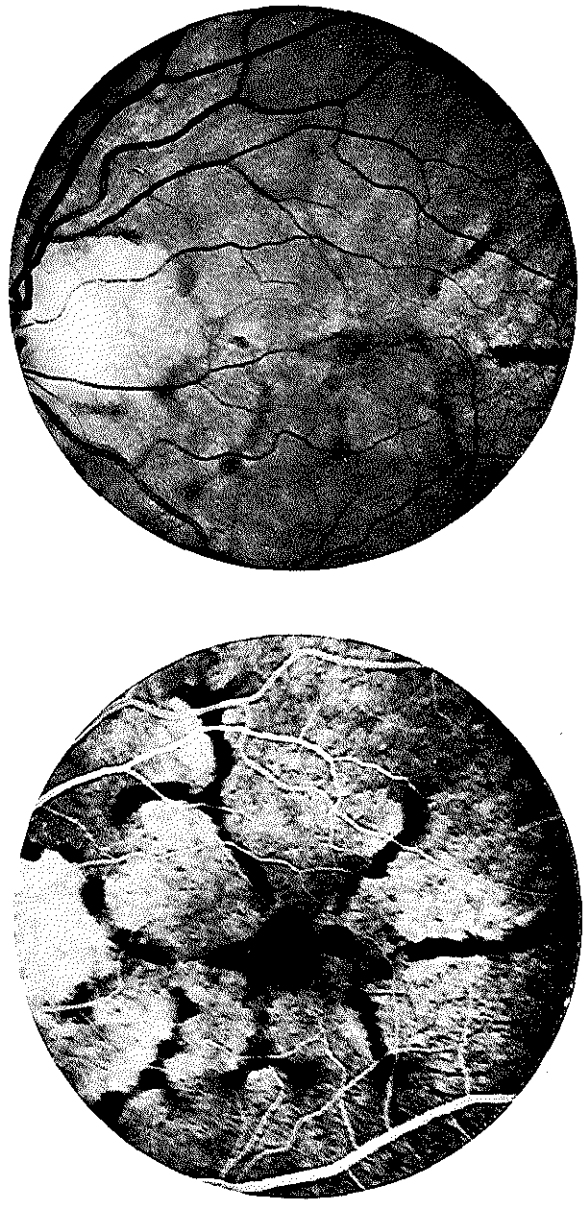


Fig. 8a-b. Conventional photograph and fluorescence angiogram of one eye of one of the three patients, described by Mesker et al., with retinal lesions resembling Sjögren's reticular dystrophy of the retinal pigment epithelium.

mosaic dystrophy" (Vogt 1930; Bron and Jones 1969) and in "mosaic dystrophy of Descemet's membrane" (posterior crocodile shagreen) (Vogt 1930; Streiff 1948); and in the retina in some forms of retinopathia pigmentosa (Franchescetti et al. 1963) and in dominant drusen (page 377). In elderly arteriosclerotic patients the retinal periphery often shows ill-defined pigmented reticular structures which are deceptively similar to Sjögren's fishing-net (fig. 6). Another net-like pattern is described in reticular cystoid degeneration of the retinal periphery (Feman and Foos, 1969).

Mosaic structures are likewise found in the corneal epithelium after applying drops of fluorescein and gentle rubbing of the closed eyelids over the cornea (Schweitzer 1967). Fischer's reflectographic "Furchenbild" (1928) also had a polygonal pattern which forms when a beam of light (preferably from a gas laser) is reflected on the cornea and then impinges on an opaque diffusing screen. It is possible that Schweitzer's corneal fluorescence pattern as well as Fischer's reflectographic "Furchenbild" result from furrows in the corneal epithelium (Schweitzer 1967). So far, no adequate explanation of the occurrence and nature of these mosaic structures has been found.

16. MODE OF TRANSMISSION

Reticular dystrophy of the retinal pigment epithelium probably has an autosomal recessive mode of transmission. Since only 7 patients from 2 families are known in the world literature, it is likely that the gene occurs very sporadically. It should be borne in mind, however, that many of these patients have normal visual acuity and are therefore unlikely spontaneously to seek ophthalmological advice, unless there are marked abnormalities of refraction. In both families the patients' parents were consanguineous. Since the parents were likewise quite normal at ophthalmoscopy, it is probable that the mode of transmission is autosomal recessive. In all likelihood the pathological gene causes only the retinal changes and not such associated conditions as deafmutism, spherophakia and diaphanous irides. These conditions were found in some relatives of the patients described by Sjögren (1950) and in a few of the patients themselves; so far as can be assessed, however, they must have been caused by other, independent genes.

The findings in the family we studied, in which the patients showed only retinal changes, support this hypothesis.

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

We found no general physical abnormalities in our patients. Sjögren (1950) and Holmgren (1950) found a probably also recessive form of deafmutism in 2 patients and in 3 other siblings. This is an interesting finding. The occurrence of retinopathia pigmentosa in association with deafness is a wellknown phenomenon (Von Graefe 1858; Liebreich 1861), which possibly reflects the common origin of the pigment epithelium and the epithelium of the organ of Corti (Franceschetti and Klein 1941). Congenital deafness is always accompanied by mutism (Usher 1914).

There is much to indicate that retinopathia pigmentosa and its accompanying deafness are produced, not by several genes but by a single pleiotropic gene (Duke-Elder 1967). Although reticular dystrophy of the pigment epithelium with deafmutism probably involves several genes, pleiotropy cannot be ruled out with certainty.

No other abnormalities were found. The Wassermann reaction was negative. Intelligence was normal. Our patients, like those described by Sjögren, had blond hair and blue eyes.

18. ASSOCIATED CONDITIONS

Sjögren (1950) found spherophakia in one of his patients and one of this patient's sisters. He observed a scleral staphyloma and diaphanous irides in a few patients. Strabismus was noted in 2 patients and 2 of their brothers. We observed the same in one of our 2 patients (III-1). High myopia was observed in only one patient (Sjögren 1950).

19. DIFFERENTIAL DIAGNOSIS

Differential diagnosis in these cases is not difficult, and encompasses the same conditions as those listed in the chapter on butterfly-shaped pigment dystrophy of the fovea (page 000).

Special mention need be made only of the reticular pigment changes frequently found in the retinal periphery of elderly individuals (fig. 6). These pigment changes are ascribed to arteriosclerosis, but they are never found in the posterior pole of the retina. Sometimes drusen and angioid streaks may show in fluorescein angiography reticular patterns too (Oosterhuis, 1970) (fig. 7ab). Furthermore the dystrophia macro-reticularis laminae pigmentosae retinae (Mesker et al., 1970) has to be differentiated. Particularly the lesions in their patient A resemble Sjögren's dystrophy. The posterior poles of their patients B and C, however, are more reminiscent of butterfly-shaped pigment dystrophy of the fovea.

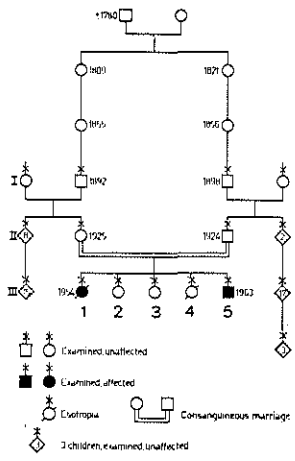
20. THERAPY

As in the other hereditary retinal affections, there is no therapy for this dystrophy, which fortunately has no or hardly any untoward effect on the retinal functions.

21. FUTURE

It will be important to make follow-up studies of patients with this rare abnormality so as to gain a better insight into the course of this dystrophy. Histological and preferably histochemical research is indispensable if the true nature of this condition is to be identified.

1. Fam. dBoe



III-1 (JdB-54.10.30) Blond girl with blue eyes.
1964: Concomitant convergent strabismus of OD. The visual acuity of the right eye is slightly diminished. Both fundi show a pigmented network in the posterior pole.
1968: Convergent strabismus OD, approximately 8 degrees.
VOD S+0.25=C+2×110° 8/10; VOS S+0.25=C+1×70° 10/10.
There is no metamorphopsia (Amsler test).
Media: Normal. No spherophakia, no diaphanous irides and no staphyloma.
Fundi: Both fundi show a pigmented fishing-net configuration in the posterior pole of the eye. The foveae reveal an irregularly shaped dark spot of about 1 disc diameter. Discs, vessels and retinal peripheries are normal. The foveal reflexes are intact. Binocular slit-lamp examination reveals that the network consists of closely packed pigment granules, which are located in the pigment epithelium (fig. 2-5).
Colour vision: Normal.
Visual fields: Normal.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 245 μV; OS 263 μV.
Phot. b-waves OD 110 μV; OS 115 μV.
EOG: OD 1.95; OS 1.85.
Fluorescein angiography: This reveals a darkly pigmented mosaic-like pattern of polygons situated in the retinal pigment epithelium in front of a brightly reflecting choriocapillaris (fig. 5). Between the threads of the network the retinal pigment epithelium appears to be hardly pigmented at all. There is no leakage of fluorescein into the subretinal space, indicating a normal Bruch's membrane (fig. 5).
Audiogram: No components of inner ear deafness are found.

III-2 and III-3 have quite normal eyes. III-4 has convergent strabismus, but normal fundi.

III-5 (KdB-63.10.05) Blond hair and blue-grey eyes.
1964: Media and fundi: Normal.
1968: VOD S+1=C+1×110° 10/10; VOS C+1×70° 10/10. No strabismus.
Media: Normal.
Fundi: A distinct dark spot of approximately 0.5 disc diameter, surrounded by some pigmented thread-like figures, located in the deeper retinal layers. Discs, vessels and retinal peripheries are normal (fig. 1).
Colour vision: Normal.

Summary: A sister and her brother from the Dutch former Zuider Zee island of Urk, suffering from reticular dystrophy of the retinal pigment epithelium. The parents of the affected children are unaffected and have a

consanguineous marriage. This dystrophy was not present in the boy at the age of 1 year. From this we can conclude that the condition is developing during infancy, and that possibly this condition is never present at birth.

Inner-ear deafness, spherophakia, diaphanous irides and staphyloma, conditions described by Sjögren himself, were not present in this family.

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X

Butterfly-shaped pigment dystrophy of the fovea

1. INTRODUCTION

So far as we know, there is only one report on butterfly-shaped pigment dystrophy of the fovea in the literature (Deutman et al. 1970). We have been unable to find in the literature another instance of a dystrophy showing even some resemblance to this condition.

In 1965, Van Blommenstein in Aruba saw an 11-year-old white Dutch boy who presented with slightly diminished visual acuity; he found an oddly shaped pigmentation in the foveal area ODS (fig. 1). The boy's father likewise proved to have these peculiar pigmentations in both foveae, in spite of normal visual acuity (fig. 2). Encouraged by Waardenburg, who had never encountered this picture, we investigated the remainder of the family, living in The Netherlands. We found three more relatives with a similar pigment structure in the retinal centre. In 4 of these patients the pigmentation closely resembled a butterfly in shape (figs. 1-4), and in view of this resemblance the condition was named butterfly-shaped pigment dystrophy of the fovea.

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

Butterfly-shaped pigment dystrophy of the fovea probably becomes ophthalmoscopically visible in the course of childhood. We found one 11-year-old boy with ophthalmoscopic changes, but none of the other 9 children of affected persons (aged from 1 to 15) showed any ophthalmoscopic changes. It seems likely that a few of these children may develop this foveal affection, because autosomal dominant transmission may be accepted for a condition found in a father and his son. It is probable that the butterfly is never in evidence at birth.

In the majority of cases the condition will be found in individuals with normal or nearly normal visual acuity. Metamorphopsia may be a first symptom in some cases, and the patients show unmistakable photophobia.

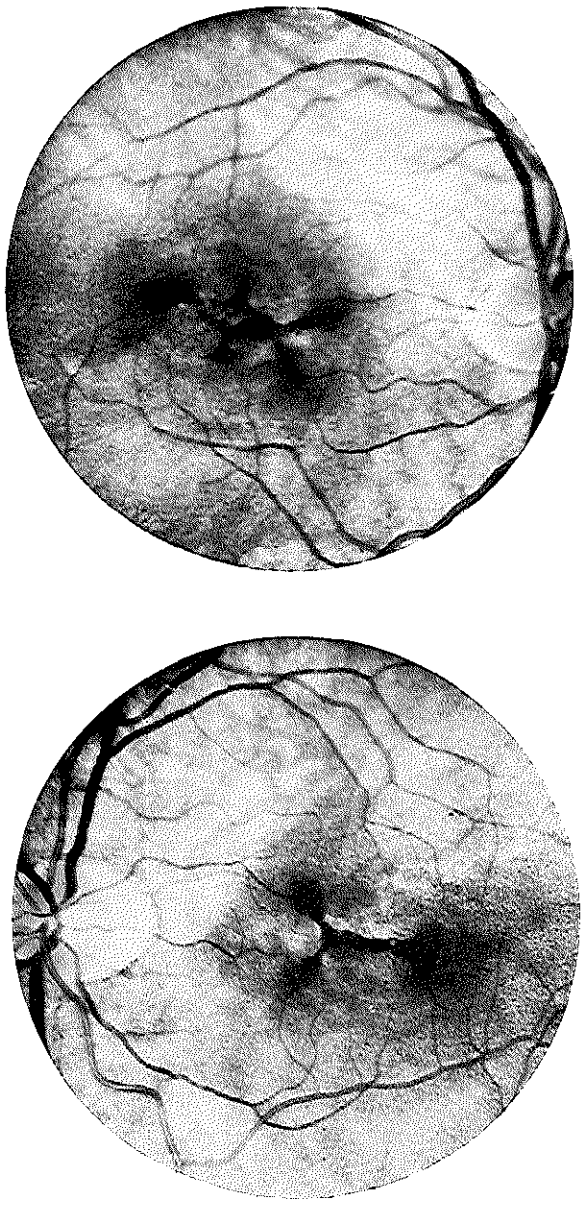


Fig. 1*a-b*. Butterfly-shaped pigment dystrophy of the fovea in the eyes of our proband, a 16-year-old boy (Fam. Ca). These photographs were made on panchromatic film.

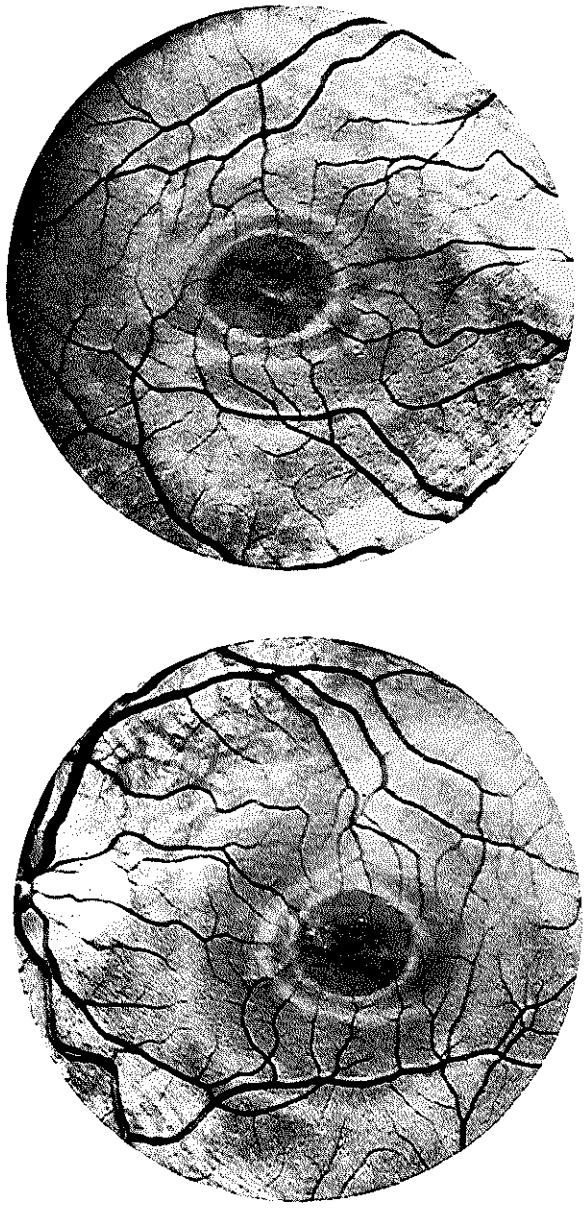


Fig. 1c-d. Butterfly-shaped pigment dystrophy of the fovea in the proband filmed on orthochromatic film. On these pictures the foveal reflexes appear to be normal while the pathological structures are hardly visible.

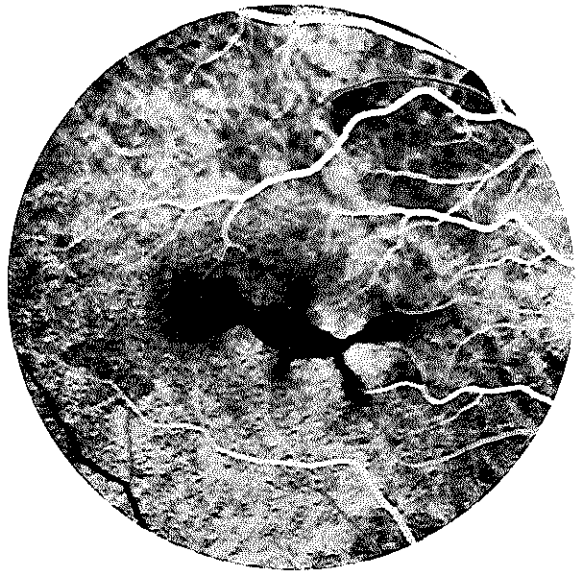


Fig. 1c. Fluorescence photograph of the right eye of the proband, showing a striking pigmented structure in front of a brightly fluorescent choroid.

The course of this condition is very slowly progressive, the progression being exceedingly small. Marked diminution of vision, if any, can be expected only at a more advanced age. The oldest of our patients (age 43) still had quite normal visual acuity.

So far as can be established this pigment alteration, which is almost certainly localized in the pigment epithelium, hardly tends to involve the layers anterior and posterior to the pigment epithelium.

Apart from peripheral retinal changes, no other ophthalmological or general pathological changes have been found. Strabismus and nystagmus were not observed. As in the other dystrophies discussed in this study, there is no particular colour of hair or irides that characterizes the patients. The refracting media are quite normal.

3. FUNDUS (OPHTHALMOSCOPIC FEATURES)

The most conspicuous feature of the fundus picture is a virtually symmetrical bilateral pigmentation localized in the deeper layers of the central retina. This pigmentation is polymorphous but in most cases takes the shape of a butterfly (figs. 1-4). Binocular slit-lamp examination clearly shows that the pigmentation is localized in the deeper retinal layers in or quite near the pigment epithelium. The retinal vessels continue their course undisturbed across the pigment butterfly. The

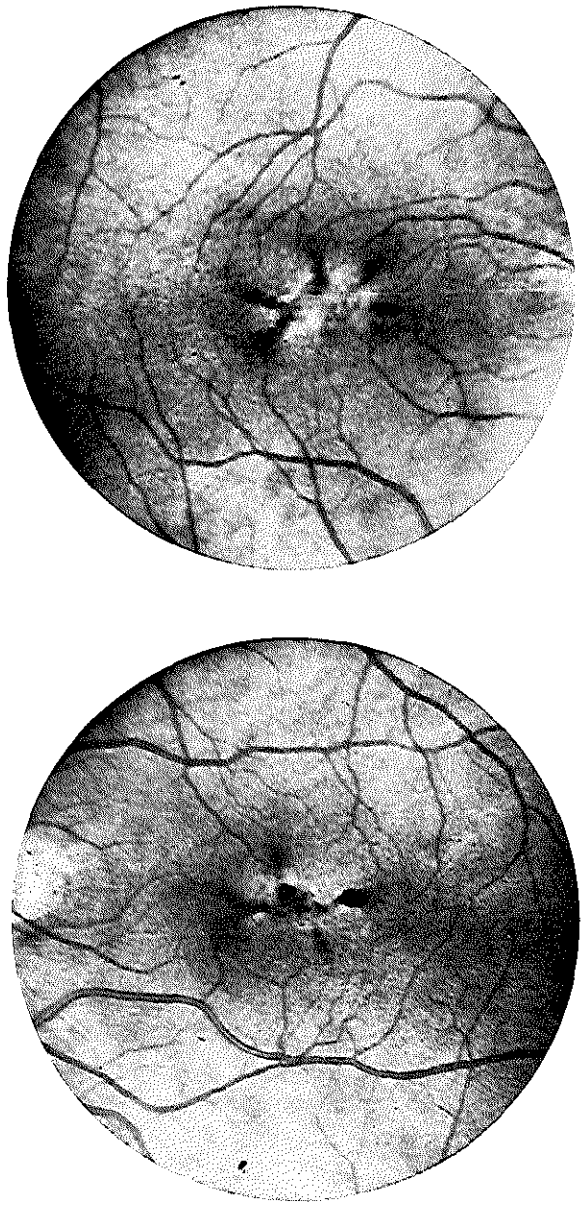


Fig. 2a-b. Two black butterflies in the eyes of one of the affected brothers (II-1) filmed on panchromatic film.

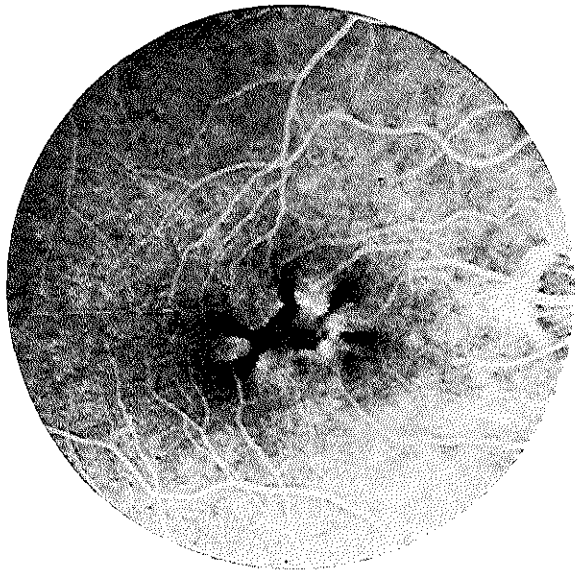


Fig. 2c. Fluorescence photograph of the right posterior pole of patient II-1, showing distinct butterfly-shaped pigmentation surrounded by bright fluorescence of the underlying choroid.

pigmentation seems to be made up of closely packed pigment granules which have migrated from the perifoveal area to the centre.

At examination with red-free light the pigmentation is less clearly visible, and this also indicates a localization deep in the retina. The superficial retinal layers are normal, as are the foveolar and foveal reflexes. The macular yellow shows a somewhat uneven distribution.

Slight drusen-like changes are visible in the posterior pole in some patients. The choroid seems normal so far as can be established.

Disc and retinal vessels are quite normal; in 2 patients (those with the darkest complexion) there were unmistakable peripheral changes in the form of spider-like lumps of pigment (fig. 6) as well as white-mottled rarefactions (fig. 7).

4. REFRACTION

Refraction was hypermetropic with astigmatism in 3 cases, emmetropic in one case and astigmatic with low myopia in one case.

In general hypermetropia with or without astigmatism proved to be quite common in the dystrophies of the central retina, which occur in the pigment epithelium.

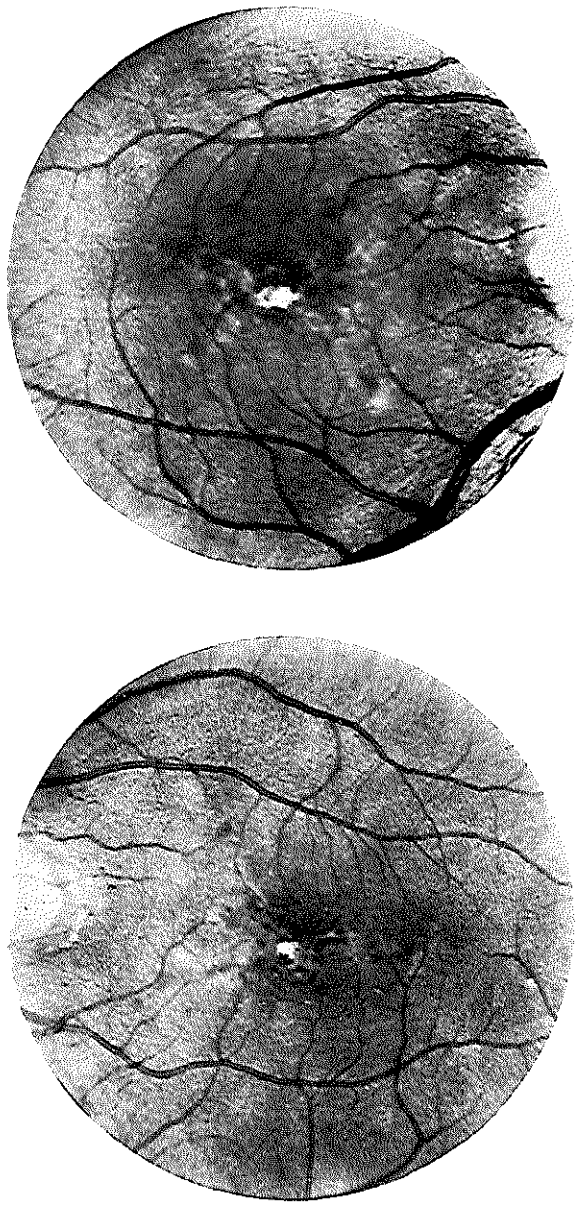


Fig. 3a-b. A more or less butterfly-shaped, slightly pigmented, and partly yellowish structure at the level of the pigment epithelium in the foveae of II-2.

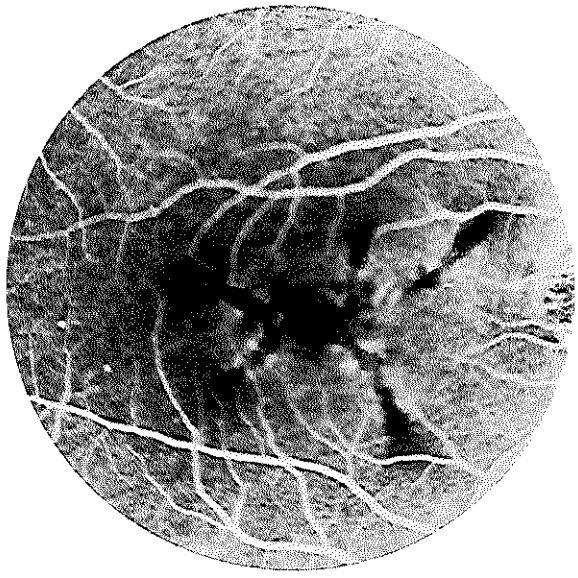


Fig. 3c. Fluorescein angiography of the right eye of II-2. showing a much more distinctive pigmented structure than is visible on the conventional photographs shown in fig. 3a-b.

5. VISUAL ACUITY

Visual acuity is virtually normal or very slightly diminished. The lowest vision recorded was 8/10. More serious loss of vision may occur at a more advanced age, when the neuroepithelium at the site of the fovea becomes more seriously affected as a result of the dystrophy of the pigment epithelium.

6. VISUAL FIELDS

The visual fields are quite normal as to peripheral boudaries. Central sensitivity is somewhat diminished in all cases, but we have been unable to demonstrate a central scotoma with the Goldmann perimeter.

7. COLOUR VISION

Colour vision is quite normal in all cases. This is consistent with out findings in other foveal dystrophies, in which colour vision diminished only when vision was distinctly diminished.

8. DARK ADAPTATION

The dark adaptation curve showed a quite normal course in all patients.

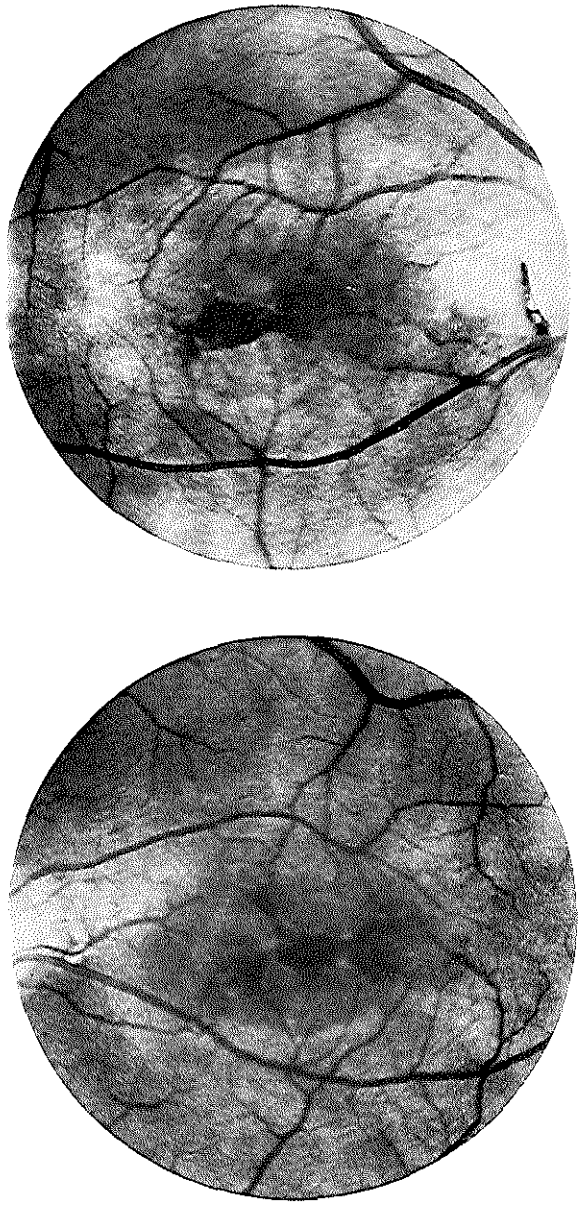


Fig. 4a-b. The foveae of II-5, a 32-year-old man, showing distinct butterfly-shaped structures, filmed on panchromatic film.

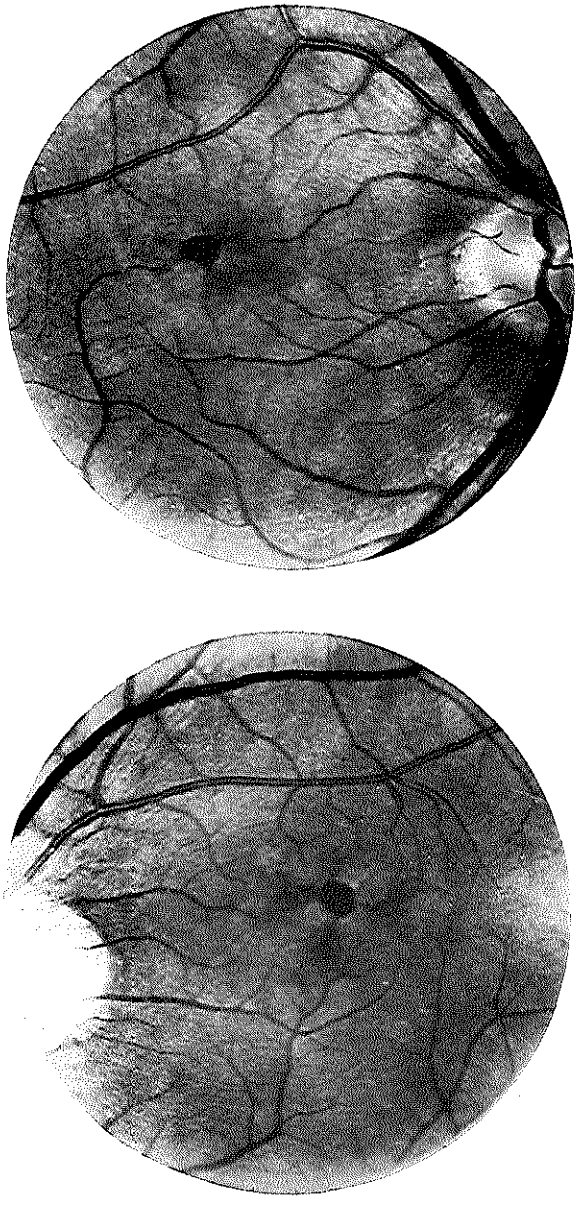


Fig. 5a-b. The foveae of II-3, a 38-year-old man, showing pigmentations which are not really butterfly-shaped.

9. ELECTRORETINOGRAPHY

The ERG is quite normal in these cases. The F-ERG was recorded in one patient (III-2) and showed a normal response. The OP were tested in the same patient and found to be entirely normal also.

10. ELECTRO-OCULOGRAPHY

The EOG is pathological in 4 of the 5 patients. Only II-5 showed an Lp/Dt-ratio which, although low, was within normal limits. In a few patients the increase of the potential in light adaptation was so slight that a marked similarity to the EOG in vitelliform dystrophy was noted.

The finding of virtually normal visual acuity, accompanied by normal colour vision, normal visual fields, dark adaptation and ERG findings, indicates intactness of the photoreceptors and the innermost retinal layers. The finding of a disturbed EOG in that case almost certainly indicates a diffuse disturbance in the function of the pigment epithelium or more deeply located structures. Since ophthalmoscopic, fluorescein-angiographic and photographic studies show that the pigment epithelium is the site of the pigment changes, and that layers outside the pigment epithelium are unaffected, we again have a strong indication that the Lp/Dt-ratio of the EOG is an index of the function of the pigment epithelium.

The peripheral retinal changes found in II-2 and II-3, support the view that the EOG is a function test of the entire retina, and not of the central retina only.

11. PHOTOGRAPHY

The pigmented butterfly-shaped lesions are much more clearly visible on panchromatic graphic film than on orthochromatic graphic film (fig. 1).

This finding is in favour of localization of the foveal changes in the pigment epithelium.

12. FLUORESCEIN ANGIOGRAPHY

Fluorescein angiograms were obtained in 3 cases (II-1, II-2 and III-2). In patients II-1 and III-2 the foveal changes (already clearly visible on the photographs) were even more clearly outlined by the choroidal fluorescence: the pigmented structures stood out as if held in front of a light box (figs. 1e, 2c and 3c).

The not readily visible pigment change in the right eye of II-2 was much more clearly seen at fluorescein angiography; there proved to be more lesions than were discernible at normal ophthalmoscopy (fig. 3ae). It is evident that pigment granules have migrated to the centre, there to form a dense papilionaceous pigment filter in the pigment epithelium. As a result, the choroidal fluorescence is invisible at the centre. Perifoveally there are some drusen-like alterations. Otherwise, defects in

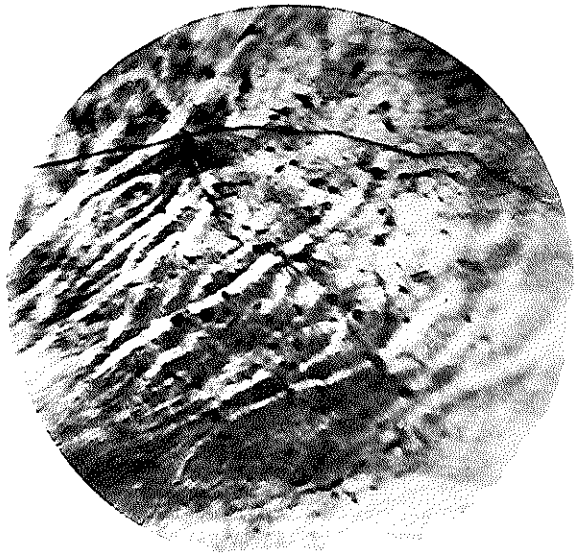


Fig. 6. Small spider-like pigmentations in the retinal periphery of one of the affected brothers (II-3).

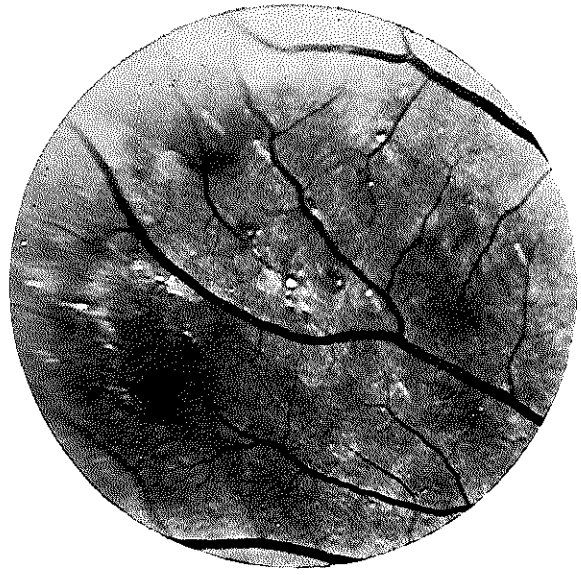


Fig. 7. Small circular white spots with pigmented borders in the retinal periphery of II-2.

the pigment layer are hardly discernible, and since no leakage of fluorescein occurs we may assume that Bruch's membrane is intact.

In summary: the fluorescein angiograms are indicative of localization of the pigmented butterfly-shaped structures in the pigment epithelium.

13. CARRIERS

Too little is known as yet about this dystrophy to establish whether there are ophthalmoscopically normal carriers of butterfly-shaped pigment dystrophy.

14. HISTOLOGICAL FINDINGS

As might be expected, no histological study has so far been made of this dystrophy.

15. PATHOGENESIS

The pathogenesis of this condition is obscure. This dystrophy would seem to show some similarity to Sjögren's dystrophia reticularis laminae pigmentosae, which likewise seems to involve migration of pigment granules in the pigment epithelium, resulting in a specific configuration of pigment. Therefore it seems to be a primary dystrophy of the retinal pigment epithelium, in which the cells of the pigment epithelium remain largely intact so that adjacent structures (retina, Bruch's membrane and choroid) are not pathologically affected.

16. MODE OF TRANSMISSION

It is still too early to formulate conclusions on the mode of transmission of butterfly-shaped pigment dystrophy of the fovea. The fact that this abnormality was found in a father (II-1) and his son (III-2), while father and mother were not consanguineous, is an argument in favour of autosomal dominant transmission. Unfortunately, no patients have as yet been identified in a third generation. Since visual acuity shows no or only very slight diminution, it is impossible to trace patients anamnestically.

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

All patients are in good health and show no abnormality other than the foveal lesions. The only one of the 5 brothers with no-retinal affection (II-4) is suffering from multiple sclerosis.

The colour of the hair and the irides shows no specific peculiarities in the affected members of the family. Two (II-1 and III-2) are blonds; two (II-2 and II-3) are brunets; and one (II-5) has red hair.

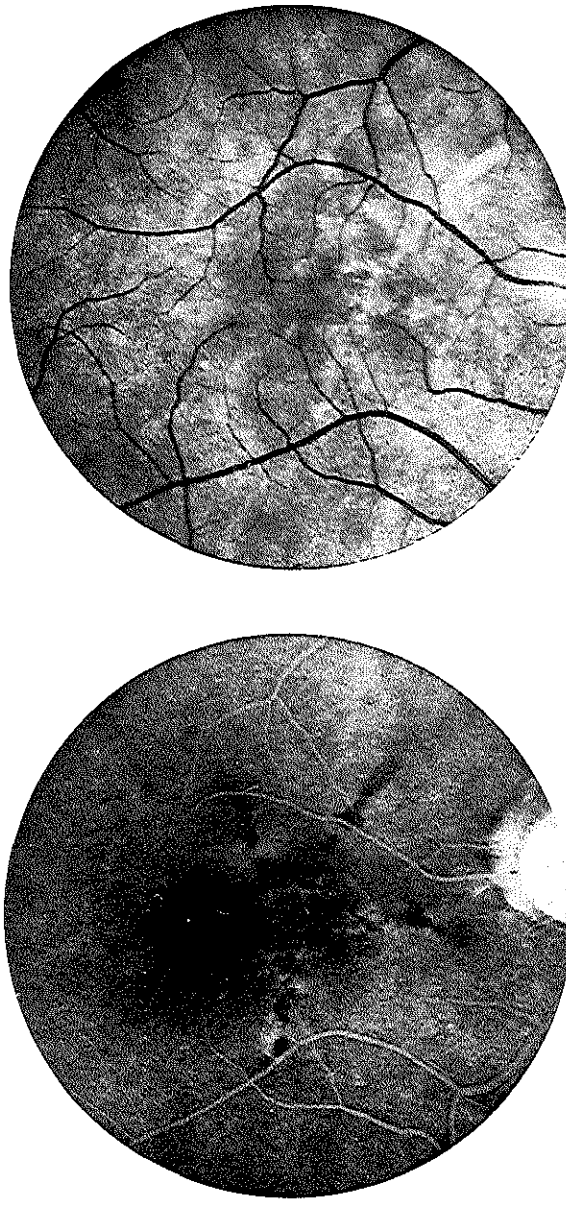


Fig. 8ab. Conventional and fluorescence photograph of one of the eyes of the 3 patients described by Mesker et al. with retinal lesions resembling Sjögren's reticular dystrophy of the retinal pigment epithelium.
In our opinion this structure resembles butterfly-shaped pigment dystrophy strikingly

Fig. 9. Rubeolar retinopathy, complicated by a foveal haemorrhage, in a 10-year-old deaf boy.

18. ASSOCIATED CONDITIONS

As the above paragraph indicates, there are no affections which occur in association with butterfly-shaped pigment dystrophy.

19. DIFFERENTIAL DIAGNOSIS

Differential diagnosis of butterfly-shaped foveal dystrophy encompasses all foveal affections and, since this dystrophy is bilateral, it must be differentiated in particular from the other hereditary dystrophies of the central retina and choroid. However, there is hardly any known foveal abnormality which shows even the faintest resemblance to the ophthalmoscopic aspect of the pigmented butterflies. Differential diagnosis will therefore offer little difficulty.

a. A possible exception is to be found in *the cases recently reported by Mesker et al.* (1970); in these cases irregular pigment structures occurred in the posterior pole which were also more clearly visible at fluorescein angiography. The mode of transmission of this condition is still obscure (fig. 8).

b. Occasionally, marked pigmentation in the posterior pole can be observed in *Stargardt's disease* or *vitelliform foveal dystrophy*. But this will always be readily distinguishable from the butterflies discussed in this chapter, on the basis of fundus picture, visual acuity and family study.

Differentiation must also be made from the group of affections in which marked pigmentations are observed in fundo in the absence of any significant disturbance in retinal function.

c. *Sjögren's dystrophia reticularis laminae pigmentosae retinae* (1950), which is autosomal recessive, shows a network of pigmentations at the level of the pigment epithelium, with intact retinal functions (Deutman and Rümke 1969). The fovea shows a black lump the size of 1 dd, surrounded by a network which extends to about 6 dd from the retinal centre. No butterfly-shaped pigmentations are seen.

d. *Grouped pigmentations of the fovea* consist of sharply defined spots of pigment in the pigment epithelium, which do not affect visual acuity. Sometimes there is a white halo around the pigmentations, which are usually seen in the retinal periphery but can also occur in the centre (Loewenstein and Steel 1941; Chan 1951). Hereditary occurrence of this condition has been suggested only by Forgacs and Bozin (1966), who found grouped foveal pigmentations in two sisters (page 365). Perhaps the patients described by Torres-Lucena (1950) also come under this heading. Five cases were described in which round pigmentations occurred in the posterior pole with no disturbance of retinal function.

e. In *rubeolar retinopathy* (pseudoretinopathia pigmentosa viralis congenita) there are usually diffuse granular pigmentations in the retinal periphery, the highest density of pigment accumulation usually occurring in the posterior pole of the eye (fig. 9). This affection is confined to the pigment epithelium and consists of localized areas of atrophy combined with areas of increased or decreased pigmentation. The neuro-epithelium of the retina and the choroid are normal, and visual functions show no or very little diminution. Visual acuity, visual fields, colour vision, dark adaptation, ERG and EOG are usually normal (Krill 1967). Many patients suffer from deafness as well.

f. *Fundus pulverulentus* is a hereditary affection of the pigment epithelium without disturbance of retinal functions, described by Slezak and Hommer (1969). Mottled and granular pigmentations occur in the posterior pole and central to the equator. These changes are symmetrical. The authors mentioned 5 cases, including a man and 2 of his daughters.

Disc, retinal vessels, visual acuity, visual fields, dark adaptation and ERG are normal. The EOG has not been recorded in this not yet exactly defined entity. More fundus photographs and fluorescein angiograms of this condition will have to be published, and a more extensive family study is required, in order to obtain a more exact impression of this abnormality of the pigment epithelium.

g. *Pigmented paravenous chorioretinal dystrophy* is characterized by fragmentary pigmentations along the large retinal veins, while the fovea is generally unaffected and visual acuity therefore intact. Hereditary factors have not so far been demon-

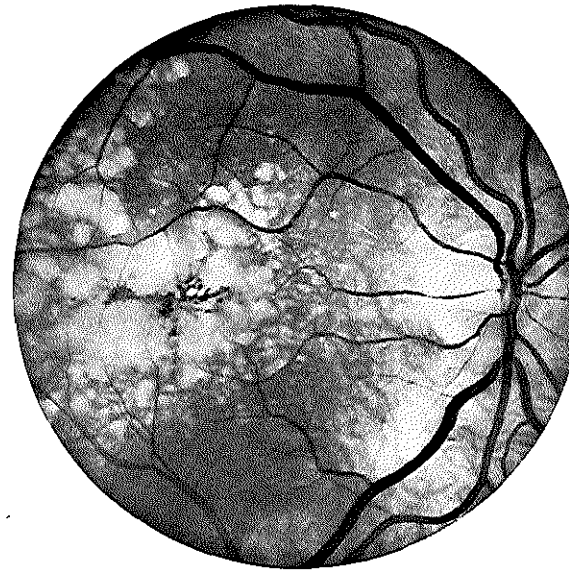


Fig. 10a. Drusen in the posterior pole of the right eye of a 70-year-old man.

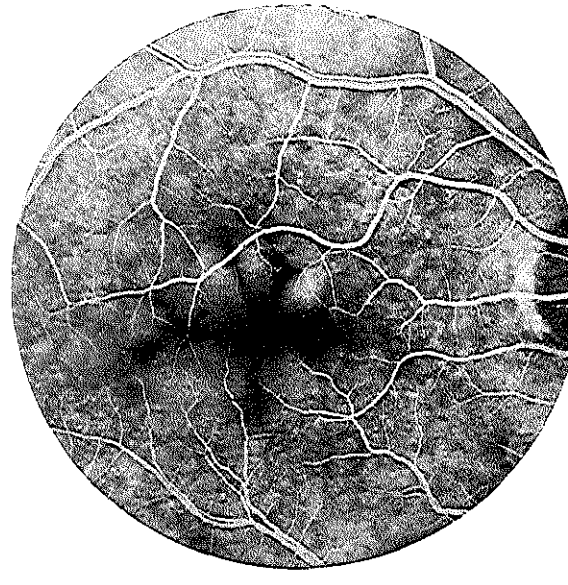


Fig. 10b. Fluorescein angiography shows a figure resembling the butterflies depicted in the foregoing figures (after Oosterhuis).

strated in this condition (Brown 1937; Weve 1957; Amalric and Schum 1968; Baquis, 1968; Bonamour and Ravault, 1968) (see page 193).

There is also a group of affections which can involve extensive pigmentations in fundo but which differ from the abovementioned group in that extensive changes in retinal function do occur. Of this group we mention the pigmentations in the foveal and retinal periphery (Potts 1966) caused by drugs such as phenothiazine derivatives (Boet 1970) and chloroquine derivatives (Butler 1966), pseudoretinopathia pigmentosa viralis acquisita (measles, vaccinia) (Hentsch and Külz 1969; Bücklers 1969), and diffuse and pericentral retinopathia pigmentosa. In these affections one generally finds pale discs, constricted retinal vessels and disturbed retinal function tests. The extensive pigmentations which can occur following chorioretinitis, are likewise differentiated without difficulty.

In addition, drusen may be mentioned as a less obvious possibility of differential diagnosis. We saw a woman with drusen in whom the fovea showed a butterfly-shaped structure among the drusen (fig. 10). In fluorescein angiograms in particular this papilionaceous structure was clearly visible because the numerous drusen surrounding the structure did not filter away the choroidal fluorescence. In butterfly-shaped pigment dystrophy of the fovea there is extra filter action at the site of the central butterfly structure, while the surrounding retina is normal or slightly deprived of pigment.

20. THERAPY

There is no therapy, and in nearly all cases the functional loss is so small that no effort at therapy need be made.

21. FUTURE

The follow-up on this family will be made with great care in an effort to ascertain the mode of transmission. This will also supply data on the long-term progression of the foveal process. Meanwhile, attempts are being made to trace further members of this family.

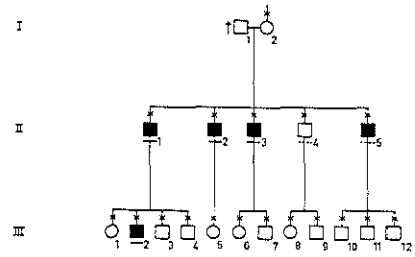
22. CASE HISTORIES

1. Fam. Ca

I-1 (JDC-98.08.03) Is reported to have had good vision. Died in 1950 from heart disease.

I-2 (CHCvD-99.05.27) VODS 10/10.
Fundi: OD normal. Some drusen in the foveal area of OS.

II-1 (HCLC-25.02.01) Sandy hair and blue-green eyes. No visual complaints. Was examined when a peculiar butterfly-shaped pigmentation was found in the foveae of one of his sons.
VOD S+3.50=C+0.50×92° 10/10; VOS S+4=C+0.50×85° 10/10.
Amsler test: OD slight metamorphopsia. OS normal.
Media: Normal.
Fundi: Normal foveal reflexes. Discs, vessels and retinal peripheries are normal. Both foveae show a pigmented butterfly-shaped structure. This structure has not changed during 3 years of observations.



Binocular slitlamp examination reveals closely packed pigment granules at the level of the pigment epithelium (fig. 2).
Colour vision: Normal.
Visual fields: Normal peripheries. Slightly decreased central sensitivity.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 285 μV; OS 305 μV; Phot. b-waves OD 125 μV; OS 120 μV.
EOG: OD 1.60; OS 1.50.
Fluorescein angiography: The pigmentation in the fovea is more easily distinguished because of the fluorescence of the underlying choroid. Around the pigmented structure there are defects in the retinal pigment epithelium (fig. 2c).

II-2 (CLG-26.03.30) Dark brown hair and brown irides. No visual complaints.
VODS S+1=C+1×90° 10/10. No metamorphopsia (Amsler test).
Media: Normal.
Fundi: In each fovea there is a more or less butterfly-shaped, slightly pigmented, and partly yellowish structure at the level of the pigment epithelium (fig. 3). This is the only case in this family in which the foveal structure is not darkly pigmented. The foveal reflexes are normal. The retinal peripheries are partly spotted with pigment dots and small circular white spots with a pigmented border (fig. 7).
Visual fields: Slightly decreased central sensitivity.
Colour vision and dark adaptation: Normal.
ERG: Scot. b-waves OD 205 μV; OS 285 μV. Phot. b-waves OD 135 μV; OS 110 μV.
EOG: ODS 1.00.
Fluorescein angiography: The pigmentations in the right fovea are much more distinctive because of the underlying fluorescing choroid. Some minor defects in the pigment epithelium are visible (fig. 3c). There is no leakage of fluorescein.

II-3 (JDC-30.02.05) Dark brown hair, brown irides. Without visual complaints. No metamorphopsia.
VODS S+0.75=C+3×90° 10/10.
Media: Normal.
Fundi: Darkly pigmented structure in each fovea (fig. 5). The structures are not butterfly-shaped. The foveal reflexes, discs and vessels are normal. The retinal peripheries reveal small spider-like pigmentations with uneven distribution (fig. 6).
Visual fields: Slightly decreased central sensitivity.
Colour vision and dark adaptation: Normal.
ERG: Scot. b-waves OD 325 μV; OS 345 μV. Phot. b-waves OD 135 μV; OS 135 μV.
EOG: ODS 1.30.

II-4 (WCC-34.05.21) Patient suffers from multiple sclerosis.
VODS S+1.50 10/10. No metamorphopsia.
Media and fundi: Normal.
Visual fields, colour vision and dark adaptation: Normal.
ERG: Scot. b.-waves OD 335 μV; OS 315 μV. Phot. b-waves OD 130 μV; OS 105 μV.
EOG: ODS 2.00.

II-5 (HLC-36.05.04) Reddish hair, blue eyes. No visual complaints.
VOD C−1×180° 9/10; VOS C−1×180° 10/10.
Media: Normal.

Fundi: Butterfly-shaped pigment structure at the site of each fovea (fig. 4). The foveal reflexes are normal. In 1965 and in 1968 this man was examined and photographs were made of the foveal area. Compared to the more closely grouped pigmentation in the butter-fly-shaped structure on the photographs of 1965, the pigmentation on the photograph of 1968 seems to be slightly dissolved. Discs, vessels and retinal peripheries are normal.
Visual fields: Slightly decreased central sensitivity.
Colour vision and dark adaptation: Normal.
ERG: Scot. b-waves OD 320μV; OS 260μV. Phot. b-waves OD 130μV; OS 120μV.
EOG: OD 1.80; OS 1.76 in 1965. In 1968: OD 1.85; OS 1.95.

III-2 (AC-54.06.18) Blond, blue-eyed boy. No metamorphopsia.
VODS 8/10, emmetropic.
Media: Normal.
Fundi: Pigmented structure in the shape of a butterfly in both foveal areas (fig. 1). This structure has not changed during the last 3 years. The foveal reflexes, discs, vessels and peripheries of the retina are normal.
Visual fields: Slightly decreased central sensitivity.
Colour vision and dark adaptation: Normal.
ERG: Scot. b-waves OD 435μV; OS 355μV.
Phot. b-waves OD 145μV; OS 120μV.
EOG: OD 1.40; OS 1.45.
Fluorescein angiography: The right eye shows a darkly pigmented structure in front of a brightly fluorescing choroid. There is no leakage of fluorescein (fig. 1e).

Summary: Four of five white brothers and a son of one of them were found to have peculiar, butterfly-shaped pigmentations in the foveal area. During 3 years of observation the foveal structures hardly changed. Four of the five affected individuals have a pathological EOG, which reflects diffuse abnormality of the retinal pigment epithelium. At ophthalmoscopy only 2 of the 5 affected individuals have peripheral alterations. Probably this condition is transmitted as an autosomal dominant. (It is of interest to note that when II-1 saw the photograph of the foveal butterfly he said: "I can see this butterfly-shaped structure myself and I have seen it all my life").

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XI

Grouped pigmentations of the foveal area

1. INTRODUCTION

The term grouped pigmentations of the retina was introduced by Höeg (1911) after publications on localized retinal pigmentations by Mauthner (1868) and Jaeger (1869), who had used different designations. Grouped pigmentations of the retina, also known as melanosis retinae or congenital grouped melanosis retinae (Waardenburg et al. 1963), are not too uncommon. The lesions are often unilateral, but bilateral cases are by no means exceptions (Hoeg 1911; Ciotola 1938; personal observation). However, grouped pigmentations are rarely found in the fovea (Perera 1939; Loewenstein and Steel 1941; Chan 1951; Meunier and Boursin 1951).

Familial cases were unknown until Forgacs and Bozin (1966) described two sisters with grouped pigmentations in the foveal area. We have made no personal observations on familial cases, nor on pronounced grouped pigmentations in the fovea or its immediate surroundings. But several times we did see both unilateral and bilateral grouped pigmentations in the retinal periphery.

The cases published by Forgacs and Bozin (1966), however, may be instances of dystrophy of the pigment epithelium rather than a congenital non-progressive affection like the classical grouped pigmentations of the retina. It is therefore questionable whether the term grouped pigmentations was properly used in the cases of Forgacs and Bozin (1966).

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

The patients are generally without complaints, and these lesions are found incidentally. It is assumed that these pigmentations are congenital and show no progression whatever. However, Forgacs and Bozin (1966) found slight metamorphopsia in one of their patients, and in another (female) patient the ERG showed a rather low response and visual acuity was slightly diminished.

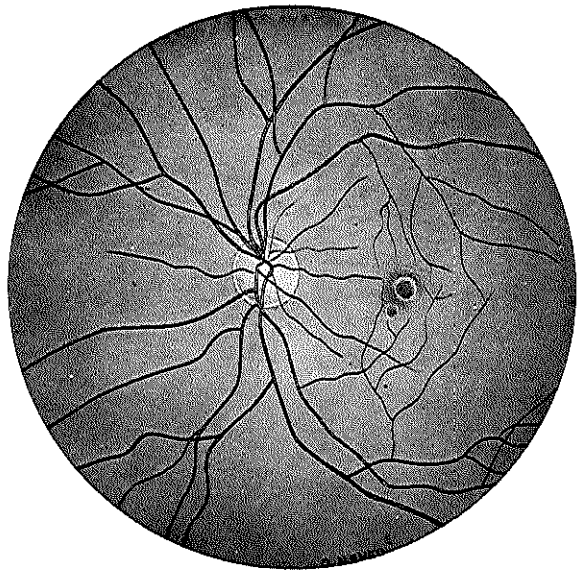

Fig. 1. Small, round pigmentations surrounded by a light halo localized in the foveal area (after Forgacs and Bozin).

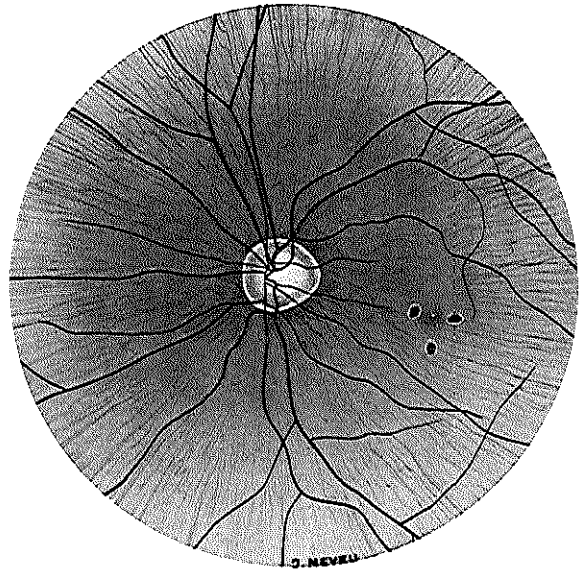

Fig. 2. Another case with small round foveal pigmentations (after Forgacs and Bozin).

3. FUNDUS (OPHTHALMOSCOPIC FEATURES)

The cases described by Forgacs and Bozin showed small, round pigmentations, always surrounded by a light halo. These pigmentations were localized in the fovea or its immediate surroundings (fig. 1, 2). Loewenstein and Steel (1941) also described such foveal pigmentations surrounded by a light halo.

Classical grouped pigmentations of the retina, however, are found in the retinal periphery and have no halo. They are often found in a triangular area, the apex of which points to the centre of the retina. Their diameter ranges from 0.1 to 1.0 dd; they are often of irregular shape, ill-defined, and can vary considerably in number (fig. 3). They are very reminiscent of animal tracks ("bear tracks") or footsteps in the snow.

4. REFRACTION

The available data on refraction are sparse and warrant no far-reaching conclusions.

5. VISUAL ACUITY

Visual acuity is generally normal.

6. VISUAL FIELDS

The visual fields are normal.

7. COLOUR VISION

Colour vision is normal.

8. DARK ADAPTATION

Dark adaptation is normal.

9. ELECTRORETINOGRAPHY

The ERG is normal, except in one of the cases described by Forgancs and Bozin (1966), in which it was slightly subnormal.

10. ELECTRO-OCULOGRAPHY

There are no data on the EOG in grouped pigmentations of the fovea. However, it would not be surprising if the EOG were normal, for at least ophthalmoscopically a localized affection is involved, and in general there are no signs of a progressive dystrophy.

Fig. 3. Melanosis retinae, or congenital grouped pigmentation of the retina, resembling bear tracks and footsteps in the snow.

11. PHOTOGRAPHY

Photography may well produce results identical to those obtained in butterfly-shaped pigment dystrophy of the fovea, and in reticular dystrophy of the pigment epithelium.

12. FLUORESCEIN ANGIOGRAPHY

Fluorescein angiography, too, may disclose similar features as the abovementioned conditons. No fluorescein angiography was performed in the cases presented by Forgacs and Bozin (1966).

13. CARRIERS

Such carriers of this condition as may exist, are quite normal.

14. HISTOLOGICAL FINDINGS

Parsons (1904) based himself on a histological study when he ascribed the grouped pigmentations to an accumulation of pigment epithelium cells.

15. PATHOGENESIS

Ida Mann (quoted by Sukumlyn 1946, 1957) assumed that the pigmentations arise from "atypical differentiation of isolated cells of the inner wall of the optic cup, each of which has developed pigment and then divided to form the small clump of cells seen as the pigmented spot".

In the cases of Forgacs and Bozin (1966), however, dystrophy of the pigment epithelium cannot be ruled out; in other words: the pigment spots in their cases may not be congenital.

16. MODE OF TRANSMISSION

Too little is as yet known of this condition to reach any conclusion on the mode of transmission. In view of the low incidence of this affection, autosomal recessive transmission is among the most plausible of the possibilities (fig. 4; pedigree).

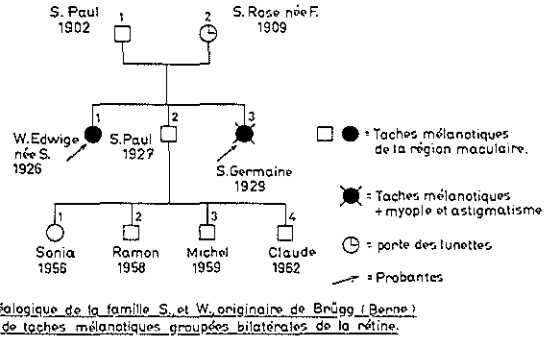

Fig. 4. Pedigree of the family described by Forgacs and Bozin (1966).

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

The patients described by Forgacs and Bozin (1966) displayed no general physical abnormalities.

18. ASSOCIATED CONDITIONS

The patients described by Forgacs and Bozin (1966) showed no abnormalities other than the foveal pigmentations. However, there are reports on incidental concomitance of grouped pigmentations with the following conditions: maculocerebral degeneration (Schwarz 1943); pseudocoloboma of the macula (McGregor 1945); Coats' disease (Paufique et al. 1951); duplicate disc (Collier 1959); Fröhlich syndrome (Hoppenbrouwers 1956); syndactylism (Lopez 1948); dyschondroplasia (Collier 1961).

19. DIFFERENTIAL DIAGNOSIS

The differential diagnosis discussed in the chapter on butterfly-shaped pigment dystrophy of the fovea fully applies to familial grouped pigmentations of the foveal

area (page 354). The principal differentiation, in our opinion, is that from fundus pulverulentus (Slezak and Hommer 1969), although we believe that this entity requires a more exact definition.

20. THERAPY

Therapy need not be discussed in this context.

21. FUTURE

Family studies on grouped pigmentations in the fovea or elsewhere in the retina will be required to obtain more information on the hereditary factors which may play a role in this condition.

22. CASE HISTORIES

We have no case histories of our own.

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ADDENDUM

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XII

Dominant drusen of Bruch's membrane

INTRODUCTION

Hyaline structures, also known as corpora amylacea, can occur in various retinal layers and in the optic nerve. Their presence has no specific significance. In advanced age and in pathological conditions they can develop from degenerating nerve fibres, and they are also seen in degeneration of retinal astroglia, perivascular glia or ganglion cells (Wolter 1959). In addition they can occur as hyalinized micro-aneurysms in terminal stages of diabetic retinopathy, and they have been observed also at the site of the internal limiting membrane (Vrabec 1953). All these hyaline bodies are histologically very much alike. They are all eosinophile and often show distinct lamellae which give them some resemblance to cells. We prefer the term hyaline bodies to corpora amylacea because the substance of these structures is hyaline, not amyloid.

Large hyaline structures are also known as drusen or colloid bodies. These drusen are found in the optic disc (fig. 1) and in Bruch's membrane (fig. 2). The drusen of the disc differ histochemically from those of Bruch's membrane, and this is understandable in view of the fact that the former are products of nerve fibre degeneration, while the latter are products of degeneration of pigment epithelium (Seitz and Kersting 1962; Seitz 1968).

After a study of relatives of 49 patients with drusen of the disc, Lorentzen (1966) postulated that this condition has an irregular dominant mode of transmission.

Drusen of Bruch's membrane, however, are found in numerous degenerative conditions and systemic diseases, and they are quite frequently seen in advanced age. Not infrequently, they are a sequel of primary hereditary dystrophy. Drusen of Bruch's membrane can be generally divided into a) *degenerative*, and b) *hereditary drusen*.

Drusen of the disc and drusen of Bruch's membrane are not usually seen in the same eye, but Lorentzen (1966) published a splendid photograph of such a rare coincidence.

Degeneration products in the form of drusen of Bruch's membrane can occur in chronic uveitis, detachment of the retina, tumours and vascular retinal disorders.

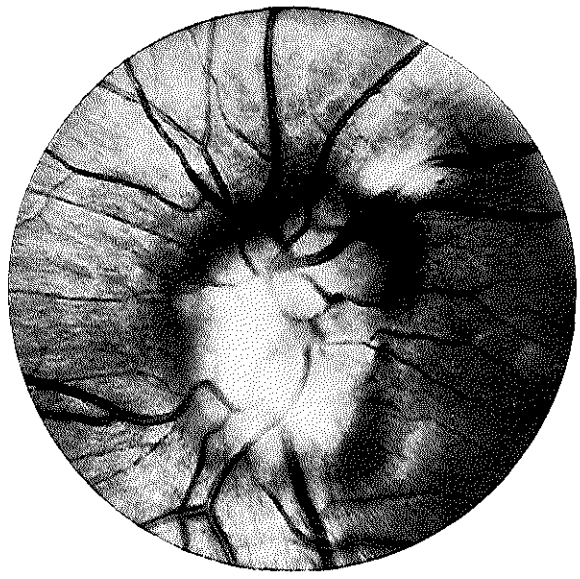


Fig. 1a. Drusen of the optic disc causing the picture of pseudo-papilloedema.

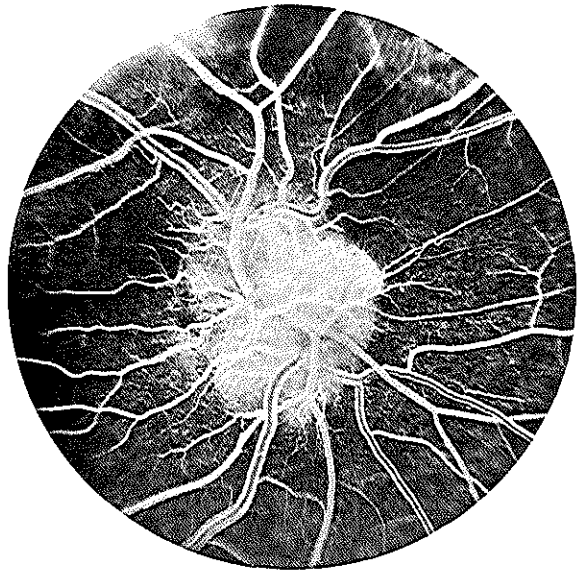


Fig. 1b. Fluorescein angiography reveals no marked capillary dilatation and tortuosity as is seen in papilloedema.

Fig. 1c. Late fluorescein phase, showing staining in areas of drusen. There is no leakage of fluorescein as is seen in the case of papilloedema.

Drusen are also observed in more general affections such as Groenblad-Strandberg pseudoxanthoma elasticum (Verhoeff 1931; Zeeman 1933; Bischler 1955; Shimizu 1961); Rendu-Osler familial haemorrhagic angiomatosis (Cuendet et al. 1953; Calmettes et al. 1957); scleroderma (Hartmann et al. 1948); polyserositis (Michaelson et al. 1959); hypercholesteraemia (Salvati, 1926 and Lijo Pavia, 1952, 1953; Montanelli 1954); and dysproteinaemia (Scorciarini-Coppola 1957). Drusen of Bruch's membrane also occur in some 50% of cases of Urbach-Wiethe hyalinosis cutis et mucosae (Jütte 1961, 1962; François et al. 1966; Rosenthal et al. 1967).

As pointed out, drusen not infrequently manifest themselves as a result of primary hereditary drystrophy of the central retina. This dystrophy has an autosomal dominant mode of transmission and is known under a variety of names, which might suggest a variety of entities. The designations found are: Hutchinson-Tay choroiditis; guttate choroiditis (Nettleship 1884; Juler 1893); Holthouse-Batten superficial chorioretinitis; family choroiditis (Doyne 1910); Doyne's honeycomb dystrophy; malattia leventinese; crystalline retinal degeneration (Evans 1950); iridescent crystals of the macula (Lijo Pavia 1953); and hyaline dystrophies (Duke-Elder 1967).

A conspicuous characteristic of these dominant drusen of Bruch's membrane is the intrafamilial uniformity and interfamilial variation in ophthalmoscopic features, which are frequently observed. One may find very large (fig. 2) or very small drusen (fig. 3). Fuchs (1956) supposed that these differences are geographically determined.

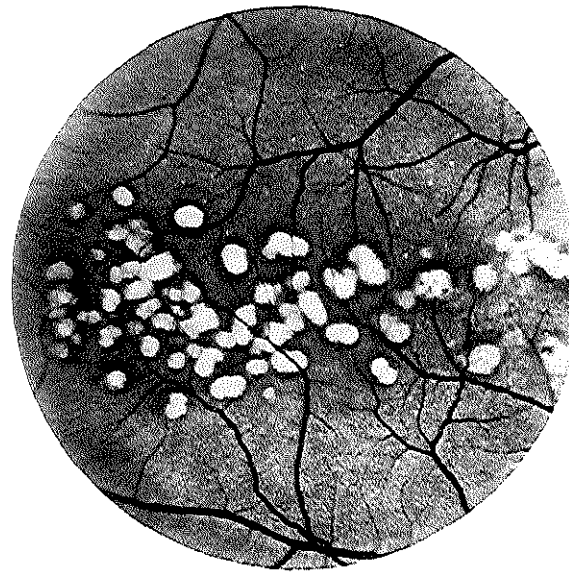


Fig. 2. Large drusen of Bruch's membrane, clearly situated beneath the retinal vessels.

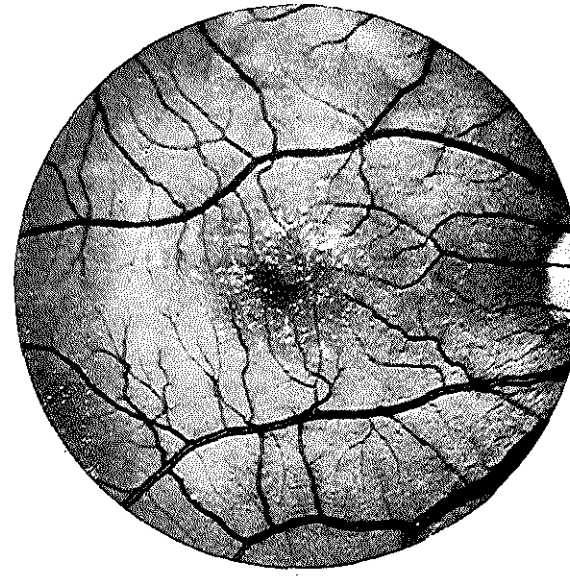


Fig. 3. Tiny drusen-like structures in the fovea of a 47-year-old female.

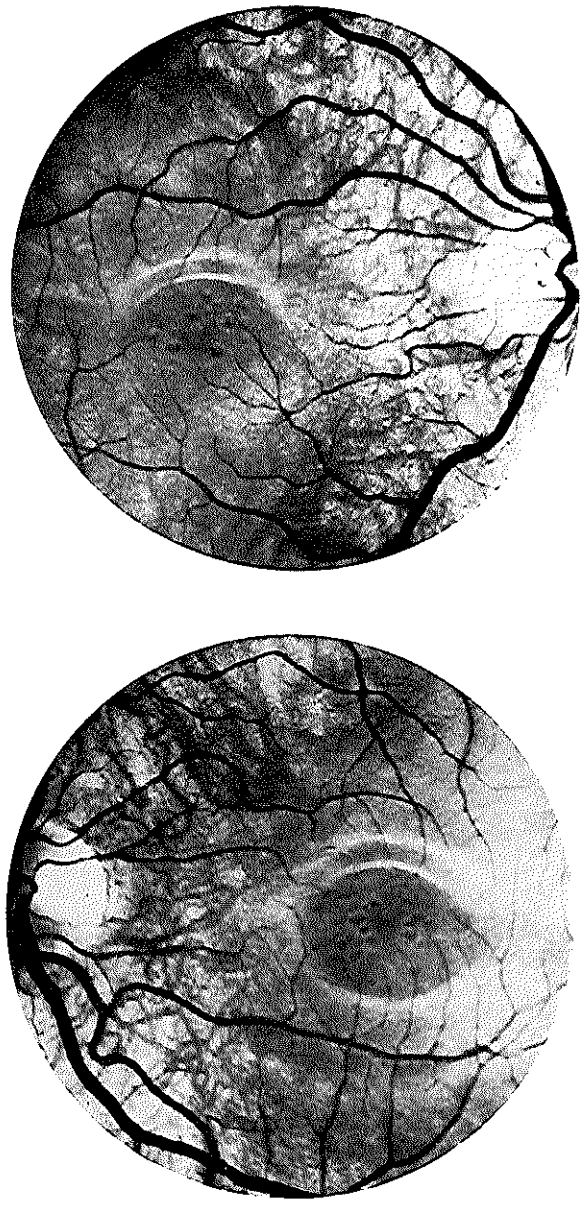


Fig. 4a-b. Incipient dominantly inherited drusen of Bruch's membrane in a 12-year-old boy (Fam. G-S.) The drusen are not white, indicating that the overlying pigment epithelium is not yet destroyed.

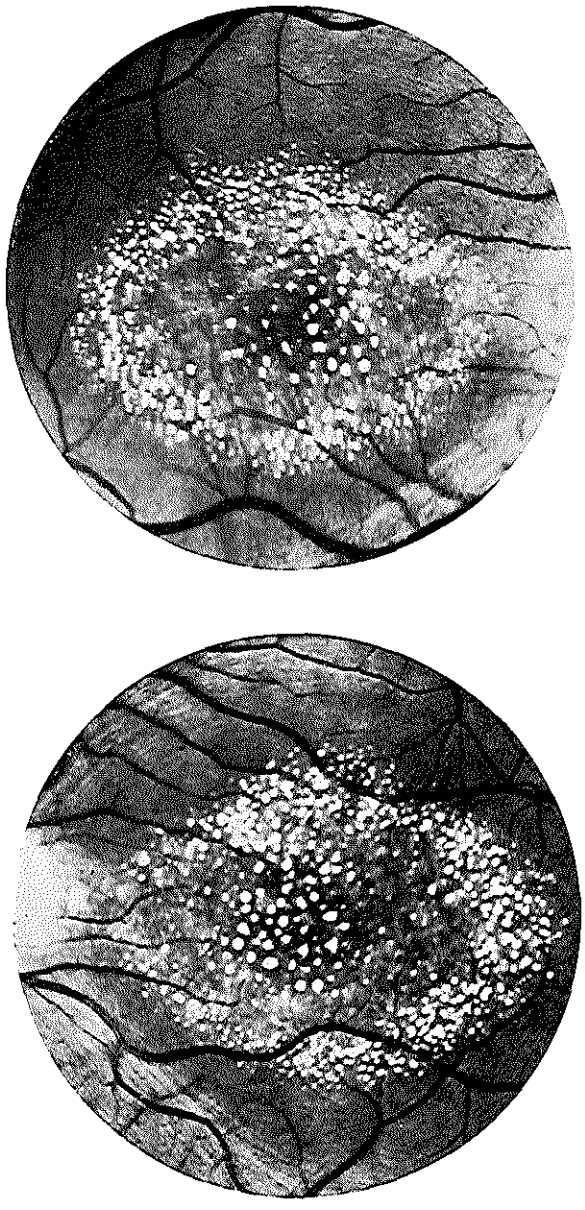


Fig. 3a-b. Symmetrical lesions in the posterior poles of one of identical twins, caused by numerous drusen (Fam. G-S).

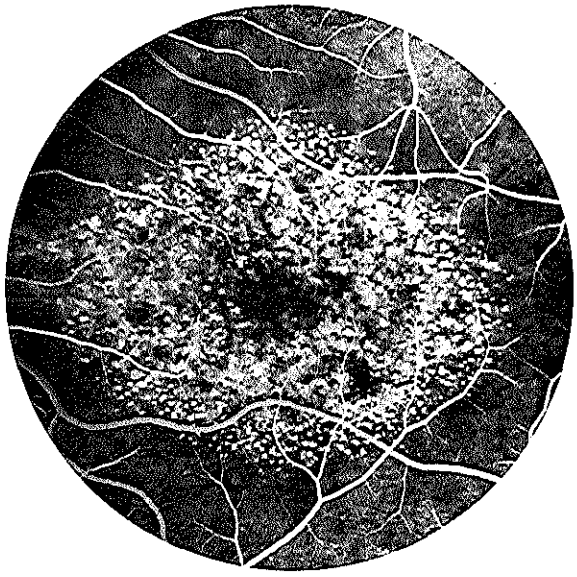


Fig. 5c. Fluorescence photograph of the fundus depicted in fig. 5b, indicating multiple defects in the retinal pigment epithelium. There is a horizontally ovoid zone of atrophic pigment epithelium. Many drusen show confluence.

The families we studied (families G-S and W-H) clearly illustrate the interfamilial variation. Franceschetti, François and Babel (1963) described four different types of these hereditary drusen: Hutchinson-Tay choroiditis, Holthouse-Batten superficial chorioretinitis, Doyne's honeycomb dystrophy, and malattia leventinese. They nevertheless maintained – with Waardenburg (1948), Krill and Klien (1965) and Duke-Elder (1967) – that there is one entity of hereditary drusen, caused by one specific pathological gene.

No designation has so far been generally accepted for this entity, which Franceschetti et al. (1963) and Duke-Elder (1967) describe as "hyaline dystrophies".

Familial occurrence of drusen was first described by Hutchinson and Tay in 1875. They found drusen in the posterior pole of the eye in 3 sisters (respective ages: 57, 48 and 40). Some authors regard these cases as a specific presenile form of hereditary drusen, although nothing is known of the fundus features during the years preceding the abovementioned study. The mode of transmission was not discussed either, but dominant transmission is quite possible because the father of the three women had poor vision. In my opinion there is no reason why Hutchinson-Tay choroiditis should be regarded as a separate entity; its features are in no way distinct from those of the other types of hereditary drusen.

Holthouse and Batten (1897) described a 25-year-old woman with white spots in the central retina. No relatives of this patient were examined. In my opinion there is again no reason why this patient should be considered a case representative of a

specific condition. The fundus features described do not differ in any way from those of the generally accepted picture of drusen.

Doyne's honeycomb dystrophy and malattia leventinese, however, are well-defined entities. Doyne's honeycomb dystrophy was first described by him in 1899: "honeycomb appearance of white spots affecting almost entirely the disc-macular region" in 4 sisters.

In 1910 he reported on two more large families in which he had observed this "closely grouped guttate choroiditis". Other English reports on Doyne's disease in more than two generations have been presented by Tree (1937) and Pearce (1967, 1968); familial cases were described by Butler (1910), Foster (1932) and Evans (1950). More families were described outside England: in The Netherlands (Waardenburg 1948), Belgium (François 1950), Czechoslovakia (Pajtáš 1950, 1957), the USA (Alper and Alfano 1953), Austria (Fuchs 1956) and Italy (Sanna 1957). There are more known reports on Doyne's honeycomb dystrophy, but these were all solitary cases in which the diagnosis was not established with certainty (Bickerton 1900; Malbrun et al. 1936; Tanaka 1938; Krückmann 1941; Pisano 1952; Montanelli 1954).

Malattia leventinese was first noted by Erb, a Lugano ophthalmologist, and Vogt (1925) devoted the first publication to this condition. Later, several others wrote about this dominant affection, which originates from the Leventine valley in the Tessino Canton of Switzerland (Klainguti 1932; Vogt 1940; Huber 1943; Wagner et al. 1943, 1944; Forni et al. 1957, 1962; Zuccoli 1962; Babel and Farpour 1968). Klainguti (1932) initially called this condition retinitis circinata, and later retinitis airolensis (after the village of Airolo) before he ultimately decided on malattia leventinese.

Other solitary cases which probably come under this heading were described by many other authors (Nagel 1875; Nettleship 1884; De Schweinitz 1894; Hirschberg 1889; Juler 1893; Blair 1901; Schneidemann 1904; Nuel 1908; Mould 1910; Morelli 1928; Pampichler 1928; Bonnet and Chauviré 1943; Tiscornia and Nano 1948; Safar 1949; Lijo Pavia 1952, 1953; Bedell 1954; Neame 1954; Dzodzo-Kukoc 1962; Krill and Klien 1965; Ernest and Krill 1966; Lorentzen 1966; Kojima et al. 1968).

A review of the entire literature on "hereditary drusen" warrants the conclusion that all these descriptions of hereditary hyaline dystrophies concern the same disease: dominant hyaline dystrophy of the central retina. Clinical, histological and hereditary characteristics are the same in Doyne's honeycomb dystrophy as in malattia leventinese. The differences sometimes seen in ophthalmoscopic terms must undoubtedly be due to the interfamilial variability, caused by a difference in expressivity. Forni and Babel (1962) also reached this conclusion. Franceschetti (1962), who investigated both diseases, reported that no distinction can be made between the two in the initial stages. Only in advanced stages, he maintained, the almost rectangular plaques which encompass the optic disc can show an appearance more or less characteristic of malattia leventinese. However, Pearce (1968) demonstrated exactly the same plaques in advanced cases of Doyne's honeycomb dystrophy.

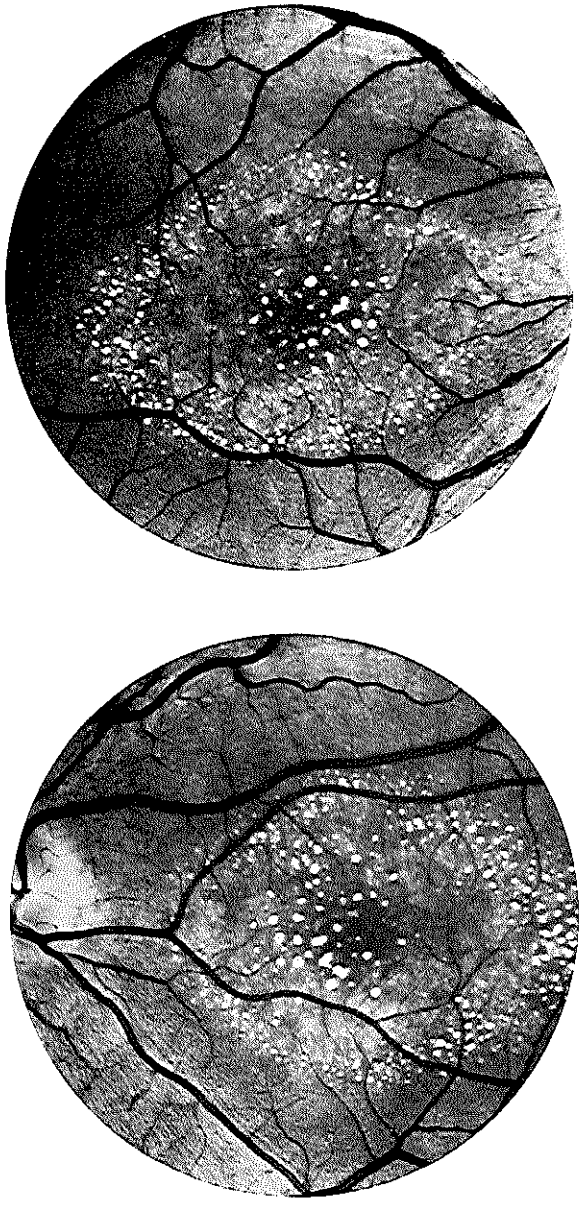


Fig. 6a-b. Right and left posterior poles of the other of the identical twins. Numerous tiny drusen with increasing diameter towards the centre of the retina (Fam. G-S).

Our conclusion is that, if any difference exists, it is geographically determined. Doyne's families came from a mid-England area bounded by Maidenhead and Reading in the South, Beaconsfield in the East, Aylesbury in the North and Oxford in the West (Pearce 1967). Malattia leventinese has its origin in the Leventine valley in the North of Tessino, extending from the foot of St. Gotthard to Biasca, where the Tessino valley joins the Blenio valley (Forni and Babel 1962).

Since we now know that hereditary drusen of Bruch's membrane do not occur exclusively in England and Switzerland, we consider it useful to introduce the designation "dominant drusen of Bruch's membrane" (in brief: "dominant drusen") for all cases in which primary hyaline dystrophy shows an autosomal dominant mode of transmission (Deutman and Jansen, 1970). Differential diagnosis between Doyne's honeycomb dystrophy and malattia leventinese is impossible; and complicated designations such as Hutchinson-Tay choroiditis, Holthouse-Batten chorioretinitis, Doyne's honeycomb dystrophy and malattia leventinese are best avoided. Of course these terms will retain their historical value, but in actual practice they produce avoidable confusion. Dominant drusen of Bruch's membrane represents one of the hereditary dystrophies of the central retina and can be distinguished on several points as an unequivocal separate entity.

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

The age of onset of dominant drusen is generally reported to be over 20 (Franceschetti et al. 1963; Duke-Elder 1967; Pearce 1968); but we ourselves observed early stages of this condition in a boy aged 12 and another aged 14 (IV-4 and IV-12 fam G-S) (fig. 4). Evans (1950) mentioned an 8-year-old girl with "crystalline retinal degeneration" in a family in which three generations were affected. In this family there was probably dominant drusen of Bruch's membrane. Krill (1969) observed this affection in a 10-year-old child.

There is no male or female predominance. The bilateral condition is usually observed before there are any changes of vision. As in most hereditary retinal affections, the more or less pronounced symmetry of the lesions is a striking feature. There is one report on a unilateral case of Doyne's honeycomb dystrophy (Montanelli 1954); since this was a solitary, non-familial case, it is doubtful whether the diagnosis was correct.

3. FUNDUS (OPHTHALMOSCOPIC FEATURES)

Usually between age 20 and age 30, but sometimes earlier, a few round, brown-yellow, later whitish structures appear in the deeper retinal layers of the posterior pole in both eyes (fig. 4). The subsequent course is usually characterized by striking symmetry (fig. 5, 6), although in some cases this is less marked (fig. 7). In middle age the posterior pole is usually already covered by many round white spots, which can be arranged in a mosaic or honeycomb pattern (fig. 7b), although the typical honeycomb structure described by Doyne (1899) is relatively uncommon in dominant

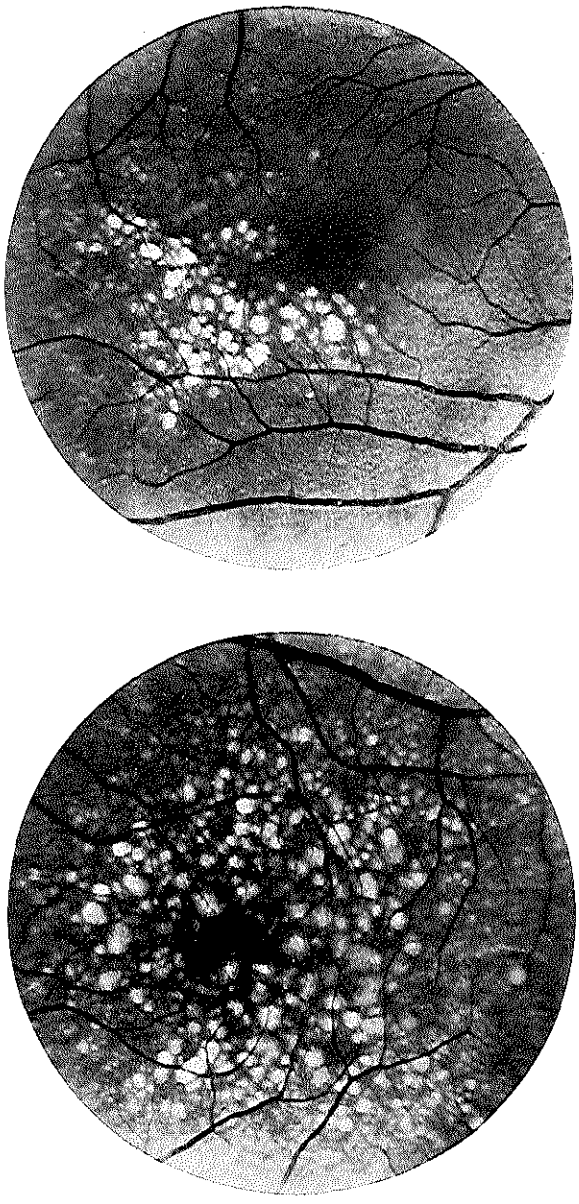


Fig. 7a-b. Dominant drusen in a 45-year-old female (Fam. W-H). There is no exact symmetry. The drusen in the right eye are eccentrically located. The drusen in the left eye are more numerous and centrally located. They are arranged in a honeycomb pattern.

Fig. 8. Confluence of large drusen in the foveal area of a 55-year-old man (Fam. v.R.).

drusen. Later, these spots show confluence (fig. 8) and the retina in front of them becomes thin and atrophic, while pigmentation and choroidal atrophy ensue. The lesions are not always found in the exact centre of the fundus (fig. 9). The finding of drusen on the nasal side of the disc in more advanced cases can be interpreted as more or less pathognomonic of dominant drusen (Forni and Babel 1962; Pearce 1968). We had occasion to confirm this (fig. 10, 11).

In advanced stages the oval-shaped or almost rectangular white plaques which surround the disc are characteristic. In the central area the pigment epithelium has totally disappeared, and so far as can be ascertained the choroid seems atrophic. The total area involved rarely exceeds a diameter of 6 dd. The optic disc, retinal vessels and retinal periphery usually remain normal.

4. REFRACTION

In our material, refraction was emmetropic or slightly hypermetropic.

5. VISUAL ACUITY

Visual acuity usually remains intact for some considerable time even in the presence of unmistakable, large drusen. For example, vision in III-6 and III-7 fam. G-S was still 9/10 although extensive changes were observed in fundo (fig. 5, 6). This can only be explained by assuming that the neuroepithelium is involved only in far advanced stages. It often takes over 10 years before the drusen inflict the first

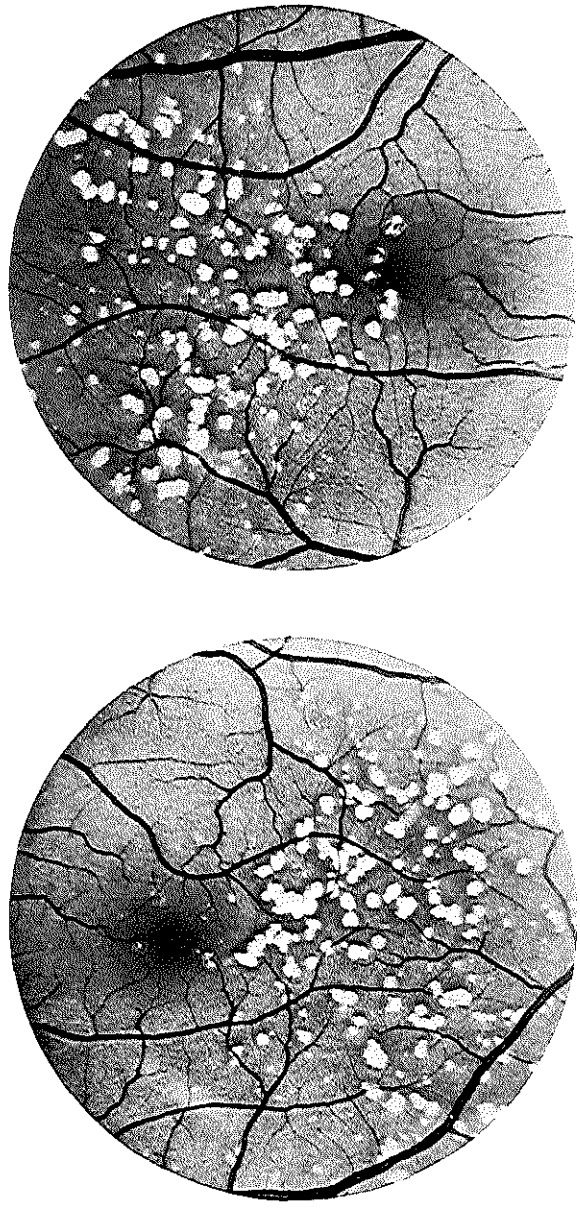


Fig. 9a-b. Eccentrically located symmetrical lesions, caused by drusen of varying size in the posterior poles of the eyes of a 49-year-old female.

damage upon the photoreceptors. Metamorphopsia can then occur. Diminution of vision is rarely seen before age 40. Ultimately, however, a central scotoma occurs with, of course, marked diminution of vision. This was the case in our female patient II-4 fam. W-H (fig. 12).

6. VISUAL FIELDS

The visual fields always retain their normal peripheral boundaries, and in advanced cases a central scotoma occurs which is initially relative but can later become absolute. Diminished central sensitivity is found fairly early but may well be accompanied by 10/10 vision.

7. COLOUR VISION

Colour vision is usually normal until the fovea is affected. Diminished red sensitivity is then often found as the first anomaloscopic change. The HRR test discloses red-green dyschromatopsia, and in advanced stages blue-yellow dyschromatopsia can be found also (II-4 fam. W-H). Franceschetti et al. (1963) described as principal characteristic a blue-yellow dyschromatopsia preceding loss of vision. We did not observe this in our patients (see Case histories). Krill and Klien (1965) did not either.

8. DARK ADAPTATION

Dark adaptation was normal in virtually all cases presented in the literature (Forni and Babel 1962) and in the cases we examined. Only Pajtáš (1950, 1957) described patients who showed true nightblindness as early as age 14.

Krill and Klien (1965) found slight changes in the dark adaptation curve in a few cases: delay in attaining ultimately normal cone and rod thresholds. We observed this in only one female patient (II-4 fam. W-H).

9. ELECTRORETINOGRAPHY

The ERG is normal in virtually all cases of dominant drusen (Forni and Babel 1962); this is consistent with the fact that the ERG is an overall response of the entire retina. Only in cases in which drusen occupy a large part of the retina and have damaged considerable proportion of the photoreceptors can a photopically as well as scotopically subnormal ERG be expected. We found a quite normal ERG in 4 patients.

Krill and Klien (1965) found a delay in attaining a maximum b-wave (which showed normal values). In only one patient (II-4 fam. W-H) did we obtain a subnormal ERG, but at her age this might also be ascribed to senile degenerative changes.

F-ERG and VER

As expected, the F-ERG was normal in the early stages, but became very subnormal in advances stages with involvement of the photoreceptors.

The VER more or less parallel the results of the F-ERG.

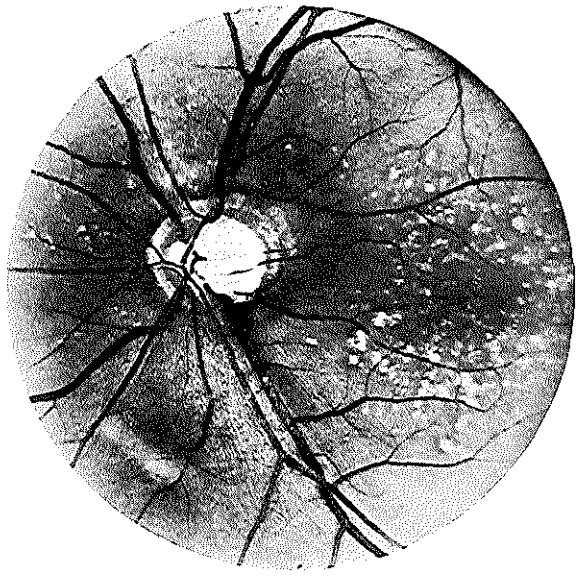


Fig. 10. Small drusen located on both sides of the optic disc.

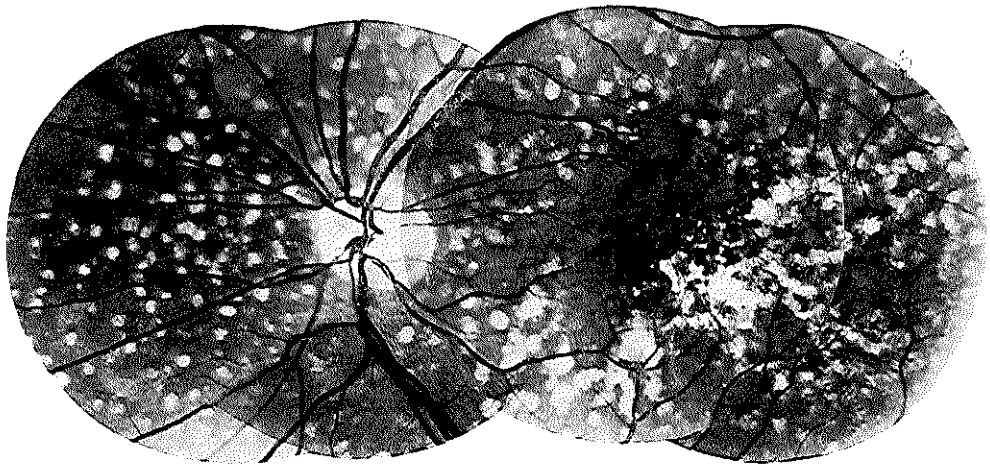


Fig. 11. Large drusen surrounding the optic disc and showing confluence in the perifoveal area (Fam. v.R.).

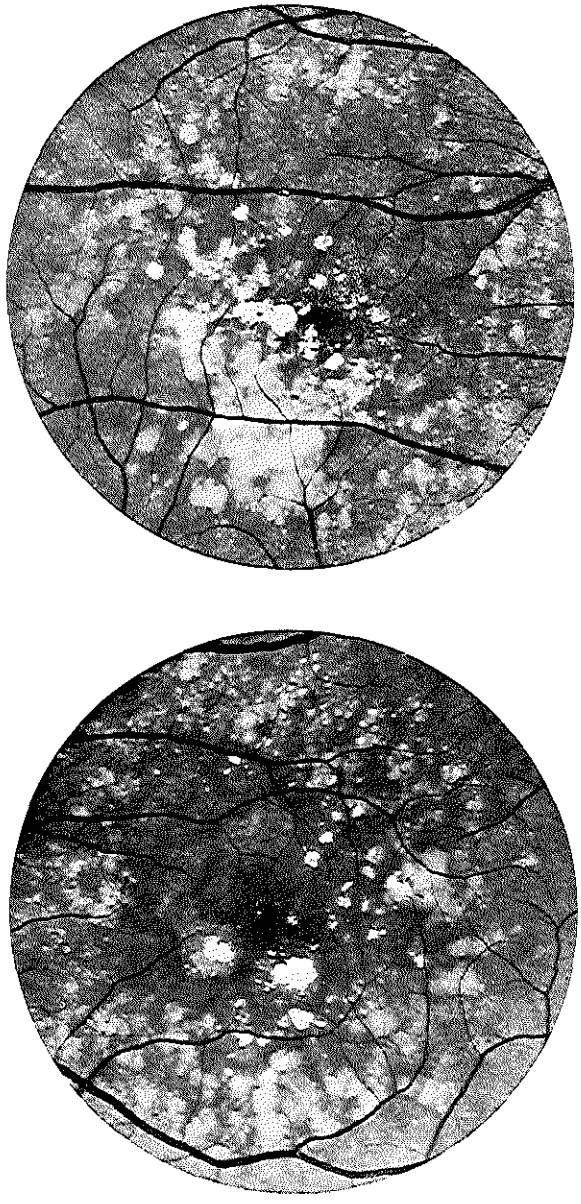


Fig. 12a-b. Confluence of drusen of long standing in the eyes of a 67-year-old female (Fam. W.H.), filmed on orthochromatic film.

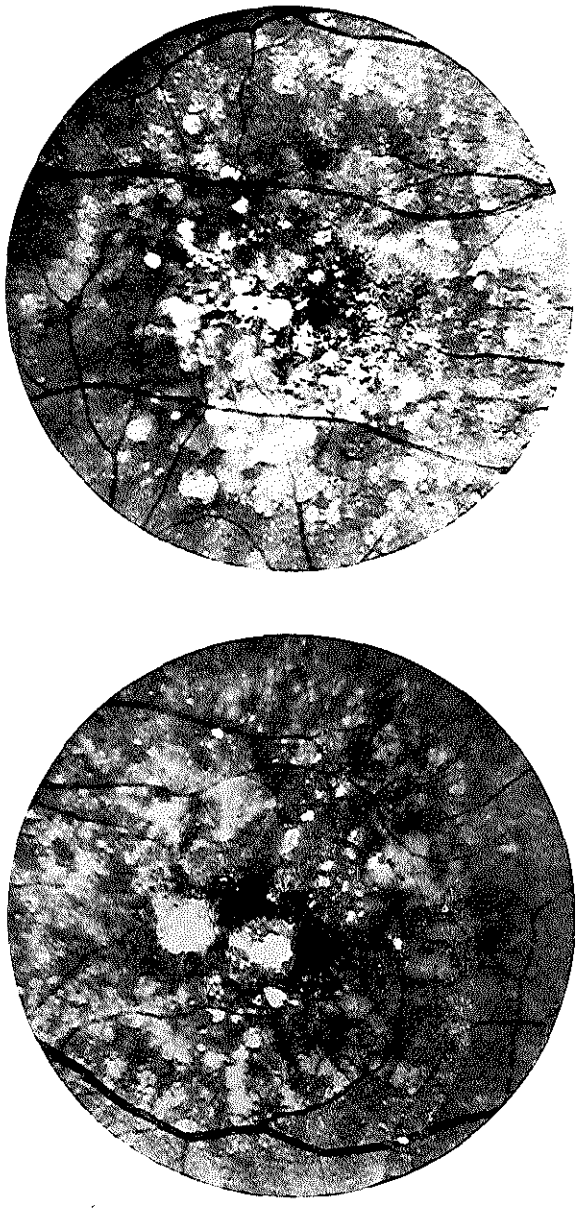


Fig. 12c-d. The same eyes as depicted in fig. 12a-b filmed on panchromatic film. More pathological structures are visible.

OP

We know of no data on OP in the literature. They were normal in one of our patients with drusen (fam. vR).

10. ELECTRO-OCULOGRAPHY

The EOG is normal in the initial stages but ultimately develops a degree of subnormality which depends on the extent of the retinal involvement. Krill and Klien (1965) found a subnormal EOG in 4 of the 8 patients examined.

The family we examined (GS) showed no subnormal Lp/Dt-ratio, but in fam. W-H both patients had a pathological EOG. In the presence of normal visual fields, colour vision, dark adaptation and ERG, as in patient III-3 fam. W-H, this indicates an intact neuroepithelium and diffusely disturbed pigment epithelium (and/or Bruch's membrane and/or choriocapillaris).

In the lastmentioned family (fig. 7, 12) the lesions were much more extensive than in the former family (fig. 4-6), and this might explain the difference in EOG values. The drusen are localized on the inside of the Bruch membrane and therefore tend to cause early damage to the pigment epithelium.

The fact that the EOG becomes subnormal before dark adaptation and ERG do (clearly demonstrated in III-3 fam. W-H) suggests an important correlation between the Lp/Dt-ratio of the EOG and the integrity of the pigment epithelium. In other primary disorders of the pigment epithelium, such as fundus flavimaculatus certainly is and vitelliform dystrophy of the fovea probably also, a pathological EOG is likewise found in combination with often normal dark adaptation and ERG (Krill et al. 1966; François et al. 1966, 1967, 1968; Deutman 1969).

Krill and Klien (1965) classified fundus flavimaculatus, fundus albipunctatus and dominant drusen under the joint heading "flecked retina syndrome", because the clinical similarities (ophthalmoscopy and retinal function tests) were so striking. Nevertheless they themselves admitted that these three entities can be clearly distinguished on the basis of ophthalmoscopic features, fluorescein angiography and mode of transmission.

11. PHOTOGRAPHY

Panchromatic film discloses more of the abnormal retinal structures than orthochromatic film. Panchromatic film is more sensitive to light of longer wavelength, and because the longer wavelengths penetrate deeper into the retina it is understandable that the deeper retinal layers, in which the lesions are mainly localized in dominant drusen, are more clearly visualized on panchromatic film. The difference in contrast sensitivity between the two films probably plays the principal role in the difference between the photographs. The difference between a panchromatic and an orthochromatic photograph is best demonstrated by a comparison between fig. 12cd and fig. 12ab.

12. FLUORESCEIN ANGIOGRAPHY

During the arterial phase, fluorescein angiography reveals the occurrence of multiple sharply defined fluorescent spots, the contours of which correspond to the lesions observed at normal ophthalmoscopy. Fluorescein angiography often discloses several abnormal areas (fig. 5c), but this need not always be the case (fig. 13). The majority of fluorescent areas persist after the venous phase and show no change of size. There is no extravasation of fluorescein, and therefore nothing to indicate disturbances in Bruch's membrane and the choriocapillaris. The visualization of the drusen is undoubtedly made possible by the presence of defects in the pigment epithelium (in front of the drusen or not), which results in increased visibility of the choroidal fluorescence behind them (Norton et al. 1965; Ernest and Krill 1966; Amalric 1967, 1969).

Confluence of fluorescent areas is fairly common in dominant drusen, although less frequent than in fundus flavimaculatus. Areas encompassing large drusen sometimes show hardly any fluorescence (fig. 13). This is explained by the assumption that the structure of these drusen has so changed as to cause them to act as filters instead of passing the fluorescence.

The after-fluorescence (i.e. the fluorescence after disappearance of the fluorescein from the choroidal and retinal vessels) may be due to absorption of fluorescein in the drusen (Rubinstein and Paton 1966; Babel and Farpour 1968). Norton et al. (1965) doubt this, however, and maintain that the drusen continue to fluoresce as long as a sufficient amount of circulating fluorescein is available. Another possibility is that scleral fluorescence causes the after-fluorescence, for Sollom and Brown (1967) and Sollom and Adlakha (1968) demonstrated that the sclera can bind fluorescein. However, this is hardly conceivable in view of an intact choroid. The most plausible explanation seems to be that after-fluorescence is visible because we look through the defects in the pigment epithelium upon the fluorescein which normally escapes from the small vessels of the choriocapillaris (Wessing, 1970).

13. CARRIERS

We have identified no carriers in our material, because no skipping of a generation occurred. Virtually all authors describe the mode of transmission as regular dominant.

14. HISTOLOGICAL FINDINGS

Histological examination discloses round accumulations of hyaline in the pigment epithelium. These hyaline bodies are connected with the inner layer of Bruch's membrane (Treacher Collins 1913; Wolter 1957, 1958, 1959; Forni and Babel 1962; Zuccoli 1962).

The choroid and neuroepithelium are normal in the initial stages but in advanced stages these structures can show marked atrophy.

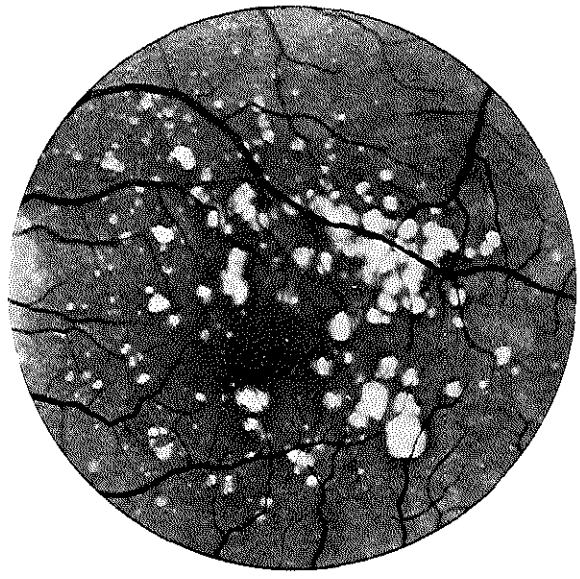


Fig. 13a. Large drusen, mainly located in the perifoveal area.

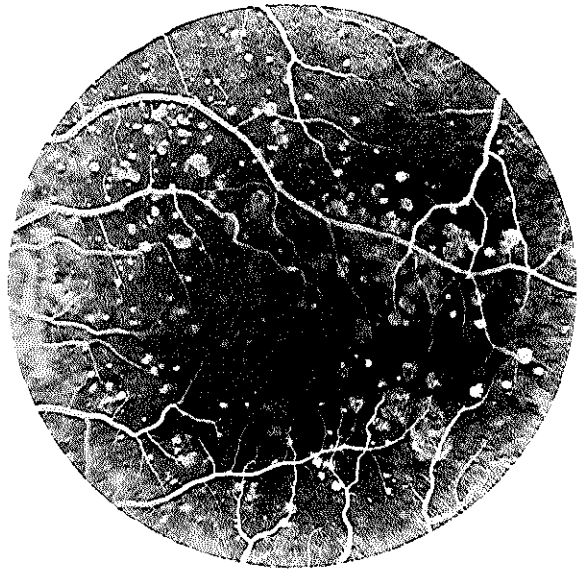


Fig. 13b. Fluorescein angiography shows defects in the retinal pigment epithelium at the site of the drusen. It is of interest to note, that some of the larger drusen hardly show pathological fluorescence.

The eosinophile hyaline bodies show a stratified structure. Histochemical examination shows that these structures are made up of carbohydrate compounds, proteins and minute quantities of nucleoproteins.

Drusen of the optic disc likewise consist of carbohydrate compounds, proteins and small amounts of nucleoproteins (ribonucleic acid) (Seitz 1968). The only difference from the drusen of Bruch's membrane is the argyrophilia of the disc drusen (Seitz and Kersting 1962).

15. PATHOGENESIS

The probable origin of this dystrophy is an inborn error of metabolism, probably localized in the cells of the retinal pigment epithelium. One of the sources for this conclusion is found in studies by Wolter (1957), who found two different developmental types of drusen:

1. The development of drusen by accumulation of hyaline substance within slowly degenerating cells of the pigment epithelium.
2. The development of drusen by extracellular deposition of hyaline substance beneath the pigment epithelium on Bruch's membrane.

Already in the early years of this century Coats (1904-1905) postulated a pathogenesis of drusen on the basis of transformation or deposition. Both types of drusen occur together, and both result in large hyaline structures on Bruch's membrane and destruction of adjacent cells of the pigment epithelium. Since both the choroid and the neuroepithelium are normal in the initial stages, the pathogenesis of dominant drusen of Bruch's membrane must be assumed to be a hereditary dystrophy primarily localized in the pigment epithelium.

Histochemical and possibly biochemical research may in future lead to identification of the absent or deficient enzyme.

16. MODE OF TRANSMISSION

The mode of transmission is doubtless autosomal dominant with variable expressivity. After an exhaustive study of 76 cases of Doyne's honeycomb dystrophy, Pearce (1967) concluded that the transmission was regular dominant. Tree's pedigree (1937) suggests an irregular dominant transmission with skipping of a generation. Many other pedigrees with affected individuals in three generations, however, are more suggestive of regular dominance (Doyne 1910; Pajtáš 1950, 1957; Evans 1950; Alper and Alfano 1953; Fuchs 1956; Forni and Babel 1962).

Factors indicating the plausibility of an autosomal dominant gene as causative of the dystrophy are:

a. Patients always have an affected parent (so far as available for examination).
b. Many families include patients in three generations.
c. The number of affected males and females does not differ much.
d. The number of affected persons and non-affected persons per family does not differ much (Pearce 1967).

The families we examined also suggested regular autosomal dominant transmission. While it is true that no patients have so far been found in the third generation in fam. W-H, transmission from mother to daughter confirms the likelihood of autosomal dominance.

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

General physical examination usually discloses no significant abnormality. In female patient (III-6 fam. GS) we found no abnormality even after extensive laboratory studies. Lipid and protein patterns were quite normal. In our 67-year-old female patient II-4 (fam. WH), we found slight hyperlipidaemia and a slightly disturbed liver function.

However, hyperlipidaemia is a so common finding in persons of this age that it is inconclusive in this case.

In a 54-year-old man (fam. vR) with extensive drusen of the posterior pole we also found slight hyperlipidaemia; a family study was unfortunately impossible. Lijo Pavia (1953) and Montanelli (1954) also reported hypercholesteraemia in patients with dominant drusen. Lijo Pavia (1953) administered large quantities of cholesterol to rabbits, whereupon drusen developed in the posterior pole of the eye; when he added thyroxine, the drusen disappeared. Salvati (1926) produced fundus changes in dogs by giving them cholesterol. This indicates that drusen can occur in the presence of hypercholesteraemia, but it does not prove that dominant drusen of Bruch's membrane and hypercholesteraemia are inevitably concomitant (patient III-6 fam. GS also demonstrated this).

18. ASSOCIATED CONDITIONS

Dominant drusen of Bruch's membrane generally occur without associated diseases. A disease associated with dominant drusen through several generations has not so far been found or reported.

There are reports, however, on drusen combined with essential iridal atrophy (Nano et al. 1968), drusen of the optic disc (Lorentzen 1966), hypercholesteraemia (Lijo Pavia 1953; Montanelli 1954; personal observations) and conditions mentioned earlier, such as pseudoxanthoma elasticum (Bischler 1955; Shimizu 1961), familial haemorrhagic angiomatosis (Cuendet et al. 1953; Calmettes et al. 1957), scleroderma (Hartmann et al. 1948), polyserositis (Michaelson et al. 1959), dysproteinaemia (Scorciarini-Coppola 1957) and hyalinosis cutis et mucosae (Jütte 1961, 1962; François et al. 1966; Rosenthal et al. 1967).

19. DIFFERENTIAL DIAGNOSIS

Dominant drusen of Bruch's membrane must be differentiated from those conditions that likewise involve white spots in the posterior pole of the eye.

Fundus flavimaculatus and fundus albipunctatus are among these conditions and, although they are readily distinguishable ophthalmoscopically, show a retinal function profile almost identical to that in dominant drusen. For this reason Krill and Klien (1965) brought these three conditions under the collective heading "flecked retina syndrome". The mode of transmission of fundus flavimaculatus and fundus albipunctatus is autosomal recessive.

a. *Fundus flavimaculatus* shows yellow-white, ill-defined fish- and sharkfin-shaped spots in the posterior pole, unlike the drusen which are round and sharply defined.

b. *Fundus albipunctatus* (Lauber 1910) shows very small (usually less than the diameter of an arteriole) round, white spots in a large area of the fundus, with maximum density in the equatorial region, the central retina remaining unaffected in contrast to what is observed in dominant drusen. Dark adaptation is much more severely disturbed in these cases (fig. 14, 15).

c. *Stargardt's disease* must also be differentiated. If in this disease many perifoveal white spots are present, then the fundus picture is almost indistinguishable from that of fundus flavimaculatus, in which the fovea is affected. If the retinal periphery becomes involved in Stargardt's disease, then whitish, ill-defined spots with central pigment accumulations often occur in the periphery.

The following conditions must be differentiated also:

d. *Retinitis punctata albescens* (Mooren 1882; Nettleship 1908; Lauber 1910).

e. and *Bietti's tapetoretinal dystrophy with marginal corneal dystrophy* (Bietti 1937, 1942; Bagolini and Ioli-Spada 1968), which likewise show small white spots in the retina, but in these cases there is an unmistakable progressive tapetoretinal dystrophy; the ERG is soon no longer recordable and dark adaptation is markedly disturbed. Moreover, the posterior pole is usually unaffected in these cases.

f. *Kandori's "fleck retina with congenital hemeralopia"* (Kandori 1959, 1960; Kandori et al. 1965, 1966, 1969; Kurimoto and Fukunaga 1969) is another entity to be differentiated. Klien and Krill (1967) believed that these cases probably come under the fundus flavimaculatus heading. This is possible but doubtful for the time being, because congenital hemeralopia has not been clearly demonstrated in fundus flavimaculatus; and the spots described by Kandori are much larger than the small pisciform lesions usually seen in fundus flavimaculatus. Moreover, Kandori's spots are observed chiefly in the equatorial region. Nevertheless it is advisable to make another careful comparison between Kandori's patients and patients suffering from fundus flavimaculatus (fig. 16).

g. The *focal central punctate chorioretinopathy* described by Yaetes (1960) and

Fig. 14. Conventional photograph of fundus albipunctatus. There are tiny round white spots, evenly distributed over the retina. The foveal area is unaffected. (after Kandori).

Fig. 15. Fluorescence photograph of fundus albipunctatus, showing small round defects in the retinal pigment epithelium.

Fig. 16*a*. Conventional photograph of Kandori's fleck retina, showing rather large cloud-like yellowish patterns in the mid-periphery of the fundus (after Kandori).

Fig. 16*b*. Fluorescence photograph of Kandori's fleck retina. There are large defects in the retinal pigment epithelium. These defects correspond with the ophthalmoscopically visible lesions (after Kandori).

h. the *capillarosis* which probably occurs on the basis of capillary insufficiency (Bailliart 1934, 1939, 1953) show exceedingly small round white spots in the retina, on the basis of which they can be differentiated. The capillarosis spots are seen in the retina on the inside of the pigment epithelium instead of at the level of the pigment epithelium or in a more external position, as dominant drusen are.

i. In rare cases, *multiple vitelliform lesions* can be observed. These have a yellow-orange colour and are virtually round, varying widely in size. The EOG is decidedly pathological in these cases (hardly any increase in standing potential at light adaptation), and family-studies can also confirm the diagnosis.

j. *Chorioretinitis disseminata* (tuberculous or syphilitic) is not easily mistaken for drusen. Its spots are more diffuse and irregular, more pigmented and more polymorphous than those in dominant drusen. These cases lack the symmetry of the hereditary dystrophies.

k. "*Dyshorische Herdchen*" are likewise white spots, usually found in the retinal periphery of elderly people. They are ascribed to arteriosclerotic processes, are sharply defined and show a thin black border.

l. In *angioid streaks*, "le fond d'oeil moucheté multicolore" has been described by Bischler (1955). Many drusen-like white and darker points are visible in the retina (Groenblad 1929; Renard 1947).

20. THERAPY

There is no known therapy against dominant drusen.

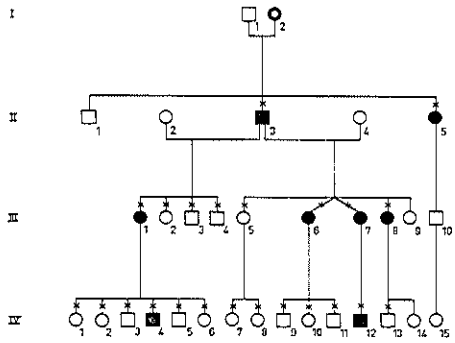
21. FUTURE

Future histochemical research may demonstrate an enzymatic disorder in the pigment epithelium as the cause of dominant drusen.

22. CASE HISTORIES

1. Fam. GS
Examined in 1968 and 1969.
II-3 (S) VODS: counting fingers.
Posterior poles: Extensive chorioretinal atrophy.

II-5 (GS-90.02.14)
1968: VOD S+1.25=C+0.25×180° 4/10; VOS S+0.75=C+1.50×180° 5/10.
Posterior poles: Confluent drusen and diffuse granular pigmentation.



III-1 (JS-10.01.22)
VODS: S+0.25 10/10.
Posterior poles: Non-confluent drusen, surrounded by a fine mottling of pigment. Most drusen are located around the foveal.
Visual fields, colour vision and dark adaptation: Normal.

III-6 (WGS-34.12.13)

III-6 and III-7 are identical twins.
Some metamorphopsia in the right eye (Amsler test).
VOD S+0.25 9/10; VOS S+0.50 9/10.
Posterior poles: Numerous fine, round, white and yellowish-brown drusen. The diameter of the drusen decreases from the centre of the fovea to the perifoveal area. The drusen are located in the deeper retinal layers beneath the retinal vessels. Foveal and foveolar reflexes are absent. (Fig. 5ab).
Visual fields: Small relative central scotomata of about 5°.
Colour vision: Slight red-green dyschromatopsia (HRR). Diminished sensitivity to red (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 225μV; OS 270μV.
Phot. b-waves OD 110μV; OS 115μV.
EOG: OD 1.86; OS 2.18.
Fluorescein angiography: Fluorescence in the arterial phase, increasing in the venous phase. The central drusen show confluence while the perifoveal drusen remain solitary. More defects are visible in the pigment epithelium than with normal ophthalmoscopy (fig. 5c). The fluorescent areas persist with no change in size for 12 minutes beyond the venous phase.
Systemic examination: Normal. Normal protein and lipid spectra.

III-7 (MWS-34.12.13) The other half of the identical twins. Some metamorphopsia in the right eye (Amsler test).
VODS 9/10, emmetropic.
Posterior poles: Many fine drusen. Striking symmetry of both eyes. Somewhat less drusen than her twin-sister (fig. 6).
Visual fields: Small relative central scotomata.
Colour vision: Mild red-green dyschromatopsia (HRR). Decreased sensitivity to red (anomaloscope).
Dark adaptation: Normal.
ERG: Scot. b-waves OD 280μV; OS 305μV.
Phot. b-waves OD 120μV; OS 95μV.
EOG: OD 2.06; OS 2.15.

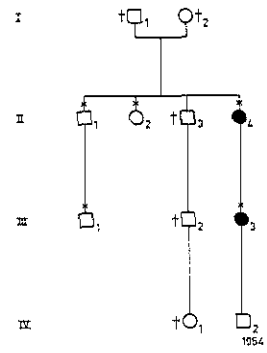
III-8 (HS-36.02.21)
VODS S+1.25 6/10.
Media: Coralliform cataract.
Posterior poles: Small round drusen in the parafoveal region. Fine granular pigmentations at the fovea.
Visual fields: Some decreased central sensitivity.
Colour vision and dark adaptation: Normal.

IV-4 (ThJ-55.10.20)
VODS: 9/10, emmetropic.
Posterior poles: Some yellowish-brown drusen and granular pigmentation at the fovea.
Visual fields, colour vision and dark adaptation: Normal.

IV-12 (GG-57.06.21)
VODS S+0.50 10/10.
Posterior poles: Normal foveal and foveolar reflexes. Yellowish-brown drusen in the foveal area (fig. 4).
Visual fields, colour vision and dark adaptation: Normal.

Summary: Drusen, inherited following a regular dominant pattern in 8 members and 3 generations of one family. The drusen are small as compared to the dominant drusen generally known. Interesting features are the finding of drusen in identical twins and the presence of drusen already in a 12- and 14-year-old boy. In all affected members, the symmetrical appearance of the lesions is remarkable. Furthermore, the intrafamilial ophthalmoscopic patterns are very much alike, in contrast to the interfamilial ophthalmoscopic patterns (see fam. WH).

2. Fam. WH



I-1, 2 Nothing is known about the visual acuity of these individuals. They died when II-4 was a young girl.

II-4 (AWH-02.02.10)
1967: VOD C+0.50×180° 10/10; VOS C+0.50×180° 10/10.
Posterior poles: Many large drusen, showing confluence in the centre of the retina.
1968: VODS 8/10, emmetropic.
Posterior poles: Many confluent drusen in an area of about 6 disc-diameters. Furthermore solitary drusen, fine pigmentations and glistening reflexes.
Visual fields: Relative central scotomata of about 5-10 degrees.
Colour vision: Mild red-green and blue-yellow dyschromatopsia.
Dark adaptation: Delayed Kohlrausch kink. The curve is slightly too high, but ends normally.
ERG: Scot. b-waves OD 175μV; OS 155μV.
Phot. b-waves OD 120μV; OS 100μV.
EOG: OD 1.65; OS 1.46.
Photography: Panchromatic films give photographs with more extensive lesions, than do orthochromatic films (fig. 12).
Systemic examination: Slightly disturbed lipid spectrum: Cholesterol 281 mg% (normal 200 mg%). Triglycerids 13.6 meq/l (normal 10 meq/l). Total lipid 1005 mg% (normal 800-900 mg%).
1969: VODS 6/10, emmetropic.
Posterior poles: Unchanged.

III-3 (EdMvdR-24.11.08) No visual complaints. No strabismus. Some photophobia.
1969: VOD S+0.50 11/10; VOS S+2=C+0.75×180° 2/10.

Posterior poles: Large drusen with a honeycomb appearance (fig. 7). Foveal and foveolar reflexes are normal.
Visual fields: Normal peripheral limitations. Slightly decreased central sensitivity in OS.
Colour vision: Normal.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 270μV; OS 220μV.
Phot. b-waves OD 135μV; OS 150μV.
EOG: OD 1.55; OS 1.64.

Summary: A mother and her daughter with drusen in the posterior poles of both eyes. In this family inheritance is probably dominant. So far no third affected generation has been found in this family. The large drusen in both individuals have resulted in a subnormal EOG together with a normal ERG and normal dark adaptation in III-3, and a subnormal EOG, with a slightly subnormal ERG and dark adaptation in II-4. This indicates the important relationship of the EOG to the integrity of the pigment epithelium. The drusen, found in this family are much larger than those in fam. GS. The families GS and WH demonstrate the fact that the intrafamilial ophthalmoscopic patterns are very much alike, whereas interfamilial patterns differ considerably.

3. **AvR** *(14.12.06)*
1959: VOD S+0.50 8/10; VOS S+0.75=C+0.50×45° 8/10.
1966: VODS S+1 8/10.
Posterior poles: Many large drusen.
1969: VODS S+1 8/10.
Posterior poles: Many large drusen, showing confluence in the centre of the retina. Solitary drusen also on the nasal side of the disc (fig. 8, 11).
Visual fields: Small relative scotomata.
Colour vision and dark adaptation: Normal.
ERG: Scot. b-waves OD 215μV; OS 225μV.
Phot. b-waves ODS 130μV.
F-ERG and VER: Normal.
OP: Normal.
EOG: OD 2.53; OS 2.15.
Systemic examination: Normal, with the exception of the total amount of lipids in the blood (1130 mg%, 800 mg% being normal).

Summary: A man with extensive drusen in the posterior pole of both eyes. It was not possible to examine all his relatives. Two of his sons were found to be normal. This man probably suffers from dominant drusen of Bruch's membrane.

The patients MBK (18.04.03) (fig. 13); SvD (21.05.31) (fig. 9); CLK (23.11.05) (fig. 3); JL (49.10.21) (fig. 10); and AGMSS (27.05.13) (fig. 2) have drusen in both posterior poles, which show a striking symmetry. The relatives of these individiuals have not been examined.

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ADDENDUM

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XIII

Pseudo-inflammatory dystrophy (Sorsby)

I. INTRODUCTION

In 1949 Sorsby, Joll Mason and Gardener reported on five families with "a fundus dystrophy with unusual features". The patients in the Randall, Carver, Ewbank, Kempster and Cranston families showed acute loss of vision while in fundo there were symmetrical bilateral changes very reminiscent of an inflammatory process of the posterior pole of the eye.

Families with this affections have also been described by others (Burn 1950; François 1958; Seedorff 1962; Rosen and Leighton 1968), and what Bedell (1961) described as "progressive bilateral chorioretinitis" in a man and his daughter may also have been in this category.

The entity described by Sorsby seems to be fairly uncommon. In the patients we examined we have been unable to demonstrate this dystrophy with certainty. We bear in mind that a very prolonged follow-up is required to demonstrate dominant transmission of an affection which does not occur until about age 40.

The cases of Hutchinson and Tay (1875), Lutz (1911), Blue (1911), Behr (1920), Cavara (1924) and Mazzi (1934), interpreted as cases of pseudo-inflammatory macular dystrophy by Franceschetti et al. (1963) and Duke-Elder (1966), do not really come under this heading in my opinion. Lutz (1911) and Cavara (1924) described patients with Stargardt's disease, and Blue (1919) described a possibly dominant progressive foveal dystrophy. The cases of Behr (1920) do not resemble Sorsby's entity either. The cases described by Mazzi (1934) are in my opinion instances of vitelliform dystrophy of the fovea, and the patients described by Hutchinson and Tay (1875) were suffering from dominant drusen of Bruch's membrane.

Since differential diagnosis from "disciform macular degeneration" on the basis of the ophthalmoscopic features is difficult, we are not inclined to attach any value to publications on "Sorsby's pseudo-inflammatory dystrophy" which fail to demonstrate unequivocal dominant transmission (Perdriel et al. 1968).

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

The condition usually becomes manifest about age 40. Visual acuity diminishes, sometimes to very low values, within a few months. There are no subjective symptoms beyond poor vision. A positive family history enhances the likelihood of Sorsby's pseudo-inflammatory dystrophy when inflammation-like changes are observed in the posterior pole of the eye.

3. FUNDUS (OPHTHALMOSCOPIC FEATURES)

The first changes consist of oedema, haemorrhages and exudates in the central retina ODS. Next, cicatrization occurs with a varying degree of pigment proliferation. Marked atrophy of the pigment epithelium occurs after some time, so that the choroidal vessels are exposed and become visible. In the course of the years the process extends to the periphery, and differentiation from choroidal sclerosis becomes difficult.

Exudates and glistening drusen-like structures can still be in evidence in this stage. Ultimately the choroidal vessels disappear over a large area and the sclera becomes visible. In many cases marked pigmentations are observed in addition. We saw a 37-year-old woman with bilateral posterior pole changes somewhat reminiscent of the fundus patterns in Sorsby's disease (fig. 1ab). The family history was positive, however, a diagnosis of pseudo-inflammatory dystrophy could not yet be established with certainty.

4. REFRACTION

Too few data are available to identify a given anomaly of refraction as typical of this condition.

5. VISUAL ACUITY

Visual acuity diminishes rapidly and almost total blindness ultimately results (Sorsby 1955).

6. VISUAL FIELDS

The peripheral visual field is intact. A central scotoma soon occurs and progressively increases in size and intensity until finally a large part of the central visual field is involved.

7. COLOUR VISION

Colour vision is normal in the initial stages. Various types of dyschromatopsia have been described. Cox (1960, 1961) found blue-yellow dyschromatopsia in 2 of 4 persons examined, while Franceschetti et al. (1963) found red-green dyschromatopsia in one of their patients. Verriest (1964) demonstrated this in 2 patients.

Fig. 1a. Disciform degeneration of the right posterior pole, resembling Sorsby's pseudo-inflammatory dystrophy, in a 37-year-old female (Fam. Ot).

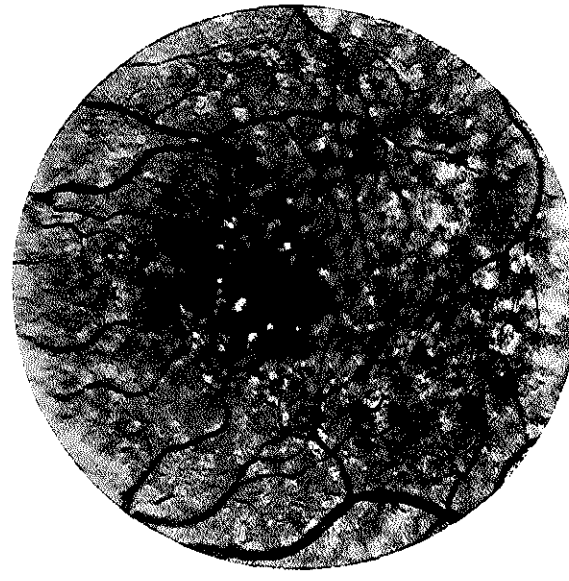

Fig. 1b. Flecked retina aspect of the left posterior pole resembling initial stages of Sorsby's pseudo-inflammatory dystrophy.

Fig. 1c. Fluorescence photograph of the right eye showing multiple defects of the retinal pigment epithelium surrounding a disciform area of pathological fluorescence suggestive of fluorescein leakage through Bruch's membrane.

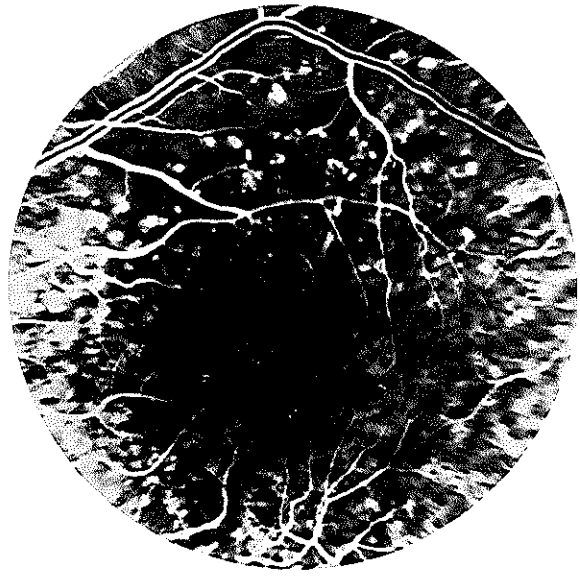

Fig. 1d. Fluorescein angiography of the fundus depicted in fig. 1b showing a pattern indicative of defects in the retinal pigment epithelium.

8. DARK ADAPTATION

Dark adaptation is generally unaffected. Franceschetti et al. (1963), however, described a slightly delayed dark adaptation curve in 2 patients.

9. ELECTRORETINOGRAPHY

The ERG is normal in early stages, but becomes subnormal in advanced stages when a fair part of the retina is involved (François 1952).

10. ELECTRO-OCULOGRAPHY

So far as we know, no EOG's have been recorded in Sorsby's pseudo-inflammatory dystrophy. In advanced stages with extensive atrophy of the pigment epithelium and choroid, pathological EOG's are bound to be found.

11. PHOTOGRAPHY

Except in Bedell's article (1961), none of the publications have so far presented photographs of Sorsby's dystrophy: nearly all publications present drawings (Sorsby et al. 1959; Burn 1950; Franceschetti et al. 1963).

12. FLUORESCEIN ANGIOGRAPHY

Rosen and Leighton (1968) presented fluorescein angiograms of Sorsby's dystrophy. They disclosed extensive defects of the pigment epithelium and pigmentations. Two individuals not immediately identifiable as patients showed slight but unmistakable changes of the pigment epithelium. The results of this method of examination, it should be borne in mind, are largely dependent on the stage which the dystrophy has reached. In exudative processes, as in disciform macular degeneration (Junius Kuhnt), diffuse fluorescein leakage will certainly be visible. The fluorescence photographs of our patient with bilateral lesions resembling Sorsby's pseudo-inflammatory dystrophy are seen in fig. 1cd.

13. CARRIERS

Regular dominant transmission occurred in the families so far described, and carriers have therefore not been identified.

14. HISTOLOGICAL FINDINGS

Ashton and Sorsby (1951) made a histological examination of the eyes of 2 patients (aged 70 and 71) with Sorsby's pseudo-inflammatory dystrophy. A by no means negligible objection lies in the fact that precisely in these patients' families dominant transmission was not demonstrable. They found the following histological changes:

1. Sclerosis and atrophy of the choroid with fibrous mural degeneration of the remaining vessels.
2. Numerous ruptures of Bruch's membrane in the posterior fundus with degeneration of the elastic layer in the same area.
3. Subretinal newly formed vascular tissue, originating from the choroid and related to the dehiscences in Bruch's membrane.
4. Disturbance of the pigment epithelium.
5. Destruction of the outer layers of the retina with glial replacement.

Babel (1958) examined the eyes of a 52-year-old man with a 12-year history of diminishing vision, whose condition had been diagnosed as Sorsby's pseudo-inflammatory dystrophy. The choriocapillaris of the right eye had largely disappeared. The corresponding pigment epithelium was atrophic but also showed areas of proliferation. The neuroepithelium and outer retinal layers likewise showed atrophy. The large choroidal vessels were either fibrotic or hyalinized.

Bruch's membrane was greatly changed: irregular rarefactions and deposits of fine granulations. Circumscribed exudates were found between the more or less marked pigment epithelium changes and the external limiting membrane, and small localized haemorrhages were visible in the inner retinal layers. The left eye showed a less completely affected choriocapillaris, and its neuroepithelium showed unmistakable degenerative changes.

Histopathological studies thus disclosed changes of the type usually found in disciform macular degeneration and angioid streaks. The principal common lesion in these 3 conditions is degeneration and rupture of Bruch's membrane, followed by formation of subretinal tissue.

15. PATHOGENESIS

The above indicates that in Sorsby's pseudo-inflammatory dystrophy the fundamental pathology seems to be a primary dystrophic change of Bruch's membrane, followed by secondary organization of subretinal haemorrhages and exudates originating in the choriocapillaris and passing through the ruptures in Bruch's membrane.

Nevertheless, the physicochemical changes which lead to involvement of the elastic tissue of Bruch's membrane are still obscure, and the possibility remains that this involvement results from pathological alteration of the choroid or the choriocapillaris proper. Histological examination in early stages of this dystrophy may lead to a solution of this problem.

For the time being it seems best to follow Ashton and Sorsby's suggestion (1951) and assume that pseudo-inflammatory dystrophy is primarily caused by genetically determined defects in Bruch's membrane, thus indicating a histopathological relationship of this condition to angioid streaks and disciform macular degeneration.

16. MODE OF TRANSMISSION

The mode of transmission of this condition is probably always autosomal dominant (Sorsby 1940: Kr family; Sorsby et al. 1949: 4 families, including the Randall family with 16 patients in 4 generations, the Ewbank family with 10 patients in 2 generations, the Carver family with 25 patients in 4 generations, and the Kempster family with 16 patients in 3 generations; Burn 1950: 11 cases in 3 generations; François 1958: 5 patients in 2 generations; Bedell 1961: father and daughter).

In the literature, an autosomal recessive mode of transmission is considered not impossible in view of some publications, but data so far available are too scanty to permit of a definite conclusion on the mode of transmission.

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

No characteristic abnormalities have been found in these cases at general internal examination. Only Seedorff (1962) found renal glycosuria in a family suffering from a central macular degeneration, which resembled Sorsby's pseudo-inflammatory dystrophy.

18. ASSOCIATED CONDITIONS

No associated conditions have been described in patients.

19. DIFFERENTIAL DIAGNOSIS

Differential diagnosis of Sorsby's pseudo-inflammatory dystrophy encompasses the other dystrophies of the central retina and choroid discussed in this study, none of which shows really marked similarities to the entity Sorsby described.

Vitelliform dystrophy of the fovea can show exudative changes and must therefore be borne in mind in differential diagnosis. Oedema, haemorrhages, exudates, drusen, gross pigment changes and subsequent generalized chorioretinal atrophy are more reminiscent of the complications of *angioid streaks* or of *disciform macular degeneration* and *chorioiditis disseminata* can also show similarities to this condition.

The entities thus defined are not accompanied by angioid streaks, and disciform macular degeneration usually is confined to the retinal centre, not affecting the retinal mid-periphery. Also, disciform macular degeneration rarely occurs before age 55 and has no dominant transmission.

In chorioretinitis disseminata an infectious cause can often be found, and hereditary factors are not at all involved.

In terminal stages an extensive choroidal atrophy may call for differentiation from one of the forms of choroidal atrophy, choroideremia, gyrate atrophy or chorioretinal atrophy associated with high myopia. For the more comprehensive differential diagnosis of these conditions, I refer to the differential diagnosis of central areolar choroidal dystrophy.

20. THERAPY

No therapy has been described. Photocoagulation of dehiscences in Bruch's membrane (demonstrated by fluorescein angiography) might prevent further progression of the process.

21. FUTURE

Further reports on families with this affection are required for better analysis of this entity. Very few families with this affection have so far been described and the clearly detailed descriptions pertain only to families in England.

It should be stressed once again that only unequivocally familial cases (and probably only those with autosomal dominant transmission) warrant a diagnosis of pseudo-inflammatory dystrophy. In solitary cases not diagnosable with certainty, the diagnosis "Sorsby's pseudo-inflammatory dystrophy" should not be used as a "diagnosis of convenience".

22. CASE HISTORIES

1. Fam. Ot

EOB-32.01.05 At the age of 37 a rather sudden impairment of visual acuity in the right eye.
VOD 1/60; VOS 8/10; emmetropic.
Media: Normal.
Fundi: In the posterior pole of OD a large disciform exudative process, surrounded by small drusenlike configurations (fig. 1a). In the posterior pole of the left eye a flecked retina, which resembles the initial stages described in Sorsby's pseudo-inflammatory dystrophy (fig. 1b).
Fluorescein angiography: The fluorescein angiograph of the posterior pole of the right eye shows a fluorescein pattern resembling disciform macular degeneration (fig. 1c). The left eye shows a pattern such as that seen in drusen and fundus flavimaculatus (fig. 1d).
Family history: The family is reported to have some more members with similar eye affections. A comprehensive family study has not so far been possible.

Summary: A 37-year-old woman with a foveal affection, resembling Sorsby's pseudo-inflammatory dystrophy.

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XIV

Central areolar choroidal dystrophy

1. INTRODUCTION

Central areolar choroidal dystrophy (atrophy) is one of several forms of choroidal dystrophy, often described as choroidal sclerosis. The recognized forms of choroidal dystrophy are:

1. diffuse, generalized choroidal dystrophy;
2. peripapillary choroidal dystrophy;
3. central areolar choroidal dystrophy.

Solitary as well as familial cases of all three forms have been described. Another form is circinate choroidal dystrophy, in which an atypical chorio-retinal atrophy is limited to a circular area around the macula in both eyes (Knapp, 1907; Schocket and Ballin, 1970). Generalized choroidal dystrophy has been described by such authors as Morton (1885, 1893), Frost (1896), Bednarski (1900), Harman (1902), Levinsohn (1903), Holloway (1914); familial cases have been reported by François (1949), Sorsby and Davey (1955) and Stankovic (1958).

Haab (1895), Harman (1902), Haab (1928) and Di Marzio (1937) described peripapillary choroidal dystrophy, and familial cases were reported by Cuperus (1903), Guglianetti (1908, 1909), Gilbert (1938), Sorsby (1939) and Waardenburg (1952).

Central areolar choroidal dystrophy was observed in a 60-year-old woman by Jaeger (1855, 1869). Other reports on this condition were published by Nettleship (1884) in a woman of 60, Retze (1902) in a man of 66, and Thompson (1905) in a woman of 63.

Central areolar choroidal dystrophy is characterized in terminal stages by a bilateral, symmetrical, sharply defined areolar or oval-shaped area of choroidal atrophy, visible because pigment epithelium and choriocapillaris have disappeared at the site of the posterior pole.

Sorsby (1935, 1939) was the first to call attention to the hereditary nature of central areolar choroidal dystrophy in two brothers. The family described by De Haas

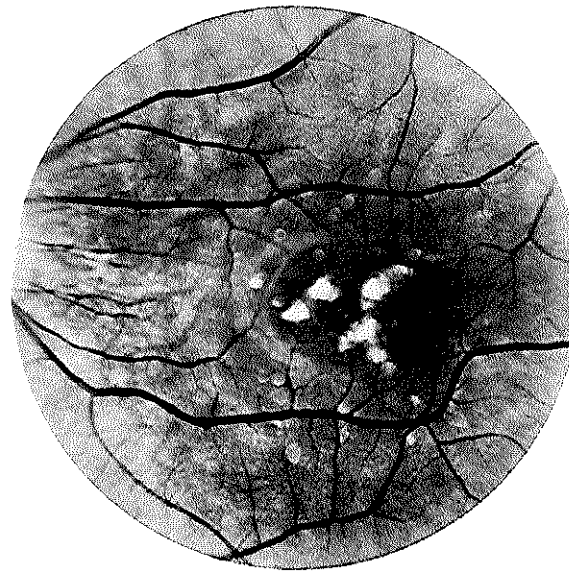


Fig. 1a. Irregularly shaped whitish flecks in the fovea of a 20-year-old girl (Fam. Fr). The pigment epithelium and the choriocapillaris appear to be absent in the pathologically changed areas.

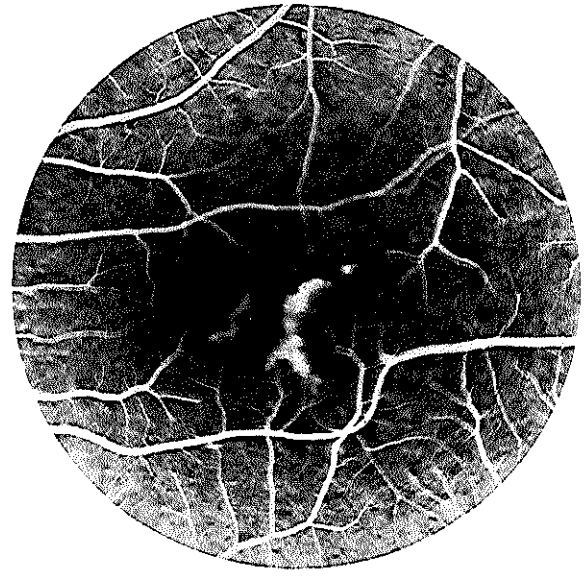


Fig. 1b. Fluorescein angiography reveals defects in the pigment epithelium and presumably in the choriocapillaris. The fluorescence is less intensive than the one usually seen in cases with defects in the retinal pigment epithelium.

(1931), in which a man and three of his sons showed sharply defined white plaques with sclerotic choroidal vessels, probably also comes under this heading.

Sorsby and Crick (1953) published 4 families in which central areolar choroidal dystrophy occurred, and a follow-up on 2 brothers described in 1935: a total of 14 cases in 5 families. In 4 of these families the condition was observed only in siblings but the fifth family included an affected mother and her affected daughter.

Friemann (1953) observed this condition in 2 brothers out of 7 siblings, and in a second family 3 persons in 2 generations seemed to be affected.

A detailed study was published by Sandvig (1955, 1959), who described a dominant form of central areolar choroidal dystrophy in 13 patients in 4 generations, and 4 additional cases, including a brother and sister (1959).

Howard and Wolf (1964) observed this condition in a sister and two brothers, aged 56, 51 and 47 years.

Carr (1965) described this condition in a 57-year-old woman and her 2 daughters (aged 22 and 15).

The nomenclature of this condition is controversial. It was originally known as choroidal atrophy, and later the term choroidal sclerosis was introduced in view of the ophthalmoscopic features (Sorsby 1935, 1939; Sorsby and Crick 1953).

Histopathological studies by Ashton (1953) demonstrated that the condition entails no sclerosis but atrophy of the choroidal vessels. These findings showed that the term atrophy is to be preferred to sclerosis. However, atrophy pertains to a state which occurs after some time; in initial stages and during the course of the process it is best to speak of choroidal dystrophy.

Waardenburg et al. (1961) were right in introducing this designation, but the term central areolar choroidal atrophy is still general usage and correctly describes the unmistakable ophthalmoscopic picture of the terminal stages.

However, the question arises whether central areolar choroidal dystrophy is in fact always a separate entity. The reports by Sorsby and Crick (1953), Sandvig (1955) and Carr (1965), which describe early stages of this condition, mention only slight pigment changes in the fovea and already notable disturbances of vision. The diagnosis was then made in view of older members of the family who showed the characteristic atrophic choroidal area. Without these older members, the diagnosis could have been Stargardt's disease in the case of recessive transmission, or dominant progressive foveal dystrophy in the case of dominant transmission.

We observed Stargardt patients who developed central choroidal atrophy later in life, and found this atrophy fully developed in others.

On the other hand, there are reports on central areolar choroidal dystrophy (CACD) occurring at a later age and almost immediately assuming the atrophic aspect (De Haas 1931; Sandvig 1959) (fam. Kou, fam. Meu).

2. GENERAL CLINICAL PICTURE IN THE PATIENTS

Patients with incipient CACD are usually found in age group 20-50 (De Haas 1931;

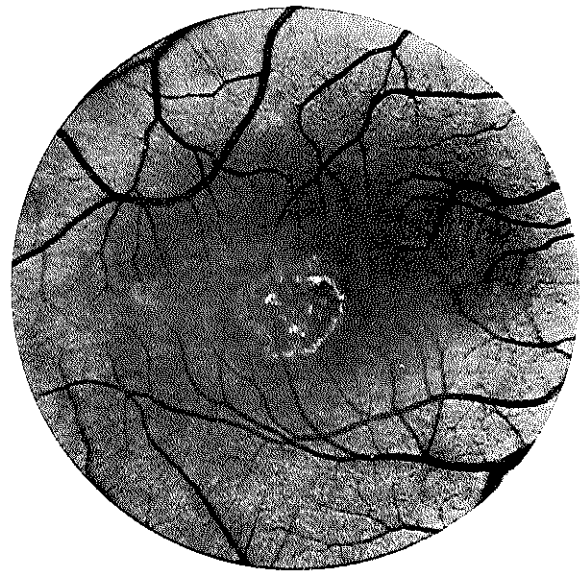


Fig. 2a-d. Development of central areolar choroidal atrophy in the right eye of a man in his forties (Fam. Kou).

Fig. 2a. Posterior pole on August 2, 1967.

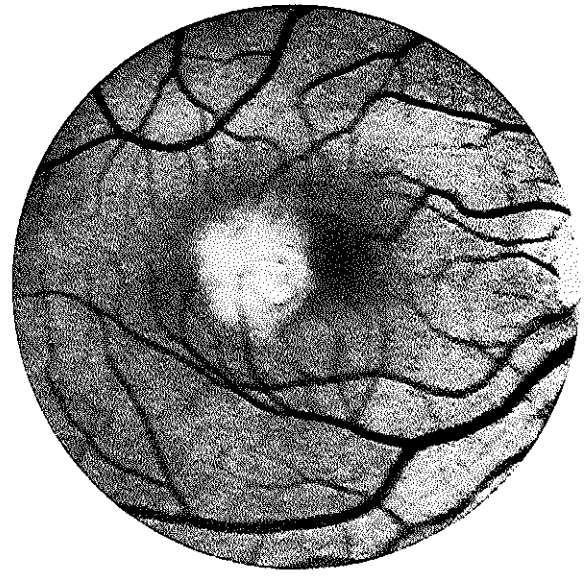


Fig. 2b. Posterior pole on August 25, 1967.

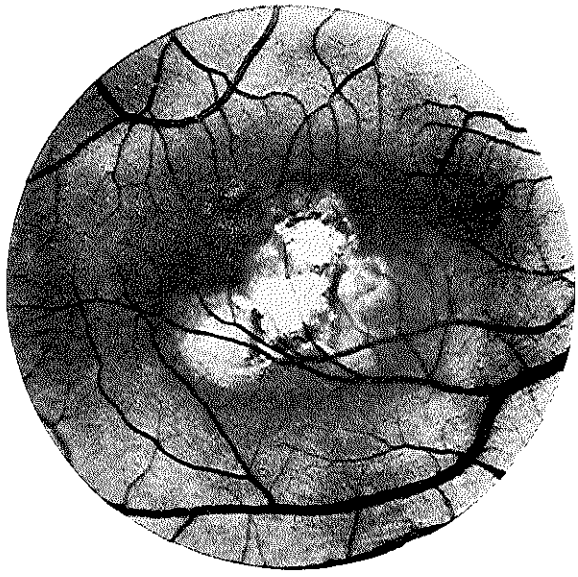


Fig. 2c. Posterior pole on July 3, 1968.

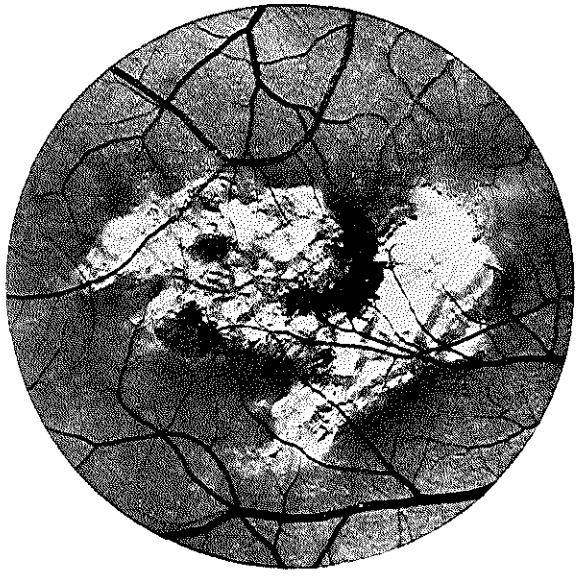


Fig. 2d. Posterior pole on April 4, 1970.

Fig. 2e. The posterior pole of the left eye of the same patient as seen in fig. 2a-d. There is a well defined areolar area of extensive atrophy of the retinal pigment epithelium and choriocapillaris. Only some of the larger choroidal vessels have not yet disappeared.

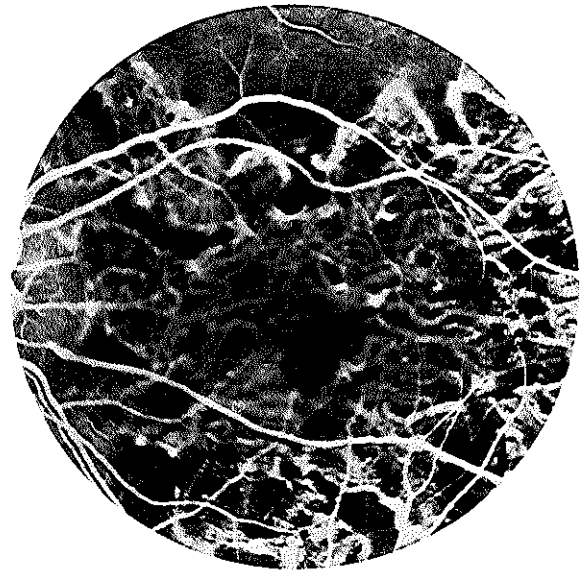


Fig. 2f. Fluorescence photograph of the same fundus as depicted in fig. 2e. Extensive chorioretinal atrophy in the centre surrounded by a normally appearing retina.

Sorsby and Crick 1953). The initial symptoms can be mild but later, usually about age 60, there is progressive loss of visual acuity resulting in a central scotoma. The condition is bilateral and symmetrical, and familial occurrence is frequently observed.

3. FUNDUS (OPHTHALMOSCOPIC FEATURES)

Initially, a slight exudative oedematous reaction can be observed in previously normal fundi; but non-specific changes in the pigment epithelium in the form of pigmentations or white or variegated spots can also herald the beginning of the dystrophic process (fig. 1, 2). The specific character of this condition is not recognizable in the early stages. Only after many years does the pathognomonic circular or oval areolar area of atrophy occur in the posterior pole. Pigment epithelium and choriocapillaris have disappeared, and the large choroidal vessels are visible in a pale area which stands out clearly from the adjacent normal retina (fig. 2-4).

4. REFRACTION

Myopia as well as hypermetropia with or without astigmatism have been described, but in many cases no mention is made of refraction.

5. VISUAL ACUITY

There is fairly rapid progressive loss of central visual acuity in CACD. Vision diminishes to 1/10 or even lower.

6. VISUAL FIELDS

The peripheral visual fields remain quite intact, while a central scotoma develops which is initially relative but ultimately absolute.

7. COLOUR VISION

Colour vision changes as soon as visual acuity shows marked diminution. Both acquired blue-yellow dyschromatopsia and acquired red-green dyschromatopsia have been described in the patients (Franceschetti et al. 1963).

8. DARK ADAPTATION

As could be expected in an ophthalmoscopically purely central abnormality, dark adaptation is generally undisturbed (Carr 1965). It was undisturbed in our patients. However, there have been reports on disturbed dark adaptation curves (Thompson 1905; Guglianetti 1908; François et al. 1956; Sandvig 1959).

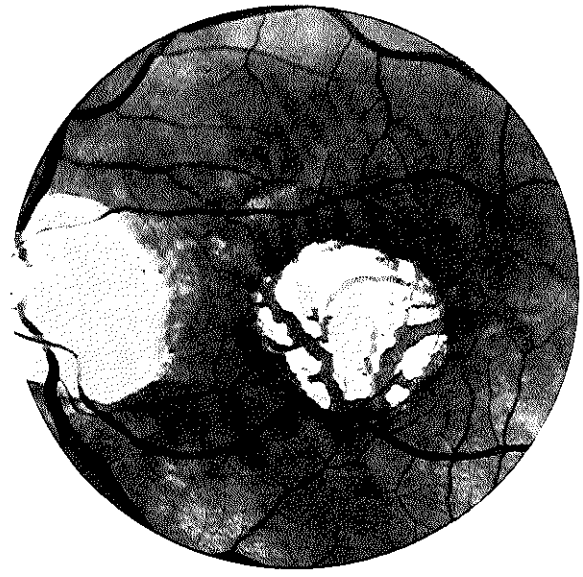


Fig. 3a. An acquired, well-defined round area of chorio-retinal atrophy in the left fovea of a 75-year-old man, filmed on orthochromatic film (Fam. Meu).

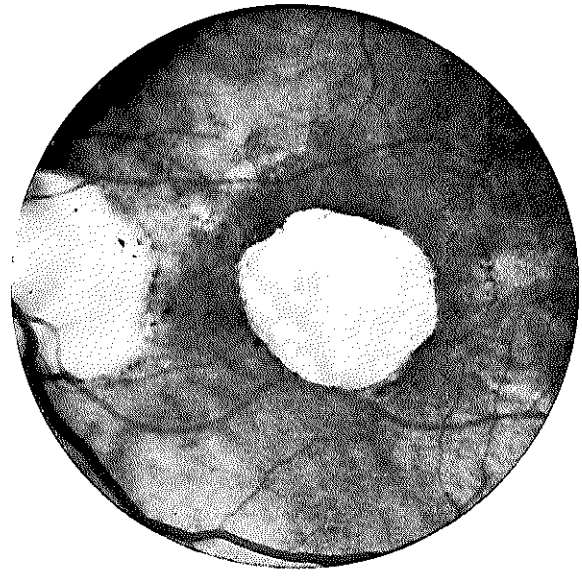


Fig. 3b. The same fundus as depicted in fig. *3a* filmed on panchromatic film.

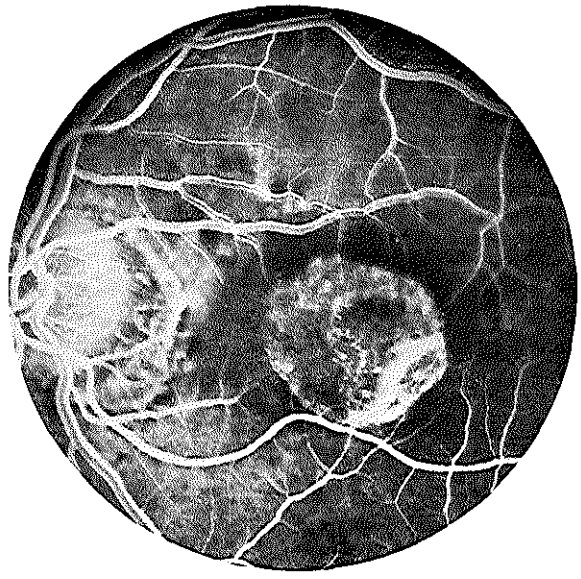


Fig. 3c. Fluorescein angiography is consistent with a sharply defined area of chorioretinal atrophy.

9. ELECTRORETINOGRAPHY

The ERG is generally normal in affections of the central retina, and it also is normal in CACD (Carr 1965). In cases in which a large part of the retina is involved, a subnormal ERG can be expected (Franceschetti et al. 1963; François et al. 1969). We have recorded no F-ERG, but undoubtedly this must be subnormal in this condition.

10. ELECTRO-OCULOGRAPHY

The EOG shows normal or slightly subnormal results (Carr 1965; François et al. 1969), as personal observations confirm (fam. Kou).

11. PHOTOGRAPHY

Not many photographs of CACD have been published (Sandvig 1955, 1959; Carr 1965). Sandvig (1959) illustrated her article with very beautiful photographs. Our study disclosed that orthochromatic graphic film gives a much more exact picture of this condition than does panchromatic graphic film (fig. 3ab).

12. FLUORESCEIN ANGIOGRAPHY

After injection of fluorescein, some slight fluorescence occurs in the area where few choroidal vessels are left; no fluorescence occurs where choroidal vessels are lacking.

This is clearly visible because pigment epithelium and choriocapillaris have quite disappeared at the site of the focus (figs 2f and 3c). At the site of persistent remnants of the choriocapillaris, the small vessels leak fluorescein but the large vessels are impermeable to this dye (Maumenee 1968). If there were only a defect in the pigment epithelium, diffuse fluorescence of the choriocapillaris would be seen; an intact pigment epithelium would of course show no pathological fluorescence. If CACD is purely choroidal in origin, then it is probable that in its early stages normal fluorescein patterns still prevail.

Krill et al. (1968) made a fluorescein-angiographic study of a carrier of choroideremia, and found widely scattered defects in the pigment epithelium. Partly on this basis they postulate that the original basic defect of this condition is to be found in the pigment epithelium. A similar situation might well be involved in CACD.

Follow-up fluorescein-angiographic studies of patients with incipient CACD are required to obtain more conclusive data on this question. Perhaps such an incipient picture is involved in our female patient Fr (fig. 1), but the problem is that the ultimate development of an ophthalmoscopic pattern is not predictable. Investigation and follow-up in a family in which this condition is dominant, however, could overcome this difficulty.

13. CARRIERS

Too little is so far known of the transmission of CACD to conclude with certainty that irregular dominance occurs. In the cases in which recessive transmission was described, the parents were (of course) quite normal. Since no specific changes in retinal function tests occur in CACD, nothing can be expected of such tests in carrier investigation.

14. HISTOLOGICAL FINDINGS

Ashton (1953) had occasion to make a histological examination of the eyes of a 56-year-old woman from a family described by Sorsby and Crick (1953). His findings were the following.

a. A well demarcated avascular zone extending from the submacular region to the disc was present in the posterior choroid.
b. Histologically this avascular zone was found to be atrophic and fibrosed. No arteriosclerotic changes were found either in the affected area or elsewhere in the choroid. Dissection of the posterior ciliary arteries failed to reveal constriction or occlusion.
c. The outer layers of the retina together with the pigment epithelium had disappeared without glial replacement, in an area exactly corresponding to the underlying choroidal atrophy.
d. Bruch's membrane was little affected by the failure of the choroidal blood supply.

Babel (1958) examined the eyes of a 70-year-old man with CACD and found numerous

Fig. 4. Areolar pattern of chorioretinal atrophy. There are some small areas of preserved pigment epithelium centrally (Fam. Lod).

drusen surrounding the atrophic area from which choriocapillaris, pigment epithelium and neuroepithelium had disappeared. Bruch's membrane showed secondary irregularities, ruptures and a lamellar structure. Babel ascribed the clinical features of vascular sclerosis to the sharp contrast between the remaining choroidal vessels and the atrophic area.

Klien (1964) described the histological features of CACD in the eye of a 71-year-old man: "The macular area showed grossly an area 2.0 by 2.0 disc diameter in size, of pigmentary and choroidal atrophy, beginning near the temporal edge of the disc. Histologically this lesion represented a rather well-defined macular defect of the neuroepithelium, pigment epithelium and choriocapillaris. These three structures had normal appearance up to the edges of the defect where they ceased rather abruptly. In the peripheral portion of the atrophic area a few scattered lumens of capillaries were still visible, while in the central portion all of these and the medium-sized vessels had disappeared, leaving only a few arteries surrounded by fibrosed stroma. No breaks were found in Bruch's membrane".

This man's family had no history of eye diseases. Klien also stated: "The histopathologic findings in this eye resemble closely those described by Ashton in central areolar choroidal atrophy and they serve well to contrast the findings in primary heredo-degeneration of the first retinal neuron, described elsewhere (Klien 1950), in which no choroidal defects could be demonstrated". However, it is our impression

that in longstanding dystrophies of the first retinal neuron the choroid also becomes atrophic.

Howard and Wolf (1964) carried out a histopathologic study in one case. They found atrophy and loss of the choriocapillaris, beginning near the equator and becoming more pronounced at the posterior pole. There were degenerative changes in Bruch's membrane and retinal pigment epithelium. A selective loss of the outer retinal elements was more marked posteriorly.

15. PATHOGENESIS

The pathogenesis of this condition is probably to be found in primary dystrophy of the choroidal vessels, although primary tapetochoroidal dystrophy or primary dystrophy of the pigment epithelium with secondary choroidal involvement cannot be ruled out. Sclerosis of the choroidal vessels as causative factor is unlikely in view of the histological absence of sclerotic vessels.

However, considering the early stages of this condition in which only slight pigment changes of the macula are seen with already markedly diminished vision (Sorsby and Crick 1953; Sandvig 1955; Carr 1965), the question arises whether this condition does not involve a primary tapetoretinal lesion, as does progressive foveal dystrophy.

16. MODE OF TRANSMISSION

There are reports on families with autosomal dominant transmission of CACD as well as on families in which an autosomal recessive pattern seems to prevail. In the patients we examined we were unable to demonstrate a hereditary factor. It should be pointed out that no complete family study could be made in these cases.

Dominant transmission is suggested by several case reports (De Haas 1931: father and 3 sons; Sorsby and Crick 1953: mother and daughter; Friemann 1953: 3 persons in 2 generations; Sandvig 1955:13 patients in 4 generations; Carr 1965: mother and daughter). In other cases, recessive transmission seems probable (Sorsby 1935, 1939: 2 brothers; Sorsby and Crick 1953: siblings of 4 family members; Friemann 1953: 2 brothers; Sandvig 1959: brother and sister).

17. GENERAL PHYSICAL AND LABORATORY FINDINGS

General physical and laboratory findings are generally normal, as they were in the patients we examined.

18. ASSOCIATED CONDITIONS

Central areolar choroidal dystrophy is generally observed as an isolated condition.

Kapuscinski (1934), however, described a progressive choroidal atrophy, not entirely confined to the central retina, in 2 sisters who suffered from Friedreich's

ataxia. And Tiberi and Cuccagna (1959) reported on 2 brothers with CACD, one of whom (in a consanguineous marriage) sired 3 children with Stargardt's disease. The occurrence of these two different affections in the same family may have been a coincidence. The ophthalmoscopic features of an advanced stage of Stargardt's disease, however, can closely resemble those of CACD, as demonstrated on page 117. Therefore, a recessive or dominant progressive foveal dystrophy cannot be ruled out in the cases of Tiberi and Cuccagna. Also, these cases are very similar to that described by Carr (1965) in a woman with CACD and her 2 daughters with Stargardt-like changes.

In terminal stages of vitelliform foveal dystrophy and Sorsby's pseudo-inflammatory dystrophy, too, a more or less marked form of choroidal atrophy can be observed.

19. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of CACD encompasses the following conditions, the first two of which have been mentioned in the introduction.

a. *Diffuse, generalized choroidal dystrophy.*

b. *Peripapillary choroidal dystrophy* and circinate choroidal dystrophy.
There are also forms which begin at the centre and spread to peripapillary or even peripheral areas, so that the diagnosis can be dependent on the developmental stage the process has reached.

c. *Sorsby's pseudo-inflammatory dystrophy* can show large areas of choroidal atrophy in the terminal stages. The extensive haemorrhages and exudates seen in early stages, however, are not observed in the more sharply defined CACD; and the overall picture is much more disorderly and less localized.

d. *Choroideremia*, also known as progressive tapetochoroidal dystrophy, shows a much more diffuse lesion than CACD. Its mode of transmission is intermediate X-chromosomal (Kurstjens 1965).

e. *Chorioretinal atrophy associated with high myopia* is most extensive in the posterior pole of the eye, like CACD, and must therefore be differentiated.

f. *Gyrate atrophy of the choroid and retina* in its initial stages shows well-defined, garland-shaped areas of choroidal and retinal atrophy in the retinal periphery; only in later stages do these areas extend in the direction of the posterior pole of the eye (Kurstjens 1965).

g. *Terminal stages of Stargardt's disease* may render differential diagnosis difficult or even impossible (page 117). Patients with dominant drusen also have central choroidal atrophy as a late development (Neame 1954).

h. *Macular colobomas* show, even at birth, well-defined ovalshaped white areas in which no vessels are discernible in the posterior pole. This means that differential diagnosis is possible on the basis of the history.

20. THERAPY

There is no therapy. Many efforts made to treat the posterior pole process with vasodilators and anticoagulants have remained as futile as has placenta implantation.

21. FUTURE

It is important that further reports be published on families with central areolar choroidal dystrophy; this will facilitate differentiation from other similar affections and enlarge our knowledge of the mode of transmission.

Differentiation from Stargardt's disease or dominant progressive foveal dystrophy still offers difficulties, for in its early stages central areolar choroidal dystrophy may show features identical to those of these conditions (Sorsby and Crick 1953; Sandvig 1955, 1959; Carr 1965), and in the terminal stages of Stargardt's disease a picture of CACD is frequently encountered.

22. CASE HISTORIES

1. Fam. Ko

PK-99.04.13 Poor visual acuity in the right eye since 1951. The family is reported to have normal eyes.
1965: VOD 1/300; VOS 8/10.
1970: VOD 1/300; VOS S+3.50=C+0.50×25° 8/10.
Media: Normal.
Fundi: An extensive area of chorioretinal atrophy in each posterior pole. The left eye shows a remnant of retinal pigment epithelium, exactly in the centre of the fovea. This is the reason of the preserved visual acuity in this eye.

2. Fam. Kou

FK-26.11.02 Since some months a black spot in front of each eye.
1967: VOD 4/10; VOS 0.5/60 Emmetropic.
Fundi: OD shows a yellowish, slightly pigmented area at the site of the fovea (fig. 2a).
OS shows an areolar area of atrophic choroid and retina (fig. 2e).
Visual fields: Central scotoma.
Colour vision: OD normal. OS unrecordable.
Dark adaptation: Normal.
ERG: Scot. b-waves OD 270μV; OS 265μV.
Phot. b-waves OD 110μV; OS 105μV.
EOG: OD 1.79; OS 1.82.
Systemic examination: Normal. There is only a slightly positive Sabin-Feldmann reaction (1:256). Has been treated with prednisone and pyrimethamine.
Family examination: Parents are not consanguineous. Three sisters, one brother and the two sons have completely normal eyes.
1970: VOD 3/60; VOS 1/300.

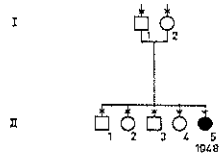
Fundi: Ovoid zone of chorioretinal atrophy in the right eye (fig. 2d). Large areolar area of chorioretinal atrophy in the left eye.
Fluorescein angiography: OS: See fig. 2f.

Summary: A man, who developed a central areolar choroidal atrophy at the age of 41. It is of interest to note the development of the ophthalmoscopic picture of the right eye (see fig. 2abcd). A yellowish-grey area, approximately 1 disc diameter in size, developed into an area of extensive chorioretinal atrophy.

3. Fam. Lod.
JJLR-08.08.04 In the last few years visual impairment. The family is reported to have normal eyes.
VOD S+2.25=C+0.50×100° 6/10; VOS S+3=C+0.50×100° 6/10.
Media: Mild incipient senile cataract.
Fundi: Extensive areolar chorioretinal atrophy in each eye (fig. 4).
Visual fields: Central and paracentral scotomata.
Dark adaptation: The curve is approximately 2/3 log. U. too high.
ERG: Scot. b-waves OD 285μV; OS 220μV.
Phot. b-waves OD 65μV; OS 80μV.
EOG: OD 1.92; OS 1.30.

4. Fam. Meu
GJM-94.12.04
1967: VOD S+1.50=C+1×30° 7/10; VOS 6/10, emmetropic.
1968: VOD 8/10; VOS 3/60.
Media: Incipient senile cataract ODS.
Fundi: Mild pigmentary disturbances in the right fovea. A sharply defined area of chorioretinal atrophy in the posterior pole of the left eye (fig. 3).
Fluorescein angiography: The pigment epithelium and the choriocapillaris have disappeared completely in a centrally located round area, which is slightly larger than 1 disc diameter. Some of the larger choroidal vessels are left (fig. 3c).

5. Fam. Fr.



II-5 (MJF-48.05.09) Has suffered from acute poliomyelitis and acute rheumatism.
1965: Observes some tiny flecks with OS.
1967: Same complaints with OD.
1968: VOD S−4 11/10; VOS S−4.75=C−0.50×50° 11/10.
There is some metamorphopsia (Amsler test).
Fundi: Symmetrical foveal lesions. Whitish, capricious flecks, suggestive of defects in the retinal pigment epithelium and the underlying choriocapillaris (fig. 1a).
Visual fields: Normal.
Colour vision: Normal.
Dark adaptation: Normal.
ERG: Scot. b-waves ODS 400μV; Phot. b-waves OD 95μV; OS 110μV.
EOG: OD 1.95; OS 1.97.
Fluorescein angiography: Pathological fluorescence at the site of the lesions visible with normal ophthalmoscopy. The fluorescein pattern indicates defects in the retinal pigment epithelium and some atrophy of the choriocapillaris (fig. 1b).
Systemic examination: Slightly disturbed capillary resistence. No other abnormalities.

Summary: A fairly young female patient with irregularly shaped whitish flecks in both foveae. A definite diagnosis is impossible at this stage. The whitish flecks, located deeply in the retina are suggestive of chorioretinal atrophy. An incipient central areolar choroidal atrophy seems to us one of the most likely of the few diagnostic possibilities.

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XV

Comment and conclusions

This study of 240 patients with hereditary dystrophies of the posterior pole and several times as many relatives shows that the hereditary dystrophies of the central retina and choroid include several readily distinguishable entities.

The classification presented on page 39 and repeated here (fig. 1) is very useful in general, and in clinical practice in particular, and easily lends itself to extension should new dystrophies be reported. On the other hand, if necessary, it can just as easily be restricted.

The long-accepted view that many different manifestations of hereditary foveal dystrophies are all expressions of the same basic dystrophic process is quite untenable in my view, and I am confident that this study has demonstrated this. The characteristics which the various affections have in common are mainly determined by the localization of the pathological process, which is the same in all these dystrophies. Some of these common characteristics are:

1. familial, bilateral, symmetrical involvement of the posterior pole of the eye;
2. more or less marked diminution of visual acuity;
3. no general physical or laboratory abnormalities;
4. a generally early age of onset.

The classification presented here might suggest that there are no more problems concerning the dystrophies of the posterior pole. However, there are still a few questions which remain moot points. A few of these may be briefly reviewed here.

It is difficult sharply to differentiate between Stargardt's disease with perifoveal yellow-white spots and fundus flavimaculatus. My own impression is that in Stargardt's disease the dystrophic foveal process occurs first, to be followed by the development of perifoveal spots, whereas in fundus flavimaculatus numerous spots are already in evidence in the posterior pole before the fovea is affected ("Stargardt inversa"). Moreover, the spots in fundus flavimaculatus are generally much more numerous.

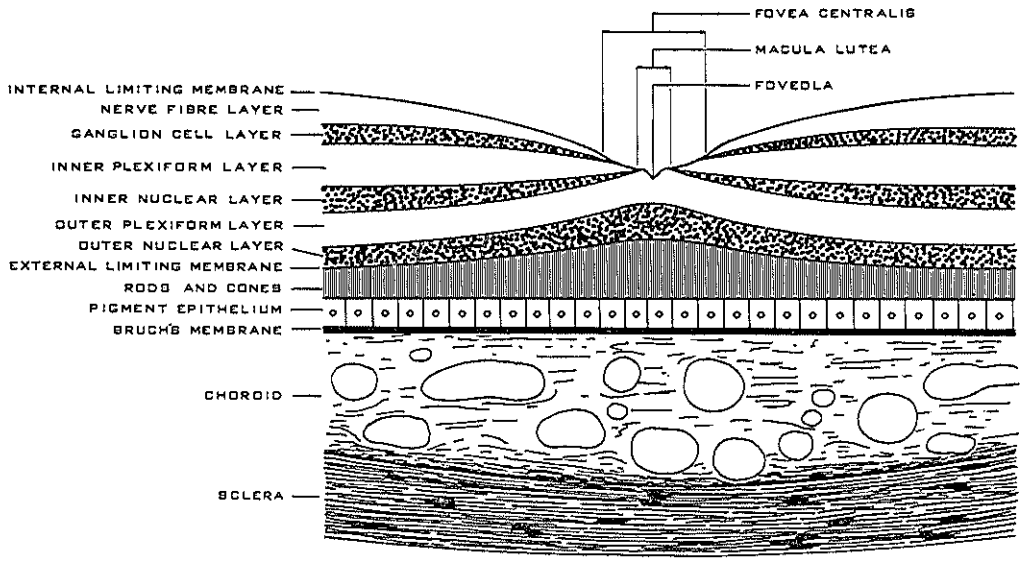


Fig. 1.

Classification with regard to the tissue mainly and primarily affected.

Nerve fibre layer	-	sex linked juvenile retinoschisis
Neuroepithelium	-	Stargardt's disease
	-	dominant progressive foveal dystrophy
	-	progressive cone dystrophy
	-	central retinopathia pigmentosa
Pigment epithelium	-	vitelliform dystrophy of the fovea
	-	fundus flavimaculatus
	-	reticular dystrophy of the retinal pigment epithelium
	-	butterflyshaped pigment dystrophy of the fovea
	-	grouped pigmentations of the foveal area
Bruch's membrane	-	dominant drusen of Bruch's membrane (hyaline dystrophies)
	-	pseudo inflammatory foveal dystrophy (Sorsby)
Choroid	-	central areolar choroidal dystrophy

Likewise, the difference between some forms of central areolar choroidal dystrophy and terminal stages of Stargardt's disease is not always marked, because in terminal stages of Stargardt's disease there is often marked choroidal atrophy. Also, initial stages of what later becomes an extensive central areolar choroidal dystrophy are sometimes characterized by very inconsiderable changes in fundo. These facts once again emphasize the importance of follow-up studies on hereditary dystrophies of the posterior pole.

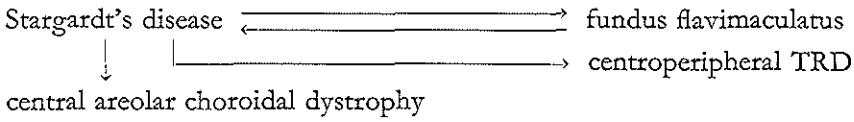
Nor is it quite certain whether Stargardt's disease with dystrophy confined to the posterior pole and Stargardt's disease with involvement of the retinal periphery in the dystrophic process (centroperipheral tapetoretinal dystrophy) are essentially different conditions or merely different manifestations of the same genotype. We

Table I. The results obtained by the various methods of investigation in all the condition studied.

	VISUAL FIELD	COLOUR VISION	DARK ADAPTATION	ERG	EOG	PHOTOGRAPHY ORTHO-PAN	FLUORESCEIN ANGIOGRAPHY
SEX LINKED JUVENILE RETINOSCHISIS	central scotoma often peripheral constriction	R-G dyschromatopsia	cone- and rod-systems pathological	a-waves normal b-waves pathol.	normal	ortho better results	normal
STARGARDT'S DISEASE	central scotoma	R-G dyschromatopsia	normal	normal	normal	not much difference	defects in ret. pigm. epithel.
STARGARDT'S DISEASE WITH PERIPHERAL INVOLVEMENT	central scotoma and concentric decrease of sensitivity	R-G and B-Y dyschromatopsia	cones and rods pathological	a- and b-waves pathol.	pathol.	not much difference	defects in ret. pigm. epithel.
DOMINANT PROGRESSIVE FOVEAL DYSTROPHY	central scotoma	R-G dyschromatopsia	normal	normal	normal	not much difference	—
PROGRESSIVE CONE DYSTROPHY	central scotoma	R-G dyschromatopsia → achromatopsia	cone- and rod-systems pathological	photopic pathol.; scot. norm.	normal	not much difference	—
CENTRAL RETINOPATHIA PIGMENTOSA	pericentral annular scotoma	R-G and B-Y dyschromatopsia	normal	normal → subnormal	normal → subnormal	not much difference	defects in ret. pigm. epithel.
VITELLIFORM DYSTROPHY OF THE FOVEA	central scotoma	R-G dyschromatopsia	normal	normal	pathol.	more pathol. details on pan	defects in ret. pigm. epithel.
FUNDUS FLAVIMACULATUS	often central scotoma	often R-G and B-Y dyschrom.	normal	normal	normal → subnormal	„	defects in ret. pigm. epithel.
RETICULAR DYSTROPHY OF THE RETINAL PIGMENT EPITHELIUM	normal	normal	normal	normal	normal	pan better results	condensation of pigment
BUTTERFLYSHAPED PIGMENT DYSTROPHY	decreased centr. sensitivity	normal	normal	normal	pathol.	pan better results	condensation of pigment
GROUPED PIGMENTATIONS OF THE FOVEAL AREA	normal	normal	normal	normal	—	pan better results	condensation of pigment
DOMINANT DRUSEN	central scotoma	R-G and B-Y dyschromatopsia	normal	normal	normal → subnormal	more pathol. struct. on pan	defects in ret. pigment epithelium
PSEUDO-INFLAMMATORY DYSTROPHY	central scotoma	„	normal	normal	normal → subnormal	not much different	defects in ret. pigm. epithel.
CENTRAL AREOLAR CHOROIDAL DYSTROPHY	central scotoma	„	normal	normal	normal → subnormal	ortho better results	defects in ret. pigment epith. and choroid

tend to prefer the latter possibility because follow-up studies have disclosed transitional forms and transitions.

The relations between the above discussed affections might be schematically presented as follows:



Centroperipheral tapetoretinal dystrophy which diffusely affects the rods and cones throughout the retina, occupies an interesting position intermediate between progressive cone dystrophy, in which only the cones are involved, and retinopathia pigmentosa in which it is chiefly and primarily the rods that are affected (Berson et al. 1968).

In this study, the value of various retinal function tests and modern photographic techniques has proved to be unmistakable. Especially the electrophysiological and photographic techniques used in this study have made it possible to differentiate the various conditions, and have given a more profound insight into the localization in depth of the various conditions and their extent through the retina.

Table I presents the results obtained by the various methods of investigation in all the conditions studied. The value of these methods will be discussed once again briefly, with special reference to their value in studying the dystrophies of the posterior pole. The various methods have on the one hand taught us more about the nature and localization of the various dystrophies, and on the other hand have given us a broader and more profound understanding of the basic retinal processes involved.

The methods used to examine the retina were methods to determine visual acuity, visual fields, colour vision and dark adaptation, and also included electroretinography, electro-oculography, photography with orthochromatic and panchromatic graphic film, and fluorescein angiography. The results and significance of these methods will be briefly recapitulated.

Visual acuity largely depends on the primary localization of the pathological process. Dystrophies which primarily involve the photoreceptors show rapid progressive diminution of vision, while dystrophies of the pigment epithelium cause slow or very slight diminution of vision. Conditions which involve Bruch's membrane and the choroid, can likewise cause rapid diminution of vision due to dehiscences in Bruch's membrane or deficient nutrition of the photoreceptors. In sex-linked juvenile retinoschisis, visual acuity is probably already affected at birth, and shows gradual further loss during life.

It is of importance that there is no parallel between the ophthalmoscopic features of the posterior pole and visual acuity. In fact, conditions with the least conspicuous

ophthalmoscopic changes often show the most marked diminution of vision, whereas extensive ophthalmoscopic changes can be found in association with 10/10 vision (intact vitelliform disc).

Refraction is inextricable from determination of visual acuity, and certain conditions prove to be associated with specific anomalies of refraction.

In sex-linked juvenile retinoschisis and in vitelliform dystrophy of the fovea, one nearly always finds hypermetropia, often with astigmatism.

The other dystrophies originating in the pigment epithelium are likewise often accompanied by hypermetropia, with or without astigmatism; in conditions primarily involving the photoreceptors, low myopia seems to be prevalent, not infrequently with astigmatism.

The *visual fields* are usually characterized by an intact periphery and a central scotoma which increases in size and depth as the dystrophy progresses. In sex-linked juvenile retinoschisis there are often limitations in the peripheral visual field, especially in the upper nasal quadrant, but normal peripheral boundaries and very markedly reduced visual fields are also observed. In centroperipheral TRD, concentric limitation of sensitivity is always observed besides a central scotoma. Loss of peripheral visual fields is occasionally seen in these cases. In progressive cone dystrophy, the visual fields are much better under scotopic than under photopic conditions.

Colour vision shows comparable results in all the various posterior pole dystrophies. No results specific for a given type of dystrophy are found, and differential diagnosis of these conditions is therefore not possible on the basis of disturbances in colour vision. Since acquired disturbances of colour vision are generally given little attention, they may be discussed in some detail here.

The generally accepted view is that the human retina contains three different pigments (red = protos; green = deuteros; blue = tritos), probably localized in three different types of cone. Congenital defects of colour vision must probably be ascribed to deficiency or absence of certain pigments or cones, and are designated according to the deficient pigments. Thus we have such terms as protanomaly (partial red pigment defect), protanopia (total red pigment defect) and protan defect (unspecified red pigment defect).

Acquired defects of colour vision are not present at birth but occur in the course of life in response to such influences as eye diseases, general diseases or drugs. Their classification of necessity differs from that of congenital defects of colour vision, because the acquired dyschromatopsias cannot be so sharply differentiated, and because various forms can occur in combination. The acquired dyschromatopsias are generally divided into red-green and blue-yellow dyschromatopsias, but a more detailed subdivision is also possible.

In his comprehensive study "Les déficiences acquises de la discrimination chromatique", Verriest (1964) distinguished the following forms:

a. Type I acquired red-green dyschromatopsia.
b. Type II acquired red-green dyschromatopsia.
c. Acquired blue-yellow dyschromatopsia.
d. Acquired dyschromatopsia with no specific axis.

re a. This form is found in the hereditary dystrophies of the posterior pole. The anomaloscope indicates reduced sensitivity to red, and the spectral sensitivity curve shows displacement to the short waves of the spectrum. Ultimately, when all the cones in the posterior pole have disappeared and acquired achromatopsia develops, the spectral sensitivity curve assumes a scotopic character.

re b. This form is found in affections of the optic nerve. The anomaloscope findings are the same as those found in congenital deutan defects, and the spectral sensitivity curve is normal. In the case of extensive optic nerve lesions, achromatopsia can then be found while the spectral sensitivity curve is normal.

re c. This form is often observed in affections of the retinal periphery in which dark adaptation and the scotopic ERG are affected also. It is also found in degenerative (not dystrophic!) posterior pole lesions, e.g. central serous choroidopathy and disciform degeneration of the posterior pole, and also in dominant optic nerve atrophy. A dyschromatopsia resembling a congenital tritan defect is found also in clouding of the refracting media.

re d. This is an ill-defined form which often shows trichomatic defects as a result of a wide variety of pathological changes.

As we mentioned, type I acquired red-green dyschromatopsia is observed in the hereditary posterior pole dystrophies, while an acquired tritan defect can also be observed in conditions in which the retinal periphery is involved as well. This is seen specifically in Stargardt's disease with peripheral involvement (centroperipheral TRD). The marked decrease in red sensitivity in hereditary posterior pole dystrophies must probably be ascribed to the fact that the red-sensitive cones are for the most part localized in the posterior pole. However, selective affection of the red-sensitive cones in early stages cannot be ruled out (Verriest 1964). In investigating acquired dyschromatopsias, it must always be borne in mind that congenital dyschromatopsias occur in about 8% of all males and some 0.5% of all females (Krill 1968).

Dark adaptation is generally normal in hereditary dystrophies of the posterior pole. Of the conditions discussed in this study, only sex-linked juvenile retinoschisis and the centroperipheral TRD are associated with an unmistakable delay in dark adaptation. The curve is rarely more than 1-2 log U too high, and in both conditions the photopic as well as the scotopic system is affected. Progressive cone dystrophy shows delayed adaptation of the photopic mechanism but an entirely normal scotopic mechanism. In our study the retina has always been tested in its totality. When even a small portion of the retina is still intact, a normal dark adaptation curve may be found. This is the case, for example, in chloroquine retinopathy in which some retinal areas remain intact while other areas are severely affected. In such cases a

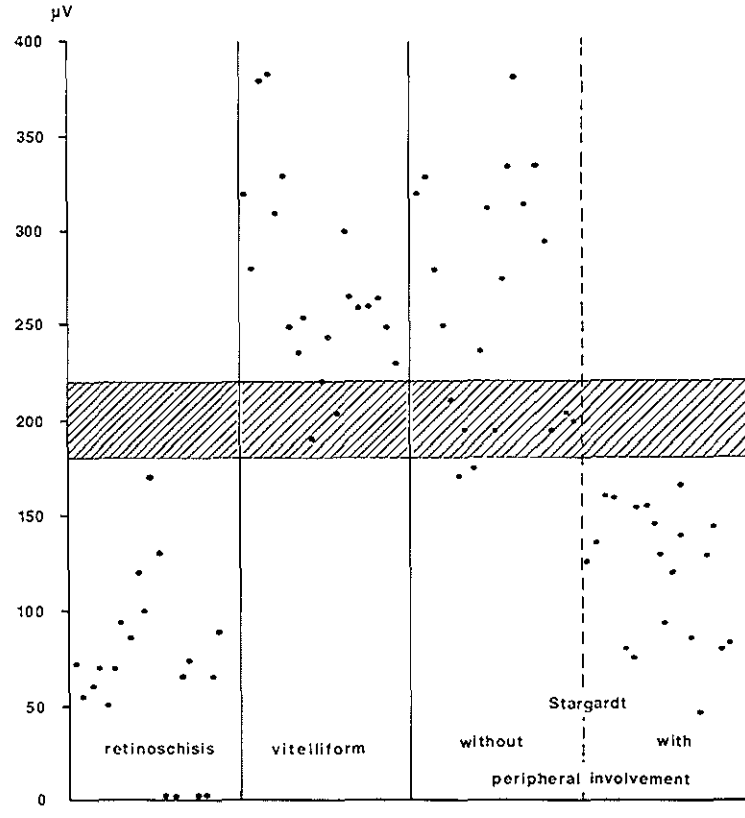


Fig. 2. ERG b-waves in sex linked juvenile retinoschisis, vitelliform dystrophy and Stargardt's disease. The latter designed separately with and without peripheral involvement as seen ophthalmoscopically. The results of 10 unselected patients (20 eyes) per entity are given (every black point means one eye).

decidedly pathological ERG and EOG can be obtained while the dark adaptation curves are virtually normal (Gouras and Gunkel 1963).

If the dark adaptation of localized retinal areas were tested, either normal or pathological results could be expected. Therefore, the fact that a pathological curve is obtained in sex-linked juvenile retinoschisis and centroperipheral TRD indicates that the whole retina is involved and that no islets of intact retinal function remain.

The *electroretinogram* (ERG) gives information on the overall function of the retina. The ERG is a rapid change in potential which follows a change in retinal illumination. The principal components of this response are the a-wave and the b-wave. The corneal negative a-wave seems to arise in the photoreceptors, and the corneal positive b-wave in the bipolar cells.

The principal argument for the assumption that the source of the a-wave is in the

photoreceptors is the fact that it survives occlusion of the central retinal artery. In several patients with such occlusion we observed normal a-waves with distinctly subnormal b-waves. Moreover, the a-waves are best recorded by micro-electrodes placed close to the photoreceptors (Brown and Wiesel 1961).

The assumption that the b-wave arises in the bipolar cells is based on micro-electrode probings (Brown and Wiesel 1961) and on the fact that destruction of most of the inner nuclear layer, be it by ligation of the central retinal artery (Noell 1953, 1954; Brown et al. 1961; Gouras and Carr 1965) or by administration of glutamate (Potts et al. 1960), causes disappearance of the b-wave. In general, however, b-waves are more susceptible to noxae than a-waves (Fujino and Hamasaki 1965; Gouras 1968).

In hereditary dystrophies limited to the fovea the ERG is normal, photopically as well as scotopically. The fovea contains only 110,000 of the total of 7 million cones, and the central retinal area with its diameter of 5 mm contains only 650,000 cones (Polyak 1941). If a subnormal photopic ERG is found in foveal dystrophies, this means only that the involvement of the photopic system is greater than would be expected in view of ophthalmoscopic findings, because changes confined to the fovea produce no changes in the diffuse ERG. Jacobson et al. (1960) demonstrated this in monkeys whose maculae had been photocoagulated; Ponte (1962) demonstrated this in human individuals suffering from retinopathia heliocliptica (solar retinopathy).

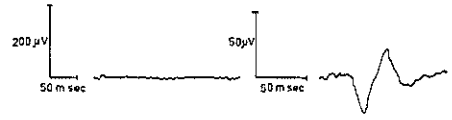


Fig. 3. Scotopic (left) and photopic (right) ERG in a 50-year-old man with X-linked juvenile retinoschisis. The scotopic b-waves are unrecordable. The photopic a-waves are almost normal, whereas the photopic b-waves are definitely subnormal. (Stimulus onset 20 msec after the start of the sweep of the CAT).

Noell (discussion to Jacobson et al. 1960), however, maintained that "in every case in which there is a circumscribed lesion of disc-size or larger we find ERG changes which mainly concern to varying degrees the a-wave, the response to flicker, the response to red light and with regard to various other phenomena".

François and De Rouck (1966) found changes in the photopic ERG only when the size of the posterior pole lesions exceeded 3 disc diameters. We obtained a pathological photopic and scotopic ERG only in sex-linked juvenile retinoschisis and in centroperipheral TRD (Stargardt's disease with involvement of the periphery) (fig. 2). In sex-linked juvenile retinoschisis the a-waves proved to be normal or slightly subnormal, while the b-waves were decidedly subnormal (fig. 3). In centroperipheral TRD both the a-waves and the b-waves were subnormal.

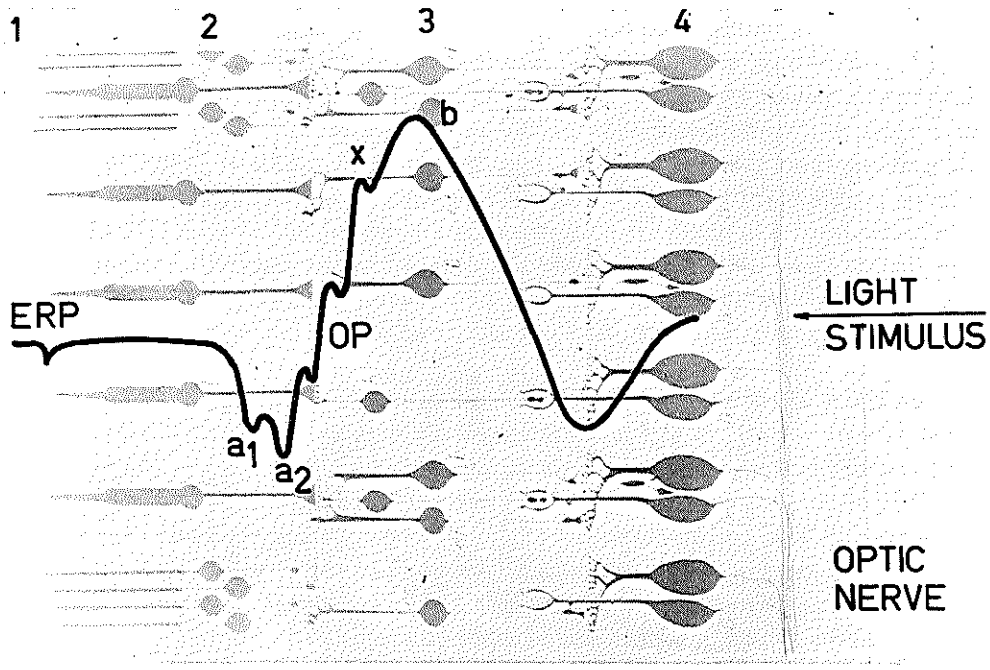


Fig. 4. Section through the retina (after Polyak) with the different components of the ERG. The localization of the ERG-components is shown in relation with their presumed anatomical origin.

ERP = early receptor potential
a_1 and x = photopic components
a_2 and b = scotopic components
OP = oscillatory potentials

1 = pigment epithelium
2 = photoreceptor layer
3 = bipolar cell-layer
4 = ganglion cell-layer

(after Henkes).

Progressive cone dystrophy proves to be characterized by a quite normal scotopic and a distinctly subnormal photopic ERG (Berson et al. 1968).

The other conditions discussed in this study have a normal ERG, although subnormal results are occasionally observed in the case of marked peripheral spread of the lesions.

In view of the fact that a-waves arise in the photoreceptors and b-waves in the bipolar cells, the localization of pathological processes can be determined in some cases (fig. 4). For example, in sex-linked juvenile retinoschisis, in which the a-waves are normal while the b-waves are very subnormal, the principal pathological changes would seem to be in the superficial retinal layers, near the bipolar cells (fig. 3).

The local ERG of the fovea (F-ERG) and the visually evoked responses (VER) are subnormal in all cases showing unequivocal diminution of vision. These data, therefore, are not very informative and certainly are of no use in differential diagnosis of the various posterior pole dystrophies.

We never observed a subnormal F-ERG in the presence of normal visual acuity,

but in several cases of sex-linked juvenile retinoschisis there was a typical broadening of the curve (fig. 5). The great importance of the F-ERG combined with the VER lies in differential diagnosis of cases of loss of vision not accompanied by distinct ophthalmoscopic changes. There are incipient forms of foveal dystrophy, e.g. Stargardt's disease, in which there are no or hardly any ophthalmoscopic changes. Likewise there are affections of the optic nerve in which the disc shows a normal appearance. If in such cases we find a markedly subnormal or absent F-ERG, we can assume that foveal dystrophy is involved, even though we must bear in mind that poor fixation can be the cause of subnormal findings in young children.

The finding of a normal F-ERG with subnormal or absent VER warrants the assumption that conduction is disturbed, generally in the optic nerve. In two young patients in whom an unexplained low vision had been observed and who showed a

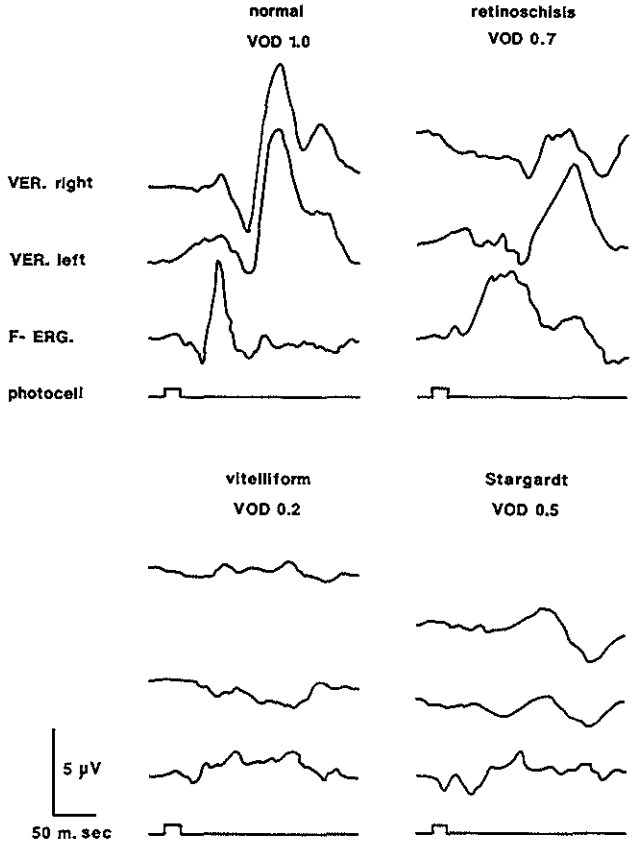


Fig. 5. The local ERG of the fovea and the visually evoked responses (VER) of the fovea in a normal individual, in a patient with sex-linked juvenile retinoschisis, in a patient with vitelliform dystrophy and in a patient with Stargardt's disease.

normal F-ERG as well as normal VER, reduplication of skiascopic examination disclosed a marked anomaly of refraction. Observations of this kind merely emphasize the value of this method of investigation.

The oscillatory potentials (OP) were examined in a few cases and showed a degree of parallelism with the b-waves of the ERG. The OP were normal in Stargardt's disease, vitelliform dystrophy of the fovea, butterfly-shaped pigment dystrophy and dominant drusen, but subnormal in sex-linked juvenile retinoschisis and Stargardt's disease with peripheral involvement. The OP generally proved to be more vulnerable than the b-waves. These findings are consistent with Algvere's conclusions (1968).

The *electro-oculogram* (EOG) proves to be made up of two different potentials: one sensitive and the other insensitive to light. The light-insensitive potential depends on the condition of the retinal pigment epithelium, but also represents some extraretinal structures such as the cornea, lens and ciliary body (Noell 1952, 1963; Lasansky and De Fisch 1966). This potential can be measured in dark adaptation and supplies information on the function of the pigment epithelium without requiring stimulation of the photoreceptors. Unfortunately, the potential can be measured only indirectly, and consequently it depends on too many factors to be of much clinical value.

The light-sensitive responses of the EOG can be divided into two components (Gouras 1968). The only component clinically studied is the large, slow, corneal positive response which develops within a few minutes of photic stimulation of a previously dark-adapted eye; it reaches a peak after 8-10 minutes and then oscillates in a damped sinusoidal manner (Kris 1958). The other component of the light-sensitive EOG potential is a much smaller corneal negative response which is maintained throughout photic stimulation and becomes apparent once the large positive response is abolished (Gouras and Carr 1965). This response is probably part of the a-wave of the ERG, which persists after occlusion of the central retinal artery (Gouras 1968). The exact site in the retina where the large, slow light-sensitive corneal positive response of the EOG originates has not so far been established with certainty. Arden (1962), Arden, Barrada and Kelsey (1962), Arden and Fojas (1962) and Arden and Kolb (1964) assumed on the basis of data obtained in examination of patients with various affections, that this response reflects the activity of the pigment epithelium. Klien and Krill (1967) and Krill (1968) reached the same conclusion, in part on the basis of their findings in a patient with fundus flavimaculatus. The only pathological funcion test was a subnormal Lp/Dt-ratio of the EOG; histological examination disclosed changes only in the pigment epithelium.

After artificial interruption of the central retinal artery in monkeys, Gouras and Carr (1965) observed disappearance of the increase in the standing potential of the light-adapted eye, and in addition disappearance of the b-waves and intactness of the a-waves of the ERG. We made the same observation in three patients with occlusion of the central retinal artery. These findings indicate that the light-sensitive corneal

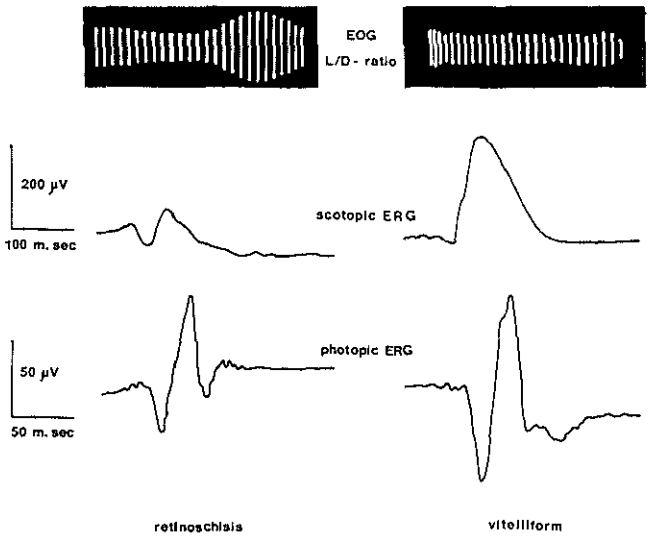


Fig. 6. Representative EOG- and ERG recordings of an individual with X-linked juvenile retinoschisis, and of an individual with vitelliform dystrophy. Stimulus onset 20 msec after the start of the sweep of the CAT. (Note the differences in analysis time).

positive response of the EOG seems to depend on the inner nuclear layers of the retina, because these layers are destroyed upon occlusion of the central retinal artery; and on the photoreceptors, because this response is elicited by light. Gouras and Carr (1965) maintained in view of their findings that this light-sensitive potential of the EOG, like the b-waves of the ERG, must arise in or very close to the bipolar cells. However, when Carr et al. (1966) examined a patient with a recessive form of congenital night blindness and found a normal Lp/Dt-ratio of the EOG and normal ERG a-waves besides markedly reduced b-waves, they suggested that the EOG-light-rise must originate somewhere in a retinal structure interposed between the structures responsible for the a- and b-waves.

The results obtained in patients with vitelliform foveal dystrophy (normal ERG, absent EOG light rise; fig. 6, 7), however, do not support this suggestion. But we may conclude that the EOG-lightrise and the ERG b-waves are independent of each other and therefore arise in different retinal structures. This was demonstrated not only in vitelliform foveal dystrophy, but also in sex-linked juvenile retinoschisis (fig. 6, 7), in which we obtained virtually the same results as Carr et al. (1966) reported in a recessive form of congenital hemeralopia (normal EOG-lightrise, normal ERG a-waves and subnormal scotopic ERG b-waves). A similar situation (normal EOG and subnormal photopic ERG b-waves) is encountered in achromatopsias. In sex-linked juvenile retinoschisis, like in sex-linked hemeralopia (hemeralopia-myopia syndrome) we found normal EOG, normal photopic a-waves and subnormal photopic and scotopic b-waves.

If we follow the reasoning of Gouras and Carr (1965) and Carr et al. (1966), the site of origin of the EOG-lightrise should be localized, in view of the findings in vitelliform foveal dystrophy, on the outside of the structures responsible for the ERG a- and b-waves, that is to say: in or very near the pigment epithelium. Since the choroid and Bruch's membrane show a normal appearance in vitelliform foveal dystrophy at fluorescein angiography, it is likely that only the pigment epithelium is dysfunctional. This would warrant the conclusion that the EOG-lightrise originates in the pigment epithelium. In that case, however, it remains difficult to explain the fact that the EOG-lightrise disappears upon occlusion of the central retinal artery. It is possible that a more extensive functional affection of the deeper retinal layers develops than histological findings would seem to suggest.

Arden (1962) postulated oedema due to retinal ischaemia, giving rise to what might be called functional detachment. Carr and Siegel (1964) postulated a spasm of the proximal segment of the affected artery. "In this way there might be a transient effect on the posterior ciliary artery supply to the choroid, sufficient to eliminate the d-c potential but not sufficient to affect the photoreceptors, thus accounting for the presence of the ERG."

As long as no further data are available it seems best to assume that the light-induced EOG response is produced in the pigment epithelium under the influence

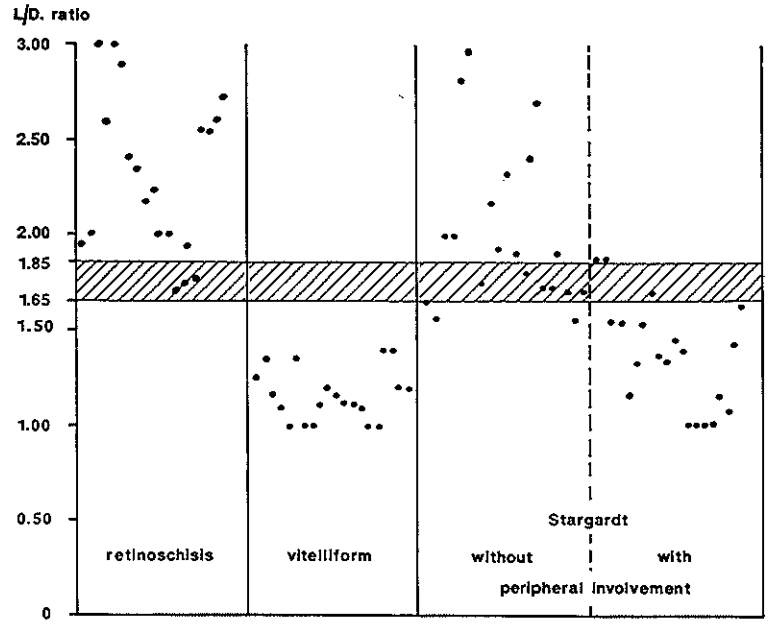


Fig. 7. EOG light peak/dark trough ratio's in the three most common hereditary foveal dystrophies of childhood. The results of 10 unselected patients (20 eyes) per entity are given (every black point means one eye).

of the photoreceptors (fig. 8). Thus, the finding of a subnormal Lp/Dt-ratio of the EOG warrants the assumption that a diffuse dysfunction of the retinal pigment epithelium is present.

This means that a normal EOG is to be expected in conditions ophthalmoscopically confined to the fovea or posterior pole. If a pathological EOG is nevertheless found, then we must assume that diffuse dysfunction of the pigment epithelium exists. A pathological EOG is observed in centroperipheral TRD, vitelliform foveal dystrophy, butterfly-shaped pigment dystrophy of the fovea, and somewhat advanced cases of fundus flavimaculatus and drusen. In the remaining conditions we usually find a normal EOG, although a subnormal EOG can occasionally occur in advanced age and upon peripheral spread of the processes.

Centroperipheral TRD, fundus flavimaculatus and dominant drusen are conditions in which large retinal areas are ophthalmoscopically affected. In vitelliform dystrophy and butterfly-shaped pigment dystrophy, however, the changes are virtually confined to the central retina. The sporadic multiple vitelliform structures, however, support the theory of a diffuse affection of the pigment epithelium, as does the occurrence of unmistakable clumps of pigment in the retinal periphery in two patients with butterfly-shaped pigment dystrophy of the fovea.

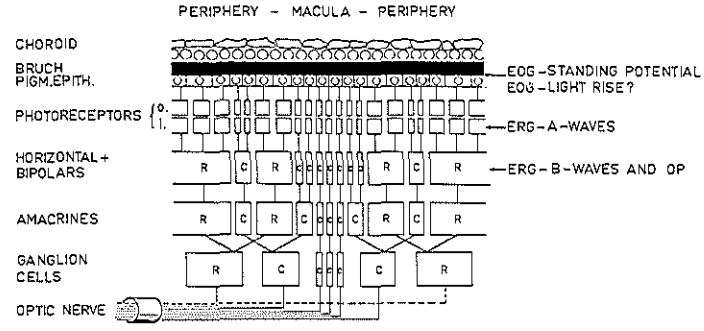


Fig. 8. A tentatively proposed model of the presumed sources (anatomical localization) of the different components of the ERG and EOG.

The fact that the EOG is decidedly pathological in ophthalmoscopically normal carriers of the pathological gene of vitelliform dystrophy of the fovea, likewise indicates that a pathological EOG does not result from localization of the vitelliform lesion in the foveal area, as François et al. (1967) assumed. A quite normal EOG is usually found also in other foveal affections such as central serous choroidopathy, central choroiditis and foveal lesions in angioid streaks (page 240). Stargardt's disease, too, demonstrates that the EOG is a test of the retina in its totality: the EOG is normal in the purely central, and pathological in the centroperipheral form (fig. 7) (Table II).

Table II. The results of the ERG b-waves and the EOG L/D-ratio's in the three most frequently occurring juvenile hereditary foveal dystrophies. Note that differentiation is possible on the basis of electrophysiological tests.

	ERG – b – wave	EOG – $^{L}/_{D}$ – ratio
X – linked juvenile retinoschisis	–	+
vitelliform dystrophy	+	–
Stargardt's disease – without peripheral involvement	+	+
Stargardt's disease – with peripheral involvement	–	–

It can be concluded that electro-oculography is a very important method of investigation in hereditary retinal affections, and that its importance is very evident especially in depth localization of pathological retinal processes.

This is clearly illustrated by sex-linked juvenile retinoschisis and vitelliform dystrophy of the fovea. In the former the EOG is normal, and this condition proves to be localized in the nerve fibre layer of the retina; in the latter the EOG is decidedly pathological, and all investigations point in the direction of localization in the pigment epithelium (fig. 6, 8).

Photography of fundi, using orthochromatic and panchromatic graphic film (Craandijk and Aan de Kerk 1969) has yielded interesting results. It was found that particularly pathological changes localized in the pigment epithelium are more clearly shown on panchromatic than on orthochromatic film (fig. 9). For example, the lesions of reticular pigment epithelium dystrophy (Sjögren) and butterfly-shaped pigment dystrophy are best seen on panchromatic film. In vitelliform dystrophy, fundus flavimaculatus and dominant drusen, both types of film give good photographs, but panchromatic film discloses more extensive pathological changes than orthochromatic film. One obtains results comparable to those obtained with the aid of monochromatic light (Behrendt and Wilson 1965; Potts 1965; Behrendt and Duane 1966; Krill et al. 1966).

It is not quite clear why the pigment epithelium is so much more clearly shown on

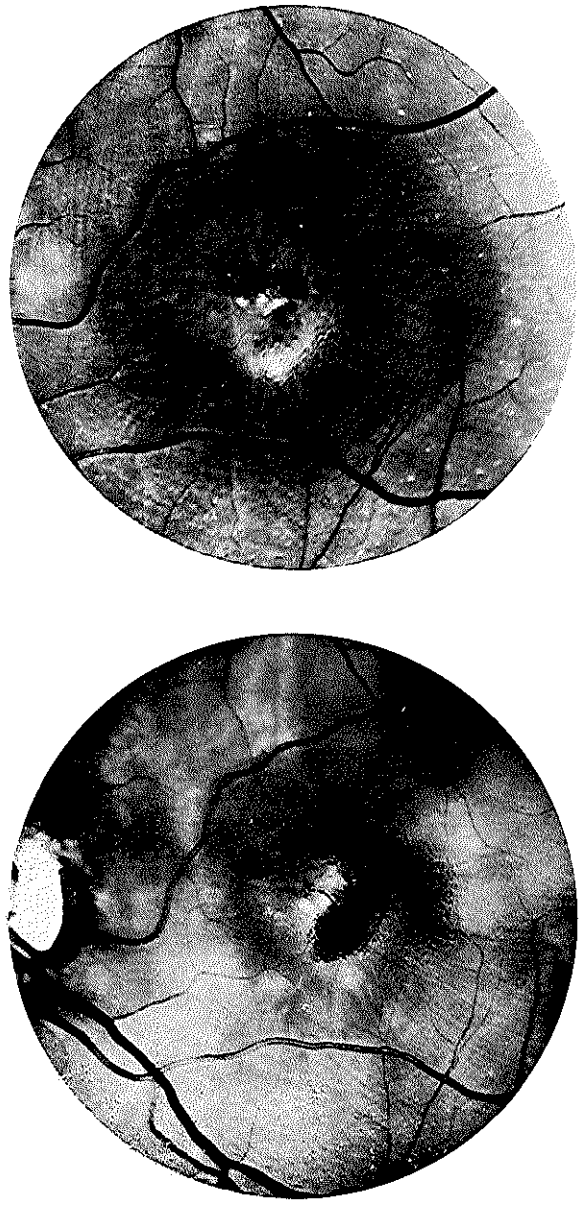


Fig. 9a-b. An individual with vitelliform dystrophy complicated by retinal detachment. The hole in the retinal pigment epithelium is beautifully visible on panchromatic film (see bottom), whereas the more superficially localized structures (folds etc.) are better visible on orthochromatic film (see top).

panchromatic film. Longer wavelengths penetrate deeper into the retina than shorter wavelengths (Behrendt and Duana 1966) (fig. 10), and panchromatic film has its maximum sensitivity at a longer wavelength than orthochromatic film. The better penetration of the longer wavelengths into the retina might partially explain the differences between orthochromatic and panchromatic film. It is probably not the only explanation, however, but contrast and absorption-reflection mechanisms are likely also to play a role. For example, the choroidal vascular pattern is sometimes better visible on orthochromatic than on panchromatic film. Also, orthochromatic and panchromatic films of a colour slide give the same results as those made directly of the patient. The difference in result, therefore, cannot be ascribed solely to a difference in retinal penetration.

Whatever may be the exact mechanism underlying the marked difference in results between orthochromatic and panchromatic film, it is a fact that changes at the level of the pigment epithelium are especially clear on panchromatic film, while more superficially localized changes are shown in more detail on orthochromatic film.

Fluorescein angiography makes an important contribution in the assessment of the various hereditary affections of the posterior pole of the eye.

No pathological fluorescence is visible in processes which leave the pigment epithelium and deeper layers intact, such as sex-linked juvenile retinoschisis initially is. In affections of Bruch's membrane, leakage of fluorescein through the membrane forward can be observed, e.g. in central serous choroidopathy. But this is not seen in the hereditary dystrophies of the posterior pole discussed here. This might be found in Sorsby's pseudo-inflammatory dystrophy, because histological examination has revealed ruptures in Bruch's membrane in these cases.

Defects of the pigment epithelium are demonstrable in many of the conditions discussed in this study (Stargardt's disease, vitelliform dystrophy of the fovea, fundus flavimaculatus, and dominant drusen). In other conditions, however, the pigment epithelium shows densifications (reticular dystrophy of the pigment epithelium and butterfly shaped pigment dystrophy).

If there are defects of the pigment epithelium, it is possible to see the choriocapillaris and the large choroidal vessels, and sometimes even the sclera (central areolar choroidal dystrophy).

Fluorescein angiography is an important aid in the follow-up of hereditary dystrophies, and can enhance our knowledge of primarily affected retinal structures. As long as the retinal pigment epithelium is intact, however, pathological fluorescein angiograms can hardly be expected. Fluorescein angiography often reveals more pigment epithelium defects than can be disclosed by normal photography. A comparison of ophthalmoscopic findings with fluorescein angiograms can improve our interpretation of ophthalmoscopic features, for fluorescein angiograms clearly show what is hardly discernible at ophthalmoscopy. Much of the value of fluorescein angiography also lies in the fact that the various dystrophies discussed here can be differentiated with greater confidence on the basis of the fluorescein pattern.

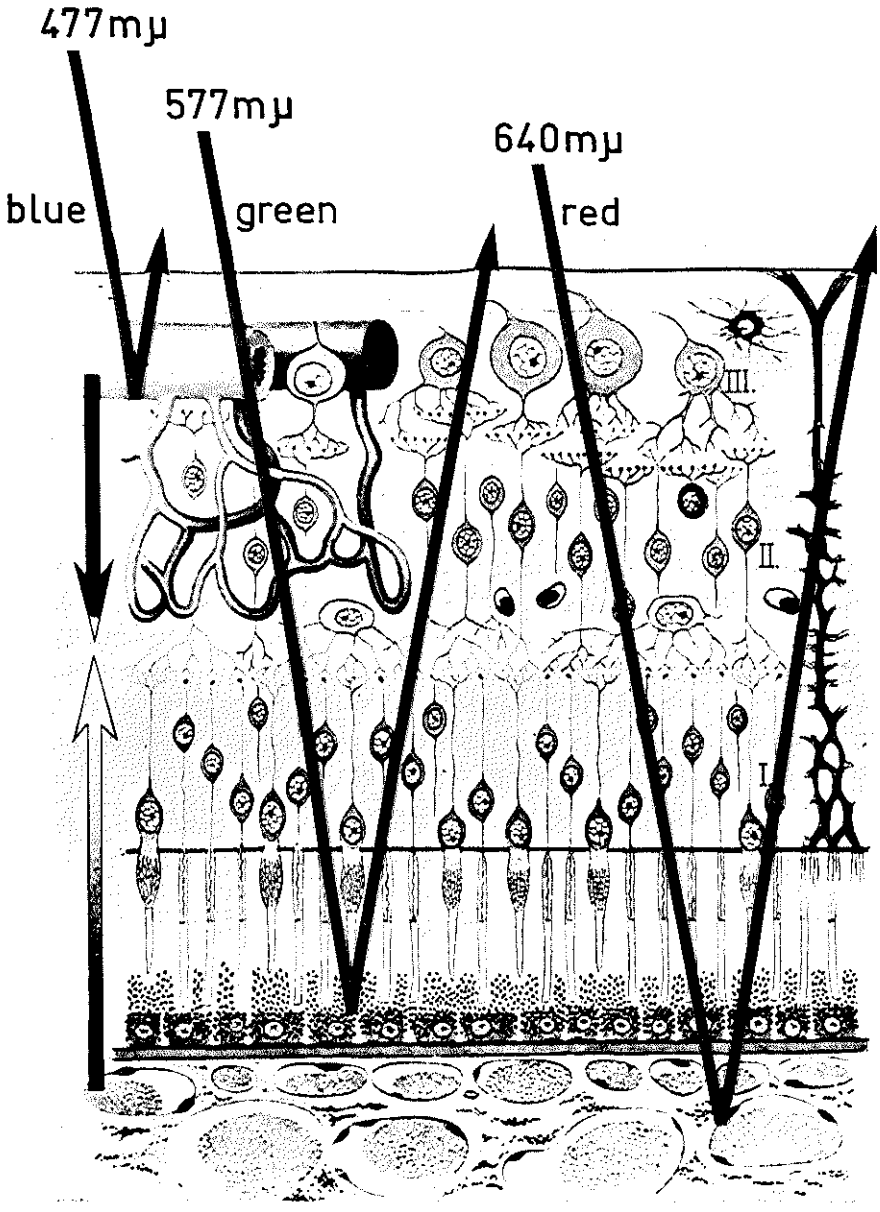


Fig. 10. Model of the depth-penetration of monochromatic light into the different retinal structures (after Thiel and Behrendt).

We are hopeful that this study may have removed some of the confusion which prevails in the intricate field of the hereditary dystrophies of the posterior pole, and that it may have demonstrated that this group includes several essentially different conditions.

The classification presented in this study purports to be useful in actual practice, and readily lends itself to such expansion or restriction as may be necessary.

Histochemical and biochemical research, it is hoped, will in future yield more information on the pathological changes underlying this group of conditions. Histological examination, if possible, can teach us much in particular if the eyes examined are still free from senile changes.

It is a pleasure to observe that electrophysiological and photographic techniques can make a valuable contribution to a better understanding of the various conditions, thus facilitating correct differential diagnosis.

Unfortunately, future expectations are less hopeful in therapeutic terms. There is as yet very little that can be done beyond genetic counselling. Only in sex-linked juvenile retinoschisis is surgical intervention occasionally a sensible measure. Optical aids often make a grateful patient, and in many cases restore the patient's ability to read. It is an important assurance to the patient that virtually none of the conditions discussed here will lead to total blindness. Many patients prove capable of leading useful and happy lives in spite of their visual handicaps. Hospitalization and a comprehensive physical and neurological examination are quite unnecessary once the diagnosis is established. As long as no truly effective therapies are available, it will be much to the patients' benefit to observe the following rule, formulated by Berkley and Bussey (1949): "Much assistance to the patient may be offered in the form of correcting of refractive error, assurance that blindness will not ensue, and elimination of unnecessary empirical approaches to therapy".

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Samenvatting

Op het gebied van de erfelijke dystrofieën van de achterpool van het oog bestaat in de hedendaagse literatuur nog een aanzienlijke mate van verwarring. Aangezien na het werk „The dystrophies of the macula" van Sorsby (1940) er geen studie meer speciaal aan dit onderwerp is gewijd werd het wenselijk geacht een zo uitgebreid mogelijk eigen onderzoek uit te voeren.

Franceschetti, François en Babel (1963) gaven in hun uitgebreide studie „Les hérédo-dégénérescences choriorétiniennes" als hun mening te kennen, dat al de verschillende manifestaties van de erfelijke dystrofieën van de achterpool van het oog in wezen slechts uitingen van een en hetzelfde ziekte-proces waren. Duke-Elder (1967) handhaafde deze door Behr (1920) naar voren gebrachte monistische opvatting in „The Retina", een van de delen van zijn „System of Ophthalmology".

Waardenburg (1963) gaf echter in zijn standaardwerk „Genetics and Ophthalmology" aan, dat er verschillende van elkaar te differentiëren aandoeningen zijn onder de achterpool-dystrofieën, een opvatting die eerder door Stargardt (1917) naar voren was gebracht. Waardenburg stelde, dat er nog te weinig gegevens beschikbaar waren om een aanvaardbare classificatie op te stellen.

Om een eigen standpunt in te kunnen nemen bij deze divergerende opvattingen, werd een zo uitgebreid mogelijke literatuurstudie verricht, terwijl tevens een zo groot mogelijk aantal patiënten werd opgespoord. Deze patiënten werden aan een diepgaand onderzoek onderworpen, waarbij naast conventionele onderzoekingsmethoden van de retinafunctie als gezichtsscherpte, gezichtsveld, kleuren zien en donkeradaptatie, moderne en verfijnde electrofysiologische (electro-oculografie, electro-retinografie van de retina in zijn totaliteit en selectief van de fovea, visueel opgewekte corticale responsies en oscillatory potentials) en fotografische (fluorescentie angiografie, fotografie met ortho- en panchromatische films) technieken werden toegepast.

Meer dan 240 patiënten met een erfelijk bepaalde achterpoolafwijking werden

onderzocht, terwijl vele malen dit aantal aan familieleden werd nagekeken. Bij dit onderzoek bleek, dat in vrij veel gevallen ten onrechte een infectieus proces als oorzaak van de oogaandoening was aangenomen. De grote waarde van familie-onderzoek bij moeilijk te diagnosticeren retina-afwijkingen werd aldus vastgesteld.

Aan de hand van onze studie hebben we in tegenstelling tot de wijd verbreide mening aan kunnen tonen, dat er een aantal, verschillende erfelijke dystrofieën van het centrale gedeelte van het netvlies en het vaatvlies bestaat. Deze dystrofieën zijn op velerlei wijze te onderscheiden, onder meer op grond van overervingsmodus, ophthalmoscopisch beeld en retinafunctie.

In het eerste hoofdstuk wordt de afgrenzing van het studiemateriaal besproken, waarbij nadrukkelijk wordt gesteld, dat een zeer stricte afscheiding van de te bestuderen afwijkingen moeilijk te maken valt. Slechts die aandoeningen werden in deze studie opgenomen, waarbij de achterpoolafwijking als enige aandoening voorkomt, of waarbij deze in het ziektebeeld een dominerende plaats inneemt. Vervolgens worden enkele begrippen als fovea, dystrofie en carrier aan een nadere beschouwing onderworpen.

De classificatie, die uit het onderzoek naar voren is gekomen wordt dan besproken. Het blijkt dat de veelal gebruikte classificatie op basis van de leeftijd waarop de aandoeningen zich gewoonlijk manifesteren niet voldoet. Onze classificatie is gebaseerd op grond van de uit ons onderzoek naar voren gekomen vermoedelijke primaire localisatie van de dystrofieën in de verschillende lagen van de retina en chorioidea:

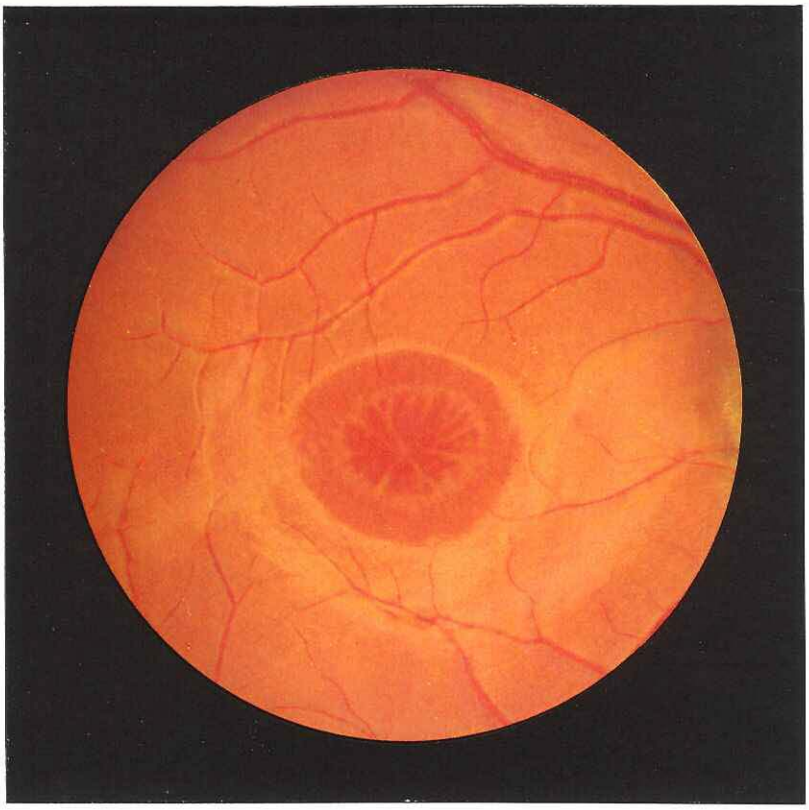
zenuwvezellaag	– geslachtsgebonden juveniele retinoschisis
neuro-epitheel	– ziekte van Stargardt
	– dominante progressieve fovea dystrofie
	– progressieve kegel dystrofie
	– centrale retinopathia pigmentosa
pigment epitheel	– vitelliforme fovea dystrofie
	– fundus flavimaculatus
	– reticulaire pigment epitheel dystrofie (Sjögren)
	– vlindervormige pigment dystrofie van de fovea
	– gegroepeerde pigmentaties in de achterpool
membraan van Bruch	– dominante drusen
	– pseudo-inflammatoire fovea dystrofie
chorioidea	– centrale areolaire choroidea dystrofie.

In de hierop volgende hoofdstukken worden de in deze classificatie genoemde dystrofieën successievelijk behandeld. Bij deze dystrofieën worden enkele uiterst zeldzame aandoeningen zoals de reticulaire pigment epitheel dystrofie en de vlindervormige fovea dystrofie uitvoerig besproken.

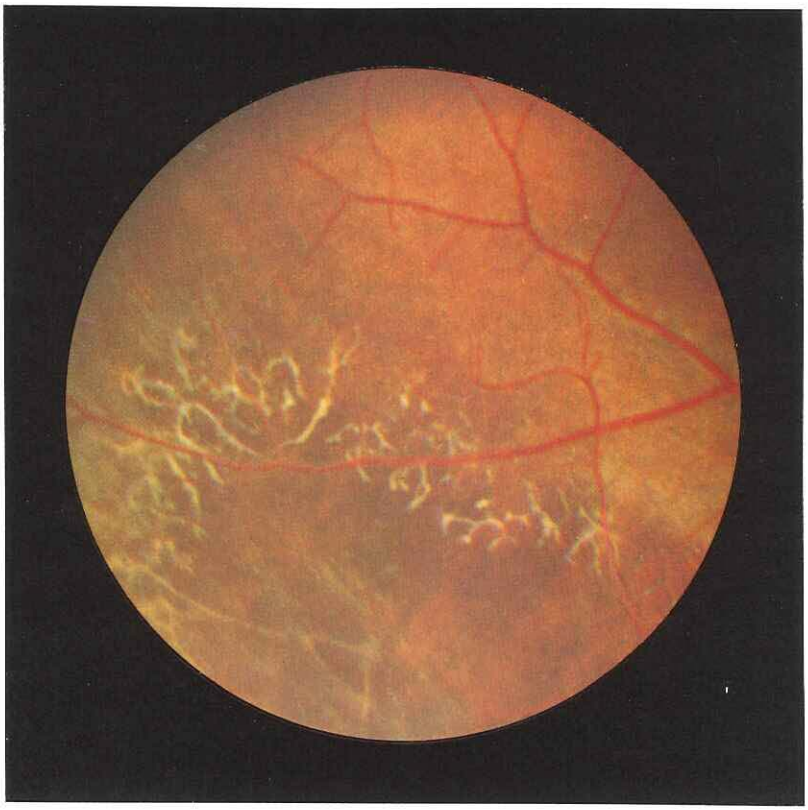
In het laatste hoofdstuk wordt diep ingegaan op de betekenis van de verschillende onderzoekingsmethoden van de retinafunctie. Het belang van electrodiagnostisch onderzoek wordt onder meer geïllustreerd door het uit deze studie naar voren gekomen feit, dat ophthalmoscopisch geheel normale dragers van het gen van de vitelliforme fovea dystrofie met behulp van het electro-oculogram als carrier kunnen

worden ontdekt. Het belang van fluorescentie angiografie wordt onder meer geïllustreerd bij de vlindervormige pigment dystrofie van de fovea, waarbij met normaal oogspiegelonderzoek somtijds nauwelijks opvallende structuren duidelijk naar voren komen. De waarden en beperkingen van de moderne electrodiagnostische en fotografische technieken, vooral in het kader van de dieptelocalisatie van de verschillende dystrofieën in de retina en chorioidea, worden in dit laatste hoofdstuk uitvoerig besproken.

Colour-plates

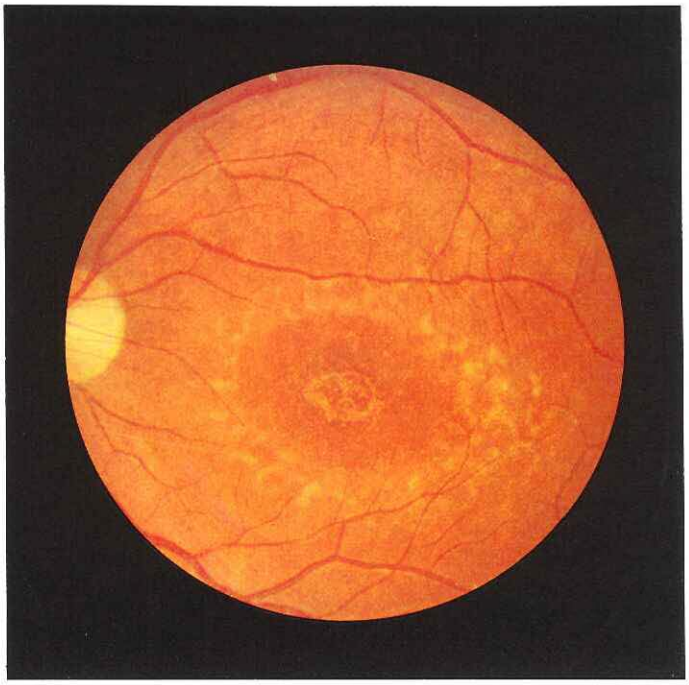


I The pathognomonic foveal retinoschisis of X-linked juvenile retinoschisis, showing a radiate striation.

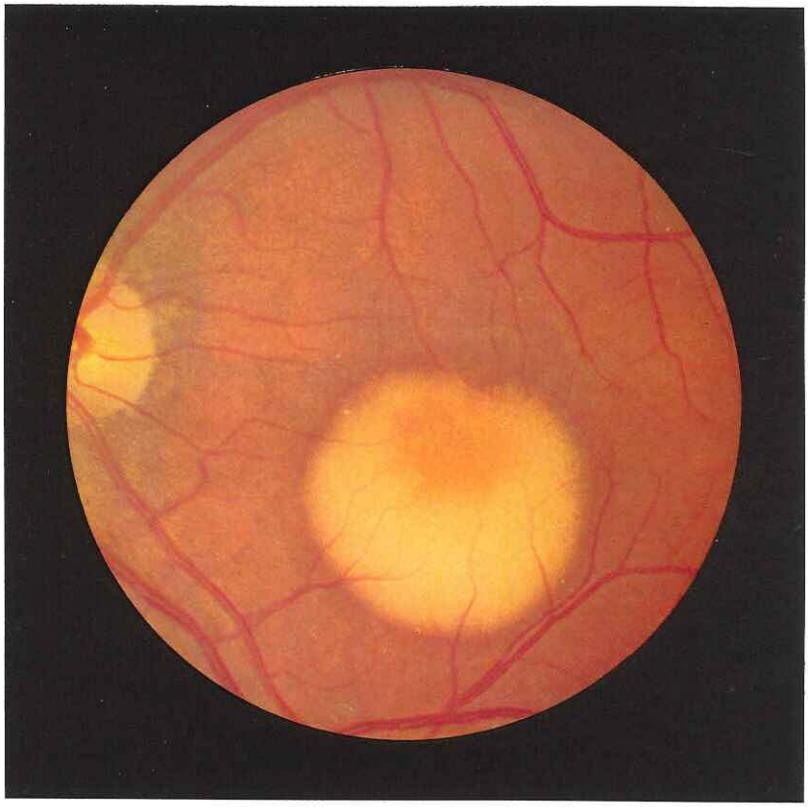


II Preretinal dendritiform structures and retinoschisis in the midperiphery of the retina in X-linked juvenile retinoschisis.

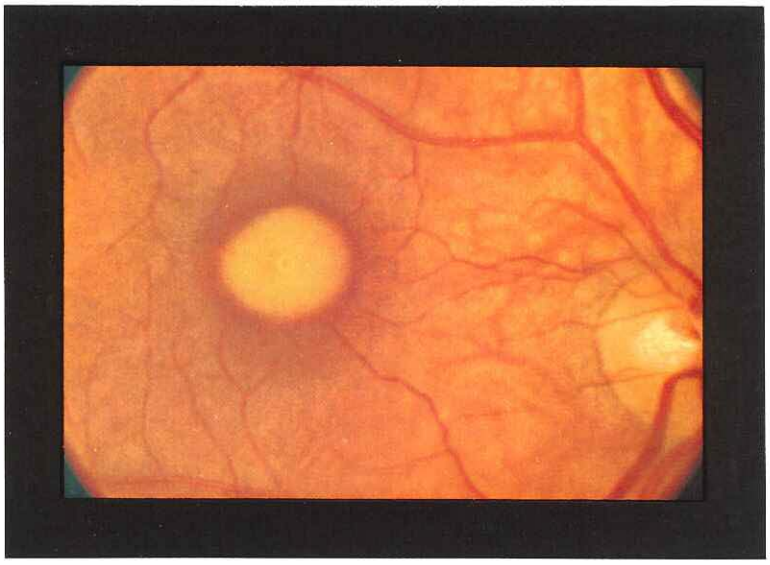
III Vitreous veil and a small haemorrhage in X-linked juvenile retinoschisis.



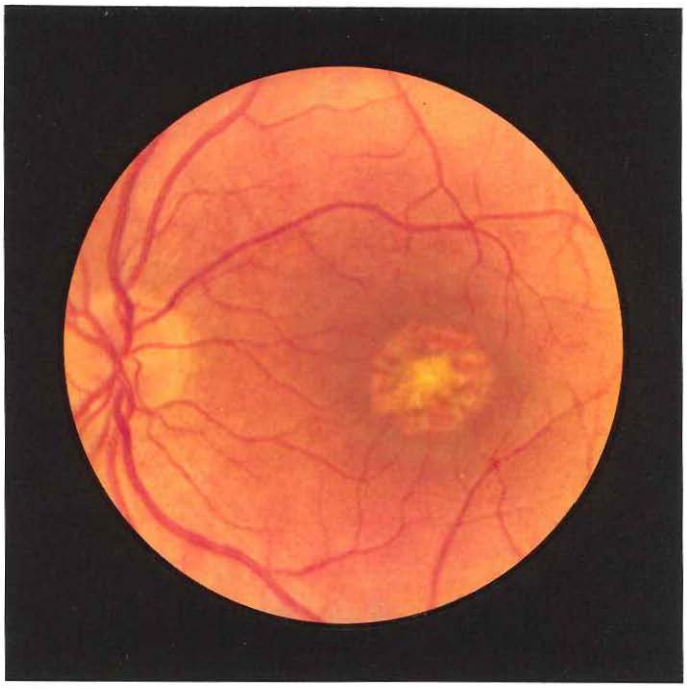
IV Classic case of Stargardt's disease: a central area of beaten bronze atrophy surrounded by a horizontal oval of yellowish flecks.



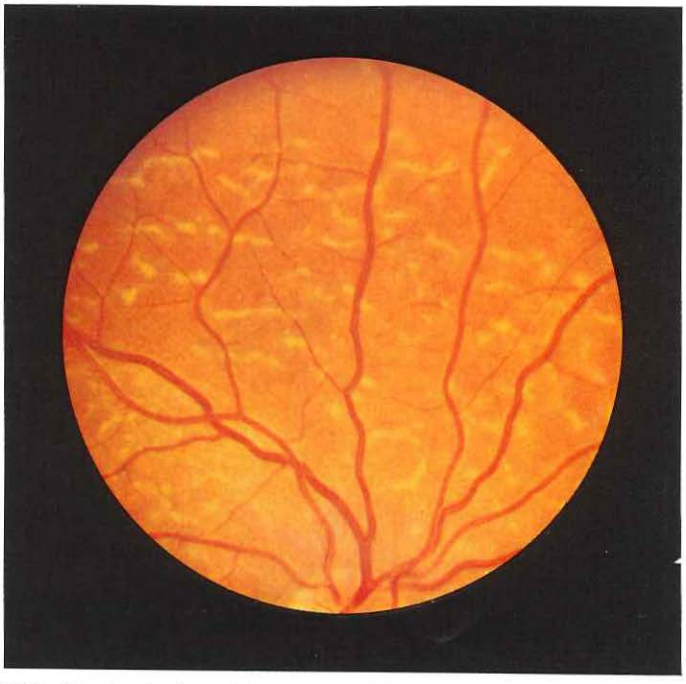
V Vitelliform dystrophy with almost normal visual acuity.



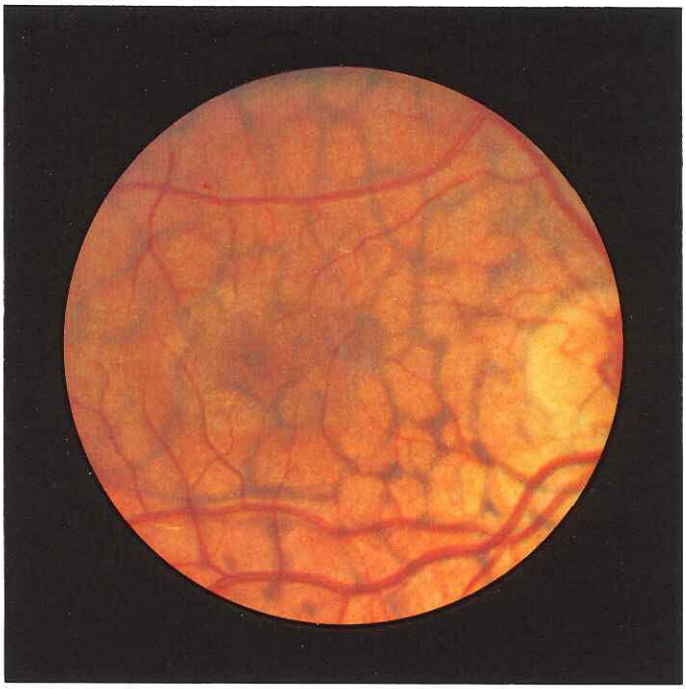
VI The intact "egg-yolk"-stage in vitelliform dystrophy.



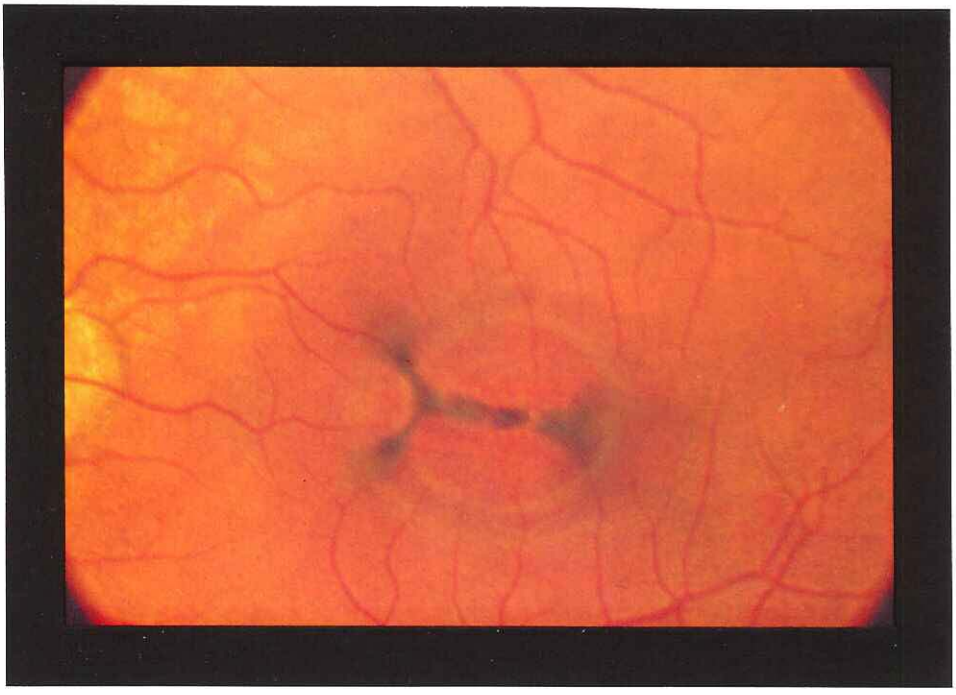
VII "Scrambled-egg"-appearance in vitelliform dystrophy. Around the yellow centre there is atrophic pigment epithelium.



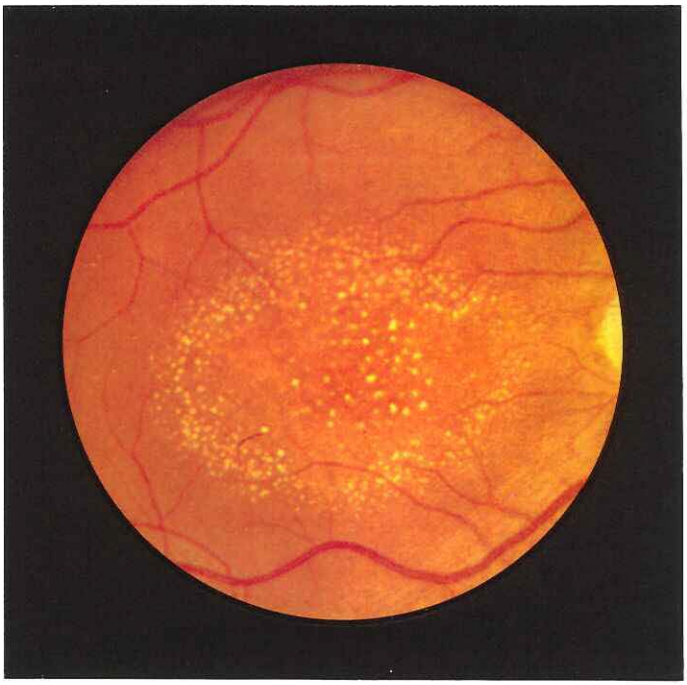
VIII Fundus flavimaculatus, showing the characteristic rather ill-defined pisciform lesions.



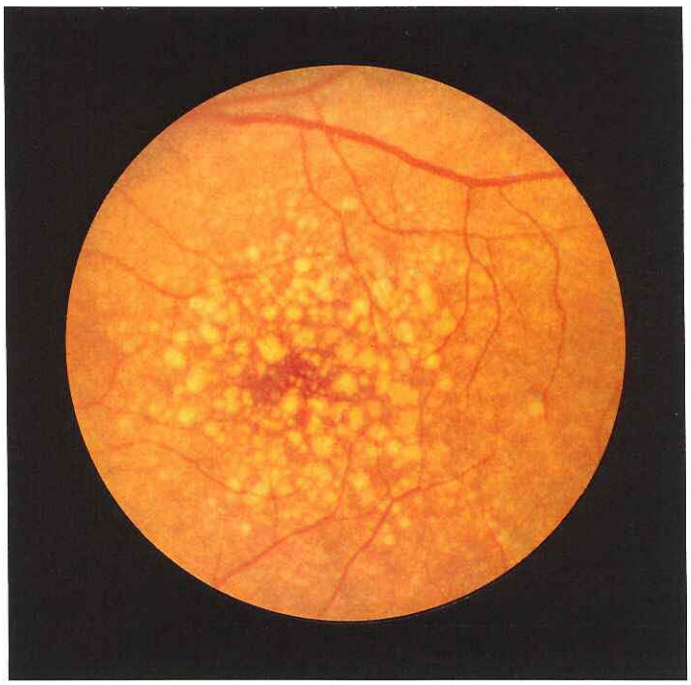
IX Reticular dystrophy of the retinal pigment epithelium (Sjögren).



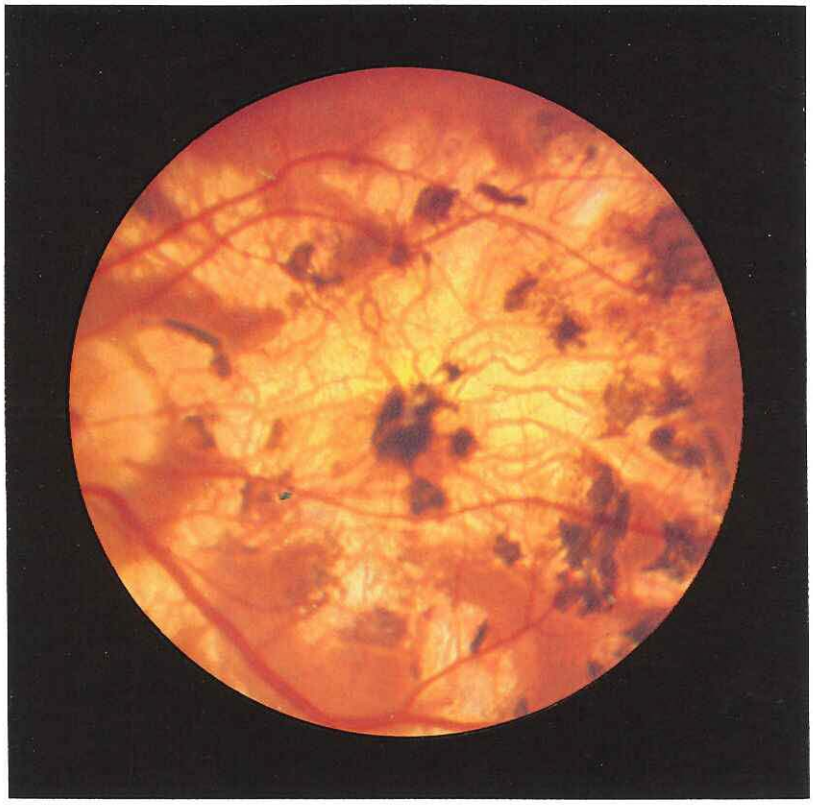
X Butterfly-shaped pigment dystrophy of the fovea.



XI Numerous tiny drusen in dominantly inherited drusen of Bruch's membrane.



XII Dominant drusen of Bruch's membrane in a honeycomb pattern.



XIII Central areolar choroidal dystrophy, showing extensive atrophy of the retinal pigment epithelium and choriocapillaris.

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CURRICULUM VITAE

op verzoek van de Medische Faculteit

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