THE EYE IN THE MARFAN SYNDROME*

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INTRODUCTION

IN 1972 MCKUSICK,[1] IN DISCUSSING THE BASIC DEFECT OF THE MARFAN SYNDROME IN his textbook entitled *Heritable Disorders of Connective Tissue,* wrote the following: "What the suspensory ligament of the lens has in common with the tunica media of the aorta is obscure. If this common factor were known the basic defect of the Marfan syndrome might be understood." Is this a valid premise for the study of the Marfan syndrome, or are the zonular fibers only secondarily involved? Prior to addressing the question of the basic defect of the Marfan syndrome, however, we should consider the problems of diagnosis and management of these patients from an ocular and systemic point of view. The question of possible correlation, and thus predictive value, between the ocular and systemic findings has never been analyzed, nor has the correlation of individual ocular signs. In this thesis, I will attempt to do this.

BACKGROUND

Probably the first description of a family with the Marfan syndrome was made in a report to the American Ophthalmological Society at its 11th annual meeting in Newport, RI, in July 1875 by E. Williams[2] of Cincinnati, under the title "Rare Cases, With Practical Remarks." Under that heading he described a brother and sister who probably had the syndrome of dislocated lens and pupil, and a brother and sister and their identically affected father who all had dislocated lenses and generalized loose-jointedness. The eyes were characterized by divergence strabismus, small and sluggish pupils, trembling irides, and deep anterior chambers in addition to the upward dislocation of the lenses in the three affected. The sister had a spontaneous unilateral retinal detachment at the age of 28 years. The brother, at 26 years, was described as being large and loose-jointed like his sister. Unfortunately no further comments about their physical findings were made. That author did not include photo-

*This investigation was supported in part by grant 01773 from the National Eye Institute, Bethesda, Md.

graphs of the patients; this is probably why his description went unnoticed and why we now use the eponym "Marfan syndrome" instead of "Williams syndrome" for this heritable disorder of connective tissue, which the French pediatrician Marfan described in 1896 in a 5½-year-old child who had long, thin extremities.[3] Marfan coined the term "dolichostenomelia." The same child was reexamined at the age of 11½ years, and a follow-up report was published by Méry and Babonneix.[4] At neither time were ocular or cardiovascular complications noted. The patient had fibrous contractures of the fingers and a marked scoliosis on reexamination.

In 1902 the condition was renamed "arachnodactyly" by Achard.[5] Both the terms "dolichostenomelia" and "arachnodactyly" continue to be used to denote the Marfan syndrome. The Marfan designation seems preferable, however, because it does not describe only the skeletal findings of this entity; but even the term "Marfan syndrome" will probably be displaced when the basic defect of this condition becomes known. I will use the term "Marfan syndrome" throughout this text. The term "Marfan syndrome" was first introduced by Weve,[6] of Utrecht, The Netherlands, who used the term "dystrophia mesodermalis congenita, typus Marfanis," conceiving of it as a generalized defect of mesenchymal tissues. Weve[6] first pointed out the presence of atypical cases or "formes frustes" in this syndrome, using this term for mildly affected secondary cases in families with a severely affected proband. Thus, the variable expressivity of this syndrome between cases and within families was observed early. Many case reports describing the various manifestations of this disorder have since been published.

Patients with the Marfan syndrome show, in addition to the eye changes, abnormalities in two areas: the skeletal system and the cardiovascular system. The changes in the skeletal system include excessive height caused by excessive length of the distal limbs, loose-jointedness, scoliosis, and anterior chest deformities. The skeletal proportions are unusual, with an increased arm span in relation to body height, and an elongated lower segment (pubis to sole) compared with the upper segment (pubis to vertex). The absolute height is not as important as the patient's relative height, given the family background. These patients will be the tallest in their families. Many extremely tall patients, however, have also been described. Marfan first defined the condition as an abnormality of the skeleton, and thus the subsequently described early cases had very striking skeletal changes. Marfan patients, however, may develop adequate adipose tissue with age and even become obese, thus masking the skeletal abnormalities evident at a younger age; others, at birth, may not show the characteristic dolichostenomelia, but may develop it with growth.

The major cardiovascular complications of aortic dilatation, dissecting aortic aneurysm, and "floppy mitral valve" were first clearly described in 1943 by Baer et al[7] and Etter and Glover.[8] The cardiovascular complications of this entity are most marked in the ascending aorta and in the mitral valve. The defects are presumably due to an inborn weakness of the vascular tissues, with subsequent degeneration, since the vascular tissues mainly involved are those under high vasodynamic stress, such as the ascending aorta and the mitral valves. In the aorta, dilatation usually begins at the base, particularly the sinuses of Valsalva and the lines of attachment of the aortic cusps. Severe aortic regurgitation may occur before clear signs of aortic dilatation can be demonstrated. The aortic dilatation is usually progressive, and the course may simulate the one seen in syphilitic aortitis. Aortic aneurysms most commonly involve the ascending aorta, but Weve[6] described the presence of a large abdominal aneurysm in a 36-year-old proband. The mitral cusps and chordae tendineae may be redundant, with resulting mitral regurgitation. Involvement of the mitral valves, with regurgitation, may be the main cardiovascular lesion in the Marfan syndrome and may lead to early death (prior to the age of 10 years). Later death is commonly associated with dissecting aortic aneurysms.

Weve's[6] oldest patient was alive at the age of 62. McKusick's[1] oldest patient died at 61 years of age with severe aortic regurgitation. Bowers described two patients with the Marfan syndrome who were still living at 61 and 66 years of age respectively.[1] Stillborn children with the Marfan syndrome were reported by Capotorti et al.[9] Bowers found the average age at death to be 43 years in males and 46 years in females.[1] Murdoch et al[10] analyzed 257 cases of the Marfan syndrome by the life-table method for survivorship curves and found that 50% of all male patients were dead by the age of 41, and 50% of all female patients were dead by the age of 49. Cardiac problems led to 52 of the 56 deaths of known cause, with complications of aortic dilatation accounting for about 80% of the deaths.

Weve[6] clearly pointed out the often familial nature of this disorder, and he defined the inheritance as autosomal dominant. The penetrance appears to be nearly complete, and both sexes are affected equally often. However, Marfan's original patient and many additional patients reported subsequently were isolated cases in their families and were interpreted as representing new autosomal dominant mutations. Viewed retrospectively, many of these patients may have suffered from homocystinuria. Lynas[11] estimated the mutation rate as 5×10^{-6} per gamete per generation in the population of Northern Ireland, and estimated a prevalence figure

for the Marfan syndrome as 1.459/100,000 of the population. Most recently, Pyeritz and McKusick[12] gave a prevalence estimate of 1/20,000 for the United States population.

Boerger,[13] a pediatrician, was the first to point out that ectopia lentis is part of the clinical manifestations of the Marfan syndrome. The lenses in both of his cases were bilaterally dislocated upward. The retina was apparently attached. Many reports have referred to iridodonesis as a sign of lens dislocation. Several reports describe microspherophakia.[14-16] Moderate to high myopia is usually seen. No measurements are in the literature to indicate whether this myopia is of lenticular or axial origin. Megalocornea[17] and keratoconus[18] have been described. The presence of angle abnormalities is discussed by Burian,[19] Burian et al[20] and by von Noorden and Schultz.[21] These angle changes, however, do not appear to be pathognomonic of the Marfan syndrome, because they are seen in many abnormalities of connective tissue and even in normal patients. In Williams' case[2] and others since, an increased prevalence of retinal detachments has been reported. Cross and Jensen[22] found a retinal detachment in 9% of the phakic patients and in 19% of the aphakic eyes. Among Jarrett's 24 cases with the Marfan syndrome,[23] a retinal detachment had occurred in 54% of the patients: prior to lens extraction in eight eyes, after lens extraction in three eyes, and after peripheral iridectomy in two eyes. Twenty-six eyes had had a lens extraction. These patients had all been admitted to the hospital because of dislocated lenses, and I presume that he is therefore dealing with a biased series.

Several authors describe glaucoma in the Marfan syndrome and discuss the relationship to dislocation of the lens.[24,25] Various estimates of the prevalence of dislocated lenses in the Marfan syndrome have been given, ranging from 79% of the patients[22] to close to 100%.[1] Jarrett[23] reviewed 166 patients with ectopia lentis admitted to the Johns Hopkins Hospital. Twenty-four of these patients had the Marfan syndrome. The dislocation was caused by trauma in 85 cases; among those, 27% had a positive serology for syphilis. A list of causes of ectopia lentis is given in Table I.

Chandler,[25] in a paper entitled "Choice of Treatment in Dislocation of the Lens," concludes with the question "If vision is impaired, will we in the long run improve vision by removing the lens?" I will try to answer this question as we proceed with discussion of the data.

HISTOPATHOLOGIC FINDINGS

The first histopathologic report on the eyes of a patient with the Marfan syndrome was made by Dvorak-Theobald[26] and read before the American Ophthalmological Society at Hot Springs, Va, June 3 to 5, 1940. The

TABLE I: DIFFERENTIAL DIAGNOSIS OF ECTOPIA LENTIS

Genetic:
- Without systemic manifestation
  - Simple ectopia lentis
    - (1) congenital (recessive and dominant varieties reported)
    - (2) delayed onset (recessive and dominant varieties reported)
  - Ectopia lentis et pupillae (recessive)
  - Aniridia (several varieties)
  - Megalocornea (most commonly x-linked; dislocation of the lens a rare complication)
- With systemic manifestation
  - Marfan syndrome
  - Homocystinuria
  - Weill-Marchesani syndrome
  - Hyperlysinemia
  - Sulfite oxidase deficiency

Nongenetic:
- Trauma
- Luetic
- Persistent hyperplasia primary vitreous

report concerned a 27-month-old child who had died from an unrelated cause. On an earlier ocular examination the patient had been found to have megalocornea, miotic pupils, and iridodonesis with superonasally dislocated lenses. The most striking feature on pathologic evaluation was the extreme size of the globe, with an anteroposterior dimension of 33 mm, and a corneal diameter of 12.5 mm horizontally and 12 mm vertically. The distance from the limbus to the center of the insertion of each rectus muscle was markedly increased, measuring as follows: superior rectus, 11 mm; medial rectus, 8 mm; inferior rectus, 8.6 mm; and external rectus, 8.9 mm. There were no folds in the iris. The dilator of the pupil was not formed. The lens was displaced 0.5 to 1.5 mm behind the iris. The lens fibers appeared to be normal. The anterior angle was wide open, but Schlemm's canal was displaced with respect to the normal angle structures.[26] There were pectinate ligaments, interpreted as incomplete separation of iris and trabecular meshwork, and the circular fibers of the ciliary muscle were scarce. The choroid was thin, comprising only one or two layers of vessels. The pigment epithelium beneath the retina was absent in some places. Anteriorly the retina was stretched. Behind the equator, however, the retinal layers were well differentiated and there appeared to be normal development of the macula. The optic nerve appeared to be normal, but there was a large temporal crescent.

Further pathologic reports since then have pointed out the same features.[27,28] In addition, Wachtel[29] saw a small lens, and he again commented on the unusual depth of the anterior chamber and that the iris was attached to the ciliary body in a far posterior position. Allen et al[30] also stated the following:

> The ocular enlagement appears to be a common, if not invariable, feature of the Marfan syndrome . . . . The degree of ocular enlargement was not uniform in all dimensions, and in the two cases where enlargement was most pronounced the measurements were disproportionately great in the vertical and horizontal diameters. In two cases the corneal scleral groove appeared exaggerated, and in the third case it was distinct. In all three cases it was located far more anteriorly than normal . . . . It is interesting to know that despite the remarkably thin sclera, scleral staphylomata were not present in the pathologic specimens.

Ramsey et al[31] found similar changes on histologic evaluation. In addition, they state that the sample of the zonule examined by light microscopy had a normal structure, as did the ciliary epithelium. On scanning electron microscopy, however, the anterior zonule-lens capsule relationship was changed; there appeared to be a lack of widespread separation of the zonular fibers into a fan of filaments, and the fibers became attenuated toward the lens capsule. Farnsworth et al[32] examined the lens that was extracted from a patient with the Marfan syndrome. It showed, on scanning electron microscopic evaluation, that the capsular fibers were abnormally large and grossly granular, and so were the zonular fibrils, which maintained the normal parallel orientation, however. Those authors conclude that the basic defect lies in a structural protein that plays an important role in zonular and capsular construction.

Henkind and Ashton[33] performed the histologic examination on four eyes from three patients with homocystinuria, and they found consistent changes among these cases in the region of the zonular area of the ciliary body and the pars plana. The main abnormality consisted of deficiency of the zonular fibers adjacent to the lens. The fibers had retracted to the surface of the ciliary body, where they lay matted into a feltwork. Among cases of homocystinuria reported by Ramsey et al,[34] there were similar changes of the lens fibrils, and also an atrophic or underdeveloped ciliary body and anterior dislocation of the lens. No comment is made in either report about enlargement of the globe. Seland[35] described the changes seen in the zonular fibers of a patient with autosomal dominant congenital simple ectopia lentis. He found that the ultrastructure of the lens capsule was normal. However, it was completely devoid of zonular fibers in most areas, with some irregular remnants remaining in others. The capsular attachment fibers were underdeveloped, and he concluded that the con-

genital ectopia is the result of defective development of the zonular apparatus. Farnsworth et al[36] examined the lens from a patient who had presumably an identical diagnosis, and they saw similar findings. The primary abnormality in this patient, however, was in the reduction of size of the lens fibers to 20% of their normal cross-sectional area. We may be dealing with different entities in those two reports. Certainly there would be no confusion between the histologic changes of those cases compared with the changes seen in the Marfan syndrome.

The histologic evaluations of the vascular system of patients with the Marfan syndrome show mainly changes in the tunica media of the great vessels and in the heart valves.[37] The advanced changes seen in the aorta consist of fragmentation and sparsity of elastic fibers, irregular whorls of hypertrophied and perhaps hyperplastic smooth muscle, increase in collagen, and pronounced increase in vascularity of the tunica media with wide dilatation of the vasa vasorum. In both the adventitia and the media, there were cystic spaces occupied by metachromatically staining material. Takebayashi et al[38] described the light microscopic changes of this lesion as "cystic medionecrosis," a change that is not peculiar to the Marfan syndrome. They did not find ultrastructural changes of the collagen fibers in the arterial wall specific for the Marfan syndrome. However, this does not exclude impaired cross-linking, which would not have been diagnosed under this methodology. No histologic abnormalities were found in the elastic tissues of trachea, skin, spinal ligaments, and in vertebral discs, all primarily composed of elastic fibers.

BASIC DEFECT

The basic defect of the Marfan syndrome is still unknown. In what element of connective tissue is the defect of the Marfan syndrome located? The histologic appearance of the aorta suggests that the primary defect may be in the elastic fibers. However, the histologic changes are not inconsistent with the possibility that the priimary defect involves collagen. There is more collagen than elastic tissue in the aorta, and by interconnecting the elastic lamellae the collagen fibers may be important to the structural integrity of the skeleton of the aortic media. The fact that no changes were found in tissues primarily composed of elastic fibers, such as the spinal ligaments and vertebral discs, also implies a more likely primary defect of collagen fibers. To date, it is unclear in which tissue the primary defect resides.[1]

MATERIALS AND METHODS

PATIENT COLLECTION AND DIAGNOSIS

A variety of medical specialists refer between 150 and 200 patients annually to our clinic for ocular evaluation to assist with the diagnosis and management of patients with presumed Marfan syndrome. The referring specialists include ophthalmologists, orthopedists, pediatricians, internists, and cardiologists. Similarly, patients referred to us for evaluation by an ophthalmologist are referred on to the departments of pediatric genetics or medical genetics, depending upon the age of the patient, for further systemic evaluation and management.

In the present study, all patients suspected of being affected by the Marfan syndrome received a thorough physical examination including measurements of body proportions, chest auscultation, chest roentgenogram, and echocardiogram as the minimum procedures.

The diagnosis of the Marfan syndrome is based on four criteria: ocular, cardiovascular, skeletal disease, and familial occurrence. In a patient with the classic Marfan syndrome the diagnosis is certain, and frequently three or four of these criteria are fulfilled. However, some mildly affected patients are seen in families, or sporadically, and in these a definite diagnosis may be difficult. No laboratory examination or test exists to confirm or negate this diagnosis. In mild cases, the presence of at least two of the clinical criteria was required to make the diagnosis. No patient with a questionable diagnosis was included in this study, nor was lens dislocation alone considered a sufficient criterion for inclusion, even if the family history was positive for lens dislocation, since this is seen on a familial basis as isolated dislocation of the lens, and as dislocated lens and ectopic pupil. To determine which of the patients with mild connective tissue disease have the Marfan syndrome, a definition of "hard" vs "soft" clinical features was obtained.[12] The hard (or primary) manifestations include subluxed lenses, aortic dilatation, severe kyphoscoliosis, and deformity of the anterior thorax. The soft (or lesser) features include myopia, mitral valve prolapse, tall stature, joint laxity, and arachnodactyly. Unfortunately, the diagnosis of the Marfan syndrome in patients with a mild connective tissue disease remains one of clinical judgment, depending also on the age of the patient. The diagnosis of homocystinuria was excluded in all patients.

Family histories with regard to Marfan syndrome, including its ocular and systemic complications, were obtained in all instances. However, only probands are included in this study. Secondary cases are not in-

cluded unless the patients were individually referred and were then reclassified as probands.

OCULAR EVALUATION

The extent of ocular evaluation and ocular measurements depended upon the age and cooperation of the patient. Wherever possible, the examination included the following: inspection of the ocular adnexae, measurement of the corneal diameter, measurement of best corrected visual acuity, retinoscopy and manifest refraction, evaluation for the best type of optical correction (phakic or aphakic, glasses vs contact lenses), keratometer reading, pachometer reading (in 11 patients), accommodation (in 11 patients), slit-lamp examination including appearance of the iris and transillumination, gonioscopy, evaluation of the lens position and shape before and after pupil dilatation, Goldmann perimetry, evaluation of the retinal status, and measurement of the ocular axial length. The various methods used for the ocular evaluation will be described under each heading. The data were graded and computerized for statistical analysis, and the details will be given under each heading.

RESULTS

PATIENT DISTRIBUTION BY AGE AND SEX

One hundred sixty consecutive patients with an unquestionable diagnosis of the Marfan syndrome were included in this study. There were 74 male and 86 female patients (difference not significant). Their ages at their last visit ranged from less than 3 years to less than 60 years. Forty-four patients (27.5%) were less than 10 years of age at the time of their last visit (Table II). Sixty-four patients (40%) were seen more than once (Table III)

TABLE II: DISTRIBUTION OF PATIENTS WITH THE MARFAN SYNDROME BY SEX AND AGE AT THEIR LAST VISIT (INCLUDING PATIENTS SEEN ONLY ONCE)

SEX	AGE (YR)								
	0-3	4-5	6-9	10-19	20-29	30-39	40-49	50-59	TOTAL
Male	5	5	8	23	9	15	6	3	74
Female	3	7	16	29	11	10	2	8	86
Total	8	12	24	52	20	25	8	11	160

TABLE III: TABULATIONS OF EXAMINATIONS OF 160 PATIENTS WITH THE MARFAN SYNDROME BY NUMBER OF VISITS AND INTERVAL BETWEEN VISITS IN MONTHS

	NO. OF EXAMINATIONS PER PATIENT							
	1	2	3	4	5	6	7	8
No. of patients	96	35	11	6	4	3	4	1
Range of time interval between 1st and last visit (mo)	0	1-60	1-78	26-63	32-81	25-131	19-83	69
Mean time interval		22.6	35.4	41.8	59.8	74.3	53.8	69

and had been first seen prior to the date when this specific study was started. Thus, results on a total of 297 visits of the 160 patients are included in this material. The maximum number of follow-up evaluations per patient was eight; the longest time of follow-up was 6 years and 11 months. Some patients were seen repeatedly at short intervals because of unsatisfactory results of refraction or follow-up for amblyopia, whereas others were seen in annual follow-up; thus the length and intensity of follow-up were variable.

OCULAR CRITERIA

Adnexae

On inspection of the ocular adnexae of patients with the Marfan syndrome, a clinical appearance of enophthalmos is often very striking, especially in severely affected children; to some extent this is noticeable in adults also (Fig 1). The enophthalmos may be caused by reduced or

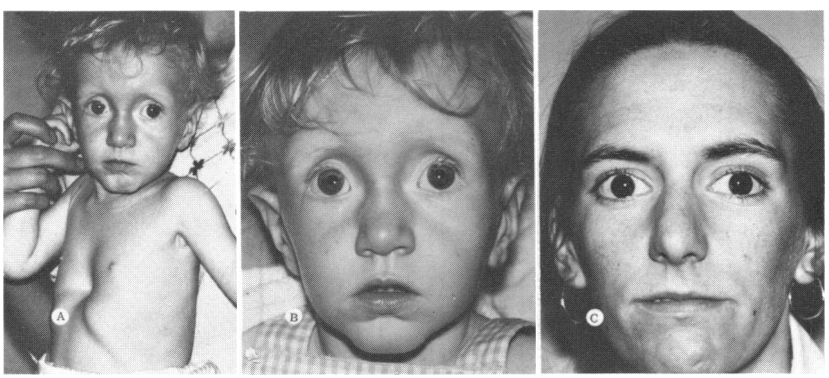


FIGURE 1
Enophthalmos and "myopathic" facies in a severely affected 18-month-old infant (A, B) and a young adult (C).

absent retrobulbar fat. This was considered a soft sign, and no attempt at grading of severity of enophthalmos was made. Usually some degree of frontal bossing is present, which in the absence of subcutaneous fat, combined with flat malar areas and hypoplastic facial muscles, will give these patients a characteristic facial "myopathic" appearance.

Corneal Diameter

The corneal diameter in the Marfan syndrome is, classically, increased. Many of the patients give the appearance of megalocornea (Fig 2). This appearance is further enhanced by the miotic pupil. Corneal diameters of up to 13 mm were measured without evidence of increased intraocular pressure such as tearing, photophobia, breaks in Descemet's membrane, or cupping of the optic disc. However, measurements of the corneal diameter were not computerized because of their poor reproducibility.

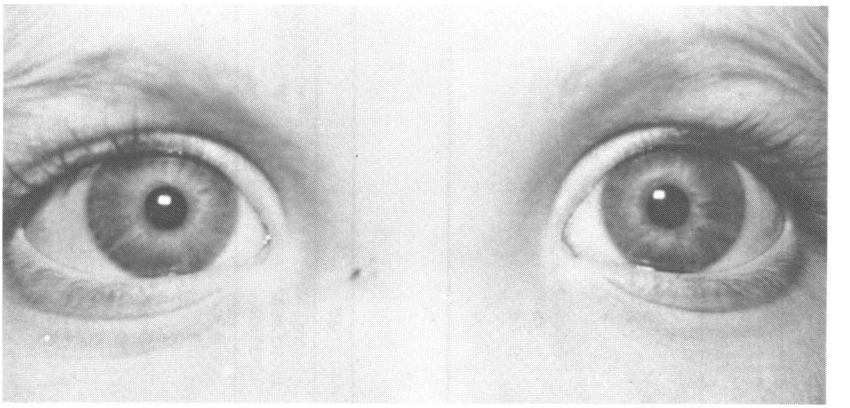


FIGURE 2
Megalocornea and slight ectopia of pupils.

Thus, a mean corneal diameter and standard deviation are not recorded for this patient population. Although megalocornea is common, normal corneal diameters are seen in this syndrome.

Visual Acuity

Among the 160 patients, the visual acuity of 151 patients (302 eyes) at the time of their *first* visit is given in Table IV. There are an additional 9 patients below 5 years of age on whom no reliable acuity could be obtained at their first visit. Seven of these nine patients were followed up, with the development of good visual acuities under conservative management. In the 151 patients, 70.5% of all eyes measured for visual acuity at the time of the patient's first visit had an acuity of $\geq$ 20/40, and 89.4% of all eyes had an acuity of $>$ 20/200. Fifteen (5.0%) of all eyes had an acuity ranging from 4/200 to no light perception (NLP) vision, or an enucleation had been performed. In Table V, the visual acuities for the same patients are described at the time of their last visit (which is equal to the first visit for patients seen only once). The proportion of eyes with legal blindness (20/200 or less) changed from 10.6% of the total at the time of the patient's first visit, to 8.5% at the last visit. This change is due to such measures as careful refraction and treatment of amblyopia, repair of retinal detachment, or extraction of a cataractous lens. Under our management, no patient had had removal of a clear dislocated lens because of reduced visual acuity. When only the better eye is considered for a given patient (Table VI), 84.6% of the patients had a visual acuity of $\geq$ 20/40 at the time of

TABLE IV: VISUAL ACUITY BY AGE AT FIRST VISIT (EYES)

AGE RANGE (YR)	NO. OF PATIENTS	NO. OF EYES	20/20	20/25-20/40	20/50-20/70	20/80-20/160	20/200-5/200	4/200 LIGHT PERCEPTION	NO LIGHT PERCEPTION	NO ACUITY MEASUREMENT AVAILABLE
0-3	16	32	5	7	4					16
4-5	14	28	4	2	5	8	7			2
6-9	20	40	9	19	4	4	3	1		
10-19	52	104	59	19	15	3	4	1	3	
20-29	18	36	20	8	2	3	2		1	
30-39	21	42	25	12	3	2				
40-49	9	18	8	4		2		2	2	
50-59	10	20	5	7	2		2	3	1	
Total	160	320	135	78	35	22	18	7	7	18

TABLE V: VISUAL ACUITY BY AGE AT LAST VISIT (EYES), ONLY VISITS INCLUDED

AGE RANGE (YR)	NO. OF PATIENTS	NO. OF EYES	20/20	20/25-20/40	20/50-20/70	20/80-20/160	20/200-5/200	4/200-LIGHT PERCEPTION	NO LIGHT PERCEPTION	NO MEASUREMENT AVAILABLE
0-3	8	16	4	6	4	0	0	0	0	2
4-5	12	24	4	8	3	4	3	0	0	2
6-9	24	48	8	25	6	6	2	1	0	
10-19	52	104	63	21	10	2	3	3	2	
20-29	20	40	23	8	3	2	2	0	2	
30-39	25	50	27	17	4	2	0	0	0	
40-49	8	16	5	5	0	2	1	1	2	
50-59	11	22	6	9	1	1	1	3	1	
Total	160	320	140	99	31	19	12	8	7	4

TABLE VI: VISUAL ACUITY BY AGE AT LAST VISIT FOR BETTER EYE

AGE	VISION								
	20/20	20/25-20/40	20/50-20/70	20/80-20/160	20/200-5/200	4/200- LIGHT PERCEPTION	NO LIGHT PERCEPTION	NO MEASUREMENT AVAILABLE	TOTALS
0-3	2	3	2					1	8
4-5	2	5	2	2				1	12
6-9	6	13	3	2					24
10-19	34	10	6	1			1		52
20-29	12	5		1	2				20
30-39	16	8	1						25
40-49	4	2		2					8
50-59	4	6			1				11
Total	80	52	14	8	3		1	2	160

their last visit (which, as mentioned, is equal to the first visit if a patient was seen only once). Four patients were legally blind. Of these four, a 14-year-old patient had had removal of the right and left lenses at 6 and 7 years of age respectively, resulting in panophthalmitis with enucleation of the right eye and a phthisical left eye. The details of the surgical procedures are not available. A now 25-year-old patient had had bilateral spontaneous retinal detachments with loss of one eye, and glaucoma in the other eye at a later stage. A 29-year-old patient had had ocular surgery at 6 years of age, resulting in a phthisical eye; at 24 years of age he had had a spontaneous retinal detachment in his other eye, with a successful repair but with vision fluctuating between 20/100 and 20/200. Glaucoma has since developed in that eye. The last of these four legally blind patients had a retinal detachment in one eye, for which she refused surgical intervention, and had a disciform macular lesion and dense cataract in the other eye. The causes for visual acuity of $\leq$ 20/200 in the 27 eyes noted in Table V are distributed as follows (Table VII): 14 cases of retinal detachment (nine had had no prior lens surgical treatment, five had had lens aspirations), eight cases of amblyopia, five cases of glaucoma, one case of expulsive choroidal hemorrhage, one unrelated case of trauma, and one disciform macular process in a cataractous eye. In three eyes, more than one cause is given for the legal blindness. Among the eight amblyopic eyes are three patients with high anisometropia. The expulsive choroidal hemorrhage occurred in an eye that had an intraocular pressure of more than 50 mm Hg, a totally dislocated lens floating in the vitreous cavity, uveitis, and a retinal detachment. The pupil did not dilate. An optical iridectomy was attempted to improve visualization. At that point the choroidal hemorrhage occurred, and the visual result was light per-

TABLE VII: CAUSES FOR VISION $\leq$ 20/200 FOR 27 EYES IN 23 PATIENTS*

Retinal detachment without lens surgery	9
Retinal detachment after lens surgery	5
Amblyopia	8
Glaucoma	5
Expulsive choroidal hemorrhage	1
Trauma	1
Disciform degen. and cataract	1

*In three instances, more than one contributory cause was found.

ception only at the time of patient discharge. Seventy eyes had a visual acuity of < 20/20 at the first visit and could be followed up for at least 12 months (Table VIII). Some of the age groups had to be combined in order to have significant entries in each category. An improvement in visual

TABLE VIII: CHANGE IN VISUAL ACUITY BETWEEN FIRST AND LAST VISIT FOR EYES WITH VISUAL ACUITY < 20/20 INITIALLY*

VISUAL ACUITY	AGE GROUPS (YR)					TOTAL
	1-5	6-9	10-19	20-29	30+	
No improvement	3	4	14	9	9	39
Improvement	10	8	8	3	2	31
Total	13	12	22	12	11	70

*By age at first visit; follow-up at least one year; improvement of at least one line.

acuity could be achieved at all age levels, even above the age of 20 years. The proportion of eyes improved is significantly larger for the younger age groups (χ^2 test with 4 df = 13.45; $P < .01$); if analyzed for linear trend, the improvement was significant at $P < .001$, χ^2 with 1 df = 12.51). When the visual acuity is plotted vs lens dislocation (Table IX) for the better eye at the last visit (or only visit when seen once), we see that dislocation of the lens entails a significantly worse visual acuity (χ^2 with 3 df = 29.63; $P <$ .001). The effect is even more significant when both eyes are included (Table X), and it remains significant when surgical cases are excluded (Table XI). Lens extraction had occurred in 18 eyes of 11 patients prior to their first visit, with good visual results in 10 eyes, and 20/200 vision in one eye, hand motion in one eye, and NLP in six eyes, occurring at

TABLE IX: VISUAL ACUITY VS LENS POSITION FOR BETTER EYE AT LAST VISIT*

LENS POSITION	VISUAL ACUITY				TOTAL
	20/20	20/25-20/40	20/50-20/70	<20/80	
Normal	49	11	3	1	64
Dislocated	31	41	11	11	94
Total	80	52	14	12	158†

*First visits are included if seen only once.
†Two patients: no acuity measurement available.

various intervals after surgery. Table XII gives this information from another viewpoint. This visual acuities of 53 patient (102 eyes) with dislocated lenses who have been seen more than once are given for their first and last visits. They are grouped by age. An improvement in visual acuity could be obtained at all age levels, and also the final visual acuities were the best when the patients were first seen at a young age. With age, the proportion of patients with secondary complications increases. In the young age group, a major cause of reduced visual acuity is delayed and inadequate refraction and the development of amblyopia, often bilaterally.

One additional interesting feature becomes evident: there are two periods in which there are more eyes with dislocation of the lens in the follow-up group than there were at the first visit. This concerns the age group from 0 to 5 years and again in the age group from 10 to 19 years. In the first age group, it is possible that the first examination was inadequate and that some cases with slight dislocation of the lens were undiagnosed. However, this interpretation is unlikely in the age group of 10 to 19 years where true new dislocations appear to have occurred in six eyes. Significant improvement in vision could be achieved in this latter group in eyes

TABLE X: VISUAL ACUITY VS LENS POSITION FOR BOTH EYES AT LAST VISIT (INCLUDING SURGICAL CASES)*

LENS POSITION	VISUAL ACUITY				TOTAL
	20/20	20/25-20/40	20/50-20/70	<20/80	
Normal	87	27	6	3	123
Dislocated	53	72	25	43	193
Total	140	99	31	46	316

*First visits are included if seen only once.

TABLE XI: VISUAL ACUITY VS LENS POSITION FOR BOTH EYES AT LAST VISIT (WITHOUT SURGICAL CASES)*

LENS POSITION	VISUAL ACUITY				TOTAL
	20/20	20/25-20/40	20/50-20/70	<20/80	
Normal	87	27	6	3	123
Dislocated	50	66	25	34	175
Total	137	93	31	37	298

*First visits are included if seen only once.

TABLE XII: VISUAL ACUITY OF PATIENTS WITH DISLOCATED LENSES ON FIRST (A) AND LAST (B) VISITS; BOTH EYES*

AGE AT FIRST VISIT	NO. OF PATIENTS	NO. OF EYES	VISIT	20/20	20/25-20/40	20/50-20/70	20/80-20/160	20/200-5/200	4/200-LIGHT PERCEPTION	NO LIGHT PERCEPTION	NO ACUITY MEASUREMENT AVAILABLE
0-3	4 (1)†	8 (2)	A	1	1 (2)						6
	6	12	B	1	10		1				
4-5	5 (1)	9 (2)	A			2	5	2 (2)			
	6	12	B		7	2	2				
6-9	9	16	A	2	7	2	3	2			
	9	16	B	7	1	3	4				
10-19	15	29	A	6	8	10	3	1	1	1	
	18	35	B	11	14	5	2	1	1	1	
20-29	7	13	A	3	5	1	3	1			
	7	14	B	4	6	1	3				
30-39	3	6	A	2	1	2	1				
	3	6	B	2	1	3					
40-49	3	5	A		2		1		1	1	
	1	2	B		2		1	1		1	
50-59	3	5	A	1					1		
	1	2	B		1				1		
Total	51	97									

*Only patients who have been seen more than once are included.
†Number in parentheses ( ) refers to patients or eyes with questionable lens dislocation.

which probably had been adequately corrected in early childhood, but in which undercorrection of the refractive errors had occurred due to growth of the globe around puberty.

Refractive Error

The distribution in percent of refractive power measured as spherical equivalent for this Marfan population is shown in Table XIII and Fig 3,

TABLE XIII: DISTRIBUTION IN PERCENT OF REFRACTIVE POWER FOR THE MARFAN POPULATION COMPARED WITH THE NORMAL POPULATION*

REFRACTIVE POWER (DIOPTERS)	MARFAN (%)	NORMAL (%)
−45.00−		
−15.00	4.5	
−13.00−		
−14.99	1.4	
−11.00−		
−12.99	1.4	0.3
−9.00−		
−10.99	4.2	
−7.00−		
−8.99	4.8	
−5.00−		
−6.99	6.9	0.5
−3.00−		
−4.99	6.2	1.0
−1.00−		
−2.99	15.5	3.0
−0.99−		
0.99	33.5	69.0
1.00−		
2.99	3.1	25.4
3.00−		
4.99	3.1	0.5
5.00−		
6.99	3.8	0.3
7.00−		
8.99	1.7	
9.00−		
10.99	2.8	
11.00−		
12.99	1.0	0.1
13.00−		
14.99	4.4	
>15.00	1.7	
Total	100.0	100.0

*"Normal Population" material from Stromberg.[39]

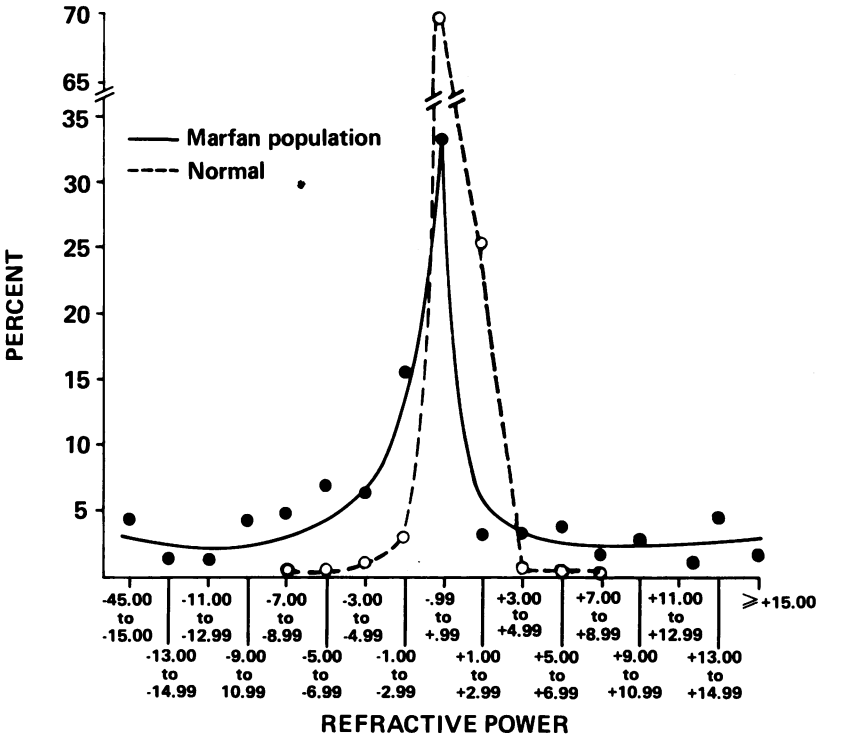


FIGURE 3
Distribution of ocular refractive power in 160 patients with Marfan syndrome (present study) compared with normal distribution (Stromberg[39]). Note difference in scale for Marfan population (solid line) and normal population (dotted line).

and is compared with the distribution of the normal population using the data by Stromberg.[39] It is evident that among the Marfan patients there is a much wider distribution of ocular refractive power than in the normal population and a flatter peak and a higher proportion of extreme refractive errors. Four and one-half percent of all these Marfan patients have a myopic refractive error > -15 D, and 16.3% of all these patients have a myopic refractive error of -7.00 D or more, compared with 0.3% in the normal population. Fifty-four of 290 eyes (18.6%) in our study wore an aphakic prescription. All patients in the age group of 0 to 3 years measured virtually emmetropic on retinoscopy. In the 4- to 5-year-old age group, cases of high myopia were present, and also eyes with moderate to high hypermetropic refractions. In the 4- to 9-year-old age group 27% of

the patients wear an aphakic prescription with refraction around the dislocated lens. The proportion of patients wearing an aphakic prescription drops to 13% in the 10- to 19-year-old group and then reaches 25% in the age group of 30 to 39 years. The latter age group combines patients who wear an aphakic prescription because of surgical aphakia after extraction of a cataractous lens and patients who wear an aphakic correction prescribed around a dislocated lens. The amount of astigmatism measured on manifest refraction or on retinoscopy at the patients' last visit is given in Table XIV. The mean astigmatism measures 1.47 D, with a standard deviation of 1.51 D. More than 7 D of astigmatism was seen in two patients, and 33.4% of the eyes (107/320) had less than 0.50 D of cylinder.

Whenever possible we tried to give a phakic prescription, especially to young children, as long as reasonable retinoscopic values could be obtained. We have, however, placed children as young as four years on an aphakic prescription with good final visual results. Most patients who wore an aphakic prescription (with lens dislocation) had a large enough aphakic pupillary space without long-term mydriatic therapy; however, if this therapy was necessary, one drop of atropine sulfate 1% per day (or as needed) was prescribd. Many patients tolerated a hard contact lens well, and the Marfan syndrome was not considered a contraindication to the use of a hard contact lens. One patient wore a soft contact lens successfully with first fitting prior to the age of ten years, with spectacle overcorrection of her astigmatism.

Keratometry

Using the Haag-Streit ophthalmometer, calibrated in terms of refractive power and units of prism diopters, the largest and smallest radii of curvature were measured and the power and axis noted. The average value of the reading for each eye was used as a measure of corneal power. The absolute value of the difference between these two readings was used as the amount of corneal astigmatism. Given the wide variation in keratometer readings in our patient population, the mean corneal power was not computed for males and females separately. The mean corneal power (Table XV) of 137 eyes in our group was 41.38 D with a standard deviation of 2.04 D, compared with keratometer readings of 43.44 ± 0.19 and 44.00 ± 0.19 for the normal USA male and female population as calculated from data reported by Mash et al,[40] and 43.00 to 43.24 D reported by Ellerbrook[41] in 1963. Nineteen percent of eyes had keratometer readings below or equal to 40 D (26 out of 137). The lowest average keratometer reading (K) was 35.95 D for a radius of 9.36 mm, compared with a

TABLE XIV: ASTIGMATISM (CYLINDER IN DIOPTERS) FROM MANIFEST REFRACTION OR RETINOSCOPY FOR BOTH EYES AT LAST VISIT

CYLINDER (DIOPTERS)	AGE (YR)								TOTAL
	0-3	4-5	6-9	10-19	20-29	30-39	40-49	50-59	
0	5	6	15	40	10	14	7	4	101
0.01-0.49	3	1	2	0	0	1	0	1	8
0.50-0.99	2	5	1	16	7	9	1	4	45
1.0-1.99	2	5	6	15	7	13	3	4	55
2.0-2.99	0	2	8	12	7	3	2	1	35
3.0-3.99	0	0	8	6	3	4	1	1	23
4.0-4.99	0	1	5	0	2	2	0	0	10
5.0-5.99	0	0	1	3	2	1	0	1	8
6.0-6.99	0	1	2	2	0	1	0	6	12
>7.00	0	1	0	1	0	0	0	0	2
N/A	4	2	0	6	0	2	0	7	21
Total	16	24	48	101	38	50	14	29	320

TABLE XV: MARFAN SYNDROME: MEAN KERATOMETER READING BY AGE

AGES	NO. PATIENTS IN AGE CATEGORY	NO. EYES MEASURED	MEAN	SD
1-8	40	37	40.90	2.42
1-14	76	65	40.84	2.26
15+	84	72	41.86	1.71
Total	160	137	41.38	2.04

radius of 7.71 mm for the US mean K of 43.72. Thus, the corneas in these Marfan patients are considerably flattened. The mean corneal astigmatism was 1.39 ± 1.07 D. Thirty-three eyes had corneal astigmatism of more than 2 D. The difference in astigmatism between the two eyes was less than 1D in 81.5% of the cases; values equal to or above 2 D of difference were seen in four patients only.

The flatter average K readings did not necessarily correlate with the higher amounts of astigmatism. No patient with keratoconus or keratoglobus was seen among the 160 patients.

The power and axis of the cylinder measured on keratometer readings closely corresponded to the retinoscopic and manifest refractions as demonstrated in the example of the following patient, a 6-year-old girl, with temporal and upward dislocation of the lenses bilaterally: On K readings a measurement of 39.70–43.00 axis (@) 100 was obtained for the right eye and 40.30–43.50 @ 70 was obtained for the left eye, which equals a cylinder of 3.30 and 3.20 at axes 100 and 70 for the right and left eyes respectively. Her final refraction amounted to $-9.00 + 4.25 \times 110$ and $-10.50 + 5.00 \times 70$. When spectacle distance was corrected, a value of $-8.10 + 3.50 \times 110$ and $-9.30 + 4.20 \times 70$ was obtained. Thus, for the right eye there was close agreement between keratometer readings and final refraction, and the agreement is approximate for the left eye.

Interestingly, we often observed that the axis of the plus cylinder corresponded to the direction of the dislocation of the lens. In the previously described child, for example, the lenses were dislocated upward and temporal, bilaterally.

In not all cases, however, does the amount and axis of astigmatism measured on retinoscopy or manifest refraction or both correspond to the keratometer reading. In such instances the combination of corneal and lenticular astigmatism leads to complex retinoscopies. This was commonly observed in eyes in which the lens was displaced to the point that an aphakic prescription could be given.

Pachometry

Pachometer readings were performed on 11 patients. No difference from the normal population was found, and no further measurements were taken.

Accommodation

Accommodation was measured on 11 patients using a Prince's rule and a letter target, which was advanced to blurred vision and pushed back to the point where the patient could again read the target. The distance was measured in diopters for each eye separately and used as measure of amplitude of accommodation. The patients were wearing their distance refraction. The amplitude of accommodation was normal for age in all 11 patients. All patients had dislocation of the lens, but they still had an intact zonular complement. No routine measurements were obtained thereafter.

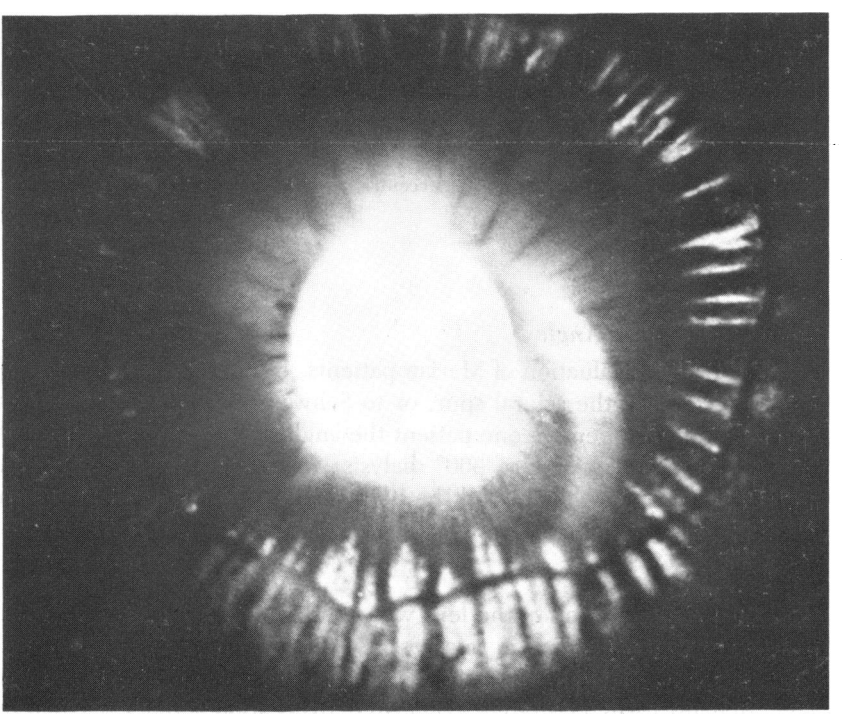


FIGURE 4
Iris transillumination seen in patient with mild upward dislocation of lens.

Iris

The appearance of the iris is often striking in patients with the Marfan syndrome. In approximately 10% of the patients there was iris transillumination (Fig 4), more marked at the base of the iris. The anterior iris leaf was commonly homogeneous in its appearance, having a decreased number of circumferential ridges and furrows and an absence of crypts, thus giving it a velvety appearance. Occasionally the pupil was eccentric (Fig 5), and very commonly it was miotic and difficult to dilate.

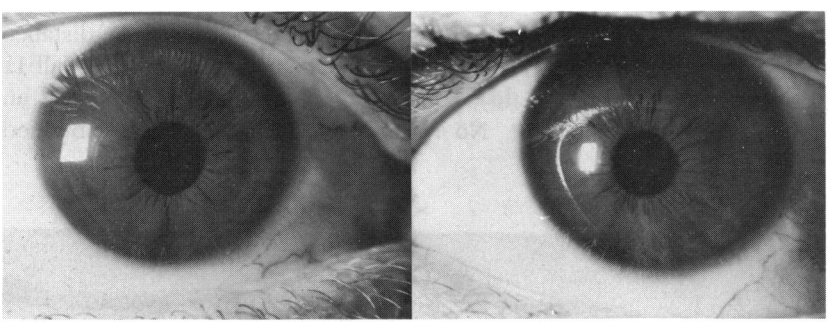


FIGURE 5
Rarefaction of iris surface pattern and eccentric pupil in both eyes of one patient.

Anterior Chamber Angle

On gonioscopic evaluation of Marfan patients, frequently iris strands are seen to extend to the scleral spur, or to Schwalbe's line. The angle was usually grade IV open. In one patient the angle appeared bilaterally as if the patient had sustained a 360° dialysis. Iridodonesis was often seen under gonioscopic evaluation of the peripheral iris, even if not noted on slit-lamp examination.

Lens

Diagnosis of dislocation of the lens was attempted through the undilated pupil, with special attention to assessment of the adequacy of the pupillary space for an aphakic refraction in cases of major dislocation of the lens. In many cases a tentative diagnosis of dislocation of the lens could be made using decentralization of the Y sutures and iridodonesis, more easily visible under the slit lamp, as diagnostic aids. All pupils were

dilated prior to final diagnosis of presence or absence of dislocation of the lens. A notch (Fig 6), most commonly located inferonasally, was considered a minimal sign of dislocation of the lens. This has been referred to in the literature as lens coloboma.

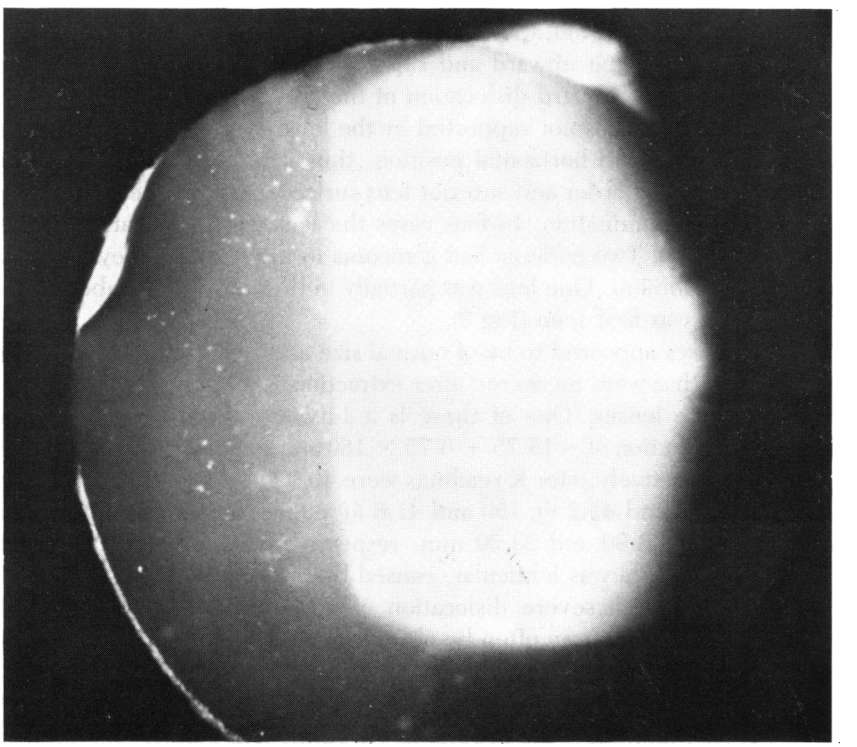


FIGURE 6
Notch in lens border, here located superotemporally, is most commonly found inferonasally and is used as minimal sign of dislocation of lens in Marfan syndrome.

Dislocation of the lens was observed in 193 eyes, or 60.3% of all of our patients. In the total population, 47.5% of the patients were male, and 44.0% of all dislocations were found in male patients (this difference is not statistically significant). If dislocation is plotted by age (Table XVI), a nonsignificant decrease in the proportion of patients with dislocation of the lens is seen with age.

Severity of dislocation of the lens was not graded, for two principal reasons: (1) Since the difference between minor and major dislocation is gradual, no logical cut-off points could be defined. (2) The absolute value of presence or absence of dislocation seemed more significant for evaluation of intrafamilial and interfamilial variation of ocular signs than the amount of dislocation.

All directions of dislocation of the lens were observed, the most common direction being upward and superotemporally (Fig 7 and 8). Also common was a backward dislocation of the lens, in which the pupillary border of the iris was not supported by the lens, even if the lens was in a normal vertical and horizontal position, thus leaving a definite gap between pupillary border and anterior lens surface, which was easily visible on slit-lamp examination. In four cases the lens was free-floating in the vitreous cavity. Two patients had glaucoma in the respective eye, with a retinal detachment. One lens was partially in the anterior chamber when the patient was first seen (Fig 9).

Most lenses appeared to be of normal size and shape; this was true for two lenses that were measured after extraction. Two patients had microspherophakic lenses. One of these is a 14-year-old patient who had a manifest refraction of $-15.75 + 0.75 \times 180$ and -14.50 for the right and left eye respectively. Her K readings were 40.9 @ 84 and 42.0 @ 175 for the right eye and 41.2 @ 150 and 41.6 @ 60 for the left eye. Her axial lengths were 23.90 and 23.20 mm, respectively. In this case the total amount of myopia was lenticular, caused by the spherophakic lens.

In patients with severe dislocation of the lens, a numerically good zonular complement can often be observed even though there is rarefaction of the zonules—resulting, if the rarefaction is in an irregular pattern, in a crenellated lens border (Fig 4 and 7 A, C). In two patients below 10 years of age, matting of the zonular fibers on the lens surface and marked irregularity of the zonular pattern occurred (Fig 10). (Both of these changes are commonly considered signs of homocystinuria.) The lenses were bilaterally dislocated downward in one of these two patients, and upward in the other. The patient with downward dislocation of the lens had definite evidence of progressive dislocation. This patient had originally had a phakic refraction bilaterally, then wore a unilaterally aphakic prescription, and now has bilateral aphakic prescriptions.

Usually the amount of dislocation was stable from early childhood. A total of 53 patients were seen more than once. Among these, seven patients (13.2%) had definite evidence of progression of the dislocation, either on photographic data or by comparison of drawings or because the refractive mode had to be changed from phakic to aphakic or a combina-

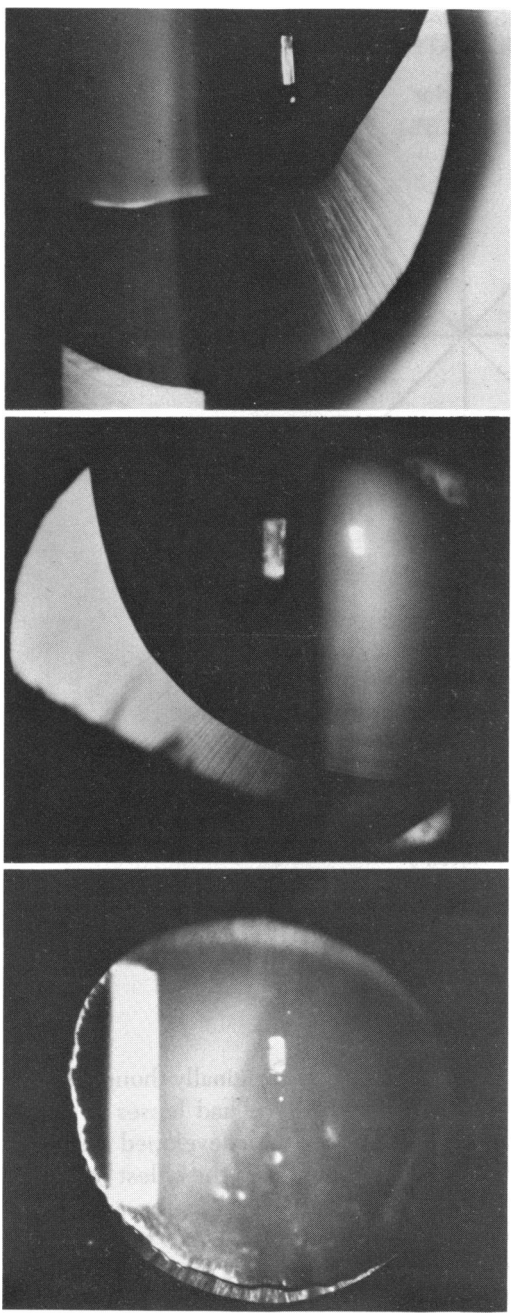


FIGURE 7
Superotemporal dislocation of lens in three unrelated patients. Note parallel alignment of zonular fibers in eyes.

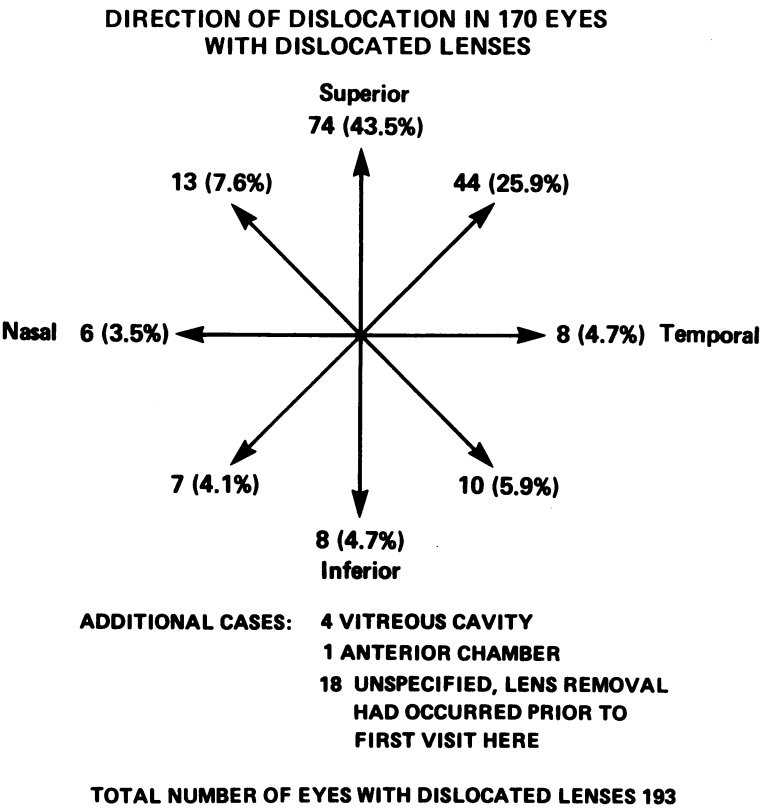


FIGURE 8
Analysis of direction of dislocation of lens in 170 eyes, with 23 other cases as noted.

tion of those methods. Three of these patients were originally thought not to have a lens dislocation. In addition, four patients had lenses in the vitreous cavity on first evaluation. By history this had developed during their lifetime. The youngest patient was 7 years old and the oldest was 58 years at the time of visit here. One patient had a lens in the anterior chamber when first seen, a secondary development. Thus a total of 12 patients had evidence of progression, or 7.5%, using historical information as well, in the total of 160 patients.

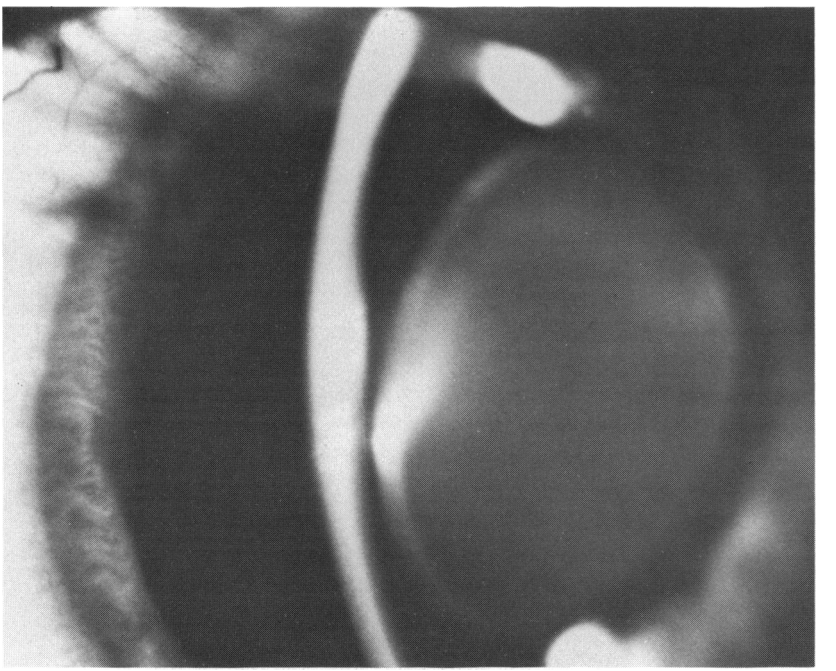
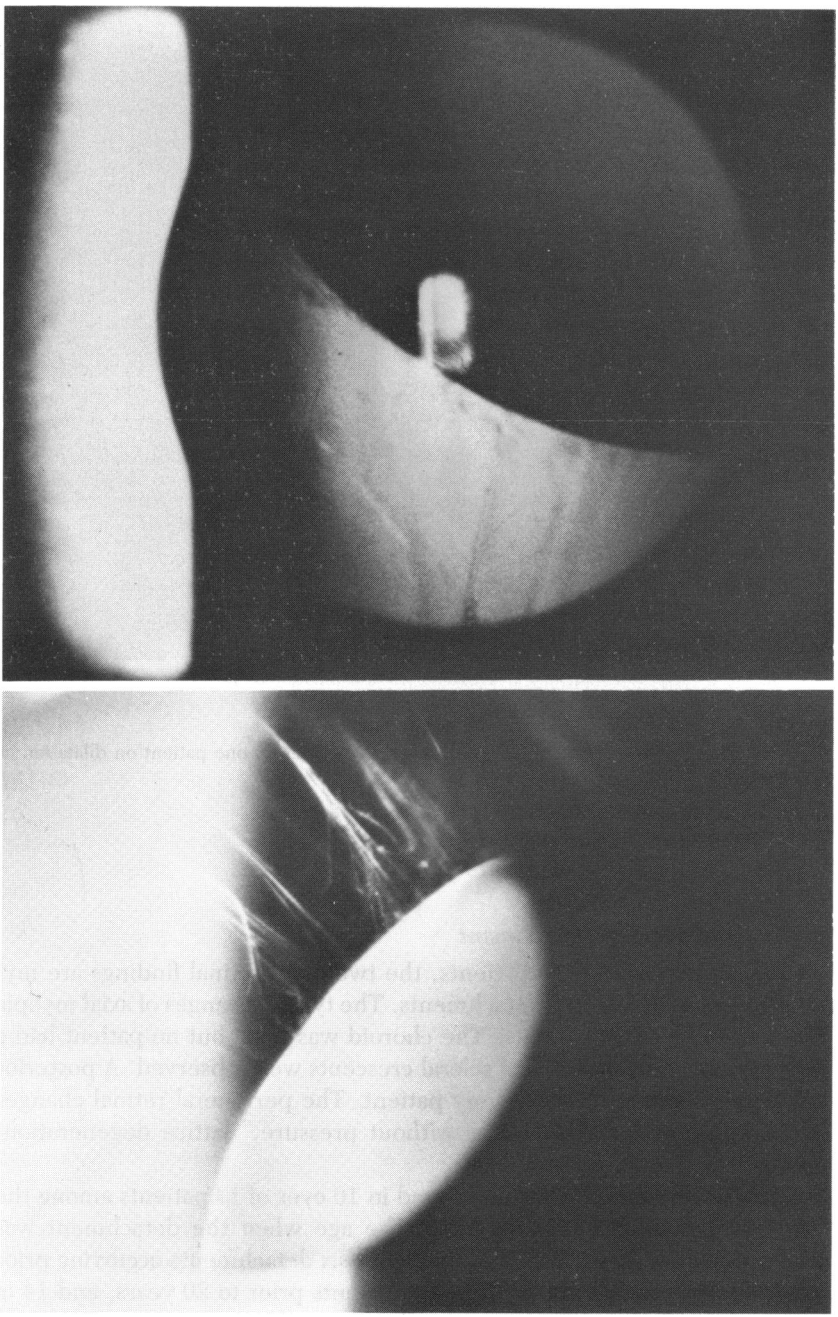


FIGURE 9
Forward tilting of lens with corneal touch and edema seen in one patient on dilatation of pupil.

Retina and Retinal Detachment

In the Marfan syndrome patients, the two main retinal findings are myopic changes and retinal detachments. The typical changes of axial myopia were seen in many patients. The choroid was thin, but no patient had a Fuchs' spot. Various sizes of scleral crescents were observed. A posterior staphyloma was not seen in any patient. The peripheral retinal changes consisted of prominent "white without pressure," lattice degeneration, and retinal holes.

A retinal detachment had occurred in 16 eyes of 13 patients among the 160 Marfan patients under study. The age when the detachment was diagnosed varied from 5 to 57 years, with six detachments occurring prior to 10 years of age, 11 of the 16 detachments prior to 20 years, and 14 of



the 16 prior to 30 years. In two additional eyes the detachment occurred after the age of 30. Thus, nearly 70% of the detachments occurred prior to the age of 20. The sex ratio was 4:9, male to female. All 13 patients had dislocation of the lens also.

The final visual acuity after retinal reattachment procedures was 20/40 or better in only three eyes; the vision in four of the 16 eyes was ≥ 20/100; in an additional two eyes the visual acuity was between 20/200 and 5/200, in five eyes the vision was 4/200 to light perception, and five eyes had NLP vision.

The keratometer readings of fellow eyes of these 13 patients with retinal detachment varied from 36.70 to 44.05 D with a mean of 40.41. Patients with bilateral retinal detachments are excluded from these fellow-eye measurements. The axial length measurements of the fellow eye in six of the 13 patients ranged from 24.00 to 30.34 mm. The mean axial length of fellow eyes of patients who had a retinal detachment and who were more than 11 years old was 28.47 mm; including only patients who had had intraocular surgery the mean axial length was 28.54 mm.

Previous intraocular surgery had been performed on five eyes of four patients. The interval between intraocular surgery and the diagnosis of retinal detachment was less than six months in three patients (four eyes) and was seven years in one patient. (In this latter patient a detachment in her second aphakic eye has developed recently, eight years after intraocular surgery.) Six patients had a positive family history for retinal detachments in other family members with the Marfan syndrome (Fig 11). Intraocular surgery had been performed on 18 eyes in this series of 160 patients. Six retinal detachments have occurred in four patients who had previous intraocular surgery. One eye was lost from panophthalmitis.

Axial Length Measurements

Axial length measurements were obtained using the Digital Biometric Ruler 300 (A scan) and a computer velocity averaging potential. Measurements on 86 eyes were obtained (Table XVII). Twenty eyes were measured in patients younger than 9 years of age, and their mean axial length

FIGURE 10

Irregular arrangement of broken zonular fibers, which are in part matted on lens surface. (Eyes are from unrelated patients; one lens is dislocated temporally upward and one temporally downward.)

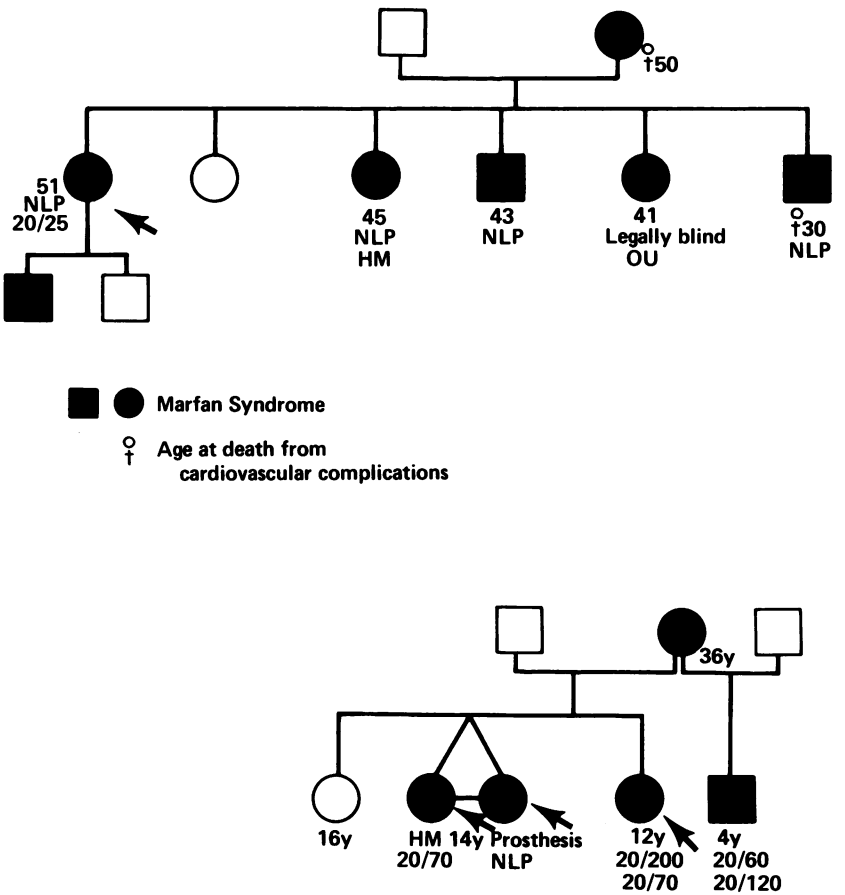


FIGURE 11
Pedigrees of two families with Marfan syndrome, in which several members have sustained retinal detachments.

TABLE XVI: MARFAN SYNDROME: 160 PATIENTS: LENS DISLOCATION BY AGE FOR 320 EYES

AGE (YR)	DISLOCATED	IN PLACE	TOTAL	% DISLOCATED
0-3	2	14	16	12.5
4-5	18	6	24	75.0
6-9	36	12	48	75.0
10-19	59	45	104	56.7
20-29	26	14	40	65.0
30-39	32	18	50	64.0
40-49	9	7	16	56.3
50-59	11	11	22	50.0
Total	193	127	320	60.3

was 23.49 mm ± 0.78 mm. A total of 43 eyes were measured in patients younger than 15 years, and their axial length was 24.03 mm ± 1.68 mm. An additional 43 patients were 15 years and older, and their mean axial length was 25.26 mm ± 2.50 mm. When all ages were pooled, the axial length measurements were 24.65 mm ± 2.21 mm. A mean of 23 mm has been found in normal children at the age of 3, and a range of 23.47 to 24.74 mm has been found in normal persons 15 years old and older for eyes with refractive errors of less than 4 D of myopia.

Six patients with the Marfan syndrome had two axial length measurements that were separated by an interval of 9 to 23 months. Three of these patients were 25 years and older; the three younger patients were 4, 5, and 12 years of age at the time of first evaluation. An increase in size of 0.51 mm for the right and left eye respectively over a 19-month period was seen in the child who was 4 years old at the time of first evaluation. Evidently, measurement error may well have played a role in such a young child. All other changes were negligible.

As mentioned, 13 patients had had a retinal detachment. In ten patients the detachment was uniocular. The axial length was measured in the fellow eye of seven of these 10 patients, and it varied in length from

TABLE XVII: AXIAL LENGTH VS AGE: MEAN AND STANDARD DEVIATION

AGES	NO. PATIENTS IN AGE CATEGORY	NO. EYES MEASURED	MEAN	SD
1-8	40	20	23.49	0.78
1-14	76	43	24.03	1.69
15+	84	43	25.26	2.50
Total	160	86	24.65	2.21

24.00 mm in a 7-year-old to 30.98 mm in a 19-year-old. Two of those who originally had uniocular detachments have since had a detachment in the fellow eye. The axial length in these two patients was 29.90 mm at the age of 10 and 27.92 mm at the age of 15.

We compared axial length measurements of patients without dislocation of the lens with those with dislocation of the lens; the mean axial length for patients without dislocation was 23.39 mm, and for those with dislocation, 25.96 mm. This difference was statistically significant at $P < .01$.

SYSTEMIC FINDINGS: CARDIOVASCULAR AND SKELETAL SYSTEMS

All patients were evaluated by an internist or a cardiologist or both, clinically and by auscultation. They also had an echocardiogram and a chest roentgenogram.

The cardiovascular changes were classed as grade 0 or normal if there was neither clinical nor auscultatory evidence of valvular insufficiency and if an echocardiogram was within normal limits. The patient was classified as having grade 1 cardiovascular changes if there was either a diastolic murmur or a positive echocardiogram as evidence for enlargement of the aorta. Grade 2 was assigned if the patient had aortic regurgitation or aortic surgery.

The skeletal changes were classed as grade 0 if normal, and grade 1 + if there were only previously defined soft clinical features such as tall stature, mild to moderate joint laxity, and mild to moderate arachnodactyly. A patient was graded as having grade 2 skeletal changes if there was severe kyphoscoliosis, deformity of the anterior thorax, or both. There were no patients with tall stature, severe joint laxity, and severe arachnodactyly who did not have kyphoscoliosis or an anterior chest deformity, either a pectus carinatum or a pectus excavatum. Among the 160 patients, 4 had grade 0, 61 had grade 1, and 95 had grade 2 skeletal changes. Nineteen had grade 0, 87 had grade 1, and 54 had grade 2 cardiovascular disease.

FAMILY HISTORY

Of the 160 patients, 111 had a positive family history—that is, there was at least one additional affected person in the family. In case of only two affected members in a family, the affected were a parent and a child. All pedigrees were compatible with an autosomal dominant inheritance. Forty-six patients had no family history and three probands had an inconclusive family history from the information obtainable. Thus, 29.3% of all cases apparently occurred as sporadic cases. In 24 instances more than

one family member was included in the study. The presence or absence of dislocated lenses as a sign of ocular manifestations was consistent in all members in 19 of these families; in five families there was discordances. There were far fewer discordances among family members for ocular complications than for cardiovascular or for skeletal manifestations.

DISCUSSION

DIAGNOSIS

The patient with the Marfan syndrome who has the classic ocular, skeletal, and cardiovascular findings and a positive family history is readily recognized. If the family history is negative, a differential diagnosis from homocystinuria is confirmed with a urinary nitroprusside screening test and, if necessary, by serum chromatography.

Of how much help can the ophthalmologist be in making the diagnosis of the Marfan syndrome? The ocular findings are quite characteristic and readily differentiated from the ocular findings seen in other syndromes with dislocated lenses (Table I), with the exception of congenital hereditary dislocated lenses that have a virtually identical clinical appearance of deep anterior chambers, often with upward dislocation of the lenses. These patients are also subject to development of presenile cataracts. However, unlike the eyes of the Marfan syndrome, retinal detachments are not more frequent than among normal eyes. No measurements of keratometry or axial length are available to me on congenital hereditary lens dislocation, which usually is an autosomal dominant disorder.

Congenital dislocation of the lens associated with corectopia may be a confusing entity, because a displaced pupil can be seen in the Marfan syndrome and may be absent with a dislocated lens. In four cases of corectopia measured by us, the keratometer readings actually showed steep readings.

Spontaneous, delayed-onset lens dislocation is an occasionally seen and poorly understood entity. Neither it nor corectopia has systemic findings. Delayed onset of dislocation of the lens until 40 to 50 years of age is not a feature of the Marfan syndrome, and the validity of inclusion of such patients under the heading of the Marfan syndrome is dubious, even if they have cardiovascular or skeletal signs. Such patients probably have a connective tissue defect of another origin.

The entities with ocular malformations in which dislocation of the lens is a complicating feature are readily recognized because of the associated ocular features. The eye in homocystinuria is normal up to the age of four

or five years, at which stage progressive myopia develops, followed by progressive downward dislocation of the lens. The zonular fibers break and lie matted on top of the lens, a finding that, however, can occasionally be seen in the Marfan syndrome (Fig 10). Patients with homocystinuria also have an increased tendency toward retinal detachment, and this occurred in one of eight homocystinuric patients followed up in this study. Keratometer readings have been obtained on two patients and were within normal limits. In homocystinuria the lens may readily dislocate into the anterior chamber, at the stage when most or all zonular fibers are broken. This is not a common feature in the Marfan syndrome. It has occurred in four eyes of three patients of our Marfan population of 160 cases. Cross and Jensen[22] observed this anterior dislocation in four eyes of 115 patients (1.7% of eyes) with the Marfan syndrome, and in 19% of their patients with homocystinuria. It has occurred in two of our eight patients with homocystinuria. The lens in homocystinuria is commonly microspherophakic. Even though the zonular fibers may appear totally broken, I have noticed that the lens may still be attached to Wieger's ligament.

The eye in the Weill-Marchesani syndrome will show an extremely shallow anterior chamber with microspherophakia, and with pupillary block glaucoma as a common complication. The ocular appearance is very characteristic, and is not readily confused with the eye in the Marfan syndrome and in homocystinuria. In the differential diagnosis, sulfite-oxidase deficiency is a rare entity in which children are mentally retarded and have severe failure to thrive. Only a few patients have been described in the literature and we have not seen a case. Hyperlysinemia is similarly rare.

Can the ophthalmologist be of help in making the diagnosis in a patient with mild skeletal or cardiovascular features suggesting the Marfan syndrome? For examination such a patient needs pupillary dilatation, and mild lens dislocation may become evident. Also, the mean K reading in our Marfan patient population with dislocation of the lens was 41.26 ± 1.65, and in our Marfan population without dislocation of the lens the reading was 42.43 ± 2.30. The difference in mean K readings between the normal population and patients with the Marfan syndrome without dislocation of the lens was significant at the $P < .001$ level ($t = -13.245$). The difference in mean K reading for patients with dislocation of the lens compared with patients without dislocation of the lens was also significant (χ^2, 5 df = 15.73, $P < .01$). Thus, in the absence of dislocation of the lens, the unusual flattening of the cornea may be considered characteristic for the Marfan syndrome, which will become more marked when the

lens is dislocated. Keratometer readings have their shortcomings, because they are taken on a small area of the corneal surface only. Holography may be useful in the future in defining unusual stretch patterns of the cornea in this syndrome.

VISUAL ACUITY

Reduced visual acuity in the Marfan syndrome has been given as indication for lens extraction,[42,43] and improved postoperative visual acuity is given as justification. Of our 160 patients, 82.5% had an acuity of ≥ 20/40 in their better eye under conservative management (Table VI). Table IX shows that 76.6% of our Marfan patients with dislocated lenses had a visual acuity of 20/40 or better in the better eye. An improvement in visual acuity of at least one line on the Snellen chart could be achieved at all age levels in Marfan patients, and in the highest proportion before the age of 6 years (Table VIII). Unfortunately, patients are commonly seen for the first time at the beginning of school, at which stage unilateral or bilateral amblyopia has developed, and it may be difficult or impossible to significantly improve their vision with conservative methods at that age because of deep amblyopia. The vision may have been stimulated sufficiently in one eye, but this is not always the case, and patients with bilateral amblyopia are also seen. Certainly with repeated careful refractions and correction, good bilateral form vision stimulation and good visual acuity can be achieved in these patients.[44]

It is useful to obtain a keratometer reading prior to retinoscopy in these patients to obtain an approximation of the size and direction of corneal astigmatism in these patients. We have not hesitated to prescribe an aphakic prescription in children even as young as 4 years to achieve development of good visual acuity. The following patient may serve as an example: The patient was 4 years old at the time of her first aphakic prescription. Her visual acuity now, at the age of 8, is 20/25+ OU with $+11.50 + 1.25 \times 110$ and $+12.00 + 1.00 \times 75$ correction, respectively. The size of the aphakic pupillary space present without mydriatic agents, under slit-lamp examination, is shown (Fig 12).

Adequate retinoscopic findings are easily obtained on patients with mild dislocation of the lens. In case of severe luxation when no meaningful retinoscopic findings can be obtained, an aphakic refraction is easily achieved. We have therefore not removed the lens in any of our Marfan patients for optical reasons. Also, we have not hesitated to sedate a child when an adequate refraction could not be obtained otherwise. It appears unlikely that a better visual result would be obtainable by extraction of the lens, than would be obtained if they are given the benefit of a detailed

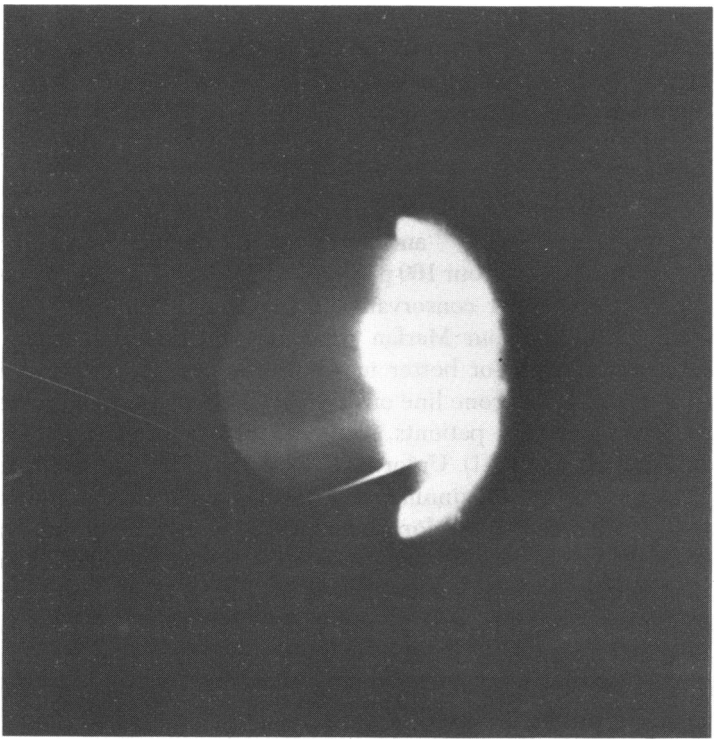


FIGURE 12
Size of aphakic pupillary space under slit-lamp examination, without use of mydriatic agents, which is adequate for optimal visual acuity with lens subluxation.

refraction—whether through the lens in minor amounts of dislocation or through the aphakic space if the dislocation is considerable. The most common cause for reduced visual acuity in patients with dislocated lenses is amblyopia; the most deleterious cause of reduced acuity is a retinal detachment.

ACCOMMODATION AND ZONULAR APPARATUS

Strikingly, accommodation was normal in our patients with subluxated lenses. On slit-lamp examination one sees a good zonular complement, with tight zonular fibers and not redundant and loose ones, as often described for the Marfan syndrome. This finding corresponds to the

surgical observation that the zonular fibers do not readily break if a subluxed lens in a Marfan patient has to be removed. Thus, in many instances we are dealing with functional zonular fibers on a partly displaced lens.

The overyling iris is not normally supported in Marfan patients, and iridodonesis is evident. The iris also will show a smooth velvety appearance; and about 10% of our patients showed peripheral iris transillumination, which may be very striking a times (Fig 4). On histologic examination, absence or hypoplasia of the dilator muscle is commonly seen.[26-30] Pharmacologic agents that stimulate the dilator muscles may be of no help in achieving pupillary dilatation, and thus the use of sympathomimetic drugs seems contraindicated in the Marfan patients, who may have significant cardiovascular disease.

DISLOCATION OF THE LENS

The lens was dislocated in only 60.3% of our patients, which shows our readiness to make the diagnosis of the Marfan syndrome in the absence of dislocation of the lens. A dislocated lens was usually of normal size, although a microspherophakic lens was seen in both eyes of two of our Marfan patients with severe congenital skeletal and cardiovascular changes. In both cases the lenses were, concurrently, slightly dislocated upward. As a minor sign of dislocation of the lens, we frequently see a slight notch in the lens, most commonly inferiorly. The lens was often dislocated slightly backward, in addition to the vertical and horizontal dislocation, leaving a gap between the pupillary border and anterior lens surface. In one patient the lens would tilt into the anterior chamber on pupillary dilatation, and corneal edema would result. This apparently also occurred spontaneously at night. One other patient showed at a short time interval in the two eyes progressive dislocation of the lens with entrapment of the lens in the pupillary space. Still another patient had had, by history, a dislocation of the lens into the anterior chamber. It had been removed prior to his first visit here. In four eyes the lens was found in the vitreous cavity, which was well tolerated in two of these eyes over many years. In the other two eyes the dislocation was accompanied by uveitis, retinal detachment, and markedly increased intraocular pressure. The lens was dislocated upward, or superonasally, or superotemporally in 77% of our cases, thus making the prime direction of dislocation upward, a direction never seen in homocystinuria.[22] The lens dislocation was progressive in between 7.5% and 13.2% of our patients, using for the lower figure personal observation and for the greater figure historical information as well.

By history, there was no relation between lens dislocation and trauma, and there was a smaller proportion of men (but statistically nonsignificant) who had a dislocated lens. Men presumably are more physically active; thus there is no evidence that this leads to an increased rate or progression of dislocation of the lens in Marfan syndrome patients. There is also no evidence that children with dislocated lenses should be excluded from participation in sports because of danger of progression of dislocation of the lens. However, the participation in contact sports does appear contraindicated because of the increased tendency toward retinal detachments in Marfan syndrome patients. The less frequent dislocations in the older age groups was noted (Table XVI). This can be interpreted in two ways: (1) It is possible that patients with dislocation of the lens are likely to be more severely affected systemically, and therefore die at an earlier age, than patients who do not have dislocation of the lens. This would lead to a decreasing proportion of patients with dislocation of the lens with increasing age. (2) Similarly, this decrease may be spurious and be due to the fact that patients in the older age group were likely to be discovered as the result of the diagnosis of severe disease in an offspring. Patients that have married and had children are likely to be more mildly affected than is the typical patient with the Marfan syndrome. Such late discovery of mildly affected adults in conjunction with more severely affected children could produce a bias in the patient distribution with regard to lens dislocation.

RETINAL DETACHMENTS

A retinal detachment had occurred in 16 eyes of 13 patients among 160 consecutive patients with the Marfan syndrome. To answer the question of whether every patient with the Marfan syndrome is at an equal risk of having a retinal detachment, the following studies were analyzed.

Keratometer Readings

The K readings of six fellow eyes from patients with retinal detachments varied from 36.70 to 44.50 with a mean of 40.41. The mean K reading of 96 eyes with dislocation of the lens was 41.26. The difference was not significant, although there evidently was a trend toward more marked flattening of the corneas in patients with retinal detachments.

Axial Length Measurements

The axial length measurements of the fellow eye in six patients with a detachment ranged from 24.00 to 30.34 mm. The mean axial length in

patients 12 years and older with a retinal detachment was 28.47 mm vs a mean of 24.90 mm for 40 eyes of patients 15 years and older with the Marfan syndrome but without a retinal detachment. This difference was significant ($t = 4.86$, $P < .01$) despite the small number of patients. Conversely, there was no patient with a normal axial length in whom a spontaneous retinal detachment had developed (the measurement of 24.00 mm had been obtained in a 7-year-old child). Previous intraocular surgery had been performed elsewhere on five of these eyes with a retinal detachment in four patients. Among the 160 patients with Marfan syndrome, the lens had been surgically removed in 18 eyes prior to the patient's first visit here. Five detachments occurred prior to or during the collection of data for the study. One additional detachment occurred recently in the second eye of one of these patients. Six patients had a positive family history for retinal detachments and two pedigrees are shown in Fig 11. All patients with detachments had dislocated lenses. An increased prevalence of retinal detachments after intraocular surgery in the Marfan syndrome has been reported.[22,23,25] This is confirmed in our series, in which a retinal detachment has developed in over 30% of the patients who had intraocular surgery. Correlation analysis between retinal detachments and skeletal and cardiovascular changes respectively was not statistically significant, and thus the most significant values for retinal detachment in our series were increased axial length, positive family history, prior intraocular surgery, and dislocated lenses.

LENS SURGERY

Two indications for lens surgery in the Marfan syndrome are lens opacities and lens touch of the corneal endothelium by a forward-tilted lens. Another relative indication is imminent complete luxation of the lens. The lens dislocated into the vitreous cavity is occasionally well tolerated for many years, but there are definite cases in which the development of poorly controlled glaucoma occurs.

If a markedly dislocated lens is cataractous, we do not remove the cataract but give the patient an aphakic prescription. In case of minor dislocation when an adequate aphakic pupillary space cannot be achieved, a planned extracapsular cataract extraction is performed. The zonular fibers are tight enough in such a case, and the anterior capsulotomy can be done with the cystotome in the usual manner. (However, if the fibers do not prove strong enough, an anterior capsulotomy could be completed using scissors.) Thereafter the nucleus is removed with the cryoprobe. The cataracts seen in these patients are nuclear-sclerotic, and the nucleus is easily removed with the cryoprobe after anterior capsulotomy. The

residual cortical material is then irrigated and aspirated. A posterior capsulotomy is performed using a bent needle tip. No long-term results are available for this procedure, but the early postoperative results are good (Fig 13). Whether the rate of retinal detachments will be similarly high remains to be determined.

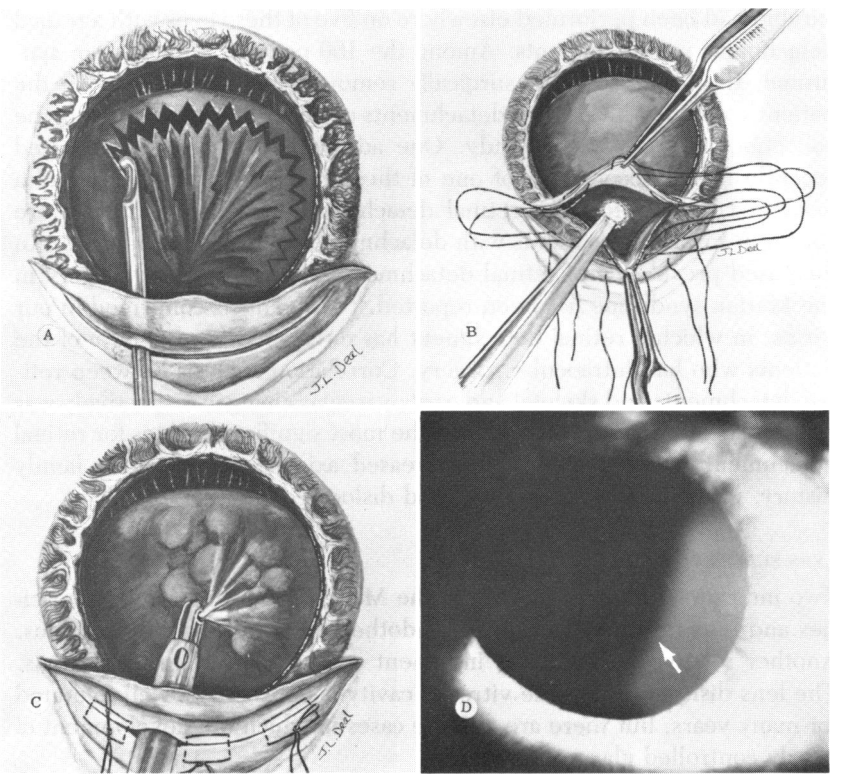


FIGURE 13
Planned extracapsular extraction in Marfan patient with dislocated lenses using A: cystotome, B: cryoprobe, C: irrigation-aspiration, and D: result after primary capsulotomy (arrow at edge of capsulotomy site).

GLAUCOMA

Glaucoma was not a common problem in our patient population. Glaucoma occurred in five eyes of five patients. All had a concomitant or previous retinal detachment. All five patients had dislocated lenses, two

into the vitreous cavity. One patient refused all therapy, one eye was lost from intraocular surgery and an expulsive hemorrhage, and three eyes were well controlled on medical therapy. The angles were open in all cases. Could it be that the glaucoma led to further stretching of the globe followed by the development of a retinal detachment in at least some of these cases? The histories would be compatible with such a development in two cases.

PATHOPHYSIOLOGIC CHANGES OF LENS DISLOCATION

When K readings were computed against dislocation of the lens, a highly significant linear trend was found: X^2 with 1° of freedom = 10.92; $P < .001$. Thus, the flatter the keratometer reading, the more likely a patient will have a dislocated lens (Table XVIII).

When axial length was measured against lens position in the Marfan patients older than 14 years, we saw that the mean axial length of Marfan patients with normal lenses was significantly shorter than the mean axial length of Marfan patients with dislocated lenses ($F = 4.35$, $P < .01$). Thus, patients with a dislocated lens had a significantly lengthened globe with flattened K readings. Why would the K readings be flat and not steep if this correlation is caused by excess stretching of the globe under normal pressure? The most obvious explanation is that the eyes "give" at the scleral ring and that the scleral tunic, in general, stretches under the intraocular pressure; this leads to flattening of the cornea with the appearance of megalocornea and to a lengthened globe. Histopathologic reports are compatible with such an explanation.[26-30] The thickness of the cornea was not reduced in any of the patients measured. Thus the cornea as such does not appear to "give." This stretching of the globe may lead to stretching of the zonule, which will "give" and lead to rarefaction of zonular fibers and dislocation of the lens. Support for such an interpretation comes from experimental work by McKanna and Casagrande,[45] who compared fellow eyes from tree shrews that had been deprived of pattern vision from infancy by unilateral lid sutures. Axial myopia with poorly developed ciliary zonules developed in these eyes. The lenses in these eyes weighed significantly less than the lenses in the fellow eyes. Evidently the changes in the zonule were environmentally induced under genetically controlled conditions. The assumption that definition of the basic defect of the Marfan syndrome will come from knowledge about the biochemistry of the zonular fibers is not necessarily true. The fibers might be biochemically normal but secondarily altered, depending upon scleral pathologic changes. Also, why do the lenses usually dislocate upward? The zonules are likely to yield where they are the weakest, which could

TABLE XVIII: KERATOMETER READINGS VS LENS DISLOCATION*

LENS POSITION	DIOPTERS						TOTAL†
	<40.00	40.00-40.99	41.00-41.99	42.00-42.99	43.00-43.99	>44.00	
Normal	5	5	9	5	6	11	41
Dislocated	21	18	27	17	8	5	96
Total	26	23	36	22	14	16	137 eyes

*K readings per eye, based on the average of two readings.
†$\chi^2 = 15.73$; 5 *df*; $P < .01$ linear trend $\chi^2 = 10.92$, 1 *df*; $P < .001$.

be in the area of closure of the optic vesicle. Certainly this is hypothetical, however, and no proof for this hypothesis exists.

Are any of the ocular parameters so far measured predictive of the Marfan patients' cardiovascular or skeletal manifestations?

When dislocation of the lens was plotted against cardiovascular manifestations, no significant association was found, nor was an association found between lens dislocation and skeletal manifestations. Similarly, the K readings were not statistically associated with the cardiovascular manifestations or the skeletal manifestations. Searches for a relation between the axial length ocular measurements and the cardiovascular and skeletal manifestations were equally negative. This lack of a statistical relation is unfortunate, but the result was to be expected from the clinical data. We observed all permutations possible between mild and severe ocular, cardiovascular, and skeletal changes. However, the phenotype was more consistent within families than between families. This lack of correlation is unfortunate, because had such correlations been present, they might have helped us to predict in a given patient the natural history of his disease.

GENETIC ANALYSIS

The absence of consistent correlation between the degree of ocular, cardiovascular, and skeletal changes is best explained by the probable existence of genetic heterogeneity in the Marfan syndrome. The collagen molecule is formed by a triple helix, and by definition is therefore dependent upon the action of genes at three different loci. Evidently, in such a system there is ample space for different mutations to occur, which may lead to biochemically distinct diseases with overlapping phenotypic variations. Do we have any evidence in our study for such an explanation? We analyzed our 84 familial cases, which were distributed in 24 families. We see that there is a marked degree of intrafamilial consistency in ocular findings, in contrast to a lesser amount of interfamilial consistency: There were six families in which all affected had normal eye findings, and there were 13 families in which all affected had definite ocular changes. There were five families, however, with internal discrepancies among the members. There was no family in which there were severe ocular changes in one member and no ocular changes in others.

When we look at the distribution of sporadic cases vs familial cases, we see that 29.3% were presumably caused by a new mutation. The penetrance of the Marfan syndrome appears to be close to 100%, and even mildly affected patients are quite easily recognized when there is clinical suspicion because of other family members who are severely affected.

If the general population is at equilibrium regarding the Marfan syndrome, that is, if the prevalence in the general population does not change from generation to generation, the mutation rate can be estimated from reduction in fertility (or its complement, selection) of affected persons. Haldane[46] devised the following formula for estimation of the mutation rate u in a given disease: $u = \frac{1}{2} \times (1 - f)\, p$, where f corresponds to the effective fertility of Marfan patients, and p is the prevalence of patients with a given disease in the population. Since the mutation rate is defined per gamete and not per zygote, the prevalence of the syndrome seen in the population corresponds to twice the mutation rate. If a prevalence of 1 per 20,000 is used and f values of 0.5, 0.6, and 0.7, mutation rates of 1.25×10^{-5}, 1×10^{-5}, and 7.5×10^{-6} are calculated. When the mutation rate is estimated from the prevalence of sporadic cases, a value of 7.4×10^{-6} is calculated. The fertility value, however, is poorly defined. When we looked at our actual families, we obtained a fertility value of close to 1, but this is an evident overestimate, given the fact that only patients with mild Marfan syndrome live to and beyond reproductive age and have children and thus have established pedigrees. The mutation rates estimated by using directly the prevalence of sporadic cases in our population, and by using estimates based on reduction of fertility of patients with the Marfan syndrome, give, however, similar estimates of mutation rate. These values are compatible with the mutation rates seen for other human point-mutation diseases. However, the estimated rates are compatible with admixture of two to three diseases caused by separate allelic or nonallelic mutational events.

SUMMARY

One hundred sixty consecutive patients with the Marfan syndrome were reviewed for ocular, cardiovascular, and skeletal abnormalities, and were graded by severity.

The most striking ocular abnormality was enlargement of the globe, presumably caused by scleral stretching. Staphylomata were not a feature of any of the patients seen, nor was keratoconus. The cornea, in fact, was flattened but not thinned. Among the 160 patients, 193 eyes showed dislocation of the lens. Dislocation of the lens was positively correlated with increased ocular axial length and with decreasing K readings. We postulate that the ocular pathologic changes are primarily caused by stretching of the tunica scleralis, and that the zonular fibers (thus under

stress) may "give" or may rupture in their area of presumably least density which may be the area of developmental fusion of the optic vesicle. In a small proportion of cases the lens dislocation was progressive.

There was no correlation between ocular findings, on one hand, and the skeletal and cardiovascular abnormalities on the other. However, there was a good degree of intrafamilial consistency with regard to absence or presence of ocular pathology. The absence of correlation between the ocular and systemic findings in our data on these 160 patients is best explained by the existence of more than 1 point mutation, which may give rise to different but clinically similar phenotypes. The results of our calculations of mutation rate were compatible with such an explanation.

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