ANTERIOR LENTICONUS AND ALPORT'S SYNDROME*

BY

E. J. ARNOTT, M. D'A. CRAWFURD, AND P. J. TOGHILL

University College Hospital and Galton Laboratory, University College, London

IN 1927 Alport drew attention to the syndrome of hereditary nephritis and perceptive deafness which has since borne his name. Following this original description many other families with these two associated features have been extensively studied.

The renal lesion is characterized by a chronic form of nephritis, presenting often in childhood or early adult life with proteinuria or haematuria or both, with little disturbance of renal function. In males, after a variable latent period, the disease usually progresses to death from uraemia by the age of 30 years, and females usually have a less severe, not necessarily fatal, form. The majority of authors have considered the basic renal disorder to be a chronic glomerulonephritis, although some have believed the histological changes to represent pyelonephritis (Perkoff, Stephens, Dolowitz, and Tyler, 1951). The progressive nature of the disease is shown by the presence, in a child with abnormal urinary findings, of benign histological features on renal biopsy, compared with the advanced changes in adults dying from the disease (case records of Massachusetts General Hospital, 1957). Attention has been drawn to the frequency of renal foam cells in some families with hereditary nephritis and deafness (Perkoff and others, 1951; Goldbloom, Fraser, Waugh, Aronovitch, and Wiglesworth, 1957), but other authors have pointed out the non-specificity of these cells which occur in other chronic renal disorders (Whalen, Huang, Peschel, and McIntosh, 1961).

Approximately half the affected patients in the reported series have had perceptive deafness though there is a wide variation in the families, from only one in ten in Chappell and Kelsey's (1960) family, to all of the affected in one of the families of Mettier (1961).

Other authors have described families in which, in addition to the hereditary nephritis and deafness, there have been ocular lesions involving the lens and its capsule (Table, opposite), and recently a high incidence of lenticonus has been noted. In view of this association another family with Alport's syndrome, in which lenticonus was found, is described.

Case Report

A 20-year-old male student from Ceylon first attended University College Hospital, London, on June 1, 1964, complaining of headaches and anorexia for three months and intermittent vomiting for one month. He had had no urinary symptoms and in particular had never noticed haematuria.

* Received for publication April 27, 1965.

TABLE I
ALPORT FAMILIES WITH LENS DEFECT

Author	No. of Cases of Syndrome	No. of Cases with Lens Defect	Description of Lens Defect
Reyersbach and Butler* (1954) Case records, Massachusetts General Hospital (1957)	28	4	1 Cataract, 3 unspecified
Sohar (1956)	8	4	Spherophakia Spherophakia Congenital posterior cortical cataract Congenital posterior cortical cataract
Goldbloom and others (1957)	4	1	Bilateral anterior subcapsular cataract
Nieth (1959)	6	1	Bilateral lenticonus
Shaw and Glover* (1961)	33	2	Cataracts
Mettier (1961)	3 5	1 1	Bilateral anterior lenticonus Bilateral anterior lenticonus
Howe and Smythe (1962)	23	4	1 Anterior lenticonus, 3 Blind from early life
Ohlsson* (1963)	3	3	Myopia
Brownell and Wolter (1964)	7	6	3 Anterior punctate subcapsular opacities 1 Posterior lenticonus with anterior polar cataract 2 Bilateral anterior lenticonus
Asperti* (1964)	1	1	Bilateral anterior and left posterior lenticonus
Dubach and Gsell* (1962)	9	1	Cataract at age 10
Gregg and Becker* (1963)	?	1	Ruptured lens capsule—right eye Small bleb on left lens followed by an anterior polar cataract
Perrin* (1964)	? ? ?	2 2 2	Bilateral anterior and posterior lenticonus with nystagmus Bilateral congenital cataracts Bilateral anterior and posterior subcapsular cataract Coronal cataract Nuclear cataract
Present report (1965)	8	2	Bilateral anterior lenticonus Posterior lenticonus

* Cases not included in genetic analysis for reasons given in the text.

For some years there had been a steady deterioration in his hearing. He had had increasing difficulty with reading for three years; spectacles had originally been prescribed two years previously, and the prescription changed after one year. He had not had any serious illnesses in the past.

Family History.—Three brothers had had similar illnesses. The eldest died at the age of 18 years

in 1956 from progressive renal failure, having had proteinuria and microscopic haematuria for two years and deafness for eight years. Another brother died at the age of 22 years in 1964 from renal failure following a short history of proteinuria. He also had been deaf and had posterior lenticonus. A younger brother, now 14 years old, has a four-year history of deafness and proteinuria. His father is in good health at the age of 55 years. His mother, aged 53 years, has been deaf for eight years and was found to have proteinuria and a raised blood urea one year ago. A maternal aunt who died aged 43, and her son who died aged 18, both had nephritis and deafness for four years prior to death. There is no consanguinity in the family. The family pedigree is shown in Fig. 1.

FIG. 1.—Pedigree of patient's family, showing distribution of nephritis, perceptive deafness, and lens defect.

Examination.—Routine physical examination showed the patient to have a mild hypertension with a blood pressure of 160/90 mm. Hg. There was no cardiomegaly. There were no other abnormal findings apart from those detailed below.

Ophthalmological Findings:

Right eye: Visual acuity 6/18 without glasses. 6/12 with + 3 D sph.; also 6/12 with −12 D sph., −3 D cyl., axis 180°.

Left eye: Visual Acuity 6/24 without glasses. 6/12 with + 0.75 D sph.; also 6/12 with −12 D sph., −3 D cyl., axis 180°.

N6 was read with the myopic correction. There had been an increase in the central myopia of −3 D sph. during the previous year. There was arcus juvenilis of both corneae. The pupils reacted sluggishly to light. The anterior surface of the lens protruded into the anterior chamber of both eyes (Fig. 2, opposite). Direct illumination showed the typical appearance of a "globule of oil in water" in the centre of the pupillary area. Apart from anterior lenticonus the lens appeared healthy with no opacities in the cortex or capsule. Both fundi appeared normal. The ocular tension and the visual fields were normal.

Aural Examination: Audiometry (Dr. D. Birt) revealed bilateral perceptive deafness of 60–80 decibels. Caloric responses were normal.

Investigations.—Haemoglobin 76 per cent. (11.2 g. per cent.). W.B.C. 9,000/c. mm. (normal differential). E.S.R. 31 mm. at 1 hour (Westergren). Plasma urea 177 mg./100 ml. Plasma electrolytes: Na = 141, K = 4.7, Cl = 112.5, CO₂ capacity = 15.9 mEq./l.

Electrophoresis of the plasma proteins showed a moderate decrease in albumin and a slight increase in the alpha₂ and gamma-globulins.

FIG. 2.—Painting of right eye under slit lamp illumination showing arcus juvenilis and anterior lenticonus.

FIG. 3.—High-power view of kidney showing several stages of glomerular disease and tubular casts.

Serum calcium 9.0 mg./100 ml. Plasma phosphorus 5.8 mg./100 ml. (S.G. 1024). Alkaline phosphatase 4.8 K.A. units.

Mid-stream specimen of urine: 3.6 g./litre protein; 3 pus cells and 4 red cells per high-power field; occasional granular and hyaline casts; culture sterile. Urinary amino-acid chromatogram showed a non-specific glycine pattern. The urine contained 0.5 g. glucose/100 ml., but a glucose tolerance curve showed this to be due to a low renal threshold.

Chest x ray was normal.

Progress.—Initially treatment with a low protein diet and high fluid intake produced a satisfactory response with lowering of the blood urea to 56 mg./100 ml. After discharge from hospital the patient's condition again deteriorated and he died on November 8, 1964.

Post-mortem Examination (Dr. P. M. Sutton).—This showed the immediate cause of death to be pulmonary oedema. The heart was enlarged (350 g.) with considerable left ventricular hypertrophy, the ventricular wall being 2.2–2.6 cm. thick. Both kidneys were uniformly small (left, 80 g.; right, 80 g.) with a fine surface granularity and capsular adhesions. On section the cortices were reduced in depth and were a yellow colour, with a few bright yellow streaks. The renal medullae, calices, and pelves were normal, as were the renal vessels. Other macroscopic findings were normal apart from some enlargement of the parathyroid glands.

Histological examination of the kidneys showed the changes of chronic nephritis (Fig. 3). Almost all the glomeruli were abnormal. Some were large and cellular showing many capsular adhesions and great capsular epithelial proliferation. Other glomeruli showed progressive fibrosis and some were completely hyalinized. The tubules contained pink-stained casts. There was medial hypertrophy of arteries with intimal proliferation and hyaline change in the arterioles. Patchy lymphoid proliferation was present. No foam cells were seen.

Sections stained for fat (Oil Red O) showed that lipid was distributed focally throughout the kidney, being found in some of the walls of the tubules, in a few glomeruli and arteries, and a little in the casts themselves.

Pathological Report on the Eye (Dr. G. Morgan, Institute of Ophthalmology, London).—On macroscopical examination the globe was soft and the lens showed slight lenticonus (Fig. 4). On microscopical examination the eye appeared normal except for the presence of a thinned lens capsule centrally with slight protrusion forward of lens substance (anterior lenticonus). Occasional pigment clumps were seen on the corneal endothelium.

FIG. 4.—Sagittal section of anterior segment of the eye showing the anterior lenticonus of the lens.

Discussion

Anterior lenticonus is a rare condition in which there is a conical or spherical protrusion of the anterior lens surface into the anterior chamber. At the present time some 42 cases have been reported (Table II), representing 30 per cent. of the total cases of both anterior and posterior lenticonus known in the literature.

Using oblique illumination a conical or spherical protrusion of the centre of the anterior surface of the lens into the anterior chamber can be observed; the protrusion is sharply localized and its base is circular varying from 2.5 mm. to 4 mm. diameter (Marback, 1943; Ehrlich, 1946). By direct illumination a distortion of the fundus reflex is seen; in the centre of the pupillary area there is a dark disc resembling in appearance an effect which has been likened to a globule of oil in water. This is due to the fact that none of the rays from the central area of the pupil reach the observer's eye, owing to prismatic refraction by the excessively curved anterior region of the lens. As a consequence of the increased curvature of the anterior surface of the lens the central pupillary area may be highly myopic (up to -30 D sph. has been recorded) while the periphery may be emmetropic or even hypermetropic. With indirect ophthalmoscopy it is possible to obtain two images of the fundus, an erect virtual through the periphery and a small real inverted image through the axial area. The Purkinje images of the lens are altered.

Anterior lenticonus involves the axial portion of the lens capsule, the subcapsular epithelium, and the anterior cortex. The foetal nucleus is always spared, as is usually the adult nucleus, only two cases having been described in which this was involved. In a report by Urrets Zavalía and Obregón Oliva (1939) of two brothers with anterior lenticonus, the lens of the elder brother showed a concavity in the

TABLE II
PUBLISHED CASES OF ANTERIOR LENTICONUS

Author	Sex	Age (yrs)	Comment
Webster (1874)	M	24	Bilateral anterior lenticonus, posterior lens opacities
Van der Laan (1880)	M	23	Bilateral anterior lenticonus for 8 years, high myopia
Venneman (1891)	F	20	Bilateral anterior lenticonus and myopia for 6 years
Jaworski (1910)	M	32	Bilateral anterior lenticonus and high myopia; chronic nephritis
de Schweinitz and Wiener (1919)	M	20	Bilateral anterior lenticonus, poor visual acuity since childhood
Frey (1922)	M	?	Bilateral anterior lenticonus, marked central myopia and peripheral hyperopia
Riedl (1923)	M	36	Bilateral anterior lenticonus, myopia 7D, radial opacity in right lens
Weiss (1927)	M	29	Bilateral anterior lenticonus, poor vision since childhood
Kienecker (1929)	M	42	Bilateral anterior lenticonus; decreasing vision and nephritis for 8 years
Tsukahara (1930)	M	17	Right anterior lenticonus and cataract; anterior capsular cataract; juvenile arcus, left eye
Feigenbaum (1932)	M	10	Bilateral anterior lenticonus; later granular opacities, later polar cataract only on left
Moulton (1936)	M	33	Bilateral anterior lenticonus and minute anterior opacities
Rauh (1936)	M	48	Bilateral anterior lenticonus
Knobloch (1938)	M	20	Bilateral anterior lenticonus
Urrets Zavalía and Obregón Oliva (1939) (2 cases)	M M	23 15	Two brothers; bilateral anterior lenticonus in elder; unilateral anterior lenticonus in younger with capsular cataract in other eye. Parents were cousins
Ter-Artuniantz and others (1940) (2 cases)	?	?	1 case of posterior lenticonus and 1 of anterior lenticonus
Harris (1940)	M	?	Bilateral anterior lenticonus; punctate cataracts just behind centre of nucleus
Damel and Garbarino (1942)	M	24	Bilateral anterior lenticonus
Rocha and Coscarelli (1943)	F	30	Bilateral anterior lenticonus

Continued overleaf

TABLE II—*continued*

Author	Sex	Age (yrs)	Comment
Marback (1943)	M	23	Bilateral anterior lenticonus with microphakia
Ehrlich (1946)	M	12	Right anterior lenticonus with rupture of capsule and anterior cataract; capsular cataract left eye. Nephritis
Sen (1948)	M	14	Acute right visual defect, anterior lenticonus with herniation of lens through capsule
Litricin (1952)	F	?	Bilateral anterior lenticonus
Straatsma and others (1954)	?	?	Bilateral anterior lenticonus in a young adult, preceded by mild trauma
Shank (1954)	?	?	Monocular anterior lenticonus, posterior keratoconus and congenital nuclear cataracts
Unger (1957)	?	?	Bilateral anterior lenticonus associated with nephritis
Vancea and Lăzărescu (1958) (2 cases)	? ?	? ?	Bilateral anterior and posterior lenticonus in 1 case Unilateral lenticonus with anterior lens opacity in other eye in other case
Nieth (1959)	M	17	Bilateral lenticonus. Alport's syndrome
Mettier (1961) (2 cases)	M M	13 28	Bilateral anterior lenticonus. Alport's syndrome Bilateral anterior lenticonus. Alport's syndrome
Gregg and Becker (1963)	M	14	Ruptured capsule right eye; small bleb anterior polar cataract left eye. Alport's syndrome
Sand and Abraham (1962)	M	4	Unilateral anterior lenticonus
Johnstone (1963)	?	?	Unilateral anterior lenticonus
Howe and Smythe (1962)	?	?	Anterior lenticonus. Alport's syndrome
Perrin (1964) (2 cases)	M M	25 ?	Bilateral anterior and posterior lenticonus and congenital nystagmus. Alport's syndrome Bilateral anterior and posterior lenticonus with posterior subcapsular cataract. Alport's syndrome
Brownell and Wolter (1964) (2 cases)	M M	27 12	Bilateral anterior lenticonus. Alport's syndrome Brother; bilateral anterior lenticonus, nerve deafness. ? Nephritis
Asperti (1964)	M	24	Bilateral anterior lenticonus and pigment granules on anterior capsules
Crawford (1964)	M	20	Bilateral anterior lenticonus and pigment granules on anterior capsules
Present case (1965)	M	20	Bilateral anterior lenticonus. Alport's syndrome. Brother posterior lenticonus

usually convex surface of the anterior band of the adult nucleus. In the other case (Marback, 1943) the anterior portion of the senile nucleus was involved.

The structural pattern of the conus may have one of two forms. In most of the cases reported, including that described in this paper, there was a marked thickening of the anterior lens cortex (Kienecker, 1929; Moulton, 1936; Harris, 1940; Rocha and Coscarelli, 1943), over which curved the anterior lens capsule and the anterior band of disjunction. These two bands were sharply deflected at the base of the conus, and while arching over the prominence, though remaining approximately parallel to each other, had a decreased radius of curvature. In other cases (Knobloch, 1938; Ehrlich, 1946; Straatsma, Cancilla, and Hohn, 1954) there was a local blister-like bulge at the anterior pole of the lens over which the anterior lens capsule was deflected, while the underlying anterior band of disjunction took no part in the lens deformity.

While in the majority of cases of anterior lenticonus the lens is clear, other aberrations in lens morphology may be present, and in some cases there has been associated posterior lenticonus (Shank, 1954; Vancea and Lăzărescu, 1958; Perrin, 1964; and Asperti, 1964). Various associated lens opacities have been described (Webster, 1874; Jaworski, 1910; de Schweinitz and Wiener, 1919; Riedl, 1923; Rocha and Coscarelli, 1943; and Harris, 1940), including fine subcapsular cataracts in the axial area and the anterior capsular opacities (Moulton, 1936). In several cases of anterior lenticonus localized anterior opacities have appeared (Jaworski, 1910; Tsukahara, 1930; and Feigenbaum, 1932). In one case Feigenbaum claimed that increase in convexity at the anterior pole of the lens caused the capsule to burst in one place, resulting in a localized opacity. For the opacity to have remained so localized the rupture of the capsule must have been small and sealed quickly. That rupture of the lens capsule can occur in anterior lenticonus is conclusively demonstrated by a case of Ehrlich (1946), in which, after a three-year history of anterior lenticonus in the right eye, the capsule ruptured with protrusion of lens cortex into the anterior chamber, the whole lens finally becoming cataractous. Later a grey raised horseshoe-shaped anterior capsular opacity appeared in the left eye. Gregg and Becker (1963) reported the case of a boy of 14 with Alport's syndrome who ruptured the capsule of the right eye and was later observed to have a small bleb on the anterior surface of the left lens.

Unlike posterior lenticonus in which there are often other anomalies in the eyes, apart from the lenticular change, the other ocular structures are usually normal.

Anterior lenticonus commonly occurs in males, only three cases in a female having been reported (Venneman, 1891; Rocha and Coscarelli, 1943; and Litricin, 1952); in over 75 per cent. of cases it is bilateral and in many of the unilateral cases some change in the region of the anterior capsule of the other eye has been present.

The average age at time of diagnosis is 26 years with extremes of 10 to 48 years being reported. There is usually a history of gradual deterioration of vision over several years, with the development of axial myopia. Optical correction does not markedly improve the visual acuity. Since the other ocular tissues are normal, lens extraction should give a good visual result if the visual acuity has been affected seriously enough to merit surgery.

Many theories as to the cause of anterior lenticonus have been postulated. Rones (1934) divided anterior lenticonus into congenital and acquired, but this division

does not preclude the possibility that the acquired condition could be genetically determined, or that the congenital form could be the result of environmental influences.

One theory has related anterior lenticonus to a delayed or abnormal separation of the lens vesicle from the surface ectoderm (Venneman, 1891; Krusius, 1910; and Mohr, 1910). Rones (1934) was the first to disprove this theory by stating that the lens capsule and anterior epithelium of the lens were often clear and the foetal nucleus intact; furthermore, the whole concept of the lens formation from a plaque of surface ectoderm has been challenged by Russian and English workers who contend that lens elements really arise from "neural" cells beneath the surface epithelial layer. Webster (1874) considered that a distension of the lens vesicle was the cause of anterior lenticonus. Mohr (1910) and Jaworski (1910) held the view that anterior lenticonus was the result of adhesion between the cornea and the anterior capsule.

Seefelder and Wolfrum (1907) found in a four-month foetus a protein-rich coagulum between the lens fibres and the anterior epithelium of the lens; Rones (1934) also found a similar defect in a foetus and contended that anterior lenticonus is probably the result of a congenital or acquired disturbance of the pressure relationship of the lens system.

Many authors have correlated anterior lenticonus with an inherent weakness of the anterior capsule or an anomaly of the zonular system, an imbalance between resistance of the capsule and the intracrystalline pressure. The physio-chemical changes of puberty or mild trauma in association with a weak anterior capsule have been implicated as causatory factors. Duke-Elder (1964) has suggested that it may arise from a weakness and a consequent stretching of the lens capsule, which in turn may be due to maldevelopment of the anterior part of the zonule. If the anterior capsule is weak a lenticonus develops, if it is deficient an anterior polar cataract is formed. According to Duke-Elder, both deformities are two stages of the same process.

Many of the cases of anterior lenticonus reported in the literature have occurred in patients with Alport's syndrome. It is possible that the occurrence of arcus juvenilis in the patient reported here is significant, as this was also reported by Tsukahara (1930) in his patient with anterior lenticonus.

Jaworski (1910) and Keinecker (1929) thought that a disturbance of water metabolism in renal disease was the cause of the lenticonus, associated with a predisposing anterior capsule weakness. It is doubtful whether disturbance of water metabolism in Alport's syndrome produces lenticonus, as renal failure is a late manifestation of the syndrome and lenticonus can be present at a time when renal function is still normal. The presence of anterior lenticonus in some cases and anterior capsular opacities in other cases would suggest that there is an inherent weakness in the anterior capsule. In the patient described by Goldbloom and others (1957) both lenses showed anterior capsular opacities. Though other types of lens changes have been described in Alport's syndrome, notably spherophakia and posterior lenticonus (both of which conditions may be similarly associated with changes in the lens capsule), anterior lenticonus is the commonest lenticular manifestation. In many cases it would appear to be one of the inherited characteristics, and may be fundamental to the classification of Alport's syndrome.

Several conflicting views have been expressed regarding the mode of inheritance of Alport's syndrome and attempts have been made to subdivide this syndrome.

Several recent authors have favoured an autosomal dominant mode of inheritance with different expression in the male and female (Gobin, Porge, and Maréchal, 1958; Howe and Smythe, 1962; and Perrin, 1964). Other views have included partial sex-linkage (Stephens, Perkoff, Dolowitz, and Tyler, 1951; Perkoff, Nugent, Dolowitz, Stephens, Carnes, and Tyler, 1958), a form of inheritance so far unproven in man. The unique concept of autosomal dominant inheritance, with preferential migration of the chromosome carrying the abnormal gene to the oocyte rather than to the polar body in oogenesis, or to the X-bearing rather than the Y-bearing sperm during spermatogenesis, has been postulated by Shaw and Glover (1961), Cohen, Cassady, and Hanna (1961), and Mulrow, Aron, Gathman, Yesner and Lubs (1963).

Attempts to subdivide the syndrome have hitherto rested on clinicopathological differences in the renal lesion, in particular a division into hereditary glomerulonephritis or haematuria on the one hand, and hereditary pyelonephritis on the other, but such differences have not been consistent within families (Perkoff, 1964). A different distinction can be made by classifying families into those with or those without lens defect. Such a division cannot be absolute, as the manifestation of lens defect is not complete, and in small families with this tendency the lens defect may not appear. We have taken lenticonus, spherophakia, or polar cataract as constituting lens defect, and designated the families with any of these defects as group A. The families without lens defect we have designated as group B.

The details given of families in reports so far published, together with the family reported here, have been examined for any other differences between these two groups (Table III, overleaf). For this purpose the family of Shaw and Glover (1961) has been excluded, as the two cataracts reported may have been of the senile variety. The families of Reyersbach and Butler (1954), of Perrin (1964), and of Dubach and Gsell (1962) have been excluded because the published data are not adequate for comparison. We have also left out reports of single cases, of Ohlsson's (1963) family (which shows differences from other published families in the clinical features of both eye and renal lesions), and the families in which hyperprolinaemia has been described (Schafer, Scriver, and Efron, 1962; Fuhrmann, 1963; and Kopelman, Asatoor, and Milne, 1964).

In an analysis of family data patients with nephritis, perceptive deafness, or lenticular lesions were accepted as being affected. The data were analysed to determine the proportion of members affected and the proportion of the affected members with defects of hearing and of the lens, and the sex incidence in parents and offspring.

The proportion of affected members with lens defect of group A itself is 0.35 (range 0.17 to 0.92) and for the two groups taken together 0.03. Applying this mean value for group A to group B "expected" numbers of affected members with lens defect for each family were calculated and are shown in Table III.

The difference in the ratio of affected to unaffected members in the two groups (64 : 64 in group A and 589 : 974 in group B) is highly significant. $\chi^2 = 38.1$, for 1 degree of freedom, $P < 0.001$ (Table III).

TABLE III
FAMILIES WITH ALPORT'S SYNDROME IN GROUPS A AND B

Author	No. of Affected Members of Family	No. of Unaffected Members	Incidence in Affected Members of		Affected	
			Deafness	Lens Defect	M	F
<i>Group A</i>						
Sohar and others (1956)	8	5	7	4	6	2
Goldbloom and others (1957)	4	11	2	1	3	1
Nieth (1959)	6	5	4	1	4	2
Mettier (1961) (2 families)	3 5	3 6	3 2	1 1	3 3	0 2
Howe and Smythe (1962)	23	7	11	4	?	?
Brownell and Wolter (1964)	7	4	3	6	4	3
Present report (1965)	8	23	5	2	6	2
Total	64	64	37	20	29	12
<i>Group B</i>						
Alport (1927)	21	6	11	7	8	13
Poli (1953)	32	36	4	11	17	15
Hamburger and others (1956)	13	16	4	5	7	6
Bouchet and Paquelin (1956)	12	20	4	4	7	5
Robin and others (1957)	17	12	?	6	11	6
Perkoff and others (1958)	81	183	21	28	30	51
Sturtz and Burke (1958) (2 families)	18 4	214 14	9 1	6 1	8 1	10 3
Gobin and others (1958)	11	3	5	4	7	4
Klotz (1959)	8	0	3	3	3	5
Chappell and Kelsey (1960)	10	8	1	4	3	7
Whalen and others (1961)	19	27	8	7	7	12
Williamson (1961) (3 families)	6 4 4	10 10 4	3 2 2	2 1 1	4 3 1	2 1 3
Cohen and others (1961) (5 families)	8 47 40 26 85	9 38 63 36 117	7 14 19 5 25	3 17 14 9 30	4 24 15 10 37	4 23 25 16 48
Mulrow and others (1963)	28	27	5	10	12	16
Schneider (1963)	18	32	6	6	8	10
Giacomelli (1963)	10	7	5	4	6	4
Rosenkranz (1963) (2 families)	9 6	16 2	5 4	3 2	5 4	4 2
Tiliakos and others (1963) (2 families)	10 14	16 16	7 4	4 5	4 7	6 7
Peters (1964)	22	21	10	8	14	8
Ellis and Yaffe (1964)	6	11	4	2	2	4
Total	589	974	198	207	269	320
Grand Total	653	1038	235	227	298	332

The incidence of perceptive deafness in affected members is higher in group A at 0.62 (37/64) than in group B at 0.44 (198/572). This difference also is significant. $\chi^2 = 12.7$, for 1 degree of freedom, $P < 0.001$ (Table III).

The mean sex ratios of affected members of the families of groups A and B are 2.3 and 1.04 respectively, whereas for unaffected members the ratios are 1.0 and 1.2.

Taking the total numbers of affected males and females in the two groups (29 and 12 in group A and 269 and 320 in B, respectively) the differences here also are significant. $\chi^2 = 9.6$ to 1 degree of freedom with $0.005 < P < 0.001$ (Table III).

The distribution of affected and unaffected sons and daughters among the children of parents who transmit the gene (Table IV) strongly suggests not partial sex-linkage, but rather autosomal dominant inheritance in both groups, with modification by a sex-linked gene leading to reduced penetrance and expression. Such a sex-linked modifying gene would have to have a high frequency in the population. A maternal carrier for Alport's syndrome with a modifying gene on her X-chromosome would appear unaffected or only very mildly affected. Her sons or daughters would also carry the Alport gene, and the modifying gene, that is, one-quarter of each, would also be apparently unaffected or only mildly affected. This would give an excess of unaffected or very slightly affected sons and daughters. Similarly, a paternal carrier of the modifier may appear unaffected and will pass on the modifier to all his daughters but not to any of his sons, leading to an apparent excess of unaffected daughters. As will be seen from the table the actual findings agree well with these expectations for a sex-linked modifying gene. Inheritance of the modifier may, of course, take place from the non-transmitting parent. It is also still necessary to assume a more severe manifestation in males, producing greater morbidity in those affected and an early loss of affected male foetuses in the absence of the modifier.

While differential migration of the abnormal autosome with the X-chromosome during meiotic division of spermatogenesis is possible, the hypothesis proposed above provides a more satisfactory explanation of the findings.

TABLE IV
SEX DISTRIBUTION OF OFFSPRING OF TRANSMITTING PARENTS

Group	Transmitting Parents		Offspring			
			Sons		Daughters	
			Affected	Unaffected	Affected	Unaffected
A	Fathers 0	Affected —	—	—	—	—
		Unaffected —	—	—	—	—
	Mothers 8	Affected 7	18	5	5	7
		Unaffected 1	1	2	0	1
B	Fathers 95	Affected 90	34	95	88	61
		Unaffected 5	4	7	5	7
	Mothers 176	Affected 142	170	140	160	162
		Unaffected 34	21	36	31	52

A further paper is in preparation in which more families are investigated and linkage studies and a more detailed genetic analysis carried out. In the meantime we consider that the evidence presented here strongly favours the view that these two groups are either determined by two genes at different autosomal loci, or more probably by two alleles at the same locus, and are both inherited as autosomal dominants with sex influence, most marked in the group with lens defect and showing in both groups the action of a sex-linked modifying gene that suppresses or reduces the manifestation of the main gene. The possibility, especially within group B, of further heterogeneity is not excluded.

Summary

A case is reported of anterior lenticonus in a patient with Alport's syndrome. Attention is drawn to the frequent association of these two conditions and the possible reasons for this association are discussed. The literature concerning anterior lenticonus and Alport's syndrome with lens defects is reviewed. It is suggested that the mode of inheritance in Alport's syndrome is usually autosomal dominant, and that the manifestation of the gene concerned may be weakened in some persons by the presence of a sex-linked modifying gene of high incidence in the general population.

We thank Dr. J. F. Stokes, under whose care this patient was admitted, for permission to publish this report, and Prof. L. S. Penrose for much helpful criticism and advice. We also thank Mr. T. Tarrant of the Institute of Ophthalmology, London, for the drawing of Fig. 2.

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