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WAGNER'S SYNDROME

(DEGENERATIO HYALOIDEO-RETINALIS HEREDITARIA)

by

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Wagner was the first to describe degeneratio hyaloideo-retinalis hereditaria; he observed this hitherto unknown disease in 16 cases in 3 successive generations (WAGNER 1938). Subsequently 10 more cases were observed in the same family (BÖHRINGER, DIETERLE & LANDOLT, 1960). The concept of vitreoretinal degeneration was introduced only after the publication of Wagner's paper (RICCI 1960). This term includes hereditary changes of the vitreous, involving in particular the outer limiting membrane of the vitreous body and retina, accompanied by retinal changes. Ricci distinguishes 3 forms of vitreoretinal degeneration which differ both in their symptomatology and idiotypical heredity:

a. the idiopathic retinoschisis of young men, with recessive X-chromosomal heredity. (MANN & MACRAE 1938, 1954; JULER 1947, 1951; KLEINERT 1953; JAGER 1953 a,b; GIESER & FALLS 1961; DEUTMAN 1971).
b. Degeneratio hyaloideo-retinalis hereditaria with dominant autosomal heredity (WAGNER 1938).
c. Recessive hyaloideo-tapeto-retinal degeneration (FAVRE 1958; BLANCK 1973; STANKOVIC 1973; FRANÇOIS 1974).

Our experience with cases of Wagner's syndrome is based on two families, already referred to by JANSEN (1962, 1966) and PINCKERS (1970). The number of cases is well over forty, sufficient to give some idea of the course of this syndrome. The purpose of this paper is to give a summary of the findings in Wagner's syndrome, supplementing JANSEN'S thesis (1966).

The symptomatology of Wagner's syndrome is very varied; we will sum it up by describing the case of a hypothetical outpatient as seen by an oculist.

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The patient complains of loss of visual acuity and floating spots. It appears that retinal disease and cataract are a familial trouble, transmitted from father to son (Fig. 1: V-1 to VI-2), from father to daughter (V-1 to VI-1), from mother to daughter (VI-1 to VII-1) and from mother to son (V-8 to VI-25, i.e. of domi-

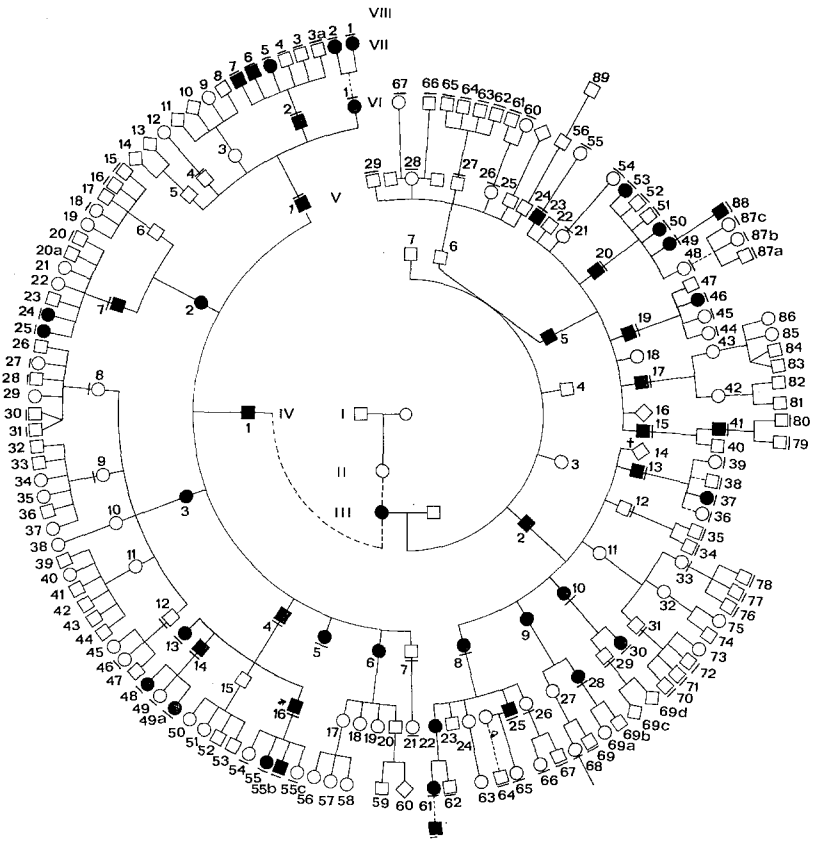

Fig. 1
Pedigree of Wagner's syndrome (cfr. JANSEN 1966 Family B).

nant autosomal nature. Important evidence for dominance is the transmission from father to son (V-1 via VI-2 to VII-7) and also absence of symptoms in descendants of individuals not affected by the disease (V-27 to VI-62-65 incl.).

a. Refraction

Strabismus divergens is often evident, commonly associated with often serious myopia. The fundus also shows changes corresponding to serious myopia. But as these fundus changes are also inherent to Wagner's syndrome, it is particularly difficult to ascertain how far these changes should be considered as due to pathological myopia. We shall revert to this point later. Refraction measurements usually indicate myopia in conjunction with astigmatism.

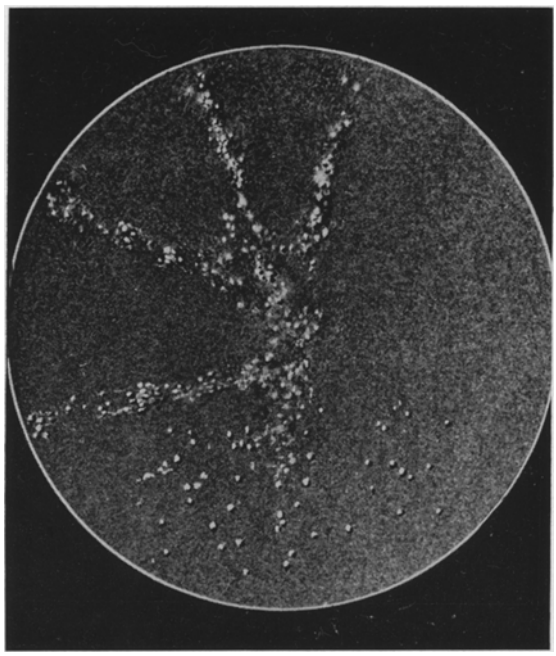

Fig. 2
Wagner's syndrome: artist's drawing of punctated stellate posterior subcapsular cataract in a 24 year old female.

b. Slit lamp

The media show characteristic changes. Clouding of the lens is observed in practically all cases. Punctated clouding of the posterior cortex of the lens can be observed already in children of 10 years, the arrangement of the dots being sometimes stellate. The clouding increases with the patient's age. The

adult develops a complicated cataract, while the myopia moreover favours the formation of a nuclear caratact. It is thus no coincidence that the family history refers to cararact as cause of poor vision.

Changes in the vitreous are important signs in the clinical picture .Slit lamp examination through a dilated pupil will show behind the lens an optically empty space; the first impression is that structures behind the lens are absent, but careful inspection discloses in this optically empty space a limited number of filaments with fine membranous fragments.

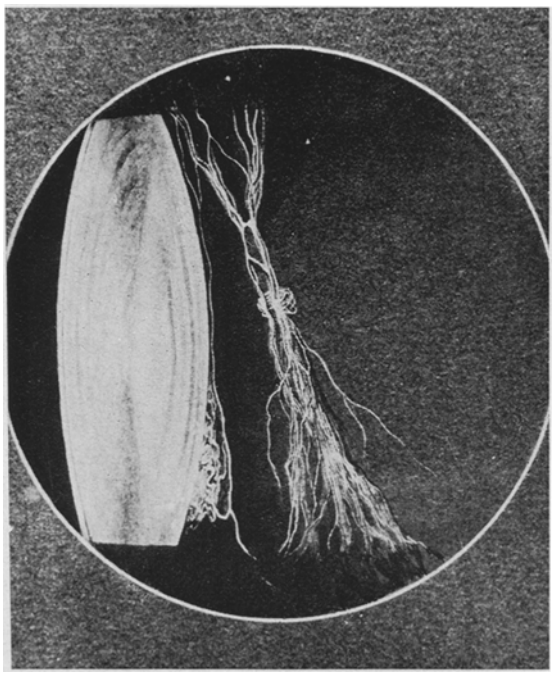

Fig. 3

Wagner's syndrome: artist's drawing of lens and vitreous in a 24 year old female. The vitreous is an optically empty space with some floating filaments.

c. Fundus inspection

Changes in the vitreous humour are an indication to look for an almost pathognomic phenomenon in the retinal equator: in this region will be seen a thin, shiny greyish-white line on or in front of the retina, often forming a practically continuous circle. The line may be wide enough to be called a band. Further inspection discloses the myopic changes in the posterior pole, already referred to; apart from a conus temporalis and slight to severe atrophy of the chorio-

capillaris and choroid the nasal papilla margin often has no sharp delimitation because of an inverse vascular emersion.

In the retinal periphery pigment accumulations, depigmentations and local choroidal atrophy are rarely absent; at an early stage these phenomena are also observed in the equatorial region. Pigmentations may form solitary spots, hardly ever in the shape of bone corpuscles, but often close together looking like a broad band of pigment. Depigmentations may be associated with pigment accumulations; there may be sharply defined atrophic patches not unlike chorioretinitis scars, called 'Pflastersteine' by Heinzen.

Retinal ruptures should be looked for in the equatorial region, where signs of spontaneous cicatrisation may also be present.

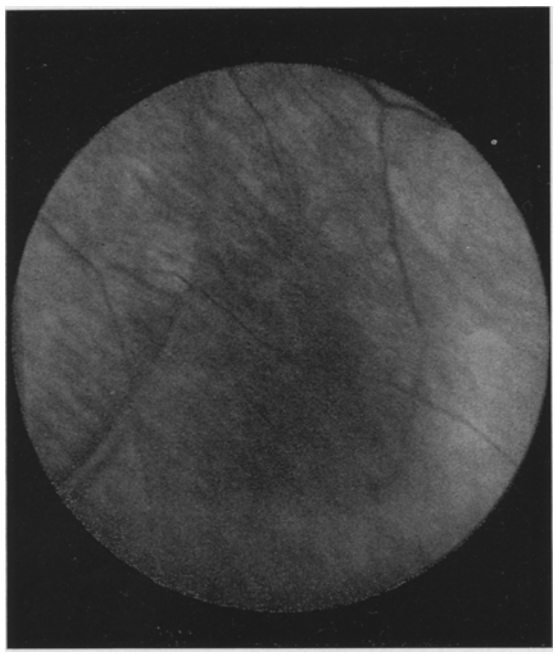

Fig. 4
Wagner's syndrome: preretinal greyish-white line.

d. Intraocular Pressure

In more than half of our Wagner patients the intraocular pressure was 22 mm Hg or more (JANSEN 1966). Observations with the Schioetz tonometer vary with scleral rigidity, hence pressure measurements by one or other form of applanation tonometry are necessary.

a. Electroretinography (ERG)

For all eyes tested (n = 34) the result was subnormal (JANSEN 1966). There was no selective involvement of the cone system or rod system (BÖHRINGER, DIETERLE, LANDOLT 1960; JANSEN 1966). Subsequently we studied another 16 eyes; only twice (in one patient) was the ERG normal. Altogether we examined 50 eyes by ERG. In three eyes the rod function was diminished with normal cone function, which indicates that the primary receptor lesion is in the region where the first ophthalmoscopic changes are observed. i.e. the equatorial region. We found no indication that the a-wave decreased before the b-wave.

b. Dark adaptation measurements by the Goldmann-Weekers method

WAGNER (1938) obtained a dark adaptation curve varying between practically normal and more or less disturbed. BÖHRINGER, DIETERLE & LANDOLT (1960) observed in the same family later a 'practically normal' dark adaptation curve. JANSEN (1966) considered that dark adaptation was generally not disturbed, but

Fig. 5
Wagner's syndrome: artist's drawing of the characteristic shiny line found in all our cases; sometimes this line only is recognized by careful examination.

cases of advanced retinal atrophy associated with considerable restriction of the visual field show some slight disturbance.

c. Electrooculography (EOG)

The EOG can be disturbed even in the young patients (PINCKERS 1970). So far 39 eyes have been examined: The Lp/Dt ratio was normal in 15 cases, disturbed in 24. Evaluation by the A-criterion (PINCKERS, THIJSSEN 1969) resulted in only 8 eyes being normal; 2 patients with normal EOG were over 15 years old. Our tests did not show clearly whether the EOG is disturbed before the ERG, because we observed a lower A-value in only one patient when the ERG was normal.

d. Colour vision

Colour vision is normal or slightly disturbed without distinct axial direction. If in cases of a non-detached retina an acquired blue-yellow defect occurs, this will generally be due to the simultaneous presence of nuclear cataract (PINCKERS 1970).

e. Visual fields

Even in the absence of retinal detachment we may expect extensive visual field defects, always associated with severe retinal and choroidal atrophic changes, and often also with glaucoma (JANSEN 1966). In some cases the visual field changes are very much like those observed in dystrophia retinae pigmentosa.

f. Ultrasonography

TABLE

Ultrasonographic measurements of longitudinal axis in some Wagner syndrome eyes.

Refraction	Corneal power (dioptres)	Cornea-posterior lens surface	posterior lens surface-retina	total length
$+ 3.25^{cyl} - 1.0$ at 20°	45.00 × 43.26	7.6 mm	15.3 mm	22.9 mm
$+ 2.00^{cyl} + 0.5$ at 180°	44.00 × 44.75	7.0 mm	14.0 mm	21.0 mm
+ 1.50	44.00 × 44.50	7.5 mm	14.0 mm	21.5 mm
$+ 1.25^{cyl} - 1.25$ at 150°	44.29 × 43.55	7.6 mm	14.8 mm	22.4 mm
$- 1.00^{cyl} - 1.5$ at 180°	45.25 × 45.75	7.8 mm	13.3 mm	21.1 mm
$- 5.00^{cyl} - 1.0$ at 175°	44.50 × 45.75	7.5 mm	16.5 mm	24.0 mm
$- 5.50^{cyl} - 0.5$ at 180°	44.50 × 46.00	7.0 mm	17.0 mm	24.0 mm
$- 7.50^{cyl} - 2.0$ at 140°	43.00 × 44.00	7.5 mm	18.0 mm	25.5 mm

Although the number of eyes so measured is still small, the findings indicate enlargement of the posterior ocular segment concurrent with increasing myopia. It thus seems that the axial length of the eye increases in accordance with the findings in myopia (FRANÇOIS & GOES 1973).

g. Pathological anatomy

The first anatomo-histological examination was applied to a Wagner patient (1941). The pre-retinal membrane is covered with a monolayer of cells having partly stretched nuclei; where the membrane is attached to the retina, the latter shows thickening, pigment proliferation and deficiency of distinct separate layers, i.e. retinal atrophy. There are no signs of inflammation. Perivascular accumulations of pigment and absence of sensory epithelium must be considered as secondary changes (LANDOLT 1958). ALEXANDER & SHEA (1965) observed considerable changes both in choroidal and retinal vessels.

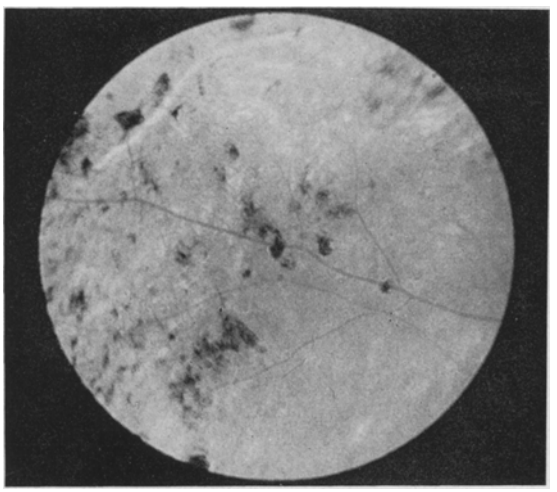

Fig. 6
Wagner's syndrome: peripheral pigment accumulations, depigmentations and local choroidal atrophy.

D. FURTHER STUDIES

The families described by JANSEN (1962, 1966) have been further examined (internal-neurological tests, EEG, chromosome pattern, urine and blood), but no striking or regularly occurring changes were observed.

As subsequently two families were described with a striking physiognomy,

palatoschisis and autosomal dominant hereditary vitreoretinal degeneration (FRANDSEN 1966, FALGER et al. 1970) we looked for similar phenomena in several other cases but were unable to find any. This may mean that either these phenomena are not inherent in Wagner's syndrome or that Frandsen and Falger described a syndrome not identical with Wagner's. The latter seems more likely because in a discussion with Falger, Jansen pointed out that the most important symptoms of Wagner's syndrome were absent in Falger's patients, i.e. these patients were not cases of Wagner's syndrome according to Jansen. Considering Frandsen's description, at least two of the four cases did not show the pathognomic white line; here also the diagnosis Wagner's syndrome appears to be doubtful. Possibly the cases described by Frandsen and Falger represent a transition to the syndrome of Pierre Robin, as SMITH et al. (1960) described cases with glaucoma, retinal detachment, posterior subcapsular cataract and severe myopia. The findings by KNOBLOCH & LAYER (1972) also point in this direction.

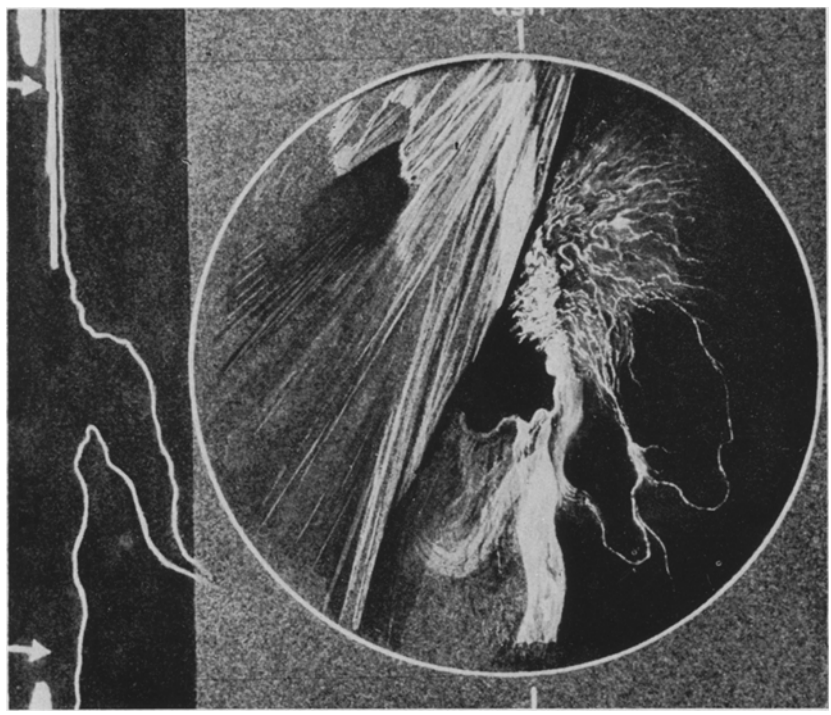

Fig. 7

Wagner's syndrome: artist's drawing of vitreous after intracapsular cataract extraction in a 49 year old male.

E. COMPLICATIONS AND TREATMENT

As already mentioned, the most common complications are: strabismus, cataract, glaucoma and retinal detachment.

a. Strabismus

Strabismus divergens is due to underdevelopment or breakdown of the binocular function owing to severe fundus changes; strabismus divergens is not uncommon in myopia. It is thus not surprising that because of multiple organic changes 'amblyopia treatment' often proves quite ineffective.

b. Cataract

As stated, cataract is a common feature, so a Wagner patient will be at a relatively early age likely to attract attention with a view to its extraction. As glaucoma may be present and the vitreous humour is degenerative, cataract extraction becomes a delicate operation. Possible complications are (JANSEN 1966): loss of vitreous humour, expulsive haemorrhage, post-operative chemosis, shallow anterior chamber and secondary glaucoma.

c. Glaucoma

This can also become manifest at an early age; as so far we have found no difference between glaucoma in Wagner's syndrome and primary glaucoma simplex, we treated all cases as glaucoma simplex. The possible presence of watery vitreous humor must be allowed for in any filtering operation.

d. Retinal detachment

This is the most serious complication for the patient. Operative results are generally unfavourable. It is known that prophylactic treatment of solitary ruptures adjoining a contiguous retina, by coagulation therapy (diathermy or cryo-, xenon, or laser coagulation) is preferable to an expectant attitude. Many defects cicatrise spontaneously, but one that fails to do so poses a difficult therapeutic problem. HIROSE et al. (1973) advise prophylactic treatment before cataract develops; we have already pointed out that Wagner syndrome cases develop a troublesome cataract at a relatively early age.

F. DIFFERENTIAL DIAGNOSIS

Wagner's syndrome is characterized by an extensive symptomatology, including several non-specific symptoms. There is a risk of missing the true diagnosis owing to this polymorphy, (GILLESPIE & GOVELLI 1963). Even at present in many

cases the first diagnosis is wrong. Certain features (cataract, myopia, detachment of the retina) are so prominent that phenomena like the white equatorial line are not sufficiently considered. On the other hand, there is too much inclination to diagnose a dominant vitreo-retinal degeneration associated with a non-ophthalmic phenomenon as a case of Wagner's syndrome (FRANDSEN 1965, FALGER 1970), whereas the symptomatology of this disease points more to a systematic disease with transition to Pierre Robin's syndrome (SMITH et al. 1960, KNOBLOCH et al. 1972). Classification becomes still more difficult when we consider that Pierre Robin's syndrome is not a true syndrome, but that the combination palatoschisis, micrognathia and glossoptosis is a non-specific symptom complex observed in several diseases (COHEN 1973). For the present, Wagner's syndrome should be considered as a disease with exclusively ophthalmic symptoms, although transition to pluri-malformation syndromes must also be borne in mind. For example, in a family pedigree by DELANEY et al. (1963), palatoschisis is described in association with vitreous humour degeneration and detachment of the retina; there are cases of detachment with palatoschisis and cases of palatoschisis without detachment. The pedigree gives no indication as to whether palatoschisis and detachment are symptoms of a pluri-malformation syndrome with variable manifestation rather than an accidental meeting of two phenomena in one family.

As regards the vitreous humour abnormalities, we must differentiate between myopic and senile vitreous degeneration and the degenerative structural changes in primary detachment of the retina and tapetoretinal degenerations as well as differentiation of the recessive X-linked juvenile retinoschisis and vitreo-retinal degeneration of Goldmann-Favre. The typical equatorial circular line structure is hardly ever seen in such cases. If in some individual case diagnosis is difficult, a study of the family will provide information as to the hereditary process.

G. MYOPIA IN WAGNER'S SYNDROME

In the discussion on refraction (B, a) it has been already suggested that it is difficult to know how far myopia and thus the fundus changes resembling pathological myopia are inherent in Wagner's syndrome. In an earlier paper (PINCKERS 1970) Wagner's syndrome cases and cases with severe myopia were tested by EOG and for colour vision. The following conclusions were arrived at:

a. The EOG is usually disturbed (75%) in cases of Wagner's syndrome. In severe myopia the EOG is sometimes supranormal, unless extensive ophthalmoscopically visible lesions are present (FRANÇOIS, VERRIEST, DE ROUCK 1957).

b. Colour vision is often disturbed (50%), although only a distinct axis direction is present in the form of a blue-yellow defect, if associated with a nuclear cataract. In myopia colour vision (100 Hue) is within the age limit.

Figure 8 shows the refraction of all the family members examined, viz: refraction of Wagner syndrome cases (n = 70) and refraction of family members not being Wagner syndrome cases (n = 141). It will be seen that the refraction distribution of the Wagner syndrome cases differs essentially from that of the members without the Wagner syndrome. Refraction plotted against age (Fig. 9) does not give the impression that the older patients show maximum myopia; in other words, in the Wagner syndrome cases myopia is practically stationary. Nevertheless vision decreases with increasing age.

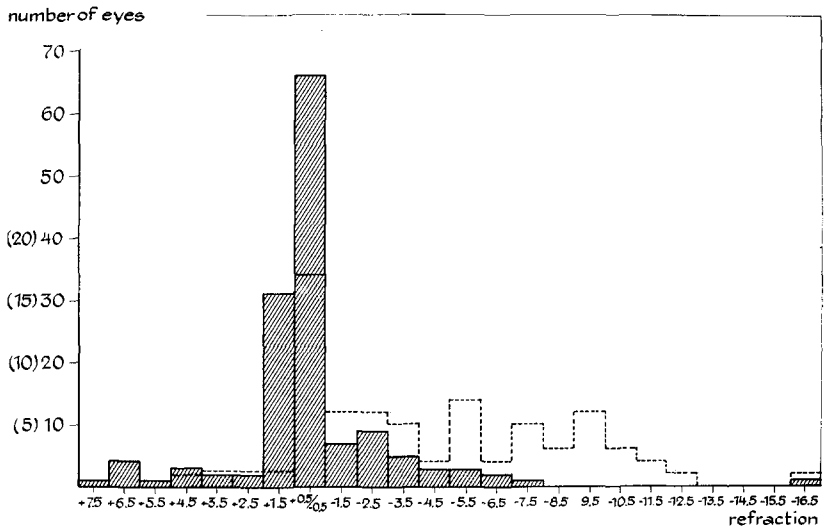

Fig. 8

Refraction of Wagner's syndrome cases (n = 70, dotted lines, number of eyes indicated between parentheses) and refraction of not affected family members (n = 141, hatched groups, no parentheses).

ALEXANDER & SHEA (1965) do not consider the Wagner syndrome to be a variant of severe myopia because neither Wagner's cases nor their own cases had high myopia. But the figures 8 and 9 show that a high myopia (over 6 dioptres) is no rarity in our cases, so this argument does not hold good. We are convinced that the myopia problem in Wagner's syndrome is so complex that it cannot be solved either statistically or by present test techniques. The table seems to

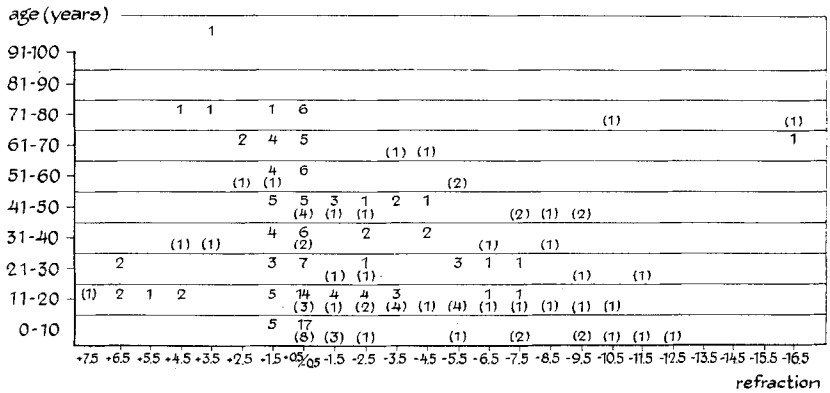

Fig. 9

Refraction plotted against age; the numbers between parentheses represent cases with Wagner's syndrome (n = 70), the other numbers the not affected family members (n = 141).

indicate that even more extensive ultrasonographic longitudinal axis measurements of Wagner syndrome eyes will not give findings different from those for myopic eyes (FRANÇOIS & GOES 1973).

For a thorough understanding of this myopia we must bear in mind that myopia is not only common in Wagner's syndrome but also in several hereditary

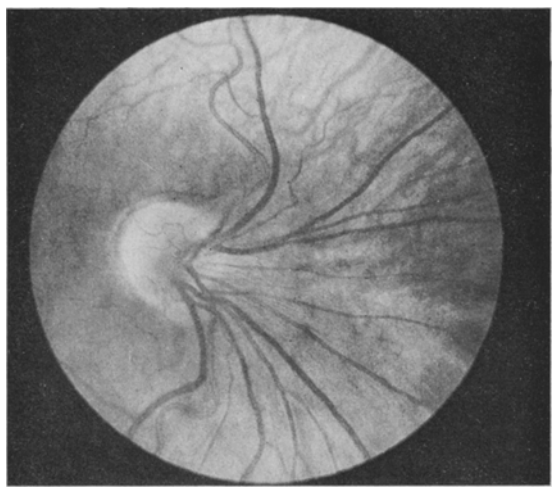

Fig. 10

Wagner's syndrome: inverse emersion of retinal vessels

eye troubles, e.g. recessive X-linked choroideremia, achromatopsia and hemeralopia. But hyperopia is found in vitelliform macula degeneration and X-linked juvenile retinoschisis (DEUTMAN 1971).

The picture of inverse retinal vessel emersion is nothing unusual in Wagner's syndrome and occurs in other diseases, e.g. retrolental fibroplasia and myopia of premature born infants. The characteristic vessel emersion in retrolental fibroplasia is due to a disturbed oxygenation (WEEKERS, WATILLON, THOMAS-DECORTIS 1961). The question arises whether the cause of the phenomenon in Wagner's syndrome is disturbance of the haemodynamics. The histological findings of ALEXANDER & SHEA (1965) could fit the picture, but then we must prove that the vascular changes are primary and not a reaction to some process or other, not yet understood.

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