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CHOROIDEREMIA AND GYRATE ATROPHY OF THE CHOROID AND RETINA

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With 37 figures, 16 photographs and 5 tables

Introduction*

Until recently, choroideremia (progressive tapetochoroidal degeneration; see page 41) and gyrate atrophy of the choroid and retina were regarded as uncommon hereditary ocular affections. Only since 1942 have some publications on choroideremia appeared in the Netherlands, and reports on gyrate atrophy of the choroid and retina have been largely confined to casuistics.

Very little is known as yet about the clinical picture of the early stages of both these affections. Consequently they are frequently confused with each other or with (fundus) anomalies such as choroidal sclerosis and tapetoretinal degeneration.

The object of this study was:

1. To trace as many cases as possible in order to gain an impression of the incidence of choroideremia and gyrate atrophy of the choroid and retina in the Netherlands. In addition, to enlarge our knowledge of the clinical picture of these two conditions, especially in their early stages, by an exhaustive and exact investigation.
2. To make an objective analysis of the genetic aspects of these two clinical entities.

The study was carried out with the support of the Netherlands General Association for Prevention of Blindness which, together with the ophthalmological clinics and many ophthalmologists, co-operated in collecting the material. The genealogical research was done by Ir. T. W. SIERTSEMA, the Association's genealogist.

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PART I

CHOROIDEREMIA

Brief historical review

MAUTHNER was the first (1872) to describe the clinical picture, which he designated "choroideremia" because he interpreted the findings as congenital absence of the choroid. It was later found that the disease is progressive, and it is still dubious whether it can be congenital. SORSBY et al. (1952) consequently referred to "progressive choroidal atrophy", while WAARDENBURG (1958) and PAMEIJER et al. (1960) described the condition as "progressive tapetochoroidal dystrophy". The motives behind these designations will be discussed later (page 40).

MAUTHNER's report was followed by descriptions of a large number of isolated cases, all encountered in males, by such authors as COWGILL (1892), LANDMAN (1906), MARBAIX (1908), SMITH & USHER (1916; cf. RIDDELL 1933–1934), CONNOR (1919), ZORN-SCHUTZBACH (1920–1938), BECKERSHAUS (1926), DIMMER & PILLAT (1927), PARKER & FRALICK (1931), DE SCHWEINITZ (1931), BAHN (1932), BHADURI (1934), WILMER (1934), BENEDICT (1937), WÜRDEMANN (1937), DI MARZIO (1937), FRIEDMAN (1940), MAGDER (1945), MEYRAN (1948) and others.

Familial occurrence of the condition in brothers was described by KÖNIG (1874), BULLAR (1898), THOMPSON-WARDALE (1899–1906), ALEXANDER (1910), WOLF (1930), WERKLE (1931), BEDELL (1937), BENCINI (1938), SORSBY (1939; originally reported as choroidal sclerosis), SCOBEE (1943) and ESTERMAN (1947). A number of these reports were based on anamnestic data.

The confusion with other hereditary affections of the choroid and retina was ended in 1942, when two Dutch ophthalmologists – GOEDBLOED and WAARDENBURG – demonstrated in independent studies that choroideremia is subject to intermediate X-chromosomal transmission. This discovery greatly contributed to a more accurate definition of the place of choroideremia in the group of choroidal and retinal dystrophies. GOEDBLOED reached his conclusion on the basis of personal observations in a family including one patient and two women showing only slight fundus changes, and consequently considered to be carriers of the mutant gene, and also on the basis of an analysis of the pedigree of ZORN-SCHUTZBACH. WAARDENBURG formed his conclusion on the basis of a penetrating analysis of the literature, after having had occasion to re-examine SMITH & USHER's patient in 1939. GOEDBLOED and WAARDENBURG based their postulate upon, among other things, the fact that males show the complete clinical

picture, whereas females show striking but much less pronounced fundus changes which cause no subjective complaints.

Pedigrees published much later have completely confirmed the postulate of intermediate X-chromosomal transmission of choroideremia. A spectacular contribution was made by J. C. and R. J. P. McCULLOCH (1948). They published two pedigrees: a large one covering six generations with over 600 relatives, and a small one covering three generations with 18 relatives. Their two pedigrees include a total of 33 patients and 53 carriers.

LOWE (1951) reported on three generations of a family, with two patients and one carrier, and SPEAR & STEPHENS (1952) on a family with five patients and 13 carriers. SORSBY et al. (1952) described three pedigrees covering three generations; the first pedigree included five patients and eight carriers, the second three patients and eight carriers (including a pair of monozygotic twins), and the third included two patients and five carriers. WESTERLUND (1956) found two families: the first included one patient and four carriers, and the second included two patients and one carrier. FRANÇOIS (1958) mentioned a family including one patient and two carriers. WAARDENBURG discussed (1958) four generations of a family with one patient and three carriers; the ophthalmoscopically verified carriers occurred in three consecutive generations, and the anomaly was not manifested because males were absent. KAVKA (1960) found three patients and seven carriers. PAMEIJER et al. (1960) mentioned two families: one with two patients and four carriers and another with one patient and three carriers.

The family examined by PÖLLOT (1912) and described by him as suffering from "Atypische Chorioretinitis pigmentosa hereditaria" is a typical example of an erroneous diagnosis due to unfamiliarity with the clinical picture. Upon WAARDENBURG's request (1962) the family was re-examined by JAEGER & GRÜTZNER (1962), who confirmed WAARDENBURG's suspicion that the subjects in question were suffering from choroideremia (four generations with four patients and three carriers). JAEGER & GRÜTZNER also published two other pedigrees: one covering seven generations with 15 patients and 32 carriers, and one covering four generations with three patients and two carriers.

Seemingly contradicting the postulate of X-chromosomal transmission were reports by DI MARZIO (1937) and BENCINI (1938) on transmission from father to son. Both reports, however, are open to question (WAARDENBURG, 1942 and 1961). The same applies to the description (SCHUTZBACH, 1938) of an affected male whose father was asymptomatic and whose paternal uncle was a patient (WAARDENBURG, 1942, 1961; FRANCESCHETTI, FRANÇOIS & BABEL, 1963).

SORSBY et al. (1952) pointed out an irregularity in the pedigree described by the MCCULLOCHS (1948), in which a normal man had a carrier daughter, while another normal man had a carrier daughter and an affected son. Both instances proved to be due to consanguineous marriages, the wives of both men being carriers.

SPEAR & STEPHENS (1952) observed a carrier without fundus changes. They mentioned that this carrier's father was reported to have been a patient only anamnestically. The literature also discloses a few cases of choroideremia in females, described by THOMPSON (1899), HUTCHINSON (1900), GRIMSDALE (1917), SHAPIRA & SITNEY (1943) and FORNÉS PERIS (1947); all these cases, however, must be regarded as doubtful (WAARDENBURG, 1961; FRANCESCHETTI, FRANÇOIS & BABEL, 1963).

Clinical picture of the patient

Fundus

On the basis of the fundus findings it is possible to distinguish, broadly, three stages.

Initial stage. In the youngest patient examined – a boy aged 22 months – the MCCULLOCHS (1948) observed "typical brilliant yellow areas associated with groups of pigment granules". There was nothing like a thorough examination of this child; the authors report only a fleeting glance into the fundus. In a 6-year-old boy, the same investigators found that a broad band of choroidal atrophy had already formed, with fine pigment granules in the equator of the fundus.

The fundus changes described by SORSBY et al. (1952) in a patient aged 6½, consisted of some peripheral and peripapillary atrophic areas with more clearly defined choroidal vessels accompanied by fine peripheral pigmentations. In an 18-year-old male, these investigators observed peripheral pigment changes of the pepper-and-salt type, reminiscent of similar changes found in carrier women.

Identical fundus pictures were seen by FRANCESCHETTI, FRANÇOIS & BABEL (1963) in a male aged 42. In view of his age, the changes can hardly be interpreted as an initial stage unless in this man the affection took an exceedingly protracted course.

The *second stage* is characterized by atrophy of the choroidal vessels and the pigment epithelium, progressive from the periphery to the centre.

PAMEIJER & WAARDENBURG (1960) examined the fundus in an 8-year-old patient, both with Thorner's binocular ophthalmoscope in red and red-free light and with the fundus contact glass. They found that this

young patient already showed extensive pigment changes in the periphery of the fundus with, in addition, a fine pigment mottling at the posterior pole. There was no migration of pigment to the anterior layers of the retina, such as would characterize tapetoretinal degeneration, and no typical sclerosis of the choroidal vessels; however, there was a peripapillary ring of choroidal dystrophy.

FRANCESCHETTI, FRANÇOIS & BABEL (1963) maintain that the fundus features in this stage are strongly reminiscent of those found in gyrate atrophy of the choroid and retina. The differential diagnosis between the two conditions will be discussed in detail in the chapter on gyrate atrophy of the choroid and retina (page 85).

Terminal stage. This stage is characterized by the further gradual dissolution of choroidal vessels and pigment epithelium, progressing from the periphery to the centre. The choroidal structure as a rule remains intact longest in the macula until, between the age of 40 and 50, it is no longer discernible there either. The terminal picture is characterized by a yellowish-white fundus (a result of atrophy of the retina and choroid) with brownish discoloration of the macular region and scattered irregular pigment accumulations over the entire fundus (no typical bone trabeculae).

A striking fact is that the aspect of the disc and the retinal vessels is generally described as normal even in advanced stages.

Vision and refraction

Since the macula is not affected until later, vision as a rule remains reasonably good until the age of 40, after which there is gradual deterioration to the point of complete loss of vision.

On the basis of data from the literature, WAARDENBURG (1942, 1961) ventured to conclude that some correlation exists between choroideremia and milder degrees of myopia. The combination of choroideremia with myopia was mentioned by such authors as PÖLLOT (1912; cf. page 3), GOEDBLOED (1942), SCOBEE (1943), MAGDER (1945), ESTERMAN (1947), SPEAR & STEPHENS (1952), WESTERLUND (1956) and PAMEIJER et al. (1960).

MCCULLOCH & MCCULLOCH (1948) held that myopia frequently develops in the course of the disease.

The possibility of other refractions was confirmed by, among others, SORSBY et al. (1952), who in patients in three choroideremia families encountered hypermetropia and emmetropia as well as myopia.

Field of vision

Various forms of visual field defects have been described. Some authors found an annular scotoma (BULLAR, 1898; ALEXANDER, 1910; PÖLLOT,

1912 (page 3); SMITH & USHER, 1916; WERKLE 1931; SCHUTZBACH, 1938; SCOBEE, 1943; SAEBÖ, 1948; J. C. & R. J. P. MCCULLOCH, 1948; LOWE, 1951; SORSBY et al., 1952; FRANCESCHETTI & DIETERLE, 1957; FRANCESCHETTI, FRANÇOIS & BABEL, 1963); others found a concentric limitation of the visual field (MAUTHNER, 1872; KÖNIG,1874; THOMPSON-WARDALE, 1899–1906; LANDMAN, 1906; MARBAIX, 1908; CONNOR, 1909; ZORN, 1920; BECKERSHAUS, 1926; WOLF, 1930; PARKER & FRALICK, 1931; DE SCHWEINITZ, 1931; BHADURI, 1934; BEDELL, 1937; BENCINI, 1938; FRIEDMAN, 1940; GOEDBLOED, 1942; MAGDER, 1945; ESTERMAN, 1947; SPEAR & STEPHENS, 1952; BOUNDS & JOHNSTON, 1955; WESTERLUND, 1956; JACOBSON & STEPHENS, 1962).

PAMEIJER et al. (1960) found reduced retinal sensitivity at the equator and an enlarged blind spot, whereas central sensitivity was relatively intact. These authors were unable to demonstrate an annular scotoma.

Freakishly shaped visual field defects were described by SORSBY et al. (1952) and JAEGER & GRÜTZNER (1962). Only a small central and a narrow peripheral visual field remnant remains in the terminal stage (JAEGER & GRÜTZNER, 1962).

Dark adaptation

Night blindness as a rule develops at an early age. In patients described by BEDELL (1937), SCOBEE (1943), MAGDER (1945), SAEBÖ (1948) and SORSBY et al. (1952) the night blindness did not become manifest until after the age of 20.

The scotopic and photopic thresholds of the adaptation curve are generally too high (PAMEIJER et al., 1960; FRANCESCHETTI, FRANÇOIS & BABEL, 1963). In the terminal stage, the adaptation curve can usually no longer be recorded. A normal dark adaptation curve was mentioned by JAEGER & GRÜTZNER (1962) in a 31-year-old patient with fundus features closely resembling those of a carrier. JACOBSON & STEPHENS (1962) found a sufficiently adapted cone system only in two patients with choroidoretinal degeneration (designation probably referring to choroideremia).

Colour vision

PAMEIJER et al. (1960) demonstrated a protan defect by means of the Farnsworth dichotomous test (D-15 panel) in one patient in whom examination with the Nagel anomaloscope revealed no changes. JAEGER & GRÜTZNER (1962), studying the sensitivity to differences in colour, found disturbances in the blue-green part of the spectrum even in the early stages. With progressive degeneration of the retina and choroid, the blue-

green sensitivity continued to diminish until finally, as a result of reduced vision and loss of visual field, colours were no longer distinguished. FRANCESCHETTI, FRANÇOIS & BABEL (1963) and VERRIEST (1964) demonstrated dyschromatopsia in the blue-yellow axis in two patients.

Electroretinography

In the majority of cases in which an ERG examination was mentioned, the choroideremia had reached an advanced stage. In none of these cases was the ERG recordable (BOUNDS & JOHNSTON (1955), in two patients; FRANCESCHETTI & DIETERLE (1957), in one patient; STRAUB (1961), in three patients; JACOBSON & STEPHENS (1962), in one patient; FRANCESCHETTI, FRANÇOIS & BABEL (1963), in three patients).

Two juvenile patients in the material studied by PAMEIJER et al. (1960) showed a virtually undisturbed photopic response, both in the single-flash and in the flicker ERG, whereas the scotopic activity was absent. In one patient with a far advanced stage of choroideremia, only selective amplification of the flicker ERG made it possible to obtain a rudimentary photopic response.

JACOBSON & STEPHENS (1962) saw that in young patients the ERG became negative with an enlarged a-wave, probably as a result of the disappearance of a compensatory, chiefly positive, scotopic component (b-wave).

Anterior segment of the eye

ESTERMAN (1947) mentioned transparency of the irides on transillumination, as in albinotic eyes. PAMEIJER et al. (1960) emphasized that there was no transparency in their cases. The literature makes no mention of this aspect.

Opacities of the lens were described by DE SCHWEINITZ (1931) and WERKLE (1931). In DE SCHWEINITZ's patient these had finally led to cataract extraction. It is not clear, however, whether a complicated cataract existed in this case. This form of cataract, which frequently occurs in gyrate atrophy of the choroid and retina, is no part of the clinical picture of choroideremia. Opacities of the lens existed in a few cases in the MCCULLOCHS' material (1948).

MAUTHNER (1872) found floating punctiform and fibrillar opacities in the vitreous body. In two patients of the families described by ZORN-SCHUTZBACH (1920–1938), fine greyish-white cholesterol-like crystals were found in the vitreous body. SCOBEE (1943) found irregular bundles of fibres amidst optically empty spaces in the anterior part of the vitreous body;

numerous fine brown globules, interpreted as pigment, were localized in the fibres and slowly migrated with the ocular movements. The features were reminiscent of asteroid hyalitis. Immediately behind the lens he saw vitreous strands, vertically suspended and executing undulating movements, with a striated appearance. The vitreous body in the patients described by J. C. &. R. J. P. McCULLOCH (1948) sometimes showed a few fibrillar changes.

Clinical picture of the carrier

Even before the discovery of the intermediate X-chromosomal mode of transmission, several authors (PÖLLOT, 1912, cf. page 3; SMITH & USHER, 1916; ZORN, 1920; WERKLE, 1931; SCHUTZBACH, 1938; BENCINI, 1938; RIDDELL, 1939) had observed fundus changes in female relatives of patients with choroideremia. These changes were as a rule described as pigment anomalies of the pepper-and-salt type, with or without associated choroidal atrophy. They were interpreted as tapetoretinal degeneration (SMITH & USHER (1916), and others).

Fundus

The fundus changes in choroideremia carriers were described at length and in exact detail by WAARDENBURG (1958) and PAMEIJER et al. (1960). These authors examined the fundus with Thorner's binocular ophthalmoscope, both in red and in red-free light. In some cases the fovea showed a delicate pigment mottling, but this was less pronounced than that found in patients. At the periphery the changes were more gross than those at the posterior pole. It is emphasized that the pigment changes were localized deep in the retina, at the level of the tapetum nigrum. The other layers of the retina were free of pigment. The ophthalmoscopic features, therefore, differed from those of tapetoretinal degeneration. Some choroidal vessels were lacking; in others, no blood column was seen. These changes were much less pronounced than those in patients. In one carrier the macular yellow was diminished. The disc and retinal vessels were normal.

The McCULLOCHS (1948) described an unusual combination of pigmentations and depigmentations, chiefly at the equator and the periphery of the fundus. The pigment granules were of irregular shape and varied in size. In contrast to WAARDENBURG's and PAMEIJER's findings, the pigmentations in the McCULLOCHS' patients were localized superficially in the retina, in front of or behind the retinal vessels. This, however, was not established with the fundus stereoscope.

FRANCESCHETTI, FRANÇOIS & BABEL (1963) also found small white foci in the macular region, which did not influence vision.

In a 64-year-old carrier JAEGER & GRÜTZNER (1962) encountered an unusually pronounced choroidal sclerosis which, however, had produced no functional disturbances.

The fundus changes in carriers are regarded as probably connatal and as stationary. No relation is believed to exist between the intensity of the fundus changes and the carrier's age; minor changes have been found in older carriers, and severe pigmental disorders in younger ones (MCCULLOCH & MCCULLOCH, 1948; SORSBY et al., 1952).

The youngest carrier examined was a girl aged 4½ months, in whom the MCCULLOCHS' (1948) believed they could see a few anomalous pigmentations in the retinal periphery. In a girl aged 3 years, these authors observed pigmental changes with greater certainty. SORSBY et al. (1952) also observed pigmental changes in a girl not older than 3½ years.

Vision and refraction

Vision is generally described as good. No preponderance of myopia has been found.

Field of vision

Apart from a concentric limitation (ZORN-SCHUTZBACH, 1920–1938; LOWE, 1951) and slight enlargement of the blind spot (LOWE, 1951; PAMEIJER et al., 1960), no visual field defects are mentioned.

Dark adaptation

PÖLLOT (1912, cf. page 3), ZORN-SCHUTZBACH (1920–1938) and WERKLE (1931) found hemeralopia in one carrier.

SORSBY et al. (1952) mentioned two cases with a dubiously raised dark adaptation curve (measured with the Della-Casa and with the Crookes adaptometer). PAMEIJER et al. (1960) observed a slightly raised sensitivity threshold of the scotopic retinal system in four carriers. FRANCESCHETTI, FRANÇOIS & BABEL (1963) observed a subnormal dark adaptation curve in a 75-year-old carrier. In other cases the dark adaptation curve showed a normal course.

Colour vision

Only JAEGER & GRÜTZNER (1962) found disturbances in the blue-green range of the spectrum when examining the sensitivity of carriers to differences in colour hues. These disturbances were so slight as to leave the carriers unaware of them.

Electroretinography

Normal ERG findings were reported by BOUNDS & JOHNSTON (1955, in three carriers), VON BURSTIN (1958, in two carriers), FRANÇOIS & DE ROUCK (1958, in two carriers), JACOBSON & STEPHENS (1962), FRANCESCHETTI, FRANÇOIS & BABEL (1963, in one carrier). PAMEIJER et al. (1960) observed a slight dysfunction of the scotopic retinal system in a few carriers, whose photopic responses were normal. FRANCESCHETTI, FRANÇOIS & BABEL (1963) found a subnormal ERG in the above-mentioned 75-year-old carrier. JACOBSON & STEPHENS (1962) mentioned that one carrier showed no increase of the scotopic b-wave during dark adaptation.

Electro-oculography

FRANCESCHETTI, FRANÇOIS & BABEL (1963) saw a normal EOG in one carrier.

Association of choroideremia with other affections

BECKERSHAUS (1926) described the familial occurrence of choroideremia and tapetoretinal degeneration, but gave no details about the patients with tapetoretinal degeneration. WAARDENBURG (1942) presumed that a coincidence was involved and that dominant tapetoretinal degeneration was the result of a new mutation.

SORSBY et al. (1952) found central choroidal sclerosis in two brothers whose mother showed no fundus changes. They remarked that "there is nothing to suggest choroideremia in the sons, the elder of whom also shows lens changes".

VALK & BINKHORST (1956) described the association of choroideremia with familial dwarfism, myopia, posterior polar cataract and zonular cataract. The nature of the fundus changes and the incompleteness of the family study throw considerable doubt on the diagnosis of choroideremia in this case.

If choroideremia constitutes part of the syndrome found in two brothers by VAN DEN BOSCH (1957, 1959), then one would be inclined to think of a more gross chromosomal anomaly, because the family in question in addition showed the following symptoms: mental deficiency, nystagmus, high myopia, verruciform-like acrokeratosis, skeletal and dental deformations, general retardation in growth, no local sweat reaction on injection of 0.1 ml of a solution of 1% acetylcholine, and according to WAARDENBURG (1961) also microblepharia and a mild degree of blepharophimosis.

Pathology

Only four eyeballs have been submitted to pathological examination; they were obtained from two elderly men in whom the disease had reached a far advanced stage (J. C. McCULLOCH, 1950). One of the four eyes showed glaucoma in addition.

The pigment epithelium of the iris and the ciliary body was generally intact. At the ora serrata the retina showed some cystic degeneration. The pigment epithelium and the choroid were present, but the choroidal vessels – particularly those at the periphery – were for the most part thickened and hyalinized; the inner capillary network seemed to be relatively normal. Towards the posterior pole there was increasing sclerosis with marked stenosis of the lumina of the choroidal vessels, and progressive degeneration of the choroid and the pigment epithelium. The latter degenerated to a pigmented line. At the equator the choroid and pigment epithelium were completely absent; at this site the retina rested directly upon the sclera. Retinal layers present were the bipolar cellular layer, the inner molecular layer, an incomplete ganglion cell layer, the layer of nerve fibres and the internal limiting membrane. At the posterior pole, remnants of choroid and pigment epithelium were found at the level of the macula. At several sites the proliferation of pigment epithelium had produced accumulations on the outside of the bipolar cellular layer. The ciliary arteries showed no discernible changes.

The pathological findings corresponded with the ophthalmoscopic findings. According to McCULLOCH, the choroid was the primary localization of the affection (page 40). FRANCESCHETTI, FRANÇOIS & BABEL (1963) had occasion to re-examine these sections and, although less positive in their conclusion, also suspected that the primary sites of the affection were to be found in the choroid.

Re-examination of a section from a case described as choroideremia by FORNÉS PERIS (1947) led FRANCESCHETTI, FRANÇOIS & BABEL (1963) to the conclusion that the diagnosis had been erroneous.

Theories on the pathogenesis

As has been pointed out, MAUTHNER (1872) and later KÖNIG (1874) believed they were dealing with congenital aplasia of the choroid. This view was maintained for some considerable time. In 1938, DUKE ELDER still classified choroideremia among the congenital, stationary developmental anomalies. In his "System of Ophthalmology" (1964), he again classified the condition under the heading of congenital anomalies, but this time he also mentioned progressivity. MANN (1957) also believed that

the condition is based on a congenital developmental anomaly; she believed it to be caused by "failure of the ciliary arteries to bud out from the ophthalmic artery or a failure of the optic cup to produce pigment, with a consequent absence of capillary outgrowth even if the arteries began to develop".

The possible existence of an abiotrophic process was considered even in the past (LEBER, 1916; and others). It was believed, however, that the disease belonged to the group of retinal pigment dystrophies (BECKERSHAUS, 1926). VERHOEFF (1942) erroneously presumed that the supposed features of choroideremia frequently (as probably in BEDELL's cases) conceal a retinitis pigmentosa with extensive glial proliferations of the retina, causing the choroid to become invisible.

According to CUTLER (1895), SMITH & USHER (1916), BÖHM (1919), WERKLE (1931) and others, choroideremia represents a late stage of gyrate atrophy of the choroid and retina. According to current views, and on the basis of current knowledge regarding the genetic behaviour of the condition, choroideremia must be regarded as a clinical entity of a progressive character, to be included in the group of the abiotrophic processes; it has not yet been established whether its initial symptoms can be present at birth.

It has been pointed out that SORSBY et al. (1952) suggested the designation "progressive choroidal atrophy". On the other hand, WAARDENBURG (1958) and PAMEIJER et al. (1960) considered the fact that the pigment epithelium of the retina (tapetum nigrum) is also affected – and even in an early stage – an essential feature of this disease. They called it "progressive tapetochoroidal dystrophy", chiefly in view of the fact that in carriers the changes in the tapetum nigrum become so prominent that the choroidal changes are negligible in comparison.

PRESENT INVESTIGATION OF CHOROIDEREMIA

Material

An attempt was made to ensure the fullest possible coverage of cases of choroideremia occurring in the Netherlands.

a. Reports published earlier in the Netherlands furnished three families, namely:

   Family B: one patient and four carriers; WAARDENBURG & HARTOGS (1958); pedigree E in the present investigation.

   Family V: two patients and three carriers; PAMEIJER et al. (1960); pedigree G in the present investigation.

Family G: one patient and three carriers; PAMEIJER et al. (1960); pedigree B in the present investigation.

The fourth family described earlier (GOEDBLOED, 1942) could no longer be traced.

b. An inquiry among ophthalmological clinics and ophthalmologists yielded seven probands: six patients (A″VIII, 58; A‴VI, 20; A⁗VII, 59; F III, 6; H III, 7, and one patient who dropped out due to insufficient co-operation on the part of the family) and one carrier (D IV, 24).

c. Three reports filed at ophthalmological clinics under a different diagnosis were identified as referring to two choroideremia patients and one carrier, and could be added to the material as probands (A′VIII, 11; J III, 13 and C III, 5).

Taking as starting-points the nine probands mentioned under b) and c), nine pedigrees were charted, and the three known pedigrees mentioned under a) were further elaborated.

The twelve pedigrees thus obtained were verified on the basis of civil registry data. There followed an exhaustive genealogical investigation of all pedigrees, both in the male and in the female line. This investigation made it possible to combine four pedigrees into a single large (nine-generation) pedigree (pedigrees A′, A″, A‴ and A⁗), thus reducing the total number of pedigrees to nine. These pedigrees proved to include in part anamnestic 52 patients and 96 carriers, of whom 45 patients and 61 carriers were visited in their homes over a period of about two years. In addition, the largest possible number of relatives were included in this part of the investigation; the total number of individuals visited was 314.

Patients and carriers alike were requested to report to an ophthalmological clinic for further examination. If this was impossible, the individuals were examined ophthalmologically in their homes as extensively as possible.

Methods

The ophthalmological examination to which every individual was submitted in the clinic, included:

History, with special reference to the onset of symptoms of hemeralopia, visual field defects, diminished vision, disturbed colour vision, etc.

Fundus examination. The fundus contact glass was used in examining 10 patients. To record fundus changes, fundus photographs were made of the majority of patients and carriers.