THE GENETICS OF RETINOBLASTOMA*

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I.—The incidence of retinoblastoma at the Royal Eye Hospital, 1894-1943

(1) *Sporadic cases.*—Retinoblastoma is a rare tumour and hereditary manifestations of it are rarer still. At the Royal Eye Hospital, London, there were seen 59 children with retinoblastoma during the 50 years 1894-1943, and among these there was only one familial group, now observed over three generations. This group has supplied 6 instances of the affection, the remaining 53 being isolated sporadic cases. Amongst these 53 isolated cases there were eight bilateral cases (15·1 per cent.). The subjoined table gives the salient features as to sex and age distribution of the sporadic cases.

Age at which child was first seen	Unilateral		Bilateral	
	Male	Female	Male	Female
0– 3 months ...	0	0	2	1
4– 6 months ...	2	2	–	–
7– 9 months ...	2	2	1	1
10–12 months ...	4	3	–	–
13–18 months ...	3	1	1	1
19–24 months ...	4	4	–	–
25–30 months ...	3	0	1	–
31–36 months ...	3	0	–	–
Over 36 months	6	6	–	–
	27	18	5	3

The right eye was involved 12 times and the left 15 times in the 27 cases of unilateral retinoblastoma in boys. For the 18 girls, the retinoblastoma was right-sided 4 times and left-sided 14 times.

In estimating the frequency of retinoblastoma, the ratio of retinoblastoma cases to the total number of patients seen at the particular hospital is generally given. On this basis, the following rates of incidence have been recorded:—

London (*a*) Royal London Ophthalmic Hospital 1:9614 (Berrisford, 1916); (*b*) Royal Eye Hospital 1:10,433 (Letchworth, 1928). Paris 1:14,444 (Morax, 1926). Berlin 1:5,832 (Adam, 1911). Osaka (Japan) 1:848 (Nomoto, 1937).

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Wintersteiner in his exhaustive monograph of 1897 records a whole series of such ratios from the older literature.

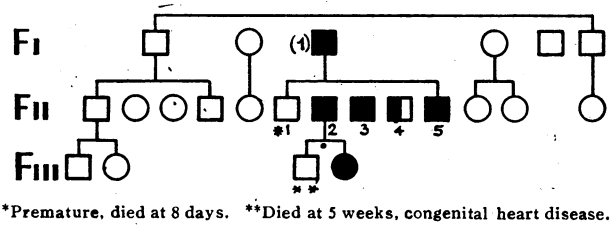
Such computations are apt to be fallacious as they ignore the variable age-structure in different countries and at different times and the rather erratic modes of registering new attendances at different hospitals. Hemmes (1931) more reliably computed the incidence at 1 in each 34,000 live births in Holland, basing himself on the occurrence of 12 actual new cases and a total of 16 computed cases seen over a period of three years by Dutch ophthalmologists. If the 59 cases seen at the Royal Eye Hospital during the past 50 years are taken to represent the incidence of the affection in London, South of the Thames—and it is permissible to do so, since some 70 per cent. of all the eye patients seen South of the river (35,476 out of 49,139 in 1938) come to this hospital and in addition there are a considerable number from outside the London area—an incidence of 1: 32,793 births is obtained, as there were 1,934,764 births (1,915,374 recorded births 1894-1942 and 19,390 computed births in 1943) in South London during this period.

In assessing the frequency of retinoblastoma the following data are of some interest:

(1) Retinoblastoma as a cause of blindness in infants under 5 years of age. During the period 1920-43 there were admitted 600 children to the Sunshine Homes for Blind Babies. Retinoblastoma (presumably bilateral) was the cause of blindness in 27 out of the 549 (=4·9 per cent.) for whom the cause of blindness was known.

(2) Mortality statistics for England and Wales 1936-41. During these five years there were recorded 14 male deaths and 4 female deaths from "glioma of the eye." The 1942 returns showed 5 male deaths, with the female deaths not as yet ascertained. (Registrar-General, 1943.)

(2) *A familial group.*—The pedigree recorded here has been reported in part on three previous occasions (Letchworth, 1928; Griffith, 1933, 1934, 1937; Hine, 1937). It is now possible to extend and amplify the previous observations of retinoblastoma in two generations to the observed occurrence of this condition in a member of the third generation.



*Premature, died at 8 days. **Died at 5 weeks, congenital heart disease.

FIG. 1.

Pedigree chart of the S. Family.

F1. (1) Ernest W. S., born 1895. Seen at the Royal Eye Hospital in May, 1897, aged 2 years and 3 months, when the left eye was removed by Malcolm McHardy for glioma. According to the history obtained by M. L. Hine (1937) removal of the right eye was advised but declined. The fundus appearances in this eye in 1937 are interpreted by Hine as those of spontaneously healed glioma.

F2. (1) Premature male infant (7 months). Died on 8th day.

(2) Frederick S., born 1917. A full account of this patient has been given by Hine who regards his fundi as showing spontaneous cure of bilateral glioma. Vision with correction is R: 6/6. L: 6/12. His daughter F3. (2) is affected.

(3) Leonard S., born 1919. Brought to the Royal Eye Hospital in August, 1921, at the age of 2 years. His mother had noticed "a white speck" in the right eye when the child was 7 months old. Glioma was diagnosed and the eye excised by Mr. T. W. Letchworth. Glioma in the left eye was observed in

January, 1923; at operation, the orbit was found invaded and, in spite of exenteration there was a recurrence and death in the same year.

(4) Walter S., born 1921. Seen by Mr. Letchworth in December, 1921, when the child was 3 months old. Glioma of the right eye was found and the eye was excised in January, 1922. He has been under constant observation since. The left eye is normal and in 1935 a Hess operation for ptosis of the right upper lid was done.

(5) Ernest Cyril S., born 1928. Seen in April, 1928, when 9 weeks old and suffering from glioma of the right eye (Letchworth). The left eye was then normal. The right eye was excised in May, 1928. Glioma of the left was diagnosed in July, 1929. Radium treatment was instituted and an account of initial success in this case with subsequent disappointment from the appearance of fresh foci of growth has been given by one of us (Griffith, 1933). Exenteration of the left orbit was done in April, 1931 (A. D. Griffith). The child died from recurrences in August, 1931.

F3. (1) Died at 5 weeks from "congenital heart disease."

(2) Helen S., born July 2, 1943. Brought to the Royal Eye Hospital at the beginning of September, 1943, when 9 weeks old. The left globe was almost filled with a tumour mass. Eye excised by Mr. Hine at the Royal Westminster Ophthalmic Hospital. The right eye was then normal, but subsequently a rapidly growing glioma developed necessitating excision of the eye in February, 1944 (Hine, 1944).

The points of interest in this history are:—

(1) The occurrence of glioma over three generations.

(2) The early age at which tumours were observed.

In the grandfather (F1. (1)) the tumour was noted at the age of 2 years and 3 months. In Frederick (F2. (2)) the age of onset is unknown. In Leonard (F2. (3)) it was 7 months; in Walter S. (F2. (4)) 3 months; in Ernest Cyril (F2. (3)) 9 weeks; and in Helen (F3. (2) also 9 weeks. (Early onset seems also to be a characteristic of the sporadic bilateral cases.)

(3) The presumably spontaneous cure in the right eye of the grandfather (F1. (1)) and in the two eyes of one of his sons (F2. (2)).

(4) The heavy tendency towards bilateral involvement in this family (in only one of these six patients (F2. (4) has the lesion been unilateral).

II.—The genetic behaviour of retinoblastoma

1. *Sporadic retinoblastoma.*—Evidence that retinoblastoma does occur as a sporadic affection is supplied by the observation of 51 sporadic cases at the Royal Eye Hospital and is supported by the following data:—

(1) Davenport (1926), Stock (1936) and Keller (1938), all report negative family histories in their series of 27, 28 and 13 cases respectively (though the possibility of inheritance could not be excluded in one of Stock's cases).

(2) Adam (1911) found no evidence of the disease in ancestral or collateral lines and in siblings in 41 cases (though in addition he noted three pairs of affected siblings). Lange (1938) found an affected parent twice in his series of 36 cases, studied over 22 years at Halle. Heijl's series of 45 cases contained only one in which

another member of the family (the patient's mother) was affected. From 1871 to 1924 there were seen at the Royal London Ophthalmic Hospital (Lawford and Collins, 1890; Marshall, 1897; Owen, 1905; Berrisford, 1915; Davenport, 1926) 163 cases of glioma, and these included two familial groups: three cases in one sibship reported by Marshall (1897), and six (more strictly five in the period under review) in another family (Owen, 1905, and Berrisford, 1915).

Reiser's (1937) observations are only slightly less negative. Sixteen patients, coming from 16 families with a total of 64 children, showed no affected sibs, and in only one instance was a parent found to have had an eye affected. Reiser stresses the rarity of hereditary retinoblastoma by pointing out that there are probably 1,000 cured patients throughout the world, and that many by now must have had children who have apparently not come to ophthalmic observation.

(3) Hemmes (1931) obtained completely negative results in an exhaustive genetic study of 48 cases. Not one of the parents had had an eye enucleated. Nine cured patients who had had unilateral retinoblastoma were older than 25 years at the time of Hemmes' study, and four of them had become parents, having nine children in all—all of them healthy. The 48 patients had 211 sibs over the age of five years and none of them were affected, nor was there evidence of the affection in 31 sibs who had died before reaching the age of 6 and in 11 who were alive but under the age of 6 years. The collateral lines were clear: 24 of the retinoblastoma patients had 76 sibs who were the parents of 281 children, in none of whom the affection had appeared. Consanguinity was noted three times in the parents of the 48 cases: in two instances the parents were first cousins, and in the third the affected child was the product of incestuous relationship between father and daughter.

2. *Retinoblastoma in fraternities with clear antecedents.*—The earliest record of affected sibs is that of Lerche in 1821; of seven children three sons and one daughter were affected. Sichel in 1859 reported on four out of five children affected. These cases and the familial groups reported subsequently are shown in Chart I, on which the following table (Table I) is based:—

The following points are noteworthy:—

(1) That there was no consanguinity in the parents is stated by Schoenemann (1880) and Marshall (1897). Consanguinity was noted only in one instance (Waardenburg, 1932), the parents being first cousins. In the other reports no mention is made.

(2) Whilst affected sibships with clear antecedents suggests recessive inheritance, an incidence of 47·8 per cent. against the theoretical 25 per cent. and the negative evidence on consanguinity speak against this view, as does the appearance of an affected

TABLE I—*Retinoblastoma in Affected Sibs with Clear Antecedents*

1.—COMPLETE SIBSHIP

Year	Author	Number in family			Number affected											
					Male				Female				Sex not stated			
					Eye affected				Eye affected				Eye affected			
		M.	F.	Not stated	R.&L.	R.	L.	Not stated	R.&L.	R.	L.	Not stated	R.&L.	R.	L.	Not stated
1929	Benedict ...	2	2	–	–	–	–	–	1	–	1	–	–	–	–	–
1898	Boyd	1	1	3	–	–	–	1	–	–	–	1	–	–	–	1
1891	Brown ...	7	1	–	1	–	2	–	–	–	–	–	–	–	–	–
1910	Calderaro ...	2	3	–	–	2	–	–	1	1	–	–	–	–	–	–
1867	Calderini ...	–	3	8	–	–	–	–	–	–	1	2	–	–	–	–
1920	Comas ...	2	3	6	1	–	–	1	–	–	–	3	–	–	–	–
1915	Dabney ...	–	–	6	–	–	–	–	–	–	–	–	2	–	–	1
1930	Ernrooth ...	–	–	4	–	–	–	–	–	–	–	–	–	–	–	3
1893	Fuchs ...	2	–	1	–	–	–	2	–	–	–	–	–	–	–	–
1868	v. Graefe ...	–	–	6 (or 7)	–	–	–	–	–	–	–	–	–	–	–	2
1932	Hemmes[2] ...	1	–	7	–	–	–	–	–	–	–	–	–	–	–	4
1916	Leber ...	–	–	9	–	–	–	–	–	–	–	–	3	–	–	–
1821	Lerche ...	3	4	–	–	–	3	–	1	–	–	–	–	–	–	–
1885	Macgregor ...	1	–	4	1	–	–	–	–	–	–	–	2	–	–	–
1902	Maher[1] ...	2	2	–	1	–	–	–	1	–	1	–	–	–	–	–
1897	Marshall ...	2	4	–	–	1	–	–	1	–	–	1	–	–	–	–
1930	Mazzei ...	1	1	2	–	–	1	–	–	–	1	–	–	–	–	–
1937	Nemoto ...	–	–	7	–	–	–	–	–	–	–	2	–	–	–	–
1915	Purtscher[2] ...	6	5	–	2	–	–	–	1	–	–	–	–	–	–	–
1880	Schoenemann	3	–	3	–	1	1	–	–	–	–	–	–	–	–	–
1859	Sichel ...	2	1	2	–	1	1	–	–	–	–	–	–	–	–	2
1904	Snell (1) ...	2	1	–	1	–	–	–	1	–	–	–	–	–	–	–
1905	Snell (2) ...	1	1	–	1	–	–	–	1	–	–	–	–	–	–	–
1900	Steinhaus[2] ...	2	2	6	–	–	–	1	–	–	–	2	–	–	–	–
1939	Townsend ...	–	3	–	–	–	–	–	–	3	–	–	–	–	–	–
1903	Valenti ...	1	–	2	–	–	–	1	–	–	–	–	–	–	–	1
1932	Waardenburg	2	–	9	2	–	–	–	–	–	–	–	–	–	–	–
1941/2	Weller-Falls	5	5	–	1	1	–	–	2	–	2	–	–	–	–	–
1872	Wilson ...	–	1	7	–	–	–	–	–	–	–	–	–	–	–	3
1875/7	Zinke ...	2	–	3	1	–	1	–	–	–	–	–	–	–	–	–
		52	43	95	12	6	9	6	10	4	6	11	7	–	–	17
							33				31				24	

2.—INCOMPLETE SIBSHIP

1911	Adam (1) ...	1	1	?	1	–	–	–	1	–	–	–	–	–	–	–
	Adam (2) ...	2	?	?	–	2	–	–	–	–	–	–	–	–	–	–
	Adam (3) ...	2	?	?	–	1	1	–	–	–	–	–	–	–	–	–
1922	Adams ...	1	1	?	1	–	–	–	1	–	–	–	–	–	–	–
1895	Feinstein[2] ...	2	2	?	–	–	–	1	–	–	–	–	2	–	–	–
1891	Flexner ...	?	?	3	–	–	–	–	–	–	–	–	1	–	–	2
1897	Wintersteiner	2	?	?	–	1	–	1	–	–	–	–	–	–	–	–
					2	4	1	2	2	–	–	–	3	–	–	2

Total number of children in 31 complete sibships : 190.

Total number of children affected in these sibships ; 88=46·3 per cent.

Total number of children with glioma in complete and incomplete sibships : 104.

Number of recorded bilateral cases, 38*=36·5 per cent. Number with right eye affected, 14. Number with left eye affected, 16. Number affected without nearer specification, 36.†

(1) Glioma appeared in a child of one of these sibs. See Maher-Pockley pedigree in Chart II.

(2) Glioma appeared in children of unaffected sibs. See appropriate pedigrees in Chart III.

*This table shows only 36, but there were at least 38 as in Comas' cases there must have been 3 patients with bilateral glioma since 8 enucleations were done on 5 patients.

† This table shows 38 for the same reason.

descendant in one of Maher's patents and in several offspring of unaffected sibs of patients (Hemmes, 1932; Purtscher, 1915; Steinhaus, 1900).

3. *Retinoblastoma with direct inheritance.*—In 1896-1910 de Gouvea reported the occurrence of bilateral glioma in two children out of seven born to a father who had the right eye excised by him in 1872. Owen, in 1905, reported on the occurrence of right-sided glioma in a boy aged 3 years in 1898, whose father had a left eye removed at 5 months for glioma in 1859 (by Bowman). In 1908 v. Hoffmann reported the occurrence of bilateral glioma in a child aged 1 year, whose mother had had her right eye enucleated for glioma 28 years earlier by the reporter's father. Additional reports of such inheritance have since accumulated. Chart II gives these family trees, and the essential features are brought out in the subjoined Table :—

TABLE II—*Direct Inheritance of Retinoblastoma*

1.—COMPLETE SIBSHIPS

	Year	Author	Number in family			Number affected											
						Male				Female				Sex not stated			
						Eye affected				Eye affected				Eye affected			
			M.	F.	Not stated	R.&L.	R.	L.	Not stated	R.&L.	R	L.	Not stated	R.&L.	R.	L.	Not stated
Father affected	1896	de Gouvea ...	—	3	4	—	—	—	—	3	—	—	—	—	—	—	—
	1926	van der Hoeve ...	—	—	12	—	—	—	—	—	—	—	—	—	—	—	2
	1938	Lange (1)	2	—	—	2	—	—	—	—	—	—	—	—	—	—	—
		Lange (2)	1	—	3	1	—	—	—	—	—	—	—	—	—	—	—
	1929	Meyer-Riemsloh	1	—	—	—	—	1	—	—	—	—	—	—	—	—	—
	1936	Stallard	2	—	—	2	—	—	—	—	—	—	—	—	—	—	—
	1928	Sym	1	2	—	1	—	—	—	1	—	—	—	—	—	—	—
	1919	Traquair	1	1	—	1	—	—	—	—	—	1	—	—	—	—	—
	1941	Weller-Sleight ...	—	2	—	—	—	—	—	1	—	1	—	—	—	—	—
	1902 1919	Maher-Pockley ...	—	—	1	—	—	—	—	—	—	—	—	—	—	—	1
		Present series (1)	5	—	—	3	1	—	—	—	—	—	—	—	—	—	—
		Present series (2)	1	1	—	—	—	—	—	1	—	—	—	—	—	—	—
			14	9	20	10	1	1	—	6	—	2	—	—	—	—	3
Mother affected	1911	Caspar	—	1	—	—	—	—	—	1	—	—	—	—	—	—	—
	1925	Fietta	—	1	—	—	—	—	—	—	1	—	—	—	—	—	—
	1917	Griffith	1	2	—	—	1	—	—	1	1	—	—	—	—	—	—
	1917 1923	Griffith-Bride ...	4	3	—	3	—	—	—	2	—	—	—	—	—	—	—
	1908 1916	v. Hoffmann-Leber	2	—	1	2	—	—	—	—	—	—	—	—	—	—	—
	1937	Reiser	1	1	—	—	—	1	—	—	—	—	—	—	—	—	—
			8	8	1	5	1	1	—	4	2	—	—	—	—	—	—
Sex of affected parent not stated	1934	Best	—	—	3	—	—	—	—	—	—	—	—	—	—	2	—

2.—INCOMPLETE SIBSHIPS

Father affected	1916	De Haas	?	?	1	—	—	—	—	—	—	—	—	1	—	—	—
	1928	Heine	3	?	?	—	—	—	—	—	—	—	—	3	—	—	—
	1932	Hemmes	?	1	?	—	—	—	—	1	—	—	—	—	—	—	—
	1905 1916	Owen-Berrisford	1	1	?	—	1	—	—	—	—	—	—	—	—	—	—
Mother affected	1934	Heijl	1	?	?	1	—	—	—	—	—	—	—	—	—	—	—
	1921	Kennon	1	?	?	—	—	—	1	—	—	—	—	—	—	—	—
	1936	Melanowski ...	?	?	1	—	—	—	—	—	—	—	—	—	—	—	1
	1927	Odinzow	?	1	?	—	—	—	—	—	—	—	1	—	—	—	—
	1905 1917	Taylor	1	?	?	1	—	—	—	—	—	—	—	—	—	—	—
						2	1	—	1	1	—	—	1	4	—	—	1

Total number of children in 19 complete sibships: 63

Total number of children affected in these sibships: 38 = 60·3 per cent.

Total number of children with glioma in complete and incomplete sibships: 49.

Number of recorded bilateral cases: 32 = 65·3 per cent. Number with right eye affected: 5. Number with left eye affected: 6. Number affected without nearer specification: 6.

Number of children born to affected fathers (in complete sibships): 43* of whom 23* were affected = 53·5 per cent. (16 bilateral = 69·6 per cent.).

Number of children born to affected mothers (in complete sibships): 17, of whom 13 were affected = 76·5 per cent. (9 bilateral = 69·2 per cent.).

Number of parents affected with bilateral retinoblastoma in complete sibships: 1 (Maher-Pockley). In incomplete sibships: 1 (Heijl).

*If v. d. Hoeve's sibship of 12 with 2 affected is excluded, the respective figures are 31 children with 21 affected = 67·7 per cent.

The data in the Table permit the following conclusions:—

(1) The direct transmission of retinoblastoma is established by these 28 pedigrees.

(2) The suggestion of dominant inheritance is strengthened by the incidence of the affection in 61·1 per cent. of children in the 19 complete sibships available.

4. *Retinoblastoma in the children of parents themselves unaffected but having a family history of the affection.*—In 1868 v. Graefe, discussing the familial incidence of neuroblastoma, mentioned briefly that "several siblings" of the mother of a child with glioma had died in the first year of life from "cancer of the eye" ("*Augenkrebs*"). A more definite finding was given in 1874 by Thom[p]son and Knapp, who reported retinoblastoma in the two children of healthy parents, but noted the occurrence of the affection in a paternal cousin of the affected children, and in two cousins of the father. (Further information on this family which had meanwhile become much larger was subsequently given by Thompson in 1898). An indisputable example of the occurrence of retinoblastoma in the children of an unaffected parent who had affected sibs was recorded by Steinhaus in 1900; in a sibship of 10, a boy and two girls had been affected by glioma, and the eldest of these 10 children, himself unaffected, had two affected children. The data on these and similar instances are shown in Chart III and are summarised in the subjoined table.

TABLE III—*Retinoblastoma in Children of Parents of Affected Stock but themselves Unaffected*

1.—COMPLETE SIBSHIP

	Year	Author	Number in family			Number affected											
						Male				Female				Sex not stated			
						Eye affected				Eye affected				Eye affected			
			M.	F.	Not stated	R.&L.	R.	L.	Not stated	R.&L.	R.	L.	Not stated	R.&L.	R.	L.	Not stated
Transmitted by male carrier	1932	Hemmes	—	—	5	—	—	—	—	—	—	—	—	—	—	—	4
	1937	Nemoto	—	—	4	—	1	—	—	—	1	—	—	—	—	—	—
	1902	Newton	9	7	—	3	2	—	—	4	—	1	—	—	—	—	—
	1900	Steinhaus... ...	1	1	—	—	—	1	—	—	—	1	—	—	—	—	—
	1874 1898	Thompson and Knapp...	7	7	—	—	—	—	2	1	2	—	—	—	—	—	—
			17	15	9	3	3	1	2	5	3	2	—	—	—	—	4
Transmitted by female carrier	1905 1916	Owen-Berrisford	3	5	—	2	—	—	—	1	1	—	—	—	—	—	—
	1915	Purtscher... ...	2	—	—	2	—	—	—	—	—	—	—	—	—	—	—
	1927	Sabugin	2	—	10	2	—	—	—	—	—	—	—	—	—	—	—
			7	5	10	6	—	—	—	1	1	—	—	—	—	—	—

2.—INCOMPLETE SIBSHIP

	1868	v. Graefe[2] ...	?	?	1	—	—	—	—	—	—	—	—	—	—	—	1
	1895	Feinstein[1] ...	?	1	?	—	—	—	—	—	—	—	1	—	—	—	—
	1908	Lukens (a)[1] ...	1	?	?	1	—	—	—	—	—	—	—	—	—	—	—
		Lukens (b)[1] ...	?	?	1	—	—	—	—	—	—	—	—	—	—	—	1
	1898	Thompson and Knapp[1] (a)	1	?	?	—	—	—	1	—	—	—	—	—	—	—	—
		(b)	?	?	3	—	—	—	—	—	—	—	—	—	—	—	3

Total number of children in 8 complete sibships: 63.
Total number of children affected in these sibships: 31 = 49·2 per cent.
Number of recorded bilateral cases: 15 out of 31 = 48·4.
Number of children born to fathers of affected stock (in complete sibships): 41 of whom 23 were affected = 54·8 per cent. (8 bilateral = 34·8 per cent.).
Number of children born to mothers of affected stock (in complete sibships): 22 of whom 8 were affected = 36·4 per cent. (7 bilateral = 87·5 per cent.).
[1] Male carrier. [2] Female carrier.

III.—Discussion

1. *Varieties of retinoblastoma.*—The considerable variations in the histological structure of "gliomata" of the retina may have a bearing on the genetics of these tumours. There is as yet no general survey of the histological appearances of retinoblastoma of proved genetic origin. This is a point that requires elucidation. For the present one must assume that retinoblastoma is more frequently "sporadic" than hereditary. The rarity of the tumour and the severity of the lesions it produces make it unlikely that hereditary aspects have been overlooked in the mass of sporadic cases observed and reported.

2. *The mode of inheritance.*—The genetic analyses shown in Tables I-III justify the conclusion that glioma may appear " spontaneously " within a given sibship and be transmitted as a dominant, though " irregular " in type, as these tumours occur in children of parents derived from an affected stock but themselves free from the affection. In any particular case of " sporadic " glioma, it is at present impossible to say whether this represents the starting point of a hereditary group. A detailed study not only of the histological features of the genetic variety of retinoblastoma but of possible associated somatic stigmata is needed.

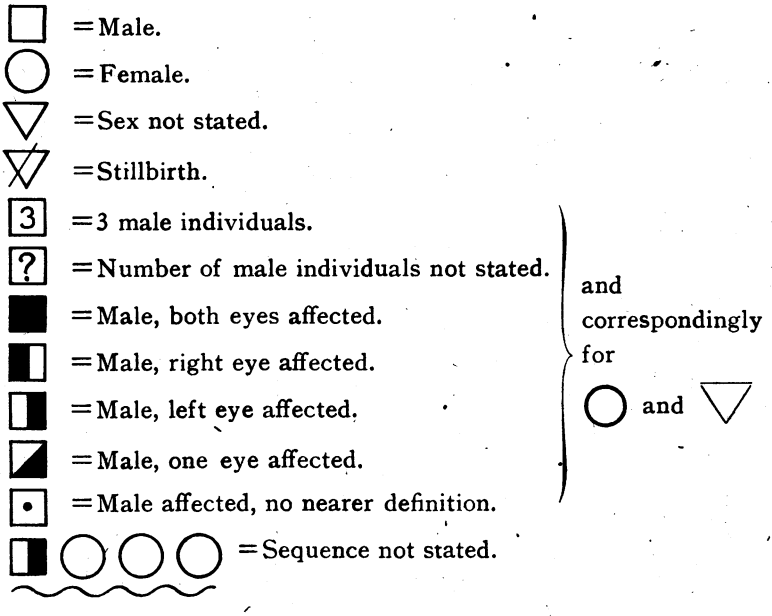
Bearing on the genetics of retinoblastoma the following observations are of interest :—

(1) The pedigree given by Lukens (1908) (Chart III) shows two paternal cousins affected, though their fathers were unaffected.

(2) In Townsend's (1939) pedigree, the three children by two husbands of an unaffected negro woman were all affected (Chart I).

(3) In contrast to Benedict's (1929) report of retinoblastoma in probably identical twins (Chart I), there is the observation of Foster Moore (1929) of healthy eyes in the twin sister, aged 2 years, of a female infant with bilateral glioma.

SYMBOLS USED



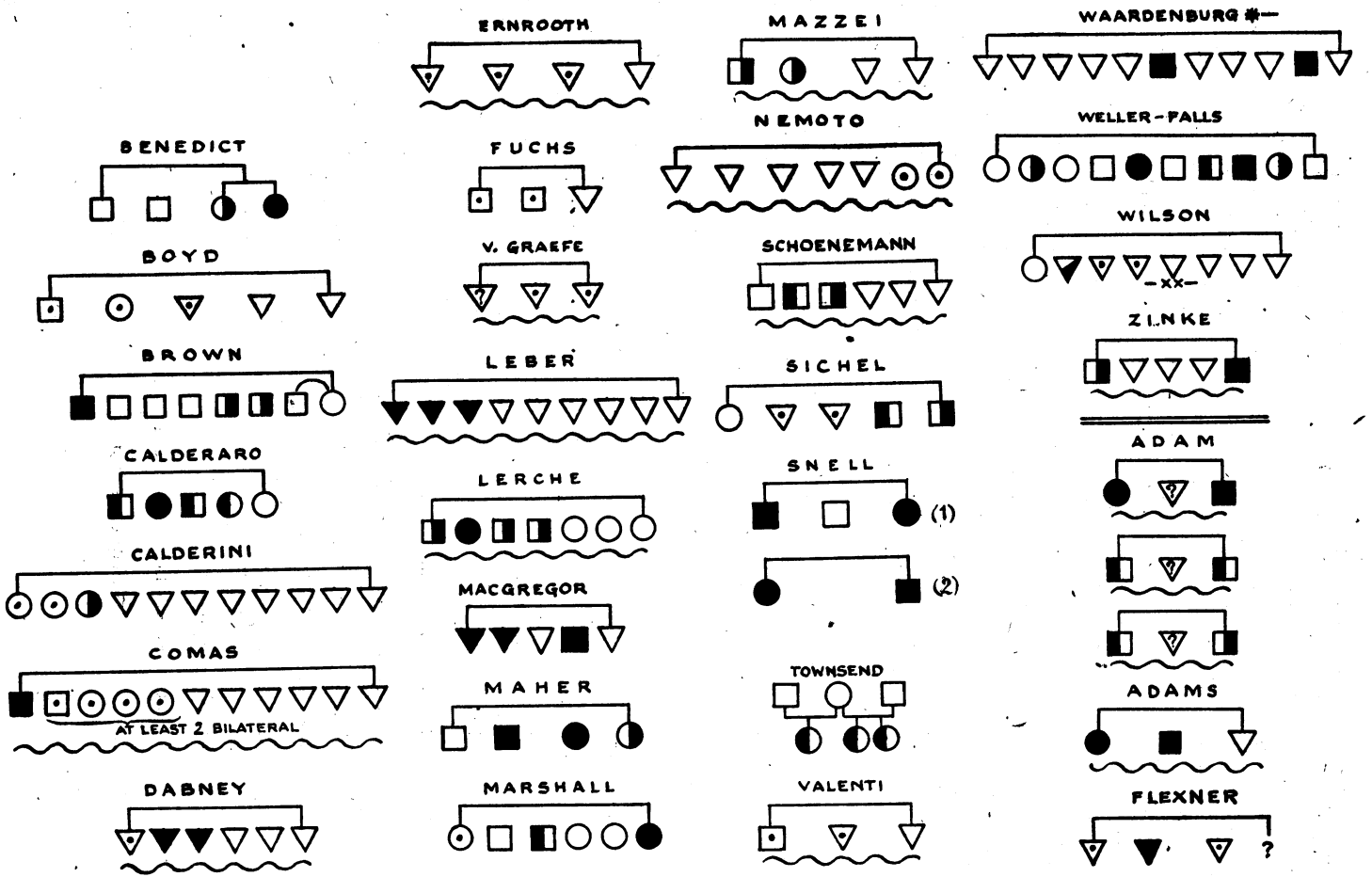


Chart I. Pedigrees of affected sibs with clear antecedants.

* ? The same familial group as van der Hoeve's (Chart II). ** Died from "scrofulous tumour at base of brain." ? Glioma. Maher—see also pedigree Maher-Pockley in Chart II. For pedigrees recorded by Feinstein, Hemmes, Purtscher and Steinhaus see Chart III.

3. *Sex incidence in hereditary retinoblastoma.*—That retinoblastoma is not sex-linked is obvious from Tables I-III. The sex distribution revealed is: males, 80; females, 63; sex not stated,

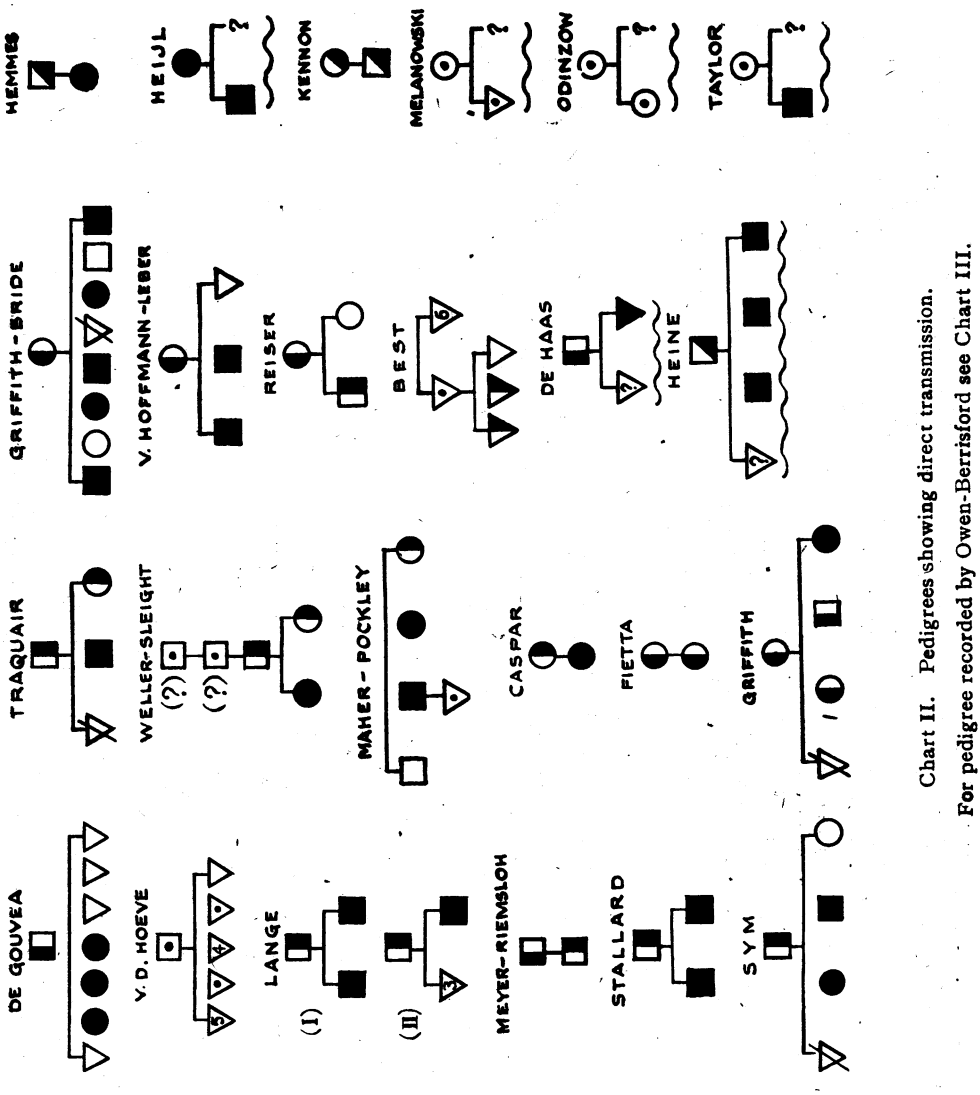


Chart II. Pedigrees showing direct transmission.

For pedigree recorded by Owen-Berrisford see Chart III.

53. The large number in which sex is not stated makes it impossible to establish whether there is a differential sex incidence in the affection—a difficulty all the more real, as similarly incomplete data apply to the sex distribution within the families as a whole. (In 429 collected areas cases of glioma in which the sex was

stated, Wintersteiner found 221 males to 208 females; in the series of cases observed at the Royal London Ophthalmic Hospital, 1871-1924, there were 98 males, 96 females, and 16 sex unstated. In the 53 consecutive sporadic cases seen at the Royal

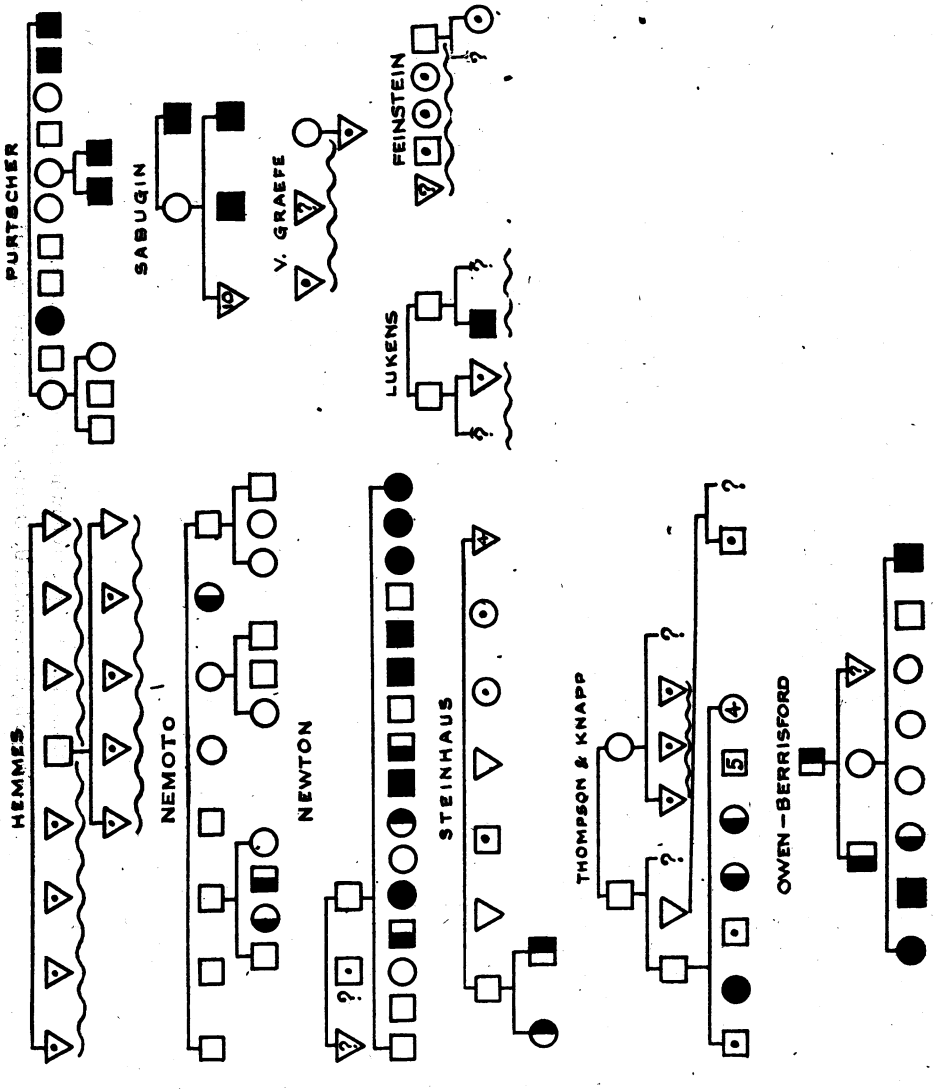


Chart III. Transmission by phenotypically healthy parents derived from affected stock.

Eye Hospital, 1894-1943, there were 32 males and 21 females.)

4. *Incidence of bilateral cases.*—In affected sibships (Table I) the incidence of bilateral retinoblastoma was 36·5 per cent. (in 38 cases out of a total of 104); in families with direct inheritance (Table II) the incidence was 65·3 per cent. (in 32 cases out of

49), and in the group analysed in Table III it was 48·4 per cent. (in 15 cases out of 31). These are distinctly higher percentages than those recorded for glioma as a whole, for which percentages between 8·5 and 21·7 have been recorded (Hirschberg, 1869: 13 times in 77 cases=16·8 per cent.; Wintersteiner, 1897: 97 times in 405 cases=19·1 per cent.; Adam, 1911: 4 times in 47=8·5 per cent.; Nomoto, 1937: 5 times in 63 cases=7·9 per cent.; Royal London Ophthalmic Hospital series: 39 out of 210=18·6 per cent., or possibly 45 cases=21·4 per cent.; Royal Eye Hospital series of sporadic cases: 8 out of 53=15·1 per cent.; Best, 1934, speaks of "not more than 15 per cent.").

If the present figures are to be taken on their face value, not only is the genetic type of retinoblastoma more prone to show bilateral involvement, but this tendency is more marked in cases with direct inheritance than in affected sibships with clear antecedents. The possibility of an abnormally high rate of miscarriage in glioma families as a result of intensifying lethal influences in embryonic life requires investigation.

5. *Sex of the transmitting parent.*—Judging by Table II, more affected children are likely to be born to an affected mother than an affected father. This suggestion is contradicted by the findings analysed in Table III.

6. *The nature of retinoblastoma.*—The fact that retinoblastoma can be transmitted by a phenotypically healthy person of an affected stock raises the question as to the nature of the additional or missing factor in such persons that inhibits the potential development of glioma in them. Such exciting or inhibiting factor need not necessarily be genetic, as environmental as well as genetic factors may suppress or make manifest a genetic tendency. The experimental production in white mice of lesions similar to retinoblastoma (Weil and Mayer, 1941), by means of carcinogenic agents is therefore of interest.

Summary

1. The occurrence of retinoblastoma in three successive generations is recorded.

2. An analysis of the literature shows the mode of inheritance to be irregularly dominant.

3. The incidence of bilateral involvement appears to be higher in the genetic type of retinoblastoma than in sporadic cases.

4. The possibility that hereditary retinoblastoma is a distinct histological entity different from the sporadic types is suggested.

We are indebted to Mr. T. W. Letchworth for the records on the S—— family and to Mr. M. L. Hine for information on the youngest member of this family. We are grateful to Mr. L. H. Savin for his interest and helpful suggestions.

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*Indicates comprehensive studies containing reviews of the literature.

AN ENCAPSULATED ORBITAL MELANOMA*

BY

J. FOSTER

LEEDS

THE patient, a woman aged 65 years, was in good health until November, 1941. In this month she developed a paresis of the right inferior rectus, constant circumorbital pain, and slight proptosis of this eye. She was treated for six weeks with eye drops elsewhere, and when brought to me was feeling very ill and losing weight.

When examined in January, 1942, the left eye was normal, but the right showed 7 mm. of exophthalmos, displacement slightly up and in, paresis of the inferior rectus, mydriasis, and vision of 6/24.

Although no tumour could be felt, a tentative diagnosis of a metastasis of the orbit was made. All general and local investigations were negative—a slight subcostal projection of the liver was attributed to visceroptosis.

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