INHERITED HYALOIDEORETINOPATHY AND SKELETAL DYSPLASIA*

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INTRODUCTION

HEREDITARY PROGRESSIVE ARTHRO-OPHTHALMOPATHY HAS BEEN REPORTED IN A number of families with clinically apparent skeletal defects and retinal detachment. The radiographic findings in this syndrome are now well documented. However, the relationship of this disease to patients with inherited hyaloideoretinopathy and no obvious skeletal abnormalities is not defined. It is the purpose of this paper to determine if skeletal defects do occur in inherited hyaloideoretinopathy and to identify the similarities or differences of these defects to those found in arthro-ophthalmopathy.

HISTORICAL REVIEW

THE HYALOIDEORETINOPATHY

Almost from the time that detachment of the retina was recognized as a clinical entity, its occasional occurrence within families has been noted. Lang in 1885[1] reported detachment of the retina occurring in a brother and sister. In 1930, Bane reported a family in which detachment occurred in four myopic siblings.[2] Several European authors at this time were also reporting a number of families with retinal detachment and there was much speculation as to their dominant or recessive inheritance. These early investigations were hampered because the precursor of retinal detachment, that is, the hyaloideoretinopathy, was not well recognized. Without careful examination of family members or without adequate instrumentation for viewing the retinal periphery during these early years, an unwarranted assumption of recessive inheritance mode was probably made in many instances.

In a now classical paper, Wagner in 1938[3] described a large Swiss family in which 13 members in three generations suffered from an ocular disease complex that now is associated with his name. The same family was

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restudied and ten additional cases were added in 1959 by Boehringer, Dieterle, and Landolt.[4] In 1961 Ricci[5] also reviewed the family and found five additional afflicted members.

Ricci also attempted to identify and classify three main forms of inherited vitreoretinal degeneration.[6] He grouped them into sex-linked congenital retinoschisis, the recessively inherited hyaloideotapetoretinal degeneration of Goldmann and Favre, and the dominantly inherited hyaloideoretinopathy of Wagner. The congenital sex-linked retinoschisis is fairly commonly seen and is well described. The hyaloideotapetoretinal degeneration of Goldmann and Favre has been seen only occasionally and probably represents a rare entity.

Following these original descriptions of the hyaloideoretinopathy, other comprehensive reports have appeared in literature. These include those of Jansen in 1962,[7] Alexander and Shea in 1965,[8] and forty-one patients from seventeen families by Hirose, Lee and Schepens.[9] Similarities and differences occurred in the patients and families described. Despite these differences one is able to summarize the important features of Wagner's hyaloideoretinopathy as follows:

Vitreous

Syneresis or liquifaction of the vitreous apparently occurs very early in life. Jansen reported seeing this in a 2½ year old child. Fibrillar degeneration is followed by the development of large optically empty areas with visible membranes interspersed. A well developed fenestrated preretinal membrane may be evident with multiple attachments to the retina near the equator. The degeneration of the vitreous is probably the most universal finding.

Retina

Areas of "white without pressure" in portions of the peripheral retina are described. Equatorial and pre-equatorial lattice degeneration may be present. A progressive accumulation of round pigment clumps also occurs at the equator. Patchy areas of atrophy of the pigment epithelium and underlying choriocapillaris may occur. A characteristic form of this atrophy is one which follows the veins and occasionally the arteries posteriorly in a radial fashion. This radial perivascular degeneration extends posterior to the equator and may almost reach the optic nerve in some instances.

Choroid

Areas of atrophy of the choriocapillaris and the pigment epithelium with apparent choroidal sclerosis have been reported. This finding was prob-

ably more marked in Wagner's original family and has been described less in recent literature. In his patients, Wagner also described optic atrophy and vascular attenuation. These also have not been a common finding in subsequent reports.

Cataract

Cortical, posterior subcapsular, and nuclear opacities have been described, frequently occurring with the onset of puberty. Occasionally the onset of the cataract is delayed until the third or fourth decade of life. The frequency of occurrence of cataracts varies widely among affected families but is probably quite common.

Glaucoma

The occasional occurrence of open-angle glaucoma was first reported by Jansen and continues to appear in some families. No abnormalities of the angle have been described.

Refractive Error

Myopia of a moderate degree frequently occurs and is usually associated with astigmatism. Occasionally very high myopia is seen as well as emmetropia and even hyperopia. Alexander and Shea made note of the fact that none of their patients appeared to have axial myopia and that typical myopic choroidosis and posterior staphylomas were absent.

Retinal Detachment

It is of interest to note that none of the members of Wagner's original family developed retinal detachment during the sixteen years they were followed. It has been a retinal detachment that has brought most families to the attention of subsequent authors. Most are in agreement that the retinal detachments usually respond less favorably to treatment than those more commonly encountered. Multiple breaks occurring both equatorially and postequatorially are usually found. It is also characteristic that detachments may occur early in life and in these eyes giant tears of the retina or disinsertions with "roll-over retina" are frequently seen. In some instances the detachment follows removal of the cataract.

Visual Function

In Wagner's original family, reduction of central visual acuity was reported even without cataract. This apparently was related to the marked choroidal atrophy which occurred in his patients. Subsequent studies have stressed the normal central visual acuity in the absence of cataract. De-

pending upon the degree of chorioretinal degeneration that may occur, the visual fields may or may not be constricted. Likewise, dark adaptation may be normal or depressed. Depression of the ERG has also been reported in patients with large areas of the retina involved with degenerative change.

Inheritance

All of the families that have been reported have consistently shown dominant inheritance with a fairly high degree of penetrance and a marked variability of expression. Only a few chromosomal studies have been reported and these were interpreted as negative.

Pathology

Pathological material has not been readily available but Boehringer, Dieterle, and Landolt did offer some descriptions. Retinal atrophy with cystic degeneration, atrophy of the pigment epithelium and choriocapillaris with pigment dispersion and thickening of retinal vessels with perivascular accumulation of pigment were all found. One of the most interesting findings was that of a glial-like membrane on the surface of the peripheral retina that split centrally and extended forward into the vitreous cavity. Pathological material reviewed by Alexander and Shea added little knowledge of the chorioretinal degeneration because of the advanced disease state of the eyes examined. However, they did note that scleral thinning and staphylomas that may be associated with progressive myopia were not present.

Hagler and Crosswell in 1968[10] in a well-documented paper described 33 patients manifesting radial perivascular degeneration of the retina. Seventy-six percent of these patients were from families with a dominant inheritance pattern and had associated cataracts, myopia, glaucoma, and retinal detachment. The report emphasized the prominent feature of the perivascular degeneration extending posteriorly and the authors felt that this was either a variant of the hyaloideoretinopathy as originally described by Wagner or perhaps a different entity. In reviewing the literature they found a report of a case described by Brown in 1937.[11] This patient was a myopic man with marked radial perivascular chorioretinal degeneration. This is probably the first description of Wagner's dominantly inherited hyaloideoretinopathy.

THE SKELETAL DYSPLASIA

As one reviews the literature of familial retinal detachment, references to skeletal defects are encountered. In the ophthalmic literature, emphasis

is, of course, placed on the eye with only minimal reference to the skeletal system. The reverse is true if the skeletal defect provoked the investigation and the ophthalmic exam, where indicated, is only briefly mentioned. However, review of the literature does reveal an apparent common linkage between certain skeletal defects and familial retinal detachment. The skeletal defects that have been encountered can be described as follows:

Characteristic Physiognomy

As early as 1939, Friedman[12] in reporting a family with retinal detachment and cataract noted that the affected members had a peculiar resemblance to one another. He felt that their appearance was one of hyperpituitarism, but other clinical tests did not substantiate this. In the 1960s a number of reports appeared concerning a characteristic physiognomy that was seen in family members with retinal detachment.[13-19] Generally this included descriptions of a low nasal bridge with an associated short turned-up nose. A flat mid-face with hypoplasia of the maxilla was seen. A variable degree of underdevelopment of the mandible was sometimes encountered. While this physiognomy tended to be extremely variable within a given family, those members with the eye defects could usually be recognized by their facial resemblance.

Palatoschisis

Edmund in 1961[20] was probably one of the first to mention the occurrence of palatoschisis in pedigrees with retinal detachment. Subsequent reports[14-19,21] contain numerous references to its occurrence. Van Balen and Falger[22] and Knobloch and Layer[18] emphasized its very frequent occurrence with hyaloideoretinopathy and recommended that examination of the palate be done both visually and by palpation to detect the defect. The vast majority of the patients in the pedigrees have an intact soft palate with a bony separation of the posterior border of the hard palate. A bifid uvula is frequently associated.

Arthro-ophthalmopathy

In 1965 Stickler and associates[23] described a large family followed at the Mayo Clinic for many years with a dominantly inherited syndrome of generalized skeletal dysplasia, myopia, retinal detachment, flat facies, and cleft palate. In a subsequent publication[24] spondyloepiphyseal dysplasia and hearing loss were added. Three years later, Spranger[25] also described the radiographic abnormalities in this syndrome.

The skeletal defects appear early in life with widening of the joints. Hip dislocations are frequent. Irregular joint surfaces produce pain and occa-

sional limitation of motion later in life. Severely affected individuals may be slightly shorter in height. Hypermobility of some joints has also been reported.

The radiographic findings are those of a generalized spondyloepiphyseal dysplasia with flattening of the epiphyses, narrowing of the diaphyses, and flaring or widening of the metaphyses. Scheuermann's changes may appear in the spine.

Some subsequent pedigrees include individuals with the Pierre Robin defect.[26,27,28] During growth, mandibular hypoplasia becomes less evident and these individuals less easily recognized. These pedigrees, when surveyed radiographically, also revealed a similar generalized epiphyseal dysplasia.

Mild to moderate myopia appears in the families. Retinal detachment may occur early in life with large disinsertions. Cataract and glaucoma are also reported. A definitive description of the ophthalmoscopic findings has not yet appeared in the literature.

In an excellent review article describing two Canadian families with arthro-ophthalmopathy, the clinical findings of twenty-two affected individuals were summarized by Popkin and Polomeno.[29] Progressive joint degeneration was found in 85%, myopia in 83%, retinal degeneration in 61%, cleft palate in 28%, micrognathia in 17%, and sensorineural hearing loss in 9%.

In a letter to the editor of the New England Journal of Medicine, Opitz and associates[30] emphasized the variability of this syndrome and expressed the concern that it might be easily overlooked. Judith Hall[31] reported the radiographic changes of mild epiphyseal dysplasia in a child from a family with the Pierre Robin defect and dominantly inherited myopia and retinal detachment. She concluded that previously reported families with Wagner's syndrome, flat facies, and cleft palate all might have a manifestation of inherited progressive arthro-ophthalmopathy. These latter reports precipitated this present radiographic survey of families seen in our practice with dominantly inherited hyaloideoretinopathy.

METHOD OF STUDY

Roentgenograms of the hands, ankles, knees, spine, and hips were taken in forty patients. Thirty-three of the patients were selected from seven different families with inherited hyaloideoretinopathy and retinal detachment. Five of these families were felt to have fairly typical Wagner's disease. Two families with myopia, cataracts, and retinal detachments were

TABLE I: OPHTHALMIC EXAMINATION

Case	Age	Palate	Refract.	Cataract	Detach.	Vitreous	Retina	X-Rays
				ARTHRO-OPHTHALMOLOGY				
S.H.	12	SMC	Plano	O.S.	N	Syn. Memb.	Lattice RPVD	P
D.J.	20	N	−5.00	N	O.D. O.S.	Syn. Memb.	Lattice	P
				PEDIGREE ONE				
III_2	50	SMC	−1.00	O.D. O.S.	N	Syn. Memb.	Lattice RPVD	P
III_4	40	Cleft	−1.00	N	N	Syn. Memb.	Lattice RPVD	P
III_5	47	SMC	−1.75	O.S.	N	Syn. Memb.	Lattice RPVD	P
IV_{12}	22	SMC	−6.00	N	O.D O.S.	Syn. Memb.	Lattice	P
IV_{16}	16	SMC	−2.75	N	N	Syn.	Lattice RPVD	P
IV_{17}	13	SMC	−5.75	N	N	Syn.	N	P
IV_{18}	11	N	−1.50	N	N	Syn.	N	P
IV_{19}	6	SMC	−13.00	N	N	Syn.	N	P
				PEDIGREE TWO				
III_1	24	Cleft	−4.00	N	O.D.	Syn. Memb.	Lattice RPVD	P
III_4	35	N	−13.00	N	O.D.	Syn. Memb.	RPVD	P
III_5	37	N	−7.00	N	N	Syn. Memb.	Lattice	P
IV_5	18	SMC	−7.75	N	O.S.	Syn. Memb.	Lattice	P
				PEDIGREE THREE				
I_1	66	N	Myopic	O.D. O.S.	O.D.	Syn. Memb.	Lattice RPVD	P
II_1	42	N	−6.50	O.D. O.S.	O.S.	Syn. Memb.	Lattice RPVD	P
III_1	17	N	−11.00	O.D. O.S.	N	Syn. Memb.	Lattice RPVD	P
III_2	13	N	Plano	N	N	N	N	N
				PEDIGREE FOUR				
II_1	51	SMC	Myopic	O.D. O.S.	O.D. O.S.	Syn. Memb.	Lattice RPVD	N
III_2	22	SMC	−16.75	N	O.S.	Syn.	Lattice	P
III_3	17	SMC	−9.50	N	O.D.	Syn.	Lattice	P
III_4	12	SMC	−12.00	N	N	Syn.	Lattice	P

SMC Submucous Cleft
Syn. Syneresis
Memb. Membrane
RPVD Radial Perivascular Degeneration
N Normal
P Positive

TABLE I: *(Continued)*

Case	Age	Palate	Refract.	Cataract	Detach.	Vitreous	Retina	X-Rays
				PEDIGREE FIVE				
III_5	46	SMC	Myopic	O.D.	O.S.	Syn. Memb.	Lattice RPVD	P
IV_5	13	SMC	−8.00	N	O.D.	Syn. Memb.	Lattice RPVD	P
				PEDIGREE SIX				
III_4	65	N	Myopic	O.D. O.S.	N	Syn	Myopic Choroid-osis	P
IV_{10}	46	N	Myopic	O.D. O.S.	O.D. O.S.	Syn. Memb.	Myopic Choroid-osis	N
V_6	15	N	−25.00	N	O.D. O.S.	Syn.	Lattice	N
V_7	13	N	−23.00	N	N	Syn.	N	N
V_8	11	N	Plano	N	N	N	N	N
V_9	10	N	Plano	N	N	N	N	N
				PEDIGREE SEVEN				
III_2	41	N	−4.25	O.D. O.S.	N	Syn.	Lattice	N
III_5	31	N	−2.00	O.D. O.S.	N	Syn.	Lattice RPVD	N
IV_1	15	N	−12.00	N	O.D. O.S.	Syn.	Lattice	N
IV_7	8	N	−1.00	N	N	Syn.	N	N
IV_8	4	N	Plano	N	N	N	N	N
				INDIVIDUAL PATIENTS				
W.F.	44	N	−4.00	O.D. O.S.	O.S.	Syn.	Lattice	N
D.M.	55	Cleft	−3.00	O.D. O.S.	O.S.	Syn.	Lattice	N
M.W.	19	N	−17.00	N	O.S.	Syn.	Lattice Choroid-osis	P
E.A.	48	N	−7.00	N	O.D.	Syn.	Lattice RPVD	N
J.K.	13	N	−8.00	N	O.S.	Syn.	N	N

SMC Submucous Cleft
Syn. Syneresis
Memb. Membrane
RPVD Radial Perivascular Degeneration
N Normal
P Positive

TABLE II: X-RAY RESULTS

Patient	Hands	Ankles	Knees	Spine	Hips
		ARTHRO-OPHTHALMOPATHY			
S.H.	++ AO	+++	++	+++	++ CV
D.J.	+++	+++	++	+++	+++ CV
		PEDIGREE ONE			
III_2	+ AO	−	−	−	−
III_4	+ AO	+++	−	−	++
III_5	+ AO	+	−	−	−
IV_{12}	+	+++	−	−	−
IV_{16}	++ AO	++	−	−	− CV
IV_{17}	++	++	−	−	− CV
IV_{18}	−	++	−	−	− CV
IV_{19}	+ AO	+	−	+	−
		PEDIGREE TWO			
III_1	+ AO	+	−	−	−
III_4	+ AO	−	−	−	+ CV
III_5	+ AO	+	−	−	−
IV_5	+ AO	++	−	−	−
		PEDIGREE THREE			
I_1	−	+	−	−	−
II_1	++ AO	+++	−	−	−
III_1	++ AO	++	−	−	−
III_2	−	−	−	−	−
		PEDIGREE FOUR			
II_1	−	−	−	−	−
III_2	++	++	−	−	− CV
III_3	−	+	+	−	− CV
III_4	++	+	+	−	− CV

− Normal
+ Degree of Abnormality
CV Coxa Valga
AO Accessory Carpal Ossicle

also evaluated. In addition, five individual patients with retinal detachment were similarly screened. These patients did not necessarily appear to have clinical Wagner's disease, but were selected as controls because of their age or family history. Two patients with typical clinical arthro-ophthalmopathy were evaluated for comparison.

A complete ophthalmic examination was performed and fundus photographs were obtained of representative lesions. Facial photographs of all patients were also taken. A general examination was made to detect any skeletal abnormalities with special reference to joint thickening or any evidence of hypermobility. The hard and soft palate were also examined for palatoschisis.

TABLE II: *(Continued)*

Patient	Hands	Ankles	Knees	Spine	Hips
			PEDIGREE FIVE		
III_5	+	++	−	−	− CV
IV_5	−	−	+	−	− CV
			PEDIGREE SIX		
III_4	−	+	−	−	−
IV_{10}	−	−	−	−	−
V_6	−	−	−	−	− CV
V_7	−	−	−	−	− CV
V_8	−	−	−	−	−
V_9	−	−	−	−	−
			PEDIGREE SEVEN		
III_2	−	−	−	−	−
III_5	−	−	−	−	−
IV_1	−	−	−	−	−
IV_7	−	−	−	−	−
IV_8	−	−	−	−	−
			INDIVIDUAL PATIENTS		
W.F.	−	−	−	−	−
D.M.	−	−	−	−	−
M.W.	+	+++	+	+	− CV
E.A.	−	−	−	−	−
J.K.	−	−	−	−	−

− Normal
\+ Degree of Abnormality
CV Coxa Valga
AO Accessory Carpal Ossicle

RESULTS

A summary in tabular form of the ophthalmic examination of all patients is presented in Table I. Palate defects, when found, are also indicated and the roentgenograms are reported as positive or negative for skeletal dysplasia. A complete summary of the roentgenographic findings is tabulated in Table II. The degree of dysplasia is indicated and the presence of coxa valga or an accessory carpal ossicle is noted. The patients are grouped by family as shown on the pedigrees that precede the description of each family. Individual patients that were examined are summarized last. The first two patients in the tables are two unrelated patients with clinical arthro-ophthalmopathy. The results of their examinations will be described first for sake of comparison.

ARTHRO-OPHTHALMOPATHY

The first patient, S.H., is a male age 12. He is related to the original family described by Stickler and the presence of the disease was suspected

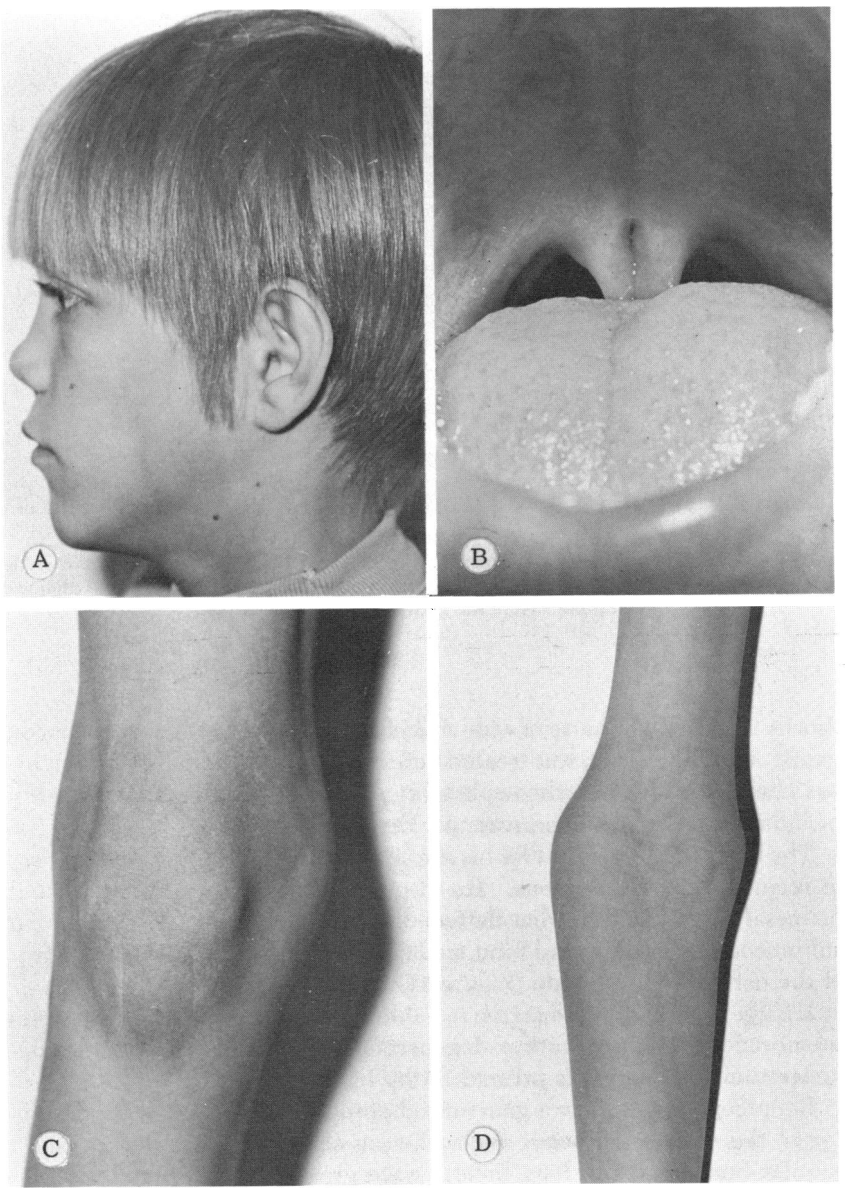

FIGURE 1

A: Patient S.H. Arthro-ophthalmopathy patient. Note flat mid-face with maxillary hypoplasia. Low nasal bridge with short nose. B: Submucous cleft palate with bifid uvula. C: and D: Widening of the knee and elbow joints.

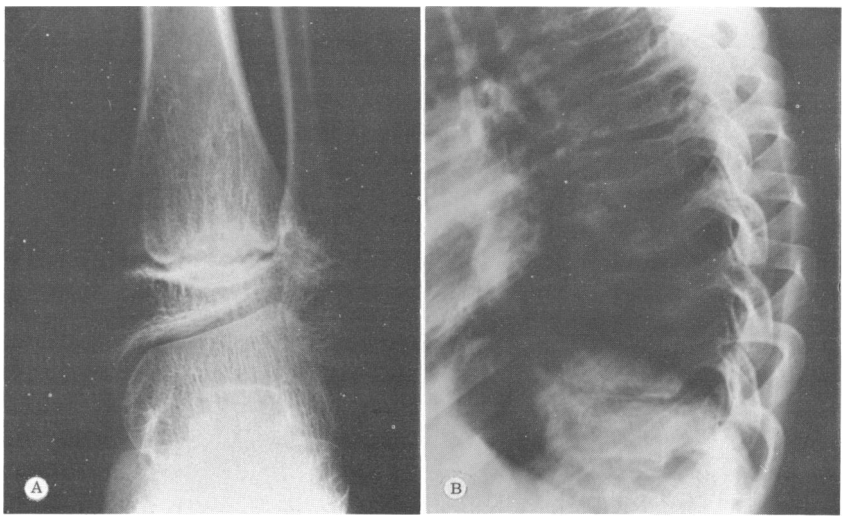

FIGURE 2
A: Patient S.H. Hypoplasia of the lateral portion of the distal tibial epiphysis. Widening of the metaphysis. B: Patient S.H. Epiphyseal and apophyseal irregularity of thoracic vertebrae. Note the flattening of the vertebrae.

shortly after birth because of widening of the wrist, knee, elbow, and ankle joints. His father, who was treated here for unilateral retinal detachment, has clinically obvious arthro-ophthalmopathy with hyaloideoretinopathy including marked radial perivascular degeneration.

The boy's stature is short for his age and he has a defect in gait secondary to recurrent hip dislocations. He displays mild mid-face flattening and his nasal bridge is somewhat flattened with a short nose (Figure 1A). A submucous cleft palate and bifid uvula is present (Figure 1B). The joints of the extremities are wide (Figure 1C and D).

His eye defects as summarized in Table I include vitreous syneresis with membranes, equatorial lattice degeneration, and radial perivascular degeneration. A cataract is present in the left eye.

Roentgenograms show a generalized epiphyseal dysplasia with flattening of the metacarpal heads and widening of the diaphyses of the short tubular bones and the long bones. Overgrowth of the growth centers appear to account for the widening of the joints seen clinically. The ankle roentgenogram (Figure 2A) shows a dysplasia of the lateral portion of the distal tibial epiphyses resulting in ankle tilting. Spondyloepiphyseal dysplasia of the spine is also present (Figure 2B).

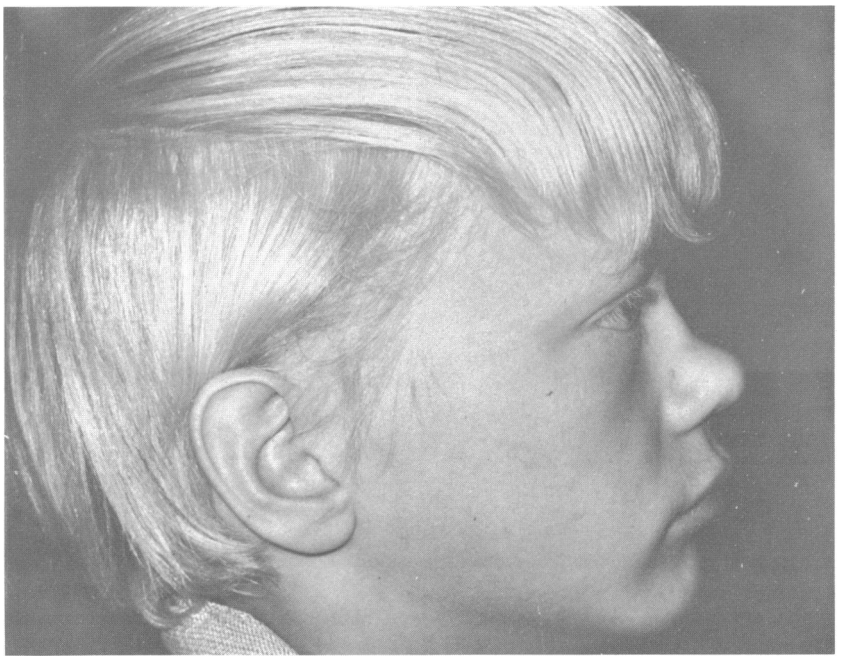

FIGURE 3
Patient D.J. Maxillary hypoplasia with low nasal bridge and short nose. Notice the remarkable similarity to the other unrelated arthro-ophthalmopathy patient in Figure 1.

The second patient, D.J., is a 20 year old male with a history of widened joints and recurrent hip dislocation since early childhood. Other members of his family have not been examined but the history is entirely negative for bone and joint disease or eye defects. He had an inoperable retinal detachment in the right eye with a large disinsertion at age 13 and a recurrent retinal detachment in his left eye beginning at age 16 that has been successfully repaired.

His clinical appearance is almost identical to that of the first patient with a reduction in height for his age, wide joints, and restricted gait. Mid-face flattening with a short nose is present (Figure 3).

Ocular examination discloses moderate myopia and vitreous syneresis with membranes attached to areas of equatorial lattice degeneration. No radial perivascular degeneration is present.

The roentgenograms demonstrate a generalized skeletal dysplasia that includes the thoracic spine. The overgrowth of the growth centers and a downward sloping of the tibial plateau is readily seen in the roentgenogram

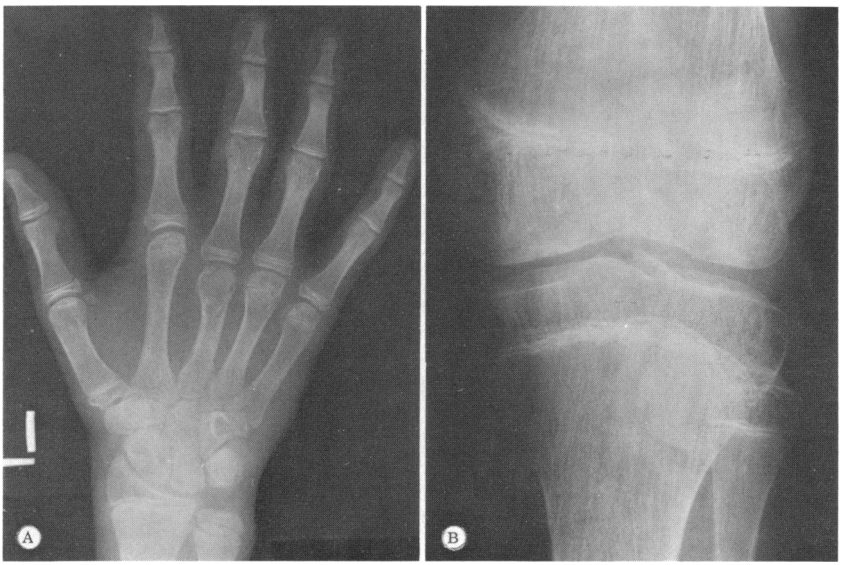

FIGURE 4
A: Patient D.J. Flattening of the metacarpal heads of the third, fourth and fifth metacarpals. Flaring of the metaphyses with wide M-P joints and proximal interphalangeal joints. Marked shortening of the third metacarpal. B: Patient D.J. Irregularity of the joint surfaces with downward sloping of the tibial plateau. Overgrowth of the growth centers with widening of the joint.

of the knee (Figure 4A). The hands are thick and short with flattening of the metacarpal heads, narrowing of the joint spaces, and flaring of the metaphyses (Figure 4B).

PEDIGREE ONE

This family has been followed here for over seven years. Affected members have myopia, hyaloideoretinopathy, and palatoschisis. Inheritance appears dominant with a high degree of penetrance. No systemic skeletal defects are present except for slightly elongated fingers. Mild mid-face flattening occurs in the young.

Vitreous syneresis is present in the younger affected individuals with membranes appearing additionally in the older members. Areas of chorioretinal atrophy occur associated with thin membranes (Figure 6A). Round pigment clumps are found equatorially and may be associated with vessels (Figure 6B and 6C). In some areas atrophy of the pigment epithelium and choriocapillaris with perivascular pigmentation extend posteriorly in a radial fashion (Figure 6D). Cataracts appear in the fifth decade. Bilateral retinal detachment with large disinsertions occurred in one patient at age 15.

Eight family members were surveyed radiographically and mild epiphyseal dysplasia was found. This is most evident in the hands and ankles (Figure 7A and 7B). Most of these patients have an accessory ossicle in the carpal bones of the hands. The youngest patient does show a very mild spondyloepiphyseal dysplasia of the thoracic spine.

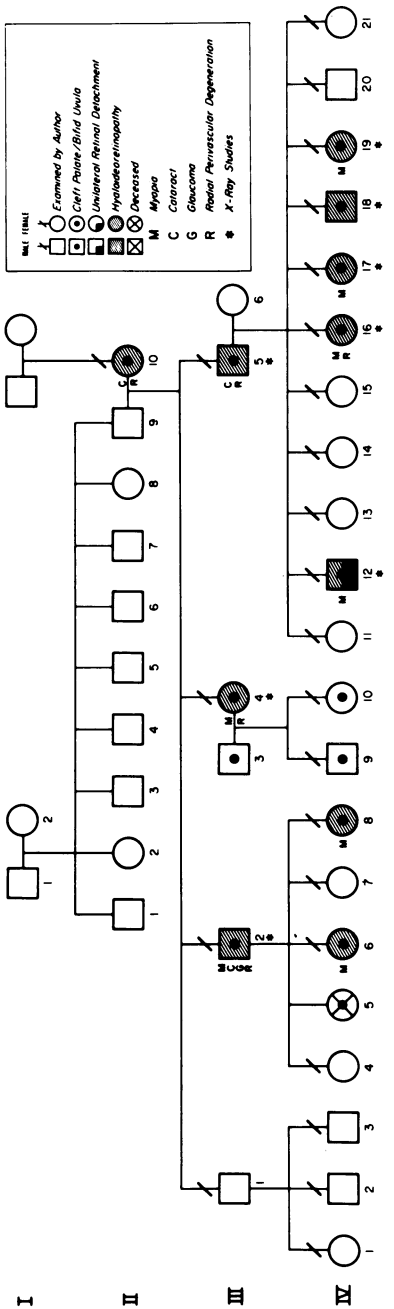

FIGURE 5 (Pedigree One)

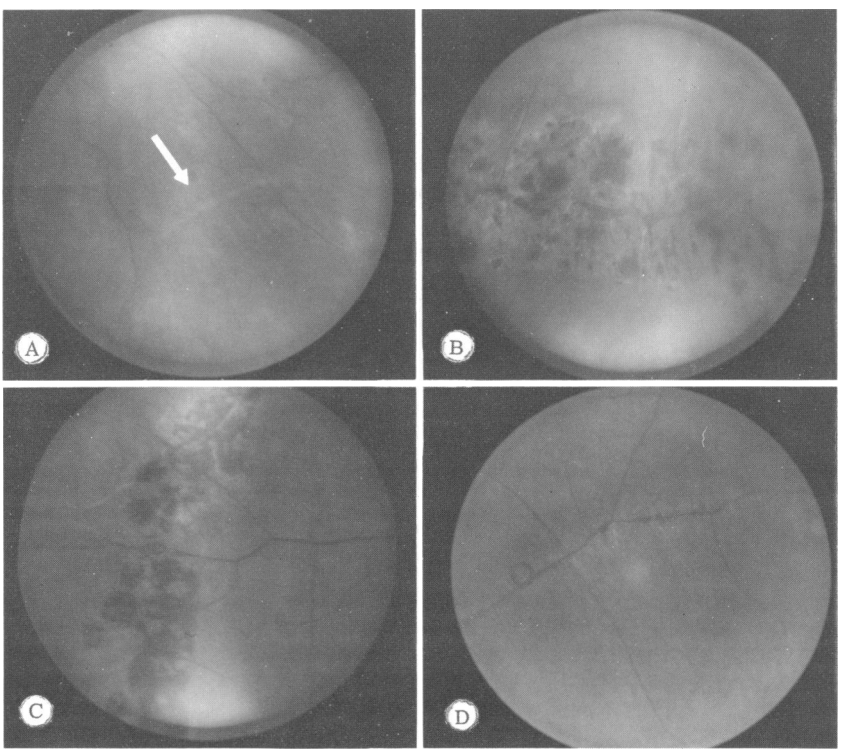

FIGURE 6

A: Pedigree One. III_4. Inferior-nasal quadrant, right eye. The arrow points to a thin membrane with an area of early pigment epithelium and choriocapillaris atrophy. B: Pedigree One. III_4. Circumferential perivascular degeneration with marked pigment clumping. Notice the sclerosis of the retinal vessels. C: Pedigree One. III_2. Circumferential clumping of the pigment in the temporal periphery of the right eye. Sheathing and sclerosis of the adjacent vessels. D: Pedigree One. III_5. Perivascular atrophy of the pigment epithelium and choriocapillaris with prominent choroidal vessels surrounding the vessel with pigment clumps occurring along the wall of the vessel.

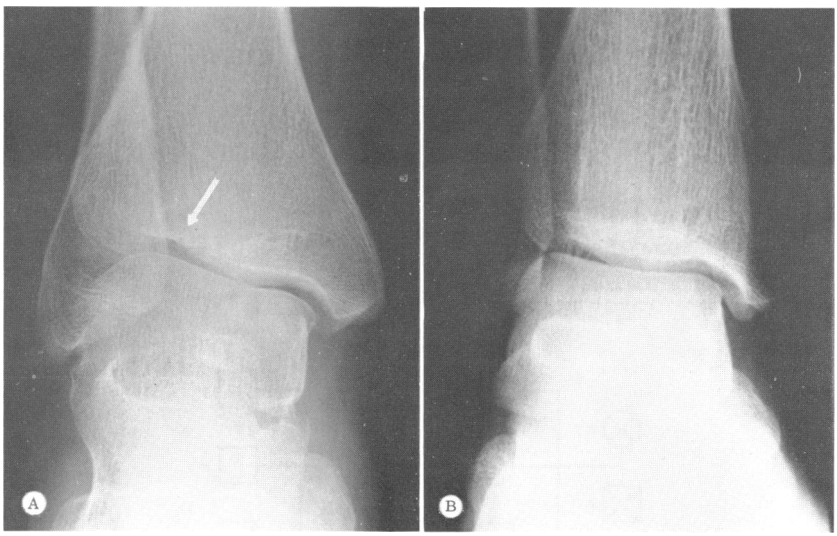

FIGURE 7
A: Pedigree One. III_4. Marked hypoplasia of the lateral portion of the distal tibial epiphysis.
B: Pedigree One. IV_{17}. Minimal hypoplasia of the lateral portion of the distal tibial epiphysis.

PEDIGREE TWO

This family with cleft palate and hyaloideoretinopathy has been followed here for seven years. Four members are evaluated in this study.

Mandibular growth is retarded (Figure 9A and 9B) and one child that died three days after birth may have had the Pierre Robin defect. The fingers are long (Figure 10) but no other skeletal defects are evident.

Moderately high myopia is accompanied by hyaloideoretinopathy with radial perivascular degeneration. Dense membranes are seen equatorially (Figure 11A) and patchy areas of atrophy of the pigment epithelium and mild choroidal sclerosis are present (Figure 11B). Retinal detachment has occurred in three members.

The radiographic survey shows all four patients to have mild epiphyseal dysplasia in the hands and ankles with accessory carpal ossicles. Flattening of the heads of the metacarpals and thinning of the diaphyses is present (Figure 12). Hypoplasia of the lateral portion of the distal tibial epiphyses occurs to a mild degree in three of the patients.

PEDIGREE THREE

This family is few in number, but three generations have been examined and each generation exhibits the ocular defects. They have been followed here for six years. Cleft palate has not been present. No facial flattening is present but both patient I_1 and II_1 have a peculiar bowing of the radius and ulna in both arms.

Retinal detachment has occurred in the two members in generation I and II. Moderately high myopia is present with vitreous syneresis, membranes, and radial perivascular degeneration increasing in severity with age (Figures 14A and 14B).

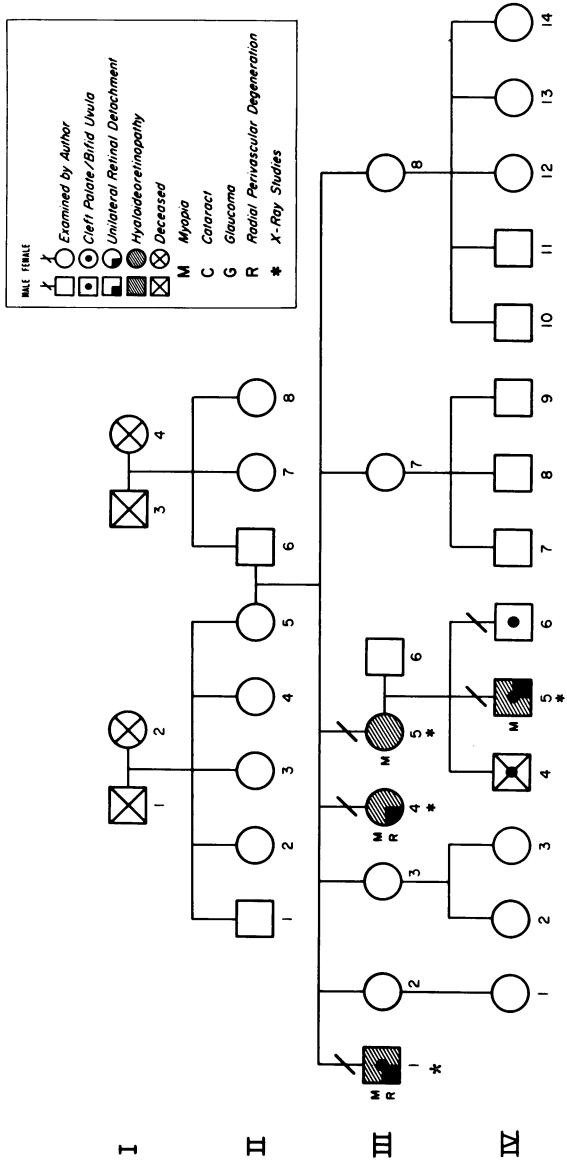

FIGURE 8 (Pedigree Two)

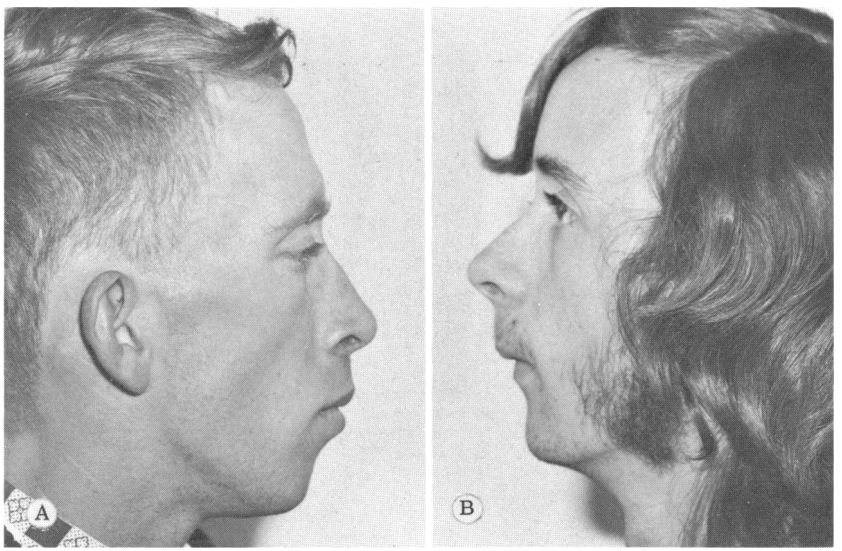

FIGURE 9

A: Pedigree Two. III_1. There is mild maxillary hypoplasia but the bridge of the nose is well developed. Mandibular growth appears to be retarded. B: Pedigree Two. V_5. This is a nephew of the patient shown in Figure 9A. Mandibular growth again appears to be somewhat retarded.

All three affected family members show epiphyseal dysplasia of the hands and ankles with the mildest dysplasia occurring in the oldest member. Accessory ossicles are present in the wrist and a Madelung deformity of the wrist that accompanies the bowing of the forearms is also present. The one unaffected member of the family (III_2) was also surveyed and found to have no dysplasia.

PEDIGREE FOUR

This family has been treated and followed here for nine years. Only two generations have been available for study. A high degree of penetrance of the defect is illustrated in generation three.

Submucous cleft palates are present as well as mid-face flattening (Figure 16). This has improved in appearance with growth. Slight widening of the wrist and elbows is present with elongation of the fingers.

All the family members except the youngest have had retinal detachments. High myopia associated with hyaloideoretinopathy is present. Only the older two members show radial perivascular degeneration. These same two individuals also have cataract and open-angle glaucoma. In the younger patients, choroidal sclerosis to a mild degree is present posteriorly. Some irregularity of the retinal vessels occurs at the disc but a true situs inversus was not seen.

Only four members were available for the radiographic survey and all exhibited mild epiphyseal dysplasia of the hands, ankles, and knees except for the oldest patient in genera-

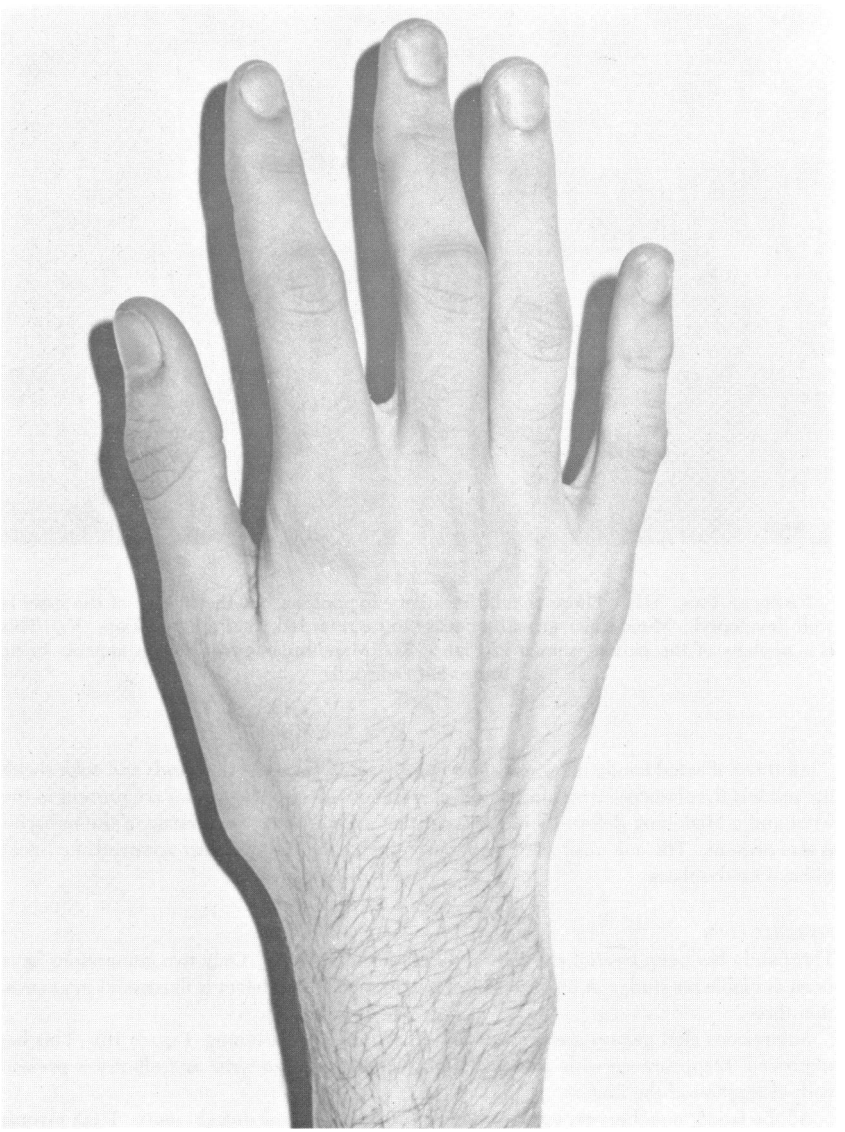

FIGURE 10

Pedigree Two. IV_5. The fingers are elongated and there is some hyperextension of the terminal phalanx.

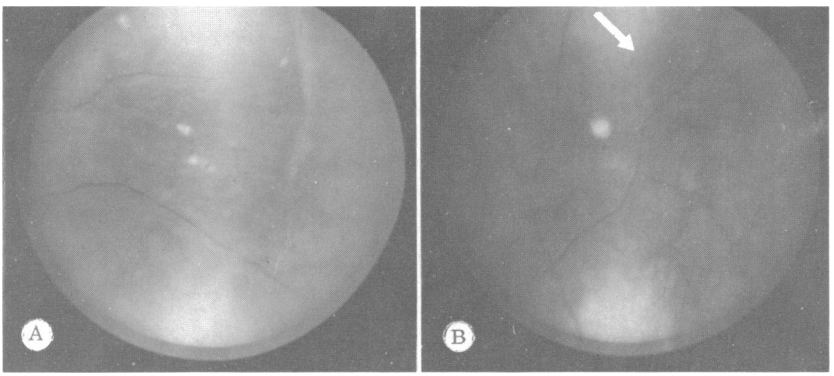

FIGURE 11

A: Pedigree Two. III_4. Dense equatorial membranes temporally, right eye. B: Pedigree Two. III_1. Patchy areas of atrophy of the pigment epithelium and choriocapillaris superiorly, left eye.

tion two whose roentgenograms were completely negative. Coxa valga is found in the hip roentgenograms of all the younger patients.

PEDIGREE FIVE

Only a few members from three generations of this family have exhibited the defects. The youngest has been treated here for retinal detachment and followed for four years.

Mid-face flattening with underdevelopment of the mandible is seen in the youngest patient (Figure 18). Submucous cleft palate and bifid uvula are also present. One sibling of the youngest patient died shortly after birth and by history may have had the Pierre Robin defect. Other than long fingers, no other skeletal defects are found.

Ocular defects include moderate myopia, cataract, retinal detachment, and a fairly severe hyaloideoretinopathy with radial perivascular degeneration.

Only two members were available for radiographic survey and their findings are summarized in Table II. The older patient has the typical epiphyseal dysplasia in the hands and ankles but the younger patient has only mild changes in the knees. Both have coxa valga.

PEDIGREE SIX

Members of this large family have been treated and followed here for seven years. Partial penetrance of the defects in four generations is illustrated.

Complete cleft palate was said to have been present in several deceased family members. Individuals that have been evaluated have a high palate with some notching of the posterior border of the hard palate but no submucous cleft or bifid uvula. No other clinically apparent skeletal abnormalities are found.

The ocular defects are summarized in Table I. Six members were selected for survey, four having ocular defects and two with normal eyes. The myopia is very high, in excess of 20 diopters. Cataracts are present in the two older members (III_4, IV_{10}). Bilateral retinal detachment has resulted in blindness in patient IV_{10} and bilateral retinal detachment with successful repair has occurred in patient V_6. This patient exhibits only lattice degeneration.

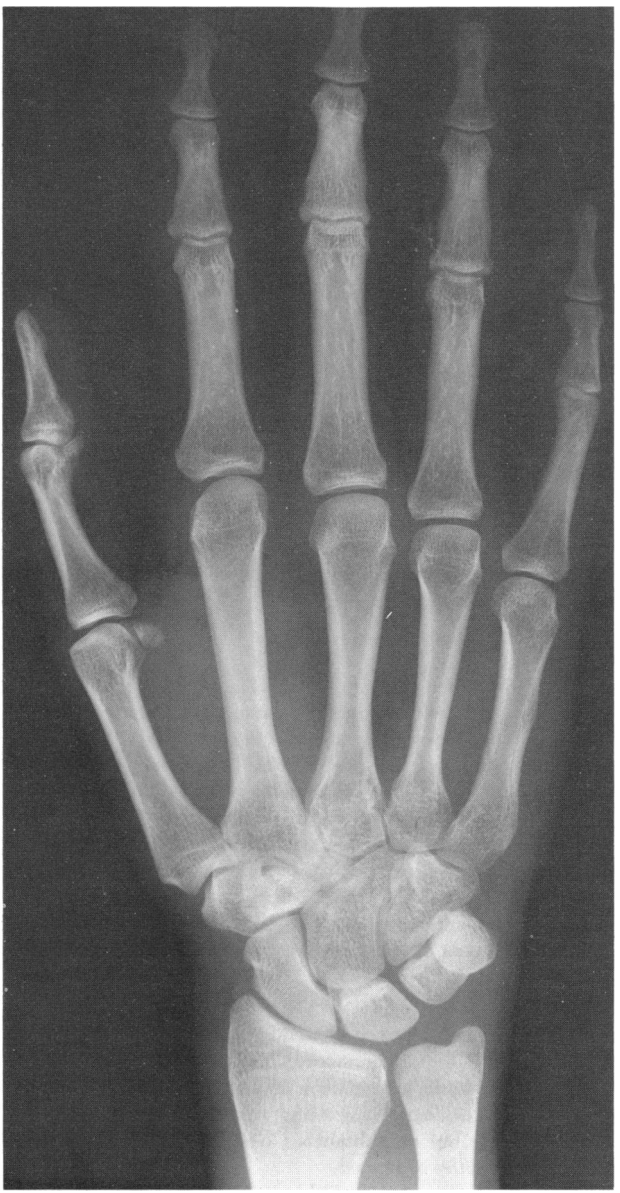

FIGURE 12

Pedigree Two. IV_5. This is the same hand as shown in Figure 10. There is flattening of the metacarpal heads of the third, fourth, and fifth metacarpals. The diaphyses are thin and there is phalangeal preponderance.

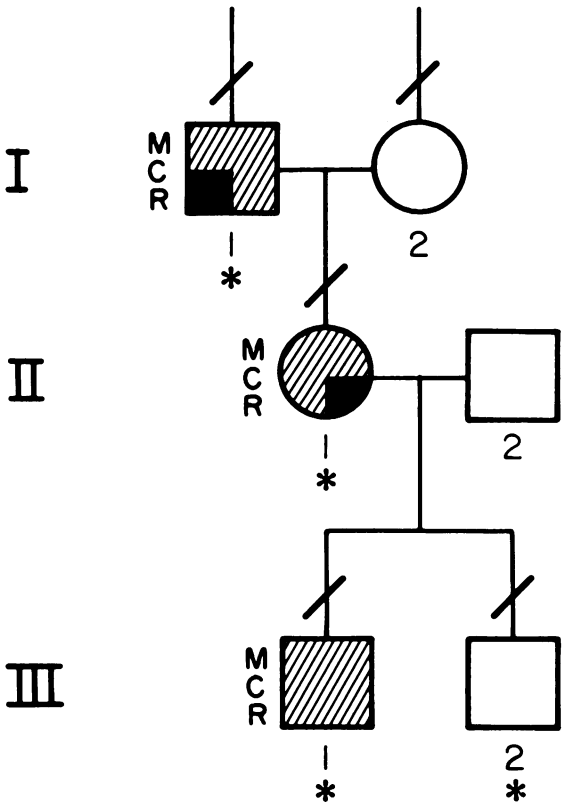

FIGURE 13 (Pedigree Three)

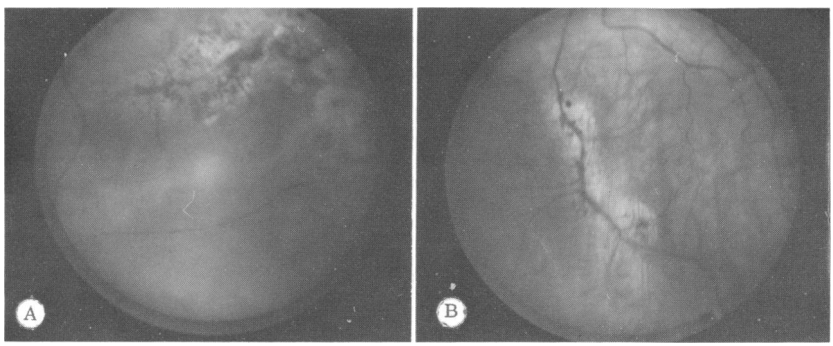

FIGURE 14

A: Pedigree Three. I_1. Radial perivascular chorioretinal degeneration, superior-temporally, left eye. B: Pedigree Three. I_1. Radial perivascular degeneration inferiorly, left eye.

Vitreous syneresis is present in the myopic patients but typical radial perivascular degeneration and patchy areas of chorioretinal atrophy are not present. In addition, in the older patients, severe myopic choroidosis involving the maculas is seen. Axial lenth measurements were obtained on two of the affected individuals and recorded as 29 and 31 mm (III_4 and V_6).

The radiographic survey found only one abnormal patient and that is the oldest patient in generation three. A marked hypoplasia of the lateral portion of the distal tibial epiphyses with ankle tilting is found.

PEDIGREE SEVEN

This family was brought to our attention because of bilateral retinal detachments in one of the younger patients occurring at the age of 12 years. A moderately high degree of penetrance of the ocular defects is illustrated in the pedigree. Five members are examined in this survey. The youngest has no ocular defects, but is included for control.

Cleft palate is not found in any of the individuals examined. The facial characteristics include only hypertelorism without mid-face flattening. There is some increase in height of the patients but no other skeletal defects are clinically apparent.

The ocular defects include myopia and vitreous syneresis without visible membranes. Cataracts occur in the fourth decade. The affected individuals also have equatorial lattice degeneration. Radial perivascular degeneration is conspicuously absent except in one patient (III_2) who has one small area in her right eye only. No patchy areas of pigment epithelium and choriocapillaris atrophy or choroidal sclerosis is seen.

The radiographic survey of the four affected members and the one normal patient are completely negative for any skeletal defect.

INDIVIDUAL PATIENTS

Five individuals are included in this survey, largely for control purposes. Each of these patients has had retinal detachment.

Patient W.F. is included because of a family history of cataracts, myopia and retinal detachment. Patient D.M. has a complete cleft of his hard palate. Only patient E.A. has

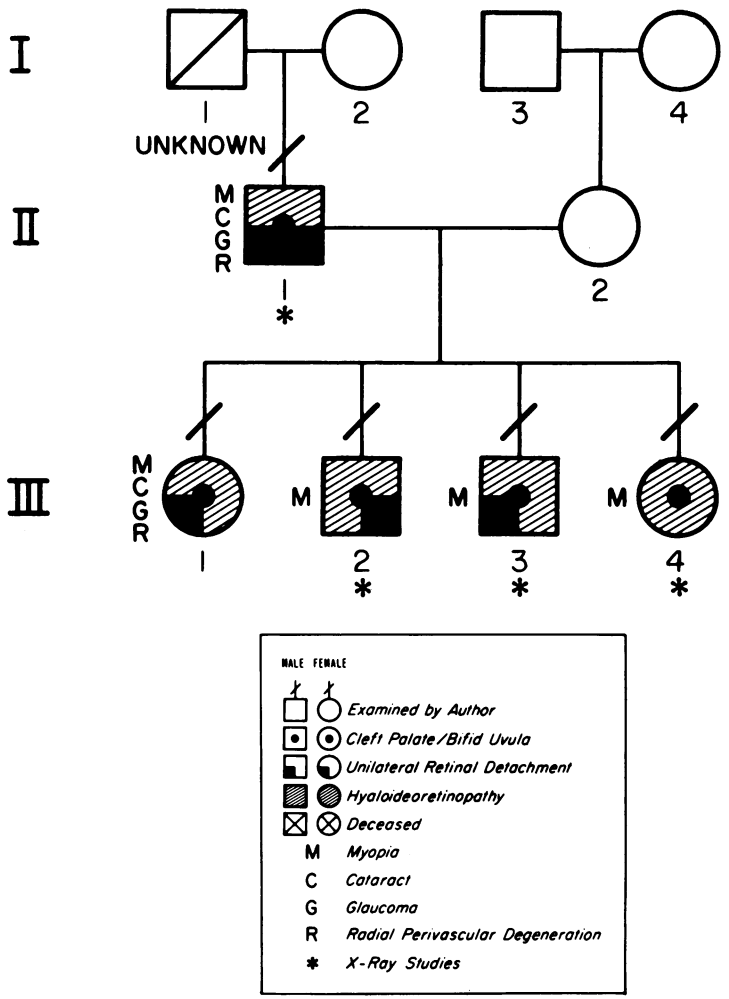

FIGURE 15 (Pedigree Four)

evidence of Wagner's hyaloideoretinopathy where vitreous syneresis without membranes is associated with radial perivascular degeneration and equatorial lattice degeneration.

All of the roentgenograms are negative for skeletal dysplasia except for patient M.W. who has the typical changes in the ankles, hands and knees. In addition, he has mild spondyloepiphyseal dysplasia of the thoracic spine. His ocular findings include very high myopia with equatorial lattice degeneration and early myopic choroidosis.

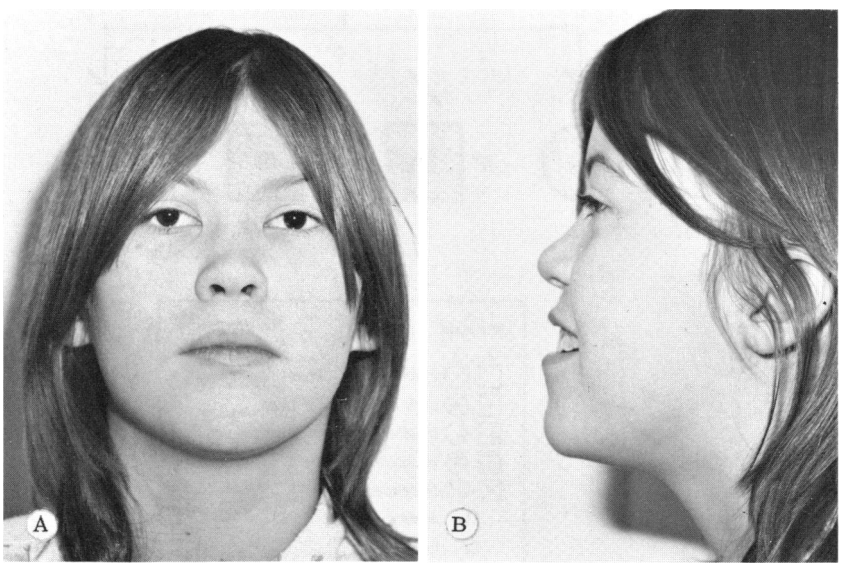

FIGURE 16

A: Pedigree Four. III_4. Epicanthal folds are present. B: Maxillary hypoplasia with a low nasal bridge resulting in mid-face flattening.

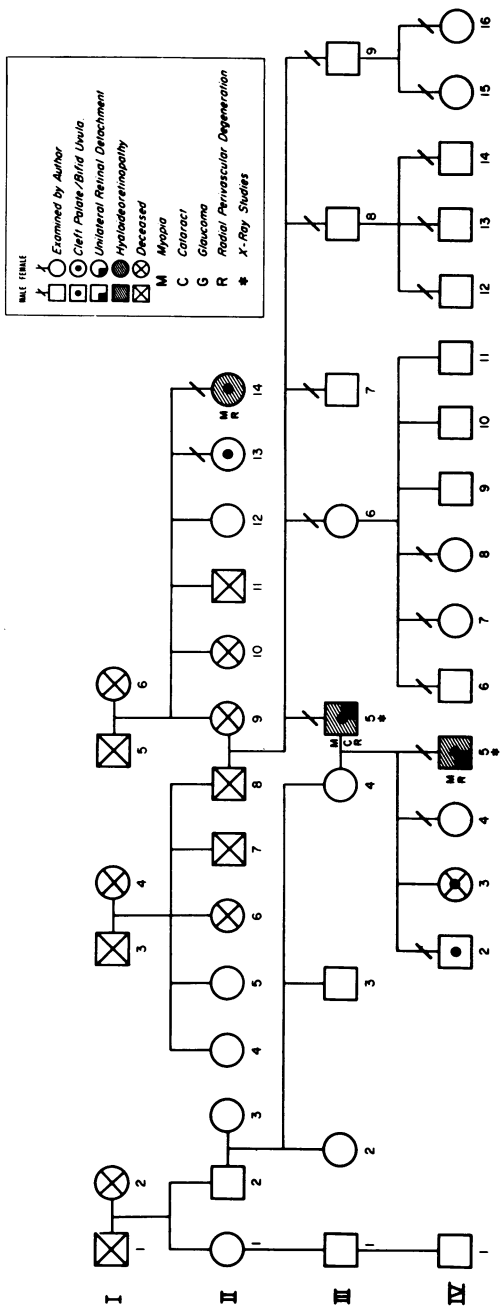

FIGURE 17 (Pedigree Five)

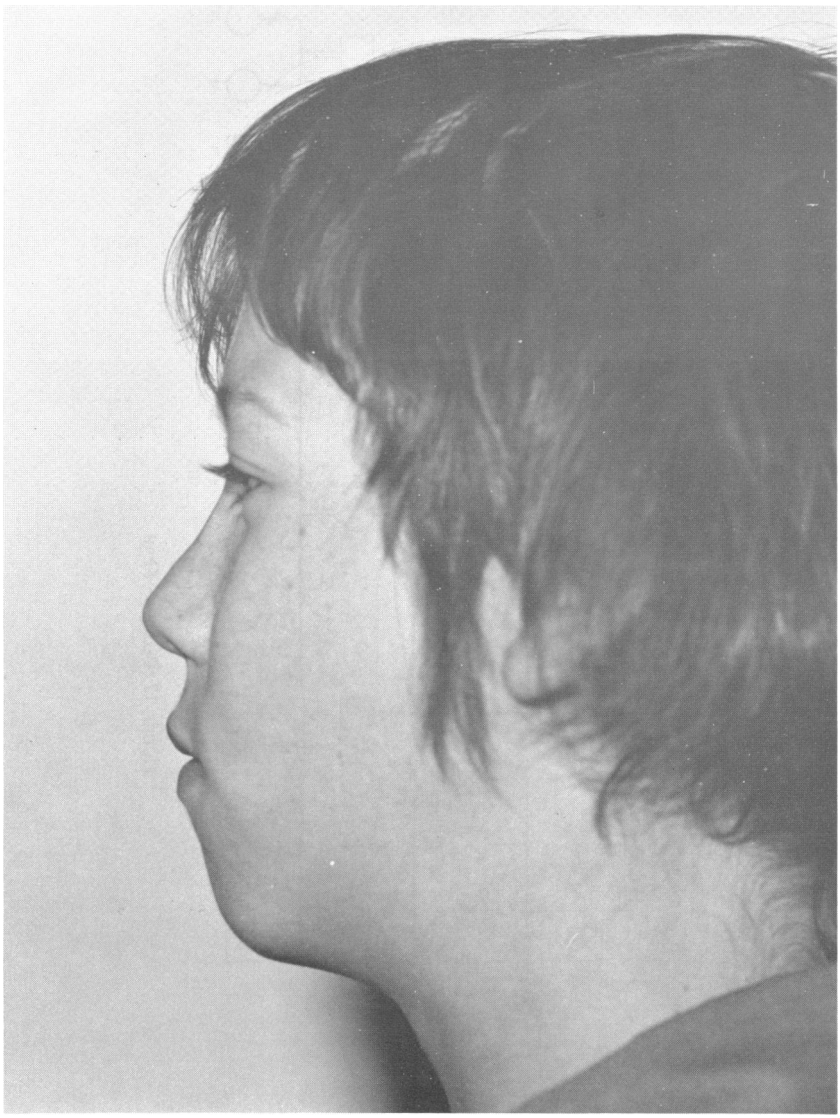

FIGURE 18
Pedigree Five. IV_5. Mid-face flattening and some retardation of growth of mandible.

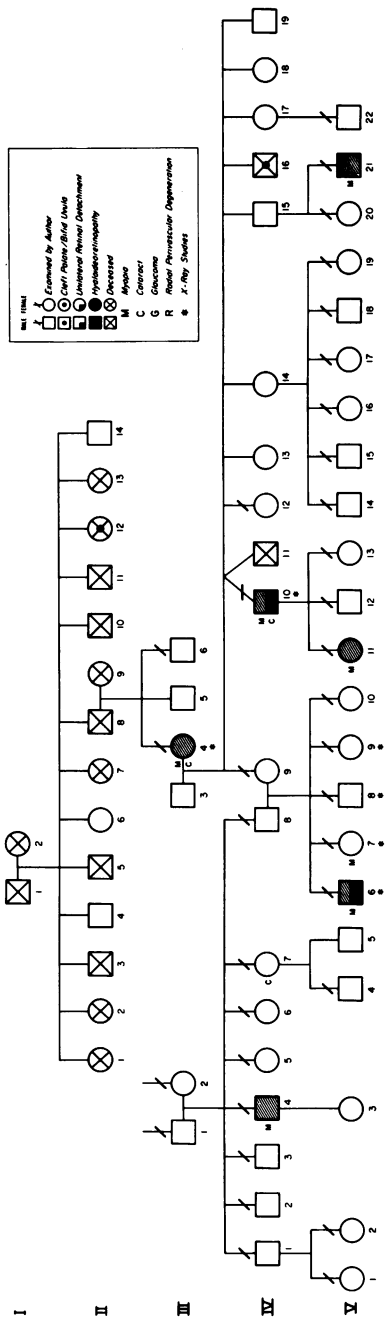

FIGURE 19 (Pedigree Five)

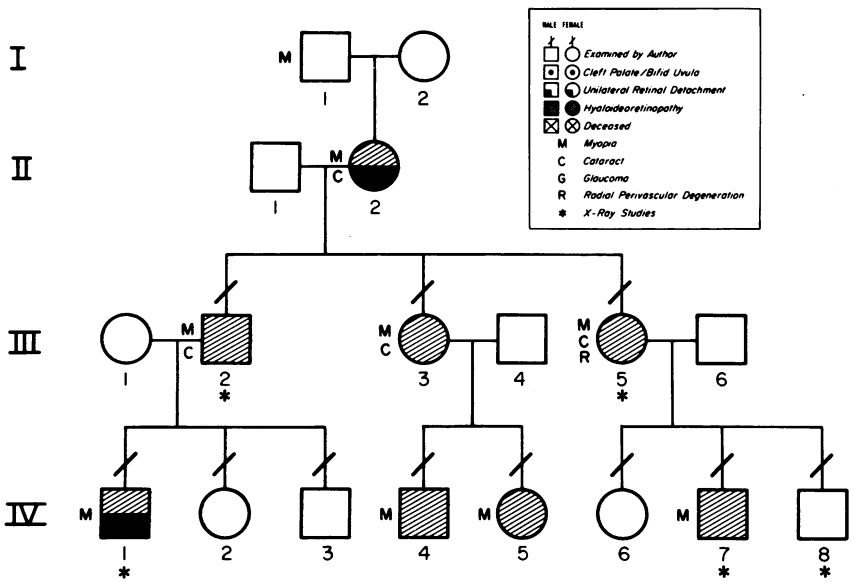

FIGURE 20 (Pedigree Six)

DISCUSSION

Despite the accumulated knowledge of Wagner's disease, confusion as to diagnostic criteria for making a definitive diagnosis persists. Cibis[32] compared the original descriptions of Wagner and the later reviewers with the findings in members of some of his families who had dominantly inherited hyaloideoretinopathy and concluded the diseases were similar. Jaffe[33] also expressed doubt that Wagner's disease and inherited myopic hyaloideoretinopathy were separate entities. In this study, I have interchanged the diagnostic terms Wagner's disease and dominantly inherited hyaloideoretinopathy. Family members whom I feel exhibit this disease consistently show vitreous degeneration with associated membranes. The most characteristic ophthalmoscopic lesion is that of radial perivascular chorioretinal degeneration associated with or preceded by patchy areas of atrophy of the pigment epithelium and choriocapillaris. Diagnosis in individual patients is still difficult despite our identification of criteria. This is largely due to the marked variability of expression of the disease between family members, with some manifesting only a portion of the syndrome.

This is especially true in the very young, as the various facets of the eye changes may not appear until later in life.

Individuals from the first five families surveyed in this report are felt to have fairly typical Wagner's disease based on the foregoing observations. Pedigree Six represents a family with high myopia with a great increase in axial length of the eyes. Missing are vitreous membranes and radial perivascular degeneration. Pedigree Seven appears to be a family with dominantly inherited equatorial lattice degeneration and cataracts and also without the other stigmata.

From these first five families with dominantly inherited hyaloideoretinopathy of Wagner, twenty-one patients with ocular defects were screened. Twenty of these have a mild generalized epiphyseal dysplasia. In the last two families without typical Wagner's disease, eight patients with ocular defects were evaluated. Seven of these do not show skeletal dysplasia but one patient does have dysplasia of the distal tibial epiphyses. Individuals with normal eyes from all seven families, evaluated as controls, have negative X-rays. A high correlation of radiographically diagnosed epiphyseal dysplasia and dominantly inherited hyaloideoretinopathy is evident.

Among the individual patients without family pedigree that were reported last in the results, one notable exception to the correlation of skeletal dysplasia with Wagner's disease was found. This patient (M.W.) has high myopia with myopic choroidosis and lattice degeneration. He does not have vitreous membranes or radial perivascular degeneration, and in our opinion does not manifest the eye changes we diagnose as Wagner's disease. Despite this, he does have a generalized epiphyseal dysplasia, including Scheuermann's changes of the thoracic spine.

Although detailed descriptions of the ocular fundus have not been given for patients with clinically apparent arthro-ophthalmopathy, some conclusions can be reached. The variable myopia, the types of retinal detachment seen and the frequent occurrence of cataracts are all defects commonly associated with Wagner's disease. I have had the opportunity to examine only three patients with arthro-ophthalmopathy, two of which have been described earlier in this report. None of these differ significantly from the criteria I have given for Wagner's disease. The oldest of the three patients, the father of patient S.H., demonstrated the very classical findings of a fenestrated vitreous membrane and radial perivascular chorioretinal degeneration. The conclusion that there is no significant difference in the hyaloideoretinopathy of Wagner and that associated with arthro-ophthalmopathy appears warranted.

In comparing the radiographic findings in patients with clinically ap-

parent arthro-ophthalmopathy with those with Wagner's disease, differences appear to exist primarily in degree of involvement. Generalized epiphyseal dysplasia is present in both groups with prominent changes in the hands and ankles. Spine and femorial head defects are much greater in the arthro-ophthalmopathy group. With age, the marked epiphyseal irregularities in the patients with arthro-ophthalmopathy are associated with degenerative joint disease. Significant hip joint degenerative disease occurs in only one of our patients with Wagner's disease. The apparent discrepancy in general physical appearance of the patients with arthro-ophthalmopathy from the members of our families (that is the tendency for short stature) can be explained by the greater epiphyseal dysplasia resulting in reduction of length of the long bones. I do not feel there is enough evidence yet to say if these differences are simply a variable expression of the phenotype with one common genotype or if, indeed, there is more than one genotype.

Our findings of epiphyseal dysplasia associated with hyaloideoretinopathy leading to retinal detachment should not be surprising. The literature contains many references to syndromes of skeletal dysplasia and ocular defects. Fraser,[34] in surveying systemic defects in 776 blind children, found skeletal dysplasia the most commonly associated handicap. I have been able to examine only one patient with spondyloepiphyseal dysplasia congenita and found her to have typical Wagner's disease.[18] The various syndromes of skeletal dysplasia have usually been considered to be quite rare. Since Wagner's disease is not at all uncommon, we can conclude that this type of skeletal dysplasia which we have described is probably one of the most frequently encountered forms.

The association of the Pierre Robin defect with the various families reported having arthro-ophthalmopathy and inherited hyaloideoretinopathy is of some interest. The name of Robin became associated with the malformation defect of cleft palate, glossoptosis, and micrognathia from his early description in 1923.[35] Associated ocular defects were analyzed by Smith and Stowe in 1960.[36] Retinal detachment and myopia were reported in one patient. Two brothers from this same study were reported in detail by W. King Smith in 1969.[37] In light of our knowledge now, the general appearance of these two patients is that of arthro-ophthalmopathy. It is generally agreed that the Pierre Robin defect is not a syndrome in itself but has a multiplicity of etiologies. In patients with skeletal dysplasia and hyaloideoretinopathy, the defect is the result of a retarded mandibular and palate development in association with a flat mid-face.

Attempts to identify a chemical abnormality in patients with arthro-ophthalmopathy or a structural tissue component irregularity in skeletal

dysplasia have not been fruitful. Biopsies of synovial tissue and chemical analyses by Stickler and associates[23] did not uncover a specific defect. Increased urinary hydroxproline excretion was reported by Popkin and Polomeno.[29] It is interesting to speculate on the possibility of the presence of a common defect responsible for the apparently disparate ocular defects and the skeletal dysplasia. As the abnormal vitreous appears to be the most universal ocular defect, an attempt should be made to analyze chemical and basic structural alterations of the vitreous in patients with inherited hyaloideoretinopathy.

SUMMARY

Twenty-one patients from five families displaying the ocular defects of dominantly inherited hyaloideoretinopathy as originally described by Wagner were surveyed radiographically for skeletal defects. A mild generalized epiphyseal dysplasia was found in twenty. A comparison of the skeletal dysplasia associated with arthro-ophthalmopathy and that found in families with Wagner's disease reveals more similarities than differences. It is concluded that Wagner's disease is a dominantly inherited syndrome of ocular defects that includes myopia, vitreous syneresis with membranes, and radial perivascular chorioretinal degeneration. It is associated with radiographically demonstrated generalized epiphyseal dysplasia that is manifested clinically by flattening of the mid-face and palatoschisis.

ACKNOWLEDGEMENTS

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