TWO PEDIGREES OF HEREDITARY BLINDNESS IN MAN

By MARGARET D. McQUARRIE, B.Sc.

(*University of Liverpool.*)

(With One Folder.)

The present paper deals with two fairly large pedigrees showing the inheritance of eye defect in man. In both cases the defect leads to blindness. Pedigree I has already been recorded in a less complete form by the Liverpool School Medical Service in their *Report* for 1929, and an outline of this present analysis of both pedigrees is being incorporated in the *Report* for 1933 now in press.

The special interest of these cases lies partly in their relative completeness, and partly in the difficulties surrounding their diagnosis. The facts shown in Pedigree I have been collected independently by the School Medical Service and by myself. The facts shown in Pedigree II were collected almost entirely by the School Medical Service, to whom I wish to express my gratitude for permission to use this pedigree as well as for much valuable help in regard to diagnosis.

Pedigree I shows the details of the inheritance of an eye defect in a Liverpool family through four generations. All the individuals recorded as affected have been examined ophthalmologically except ♂♂ A 1, B 3, B 5; ♀♀ B 2, C 25, C 27, D 19, D 30. The first recorded member of this family was a man named Owen. This man, married to a woman with normal sight, had three children all of whom were affected. One of these, a daughter, married a man named Jones, and from this branch of the family the majority of the recorded cases have come. The family is always referred to locally as the Jones family.

Throughout this family the disease is inherited without exception as a simple Mendelian dominant (see Pedigree I).

♂, D 59, both of whose parents had normal sight, was himself blind, and was at first thought to show an exception to the Mendelian rule, but a special examination showed him to be suffering from a type of blindness entirely different from that of the rest of the family.

The eye defect of this family was originally diagnosed as Hereditary Optic Atrophy (Leber's disease), and as such was recorded in the 1929

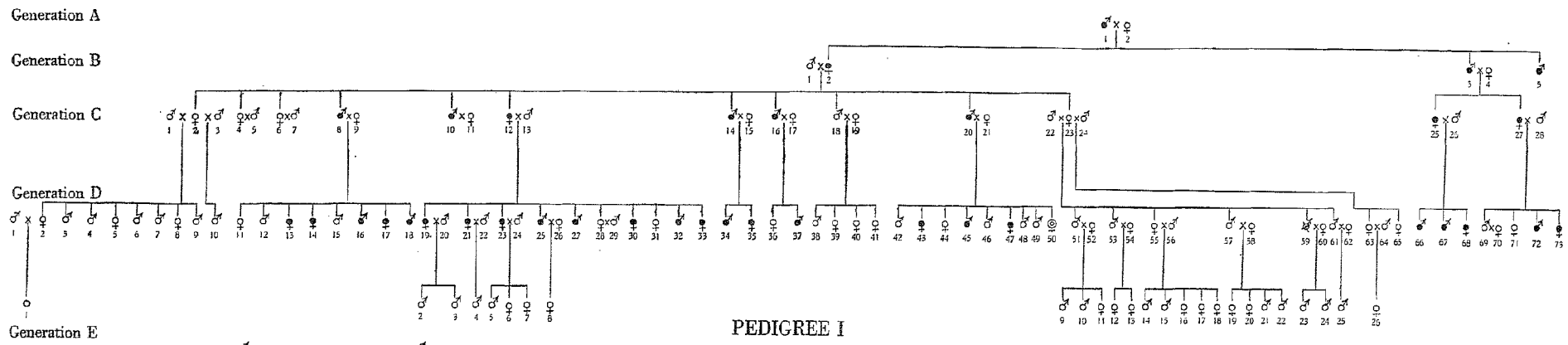
Report of the School Medical Service. That, at the time, was of interest, because most previous records of the disease describe its inheritance as recessive and frequently sex-linked (Nettleship, 1909; Julia Bell, 1931; Waardenburg, 1932). There is a suggestion that it may sometimes behave as a simple Mendelian dominant (Julia Bell, 1931).

Shortly after the publication of the 1929 *Report*, one of the children of the family under discussion was re-examined, and was stated to be suffering not from Leber's disease but from retinitis pigmentosa; and many other members of the family were then re-examined with the same result. Now if this second diagnosis were a correct one, the family would provide yet another example of retinitis pigmentosa inherited in the manner which has been most frequently demonstrated, namely, as a Mendelian dominant not sex-linked. (For a further discussion of the inheritance of retinitis pigmentosa see below.)

Early last year, however, owing to the interest of the case several of the children were brought before a local meeting of the Ophthalmological Society. There, the disease was pronounced to be neither Leber's disease nor retinitis pigmentosa, but macular degeneration, with no affection of the cerebral region.

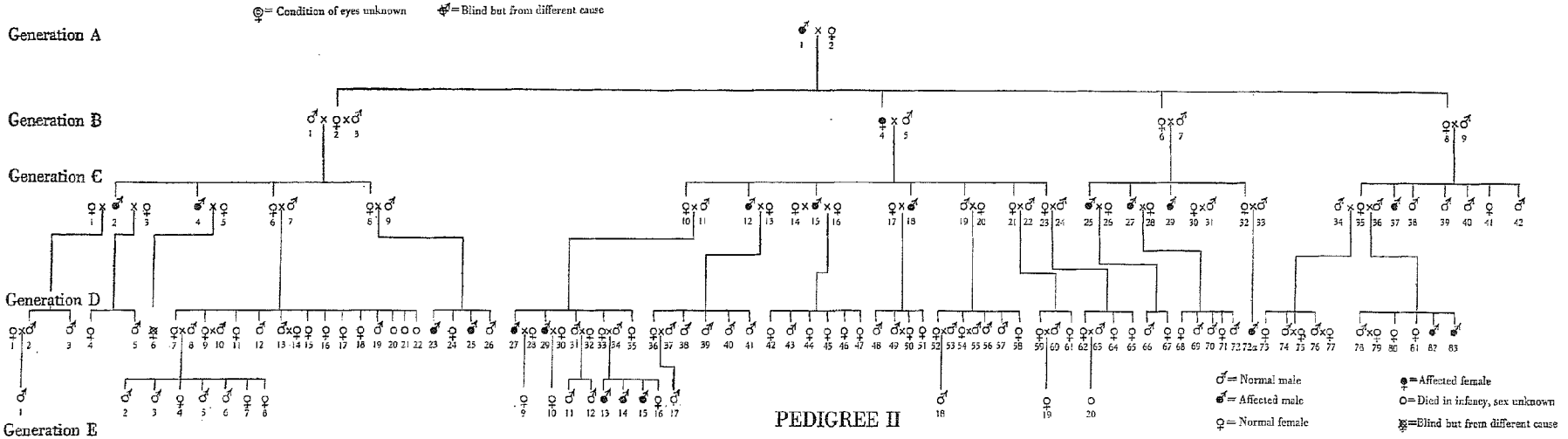
The literature dealing with the inheritance of macular degeneration is interesting. In the earlier papers which describe the disease no agreement is reached as to its mode of inheritance. Behr (1920, 1921) links together a number of allied diseases which he calls Heredodegeneration of the Macula. Ruggles Gates (1929) and Bickerton (1934) say little about its inheritance, but draw attention to its close association with amaurotic family idiocy, a condition largely confined to Jews. Oatman (1911) distinguishes between the cerebral and non-cerebral type and concludes that macular degeneration occurs sporadically and is familial, but is not an inherited disease. On this latter characteristic he bases his principal distinction between macular degeneration and retinitis pigmentosa. Macklin (1917), however, claims that the disease is an inherited one, and the work of later writers confirms this (Waardenburg, 1932; Behr, 1920, 1921; Clausen, 1921; Halbertsma, 1927). Some records show the disease to be inherited as a simple dominant (Behr, 1920; Clausen, 1921), others as a sex-linked recessive (Halbertsma, 1927).

The difficulty of diagnosis in regard to the Jones family is evidently a very real one. It is practically certain that it is one and the same disease which appears in all those members of the family recorded as affected in Pedigree I; but during the course of this investigation there



♂ = Normal male
♀ = Normal female
◎ = Condition of eyes unknown
♂ = Affected male
♀ = Affected female
♂ = Blind but from different cause

PEDIGREE I



♂ = Normal male
♂ = Affected male
♀ = Normal female
♀ = Affected female
O = Died in infancy, sex unknown
⊗ = Blind but from different cause

PEDIGREE II

have been three different diagnoses of that disease, and on no occasion have all the authorities been in complete agreement.

The similarity in the symptoms of the three diseases in question is shown in Table I below.

That these symptoms are liable to variation in all three diseases is an acknowledged fact, confirmed by many authorities from their own experience.

In the Jones family the children's eyes are regularly examined by the School Medical Authorities; but the older patients had passed through the early stages of the disease before this investigation was begun. The information given below is therefore incomplete.

The age of onset is early (under 10 years) when the first stages have been scientifically observed, but some of the older affected members, when asked about the time of onset in their own cases, gave a much later age.

Among those examined, about a third show general pigmentation of the retina and this varies in degree from slight to profuse. In most cases, however, there is a pigmentation of the macular region followed by atrophy of the yellow-spot; and in many the optic nerve is atrophied and the disc affected. Night blindness has not been observed, and none of the patients show any sign of mental defect.

There is no information with regard to colour-blindness nor have accurate records been made of the range of visual fields. Such records can only be obtained in the primary stages of the disease, and, since in the Jones family the age of onset is early (under 10 years), the difficulties in the way of carrying out exact tests are obvious. Among the patients who are older, and might therefore be expected to yield more satisfactory results, the disease has progressed too far for an accurate diagnosis to be made.

The early onset-time of the disease and the absence of night-blindness suggest macular degeneration, and this is actually the latest diagnosis. It is not a unanimous one, however, and it is still possible that the disease may be retinitis pigmentosa.

Pedigree II shows the inheritance through five generations of an eye defect resulting in blindness. All the individuals recorded as affected have been examined ophthalmologically except ♀ B 4; ♂♂ A 1, C 12, C 18, C 27, D 83. In this case the diagnosis appears to be a straightforward one of retinitis pigmentosa. All the individuals examined show the characteristic retinal pigmentation, and in most cases there is a contraction

TABLE I.

	Hereditary optic atrophy	Retinitis pigmentosa	Macular degeneration
Age of onset ...	Usually 20, 23–25 years (Julia Bell, 1931). Both earlier and later.	Childhood or early adult life. Usually earlier than 20 years (N. Bishop Harman, 1912; Julia Bell, 1922)	7–12 years (Ruggles Gates, 1929). Sometimes 14–16 years (F. E. Batten, 1903; Oatman, 1911)
Ophthalmoscopic symptoms	Shrinkage of arteries and veins sometimes present (N. Bishop Harman, 1912).	Contraction and apparent diminution of vessels due to encrustation with pigment which extends along them (G. E. de Schweinitz, 1921)	Vessels small with some exudation (Oatman, 1911; F. E. Batten, 1903).
		Pigmentation of retina. Usually commences in ring midway between disc and periphery. Whole retina including macular region may be pigmented although macula not markedly so, and often invaded only at late stage.	Considerable pigmentation of the retina in the region of the yellow spot (F. E. Batten, 1903; E. L. Oatman, 1911; R. D. Batten, 1897).
		Frequently central vision unaffected until late stage (G. E. de Schweinitz, 1921).	Occasional slight pigmentation outside macular region (R. D. Batten, 1897).
	Abnormally white hue of disc (N. Bishop Harman, 1912).	As pigmentation approaches disc, nerve-head affected. Colour of disc changes, often becomes dull white and atrophic (G. E. de Schweinitz, 1921).	Discs clear, slightly pale but not markedly atrophic. Sometimes greater degree of bleaching (F. E. Batten, 1903). Atrophy of optic nerve may occur (Behr, 1920, 1921; Oatman, 1911).
Subjective symptoms	Contraction of visual fields. In typical cases, peripheral vision remains throughout life or until late stage in the disease. Optic nerve usually first seat of trouble (Julia Bell, 1931).	Gradual contraction of visual fields leading to blindness. Extreme periphery sometimes not affected until late in disease. First part affected frequently ring midway between nerve and periphery (G. E. de Schweinitz, 1921).	Peripheral vision at first fairly good. Failure of central vision. Finally complete blindness (Oatman, 1911).
	Greater or less degree of colour-blindness (Julia Bell, 1931), especially for red and green (N. Bishop Harman, 1912).	Colour vision affected. Red and green less than normal. Frequently early in disease (G. E. de Schweinitz, 1921).	Early symptom, affection of colour-vision, particularly for red and green (Oatman, 1911).
	Gradual failure of sight, particularly in evening (N. Bishop Harman, 1912).	Night blindness usually first symptom that calls attention to disease (G. E. de Schweinitz, 1921).	
	Onset in two eyes usually simultaneous and symmetrical. Sometimes in two eyes unequal in intensity (Nettleship, 1909; Julia Bell, 1931).	Occasional unilateral effect (Julia Bell, 1922).	
		Nystagmus frequent (de Schweinitz, 1921; N. Bishop Harman, 1912).	Occasional fine nystagmus (F. E. Batten, 1903).
Exceptions	"Peripheral contraction of fields may be present, with or without central scotoma, and in some instances neither symptom is present" (Julia Bell, 1931).	"Pigment may not necessarily be present although waxy disc-degeneration and contraction of vessels are evident" (G. E. de Schweinitz, 1921).	

of the visual fields, although there is no record of the late central vision often associated with the disease. Night blindness is a definite symptom in three cases only, but for this particular defect the records are very incomplete. The age of onset is later than in the previous family, being from about twelve to twenty-five years (the latter in one case only). Here, again, there is no record of mental defect, nor of deafness, a condition frequently associated with retinitis pigmentosa.

The mode of inheritance in this family is obviously that of a sex-linked recessive character, and the only individual who does not fit in with the theoretical expectation in such a case is ♀ B 4. The earliest record, here, is of a man named Henry Clifford, who, married to a woman with normal sight, had four daughters. Three of these daughters had themselves normal vision, but one, ♀ B 4, was blind. If her blindness was of the same type as her father's, she shows an exception to the sex-linked recessive type of inheritance shown throughout the rest of the family. Her blindness, however, was only reported by other members of her family and, as she was not examined and is no longer alive, it is not certain that she was blind from the same cause as her father. In this connection it is significant that ♀ D 6 was at first noted as a doubtful case, and as such was another possible exception. She is blind in one eye, but hers is now known to be a different type of blindness from that of her father, ♂ C 4.

Pedigree II, therefore, shows the inheritance of retinitis pigmentosa through four generations as a Mendelian sex-linked recessive with only one possible exception.

Retinitis pigmentosa is another disease which, according to the records, shows different types of inheritance in different pedigress. It is often recorded as a simple Mendelian dominant (Julia Bell, 1922; de Schweinitz, 1921; Nettleship, 1909). It is also stated to behave sometimes as a simple recessive (Julia Bell, 1922). It is also recorded in a very few cases as a sex-linked recessive (Gasalla, 1931; Usher, 1914; Waardenburg, 1932). In regard to the latter type of inheritance the given pedigrees are small and, as is pointed out by Waardenburg (1932), it is possible in some cases that it is pure chance that males only are affected. Nevertheless, there do appear to be one or two records which show undoubted sex-linkage; and Pedigree II provides another example of the same phenomenon. Here, too, the numbers are large enough to rule out the possibility that it is merely chance that males only show the disease. The relevant facts are known for 152 individuals, and of these twenty-one are recorded as affected. Of these twenty-one affected individuals, all

are males except one, and fit perfectly into the scheme of inheritance for a sex-linked recessive character. The one exception (♀ B 4) may be a real exception, in which, for some unknown reason, the disease has developed in a heterozygous female, or, as stated above, she may only appear to be an exception through lack of exact information.

Many inherited characters, especially in man, are recorded as showing different types of inheritance in different pedigrees, and such conflicting records are particularly common in connection with eye defects.

Where the difference in type of inheritance involves only a difference in dominance, the phenomenon does not present any great difficulty; but when a character is sex-linked in one strain, and not sex-linked in another, the difficulty is more serious. Punnett (1933) has suggested that abnormal behaviour of chromosomes during maturation division might result in the transference of a factor from an autosome to an *X*-chromosome. In this way, strains might arise showing sex-linkage of characters otherwise not sex-linked within the species.

Be that as it may, there are certainly many cases recorded, especially in man, of such inconsistent behaviour of characters in inheritance, and retinitis pigmentosa seems to be a well-established case in point. Pedigree II places its inheritance as a sex-linked recessive beyond question.

But in the light of the difficulties of diagnosis which have been discussed above, in connection with Pedigree I, it seems possible that the genetical inconsistencies may be far less than at present appears from the records.

I wish to express my gratitude to Prof. Paten who first called our attention to the Jones family; to the Liverpool School Medical Department for much valuable help and co-operation; and to Mrs Bisbee for originally suggesting the research, and for her continued help and criticism throughout the course of the investigation.

REFERENCES.

Batten, F. E. (1903). *Trans. Ophthal. Soc.* **23**, 286.

Batten, R. D. (1897). *Ibid.* **17**, 48.

Behr, C. (1920). "Die Heredodegeneration der Macula." *Klin. Mon. f. A.* **65**, 465.

—— (1921). "Die Anatomie der senilen Macula." *Ibid.* **67**, 551.

Bell, Julia (1922). "Retinitis pigmentosa and allied diseases." *Treasury of Human Inheritance*, Eugen. Lab. Mem. xxi, **2**, pt. i. (edited by Pearson).

—— (1931). "Hereditary optic atrophy." *Ibid.* Eugen. Lab. Mem. xxvi, **2**, pt. iv, 325.

BICKERTON, J. M. (1934). "Menace of hereditary blindness." *Brit. Med. Journ.* Jan. 20th.

CLAUSEN, W. (1921). "Heredodegeneration der Macula." *Sitzber. Ver. Augenärzte Sachsen*, Anhalt, Thüringen. *Klin. Mon. f. A.* **67**, 117.

DE SCHWEINITZ, G. E. (1921). *Diseases of the Eye*, p. 484. Philadelphia and London: Saunders.

GASALLA, M. L. (1931). "L'hérédité dans une famille atteinte de rétinite pigmentaire." *Bull. et Mém. Soc. Franç. d'O.* **44**, 169.

GATES, RUGGLES (1929). *Heredity in Man.* London: Constable.

GRISCOM, J. M. (1921). "Hereditary optic atrophy." *Amer. Journ. Ophthal.* **4**, 347.

HALBERTSMA, K. T. A. (1927). "Ueber erbliche Entartung des gelben Fleckes, vereinigt mit Farbenblindheit (Holl.)." *Ned. T. v. Gen.* **71**, 11, 2056. Ref. *Zbl. f. O.* **19**, 492 (1928).

—— (1928). "Ueber einige erbliche familiäre Augenerkrankungen." *Klin. Mon. f. A.* **80**, 794.

HARMAN, N. BISHOP (1912). *Aids to Ophthalmology.* London: Baillière, Tindall and Cox.

MACKLIN, M. T. (1917). "Maculo-cerebral degeneration." *Canad. Med. Assoc. Journ.*, 1194.

NETTLESHIP, E. (1909). Bowman Lecture. *Trans. Ophth. Soc. U.K.* **29**.

OATMAN, E. L. (1911). *Amer. Journ. Med. Science*, **142**, July, p. 221.

PUNNETT, R. C. (1933). "An ocular Mendelian puzzle." *Trans. Ophth. Soc. U.K.*

USHER, C. H. (1914). "On inheritance of retinitis pigmentosa with a note on cases." *Roy. Lond. Ophth. Hosp. Rep.* **19**, 2, 130.

USHER, C. H. and SHENNAN, T. (1930). "Two pedigrees of retinitis pigmentosa." *Ann. Eugenics*, **4**, 215.

WAARDENBURG, P. G. (1932). *Bibliographia Genetica*, **12**, 356, 398, 445.