DYSGENESIS MESODERMALIS OF THE IRIS AND THE CORNEA

A STUDY OF RIEGER'S SYNDROME AND PETERS' ANOMALY

Proefschrift

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General Introduction

This monograph discusses two syndromes, both developmental defects of the anterior segment of the eye.

Among other subjects the study presents a detailed discussion of the many clinical aspects of dysgenesis mesodermalis of the iris (Rieger's syndrome, Axenfeld's anomaly) and dysgenesis mesodermalis of the cornea (Peters' syndrome or Peters' anomaly). Problems of classification, heredity and pathogenesis receive special attention.

The introductory chapter discusses the deep structure of the limbus corneae, because there is evidence of some discrepancy in the clinical interpretation of the prominent line of Schwalbe, which some investigators regard as a mild degree of expression of Rieger's syndrome. The author refutes this.

The closing chapter discusses the differential diagnosis of various developmental defects of the anterior segment of the eye.

The chapter headed Case Histories presents detailed reports on personal clinical observations ans summaries of the clinical picture in a few patients who could not be personally examined (family RK).

Acknowledgement

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Abbreviations

Cranial dimensions:
C: circumference in centimetres
APD: anteroposterior distance in millimetres
BPD: bi-parietal distance in millimetres
(normal range is given in brackets)

Interocular distances are always given in the same order:
CID-PLD-PD-CED-(CID/PD ratio)
CID: distance canthi interni in millimetres
PLD: distance puncta lacrimalia
PD: distance pupils or corneal centres
CED: distance canthi externi

Iris typing according to Waardenburg:
C 1-3: compact type
L 1-3: lacunar type
T: trabecular type
transillumination according to Abrams (1964).

Cornea:
refraction always given in dioptres (D).
limbus types: A 1-3 ⎫
               B 1-3 ⎬ see chapter I
               O   ⎭
order: temporal OD-nasal OD- nasal OS- temporal OS
DH: horizontal diameter in milimetres
DV: vertical diameter in millimetres

Intraocular pressure:
AT: determined by applanation tonometry, in mm Hg
S: determined according to Schiøtz, in mm Hg

"All cases are unique, and very similar to others"

T. S. ELIOT: *The Cocktail Party*

The deep structure of the corneal limbus

A. INTRODUCTION

Careful slit-lamp examination of the deep parts of the corneal periphery in the nasal and temporal limbus areas nearly always discloses a thin, semi-transparent opacity.

The most central, i.e. the most anterior part of the trabecula of the iridocorneal angle should be regarded as the substratum of this opacity. Under the conditions of slit-lamp examination, the opacity proves to be variable in extent as well as in central delimitation. Its peripheral boundary is not directly visible, owing to the opacity of the corneoscleral junction in the superficial limbus zone. If this extends relatively far centrally, then the deep peripheral opacity is not visible even under normal conditions. Nor is it visible in conditions which entail opacification of the corneal periphery (arcus lipoides, Vogt's white limbus girdle, senile degeneration of the corneal margin, persistent corneoscleral membrane, sclerocornea, etc.). This deep peripheral opacity can be seen better when viewed directly through a contact lens, which improves the optical conditions.

It was occasionally possible to follow the blood-filled canal of Schlemm virtually throughout the circumference. In that case the corneal diameter was 12.5 mm, and there was no so-called partial limbus coloboma (Asher 1941) of the type which renders the blood-filled canal of Schlemm visible in the coloboma area only.

In our case the corneoscleral junction of the superficial limbus zone was probably placed in a relatively peripheral position so that a wider strip of the trabecular system could be seen from the "outside". The relatively large corneal diameter also suggested this.

In another case the deep peripheral semi-transparent corneal opacity was covered by a brown pigmented reticulum on the posterior side, i.e. the side towards the iridocorneal angle. Gonioscopic examination disclosed a highly developed network of iridal trabeculae on the trabecular system.

The density of the deep peripheral corneal opacity generally increased towards

the periphery; and in particular at high magnification it proved not to be homogeneous but to consist of a groundwork of criss-crossed fibres which were more loosely arranged towards the centre. In a few cases this less dense, fanned-out part of the opacity contained long circular fibres which ran virtually parallel to the limbus. Burian (1966) informed me that such circular fibres were demonstrable histologically even in the most central part of the trabecula. The fibrous groundwork we observed was formed in part by delicate tendons and supporting elements of the outer layers of the trabecula. These tendinous and supporting elements were beautifully demonstrated in histological flat sections by Unger and Jankovsky (1966).

In the majority of cases the central boundary of the opacity was ill-defined. We called this type of boundary type A. In such cases the opacity gradually dissolved into the clear cornea, the fibrous and reticular aspect first becoming more pronounced and then disappearing completely. In a very small number of cases, however, the central boundary was not vague but sharply defined by a compact, slightly curving white-grey line running more or less parallel to the limbus and forming a ridge which protruded into the anterior chamber. At some sites the width of this otherwise narrow line increased so that local spindle-shaped distensions occurred. The line was occasionally accentuated by small pigment granules. We called this sharply delineated type of boundary type B. An eye in which this line is found as boundary of the deep peripheral corneal opacity, can elsewhere show the normal ill-defined pattern, and this can also be found in the contralateral eye.

1. History

A study of the literature revealed that the deep limbus opacity with the vague type A boundary was first described by Graves (1934) who, with the slit-lamp, observed in many individuals an "ill-defined textural non-vascular zone of faintly increased relucency at the extreme periphery of the posterior part of the cornea" which was "often somewhat wedge-shaped in section". In several other cases, moreover, he found a type B boundary which he described as "peripheral refractile postcorneal rim". He found this rim to be more often localized temporally, often bilateral and seldom symmetrical. In view of the relatively frequent occurrence of this type he considered it to be a normal characteristic.

A similar linear boundary was described by Biozzi and Lugli (1935) as "ringförmige, periphere Verdichtung in der Gegend der Descemet". Other reports on this type of boundary were made by: Remky (1933); Bloch (1937); Karbacher (1940), who described it as "ringförmige Zirkularleiste des Descemetrandes"; Hugger (1948); Streiff (1943, 1949), who called it "dysplasie marginale postérieure de la cornée"; Burian et al. (1955), who described it as "prominent ring of Schwalbe"; Marty (1957); Rollin (1958); Waardenburg (1961, p. 575); Forsius and Eriksson (1964); and Pearce and Kerr (1965).

The type B boundary has also been described – often as "embryotoxon corneae posterius" – in association with many connatal or congenital ocular anomalies and in syndromes involving some ocular changes. It is very difficult to establish whether the incidence of this type B is higher in these defects and syndromes than in normal eyes without studying a large series of cases. The impression is meanwhile that the prominent line of type B – if present – is usually more pronounced and extensive in the abnormal than in the normal eyes. However, this line was not looked for in the past so that a less marked type B line may have been overlooked in many cases. In the past few years its absence or presence is explicitly mentioned in an increasing number of reports. The line is very much in evidence in Rieger's syndrome of which, as will be demonstrated, it is a more or less constant characteristic. The line is also observed, though less constantly, in other developmental anomalies of the anterior chamber, e.g. aniridia (Paganelli 1951; Forsius and Eriksson 1964), coloboma of the iris and choroid (Paufique et al. 1950), keratoconus posticus (Collier 1962; Forsius and Metsälä 1963), general hypoplasia of the iridal stroma (Remky 1927; Burian et al. 1955; Forsius and Eriksson 1964), cornea plana (Kraupa 1921; Forsius 1961), but also in conjunctival naevus (Forsius 1963, case 14), megalocornea (case 6), lenticular anomalies (Franceschetti and Rickli 1951), craniofacial dysplasia (Collier 1962a) and the Van der Hoeve syndrome (Forsius 1963, case 8).

We have personally observed this line repeatedly in high myopia, marked astigmatism, glaucoma simplex, anterior keratoconus, iridal hypoplasia and partial iris coloboma. These were cases of an incidental nature which may have been chance combinations not entailing any correlation. Only Forsius (1960) observed in a comparative study a significantly higher incidence of a prominent line of Schwalbe (type B) in patients with a hypermetropia exceeding 5 D (dioptres).

An evaluation of this incidence requires correct classification of such ocular anomalies and syndromes as may entail a prominent line of Schwalbe. The pertinent publications, particularly those by Forsius (1963) and Forsius and Eriksson (1964) are not always very logical and consistent in this respect. Under the heading "iridal hypoplasia" these authors include instances of Rieger's syndrome, Peters' anomaly as well as essential progressive iridal atrophy; they rank the same syndromes under such headings as "remnants of the pupillary membrane" and "corectopia", although corectopia occurs as a separate entity (Waardenburg) and also in association with luxation of the lens (Siemens).

2. Heredity

Biozzi and Lugli (1935) observed this characteristic through two successive generations in a few instances, and once in an uncle and nephew. Waardenburg (1961) and Forsius, Eriksson and Fellman (1964) likewise observed the line through two successive generations in several instances. Stephenson's family

(1910, cited by Marty 1957) showed, not a prominent line of Schwalbe but bluish sclerae through several generations.

However, the investigations of Forsius (1964) yielded certain indications suggestive of a recessive transmission: 80% of the individuals they studied belonged to an isolated community, and the authors finally refrained from presenting definite conclusions concerning heredity.

3. Gonioscopy

The gonioscopic correlate of the anterior boundary of the trabecular system has been known since the studies of Troncoso (1909, 1925, 1947), Koeppe (1920), Trantas (1928), Busacca (1945) and François (1948, 1955).

Busacca described a "ligne blanche limitante antérieure" or "anneau limitant antérieur de Schwalbe". This corneotrabecular junction – normally visible as a reflex difference – cannot always be accurately located. Streiff (1949) established the probability of a direct relation between the anterior gonioscopic line and the white bounding line of the deep peripheral corneal opacity as seen with the slit-lamp.

Burian et al. (1955) made exhaustive gonioscopic studies of the deep limbus structure with a type B boundary, and formed the conclusion that the line must be considered identical to the line of Schwalbe. They therefore made the justifiable suggestion that this line be called a "prominent line of Schwalbe".

4. Histology

The prominent line of Schwalbe (1870) was already known from the histological studies of Fritz (1906) and Seefelder (1910). Fritz found this line in 20% of the eyes examined, and Seefelder mentioned an even larger percentage. Streiff (1949) found the line in only 4% of his cases, but he believed that this figure must be too low. Burian et al. (1955) observed the line in 12% of their histological sections of 600 eyes with pathological changes.

The prominent line of Schwalbe consists of collections of collagen fibres alternating with elastin fibres. In a few cases the bundle is enclosed in thin extensions of the locally severed Descemet membrane. The trabecular system of the iridocorneal angle is connected with it, and iridal trabeculae (the socalled pectinate fibres of the ligamentum pectinatum in man) insert on it. The entire structure is covered by a thin layer of mesothelium (endothelium) which is a continuation of the corneal mesothelium.

5. Origin

The origin of the prominent line of Schwalbe is directly related to the embryogenesis of the trabecular system, iridocorneal angle and anterior chamber. This

embryogenesis is the subject of controversial views which in turn determine differences in the interpretation of, among other things, the prominent line of Schwalbe. For a long time it was generally believed that the formation of the iridocorneal angle chiefly depended on disappearance of the mesodermal tissue which formed the peripheral wall of the primitive anterior chamber. It was held that disturbances or inhibitions of this process of absorption and atrophy could lead to persistence of remnants of mesodermal tissue in the iridocorneal angle, where they might interfere with the outflow of aqueous humour and cause glaucoma.

In the light of this theory the prominent line of Schwalbe (type B) should be regarded as a very small unabsorbed remnant of the mesodermal tissue. This would make the line a result of an inhibition occurring late in the development of the anterior chamber.

Allen, Burian and Braley (1955) took quite a different view. They found that the anterior chamber angle is formed in the course of foetal development by a cleavage process which separates two layers of the existing mesodermal tissue, without measurable atrophy or absorption of this tissue. From this point of view, the prominent line of Schwalbe and the iridal trabeculae result from an initial excess of mesodermal tissue. We intend to revert to this subject in a more detailed later discussion.

6. Problem definition

Are there reasons to regard a type B peripheral corneal opacity as an anomaly and developmental defect (dysgenesis)? Or should we regard this as a normal condition within the range of anatomical variation?

In view of the fairly frequent occurrence in normal eyes, Graves decided in favour of the latter view as early as 1934. If the question is to be fully answered, several different approaches to the problem are required.

To begin with, an effort can be made to establish whether there are differences between individuals (or rather: eyes) with, and those without the prominent line of Schwalbe. The study discussed in the second part of this chapter was designed as a contribution to an answer to this first question.

Next, one can attempt to establish whether the incidence of the prominent line of Schwalbe is higher in eyes with various other connatal and congenital anomalies, and whether relatives of patients with such anomalies show an increased incidence of this line. This question has been among the problems which we had in mind in our clinical and genetic study of various developmental defects of the anterior chamber – in particular Rieger's primary dysgenesis mesodermalis of the iris and Peters' dysgenesis mesodermalis of the cornea – which will be described in subsequent chapters.

– Next to hypoplasia of the iridal stroma, an embryotoxon corneae posterius is an essential characteristic of primary dysgenesis mesodermalis of the iris; this is

why more detailed considerations will be devoted to the embryotoxon-like prominent line of Schwalbe. In this context we disagree with Streiff's opinion (1949) that the prominent line of Schwalbe is "une anomalie par arrêt de développement", which only gradually differs from a malformation and accordingly represents a mild degree of the developmental defect considered in this study.

<div align="center">B. PERSONAL OBSERVATIONS</div>

In order to determine the incidence of the various types of limbus structure and their extent, and to see whether a correlation might exist with other clinical ophthalmological findings, we made a preliminary study of 200 individuals with emmetropia or slight errors of refraction.

The abovementioned peripheral corneal opacity was observed temporally in 372 and nasally in 356 of the 400 eyes thus examined. There were no differences between the sexes, which were equally represented in the group. The numerical and percentual distribution of the various types is presented in table 1.

Table 1. Numerical and percentual distribution of the various types of limbus structure in normal individuals and eyes.

	200 individuals		400 eyes		800 sides		Temporal	Nasal
	Number	%	Number	%	Number	%	Number	number
Type A	175	87,5	366	91,5	692	86,5	345	347
Type B	25	12,5	32	8	36	4,5	27	9
Type O	–	–	2	0,5	72	9	28	44

The table shows that type A was found about as often temporally as nasally, whereas type B was found more often nasally (as reported also by Streiff 1949; Marty 1957; Forsius 1964). We found a nasal: temporal ratio of 3:1. The type B line was observed only between 1 and 5 o'clock or between 7 and 11 o'clock – usually in a more limited and never in a more extensive area. According to the width of the opacity, we refined the classification by adding a number to the type letter: 1 for narrow, 2 for wider and 3 for very wide. When the opacity was absent, or rather: invisible, we used the designation type O. Of course this division by width was made merely to give an impression and cannot claim an objective metrical significance.

Table 2 gives the distribution of the three types and subtypes according to extent, number and percentage.

The table shows that, as type A becomes wider, its temporal incidence begins to prevail over the nasal incidence, as is the case with type B also.

Considering the group of 25 individuals with a limbus structure which at some site was of type B, we find that the feature was unilateral in 18 and bilateral in 7

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Type	Total		Temporal		Nasal	
	Number	%	Number	%	Number	%
A 1	295	36,9	99	12,4	196	24,5
A 2	275	34,4	144	18	131	16,4
A 3	122	15,3	102	12,8	20	2,5
B 1	12	1,5	9	1,1	3	0,4
B 2	14	1,7	9	1,1	5	0,6
B 3	10	1,2	9	1,1	1	0,1
O	72	9	28	3,5	44	5,5

cases. This differs from Streiff's findings (1949), which indicated bilaterality in nearly all cases. In one individual we found type B both temporally and nasally ODS.

For further comparison, we compared the 25 individuals with a type B boundary in the deep limbus structure to 25 others with a type A (ill-defined) boundary. The two groups were comparable as to age and sex distribution; all had full visual acuity ODS (after correction) and none had eye diseases or abnormalities. The first group included 32 eyes with type B, and the second group had 50 eyes of type A. These two groups of eyes were compared for further study.

1. Refraction

The groups did not differ in refractions and their distribution.

2. Cornea

The corneoscleral membrane as manifest in the architecture of the limbus zone was normal in size and development in both groups.

Type A and type B eyes did not significantly differ in corneal size or distribution of corneal size. The average value of the horizontal corneal diameter was 11.4 mm in the type A and 10.9 mm in the type B eyes, the difference being non-significant.

The two groups did differ in corneal refraction (table 3), but the limited number of type B eyes makes it impossible to attach definite significance to this difference. The corneal refraction of type A eyes was 43.2 D (radius of curvature 7.8 mm); like distribution and range, this value was in accordance with predicted values. The corneal refraction of type B eyes averaged 42.2 D (radius 8.0 mm). The distribution over the various sizes suggested a diphasic curve, but larger groups of

Table 3. *Distribution of corneal refraction (over 11 categories) in two types of limbus structure in normal eyes.*

Corneal refraction (dioptres).												Average
	38	39	40	41	42	43	44	45	46	47	48	49	
A %	0,75	3	7^5	17	17	26	16^5	7	3	0,75	1,5		43,2 D
B %			10	17	32	8	5^5	16	5^5	2	4		42,2 D

patients with limbus type B will have to be examined for further information in this respect.

3. Iris

The two groups did not differ in iridal colour, the colour distribution being:

type	blue blue-grey	green green-grey	brown dark brown
A	56%	20%	24%
B	53%	25%	22%

The two groups showed some differences in type of iridal structure, namely:

type*	C 1	C 1-2	C 2	L
A	76%	12%	8%	4%
B	53%	6%	25%	16%

* according to Waardenburg (1961, p. 653).

Type C1 was somewhat less frequent in group B, in which types C2 and L were decidedly more frequent. It might be that in this group absorption of the anterior layer of the iridal stroma has been slightly more intensive during embryonic development than in the eyes without a linear boundary of the deep peripheral corneal opacity.

No really distinct hypoplasia of the anterior layer of the iridal stroma was observed. In 4 of the 32 type B eyes, however, there was some general hypoplasia; both individuals had irides of structural type L ODS. In all other cases in both groups the structure of the iridal stroma was normally developed.

According to Allen *et al.* (1955), the prominent line of Schwalbe is often associated with hypoplasia of the anterior layer of the iridal stroma. Local hypoplasia in the line area was described by Kayser (1922) and Remky (1927); in their subjects,

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too, no other ocular abnormalities existed. Neither Marty's findings (1957) nor our own observations confirm this frequent association of hypoplasia of the iridal stroma.

Neither in type A nor in type B eyes was the pigment layer of the iris diaphanous.

The pupils were of normal shape and localization in all cases and showed an adequate response to light; no abnormalities of the pupillary zone were observed.

In both groups, the refracting media and fundi were free from abnormalities.

4. Intraocular pressure

Many authors maintain that eyes with a prominent line of Schwalbe show an increased predisposition to glaucoma (Gasteiger, Streiff, Burian). The intraocular pressure was normal in all the eyes examined; it averaged 15.5 mm Hg (AT) in type A eyes, at an average age of 40, and 16 mm Hg (AT) in type B eyes, at an average age of 41 years.

In a subsequent study of 100 patients with glaucoma simplex (average age 64 years) we found a type B deep limbus structure or prominent line of Schwalbe in 18 out of 200 eyes (9%). This did not differ significantly from what we expected in view of the frequency we established in normal eyes (8%). With Marty's findings (1957) also in mind, we concluded that there is no evidence to warrant the assumption of a glaucomatous predisposition in eyes with a type B deep limbus structure.

5. Gonioscopy

All eyes in both groups examined had normal open iridocorneal angles and normal gonioscopic features. The anterior gonioscopic line (separating the cornea from the trabecula) was invariably present in type B eyes, in which it was more extensive and thicker than in the 50% of type A eyes in which it was found. In the majority of cases the boundary between trabecula and cornea could be located on the basis of differences in optical qualities (expressed in different light reflections) between the two structures. In these cases, however, there was no distinct linear boundary relucence as with the prominent line of Schwalbe. The two groups did not differ in the incidence of iridal trabeculae; these were found in 58% of type A and 53% of type B eyes.

The iridal root in type B eyes was hypoplastic in 70%, while only 38% of type A eyes showed this hypoplasia.

The visibility of blood vessels in the periphery of the iridal root likewise showed a higher incidence in type B eyes. The colour of the iris – an important factor in the visibility of iridal vessels in the iridocorneal angle (Henkind 1964) – in our groups played no role in explaining the difference, because both groups showed a similar distribution of iris colours.

6. Conclusions

The prominent line of Schwalbe (type B deep limbus structure) found in 8% of the eyes examined, is not an anomaly but should be regarded as a variant in the structure of the iridocorneal angle within the normal range of variation in the development of the anterior chamber and iridocorneal angle. The findings obtained did not corroborate a glaucomatous predisposition.

Individuals with a prominent line of Schwalbe (type B) did not differ from those without this linear boundary of the peripheral corneal opacity (type A) in terms of refraction, corneal size, iridal colour, form and localization of the pupil, intraocular pressure and clarity of refracting media and fundus.

They did show some differences in corneal refraction and structure of the iridal stroma. The corneal refraction was slightly lower in type B eyes, in which the radius of curvature averaged 0.2 mm more (indicating a lesser average curvature). Iridal structure types L and C_2 were more frequently found in type B eyes. Further investigations into the incidences of these three factors will be made in order to establish possible correlations. Correlation is not excluded, for a prominent line of Schwalbe, flat corneae and changes in iridal structure are features which, in the light of the development of the anterior chamber and its pathology, may be interrelated.

Primary dysgenesis mesodermalis of the iris

Rieger's syndrome

1. INTRODUCTION

As we mentioned in passing, the prominent line of Schwalbe is not always an isolated ophthalmological entity. Reports on pigment granules and lumps marking the line are not uncommon (Remky 1927; Graves 1934; Gasteiger 1937, 1939; Schmidt 1943; Forsius and Eriksson 1964). In less common cases, tattered filaments were seen to extend from the line into the anterior chamber (Streiff 1949). In a few cases there was local hypoplasia (Kayser 1922; Remky 1927) or general hypoplasia (Remky 1933; Schmidt 1943; Burian *et al.* 1955; Forsius and Eriksson 1964) of the anterior mesodermal layer of the iris.

These changes can be regarded as "transitions" to a developmental defect of the anterior chamber which Axenfeld described in 1920. He demonstrated a boy with a white annular line ODS at 1 mm from the limbus, at the level of Descemet's membrane; at this level, a semi-transparent opacity was observed between the line and the limbus. From the anterior layer of the poorly developed iridal stroma (partial iris coloboma), a number of delicate fibrillae traversed the anterior chamber towards this line. Axenfeld described this abnormality as "*embryotoxon corneae posterius*". Isolated cases of a prominent line of Schwalbe with adhesions between this line and the hypoplastic iridal stroma, with or without glaucoma, have since been described by several authors (Thier 1921; Mann 1933; Gasteiger 1937; Hagedoorn 1937; Delmarcelle *et al.* 1958; Nenquin and Brihaye 1959; Wuest and Erdbrink 1961; Royer and Géhin 1963; Forsius and Eriksson 1964; Ernyei 1965; Haye and Blanck 1965; Meyer 1965; Sugar 1965); and we have repeatedly observed such cases.

We found several patients with this combination of abnormalities among the relatives of patients with more severe and extensive developmental defects of the anterior chamber.

The anomaly described by Axenfeld represents a mild expression of the developmental defect of the anterior chamber which Rieger elucidated. In Vienna, in

1934, Rieger demonstrated two patients whose cases he subsequently described (Rieger 1935). These patients combined connatal anomalies of the pupil (ectopia, dyscoria, slit-pupil) with unmistakable hypoplasia of the anterior layer of the iridal stroma. Moreover, there were adhesions between the iridal stroma and the posterior aspect of the corneal periphery, and at several sites the iridocorneal angle and its immediate surroundings were filled by grey-yellow or brown-yellow tissue. Opacities of the corneal parenchyma were observed at these sites. The sclerocorneal junction was ill-defined so that the limbus was vague (persistent corneoscleral membrane). In one patient the intraocular pressure was considerably increased. In this publication Rieger also reviewed the literature on many cases of iridopupillary malformation of a connatal type, and he concluded that both embryotoxon corneae posterius (Axenfeld) and iridal hypoplasia are aspects of the same developmental defect, which he described as *"dysgenesis mesodermalis corneae et iridis"*. Partly in recognition of the merit of this description, the syndrome was later given Rieger's name.

In 1949, Kleinert described similar changes in a daughter of one of Rieger's patients.

Rossano (1934) had previously observed and described similar changes in a father and son; the father showed hypertelorism, a rather strange face with a remarkably flat nose, small horizontally oval corneae with poorly marked limbus, hypoplasia of the iridal stroma, ectopic pupils, pseudopolycoria and glaucoma; the son likewise showed hypertelorism and a broad nose, small corneae, an ill-defined limbus and iridal hypoplasia. The son in addition was described as having large, yellow, malposed teeth.

In 1963 Saraux (1966) examined the third generation of this family in the person of a 20-year-old man, who only later proved to be the grandson and son of the patients described by Rossano. With regard to this patient, Saraux wrote in a personal communication to us: "He showed chronic glaucoma and atrophy of the mesodermal layer of the iris, which was reduced to a thin greyish lamina with no configuration. There was no embryotoxon and no polycoria. With regard to the teeth and face we have made no notes, and slight abnormalities may have escaped our attention".

Rossano's publication (1934) was the first in the literature to mention a hereditary syndrome of developmental defects of the anterior chamber, which was to become more generally known through Rieger's publications. In 1935 Rieger demonstrated a mother with two children (fig. 39, table 16) who, besides "dysgenesis mesodermalis corneae et iridis", showed an unusual and relatively rare dental anomaly. This *anodontia partialis vera* and the ocular abnormalities in this family were described in detail by Mathis (1936). In a later publication (1941) Rieger re-emphasized the connection between the two congenital anomalies.

This connatal, hereditary ocular syndrome, which we call *primary dysgenesis mesodermalis of the iris*, is the central subject of this monograph.

For further definition of the syndrome we made a study of the literature and carried out an exhaustive clinical-genetic investigation.

For the diagnosis of primary dysgenesis mesodermalis of the iris we used three criteria, which represent the principal symptoms, namely:

– hypoplasia of the iridal stroma;
– abnormalities of the iridocorneal angle:
    – embryotoxon corneae posterius (pathologically prominent line of Schwalbe)
    – adhesions between this line and the iridal stroma, with or without tissue in the iridocorneal angle;
– bilaterality.

We culled 151 cases of this syndrome from the literature which, with our own material of 12 patients, made a total of 163 patients (326 eyes) showing the anomaly. Sufficient clinical data were available on these patients for analysis in this study.

Of a group of 178 patients with primary dysgenesis mesodermalis of the iris, the sex was known: 92 were female and 86 were male patients. This distribution did not significantly differ from the expected. The sex distribution in 130 familial cases was: 64 female and 66 male patients. Rieger's syndrome can therefore be described as showing no male or female predominance.

2. REFRACTION

Of 144 of the 326 eyes with primary dysgenesis mesodermalis of the iris we know the refraction (i.e. 44% of cases). Of these eyes, 70 showed astigmatism ranging from 0.5 to 5 D. Tables 4 and 5 present the distribution of the refractions found.

Table 4. Distribution of the refraction in clinical groups in primary dysgenesis mesodermalis of the iris (Rieger's syndrome)

Refraction	Number	%
Emmetropia	9	6
Astigmatism	24	17
Myopia	69	48
Hypermetropia	42	29
Total	144	100

Table 6. Distribution of the refraction in number and percentage in primary dysgenesis mesodermalis of the iris (Rieger's syndrome) and in normal eyes.

Refraction	Number	%	% (Normal)
$\geqslant + 4$	16	13	1
$+ 1 < + 4$	23	19	26
E $\leqslant + 0,75$	12	10	63
$- 0,25 \geqslant - 4$	33	28	8
$> - 4$	36	30	2
Total	120	100	100

Table 5. Distribution of the refraction (18 dioptric categories) in primary dysgenesis mesodermalis of the iris (Rieger's syndrome).

Dioptres	0,5-1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	22	
Astigmatism	25	19	17	8	1														70
Myopia	14	10	6	3	3	3	2	3	1	2	4	5	2	3	4	2	1	1	69
Hypermetropia	9	12	5	5	4	2	2			1	1	1							42

Comparing these data with the distribution of refractions in a normal population as reported by Strömberg (1936), we find that eyes with Rieger's syndrome show a considerably higher incidence of refraction abnormalities than normal eyes: 13 times more hypermetropia exceeding 4 D, at least 3 times more myopia below 4 D and 15 times more myopia exceeding 4 D, and 6 times less emmetropia (table 6).

In Rieger's syndrome, therefore, there is a considerably higher incidence of *astigmatism and marked ametropia.*

3. BULBUS SIZE

Very little is known about the size of the bulbi in primary dysgenesis mesodermalis of the iris. Bulbus size was explicitly described as normal in some 40 eyes.

Microphthalmos was described by Braendstrup (1948) in 4 eyes in her family with the syndrome, and unilateral microphthalmos occurred in a patient described by Bartolozzi et al. (1964). Microphthalmos is sometimes deduced from the presence of microcornea, but since we know that there are eyes of normal size with microcorneae (Gernet 1965) or macrocorneae, and that microphthalmos occurs with normocornea and even macrocornea, while macrophthalmos with microcorneae can also occur (Friede 1933a, 1933b; Waardenburg 1949), the diagnosis of microphthalmos requires other criteria. In dubious cases, exact determination by means of echometry is the best solution.

Hydrophthalmos was observed in 22 cases (Maxwell 1936; Falls 1949; Weekers and Weekers 1950; Sivasubramanian and Hoole 1955; Nenquin and Brihaye 1959; Gassler and Berthold 1960; Haye and Blanck 1965; Belmonte 1966; Delmarcelle et al. 1958, 1968).

In our own material, hydrophthalmos was observed in two sisters in pedigree BR (IV-1 and IV-2).

4. MOTILITY

Data on motility were available on 69 individuals with primary dysgenesis mesodermalis of the iris. Of these, 12 patients showed *connatal nystagmus* only; 6 showed nystagmus associated with concomitant strabismus; 38 showed concomitant strabismus only; and in 13 the motoricity was described as normal.

Of the 44 patients with concomitant strabismus, 28 showed *exotropia* and 16 showed *esotropia.* This considerably higher incidence of ocular motor disorders is not surprising, because such disorders are frequently observed in association with various ocular abnormalities (Waardenburg et al. 1963). The greatly increased incidence of refraction abnormalities found in primary dysgenesis mesodermalis of the iris may have contributed to this also.

Several patients with hypertelorism and Rieger's syndrome showed abnormalities of motility (Rossano 1934; Lemmingson 1961; Von Noorden and Baller

1963; Marx 1965; and the proband of pedigree SD in our own material: fig. 27); these abnormalities consisted of exotropia or connatal nystagmus. Hypertelorism as a cause of exotropia is mentioned by several authors, and was observed in our study (CM-V-5; fig. 58).

As will be seen later, several patients with dysgenesis mesodermalis of the iris showed mild disorders of cranial development; the increased incidence of ocular motor disorders can in part be regarded as an aspect of the cranial abnormalities.

5. CONJUNCTIVA

Virtually no publication on primary dysgenesis mesodermalis of the iris makes special mention of the conjunctiva. Conjunctival changes were observed in the form of *conjunctival xerosis* (*Bitot*) by Bietti (1943, 1963) in a female patient with slit-pupils and in a mother and son who showed Rieger's syndrome. Meyer (1965) also observed conjunctival xerosis in a young patient with primary dysgenesis mesodermalis of the iris. We found no such conjunctival changes in our patients with Rieger's syndrome. It is very remarkable that this conjunctival xerosis (Bitot) has also been described – without vitamin A deficiency – in other developmental defects of the anterior chamber, e.g. aniridia (Bietti 1963; Delleman 1966; Castellazzo and Vittone 1967; Alkemade 1968), cornea plana (Gasteiger 1945-1946) and sclerocornea (Merz 1964).

Bietti's contention (1963) that these cases involved a new syndrome – "iridopupillary anomalies and conjunctival xerosis" – is not justifiable in our opinion. The entities described as occurring in association with conjunctival xerosis differ not only clinically and genetically but also as to pathogenesis. However, all these conditions are indeed developmental defects of the anterior chamber.

In view of these facts, conjunctival xerosis (Bitot) must be regarded as a less frequent but more general aspect of these developmental defects. The same applies to the occurrence of blue sclerae in association with various developmental defects of the eye (Alkemade 1968).

6. SCLERA

Only a few of the reports in the literature present data on the sclera in primary dysgenesis mesodermalis of the iris, and only Henkes (1965) considered the sclera in detail.

Blue sclerae or a blue translucent scleral band were described several times in patients with Rieger's syndrome (Lisch 1938; Falls 1949; Kittel 1956; Collier 1962; Forsius and Metsälä 1963; Henkes 1965; Marx 1965; Dark and Kirkham 1968); we observed this condition in a few cases (HO-III-6; SD-III-2; SD-IV-1 and others).

The bluish "discoloration" in these cases arises from the fact that the uveal pigment in visible through the sclera. In many cases the sclera is not thinner but

merely more transparent, due to a change in the mesenchymal ground substance (Oerkermann and Behnke 1966). In patients with hydrophthalmos, who regularly show blue sclerae, the hyperextension and associated thinning of the sclera probably plays the principal role. Differentiation in this respect is therefore necessary.

Apart from the Van der Hoeve syndrome (osteogenesis imperfecta), blue sclerae are chiefly found in eyes with a developmental defect of the anterior chamber. As we saw, these defects include primary dysgenesis mesodermalis of the iris and primary hydrophthalmos, but also aniridia (Mohr 1895; Duggan 1927; Beattie 1947; Grove 1961; Alkemade 1968) and cornea plana (Gasteiger 1945-1946; Straub 1950). We personally observed blue sclerae also in eyes with a congenital cataract – with or without microphthalmos – and in iris coloboma and limbus dermoid with secondary dysgenesis mesodermalis of the iris (CM-V-5; plate VI).

Blue sclerae and congenital cataract with or without microphthalmos or microcornea have been described fairly frequently in association with dyscephaly (Hallermann-Streiff syndrome), remnants of the pupillary membrane (Waardenburg 1949) or iridopupillary anomalies in the oculo-cerebro-renal syndrome of Lowe.

Microphthalmos and iridopupillary anomalies as well as blepharophimosis, nystagmus and iridopupillary changes have been observed in combination with blue sclerae in patients with the Cornelia de Lange syndrome (Ptacek et al. 1963; Zweymüller 1957; Nicholson and Goldberg 1966).

Bonnet (1953) and Beattie (1968) described blue sclerae in the Ehlers-Danlos syndrome. The same combination, with microcorneae and glaucoma, was described by Durham (1953), and with subluxation of the lens by Johnson (1949). Hypertelorism and partial anodontia (Blodi 1957), the Toni-Fanconi syndrome and the Turner syndrome, sometimes associated with cataract, corneal opacities and epicanthus, can involve blue sclerae (Lessell and Forbes 1966).

Padovani (1932), Rados (1942) and Von Noorden and Schultz (1960) mentioned blue sclerae in association with the Marfan syndrome, in which developmental defects of the iridocorneal angle (secondary dysgenesis mesodermalis of the iris) are known to be very common (Theobald 1941; Starke 1951; Reeh and Lehman 1954; Burian 1958; Schocket 1967).

Thus we find that, when blue sclerae are described apart from the Van der Hoeve syndrome, some developmental defects of the anterior chamber are usually present also. In the context of developmental defects of the anterior chamber, therefore, blue sclerae can be of no aid in differential diagnosis. In these cases the blue sclerae must be regarded as an aspect of the developmental defects. In the Van der Hoeve syndrome and the Ehlers-Danlos syndrome, the blue sclerae in part represent the general disturbance in the primordium of the mesenchymal tissue (and in part this also applies to their combination with the Marfan syndrome).

PLATE II. Primary dysgenesis mesodermalis of the iris with embryotoxon corneae posterius, hypoplasia of the iridal stroma and temporal partial limbus coloboma (SD-IV-1, left eye).
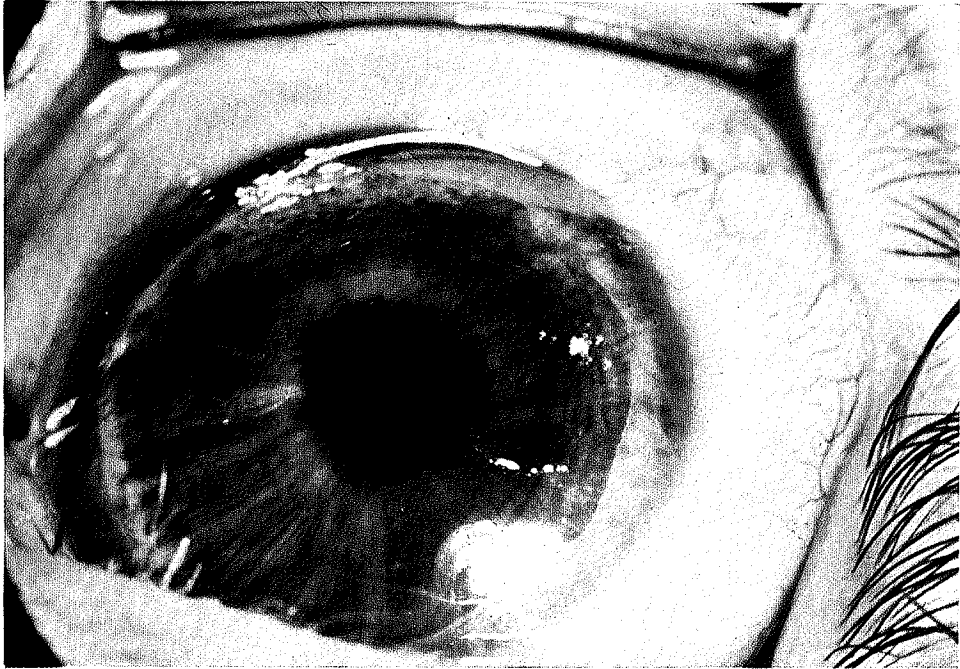
a. *Architecture of the limbus*

In his patients with primary dysgenesis mesodermalis of the iris, Rieger observed an *ill-defined limbus* due to abnormally far encroachment of the corneoscleral membrane on the cornea. In these cases, however, the situation is more precisely described as less marked regression of this zone during embryonic development. This limbus anomaly – also known as *persistent corneoscleral membrane* – should therefore be regarded as a malformation due to developmental arrest. According to Fischer (1931), this membrane begins to be subservient to vision in an embryo of 24 mm; and in an embryo of 17 cm its regression is already so far advanced that at that time there is a direct and fairly sharply defined sclerocorneal junction. The limbus anomaly in question is frequently observed in several developmental defects of the anterior chamber: cornea plana, Peters' anomaly, sclerocornea, aniridia and (personal observation) microphthalmos and iridochorioretinal coloboma (HC-IV-8; plate V).

In a large proportion (16/24) of our own cases of Rieger's syndrome, this ill-defined sclerocorneal junction was observed. The limbus architecture is discussed in only a minority of the cases reported since Rieger's studies. Pertinent data are available on 102 of the 326 eyes. An ill-defined corneoscleral boundary was observed in 83 instances; a crescent-shaped broadening of the superior corneo-

Fig. 1. Primary dysgenesis mesodermalis of the iris, ill-defined corneoscleral boundary (BR-IV-2).

scleral junction was seen 4 times (Rossano 1934); the boundary was sharply defined in 4 cases (Gassler and Berthold 1960) and a normal boundary was observed 10 times (Gassler and Berthold 1960; and personal observations: figs. 1, 2, 3, 4, 6, 10, 13, 15, 16 and 18).

An ill-defined corneoscleral boundary is an important factor in determining corneal size, and can cause errors of determination. The corneal diameter may seem too small so that microcornea is erroneously diagnosed (pseudomicrocornea).

b. Corneal size

Microcornea is often mentioned as an essential characteristic of primary dysgenesis mesodermalis of the iris. Rieger (1935) wrote that, in dysgenesis mesodermalis corneae et iridis, there is a slight degree of microcornea even when the opaque streak is taken into account. Subsequent authors have often accepted this statement and repeated it, but have seldom corroborated it.

Peter (1924) measured the corneae in 512 individuals and computed a mean horizontal diameter of 11.67 mm ($\pm$ 2.5 mm). She observed that no corneal growth occurred after the age of 5 years. On the basis of repeated measurements in 526 eyes, Jöhr (1954) computed the mean corneal diameter as 11.03 mm (with 95% of the values between 9.26 and 12.80 mm).

In view of the abovementioned data and personal observations we accept a value of 9.5 mm as indicating the borderline between normocornea and microcornea. The designation macrocornea is justifiable at values exceeding 12.5 mm, while values below 9.5 mm warrant the designation microcornea.

In our own patients and their relatives, the corneal diameter was measured in various ways (Wessely's keratometer; dividers and ruler), and the results were compared. Such authors as did specify corneal size in their patients' eyes, seldom if ever specified the measuring method used. We believe, however, that values measured by different methods are nevertheless comparable.

Data on the corneal diameter are available on 236 of the 326 eyes (70%). The mean value in this group was 11.55 mm, which is slightly above the mean indicated by Jöhr but otherwise consistent with the value described as normal mean (11.6 mm) by other authors (Peter 1924; Oppel 1956, and others).

Table 7. Number and percentage of corneal diameters in clinical groups in primary dysgenesis mesodermalis of the iris (Rieger's syndrome) and in normal eyes.

	Horizontal diameter of the cornea (mm)		Number	% Rieger's syndrome	% Normal
Microcornea	9		8	3,5	0
Boundary	9,5		13	5,5	0,5
Normocornea	> 9,5	$\leqslant 12^5$	153	65	99
Macrocornea		$> 12^5$	62	26	0,5

18

Table 8. Number and percentage of corneal diameters, divided into 13 categories, in primary dysgenesis of the iris (Rieger's syndrome) and in normal eyes.

Horizontal diameter of the cornea (mm)	9	9^5	10	10^5	11	11^5	12	12^5	13	13^5	14	15	16	Total
Number	8	13	21	13	49	24	29	17	33	11	13	4	1	236
% Riegers' syndrome	3,5	5,5	9	5	21	10	13	7	14	5	5	1,5	0,5	100
% Normal	0	0,5	1	12	50	28	7	1	0,5	0	0	0	0	100

Considering a corneal diameter of 9.5 mm as microcornea, we find (table 7) that 9% of the eyes with primary dysgenesis mesodermalis of the iris showed *microcornea*. However, when stricter diagnostic criteria are applied we find a microcornea incidence of only 3.5%. In the former case, 65% of the eyes with primary dysgenesis mesodermalis of the iris showed normocornea, while 26% showed macrocornea.

Table 8 presents a more differentiated picture of the number and percentage of corneal diameters, divided into 13 categories. Comparing our percentages in eyes with Rieger's syndrome (top column) with percentages based on a personal study of 200 normal eyes, we find that smaller corneal diameters are more prevalent in primary dysgenesis mesodermalis of the iris, but also that more large corneae and fewer corneae of average size are included in this group. This means that the range of corneal diameters was considerably wider in the eyes with Rieger's syndrome than in normal eyes.

Apart from this it is clear that eyes with Rieger's syndrome show a significantly higher incidence of microcornea than normal eyes.

However, while microcorneae are regularly mentioned in association with many developmental defects of the anterior chamber (e.g. aniridia, cornea plana, iris coloboma, Peters' anomaly, etc.), exact data on incidence are unfortunately lacking so that comparison is impossible. We have meanwhile gained the impression that microcornea occurs in a varying percentage of all these developmental defects – being a typical characteristic of some but a less relevant aspect of other defects.

In primary dysgenesis mesodermalis of the iris, microcornea is neither an essential nor a frequently observed characteristic. Corneal diameters of 9.5 mm were described by Mathis (1936), Braendstrup (1948), Riethe and Lemmingson (1958) and Henkind *et al.* (1965) in Rieger's syndrome; corneal diameters of 9 mm were reported in this syndrome by Rossano (1934), Rejchrt and Miksa (1952), Unger (1956), Gassler and Berthold (1960), Frandsen (1963) and Shaffer (1965).

Smaller cornea such as those found in microphthalmos and in such conditions as the oculodentodigital syndrome, were never described or observed in association with primary dysgenesis mesodermalis of the iris.

Corneal diameter (mm)		9	9^5	10	10^5	11	11^5	12	12^5	13	13^5	14	15	16	Total
Without glaucoma	Number	2	7	7	5	23	11	10	9	15	3	3			95
	%		10				68					22			100
With glaucoma	Number	6	4	11	5	21	10	18	8	18	8	8	4	1	122
	%		8				60					32			100
Corrected for hydrophthalmos	Number	6	4	11	5	21	10	16	8	14	5	3	3	1	107
	%		10				66					24			100

Rieger's syndrome has a significantly higher incidence of *macrocornea* than is found in normal eyes. In an effort to establish whether glaucoma plays a role in this increased macrocornea incidence (and if so, which role), a group of 122 eyes with primary dysgenesis mesodermalis of the iris and glaucoma was compared with a group of 95 eyes with the syndrome without glaucoma.

Table 9 shows the distribution of corneal sizes in these two groups. Among other things this table shows that both groups had the same incidence of microcornea, and that the percentage of macrocornea was larger in the group with than in that without glaucoma.

Data on the corneal diameter were available on 15 of the 21 eyes with hydrophthalmos. After correction for these eyes, the group without glaucoma was found to show virtually the same incidence of macrocorea as that with glaucoma. This would seem to suggest that the macrocornea in primary dysgenesis mesodermalis of the iris is probably not a manifestation of increased intraocular pressure but an aspect of the clinical picture of this developmental defect of the anterior chamber. Hydrophthalmos in association with Rieger's syndrome will be discussed in detail in the section on the intraocular pressure in this syndrome.

c. Corneal shape

The shape of the normal cornea is that of a circle or slightly horizontal oval, the difference between the horizontal and the vertical diameter being 0.5-1 mm. In a few normal eyes the cornea has the shape of a vertical oval, as a genetically determined characteristic (Seefelder 1930).

The majority of instances of an unusual corneal shape are encountered in developmental defects of the anterior chamber. In few of these cases the peripheral boundary of the cornea may be an oblique oval or egg-shape, as we observed in our case of iridochorioretinal coloboma with Peters' anomaly (HC-IV-8; fig. 55 and plate V).

Table 10 shows that both the horizontal and the vertical diameter was known of 86 eyes with primary dysgenesis mesodermalis of the iris. Of these, 71 eyes

DH > DV in mm	Number		%
+ 2	1	} 3	3⁵
+ 1,5	2		
+ 1	10	} 71	82
+ 0,5	38		
0	23		
− 0,5	7	} 12	14⁵
− 1	5		
Total	86	86	100

(82%) had a normal corneal shape, while in 15 (18%) the corneal shape was abnormal. Of the latter, 3 showed a pronounced horizontal oval and 12 a vertical oval shape. While abnormal corneal shapes do occur in Rieger's syndrome, therefore, their incidence is relatively low. We do not know whether in this respect the syndrome differs significantly from other developmental defects of the anterior ocular segment.

Abnormalities of corneal shape were reported also in association with cranial anomalies such as oxycephaly (Patry 1906) and facial asymmetry (Swerdloff 1930, and others). Lemmingson (1961) described primary dysgenesis mesodermalis of the iris with cranial anomalies, dental anomalies and a very oblique oval shape of the cornea.

In our own material we observed that facial asymmetry and mild dyscephaly occur in association with Rieger's syndrome; consequently, there is a possibility of a correlation via other abnormalities associated or separate.

d. Corneal refraction

The literature offers few data on corneal refraction in primary dysgenesis mesodermalis of the iris. Rieger (1935) found an average value of 44 D in 10 eyes, and reported that cornea plana was a designation which did not apply to these cases.

In normal eyes, corneal refraction ranges between 39 and 49 D. The distribution and range of various corneal refractions were discussed in various studies by Steiger (1895), Waardenburg (1930) and Stenström (1949), who computed the mean corneal refraction as 43.5 D. Our personal study of corneal refraction disclosed a mean value of 43.2 D in a group of 68 eyes.

Data on corneal refraction were available on 59 eyes with primary dysgenesis mesodermalis of the iris. Table 11 reviews the percentual distribution over a

Table 11. Percentual distribution of corneal refraction over 8 categories in primary dysgenesis mesodermalis of the iris (Rieger's syndrome) and in normal eyes.

Corneal refraction	35	37	39	41	43	45	47	49	51	Total
% Riegers' syndrome	5	10	25	30	21	6	2	1		100
% Normal		0,1	6,5	36	46	10	1			100

number of categories. For comparison we refer to the second column, giving the normal distribution as found in the abovementioned population surveys.

In eyes with Rieger's syndrome, the corneal refraction averaged 41.7 D, i.e. 1.5 D lower than the mean value in normal eyes. In view of these date on distribution it can be concluded that eyes with primary dysgenesis mesodermalis of the iris more frequently have a corneal refraction < 41 D and less frequently a refraction > 43 D than have normal eyes. This implies a shift towards *flatter corneae* (as indicated also in the difference in mean values). The small numbers of cases preclude adequate determination of correlations, e.g. with the corneal diameter.

e. Corneal clarity

The *embryotoxon corneae posterius* which always accompanies primary dysgenesis mesodermalis of the iris, can manifest itself in many different ways. The embryotoxon nearly always involves the entire circumference, although it is not always entirely visible with the slit-lamp. Supplementary gonioscopic examination will usually show that, in the sector in which the embryotoxon is not visible externally, there is a highly pathological line of Schwalbe with numerous adhesions to the hypoplastic iridal stroma (figs. 8, 19-23). As a rule, the embryotoxon corneae posterius is localized peripherally, about 0.5-1 mm from the corneal limbus (figs. 5, 6, 8, 9, 13), although it may be further (1-2 mm) from the limbus (figs. 2, 3, 15, 16 and plates I-II-III); or it may occupy a relatively central position and not take a circular course (Delmarcelle 1968). The embryotoxon may be thin and regular (figs. 2, 3, 15, 16), thick and regular (figs. 5, 9) or thick and irregular (figs. 1, 6, 8 ,13, 18). Other types of embryotoxon described were characterized by tubular thickening (Delmarcelle 1968) or detachment from the posterior corneal surface, floating free in the anterior chamber (Wolter et al. 1967). We observed this in our case HH-II-4. (fig. 8).

Apart from the embryotoxon corneae posterius and the sometimes present deep peripheral corneal opacities at the site of the peripheral adhesions between the iris and the posterior corneal surface, a small proportion of eyes with Rieger's syndrome show changes of the *central* cornea (which is usually unchanged and clear in this syndrome). Explicit data on the central zone of the cornea were available on 170 eyes with primary dysgenesis mesodermalis of the iris; 108 of these eyes showed no changes, while 62 showed central corneal abnormalities.
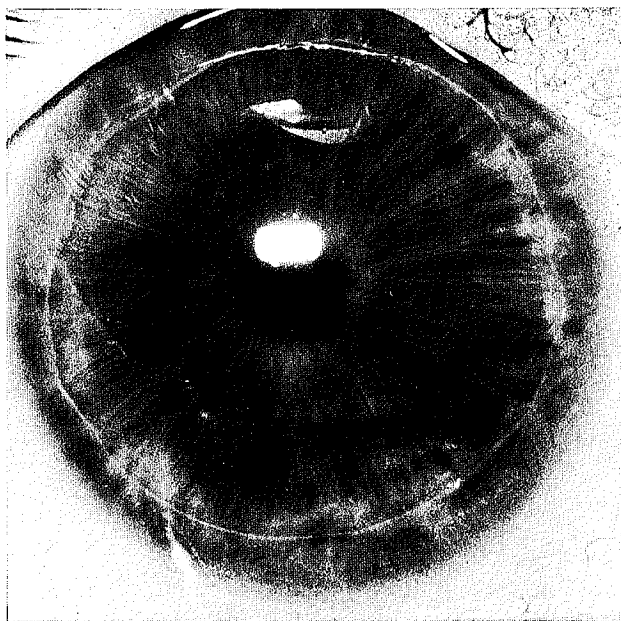
Fig. 2. Primary dysgenesis mesodermalis of the iris with marked circular embryotoxon corneae posterius, iridal hypoplasia and central pupil (SD-IV-1, right eye).
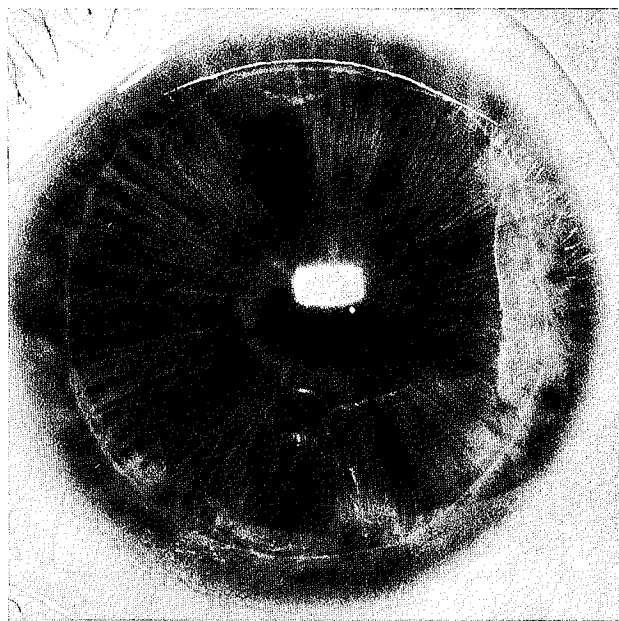

Fig. 3. Primary dysgenesis mesodermalis of the iris with marked circular embryotoxon corneae posterius, iridal hypoplasia and central pupil (SD-IV-1, left eye).
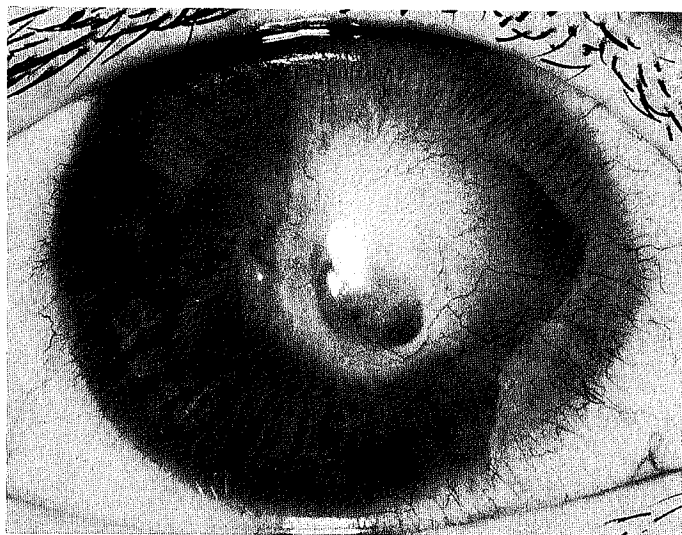
Fig. 4. Primary dysgenesis mesodermalis of the iris with secondary dysgenesis mesodermalis of the cornea (Peters' anomaly). Ill-defined limbus, horizontaloval cornea and central corneal opacity with local defect of the posterior corneal stroma (BR-IV-1).
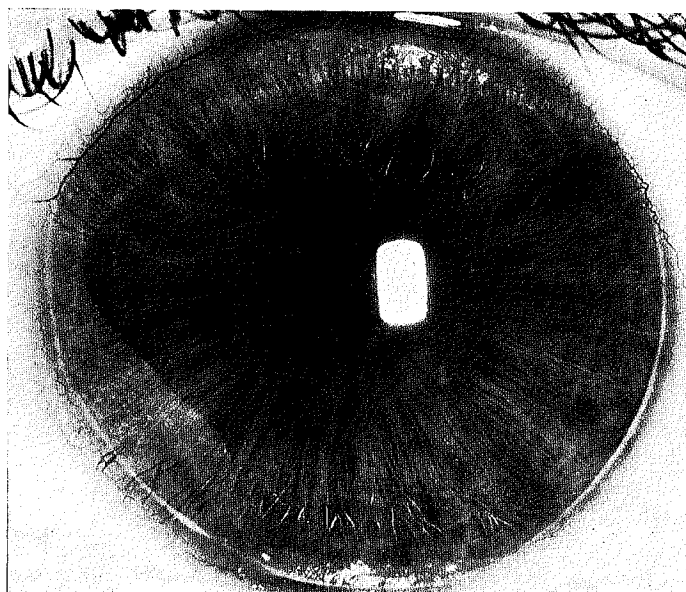
Fig. 5. Primary dysgenesis mesodermalis of the iris; aplasia of the anterior mesodermal layer and iridal frill. The pupillary sphincter muscle shimmers through. Annular posterior embryotoxon of the cornea clearly visible (BR-III-2, left eye).
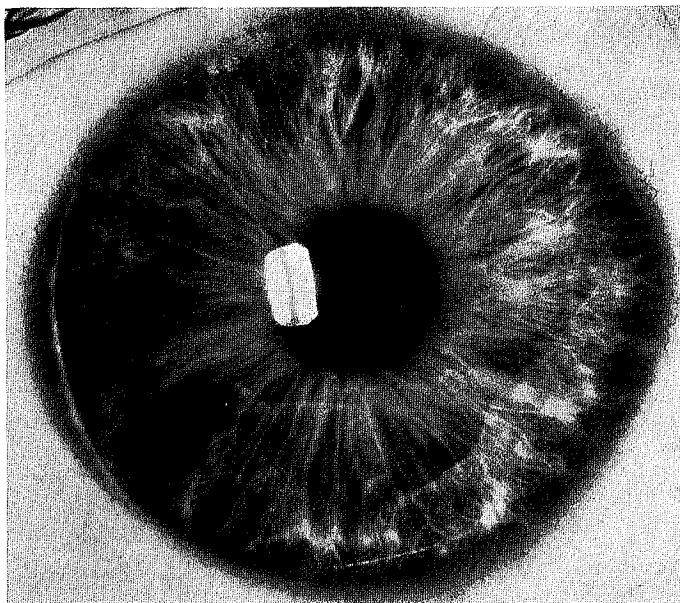
Fig. 6. Primary dysgenesis mesodermalis of the iris, illdefined limbus, well-marked posterior corneal embryotoxon and iridal hypoplasia. Normal, central pupil (PM-IV-2, right eye).

Superficial epithelial changes, opacities and secondary band-shaped corneal degeneration were observed in 12 eyes (Polte 1913; Falls 1949; Riethe and Lemmingson 1958; Levien 1966; our patient HO-III-6.

Opaque corneae were mentioned without further specification in 6 eyes (Sivasubramanian and Hoole 1955; Riethe and Lemmingson 1958; Henkind *et al.* 1965; Boles Carenini and Orzalesi 1966).

Von Grósz (1940) described keratoconus ODS, which was also mentioned by Dark and Kirkham (1968) in a patient who in addition showed Down's syndrome.

Descemet ruptures were described in patients who combined Rieger's syndrome with hydrophthalmos (Haye and Blanck 1965; Delmarcelle *et al.* 1958, 1968; our patient BR-IV-2). Unilateral descemetolysis, probably of traumatic origin, was described by Henkes (1965) in one female patient.

Cornea guttata was mentioned in 9 patients with Rieger's syndrome (Blum *et al.* 1962; Henkind *et al.* 1965).

Delicate pigmentation of the endothelium were found in 7 eyes with primary dysgenesis mesodermalis of the iris (Busch *et al.* 1960; Lemmingson and Riethe 1962; Henkind *et al.* 1965).

Central corneal leucomas were found in 19 eyes with Rieger's syndrome (Falls 1949; Paufique *et al.* 1950; Delmarcelle *et al.* 1958, 1968; Forsius 1964; Forsius and Eriksson 1964; Levien 1966; Wolter *et al.* 1967; our patients BR-IV-1, fig. 4,
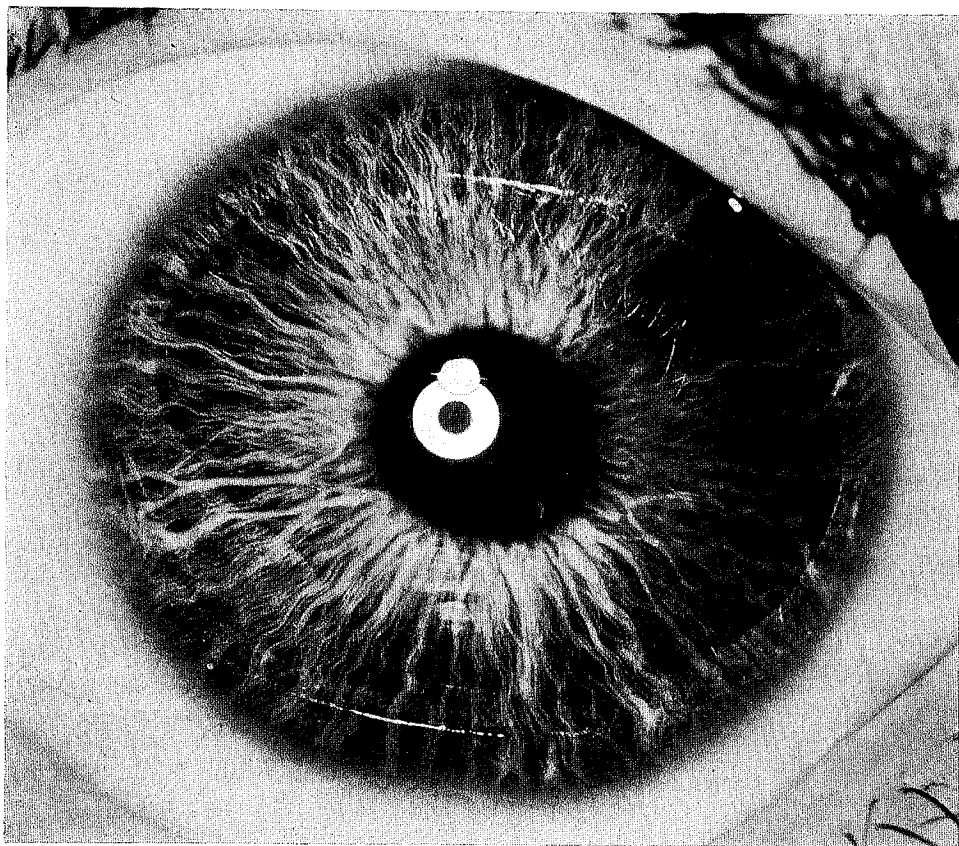
Fig. 7. Primary dysgenesis mesodermalis of the iris; hypoplasia of the iridal mesoderm with prominent posterior embryotoxon of the cornea in the nasal region (HH-III-4, left eye).

53, 54 and RK-I-1, fig. 37). Collier (1962) reported on two brothers with what was probably Rieger's syndrome, one of whom showed a deep central corneal opacity.

Corneal staphyloma was observed in the patient described by Dark and Kirkham (1968) and our patient BR-IV-1. The group of central corneal leucomas and staphylomas will be discussed in detail in the chapter on Peters' anomaly. They represent dysgenesis mesodermalis of the cornea secondary to Rieger's syndrome.

8. IRIS

a. Iridal stroma

All the eyes with primary dysgenesis mesodermalis of the iris showed *hypoplasia of the iridal stroma*. In the majority of cases this hypoplasia was very marked so that
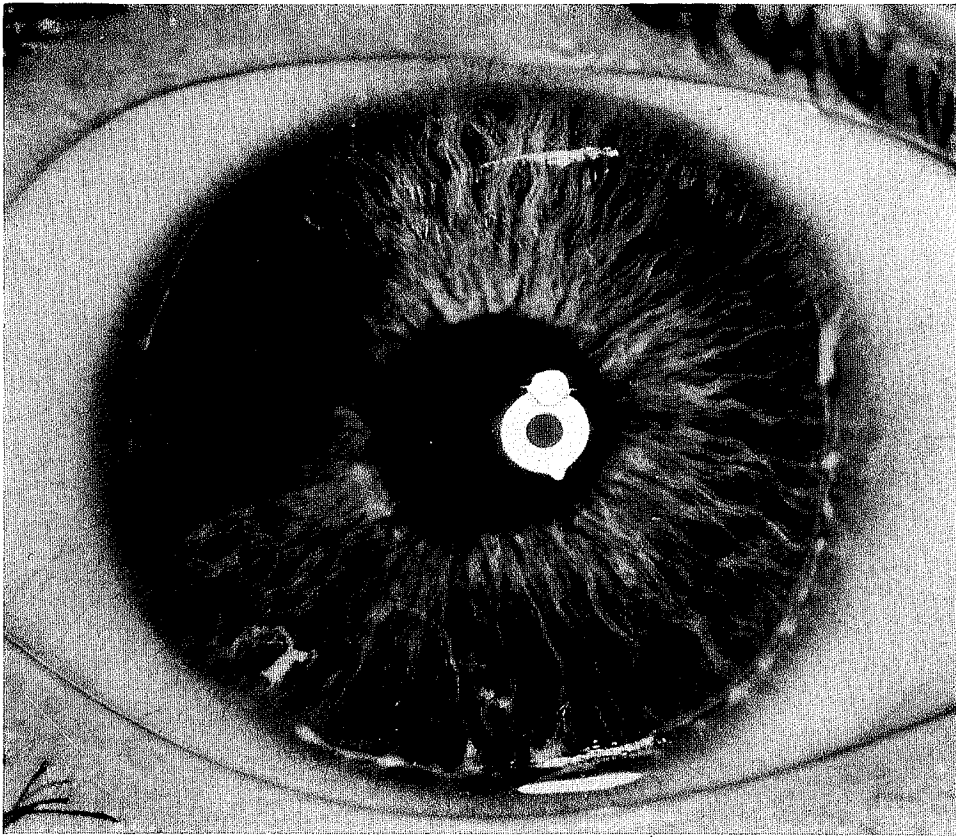
Fig. 8. Primary dysgenesis mesodermalis of the iris; hypoplasia of the iridal mesoderm and very prominent and clearly visible annular posterior corneal embryotoxon and iridocorneal adhesions in the periphery (HH-III-4, right eye).

the entire anterior mesodermal layer (Streiff's crypt layer) was absent (plates I, II, III, and fig. 2, 3, 5, 6, 9, 15-18). This hypoplastic condition was clinically manifested by a dull, sometimes rather drab iris colour. The sphincter iridis muscle was clearly visible in its entirety; it had a yellow-brown colour and formed a slight peripupillary prominence. The iridal frill was absent, as were the crypts and the contraction folds of the iris. In some cases the deep mesodermal layer with its more delicate, slender, radial structure showed changes also: the structure of this iridal tissue was rarefied so that the pigment layer shimmered through more clearly and became a more important component in the colour of the iris. This tissue was sometimes completely absent at some sites, exposing the pigment layer so that there seemed to be dark holes in the iris (fig. 11).

The hypoplasia of the iridal stroma was usually of equal intensity ODS. In cases in which the eyes differ in this respect, heterochromia may result (Burian *et al.* 1957).
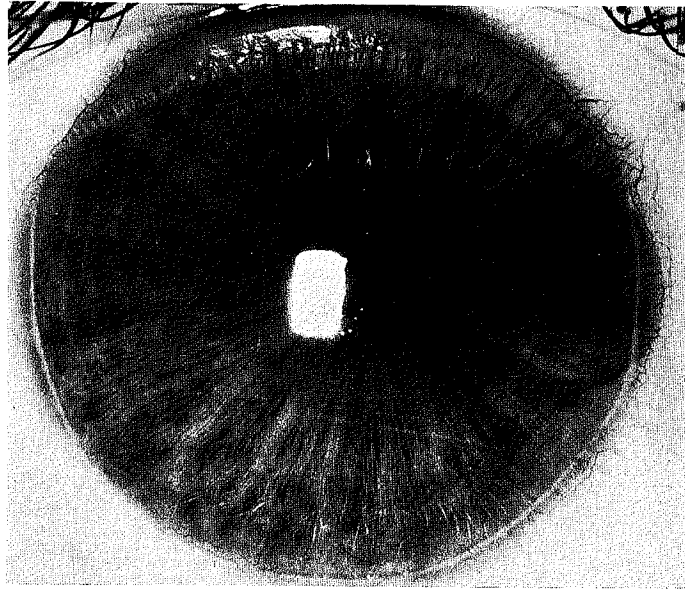
Fig. 9. Primary dysgenesis mesodermalis of the iris: besides general hypoplasia of the mesodermal iris, an annular embryotoxon corneae posterius is present; mildly ectopic pupil (BR-III-2, right eye).
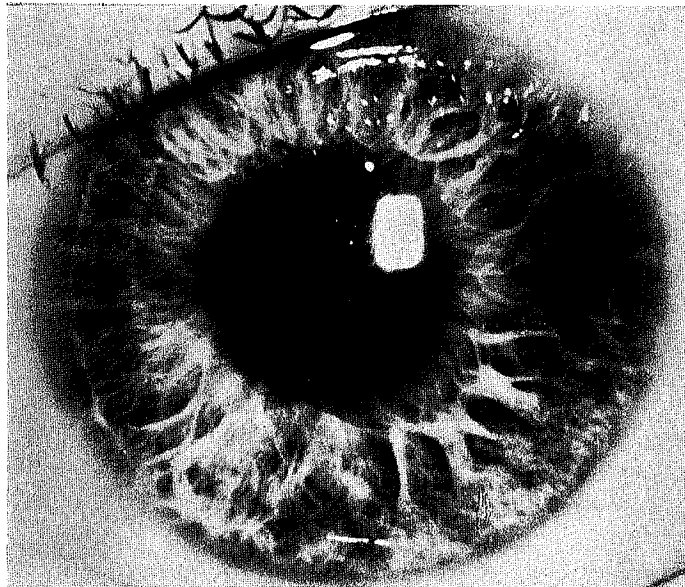

Fig. 10. Primary dysgenesis mesodermalis of the iris with thin centrad posterior corneal embryotoxon and loose, hypoplastic iridal stroma in connection with the prominent corneal ridge (HL-III-5, right eye).
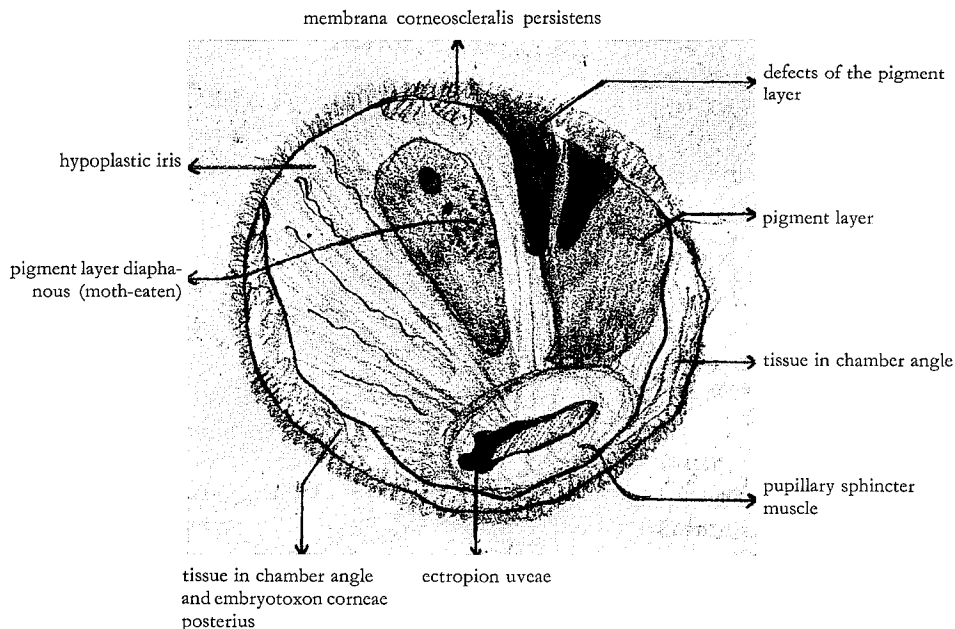
membrana corneoscleralis persistens

hypoplastic iris

pigment layer diapha-
nous (moth-eaten)

defects of the pigment
layer

pigment layer

tissue in chamber angle

pupillary sphincter
muscle

tissue in chamber angle
and embryotoxon corneae
posterius

ectropion uveae

Fig. 11. Primary dysgenesis mesodermalis of the iris, ill-defined limbus, ectopic pupil, ectropion uveae, hypoplasia of the mesodermal iris and absence of the iridal frill. Mesodermal tissue connected with the periphery of the posterior cornea fills the chamber angle. The defects in the pigment layer may be of a secondary nature (HO-III-6, right eye).

hypoplastic iris

fibrous stromal tissue

remnants of the mem-
brana pupillaris

ill-defined corneoscleral
junction

defects of the pigment
layer

pigment layer diaphanous

embryotoxon corneae
posterius

tissue in chamber angle

pigmented remnants of
tunica vasculosa lentis
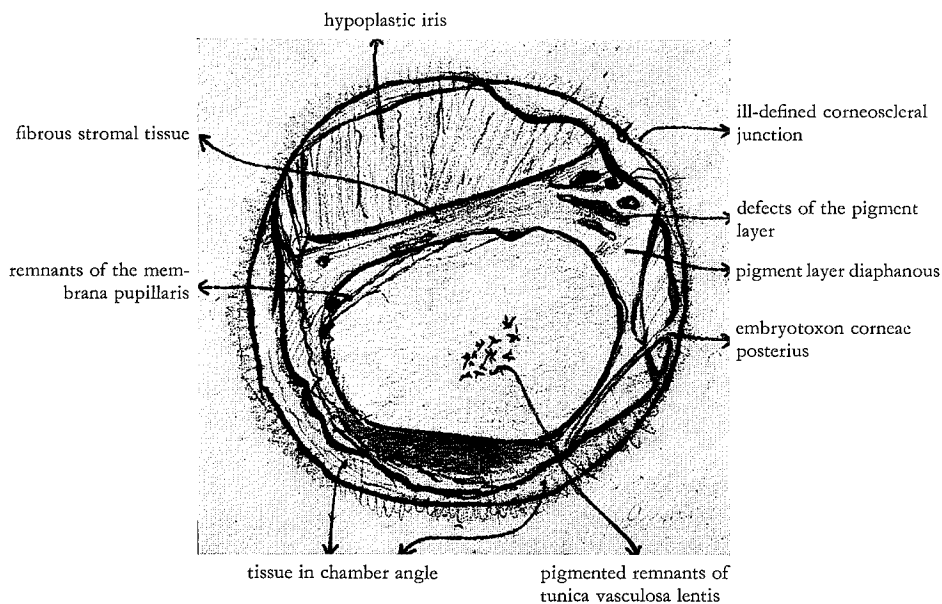
Fig. 12. Primary dysgenesis mesodermalis of the iris, ill-defined limbus, dyscoric pupil, abnormalities of the hypoplastic iridal tissue, posterior corneal embryotoxon and remnants of the pupillary membrane. Moth-eaten translucency of the pigment layer (HO-III-6, left eye).

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In a smaller proportion of the eyes with primary dysgenesis mesodermalis of the iris the hypoplasia of the iridal stroma was less pronounced, manifesting itself (fig. 10) in partial absence of the anterior mesodermal layer or a very loose, transparent structure of this layer. In many of these cases the dark brown pigment layer nevertheless shimmered through, even in the pars ciliaris of the iris.

b. Pupillary membrane

In only a few of our collection of eyes with Rieger's syndrome were persistent remnants of this embryonic membrane found (Weekers and Weekers 1950; Rejchrt and Miksa 1952; our patient HO-III-6, fig. 12).

The peculiar family described by Waardenburg (1949), with extensive membrane remnants in association with cataract of the anterior pole, microcornea, colobomas and a filamentous anterior synechia, showed a different entity in the series of hereditary developmental defects of the anterior ocular segment.

c. Pigment layer

Abnormalities of the pigment layer in patients with primary dysgenesis mesodermalis of the iris took the form of defects. For ectropion uveae, we refer to the section on the pupil.

In only 12% of eyes was the pigment layer diaphanous (however, only 51 eyes were examined specifically for this purpose). The total diaphaneity of the iris in the patient described by Hales (1968) was based on albinism.

In our own material, 24 eyes were examined with the diaphanoscope; 10 eyes were found to be positive and pathological (Abrams 1964). One patient in our series (HL-III-5) was irrelevant in this respect because he combined Rieger's syndrome with ocular albinism and totally diaphanous irides. The percentage of defects of the pigment layer in primary dysgenesis mesodermalis of the iris must therefore be considerably larger than 12%.

The combination of diaphanous irides with ectropion uveae was described in 18 eyes with Rieger's syndrome (Thye 1903; Engelbrecht 1908; Lisch 1938; Falls 1949; Sivasubramanian and Hoole 1955; Kittel 1956; Unger 1956; Forsius 1963; our figures 11, 12 and 14).

9. PUPIL

Apart from hypoplasia of the iridal stroma, other changes of the iris and pupil occur at varying rates of frequency. In primary dysgenesis mesodermalis of the iris, *pupillary anomalies* are very frequently observed (72%), although they are no prerequisite for this diagnosis.

Data on the localization and shape of the pupil were available on 298 of the 326 eyes with Rieger's syndrome, i.e. 90% of the total material.
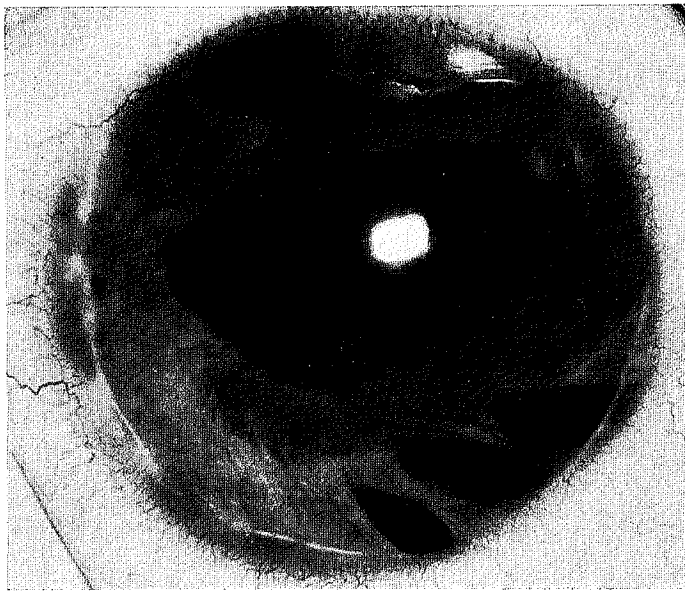
Fig. 13. Primary dysgenesis mesodermalis of the iris with hydrophthalmos, ill-defined limbus, prominent embryotoxon corneae posterius, dyscoric pupil and ectropion uveae. The hypoplastic iris shows several holes (pseudo-polycoria) (BR-IV-2, left eye).
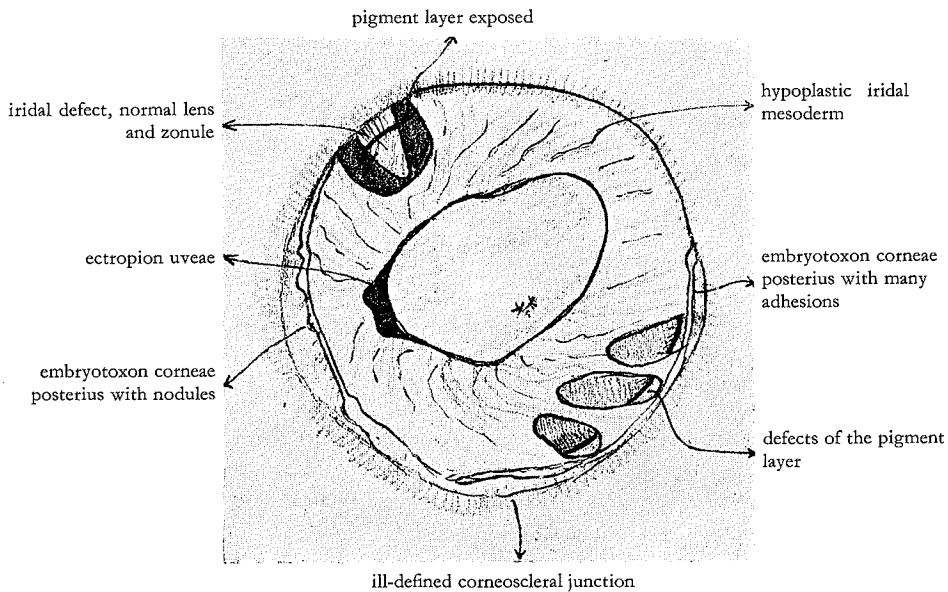

pigment layer exposed

hypoplastic iridal mesoderm

iridal defect, normal lens and zonule

ectropion uveae

embryotoxon corneae posterius with many adhesions

embryotoxon corneae posterius with nodules

defects of the pigment layer

ill-defined corneoscleral junction

Fig. 14. Schematic drawing of the same eye in fig. 13.
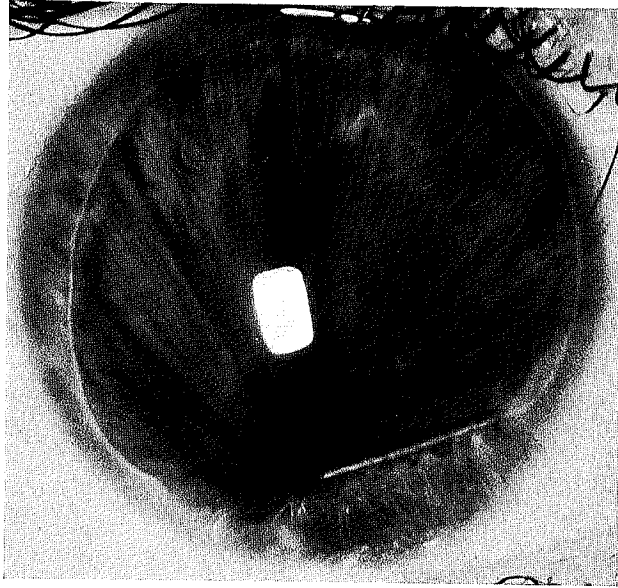
Fig. 15. Primary dysgenesis mesodermalis of the iris with marked circular embryotoxon corneae posterius, iridal hypoplasia and ectopic, dyscoric pupil (SD-III-2, right eye).

Fig. 16. Primary dysgenesis mesodermalis of the iris with marked circular embryotoxon corneae posterius, iridal hypoplasia and ectopic pupil (SD-III-2, left eye).
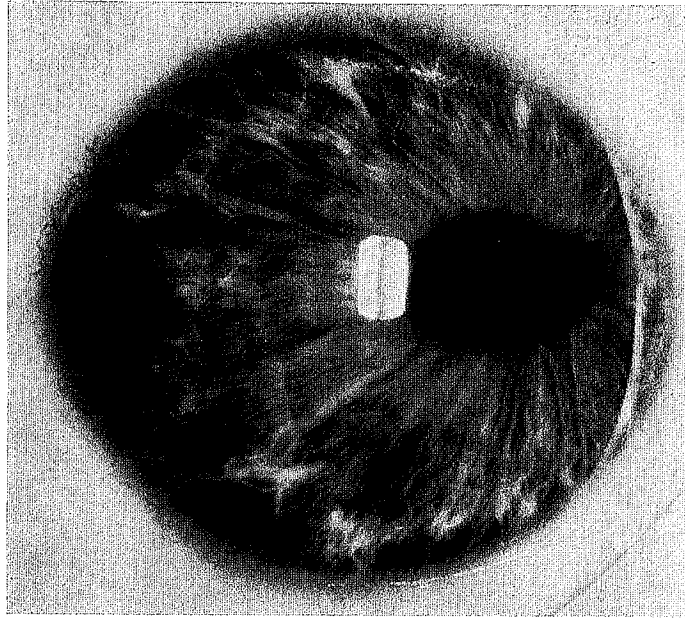
PLATE III. Primary dysgenesis mesodermalis of the iris, illdefined limbus, well-marked posterior corneal embryotoxon, iridal hypoplasia and ectopic, dyscoric pupil (PM-IV-2, left eye).

Temporal   Nasal
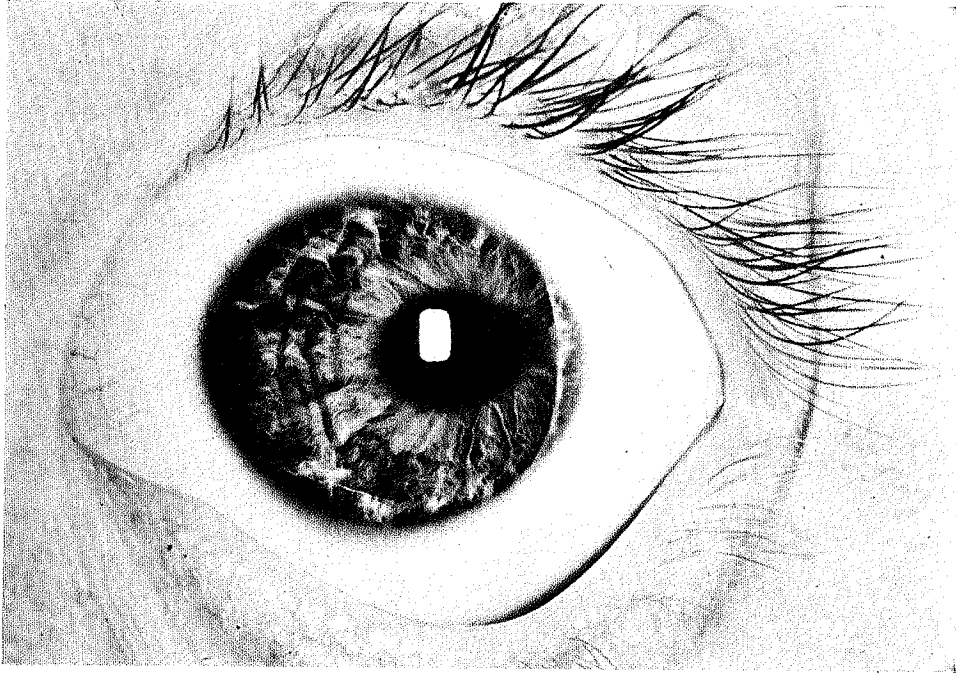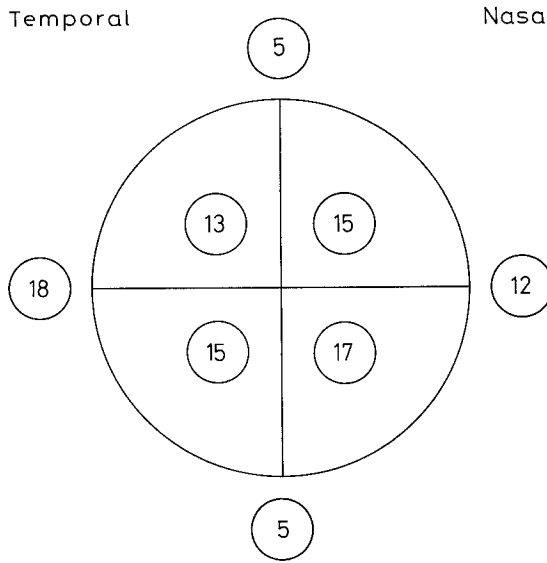
a. Localization

In 70% of the eyes with primary dysgenesis mesodermalis of the iris, the pupil was *ectopic* (figs. 11, 15-18 and plates I, III), and in 30% a *central* pupil was found (figs. 2, 3, 5, 6, 9, 10 and plate II). We define a central pupil as a pupil localized within the normal range of variation of 0.5 mm. The exact localization of the pupil was know in 164 of the 204 cases of ectopia. The percentual distribution is shown in table 12. This table shows that temporal and nasal ectopia

Fig. 17. Primary dysgenesis mesodermalis of the iris, bilateral symmetrical, ectopic pupils, hypoplasia of the mesodermal iris with clearly visible sphincter pupillae muscles and pigment layer shimmering through (BS-III-6).

Fig. 18. Primary dysgenesis mesodermalis of the iris, ill-defined limbus, well-marked posterior corneal embryotoxon, iridal hypoplasia and ectopic, dyscoric pupil (PM-IV-2, left eye).

were equally frequent, and that the pupil was as often localized above as below the horizontal line. It also indicates that the distribution over the various quadrants showed no significant differences apart from some slight predilection for the lower nasal quadrant. In Rieger's syndrome, ectopia of the pupil was three times as frequent in the horizontal as in the vertical line. Only 13% of the ectopic pupils were round (as against 88% of the central pupils).

b. Shape

Of the 298 eyes with Rieger's syndrome, 107 (36%) had round pupils while 191 eyes (64%) showed *dyscoria*: the pupil was oval, irregular, triangular, slit-shaped or egg-shaped (figs. 1, 11-16, 18 and plate III). Of the *round* pupils, 75% were central (plate II) and 25% ectopic; of the dyscoric pupils, 6% were central and 94% ectopic.

c. Pupillary border

Little is known about the pupillary border in patients with Rieger's syndrome. In a few cases this border was described as irregular. It was described as entirely normal in a total of 27 eyes.

An *ectropion uveae* was observed in 44 eyes with primary dysgenesis mesodermalis of the iris, i.e. 15% of the total number of cases (Thye 1903; Engelbrecht 1908; Rossano 1934; Rieger 1935; Mathis 1936; Lisch 1938; Braendstrup 1948; Hugger 1948; Falls 1949; Sivasubramanian and Hoole 1955; Kittel 1956; Unger 1956; Burian *et al.* 1957; Riethe and Lemmingson 1958; Delmarcelle *et al.* 1958; Forsius 1963; Guillerez 1963; Henkind *et al.* 1965; Delmarcelle 1968; our figures 11, 13 and 14).

In patients with the Rieger syndrome, ectropion uveae was invariably associated with dyscoric pupils.

10. IRIDOCORNEAL ANGLE

In eyes with primary dysgenesis mesodermalis of the iris, *anomalies of the iridocorneal angle* invariably occur although the iridocorneal angles are open and the anterior chambers are deep or of normal depth.

In the majority of cases the abnormalities of the anterior chamber angle were visible with the slit-lamp in the area of the limbus or iridal root, but in a smaller proportion of cases they can be brought to light only by gonioscopic examination.

The first gonioscopic descriptions of the iridocorneal angle in patients with Rieger's syndrome were presented by Busacca and De Pinticart (1948) and Tavolara (1949).
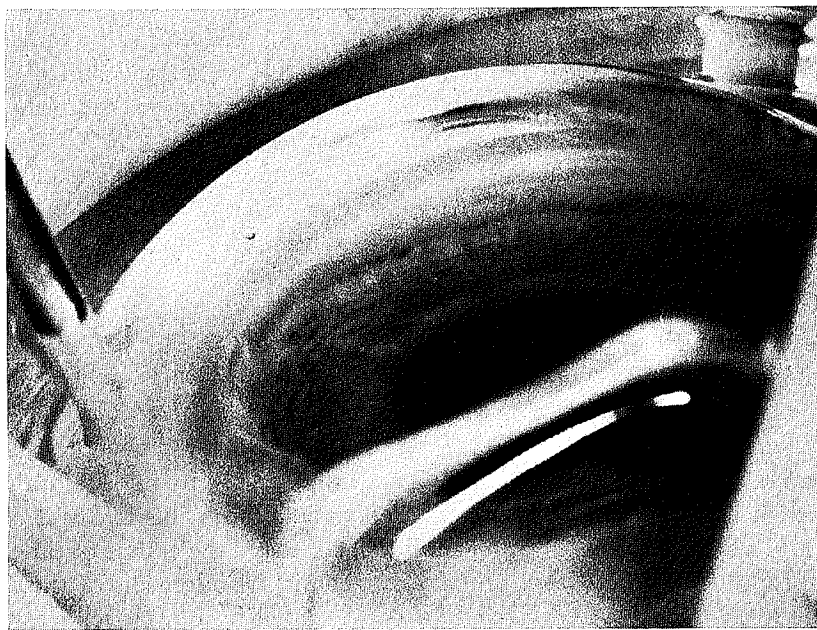
Fig. 19. Gonioscopic view in primary dysgenesis mesodermalis of the iris: peripheral connections between iris root and centrad embryotoxon corneae posterius (SD-IV-1).
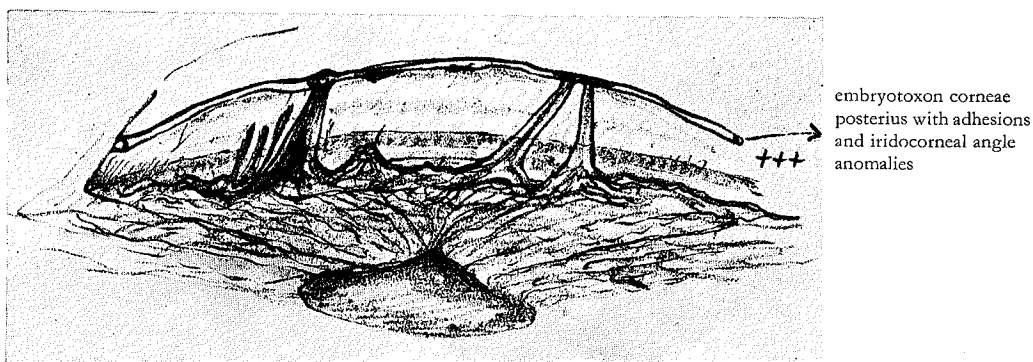
embryotoxon corneae
posterius with adhesions
and iridocorneal angle
anomalies

+++

Fig. 20. Gonioscopic view in primary dysgenesis mesodermalis of the iris: extremely prominent embryotoxon corneae posterius protruding into the anterior chamber; stroma-coloured adhesions of varying width between the iridal root and the ridge; mild dyscoria of ectopic pupil (BR-IV-1).

The angle anomalies can vary widely in extent and intensity but always consist of adhesions between the hypoplastic iridal stroma and the pathological prominent line of Schwalbe or the embryotoxon corneae posterius, which often shows centrad displacement and a broadening of the trabecular zone. These adhesions can extend from the iridal root and be so delicate and scanty as to be almost or completely invisible at slit-lamp examination. Both the width and the thickness of these "synechiae" can range from very slender, filamentous to broader conical or very broad trapezoidal or membranous structures. The adhesions always arise from the usually thickened, pronounced and externally quite clearly visible embryotoxon corneae posterius, extending to the stroma of the iridal root or traversing to the pars ciliaris (figs. 19-25).

In a few rare cases the adhesions extend towards the pars pupillaris of the iris, in which event the pupil is usually in a very ectopic peripheral position. In such cases the peripupillary zone and even the sphincter iridis muscle can be directly adherent to the embryotoxon cornea posterius (fig. 15, 16).

The tissue which makes up these adhesions, as a rule resembles the iridal stroma and has similar qualities, but in a few cases this tissue is of quite different appearance: it is white and can seem to be rigid and fibrous.

In several cases the adhesive strands seem to exert traction on the pupil, which is consequently distorted; when there are strands at several peripupillary sites, the pupil can be slitshaped or triangular. Contraction caused by miotics can greatly alter the iridal and pupillary features of an ectopic pupil. This makes it difficult to evaluate real changes of the pupil and iridal stroma in the course of time.

In a proportion of eyes with primary dysgenesis mesodermalis of the iris the space between trabecula and iridal root can be filled by brown-yellow to light yellowish-white tissue of low or high density.

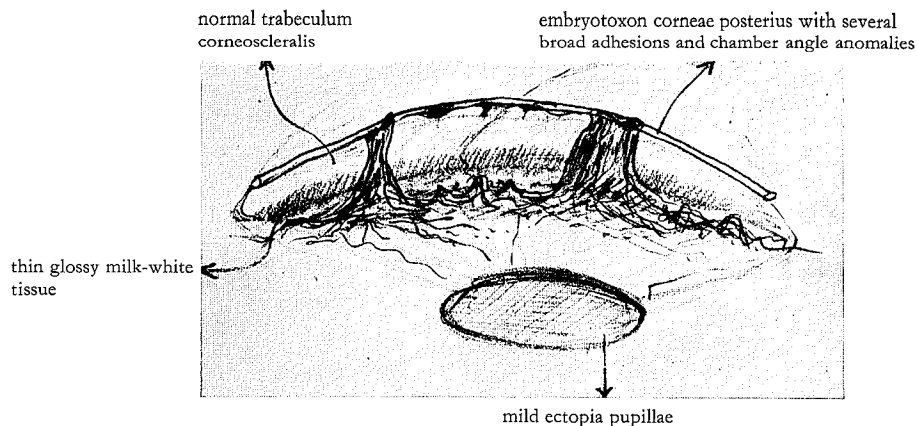The gonioscopically visible parts of the iridocorneal angle, i.e. such parts as

normal trabeculum
corneoscleralis

embryotoxon corneae posterius with several
broad adhesions and chamber angle anomalies

thin glossy milk-white
tissue

mild ectopia pupillae

Fig. 21. Gonioscopic view of primary dysgenesis mesodermalis of the iris;
posterior corneal embryotoxon with many broader and smaller pigmented
iridocorneal adhesions; the deeper parts of the chamber angle are covered
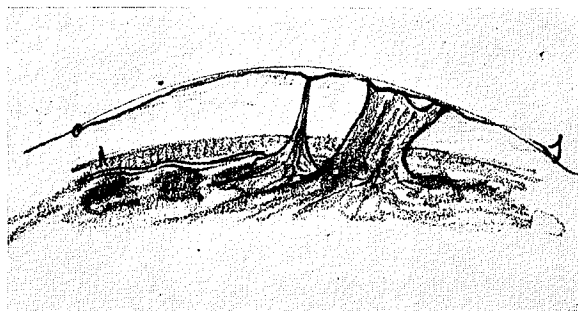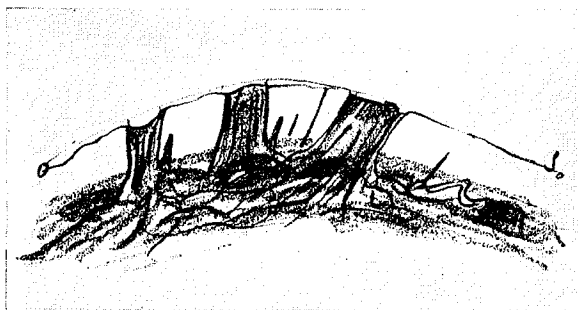by a very thin, glossy, milkywhite tissue (BR-III-2).

Fig. 22.

Fig. 23.

Gonioscopic view in primary dysgenesis mesodermalis of the iris: prominent irregular posterior corneal
embryotoxon with broad and small iridocorneal adhesions. The ciliary band was covered by a thin, glass-
like fibrous tissue which obscured the scleral spur (BS-III-6).

Fig. 24. Gonioscopic view in primary dysgenesis mesodermalis of the iris: broad connections between iris root and embryotoxon corneae posterius (BS-III-6).

are not covered by the abovementioned iridocorneal adhesions, are often quite normal, e.g. as in glaucoma simplex. In some cases, however, parts of the trabecula and the ciliary band are covered by a fine, glistening, fibrous, whitish or vitreous tissue, which forms a thin layer (BS-III-6 and BR-III-2, fig. 22, 23 and fig. 20).

When Schlemm's canal is visible or can be made visible, it proves to be in a normal position in relation to the scleral spur or ciliary band.

In our eyes with Rieger's syndrome, the insertion of the iridal root was always found in a normal localization, although in some cases it was slightly stretched. No abnormally intensive pigmentation was observed and, so far as we could establish, gonioscopic features such as those of degeneration of the pigment layer with glaucoma (pigment glaucoma or pigment dispersion syndrome) were never observed. Not even in cases characterized by extensive defects in this part of the iris (BR-IV-2).

The iridal root was often hypoplastic, with an increased frequency of visible iridal vessels and lobulation of the peripheral boundary of the pigment layer. The latter, however, is also fairly common in normal eyes without hypoplasia of the iridal stroma, and in eyes with glaucoma simplex.

II. INTRAOCULAR PRESSURE

a. Glaucoma

The clinical significance of primary dysgenesis mesodermalis of the iris is largely determined by the glaucoma which often accompanies this developmental defect.

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This secondary glaucoma, which is relatively seldom manifested as hydrophthalmos but more frequently as *juvenile glaucoma*, can cause insidious loss of function and thus lead to absolute glaucoma.

In this way Rieger's syndrome constitutes one of the causes of blindness on the basis of congenital glaucoma or glaucoma of early childhood. There are no data on the incidence of glaucoma in the syndrome, but our study revealed that this incidence is by no means negligible.

The intraocular pressure was known of 281 eyes with primary dysgenesis mesodermalis of the iris (86% of the total material). It was normal in 40% of these cases, and increased in 60%. The readings obtained ranged between 22 and 65 mm Hg.

Several patients with primary dysgenesis mesodermalis of the iris showed lower intraocular pressure during the night. Breebaart (1966) observed sharply falling intraocular pressure in his patient when she was asleep, independent of day or nighttime.

Congenital glaucoma can certainly occur in Rieger's syndrome. Hydrophthalmos was mentioned by Maxwell (1936), Falls (1949), Weekers and Weekers (1950), Sivasubramanian and Hoole (1955), Delmarcelle *et al.* (1958, 1968), Nenquin and Brihaye (1959), Gassler and Berthold (1960), Haye and Blanck (1965) and Belmonte (1966). It was observed also in Baratta's (1937) familial cases of bilateral corectopia, slitpupil, polycoria and ectropion uveae.

However, it is by no means certain whether all these cases involved real hydrophthalmos, i.e. a secondary enlargement of the bulbus as a result of connatal or very early glaucoma. As we pointed out, macrocornea without glaucoma is a fairly common finding in primary dysgenesis mesodermalis of the iris, and the same applies to macrocornea with glaucoma. This explains the tendency to diagnose incidental cases of the syndrome with macrocorneae and glaucoma as involving hydrophthalmos. This diagnosis is certainly justified, however, when there are descemet ruptures (Delmarcelle *et al.* 1958, 1968; Haye and Blanck 1965; our patient BR-III-2). If the increase in intraocular pressure occurs before age 3, then hydrophthalmos may be considered as a diagnosis even in the absence of descemet ruptures (Delmarcelle *et al.* 1958, 1968). However, when the glaucoma occurs or is diagnosed at a later age in a patient who shows macrocornea but no descemet ruptures (Maxwell 1936; Falls 1949; Weekers and Weekers 1950; Nenquin and Brihaye 1959; Belmonte 1966), then hydrophthalmos is an uncertain diagnosis; for these could be cases of juvenile glaucoma with macrocornea as another aspect associated with Rieger's syndrome.

In evaluating *glaucoma* and *macrocornea*, our starting-point was that in these cases macrocorneae cannot always be regarded as manifestation of a so-called abortive or "cured" connatal glaucoma, but may be an aspect of the developmental defect, of which the glaucoma is another aspect. In the majority of cases, therefore, there was no direct causal relation between glaucoma and macrocornea.

In the families described by Weekers and Weekers (1950) and by Delmarcelle

et al. (1958, 1968), several patients with Rieger's syndrome showed both "buphthalmos" and megalocornea. Primary hydrophthalmos and megalocornea in the same family is also a combination described several times (Veil and Sarrazin 1937; Vom Hofe 1938, 1940; Trautmann 1952; Schweitzer 1962, and others). Macrocorneae without other developmental defects of the anterior ocular segment were described by such authors as Friede (1933a, 1933b) and Rud (1960), while Kadlecová (1959) described macrocorneae without glaucoma but with gonioscopic changes.

b. *Tonography and glaucoma aetiology*

Patients with primary dysgenesis mesodermalis of the iris were submitted to tonographic examination by Nenquin and Brihaye (1959), Busch *et al.* (1960), Blum *et al.* (1962), Frandsen (1963), Guillerez (1963), Royer and Géhin (1963), Ernyei (1965), Henkind *et al.* (1965), Sugar (1965), Boles Carenini and Orzalesi (1966), Breebaart (1966), Bernardczykowa (1967) and ourselves.

Tonographic findings were available on a total of 49 eyes. They were normal in the 16 eyes with Rieger's syndrome without glaucoma ($c > 0.15$). Of the 33 eyes with the syndrome and glaucoma, 18 had pathological readings ($c \leqslant 0.10$); the values were dubious in 9 eyes ($c > 0.10 \leqslant 0.15$) and quite normal in 6 eyes.

These tonographic data show that the majority of cases of primary dysgenesis mesodermalis of the iris with glaucoma were characterized by a *reduced outflow of aqueous humour* while the outflow was normal in eyes in which the syndrome was not associated with increased intraocular pressure. These findings would seem to warrant the conclusion that the glaucoma in Rieger's syndrome is based on an increased resistance to outflow.

The adhesions between the embryotoxon corneae posterius and the iris cannot be held responsible in this respect, because they left sufficient space for an adequate outflow of aqueous humour to the iridocorneal angle and the trabecular system. Even in the cases which showed virtually total circular iridocorneal adhesion, the intraocular pressure was not necessarily increased (SD-IV-1). On the other hand there were cases with considerably increased intraocular pressure despite relatively few adhesions (BS-III-6). The iridocorneal adhesions, therefore, do not interfere with the pathogenesis of glaucoma in primary dysgenesis mesodermalis of the iris.

A further analysis of these complicated features, however, would be too far beyond the context of this study. It is therefore difficult to determine the exact incidence of connatal glaucoma in primary dysgenesis mesodermalis of the iris although this incidence is probably not very high. If all eyes with Rieger's syndrome, macrocorneae and glaucoma (39 eyes) were truly hydrophthalmic, then the incidence of descemet ruptures should be higher than that described. It is possible, however, that these ruptures (which accompany hydrophthalmos in most cases) existed but were not described in the case reports. A total of 22 eyes with Rieger's syndrome were described as "buphthalmic". Table 13 shows the

PLATE IV. Fundus in primary dysgenesis mesodermalis of the iris. Marked hypoplasia of the choroidal vessels is evident (SD-IV-1, left eye).
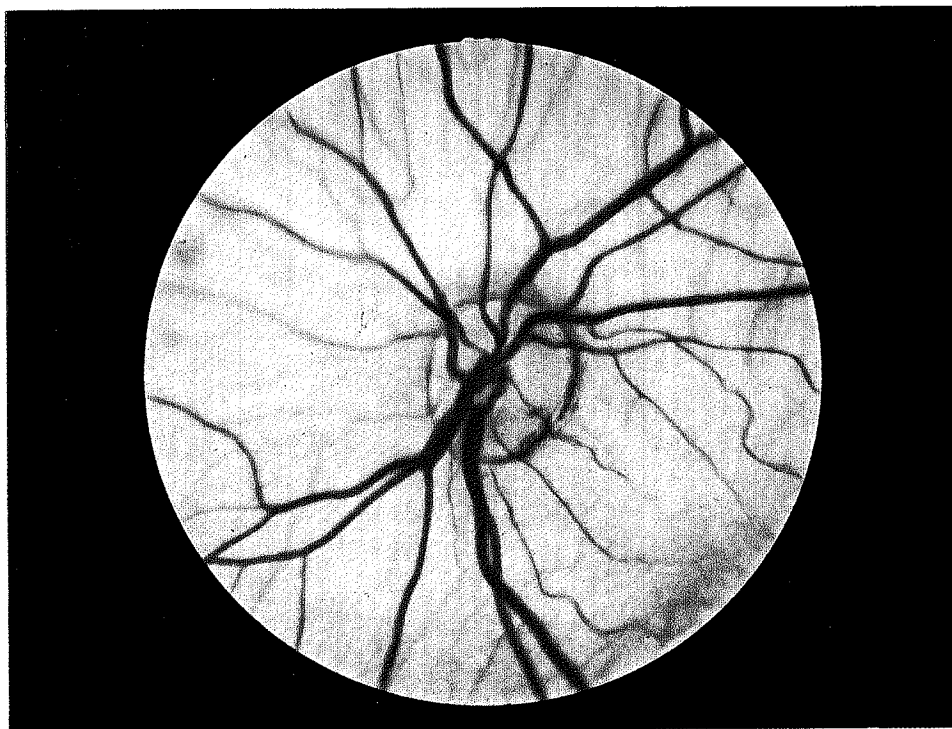

Table 13. Age distribution of patients with primary dysgenesis mesodermalis of the iris (Rieger's syndrome) with and without glaucoma.

Age in years	Glaucoma present	Glaucoma absent
0- 1	14	8
1- 2	4	---
2- 3	2	---
3- 4	2	2
4- 5	2	6
0- 5	24	16
5-10	18	19
10-15	26	25
15-20	19	6
20-30	25	19
30-40	22	15
40-50	18	9
> 50	12	8
Total	164	117
%	60	40

age distribution of the cases of primary dysgenesis mesodermalis of the iris with and those without glaucoma. The age given is that at which increased or normal intraocular pressure was first determined. The two groups show practically the same age distribution and composition.

Bearing in mind that glaucoma almost certainly became manifest at an earlier age in most cases than the age recorded, we may conclude that glaucoma in Rieger's syndrome is of the *infantile* and especially the *juvenile* type. The glaucoma classification according to age was used for practical reasons. In our opinion, there is *no essential* difference between these forms, nor between these forms on the one hand and connatal glaucoma on the other. Unilateral glaucoma is an exception in cases of primary dysgenesis mesodermalis of the iris (Falls 1949).

The cases in which, besides adhesions, tissue had remained in parts of the iridocorneal angle, were not sufficiently numerous to establish whether in these eyes the glaucoma incidence was significantly higher than in eyes without such tissue. As we established in a few cases, eyes with such tissue in the iridocorneal angle can show a normal intraocular pressure.

The thin layer of fibrous tissue sometimes observed to cover the trabecula, masking its structure, can be associated with glaucoma (BS-III-6, fig. 22, 23) or not (BR-II-2); on the other hand, there may be glaucoma while the trabecula has an entirely normal appearance.

Therefore, while gonioscopy reveals the results of a defect in the development of the iris and iridocorneal angle, these results cannot be identified as the anatomical cause of the glaucoma. It seems highly probable that the visible developmental defect of the primary dysgenesis mesodermalis of the iris extends invisibly into the trabecula and the further structure controlling the outflow of aqueous humour.

The functional disturbance observed is probably based on a defect or retardation of the structural differentiation of the corneoscleral trabecula and the anterior wall of Schlemm's canal. In this light, the glaucoma observed in Rieger's syndrome can be regarded as coming under the heading of the *developmental glaucomas* (Gorin 1964), *or teratological glaucoma* which also encompasses the juvenile glaucoma observed in such conditions as primary hydrophthalmos, aniridia, Peters' anomaly (dysgenesis mesodermalis of the cornea), Sturge-Weber-Krabbe's syndrome, microcornea, megalocornea and probably also connatal iridal hypoplasia.

The familial cases of mesodermal changes of the iridocorneal angle with glaucoma, with or without pigment dispersion, as described by Weekers and Watillon (1957, 1966) might also be brought under this heading.

The *lens* was described as normal in 93 eyes with primary dysgenesis mesodermalis of the iris, and no relevant data were available on 168 such eyes. Of the 67 eyes with Rieger's syndrome and lenticular abnormalities, 39 showed a star-shaped arrangement of brown pigment on the anterior surface of the lens; this pigment was regarded as a remnant of the embryonic vascular capsule of the lens and of the pupillary membrane (figs. 12 and 14). However, these pigmentations are fairly common also in other developmental defects, and can be observed in quite normal eyes as well.

Wolter *et al.* (1967) described luxation of the lens into the anterior chamber in a patient with Rieger's syndrome and corneal staphyloma. Subluxation of the lens – usually in a very slight degree – was described in a total of 8 patients with primary dysgenesis mesodermalis of the iris (Falls 1949; Burian *et al.* 1957; Busch *et al.* 1960; Lemmingson and Riethe 1962; Yigitsubay 1967; our patient BR-IV-2). Our patient also showed an (artificial?) coloboma of the lens; and such a coloboma was described also by Henkind *et al.* (1965).

The other lenticular changes described encompass cataracts of many types: partial lamellar (Theodore 1944), cuneiform (Falls 1949), punctate (Weekers and Weekers 1950; Burian *et al.* 1957), juvenile (Thye 1903; Falls 1949), cupuliform (Henkind *et al.* 1965), nuclear (Delmarcelle *et al.* 1958), cerulean (SD-III-2), congenital (Burian *et al.* 1957), senile and anterior polar (Falls 1949), anterior corti-cal (HO-III-6), subcapsular (Crawford 1967) and not further specified cataracts (Kittel 1956; Lemmingson and Riethe 1958; Henkind *et al.* 1965; Boles Carenini and Orzalesi 1966).

Few data were available on the *vitreous body*, which was described as normal in 72 eyes. Opaque streaks in the vitreous were observed in only one patient (Falls 1949). Although we carefully searched for them, we found no special changes in the vitreous body in our own material.

13. OCULAR FUNDUS

Normal fundi were described in 136 eyes with primary dysgenesis mesodermalis of the iris; in 95 eyes the fundi were reported to show abnormalities.

a. Optic disc and vessels

Of the optic disc changes observed in 63 eyes, 90% consisted of glaucomatous cupping. In all these cases, glaucoma was observed, and no cupping was found in the group of eyes with Rieger's syndrome without increased intraocular pressure. Coloboma of the disc was observed in 4 cases (Engelbrecht 1908; Busch *et al.* 1960; Wolter *et al.* 1967); a transverse oval disc was found in 2 patients (Unger 1956; Forsius 1963); and our patient PM-IV-2 (fig. 33) showed a large

upward heterotopic conus ODS. According to Ida Mann (1957), the lastmentioned abnormality is a developmental defect which begins between the 8 mm and the 11 mm stage (33 days); she regards it as an anomaly of the primitive epithelial disc, caused by germinal rather than exogenous factors.

Connatal vascular anomalies in the form of an abnormal origin or course of the vessels from the optic disc, were found in 15 eyes with Rieger's syndrome (Niederegger 1920; Rieger 1935; Mathis 1936; Braendstrup 1948; Callahan 1956; Henkind *et al.* 1965). Most of these cases involved a nasal displacement of the vessels or situs inversus. Connatal tortuosity of the vessels was found in 4 eyes (Rieger 1935; Gassler and Berthold 1960).

The vascular changes and connatal disc anomalies found in primary dysgenesis mesodermalis of the iris were usually of a relatively low frequency, and were of a kind repeatedly found also in normal eyes. We attach no special significance to these changes.

b. Retina and choroid

A few fundi of eyes with Rieger's syndrome showed myopic changes, and detachment of the retina was found in 2 patients.

Unilateral cystic *macular degeneration* was reported in one 40-year-old man with Rieger's syndrome (Forsius and Eriksson 1964), and pigment displacements in the macular region were observed in 3 young patients (5 eyes) in the family described by Falls (1949). Forsius (1964) mentioned macular pigmentations in combination with other fundus changes in an 11-year-old girl with primary dysgenesis mesodermalis of the iris. A striking feature was the presence of *medullated nerve fibres* in 3 patients with the syndrome (Rieger 1935; Forsius 1964; our patient HO-III-6).

Chorioretinal colobomas were observed in the patients described by Lemmingson (1961), Guillerez (1963) and Fontaine *et al.* (1963).

Markedly albinotic fundi were observed in our patient HL-III-5, who suffered from ocular albinism and Rieger's syndrome. *Choroidal hypoplasia* was mentioned by Forsius (1964), Marx (1965), and histologically indicated by Busch *et al.* (1960). The choroidal pattern of vascularization is clearly visible in individuals with a fair complexion and little pigmentation. The choroidal hypoplasia we observed in our patients SD-IV-1 (plate IV) and PM-IV-2 was a striking feature. It seems likely that in primary dysgenesis mesodermalis of the iris there is *primordial hypoplasia*, not only of the mesodermal iris but also *of the choroid*. Not only the mesodermal iris but also the choroid are known to originate from the paraxial mesoderm, which differentiates in the embryonic phase. Unlike the iridal mesodermal hypoplasia, which is always quite apparent, the choroidal hypoplasia is not always visible ophthalmoscopically. In patients with Rieger's syndrome whose fundi are blond, the degree of choroidal development must always be carefully noted.

The *clinical course* of primary dysgenesis mesodermalis of the iris is closely related to the development of the glaucoma. If increased intraocular pressure is absent or if it can be successfully controlled, then the clinical picture is quite stationary, and no structural or functional changes occur in the course of the years (SD-III-2 and BR-III-2).

In the presence of glaucoma, however, the clinical course is determined by the response of this glaucoma to therapy. In these cases there may be dynamic changes in the initially static features which existed at birth.

Progressive iridal changes of an atrophic type are seldom observed in primary dysgenesis mesodermalis of the iris and form no part of the normal clinical picture of this anomaly. Progressive essential iridal atrophy is an entirely different entity with its own clinical characteristics, and its differentiation from Rieger's syndrome is therefore not difficult. In the chapter on differential diagnosis this will be discussed in detail with reference to some of our own patients.

Iridal changes consisting of progressive thinning and rarefaction of the iridal stroma were described in only a few patient with primary dysgenesis mesodermalis of the iris (Rieger 1935; Falls 1949; Lemmingson and Riethe 1958; Busch et al. 1960; Blum et al. 1962; Forsius and Eriksson 1964). The first case of Lisch (1938) may also have shown a progressive tendency. No other mention of these progressive changes can be found; in 44 eyes with Rieger's syndrome followed up for several years, these progressive changes were explicitly ruled out (Boles Carenini and Orzalesi 1966; personal observations). The patients who did show the progressive changes as a rule had for years suffered from ill-controlled glaucoma, and in some 50% of these cases the progression did not occur until after a glaucoma operation.

In our opinion, the family described by Blum et al. (1962) suffered from primary dysgenesis mesodermalis of the iris, which is frequently described as a familial disease. Progressive changes were clearly described only in their first case, but they did not occur until after an unsuccessful glaucoma operation. Goniosynechiae not uncommonly occur or show an increase after such operations. In the clinical picture the progression observed was of subordinate importance.

The progressive iridal atrophy which Forsius and Eriksson (1964) described in a few relatives with iridal anomalies and glaucoma (which we believe to have been Rieger's syndrome), was uncharacteristic. It should be regarded as a consequence of the intractable glaucoma and the use of strong miotics.

It is not surprising that, in the presence of glaucoma, the hypoplastic iridal stroma in primary dysgenesis mesodermalis of the iris can become atrophic and rarefied; its resistance is likely to be lower than that of normal iridal stroma. That this is sometimes observed, however, does not imply that progression of iridal changes is a characteristic feature of primary dysgenesis mesodermalis of the iris, as it is of essential progressive iridal atrophy. When observed occasionally in

Fig. 25. Worst goniotomy in primary dysgenesis mesodermalis of the iris: cleavage at the level of the trabecular system by Worst goniotomy-needle (BS-III-6).

Rieger's syndrome, it always follows glaucoma of many years' standing. In progressive iridal atrophy the reverse is often seen: the progressive iridopupillary changes precede the usually intractable glaucoma.

Rieger (1935) already pointed out that slight progression (secondary atrophy of the mesodermal iris) can be a sequela of glaucoma, and chiefly in eyes with ectopic pupils in which traction could be expected to cause abnormal tensions in the stroma. This part of the iridal stroma could consequently degenerate more quickly.

The *therapy* of glaucoma in patients with primary dysgenesis mesodermalis of the iris is not always very simple; it is impossible to formulate general rules or deduce such rules from the literature. Besides the conventional conservative anti-glaucomatous therapy with miotics and agents inhibiting the production of aqueous fluid, which in some cases is sufficient, many eyes with Rieger's syndrome were treated by operation.

If by conservative means the intraocular pressure could not be normalized, then a surgical intervention was often resorted to. Operations performed with varying success have included Elliot trephination of the sclera, cyclodialysis, cyclodiathermy, sclerotomy with (Scheie) or without cauterization, iridectomy, iridencleisis, goniopuncture and operations on the iridocorneal angle according to Barkan.

While some good results have been obtained, a comparative evaluation is difficult because the literature often fails to present data on longer follow-ups. In many cases the abovementioned procedures were reported to have normalized the intraocular pressure; on the other hand, there were many failures.

Fig. 26. Primary dysgenesis mesodermalis of the iris, telecanthus, hypertelorism, broad nose, receding chin and macrocorneae (SD-IV-1).
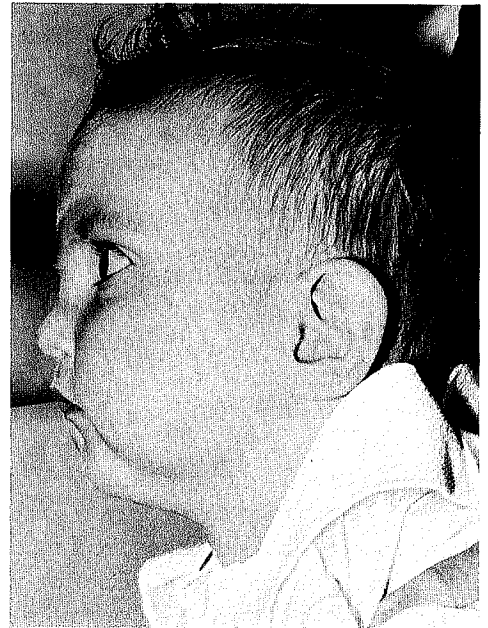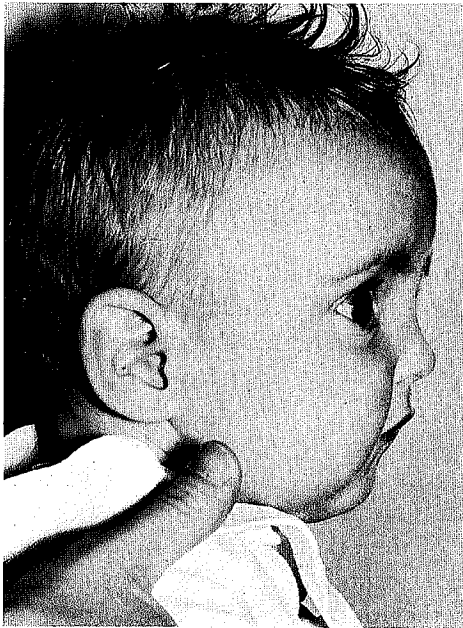
The results obtained in 3 of our patients treated by goniotomy according to Worst (1966) were initially fair, but subsequently disappointing: in patient BS-III-6 the intraocular pressure increased again and another goniotomy (fig. 25)

Fig. 27. Primary dysgenesis mesodermalis of the iris, telecanthus, hypertelorism, mandibular prognathism with underhung bite, sunken upper lip and pronounced lower lip. Esotropia OS (SD-III-2).
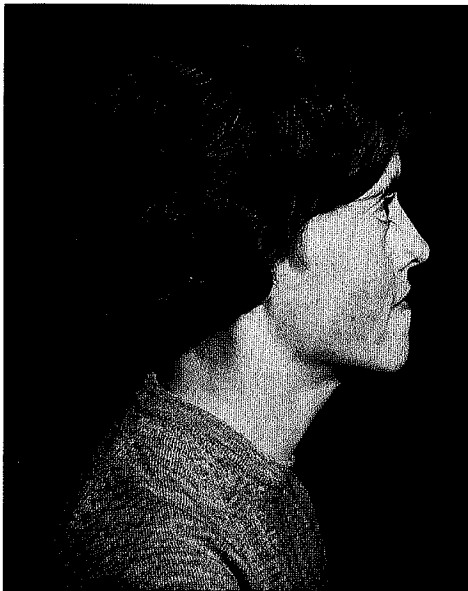
was performed, but without lasting success. While the goniotomy results in our patients BR-IV-1 and BR-IV-2 were initially hopeful, the intraocular pressure subsequently increased considerably again in these patients also, even after

Fig. 28. Primary dysgenesis mesodermalis of the iris. No abnormalities of facial dimensions (BR-IV-1).
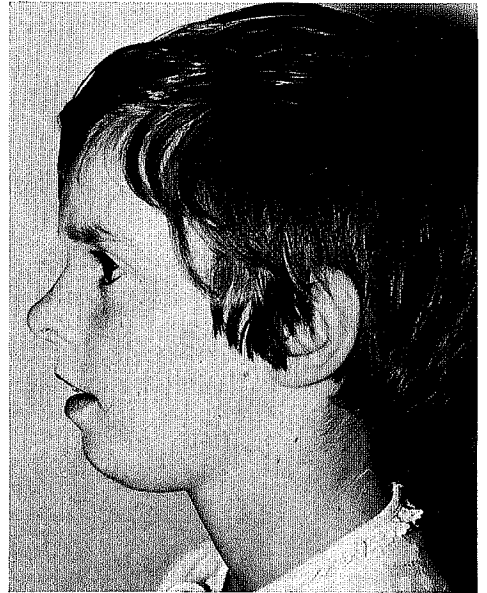
repeated goniotomy. Perhaps it is only when performed at a very early age on Rieger eyes with connatal glaucoma that this operation can yield good results.

The ultimate impression is that, for "older" patients, an ample filtering antiglaucomatous operation is most likely to be successful when conservative measures fail.

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Fig. 29. Primary dysgenesis mesodermalis of the iris. Clinical hypoplasia of the zygomatic arches; borderline case of hypertelorism and telecanthus (BR-IV-2).
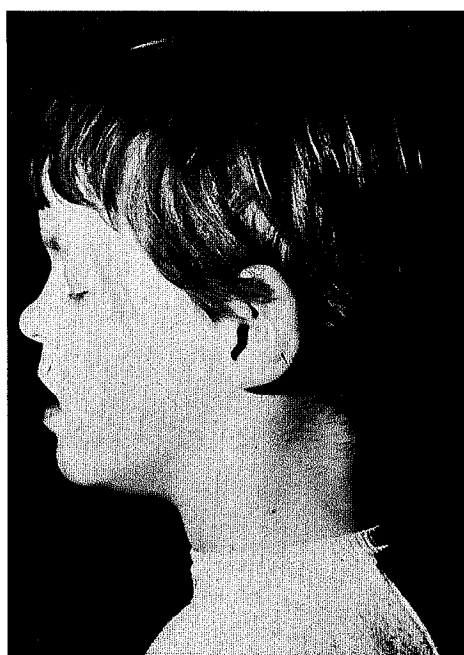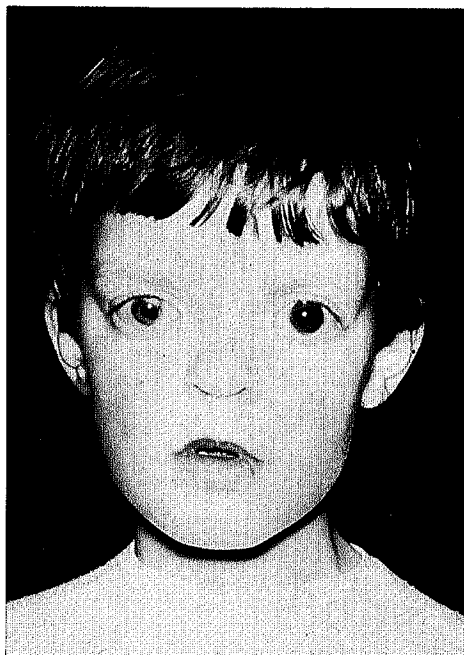
Fig. 30. Primary dysgenesis mesodermalis of the iris, no abnormalities of the face and mild blepharochalasis (BR-III-2).
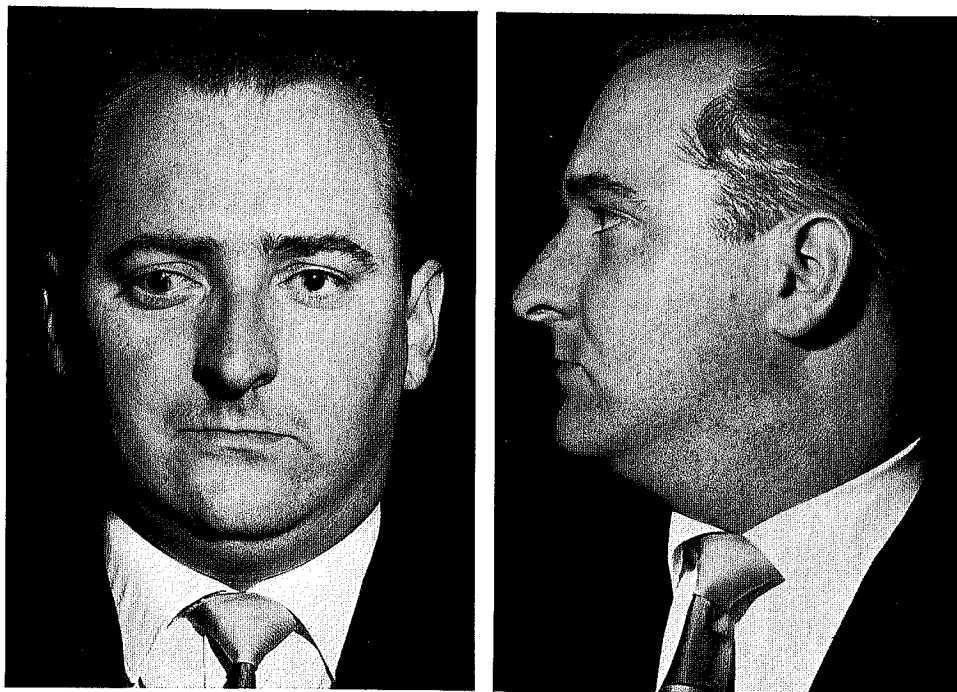
Fig. 31. Primary dysgenesis mesodermalis of the iris, no apparent facial abnormalities (HO-III-6).

15. FACE

Only in a few cases specific mention is made of the shape of the face and of typical facial characteristics. Many patients with primary dysgenesis mesodermalis of the iris have no unusual facial features, as can be seen from figures 28-35. Dark and Kirkham (1968) found no craniofacial abnormalities in their 11 cases.

It is a remarkable and striking fact that another proportion of patients in our own material and in the literature showed a fairly marked resemblance in certain respects. The photographs and descriptions often seem to suggest that all these patients are relatives.

The majority of patients with Rieger's syndrome whose photographs are available (Mathis 1936; Rejchrt and Miksa 1952; Gassler and Berthold 1960; Frandsen 1963; Von Noorden and Baller 1963; Henkes 1965; Boles Carenini and Orzalesi 1966; Delmarcelle 1968; our patients BR-IV.2, SD-III-2, RK-II-1 and RK-II-2: figs. 27, 29, 36, 38) show an *oldish appearance* in spite of their youth. Further analysis reveals that this impression is caused by the ever-present retracted and *receding upper lip*, which makes the lower lip seem more pronounced, broader and slightly everted. This gives these individuals the sunken-mouth appearance of elderly users of full dentures, with secondary mandibular and maxillary regression.

Fig. 32. Primary dysgenesis mesodermalis of the iris, no facial abnormalities present (BS-III-6).
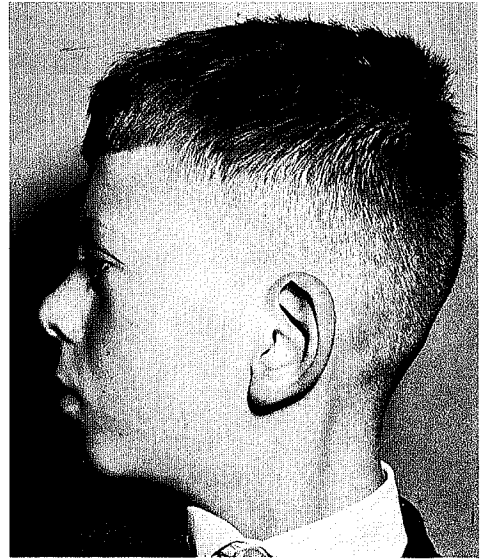
All these youthful patients with Rieger's syndrome and an oldish appearance proved to suffer from *mandibular* but particularly *maxillary hypoplasia* with *oligodontia vera*, which largely determined the above described appearance.

Perhaps the oldish appearance with sunken mouth was also the cause of the "facies myopathica" described by Busch *et al.* (1960) in patients who probably were not really suffering from what these authors reported as dystrophia myotonica.
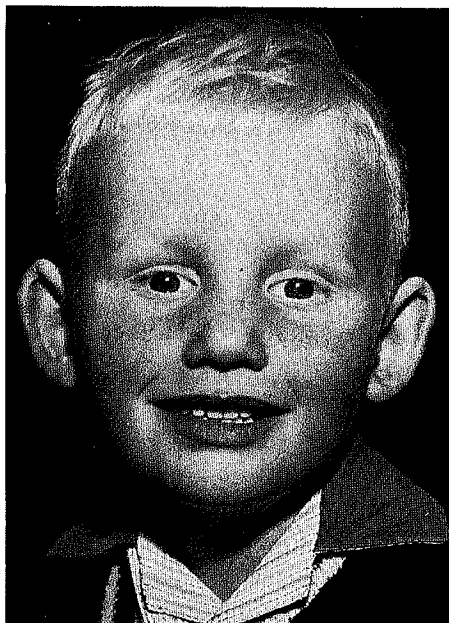
Fig. 33. Primary dysgenesis mesodermalis of the iris in a patient with Perthes' disease (PM-IV-2).
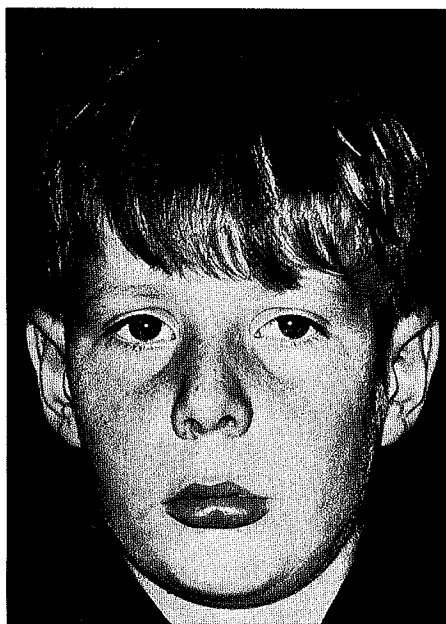
Fig. 34. Primary dysgenesis mesodermalis of the iris; normal facial structure with receding upper lip and somewhat pronounced lower lip. Ocular albinism (HL-III-5).

We also considered the *shape of the nose* in patients with primary dysgenesis mesodermalis of the iris, especially since the shape of the nose is an important feature in differentiating certain features of the Rieger syndrome from those of the oculo-dento-digital syndrome, which we shall discuss in detail later.

We know the shape of the nose from description and several photographs of patients in the literature and from our own material. In no patient with Rieger's syndrome was a conspicuously narrow, pointed nose described or observed. Both patients described by Rossano (1934) had a broad, flat nose ("le nez est aplati, étalé"), as did the patients of Rieger and Mathis (1936; fig. 39).

Broad noses were also described or depicted by Weekers and Weekers (1950), Garland (1958), Gassler and Berthold (1960), Frandsen (1963), Von Noorden and Baller (1963), Henkes (1965), Boles Carenini and Orzalesi (1966) and Delmarcelle (1968). In our own patients with Rieger's syndrome, too, the nose was usually broad (figs. 26-29, 32, 33, 38). Lemmingson's patient (1961) had a very gross, broad, thick nose, and the female patient described by Marx (1965) had a short nose. Some of these patients in addition showed a broad, flat nasal root (Gassler and Berthold 1960; Von Noorden and Baller 1963; Breebaart 1966; Delmarcelle 1968). The patients described by Shaffer (1965) and Breebaart (1966) likewise had a broad nose with short nostrils and a short nasal septum, giving the nose a somewhat unusual shape (fig. 40).
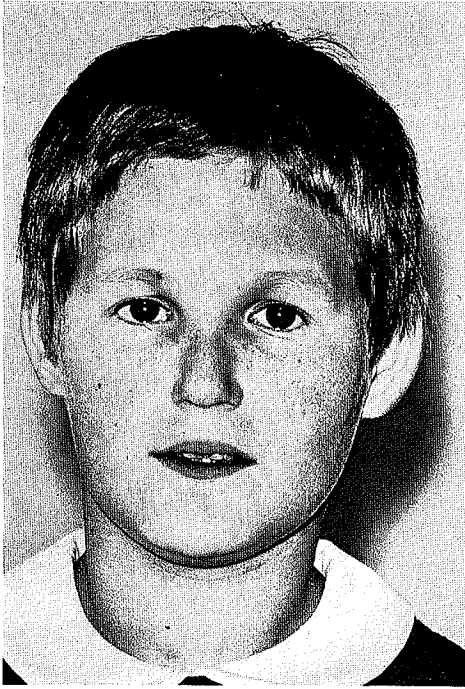
Fig. 35. Primary dysgenesis mesodermalis of the iris. No apparent facial anomalies (HH-III-4).
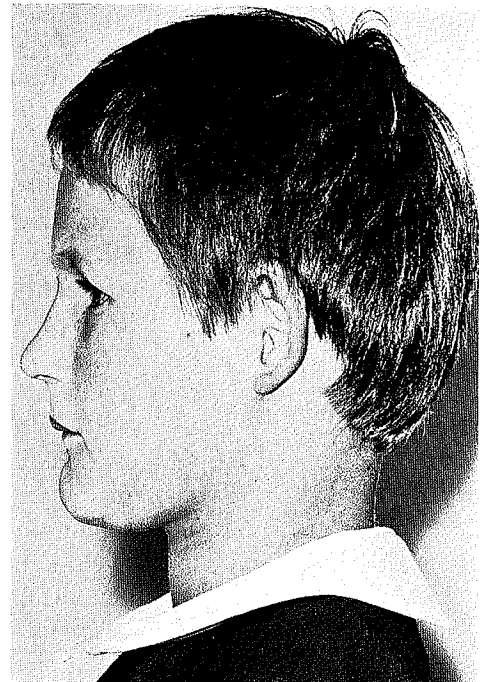
Fig. 36. Primary dysgenesis me-
sodermalis of the iris, with oli-
godontia vera, sunken upper lip
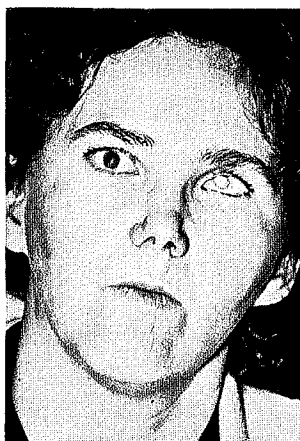and pronounced lower lip (RK-
II-1).

Fig. 37. Primary dysgenesis me-
sodermalis of the iris with
secondary dysgenesis mesoder-
malis of the cornea. Mother of
the patients in figs. 36 and 38.
(RK-I-2).

Fig. 38. Primary dysgenesis me-
sodermalis of the iris with oligo-
dontia vera, sunken upper lip,
pronounced lower lip and tele-
canthus (RK-II-2).

Braendstrup (1948) described all her patients as having a broad face with
prominent cheekbones (hardly the type of face to have a narrow nose).

Another factor determining the expressive quality of the face and probably
promoting the resemblance of these patients is the distance between the eyes and
between the internal canthi (cf. Waardenburg syndrome). The distance between
the eyes, expressed as interpupillary distance, is an aspect of the interorbital
distance, which is increased in hypertelorism (Greig). A broad nasal root, with
increased intercanthal width, can occur also in the absence of hypertelorism, i.e.
with normal interpupillary and interorbital distances. Mustardé (1963) described
"this excessive width of the soft tissue of the frontonasal process" as primary
telecanthus. In normal subjects of any age the intercanthal width seldom exceeds
0.55 of the interpupillary distance; in telecanthus the value is > 0.55, and in
plesiocanthus (Taylor and Cameron 1963) it is < 0.50. Personal observations on 100
individuals with routine anomalies of refraction confirmed this completely.

In our 12 patients with Rieger's syndrome we computed the ratio between
intercanthal width and interpupillary distance on the basis of measurements on
these patients and on their photographs. The values found proved not to differ by
more than 1-2%. Next, we were able to compute this ratio in 19 other patients
with Rieger's syndrome of whom we found usable photographs in the literature
or received them from various authors (Boles Carenini; Delmarcelle).

Table 14 shows that, of 31 patients with primary dysgenesis mesodermalis of
the iris whose ratio intercanthal width: interpupillary distance was known, 9
showed telecanthus, 18 had normal values and 4 were borderline cases.

Fig. 39. Primary dysgenesis mesodermalis of the iris in a brother and sister with oligodontia vera (Mathis, 1936).
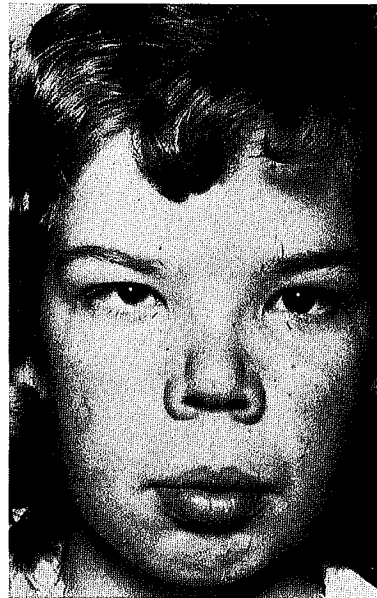

Fig. 40. Primary dysgenesis mesodermalis of the iris. Broad nose, telecanthus and pronounced lower lip (Breebaart).

On the basis of these findings the incidence of telecanthus in Rieger's syndrome can be estimated as 25%. Values of 0.56 and up are not found either in normal persons or in relatives of these patients. Only in our family HO did we find telecanthus in 4 normal members, whereas the proband – surprisingly – showed no telecanthus. The cranial size in this family (including the proband) was fairly large. It is therefore possible that we are confronted here with an association of telecanthus and macrocephaly within the family.

Table 14. Ratio intercanthal width (CID): interpupillary distance (PD) in 31 patients with primary dysgenesis mesodermalis of the iris (Rieger's syndrome).

Authors	CID/PD ratio	Telecanthus	Hypertelorism
MATHIS (1936)	0.54	—	—
	0.51	—	—
REJCHRT and MIKSA (1952)	0.51	—	—
	0.52	—	—
GASSLER and BERTHOLD (1960)	0,58	+	—
FRANDSEN (1963)	0.51	—	—
VON NOORDEN and BALLER (1963)	0.61	+	+
HENKES (1965)	0.50	—	—
SHAFFER (1965)	0.52	—	—
BREEBAART (1966)	0.61	+	—
BOLES CARENINI and ORZALESI (1967)	0.56	+	—
	0.55	—	—
	0.58	+	—
DEMARCELLE (1968)	0.62	+	—
	0.56	+	+
	0.60	+	—
	0.49	—	—
	0.62	+	—
ALKEMADE			
SD-IV-1	0.65	+	+
SD-III-2	0.59	+	+
BR-IV-1	0.55	—	—
BR-IV-2	0.56	+	+
BR-III-2	0.54	—	—
HO-III-6	0.52	—	+
BS-III-6	0.55	—	—
PM-IV-2	0.53	—	—
HL-III-5	0.52	—	—
RK-I-2	0.55	—	—
RK-II-1	0.55	—	—
RK-II-2	0.56	+	—
HH-III-4	0.54	—	—

According to Mustardé (1963), telecanthus often occurs in association with many different congenital, craniofacial anomalies and is frequently observed as a secondary feature of hypertelorism. Table 14 shows that a few cases in our own material showed this combination. Patients with primary dysgenesis mesodermalis of the iris may show telecanthus without hypertelorism or telecanthus with hypertelorism (although in a minority of cases).

All our other patients with Rieger's syndrome (figs. 30, 31, 34-36) had a normal

nose, as had the patients of Rejchrt and Miksa (1952) whose photographs we know. In all these cases, however, the nose tended more to the broad than to the narrow limit of the normal range of anatomical variation.

Rieger's female patient (1935) and her daughter who was later examined by Kleinert (1949) likewise had normal noses without conspicuous features according to a personal communication from Kleinert (1966).

In conclusion we would therefore maintain that the shape of the nose in patients with primary dysgenesis mesodermalis of the iris, if abnormal, is characterized by a *broad, flat nasal root, telecanthus* and a *broad base*, and that none of these patients shows a narrow, pointed nose with the typical characteristics described in patients with Meyer-Schwickerath's oculo-dento-digital syndrome.

Very few data are found on the *ears* in patients with Rieger's syndrome. We found no abnormalities of the external ear in our own material. The literature shows that Gassler and Berthold (1960) observed small, prominent ears in two patients, while Lemmingson (1961) found marked malformation of the external ear in his patient with pronounced facial asymmetry and dyscephaly. Crawford (1967) found a low insertion of the ears in two patients with Rieger's syndrome; and Collier (1962) described pre-auricular appendices in brothers suffering from primary dysgenesis mesodermalis of the iris.

The abovementioned abnormalities are all found incidentally described in association with other anomalies and syndromes, and also in otherwise normal individuals. The findings obtained in patients with Rieger's syndrome can therefore be regarded as chiefly coincidences.

16. SKULL

The shape of the face is determined, not only by the shape of the soft structures as discussed in the previous section, but more so by the shape of the skull. The interorbital distance and the degree of development of the various facial bones, especially the jaws, play a role of importance in this respect.

In 9 patients with primary dysgenesis mesodermalis of the iris, clinical or radiological findings were suggestive or conclusive of *hypertelorism* (Rossano 1934; Scheie 1961; Von Noorden and Baller 1963; Marx 1965, 1966; Delmarcelle 1968; our patients BR-IV-2, SD-III-2; SD-IV-1 (fig. 41); HO-III-6).

Since we are seldom fully informed about abnormalities of the face, skull, jaws, teeth, etc., not much can be said about the frequency and significance of these abnormalities in Rieger's syndrome. Henkind *et al.* (1965) ruled out cranial abnormalities on the basis of normal cranial X-rays. As can be seen from the illustrations, hypertelorism entails a broad, flat nasal root and in some cases is associated with telecanthus.

In our patients with primary dysgenesis mesodermalis of the iris we could not establish any cranial abnormality by mesuring the circumference (C), the antero-posterior distance (APD) and the biparietal distance (BPD).
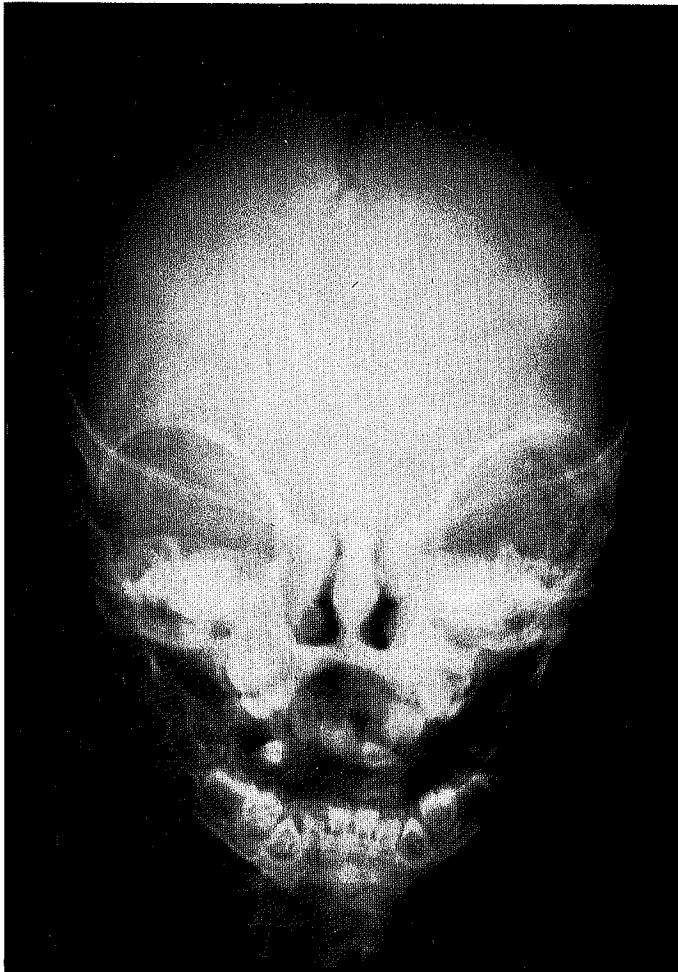
Fig. 41. X-ray of the skull in primary dysgenesis mesodermalis of the iris
with orbital hypertelorism (SD-IV-1).

Hydrocephalus was reported in patients with primary dysgenesis mesodermalis
of the iris syndrome by Saba (1927), Delmarcelle *et al.* (1958), Von Noorden and
Baller (1963) and Delmarcelle (1968), and was observed also in relatives of the
patient with Rieger's syndrome described by Morax (1963).

In this context it may be of interest to mention an observation made by De
Haas (1967), who found an iris coloboma in a patient with hydrocephalus, and of
Grover's description (1958) of this abnormality in a patient with Peters' anomaly.
The possibility of a correlation between hydrocephalus (stenosis of the aqueduct)
and developmental defects of the anterior chamber must certainly be further in-
vestigated.

Dolichocephaly was described in Rieger's syndrome by Botteri (1920).

Fissures of the face and cranium were seldom described or observed in primary dysgenesis mesodermalis of the iris (Delmarcelle *et al.* 1958; Delmarcelle 1968).

Developmental defects of the *jaws*, observed in several patients with primary dysgenesis mesodermalis of the iris, can sometimes be traced back to primordial dental disorders. For a normal primordium and development of the teeth is a primary requirement for the normal growth and development of certain parts of the jaws. Modern research in dentistry and orthodontics has disclosed that the development of the jaws above the apical base (the plane through the apices of the dental radices) is quite independent of the development of the dental germs, whereas development of the part below the apical base shows a high degree of dependence on the presence and development of the dental germs (Weil 1967).

Abnormalities of the jaws above the apical base, when found in Rieger's syndrome, are consequently not dependent on dental development but must be regarded as primary features.

Maxillary hypoplasia (retrognathia, micrognathia) was reported in patients with primary dysgenesis mesodermalis of the iris (Vossius 1883; Kittel 1956; Unger 1956; Lemmingson and Riethe 1958; Busch *et al.* 1960; Lemmingson 1961; Riethe and Lemmingson 1962; Frandsen 1963; Von Noorden and Baller 1963; Henkes 1965; Boles Carenini and Orzalesi 1966; Crawford 1967; Delmarcelle 1968), and observed by us in our patients SD-III-2, BR-IV-2 and RK-II-1 as well as RK-II-2.

Mandibular hypoplasia was observed by Marx (1965), and relative mandibular hyperplasia with malocclusion was reported by Vossius (1883), Frandsen (1963), Henkes (1965) and Boles Carenini and Orzalesi (1966), and observed by us in patients RK-II-1 and RK-II-2. As will be shown, all these cases were characterized by the presence of significant dental abnormalities.

There are indications which suggest that, in patients with Rieger's syndrome and in those with developmental defects of the anterior ocular segment in general, there may be primary developmental defects of the facial skull which can impress as dyscephalies (Marx 1965; Lemmingson 1961; Delmarcelle 1968).

For a good orientation on dyscephalies, especially their milder forms, plain cranial X-rays are not sufficient; an analysis of teleradiographs is required for this purpose. These analyses of exact measurements with certain fixed points of reference can be carried out and evaluated only with the aid of teleradiographs. An analysis of this type was made in 8 patients with Rieger's syndrome (Kittel 1956; Busch *et al.* 1960; Henkes 1965; our patient BR-IV-1) and in our patient VE-III-6. Three of Kittel's patients (1956) showed conspicuous underdevelopment of the maxilla in sagittal direction. Such a maxillary hypoplasia – which can also occur as type variant in association with a hereditary ocular anomaly and partial anodontia vera – indicates inferiority of the organ anlage of the mesiofacial area.

The four patients of Busch *et al.* (1960) likewise showed sagittal as well as

vertical maxillary hypoplasia, which was ascribed to the existing hypodontia. The mandibles (which these authors considered less dependent on dental development) were normal in these patients.

Henkes (1965) described a female patient who showed a dorsal position of the subnasale, a small maxillary apical base and a large angle between the ascending and the horizontal ramus of the mandible. An analysis of teleradiographs pertaining to our female patient BR-IV-1 revealed no abnormalities.

In summary: we found that hypertelorism with a flat nasal root and maxillary hypoplasia with mild prognathism were prominent among such craniofacial abnormalities as occurred in patients with primary dysgenesis mesodermalis of the iris. It remains difficult to attach conclusions to this finding because there are no data for comparison on a scientific level.

Evaluation is further complicated by the fact that partial anodontia vera can occur in association with Rieger's syndrome. This dental anomaly may be the cause of secondary maxillary hypoplasia. Since no abnormal ear position and no hypoplasia of the zygomatic arch were observed, it would seem to be premature at this stage to use the designation "maxillofacial dysostosis" (Peters and Hövels 1960), of which an antimongoloid eye position is an additional characteristic. This abnormality, too, was not observed in patients with primary dysgenesis mesodermalis of the iris. Only the patient described by Lemmingson (1961) showed some features reminiscent of the dysostosis reported by Peters and Hövels.

17. TEETH

Rieger (1935) and Mathis (1936) were the first to correlate the ocular syndrome described by the former with *partial anodontia vera* (oligodontia, connatal hypodontia vera, agenesis of dental elements). In the dental literature, this anomaly had long been known as an independent dental developmental defect, of dominant heredity.

It should be pointed out that dental anomalies have been described also in association with other developmental defects of the anterior chamber, e.g. familial microphthalmos (Wolf 1930), aniridia and atresia ani (Brailey 1890), Peters' anomaly and hydrophthalmos (Chosak and Rosenzweig 1966), and in reports by Forsius (1964) and Denden and Ahrens (1967). Association with other developmental defects of the anterior chamber, however, is relatively rare.

Partial anodontia vera was described in Rieger's syndrome by several authors (Vossius 1883; Rejchrt and Miksa 1952; Kittel 1956; Unger 1956; Lemmingson and Riethe 1958; Busch et al. 1960; Gassler and Berthold 1960; Lemmingson 1961; Riethe and Lemmingson 1962; Frandsen 1963; Zygulska Machowa 1964; Henkes 1965; Boles Carenini and Orzalesi 1966; Crawford 1967; our patients BR-IV-1, HO-III-6, RK-II-1 and RK-II-2: figs. 41-46).

Other dental abnormalities such as microdontia, conical teeth, poorly implanted teeth and enamel defects were often seen to accompany partial anodontia vera.
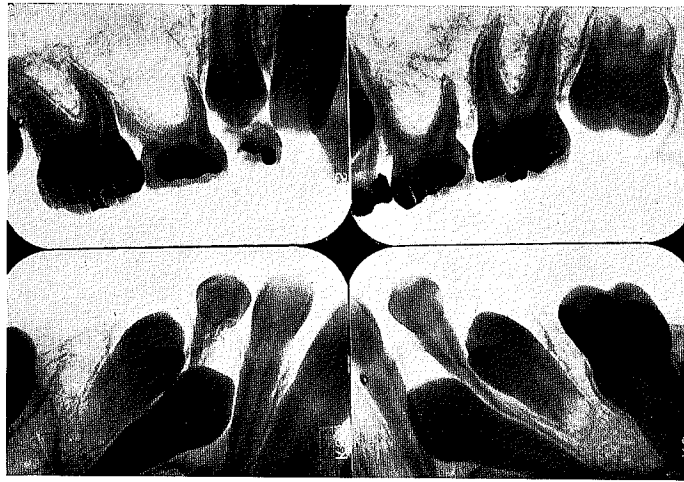
Fig. 42. X-ray of dentition in primary dysgenesis mesodermalis of the iris: agenesis of all third molars and second premolars (oligodontia vera). Css and Csd retained in mesioversion and palatine position (BR-IV-1).

Niederegger (1920) and Rossano (1934) did observe dental anomalies but offered no diagnosis of oligodontia. The patient described by Marx (1965) had an accessory tooth besides oligodontia.

The literature and our own material include a total of 31 patients with primary dysgenesis mesodermalis of the iris and partial anodontia vera. Dental anomalies were explicitly mentioned as absent in 25 cases of this syndrome (Kittel 1956; Riethe and Lemmingson 1962; Guillerez-Fontaine *et al.* 1963; Henkind *et al.* 1965; Pearce and Kerr 1965; Boles Carenini and Orzalesi 1966; personal observations). Dark and Kirkham (1968b) likewise found normal teeth.
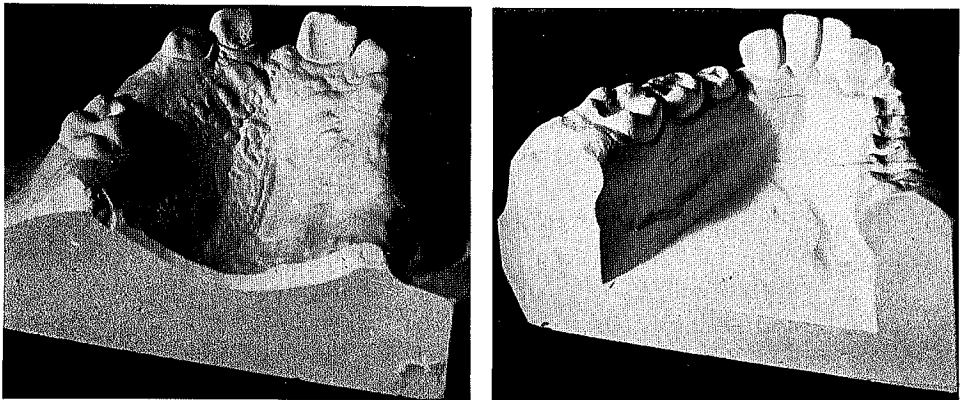
Fig. 43. Plaster casts from the same patient: deciduous teeth in phase of (belated) replacement; superior first molars not yet erupted; Iisd lost due to violence; Miss extracted.

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Fig. 44. Teeth in primary dysgenesis mesodermalis of the iris: oligodontia vera, hypoplasia of the teeth, microdontia, caries and periodontopathies (HO-III-6).
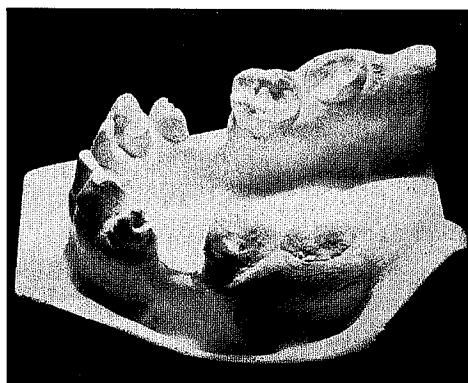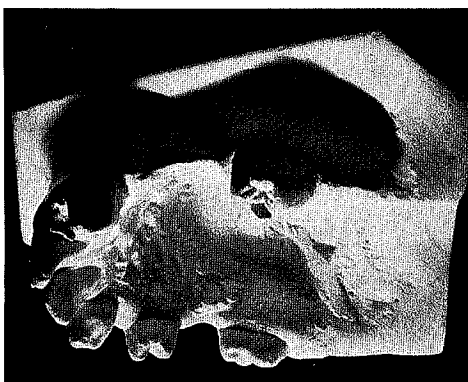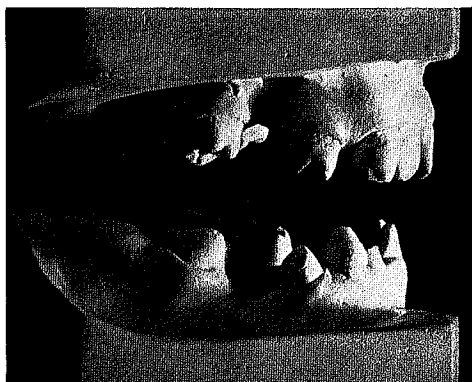
Fig. 45. Plaster casts of teeth in primary dysgenesis mesodermalis of the iris: oligodontia vera. Probably as a result of the dental reduction in the maxilla, there was maxillary retrognathia which reversed the sagittal relation of the incisors (HO-III-6).
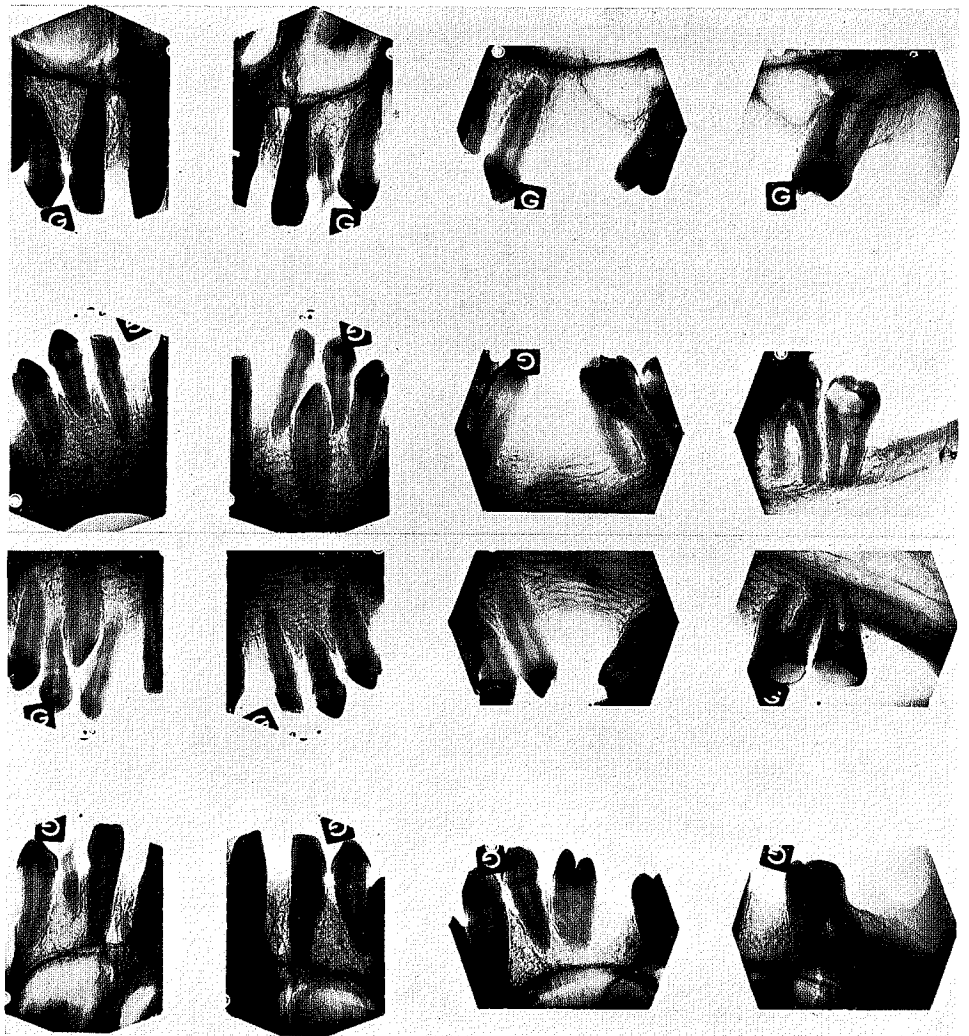
Fig. 46. X-ray of teeth in primary dysgenesis mesodermalis of the iris: agenesis of 14 dental elements (oligodontia vera) (HO-III-6).

Families with the Rieger syndrome in which none of the patients showed dental abnormalities were described by Henkind *et al.* (1965). Pearce and Kerr (1965) and Dark and Kirkham (1968). In the families described by Mathis (1936), Rieger (1935) – Kleinert (1949), Rejchrt and Miksa (1952), Unger (1956), Lemmingson and Riethe (1958, 1962), Busch *et al.* (1960) and Crawford (1967) all patients with primary dysgenesis mesodermalis of the iris in two successive generations showed partial anodontia vera. In our family BR, the mother had no anodontia vera but the daughters had (figs. 42, 43).

Is the occurrence of this dental abnormality in Rieger's syndrome a coincidence,

or is there a correlation? We believe for various reasons that a coincidence is exceedingly unlikely.

To begin with, partial anodontia vera is a rare dental abnormality; Stafnes (cited by Mathis 1935) reported an incidence of 1 per mille. Recent studies reported a rate of agenesis of dental elements of 7-30%, but these figures often included agenesis of the third molars, which frequently occurs in the normal population. Agenesis of 3 or more dental elements is decidedly an exception, and agenesis of even more elements is even less common (Weil 1967). Rieger's syndrome is probably an even less common abnormality (our conservative estimate would be 1 per 200,000 population). The chance that both abnormalities would "happen" to coincide in a single patient must be considered singularly small. The fact that concomitance of the two abnormalities was described in as many as 31 cases cannot be based on coincidence but is highly suggestive of a correlation.

This is further corroborated by another fact. Our personal observations and study of the literature have shown that families with primary dysgenesis mesodermalis of the iris include no individuals with only the dental anomaly but do include patients with only the Rieger syndrome. Both conditions are known to be separate anomalies of dominant heredity; therefore, if the two anomalies should happen to occur as hereditary conditions within the same family, then there would certainly be patients showing only the dental anomaly. Since studies in this context are usually incomplete and inaccurate, and since the available data on incidences and family studies are insufficient, no definite conclusions can as yet be reached. Moreover, not all data can be used because partial anodontia vera cannot be diagnosed exclusively on the basis of clinical findings, without resorting to radiography of dental germs (fig. 42, 46).

Anamnestic data cannot be trusted in establishing the diagnosis; and the age at which the radiological examination is made, is likewise of great importance for the degree of certainty. The ideal age for such an examination is between 5 and 9 years. A positive radiological diagnosis was made in our patients BR-IV-1, HO-III-6, RK-II-1 and RK-II-2 (figs. 42, 46).

Clinical abnormalities of the teeth (e.g. microdontia, conical teeth, diastemata) are as such fairly uncommon. Abnormalities of implantation are less uncommon in a normal population; and the caries or yellow teeth often reported in patients with Rieger's syndrome are of no special significance because they are quite common in otherwise normal individuals.

The literature not infrequently makes mention of enamelogenesis imperfecta in patients with Rieger's syndrome or with dental anomalies in general. This diagnosis, however, is exceedingly unreliable because it is never based on histological examination of dental sections; and it is on histological findings that it should be made. We had a histological study made in one of our cases (patient HO-III-6; fig. 45). Although the clinical picture of this case showed connatal oligodontia, microdontia and abnormalities of shape and colour with caries (figs. 47, 48), there was no enamelogenesis imperfecta.
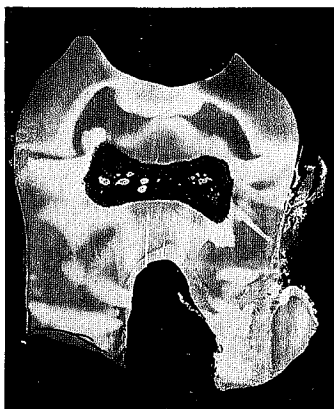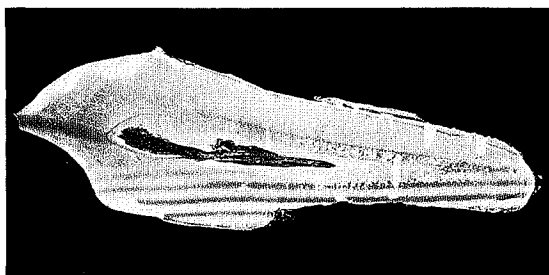
Fig. 48.

Dental histology in primary dysgenesis mesodermalis of the iris and oligodontia vera. The sections of the teeth showed no abnormal dental structure (HO-III-6).

Fig. 47.

Since a correlation between primary dysgenesis mesodermalis of the iris and partial anodontia vera is highly probable, it seemed of interest to investigate whether ocular abnormalities occur in patients with this dental anomaly.

Preliminary to a more exhaustive study, we examined a group of 22 patients aged 6-20 who showed radiologically verified partial anodontia vera of at least three teeth (not including the third molars because these are frequently absent in the normal population). The average agenesis in this group involved 5 teeth, chiefly incisors and premolars, and the group must consequently be regarded as unusual. None of these individuals showed ocular abnormalities. In particular we found no prominent line of Schwalbe, and no abnormalities of the cornea, iris or intraocular pressure. In such individuals as were examined gonioscopically we found no abnormalities.

Apart from a dental anomaly in a brother and sister, none of the relatives of the remaining patients showed dental or ocular anomalies; this was established partly on the basis of anamnestic data and in part by personal observation.

In patients who combine primary dysgenesis mesodermalis of the iris with partial anodontia, we are probably confronted with an occassionally occuring *gene linkage*, although polyphenic expression of one gene cannot be ruled out.

18. LIMBS

Very few reports on patients with primary dysgenesis mesodermalis of the iris supply data on the limbs, although in recent years some attention has been focused on these parts.

Abnormalities of the limbs, fingers or toes have been observed in many patients with developmental defects of the anterior ocular segment (Börner 1886; Coats 1910; Citola 1938; Berliner 1941; Stephens 1947; Sjögren and Larsson 1949; Lepri 1949; Bornstein 1952; Tower 1953; Duggan and Hassard 1961; Haney and Falls 1961; Goldstein and Cogan 1962; Van der Helm 1962; Collier 1963;

Forsius 1963; Zeiter 1963; Speakman and Crawford 1965; Denden and Ahrens 1967; Delmarcelle 1968). The same applies to a few patients with Meyer-Schwickerath's oculo-dento-digital syndrome.

Patients with Rieger's syndrome sometimes showed clinical abnormalities such as genua valga (Gassler and Berthold 1960), bilateral calcaneus valgus (Levien 1966), pedes plani (Nenquin and Brihaye 1959; Gasslier and Berthold 1960; Forsius 1963), congenital luxation of the hip (Breebaart 1966), clinodactyly (Collier 1962; Frandsen 1963; Breebaart 1966), and gross fingers with broad interdigital spaces between metatarsals I and II and hypoplasia of metatarsal III (Lemmingson 1961).

In some cases the abnormalities were only radiologically visible: retarded development of metacarpals (Kittel 1956), bilateral hypoplasia of metacarpals IV and V (Henkes 1965), bilateral cubical middle phalanges of metacarpal V and metatarsals IV and V (Frandsen 1963).

The hands and feet were radiologically examined in 9 of our patients with primary dysgenesis mesodermalis of the iris. We found no abnormalities apart from retarded development of the metacarpal and metatarsal bones in our patient PM-IV-2, who suffered from Perthes' disease.

These findings show that abnormalities of the limbs are seldom observed in patients with Rieger's syndrome, so that a correlation is not plausible.

19. ASSOCIATED ANOMALIES

Apart from the above discussed anomalies of the skull, face and limbs sometimes found in association with primary dysgenesis mesodermalis of the iris, other connatal and congenital anomalies have been reported in the presence of primary dysgenesis mesodermalis of the iris. In view of the relatively low incidence of these anomalies in Rieger patients, the combination should be regarded as a coincidence. The anomalies reported in the presence of Rieger's syndrome are widely diverse.

Internal conditions described in this context included goitre (Niederegger 1930), rickets (Gassler and Berthold 1960), thymal hyperplasia (Forsius 1963), kyphosis (Von Grósz 1940), funnel chest (Gassler and Berthold 1960), familial asthenia (Falls 1949), arachnodactyly (Weekers and Weekers 1950; Mills 1967), inguinal hernia (Braendstrup 1948), anal stenosis (Crawford 1967; two patients), cryptorchism (Kittel 1956; Gassler and Berthold 1960; Lemmingson 1961), and nephroptosis (Breebaart 1966).

Connatal *heart defects* were observerd in cases described by Zygulska Machowa (1964) and Haye and Blanck (1965) and in our patient PM-IV-2, who suffered from Perthes' disease.

Congenital *deafness of the middle ear* was observed and audiometrically verified in several cases (Falls 1949; Callahan 1956; Forsius 1963, 1964; Forsius and Eriksson 1964). Falls (1949) in addition mentioned several instances of bilateral *otosclerosis* in his large family, and a similar finding was reported by Levien (1966).

The *dystrophia myotonica* described by Busch *et al.* (1960) in patients with Rieger's syndrome seems very doubtful on neurological diagnostic grounds; moreover, they referred to Löhlein (1951), who reported a likewise very dubious dystrophia myotonica in a female patient with essential progressive iridal atrophy – a condition of a quite different type although is it often confused with primary dysgenesis mesodermalis of the iris. The patients described by Busch *et al.* (1960) showed no distinct muscular atrophy and no conclusive clinical-neurological symptoms; no electromyogram was recorded, and the cataractous changes which typify this myotonia (Vogt 1921; Vos 1933; Junge 1966) were not found or at least not mentioned.

Von Grósz (1940) observed *syringomyelia*; Forsius (1963) reported *poliomyelitis*, and Lemmingson (1961) and Marx (1965) mentioned left-handedness. Von Noorden and Baller (1963) saw hydrocephalus with psychomotor retardation in a patient with Rieger's syndrome, and Kittel (1956) observed a patient showing hypoplasia of the orbicularis oris muscle, epilepsy, and general and mental underdevelopment.

Mental deficiency was observed also by Niederegger (1920), Forsius (1963), Lemmingson (1961) and myself (BR-III-2). The female patient described by Ernyei (1965) was mentally disturbed (paranoia). As we pointed out, there are some links between primary dysgenesis mesodermalis of the iris and developmental defects of the ectodermal germ layer (partial anodontia vera).

Skin changes suggestive of another ectodermal defect were seldom mentioned in patients with Rieger's syndrome. Our own material contained not a single clue in this direction to which significance might be attached. Chalky nails as in family SD are by no means uncommon. A patient described by Gassler and Berthold (1960) showed hypohidrosis and mild hypotrichosis, and one of Kittel's patients (1956) suffered from hyperhidrosis and loss of hair. Premature baldness was described also by Sivasubramanian and Hoole (1955). Lemmingson (1961) found a vascular naevus on one of his patients' shoulder.

20. RELATIVES

Relatives of patients with primary dysgenesis mesodermalis of the iris not uncommonly showed other connatal or congenital anomalies, both of the *eyes* and of *other organs*. Relatives of Rieger's patients (1935) were found to show: persistent pupillary membrane (3 cases), hypermetropic astigmatism (3 cases), flocculi of the pupillary border, iridal heterochromia and facial asymmetry (2 cases) and mental deficiency (3 cases) in the form of feeblemindedness and idiocy.

Burian *et al.* (1957) reported a retinoblastoma in a nephew of their patient. Delmarcelle *et al.* (1958) and Delmarcelle (1968) found in their female proband's sister (both children of a father with Rieger's syndrome, hydrophthalmos and "wolf's mouth") iridochoroidal coloboma OD and iridal coloboma and microphthalmos OS, with dextrocardia, polycystic kidneys and polydactyly of the hands and feet.

Collier (1962 e) described abortive iridal colobomas and harelip in two of his patient's brothers; and a great-aunt of Frandsen's patient (1963) likewise showed a harelip.

The patients described by Morax (1963) had a brother with hydrocephalus and spina bifida occulta.

A brother of three patients with Rieger's syndrome described by Delmarcelle (1968) died at age 16 from a connatal heart defect.

Retinitis pigmentosa with deafness was found by Sugar (1961) in three close relatives, and this combination was reported to exist also in Breebaart's (1966) family, which also included a case of congenital hip luxation.

In our own material, too, we observed ocular abnormalities and a few other connatal anomalies in close relatives of patients with primary dysgenesis mesodermalis of the iris.

In 24 of 96 relatives submitted to ophthalmological examination, the following ocular abnormalities were found in order of diminishing frequency.

– prominent line of Schwalbe	8 cases (12 eyes)	
– partial limbus coloboma	6	-
– mild hypoplasia of iridal stroma	3	-
– remnants of the pupillary membrane	2	-
– glaucoma simplex	2	-
– exotropia and esotropia	2	-
– mild pupillary ectopia	1	-
– mild anomalies of iridocorneal angle	1	-
– bilateral congenital cataract	1	-
– pseudopapillitis	1	-
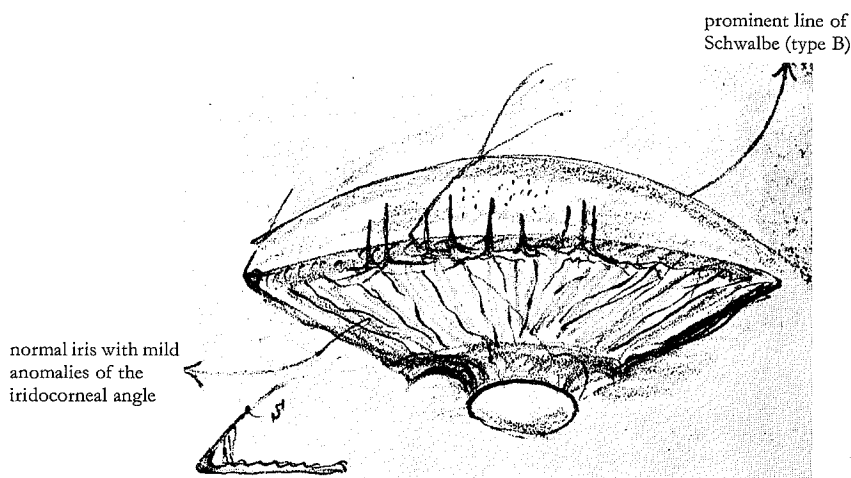
Fig. 49. Mild anomalies of the iridocorneal angle (PM-III-1).

In one instance a prominent line of Schwalbe was associated with persistent remnants of the pupillary membrane; in another case it was accompanied by mild hypoplasia of the iridal stroma while in another case a partial limbus coloboma was associated with iridal hypoplasia.

The incidence of a prominent line of Schwalbe (limbus type B) in relatives of patients with primary dysgenesis mesodermalis of the iris (8% of individuals; 6% of eyes) therefore proved not to be higher than that in our group of normal subjects (see table 1).

The incidence of glaucoma simplex, remnants of the pupillary membrane and strabismus was likewise not above normal. Nor is it probable that any significance should be attached to the single instances of mild pupillary ectopia, mild anomalies of the iridocorneal angle (fig. 49), congenital cataract and unilateral pseudo-papillitis. Mild iridal hypoplasia was observed in 3 cases. The subjects affected were always brothers or sisters of patients with Rieger's syndrome. The father of one of them (PM-IV-2) showed the above mentioned mild angle changes, although both parents otherwise had completely normal eyes and iridocorneal angles.

As we pointed out, a few instances of mild hypoplasia of the iridal stroma were observed in a group of subjects with normal eyes. Also in view of the autosomal dominant transmission of primary dysgenesis mesodermalis of the iris, it is improbable that the mild stromal hypoplasia observed in a few relatives had any relation to the syndrome. No more than the prominent line of Schwalbe can this be interpreted as a low degree of expression of abortive form of the Rieger syndrome; no more than, say, mild axis myopia can be regarded as a low expression of myopia gravior.

Partial limbus coloboma was observed in 6 instances; the same special limbus variant was found in 4 out of 50 individuals with normal eyes. So far as we know, the incidence of this anatomical variant in normal subjects has not otherwise been investigated. It seems that, also in terms of partial limbus coloboma, relatives of Rieger patients do not differ from normal subjects. Kraupa (1920) was the first to mention this limbus variant in the ophthalmological literature; he observed it in association with lamellar cataract, remnants of the pupillary membrane and corectopia. Kayser (1922) followed with two cases, in association with embryotoxon corneae posterius, hypoplasia of iridal stroma, pupillary membrane remnants and mild corectopia. Asher (1941) likewise reported partial limbus coloboma with embryotoxon, and Rice *et al.* (1956) and Burian *et al.* (1955) found partial limbus coloboma in a family with primary dysgenesis mesodermalis of the iris.

In our material we observed partial limbus coloboma in a patient with Rieger's syndrome (SD-IV-1, plate II) and in a patient with Peters' anomaly (E-II-1, fig. 56).

In summary, it can be stated that in relatives of patients with primary dysgenesis mesodermalis of the iris we did not find more ocular abnormalities than might be expected on the basis of incidence studies in a random group of normal subjects.

The prominent line of Schwalbe and mild hypoplasia of the iridal stroma should be regarded as a consequence of variation in the normal development of the ante-

rior ocular segment, and not as a feeble expression of a gene-determined developmental defect.

In our opinion there is still quite a gap between a low expression of the gene of primary dysgenesis mesodermalis of the iris and the most extreme minus variant of the normal development of the anterior chamber.

In relatives of patients with Rieger's syndrome, connatal abnormalities of *other organs* than the eye were repeatedly (but not frequently) observed and reported. We did not observe these abnormalities equally often in all families; they were encountered chiefly in families SD and HO.

In the family SD we found mental deficiency (3 cases), connatal hip luxation, mild camptodactyly with cutaneous syndactyly and imbecility.

In the family HO we found: in the paternal line (H): epilepsy; connatal aplasia of the pectoralis major muscle; cheilopalatoschisis; connatal preauricular appendix with mild facial asymmetry; in the maternal line (O): a patient with connatal hypospadias, duplication of ureters and bladder, epilepsy and imbecility.

It is difficult to establish whether a correlation existed between the anomalies on the one hand, and the primary dysgenesis mesodermalis of the iris on the other. Exhaustive studies of "normal" families and families with patients showing other developmental defects of the eye or the anterior ocular segment may yield some information on a possible (but, we believe, improbable) correlation. The presence of ocular albinism in one of our families with Rieger's syndrome (family HL) should be regarded as a coincidence.

21. HEREDITY

Several patients with Rieger's syndrome are often found in one family. When we include the family described by Dark and Kirkham (1968), we find that a total group of 175 patients with Rieger's syndrome comprises 122 patients who belong to 29 different families. Of the total group, 39 patients were known to have no relatives with ocular abnormalities. These cases can be characterized as isolated cases. For 14 patients, no data on relatives were presented. These facts warrant the conclusion that some 70% of cases of primary dysgenesis mesodermalis of the iris are familial cases, while 25% are known to be isolated cases.

Two patients with Rieger's syndrome were prematurely born (Callahan 1956; Frandsen 1963), and the same applied to the ancestor of the family described by Rossano (1934).

In nearly all (34) cases in which data were available on the mother's *pregnancy*, this proved to have been normal. Only the mother of Callahan's prematurely born female patient (1956) had suffered from nephritis during pregnancy.

Ten patients with the syndrome were explicitly described as having parents who were *not consanguineous*. In our cases, too, parental consanguineousness was ruled out so far as possible by an exhaustive family history, studies of pedigrees (family SD) and an investigation of places of birth.

There were no obvious clues to recessive autosomal transmission, such as an increased incidence of consanguineousness of healthy parents or repeated occurrence of the syndrome in a family in which both parents showed no abnormalities. Unfortunately, virtually nothing is known about the offspring of the isolated cases of Rieger's syndrome. Only the patient described by Guillerez (1963) is alleged to have two healthy sons.

In many of these cases, information on the parents is likewise lacking, and consequently it is impossible to decide whether these cases represent mutations or are phenocopies.

Table 15. Distribution of patients and normal siblings in 29 families (including 56 households) with primary dysgenesis mesodermalis of the iris (Rieger's syndrome).

Authors:	Number of patients (x)	Number of siblings (n)	x(n-1)	x(x-1)
THYE (1903)	1	3	2	0
ROSSANO (1934)	1	1	0	0
SARAUX (1965)	1	1	0	0
KITTEL (1956)	1	1	0	0
	1	1	0	0
RIEGER (1935) – KLEINERT (1949)	1	1	0	0
REJCHRT and MIKSA (1952)	1	1	0	0
UNGER (1956)	1	1	0	0
LEMMINGSON and RIETHE (1958)	1	1	0	0
ALKEMADE, family SD	2	2	2	2
MATHIS (1936) – RIEGER (1935,1941)	2	2	2	2
BRAENDSTRUP (1948)	5	8	35	20
	1	1	0	0
FALLS (1949)	2	3	4	2
	6	10	54	30
	2	3	4	2
	7	11	70	42
WEEKERS and WEEKERS (1950)	1	1	0	0
	3	3	6	6
BURIAN et. al. (1957)	4	8	28	12
BUSCH et al. (1960)	1	4	3	0
	1	6	5	0
	2	3	4	2
	2	2	2	2
BLUM et al. (1962)	3	7	18	6
BIETTI (1963)	1	1	0	0
FORSIUS and ERIKSSON (1964)	2	2	2	2
ALKEMADE, family BR	2	2	2	2
family RK	2	2	2	2
HENKIND et al. (1965)	2	6	10	2
	1	3	2	0
	1	5	4	0
	1	1	0	0
	1	2	1	0
	1	2	1	0

Authors:	Number of patients (x)	Number of siblings (n)	x(n-1)	x(x-1)
PEARCE and KERR (1965)	4	9	32	12
	3	5	12	6
	1	4	3	0
	2	2	2	2
	1	2	1	0
	1	1	0	0
BOLES CARENINI and ORZALESI (1966)	3	10	27	6
	1	5	4	0
BREEBAART (1966)	1	1	0	0
LEVIEN (1966)	2	3	4	2
CRAWFORD (1967)	2	3	4	2
WOLTER et al. (1967)	1	1	0	0
DARK and KIRKHAM (1968)	1	1	0	0
	3	6	15	6
	5	7	30	20
	1	4	3	0
	1	1	0	0
	1	2	1	0
DELMARCELLE et al. (1958)	3	5	12	6
DELMARCELLE (1968)	2	5	8	2
	1	2	1	0
Total	107	190	422	200

If we accept a gene-linkage between primary dysgenesis mesodermalis of the iris and partial anodontia vera, then we can maintain that an isolated case combining dysgenesis mesodermalis of the iris and partial oligodontia vera (HO-III-6) represents a gene mutation and may produce offspring with these anomalies.

When primary dysgenesis mesodermalis of the iris was regarded as hereditary, autosomal dominant transmission was always involved (see table 16). Von Grósz (1940) described a brother and sister with the syndrome, without supplying data on the parents.

Dominant transmission through five successive generations (the two oldest generations only anamnestically) was reported by Busch et al. (1960); Henkind et al. (1965) and Dark and Kirkham (1968). Dominant transmission through four successive generations (the oldest only anamnestically) was reported by Falls (1949), and through three successive generations by Rossano (1934) – Saraux (1965), Braendstrup (1948), Weekers and Weekers (1950), Kittel (1956), Pearce and Kerr (1965) and Boles Carenini and Orzalesi (1966). The syndrome was seen in two generations by Thye (1903), Rieger (1935) – Kleinert (1949), Mathis (1936), Rejchrt and Miksa (1952), Unger (1956), Burian et al. (1957), Delmarcelle et al. (1958). Lemmingson and Riethe (1958), Blum et al. (1962), Bietti (1963), Bartolozzi
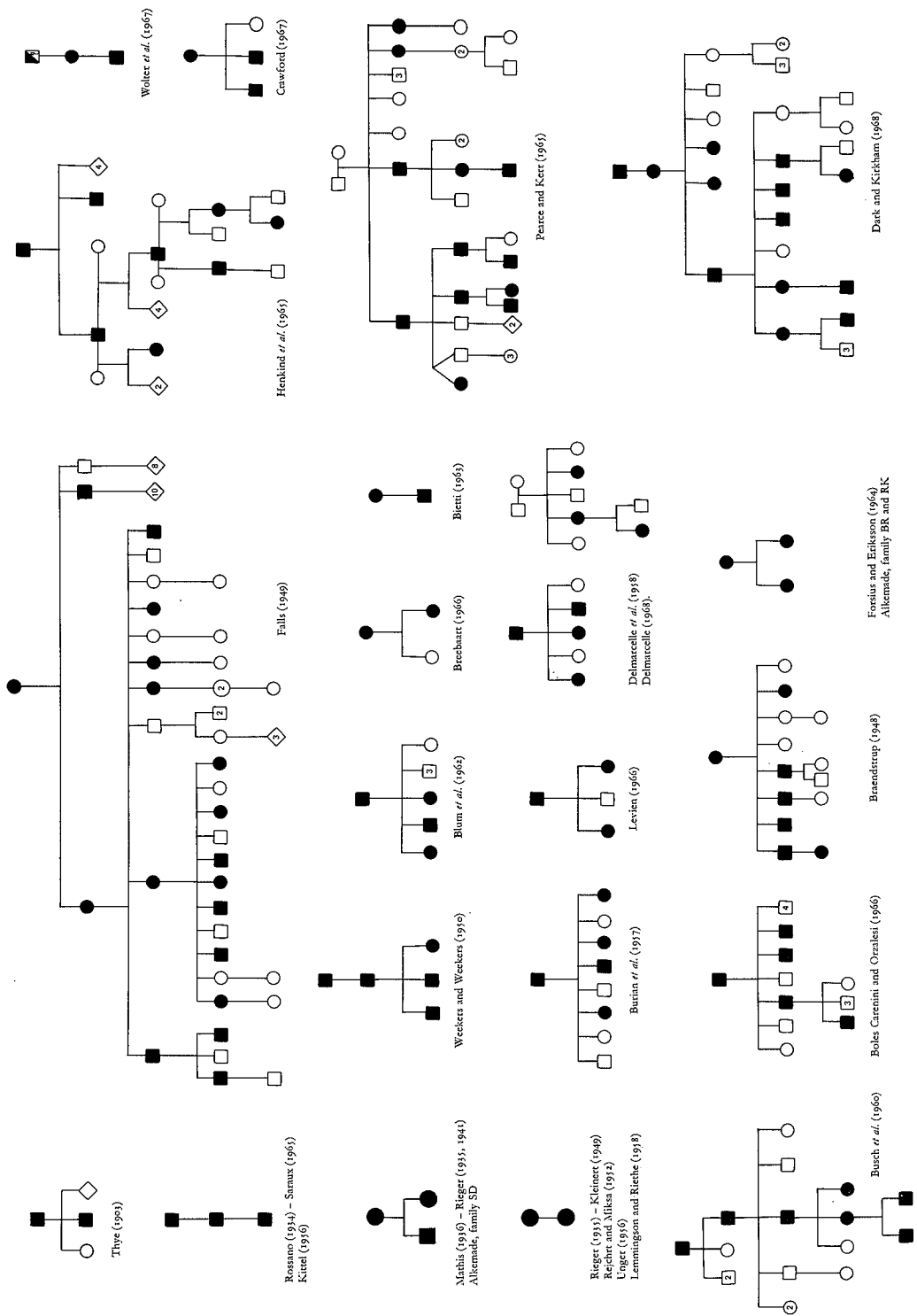
Table 16. Pedigrees of 29 families with primary dysgenesis mesodermalis of the iris (Rieger's Syndrome).

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et al. (1964), Forsius and Eriksson (1964), Breebaart (1966), Levien (1966), Crawford (1967), Wolter *et al.* (1967) and Delmarcelle (1968).

In our own material we observed three families with Rieger's syndrome in two successive generations (families BR, SD and RK), and the mother of Breebaart's patient (1966) was believed also to show the syndrome. The family described by Schmidt (1943), with embryotoxon corneae posterius, iridal hypoplasia and corectopia without angle anomalies, consisted of three successive generations.

With these data, autosomal dominant transmission of primary dysgenesis mesodermalis of the iris can be considered an established fact. The interfamilial and intrafamilial variability proves to be considerable when we compare patients within the same family and the families with each other.

Both the anomalies of the iridocorneal angle and the hypoplasia of the iridal stroma can vary considerably in intensity and extent, and the same applies to the associated glaucoma.

Intrafamilial and interfamilial variability was particularly striking in the families described by Rossano (1934), Braendstrup (1948), Falls (1949), Kittel (1956), Burian *et al.* (1957), Forsius and Eriksson (1964), Henkind *et al.* (1965), Pearce and Kerr (1965), Wolter *et al.* (1967) and ourselves.

The 29 families with primary dysgenesis mesodermalis of the iris included 56 households in which one of the parents showed the syndrome. These parents had a total of 190 children, including 107 (56%) who proved to suffer from Rieger's syndrome, and 83 without these abnormalities.

Since we are dealing with an autosomal dominant condition, this means that the pathological gene of primary dysgenesis mesodermalis of the iris has nearly *total penetrance*.

By applying Weinberg's sibling method (propositus method) this percentage (56%) is corrected. For this purpose we use Weinberg's formula:

$$P = \frac{\sum x(x-1)}{\sum x(n-1)},$$

in which P is the corrected proportion patients: siblings; x is the number of affected children in one family and n is the total number of the individuals in that family.

According to our table 15 we see the following fraction:

$$P = \frac{200}{422} \times 100 = 47.4\%.$$

This means that the penetrance of the pathological gene of primary dysgenesis mesodermalis of the iris is 95%.

The degree of expression can be described as very variable, but always within a distinctly pathological clinical picture.

Before advancing a hypothesis concerning the pathogenesis of primary dysgenesis mesodermalis of the iris, it may be useful to present a brief outline of the normal development of the anterior chamber of the eye (Barber 1955; Dejean *et al.* 1958; Duke-Elder 1963; Brini *et al.* 1965).

The development of the anterior chamber commences with the development of the lens vesicle from the superficial ectoderm (6-9 mm stage). During this period and shortly after detachment of the lens vesicle, we find between the vesicle and the superficial ectoderm a delicate fibrillar protoplasmic matrix (anterior vitreous, mesostroma), which is believed to represent the ectodermal basis of the future cornea. On the basis of exhaustive comparative embryological studies, Hagedoorn (1928-1936) established the presence and development of a delicate membrane immediately behind the superficial ectoderm. Guided by this ectodermal primitive cornea, which then serves as "directional membrane" (Richtungshäutchen), the mesodermal cornea is believed to develop next. Fairly soon after ingrowth of the first mesodermal elements at the end of the sixth week (12-13 mm stage), *no* trace of these fibrillae can any longer be found.

Initially, the mesoderm near the edge of the optic cup gives rise to a thin layer of mesodermal cells interposed between the lens vesicle and the superficial ectoderm (12 mm stage). From this layer develop, first the corneal endothelium and later the membrane of Descemet.

Next, a second wave of proliferating mesodermal cells grows between the ectodermal (meanwhile bistratal) corneal epithelium and the primordium of the corneal endothelium. From this tissue the corneal stroma differentiates in the 7th to 8th week (16-23 mm stage).

During this period a third wave of mesodermal cells begins to invade between the already formed corneal primordium and the lens body which has meanwhile developed from the lens vesicle (21-30 mm stage). From these mesodermal cells then develop the pupillary membrane and the iridal stroma, while in later months the ectodermal iris develops behind the mesodermal iris.

Since in this period the fibrillar elements of the mesostroma should have disappeared, the mesostroma will normally not be involved in or interfere with the development of the mesodermal iris.

With the development of the pupillary membrane, that of the anterior chamber of the eye begins. This is initially of limited size, and peripherally bounded by the primary mesodermal tussue at the edge of the optic cup. Some time later, the development of the iridocorneal angle will take place in this area. This begins after the fourth month of development because the various parts of the local mesoderm, the uveal trabecular tissue and the mesodermal parts of the iris and the ciliary body differ in rate and direction of growth. This change in the topography of the area leads to separation or cleavage of two different layers of mesodermal tissue, giving rise to the anterior chamber angle (Allen, Burian and Braley 1955).

Rieger (1935, 1941) regarded as the principal clue in establishing the onset of the developmental defect, the abovementioned protoplasmic adhesions between the posterior corneal and the anterior iridal surface. Since according to Fischer (1931) these must have disappeared at the latest in the 20 mm stage, Rieger believed that this was the ultimate time at which the developmental arrest could commence.

On these grounds, Rieger interpreted "dysgenesis mesodermalis corneae et iridis" as the consequence of a developmental arrest beginning in the second month of foetal development and ending in the fourth month (for the ectodermal part of the iris, including the sphincter, generally shows normal development).

Another factor which Rieger considered in determining the time of onset of developmental arrest was Mathis' postulate (1936) that partial anodontia vera resulted from developmental arrest by the 6th-7th week of foetal development, when the epithelium of the oral cavity, near what will become the alveolar process, begins to proliferate in depth – initially in circumscribed islands. The fact that the two developmental arrests commenced in the same period was used as an argument in favour of a pathogenic correlation between the two developmental defects.

Rieger thus held that the abnormalities observed had to be based on a developmental arrest which was very likely a consequence of a dominantly transmitted predisposition.

In his efforts to explain the developmental defect, Rieger focused mainly on the cause of the pupillary malformations in his cases. However, our study has demonstrated that these pupillary malformations are *no essential* feature of the syndrome; their cause, therefore, cannot be also the cause of the primary developmental defect. After all, pupillary development – like that of the iridocorneal angle – occurs at a later stage in foetal life.

In our opinion, primary dysgenesis mesodermalis of the iris should be regarded as a syndrome which is based primarily on a genetically determined primordial defect of the iridogenic mesoderm, which in part is expressed in primordial hypoplasia and poor differentiation. Later and secondarily, this primary defect gives rise to disturbances in the development of the iris and the pupil and in the cleavage process which gives rise to the definitive iridocorneal angle. If the pathological gene begins to exert its influence relatively early, then the development of the corneogenic mesoderm can be disturbed also; and this will be clinically manifested by secondary dysgenesis mesodermalis of the cornea (Peters' anomaly).

23. HISTOLOGICAL FINDINGS

Histological descriptions of eyes with primary dysgenesis mesodermalis of the iris are confined to a few instances. In the publication of Delmarcelle *et al.* (1958), Brini described one of the eyes of a 7-week-old girl with Rieger's syndrome and glaucoma: "Cornea: intact epithelium. Bowman's membrane not identifiable.

Central zone with inflammatory infiltrate. Considerable vascularization of the superficial and middle stromal layers. Distortion of the corneal lamellae due to cicatrization. Descemet's membrane, though not identifiable at some sites, seems normal. Normal endothelium. Fibrinoid exudate in the anterior chamber. The iridocorneal angle is filled by tissue which forms a low-density network connecting the anterior iridal surface with the line of Schwalbe at its point of maximum development. The very prominent line of Schwalbe, which shows an abnormal degree of development, is linked on the one hand to tissue in the iridocorneal angle, and on the other hand to a delicate membrane which is lost in the pupillary region. The Schlemm canal has the shape of an oblong lacuna which takes a course parallel to the scleral lamellae that constitute its distal wall. In all sections the canal is localized posterior to the iridocorneal angle. There is agenesis of the iridal stroma near the iridal root, with ectropion uveae and a posterior synechia. Mild anterior cataract."

Sugar (1965) described the histology of both eyes in a 13-year-old boy with primary dysgenesis mesodermalis of the iris and juvenile glaucoma: "On microscopic examination there is a mild episcleritis. The major portion of the corneal epithelium has been denuded. In the angle, the anterior border ring shows a marked thickening and hypertrophy of collagen fibers. This prominence of the terminus of Descemet's membrane is similar to that seen in posterior embryotoxon of Axenfeld. The angle, itself, appears slightly postplaced, with some of the trabecular fibers extending from the root of the iris toward the anterior border ring. The approach to the angle is somewhat narrow. A sprinkling of chronic inflammatory cells is noted in the iris. The ciliary processes are atrophic. The retina is detached due to cutting and fixing procedures. Peripheral cystic retinal degeneration and marked posterior bowing of the lamina cribrosa are present."
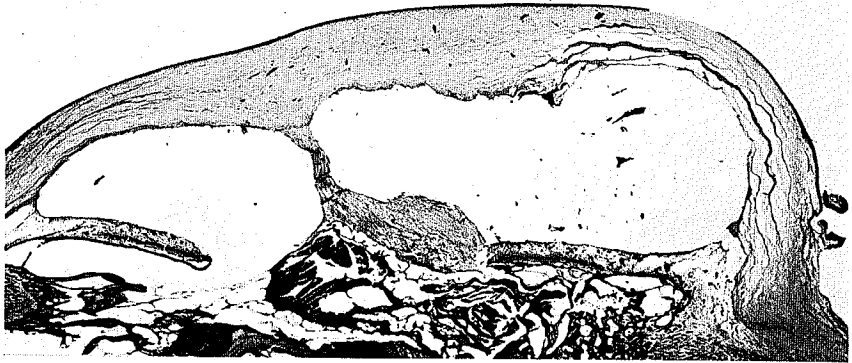
Fig. 50. Anterior segment microscopy in primary dysgenesis mesodermalis of the iris. Localized defect of the posterior corneal stroma (secondary dysgenesis mesodermalis of the cornea) is present (BR-IV-1, left eye).
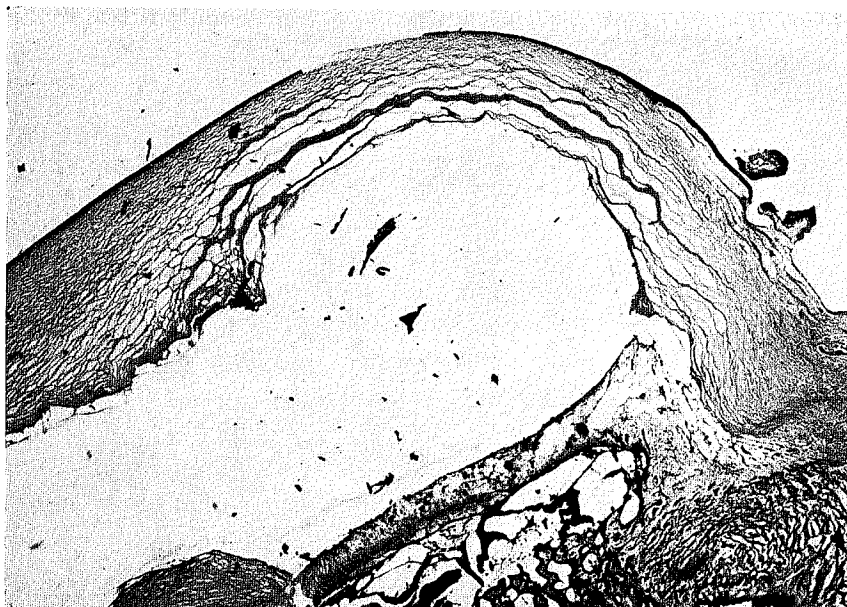
Fig. 51. Defect of the posterior corneal stroma in primary dysgenesis mesodermalis of the iris. Endothelium and Descemet were present. (BR-IV-1, left eye).

Fig. 52. Microscopy of the region of the chamber angle in primary dysgenesis mesodermalis of the iris and congenital glaucoma. Very prominent ring of Schwalbe (embryotoxon corneae posterius) with detached iridocorneal adhesions continue with loose persistent mesodermal tissue in the chamber angle. Schlemm's canal cannot be identified (57 ×) (BR-IV-1, left eye).

Wolter *et al.* (1967) described the histopathological findings obtained in the anterior chamber in a 16-day-old boy with primary dysgenesis mesodermalis of the iris, congenital glaucoma and corneal staphyloma: "Cross sections showed the extensive central corneal staphyloma, luxation of the cataractous lens into the shallow anterior chamber and hypoplasia of the iris associated with ectropion uveae more on one side than on the other. A very prominent posterior embryotoxon was represented in our cross sections by distinct nodules on the periphery of the posterior cornea. The ring-shaped structure was in firm contact with the posterior corneal surface on one side while it was separated from the cornea on the other. It was composed of a core of densely arranged collagen fibers covered by a basement membrane and a monolayer of endothelium. This layer of endothelium was continuous and was recognized to separate the substance of the posterior embryotoxon and that of the cornea everywhere – even in the zone of firm adhesion to the cornea. Complete separation of the posterior embryotoxon from the cornea was found in a large part of this anterior segment. The corneal endothelium was continuous in the area of the separated ring and this ring exhibited its own layer of endothelial cells. Schiff stain revealed a distinct glass membrane to cover the cornea in the region of the separated ring as well as on the surface of the embryotoxon itself. The iris was connected all around to the posterior aspect of the embryotoxon. This connection between iris and ring was broad in some areas while it consisted of a thin membrane in others. No canal of Schlemm was seen in any of the sections. Extensive dysplasia was found in the area of the filtering trabecula. Poorly differentiated structures somewhat resembling uveal meshwork were seen to insert on the convex aspect of the embryotoxon in many areas."

Through the good offices of Mr George Fenwick of Auckland, we received a microscopic specimen (Auckland Hospital 457/2536) of the enucleated left eye of our patient BR-IV-1. Dr Manschot, Rotterdam, was kind enough to describe this specimen for us. His description:

Microscopy: The available specimen is a single section of an eye, embedded in paraffin. The embedding has given the corneal stroma a low-density appearance (fig. 50). On one side of the cornea there is a peripheral thinning due to a defect in the inner stroma. On the inside, this defect is lined with Descemet's membrane and endothelium (fig. 51). A strand of connective tissue extends from the central cornea to a mass of connective tissue on the anterior surface of the luxated lens. Due to marked damage inflicted during processing it is uncertain whether there has been a cataract. The iridocorneal angle is irregular due to the presence of mesodermal adhesions between the peripheral iridal stroma and the cornea, more particularly the highly developed line of Schwalbe (fig. 52). Schlemm's canal cannot be identified. The peripheral iridal stroma is hypoplastic; the pupillary zone of the iris is well-developed. The iridal surface is covered by a thin layer of connective tissue. The iridal stroma contains many lymphocytes and plasma cells

PLATE V. Coloboma of the iris, central corneal opacities with defect of the deeper corneal layers (dysgenesis mesodermalis of the cornea) and secondary dsygenesis mesodermalis of the iris (HC-IV-8, right eye).
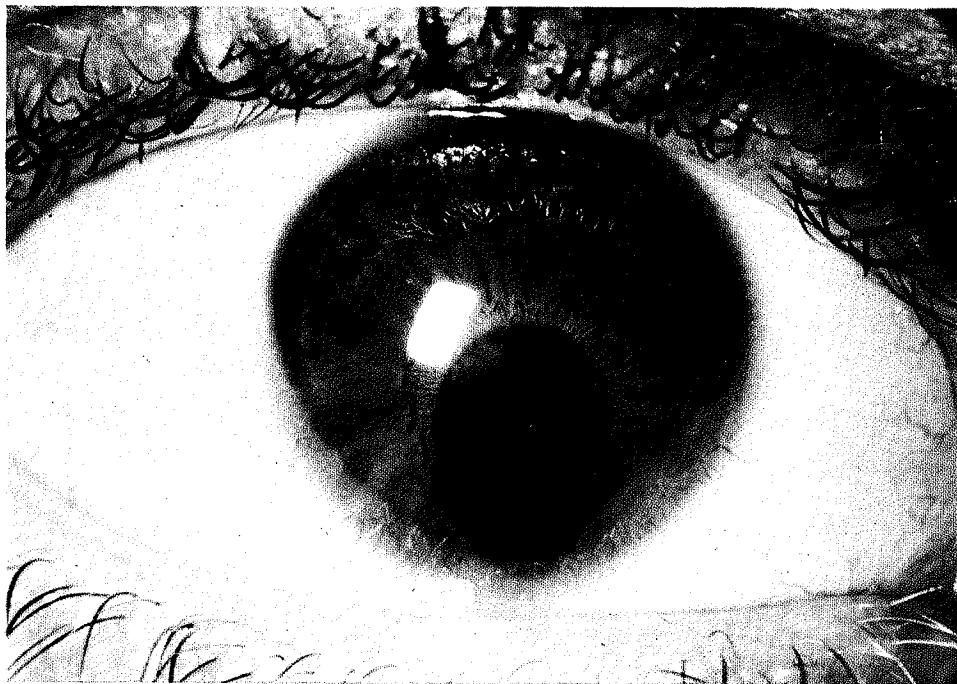
as well as a fair number of polynuclear leucocytes, mostly arranged in groups. A large amount of connective tissue is found also behind the lens; due to retraction of this tissue the ciliary processes show centrad distortion, and there is separation of the ciliary body and the peripheral retina. In the retrolenticular connective tissue as well as in the anterior part of the vitreous there is much blood. There is extensive cystic degeneration of the retina; several retinal vessels are enveloped by a lymphocytic infiltrate.

Conclusion: The section shows all the histological characteristics of Rieger's syndrome. The structure is severely disturbed by marked intraocular proliferation of connective tissue following three operations on the anterior chamber. The situation is further complicated by extensive haemorrhages in and behind the retrolenticular mass of connective tissue and by an intraocular inflammatory process. The cause of the degenerative retinal changes cannot be identified in this single section.

The above description warrants the conclusion that the most striking histological features of primary dysgenesis mesodermalis of the iris are a pathologically prominent line of Schwalbe in the form of an embryotoxon posterius with additional changes in the iridocorneal angle, consisting of adhesions between this prominence and the hypoplastic iridal stroma; these features correlate with the clinical picture of the syndrome. It is impossible to establish with certainty a demonstrable and visible anatomical basis of the increased intraocular pressure. In some specimens, however, Schlemm's canal could not be identified – a situation sometimes encountered also in eyes with primary hydrophthalmos.

The local defect found in the inner stromal portion of the cornea in our own case, was interpreted as secondary dysgenesis mesodermalis of the cornea or Peters' anomaly. The presence of endothelium and Descemet's membrane need not be inconsistent with a developmental defect in the sense meant by Peters, because secondary endothelialization is certainly possible, as we saw, in a later developmental stage.

Finally, mention should be made of the findings of Pau (1962, 1965) and Pau *et al.* (1962). In eyes with, among other abnormalities, a possible Rieger syndrome they observed changes in the form of progressive iridal atrophy and endothelial proliferation on the iris, involving the formation of glass membranes. The authors maintained that these findings corroborate their view that congenital dysgenesis mesodermalis of the iris and acquired progressive iridal atrophy are aspects of the same disease picture; the more so because such glass membranes have been repeatedly described in eyes with essential progressive iridal atrophy (Rochat and Mulder 1924; and others).

In our opinion the two conditions are of an entirely different type. We have already emphasized this in the section "Clinical course and therapy" of this chapter, and will revert to this subject in the chapter on differential diagnosis. There is a difference not only in clinical but also in pathological anatomical terms: eyes

with essential progressive iridal atrophy as a rule show no pathologically prominent line of Schwalbe. Many of the eyes available for examination have been previously submitted to several surgical interventions which may have produced marked secondary changes. The presence of glass membranes, as such, can have no differential diagnostic or diagnostic significance because these aspecific membranes have been frequently observed and described as secondary findings in eyes in the terminal stage of glaucoma, after operation and in chronic iridocyclitis (Callahan 1956; Wolter and Fechner 1962; and others).

Dysgenesis mesodermalis of the cornea

Peters' anomaly

I. INTRODUCTION

Peters (1906, 1908, 1912) described the clinical and histological features of a developmental defect of the eye which was later to become known as *Peters' anomaly* ("Peters'schen Defektbildung der Hornhaut").

The condition involved a congenital central corneal opacity with abnormalities of the deepest stromal layers and local absence of Descemet's membrane. In the case described by Peters there was hydrophthalmos also.

The affection, which can be confined to the cornea, is usually accompanied by more extensive abnormalities of the anterior ocular segment, e.g. the presence of adhesions between the edge of the defect and the pupillary zone, iridal frill or iridal stroma, and sometimes corectopia and iridal hypoplasia. Incidental findings obtained in patients showing this anomaly have been: persistent pupillary membrane, anterior polar cataract, iridal coloboma, sclerocornea, cornea plana, persistent hyaloid artery and secondary dysgenesis mesodermalis of the iris (Von Hippel 1897; Grimsdale 1903; Rübel 1912; Hoffmann 1931; Berliner 1941; Theodore 1944; Paufique *et al.* 1950; Chinaglia 1955; Badtke 1961; Forsius 1961; Goldstein and Cogan 1962; Henry 1962; Collier 1963; Forsius and Metsälä 1963; Bloch 1965; Reese and Ellsworth 1966; Godde-Jolly and Bonnin 1966; and others).

Our own material includes a patient with Peters' anomaly and iridochorioretinal coloboma (HC-IV-8 plate V), one with the anomaly and adhesions between the edge of the defect and the iris (E-II-1), one with corneal leucoma and adhesions between the opacity and the lens, as in the case described by Dudinow (1933), and one with the anomaly in association with Rieger's syndrome and glaucoma (BR-IV-1; figs. 55-57).

However, the condition known as Peters' anomaly or Peters' syndrome is not, in our opinion, a pathogenic entity. The developmental defect of the cornea

Fig. 53. Secondary dysgenesis mesodermalis of the cornea in primary dysgenesis mesodermalis of the iris. Ill-defined limbus, horizontal-oval cornea and central corneal opacity with local defect of the posterior corneal stroma (BR-IV-1).

described by Peters (which we wish to call dysgenesis mesodermalis of the cornea) can become manifest in two different ways, as:

1. primary dysgenesis mesodermalis of the cornea: an entity which takes the form of a relatively rare, genetically determined, recessively transmitted developmental defect of the cornea;
2. secondary dysgenesis mesodermalis of the cornea: a clinically similar corneal abnormality, but observed as an associated anomaly in the context of a primary developmental defect of the eye or of a more general syndrome.

2. CLINICAL PICTURE

Clinically, Peters'anomaly is a developmental defect of the anterior ocular segment with corneal changes as predominant feature. The severity of the corneal changes, like that of associated anomalies of the anterior chamber, can vary considerably.

It is possible (but not certain) that *keratoconus posticus circumscriptus (posterior*

84
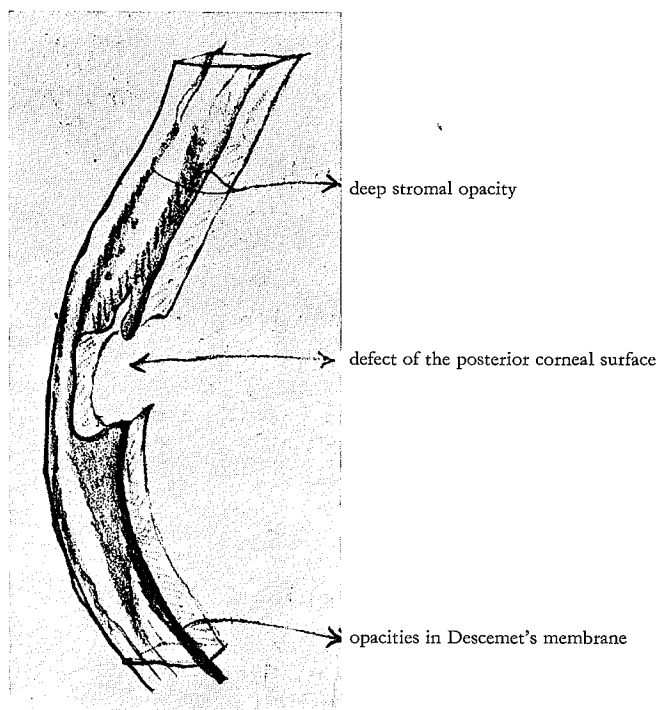
Fig. 54. Drawing of slit-lamp picture of the central corneal area in primary dysgenesis mesodermalis of the iris and dysgenesis mesodermalis of the cornea (BR-IV-1, see figs. 4 and 53).

keratoconus) constitutes the mildest degree of Peters' anomaly. It is characterized by a normal anterior corneal curvature and defect of stromal substance in a well-defined area of the deepest corneal parenchyma (Karlin and Wise 1961; Haney and Falls 1961; Collier 1962a, 1962b, 1963; and others). The abnormality is often bilateral and centrally localized, but can be unilateral and/or paracentral. Wolter and Haney (1963) described the histological features. In their case there was general rarefaction of Descemet's membrane with many minute ruptures of this membrane (which was not entirely absent). The presence of endothelium and its derivative Descemet membrane need not be inconsistent with the diagnosis of Peters' anomaly, for an initial defect can secondarily have become endothelialized.

The next, classical stage of *Peters' anomaly* consists of a defect of the deepest stromal layers of the cornea and Descemet's membrane, corneal opacities with or without adhesions or remnants of adhesions to the iris.

This was the picture encountered in our patients HC-IV-8 (fig. 55) and BR-IV-1, (figs. 4, 53) and also in patients described by Berliner (1941), Theodore (1944) and Forsius and Metsälä (1963). The lastmentioned authors referred to it by the

pear-shaped cornea

defect of the posterior
corneal surface (Peters'
anomaly) bordered by
lumps of pigment

iridal frill with several
stalks of brown-pig-
mented stroma poin-
ting towards the cor-
neal pigment lumps

12 mm

10°

scleral overriding

bridge-coloboma of the iris and pupil
distortion
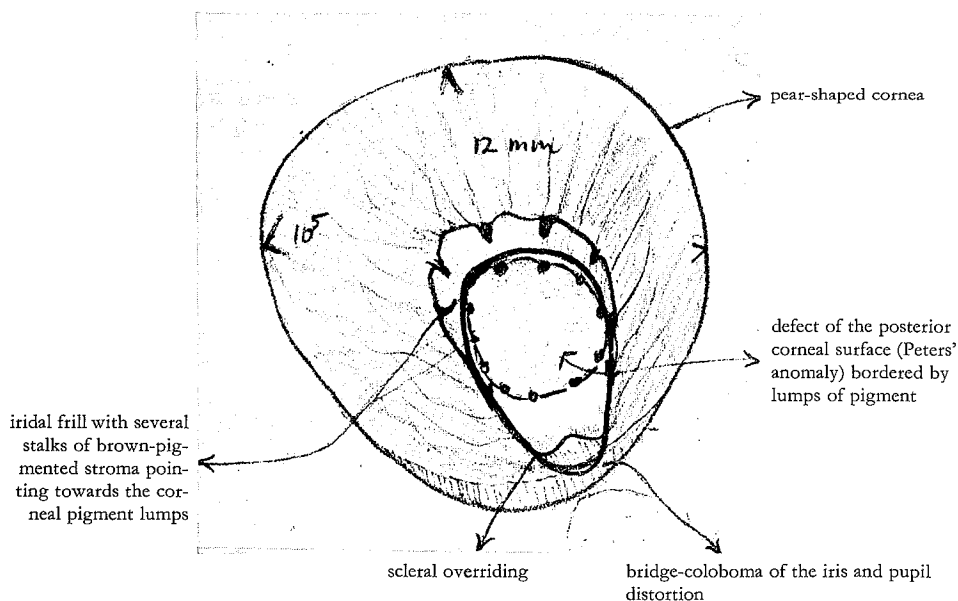
Fig. 55. Schematic drawing of the anterior segment in a patient with iridochoroidoretinal colo-
boma, dysgenesis mesodermalis of the cornea, secondary dysgenesis mesodermalis of the iris, hetero
chromia, and anomalies of the ear and face (HC-IV-8, right eye).

area of abscence of the deepest corneal
layers and presence of corneal opacities

scleral overriding (membrana
corneoscleralis persistens)

brown star-shaped pig-
mentation of the lens

partial limbus
coloboma (Asher)

adhesions between the
upper and lower margins
of the corneal defect and
the otherwise normal iris

section plane of fig. 57
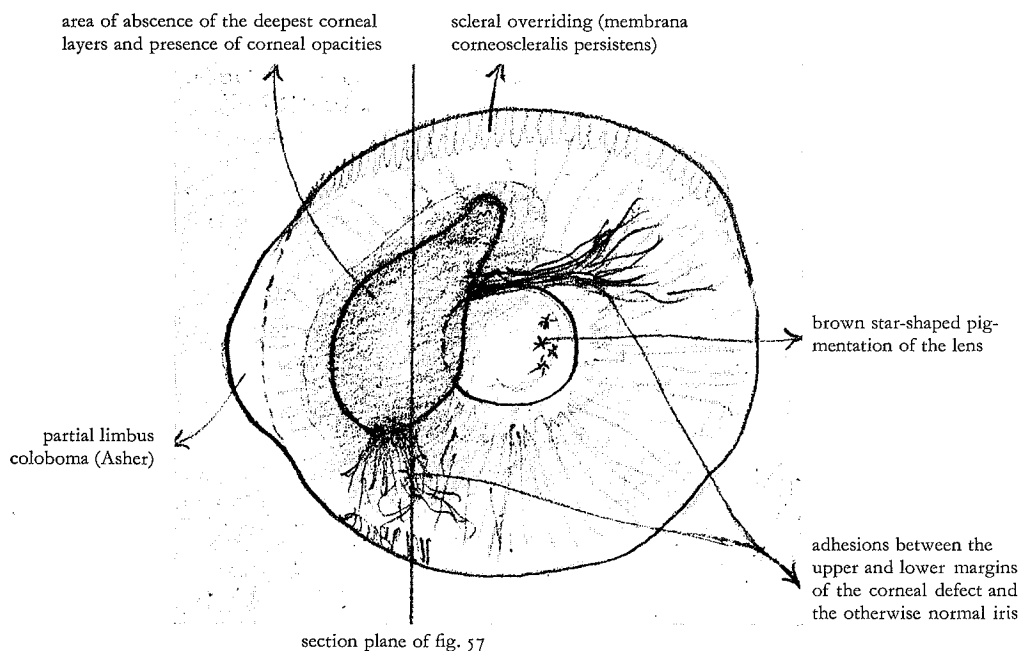
Fig. 56. Schematic drawing of dysgenesis mesodermalis of the cornea, with central iridocorneal
adhesions and partial limbus coloboma (E-II-1, left eye).

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scleral overriding

corneal opacities

defect of the deepest corneal layers

anterior chamber

central iridocorneal adhesions

irregularity of Descemet's membrane

iridocorneal adhesions in the periphery
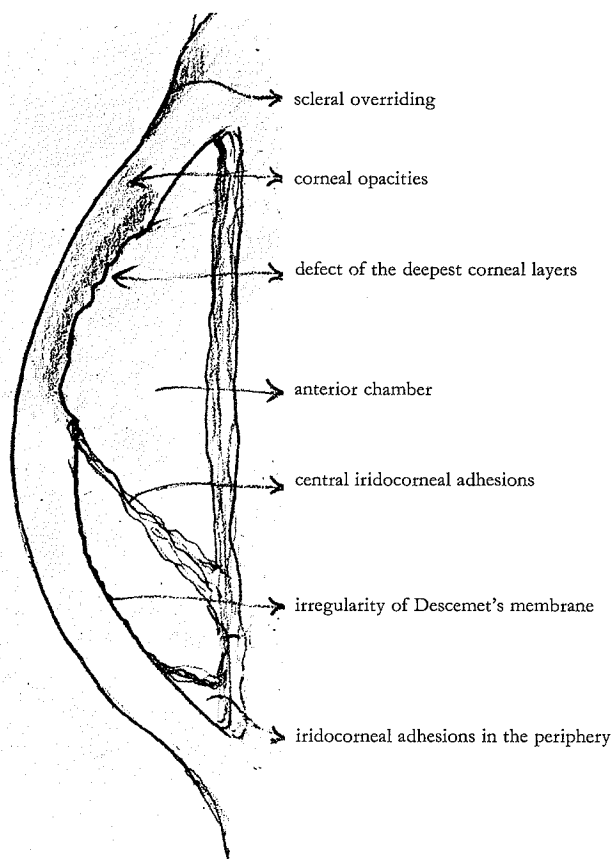
Fig. 57. Cross section of the same eye as in fig. 56. Dysgenesis mesodermalis of the cornea (E-II-1, left eye).

misnomer "keratoconus posticus". The abovementioned corneal opacities in dysgenesis mesodermalis of the cornea can be dense and remain leucomatous; or they may clear up considerably in the course of the years. We observed the latter in our patient E-II-1, who at birth showed a white pearl on the cornea which gradually became more transparent until finally only a slight nebula remained (fig. 56, 57).

The *connatal corneal leucomas*, with or without sclerocornea and other associated connatal anomalies, as described by Franceschetti and Valerio (1945), Straub (1950), Verrey (1950), Chinaglia (1955), Goldstein and Cogan (1962), Copper (1963), Nath *et al.* (1964), Franceschetti *et al.* (1964). Bloch (1965), Speakman and Crawford (1965), Reese and Ellsworth (1966) and Godde-Jolly and Bonnin (1966), are closely related if not identical to the more severe forms of Peters' anomaly.

Connatal corneal staphylomas with glaucoma (Crompton 1840, Krückow 1875,

Steinheim 1897, Peters 1912, 1923, 1926, Bouwman 1939; Donahue 1952; Weizenblatt 1954; Delmarcelle and Pivont 1957; Grover 1958; Badtke 1965; Hamburg 1965; Tanenbaum and Rosen 1966; Ing 1967; Heimann 1968; and others) represent the most severe from of Peters' anomaly.

We next present a summarizing survey of what is clinically known about Peters' anomaly, and a few differences from primary dysgenesis mesodermalis of the iris will be discussed. In some 20% of cases Peters' anomaly has been found as a *unilateral* condition.

Unlike Rieger's syndrome, Peters' anomaly is frequently found to be associated with *microphthalmos*.

A few authors, e.g. Appelmans *et al.* (1950), have described *blue sclerae* in association with Peters' anomaly. This anomaly is relatively often accompanied by *cornea plana* with *sclerocornea* and shallow anterior chambers (Copper 1963). In primary dysgenesis mesodermalis of the iris there is only a very mitigated and less frequent indication of these anomalies, and the anterior chamber is nearly always of normal depth.

While Rieger's syndrome is sometimes characterized by peripheral corneal opacities and invariably by embryotoxon corneae posterius, Peters' anomaly always shows central corneal opacities or leucomas, and embryotoxon corneae posterius is seldom observed. A prominent line of Schwalbe with iridocorneal adhesions has been mentioned as a histological finding (Zimmerman 1962, cited by Reese and Ellsworth 1966), and we established this gonioscopically in our patient HC-IV-6 (figs. 64, 65).

In primary dysgenesis mesodermalis of the iris, the iridocorneal adhesions are localized *peripherally* in the iridocorneal angle area, whereas in Peters' anomaly these adhesions are chiefly found in *central* position (figs. 56, 57), extending from the corneal opacity to the pupillary zone or the zone around the iridal frill. General hypoplasia of the iridal stroma – characteristic par excellence of Rieger's syndrome – is as rare as are pupillary anomalies (Ueno 1936) in Peters' anomaly; it should be borne in mind, however, that a thorough examination of the anterior chamber is not always feasible in these cases. Histological evidence of atrophy of the iridal stroma has been described in a few cases.

It is highly likely that over 50% of patients with Peters' anomaly show *glaucoma*, as do patients with primary dysgenesis mesodermalis of the iris. The incidence of connatal glaucoma seems to be considerably higher in Peters' anomaly, however. Exact comparison is precluded by the heterogeneity of the available material and the lack of detailed data on eyes with Peters' anomaly.

It seems that Peters' anomaly sometimes also involves the *lens*; apart from anterior polar cataract, there are reports on other types of connatal cataract (Hilbert 1892; Seefelder 1905), and on connatal aphakia (Manschot 1963), pseudo-aphakia (Von Hippel 1918) and microphakia (Maschimo 1923; Marchesani 1930). Remnants of the hyaloid artery have been found in several cases. Little is know about the retina in Peters' anomaly.

We know of a few isolated cases which showed the complete or nearly complete pictures of both developmental defects of the anterior ocular segment: Rieger's syndrome as well as Peters' anomaly; the clinical pictures in these cases represented a mixed form.

Secondary dysgenesis mesodermalis of the iris in the form of iridal and irido-corneal angle changes is involved in these cases of Peters' anomaly characterized by central corneal opacities, defects of Descemet's membrane, sclerocorneae and central iridocorneal adhesions (Ueno 1936; Cassuto 1938; Theodore 1944; Grignolo 1949; Paufique et al. 1950; Rossetti 1952; Rama and Caffi 1958; Forsius 1963; Speakman and Crawford 1965).

In view of the diagnostic uncertainty these cases were not counted among the instances of primary dysgenesis mesodermalis of the iris in compiling the material which was discussed in the preceding chapter. However, the mixed form was occasionally observed in families with the dominantly hereditary Rieger syndrome (Falls 1949; Forsius and Eriksson 1964; Levien 1966; Wolter et al. 1967; our families BR and RK). Here, Peters' anomaly occurred as secondary dysgenesis mesodermalis of the cornea in patients suffering from primary dysgenesis mesodermalis of the iris.

In the family described by Falls (1949), the many patients with Rieger's syndrome included four with this syndrome and connatal central corneal opacities, cornea plana without hydrophthalmos. One female patient with unilateral corneal opacities had a brother with Rieger's syndrome, two daughters with the syndrome, and two children with the syndrome and connatal central corneal opacities. One of the daughters without corneal changes had a number of children with primary dysgenesis mesodermalis of the iris and a daughter with Rieger's syndrome and unilateral central corneal opacity.

Forsius and Erikson (1964) used the designation "familial progressive iridal atrophy" in describing a family of a mother and two daughters with primary dysgenesis mesodermalis of the iris. One of the daughters showed mild opacity of the central part of the posterior corneal surface OS.

Levien (1966) briefly mentioned a patient with Rieger's syndrome who had two daughters with congenital anomalies and one healthy son. The elder daughter had bilateral corneal leucomas with nystagmus; the younger daughter showed primary dysgenesis mesodermalis of the iris with glaucoma, in combination with a large central corneal leucoma OS.

Wolter et al. (1967) described a patient with the combined anomaly OD and corneal staphyloma with severe anomalies of the anterior chamber OS. This patient's mother showed primary dysgenesis mesodermalis of the iris without glaucoma.

Our family BR in this respect also showed a remarkable and strikingly similar picture. The mother had primary dysgenesis mesodermalis of the iris ODS without glaucoma or dental anomalies (figs. 5, 9, 21, 30). The elder daughter showed infantile glaucoma ODS, corneal leucoma with defect of the deepest corneal

stroma OD (figs. 4, 20, 28, 53), and connatal corneal staphyloma OS. Her sister had primary dysgenesis mesodermalis of the iris ODS, with congenital glaucoma but no sign of Peters' anomaly (figs. 1, 13, 14, 29). The elder suffered from oligodontia vera (figs. 42, 43), and the younger probably had the same anomaly.

The mother (fig. 37) of the Rieger children (figs. 36 and 38) in pedigree RK (Leffertstra 1955) showed bilateral congenital corneal opacities, multiple anterior synechiae, hypoplasia of the iridal stroma, pupillary anomalies and glaucoma absolutum.

Secondary dysgenesis mesodermalis of the cornea (Peters' anomaly) occurs not only in patients with Rieger's syndrome but also in association with other developmental defects of the anterior ocular segment and the eye. In addition, it can be observed as a component of a more extensive, general and often hereditary syndrome.

Haney and Falls (1961) described keratoconus posticus circumscriptus as a component of a new syndrome which consisted of hypertelorism, mongoloid eyes, brachydactyly, pterygium colli and mental as well as physical retardation in two children from normal parents.

Pinsky *et al.* (1965) observed a hereditary oculocerebral syndrome with connatal microphthalmos, corneal opacities, mental retardation and spastic paralysis.

Mietens and Weber (1966) described four children in a consanguineous marriage who showed a syndrome characterized by connatal corneal opacities, nystagmus, flexion contracture of the elbows, growth disorders and mental retardation.

Cross *et al.* (1967) reported a new oculocerebral syndrome with hypopigmentation in four of ten children from healthy parents. The ocular changes were connatal microphthalmos, corneal leucomas, sclerocornea and synechiae with the iris in one case.

Saraux *et al.* (1967) observed Peters' anomaly in their family, in which autosomal recessive pseudo-glioma and brittle bones occurred.

Connatal anomalies of other organs and organ systems are frequently observed in association with or concomitant with Peters' anomaly. Such combinations more frequently involve dysgenesis mesodermalis of the cornea than primary or secondary dysgenesis mesodermalis of the iris. We classified the combined anomalies as involving the central nervous system, the cardiovascular system, the urogenital system, the digestive system, the skull and face, and the limbs.

Central nervous system. There are reports on mental deficiency (Appelmans *et al.* 1956; Copper 1963; Speakman and Crawford 1965), subcortical cysts in the white matter (Speakman Crawford 1965), spina bifida occulta (Bloch 1965), cerebellar dysfunctions (Goldstein and Cogan 1962), hydrocephalus (Grover 1958; Heimann 1968) and deafness (Goldstein and Cogan 1962).

Cardiovascular system. Ventricular septal defect (Rossetti 1952; Heimann 1968), pulmonary stenosis (Riise 1964; two cases), patent ductus arteriosus (Forsius and Metsälä 1965) and congenital heart defect (Appelmans *et al.* 1956).

Urogenital system. Hypospadias (Appelmans *et al.* 1956; Speakman and Crawford 1965), cryptorchism (Goldstein and Cogan 1962; Riise 1964; Heimann 1968), ureteral stenosis, hydroureter, hydronephrosis and phimosis (Heimann 1968), ureteral duplication (Ing 1967).

Digestive system. Umbilical hernia (Riise 1964) and distal intestinal atresia (Appelmans *et al.* 1950).

Skull and face. Facial hemihypoplasia (Purtscher 1921; Riise 1964); mild craniofacial dysplasia (Jaeger 1959; Collier 1962a; Goldstein and Cogan 1962; Bloch 1965; Heimann 1968), hypertelorism, micrognathia and pterygium colli (Heimann 1968), epicanthus (Badtke 1965), microcephaly (Appelmans *et al.* 1956; Godde-Jolly and Bonnin 1966), palatoschisis (Appelmans *et al.* 1950; Riise 1964; Heimann 1968), abnormalities of the external ear (Franceschetti and Valerio 1945; Goldstein and Cogan 1962; Riise 1964; Bloch 1965; Godde-Jolly and Bonnin 1966; Heimann 1968; our patient HC-IV-6).

Limbs. Syndactyly (Berliner 1941; Goldstein and Cogan 1962), camptodactyly (Jaeger 1959; Collier 1962a), clubfoot (Speakman and Crawford 1965) and polydactyly (Heimann 1968).

3. HEREDITY

Investigations made by Kleberger and Nachtsheim (1965) and Kleberger (1968) have shown that, in rabbits, Peters' anomaly is determined by a *recessive* hereditary factor. Besides the principal gene, other genes also were responsible for the manifestation of this anomaly.

A strong argument in favour of recessive transmission in man is the occurrence of Peters' anomaly in several children from parents with normal eyes. Parental consanguineousness was occasionally established, and this enhances the probability of recessive heredity.

As early as 1875 Krückow described Peters' anomaly in two brothers with healthy consanguineous parents; he cited Crompton (1840), who had observed connatal corneal opacities OD and corneal staphyloma OS in two brothers.

Baas (1894) mentioned three children (from normal parents) with changes closely resembling sclerocornea with Peters' anomaly; he cited Ferras, who found the same anomaly in three children in one family. Steinheim (1897) and Von Hippel (1900, 1906) likewise observed the anomaly in children from healthy parents (4 out of 5, 2 out of 6, and 3 out of 7 children, respectively). The 8 cases reported by Lacompte (1912) included a pair of male twins who both showed Peters' anomaly ODS.

The anomaly was observed unilaterally with microcorneae and facial hemihypo-

Authors	Number of patients (x)	Number of siblings (n)	x(n-1)	x(x-1)
KRÜCKOW (1875)	2	6	10	2
BAAS (1894)	3	10	27	6
STEINHEIM (1897)	4	5	16	12
VON HIPPEL (1900)	2	6	10	2
VON HIPPEL (1906)	3	7	18	6
LACOMPTE (1912)	2	7	12	2
PURTSCHER (1921)	2	5	8	2
THEODORE (1944)	2	2	2	2
BAQUERO HEIN (1960)	2	7	12	2
Total	22	55	115	36

plasia in two brothers (Purtscher 1921); in two sisters (Theodore 1944); and in a brother and sister mentioned in a "Redactional note", Britisch Journal of Ophthalmology (1949). It was reported by Baquero and Hein (1960) in two brothers and a sister whose parents and five other brothers and sisters were healthy.

Jaeger (1959) observed Peters' anomaly in three children from consanguineous parents, and Copper (1963) reported the anomaly in two sisters whose (non-consanguineous) parents were normal.

In addition there have been many reports on *isolated* cases of dysgenesis mesodermalis of the cornea, in patients whose parents were healthy and had normal eyes so far as could be established (Samelson 1880; Makrocki 1885; Zirm 1890; Mager 1895; Wüstefeld 1900; Van Duyse 1902; Grimsdale 1903; Herbst 1906; Coats 1910; Mayou 1910; Reis 1911; Kraupa 1921; Remky 1933; Bouman 1939; Chang 1949; Straub 1949, 1950; Appelmans *et al.* 1950; Verrey 1950; Donahue 1952; Beckett 1953; Weizenblatt 1954; Appelmans *et al.* 1956; Grover 1958; Karlin and Wise 1961; Collier 1962a, 1962b; Forsius and Metsälä 1963; Nath *et al.* 1964; Riise 1964; Speakman and Crawford 1965; Tanenbaum and Rosen 1965; Reese and Ellsworth 1966; Godde-Jolly and Bonnin 1966; Ing 1967; Hamburg 1967; Heimann 1968).

In view of the above findings there are several indications which warrant the assumption that Peters' anomaly (primary dysgenesis mesodermalis of the cornea) is a recessive hereditary condition, although a few cases and other findings seem to contradict this.

The 9 families which included several instances of Peters' anomaly among their known numbers of children, totalled 55 children, Given a recessive mode of

transmission, it might be predicted that 25% (say, 14 children) would show the anomaly. However, no fewer than 22 of these 55 children (40%) were found to show the anomaly, and this exceeds the prediction.

By applying Weiberg's sibling method (propositus method) this percentage (40%) is corrected. For this purpose we use Weiberg's formula:

$$P = \frac{\sum x(x-1)}{\sum x(n-1)}.$$

According to our table 17 we see the following fraction:

$$P = \frac{36}{115} \times 100 = 31.3\%.$$

Irregular dominant transmission might be considered: Von Hippel (1918) observed the anomaly also in his patient's aunt; Berliner (1941) reported the anomaly in two cousins, and Delmarcelle and Pivont (1957) saw four instances of the anomaly in the first, and two in the third generation. An argument in favour of dominant transmission might be the occurrence of unilateral central annular leucoma of the cornea with adhesions between the leucoma and the iridal frill in a child, and of unilateral iridocorneal adhesions in its mother (Reese and Ellsworth 1966). A slight bilateral keratoconus posticus circumscriptus was reported in a father and his son by Jacobs (1957), and in a mother and her daughter by Collier (1962a).

4. PATHOGENESIS

Von Hippel on the one hand, and Peters and Seefelder on the other, initially long held controversial views on the *pathogenesis* of Peters' anomaly.

Von Hippel (1897, 1905, 1906, 1908, 1918) believed that the condition involved an intrauterine inflammation or "ulcus internum corneae" with secondary anterior synechiae, ectasia of the cornea, and glaucoma. In a few cases such an intrauterine process could not be ruled out with certainty, but numerous cases in which histological examination was possible, showed nothing to suggest an infectious aetiology. The cases of Manschot (1966) and the interesting case described by Hamburg (1967) likewise failed to yield such clues.

Peters and Seefelder always maintained that the connatal anomaly resulted from a developmental defect. The plausibility of this view has been confirmed by later investigations in the field of experimental teratology (Badtke 1962a, 1962b, 1965; Kleberger and Nachtsheim 1963; Kleberger 1968) and by the many reports on familial cases.

Peters (1923, 1926) sought an explanation in a disturbance of the separation of

the primary lens vesicle from the superficial ectoderm, i.e. delayed separation. This view had been advanced earlier by Steffan (1867).

Seefelder (1905, 1906, 1920) was more inclined to accept a primary disorder in the development of the endothelium of the anterior chamber, in the form of three waves of disturbance in the spatial and chronological course of mesodermal ingrowth. Ida Mann (1933) agreed with Seefelder. A few arguments in favour of this view are: a not always central localization of the defect in the deep corneal layers, of Descemet's membrane and of the corneal opacity (figs. 55-57 and plate V); the absence of any opacity of the lens (cataractous changes are very frequent in disorders which only partly and temporarily involve the lens); and the occurrence of glaucoma. The increased intraocular pressure in these cases possibly indicates a developmental defect of the mesodermal corneoscleral trabecula, the irido-corneal angle and Schlemm's canal. The latest investigations of Kleberger (1968) support the contention of a mesodermal pathogenesis on the basis of animal experiments.

However, it is an undeniable fact that in several cases the separation of the lens vesicle is disturbed and that this must probably be held responsible for the sub-sequent developmental defects of the cornea and sometimes also the iris in dysgenesis mesodermalis of the cornea (Steffan 1867; Grimsdale 1903; Mayou 1910; Maschimo 1923; Mans 1926, 1928, 1933; Hoffmann 1931; Hagedoorn and Velzeboer 1959; Copper 1963; Hamburg 1967; Heimann 1968).

Badtke's studies in experimental teratology (1962, 1963) (rabbit and mice) lent support to the view that a defect in lens development is the cause of malformations of the anterior ocular segment in the sense of Peter's anomaly. It can be accepted as certain that the fourth week in the development of the human embryo is the critical phase for the occurrence of connatal corneal opacities in dysgenesis mesodermalis of the cornea and for the corneal staphyloma (Badtke 1962; Badtke and Degenhardt 1963).

Animal experiments carried out by Kleberger and Nachtsheim (1963) initially indicated that both processes might play a role in the pathogenesis of this develop-mental defect, which is believed not to be too uncommon in animals. In their rabbit strains, cataract as well as hydrophthalmos were observed separately as well as associated with mesodermal, peripheral and central iridocorneal adhesions.

Later investigations (Kleberger 1968) revealed, however, that the occasionally observed combination of Peters' anomaly with cataract depended on the presence of another, separate gene for this cataract.

Historical data and clinical observations, in part recorded in this study, would seem to us to warrant the conclusion that Peters' anomaly (dysgenesis mesoder-malis of the cornea) is the consequence of a disturbance in corneal development which can occur in several different ways. The controversial views reported in the literature are not actually contradictory but merely represent different modes of development which do not necessarily exclude each other.

It is an error to use a single designation with reference to a condition which can

result from different pathogenic developments; for this would suggest a single pathogenic mechanism. It is likewise an error to follow a certain "trend towards simplification in medicine" to the extent that different disturbances of the developmental process, leading to different clinical entities, are brought under a single heading which clearly designates one well-defined developmental process but ignores the other processes.

In this context we refer to Reese and Ellsworth (1966) who, with respect to a number of patients with congenital corneal opacities, suggested that the group of various clinical syndromes of the anterior ocular segment be collectively described as "anterior chamber cleavage syndrome", because all these syndromes could be ascribed to "faulty cleavage". In the latter designation these authors summarized a variety of factors such as imperfect differentiation, absorption and even shifting or mobilization of tissue in its developmental stage. In our opinion this renders the suggested designation highly debatable, for the term "cleavage" (particularly when used in the context of the development of the anterior chamber) denotes a particular and well-defined process (Allen *et al.* 1955). The syndromal designation therefore suggests that the development of the anterior chamber is based *exclusively* on a cleavage process. Even apart from these objections, it would have been more suitable to speak of *"faulty* cleavage syndrome of the anterior chamber".

Allen, Burian en Braley (1955) have demonstrated that later stages in the development of the anterior chamber (4th-6th month) are characterized by the occurrence of cleavage phenomena resulting from differences in the rate and direction of growth; it is this process that is *largely* responsible for the development of the definitive iridocorneal angle.

In the early stages of the development of the anterior chamber, however, there is as yet no cleavage in this sense. This period is characterized by invasion of mesodermal elements in several "waves" between the primitive superficial ectoderm and the just recently separated primary lens vesicle. In this area one finds initially a delicate protoplasmic ectodermal tissue (mesostroma, anterior vitreous); this has been identified by Hagedoorn (1928-1936) and other investigators.

In this early stage there is a gradual process of cell displacement, ingrowth and condensation, which is associated with dissolution of mesodermal tissue (atrophy). This atrophying process *continues* well into the phase in which the abovementioned cleavage process was demonstrated. Absorption of mesodermal elements in the anterior chamber is a normal embryological phenomenon (e.g. disappearance of the pupillary membrane as the iridal frill develops). It is an established fact that, during the first few years of life, considerable remnants of the mesodermal pupillary membrane can still recede and even disappear completely.

Since *both* processes play an important role in the development of the anterior chamber, the designation "cleavage syndrome" gives rise to confusion and is open to misinterpretation – quite apart from the fact that the word "syndrome" is a misnomer in this context.

If for didactic purposes the various connatal clinical syndromes of the anterior ocular segment are to be summarized, then the term "developmental defects of the anterior ocular segment" presents itself as most appropriate; and it is this term that we prefer to use.

Many different factors may interfere in the course of the development of the anterior ocular segment and the eye. These factors may be endogenous, i.e. genetically determined, or exogenous; for the most part, however, they occur in combinations.

During development there is usually an active complex of influences, one of which is predominant. The phenotypical result is dependent on the quality and quantity of the complex and on the time of its activity. These properties or characteristics can in turn be influenced by modifying factors, which thus become partial determinants of the end-product. In this way the clinical picture can vary widely. This is known for such conditions as congenital cataract and also aniridia, which have been described as clinically very variable by Drenckhahn and Behnke (1961) and other authors.

In view of these facts it is not surprising that the severally known clinical entities and component symptoms of various developmental defects of the anterior ocular segment can overlap in an individual (Srivastava 1961) or within a family.

The frequency of such overlaps is generally fairly low, although several combinations of these developmental anomalies of the anterior ocular segment have been described, and were observed by ourselves. In some cases it is easy, but especially in isolated cases it is often difficult to decide which changes are primary and which are secondary; which are the main characteristics and which are subordinate.

Aniridia, iridal coloboma, primary hydrophthalmos, megalocornea, primary dysgenesis mesodermalis of the iris, Peters' anomaly, microcornea, cornea plana, sclerocornea, connatal iridal hypoplasia and persistent pupillary membrane – these are all developmental defects of the anterior ocular segment, and as such they form a group which can be divided into several subgroups on the basis of the specific occurrence of certain characteristics or combinations of characteristics, and especially on the basis of a typical pattern of hereditary transmission.

If we maintain that the development of the anterior ocular sigment is determined by early organization and differentiation of mesodermal and possibly also ectodermal structures, with subsequent detailed structuration of the anterior chamber and iridocorneal angle in which cleavage plays a predominant role, then we must consider the possibility that the cause of an error of cleavage may lie in primary, usually genetically determined, early disorders in the primordium and differentiation of the mesoderm and/or ectoderm. We believe that the condition which prevails during the period in which cleavage begins to play a role, largely determines the ultimate clinical features of an anomaly or syndrome. And this condition (or situation) is determined by a complex of factors.

In primary dysgenesis mesodermalis of the cornea, primary dysgenesis mesoder-

PLATE VI. Secondary dysgenesis mesodermalis of the iris in a patient with unilateral epibulbar dermoid, paramedian facial fissure and connatal anomalies of the palpebrae and lacrimal apparatus (CM-V-5, left eye).
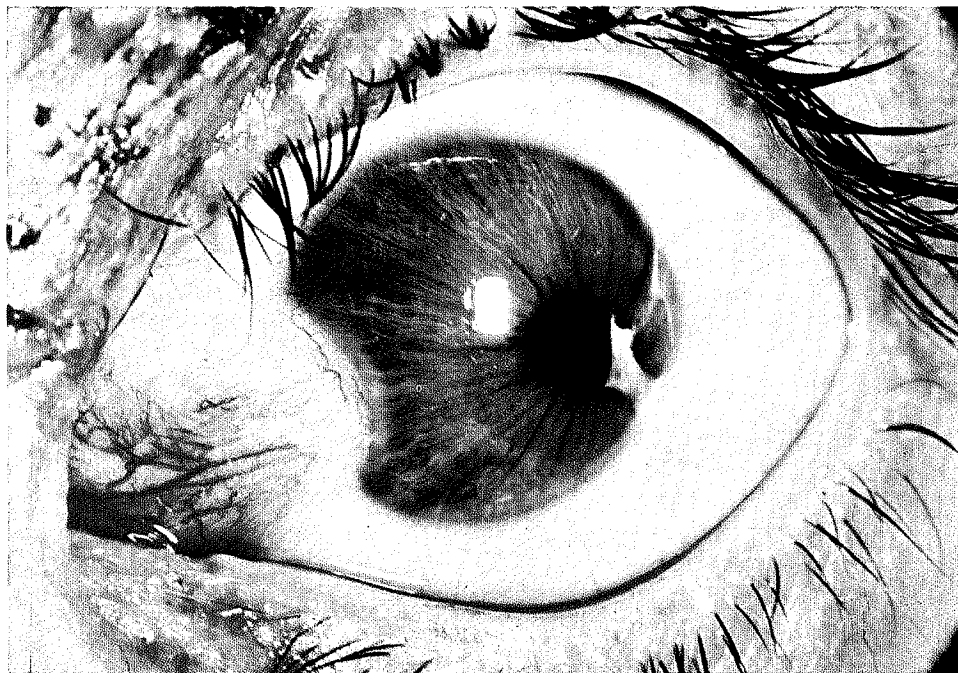
malis of the iris, primary hydrophthalmos and other anomalies of this kind, different gene-determined influences play a predominant role.

In our opinion, primary dysgenesis mesodermalis of the cornea is an anomaly which depends primarily on a genetically determined disorder of the primitive organization of the corneogenic mesoderm. When the effect of the pathological gene commences relatively late or persists relatively long, the development of the iridogenic mesoderm can be disturbed also; and this is clinically manifested as secondary dysgenesis mesodermalis of the iris.

Anomalies of other organs found several times in association with developmental defects of the anterior ocular segment should be briefly discussed also. It is possible that factors which give rise to developmental defects of the eye, also exert an influence on the development of other organs. As we mentioned, our distinct impression was that a higher incidence of more numerous and more severe connatal anomalies of other organs is found in Peters' anomaly than in Rieger's syndrome and in primary hydrophthalmos. In deceased neonates with a variety of connatal anomalies, histological examination of the eyes not infrequently discloses Peters' anomaly (Manschot 1966).

This supports our opinion that dysgenesis mesodermalis of the cornea is, in a large number of cases, a component of a more general developmental defect or syndrome, of which it should be considered a secondary aspect.

Since many organs and regions (facial fissures) must pass a critical phase in which development tends to be vulnerable, certain combinations are observed more frequently than others. For example, oligodontia (partial anodontia vera) is never mentioned in combination with Peters' anomaly, but is frequently found in patients with Rieger's syndrome.

Experimental embryology and teratology afford some information on the pathogenesis of general developmental defects, among which craniofacial and ocular defects occupy a special position. Lund et al. (1961) and Degenhardt (1961, 1963) used oxygen deficiency or roentgen irradiation as teratogenic factors in their experiments. In rabbits and mice they observed craniofacial dysplasias and developmental defects of the eye such as microphthalmos, aphakia, microphakia, disorders in the separation of the primary lens vesicle from the superficial ectoderm, defects of the deepest corneal stroma and Descemet's membrane, iridal malformations and adhesions between the iris and the posterior corneal surface (Badtke 1962). They established that the craniofacial dysplasias and ocular developmental defects were based on a complex interaction between gene influences and subtle environmental factors during the early ontogenic period of development.

That gene factors determine the threshold of the embryo's sensitivity to teratogenic factors was demonstrated by, among other things, the significantly higher incidence of developmental defects in test animals of an in-bred strain than in those of a control strain.

Further investigations will have to show whether possible correlations between

developmental defects of the anterior ocular segment and other connatal anomalies (dyscephaly, hydrocephalus, facial fissures, and developmental defects of the limbs, urogenital apparatus, etc.) might be based on the influence of the gene which causes the ocular anomaly. Clinical genetic studies of families with hereditary syndromes of a general type may elucidate the extent to which the pathological genes of these syndromes can influence the development of the eye. As we mentioned, both dysgenesis mesodermalis of the iris and dysgenesis mesodermalis of the cornea can be an aspect of the polyphenia of these pathological genes.

IV

Differential diagnosis

I. SECONDARY DYSGENESIS MESODERMALIS OF THE IRIS

Abnormalities of the iridal stroma and the iridocorneal angle which are an essential component of primary dysgenesis mesodermalis of the iris, can occur also (be it in an aspecific or mitigated form) in patients showing quite different anomalies and developmental defects. The abnormalities cannot be regarded as aspects of Rieger's syndrome in these cases, for this syndrome is a primary clinical entity.

The iridal abnormalities and changes of the iridocorneal angle in these cases are constituents of another syndrome or an aspect of another developmental defect, and should therefore be qualified as "secondary".

Secondary dysgenesis mesodermalis of the iris takes its clue, so to speak, from the syndrome of which it is a constituent. If the primary disorder is of a general type, then the secondary dysgenesis mesodermalis of the iris is often bilateral; if the primary disorder is of a local type, then it is often unilateral. The same applies to heredity: secondary dysgenesis mesodermalis of the iris follows the hereditary pattern of the primary anomaly, and therefore can be "recessive". However, we believe that it is not meaningful to use the term "recessive heredity" in this context, because secondary forms as such have no hereditary pattern. One could hardly maintain, for example, that besides the classical recessive form of congenital glaucoma (primary hydrophthalmos) there is a dominant form of this glaucoma, which occurs secondarily in dominant hereditary anomalies such as aniridia or Rieger's syndrome (Delmarcelle 1968).

Abnormalities of the iridocorneal angle, hypoplasia of the iridal stroma and pupillary changes are regularly described in various abnormalities and developmental defects of the *eye*. As we mentioned, secondary dysgenesis mesodermalis of the iris can occur in patients with Peter's anomaly (Theodore 1944; and others); and changes of this type have been described also in congenital miosis (Veirs and Brown 1961) megalocornea and congenital glaucoma (Friedman and Etzine 1961), unilateral retinal dysplasia (Hunter and Zimmerman 1965; Hunter 1966), neuro-ectodermal developmental defects of the eye (Klien 1961, 1963), cornea plana

Fig. 58. Patient with paramedian facial fissure, uni-
lateral epibulbar dermoid and homolateral secondary
dysgenesis mesodermalis of the iris and other ocular
anomalies (CM-V-5).
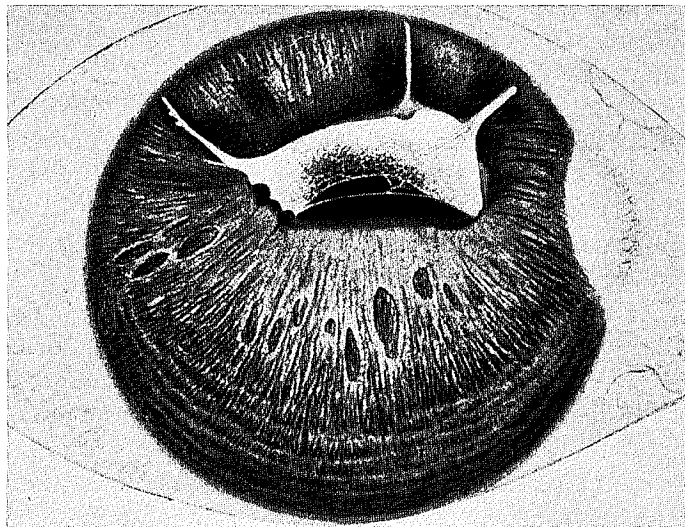
Fig. 59. Wolfrum's (1915) case with unilateral epibulbar dermoid and
secondary dysgenesis mesodermalis of the iris.
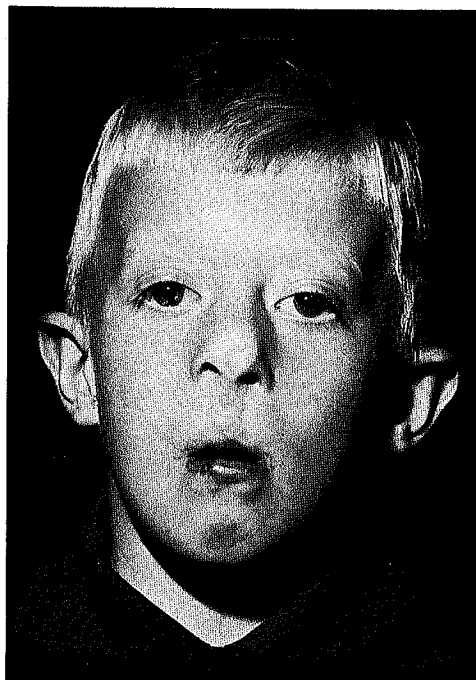
Fig. 60. Secondary dysgenesis mesodermalis of the
iris in a patient with bilateral, total cheilognatho-
palatoschisis and dental anomalies (VE-III-6).

(Forsius 1961), congenital non-attachment of the retina (Foos *et al.* 1968), foetal uveitis (Stucchi 1960), and Wagner's syndrome (Frandsen 1966).

Epibulbar limbus dermoid, whether isolated or occurring as a component of the oculo-auriculo-vertebral syndrome (Goldenhar 1952), is sometimes also accompanied by developmental anomalies in the sense of secondary dysgenesis mesodermalis of the iris (Bollack and Offret 1937; Garner 1951; Sugar 1967; Proto and Scullica 1966; personal observations).

Features closely related to or identical with those of our own case CM-V-5 (fig. 58, 71-73, plate VI) were described by Wolfrum (1915) in a normal girl from a healthy family who showed a unilateral limbus dermoid. In addition Wolfrum reported a transverse oval pupil and a white fibrous membrane extending from the superior pupillary zone to the iridocorneal angle and corneal periphery (fig. 59). This membrane and its trabeculae in turn adhered to the iridal stroma by numerous delicate fibres. The superior part of the iris lacked crypts and contraction folds. There was no microcornea or microphthalmos. Wolfrum regarded the anomaly as a secondarily greatly changed remnant of the pupillary membrane.

Whether the combined oculocraniofacial abnormalities in our patient CM-V-5 (fig. 58) and the hydrocephalus with abnormalities of the limbs in her cousin were
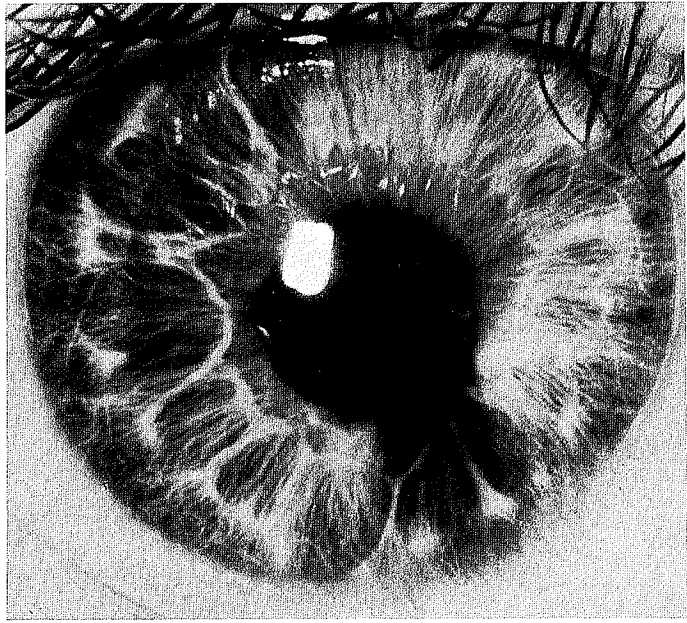
Fig. 61. Secondary dysgenesis mesodermalis of the iris in a patient with bilateral total cheilognathopalatoschisis and dental anomalies (VE-III-6, right eye).
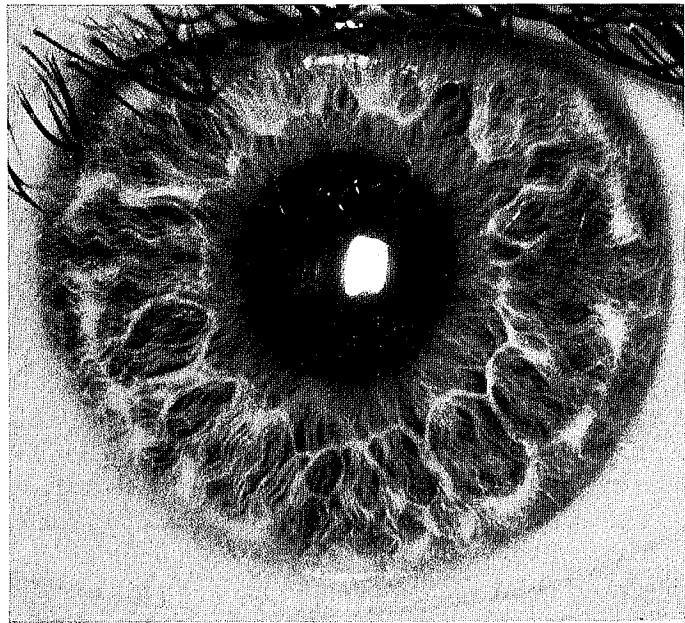
Fig. 62. Normal left eye in the same patient of fig. 61.

related to torticollis with facial hemihypoplasia, cannot be established with certainty. Our patient showed similarities to two patients described by Forsius (1963). The first was a 6-month-old boy with cheilognathopalatoschisis, nystagmus, bilateral microphthalmos, glaucoma, limbus tumour, corectopia, embryotoxon corneae posterius and adhesions to the partly atrophic iridal stroma and the lens. The second was a 15-year-old girl with facial hemihypoplasia, a broad asymmetrical nose and nasal root, anomalies of the teeth and toes, bilateral limbus tumour, microcornea OS, corectopia and hypoplasia of the iridal stroma.

In all these patients the developmental defect of the iridal mesoderm was part of a more extensive *ocular* developmental anomaly, so that the pertinent changes in

Fig. 63. Patient with iridochoroidoretinal coloboma, dysgenesis mesodermalis of the cornea, secondary dysgenesis mesodermalis of the iris, heterochromia, and anomalies of the ear and face (HC-IV-8, right eye).

embryotoxon corneae posterius and brown-pigmented tissue network

Schlemm's canal

bridge-coloboma and pear-shaped pupil
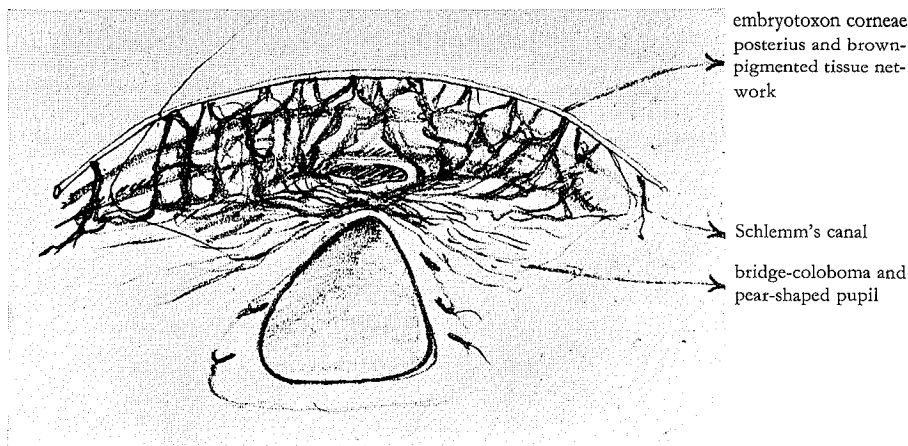
Fig. 64. Gonioscopic view showing secondary dysgenesis mesodermalis of the iris: very prominent line of Schwalbe, meshwork of iridocorneal mesodermal adhesions in the direct neighbourhood of the bridge coloboma of the iris (HC-IV-8, right eye).

these cases must be regarded as secondary dysgenesis mesodermalis of the iris. We also observed secondary dysgenesis mesodermalis of the iris in a young patient with disturbed cranial development, dental anomalies and partial iridal coloboma (Guggenheim 1925; VE-III-6: figs. 60-62).

Secondary dysgenesis mesodermalis of the iris was observed by us also in a patient with facial asymmetry, abnormalities of the external ear, and ocular abnormalities: iridochorioretinal coloboma, Peters' anomaly, cornea plana and heterochromia (HC-IV-8; figs. 55, 63-65 and plate V).

Secondary dysgenetic changes of the mesodermal part of the iris have been frequently reported also as features of *general*, hereditary or non-hereditary syndromes. Examples are: Crouzon's syndrome (Calmettes *et al.* 1958), Marfan's syndrome (Theobald 1941; Starke 1951; Reeh and Lehman 1964; Rossetti and Betetto 1956; Burian 1958; Schocket 1967), an atypical Marfan syndrome (DiTizio and Melchionda 1965), Weil-Marchessani's syndrome (Duque Estrada 1961; Collier 1962), connective tissue disorders such as idiopathic scoliosis, idiopathic genu varum, Osgood-Schlatter's disease and Perthes' disease (Burian *et al.* 1960), Klinefelter's syndrome (Amalric *et al.* 1966), Turner's syndrome (Royer and Géhin 1963), 13-15 trisomy (Heimann 1968) and some patients with the oculo-dentodigital syndrome (see the pertinent heading). Other instances of secondary dysgenesis mesodermalis of the iris have been reported in patients with congenital progressive oculo-acoustico-cerebral degeneration or Norrie's disease (Warburg 1961; Andersen and Warburg 1961; Warburg 1966; personal observation).

norma anterior goniosco-
pic line of Schwalbe

Schlemm's canal

abortive iridal root
coloboma

local hypoplasia of iris exposing the pigment layer
in the periphery
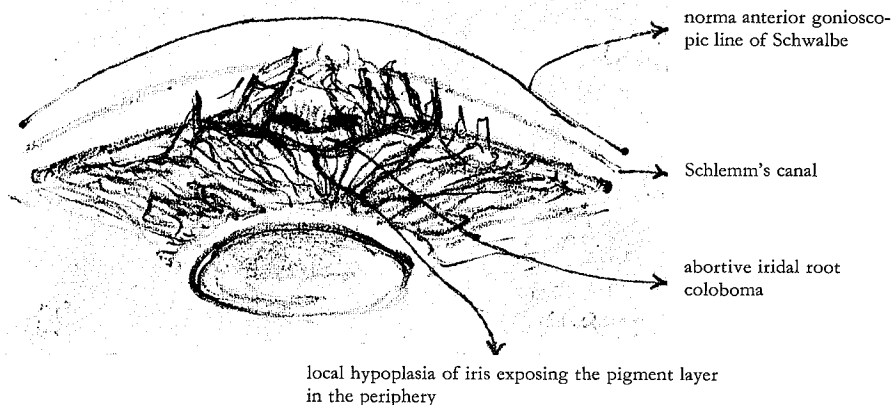
Fig. 65. Gonioscopic view showing mild secondary dysgenesis mesodermalis of the iris in the region of the externally visible area of iridal hypoplasia (abortive iridal root coloboma) (HC-IV-8, left eye).

2. ESSENTIAL PROGRESSIVE IRIDAL ATROPHY

The more fully developed clinical picture of this condition can show some resemblance to those of Rieger's syndrome. There can be an atrophic iridal stroma with defects of the pigment layer, corectopia, dyscoria and glaucoma, and abnormalities of the iridocorneal angle may develop.

Essential progressive iridal atrophy, however, is an acquired condition which is usually unilateral, without predilection for either the one or the other eye, and shows a female predominance (Rochat and Mulder 1924; Csillag 1937; Goedbloed 1941; Scharf 1941; Czukrasz 1947; Saudax *et al.* 1966). Unilateral cases have also been repeatedly described in male patients (Harms 1903; Licsko 1923; Mohr 1928; Plas 1950; De Ferrari 1954).

Bilateral cases, which are more frequent in males, were reported by various authors (Kubik 1924; Hambresin 1929; De Almeida 1930; Fine and Barkan 1937; Csillag 1938; Czukrasz 1947; Plas 1950; Tarkkanen and Forsius 1963; Varge 1964; Saudax *et al.* 1966; and others).

However, since these clinical pictures are not strictly separated and can overlap, Huerkamp's (1952) division into two types of essential progressive iridal atrophy is too schematic.

The disease begins in an initially quite normal eye, by mild distortion and displacement of the pupil, accompanied by rarefaction and atrophy of the iridal stroma. Next, the pigment layer of the iris begins to show defects, which may become confluent. Finally, large parts of the iris degenerate and the features of secondary iridal destruction develop. Parts of the detached and atrophic iridal
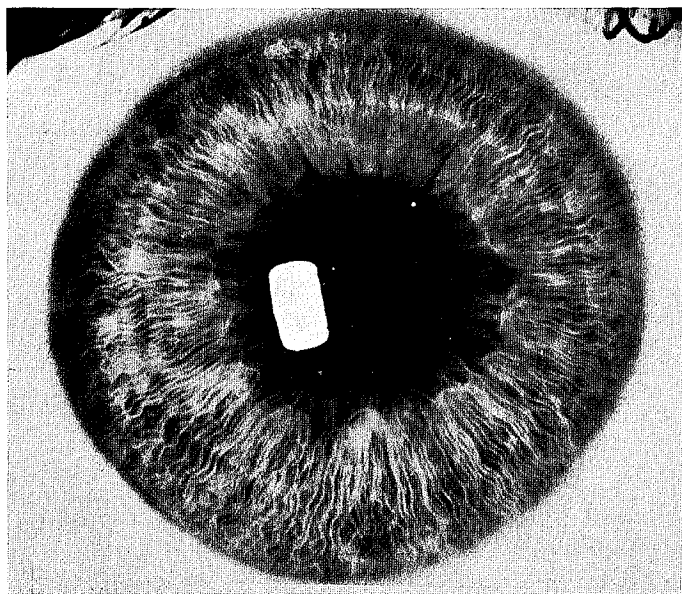
Fig. 66. Normal eye in a patient with essential progressive iridal atrophy.
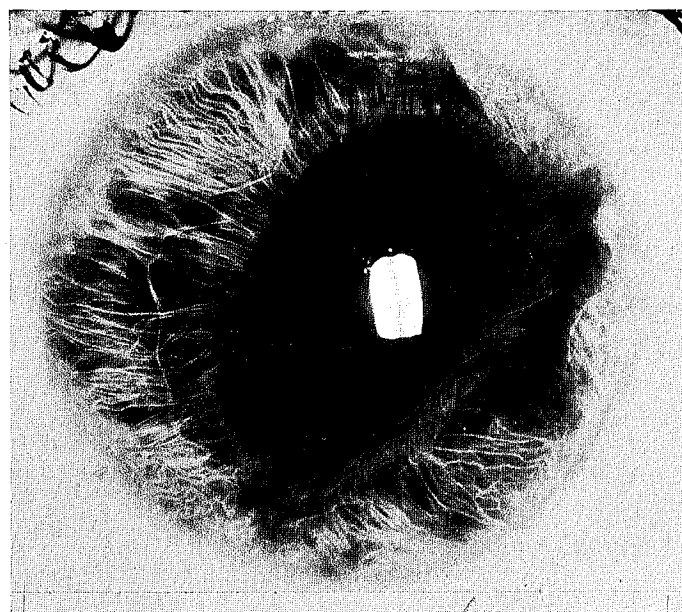
Fig. 67. Advanced stage of essential progressive iridal atrophy in the other eye.

stroma coil up against the posterior corneal surface and in the iridocorneal angle, where they may secondarily form adhesions (Scharf 1941; Van Beuningen 1952).

As these changes are developing, secondary glaucoma nearly always occurs. The usually very greatly increased intraocular pressure proves to be highly refractory to various therapeutic measures, and glaucoma absolutum as a rule results.

We ourselves had occasion to examine two female patients who developed this condition unilaterally at the age of 28-30 years. The first showed formation of the goniosynechiae, pupillary changes and mild irritation of anterior chamber during the process of progressive iridal atrophy. Her intraocular pressure was initially normal but gradually increased in spite of conservative antiglaucomatous therapy. The iridal stroma showed what might be described as a shrinking towards the iridocorneal angle. This patient's parents and her two daughters showed no ocular anomalies. In the second patient a similar process was accompanied by progressive iridopupillary changes and glaucoma (figs. 66, 67); these changes developed in the course of a few years.

Apart from the abovementioned cases, the literature supplies several reports on this typical clinical picture, the aetiology of which is still obscure (Kaminsky 1928; Sakic 1952; Winkelman 1956; Forsius and Tarkkanen 1961; Miron 1961; and others).

Because the changes in a given stage of essential progressive iridal atrophy are similar to those of Rieger's syndrome, some authors have sought a correlation between the two conditions and in this context have formed confusing conclusions (Scharf 1941; Wagenaar 1954; Pau 1962, 1965; Pau et al. 1962; Leydhecker 1960). We believe that there are no arguments in favour of regarding the two conditions as identical, for there are several conspicuous differences. To begin with, primary dysgenesis mesodermalis of the iris is connatal or congenital, rather than acquired; it is usually stationary rather than progressive; it is always bilateral, shows no male or female predominance and is not always associated with glaucoma.

In Rieger's syndrome the iridal stroma often shows regular, diffuse hypoplastic changes, whereas in essential progressive iridal atrophy the iridal stroma shows irregular rarefaction. Defects of the pigment layer of the iris do occur in primary dysgenesis mesodermalis of the iris, be it less frequently, but they are seldom progressive.

The sphincter pupillae muscle is most resistant to the atrophic forces, but nevertheless frequently yields to the ruthless process of degradation. So far as we could establish, abnormalities of the sphincter pupillae muscle are an exception in Rieger's syndrome.

Finally, there are marked differences in gonioscopic features. In Rieger's syndrome the connatal iridocorneal adhesions usually extend from the hypoplastic iridal stroma to the ever-present embryotoxon corneae posterius and the trabecular system, with conical, pointed extensions. If there are adhesions to the

posterior corneal surface centrad to the embryotoxon corneae posterius (cf. Peters' anomaly), then there are deep, dense corneal opacities at the sites of these adhesions. In essential progressive iridal atrophy the gonioscopically visible secondary anterior synechiae are broad and flat in their adherence to the cornea, ignoring the boundary between the cornea and the trabecular system; there is no embryotoxon corneae posterius, and no dense, deep corneal opacities are visible at the sites of adhesion.

To summarize: the gonioscopic features of essential progressive iridal atrophy are acquired, dynamically variable and evolutional, while those of primary dysgenesis mesodermalis of the iris are congenital, stationary and invariable.

Heredity plays a role of predominant importance in the pathogenesis of primary dysgenesis mesodermalis of the iris, but is of only subordinate importance in that of essential progressive iridal atrophy. In very exceptional cases, essential progressive iridal atrophy or a very similar condition has been described as hereditary (Frank-Kamenetzki 1925; Gedda and Bérard-Magistretti 1959).

The families reported by Blum *et al.* (1962) and by Forsius and Eriksson (1964) did not show essential progressive iridal atrophy, as they maintained, but should in our opinion be regarded as suffering from Rieger's syndrome.

The Russian family with X-chromosomal recessively inherited juvenile glaucoma and iridal atrophy described by Frank-Kamenetzki (1925) can be brought under the heading of essential progressive iridal atrophy. Makarow (1937) described another Russian family with X-chromosomal hereditary juvenile glaucoma, but supplied on data on the condition of the irides.

The large family (incest community) of which Gedda and Bérard Magistretti (1959) made an exhaustive study, showed an autosomal dominant form of bilateral, sometimes progressive iridal atrophy and hypoplasia with some of the characteristics of the atrophy described by Frank-Kamenetzki. They reported virtually complete penetrance and variable expression. However, the pattern of heredity was quite different from that observed by Frank-Kamenetzki. Whether the family described by Gedda and Bérard-Magistretti was in fact suffering from the likewise dominantly inherited Rieger syndrome remains uncertain and seems improbable. Few of their patients showed a typical embryotoxon corneae posterius, and changes in the iridocorneal angle were not prominent features of their cases. They made no mention of an ill-defined limbus or macrocornea, and they diagnosed hydrophthalmos exclusively on the basis of anamnestic data.

In none of the other known and published cases of essential progressive iridal atrophy was heredity demonstrated. Many were isolated cases in otherwise normal, healthy families.

3. CONNATAL IRIDAL HYPOPLASIA

A congenital form of marked hypoplasia to virtual aplasia of the mesodermal iridal stroma was described by Rübel (1913), who mentioned no other characteris-

tics suggestive of primary dysgenesis mesodermalis of the iris. Streiff (1915) described hypoplasia of the anterior mesodermal layer of the iridal stroma in a woman and her grandson. He ascribed this hypoplasia to marked regression of the pupillary membrane. It is difficult if not impossible to judge, however, whether the primordium of the iris was hypoplastic or whether abnormally marked regression occurred in the course of development, or whether both factors played a role.

Glüh (1927) observed marked hypoplasia or even aplasia of the iridal stroma in a father and two children, one of whom in addition showed bilateral corectopia and dyscoria (slit-pupils), suggestive of Rieger's syndrome.

Leffertstra and Waardenburg (Waardenburg *et al.* 1961) found a similar anomaly, with embryotoxon corneae posterius and abnormalities of the iridocorneal angle, in a father and five of his eight children. We believe that this family showed primary dysgenesis mesodermalis of the iris.

We ourselves observed aplasia of the anterior layer of the iridal stroma and hypoplasia of its posterior layer in two generations, but in these cases there was no embryotoxon corneae posterius and the iridocorneal angle showed no abnormalities.

The clinical features of connatal iridal hypoplasia, which can occur as a dominantly inherited condition, thus show a resemblance to Rieger's syndrome, especially when juvenile glaucoma is observed also (Hambresin and Schepens 1946; McCullog and MacRee 1950).

It is of importance in this context to mention the family R, with dominantly inherited juvenile glaucoma and iridal hypoplasia. We examined several members of this family and found that some patients showed only iridal hypoplasia, whereas others in addition showed embryotoxon corneae posterius with abnormalities of the iridocorneal angle in the form of adhesions between the iris and the embryotoxon. It is possible that these were mitigated expressions of primary dysgenesis mesodermalis of the iris. An argument against this possibility is that features reminiscent of Rübel's connatal iridal hypoplasia have not been observed in families with Rieger's syndrome, neither in the literature nor in our own material. For this reason we are inclined for the time being to regard connatal iridal hypoplasia as a separate entity.

4. PRIMARY HYDROPHTHALMOS

As we pointed out, primary dysgenesis mesodermalis of the iris can be a condition predisposing to glaucoma, wich in these cases can manifest itself as secondary or associated hydrophthalmos.

In these cases, therefore, we can differentiate between the clinical picture of primary hydrophthalmos and the secondary hydrophthalmos in Rieger's syndrome. Slit-lamp examination and gonioscopy can yield the decisive findings.

In primary hydrophthalmos there is no corneal embryotoxon posterius.

The iris is cryptless and usually slightly atrophic, and this is generally regarded as a secondary phenomenon. It is not certain whether primary iridal hypoplasia also underlies the atrophic aspect. In primary hydrophthalmos, the atrophic aspect is generally more pronounced at the periphery than in the peripupillary region.

Pupillary anomalies – very common in primary dysgenesis mesodermalis of the iris – are not found in primary hydrophthalmos.

Gonioscopy also fails to reveal the pathologically prominent line of Schwalbe that is so characteristic of Rieger's syndrome. In primary hydrophthalmos the wide iridocorneal angle is characterized by the presence of delicate, semi-transparent tissue stretched between the iridal root with its relatively high insertion, and the corneotrabecular junction (line of Schwalbe). There are no broad or narrow adhesions between the iris and this area, but in Rieger's syndrome these are a constant feature. If a patient with hydrophthalmos has a normal contralateral eye, then a diagnosis of primary dysgenesis mesodermalis of the iris is virtually excluded.

The two conditions also differ in the pattern of hereditary transmission: transmission of primary hydrophthalmos is usually autosomal recessive, and familial occurrence is rare; transmission of the Rieger syndrome is autosomal dominant and familial occurrence is very common.

5. OCULO-DENTO-DIGITAL DYSPLASIA

It seems of importance to discuss the oculo-dento-digital syndrome in the context of the differential diagnosis of primary dysgenesis mesodermalis of the iris, because a relation between the two syndromes has been suggested (Waardenburg *et al*. 1961: p. 576; Henkes 1965). This was done partly in view of the abnormalities of the teeth and limbs which are sometimes observed in patients with Rieger's syndrome (Lemmingson 1961; Frandsen 1963; Henkes 1965). Otherwise, dento-digital anomalies are exceedingly rare in patients with developmental defects of the anterior ocular segment (Denden and Ahrens 1967), and their incidence is very low in other syndromes without ocular anomalies (Zifferblatt and Radasch 1929; Trauner 1933). We personally observed a 6-year-old girl with a fissure confined to the red part of the lip, dental anomalies and cutaneous syndactyly, without ocular abnormalities.

In 1957 Meyer-Schwickerath, Grüterich and Weyers described a new syndrome which they called "dysplasia oculo-dento-digitalis". This syndrome combined abnormalities of the eyes, teeth and extremities in patients who showed a typical facial expression determined by a characteristic narrow, straight, pointed nose with short nostrils. With the latter characteristic in mind it might be better to speak of an oculo-*naso*-dento-digital syndrome, particularly since other authors have also mentioned the typical shape of the nose as an important characteristic of this syndrome.

As early as 1920, Lohmann described two patients with the same typical shape

of the nose, ocular hypotelorism, camptodactyly, syndactyly and microcorneae; and Pitter and Svejda (1952) mentioned a young patient whose abnormalities closely resembled those in the patients of Meyer-Schwickerath *et al.* (1957). The remaining literature on this syndrome is relatively scanty (Cowan 1959; Gorlin *et al.* 1963; Gillespie 1964; Kurlander *et al.* 1966; Nguyen 1966; Rajic and De Veber 1966; Sugar *et al.* 1966; Pfeiffer *et al.* 1968). We believe that the case described by Sörgel and Heidrich (1965) does not come under this heading.

Summarizing the cases of oculo-dento-digital syndrome so far described, we find the following principal symptoms:

- *microcornea* and *microphthalmos*: bilaterally present.
- *mild dyscephaly*: hypotelorism, small orbits, narrow skull, narrow pointed nose with short nostrils.
- *dental anomalies*: enamelogenesis imperfecta or enamel dysplasia, microdontia and possibly sometimes oligodontia.
- *anomalies of the limbs*: camptodactyly, syndactyly, hypoplasia and aplasia of metacarpals and middle phalanges.
- *hypotrichosis* and *cutaneous atrophy*.

The information on the development of the anterior ocular segment in these cases is generally poor. It can be concluded, however, that iridal anomalies, pupillary abnormalities and changes in the iridocorneal angle – with or without glaucoma – should *not* be regarded as features of this syndrome.

No pupillary anomalies were observed. In a few cases there was some hypoplasia of the iridal stroma (Meyer-Schwickerath *et al.* 1957); in other cases the structure of the iridal stroma was slightly hyperplastic, with remnants of the pupillary membrane (Lohman 1920; Gorlin *et al.* 1963). In the majority of cases of the oculo-dento-digital syndrome, however, the iris was described as normal (Lohman 1920; Gillespie 1964; Sugar *et al.* 1966; Pfeiffer *et al.* 1968). Two patients showed glaucoma. Gonioscopy was carried out in a few cases (Meyer-Schwickerath *et al.* 1957; Sugar *et al.* 1966; Pfeiffer *et al.* 1968).

One of the patients of Meyer-Schwickerath *et al.* (1957) showed a broad, vascularized goniosynechia in one eye – probably secondary to acute glaucoma. The remaining patients showed no abnormalities of the iridocorneal angle.

Microphthalmos and *microcorneae* were observed in all patients; the corneae were very small (diameter 6-8 mm).

Abnormalities of the lens were not reported, except by Gorlin *et al.* (1963).

Dominant heredity of the oculo-dento-digital syndrome seems probable (Rajic and De Veber 1966; Pfeiffer *et al.* 1968); if this is to be reconciled with Gillespie's observation (1964), incomplete penetrance or no penetrance must be accepted; for Gillespie observed the syndrome in two children whose parents were healthy.

In differentiation between this syndrome and primary dysgenesis mesodermalis of the iris, an outstanding fact is that abnormalities of the limbs are a constant

feature of the oculo-dento-digital syndrome but are an exception in Rieger's syndrome. In fact our study disclosed that none of the patients with primary dysgenesis mesodermalis of the iris (from different families) showed any clinical or radiological evidence of abnormalities of the limbs.

The two syndromes show essential differences also in iridal structure. Extreme microcorneae and microphthalmos are not observed in Rieger's syndrome.

The shape of the nose in patients with the oculo-dento-digital syndrome is fairly specific; it has never been described in primary dysgenesis mesodermalis of the iris, in which the nose is more likely to be broad. Among relatives of patients with Rieger's syndrome, moreover, we found none who resembled patients with the oculo-dento-digital syndrome. Nor was further evidence found of any relation between the two syndromes, which we should therefore regard as entirely *different* entities.

It can be maintained that the oculo-dento-digital syndrome is a general syndrome accompanied by ocular changes, whereas primary dysgenesis mesodermalis of the iris as well as primary dysgenesis mesodermalis of the cornea are specifically ophthalmological syndromes, which are sometimes accompanied by non-ocular abnormalities.

V

Summary

CHAPTER I

As a preliminary to a study of primary dysgenesis mesodermalis of the iris (Rieger's syndrome), the significance of the prominent line of Schwalbe was investigated. An attempt was made to establish whether a relation exists between the prominent line of Schwalbe and embryotoxon corneae posterius, which is a characteristic feature of primary dysgenesis mesodermalis of the iris.

The prominent line of Schwalbe – the deep limbus type B which we described as found in 8% of the eyes – is not an anomaly or dysplasia but should be regarded as a variant of iridocorneal angle structure within the range of variation of the normal development of the anterior chamber and of the iridocorneal angle in particular. The findings obtained in these eyes did not confirm a predisposition to glaucoma.

CHAPTER II

Individuals with a prominent line of Schwalbe were not more frequently found in families with primary dysgenesis mesodermalis of the iris than in the normal population.

The prominent line of Schwalbe, therefore, should not be interpreted as a minimal expression of Rieger's syndrome.

The principal and most constant features of primary dysgenesis mesodermalis of the iris are hypoplasia of the iridal stroma and an embryotoxon corneae posterius with adhesions to this iridal stroma. These abnormalities represent a disturbance in the development of the irido corneal angle which is typical of primary dysgenesis mesodermalis of the iris.

Rieger's syndrome is encountered as frequently in female as in male patients. Patients with this syndrome show a considerably higher incidence of astigmatism and marked ametropia, and a considerably lower incidence of emmetropia, than normal subjects.

Like other congenital ocular anomalies, Rieger's syndrome has a distinctly increased incidence of oculomotor disorders.

Neither conjunctival xerosis nor blue sclerae can be described as typical or specific abnormalities of this syndrome. A poorly defined limbus structure (persistent corneoscleral membrane) was found in some 75% of the eyes with primary dysgenesis mesodermalis of the iris.

Microcornea was observed in 9% and macrocornea in 26% of cases of Rieger's syndrome.

The shape of the cornea was abnormal in 8% of cases (75% of the abnormal shapes were vertical ovals). As compared with normal eyes, the eyes of patients with primary dysgenesis mesodermalis of the iris had less marked corneal curvatures.

Central corneal opacities and defects were observed in a small proportion of the eyes with the syndrome. These changes represented secondary dysgenesis mesodermalis of the cornea (Peters' anomaly) in Rieger's syndrome.

Remnants of the pupillary membrane were not more frequently found in the syndrome than in normal subjects. No hyperplastic iridal features were observed. Defects of the pigment layer were regularly encountered in Rieger's syndrome.

Pupillary anomalies (dyscoria and corectopia) were very frequently observed in primary dysgenesis mesodermalis of the iris and constituted an important aspect of the clinical picture. Ectropion uveae was found in addition in some 15% of the total number of cases.

Primary dysgenesis mesodermalis of the iris is a typical condition suitable for early development of glaucoma, which was found in 60% of cases. The glaucoma was usually of the infantile or juvenile type, but congenital glaucoma with hydrophthalmos was diagnosed in several cases.

In the majority of cases of the syndrome there was no direct causal relation between the glaucoma and the macrocornea. The glaucoma in these patients was determined by increased resistance to the outflow of aqueous humour, and the visible abnormalities of the iridocorneal angle probably played no role in this respect.

Specific lenticular abnormalities were not found in Rieger's syndrome.

The vitreous body was always normal.

The *choroidal hypoplasia* observed in several cases might be regarded perhaps as pathogenically correlated with the characteristic hypoplasia of the mesodermal iris.

The clinical course and prognosis of Rieger's syndrome are largely dependent on the possibility of adequate therapy of the glaucoma, if any. When the intraocular pressure is not increased, primary dysgenesis mesodermalis of the iris is a stationary affection. Only under special circumstances can progressive changes of the iris occur.

With regard to treatment it can be maintained that, if conservative anti-glaucomatous measures fail, an ample filtering glaucoma operation is the procedure of choice to ensure long-term normalization of the increased intraocular pressure.

The facial configuration in patients with Rieger's syndrome often shows typical characteristics, determined by the nose and nasal root, the interorbital distance and the condition of the jaws and teeth. In a considerable number of cases the nose is on the broad side of normal; it is never narrow. The nasal root is broad as a result of the frequently observed telecanthus and the occasional hypertelorism. Partial anodontia vera is relatively common in patients with primary dysgenesis mesodermalis of the iris. It seems probable that we are dealing here with an occasional gene linkage, although polyphenic expression of one gene cannot be ruled out.

Abnormalities of the jaws are largely confined to maxillary hypoplasia, although mandibular hypoplasia is occasionally also observed. This hypoplasia can be ascribed to the anomaly of the dental primordium in a proportion of cases, but primary hypoplasia has been observed in a few cases.

We do not regard abnormalities of the limbs as a component of Rieger's syndrome.

In view of the relatively low incidence of combinations with anomalies of other organs or organ systems, their concomitance with primary dysgenesis mesodermalis of the iris should be regarded for the time being as a coincidence. A special link with dystrophia myotonica is singularly improbable.

No definite conclusions have been reached concerning the significance of the occurrence of other connatal or congenital abnormalities in families with Rieger's syndrome. These families do not show a higher incidence of the prominent line of Schwalbe (limbus type B) discussed in the first chapter. In some 75% of the total number of patients with primary dysgenesis mesodermalis of the iris, the condition was a familial one. Whenever the syndrome was considered to be hereditary, autosomal dominant transmission was involved.

There is 95% penetrance of the pathological gene with varying degrees of expression within an unmistakably pathological clinical picture.

With regard to pathogenesis, we consider primary dysgenesis mesodermalis of the iris to be a condition which results from a genetically determined disorder of the primordium of the iridogenic mesoderm, giving rise to developmental defects of the iris, pupil and iridocorneal angle.

CHAPTER III

In view of clinical genetic considerations, we wish to distinguish a primary and a secondary form of Peters' anomaly. Primary dysgenesis mesodermalis of the cornea is a separate entity in the form of a relatively rare, genetically determined recessive hereditary developmental defect of the cornea; secondary dysgenesis mesodermalis of the cornea occurs in the context of a developmental defect of the eye (e.g. Rieger's syndrome) or as a component of a more general syndrome.

The clinical picture is variable, ranging from mild corneal changes via connatal

corneal opacities and leucomas, with or without anterior synechiae, to corneal staphyloma. Microphthalmos, cornea plana, sclerocornea and glaucoma are relatively frequent features, and developmental defects of the iris, pupil and irido-corneal angle (secondary dysgenesis mesodermalis of the iris) are likewise regularly observed.

Connatal anomalies of other organs or organ systems are frequently seen in combination or in association with Peters' anomaly.

If it occurs as a hereditary condition (which it does much less frequently than primary dysgenesis mesodermalis of the iris), then recessive transmission seems the most probable.

Peters' anomaly is a developmental defect of the mesodermal cornea which can arise from a disturbance in the separation of the primary lens vesicle from the superficial ectoderm. The primary form probably involves a genetically determined defect in the primordium of the corneogenic mesoderm.

The development of the anterior chamber is characterized by an initial phase of differentiation and organization, followed by a period dominated by a secondary cleavage process.

In our opinion, both primary dysgenesis mesodermalis of the iris and primary dysgenesis mesodermalis of the cornea are disorders in the primordium, differentiation and organization of the mesoderm, creating a situation in which subsequent cleavage is incomplete and disturbed.

CHAPTER IV

The differential diagnosis of primary dysgenesis mesodermalis of the iris is discussed with reference to, successively: secondary dysgenesis mesodermalis of the iris; essential progressive iridal atrophy, which is an entirely different syndrome; connatal iridal hypoplasia, which is probably closely related to Rieger's syndrome; primary hydrophthalmos; and the oculodento-digital syndrome, which is discussed chiefly for historical reasons.

GENERAL LEGEND
OF PEDIGREES OF CASE HISTORIES

○ – female
□ – male
☼ ☼ – examined
○ □ – normal eyes in history
◌ – still-born
↓ – abortion

○⌒○ – twin DZ
② ⑤ – two daughters and five sons
◈ – three children
↗ – probandus (a)
♀ ♂ – no offspring
□═○ – consanguinity
┊ – illegitimate
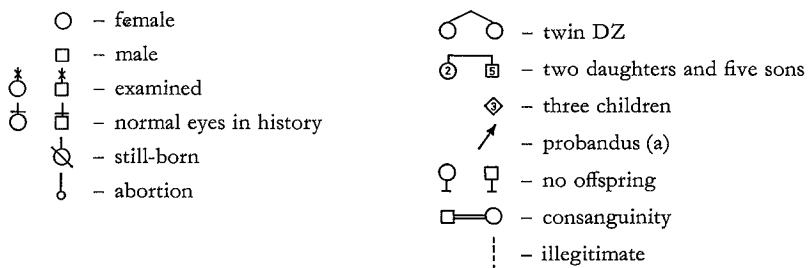
Case histories

SD-IV-1. *Female proband aged 1. Born 1965, 1st October.*
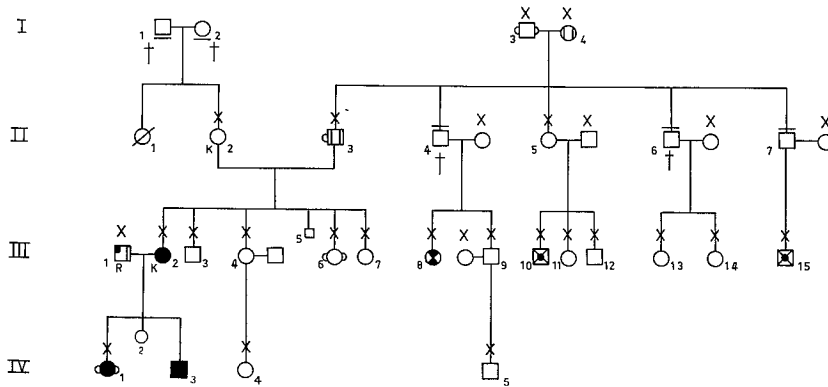
● – primary dysgenesis mesodermal is of the iris

▥ – prominent line of Schwalbe (type B) ODS

◖ – partial limbus coloboma ODS

▥R – iris bicolor with remnants of the pupillary membrane

◑ – connatal luxation of the hips, camptodactylia and syndactylia

⊗ – debilitas mentis

K – nail anomalies

The mother's pregnancy had been characterized by some loss of blood during the second month and a few febrile episodes without other symptoms during the final months. The parents were not consanguineous (confirmed by study of ascendants). The girl was born at term in occipital presentation, with a normal birth weight of 3260 g. Because the facial configuration was abnormal, radiographs were obtained which indicated the likelihood of mandibular luxation and orbital hypertelorism. Encephalographic findings were normal. The consultant ophthalmologist found "peripheral thickening of the corneae

Fig. 68. Normal chromosomal pattern in primary dysgenesis mesodermalis of the iris (SD-III-2).

with a white line on the posterior aspect. The irides were normal". Since Rieger's anomaly was suspected, the mother was examined also. She too showed considerable abnormalities of the anterior chamber ("dystrophy of the iridal stroma, bands from the iris to the cornea, white line on the cornea"), which seemed to corroborate the diagnosis.

A chromosome analysis (fig. 68) *revealed:* normal number of 46 chromosomes; sex chromosome combination XX; no structural abnormalities.

Examination in January 1966:
Both eyes showed a sharply defined, narrow annular corneal opacity about 1-1.5 mm from the limbus and concentric with it. Examination under focal illumination disclosed numerous yellowwhite adhesions between this ring and the periphery of the iris. The irides were of a dull, slate-like blue-grey colour. The central pupils responded well to light. The otherwise normal corneae had normal diameters (11-12 mm) and showed typical temporal limbus colobomas (Asher). The eyes were positively too far apart, the distance between the internal canthi being 33 mm (normal for age 18 months). The position of the palpebrae was normal. The root of the nose was broad and of slightly pronounced flatness; the nose was somewhat broad. The face was otherwise symmetrical, with the ears inserted low. No clinical abnormalities of the fingers, toes and jaws were observed.

Examination in August 1966:
The parents reported that the eyes had increased in size in the course of the months. They had not been red and not clouded, and no photophobia had been noticed. The patient was hospitalized for observation.

Hairgrowth was normal, the hair colour being medium blond.

Internal examination by the paediatrician disclosed no abnormalities.

Cranial dimensions: Circumference 44.5 cm (41.5-48). APD 152 mm (132-160); BPD 120 mm (114-134).

Interocular distances: 38-45-58-84 (CID/PD = 0.65); the normal maximum values at this age are 29-31-48-72.

The clinical features were those of hypertelorism and telecanthus (figs. 1-3). The distance between the lateral orbital margins was 92 mm.

Radiological findings:

Skull: Hypertelorism (fig. 41); slightly oval orbits with some slight superotemporal tilt of the axis; facial skull slightly too small in relation to the craniofacial skull. Mandibular width normal. Dorsum sellae somewhat steep. No mandibular luxation.

Hands and feet: No abnormalities.

The four incisors had erupted. The eye position was normal. There were no oculomotor changes, specifically no nystagmus. Fixation was good and objects moving at a distance of 2 m were followed well.

   The conjunctivae were normal. Both sclerae showed a bluish tinge, especially over the pars plana. The sclerocorneal boundary was not sharply defined.

Corneae: In the lateral view (fig. 26) the corneae seemed very flat, their convexity not exceeding that of the bulbi (cornea plana?); the sulci were effaced. The horizontal diameters were 13.5 mm OD and 13.25 mm OS; the vertical diameters were 13.25 mm OD and 12.5 mm OS. Ruptures of Descemet's membrane were not found. Temporal limbus colobomas ODS (plate II = OS). On the posterior aspect of the cornea, 1.5 mm from the limbus and concentric with it, there was a narrow, sharply defined yellow-white opacity of irregular width. Many yellow trabeculae and band-like tissue strands linked this opacity to the peripheral stroma, which it elevated slightly. The anterior chamber was separated from the iridocorneal angle by this incomplete and rather narrow wall of tissue between cornea and iris. Between the ring and the limbus the deepest corneal layers were semi-transparent and in this zone there were likewise numerous filamentous adhesions to the iridal root. Otherwise the cornea was entirely clear (figs. 2, 3).

Irides: The colour was a slate-like grey-blue. The stroma was hypoplastic; the anterior mesodermal stromal layer (cryptlayer) was absent, as was the iridal frill (collarette). The available stroma was thin and of a radial structure, with a cloudy aspect at scattered sites and local rarefactions where the pigment layer shimmered through more conspicuously: OD at 4 o'clock (fig. 2) and OS at 5, 6 and 11 o'clock (fig. 3 and plate II). The pupillary sphincter muscles were visible as narrow bands on both sides, and a few flimsy remnants of the pupillary membrane were present. Both central pupils responded well to light. In mydriasis they were not round but showed a superonasal pear-shaped dyscoria. The pupillary borders were normal. Contraction folds were absent. In transillumination the pigment layer of the iris was unmistakably diaphanous, not diffusely but in a moth-eaten pattern with its maximum in the peri pupillary zone.

Lenses: Clear, with no abnormalities of localization.

Fundi: Both fundi showed identical features (plate IV). The retinal vessels and optic discs were normal. There was extreme pigment paucity throughout the fundus, and the choroid showed very *poor vascularization.* Consequently the entire fundus had a yellow-white colour which was even more striking than the colour photograph suggests. Slight superficial pigmentation was seen in the macular region and also in the peripheral zone. Macular and foveal reflexes were not elicited, and no macular yellow was perceptible in red-free light. Both optic discs had a slight cone of pigment.

Refraction: ODS about S+12.

Gonioscopy: The iridocorneal angle was not surveyable owing to the presence of a wall-

like membrane between the cornea and the periphery of the iris, giving rise to a so-called pseudo-iridocorneal angle. This wall consisted of delicate whitish stroma-like fibres, and its base elevated the iridal stroma towards the thickened, prominent, centradly displaced line of Schwalbe (posterior corneal embryotoxon) (fig. 19). The membrane was discontinuous at scattered sites. The delicate tissue strands behind it further precluded a survey of the iridocorneal angle.

Intraocular pressure: OD 15 mm Hg and OS 16 mm Hg (S).

Summary:
- Rieger's syndrome
- macrocornea ODS
- partial limbus coloboma ODS
- blue sclera ODS
- cornea plana? ODS

- marked hypermetropia ODS
- general choroidal hypoplasia ODS
- hypertelorism
- telecanthus

SD-III-2. *Female aged 26. Born 1940.*
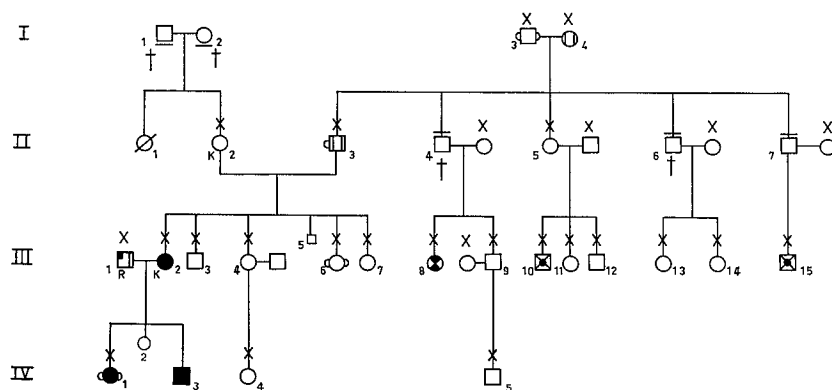
● – primary dysgenesis mesodermal is of the iris

▥ – prominent line of Schwalbe (type B) ODS

⬠ – partial limbus coloboma ODS

▣R – iris bicolor with remnants of the pupillary membrane

⊗ – connatal luxation of the hips, camptodactylia and syndactylia

⊗ – debilitas mentis

K – nail anomalies

The patient was born at term with a normal birth weight. The mother had not been ill during pregnancy and had received neither medication nor irradiation. The ocular anomaly was discovered a few weeks after birth.

Examination:
The patient (fig. 27) gave an impression of mild mental deficiency but was reported to be in good health. The hair colour was medium blond. Clinical facial features included receding zygomatic arches, giving the eyes the appearance of protruding slightly. There

was unmistakable mandibular prognathism with underhung bite. Maxillary hypoplasia may have resulted from regression, the patient having used full dentures since age 17. Whether partial anodontia had existed could not be ascertained. Her dentist did write, however, that he had found only a few remaining radices when treating the patient. Perspiration was normal.

The ears were normal; the nose was gross and broad. The temporal hairline merged with the lateral ends of the eyebrows.

Cranial dimensions: Circumference 53.5 cm (51-57). APD 194 mm (165-195); BPD 140 mm (135-156).

Interocular distances: 40-55-70-97 (0.59); normal maximum values 36-46-70-89. Clinical evidence of hypertelorism and telecanthus. No clinical abnormalities of the hands and feet. The toe-nails were whitish and thickened (chalky nails).

Radiological findings:
Skull: Hypertelorism.
Hands and feet: No abnormalities.
VOD: 10/10; refraction S + 2.5.
VOS: 0.5/60 inc.; refraction?; amblyopia.
Motility: Manifest esotropia OS 30°.
Intraocular pressure: Repeatedly determined values ODS ranged between 10 and 15 mm Hg (AT).
Conjunctivae and sclerae showed no abnormalities.
Cornea: The horizontal diameters were 11 mm OD and 11.5 mm OS; the vertical diameters were 11 mm ODS.
Refraction: OD: 41 × 150° and 40.75 × 60°. OS: 39 × 140° and 42.5 × 150°.

The posterior aspect of the corneal periphery showed a white, irregular annular opacity, more or less concentric with the limbus and unmistakably protruding into the anterior chamber. This opacity constituted the central boundary of a dense membranous opacity of the deepest corneal periphery. Its temporal distance from the limbus ranged from 0.5 to 2 mm (figs. 15, 16 and plates I).

The corneae were otherwise clear and the endothelium showed the normal mosaic structure. Sensibility (Chochet and Bonnet) was normal.

Iris OD: The pupil was localized ectopically in the lower temporal quadrant (fig. 15). It was pear-shaped, with the apex at 6 o'clock and adherent to the corneal ring which at this site was much thickened and opaque. Under normal conditions the longitudinal axis of the pupil formed an angle of some 30° with the vertical meridian. In that case the length was 3.5 mm and the width 1.5 mm; in mydriasis these respective dimensions were 5 mm and 3 mm. Normal responses to light and convergence. Pupillary border normal. The iris had a green-blue colour with an orange-brown pupillary zone. The anterior mesodermal layer was hypoplastic, and the posterior mesodermal layer had a structure of such low density that the pigment layer was exposed at a few sites. The deep iridal stroma and the peripheral remnants of the anterior mesodermal layer were connected with the prominent corneal ring by tissue which was virtually continuous between 3 and 9 o'clock, whereas between 9 and 3 o'clock there were several broad trapezoidal trabeculae, some of which were vascularized. The iridal stroma had a fragile and peculiarly swollen appearance. The sphincter muscle was clearly visible in the pupillary zone of the orange-brown pigmentation. At several peripheral sites, but especially at 6 o'clock, the region of the iridocorneal angle contained an accumulation of lightcoloured tissue resembling iridal stroma. Diaphanoscopy disclosed that the pigmented layer of the iris showed many defects of varying degrees of severity (moth-eaten appearance).

Iris OS: The pupil was slitted (fig. 16, plate I) and localized ectopically between 7 and 7.30 o'clock, where it was adherent to the peripheral corneal ring. Responses to direct

and indirect light were normal, but in mydriasis the pupil dilated only in upward direction. The transverse dimension was 5 mm, and the height was 2 mm (5 mm in mydriasis). The curving superior margin of the pupil had an irregular pigment border with a sphincter clearly visible through the thin iridal stroma. The inferior margin was straight, with no distinct pigmented zone or sphincter tissue but characterized by a band of taut fibrous strands which showed no reactions. At numerous sites the iridal stroma was more or less broadly adherent to the peripheral corneal ring; at 5 and at 7.30 o'clock there were likewise accumulations of light-coloured tissue in the iridocorneal angle. The structure and colour of the iridal stroma were otherwise the same as in the right eye. At 7.30 o'clock, a ragged patch of pigment lay against the adhesion to the posterior aspect of the peripheral cornea. The pigment layer of the iris was likewise more or less diaphanous in several larger and smaller, ill-defined areas.

Lenses: Some brown pigment marked a star-shaped area in the region of the ectopic pupil OD. Very slight blue cataract OS.

Gonioscopy ODS: The iridocorneal angle was not always surveyable owing to broad adhesions between iris and corneal periphery. The visible portion of the corneoscleral trabecula was normal. There were very abundant, broad and trapezoidal or narrow goniosynechiae of varying length. These connected the stroma of the iridal root, periphery and pupillary zone with the very prominent ridge of the abnormally thick and ectopic, irregular line of Schwalbe, which for the most part was highly pigmented. At 7.30 o'clock the OS showed an ectropion uveae, of which the pigment was locally adherent to the thickened corneal ring.

Funduscopy: The fundi were decidedly blond (fundus flavus), particularly the left. The discs showed some temporal pallor and slight cupping. No other abnormalities. Normal maculae and vessels. The choroidal vascularization was poor ODS.
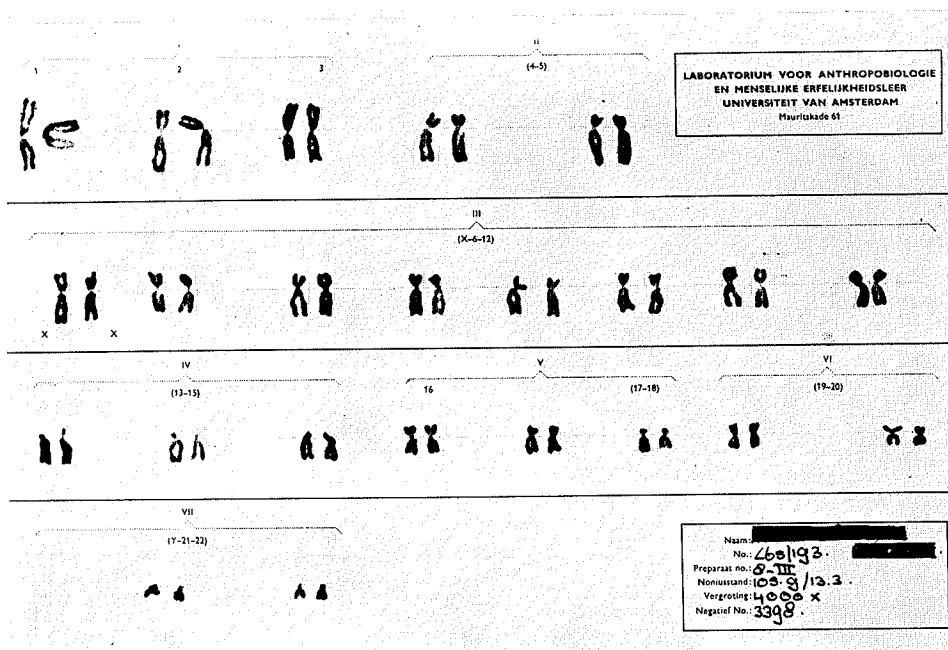
Fig. 69. Normal chromosomal pattern in primary dysgenesis mesodermalis of the iris (SD-IV-1).

Colour vision: HRR: mild red-green defect. Anomaloscope: deuteranomaly.
Chromosome analysis: Normal number of 46 chromosomes with no clues to a chromosomal anomaly. The phenotypical sex was consistent with the sex chromosome combination: XX (fig. 69).

Summary:
- Rieger's syndrome
- esotropia and amblyopia OS
- hypertelorism and telecanthus
- secondary maxillary hypoplasia
- choroidal hypoplasia ODS
- chalky nails

SD-II-*2*. *Female aged 49. Born 1917, 6th January.*
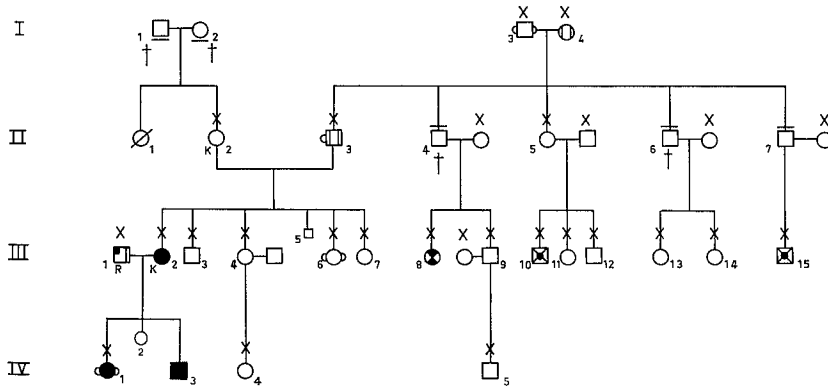
- ● – primary dysgenesis mesodermal is of the iris
- ▥ – prominent line of Schwalbe (type B) ODS
- ◌ – partial limbus coloboma ODS
- � – iris bicolor with remnants of the pupillary membrane
- ◑ – connatal luxation of the hips, camptodactylia and syndactylia
- ⊗ – debilitas mentis
- K – nail anomalies

The patient was a healthy woman with medium blond hair. There was no history of illness but the teeth had been very poor at an early age; full dentures had been introduced as early as age 14. Partial anodontia could not be traced.
Skull, face, jaws, ears, nose and skin were normal. Perspiration was normal. The finger-nails were normal but the toe-nails were whitish, thickened and brittle.
Cranial dimensions: Circumference 54 cm: normal. APD 188 mm: normal; BPD 140 mm: normal.
Interocular distances: 35-47-65-89 (0.54): upper limit of normal.
The bulbi, conjunctivae and sclerae showed no demonstrable abnormalities. Motility: concomitant alternating exotropia 10°.
VOD: 10/10 refraction: emmetropic.
VOS: 10/10 refraction: emmetropic.
Intraocular pressure: 15 mm Hg ODS.

Corneae: Smooth, glossy and clear; limbus girdle (Vogt) ODS; horizontal diameters 11.5 mm ODS; vertical diameters 11 mm ODS. Limbus type A2OO A1: normal.
Refraction: OD 41.5 × 75° and 42.5 × 165°. OS 41.5 × 0° and 42.5 × 90°.
Irides: Blue-grey, structural type C1. Not diaphanous at transillumination. The central, round pupils responded well to light and convergence and had a normal pupillary border.
Refracting media: Clear.
Fundi: Physiological cup ODS.
Gonioscopy: Normal open iridocorneal angle ODS; no prominent line of Schwalbe. Some filamentous iridal trabeculae in the lower quadrant. Remaining structures quite normal. Schlemm's canal not visible.
Colour vision: HRR: normal.

Summary:
– normal eyes   – chalky nails

SD-II-3. *Male aged 53. Born 1913, 26th October.*
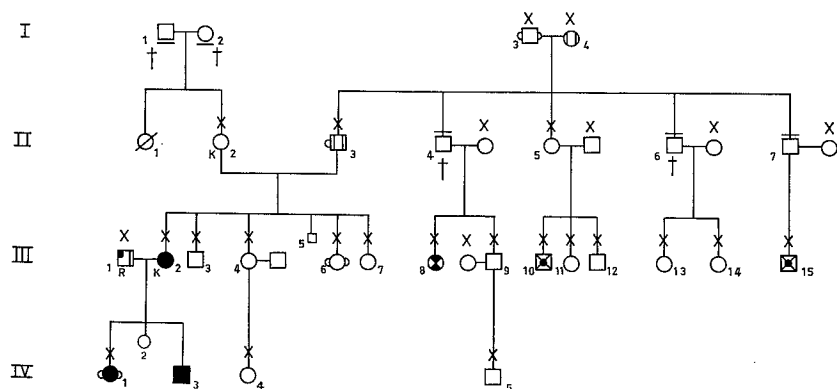
● – primary dysgenesis mesodermal is of the iris
▥ – prominent line of Schwalbe (type B) ODS
◯ – partial limbus coloboma ODS
▧R – iris bicolor with remnants of the pupillary membrane
◐ – connatal luxation of the hips, camptodactylia and syndactylia
⊗ – debilitas mentis
K – nail anomalies

The patient was a rigid man with many psychosomatic gastric complaints but reported to be otherwise healthy.
Skull, face, nose, skin, nails and extremities were normal. The dark blond hair had normal flexibility. Perspiration was normal. Dentition was reported to have been complete. The earlobes were not detached.
Cranial dimensions: Circumference 58 cm: normal. APD 205 mm (194); BPD 155 mm (156).
Interocular distances: 32-45-65-89 (0.50): normal.

The bulbi, conjunctivae and sclerae were normal. Motility was intact.

VOD: 11/10 refraction: S-0.5 = C-0.5 × 30°.

VOS: 10/10 + refraction: emmetropic.

Intraocular pressure: 14 mm Hg OD and 16 mm Hg OS (AT).

Corneae: Smooth, glossy and clear. Slit-lamp examination disclosed numerous inactive subepithelial foreign bodies (explosion in 1946). Partial temporal limbus coloboma OD. Horizontal diameters 11.5 mm ODS. Limbus type B2A2A1B2; normal. Prominent line between 7 and 10 o'clock OD and between 8 and 11 o'clock OS.

Refraction: OD 42 × 15° and 43 × 105°. OS 41.75 × 10° and 43 × 100°.

Irides: Blue, structural type C1. No peculiarities. Pigment layer not diaphanous. The central, round pupils responded well to light and convergence and had an irregular pupillary border.

Refracting media: Clear.

Fundi: No abnormalities.

Gonioscopy: ODS pigmented open iridocorneal angle; distinctly prominent anterior line of Schwalbe; normal trabecula and Schlemm's canal. Scleral spur and ciliary band normal. The iridal root OD was thickened by circular vessels between 5 and 7 o'clock, where it adhered by a thin filamentous adhesion to the prominent line of Schwalbe.

Colour vision: HRR: red-green defect.

Anomaloscope: Deuteranomaly.

Summary:
– prominent line of Schwalbe ODS
– partial limbus coloboma OD
– deuteranomaly

SD-III-1. *Male aged 28. Born 1938.*
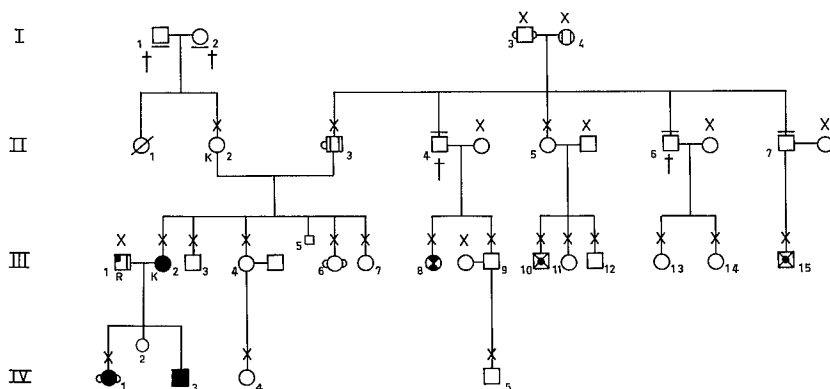
● – primary dysgenesis mesodermal is of the iris

▥ – prominent line of Schwalbe (type B) ODS

◍ – partial limbus coloboma ODS

▦R – iris bicolor with remnants of the pupillary membrane

⊗ – connatal luxation of the hips, camptodactylia and syndactylia

⊗ – debilitas mentis

K – nail anomalies

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Dark blond hair. Normal craniofacial configuration. Normal nose. Palpebrae slightly mongoloid. Normal ears. Regular teeth.

Cranial dimensions: Circumference 55 cm (51-57). APD 184 mm (168-195); BPD 142 mm (135-156).

Interocular distances: 32-44-62-82 (0.51): normal.

VOD: 10/10 + refraction: S-5.75 = C-1.75 × 35°.

VOS: 9/10 refraction: S-7 = C-0.5 × 10°.

Intraocular pressure: 14 mm Hg ODS.

The conjunctivae and sclerae showed no abnormalities.

Corneae: Clear. Prominent line of Schwalbe (type B) between 2 and 4 o'clock OD. Horizontal diameters 11.5 mm OD and 11 mm OS.

Refraction: OD 44.25 × 35° and 46 × 125°. OS 45.25 × 10° and 46.5 × 100°.

Irides: OD iris bicolor; the segment between 8 and 12 o'clock showed dark brown pigmentation (hyperchromatism) with an otherwise light brown colour (also entire iris OS). Pupillary membrane adhered to the lens at 10.30 o'clock.

ODS structural type C1. The peripheral iridal structure was of considerably diminished density, with lacunae and the non-diaphanous pigment layer shimmering through. Flimsy remnants of the pupillary membrane, originating from the iridal corona.

Lenses: Clear. OD: the temporal portion of the pupillary part of the lens contained a star-shaped area of brown pigment and there were some delicate adhesions to persistent pupillary membrane remnants.

Pupils: Central, round, adequately responsive pupils ODS.

Fundi: Normal; vitreous body clear.

Gonioscopy: No abnormalities. The iridal root was slightly hypoplastic. The localization of Schlemm's canal was normal.

Colour vision: HRR: normal.

Internal examination: Mild pulmonary stenosis; congenital thoracolumbar kyphoscoliosis.

Summary:
– myopia and astigmatism ODS
– iris bicolor OD
– remnants of pupillary membrane ODS

– peripheral marginal iridal atrophy ODS
– prominent line of Schwalbe OD

SD-III-6. *Female aged 17. Born 1949, 2nd August.*

This was a healthy girl with dark blond hair, showing no abnormalities of the skull, face, nose, ears, jaws, teeth, skin, nails or extremities.

Cranial dimensions: Circumference 55 cm (50.5-56.5). APD 192 mm: normal; BPD 143 mm: normal.

Interocular distances: 32-41-63-86 (0.51): normal.

The bulbi, conjunctivae and sclerae were normal, and motility was intact.

VOD: 11/10 refraction: emmetropic.

VOS: 11/10 refraction: S + 0.5.

Intraocular pressure: 14 mm Hg OD and 15 mm Hg OS: normal.

Corneae: Smooth, glossy and clear. Horizontal diameters 11.5 mm ODS and vertical diameters 11 mm ODS. Limbus type A3A1A1A3. Partial limbus coloboma ODS.

Refraction: OD 41 × 0° and 41.5 × 90°. OS 41 × 0° and 41.25 × 90°.

Irides: Grey-blue, of structural type C1. Pigment layer not diaphanous. Central round pupils responding well to light and convergence, with a normal pupillary border. The iridal frill showed a light orange-brown pigmentation at some sites.

Refracting media: Clear.

Fundi: Normal.

Gonioscopy: Normal open iridocorneal angle ODS. Very lightly pigmented trabecula with pigment accentuating the anterior gonioscopic line, which was prominent between 9 and 11 o'clock OD. No other peculiarities.

Summary: – partial limbus coloboma ODS.

SD-III-10. *Female aged 20. Born 1946.*
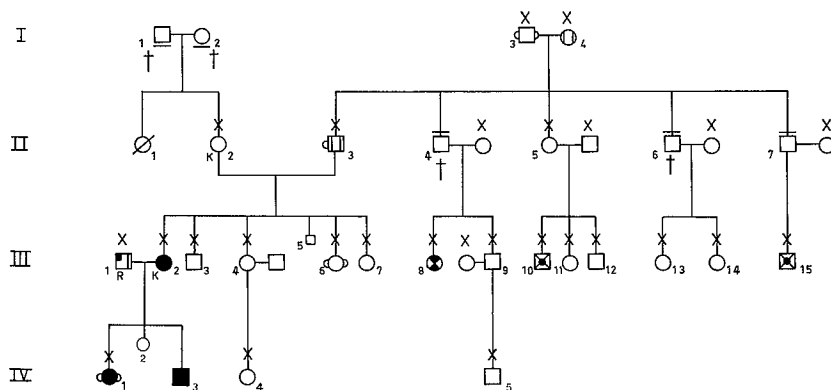
● – primary dysgenesis mesodermal is of the iris
▥ – prominent line of Schwalbe (type B) ODS
◖ – partial limbus coloboma ODS
▨ R – iris bicolor with remnants of the pupillary membrane
⊗ – connatal luxation of the hips, camptodactylia and syndactylia
⊗ – debilitas mentis
K – nail anomalies

The child was born in breech presentation after an uneventful pregnancy; birth weight 2000 g. She was rather pale at birth. The mother reported that development had always been slow. At age 14 months the family doctor diagnosed congenital luxation of the left hip, treated by a plaster hip spica which was left in situ for a year. When seen, the patient was a small hunchback with poor and incomplete dentition. The limbs were atrophic. Thoracic kyphoscoliosis with curvature to the right.
The above abnormalities were found when we examined the patient in a home for mental defectives. The craniofacial configuration was asymmetrical. Ears, nose and face showed no other abnormalities. There were hardly any teeth left; many extractions were reported. Imbecility. The nails were normal, and the body hairgrowth showed the normal pattern. Menstruation was regular and normal.
Mild cutaneous syndactyly III-IV left, and mild camptodactyly V right.
Cranial dimensions: Circumference 48 cm (51-57). APD 165 mm (168-195); BPD 138 mm (135-156).
Interocular distances: 32-37-57-76 (0.56): normal.

Radiological findings:
Left: Features of congenital luxation of the hip.
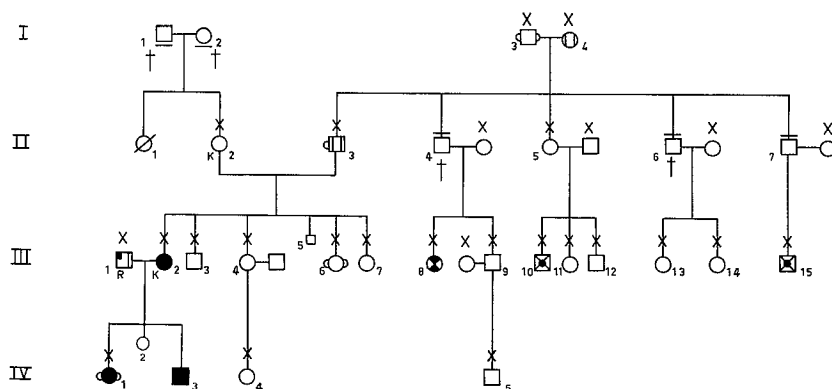
- primary dysgenesis mesodermal is of the iris
- prominent line of Schwalbe (type B) ODS
- partial limbus coloboma ODS
- iris bicolor with remnants of the pupillary membrane
- connatal luxation of the hips, camptodactylia and syndactylia
- debilitas mentis
K - nail anomalies

Right: High thoracic convex torsion scoliosis. Transverse process L5 adherent to the sacrum.

Skull: Small sella; left frontal sinus ample, but right frontal sinus small; slight pneumatization of the mastoids.

Hands: Minus variant of the R ulna; R metacarpus showed ulnad displacement in relation to the radius.

No other abnormalities.

Far vision was reported to be good, the patient being able to discern the smallest details. Conjunctivae and sclerae were normal.

Corneae: Clear and of normal size (10.5-11 mm).

Irides: Normal structure (type C2) ODS. Anterior mesodermal layer and contraction folds in evidence. Pupil OD somewhat distorted but with a normal pupillary border. Iridal colour was blue.

Refracting media: Clear.

Funduscopy: Adequate funduscopy precluded by slightly aggressive behaviour.

Summary:
- mild dyscoria OD   – congenital luxation L hip
- mild microcephaly and cranial asymmetry – mild cutaneous syndactyly L
- imbecility   – mild camptodactyly R

BR-IV-1. *Female aged 11. Born 1955, 22nd July.*

Normal birth at term, with average birth weight. During pregnancy the mother had not been ill and had received neither medication nor irradiation. Connatal opacity ODS; OD white with deformed cornea showing conical protrusion. No other connatal anomalies. Patient's physical and mental development was uneventful, with a few of the childhood

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● – primary dysgenesis mesodermalis of the iris

◎ – secundary dysgenesis mesodermal is of the cornea (Peters' anomaly)

▫ – prominent line of Schwalbe (type B)

⊠ – connatal anomalies of the limbs and cataract

⊘ – connatal cataract ODS
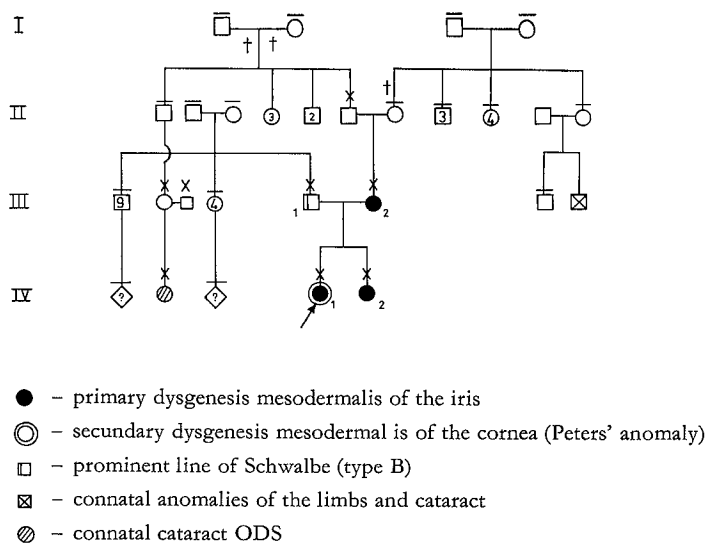
diseases. She attended a school for blind and visually defective children in New Zealand, from where an ophthalmologist wrote us the following details of her past history.

"At birth the cornea of each eye was opaque. This opacity involved almost the whole of the cornea, but during the first few weeks the opaque areas became slightly smaller. The intraocular pressures were normal. On 10-11-1955 an optical iridectomy was performed on the left eye. In 1957 an elevation of intraocular pressure was found in the left eye, and cyclodiathermy was done, and later, goniopuncture; however, this eye deteriorated, and was removed in December 1957. By 1958 the pressure of the right eye had risen, and in May of that year a goniopuncture and cyclodiathermy was performed. In April 1964 goniopuncture was done again on the right eye. In recent months the pressure of this eye has been around 25 mm Hg, and she is using pilocarpine eye drops 3% 3dd and laevo-adrenaline once a day. She also takes half a tablet of dichlorphenamide daily". (December 1966). For the histological findings see chapter II, 23.

At examination in 1967 we found no abnormalities of the skull, face and extremities. The skin was normal. Perspiration was normal. Hairgrowth was normal, the hair colour being brown. Despite her visual handicap the girl's intelligence was normally developed. General examination disclosed no abnormalies (fig. 28).
Cranial dimensions: Circumference 53 cm (50-56). APD 179 mm (164-192); BPD 142 mm (133-155).
Interocular distances: 34-43-62-83 (0.55); normal maximum values 35-45-63-88.
Orthodontic examination: External aspect: no peculiarities; normal labial relation; normotonic musculature. Internal aspect: deciduous teeth in phase of (belated) replacement: inferior cuspids and superior first molars not yet erupted (fig. 43). I1sd lost due to violence. M1ss extracted.

Radiological findings:
Agenesis of all third molars and second premolars (oligodontia vera). Css and Csd retained in mesioversion and palatine position (fig. 42).
Skull (tele): No visible abnormalities; tracing and analysis disclosed no gross changes.
Hands and feet: No abnormalities.

Ophthalmological examination:
The right eye seemed enlarged; secondary anophthalmia on the left (glass eye). Palpe-

brae, cilia and eyebrows normal. Conjunctivae normal. At a few scleral sites the uvea shimmered through with a bluish tinge (cyclodiathermy) (fig. 28). The right eye showed a predilection for adduction; vision was poor (=3/60 inc.). Refraction – established funduscopically – was about S-15. Nystagmus of varying severity was reported to have been present since birth.

Cornea: Reduced sensibility in superonasal area (Chochet and Bonnet). The horizontal diameter was 13.5 mm and the vertical diameter 12.5 mm. Refraction: marked irregular astigmatism. The limbus was ill-defined in the entire circumference and the cornea had an unmistakable horizontal oval shape (fig. 4). It was opaque between 11 and 5 o'clock, the opacity becoming more intensive and whiter towards the centre. It was present in all layers, with densifications at the levels of th very superficial, the central and the deepest stroma. It was associated with superficial and sometimes also deeper vascular invasion from the limbus region. The endothelium in the opaque region could not be evaluated. Elsewhere in the cornea the stroma was clear and the endothelium showed a normal pattern.

The opaque part of the cornea had included since birth a paracentral rarefaction measuring 3 × 2 mm, at 4.30-5 o'clock (figs. 4, 53). Slit-lamp examination with the narrow beam disclosed a punched-out defect of the deep corneal layers at this site (fig. 54). The posterior two-thirds of the cornea and Descemet's membrane were lacking here. The defect had a centrad intralamellar extension of 0.7 mm length. Around the defect the entire cornea was slightly thickened, and there were no central connections between cornea and iris in this area. The anterior chamber had a normal depth. With the slit lamp it was possible to discern, through the temporal portion of the persistent corneoscleral membrane, something of a white annular opacity in the deepest corneal layers.

The corneal surface was otherwise smooth and glossy, and could not be stained with fluorescein.

Iris: The colour was a light green-blue. The stroma was hypoplastic; the anterior mesodermal layer was absent, as were the iridal frill and contraction folds. The thin stroma showed a diffuse light brown pigmentation and a radial fibrous structure. The pupillary sphincter muscle was clearly visible and shimmered through yellow-brown. At numerous sites between the stromal fibres the non-diaphanous pigment layer was also visible. Slit-lamp examination revealed no peripheral connections between the cornea and the hypoplastic iris.

The central pupil showed slight pear-shaped dyscoria in temporal direction, responded well to light and had a narrow pupillary border (fig. 53).

Lens: It was clear so far as could be established, and the fundus could be examined without difficulty. It was a blond fundus with a normal macular reflex. The disc was slightly atrophic and showed glaucomatous cupping. There were no myopic fundal changes.

The intraocular pressure was 30 mm Hg (AT), although the patient was using 3% pilocarpine 3 dd.

Gonioscopy (fig. 20): Gonioscopy was feasible only for part of the circumference, owing to the extensive cornal opacity. The first conspicuous feature was an extremely prominent anterior gonioscopic line of Schwalbe which formed a pearlcoloured ridge protruding into the anterior chamber. The line was of varying thickness, and occasionally accentuated by pigmentations. Between 12 and 6 o'clock, the broadened trabecula and the ciliary band were covered almost entirely by a white, semi-transparent fibrous tissue, which adhered tot the ridge by delicate extensions. Moreover, at 6 o'clock there were some stroma-coloured adhesions of varying width between the stroma of the iridal root and the ridge. Between 12 and 3 o'clock a very wide adhesion linked the iris to the ridge over an entire segment. Otherwise the iridal root was hypoplastic.

Therapy: In January 1967, a Worst goniotomy was performed between 1 and 5 o'clock.

A small haemorrhage in the anterior chamber occurred during this operation. The postoperative course was uneventful. Subsequent gonioscopy showed that an opening had been made between 1 and 3 o'clock, where the adhesions between iris and ridge proved to have been abolished.

One week after the operation the intraocular pressure varied around 25 mm Hg so that a second goniotomy was performed between 4 and 8 o'clock. This lowered the pressure to 20 mm Hg, but subsequently this value increased considerably.

Summary:
- Rieger's syndrome
- Peters' anomaly ODS
- macrocornea OD
- infantile-juvenile glaucoma ODS
- high myopia ODS
- oligodontia vera

BR-IV-2. *Female aged 6.5. Born 1960, 17th July.*
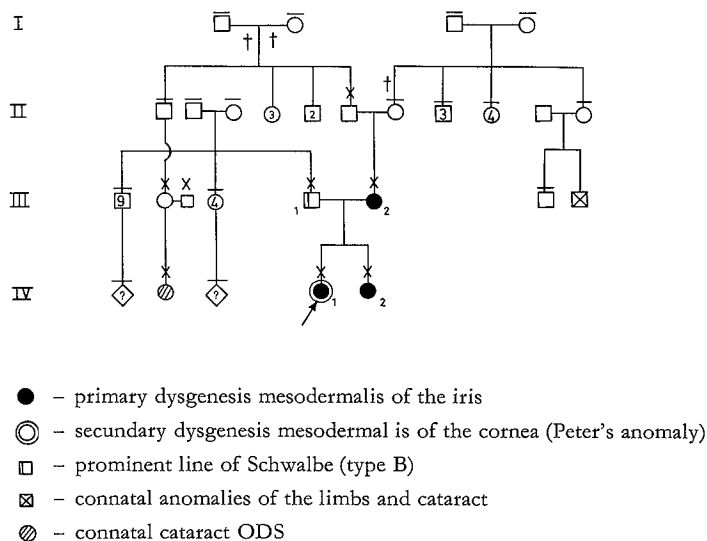
● – primary dysgenesis mesodermalis of the iris
◎ – secundary dysgenesis mesodermal is of the cornea (Peter's anomaly)
▢ – prominent line of Schwalbe (type B)
⊠ – connatal anomalies of the limbs and cataract
⊘ – connatal cataract ODS

Normal birth at term, with average birth weight. During pregnancy the mother had not been ill and had received neither medication nor irradiation. Connatal opacity ODS, as in this patient's sister (BR-IV-1). No abnormalities of other organs.

The patient's development was slower than her elder sister's and her behaviour during clinical observation suggested feeblemindedness. She attended the same school as her sister and learned the braille system. The parents were not consanguineous. The abovementioned ophthalmologist sent the following details of the past history from New Zealand.

"At birth the cornea of each eye was opaque and intraocular pressure raised. Had several surgical operations, goniotomy, cyclodiathermy, Lagrange sclerotomy on both eyes, followed by hyphaema in the right eye. In 1962 tonometer readings were 26 mm Hg in each eye, and pilocarpine drops were used. In 1964 a cautery-iridectomy operation was done on the left eye (fig. 13; 11 o'clock?). In 1966 the readings were: Right eye 30 mm Hg, Left eye 18 mm Hg. The optic discs are cupped and the right disc is distorted. She is using pilocarpine drops 2% 3 dd". (December 1966).

At examination early in 1967 we found no clinical abnormalities of the extremities. The skull showed the clinical features of hypoplasia of the zygomatic arches (fig. 29) and the eyes seemed too far apart. Skin and hair appeared to be normal, as was perspiration. The hair colour was dark blond.

Cranial dimensions: Circumference 52 cm (49-55). APD 181 mm (160-188); BPD 138 mm (131-152).

Interocular distances: 34-43-63-88 (0.56); normal maximum values 34-43-61-86. Borderline case of hypertelorism and telecanthus. Distance between lateral bony orbital margins 89 mm.

Orthodontic examination: The child's behaviour precluded a full radiological examination. Possible agenesis of M2ss. No other clinical peculiarities.

Radiological findings: The skeleton of the hands and feet showed no abnormalities or peculiarities.

Ophthalmological examination:

We found bilateral hydrophthalmos with (connatal) nystagmus of varying severity. Palpebrae, cilia and eyebrows were normal, as were conjunctivae and sclerae. It was impossible to determine vision, but it must have been very poor (less than a few sixtieths). Refraction ODS in the range of high myopia (S-12 to 15).

Right eye: The condition of this eye was greatly changed, probably a as result of the many operations. The anterior chamber was relatively shallow.

Cornea: The horizontal and vertical diameters were 13 and 13 mm, respectively. Refraction: irregular astigmatism. Normal central clarity but peripheral opacities with a white, peripheral ridge-like opacity of the deepest corneal layers between 1 and 11 o'clock, protruding into the anterior chamber. There were also some artificial corneal scars. No defect of stroma or Descemet's membrane was found. The corneoscleral boundary was ill-defined (fig. 1).

Iris: The colour was blue-green-grey. Absence of the iris between 6 and 8 o'clock. The iridal stroma was very hypoplastic, the pigment layer shimmering through in many places. Anterior mesodermal layer and iridal frill were absent. The dyscoric, dilated pupil had an irregular pupillary border and did not respond to light. Transillumination revealed a peripheral (iatrogenic?) defect at 10 o'clock.

Lens: Superonasal displacement, with an irregular equatorial boundary in the visible part, where the zonular fibres were long and sparse. There were some slight, non-compact opacities which could not be localized exactly but were definitely not lying superficially in the cortex.

Fundus: The fundus was blond. The disc showed pronounced atrophic-glaucomatous cupping. There were no myopic degenerative changes and no signs of myopic stretching.

Gonioscopy: Very prominent anterior line of Schwalbe, with adhesions between this line and the iridal root and structures of the iridocorneal angle, of which little was observed although the iridocorneal angles were open.

Intraocular pressure: 34 mm Hg (AT) despite 2% pilocarpine.

Left eye: The condition of this eye was better than that of the right eye. The defect at 11 o'clock, although not looking like an operative coloboma, must be interpreted as such in view of the surgical history (fig. 13, 14).

Cornea: Horizontal and vertical diameters both 14 mm. Smooth, glossy surface with astigmatism. The corneoscleral boundary was ill-defined. Clarity was normal and there were no stromal defects. Ruptures of Descemet's membrane were in evidence. The deepest corneal layer showed a white, irregularly thickened ridge-like opacity more or less concentric with the limbus; the ridge protruded far into the anterior chamber. At many thickened sites there were filamentous adhesions between this ridge and the peripheral iridal stroma.

Iris: The colour was green-grey and the structure very hypoplastic, with the pigment layer shimmering through. Contraction folds and iridal frill were absent. At 11 o'clock there was a peripheral stromal defect above a narrower, triangular defect in the pigment layer, which was therefore in part exposed (fig. 13). Between 3 and 5 o'clock there were three total oval-shaped iridal holes through which the normal lens contours were visible; development of the zonular fibres proved to be normal.

There was a large, central, dyscoric (oval) pupil with a poor response to light. Only at a few sites was the pupillary sphincter muscle visible. A small ectropi on uveae was seen between 8 and 9 o'clock (fig. 14). Only the holes lit up at transillumination.

Lens: Normal localization and clarity. Some star-shaped pigment spots at 4.30 o'clock on the anterior surface of the pupillary region (fig. 14).

Fundus: A very blond fundus without myopic changes. The optic disc was pale and showed distinct glaucomatous cupping.

Gonioscopy: Like the sister and the mother (figs. 20 and 21) this patient had numerous filamentous and trapezoidal adhesions connecting the posterior corneal embryotoxon with the hypoplastic iridal periphery. The iridocorneal angles were open and the structures were in part covered by light brown-yellow trabecular tissue which later, at goniotomy, was severed.

Intracoular pressure: 30 mm Hg despite the use of pilocarpine.

Therapy: Repeated goniotomies (Worst) in January and February. The postoperative intracular pressure was often satisfactory but always rose again.

Summary: Rieger's syndrome
– pupillary pseudopolycoria OS
– congenital glaucoma ODS
– high myopia ODS

– hypertelorism and telecanthus (borderline case)
– oligodontia vera?
– mild mental deficiency

BR-III-2. *Female aged 38. Born 1928.*
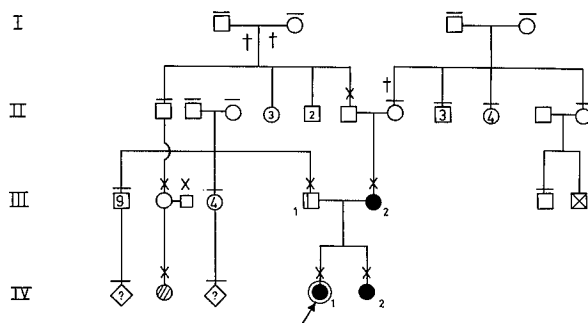
● – primary dysgenesis mesodermal is of the iris
◎ – secundary dysgenesis mesodermal is of the cornea (Peters' anomaly)
▯ – prominent line of Schwalbe (type B)
⊠ – connatal anomalies of the limbs and cataract
⊘ – connatal cataract ODS

The subject was a healthy woman of normal height, with dark blond hair. During pregnancy the mother had not been ill and had received neither medication nor irradiation. Parturition took a normal course and the birth weight was normal. The mother (BR-II-4) died from puerperal fever a few days later. The subject was reported to have had no ocular abnormalities but was occassionally troubled by the right eye, in which vision seemed to differ from that in the left eye. The parents were not consanguineous. Skull, face (fig. 30) and extremities were normal. Mild blepharochalasis existed. Nose and ears showed a normal shape. No cutaneous changes, normal nails and normal perspiration. The subject's intelligence was good.

Cranial dimensions: Circumference 56 cm (51-57). APD 188 mm (167-195); BPD 148 mm (135-156).

Interocular distances: 33-41-61-84 (0.54): normal.

Orthodontic examination: Normal skull and maxillomandibular relations. All teeth present, and of normal shape and position. No other abnormalities in the context of dentomaxillary orthopaedics.

Radiological findings:

Skull: Normal.

Hands and feet: Normal.

Ophthalmological examination:

The external appearance of the bulbi was normal. Conjunctivae and sclerae showed no abnormalities.

VOD: 10/10 refraction: S + 0.5.

VOS: 10/10 refraction: emmetropic.

Motility: Alternating hyperphoria and alternating suppression.

Corneae: Normal sensibility. Ill-defined limbus due to persistence of the corneoscleral membrane. A continuous, fairly thick conjunctival boundary vessel took its course in the superior part of the central boundary area of the superficial limbus ODS.

The horizontal diameters were 12.25 mm OD and 12 mm OS; the vertical diameters were 12 mm ODS.

Refraction ODS: 40.5 × 0° and 41° × 90°.

The deepest corneal layer ODS showed a conspicuous, thick, white, irregular ridge-like peripheral opacity which protruded into the anterior chamber (figs. 5, 9), between 2 and 10 o'clock. This annular ridge on the posterior aspect of the corneal periphery showed a sharply defined central delimitation from the clear cornea and, peripherally, merged with a semi-transparent opacity of low density in the deepest corneal layers. At several sites this line was thickened and pigmented. Several brown-pigmented strands resembling iridal stroma connected these sites with the iridal root and iridal periphery at the level of the white line.

Irides: The pigment layer ODS was no diaphanous. Both irides were brown-pigmented and hypoplastic, with the pupillary sphincter muscle shimmering through (figs. 5, 9). Anterior mesodermal layer and iridal frill were absent, as were contraction folds. The available iridal stroma consisted of thin, radial fibres showing a diffuse brown pigmentation, with the dark brown pigment layer shimmering through in places. At a few sites (3, 5, 8 and 9 o'clock OD; 5, 7, 8 and 9 o'clock OS) on the periphery of the iris, the iridal stroma adhered to the white peripheral corneal opacity, the adhesions slightly elevating the stroma. The pupil OD (fig. 39) showed a slightly ectopic nasal localization. It had a normal pupillary border, which the OS virtually lacked. Both pupils were round, isocoric; both responded well to light and mydriatics.

Refracting media: Clear.

Fundi: Normal.

Lenses: The pupillary area of the anterior lens capsule OS contained five star-shaped brown pigmentations.

Intraocular pressure: Normal (15-17 mm Hg) ODS.

Tonography: Normal (OD: $c = 0.16$; OS: $c = 0.13$).

Goldmann perimetry: Normal visual fields.

Gonioscopy: A very prominent, thick, ridge-like anterior limiting line of pearly sheen and colour protruded into the anterior chamber ODS. This ridge of irregular thickness showed several scattered wart-like swellings and prominences of brown pigmentation (fig. 21). In apposition to many of these processes the brown stroma of the iridal root likewise showed prominences. The impression was strong that the two types of processes had originally been connected. Broader and smaller adhesions between the stroma of the iridal root and the thick circular ridge were present at five sites ODS. At several scattered sites of the circumference of the iridocorneal angle, moreover, brown-pigmented adhesions connected the stroma of the most peripheral part of the iridal root with the greatly broadened trabecula. The structures of the deeper parts of the otherwise normally open iridocorneal angles (trabecula, scleral spur and ciliary band) were not clearly distinguishable owing to the presence of very thin, glossy, milky-white tissue.

Summary: – Rieger's syndrome.

BR-II-3. *Male aged 66. Born 1901.*

● – primary dysgenesis mesodermalis of the iris

◎ – secundary dysgenesis mesodermal is of the cornea (Peter's anomaly)

▫ – prominent line of Schwalbe (type B)

⊠ – connatal anomalies of the limbs and cataract

⊘ – connatal cataract ODS
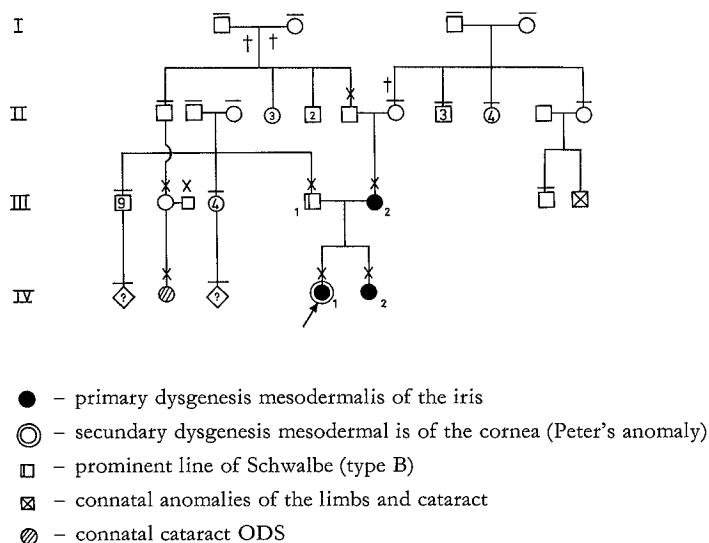
The subject was a healthy man with greying blond hair. Skull, face, teeth, ears, nose and extremities were normal.

Cranial dimensions: Circumference 60 cm. 158-198 mm. Slight macrocephaly.

Interocular distances: 36-45-65-79 (0.55): normal.

Motility: Normal.

VOD 10/10 (S + 2).

VOS 10/10 (S + 2.5).

Conjunctivae and sclerae showed no abnormalities.

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Corneae: Clear, with normal limbus type B1A1A1O. Horizontal diameters 11.5 mm ODS.
Refraction: OD 42.5 × 15° and 42.75 × 105°. OS 42.5 × 0° and 42.75 × 90°.
Irides: Colour brown, with dark brown-pigmented pupillary zone ODS. Structure type c1. Some contraction folds. The central pupils responded well to light and convergence. The round, isocoric pupils had a normally developed pupillary border. The pigment layer was not demonstrably diaphanous.
Refracting media: Normal.
Fundi: Normal.
Intraocular pressure: 19 mm Hg OD and 20 mm Hg OS.
Gonioscopy: Normal, open iridocorneal angles. Visible line of Schwalbe.

Summary:
– mild hypermetropia
– slight macrocephaly

BR-III-1. *Male aged 42. Born 1925.*
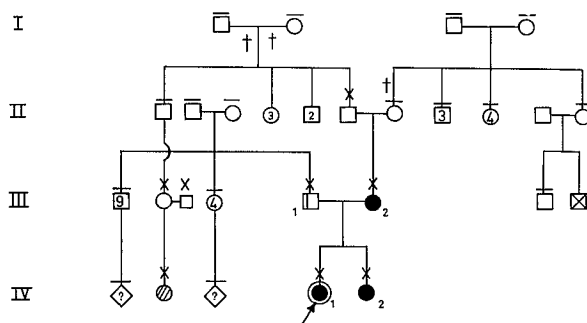
● – primary dysgenesis mesodermalis of the iris
◎ – secundary dysgenesis mesodermal is of the cornea (Peters' anomaly)
▢ – prominent line of Schwalbe (type B)
⊠ – connatal anomalies of the limbs and cataract
⊘ – connatal cataract ODS

A healthy man with dark blond hair. Skull, face, teeth, ears, nose and extremities normal.
Cranial dimensions: Circumference 57 cm. 151-190 mm: normal.
Interocular distances: 32-44-65-88 (0.50): normal.
Motility: Normal.
VOD = VOS: 10/10 (S + 1).
Conjunctivae and sclerae were normal.
Corneae: Normal clarity and sensibility. Limbus type A2B2A2A3. Horizontal diameters 11.5 mm ODS.
Refraction: OD 43 × 80° and 42.5 × 170°. OS 42 × 25° and 43 × 115°.
Irides: Grey-blue colour, structural type c1, with irregular iridal frill ODS. Some peripheral marginal iridal atrophy. Normal contraction folds. Some scattered small, light brown pigment spots on the pars ciliaris of the iris. The central, round, isocoric pupils with a normal pupillary border responded well to light and convergence. The pigment layer was not diaphanous.

Refracting media: Normal.
Fundi: Normal.
Intraocular pressure: 12 mm Hg OD and 14 mm Hg OS (AT).
Gonioscopy: ODS normal open iridocorneal angles with a normal anterior line of Schwalbe.

Summary:
– prominent line of Schwalbe OD.

BR-IV-3. *Male aged 4 months. Born 1966, 28th October.*

● – primary dysgenesis mesodermalis of the iris
◎ – secundary dysgenesis mesodermal is of the cornea (Peter's anomaly)
▫ – prominent line of Schwalbe (type B)
⊠ – connatal anomalies of the limbs and cataract
⊘ – connatal cataract ODS
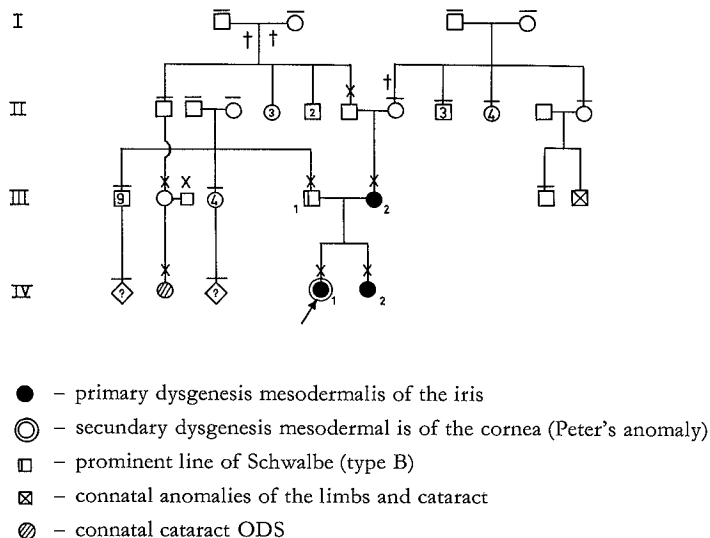
Normal birth at term, with a birth weight of 5260 g. Slight cyanosis postpartum. After a few months the parents noticed that the baby's eyes showed a white opacity and that vision was poor. The mother's pregnancy had been normal and she had received neither medication nor irradiation. There was no family history of ocular anomalies apart from two female second cousins (BR-IV-1 and BR-IV-2). The parents were not consanguineous.
Further development was normal but the child's eyes did not follows moving lights and the boy habitually rubbed his fists in his eyes. At general examination the paediatrician found no abnormalities. A detailed examination of the mother failed to disclose any clues to an infection during pregnancy.
Skull, face, jaws, ears, nose and extremities showed no external abnormalities. Skin, hair and nails were normal. Hearing was likewise normal.

Ophthalmological examination:
The bulbi seemed of normal size and there was no nystagmus.
Conjunctivae and sclerae seemed normal.
Corneae: Clear and not conspicuously small.
Irides: Of normal structure. The round, central pupils responded well to light and mydriatics.

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Lenses: Cataractous ODS, with pronounced calcareous thickening of the cataract in the central part of the anterior cortical layers. The remainder of the lens showed a diffuse milky opacity, most pronounced on the left.
Fundi: Normal so far as could be established.
Both parents (BR-III-5 and BR-III-6) were free from ophthalmological abnormalities apart from some hypermetropia in the father; the lenses were clear.
Therapy: We advised an operation ODS, soon to be performed.

Summary:
– connatal cataract ODS.

HO-III-6. *Male aged 27. Born 1938, 29th August.*
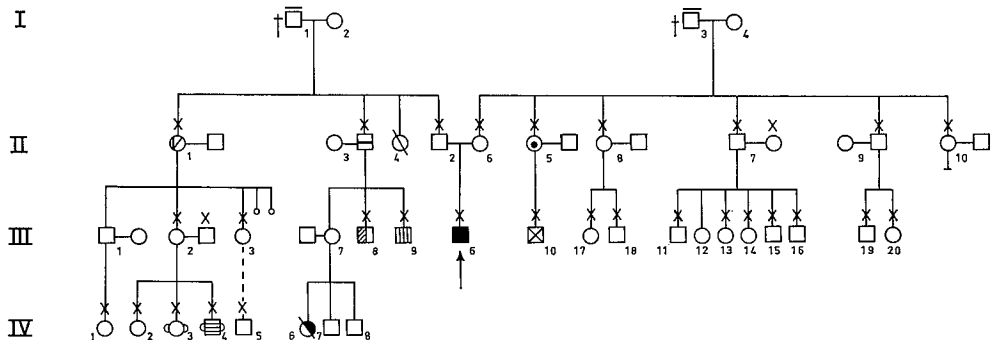
■ – primary dysgenesis mesodermalis of the iris with oligodontia vera
⊙ – mild ectopia pupillae ODS
▥ – connatal aplasia of the pectoral maior muscle
◐ – prominent line of Schwalbe OD
▤ – appendix auricularis and mild frontal asymmetry
⊡ – partial limbus coloboma
◗ – bilateral cheilopalatoschisis, still-born
▨ – pseudo-papillitis OD
⊟ – glaucoma simplex?
◩ – urogenital deformities, epilepsy and imbecilitas mentis
◪ – epilepsy

The patient was born with abnormal eyes, to which little attention was paid at first. Ophthalmological examination when he was 12 years old revealed the following.
VOD: 1/10
VOS: 9/10 with S + 0.5.
Both eyes showed an anomaly of the anterior segment: OD pseudopolycoria and ectopic pupil; OS ectopic pupil. Deep anterior chamber ODS, with some sort of connective tissue in the chamber curves, temporal as well as nasal. The intraocular pressure was considerably increased (40 mm Hg ODS). Peripapillary medullated nerve fibres OD. The Wassermann and toxoplasmin reactions were negative and general examination

disclosed no abnormalities. Cranial X-rays revealed no orbital abnormalities but showed that only a few dental germs were present. The intraocular pressure remained too high for years, despite various conservative measures and medications. There were occasional periods of blurred vision. The corneae became gradually less transparent. In 1953 the patient was demonstrated to the 128th meeting of the Netherlands Ophthalmological Society in Rotterdam (Horst 1954).

1957-1958: OD: Inferonasal ectopia of the pupil with iridal defects at 1 and 2 o'clock. Marked atrophy of the iridal stroma. Circular adhesion of the iris to the cornea periphery with the exception of the superior apart. The iridocorneal angle was filled with tissue. OS: Large ectopic pupil at 6 o'clock, stromal atrophy, ectropion uveae, circular adhesion of the iridal stroma to the corneal periphery.

The irides were rather far in front of the lenses. In the course of the years there had been no change in the irides and the condition of the anterior chamber. Both optic discs were slightly cupped, and glaucomatous visual field changes occurred.

1958: Sclerotomy and iridectomy OD with Elliot trephination.

1960: Goniopuncture at 12 o'clock, to which the intraocular pressure initially responded well (OS). In the course of the years there were many recurrent periods of increased intraocular pressure OD, associated with gradual opacification of the cornea. Vision was gradually lost, and as early as 1959 this eye was described as blind.

We have observed this patient since 1964. The intraocular pressure has been fair in recent years (< 20 mm Hg) with PJJ 0.125% i dd OS. In November 1966 the reading was as low as 12 mm Hg.

Investigation:

There was reportedly no family history of this congenital ocular anomaly. Patient received no ophthalmological treatment until later in life. The parents were not known to be consanguineous. The mother's pregnancy had been uneventful, she had been given neither medication nor irradiation.

General examination: The patient was a fairly short (162 cm), robust and slightly stout (72 kg) man of compact build with dark blond hair. The scalp hair was thin, showing incipient baldness. Body hair and beard showed normal growth. The skin was normal, as was perspiration. The slightly increased blood pressure (180/100) was emotion-dependent. Besides a mild disturbance of capillary resistance, internal examination also revealed a slight abnormality in the fat composition of the blood. The face (fig. 31) was somewhat moon-like with normal nose and ears. The eyebrows met above the nose. The fingers were relatively short (brachydactylia) and the feet were high-arched. The nails were normal. Normal intelligence.

Cranial dimensions: Circumference 57.5 cm. APD 192 mm; BPD 154 mm (upper limit of normal).

Interocular distances: 34-46-66-90 (0.52): upper limit.

Orthodontic examination: "The patient showed oligodontia on a genetic basis. The following 14 teeth were absent due to what radiological examination revealed to be agenesis (fig. 46): M3id-P2id-I1id-I1is-P2is-M3is-M3ss-M2ss-P2ss-I2sd-P2sd-M2sd-M3sd. There was marked hypoplasia of the teeth (fig. 44). Probably as a result of the dental reduction in the maxilla, there was maxillary retrognathia which reversed the sagittal relation of the incisors (figs 45). Caries and periodontopathies were accompanied by microdontia and dental deformities."

Dental histology: "Neither the ground sections nor the paraffin sections (figs. 47, 48) showed abnormal dental structures. There were no signs of temporary growth disturbances. The absence of the neonatal line indicated that calcification of teeth did not occur until after birth; a prenatal disturbance could therefore not be manifest in these teeth."

Radiological findings:
Skull: Orbits too far apart; ethmoid very broad; right orbit seemed slightly larger than left; small sella turcica; features of the jaws inconclusive.

Ophthalmological examination:
Moderate ptosis OD: Hertel 23-103-20, so that the palpebral fissure OD (31 mm) was slightly larger than that of OS (30 mm).
Motility: Concomitant exotropia OD 30°; limited adduction and mild hypotropia.
VOD: No perception.
VOS: 10/10, refraction: S-0.5 = C-2 × 15°.
Intraocular pressure: 48 mm Hg OD and 17-22 mm Hg OS (AT). *Right eye* (fig. 11):
No conjunctival abnormalities. Thin sclera, causing slight bluish discoloration mainly of the superior segment. Incipient staphyloma formation (probably resulting from operations).
Cornea: The horizontal diameter was 11 mm, and the vertical diameter was 10.5 mm. Marked hypoaesthesia of the entire corneal surface. Curvimetry disclosed highly irregular astigmatism. The irregularity of the corneal surface was caused by vesicular-bullous dystrophy of the corneal epithelium, with occasional spots which stained with fluorescein. The stroma was thickened (in part due to oedema) and showed flat white-grey opacities extending in all layers. The endothelium, when visible, was like wise dystrophic with a guttate appearance and pigment deposits; there were white spotty changes at the level of Descemet's membrane. The posterior aspect of the corneal periphery adhered by three-quarters of its circumference to the iridal stroma and the greyish tissue which filled the irodocorneal angle. The limbus was ill-defined.
Iris: It was found impossible to photograph the iris either in normal or in infra-red light, but slit-lamp examination facilitated examination and drawing (fig. 11). The ectopic pupil was localized between 4.30 and 6 o'clock, 2 mm from the limbus, and proved to be slit-shaped with its longitudinal axis (3 mm) parallel to the limbus and its transverse axis (1.5 mm) perpendicular to it. On the temporal side the normal pupillary border showed a small multiloculate ectropion uveae. The pupil was surrounded by an ill-defined, slightly elevated yellow rim in which the pupillary sphincter muscle was identified. The pupil did not respond to light.
Iridal frill and contraction folds were absent. Inferior to the pupil the iris could not be clearly observed due to the grey-white cloudy substance filling the iridocorneal angle. This tissue was most extensive, and the zone widest, in the nasal and temporal areas. The anterior aspect of the tissue was adherent to the posterior corneal surface, and in centrad and posterior direction it merged with scanty, grey-brown, hypoplastic iridal stroma. In the iridal area superior to the pupil the thin, taut, glistening stroma fanned out to the periphery and the iridocorneal angle. Between 10.30 and 12 and between 12.30 and 2.30 o'clock the stroma was virtually absent so that the pigment layer was exposed. It was exactly at these sites that transillumination disclosed moth-eaten diaphaneity. Between 1 and 2 o'clock there were two large total iridal defects, with in addition a few extremely peripheral, small total defects at 11, 1 and 2 o'clock.
Lens: Evaluation was impossible, but at least there was no distinct cataract.
Fundus: The fundus showed no red light.
In 1961 the lens was still clear and funduscopy possible; at that time there were constricted veins and arteries and the optic disc showed glaucomatous cupping.
Left eye (fig. 12):
The conjunctiva was normal, and the sclera appeared to be normal also.
Cornea: The limbus was ill-defined and the cornea was not round. Between 3 and 6 o'clock the sclera encroached far upon the cornea: marked form of persistent corneo-scleral membrane. The horizontal diameter was 10.5 mm; the vertical diameter was 10 mm.

Refraction: 38.8 × 15° and 41 × 110°.

The corneal surface was smooth and glossy apart from a few temporal and nasal epithelial vesicles. On the nasal side there were signs of incipient secondary band-shaped corneal degeneration. The fairly clear stroma seemed thickened and its central portion in particular showed endothelial dystrophy with numerous guttae. On the nasal posterior aspect of the corneal periphery there were ridge-like opacities, with adhesions between the cornea and the stroma-like tissue filling the iridocorneal angle.

Iris: The very large ectopic pupil of transverse oval shape (6 × 4.5 mm) occupied more than the lower half of the iris and did not respond to light (ecothiopate iodide). The pupillary circumference was angular, with linear and curvilinear segments (fig. 12). Between 5 and 7 o'clock the pupillary border was absent; the zone was otherwise very irregular, with occasional wart-like thickenings. The pupil was surrounded by a band of fibrous stromal tissue which parallelled the pupillary zone. In the superior part of the iris the thin, hypoplastic, taut iridal stroma fanned out to the periphery of the posterior corneal aspect and a mass of tissue which filled the iridocorneal angle. Between 2 and 3 o'clock the periphery of the iris contained a few total iridal defects which, like the peripheral dialysis at 3 o'clock, lit up red at transillumination. The chamber curve between 4 and 10 o'clock was likewise filled with floccular, grey-yellow tissue, in part adherent to the deep peripheral corneal opacity which was interpreted as posterior corneal embryotoxon (fig. 12). A few thin remnants of the pupillary membrane were seen in the superonasal portion of the pupillary aperture.

Lens: There were delicate diffuse superficial opacities in the outer layers of the lens, and also a finely diffuse group of star-shaped pigmentations on the anterior capsule. Normal localization.

Fundus: Normal vessels, macula and periphery. Cupped disc with a moderately sharp edge. Medullary flames extending down from the disc margin.

Visual field: Loss of sensitivity in the superior part.

Summary:
- Rieger's syndrome
- juvenile glaucoma ODS
- medullated nerve fibres OS
- oligodontia vera
- hypertelorism

HO-II-1. *Female aged 57. Born 1909, 15th July.*

The patient was a grey-haired former blonde who for the past few years had had epileptic absences (petit mal), in view of which she was under neurological supervision. The EEG showed changes. She was reported to be otherwise in good health. The parents were not consanguineous. There was a maternal family history of epilepsy (brothers, and one brother's daughter).

The skull, face, nose, ears, jaws, skin and extremities were normal. Dentition was reported to have been complete. Normal intelligence.

Cranial dimensions: Circumference 56 cm: normal. APD 182 mm; BPD 150 mm: normal.

Interocular distances: 31-44-63-85 (0.50): normal.

Bulbi, conjunctivae and sclerae showed no abnormalities. The motility was normal.

VOD: 10/10 refraction: S-1.5.

VOS: 10/10 refraction: S-1.5.

Intraocular pressure: Normal ODS.

Corneae: Smooth, glossy and clear. Limbus type B2A2A1A1; normal. Horizontal diameters 10.5 mm ODS.

Irides: Grey-blue, structural type C1-2. No hypoplasia. Central round, adequately responsive pupils.

Refracting media: Clear.
Fundi: Central, physiologically cupped disc ODS.

Summary:
– mild myopia ODS   – epilepsy (petit mal)
– prominent line of Schwalbe OD (type B)

HO-II-2. *Male aged 54. Born 1912, 29th February.*
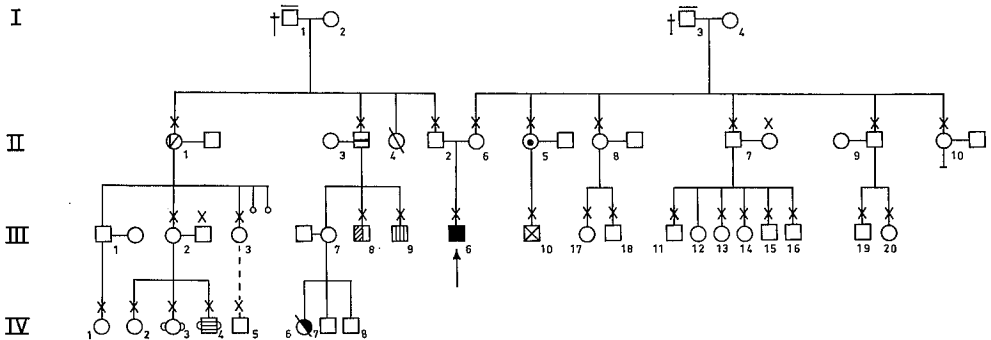
■ – primary dysgenesis mesodermalis of the iris with oligodontia vera
⊙ – mild ectopia pupillae ODS
▥ – connatal aplasia of the pectoral maior muscle
◐ – prominent line of Schwalbe OD
▤ – appendix auricularis and mild frontal asymmetry
⬡ – partial limbus coloboma
◖ – bilateral cheilopalatoschisis, still-born
▨ – pseudo-papillitis OD
▤ – glaucoma simplex?
◨ – urogenital deformities, epilepsy and imbecilitas mentis
▧ – epilepsy

Healthy man with medium blond hair. Skull, face, teeth, ears, nose, skin, nails and extremities showed no demonstrable abnormalities.
Cranial dimensions: Circumference 58 cm. APD 195 mm; BPD 158 mm (slight macrocephaly).
Interocular distances: 38-51-67-95 (0.57): all except PD too much.
Bulbi, conjuntivae and sclerae were normal, as was the motility.
VOD: 10/10 refraction: S-1.5 = C-0.75 × 75.°
VOS: 10/10 refraction: S-1.5 = C-0.5 × 105°.
Intraocular pressure: 18 mm Hg OD and 19 mm Hg OS (AT).
Corneae: Smooth, glossy and clear. Limbus type A20A1A1; normal. Horizontal diameters 11.5 mm ODS.
Refraction: OD 44 × 150° and 43.25 × 60°. OS 43 × 170° and 42.5 × 80°.
Irides: Grey blue, of structural type C1 ODS. The anterior stromal layer was compact,

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with an intact anterior limiting membrane and five contraction folds. Ten spots of brown pigmentation were seen scattered on this stroma. Slight peripheral marginal atrophy. The central, round pupils responded well to light and convergence and had irregular pupillary borders Clusters of pigment granules were seen next to these zones. No diaphaneity.

Refracting media: Clear.

Fundi: Normal OD; flat optic cup OS.

Gonioscopy: Open iridocorneal angles ODS. The slightly prominent anterior gonioscopic line of Schwalbe was slightly pigmented on the corneal and the trabecular side. Schlemm's canal and scleral spur of normal localization. The ciliary band was covered by fibrous tissue with a whitish gloss, which extended from the iridal root to the trabecular base. Hypoplasia of the iridal root. No adhesions between the line of Schwalbe and the iris.

Summary: – mild myopia and astigmatism ODS.

HO-II-3. *Male aged 53. Born 1913, 6th November.*
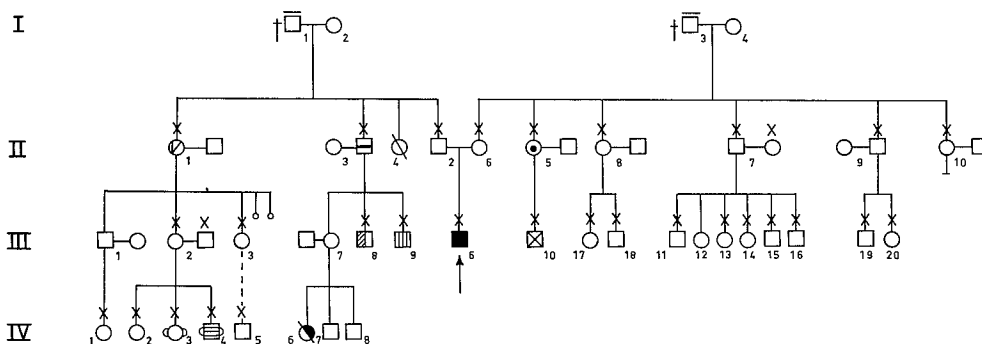
■ – primary dysgenesis mesodermalis of the iris with oligodontia vera

⊙ – mild ectopia pupillae ODS

▥ – connatal aplasia of the pectoral maior muscle

◑ – prominent line of Schwalbe OD

▤ – appendix auricularis and mild frontal asymmetry

⊡ – partial limbus coloboma

◭ – bilateral cheilopalatoschisis, still-born

▨ – pseudo-papillitis OD

▤ – glaucoma simplex?

◨ – urogenital deformities, epilepsy and imbecilitas mentis

▨ – epilepsy

Glaucoma simplex was suspected in 1965 (pressure 28-26 mm Hg). No therapy was instituted because subsequently the intraocular pressure remained between 18 and 23 mm Hg.

The patient was a healthy, somewhat stout man with medium blond hair. Skull, face, nose, ears, skin and extremities were normal, as were the nails. The patient had full dentures but dentition was reported to have been normal.

Cranial dimensions: Circumference 60.5 cm. APD 209 mm (166-196); BPD 162 mm (135-155): all dimensions decidedly above the upper limit of normal.
Interocular distances: 31-44-66-93 (0.47): normal.

Ophthalmological examination:
Bulbi, conjunctivae, sclerae and motility were normal.
VOD: 10/10 refraction: S-7.5.
VOS: 10/10 refraction: S-8.5.
Intraocular pressure: 18 mm Hg OD and 19 mm Hg Os.
Corneae: Clear, smooth and glossy, with normal sensitivity ODS. Limbus type A10A10; ill-defined. Horizontal diameters 11.5 mm OD and 11 mm OS.
Refraction: OD 44 × 10° and 43.5 × 100°. OS 44.25 × 70° and 43.5 × 160°.
Irides: Grey-blue, of structural type C1 ODS. Ill-defined corona and no contraction folds. The anterior mesodermal layer was thin, and the sphincter muscle of the iris was clearly visible. The pigment layer was not diaphanous. The central, round pupils responded well to light and convergence and had a slightly irregular pupillary border.
Refracting media: Clear.
Fundi: Slightly cupped disc ODS.
Goldman perimetry: Normal visual field ODS.
Gonioscopy: Open iridocorneal angles ODS. Finely pigmented anterior gonioscopic line, which was not prominent. No abnormalities of the other structures of the iridocorneal angle. Considerable hypoplasia of the iridal root with many concentric vessels.

Summary:
– marked myopia ODS   – dubious glaucoma simplex ODS.

HO-III-5. *Female aged 61. Born 1905, 14th October.*
A healthy middle-aged woman with grey hair (used to be medium blond). Her 64-year-old husband had myopia ODS (S-4) and disseminated black-pigmented scars of chorio-retinitis in the retinal periphery.
VODS: 10/10. Intraocular pressure 17 mm Hg (S).
Her father (HO-I-3) had good eyes until his death from pulmonary carcinoma at age 76. In January 1966, ophthalmological treatment for corneal herpes OD.
Skull, face, teeth and extremities were normal, as were the nose and ears.
Cranial dimensions: Circumference 55 cm: normal. APD 190 mm; BPD 144 mm: normal.
Interocular distances: 34-44-60-86 (0.58): high normal.
Conjunctivae, sclerae and palpebrae showed no abnormalities.
Motility: Intact.
Intraocular pressure: 17 mm Hg ODS (S).
Corneae: Of normal clarity; horizontal diameters 11 mm ODS. No posterior embryo-toxon or prominent line of Schwalbe. Normal sensitivity OS. Hypoaesthesia OD.
Irides: Blue, of normal structure (type C2-3) with regular iridal frill and without signs of hypoplasia ODS. Slight nasal ectopia of the pupil. The otherwise round pupils responded well to light and convergence.
Refracting media: Normal.
Fundi: Normal.
VOD: 10/10 refraction: S + 1 = C + 0.5 × 90°.
VOS: 10/10 refraction: S + 1 = C + 0.5 × 90°.

Summary:
– slight pupillary ectopia ODS   – telecanthus
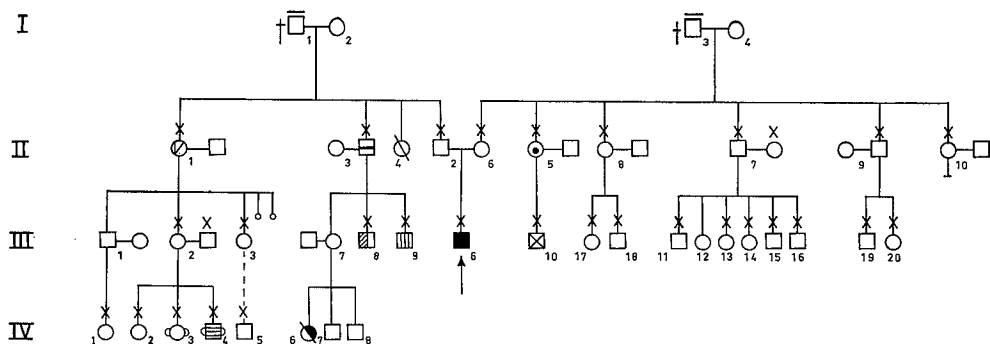
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III □ ○₁ □ ○₂ ₃ ○ □ ○₇ ▨₈ ▥₉ ■₆ ⊠₁₀ ₁₇ ○ ○₁₈ □ ₁₁ □ □ ○ □ □ ₁₂ ₁₃ ₁₄ ₁₅ ₁₆ □ ○ ₁₉ ₂₀

IV ○₁ ○₂ ○₃ ⊟₄ □₅ ₆ ◖₇ □ □₈

■ – primary dysgenesis mesodermalis of the iris with oligodontia vera
⊙ – mild ectopia pupillae ODS
▥ – connatal aplasia of the pectoral maior muscle
◐ – prominent line of Schwalbe OD
⊟ – appendix auricularis and mild frontal asymmetry
⊡ – partial limbus coloboma
◖ – bilateral cheilopalatoschisis, still-born
▨ – pseudo-papillitis OD
⊟ – glaucoma simplex?
⊠ – urogenital deformities, epilepsy and imbecilitas mentis
▧ – epilepsy

HO-III-8. *Male aged 26. Born 1940, 20th September.*
Normal birth after an uneventful pregnancy. Normal development. The subject was a healty man with blond hair. Skull, face, nose, ears, teeth, skin and extremities were normal.
Cranial dimensions: Circumference 58 cm: slightly too large. APD 193 mm (167-196); BPD 151 mm (136-155).
Interocular distances: 33-46-67-94 (0.50): high normal.
Palpebrae, bulbi, conjunctivae and sclerae were normal.
Motility: alternating concomitant exotropia 8°.
VOD: 10/10 refraction: S-1.5 = C-1.5 × 10°.
VOS: 10/10 refraction: S-1.75 = C-1.5 × 10°.
Intraocular pressure: 16 mm Hg OD and 15 mm Hg OS.
Corneae: Clear, smooth, glossy and of normal sensitivity. Horizontal diameters 11 mm ODS. Limbus type AOO1O; ill-defined.
Refraction: OD 43 × 10° and 45.5 × 100°. OS 44 × 170° and 45 × 80°.
Irides: Grey-green of structural type C2 ODS. Normal frill and contraction folds. Light brown-yellow pigmentation of the corona. The superficial stromal layer was relatively thin. The central, round pupils responded well to light and convergence. The pupillary borders showed normal development. No diaphaneity.
Refracting media: Clear.
Fundi: Ill-defined disc with thick edge: pseudopapillitis OD. Normal fundus OS. The patient had for years been aware of these facts.
Gonioscopy: Normal open iridocorneal angles with hypoplasia of the iridal root ODS.

Summary:
- myopia and astigmatism
- exotropia
- pseudopapillitis OD

HO-III-9. *Male aged 18. Born 1948, 15th March.*
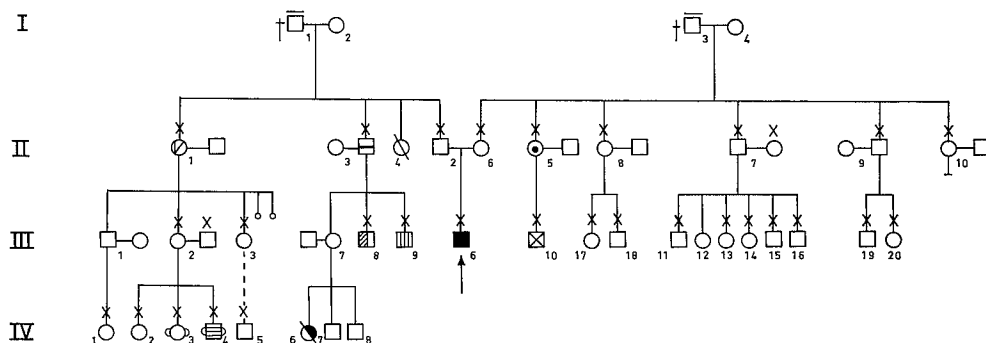
■ – primary dysgenesis mesodermalis of the iris with oligodontia vera
⊙ – mild ectopia pupillae ODS
� – connatal aplasia of the pectoral maior muscle
① – prominent line of Schwalbe OD
▤ – appendix auricularis and mild frontal asymmetry
⊡ – partial limbus coloboma
◖ – bilateral cheilopalatoschisis, still-born
▨ – pseudo-papillitis OD
▤ – glaucoma simplex?
⊠ – urogenital deformities, epilepsy and imbecilitas mentis
▨ – epilepsy

Normal birth after an uneventful pregnancy. The parents were not consanguineous. The right pectoralis muscle was absent at birth; no other congenital abnormalities. The patient developed normally to a healthy young man with medium blond hair. Skull, face, nose, ears, teeth, skin and extremities were normal. The eyebrows met in the midline. The left palpebral fissure was slightly more mongoloid than the right.
Cranial dimensions: Circumference 57 cm (51-57). APD 199 mm (194); BPD 148 mm (135-155).
Interocular distances: 31-45-53-91 (0.58): normal.
Bulbi, conjunctivae and sclerae were normal.
Motility: alternating exotropia 15°.
VOD: 11/10 refraction: S-4.75 = C-1.5 × 0°.
VOS: 11/10 refraction: S-4.25 = C-1.5 × 170°.
Intraocular pressure: 14 mm Hg OD and 15 mm Hg OS (AT).
Corneae: Limbus type A2A1A1A2. Horizontal diameters 11 mm ODS.
Refraction: OD 39.5 × 5° and 41 × 95°. OS 39.5 × 180° and 41.5 × 90°.

The corneae were clear, smooth and glossy, of normal sensitivity. Superior sickle-shaped scleralization ODS.

Irides: Blue, of structurale type C2 ODS. Towards the periphery the anterior mesodermal layer became gradually thinner, with the non-diaphanous pigment layer increasingly shimmering through. The central, round pupils responded well to light and convergence. The frill was regular and contraction folds were only vaguely visible.

Refracting media: Normal.

Fundi: Normal.

Gonioscopy: Wide iridocorneal angles ODS; broad trabecula and ciliary band; normal localization of scleral spur; invisible Schlemm's canal; line of Schwalbe normal; hypoplastic iridal root with many vessels and pigment layer exposed. No adhesions between the iris and the line of Schwalbe.

Summary:

- myopia and astigmatism ODS
- exotropia

- connatal aplasia of the right pectoralis major muscle
- telecanthus

HO-III-10. *Male aged 25. Born 1941, 2nd December.*
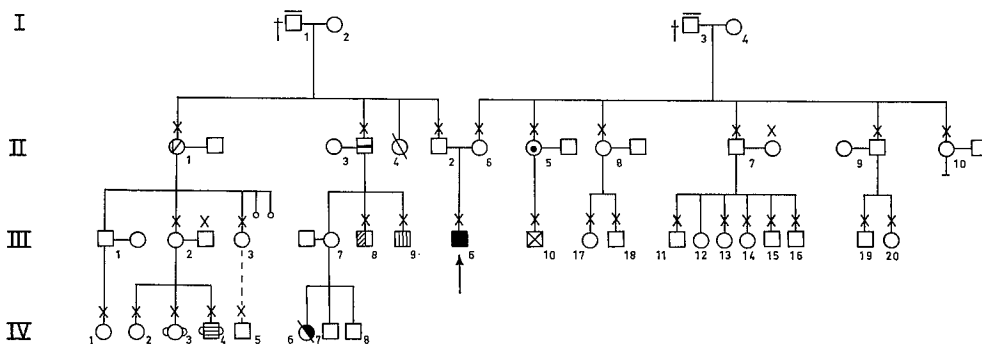
- ■ – primary dysgenesis mesodermalis of the iris with oligodontia vera
- ⊙ – mild ectopia pupillae ODS
- ▥ – connatal aplasia of the pectoral maior muscle
- ◑ – prominent line of Schwalbe OD
- ▤ – appendix auricularis and mild frontal asymmetry
- ⌑ – partial limbus coloboma
- ◥ – bilateral cheilopalatoschisis, still-born
- ▨ – pseudo-papillitis OD
- ⊟ – glaucoma simplex?
- ▨ – urogenital deformities, epilepsy and imbecilitas mentis
- ▨ – epilepsy

Normal birth at term, with a normal birth weight. No illness, medication or irradiation of the mother during pregnancy. The parents were not consanguineous. The child showed congenital anomalies of the external genitals (hypospadias) and the urogenital apparatus

(duplication of the ureters and bladder). The boy developed slowly, could hardly speak and was obviously either feeble-minded or an imbecile. He soon became subject to violent epileptic seizures with tongue-bite, thus losing many teeth which had been normally present. Reported to see well.

Cranial dimensions: Circumference 55 cm (51-57). APD 195, BPD 145 mm: normal.
Interocular distances: 28-36-62-82 (0.45): Normal.
Corneae: Clear, smooth and glossy. Horizontal diameters 12 mm ODS. Limbus type A2A2A2A2; normal.
Irides: Blue, of structural type C1. Central, round, adequately responsive pupils.
Refracting media: Clear.
Fundi: Normal. Refraction: about emmetropia ODS.

Summary:
- congenital urogenital anomalies
- epilepsey
- imbecility
- plesiocanthus

HO-IV-3. *Female aged 6. Born 1960, 12th September.*

■ – primary dysgenesis mesodermalis of the iris with oligodontia vera
⊙ – mild ectopia pupillae ODS
▥ – connatal aplasia of the pectoral maior muscle
◑ – prominent line of Schwalbe OD
▤ – appendix auricularis and mild frontal asymmetry
⊕ – partial limbus coloboma
◖ – bilateral cheilopalatoschisis, still-born
▨ – pseudo-papillitis OD
⊟ – glaucoma simplex?
◩ – urogenital deformities, epilepsy and imbecilitas mentis
◨ – epilepsy

Healthy girl with blond hair, whose development had been normal since a normal birth at term with an adequate birth weight. No illness, medication or irradiation of the mother during pregnancy. Vision was reported to be good.
Skull, face, nose, ears, teeth, skin, hair, nails and extremities were normal. Normal intelligence.

Bulbi, conjunctivae and sclerae showed no abnormalities.
Corneae: Smooth, glossy and clear. Limbus type A1A1OA1. Partial temporal limbus coloboma ODS. Horizontal diameters 11 mm ODS.
Irides: Blue, of structural type C1. Peripheral marginal atrophy of the iris with Wölflin nodules. Central, round, adequately responsive pupils.
Refracting media: Clear.
Fundi: Normal. Refraction about emmetropic ODS.

Summary: – partial limbus coloboma ODS.

HO-IV-4. *Male aged 2. Born 1964, 30th April.*
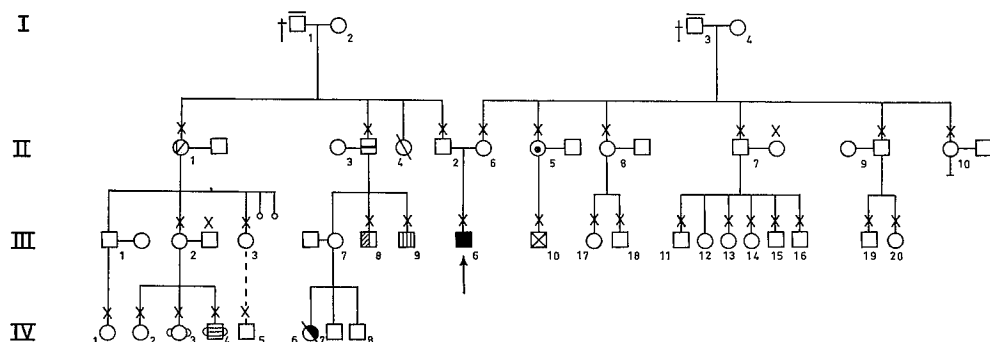
■ – primary dysgenesis mesodermalis of the iris with oligodontia vera
⊙ – mild ectopia pupillae ODS
▥ – connatal aplasia of the pectoral major muscle
◑ – prominent line of Schwalbe OD
▤ – appendix auricularis and mild frontal asymmetry
⟊ – partial limbus coloboma
◓ – bilateral cheilopalatoschisis, still-born
▨ – pseudo-papillitis OD
⊟ – glaucoma simplex?
◩ – urogenital deformities, epilepsy and imbecilitas mentis
▧ – epilepsy

A healthy boy with blond hair. Normal birth at term. Mother's pregnancy uneventful (as IV-3). At birth, the skin immediately anterior to the tragus of the left ear showed a vermiform excrescence. Such outgrowths were reported not to occur in the family. The family doctor partly removed it. Further development normal, but the boy was reported to walk with a slight limp.
Face, nose, hair, nails and extremities were normal. The forehead was slightly asymmetrical (had been much more pronounced at birth).
Cranial dimensions: Circumference 49 cm: normal. APD 174 mm (high normal); BPD 130 mm (normal).
Interocular distances: 28-32-47-70 (0.60): normal.

Bulbi, conjunctivae and sclerae showed no abnormalities.
The motility was intact (as in IV-3).
Corneae: Smooth, glossy and clear. Limbus type: no B. Suggestion of temporal limbus coloboma ODS. Horizontal diameters 10.5 mm ODS.
Irides: Blue-grey, of structural type C1. Mild peripheral marginal atrophy. Central, round pupils which responded well to light and convergence.
Refracting media: Clear.
Fundi: Normal.

Summary:
- partial limbus coloboma ODS   – slight asymmetry of the forehead
- appendix near left ear   – telecanthus

BS-III-6. *Male aged 11. Born 1955, 24th June.*
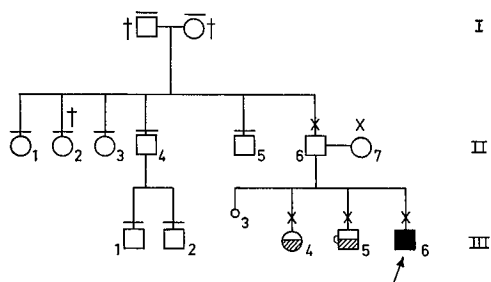
■ – primary dysgenesis mesodermalis of the iris with oligodontia vera
▨ – dysgenesis mesodermalis of the cornea (Peters)
◁ – partial limbus coloboma

Normal birth at term, with a birth weight of 3500 g. No medication or irradiation of the mother during the uneventful pregnancy. Normal physical and mental development. The parents noticed no ocular abnormalities. The school doctor referred the boy to the ophthalmologist for strabismus when he was 7 years old. The ophthalmologist found VOD 5/5 and VOS 3/60 with excentric fixation and amblyopia.
In 1963 the boy underwent an operation: recession of the rectus medialis and plication of the rectus lateralis muscle OS for concomitant esotropia. The result was good. The pupils proved to be excentric, and gonioscopy revealed abnormalities of the iridocorneal angles. The intraocular pressure ODS was increased after initially normal values. It was impossible to reduce the intraocular pressure to values below 30-35 mm Hg by conservative means. The visual fields showed no abnormalities. The condition was diagnosed as incomplete Rieger's syndrome with juvenile glaucoma. In March 1966 the patient was hospitalized for observation.
The patient was a healthy boy with blond hair. General internal examination disclosed nothing abnormal. Skull and face were symmetrical, with ears and nose of normal shape (fig. 32). The extremities and the spinal column were normal.
Cranial dimensions: Circumference 52.5 cm (50-56). APD 177 mm (165-192); BPD 149 mm (134-154).
Teeth: All primordia were normal and the germs of the third molars were also present. No odontogenous abnormalities.

Radiological findings:
Skull: No developmental anomalies. The floor of the sella was somewhat square instead of the normal semicircular form, but the dimensions were normal.
Hands and feet: Development normal for the calender age, without anomalies.

Ophthalmological examination:
The bulbi were of normal size and the palpebrae showed no abnormalities.
Interocular distances: 33-41-56-83 (0.55): the distance between the corneal centres was 60 mm, at an interpupillary distance of 56 mm.
Motility: Still slight esotropia OS 5° with excentric fixation and amblyopia.
VOD: 1/1 (S + 0.5).
VOS: 1/60 (S + 0.5).
Intraocular pressure: 26-30 mm Hg OD and 25-35 mm Hg OS (AT).
Conjunctivae and sclerae showed no abnormalities.
Corneae: Clear except for a sharply defined white opaque line in the deepest layers of the corneal periphery, where it protruded into the anterior chamber as a ridge localized 0.5-1 mm from the limbus. The central boundary of the opacity was sharp but its peripheral boundary was ill-defined. The deepest corneal layer peripheral to the opacity was likewise opaque, but in a lesser degree. The opaque line was seen between 2 and 10 o'clock OD and between 1 and 9 o'clock OS. Stromal adhesions between the line and the peripheral iridal stroma were visible at several sites.
The superficial limbus was ill-defined ODS. The horizontal diameters were 12.25 mm ODS and the vertical diameters were 12.75 mm ODS.
Refraction: OD 42 × 150° and 41.5 × 60°. OS 41 × 60° and 41.25 × 150°.
The corneal sensitivity was intact (Chochet and Bonnet).
Irides: Blue-grey colour; virtually the same symmetrical features ODS. Pronounced stromal hypoplasia; the anterior mesodermal layer was absent, as was the iridal frill, and the pigment layer shimmered through the thin, loose deep stroma at several sites. The pupillary sphincter muscle was quite conspicuous (fig. 17). The pigment layer was not diaphanous.
The pupils showed a nasal ectopia of about 1.5 mm, and a slight inferonasal pear shape. Responses to light, convergence and mydriatics were normal. The pupillary border was well-developed ODS.
Refracting media: Normal.
Fundi: Blond without other abnormalities, specifically no cupping of the discs.
Goldmann perimetry: Slight enlargement of the blind spot ODS; diminished central sensitivity OS.
Tonography: Pathological curve OS.
Gonioscopy (figs. 22, 23, 24): Open iridocorneal angles ODS. The stroma of the iridal root was very hypoplastic so that the peripheral iridal vessels and the pigment layer were visible. There were no vascular anomalies.
OD: There was a very prominent anterior gonioscopic line of Schwalbe throughout the circumference. Between 2 and 7 o'clock this line showed centrad displacement and irregular, ridge-like thickening as well as a structure reminiscent of frosted glass. The corneoscleral trabecula was broadened and the ciliary band was covered by thin, glass-like fibrous tissue which obscured the scleral spur. At 4 o'clock there was a broad stromal adhesion between the stroma of the iridal periphery and the pars ciliaris of the iris on the one hand, and the corneal periphery at the level of the above described thickened white line on the other hand. A similar but narrower adhesion was seen at 5 o'clock. Traction exerted by this adhesion on the iridal stroma caused some local elevation of the stroma and slight pear-shaped distortion of the pupil in this direction.
OS: Between 1 and 9 o'clock there was a similar prominent white line with irregular

broadened and thickened sites and centrad displacement. The broadened trabecula otherwise had a normal appearance. In this eye too a thin fibrous tissue covered the ciliary band and obscured the scleral spur. At regular intervals – roughly every hour on the hour – there were very narrow adhesions between the iridal root and the prominent white line. Between 6 and 8 o'clock these adhesions consisted of broader, conical and trapezoidal stromal strands which exerted traction on the local iridal stroma and the pupil. At 2 o'clock there was another thick, funnel-shaped adhesion made up of stroma and pigment layer.

Fundi: Normal, without glaucomatous cupping of the disc.

Lens and vireous: Normal.

Visual fields: Enlarged blind spot OD and diminished central sensitivity OS (Goldmann).

Tonography: Highly pathological (c = 0.02) OD; unreliable OS.

Therapy: In April 1966, Worst goniotomy of the nasal upper quadrant OS, during which cleavage occurred at the level of the trabecular system (fig. 25). The postoperative course was characterized by irritation which was suppressed by local application of corticosteroids. The intraocular pressure fell to 8-12 mm Hg (AT). At home after discharge, the patient developed acute glaucoma with haemorrhage in the anterior chamber (traumatic (?): jostling at school). The pressure returned to normal but in August was found to have increased again to about 28 mm Hg. Pilocarpine application was then resumed but had no perceptible effect on the intracular pressure.

Summary:
– Rieger's syndrome
– juvenile glaucoma ODS
– esotropia and amblyopia OS

BS-II-6. *Male aged 57. Born 1908, 8th October.*
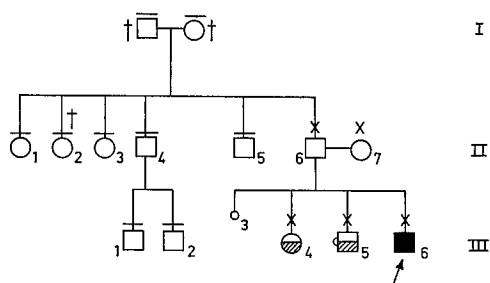
■ – primary dysgenesis mesodermalis of the iris with oligodontia vera

▨ – dysgenesis mesodermalis of the cornea (Peters)

◁ – partial limbus coloboma

Normal, healthy man with dark blond hair. Skull, face and extremities were normal. Ophthalmological findings: VODS 10/10; refraction ODS S + 1. With S + 3 OSD the patient could read the small optotypes.

Intraocular pressure: 16 mm Hg ODS.

Palpebrae, conjunctivae and sclerae were normal.

Corneae: Clear. Horizontal diameters 11.5 mm ODS. No prominent line of Schwalbe.

Irides: Blue-green, with occasional brown pigment spots. The centric pupils responded well. Structure C1.
Refracting media: Clear.
Fundi: In mydriasis: normal. No abnormalities of the discs.
Gonioscopy: Normal open iridocorneal angles ODS.

Summary:
– mild hypermetropia
– presbyopia

BS-II-7. *Female aged 51. Born 1914, 18th February.*
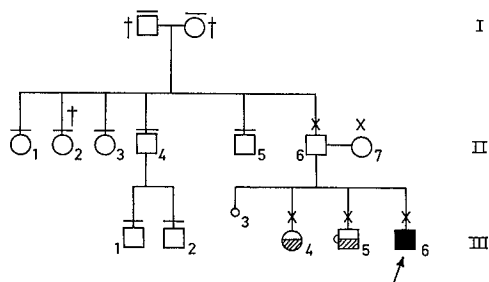
■ – primary dysgenesis mesodermalis of the iris
▨ – mild hypoplasia stromalis iridis
◁ – partial limbus coloboma

Normal, healthy woman with dark blond hair. Skull, face, skin, teeth and extremities were normal. Ophthalmological findings: VODS 10/10; refraction OD S + 0.5 = C + 1 × 90°; OS C + 1 × 90° (reading addition +2).
Intraocular pressure: 8 mm Hg OD and 12 mm Hg OS: low normal.
Motility: Normal.
Palpebrae, conjunctivae and sclerae were normal.
Irides: Grey-blue, of normal structural type C1.
Refracting media: Normal.
Fundi: Normal.
Gonioscopy: Normal open iridocorneal angles ODS.
Family history: Good eyes; grandchild of elder brother had strabismus.

Summary:
– astigmatism
– presbyopia

BS-III-4. *Female aged 15. Born 1951, 6th February.*
Normal birth at term, with an average birth weight. No illness, medication or irradiation of the mother during pregnancy. Normal development. During the past few years, constant eczema of the arms, thighs and face, which disappeared during holidays. Otherwise always in good health.

■ – primary dysgenesis mesodermalis of the iris
▨ – mild hypoplasia stromalis iridis
◁ – partial limbus coloboma
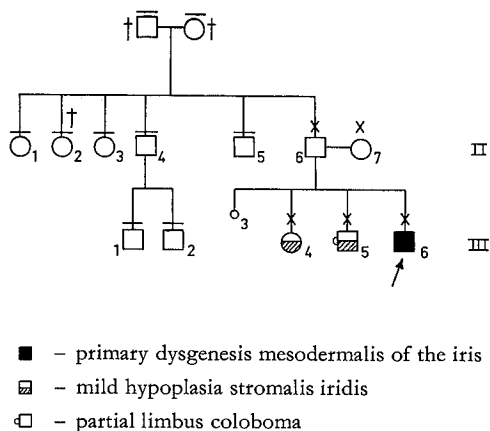
A normally developed, healthy girl with medium blond hair. Skull, face, nose, ears, hair, nails and extremities were normal.

Cranial dimensions: Circumference 53 cm (50.5-56.5). APD 176 mm (166-194); BPD 149 (135-156).

Interocular distances: 32-39-60-82 (0.53): normal.

Bulbi, conjunctivae, sclerae and motility were normal.

VOD: 10/10 refraction: S-4 = C-1 × 90°.

VOS:10/10 refraction: S-4 = C-0.75 × 90°.

Intraocular pressure: 6-7.5 mm Hg ODS (S).

Corneae: Normal, clear, smooth and glossy. Limbus type A2A1A1A2 of normal development. Horizontal diameters 11 mm ODS.

Refraction: OD 43.5 × 10° and 43 × 100°. OS 43.25 × 60° and 44 × 150°.

Irides: Grey-blue, of structural type L3 with Fuchs fissure. In the peripheral remnant of the superficial stromal layer a few contraction folds were visible. The deep stromal layer was very thin, and the non-diaphanous pigment layer was exposed at many sites. A few delicate remnants of the pupillary membrane OD. The central, round pupils responded well to light.

Refracting media: Normal.

Fundi: Normal.

Gonioscopy: Normal open iridocorneal angles without prominent line of Schwalbe ODS. Marked hypoplasia of the iridal root, with visible pigment layer and iridal vessels.

Summary:
– mild hypoplasia of iridal stroma   – remnants of pupillary membrane OD
– Fuchs fissure ODS   – myopia and astigmatism

BS-III-5. *Male aged 14. Born 1962, 24th April.*

Normal birth at term, with average birth weight, after an uneventful pregnancy. The parents were not consanguineous. Development was normal, and no severe illness occurred.

The patient was a normally developed, healthy boy with medium blond hair. Skull, face, nose, ears, skin, hair, nails and extremities normal. Good intelligence.

Cranial dimensions: Circumference 54.5 cm (50.5-56.5). APD 191 mm (166-194); BPD 155 mm (134-155.5).
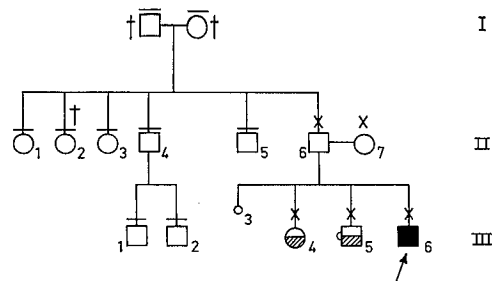
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■ – primary dysgenesis mesodermalis of the iris
▨ – mild hypoplasia stromalis iridis
◁ – partial limbus coloboma

Interocular distances: 36-43-66-82 (0.55): normal.
VOD: 10/10 refraction: emmetropia.
VOS: 10/10 refraction: emmetropia.
Bulbi, conjunctivae, sclerae and motility were normal. Intraocular pressure: 6-7.5 mm Hg (S).
*Corneae:* Normal, clear, smooth and glossy; normal endothelium. Limbus type A3A2A2 A3, ill-defined ODS; suggestion of temporal limbus coloboma OD.
Refraction: OD 44.5 × 0° and 45.25 × 90°. OS 45.5 × 0° and 45.75 × 90°.
Irides: Grey-blue and of the same structure ODS. Lacunar type, with very low-density structure of the anterior mesodermal layer, with the pigment layer and sphincter muscle obviously shimmering through. Iridal frill present OD, absent between 5 and 7 o'clock. Pigment layer not diaphanous. The central, round pupils responded well to light and convergence.
Refracting media: Normal.
Fundi: Normal.
Gonioscopy: Open iridocorneal angles ODS with very atrophic iridal root, with exposed pigmented layer and vessels. There were some iridal trabeculae but no adhesions between the iris and the normal line of Schwalbe. Schlemm's canal was normally localized. The trabecula showed no abnormalities.

Summary:
– mild hypoplasia of iridal stroma ODS
– mild partial temporal limbus coloboma OD

PM-IV-2. *Male aged 6.5. Born 1960, 3rd April.*
Normal birth, under clinical supervision in view of the mother's contracted pelvis. Birth weight 2530 g. There had been no illness, medication or irradiation of the mother during pregnancy. The parents were not consanguineous. The family history was believed to be free from ocular or pupillary abnormalities or other congenital anomalies. The greatgrandmother of the proband (I-1) was alleged to have squinted, always keeping the eye closed.
General growth and development were slightly retarded, and the patient was found to have a congenital heart defect. The cardiologist diagnosed moderately severe pulmonary stenosis and incomplete bundle-branch block.

- ■ – primary dysgenesis mesodermalis of the iris
- ▣ – m. Legg-Calvé-Perthes
- ▥ – prominent line of Schwalbe ODS
- ▨ – mild hypoplasia stromalis iridis OS
- ▩ – anomalies of the chamber angle ODS
- ⊙ – strabismus
- ℝ – remnants of the pupillary membrane
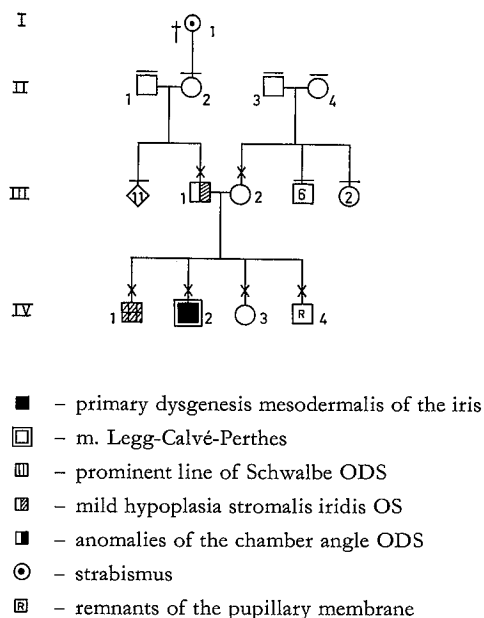
After a few weeks the right pupil was found to be excentric, and ophthalmological supervision started.

In 1966 the patient was found to suffer from Perthes' disease.

Examination 1965:
The patient was a small, slight, asthenic boy with blond hair. Skull, face, teeth and ears were normal (fig. 33). Both ears were somewhat prominent, especially the right. Hands, feet, skin, hair and nails were normal, as was perspiration. Both height and weight were considerably subnormal for his age. The intelligence was well-developed.

Radiological findings:
Skull: No abnormalities.
Hands and feet: Consistent with age 4 (the patient was 7 years old at the time). Otherwise, the changes usually seen in Perthes' disease.
Orthodontic examination: Deciduous teeth showed normal development but, without radiological examination, nothing conclusive could be said about the primordia of the permanent teeth. Oligodontia was therefore not ruled out.
Cranial dimensions: Circumference 47. 5 cm (48.5-54.5) APD 120 mm (130-152); BPD 152 (156-186).
Interocular distances: 25 (25-34)-37 (31-42)-48 (47-61)-68 (72-85) (0.53).

Ophthalmological examination:
The bulbi were of normal size. Palpebrae, cilia and eyebrows were normal.
Motility: No abnormalities; orthophoria.
VOD: 5/5 refraction: emmetropia (skiascopy).
VOS: 5/7 refraction: emmetropia
Intraocular pressure: 15 mm Hg OD and 17 mm Hg OS: normal.
Conjunctivae, sclerae, lenses and vitreous bodies showed no abnormalities.

Right eye (fig. 6):

Cornea: Smooth and glossy, without central opacities. The limbus zone was sharply defined. Horizontal diameter 11 mm and vertical diameter 10 mm. Between 7 and 12 o'clock the posterior aspect of the corneal periphery showed a thick, white, ridge-like, irregular opacity of the deepest corneal layer at varying distance from the limbus, and protruding into the anterior chamber. There were many delicate stromal adhesions between this ridge and the peripheral iridal stroma. A slight opacity of the deep corneal layers was visible between the ridge-like opacity and the limbus. The endothelium showed the normal mosaic pattern.

Iris: Green-grey-blue, with hypoplastic stroma particularly in the pars ciliaris of the iris. The anterior mesodermal layer and iridal frill were absent, and at several sites the pigment layer shimmered through between the thin fibres of the deep mesodermal iridal layer. The pigment layer was not diaphanous. The peripupillary part, which encompassed the pupillary sphincter muscle, was thicker than the very hypoplastic peripheral part. The central, round pupil responded well to light and convergence and had a slightly irregular pupillary border.

Gonioscopy: Open iridocorneal angles. Very prominent, centradly displaced line of Schwalbe which was very irregular in thickness and height. Fairly regularly distributed over the entire circumference, there were adhesions between this line and the hypoplastic stroma of the iridal root and iridal periphery. The adhesions resembled the iridal stroma in colour and appearance. The visible parts of the chamber angles showed no abnormalities.

Fundus: Blond throughout, with a very poorly vascularized choroid. Diffusely spread pigmentation, with peripheral accentuation and accumulation. Heterotopic superior conus the size of two-thirds of the optic disc diameter.

Left eye (figs 18 and plate III):

Cornea: Smooth and glossy, without central opacities. The limbus zone was not quite sharply defined. Horizontal diameter 10.5 mm and vertical diameter 10 mm. Between 1 and 6, and between 10 and 12 o'clock, the posterior aspect of the corneal periphery showed an opaque strip, the central boundary of which consisted of a white, thick, ridge-like opacity of the deepest layers; this ridge protruded into the anterior chamber and at many sites, but especially between 2 and 4 o'clock, stroma-like adhesions linked it to the iridal stroma. The endothelium was normal.

Iris: Green-grey-blue, with hypoplastic stroma as in OD. There was no iridal frill. The pupillary sphincter muscle was visible, but with difficulty, round the pupil which responded well to light and convergence. The stroma of the iridal periphery and the temporal peripupillary zone showed numerous fibres of a stromal type linking it to the corneal opacity. No diaphaneity. The transversely oval pupil was ectopic (3 o'clock) with the long axis (4 mm) horizontal and the short axis (about 3 mm) vertical. The pupil seemed to be distorted towards the temporal corneal opacity as a result of traction exerted by the adhesions. The pupillary border was irregular.

Gonioscopy: Similar features as OD, but with marked spread and density of corneo-iridal adhesions, especially in the temporal segment, where the adhesions elevated the iridal stroma towards the very prominent, thick line Schwalbe. Other findings as OD.

Fundus: Very blond, with poorly vascularized choroid as OD. The superior conus was half as large as the disc diameter.

Summary:

- Rieger's syndrome
- choroidal hypoplasia ODS
- heterotopic conus ODS

- pulmonary stenosis
- Perthes' disease
- general physical retardation

157

PM-III-1. *Male aged 43. Born 1923, 16th September.*
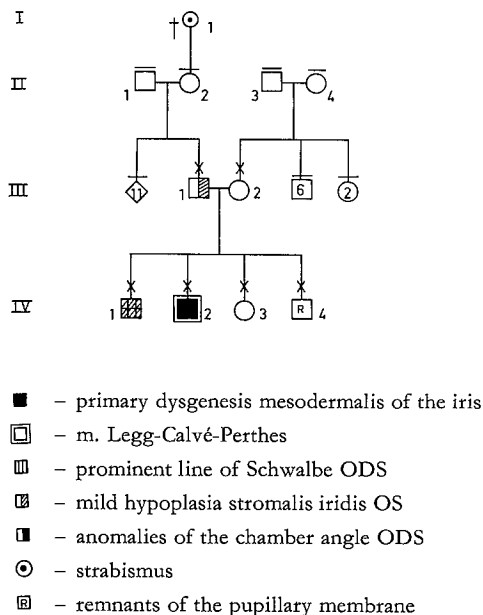
I

II

III

IV

■ – primary dysgenesis mesodermalis of the iris
▣ – m. Legg-Calvé-Perthes
▥ – prominent line of Schwalbe ODS
▨ – mild hypoplasia stromalis iridis OS
◩ – anomalies of the chamber angle ODS
◉ – strabismus
▣ – remnants of the pupillary membrane

Healthy man with medium blond hair. Skull, face, nose, ears, skin, hair, nails and extremities were normal. No consanguineousness between the parents, nor between the patient and his wife.

Cranial dimensions: Circumference 58 cm. normal. APD 196 mm; BPD 156 mm: normal.
Interocular distances: 31-45-63-85 (0.50): normal.
VODS: 10/10 + refraction: emmetropia.
Intraocular pressure: 16 mm Hg ODS (AT).
Bulbi, conjunctivae, sclerae motility were normal.
Corneae: Smooth, glossy and clear. No prominent line of Schwalbe. Limbus type $A_1A_1A_1A_1$. Horizontal diameters 11 mm ODS.
Irides: Brown, of structural type C_1. The very narrow iridal frill showed a more intensive, grey-brown pigmentation than the remainder of the iridal stroma. No visible contraction folds. Transillumination showed that the pigment layer was not diaphanous. The central, round pupils responded well to light and convergence and had a very thin pigment border.
Refracting media: Clear.   – *Fundi:* Normal.
Gonioscopy (fig. 49): Open iridocorneal angles ODS. The anterior gonioscopic line of Schwalbe was not prominent, and was accentuated only by some pigmentation. Lumps of pigment were seen scattered on the trabecula, particularly the inferior side. The scleral spur was invisible and the localization of Schlemm's canal uncertain. The ciliary band had a dark brown/black colour and was therefore sharply outlined in the iridocorneal angle. At several sites this band was covered by the light brown stroma of the iridal root. This stroma inserted at the level of the scleral spur. Between 5 and 7 o'clock, both angles contained some filiform adhesions with the features of iridal stroma, between the iridal periphery and the midportion and upper part of the corneoscleral trabecula. Lumps of pigment were seen between the sites of adhesion (fig. 49).

Summary: – mild abnormalities of the iridocorneal angle ODS.

PM-III-2. *Female aged 41. Born 1925, 19th September.*

- ■ – primary dysgenesis mesodermalis of the iris
- ▣ – m. Legg-Calvé-Perthes
- ▥ – prominent line of Schwalbe ODS
- ▨ – mild hypoplasia stromalis iridis OS
- ▮ – anomalies of the chamber angle ODS
- ⊙ – strabismus
- ▣ – remnants of the pupillary membrane
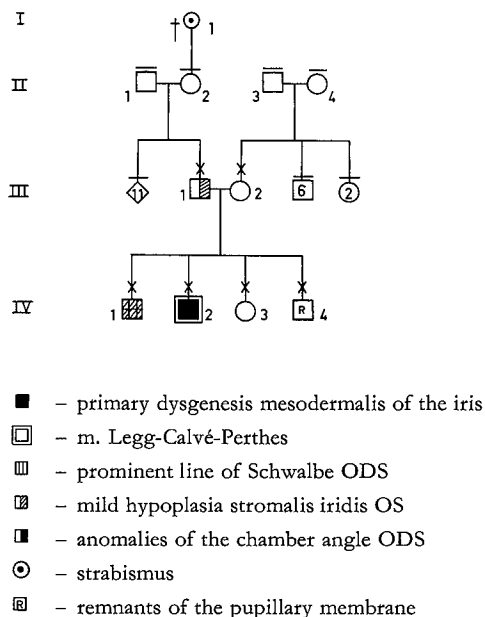
A small, healthy woman with blond hair. Skull, face, nose, ears, skin, hair, nails and extremities were normal. Reported to have had a normal and full dentition, but using dentures in the past few years. Not consanguineous with her husband .

Cranial dimensions: Circumference 55.5 cm: normal. APD 185 mm; BPD 146 mm: normal.
Interocular distances: 30-41-55-76 (0.55): normal.
VOD: 11/10 refraction: c-0.5 × 0°.
VOS: 11/10 refraction: emmetropic.
Intraocular pressure: 16 mm Hg OD and 15 mm Hg OS.
Bulbi, conjunctivae, sclerea and motility were normal.
Corneae: Smooth, glossy and clear. Limbus type A10A1A1, sharply defined. Horizontal diameters 11 mm ODS.
Refraction: OD 45 × 0° and 46 × 90°. 44.25 × 15° and 45 × 105°.
Irides: Grey-blue, of structural type C1 ODS. Anterior limiting membrane fully developed. A few contraction folds and a normal, regular iridal frill. Pigment layer not diaphanous. The central, round pupils responded well to light and convergence and had normal borders.
Refracting media: Normal.
Fundi: Blond, without abnormalities.
Gonioscopy: Normal open iridocorneal angles ODS, with a delicately pigmented non-prominent anterior gonioscopic line. The iridal root was slightly hypoplastic, with occasional visibility of an iridal root vessel.

Summary: – normal eyes.

PM-IV-4. *Male aged 1. Born 1965, 10th August.*

■ – primary dysgenesis mesodermalis of the iris
▣ – m. Legg-Calvé-Perthes
▥ – prominent line of Schwalbe ODS
▨ – mild hypoplasia stromalis iridis OS
▮ – anomalies of the chamber angle ODS
⊙ – strabismus
▣ – remnants of the pupillary membrane
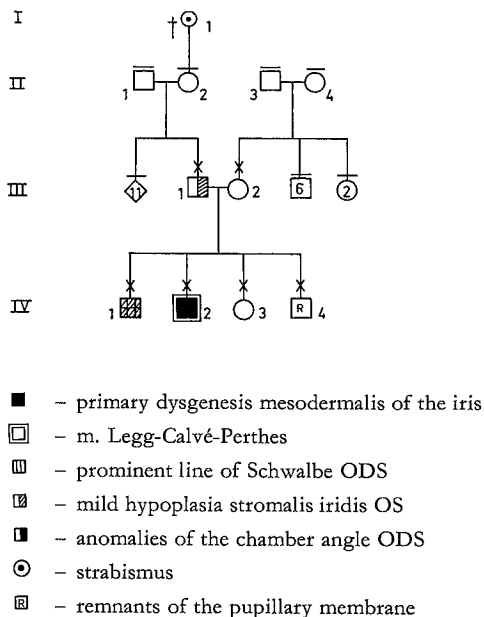
Healthy, well-developed baby with blond hair.
Cranial dimensions: Circumference 49 cm. APD 172 mm; BPD 130 mm: high normal.
Interpupillary distance: 45 mm.
Bulbi, conjunctivae, sclerae and motoricity were normal.
Corneae: Smooth, glossy and clear. Limbus normally defined; no line of Schwalbe. Horizontal diameters about 11 mm.
Irides: Blue-grey, of structural type C1 ODS. A few flimsy remnants of the pupillary membrane OD. Central, round pupils responding well to light.
Refracting media: Normal so far as could be established.
Fundi: Normal so far as could be established.

Summary:
– remnants of the pupillary membrane OD.

PM-IV-1. *Male aged 8. Born 1958, 28th December.*
Healthy, normally developed boy with dark blond hair. The mother's pregnancy had been uneventful. Skull, face, nose, ears, teeth, hair, nails and extremities were normal.
Cranial dimensions: Circumference 52 cm: normal. APD 185 mm; BPD 137 mm: normal.
Interocular distances: 29-39-54-73 (0.53): normal.
Bulbi, conjunctivae, sclerae and motility were normal.
VODS: 10/10 refractions: emmetropic.
Intraocular pressure: 14 mm Hg OD and 15 mm Hg OS (AT).
Corneae: Smooth, glossy and clear. Horizontal diameters 11.5 mm ODS. Prominent line of Schwalbe between 3 and 5 and between 9 and 11 o'clock OD, and between 8.30 and 9.30 and between 1.30 and 5 OS.

Irides: Deep-blue, of structural type C1 ODS. The peripupillary part of the iridal stroma was normal but the ciliary part was hypoplastic, with almost complete absence of the anterior mesodermal layer. The deep layer was very thin and the nondiaphanous pigment layer shimmered through vaguely. No contraction folds. The central, round pupils responded will to light and convergence and had normal borders.
Refracting media: Normal.
Fundi: Normal.
Gonioscopy: Not yet feasible.

Summary:
– prominent line of Schwalbe ODS
– mild hypoplasia of iridal stroma ODS

PM-IV-3. *Female aged 3. Born 1962, 1st June.*

■ – primary dysgenesis mesodermalis of the iris
▣ – m. Legg-Calvé-Perthes
▥ – prominent line of Schwalbe ODS
▨ – mild hypoplasia stromalis iridis OS
◨ – anomalies of the chamber angle ODS
⊙ – strabismus
Ⓡ – remnants of the pupillary membrane
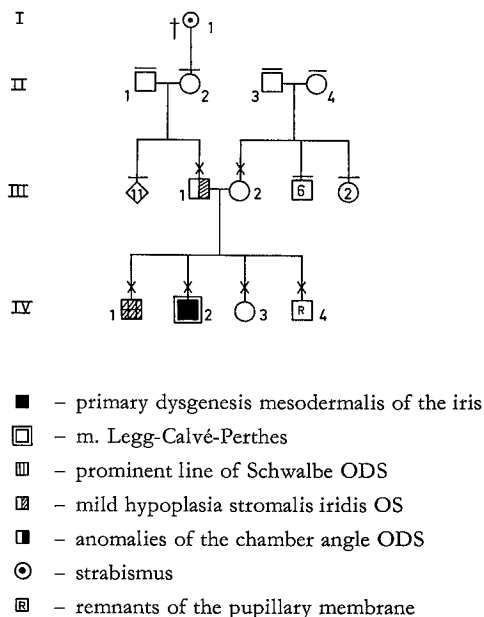
Healthy, normally developed girl with blond hair. Examination was difficult. Normal blue irides of structural type C1. Corneae normal so far as could be established; limbus normal. No gross fundal changes. The central, round pupils responded well to light. Vision was reported to be good.

Summary: – normal eyes.

HL-III-5. *Male aged 9, Born 1956, 6th October.*
Normal birth at term. No illness, medication or irradiation of the mother during pregnancy. Photophobia was noticed at birth and has since remained, though in a lesser degree. Like his older brother (familiar with ocular albinism) and two cousins (HL-III-6

☐ – ocular albinism

⊙ – carrier ocular albinism

■ – primary dysgenesis mesodermalis of the iris
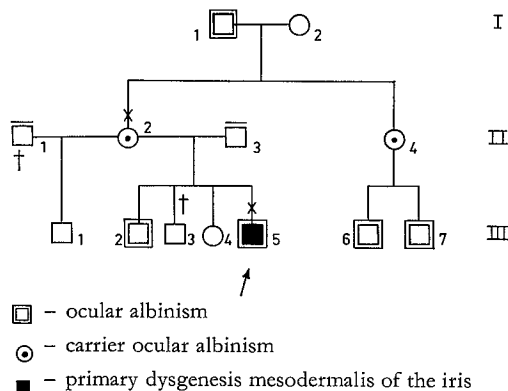
and 7), the boy suffered from poor vision and nystagmus. The maternal grandfather (HL-I-1) was reported to have shown the same abnormality. In 1962 operation for exotropia.

Examination in 1965:
The patient was a healthy boy of normal build with dark blond hair which had been lighter. Face (fig. 34), mouth, ears and nose were normal. The mixed dentition was regular. No radiological examination was made.

Hands, feet, limbs and nails showed no abnormalities. The hair was normal; the skin was normal and showed no pallor. Patient was reported to tan normally when exposed to the sun, and to perspire normally. The primary school performance was moderate but improved considerably upon transfer to a school for the visually handicapped; this indicates a normal intelligence.

Cranial dimensions: Circumference 53.5 cm (50-56).
Interocular distances: 30-39-56-80 (0.52): normal.

Ophthalmological findings:
The bulbi were of normal size. The palpebrae (rima 25 mm ODS) were normal, as were the cilia and eyebrows. There was moderate photophobia.
Motility: alternating concomitant exotropia (secondary); coarse horizontal nystagmus. Conjunctivae, sclerae, lenses and vitreous bodies were normal.
Intraocular pressure: 20 mm Hg OD and 10 mm Hg OS.
VOD: 5/30 refraction (skiascopy): c + 1.5 × 90°.
VOS: 5/30 refraction (skiascopy): c + 1.5 × 90°.
VODS with correction: 1/10 (reading: D = 0.8-0.6).
Corneae: Smooth, glossy, regular surface ODS. Normal central clarity with a peripheral opaque line on the posterior aspect of the cornea (fig. 10), of an identical type ODS. The opacity was white and consisted of a sharply defined thick ridge protruding into the anterior chamber; there were numerous fibrous adhesions resembling iridal stroma between the line and the iridal stroma of the periphery and the peripupillary region. The opacity OD could be detected with the slit lamp between 12 and 6 o'clock, and OS between 12 and 6 o'clock as well as between 7 and 11 o'clock. Between the white line and the ill-defined limbus the deepest corneal layers showed a semi-transparent opacity. The horizontal diameters were 12.25 mm ODS; the vertical diameters were 11 mm ODS. The anterior chamber was of normal depth ODS.
Irides: Grey-blue without stromal pigmentation, structural type C1 ODS. The anterior

mesodermal layer was of very low density and hypoplastic; the iridal frill was present. The deep mesodermal layer was thin, exposing the pigment layer at several sites. There were numerous delicate adhesions of iridal stroma between the peripupillary and the ciliary parts of the iris on the one hand, and the above described corneal line on the other. The sphincter muscle was clearly visible ODS.

The pupils showed slight nasal ectopia; they were round and responded well to light and convergence but lacked a pigmented border. There was mild iridodonesis. Marked general iridal diaphaneity at transillumination ODS; the peripheral shadow of the lens equator was consequently clearly visible against the red translucent iridal periphery.

Gonioscopy: Identical features ODS. Wide iridocorneal angles with a very prominent, centradly displaced line of Schwalbe; there were many adhesions of stroma-coloured fibres and tissue fasciculi between this line and the hypoplastic stroma of the peripupillary and ciliary iridal parts. Relatively many peripheral circular vessels of the iridal root were visible. The other angle structures – so far as visible – were normal.

Fundus: Identical features ODS. A very light, "albinotic" fundus with a posterior pole (20°) of a light red colour. Macular and foveolar reflexes were absent, and no areas of macular yellow were visible in red-free light. The disc OD showed a small temporal pigment conus and the disc OS had a very delicately pigmented bounding edge.

ERG and EOG: No abnormalities.

Summary:
– Rieger's syndrome   – exotropia
– ocular albinism

RK-I-2. *Female aged 37, Born 1929, 29th March.*
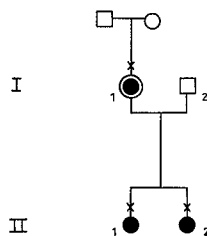
● – primary dysgenesis mesodermalis of the iris
◎ – mild hypoplasia stromalis iridis
⬡ – partial limbus coloboma

The patient (fig. 37) was born with corneal opacities ODS. There were multiple anterior synechiae ODS, associated with hypoplasia of the iridal stroma, miosis; cat's eye pupil OD. Secondary (juvenile?) glaucoma. The patient was blind ODS when examined. The anterior chamber was shallow ODS; central corneal leukoma OS. Reported to have dental abnormalities.

Summary:
– Rieger's syndrome   – glaucoma ODS
– Peters' anomaly OS   – dental anomalies?

RK-II-1. *Female aged 12. Born 1954, 3rd May (fig. 36).*
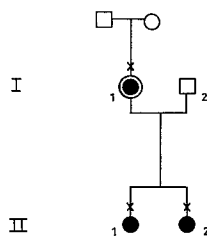
● – primary dysgenesis mesodermalis of the iris

◎ – mild hypoplasia stromalis iridis

⟨⟩ – partial limbus coloboma

Summary:
– Rieger's syndrome:
  mildly ectopic pupils
  hypoplasia of iridal stroma
  abnormalities of the chamber angle
  pseudopolycoria OS?

– juvenile glaucoma
– posterior corneal surface opaque
– high myopia ODS
– oligodontia vera (radiological diagnosis)

RK-II-2. *Female aged 9. Born 1957, 12th January (fig. 38).*

Summary:
– Rieger's syndrome:
  ectopic and dyscoric pupils
  hypoplasia of iridal stroma
  adhesions between iris and corneal periphery
  abnormalities of the chamber angle (embryotoxon corneae posterius).
– juvenile glaucoma
– oligodontia vera (radiological diagnosis)
– telecanthus

HH-III-4. *Female proband aged 12. Born 1956 (fig. 35).*
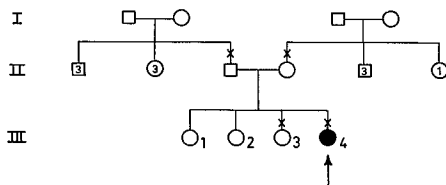
Birth at term with normal birth weight. No illness, medication or irradiation of the mother during pregnancy.
The patient gave a slightly retarded impression (she attended a special primary school). The hair colour was medium blond. Face, nose, ears and teeth were normal, as were the hands and feet.

Interocular distances: 30-42-56-76 (0.54): normal.
VOD: 0.1; refraction: S + 5.5 = C + 1.5 × 115°, amblyopia.
VOS: 1.0; refraction: S + 1.5 = C + 0.5 × 90°.
Motility: Esotropia.
Intraocular pressure: 18 mm Hg ODS (AT), later 12 mm Hg ODS.
Conjunctivae and sclerae were normal.
Corneae: Clear, of normal endothelial structure and normal sensitivity. Ill-defined limbus. Horizontal diameters 11.2 mm OD and 11.5 mm OS; vertical diameters 10.5 mm ODS. The posterior aspect of the corneal periphery ODS showed an irregular, ridge-like white opacity more or less concentric with the limbus, protruding into the anterior chamber and taking part of its course in the chamber periphery, detached from the posterior corneal surface.
Irides: Dull-blue; marked hypoplasia of the anterior and posterior mesodermal layers. The pigment layer was clearly visible through the thin anterior layer at several sites. No iridal frill. Peripherally, there were numerous trabecular adhesions between the iris and the abovementioned ridge. The pigment layer was not distinctly diaphanous. The central, round pupils were normally responsive. The pupillary borders showed small flocculi.
Lens and vitreous body: Normal ODS.
Gonioscopy: Very prominent ridge separating cornea from trabecular system, which otherwise looked normal ODS. The prominent white line, which in certain sectors was quite detached from the posterior surface of the corneal periphery, adhered at many sites to the thin stroma of the iridal root and the pars ciliaris of the iris. There was very slight pigmentation of the iridocorneal angle. The prominence was clearly visible throughout the periphery; where it adhered to the iris, the line showed fusiform swellings and a more compact structure.
Fundi: Normal.

Summary:
– primary dysgenesis mesodermalis of the iris (Rieger's syndrome)
– esotropia OD.

E-I-1. *Male aged 13. Born 1953, 6th March.*
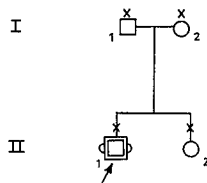
● – primary dysgenesis mesodermalis of the iris.
◎ – mild hypoplasia stromalis iridis
⟊ – partial limbus coloboma ODS

Normal birth at term, with normal birth weight. No illness, medication or irradiation of the mother during pregnancy. A "white pearl" was noticed on the left eye. In recent years this had considerably improved, and become lighter. In 1958, operation for

strabismus OS; vision OS always poor. The family was reported to be free from ocular anomalies; a paternal uncle had had a cataract operation. The parents were not consanguineous so far as could be established. Father, mother and younger sister showed no ocular abnormalities.

The patient was a normally developed, healthy boy with dark blond hair. Skull, face, nose, ears, skin, hair, nails and extremities showed no abnormalities. Slightly mongoloid palpebra OS. Regular dentition and normal labial profile.

Conjunctivae and sclerae were normal.

Intraocular pressure: 18 mm Hg OD and 16 mm Hg OS.

VOD: 5/10 refraction: S-2 = C-0.5 × 0° (skiascopy).

VOS: 1/100 with faulty light projection refraction: S + 4 = C-2 × 0° (skiascopy).

Right eye:

Cornea: Clear, smooth and glossy, with normal limbus. Horizontal diameter 11 mm. Prominent line of Schwalbe. Between 10 and 2 o'clock, palisade scleralization of the limbus zone; typical temporal partial limbus coloboma (Asher).

Iris: Green-grey, of normal structure. Small remnants of the pupillary membrane and star-shaped pigment on the anterior surface of the lens. Slight nasal ectopia of the pupil.

Fundus: Normal.

Left eye (figs. 56, 57):

Cornea: Clear, smooth and glossy. Same limbus structure as OD. Nasal partial limbus coloboma. Horizontal diameter 11.5 mm and vertical diameter 10.5 mm (transverse oval). The corneoscleral trabecula was clearly visible, unlike Schlemm's canal. The nasal half of the cornea showed superficial and deep nebulae and light corneal maculae in a more or less oval, pear-shaped area. In this area the deepest corneal layers were absent and the posterior corneal surface was very irregular, with some endothelial structure and dystrophic features, including guttae. In a wide surrounding area the Descemet membrane was thickened and irregular, while the overlying stroma was clear. There were stroma-coloured adhesions between the upper and lower margins of the corneal defect (figs. 56, 57) and the otherwise normal iridal stroma. The lower adhesions extended to the iridal periphery at 7 o'clock, while the upper adhesions took a horizontal course, traversing the anterior chamber just above the pupil, to the iris at 2.30 o'clock. No heterochromia. The central, round pupil showed only a slight response to light and had a normal pupillary border.

The anterior surface of the lens showed some brown star-shaped pigmentation, like OD.

Summary:

- Dysgenesis mesodermalis of the cornea OS
- partial limbus coloboma OS
- amblyopia OS
- partial limbus coloboma OD
- remnants of pupillary membrane OD
- slightly ectopic pupil OD

HC-IV-8. *Male aged 30. Born 1937.*

Normal birth at term with a normal birth weight. No illness, medication or irradiation or the mother during pregnancy. Connatal malformation ODS. No similar anomalies reported in the family.

The patient was a healthy man with black hair. Skull and face were clinically asymmetrical (fig. 63). The nose had a normal shape and size. The right ear was normal but the left was deformed, slightly smaller than the right and poorly developed. Skin, hair and nails

I   II   III   IV
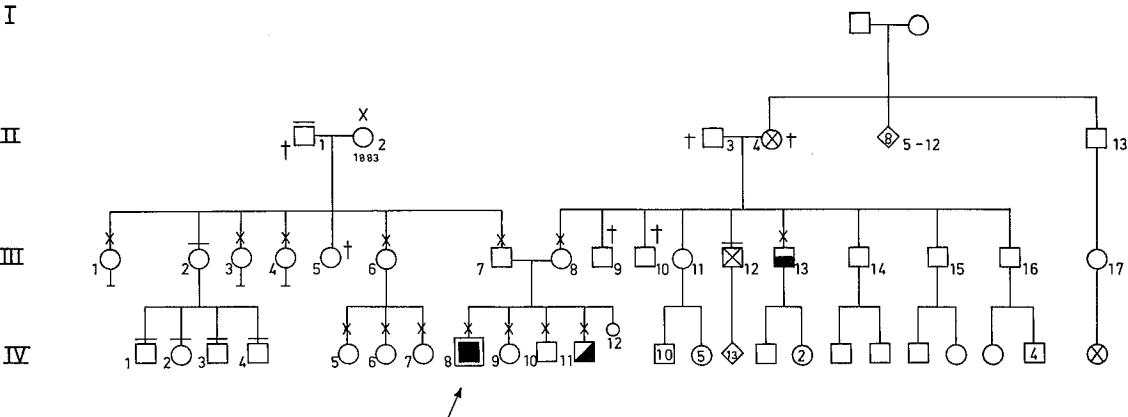
▣ -- dysgenesis mesodermalis of the cornea OS (Peters' anomaly)

■ -- secundary dysgenesis mesodermalis of the iris and coloboma iridochoroidoretinalis

▣ -- glaucoma simplex

⊠ -- peromelia

◪ -- sclerodermia "en coup de sabre"

showed no abnormalities and perspiration was normal. The extremities were clinically normal. Intelligence was not subnormal. Hearing in the left ear was very poor.

Cranial dimensions: Circumference 55 cm: normal. APD 197 mm (196); BPD 144 mm (135-157).

Interocular distances: 36-45-66-88 (0.55): high normal.

Ophthalmological examination:

The bulbus OD seemed somewhat smaller than the bulbus OS. Highly divergent, slightly superior position of OD, with limitation of adduction.

VOD: 1.5/10, inc. refraction: S + 3.

VOS: 11/10 refraction: C + 1 × 0°.

Intraocular pressure: 20 mm Hg OD and 13 mm Hg OS (AT).

Right eye (fig. 55 and plate V):

The conjunctiva and sclera were normal. The corneal limbus had a vertical oval shape with slightly oblique axis. The oval shape was irregular, with a sharper curve towards 5.30 o'clock. The sclera encroached far on the superior and inferior segments of the cornea, where a persistent corneoscleral membrane was very evident.

Cornea: Smooth, glossy, regular and of normal sensitivity. Horizontal diameter 10.5 mm and vertical diameter 12 mm.

Refraction: 36.5 × 60° and 38 × 150°.

The central cornea showed a circular nebula with a diameter of 4 mm. The opacity could be localized in the deepest corneal layers, and in the circular area these layers were found to be absent, the cornea having about three quarters of its normal thickness in this area. The endothelial mosaic was invisible at this site but was present and normal elsewhere. The posterior aspect of this round defect reflected irregularly and was bounded by about ten regularly spaced lumps of pigment (fig 55 and plate V).

Iris: Dark chestnut-brown with regular pigment distribution. The available stroma was of a normal structure with an iridal frill (type C2-3). The pupil showed some inferonasal

distortion with a bridge coloboma at 5.30 o'clock. The iridal frill was hyperplastic, with several small stalks of brown stroma pointing towards the anterior chamber. The localizations of these stalks corresponded with those of the pigment lumps on the posterior side of the cornea, thus giving the impression that originally there had been adhesions between the posterior aspect of the cornea and the iridal frill. A few contraction folds were present. The pupillary border was regular in the pupillary region, but irregular with local discontinuities in the coloboma area. The pigment layer was not diaphanous. *Lens:* Some mild cataractous changes in the outer layers of the nucleus at the site of the coloboma, in which area some superficial brown star-shaped pigmentation was also seen. In the area of the iridal coloboma the lens equator showed an indentation ("coloboma lentis"), probably as a result of the local hypoplasia of the ciliary processes and the zonule of Zinn. The lens was not ectopic.

Fundus: Large chorioretinal coloboma, with the apex half a disc diameter away from the disc and the broad base in the region of the ora serrata. At the extreme periphery there was a pigmented strip in the direction of 5.30 o'clock. The disc showed an irregular polygonal boundary with a temporal crescent. Between the deformed disc and the chorioretinal coloboma, there were perivascular glial changes. The vitreous body was normal.

Gonioscopy (fig. 64): There was a very prominent line of Schwalbe (posterior corneal embryotoxon). The entire circumference of the open iridocorneal angle was covered by a brownpigmented tissue network, localized between the peripheral iridal root and the prominent line of Schwalbe (fig. 64). The visible parts of the iridocorneal angle were normal, as was the localization of Schlemm's canal. At 5.30 o'clock the bridge coloboma of the iris with peripheral defect of the iridal root was visible.

Left eye:

Conjunctiva and sclera were normal. Crescent-shaped encroachment of the superficial sclera on the superior and inferior segments of the limbus.

Cornea: Regular, smooth, glossy and clear, with normal sensitivity and normal endothelium. Horizontal diameter 11 mm and vertical diameter 10.5 mm.

Refraction: 42.5 × 0° and 41.5 × 90°.

Iris: Its colour was determined by a brown-orange peripupillary area and a grey-green peripheral area, which was broadest temporally. The iridal frill was regular and of normal development (structural type C2). The iridal stroma was of normal structure but at 6.30 o'clock thin, with the pigment layer shimmering through. A few contraction folds were present. The pigment layer was not diaphanous. The round, central pupil showed normal responses.

Refracting media: Clear.

Fundus: Normal.

Gonioscopy (fig. 65): A normal open iridocorneal angle with a normal anterior line of Schwalbe. Schlemm's canal of normal localization. No abnormalities of the trabecula, scleral spur or ciliary band. Very slight superficial pigmentation of the trabecula, anterior line and canal zone. At 6.30 o'clock there was a peculiar dip-like depression of the iridal root with pathological broadening and stretching of the ciliary band zone, where the pigment layer was exposed. Only in this area did we find a veritable network of iridal trabeculae, extending from the iridal root to the trabeculum and circumventing (so to speak: bridging) the "abortive iridial root coloboma".

Summary:
– iridochorioretinal coloboma OD
– Dysgenesis mesodermalis of the cornea
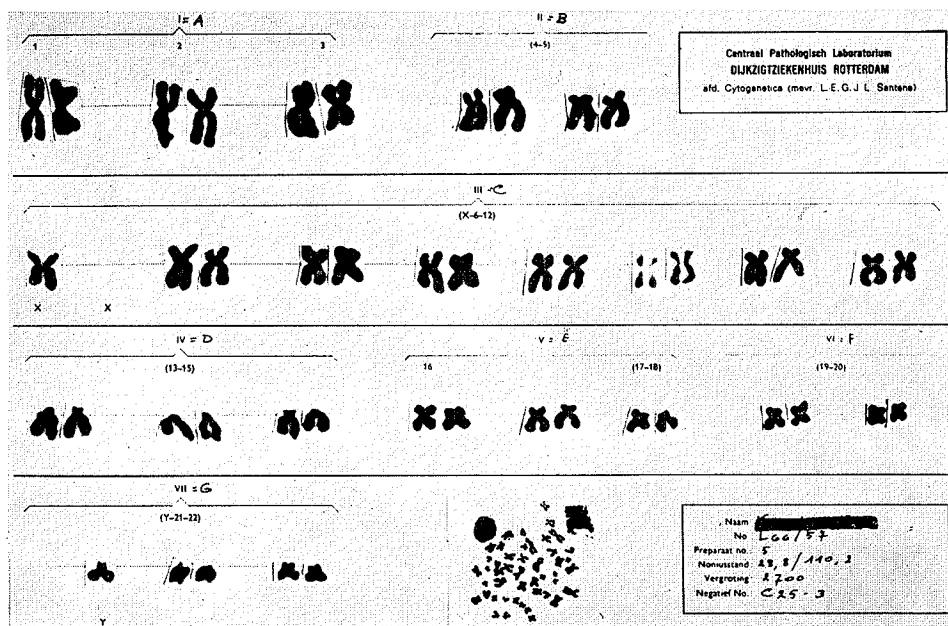
Fig. 70. Normal chromosomal pattern in primary dysgenesis mesodermalis of the iris (HO-III-6).

— posterior corneal embryotoxon OD with anomalies of the iridocorneal angle (secondary dysgenesis of the iridal mesoderm)
— hyperchromic heterochromia OD
— cornea plana OD
— exotropia and amblyopia OD
— abortive coloboma of the iridal root OS
— deformed left external ear
— facial asymmetry

CM-V-5. *Female aged 17. Born 1948, 19th June.*

The patient was born with a left-sided paramedian facial fissure (schistoprosopia) and homolateral connatal ocular abnormalities. There had been no illness, medication or irradiation of the mother during the uneventful pregnancy. The father (CM-IV-2) had died from a haemopathy a few months before the patient's birth. The parents were not known to have been consanguineous. Examination at the time disclosed: hypertelorism; contraction of the left nostril with obliteration of the entire left side of the nose; median protrusion of the nasal bone with absence of cartilage; large left glabellar region; and hairgrowth on the forehead along the defect. Radiological examination at age 1 showed absence of the lateral part of the lamina papyracea and a defect of the median cranial roof with a broadened ethmoid and extreme hyperostosis of the falx cerebri (fig. 71).
Treatment of the paramedian facial fissure consisted of a series of plastic surgical interventions in the course of the years – a series still to be completed.
Development was otherwise normal; there was a systolic souffle without cardiac abnormality. Intelligence was good, the patient attending teachers' training college.
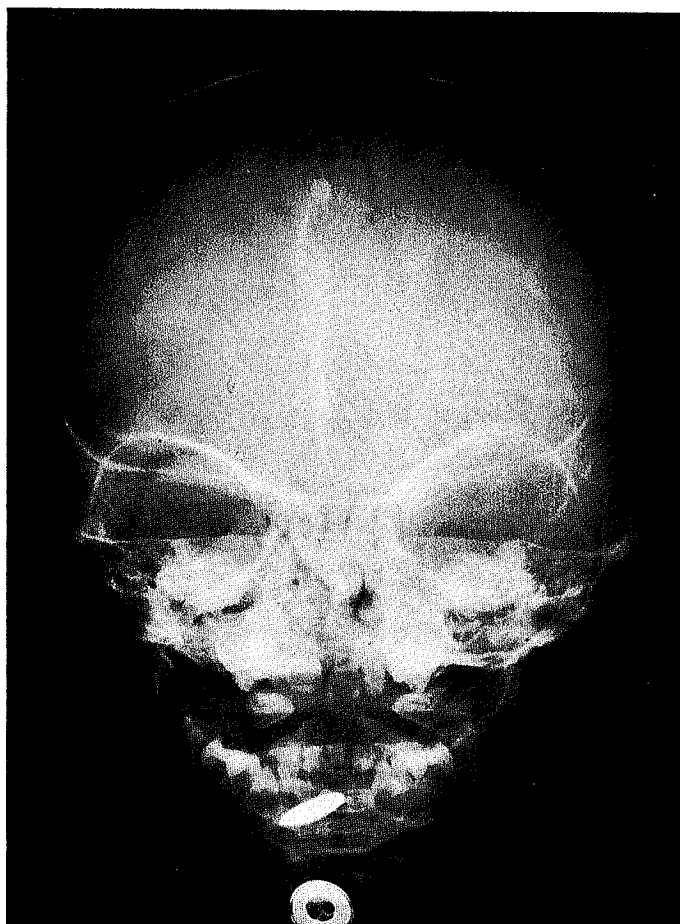
Fig. 71. X-ray of the skull (at the age of 1 year) in a patient with unilateral, paramedian facial fissure, homolateral epibulbar dermoid and secondary dysgenesis mesodermalis of the iris. Absence of the lateral part of the lamina papyracea and defect of the median cranial roof with broadened ethmoid and extreme hyperostosis of the falx cerebri (CM-V-5).

Examination:

The face (fig. 58) was broad, with a deformed nose and the eyes far apart. The left eye seemed slightly lower than the right. The girl was otherwise healthy and had dark brown hair. Hands and feet, skin and nails were clinically normal, as was perspiration. The ears showed no abnormalities and hearing was good.

Orthodontic findings: No signs of partial anodontia. P1sd was absent but the patient remembered that it had been extracted. P2sd showed transverse malposition (a common abnormality). The third molars were all present but had not erupted. Jaws and teeth showed no deformities.
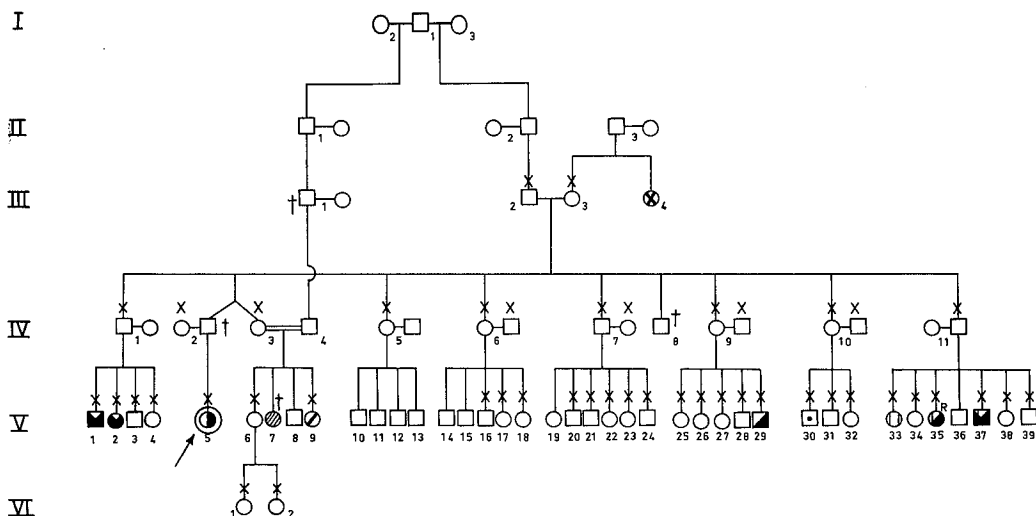
- ◑ – secundary dysgenesis mesodermal is of the iris and limbus dermoid OS
- ◎ – leftsided paramedian facial fissure
- ◪ – hemihypoplasia facieï
- ◪ – torticollis congenita
- ▯ – prominent line of Schwalbe (type B)
- ⊘ – hydrocephalus and anomalies of the limbs
- ⊘ – epilepsy and aplasia of the frontal sinus
- ⊗ – debilitas mentis
- ⊡ – esotropia
- R – remnants of the pupillary membrane

Radiological findings:

Skull: Extreme hyperostosis of the falx cerebri (osteoma of the falx).
Hand and feet: Skeletal development normal for the age, without abnormalities, although the proximal phalanges were possibly slightly too long as compared with the other phalanges of the hands.

Ophthalmological examination:

Interocular distances: 42-53-72-95 (0.58); normal maximum values 36-46-70-89.
Distance between the lateral orbital margins: 103mm (hypertelorism).
The length of the palpebral fissure was 27 mm OD and 26 mm OS; its width was 10 mm OD and 12 mm OS.
Motility: Manifest concomitant exotropia OS 30°; at dextroversion vigorous upshoot OS, and at sinistroversion vigorous upshoot OD marked V-syndrome.
VOD: 11/10 refraction: S-2 = C-0.5 × 0°.
VOS: 4/60, inc. refraction: S-3 = C-2 × 0°, amblyopia.

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Right eye:
Conjunctiva, sclera and lacrimal apparatus were normal.
Cornea: Of normal clarity and sensitivity. Horizontal diameter 11.5 mm and vertical diameter 11 mm.
Refraction: 39 × 10° and 40 × 100°. Limbus type A10.
Iris: Grey-green, of normal structure (type C2). The corona iridis was regular and showed a light orange-brown pigmentation. The pigment layer was not diaphanous. The central, round pupil responded well to light and convergence.
Lens and vitreous body: Normal.
Fundus: Slightly tessellated; the optic disc showed flat physiological cupping and a narrow superonasal conus.
Gonioscopy: Normal open iridocorneal angle with slightly pigmented anterior line. A few vessels were visible in the iridal root (normal). Other structures were normal. The intraocular pressure was 16-18 mm Hg (AT).
Conclusion: OD normal.

Left eye:
This eye had been deformed since birth. The nasal canthus was occupied by a white, bean-shaped, smooth tumour of the limbus zone (fig. 72). This tumour was firmly fixed to the subjacent layer and encroached 3 mm upon the corneal margin, pushing ahead a delicate sickle-shaped corneal opacity. A few hairs grew on the posterior surface of the tumour.
The medial one-fourth parts of the upper and lower palpebrae showed a coloboma of the palpebral edge, giving the canthus area a rounded shape (fig. 72). Even after removal of the tumour (pathology: fragment of skin and fragments of fibrous tissue without abnormal features), the nasal canthus remained open when the eye was closed.
The caruncle proved to be divided into two hypoplastic parts (fig. 73). The superior punctum lacrimale was absent; the inferior punctum was present and functioned normally.
The conjunctiva was otherwise normal; the sclera showed a bluish tinge over the ciliary body and its surroundings. The limbus was ill-defined.
Cornea: Smooth, glossy, regular surface. Horizontal diameter 11 mm and vertical diameter 10 mm.
Refraction: 36 × 10° and 40 × 100°.
Between the dense leucomatous opacity at the site of the abovementioned tumour and the delicate sickle-shaped marginal opacity there was a lucid interval. Delicate dystrophic changes were seen in the lower temporal quadrant; they consisted of very minute, irregular, reticular, grey-white pre-descemetic opacities accompanied by thin opaque spots in the deep and superficial stromal layers and the Bowman membrane.
Between 2 and 5 o'clock the posterior aspect of the corneal periphery showed a thick, white, ridge-like opacity of irregular width which protruded far into the anterior chamber. Between this opacity and the limbus the deepest layer of corneal stroma was not entirely transparent (plate VI). A white sheet of (fibrous?) tissue, 2 mm large, arose broad from this ridge and traversed part of the anterior chamber towards the temporal side of the pupil, which showed temporal ectopia. The sheet was once again adherent to the ridge by a separate white strand, and in addition there were many slender, stroma-like fibres which connected it to the subjacent iridal stroma.
Iris: Grey-green, slightly hypoplastic with the pigment layer shimmering through. The structure was radial due to prominence of the structure of the deep mesodermal iridal layer. A frill could not be localized. The thickened peripupillary region showed an orange-brown pigmentation (plate VI).
The pupil was ectopic at 5 o'clock, 2 mm away from the limbus, and had a triangular

Fig. 72. Mild coloboma of the internal canthus and nasal parts of the eyelids in a patient with unilateral epibulbar dermoid, paramedian facial fissure and secondary dysgenesis mesodermalis of the iris (CM-V-5, left eye).

Fig. 73. Encanthoschisis in the same patient with the unilateral epibulbar dermoid (removed), secondary dysgenesis mesodermalis of the iris and other connatal anomalies (CM-V-5, left eye).

shape. Its size was about 3-4 mm under average illumination. It responded normally to light and convergence and became wide and round, with a diameter of 6-7 mm, after application of a mydriatic. The pupillary border showed irregular development and local atrophy. Pigment accumulations were seen on the zone near the corners of the triangular pupil. The above described white sheet of tissue inserted on the temporal side of the pupillary zone. From this line of insertion, numerous very delicate, taut, glistening fibres extended to the anterior surface of the lens capsule in the pupillary region. The pigment layer was not diaphanous.

Gonioscopy: Open iridocorneal angle and prominent line of Schwalbe, which on the temporal side was pathologically thickened and ectopic. The white sheet could be readily located and proved to adhere to the ciliary and peripupillary parts of the iris by stroma-like adhesions. The entire iridal root was characterized by many elevations and nodular stromal prominences, and was highly vascularized. There were no adhesions between the stroma and the line of Schwalbe outside the area between 2 and 5 o'clock. The intraocular pressure was 12-18 mm Hg (AT).

Fundus: Normal disc showing non-glaucomatous cupping with a pigment edge. The disc had a deep cup which was interpreted as disc coloboma. Normal vessels and macula. Temporal peripheral detachment of the vitreous body, with differences in colour and reflexes marked by a "festooned" boundary. Some small peripheral pigment accumulutions at 3 o'clock.

Vitreous body: Of normal clarity, with some filamentous opacities extending in temporal direction.

Colour vision: HRR: normal.

Summary:
OS – secondary dysgenesis mesodermalis of the iris
   – epibulbar dermoid
   – corneal dystrophy
   – blue sclera
   – myopia and astigmatism
   – encanthoschisis
   – aplasia of the superior punctum lacrimale
   – palpebral coloboma
   – exotropia and amblyopia
   – partial detachment of vitreous body

and also
   – left-sided paramedian facial fissure
   – hypertelorism
   – telecanthus

VE-III-6. *Male aged 8. Born 1957, 7th December.*

The patient was born two weeks short of term, with a birth weight of 2050 g. Parturition was normal. No illness, medication or irradiation of the mother during pregnancy. The parents were not known to be consanguineous. No ocular abnormalities or other connatal affections known in the family.

The boy showed connatal bilateral total cheilognathopalatoschisis and a connatal irridal anomaly OD. Regular plastic surgery since 1958 and, since 1964, orthodontic therapy for the extensive anomalies of the jaws and teeth.

Development was slow allround, with a few childhood diseases (measles, chicken-pox); operation for inguinal and umbilical herniae in 1963.
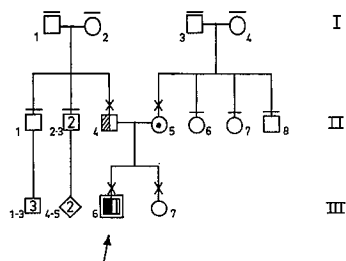
■ – secundary dysgenesis mesodermalis of the iris OD
▣ – bilateral total cheilognathopalatoschisis
▨ – iris bicolor
▢ – prominent line of Schwalbe (type B)
⊙ – exotropia

Examinations 1964-1966:
The patient was a pale, very slight boy with light blond hair, of low intelligence. The facial configuration was determined by the plastic surgery scars, due to which the otherwise normal nose was slightly flattened near the tip (fig. 60). Both ears were prominent, the left ear being inserted somewhat lower than the right. The medial portions of the eyebrows were sparse.
No abnormalities of skin, hair and nails; normal perspiration. The extremities were normal except for some slight radiad deflection of the little fingers.
Cranial dimensions: Circumference 48 cm (49.5-50.5). APD 165 mm (164-190); BPD 140 mm (135-154).
Interocular distances: 29-39-53-78 (0.56): normal.

Radiological findings:
Skull (tele): Very abnormal cranial build; analysis was not feasible because the three fixed points for analysis and tracing were abnormally localized.
Hands and feet: Normal; skeletal age not behind calendar age; no developmental disorders.
Teeth: Irregular implantation; malpositions; no oligodontia vera.

Ophthalmological examination:
Bulbi, conjunctivae, sclerae and motility were normal.
VOD: 10/10 refraction: S + 1.
VOS: 7/10 refraction: C-3 × 100°.
Intraocular pressure: 12 mm Hg OD and 13 mm Hg OS.

Right eye (fig. 61):
Cornea: Clear, smooth and glossy, of normal sensitivity. Horizontal diameter 10.75 mm and vertical diameter 10 mm.
Refraction: 47 × 15° and 48 × 105°.
Between 8 and 10 o'clock, the posterior temporal corneal periphery showed a sharply defined, thick, ridge-like white opacity which protruded into the anterior chamber about 0.5 mm from the limbus; at 8 and at 10 o'clock the line disappeared behind the

limbus in the direction of the iridocorneal angle. The ridge was the central boundary of a semi-transparent deep peripheral corneal opacity. Similar features were seen nasally, between 2 and 5 o'clock. The limbus showed a crescent-shaped broadening between 10 and 2 o'clock, but was otherwise normally defined.

Iris: The pupil was slightly wider than OS and showed slight inferonasal ectopia. The grey-blue stroma had an abnormal structure. The frill was of normal localization. For descriptive purposes the iris was divided into three sectors.

1. Sector between 11 and 4 o'clock: Normally developed stroma. Most of the anterior limiting membrane was present, especially between 11 and 2 o'clock where the anterior mesodermal layer showed a fairly compact structure. Between 2 and 4 o'clock this structure was less compact (type C1-2). The pupillary sphincter muscle was invisible at this site but its presence was demonstrated by the good local response to light. There were 7 stromal densifications (Wölfflin) and a few contraction folds. The pigment layer was not diaphanous in this area.

2. Sector between 4 and 6 o'clock: Extremely hypoplastic-to-aplastic stroma. Only a few strands of the anterior stromal layer were present, and large parts of the deep layer were likewise lacking; as a result, the local pigment layer was almost entirely exposed. The stromal periphery was somewhat more compact, with two or three densifications. There was no distinct corona iridis at this site. The thin, taut pupillary border was straight and the pupillary sphincter muscle was absent in this segment so that no photic response could be elicited. The pigment layer was locally diaphanous in a moth-eaten pattern. Peripherally, the shadow of the lens equator was even visible against the red reflex light.

3. Sector between 6 and 11 o'clock: Marked hypoplasia of the anterior mesodermal layer; the corona iridis presented itself in the form of a thickened, zig-zagging stromal strand. Trabecular type of stroma. Peripherally, the trabeculae merged into several stromal densifications (Wölfflin). The deep mesodermal layer was very thin and the pigment layer shimmered through quite distinctly. In this area the pupil responded well to light and convergence. The curved pupillary border here showed an ectropion uveae of 0.5-0.7 mm width, with maximum spread at 9 o'clock. The pigment layer was not locally diaphanous.

Gonioscopy: Open iridocorneal angle with broadened corneoscleral trabecula, centrally bounded by a prominent line of Schwalbe without adhesions to the iridal stroma. The yellow-brown ciliary band and the scleral spur were localized rather high. Schlemm's canal was invisible. The iridal root was hypoplastic with visible vessels and peripheral limitation of the pigmented layer. The stroma was virtually intact between 4 and 6 o'clock. From the peripheral densifications, stromal fibres extended towards the ciliary band. Here, the iridocorneal angle was wider because the total iridal root was deepened in posterior direction (compare with fig. 65, concerning another patient).

Refracting media: Clear.

Fundus: Normal.

Left eye (fig. 62):

Cornea: Smooth, glossy and clear, of normal sensitivity. Horizontal diameter 11 mm and vertical diameter 10 mm.

Refraction: 46 × 0° and 48.25 × 90°.

Between 8 and 10 o'clock the structure of the posterior aspect of the corneal periphery was the same as OD. Temporally the deep limbus was of structural type A2. The superficial limbus was normally defined, with a crescent-shaped broadening between 10 and 2 o'clock (like OD).

Iris: Grey-blue, type L-T, with iridal frill of normal localization. Some 20 stromal densifications were seen evenly spaced on the periphery. The deep stromal layer also showed a normal structure, with the non-diaphanous pigment layer shimmering through

at several sites. The round, central pupil responded well to light and convergence and had a broad pupillary border.

Gonioscopy: Normal open iridocorneal angle with normal structures. Clearly prominent anterior gonioscopic line, but without adhesions to the iris.

Refracting media: Clear.

Fundus: Normal.

Summary:
– secondary dysgenesis mesodermalis of the iris
– bilateral total cheilognathopalatoschisis with dental anomalies
– telecanthus

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Samenvatting

HOOFDSTUK I

Als inleiding op een studie over de primaire dysgenesis mesodermalis iridis of het syndroom van Rieger, werd een onderzoek verricht naar de betekenis van de prominente lijn van Schwalbe. Er werd nagegaan of er een relatie bestaat tussen de prominente lijn van Schwalbe en het embryotoxon corneae posterius, een kenmerkend onderdeel van de primaire dysgenesis mesodermalis iridis.

De prominente lijn van Schwalbe, het door ons beschreven diepe limbustype B, welke bij 8% der ogen kan worden aangetroffen, is geen anomalie of dysplasie, maar moet beschouwd worden als een variant der kamerhoekstructuur, welke op haar beurt uiting is van de variatiebreedte der normale ontwikkeling van het voorste oogsegment en de kamerhoek in het bijzonder. Een praedispositie voor glaucoom kon in deze ogen niet worden bevestigd.

HOOFDSTUK II

In families met de primaire dysgenesis mesodermalis iridis kwamen personen met de prominente ring van Schwalbe niet frequenter voor dan in de normale populatie.

De prominente lijn van Schwalbe is dan ook niet op te vatten als een minimale expressie van het syndroom van Rieger.

Bij de primaire dysgenesis mesodermalis iridis zijn het hypoplastische irisstroma en het embryotoxon corneae posterius verbonden met het slecht aangelegde irisstroma, de belangrijkste en steeds aanwezige kenmerken. De laatst genoemde afwijkingen representeren de gestoorde ontwikkeling der kamerhoek zoals deze typisch is voor de primaire dysgenesis mesodermalis iridis.

Het syndroom van Rieger komt evenveel bij vrouwen als bij mannen voor. Er bestaat bij de primaire dysgenesis mesodermalis iridis een aanzienlijk hogere frequentie astigmatisme en sterke ametropie en aanzienlijk lagere frequentie

emmetropie dan bij normale personen. Evenals bij andere congenitale oogafwij-
kingen, werd ook bij het syndroom van Rieger een duidelijk verhoogde frequen-
tie van stoornissen der motoriek waargenomen.

Xerosis conjunctivae, noch blauwe sclerae kunnen als typische of specifieke
afwijkingen van het syndroom worden aangemerkt. In ongeveer driekwart der
ogen met de primaire dysgenesis mesodermalis iridis werd een onscherpe limbus-
architectuur (membrana corneoscleralis persistens) waargenomen.

Microcornea werd in 9% en macrocornea in 26% der gevallen van het syn-
droom van Rieger geobserveerd.

In 8% der gevallen bestaan er afwijkingen der cornea-vorm; driekwart hiervan
betreft een staand-ovale vorm. In vergelijking met normale ogen bezitten de ogen
van patienten met de primaire dysgenesis mesodermalis iridis vlakkere corneae.

Bij een klein deel der ogen met het syndroom van Rieger werden centrale
corneatroebelingen en defecten waargenomen. Zij representeren de secundaire
dysgenesis mesodermalis corneae (anomalie van Peters) bij het syndroom van
Rieger.

Resten der membrana pupillaris komen zelden bij het syndroom van Rieger
voor, in elk geval niet meer dan onder normale omstandigheden. Hyperplastische
iriskenmerken werden niet waargenomen. Afwijkingen van het pigmentblad,
bestaande uit pigmentbladdefecten komen bij patienten met het syndroom van
Rieger regelmatig voor.

Pupilanomalieën in de vorm van dyscoria en ectopia pupillae worden zeer fre-
quent bij de primaire dysgenesis mesodermalis iridis gevonden en vormen daar-
door een belangrijk aspect van het klinische beeld der aandoening. In ongeveer
15% van het totale aantal werd tevens een ectropion uveae waargenomen.

De primaire dysgenesis mesodermalis iridis vormt een typische conditie voor
vroeg optredend glaucoom, dat in 60% der gevallen aanwezig bleek. Het glau-
coom behoort doorgaans tot het infantiele en juveniele type, doch meerdere
malen werd ook congenitaal glaucoom met hydrophthalmus vastgesteld.

In het merendeel der gevallen van het syndroom van Rieger bestaat er geen
directe causale samenhang tussen het glaucoom en de macrocornea. Het glaucoom
wordt bij patienten met de primaire dysgenesis mesodermalis iridis bepaald door
een vermeerderde afvloedweerstand van het kamerwater, waarbij de zichtbare
kamerhoekafwijkingen zeer waarschijnlijk geen rol spelen.

Specifieke afwijkingen van de lens zijn bij de primaire dysgenesis mesoder-
malis iridis niet aanwezig.

Het glasvocht is steeds normaal.

Mogelijk kan de verschillende malen door ons geobserveerde hypoplasie van
de chorioidea opgevat worden als pathogenetisch samenhangend met de ken-
merkende hypoplasie van de mesodermale iris.

Het klinisch verloop van het ziektebeeld en de prognose hangen ten nauwste
samen met de mogelijkheid het eventueel optredende glaucoom adequaat te be-
handelen. Bij afwezigheid van verhoogde intra-oculaire druk is de primaire

dysgenesis mesodermalis iridis een stationnaire aandoening. Onder bijzondere omstandigheden kunnen er voortschrijdende veranderingen van de iris voorkomen.

Voor wat de therapie betreft kan men stellen, dat indien conservatieve antiglaucomateuze therapie faalt, de ruime filterende glaucoomoperatie de meest aangewezen werkwijze is waarmee de verhoogde intra-oculaire druk op langere termijn is te normaliseren.

De vorm van het gelaat van patienten met het syndroom van Rieger heeft vaak typische kenmerken, welke worden bepaald door de neus en neuswortels, de afstand der orbitae en de toestand der kaken en tanden. In een aanzienlijk deel der gevallen is de vorm der neus breed tot normaal en nimmer smal, terwijl de neuswortel breed is door het frequent optreden van telecanthus en soms hypertelorisme. Vrij vaak zien we bij patienten met de primaire dysgenesis mesodermalis iridis het voorkomen van echte partiële anodontie. Zeer waarschijnlijk hebben we hier te maken met een zo nu en dan optredende genkoppeling hoewel polyphene expressie van één gen niet kan worden uitgesloten.

De afwijkingen der kaken bepalen zich voornamelijk tot de maxillaire hypoplasie doch soms komt ook mandibulaire hypoplasie voor. Deels is deze kaakhypoplasie op te vatten als secundair aan de tandaanlegstoornis, doch primaire gevallen zijn ook aan te wijzen.

Extremiteitsafwijkingen zien wij niet als een onderdeel van het syndroom van Rieger.

Gezien de relatief geringe frequentie van het geassocieerd voorkomen van anomalieën van andere organen of orgaansystemen, moet dit samengaan met de primaire dysgenesis mesodermalis iridis voorlopig opgevat worden als een toevallige coincidentie. Een speciale binding met de dystrophia myotonica is wel zeer onwaarschijnlijk. Over de betekenis van het voorkomen van andere connatale of congenitale afwijkingen in families met het syndroom van Rieger kunnen geen nadere uitspraken worden gedaan. De in het eerste hoofdstuk besproken prominente lijn van Schwalbe, het limbustype B, komt in deze families niet frequenter voor. In driekwart van het totaal aantal patienten met de primaire dysgenesis mesodermalis iridis was familiaal voorkomen aanwezig. Indien er van erfelijk voorkomen van het syndroom sprake was, dan was dit steeds een autosomaal dominante overerving.

Er bestaat een penetrantie 95% van het pathologische gen met wisselende expressie binnen een duidelijk pathologisch klinisch beeld.

Voor wat betreft de pathogenese zien wij de primaire dysgenesis mesodermalis iridis als een aandoening, welke het gevolg is van een genetisch bepaalde aanlegstoornis van het iridogene mesoderm, dat de basis vormt voor de ontwikkelingsstoornissen van iris, pupil en kamerhoek.

Op grond van klinisch-genetische overwegingen zouden wij bij de anomalie van Peters willen onderscheiden de primaire dysgenesis mesodermalis corneae: een aandoening sui generis in de vorm van een betrekkelijk zeldzame en genetisch bepaalde recessief erfelijke ontwikkelingsstoornis van de cornea en de secundaire dysgenesis mesodermalis corneae, welke optreedt binnen het kader van een ontwikkelingsstoornis van het oog (oa. syndroom van Rieger) of als onderdeel van een algemener syndroom.

Het klinisch beeld is variabel en verloopt van geringe cornea-afwijkingen, via connatale corneatroebelingen en leucomata, al of niet met synechiae anteriores tot het staphyloma corneae. Relatief frequent bestaat microphthalmus, cornea plana, sclerocornea en glaucoom. Ook ziet men regelmatig ontwikkelingsstoornissen van de iris, pupil en kamerhoek (secundaire dysgenesis mesodermalis iridis) optreden.

Connatale anomalieën van andere organen of orgaansystemen gaan frequent met de anomalie van Peters samen of zijn aan deze anomalie geassocieerd.

Indien van erfelijk voorkomen sprake was, bij deze anomalie in tegenstelling tot de primaire dysgenesis mesodermalis iridis in veel minder opvallende mate, dan leek de recessief erfelijke transmissie het waarschijnlijkst.

De anomalie van Peters is een ontwikkelingsstoornis van de mesodermale cornea welke tot stand kan komen door een stoornis van de separatie van het primaire lensblaasje van het oppervlakte ectoderm. Bij de primaire vorm bestaat er waarschijnlijk een genetisch bepaalde aanlegstoornis van het corneogene mesoderm. Bij de ontwikkeling van het voorste oogsegment zien we eerst een differentiatie- en organisatiefase gevolgd door een periode, welke voornamelijk door een secundair klievingsproces wordt gekenmerkt. Zowel de primaire dysgenesis mesodermalis iridis Rieger als de dysgenesis mesodermalis corneae Peters, zijn ons inziens aanleg-, differentiatie- en organisatiestoornissen van het mesoderm, welke een toestand scheppen, waarin latere klieving onvolledig en gestoord zal plaatsvinden.

In het kader de differentiele diagnostiek van de primaire dysgenesis mesodermalis iridis werden achtereenvolgens besproken: de secundaire dysgenesis mesodermalis iridis; de essentiële progressieve irisatrophie, welke een geheel ander ziektebeeld representeert; de connatale hypoplasia iridis, welke mogelijk nauw samenhangt met het syndroom; de primaire hydrophthalmus en de oculo-dento-digitale dysplasie, welke om voornamelijk historische gronden werd aangehaald.

Curriculum vitae

Alkemade, Petrus Paulus Hendrikus geboren te Naaldwijk 13 september 1935

Middelbare Schoolopleiding aan het Canisius College, afdeling H.B.S.b. te Nijmegen (1947-1952)

Inschrijving als student aan de Medische Faculteit der Universiteit van Nijmegen (sept. 1952)

Doctoraal examen in de geneeskunde te Nijmegen (jan. 1959)

Opleiding tot arts bij de Stichting Klinisch Hoger Onderwijs te Rotterdam (1959-1961)

Assistentschap interne geneeskunde bij Prof. Dr. W. J. Bruins Slot, Zuider-ziekenhuis te Rotterdam (mei-aug. 1960)

Certificaat van het Educational Council for Foreign Medical Graduates (USA), (mei 1961)

Arts-examen te Rotterdam (Universiteit van Leiden) (nov. 1961)

Militair Districtspsychiater TBZ te Breda (1962-1963)

Assistentschap oogheelkunde bij Prof. Dr H. E. Henkes, Oogziekenhuis te Rotterdam (1963-1967)

Verkreeg de door het Nederlands Oogheelkundig Gezelschap ingestelde "Waar-denburg Prijs" voor een studie over het syndroom van Rieger (juni 1967)

Als oogarts gevestigd te 's-Gravenhage (sept. 1967).

Stellingen

I

De prominente lijn van Schwalbe is geen anomalie, doch een variant der kamer-hoekstructuur, welke op haar beurt uiting is van de variatie der normale kamer-hoekontwikkeling.

II

De iridocorneale verbindingen, welke bij patienten met de dysgenesis mesoder-malis iridis worden waargenomen, spelen geen rol bij het ontstaan van glaucoom.

III

Het is niet onwaarschijnlijk, dat bij het syndroom van Rieger naast de mesoder-male iris ook de chorioidea hypoplastisch is aangelegd.

IV

Is de neusvorm bij patienten met de primaire dysgenesis mesodermalis iridis afwijkend, dan is deze breed met een vlakke neuswortel en brede neusbasis.

V

De indeling in een primaire en secundaire vorm van de dysgenesis mesodermalis corneae (anomalie van Peters) lijkt gerechtvaardigd.

VI

De door Reese en Ellsworth gebezigde term 'anterior chamber cleavage syndrome' als verzamelnaam voor verschillende ontwikkelingsstoornissen van het voorste oogsegment, moet worden verworpen.

> (Reese, A. B. en Ellsworth, R. M.: The anterior chamber cleavage syndrome.
> Arch. Ophthal. 75: 307-318, 1966).

VII

Indien ter bevordering van het wetenschappelijk onderzoek wordt besloten tot centrale registratie van erfelijke en aangeboren afwijkingen, dan zullen maatregelen moeten worden genomen ter handhaving van het medisch beroepsgeheim.

VIII

Een algemeen gebruik van het Internationaal Coderingssysteem voor Oog-aandoeningen bevordert het wetenschappelijk onderzoek.

IX

Wil men de retinale maculafunctie bestuderen aan de hand van de 'Visually Evoked Responses', dan behoort tevens het Electroretinogram te worden afgeleid en locale stimulatie te worden toegepast.

X

Indien de diagnose supravalvulaire aortastenose is gesteld, is het geïndiceerd een familie-onderzoek uit te voeren ten einde andere gevallen op te sporen.

XI

Alhoewel de dento-maxillaire orthopaedie (orthodontie) meestentijds als een discipline van de tandheelkunde wordt beschouwd, is dit medisch-biologisch specialisme nauwer geliëerd aan de kindergeneeskunde, de keel-, neus- en oorheel-kunde, de plastische chirurgie en de orthopaedie.

XII

Prognose en eugenetisch advies aan leden van families met vitelliforme dystrophie van de fovea, is niet mogelijk zonder electro-oculografisch onderzoek.

A. F. Deutman, Electro-oculography in families with vitelliform dystrophy of the fovea˙ Arch. Ophthal. 81: 305-316, 1969).