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TWO PEDIGREES OF HEREDITARY OPTIC ATROPHY

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ABERDEEN

Pedigree A. is a pedigree of Leber's disease containing three affected males in one sibship, an affected first cousin, and certainly two—one a female—but probably four affected cases in previous generations. The three brothers with the condition are members of a sibship of ten in which four are males and six females. In order of birth they come first, second, and fifth. The vision of the first-born failed at the age of 28 years, of the second-born at 21 years, and of the fifth-born at 40 years. The first-born is unmarried while the other two married and each had two children. The vision of their cousin IV 18, who is married but without issue, failed at a much earlier age than that of any of the others in the pedigree, namely, when he was 7 years of age. He is the first-born in a sibship of three, of the remaining three cases III 17, first-born in a sibship of two, married twice and by his first wife had a family of three, and by his second wife a single child. His vision failed at the age of 30 years. III 9, third-born in a sibship of eight, married and had no issue. His vision failed at the age of 30 years. III 8, second-born in the same sibship was unmarried. Her vision failed at the age of 45 years, accompanied by ptosis of the right upper lid. Catamenia continued for some years afterwards. II 5, second-born in a sibship of five, married and had two children. His vision failed at the age of 30 years. The ages of the affected individuals at the time when their vision failed range from 7 to 45 years. Of the four cases in generations II and III vision began

to fail in one of them at the age of 45 years and in the others at 30 years of age. In the three affected brothers of generation IV failure of vision occurred, taken in order of birth, at the ages of 28 years, 21 years, and 40 years, and in their cousin at 7 years of age. The order of birth in the sibships in which the eight cases of optic atrophy occur is as follows: three were the first-born, three came second, one third, and one fifth in order of birth. Six of the eight cases married and three of these had no issue. The four cases of optic atrophy with families had 10 children, of whom 6 were males and 4 females, and none of them had the family visual defect. There was no consanguinity in the parents of the affected individuals. The five sibships in this pedigree containing cases of Leber's disease had in all 28 members—11 males and 17 females—divided as follows in the individual sibships: (1) 10—4 ♂ and 6 ♀, (2) 8—1 ♂ and 7 ♀, (3) 5—2 ♂ and 3 ♀, (4) 3—2 ♂ and 1 ♀, (5) 2—2 ♂ and 0 ♀. Visual illusions were experienced by two cases (IV 18 and IV 9) and a positive central scotoma was sometimes observed by another case (III 17). The age at death of II 5 was 67 years and of III 9 47 years.

In IV 18 nystagmus was observed but only during ophthalmoscopic examination. Retinal haemorrhages were present in both eyes close to the optic disc in a case (IV 9) seen three months after the onset of the visual defect in the right eye and one month after the onset in the left eye. In a second case (IV 8) there were appearances resembling haemorrhages in the retina two months after the onset of the visual failure. In the cases of Leber's disease that were examined acuity of vision ranged from ability to see hand movements to 6/24. In comparing the conditions found after an interval of nearly eleven years in the case of IV 9 with those that were present at the first examination, vision was found to have deteriorated in the left eye, but this had occurred within eighteen months of the first examination. The periphery of the fields of vision, full at first, showed later a minor degree of contraction. The optic discs had become very pale all over, whereas at first the left optic disc seemed too red and both optic discs had shown signs of optic neuritis. The marked pallor had occurred within eighteen months of the first examination. In the case of IV 12 an examination of the blood including a Wassermann reaction and a skiagram of the sella Turcica were made.

Notes of the Cases

IV 9, R.G., male, aged 21 years, seen on January 28, 1899, clerk, the first member to become affected in sibship, noticed vision of right eye failing three months ago and of left eye one month ago. Has had no illness, no headache, feels perfectly well, no history of syphilis, throughout winter had bathed in the sea

in the early morning. Grasp equal, knee jerks present, free breathing through each nostril, no nasal discharge. Eyes: pupils, equal, contract to light, eye movements full, nothing abnormal felt in orbits; R.V.=counts fingers at one foot; L.V.=5/60 not improved by spherical lens, reads 10 J. at nine inches, field of vision full. Ophthalmoscopic examination: R.O.D. too pale, white lines along edges of vessels, cup filled in, edge of O.D. blurred. L.O.D. too red, edge blurred, white lines along vessels; after homatropine next day, R. a few small haemorrhages seen at inner edge of O.D. and black pepper appearance at Y.S., L. fine haemorrhages just beyond edge of O.D., Y.S. has black pepper appearance, on nasal side of fundus at 4 O.D. diameters from O.D. are two black square patches of pigmentation whether in retina or choroid is uncertain and excepting an occasional yellowish grey spot a little larger than those in Tay's choroiditis, fundi are otherwise normal. Urine: sp. gr. 1030, no albumen, no sugar. June 18, 1900: R.V.=counts fingers at four feet; L.V.=1/60. During the test each eye turned nasalwards; optic discs pale. Nov. 16, 1900, has subjective visual sensations chiefly at centre of fields, seen both in daylight with eyes open and at night with eyes shut. The appearances take various forms as "irregular patches of red paint" or "a little blue-black spot with a sparkle in it" and other forms. R.V.=counts fingers at two feet; L.V.=1/60, fixes with nasal portion of each retina, only extreme periphery of each field is used; oph.: R. and L. media clear, pallor, almost paper whiteness, of whole of O.D., cup partially filled in, retinal vessels of good size, edge of O.D. fairly well defined; smell normal. To give up tobacco. Dec. 18, 1909, subjective sensations continue in centre of field, cannot describe shape, but they are dark or red. R.V.=counts fingers at two feet, L.V.=1/60, oph.: appearance of O.D. in each is the same in every respect as on June 18, 1900. Absolute central scotoma for 20 mm. white square in each field. In right field it extends 20° upwards and downwards, 18° nasalwards, 20° temporalwards, and 35° up and out. In left field it extends 18° upwards and downwards, 20° temporalwards, 30° nasalwards; periphery of each field is not quite full, takes little alcohol, only beer. His son V 6, and daughter V 7, are school children (Aug., 1926), with good vision and normal eyes.

IV 8, A.G., male, aged 28 years, seen on May 26, 1904, married without children, was the second member in the sibship to lose his sight. Difficulty in reading for two months and in seeing at a distance for three weeks; sees best in dim light, had a full feeling in his brow, smokes 2½ ounces of a mixture one-half of which is twist, frequently drinks five or six glasses of whisky in an evening, sleeps well, appetite good. On examination: pupils, equal, contract to light, eye movements full; R.V.=6/60; L.V.=4/60;

absolute central scotoma for a 10 mm. red square in each, in right field it extends for 10° in all directions except on nasal side where it reaches 7° or 8° , in left field it extends in all directions for 10° , except on temporal side where it reaches 19° , periphery of fields full; oph.: R. and L. O.D. too red all over, but especially at temporal part; above and below each O.D. in the nerve fibre layer and near the large retinal blood-vessels is an appearance resembling much dilated small blood-vessels, or minute haemorrhages, edges of optic discs blurred at all parts, yellow spots normal; grasp good and equal; knee jerks readily obtained; tremor of tongue, not of fingers; smell, tested with iodoform, asafoetida, etc., is normal. No nasal discharge, no tender spots on head or pain on pressure; is an exceptionally strong man. June 20, 1904, tobacco has been discontinued, yet vision is worse, R.V.=5/60; L.V.=4/60, oph.: not much change, but R.O.D. is now paler at outer part than on rest of disc. Nothing abnormal found in the rest of his nervous system by Dr. A. W. Mackintosh. October 15, 1904: V.=2/60 in each eye; fields full with central scotomata; oph.: outer part of each O.D. too pale, edges not quite so well defined as normally. On May 26, 1908, his sister, IV10, reported that his vision was no worse.

IV 12, F.G., male, aged 40 years, seen on January 29, 1924, was the third member of the sibship to become affected; vision had gradually failed in both eyes for six months, left eye was first affected, vision was worse on a bright day. He is in good health, subject to headaches all his life, no giddiness, no sickness, tobacco given up for five months by doctor's orders, was working hard and had worry when defect began. He experiences colour sensations when his eyes are closed: (1) flashes of all colours in form of carpets or curtains, (2) a diffuse reddish yellow colour seen when in a dark room, this lasts for a few minutes. On examination: pupils, equal, contract to light, tension normal, R.V.=1/60; L.V.=2/60, absolute central scotoma for red 20 mm. square; in right field red was recognized only in lower part, the scotoma extended from 30° below fixation point and a 20 mm. red square was not recognized again above this point; the scotoma in left eye was similar, but scarcely so large, both fields showed some peripheral contraction of temporal halves when a 20 mm. white object was used, and the right field in addition had a large wedge-shaped gap up and in from the horizontal line upwards for 60° , its apex was 15° from fixation point. The left field was full except at outer part where it was contracted to 75° at the horizontal line; a McHardy perimeter was used; oph.: R.O.D. too pale at outer part, L.O.D. has a much better colour than the right one, though temporal third is too pale. His family doctor reports that an examination of the blood had been made and it was found to be normal, and Wassermann reaction negative;

radiologist reports that "the sella is 12 mm. in its greatest antero-posterior measurement and 8 mm. deep. Its outline is regular and the clinoid processes show nothing abnormal." Feb. 20: R.V.=1/60; L.V.=1/60, scotomata have same characters as on last examination, periphery of fields more contracted, they both show contraction at nasal part, more in right than left field; eye movements full; smell, tested with cloves, iodoform and peppermint, is normal; optic discs of same appearance as on last examination; fifth cranial nerves, motor and sensory, normal; seventh nerves normal; hearing normal; tongue protruded straight; soft palate moves normally; gait and movements of upper extremities are normal.

Other members of the sibship: IV 10, B.G., female, aged 29 years, seen on May 26, 1908, complains of a floating black spot, no pain in eyes and no headache, occasional indigestion, bowels and catamenia regular, looks healthy, eye movements full, R.V.=6/6 Hm. 0.75D.; L.V.=6/6 not fully, with +1D. sph.=6/6; oph.: with dilated pupils after mydriatic, right eye media clear, fundus normal, left eye media clear, fundus shows pigmentation at upper-inner and inner parts most marked near periphery, but extending nearly to optic disc. The pigment is not very dark and some of it lies in front of retinal vessels; retinal vessels are normal; choroidal vessels rather more conspicuous in the pigmented area than elsewhere, fields of vision full, no scotoma detected in any part of the fields; no night-blindness. Three months ago had severe pain in both temples lasting for two hours, then nose bled and pain was relieved, had a second attack after two weeks with a swimming feeling in head, and hands felt powerless, like a faint, became very pale afterwards, recovered. Her son, V 8, has good vision. IV 11, H.G., died of typhoid, aged 21 years; IV 13, J.G., aged 24 years (1908), has good vision, and each of her three children; V 11-13, see 6/6 with each eye (1926) and have normal fundi; IV 14, and her family, V 14, 15, and 18, are abroad; V 16 and 17, twins, died in infancy; IV 15, and her son, V 19, have normal fundi and vision=6/6 in each eye of both; Dr. A. J. Ballantyne (Glasgow) kindly examined the next four cases. IV 16, aged 36 years, had no defect in central colour vision, normal fundi, vision=5/5 and 1 J. in each eye, also V 20 and V 21 had normal fundi and no defect in central colour vision, vision=5/5 and 1 J., except in left eye of V 21, which was 5/6; V 22, aged 19 months, fundi normal. Ballantyne adds that they are all thoroughly healthy and present no anatomical defects. Father, III 6, had good sight, died, aged 59 years, no blood relationship with his wife, III 10. II 1 and II 2 had good sight, they were consanguineous, but in a degree more remote than that of first cousins. I 1, III 5 said, died at 104, could read to the last. III 1 and III 3, died unmarried, had good sight. III 2 and his family

IV 1 are abroad, none of them has defective vision. III 4, died, had good sight. IV 2, recently married, sees well. IV 3, killed at age of 24 years, had good vision. IV 4 and her daughter, V 1, aged 20 years, see well. IV 5 and her family V 2-5, the oldest is aged 14 years, all see well. III 5 has excellent vision and his ancestors for generations had good sight. IV 7 sees well. IV 6 died, aged 15 years. Mother, III 10, and five of her sisters, namely III 7, 11, 12, 13, and 14 have good sight, III 13, however has one defective eye. III 13, Mary M., R.V.=6/6; oph.: normal; L.V.=20 J. at nine inches; refraction R.H., L. my., oph.: L. choroidal atrophy adjoining O.D. and a few circular white spots in posterior part of fundus. She attributes the defect in left eye to a blow with a snowball in childhood.

III 8 a sixth sister of III 10, unmarried, intelligent, well educated female, aged 82 years (1927), with retentive memory, seen, lost her vision in the space of a few months at the age of 45 years, at this time she suffered much from headaches; catamenia continued to appear for some years after vision failed; she is second-born in the sibship of eight; drooping of right upper lid occurred at time of visual failure. On examination: a healthy active woman with 2/3 ptosis of right upper lid; pupils, equal, contract to light; tension normal; R.V.=hand movements at three feet; some contraction of field of vision (tested by hand movements), absolute central scotoma for white object of large size; L.V.=hand movements at three feet; field of vision full, absolute central scotoma for large white object—a red object, size 7 inches by $4\frac{1}{2}$ inches seen at periphery of fields as brown; no colour recognized in either field, but she knows when a colour is light or dark. Her colour vision was formerly very good; oph.: R. and L. media clear, O.D. pale, but not markedly so, some narrowing of retinal vessels, edge of O.D. not sharply defined, no lamina cribrosa seen, surface of O.D. dull in appearance; Y.S. and rest of fundus normal.

III 9, married, had no issue, died aged 47 years; at age of 30 years sight failed rapidly in both eyes at the same time and became very defective; he was a big strong man, a sail-maker, and though he continued to attend his business he was very helpless to the end of his days. II 3 drank heavily, sight good. I 2 and I 3 had good sight. The latter III 8 knew personally.

IV 18, A.S., male, aged 44 years, married, no issue, says in a letter that his vision began to fail about the age of 7 years. When first examined at age of 33 years he was told that his hereditary trouble would be transmitted by females to males, females being practically immune, "that is to say, my sisters' children run greater risks than those of my brother, especially as they are all boys." A copy of a certificate given to him by an ophthalmic surgeon on January 12, 1918, who had seen him also on May 28,

1917, shows that there was marked atrophy of both optic discs, slight persistent nystagmus seen only on ophthalmoscopic examination, refraction H. 2D. in each eye; R.V. with glass 14 J.; L.V. with glass 16 J., read 4 J. slowly with a hand magnifying glass in addition to his spectacles. He was also examined on August 28, 1915. The following notes have been received, copied from the case-book of the ophthalmic surgeon who examined him at that date: "Mr. A.W.M.S., aged 34 years. Hereditary optic atrophy. Vision discovered to be imperfect at age of 7 years, and away from school for two or three years. About this time first ordered glasses and these were revised fourteen years later. At this time he was told that he should wear glasses for near vision +2.50 sph. and later +2 sph. R. 6/60, with +2=6/24; L. 6/60, with +1.50=6/60 doubtful. Oph. very white discs with clear-cut edges, vessels of good size, no choroido-retinal changes seen, pupils smallish, equal and active. Can nearly distinguish red but it looks much paler (rose colour) opposite the centre of each eye. Peripheral field (fingers) quite full all round. Patellar reflexes normal. January 15, 1916, R. with +2.50 and L. with +2 reads 8 J., 10 J., and 12 J. slowly, with +20 reads 2 J. fairly well." IV 19 and his family V 23-24, also IV 20 and her family V 25-27 have good vision, age of V 23 is 14 years, and of V 25 is about 12 years; he wears glasses.

II 5, W.B., farmer, died, aged 67 years, vision failed in both eyes at once at age of 30 years, he could never read again, his defective vision was attributed to lifting heavy stones, he did not smoke much according to his son's statement and not at all according to his nephew III 17, his eyes "quivered," probably nystagmus. The defect of vision was said to be the same as that of III 17 only worse.

III 17, aged 65 years (1926), retired schoolmaster, seen, vision failed rapidly at age of 30 years, left eye was first affected and the right eye one or two months later. He was told to leave off smoking and this he did for a year without any improvement of vision; he had never smoked much, he is a healthy and intelligent man, he says he can see as well as anyone at dusk; with a gun he can kill birds on the wing and animals when they are moving, but not when they are stationary. R.V.=2/60; L.V.=3/60; refraction H. of low degree in each; large absolute central scotoma for red and green in both fields of vision, for blue the scotoma is smaller, a 10 mm. object was used; when he is "livery" there is a positive dark and quite circular central scotoma, fields of vision are full; oph.: R. and L. media clear, pallor of O.D., but not very marked, lamina cribrosa exposed, retinal vessels of full size, edge of O.D. well defined, macula lutea normal. Although he had such defective vision he was able to carry on his work

Leber's Disease.

A

IV. 8 should have s.p. below it

- No Consanguinity.
- sp - Married without Offspring.
- + - Seen.
- ob - Deceased.

as schoolmaster until the age for retiring. He married twice, by his first wife, III 19, he had a family of three, IV 33-35, and by his second wife, III 20, a son, IV 36, whose vision is 6/6 in each eye. All his children and grandchildren have good vision. V 30, aged 8 years, and V 31 have normal fundi. V 32-34, a family of young children with normal fundi.

III 18, farmer, with good vision, died a few months ago (1926). II 8 was the only legitimate member of the sibship II 4-8, though the other members had the same parents, II 4 died at age of 30 years. II 6, married, was without issue. None of the descendants of I 4 and I 5 is known to be affected, but not much is known about them. I 6, died aged 80 years, could read newspapers. I 7 believed to have had good sight. III 15, farmer, with good vision, fundi normal. IV 21, farm-worker, hair fair and formerly very fair, irides grey, no nystagmus, pupils sometimes red, fundi normal and pale, R.V.=6/9, refraction H. 2D. in one meridian and 5D. in opposite meridian; L.V.=6/9 not fully, refraction H. 1D. in one meridian and 4.5D. in opposite meridian. IV 22 fundi normal, vision good. IV 24, unmarried, abroad. IV 23, twin with IV 24, and his two sons V 28 and V 29 see well. In 1904, III 16, with good vision, brought her son, IV 28, aged 14 years, for examination because she thought he perhaps had the family eye affection. For two months he had been having difficulty in reading at school, though his vision was now improving. On examination R.V.=6/6 no Hm., 1 J. at 17 inches; L.V.=6/6 no Hm., 1 J. at 22 inches, fundi normal, his health had been good, no sore throat, urine, clear, no albumen, knee jerks not elicited, diagnosis cycloplegia. IV 25-32 see well. A letter from their mother, III 16 (Sept. 9, 1926), indicates that vision has not failed in any of her children. IV 25 has two sons, V 29a and V 29b, the elder is two years of age, both see well. IV 26-32 are all unmarried. IV 26 and IV 32 use glasses.

Pedigree B, contains sixteen individuals with double optic atrophy, of these fourteen are males and two females. An ophthalmoscopic examination was made in thirteen of the cases, and in the three remaining cases the histories warrant the assumption that the condition present was one of the same nature as that found in the others. All the affected individuals occur in two generations, namely, generations III and IV. The ten cases in generation III are the offspring of five unaffected sisters who presumably carry the condition. The oldest of these sisters, II 7, has four daughters and four sons, of these all of the sons are affected and none of the daughters. The next sister, II 8, had a family of nine of whom four grew up, two sons and two daughters, one of her sons was alone affected. The next sister, II 10, had fourteen children and nine of them grew up, two males and seven

females, of these one son and two daughters were affected. The next sister, II 13, had a son and six daughters, of these the son alone was affected. The youngest sister, II 18, had two sons and two daughters, of these one son died in infancy and the other was affected, neither of her daughters had any visual defect. The six cases in generation IV are all sons of unaffected females who occur in two sibships containing affected males, so that the sons have one or more affected maternal uncles.

Some of the cases marked as hereditary optic atrophy in the pedigree chart require consideration as to grouping, and more particularly those in which there is absence of a central scotoma, failure of vision in very early life, or nystagmus; and also some cases that were erroneously diagnosed as (1) tobacco amblyopia, (2) double optic atrophy cause undetermined, and (3) pressure of tumour on the chiasma.

No central scotoma was demonstrated in two instances, cases IV 10 and IV 25. The absence of such a conspicuous symptom may well cause some hesitation in grouping such cases with Leber's disease, but it has been usual to accept such cases. In one of Leber's own cases⁽¹⁾, a male, aged 21 years, with vision reduced to counting fingers with each eye, a central scotoma could not be demonstrated in the left field of vision on first examinations, but it was found later. Knapp⁽²⁾ found a case of hereditary optic atrophy in a grandfather with symmetrical central scotoma and full fields, an affected daughter and her three affected sons had no central scotoma and the peripheries of the fields were concentrically contracted. Hirsch⁽³⁾ records the case of a boy with hereditary optic atrophy in which no central scotoma was demonstrable; other three cases examined, a first cousin and two uncles, had central scotoma. Worton⁽⁴⁾ found no central scotoma in two cases of hereditary optic neuritis. There were eleven cases in three generations and he examined four of them. Clemesha⁽⁵⁾ in a pedigree of Leber's disease reported a mother and son with no central scotoma. Alexander⁽⁶⁾ found no central scotoma in three brothers with hereditary optic nerve disease. Groenouw⁽⁷⁾ found that in two-thirds of the cases there was a central scotoma only for colours or also for white. These observations are sufficient to show that absence of a central scotoma is not uncommon in cases of optic atrophy occurring in pedigrees of Leber's disease, and the two cases under discussion are, therefore, included in the pedigree as examples of the same form of optic atrophy as obtains in the cases with central scotoma.

Failure of vision in very early life. The history of the defect of vision in case IV 10 suggests that the onset occurred in early childhood, or that the visual defect was present even at birth. As

the earliest age at which the onset of visual defect occurred in the other fifteen cases was 18 years the question arises whether case IV 10 should be regarded as the same disease as the other cases, or should be discarded on account of early age at onset. Conflicting opinions have been expressed regarding cases with onset in early life. Nettleship⁽⁸⁾ in the Bowman lecture said that "cases of family or hereditary congenital optic atrophy have been described as if forming a group in some way distinct from Leber's disease. I believe that most of these are true Leber's disease setting in very early in life or perhaps sometimes before birth." More recently Drexel⁽⁹⁾ has expressed a different view. He regards early onset as being strongly against Leber's atrophy. For the present this case, IV 10, will be retained in the same group as the other cases of optic atrophy in the pedigree.

Nystagmus, in case IV 25, was observed during ophthalmoscopic examination in the left eye of a coal miner. The movements were vertical and not rapid. The right eye showed no nystagmus. He indicated that none of the men in the pit in which he worked had miners' nystagmus. One case, IV 18, in pedigree A. also had nystagmus. The condition is not unknown in the literature of hereditary optic atrophy. Doyme's cases with nystagmus have been published by Nettleship⁽⁸⁾. Waardenburg⁽¹⁰⁾ saw two children in the same family with familial optic atrophy and horizontal nystagmus. Pines and Tron⁽¹¹⁾ examined four of five brothers with Leber's disease and three of these had horizontal nystagmus of both eyes besides asymmetry of face and other abnormalities. Behr's cases of complicated hereditary familial optic atrophy of childhood also had nystagmus.

Tobacco amblyopia has not uncommonly been diagnosed erroneously in cases of Leber's disease and it is probable that this happened in case III 31. In this case, a man, aged 35 years, at onset of the visual defect in which double optic atrophy was present, sight did not improve when tobacco was discontinued. The ophthalmic surgeon who saw the case regarded the defect of vision as due to tobacco, but he was unaware of visual defects in the relatives and the presence of hereditary optic atrophy in nine of the patient's first cousins. Presumably central scotomata were found but no particulars of the fields of vision could be given.

Double optic atrophy, cause undetermined was the diagnosis made by an ophthalmic surgeon in the case of IV 83, deceased. The patient had been told elsewhere that his visual defect was a family affection. His age, 25 years, at the onset of blindness, his sex, and the fact that vision did not improve when smoking was discontinued, all support the view that the case was one of Leber's disease.

Pressure of a tumour on the chiasma in case IV 92 was on first

examination, twenty-four years ago, thought to be possibly the cause of the optic atrophy. The man is now alive and well. Bruner's⁽¹²⁾ case of hereditary optic atrophy was regarded by Dr. Hoover as probably a case of brain tumour. That pressure of a tumour on the chiasma should have been diagnosed in some cases of Leber's disease is not surprising: for bilateral central scotoma occurs as an early sign in tumour at the chiasma, as has been recorded by Nettleship⁽¹³⁾. A case with late onset of absolute symmetrical central scotoma in a male, aged 54 years, came under my own notice in which the autopsy revealed a very large, centrally situated, brain tumour, an endothelioma, that involved both frontal lobes and pressed on the chiasma. The optic discs were atrophic and had at no time shown evidence of neuritis.

This pedigree, in which some of the cases were not at first recognized, illustrates clearly the practical use for clinical purposes of information obtainable from a pedigree that has been fully traced out and from which a clue may sometimes be found to the correct diagnosis of a case. There is little doubt that had the family history and chart of this pedigree been available when certain of the cases were examined these would have presented less difficulty in diagnosis. Still, apart from any knowledge of the pedigree, a careful examination of the fields of vision by modern methods along with other clinical evidence should usually prevent confusion in distinguishing Leber's disease from tobacco amblyopia or from cases of central scotoma arising from pressure on the chiasma.

Marriages. Eleven of the sixteen cases of optic atrophy married. Two of these were intermarried. They, as well as a third case, had no issue. This leaves eight individuals who had offspring. The largest family contained ten members and the combined families numbered 37 individuals, giving an average for each family of 4.62. The intermarriage of two individuals affected with Leber's disease is a very rare occurrence. Drexel in 1922 could find in the literature no such occurrence. In this pedigree III 6 married his first cousin III 20 and both were affected by Leber's disease. There was no issue.

Age at onset. In generation III the ages of those affected at the time of onset of the optic atrophy were 33, 31, 19, 25, 20, 30, 22, 18, 20, and 25 years, giving an average of 24.3 years. In generation IV the ages at the time of onset were 38 and 25 years, early childhood or at birth, 21, 28, and 22 years, giving an average of 22.3 years when case IV 10 is included and his vision is regarded as having been defective since birth. When, however, case IV 10 is omitted for the reason that the time of onset of his defect of sight is not exactly known and only five cases in this generation are considered, then the average age is 26.8 years.

There are two sibships containing more than one case of Leber's disease. The first one, III 19-30, has three affected members and their ages at onset of visual defect given in order of birth are 33, 31, 19 years, thus showing anticipation. In the second sibship, III 1-8, are four males affected, and their ages at the onset of visual defect in order of birth are 20, 18, 25 and 22 years, so that at onset of blindness the first-born was older than the second-born, the third than the fourth, and both the third and fourth were older than the first and second.

Order of birth of the sixteen cases. Six were first, three were fourth, and two fifth in order of birth, and there was one case in each of the following places in order of birth:—second, third, sixth, eighth, and ninth.

Length of life of affected individuals. Of five who have died four lived to a good age, namely, from 62 years to 74 years. The fifth died at 33 years after an operation for appendicitis. One case, III 5, has been lost sight of. Of the ten who are alive seven are over 50 years and four are 60 years or older. The youngest case is 40 years.

There are two *females* with optic atrophy in the same sibship of generation III. Catamenia ceased in each case at the time vision failed, at 33 years and 31 years of age respectively, and it has never reappeared. They are now 67 years and 63 years of age. Both married, the former who mated with an affected cousin had no children, the latter had one child only, a daughter with normal vision.

None of the cases showed cranial deformity. Skiagrams of the sella Turcica were made in four cases, III 20, III 22, IV 89, and IV 92, and a description of each is incorporated in the notes of these cases. Headaches were complained of at the onset of the visual defect in six cases. In reference to prognosis two cases may be mentioned that were re-examined more than twenty years after the first examination so that comparison could be made of the ocular conditions found on the two occasions. In case IV 92 at the time of his first visit vision had been failing for a year in one eye and for six months in the other, after an interval of 23 years vision had scarcely altered, as on both occasions R.V.=counted fingers; L.V.=hand movements; the optic discs, though paler, retained the same appearances as on first examination; the retinal vessels were now slightly contracted; the field of vision of the right eye had contracted peripherally to some extent and the central scotoma remained. The field of vision of the left eye remained unaltered with a functioning part limited to a small area down-in.

In case IV 89, at the time of his first visit vision had been failing for four months, after an interval of 25 years vision had improved from counting fingers with each eye to R.V.=6/12 and

L.V.=6/9; each field of vision remained full with a paracentral scotoma, and the optic discs, rather too red when seen at first, were now pale. The improvement of vision took place during six months in 1902. The first examination was made on December 13, 1901. A very marked improvement of vision such as occurred in this case has been recorded in some other cases. In Pines's and Tron's case II vision became nearly normal. Hancock's⁽¹⁴⁾ case X recovered acuteness of vision=6/6 and 1 J. in each eye, and his cases IX and XI recovered nearly full vision. In one of Kawakami's⁽¹⁶⁾ cases the disease disappeared completely.

Absence of the affection from generation V and from the few individuals in generation VI may be ascribed to the young age of the members in these generations as the majority are not yet 17 years of age, many are females and some are descendants of unaffected males such as II 16. To economize space in the pedigree chart all the descendants of II 16, at least 78 in number, have in each generation been placed within an oblong, only the numbers of both sexes are indicated and not the sibships. No case of optic atrophy has occurred in this branch of the family.

With reference to II 3 in this pedigree who was reported to have been an albino and who had four sons with Leber's disease, and to IV 21 in pedigree A, who, though not a complete albino, showed marked signs of albinism, it is of interest to note that in a third pedigree of Leber's disease* an affected male had four albino children.

Notes of the Cases with Hereditary Optic Atrophy

IV 92, George S., aged 29 years (Dec. 9, 1903), seen, coal shoveller. In December, 1902, he noticed that vision was dim in his left eye. Objects directly in front of him could not be seen clearly with his left eye, though he could see objects at the sides. Had bad toothache on the evening before he discovered the defect. Some months later knocked against people on his left hand side owing to vision having got much worse. He noticed defect in vision of right eye at end of May, 1903, and a few weeks later was unable to read ordinary sized print. He describes the defect of vision in right eye as being similar to that in left eye at the onset of the defect, that is, there was blurring at centre of field. Some weeks after right eye began to fail he felt out of sorts:—Anorexia, feeling of weakness, occasional nausea, no vomiting, and frontal headache. No nasal discharge; "erysipelas" in right foot in August, 1903, was laid up for a week; previous to this was in bed for a few days, feeling nausea. Had been working up to time of admission to hospital in Dec. 9, 1903, when examination showed the following condition:—*Eyes*: R.V.=fingers at four feet, large central scotoma for red, with a large card only recognized the colour at lower and also outer peripheral parts of field, in other directions the object is much more clearly seen at periphery than at centre though he cannot recognize the colour; tension normal, pupils, equal, contract to light, eye movements full, corneal sensation normal. *Oph*: O.D. too pale, large circular cup with very pale floor, stippling well marked, edge of disc sharply cut, no white lines along retinal vessels which are not narrowed. Y.S. normal also periphery of fundus. L.V.=hand movements at one foot, eye movements full except on attempted

* Albinism in Man, Fig. 130. Karl Pearson, E. Nettleship, C. H. Usher, see also *Trans. Ophthal. Soc., U.K.*, Vol. XXIX, p. CLXXXII, 1909.

convergence when this eye does not move inwards; fundus condition similar to that of right eye except that the disc is much paler.

Previous History.—Has been strong and healthy, no syphilitic history, no constipation, does not smoke, is temperate, married, never had headaches except as stated above; never giddiness, staggering gait, or tinnitus. He is illegitimate and knows nothing of his father. His mother married someone else and had at least two children. Dr. Ashley W. Mackintosh made an examination of the nervous system. The result was almost negative. The only positive findings were some rigidity in both legs, slight Rombergism, plantar reflexes difficult to elicit, but flexor. During his stay in hospital had occipital headache once or twice. Temperature was normal throughout. Urine (Dec. 18) clear, acid, 1025, no albumen and no sugar.

March 27, 1904.—Condition practically unaltered excepting increased pallor of O.D.'s and some narrowing of retinal vessels. Fields of vision taken on several occasions on McHardy's perimeter showed on Jan. 29, 1904: R. periphery full except slight contraction below; with a 10 mm. blue square, no other colour recognized, there is an absolute central scotoma extending downwards for 12° and at sides for 10°, up-in and up-out for 20°, directly upwards no colour is seen. Left field of vision for white is practically limited to a small area in temporal half of field which extends from fixation spot outwards for 40°, down-out for 42°, downwards 26° where it encroaches for a short distance on nasal half of field, up-out it extends for 32°. On Feb. 12, right field was full, and the absolute scotoma for blue extended for 10° in lower half of field and widened upwards so that the colour was not recognized over a large area in upper part of field. In left field no colour recognized over a large area in upper part of field. In left field no colour recognized at any part. On March 27.—Right field was contracted peripherally at outer part and slightly up-in. Red, green, and yellow not recognized as such, can only say that they are not white. Absolute central scotoma for a 10 mm. blue square object extends 10° below, 40° above, 35° out, 28° in, down-out (135) 32°, down-in (120) 30°, up-out (45) 30°, up-in (45) 38°. Left field tested with a 20 mm. white square is limited to a narrow line joining the following points at 42° down, 48° down-in (120), 76° down-out (120), 32° outwards (90) 26° up-out (32). When seen again in 1926 at the age of 51 years, he said that he thought vision had got worse. Examination showed pupils, equal, contract to light, eye movements full, except left which does not move in much beyond mid-line. Marked divergence of left, no evidence of tower-skull or acromegaly. R.V.=fingers at one foot, imperfectly, in lower part of field. He worked at coal until five years ago when he had to give it up on account of the defective sight. Oph.: R. and L. O.D. very pale, greyish, edge sharply defined, retinal vessels not much narrowed, in left more than in right; Y.S. and rest of fundus normal; no white lines along vessels. Refraction low H. in each. L.V.=hand movements at six feet, limited to lower-inner part of field. Right field much contracted peripherally, 58° below, 38° above, 32° in and 80° out. An absolute central scotoma for a 10 mm. white square object extends downwards 40°, upwards 30°, inwards 28° outwards 30°. He has never smoked and does not drink alcohol. General health is good. His last and third child, a male, aged 20 years, was born a few years after his vision failed. Knee jerks equal. Report of skiagram: "The sella is regular in outline, 13 mm. A.P. and 11 mm. deep. The anterior clinoid processes are well formed, but the posterior ones are blurred and partly buried in what seems to be new bony growth. The sphenoidal sinus is well developed."

IV 89, George G., aged 22 years (Dec. 13, 1901), seen, fireman on a locomotive, noticed sight failing four months ago and that vision gradually got worse for two months and then remained stationary. Eight months ago he passed the usual railway test for eyesight. Sometime before vision failed, he had been troubled almost daily with headaches, mostly frontal, also with pain in stomach and dizziness. When smoking was discontinued two months ago the vision did not improve though it has not continued getting worse as it had been doing previously, and headache also has ceased. Does not work with lead and there are no symptoms of lead poisoning. For the last five years admits having occasionally drunk too much, but it never prevented him doing his work. Began to smoke at 16 years, and smoked about three ounces of Irish twist weekly. No history of syphilis.

Tongue and hands are tremulous; urine, amber, acid, 1020, no albumen, no sugar; no intention tremor, knee jerks present and not exaggerated, no ankle clonus, cranial nerves: I distinguishes peppermint and asafoetida, II, III, IV, VI *vid.*

infra; V, sensation of face normal; VII movements of each side of face equal; VIII hears watch with each ear at one foot, has not noticed hearing worse recently; IX, X, XI, XII nothing pointing to any affection of them. R.V.=fingers at one foot, full field, absolute central scotoma for red, with a 10 mm. object used, it was nearly circular extending to 20°, refraction estimated low H. L.V.=fingers at one foot, field full, absolute central scotoma for red, with a 10 mm. object, it extended upwards 10°, inwards 12°, downwards 10°, and outwards 30°, it is much larger external to fixation point than nasalwards, refraction estimated low H, pupils, equal, size 3.75 mm., contract to light, eye movements full, no tenderness on pressing eyeballs backwards; oph.: O.D.'s normal, or rather too red, deep physiological cupping, some of the smaller vessels are tortuous and those passing downwards from O.D. show abrupt antero-posterior bendings in the nerve fibre layer which give an appearance of small haemorrhages at the parts where they are foreshortened. Possibly there are a few minute flame-shaped haemorrhages in this region. The Y.S. and other parts of the fundus are normal. On Jan. 23, 1902, V.=fingers at two feet in each eye, fundus remains as on first examination and also pupils and eye movements. He thinks there is more mist in front of his eyes. He fixes a point to the left of the object he wishes to see with each eye. When seen again on Dec. 26, 1926, aged 49 years, vision had greatly improved. This had taken place within six months during 1902. R.V.=6/60, with +1D.=6/12, with +3.50D. reads 1 J.; L.V.=6/60, with +1.50D.=6/9, with 3.50D. reads 1 J. Says he cannot recognize people in the street although he can read very small print. Fields of vision full, large paracentral scotoma for red, green, and blue above fixation point, pupils, equal, contract to light, eye movements full. Oph.: R.O.D. pale, edge sharply defined, lamina cribrosa much exposed, large cup, vessels of good size, narrowing of inferior temporal artery on O.D., L.O.D. same appearance as R.O.D. only is paler and no contractions on vessels. Is not acromegalic and has no tower-skull. Has not again smoked a pipe, but is smoking 70 cigarettes weekly. Takes no alcohol, married at age of 27 years, is without issue; general health is good. Knee jerks present and equal. Report of skiagraph, March 29, 1927: "The sella is not quite regular in outline and its wall is thin. The clinoids, antero and postero, are small and blurred. The sella is 14 mm. A.P. and 13 deep. There is a blurred but quite distinct shadow, lying free in the sella, as if some mass, rather dense, was lying there."

III 6, *Alexander Da.*, sixth-born in a sibship of eight, aged 52 years (Oct. 27, 1909), seen, pensioner, vision failed at age of 25 years and it never got better, married his first cousin, A.R., III 20, who has double optic atrophy, had no issue; died in 1921 after operation for gastric ulcer. Smoked two ounces of tobacco weekly, saw best in dim light. R.V.=hand movements at six feet; L.V.=hand movements at six feet; fields of vision full when tested by hands, absolute central scotoma for white in each, colours not recognized anywhere in either field; pupils, equal, contract to light; eye movements full; oph.: R. and L. media clear, O.D. pale, right rather paler than left, retinal arteries distinctly narrowed, especially in right eye; lamina cribrosa exposed over most of the disc, the colour of disc is white rather than grey, no white lines along retinal vessels, some disturbance of pigment at edge of optic disc, especially right disc; some blood-vessels near the disc are more tortuous than usual; no abnormal exposure of the large choroidal vessels, no retinal pigmentation, nothing to suggest retinitis pigmentosa, diagnosis is Leber's disease.

III 4, *William Da.*, aged 73 years (1926), seen, retired coal miner, is fourth in a sibship of eight, married, had a family of ten, vision became affected at 20 years of age. He is very deaf. R.V.=hand movements at three feet; L.V.=hand movements at three feet; fields full tested by hands, central scotoma in each for large white object, no colours recognized. Oph.: L.O.D. pale, retinal vessels of fair size; R.O.D. not seen; pupils were small and conditions difficult for examination because he is so very deaf and frail; smokes one ounce of bogie roll tobacco weekly.

III 5, *John Da.* was unmarried when he went abroad and has not been heard of since, is fifth in order of birth in sibship of eight; vision failed at the age of 18 years, and though he was younger than his brother William his vision was first affected. His loss of sight is attributed to the family affection.

III 8, *Robert Da.*, coal miner, eighth born in sibship of eight, was healthy, no illnesses, hearing good, vision failed at 22 years, and he then became a pedlar. Had a twin sister Mrs. W. (III 7). He married and had a twin son and daughter,

now aged 21 years; his wife died at the birth of the twins. He died on May 14, 1921, result of injury, aged 62 years.

IV 25, Hugh W., coal miner, first-born in a sibship of nine, aged 42 years (1926), seen, vision failed in both eyes at age of 21 years, says he is strong and has had no illness, formerly smoked heavily, but has not smoked for six years; drank heavily once a week, but for last seven years has had no alcohol; has bilious attacks that last for two or three days, these come on at intervals of from one to several months; married, has a family of four daughters (V 48-51) of which the oldest is six years. R.V.=3/18 and 6 J.; L.V.=3/36 and 20 J., fields of vision full, taken with hands; no central scotoma for colour could be detected; a 4 mm. red square object was recognized by the right eye and was seen best at fixation point; nowhere in the left field of vision was a 4 mm. red or green object seen, but an 8 mm. one was seen and the colour was more marked at fixation point than elsewhere, the examination though satisfactory was made just after he had returned from work in the pit; oph.: R. and L.O.D. pale, especially the left one, lamina cribrosa exposed, retinal vessels, of about normal size in right eye, are rather diminished in left eye; during fundus examination vertical nystagmus was observed in left eye, not in right eye. He said there was no "glennie blink" (miners' nystagmus) in the men in his pit.

IV 10, John P., coal miner, third-born in a sibship of five, aged 40 years (1926), seen, does not admit that his vision is defective, though his sister, Mrs. Wi. (IV 9), said that he was very blind, is married, has three children (V 14-16). Examined in his dwelling. R.V.=4/24, 16 J.; L.V.=4/12, 4 J., refraction emm, or low H. in each, fields of vision tested by hands show no contraction, no central colour scotoma detected in either field, pupils, equal, contract to light, oph.: R. and L. O.D. pale, retinal vessels of good size, edge of O.D. well defined, lamina cribrosa visible, diagnosis double optic atrophy; no evidence of previous optic neuritis; knee jerks present. The impression he gave was that he did not wish to acknowledge any defect of vision and although it is well known to his relatives that his sight is very bad, subsequent to the examination, in reply to a letter, he sent the following: "I really do not know when my right eye became defective. As far back as I remember there has been no difference. I am sure it has been the same all my life. I have smoked black tobacco, cigarettes, and also chewed tobacco since I was fourteen years of age. I cannot remember it ever affecting my sight. I have also worked in the coal mines for 26 years using safety lamps, and I think my sight is just as good to-day as ever it was."

IV 83, William L., boxmaker, unmarried, first-born in a sibship of four, died aged 33 years, after operation for appendicitis; vision failed in both eyes at age of 25 years, had in consequence to give up his work, but did not get quite blind. He had been examined by an ophthalmic surgeon, who told me that he diagnosed double optic atrophy, but had been unable to discover the cause; no information regarding fields of vision. His aunt (III 39) said that at one time he was seen by a professor at a distance, who said it was a family disease for which there was no cure. Smoked not heavily, on advice gave it up, but vision did not improve.

III 31, John S., blacksmith, first-born in a sibship of seven, died in a poor-house in 1923, aged 74 years, causes of death certified as being "senility and cerebral haemorrhage of three days duration"; sight failed about the age of 35 years, but recovered sufficiently to allow him to get about, had to give up work as blacksmith for that of night watchman, was not a drinker, married at age of 21 years and had ten children (IV 74-82). An ophthalmic surgeon said he had taken the case for one of tobacco amblyopia and admitted that vision did not clear up when instructions were given for smoking to be discontinued and that double optic atrophy was present. Presumably central scotomata were found.

III 56, Alexander In., street porter, youngest in a sibship of four, aged 60 years (Nov., 1926), seen, vision failed rapidly when he was aged 20 years, and worsened for about nine months, he thinks that during the last twenty years vision has got very slowly worse; smoked, and still smokes one and a half to two ounces of bogie roll tobacco, always moderate with alcohol and before onset of blindness was a total abstainer; health good: when vision failed had bad headaches in temples, forehead and occiput; married twice, had two sons by first wife, a daughter and three sons by second wife: intelligent, healthy in appearance, and able to do his work which entails lifting heavy weights. R.V.=counts fingers at one foot; L.V.=counts fingers at one foot; does not fix centrally with either eye, fields of vision quite full

as tested by hand movements; large central scotoma for white in each field; red, green, blue, and yellow not recognized in any part of either field; pupils, equal, rather large, contract to light; eye movements full; tension normal; oph. : R. and L. O.D. marked pallor, lamina cribrosa exposed, edge of O.D. well or even sharply defined, retinal vessels somewhat narrowed, Y.S. and rest of fundus normal; refraction low H.; knee jerks present.

III 14, William Co., compositor, fifth in a sibship of nine, vision, good at school and even later, appears to have failed about the age of 25 years; it became very bad, though he was not blind, so that he did practically no work afterwards but loitered; health good, not subject to fits; he smoked; unmarried; died on Nov. 4, 1926, in a poor-house, aged 65 years. The medical officer kindly supplied the following information: He was admitted January 26, 1922, with chill, diarrhoea, and blindness; apart from the diarrhoea and slight temperature, with headache the only other physical signs noted were those of aortic incompetence; Wassermann negative; on February 7, 1922, discharged cured, apart from the blindness, to the main house of the poor-house; re-admitted to hospital on October 30, 1926, unconscious, doubly incontinent, and with a temperature of 102° and a right-sided hemiplegia; no post-mortem; no history of his eye condition having been thoroughly examined.

III 29, George Re., coal carrier, ninth in sibship of ten (there were four others died in infancy, order of their birth not known), aged 55 years (1926), seen, married in 1899, is without issue; vision failed at 19 years, right eye first affected, left eye soon afterwards, visual defect became stationary in about six months and has not got worse since; neuralgia in left side of face, attributed to teeth, accompanied onset of visual defect; smoked three ounces of bogie roll tobacco weekly and continues to do so, drinks beer and rum on Saturdays; had scarlet fever and enteric when in the army. Sexually no alteration when vision failed (compare cessation of menses in women); R.V.=fingers at one foot; L.V.=fingers at one foot; fields of vision full, absolute central scotoma for colours and white in each field; oph. : R. and L. O.D. pale, edge well defined, lamina cribrosa exposed, retinal blood-vessels show some localized narrowings, in left eye white lines present along some of the vessels; refraction estimated emmetropic in each eye. Sense of smell (cloves, asafoetida, peppermint) and hearing normal; knee jerks present and equal.

IV 1, William Re., labourer, unmarried, first-born in sibship of four, aged 52 years (1926), seen, vision began to fail when he was aged 38 years, got worse for about twelve months, and since then has remained stationary; pain in forehead accompanied onset of visual defect, at present can see sufficiently to walk alone in quiet back streets; told, in 1912, by an ophthalmic surgeon to leave off tobacco which he did without any improvement of vision; smoked three and a half ounces of twist and drank one or two pints of beer weekly; looks healthy, is quite intelligent, hearing and sense of smell tested and found normal, no cranial deformity; R.V.=counts fingers at one foot; L.V.=counts fingers at one foot; fields of vision full as taken by hand movements, absolute central scotoma in each field, large coloured objects not recognized in any part of fields, a 10 mm. white square was seen when moved at fixation point, but much better when removed some distance from it; oph. : R. and L. media clear, refraction estimated low H., O.D. pale, edge quite well defined, lamina cribrosa exposed, retinal arteries slightly narrowed, yellow spot and rest of fundus normal.

III 22, Mary Fo. née Re., married, fourth-born in sibship of ten (see *III 29*), aged 63 years (1926), seen, has an only child, a female (*IV 45*). Vision began to fail at the age of 31 years, at same time catamenia ceased and never reappeared; health always good; R.V.=counts fingers at one foot; L.V.=counts fingers at one foot; fields of vision full, tested by hands, absolute central scotoma for large red object in each field; refraction estimated low H. in each eye; oph. : R. and L. media clear, much pallor of O.D., edge regular and well defined, lamina cribrosa exposed, retinal arteries somewhat narrowed, no white lines along their edges; yellow spot and rest of fundus normal; report on skiagrams of sella by the radiographer: "sella is too small and there is blurring of the posterior clinoid processes by bone, sphenoidal sinus is very large. On a subsequent day another skiagram was taken when the films showed the same enlargement and deformity of the posterior clinoids as was noted in the first skiagrams. Never smoked.

III 20, Aggie Da. née Re., widow, married at age of 22 years, and had been married for forty years, no miscarriages, no stillbirths, second-born in sibship of

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ten (see III 29), aged 67 years (1926), seen, vision failed about age of 33 years, had much headache referred to vertex; visual defect, noticed first when reading, in a few months got very bad; catameria regular until vision failed, then ceased and never re-appeared; does not smoke; always had good health, no illness; sense of smell tested with peppermint, oil of cloves, asafoetida, is normal; R.V.=little more than P.L.; L.V.=hand movements at one foot; fields of vision tested by hand movements are peripherally contracted in all directions, large red object not recognized as red in any part of field, but when tested with large white object there is obviously a central scotoma in each field; oph.: R. and L., media clear, O.D. pale, edge well defined, lamina cribrosa exposed, some narrowing of retinal arteries, no white lines along their edges, nothing abnormal seen in rest of fundus; refraction estimated low H. Skiagram report: "The sella is rather irregular in outline, especially towards the posterior part. It is 15 mm. A.P. and 11 deep. Both clinoid processes are small and deformed, and are partly obscured by new bony deposits."

Unaffected Members of the Pedigree

- GEN. I.—1, Da., died abroad. 2, Mrs. Du., good vision, her husband, Wm. Du., died early, not in chart, nothing known about his sight.
- GEN. II.—3, John Da., soldier, "blin-fair" (albino), drank heavily, *ob.* 40. 4, killed 5, Grace Da., married twice, no issue by first and none known by second husband. 7, Mary Du. (Mrs. Da.), first-born in sibship, vision good. 8, Isabel Du. (Mrs. Co.), and husband, 9, saw well. 10, Agnes Du. (Mrs. Re.) and husband 11, sight good, he died, aged 68 years. 12, Wm. Du, unmarried, killed. 13, Barbara Du. (Mrs. Sm.) and husband, Wm. Sm., 14, had good vision, he died of cancer of tongue. 16, Peter Du., married twice, had two families and many descendants. 18, Catherine Du. (Mrs. In.), youngest in sibship, and her husband, 19, had good sight.
- GEN. III.—1-8 family of Da.: 1, Jessie (Mrs. Re.), *ob.* 65 of brain trouble. 2, Mary (Mrs. MacCn.), abroad. 3, Grace (Mrs. Pa.), and 7, Jane (Mrs. Wa.), vision good, 7 twin with 8. 9, died at birth of her twins. 10-18 family of Co., 10 and 11 *ob.* childhood. 12, Mrs. Le., and 13, Mrs. El., vision good. 15, Jessie, *ob.* 16. 16, her twin brother, *ob.* childhood. 17 and 18, *ob.* infancy. Only three of this family grew up. 19-30, family of Re., 28 (4 *ob.* infancy or still-born). 23, *ob.* 12 "water in head." 26, Janet (Mrs. We.), *ob.* 27, Isabella (Mrs. An.), widow, 19 (Mrs. Al.), 24 (Mrs. Fo.), 30 (Mrs. Du.) had good vision. 21, Williamson Re., phthisical, off work 12 years, R.V. 1J. close, central nebula; L.V. $\bar{c}+13D$. 1J. readily, fundi n. 31-39, family of Sm., all saw well except 31. 32 (Mrs. Ly), *ob.* 36, had illegitimate son (IV 92) by 35, later she married 37 and had two children, IV 93 and 94. 34, age 73 years, healthy. 38, married, no issue. 39, unmarried. 40-47, first family of Peter Du. (II 16), 40, Wm. and 47, Betsy, *ob.* 42, married three times, three boys of first marriage and a girl of each of the other marriages. 45, John, and 46, twins. 46, *ob.* infancy. 45, had 14 children (IV 107-120). 48-51, second family of II 16. 48, Peter and 51, Mrs. Ra., both married no issue. 50, Wilhelmina, unmarried. 49, Charles. 52-56, family of In.: 52 Isabel, has three illegitimate children (IV 131-133). 53, Maria, has illegitimate daughter (IV 134). 54, *ob.* infancy.
- GEN. IV.—1-4, Re. family. 2, John, aged 45 years. 3, Matthew, aged 43 years. 4, Grace (Mrs. Mo.), vision good in all. 5-7, MacCn. family, abroad, state of vision unknown. 8-12, Pa. family. 8, Mary (Mrs. Co.), 9, Agnes (Mrs. Wi.) and 12, James, who is abroad have good vision. 11, Jane, *ob.* aged 2 years. 13-23, Da. family all have good vision. 13, John, and 17, James, unmarried. 14 (Mrs. McEw.), 15 (Mrs. Ing.), 16, Wm., 19, Peter, and 23 Alex. have families. 25-33, Wa. family. 26, Mary (Mrs. Go.), has young family (V 52-55). 27, John, coal miner, vision 1J. in each, fundi n. 28, Minnie (Mrs. Cl.), R.V. 2J., H.As., L.V. 1J., H. 29, Grace (Mrs. Co.). 30, Jean, 31, Lizzie (Mrs. Fl.), healthy, has two boys. 32, Nettie, her child (V 63), *ob.* infancy. 33, Robina, unmarried, of healthy appearance. 34, Thomas Da., aged 21 years, seaman, vision good, 35, his twin sister, has diffuse left corneal opacity, R. vision good. 36-38, Le. family. 36, killed, aged 14 years. 37, Henry, in army, aged 40 years. says in letter, Feb. 4, 1927, his sight is quite good, has nine children, oldest is 13½ years. 38, abroad. 39, unmarried, good vision.

40-43, Al. family. 40, Annie, 41, Barbara (Mrs. Ne.), 42, Wm., married, no issue, and 43, Maggie (Mrs. Jo.), have good vision. 44, John Re., aged 25 years, scoliosis, cannot walk or read, can draw, imbecile. 45, Mrs. Hu., vision 6/6 in each, fundi n. 46-51, Fo. family. 46, imbecile, died in institution for imbeciles. 47, George, abroad, married, no issue. 48, abroad, no report of any family. 49, Elizabeth, married, 50, Lena, 51, Edwin, both unmarried, good vision in all. 52-54, We. family, 54, Joseph and 53, Mrs. Du., see well; 54, ob. 55-64, An. family, 55, Bella, 56, Nelly (Mrs. Mi.), 57, stillbirth, 58, Maggie (Mrs. St.), 59, and 61, ob. childhood; 60, Robert, 62 and 63, males, 64, Eva none with defective vision. 65-72, Du. family, father and mother (III 30) had same name, but not related. 65, Robert, and 66, Mrs. St., married; 67, ob. infancy; 69, Mrs. Macdo., married twice, only child, V 102, by first marriage, died, family of six by second marriage; 71, John; 72, Wm., aged 20 years, mentally weak. 74-82, Sm. family. 74, Wm., married twice and had two families. 76, Hugh, drowned. 77, Mrs. Du.; 78, John; 79, David, cannot smoke. 80, James; 81, Peter, abroad; 82, Bella (Mrs. No.), aged 36 years. 83-86, Lv. family. 84, Donald, baker, aged 48 years, 85, Mrs. Wi., 86, Lizzie, unmarried, all see well. 87, Harry Bu., ob. 26, influenza; 88, Dora Bu., married, no issue. 89-91, Gi. family. 90 ob., could never learn to smoke. 91, Wm., married, no issue, vision 6/6 in each eye, fundi n. 93 and 94, Gr. family were young children 30 years ago, one died, no trace of this family can be found. 95-101, Du. family. 95, Robert, abroad, 96, Mina, and 97, Peter, have families. 99, Maggie, married twice, had two families. 101, Wm., married, no issue. 102, daughter of father's first marriage, 103, Jim, 104, Ben., and 105, of second marriage and 106, daughter of third marriage of III 42. 107-120, John Du.'s family. 107, ob. childhood. 108, John, had convulsions, married, no issue. 109, Wm., 110, Lizzie, 111, Mary, 114, Nelly, 115, Jim, all married with families, 112, Aggie, and 113, Alex., married, no issue. 116, ob. infancy, 117 and 118, stillborn, 119, ob., aged 4 years, 120, ob. infancy. 121-124, twice twins all ob. young, 125, Peter, 126, Lizzie, 127, Kate, 128, Jessie have good vision. 129, male, sex of 130 unknown. 131-133, illegitimate, 131, Jean, married, no issue. 132, Kate, has family. 133, killed. 135, Wm. In., aged 35 years, married, has two sons (V 181-182). 136, Alex., unmarried. 137-140, In. family, 137, Mary In., aged 19 years, 138-140, three healthy boys, vision good.

GEN. V.—1-4, Mo. family: 1, Grace; 2, Jessie; 3, Wm., 4, another, sex unknown. 5-9 Co. family: 5, Grace; 6, James, aged 20 years; 7, Agnes; 8, John; 9, female. 10-13, Wi. family: 10 male, 11 female with epicanthus both sides, 12 female, 13 male, 14-16 are young children. 17-21, five boys, three died. 18, aged 6 years. 22-28, McEw. family: 22, 23, and 27, ob. phthisis. 24, Mrs. McF. has a child, VI 1; 25 Robert, 26 Janet, 28, four ob. infancy. 29, Elizabeth, aged 13 years; 30 Oliver, 31, Wm. lost an eye from ulceration, 32 James, 33 Robert, 34 John, 35 Charles, 36 James, 37 Lizzie, and 38 May, all see well. 39-44, 39, first-born, aged 11 years. 45, ob.; 46, Elizabeth; 47, May, good vision. 48-51, first-born, aged 6 years. 52-55, first-born, aged 12 years. 56-59, all young with good vision. 60 only child. 61 L. corneal opacity. 62, aged 10 years, R. int. con. strabismus, infantile paralysis right leg which is thin and foot small. 64-67a, Le. family of nine: first-born 13½, all see well, six have passed sight test at school. 68, abroad. 69, a family, no particulars. 70-72, three young girls. 73-76, four young children. 77, aged 6 years. 78, ob. sex unknown. 79, boy. 80-83, first-born, aged 6 years. 82, ob. ten weeks, living ones see well. 84-88, first-born, aged 14 years. 89-93, Mi. family; 89 Ella, 90, female, 91, male, ob., 92 schoolboy, 93, ob., twin with 92. 94 and 95 stillborn twins; 96 Bertie St., 97 only child. 98 and 99 boy and girl. 100 ob., aged 2 years; 101 girl. 103 and 104 twins, ob., 105, 106, 108, see well, 107, ob. 109 Fred, aged 29 years, 110 Wm., 111 John, 112 Jane, 113 Annie, 114 Frances, aged 6 years, only child of Wm. Sm.'s (IV 74) second marriage. 115, male, aged 25 years, corresponds regularly with his mother (IV 77), who says his sight is good; 116 ob. 117, Robert, aged 23 years, reads 1J., 118 John, 119 Lizzie, typist. 120-126, first-born (120), aged 21 years, 124 ob., fundus oculi n. in living members. 127 only child. 128-132, abroad, all see well. 133-140. 138, aged 7 years, 139, aged 4 years, 140, aged 2 years, others ob. infancy or in first three years of life. 141 only child; 142 ob. infancy.

male
female sign
2111 should have
ploughed male
not sign
25 and 32
ploughed male
not sign
above 9 and 10
ploughed male
not sign

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143, Barbara, aged 29 years (1916), 144 ob. infancy. 145, Charlie, aged 20 years, unmarried, fundi n., vision 6/6 in each. 146, male, ob.; 147 and 148 females. 149 a family no particulars. 150 and 151, sex not recorded, were first family, and 152 Marjory, 153 male, and 154 others number and sex not known, were second family of IV 99. 155-159 family of Wm. Du. (IV 109). 155 Wm. has phthisis, 156 Alex., 157 female ob., 158 female, 159 male, all see well. 160-162 family abroad, 160-161 male twins, 162 female. 163-166 family abroad, 163 female, others males. 167-170, 167 Catherine, 168 Margaret, 169 Jack, 170 male. Jim Du.'s family, 171 and 172 males, 173 female, see well. 174 female, 175 others no particulars. 176-180 age of first-born is 16 years. 181, aged 5 years. 182, aged 3 years.

GEN. VI.—1, a child. 2-7, first-born aged 9 years, 2, 3, 5, 6, 7, see well, 4 died. 8, only child of Wm. Du. (V 155), died. 9 and 10 abroad, son and daughter of V 160. 11 and 12 abroad, two children of V 161, sex unknown.

These two pedigrees, A and B, were being worked up for publication before it was known that they included females. This is mentioned because it has been stated that small pedigrees with only males affected are relatively common and not always recorded, but cases in females have been more generally published on account of their rarity.

I am indebted to Dr. John R. Levack for the radiographic examinations and reports.

George G., IV 89 in pedigree B, was an in-patient at the Aberdeen Royal Infirmary in 1902 and George S., IV 92 in pedigree B, in 1904.

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