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HEREDITARY OPTIC ATROPHY

AN INVESTIGATION INTO 59 CASES

WITH DOMINANT TRANSMISSION AND EARLY ONSET

THE CASES HAVE THE FOLLOWING CHARACTERISTICS:-

(a) DOMINANT MODE OF INHERITANCE

(b) GRADUAL ONSET IN EARLY CHILDHOOD

(c) PARTIAL FAILURE OF CENTRAL VISION

(d) NO PROGRESS AFTER INITIAL STAGES

THE INVESTIGATION HAS BEEN CARRIED OUT UNDER THE FOLLOWING HEADINGS:-

REVIEW OF PUBLISHED CASES

The following cases of dominant hereditary optic atrophy of early onset have been published:-

		reference nº on page 49.	
I	Doyne 1898	(1)	7 Cases
II	Knapp 1904	(2)	7 "
III	Marcus Gunn 1907	(3)	3 "
IV	Arnold Lawson 1907	(4)	2 "
V	Griscom in 1921	(5)	14 "
VI	Thomson & Cashell in 1935	(6)	16 "
VII	Riedl in 1935	(7)	9 "
			58 "

The first five were published as cases of Leber's disease.

The following are similar cases, but are not included in the present series on account of atypical features:-

VIII	Snell 1897	(8)
IX	Rifat 1906	(9)
X	Samuelson 1940	(10)

XI	Rampoldi 1883	(11)

Rampoldi's case has been quoted as an example of dominant hereditary optic atrophy of early onset, but the onset in his cases was in later life

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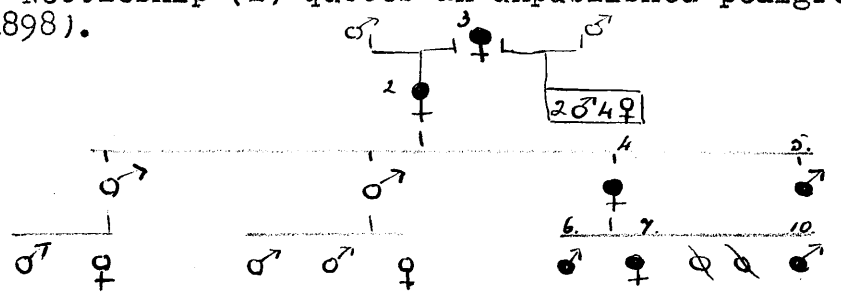
REVIEW OF SIMILAR CASES I

Nettleship (1) quotes an unpublished pedigree by Doyne (1898).



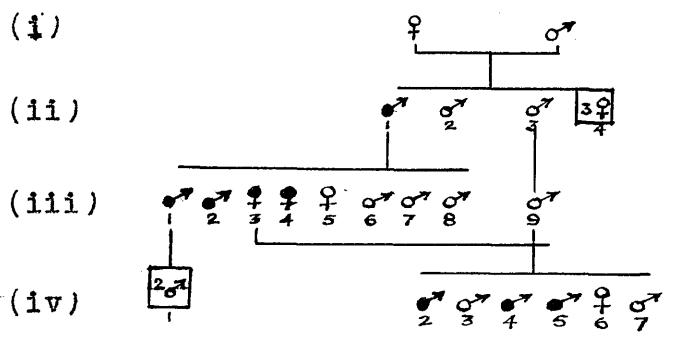
Generation	Case	
(i)	(3)	Can see to read, but has some defect of vision.
(ii)	(2)	Seen at 70. Sight failed in childhood; has remained unchanged.
(iii)	(4)	Aged 20. Born with sight as it is now.
(iv)	(6)	At 3 - sight began to fail. Now 8 - myopia - 7.00D. V.R. fingers. Disc pale. Can read J4 slowly.
	(7)	Saw well till 4. Now 5. H. + 2.00D. Disc pale. V. fingers 3'.
	(10)	At 2/12 began to see badly. Seen at 6/12. Irregular nystagmus noted. Seen at 1 10/12. Disc pale. "He bumps into tables"

NOTE:-

5 Cases seen. Sight failed about 3 or 4 years of age. In one, sight failed at 2/12, and atrophic disc seen at 1 10/12.

REVIEW OF PUBLISHED CASES

KNAPP'S CASE II



Generation	Case	
(ii)	(1)	Sight blurred suddenly at age of 24. Both parents healthy. Fields full with central scotoma. Slight recovery of sight many years later. A typical case of Leber's disease.
(iii)	(1) (2) (3) (4)	Sight was found to be poor when they went to school. Case 3 examined at age of 33. Vision R. and L. $^{6}/_{60}$. No colour vision. Fields contracted to about 20°. Disc pale on temporal half. Arteries normal.
(iv)	(2) (4) (5)	Seen at ages of 12, 10, and 8 respectively. Always had poor sight which was first noted when they went to school. In each case, vision R. and L. $^{6}/_{60}$. No colour perception. Fields contracted to about 20°. No central scotoma. Arteries normal. Disc pale on temporal half.

NOTE:-

1) Dominant transmission in 3 generations.

2) Early onset in 7 cases in 2 generations.

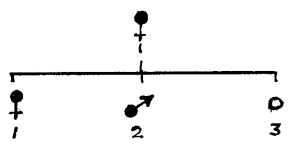
3) Peripheral contraction of fields.

4) Case (1), Generation (i) is a typical case of Leber's disease.
This case is not included as one of early onset, but raises the question as to whether dominant hereditary optic atrophy of early onset is a different form of Leber's disease.
This point will be discussed later.

MARCUS GUNN III

(i)

(ii)



Generation	Case	
(i)	(1)	Sight has always been bad, if anything, now better. R. 6/36. Central colour scotoma. L. 6/9. No central colour scotoma. Fields show marked peripheral contraction. Disc Grey-white. Vessels normal.
(ii)	(1)	Onset at 5. R. 6/12p. No colour scotoma. L. 6/18. No colour scotoma. Great peripheral contraction of fields. Disc v. Pale. Vessels normal.
	(2)	Age 4. Disc pale. Mother has noted change in past year. (+ 6.00 refraction).
	(3)	Excellent sight at $2\frac{1}{2}$.

NOTE:-

1) Dominant hereditary.

2) Early onset.

3) One eye more affected than other.

4) Peripheral contraction of fields.

REVIEW OF PUBLISHED CASES

ARNOLD LAWSON IV

(i)

(ii) 

In the mother's case, the disease had made no progress since she was examined seventeen years before (age 14) at Moorefields, and affected chiefly one eye.

R. 6/12. Normal disc. Can see colours.

L. Fingers. Disc pale and cupped in temporal half. Fields full. There is large central colour scotoma in left eye.

Son age 10. Defective since early infancy.

R. 6/60.

L. 6/36.

Not improved by glasses.
Both discs pale L. more than R. Fields normal. Central colour scotoma L. more than R.

Girl - Normal.

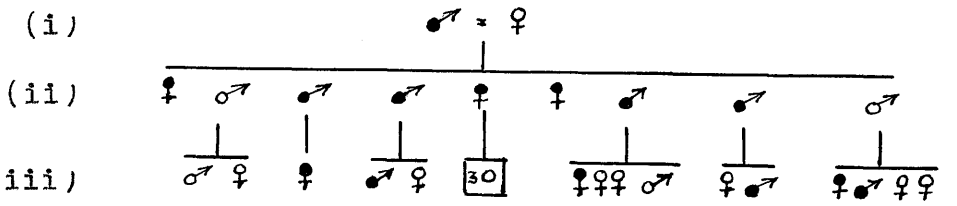
NOTE:-

1) One eye more affected than other.

2) Central colour scotoma.

3) Fields full.

GRISCOM V



14 cases of optic atrophy in 3 generations. All date from early childhood, and are presumed to be congenital. (There is no note of nystagmus). The individuals are well nourished and intelligent. There is no history of consanguinity.

Generation(ii)

	R.	L.	R.	L.	R.	L.	R.	L.
Vision	3/6	3/60	6/60	6/18	5/60	5/60	6/36	1/60
Age	46		36		34		32	

Generation (iii)

	R.	L.	R.	L.	R.	L.
Vision	6/60	6/60	6/18	6/18	6/12	6/12
Age	8		6		6	

Fields vary, but generation (ii) shows slight peripheral contraction, and some paracentral scotoma. They were not taken in Generation (iii). Discs are white with clear cut edges. Many cases show contraction of the retinal vessels, and either fine vitreous changes or scattered retinal pigmentation.

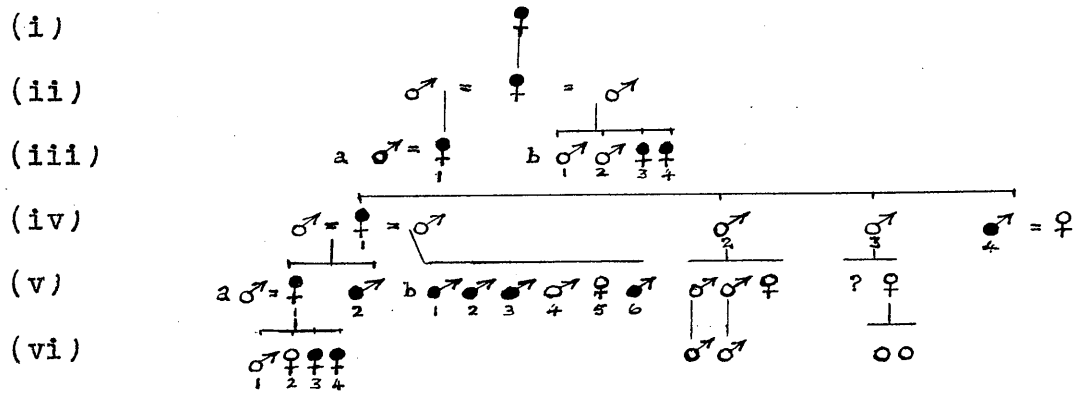
Urine W.R., X Ray sella. No abnormality.

Griscom concludes "Low grade retinal degeneration is the cause".

NOTE:-

First case (and only case) of transmission from unaffected parent. Importance requires confirmation. Is this an example of recessive inheritance in a dominant pedigree?

THOMPSON AND CASHELL (vi)



10 cases (in Generation (iv), (v) and (vi)) examined. All present nystagmus, and many have been educated at a blind school. Atrophic disc seen at age of 2 in one case. Fields present small or moderate peripheral contraction, but no central scotoma for white or colour. Discs are pale, with deep cupping and clear cut edges. Arteries are small in some cases. The disease is stationary. Vision is recorded in table. X Ray of skull, blood examinations and W.R. show no abnormality, nor was any abnormality detected in C.N.S.

THOMPSON CASES

Generation (iv)

		No. 1	No. 4
	Age	55 ish	52
Vision	R.	H. M.	1/60
	L.	H. M.	1/60

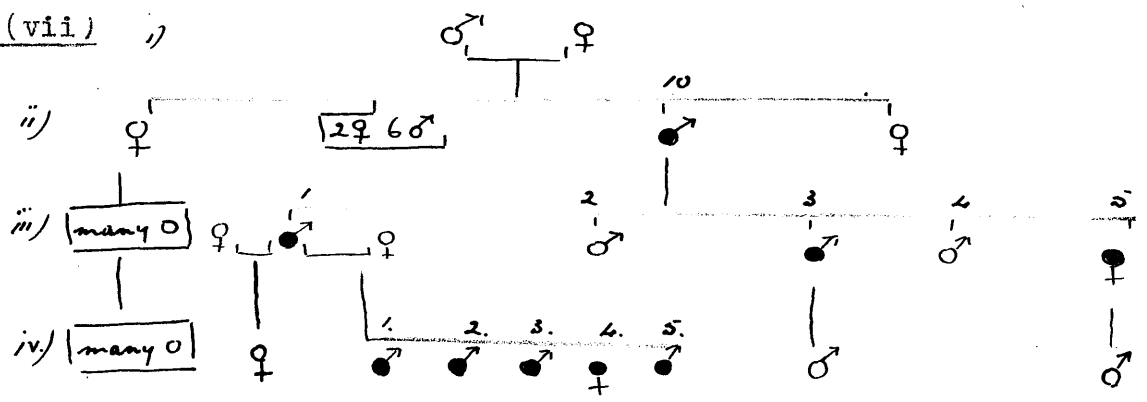
Generation (v)

		a	b1	b2	b3	b5	b6
	Age	32	28	Died at 7	24	20	13
Vision	R.	6/24	1/60	6/60	6/24	6/24	blind
	L.	6/24	2/60	6/60	6/24	6/24	blind
Colour			-			good	

Generation (vi)

Age	5	2
R.	6/36	?
L.	6/36	?
Colour		

REIDL (vii)



Generation	Case	
(ii)	(10)	His brothers, sisters, father and mother had good sight. He was exempt from military service on account of sight, and always had to hold a book very close.
(iii) Age 44	(1)	Had to sit in front at school. Can see better in the dark. Vision R. and L. counts fingers. Disc pale with deep cup. Vessels normal. X Ray of sella has been done in this case, and in all others, and no abnormality found.
(iii) Age 30	(3)	Had to sit in front at school. Can see better in the dark. Vision R. 5/60. L. counts fingers. Discs pallor of temporal half with deep cupping. Vessels normal. Fields for white contracted. Fields for colours hemianopic.
(iii)	(5)	Sight has never been good. Vision R. 5/15. L. 5/10. Disc pallor of temporal half, but not so marked as in brothers.
(iv)	(1) (2) (3) (4) (5)	The youngest is 17. All had to sit in front at school. All show pallor of disc with deep cupping. The pallor is marked in the temporal half. The only factor which varies is the fields; many cases show quadrantic or hemianopic defects for colours, and, in some cases, paracentral scotoma. A large spot had to be used, as a smaller spot was not appreciated as colour.

NOTE. 1) Dominant heredity.
2) Cases have early onset.
3) Some present hemianopia for colour fields.

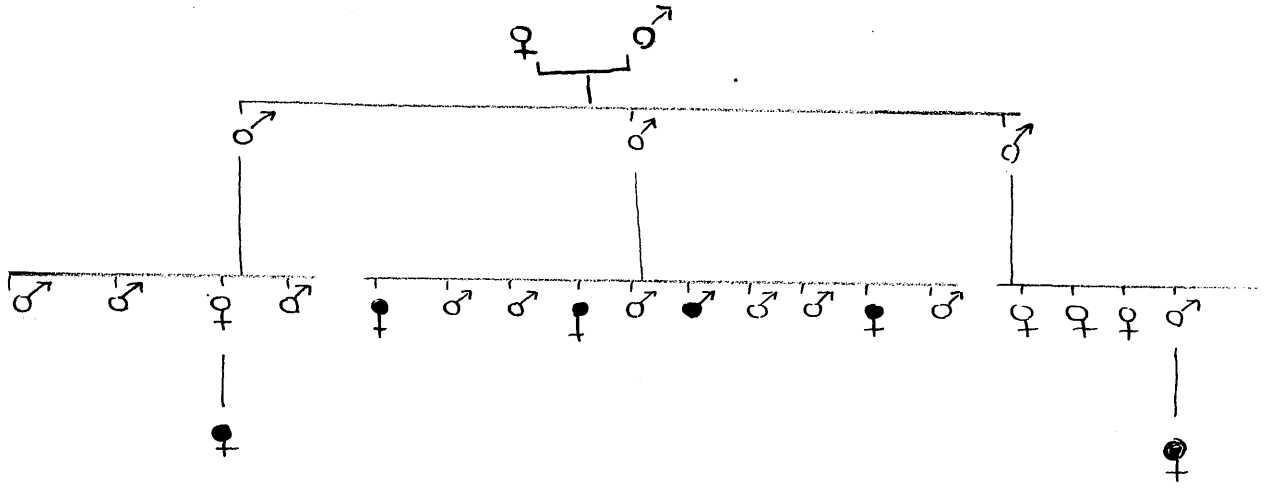
ATYPICAL CASES WITH EARLY ONSET

SPORADIC TYPE

(vii) Snell (ref 8.) in 1897 reported a family where 5 siblings of healthy parents had congenital optic atrophy with full fields and no central scotoma.

RECESSIVE TYPE

(viii) Rifat (9.) in 1906 reported 6 cases of congenital optic atrophy among cousins whose parents were healthy. W.R. was negative. There is no note of nystagmus, but it is stated all were born blind. Vision R. and L. perception of light.
Disc is pale with clear cut edges. Vessels are narrow.



ASSOCIATED WITH OTHER NERVE ATROPHIES

(IX) Samuelson (10.) in 1940 reports a mother and 3 siblings with optic atrophy of early onset, and with deafness due to atrophy of viii N, and with paresis of respiratory nerves.

It is possible that these cases should be included in the group of hereditary optic atrophy of early onset, but it is proposed to leave them aside meanwhile.

LATE ONSET.

(XI.) As the age of onset in Rampoldi's cases was about 37, they are not included.

SUMMARY OF PUBLISHED CASES

In seven families, we have reports of 58 cases of optic atrophy presenting the following points:-

1) Inheritance

In every case (except two) the atrophy is directly inherited from an affected parent; from a male in 14 cases, from a female in 10 cases.

The children of the affected parent have been affected in the following numbers:-

	Affected		Unaffected	
	Males	Females	Males	Females
Doyne	3	4	4	4
Knapp	5	2	7	5
Gunn	1	1	-	1
Lawson	1	2	1	-
Griscom	8	6	4	7
Thompson	6	10	5	1
Reidl	7	2	4	-
	31	27	25	18

Total of Males affected 31 Total affected 58
Total of Females affected 27 Total unaffected 45

In two cases (Griscom's) the affection was passed on from an unaffected parent.

In 14 cases, transmission was from affected father, in 10 cases from affected mother.

A most noteworthy exception to the mode inheritance is case (1), genertion (ii) of Knapp's family.

The history, given in full in Knapp's paper, is typical of recessive hereditary optic atrophy coming on suddenly at the age of 24. The man's parents were healthy, and no other case was known in the family.

This case raises the whole question as to whether a recessive transmission can become dominant, and whether dominant hereditary optic atrophy of early onset is a variant of the recessive type of later onset.

Alsberg reports a similar case (Ped. 903 Bell & Ref. (16)

2) Sex Incidence

Of affected cases, 31 are male, and 27 are female.

3) Age of Onset

It is difficult to record the age at which early failure of vision occurs.

If one may assume that the presence of nystagmus indicates a congenital failure of central vision, 17 cases of the 49 are congenital. 29 cases were noted at or before school age. 2 are not stated, and 1 was first noted at 14 when disc was white.

Thus there are 46 cases in which the onset was certainly before 5 years of age.

SUMMARY OF PUBLISHED CASES

4) Signs and Symptoms

No case has complained of noticing the onset of blurring of vision.

In no case is there a history of any improvement or of any marked deterioration of the condition. There are not sufficient records of visual acuity from which one can draw conclusions, but the vision of two of Griscom's cases aged 6 (V. R. and L. 6/18, and V. R. and L. 6/12) suggests that a slow deterioration may follow.

5) Fields of Vision

In cases by Knapp, Gunn and Griscom, contraction of periphery of fields is mentioned in 10 cases, of which 4 present central or paracentral scotoma.

In Thompson's cases, there is no central scotoma, but varying degrees of peripheral contraction in 8 cases. In 6 cases, fields are full.

Colour vision is said to be poor in some cases. Reidl has done very careful colour fields in his cases and finds examples of quadrantic and hemianopic defect. He states that his patients had difficulty in seeing a small spot, which was not recognised as colour.

In all cases, except Lawson's and Gunn's cases, both eyes were affected. In the great majority of cases, both eyes were equally affected.

6) Ophthalmoscopic Appearance

The fundus in all affected cases shows a pale disc with clear cut edges (the pallor being more marked on the temporal half).

In some cases the vessels are normal, and in other, they are contracted. Deep cupping is noted in most cases. The remainder of the fundus is normal except in Griscom's cases where he noted some fine scattered retinal pigmentation.

7) Association with other disabilities

There is no association with other disabilities.

X Ray of sella in many cases shows no enlargement.

No case of adiposity or of hypo-or hyper-genitalism has been reported.

PRESENT CASES

59 cases of optic atrophy have been found among three families totalling over 250 members, living in the same district; two of the families are said to be related, but this cannot be confirmed.

The individuals are healthy, industrious, and long lived, with no other family defect. There are no cases of mental deficiency or of obvious endocrine dysfunction. The causes of death present no significant factor. There are no signs of specific disease and W.R. in 6 cases is negative. No case of deafness or of loss of smell or taste was found.

I have seen 32 of the affected cases, 22 in their home, 8 as out-patients, and 2 as in-patients in hospital.

I have also examined 37 unaffected members, and found them normal in all respects.

The following points were recorded in all cases:-

1) History
2) Corrected visual acuity for distance and near
3) Colour vision by Ishihara numbers
4) Pupil reflexes and eye movements
5) Fields by hand, or by perimeter and Bjerrum screen
6) Examination of fundus R. and L.

The 10 who came to hospital had a complete examination of fields and of C.N.S. 6 had blood count and W.R. test, and 4 had X Ray of sella and sinuses. In addition, the 2 in-patients had twentyfour hour urine test, and C.S.F. examination. These tests showed no abnormality other than defects of vision.

The affected cases are all so similar that an account of one will give a picture of all. A typical history is:-

"My sight has always been bad. It was first noted when I went to school. I had to sit in front and even then had to come out to see the board. My sight has never changed. I can get about by myself and can do my work, but cannot take promotion in my job because of my sight. Another trouble is that I pass my friends in the street. Glasses are no help. I can see as well at night."

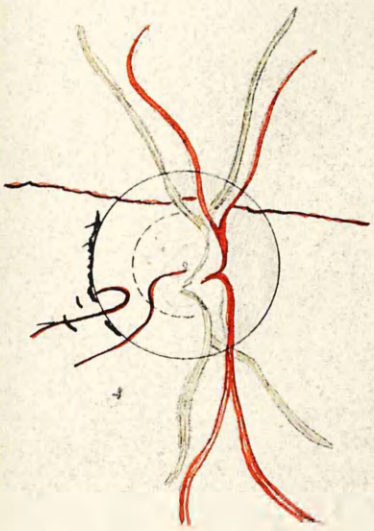
V (R. 6/60. J12. Colours very poor.
V (L. 6/60. J12. Colours very poor.

Fields are full for white and restricted for colour. There is no scotoma, central or paracentral, for white or colours. Pupils are circular and equal. They react to light and on accommodation. Consensual reflex is present. There is no nystagmus. Movements are normal.

FUNDUS EXAMINATION

The disc is of blue-white colour. The nasal half is grey and the temporal half is white. The edges are clear cut. A deep cup extends well into the temporal half. The vessels are normal. The remainder of the fundus is normal, with the important exception that no yellow area can be seen at the macula, though the usual light reflex is present. No degeneration can be detected.

Rt. disc of Case IIL. gen IV.



Rt. disc. of 9L. age 34.

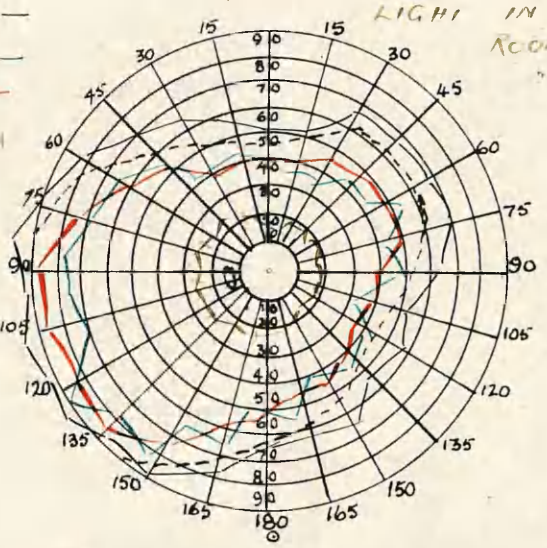
cup extends to temporal margin of disc.

Rt. disc of 10E. gen V. age 7.

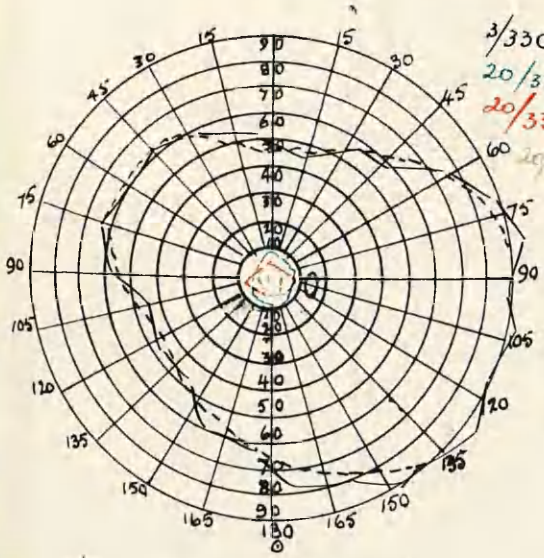
two "cups".

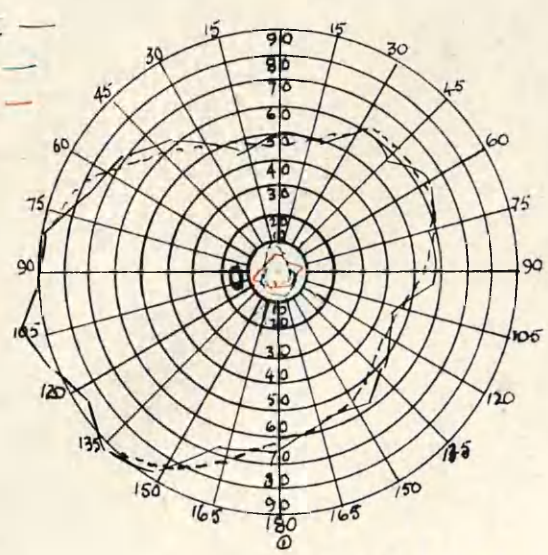
CASE 13E. gen IV.

ALL FIELDS DONE ON LISTER PERIMETER WITH "STANDARD" ELECTRIC LIGHT IN DARK ROOM.

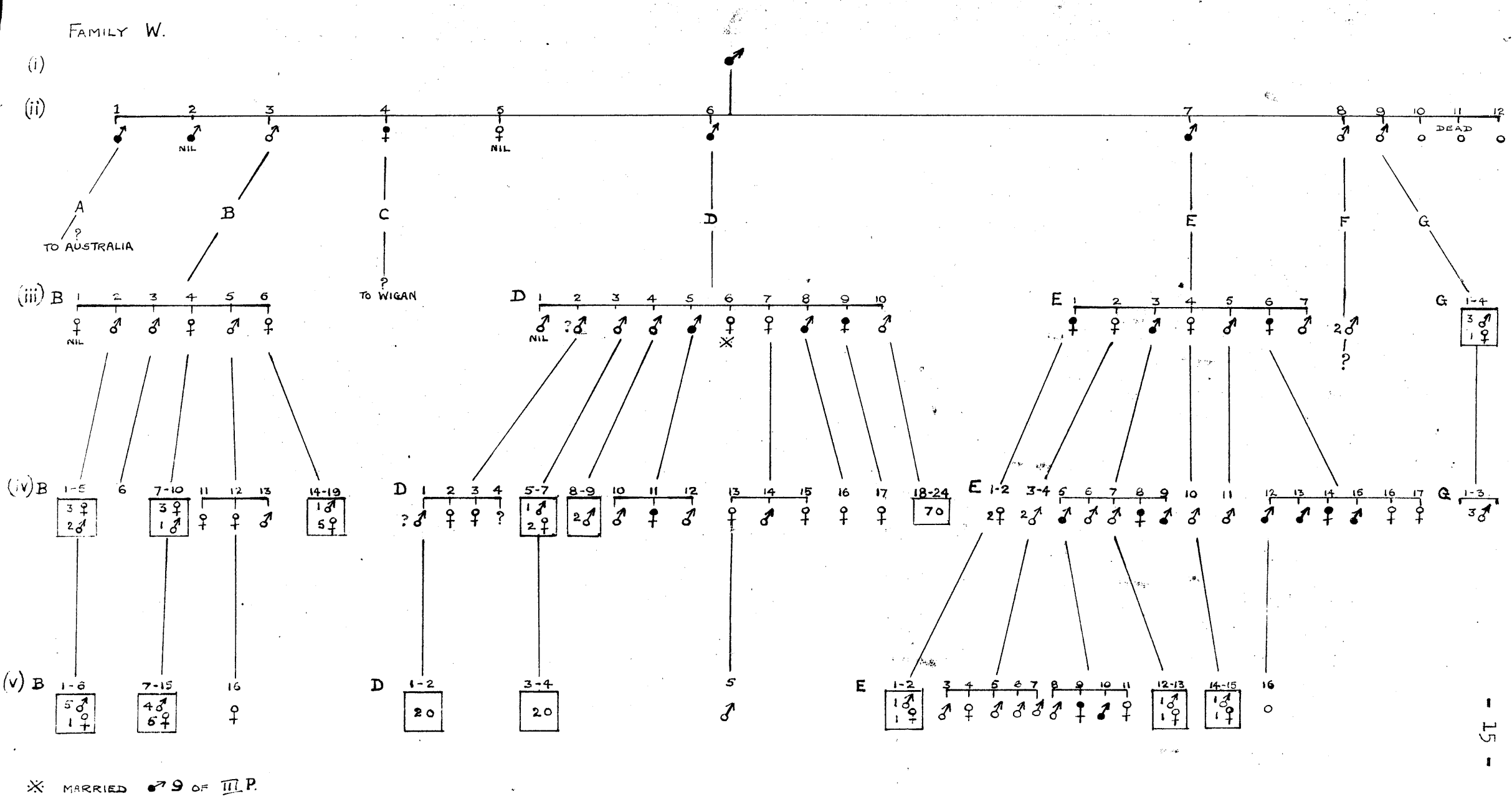


CASE IIL. gen IV.





FAMILY W.



※ MARRIED ♂ 9 OF III P.

FAMILY W

Generation (ii) are all dead, but the wife of 9, Generation (ii) is alive, and was able to give me information about the parents (Generation (i) with whom she lived for nine years.

No. 1 of Generation (i) was a preacher, and used to be able to read the Bible, but had difficulty in recognising his friends in the street. His wife was illiterate, but wore glasses and was able to see quite well. They were not related before marriage.

The same informant was able to give me the following information about the members of Generation (ii). This has been substantially confirmed by the members of Generation (iii).

GENERATION (ii)

1	Always had poor sight. Went to Australia.
2	Had poor sight but did not marry.
3	Was an engine driver and had good sight.
4	Had bad sight, and some of her children have poor sight, but they moved to Wigan, and cannot be traced.
5	Had good sight but no children.
6	Always had bad sight, which is confirmed by his daughters. Died about 70, and had diabetes in his latter years.
7	Had bad sight, and stated that it was just the same all his life. He was able to go about by himself until the last three years, when cataract developed. He died at 71 of "Old age". He stated frequently that he was able to see better at night. He found glasses no use and his sight did not change at all until cataract developed.
8	Had good sight. Went to Crewe; his two sons have good sight.
9	Had good sight. Died at 40 of pernicious anaemia.

GENERATION (iii)

5B	Age 56	Good sight. All colours. Vision R. and L. 6/9. Jl. Fundi normal. Agrees with daughter that there is no bad sight in their side of the family.
2D		This case moved to Halifax, and little is remembered about him. He has been "Bombed out" recently, and cannot be traced.

FAMILY W

GENERATION (iii)

5D Age 58

Always had poor sight. Can see better in the dark. Sees no colours.
Vision R. and L. 3/60. Can read less than J20. Fields full.
Discs white clear edges. No cupping.
Vessels normal.

6D Age 54

Vision R. and L. 6/9. J1. All colours.
Fundi normal. This was surprising as her children had atrophic discs.
It transpired that her husband, who died at 40 of peritonitis, had always had bad sight.
An investigation into the husband's family showed that hereditary optic atrophy of early onset was present.
No relationship is known or can be established by inquiry.
The children are shown in Pedigree Y.

7D Age 52

Vision R. and L. 6/9. J1. All colours.
Fundi normal.
Remembers father passing her in the street, and that his sight was always bad.

1E Age 68

Sight always poor. Worse in last ten years with cataract.
R. cataract removed when 64.
Vision R. 4/60. Reads J20.
Vision L. Hand-movements.
Disc R. white. No cupping. Edges clear cut.
Vessels slightly narrow. No degeneration at macula.
Disc L. cannot be seen due to cataract.

2E Age 66

Vision R. and L. 6/9. J2. Colours fair.
Fundi normal.

3E Age 64

Always had poor sight. First noted when he went to school. Sight has not altered.
Vision R. and L. 5/60. J12. No colours.
Fields full.
Discs white with deep cupping. Vessels normal.

4E Age 63

Good sight.
Vision R. and L. 6/9. Reads J1. All colours.
Fields full.
Fundi normal. Slight lens changes.

6E Age 60

Poor sight. Noted before she went to school.
Sight has not altered until recently, when it has become worse.
Fields tested on Perimeter and Bjerum screen.
Fields full. No central scotoma with 5mm spot (Great difficulty in seeing smaller spot).
Discs strikingly white. Deep cupping.
Central nervous system and blood pressure normal.
No deafness. X Ray shows normal sella.
W.R. negative.
Vision R. and L. 2/60. Reads less than J20.

FAMILY W

GENERATION (iii)

10E Age 40

Vision R. + 5.00/+ 1.50 at 135. 6/12. J2.
L. + 6.00. 6/6. J1.
All colours.
Fundi normal.
Internal strabismus only without glasses.

11E Age 21

In R.A.F. Reports that vision is 6/6.

12E Age 31

Always had poor sight. First noted when he went to school.
Vision R. and L. 3/60. Less than J20.
Colours x.
Fields full with 5mm spot at 330.
Finds difficulty in following spot as it approaches centre, which might denote small relative central scotoma. Central scotoma could not be demonstrated on Bjerum screen.
Fundus grey with deep white cupping extending to temporal side. Vessels normal. W.R. negative. Blood count normal. Central nervous system normal. Slit lamp shows no abnormality of cornea, iris, or lens.
(Y shaped sutures seen).

13E Age 28

Saw all right at primary school, but he found at seven that sight was poor at secondary school, and had to sit in front. Left school at 14 in standard 7. Has been working as Fitter's labourer, but could not accept promotion on account of difficulty in reading instruments.
Has noticed no variation in sight.
Vision R. and L. 6/60. J8. Colours x.
Vision in dark 4/60. R. and L.
Fields full with 3 or 1mm spot. No central scotoma on Bjerum screen for white, and no variation in brightness of colour from periphery to centre (though colour not perceived as such). Colour fields were done later on Lister perimeter, and were found to be very full for red and green with 10mm spot, but 5mm spot presented no colour in any part of field. Acuity of vision in the periphery is normal as compared with two normal cases. Tested by recognisable separation of white spots 40° out. Slit lamp shows few corneal opacities, but no I.K. or K.P.
Discs grey with deep white cupping.
Remainder of fundus normal, but no yellow area at macula. Urine no albumin, and no sugar.
C.N.S. no abnormality. W.R. negative.
X Ray-normal sella. Blood count 4,983,000 reds - 6,800 whites. Differential count Polymorphs 52%, Lymphocytes 43%, Monouclears 4%, Eosinophilles 1%, no Punctate Basophilia.
Lumbar puncture no increased pressure. Fluid clear. White cells 10 per c.m.m. Protein 30mg%, no organisms. There was no hyperaemia of disc following puncture.

NOTE:- x denotes ability to see the colours of No. 12 of Ishihara test.

xx denotes ablity to see the No. 12, but no others.

FAMILY W

GENERATION (iii)

14E Age 26

Has never been able to recognise friends in the street for as long as she can remember. Sat in front row at school. Had to come out to see the board. Glasses no help. Sight has not varied.
Vision R. 3/60. J20.
Vision L. 3/60. J12. Colours x.
Fields full with 3mm/330. No central scotoma on Bjerum screen 5/1000. Colours not appreciated, but no difference in shade of colour in periphery or centre with 20/1000.
Fundus grey with deep white cupping extending up to temporal margin. Edge clear cut.
C.N.S. no abnormality. W.R. negative.
X Ray-sella within normal limits. Blood count: no abnormality. Slit lamp: No abnormality of cornea, iris or lens.
(Y shaped sutures show clearly).

15E Age 23

Always had poor sight. Had to sit in front at school.
Vision R. and L. 4/60. J12. Colours x.
Fields R. and L. slight peripheral contraction.
No central scotoma on Bjerum screen. Pupils react to light, but sluggishly on accommodation.
There is a paresis of the right external rectus.
He had diphtheria at the age of 7. Central nervous system presents no other abnormality.
W.R. negative. Blood count normal.
Discs grey nasal half, white temporal half, deep cupping. Vessels full.

GENERATION (iv)

11B Age 36

Vision R. and L. 6/6.
Reads J1 and all colours.
Fundi normal.

12B Age 32

Vision R. 6/6. J1. All colours.
Vision L. 6/36. J8. Few colours.
Fundus R. and L. normal.
No strabismus. L. eye hypermetropic.

13B Age 20

Vision R. and L. 6/6. J1. All colours.
Fundi normal.

1D

Supposed to have bad sight, but the family have been bombed out, and it has not been possible to trace them. 11D knows him, but cannot remember if he wore glasses. She thinks his children see well.

11D Age 27

Sight has always been bad. First noted at school. Left school in standard 7.
Vision R. 6/60. J12. Colours x.
Vision L. 4/60. J20. Colours -.

12D Age 19

Vision R. and L. 6/6. J1. All colours.
Fundi normal.

13D Age 32

Vision R. and L. 6/6. J1. All colours.
Fundi normal.

FAMILY W

GENERATION (iv)

14D	Age 28	Vision R. and L. 6/6. J1. All colours. Fundi normal.
15D	Age 11	Vision R. and L. 6/6. J1. All colours. Fundi normal.
1E	Age 34	Vision R. and L. 6/6. J1. All colours. Fundi normal.
4E	Age 33	Vision R. and L. 6/6. J1. Red green blind. Fundi normal.
5E	Age 32	Always had poor sight. First noted at school. Vision R. 6/60. J12. Colours -. Vision L. 4/60. J20. Colours -. Fields full. Discs white with cupping. Remainder of fundus normal except no yellow spot seen at macula. Vessels normal.
6E		Drowned at 7. Sight was good.
7E	Age 30	Vision R. and L. 6/6. J1. All colours. Fundi normal.
8E	Age 24	Always had poor sight. First noted at school. Enjoys reading novels. Vision R. and L. 6/24. J8. Colours x. Fields full. No central scotoma. Discs notably white, more so in temporal half.
9E	Age 19	Has always had poor sight. Vision R. and L. 6/36. J8. Colours xx. Fields full. No scotoma. Discs grey. No yellow spot at macula. Vessels normal.
16E	Age 22	Vision R. and L. 6/9. J1. Colours good. Fundus normal, but bother present very deep physiological cupping. (Striking physical resemblance to mother who has optic atrophy.
17E	Age 19	Vision R. and L. 6/6. J1. All colours. Fields very full with 3mm/330 white.

GENERATION (v)

16B	Age 3	Sight stated to be perfect. Disc R. and L. normal.
5D	Age 11	Vision R. and L. 6/6. J1. Red green blind.
1E	Age 4	Sight said to be good. Can see distant aeroplane. Fundi normal. Choroidal vessels visible in periphery.
2E	Age 2	Sight said to be good. Fundi no gross abnormality (undilated).

FAMILY W

GENERATION (v)

8E Age 12

Vision R. and L. 6/6. J1. All colours.
Fundi normal.

9E Age 10

Poor sight. First noted when she went to school, when she had to sit in front. Now can sit a little further back.
Vision R. and L. 6/24. J1. Colours x.
Disc R. grey with normal cupping.
Disc L. similar, with one spot of pigment near nasal margin.
Fields full for white. Fields for red and green 25° and 10° for blue on Bjerum screen at 1m. with 22mm spot. No central scotoma for white or colours.

10E Age 7

Poor sight. First noted when he went to school when he had to sit in front.
Iris brown (from healthy mother).
Vision R. and L. 6/36. J1.
Disc R. grey nasal half, deep cupping extending to temporal margin.
Disc L. grey and pale, with normal cupping.
Fields full for white. No central scotoma for white or colour.
Colour fields 30° for red and green 20° for blue on Bjerum screen at 1m with 22mm spot.
Reads the following Ishihara numbers:-

Correct 12.8.29.5.15.2.97.5.16.-.-.26.35.

R. 12.8. 2.-.15.-.18.-. -.-.-.26.35.

Correct 12.6.57.3.74.6.45.7.73.-.-.42.96.

L. 12.8.15.8.11.8. -.-. -.-.-.42.96.

11E Age 4

Sight said to be good.
Fundi R. and L. normal.

12E Age 7

Vision R. and L. 6/6. J1. All colours.
Fundi normal. Alternating strabismus.

13E Age 4

Normal fundi.

14E Age 12

Vision R. + 5.00/+ 1.00 at 120. 6/12. J2.
Vision L. + 5.00/+ 1.00 at 120. 6/6. J1.
Colour vision R. and L. normal.
Fundus R. and L. normal.

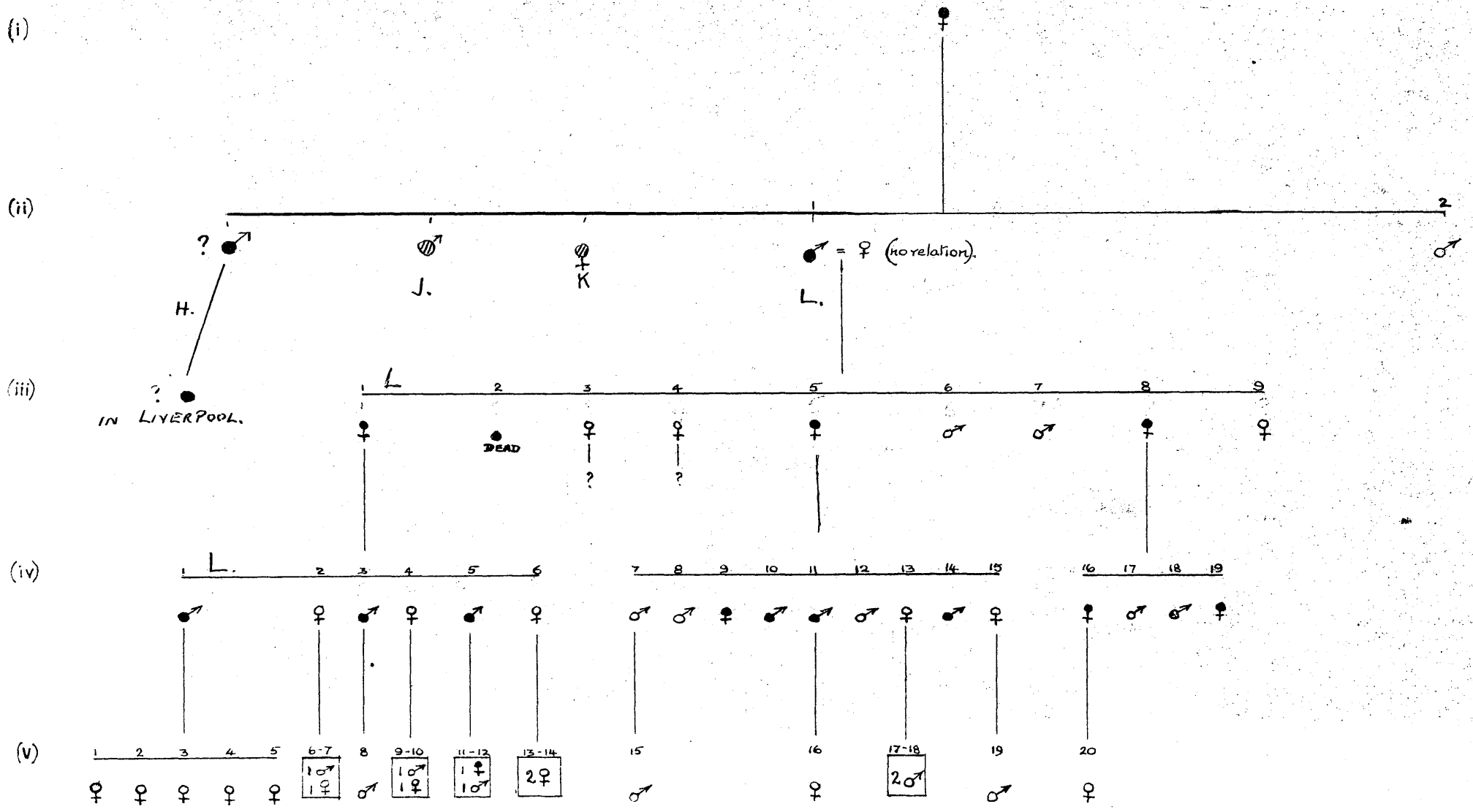
15E Age 10

Vision R. and L. 6/6. J1. All colours.
Fundi normal.

16E Age 19/12

Can see aeroplane. There is no nystagmus.
Disc R. very deep cupping. Temporal half on disc is pale, but within normal limits.
Fundus L. normal. (Examined under atropine).

FAMILY X.


(i)
(ii)
(iii)
(iv)
(v)
?
H.
?
IN LIVERPOOL.
J.
K
L.
= ♀ (no relation).
2
L
1 2 3 4 5 6 7 8 9
DEAD
?
?
L.
1 2 3 4 5 6
7 8 9 10 11 12 13 14 15
16 17 18 19
1 2 3 4 5
6-7
1♂ 1♀
8
9-10
1♂ 1♀
11-12
1♀ 1♂
13-14
2♀
15
16
17-18
2♂
19
20

FAMILY X

I am indebted to i) L of Generation (iii) (aged 74) for most of my information about generations (i) and (ii). Mrs. i) L states that her father and two uncles always had poor sight, and also her aunt.

They all inherited it from her grandmother, whom she thinks was a sister or cousin of i) generation (i) of family W.

As no one can confirm this, they have been treated as separate families.

She states that branch H of the family have many cases of "The bad sight", but can give no details, and has lost touch with them.

She can give no information about branches J and K.

I have later managed to trace the youngest son of K, who tells me that his mother's sight was good, and that none of his seven brothers or two sisters had poor sight, although he knows it runs in the family. His grandmother married twice, and he thinks she was related to family W.

FAMILY X

GENERATION 3 (L)

1 Age 74 Vision R. and L. 4/60. J20. Colours nil. Discs R. and L. white. No pigment changes. Vessels normal. Fields full. No central scotoma.

5 Age 61 Vision R. and L. 2/60. Less than J20. Colours nil.
Disc white with deep cupping. No change in vessels. Fields tested by hand, possibly contracted, but there is lack of concentration. Sight has not altered.

?8 9 Age 50 Always had poor sight. Passes husband in street, but can get around on her own.
Vision R. and L. 4/60. J20. No colours.
Discs white with deep cupping extending to temporal border. Fields full with 3mm spot/330. No scotoma on Bjerum screen with 5mm spot at 1000. Cannot see smaller spot.

GENERATION 4

1 Age ? Has always had bad sight. Was told by Specialist that nerve was dead and that no-one could help him. He declined to be examined.

3 Age 40 Vision R. and L. 6/60. J12. No colours.
Disc atrophic with deep cup. Fields full.
No scotoma.

9 Age 34 Sight always bad. Sat in front at school, but had to ask the others what was on the board. Thinks sight is worse in last five years, e.g. cannot see to read so well; she used to be able to recognise her friends in the street, but cannot do so now.
Vision R. and L. 5/60. J20. Colours nil.
Disc very atrophic. Deep cup extends to temporal margin, and well over to nasal margin, which is grey. The arterioles crossing the nasal margin do not dip. Vessels normal.
Fields full. No scotoma.

11 Age 29 Sight has always been poor. Has not altered.
Vision R. and L. 3/60. J12. Colours x.
Fundus R. and L. as illustrated (Page).
Slit lamp examination. Cornea clear. No I.K. Iris normal. No pupillary membrane.
Lens clear. Y sutures clearly seen.
Vitreous, no abnormality. Fields as illustrated (Page). Blood count normal. W.R. negative.
C.N.S. No abnormality. C.S.F. Clear fluid, no increased pressure. Cells 5 per c.m.m. protein 20 m.g.m., chlorides 780 m.g.m., no organisms W.R. negative. Lange oooooooooo.
No hyperaemia of disc after lumbar puncture.
When testing visual acuity at 3 m., the light was gradually diminished until the patient could just see the top letter. In these darkened conditions two normal persons could see no better. On increasing the light, the patient only could see no better, i.e. He can see as well in dark as in light.

FAMILY X

13L Age 24 Vision R. and L. 6/6. J1. All colours.
Fundus R. and L. deep physiological cupping.
Very marked in left fundus.

14L Age 23 Sight has always been bad.
Vision R. and L. 3/60. Less than J20.
No colours. Field full. No central scotoma. Disc white with cupping.
Vessels normal.

15L Age 21 Vision R. and L. 6/6. J1. All colours.
Fundi normal.

16L Age 24 Has always had poor sight. First noted when she went to primary school from the age of 5 to 11. She was then sent to blind school in case her sight should get worse. She is the only member in the three families who went to blind school. Her sight has never varied.
Vision R. and L. 6/60. J12. No colours.
Discs R. and L. white with deep cupping. No other abnormality. Fields very full with 3mm spot. No central scotoma on Bjerum screen.

17L Joined Army as A1. Sight presumed to be good.

18L Age 18 Has always had good sight and has noticed no change whatsoever in either eye.
Vision R. and L. 6/6. J1. Colours practically all correct.
Fundus R. striking pallor of temporal half of disc with cupping.
Fundus L. normal disc.

19L Age 13 Began school at 4. She happened to be seated near the board, and had no difficulty in seeing the letters until she moved to the "Big" school at the age of 12 (in September, 1940). She then found she could not see the board, but had previously noticed that her sight had begun to fail in the last two years since February, 1939, when she was 10. Her periods began in April, 1940. On enquiry, it was found that she had annual tests at school, and she stated that she could read to the foot of the card until June, 1940, when she could only see the top three rows; also, she used to be able to recognise friends in the street, but about two years ago noticed she could not see their faces until they were close. On being asked if she had noticed anything else, replied "I used to be able to see the colour of my friends' dresses further off than I can do now".
Vision R. and L. 6/24. J2. Colours as follows:-

orrect 12.8.6.29.57.5.3.15.74.2.6.97. 45.5.7.16.73.-.-. -.-.26.42.35.96.

. 12.8.6.28.57.5.3.15.97. 8.6.87.46.3.4.16.23.5.-.46.-.26.46.35.90.

. 12.8.5.29.57.5.8.46.97.13.6.67.48.6.7.46.-.-.-. 46.-.76. -.46. -.

Discs: pale temporal half, grey nasal half, with normal cupping. Vessels normal. Fields full with 3mm spot. No central scotoma on Bjerum screen.
Central nervous system, no abnormality.

FAMILY X

GENERATION 5

1L Age 20 Vision R. and L. $^{6}/_{6}$. J1. All colours. Fundi normal.

3L Age 16 Vision R. and L. $^{6}/_{6}$. J1. All colours. Fundi normal.

4L Age 14 Vision R. and L. $^{6}/_{6}$. J1. All colours. Fundi normal. Other two sisters have perfect vision.

8L Age 4 Appears to have good vision. Roughly $^{6}/_{12}$. Discs pale, but within normal limits.

11L Age 8 Vision R. and L. $^{6}/_{60}$. J12. Nearly all numbers.
Fundus R. and L. bluey white temporal half of disc, nasal half grey. Normal cupping.

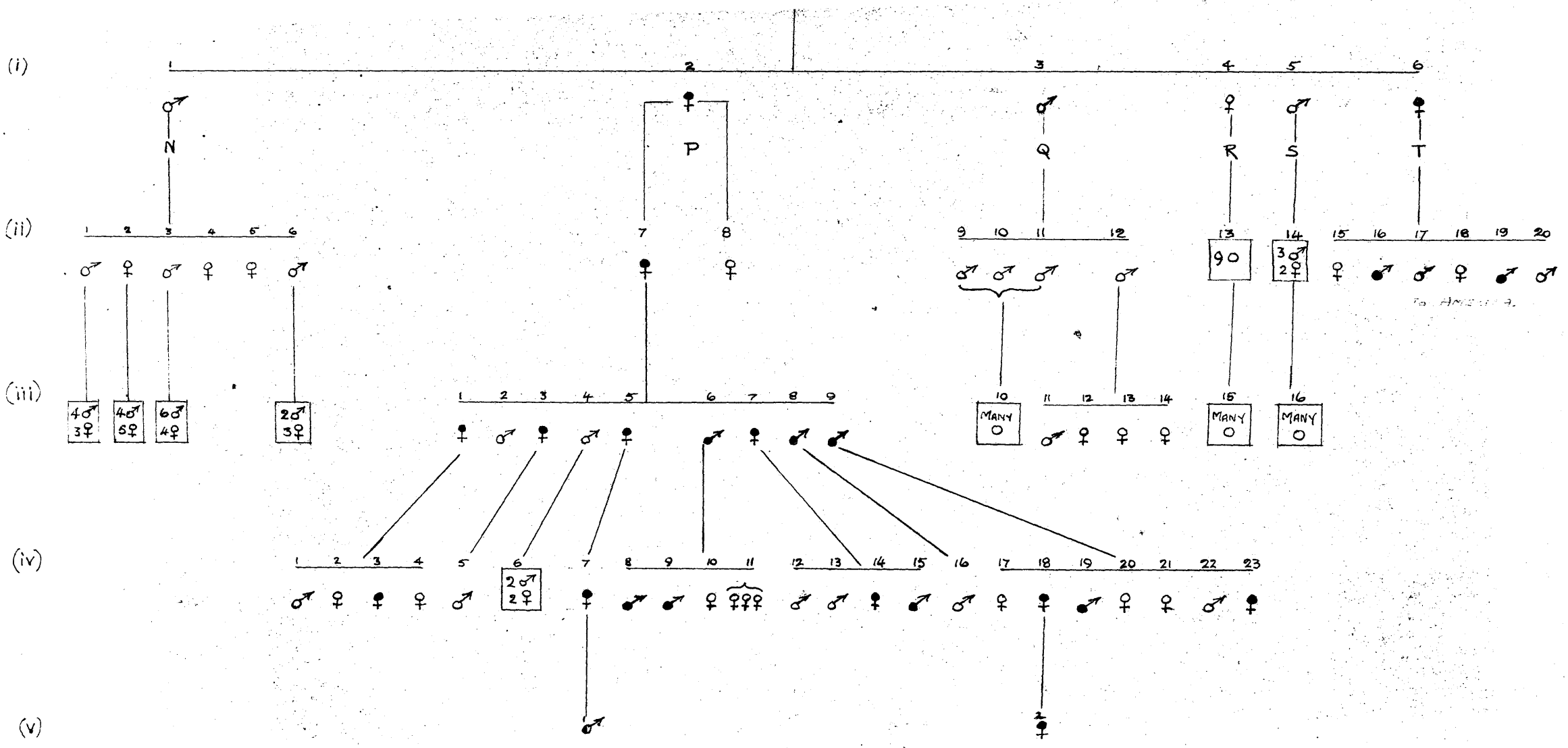
16L Age 4 Fundi examined under atropine.
Disc normal. Fundus ~~re~~presents few scattered spots of pigment.
Disc L. pale, but within normal limits. No marked cupping. No bluish appearance.

17L Age $2\frac{1}{2}$ Appears to see well.
Fundi could not be seen.

18L Age $^{4}/_{12}$ Can follow a light. No nystagmus.

19L Age $^{9}/_{12}$ Can recognise mother 300 yards away.

20L Age $1\ ^{1}/_{12}$ Fundi examined under atropine.
Discs normal. Few scattered spots of pigment in periphery of fundus.


(i)
(ii)
(iii)
(iv)
(v)
N
P
Q
R
S
T
4♂ 3♀
4♂ 5♀
6♂ 4♀
2♂ 3♀
90
3♂ 2♀
MANY
MANY
MANY
2♂ 2♀

FAMILY Y

I am indebted to Mrs. W. (5N. of Generation (ii) (Age 78) for most of my information about the earlier generations of this family.

Much of her information has been corroborated by Mr. W. the father of 7P, Generation (iv) who was in the same class as 19T. Generation (ii), and remembers the latter having to sit in front at school. Mr. W. married 5P, Generation (iii), and remembers her relations well.

Mrs. W (5N) remembers her grandfather very slightly, but has heard her father speak of the former's poor sight, and that he could not get glasses to help him.

She remembers her aunts (2 and 6 of Generation (i) who both always had poor sight.

Her own branch of the family has no eye trouble, and she has heard of none in branches Q. R. and S., where there are by now many relations.

13Q. of Generation (iii) was able to confirm this, but was unable to say how many first and second cousins she had.

Branch T. all went to America and have sent no news.

FAMILY Y

GENERATION (iii)

P8 Age 65 — Always had poor sight, which ran in the family, and came from his mother's side.
Vision R. 3/60. J20. Colours+.
Vision L. 2/60. Less than J20. Colours -.
Fundus R. atrophy of disc with cup. Vessels normal.
Fundus L. cannot be clearly seen owing to lens changes.

P9 — Died at 40 of peritonitis. Married 6D, Generation (iii) of family W. His brother (P8) states that P9 always had bad sight, and his wife knows that he could get no glasses to help him.

Q13 Age 46 — Sight has always been good, and states there is no bad sight on her side of the family. Her cousins have all good sight.

GENERATION (iv)

7P — Bad sight noticed when she went to school about 4. She was able to see when seated in front at primary school, but was unable to see the board at secondary school where the boards are higher and not so well illuminated. She can see better outside than most at night. Thinks sight is somewhat worse in last three years. She finds she cannot read her piano music, although she always had to look very closely. She taught for a few years at school, but was unable to read the children's writing.
Vision R. and L. 6/60. J6. Colours++.
Discs atrophic with deep cup. Vessels normal.

18P Age 30 — Always had poor sight.
Vision R. 6/60. J20. Colours -.
Vision L. 6/36. J12. Colours x.
Disc R. and L. white with normal cup. Vessels normal. Fields full. No scotoma.

20P Age 22 — Vision R. and L. 6/6. J1. All colours.
Fundi normal.

23P Age 17 — Always had poor sight. First noted at school.
Vision R. and L. 6/60. J12. Colours x.
Disc white with deep cup, more marked on temporal side.
There is a spot of pigment on left disc.
Fields full. No scotoma.

GENERATION (v)

1P Age 4 — Tested by his mother. Can see father at 300 yards. Sight supposed to be good.
Fundus R. very deep cup and pallor of temporal disc margin. The nasal half is a healthy pink. Appearance is frankly suspicious.
Fundus L. normal.

FAMILY Y

GENERATION (v)

2P

Happy healthy child, full of vitality.
Mother is sure her sight is good.
Disc - blue white R. and L. more marked in temporal half.
An attempt was made to test vision and colours. Both appear to be less than normal, but she can recognise her mother in the distance.

SUMMARY OF AUTHOR'S CASES

The cases have been summarised under the following headings:-

1) Mode of inheritance

2) Sex Incidence

3) Age of Onset

4) Signs and Symptoms

5) Fields of Vision

6) Ophthalmoscopic Appearance

7) Association with other disabilities

MODE OF INHERITANCE IN AUTHOR'S CASES

1) In every case the inheritance is direct from an affected father or an affected mother.

The following table illustrates this point in the three families:-

	Inheritance from	
	Male	Female
Family W	17	4
" X	5	10
" Y	7	15
TOTAL	29	29

The atrophy was inherited from a male in 29 cases, and from a female in 29 cases.

In no case did atrophy develop from an unaffected parent.

As can be seen from the table illustrating sex incidence, 32 males and 27 females are affected. This total of 59 affected cases compares with 73 unaffected cases from the affected parents.

It is presumptive that the mode of inheritance is a simple dominant, affecting males and females equally, and affecting 50% of the children of an affected parent.

In the three families, almost without exception, the colour of the iris is blue. It was wondered if the introduction of a brown iris from a healthy parent would affect the transmission. This is not so. Case 10E, Generation (v) inherits brown irides from his healthy mother, but inherits optic atrophy from his father who has blue eyes. It was also wondered if inheriting a strong family resemblance would carry the taint, but 16E, Generation (iv), is a typical member of family "W", has healthy eyes.

Cases 4E and 6E, Generation (iii), are identical in appearance, but one has optic atrophy.

2) Sex Incidence

The following table illustrates the sex incidence in the three families:-

	Affected		Unaffected	
	Males	Females	Males	Females
Family W	14	6	15	10
" X	8	8	8	15
" Y	10	13	13	12
	32	27	36	37

Of the total affected 32 were males and 27 females. The total of affected cases is 59, and the total of unaffected cases is 73.

3) Age of Onset

In view of the facts (1) that poor sight is not detected until school years, (2) that there is no nystagmus, and (3) that the youngest observed case was aged 4, it is concluded that atrophy begins between 3 months and 4 years of age, or probably about 3.

4) Signs and Symptoms

(a) History

The history in the large majority of cases is that defect of vision is usually noticed when the patient goes to school. This is despite the fact that affected mothers have been in the habit of testing their childrens' vision, e.g. by noticing at what distance they can see the home-coming father.

There is one case in Generation (v) aged 4 with marked atrophy of the discs, but whose mother thinks she has perfect sight. In a few cases the patient recollects being unable to see her friends in the street before going to school, but this history is uncertain.

In some cases the defect was not noticed until the patient went to the secondary school at about the age of 7, sight having been good enough at primary school. Quite a number of the patients state that they see better at night, and the majority say they can see as well as normal people at night. Few casesgive a history of improvement or of diminution in vision.

Considering the table of visions in the three generations, it would appear that there is a gradual deterioration of reading and colour vision, and to a lesser extent of distant vision up to the age of 10: after that, there is no progress.

4 (b) Onset

It is not possible to say whether the onset comes in one eye before the other, but considering the exceptional similarity of vision in the right as compared with the left eye, it is presumed that the onset in both eyes is equal. In a few cases, the atrophy of the disc is more marked in the right eye, but vision is not correspondingly worse.

4 (c) Corrected visual acuity for distance and near

A large majority of the cases are emmetropic or + 1.00D hypermetropia. The visual acuity for the three generations is recorded in a separate table, but can be summarised thus:-

		Average vision of Generation		
	Age	Distance	Near	Colour
Generation (iii)	50 - 74	$\frac{3}{60}$	J20	6% x
" (iv)	13 - 40	$\frac{6}{60}$	J12	50% x
" (v)	4 - 12	$\frac{6}{36}$	J8	100% x

(x denotes ability to distinguish red and blue of Ishihara No. 12)

Generation (iii)

Case No.	5D		1E		3E		6E		1L		5L		8L		8P	
	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
Snellen Type	3/60	3/60	4/60	@	5/60	5/60	2/60	2/60	4/60	4/60	2/60	2/60	4/60	4/60	3/60	2/60 @
Jaeger Type	20	20	20	-	12	12	-	-	20	20	20	20	20	20	20	-
Colour	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x	-
Age	58		68		64		60		74		61		50		65	

TABLE OF VISUAL ACUITY OF ALL AFFECTED CASES.

Generation (iv)

Case No.	11D		5E		8E		9E		12E		13E		14E		15E		3L		9L		11L		14L		16L		19L		7P		18P		23P	
	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
Snellen Type	6/60	4/60	6/60	6/60	6/24	6/26	6/36	6/36	3/60	3/60	6/60	6/60	3/60	3/60	6/60	6/60	6/60	6/60	5/60	5/60	3/60	3/60	3/60	3/60	6/60	6/60	6/24	6/24	6/60	6/60	6/60	6/36	6/60	6/60
Jaeger Type	12	20	12	20	8	8	8	8	-	-	8	8	20	12	12	12	12	12	20	20	12	12	-	-	12	12	4	4	6	4	20	12	12	12
Colour	x	-	-	-	x	x	x x	x x	x	x	x	x	x	x	x	x	-	-	-	-	x	x	-	-	-	-	xx xx	xx xx	xx	xx	-	x	x	x
Age	27		32		24		19		31		28		26		23		40		34		29		22		24		13		32		30		17	

Generation (v)

Case No.	14D		9E		10E		11K	
	R.	L.	R.	L.	R.	L.	R.	L.
Snellen Type	6/24	6/24	6/24	6/24	6/36	6/36	6/60	6/60
Jaeger Type	?	?	2	2	1	1	12	12
Colour	x	x	x	x	x x x x x x x x	x x x x x x x x	x x x x	x x x x
Age	4		12		7		8	

NOTE:- @ = cataract

The signs used in denoting colour vision are explained:-

- \- = No colours
- x = Red and blue of (12) but can see no numbers
- xx = (12) but no other numbers
- xxx = (12) and some others
- xxxx = Nearly all numbers
- xxxxx = All numbers

Page 34a

It will be seen that the distant vision varies only slightly between cases aged 4 and cases aged 74. The reading vision shows a gradual change, but it is noticeable that the younger children can see remarkably well, and that there is a little variation from 20 - 60 years. It is when we come to colour tests that the most notable differences are seen. Practically none of Generation (iii) can see any colours, but some in Generation (v) have ~~practically~~ normal colour vision, and all can distinguish bright colours with ease.

The colour test used throughout was that of the coloured numbers devised by Ishihara. The No. 12, composed of red dots on a bright blue background, presented difficulty to most. If the patient could distinguish no colours, he was marked -. If he could distinguish red and blue, but no number, he was marked x. If he could read No. 12, he was marked xx. If he could see a few of the following numbers he was marked xxx. Most numbers xxxx. All numbers xxxxx.

It was noteworthy that no case saw the "Blank" numbers, designed to be seen by the colour-blind.

Two of the normal cases were found to be red green colour blind, but the remainder had perfect colour vision.

Vision in the Dark

4 cases were tested in a very poor light, and could see nearly as well as in bright daylight.

4 (d) Pupil Reflexes

In all cases, except one who has had diphtheria, pupils are circular and equal: they react briskly to light and on accommodation. Consensual reflex is present. There is no hippus. In no case is nystagmus found. The range of eye movements is full and normal.

5) Fields of Vision

In all cases fields for white are full, and no central or paracentral scotoma is found. Some of the patients have difficulty in seeing a 1mm spot at 330mm, but all are able to see a 3mm spot. In one case, no difficulty was found with 1mm spot. The field was full and no scotoma was found.

When looking for central scotoma on Bjerum screen at a distance of 1m, a 5mm spot was used, as some patients had difficulty in seeing the 3mm spot. No scotoma could be established with a 3mm spot, or with a 5mm spot. The fields for colours were difficult to take owing to the poor colour vision. A red 22mm spot on the Lister perimeter was not visible as a colour to many.

One case (11L) shows marked contraction of colour fields, but no central scotoma for colours.

Another case (13E) has remarkable full colour fields, with no scotoma.

In the latter case, the smallest coloured spot visible was 10mm. No colour could be detected with the 5mm spot.

These fields have been charted (Page 14.).

In cases where colours could not be appreciated there was no variation in brightness as the spot was moved from the periphery to the centre.

It was endeavoured to ascertain whether visual acuity in the periphery was affected; a 5mm spot was fixed at 40° on the Lister perimeter while the patient looked at a small central fixation object. A movable 3mm spot was then moved in from the periphery until the two objects could no longer be appreciated as separate. This was compared with two normal people and found to be the same, namely spots separate at 45° (and at 55°) from spot at 40° on same meridian. No difference noted on nasal and temporal sides.

6) Ophthalmoscopic Appearance

The disc is white, and the margins are clear cut. In most cases it is deeply cupped.

Of the 32 affected cases, 29 present deep cupping, the remaining 3 present no cupping. Apart from this, all discs are very similar, and present bluish white pallor of the temporal half, and a greyness of the nasal half. The cupping extends in a varying degree towards the temporal margin. The vessels are normal in all cases, and only exceptionally is there any pigmentation or other abnormality in the periphery of the fundus.

The macula was carefully examined in all cases, and the usual light reflex was present, but in no case is there a distinct yellow area. The youngest patient seen presenting atrophy was aged 4. The oldest patient was 74. The two discs were markedly similar. There is no sign of neuritis in any case. Two cases seen at 4 are no exception, and another case seen at 4 presents a suspicious pallor of the temporal half of the disc, but no sign of neuritis.

7) Association with other disabilities

There is no such association.

COMPARISON OF PUBLISHED AND AUTHOR'S CASES

1) Inheritance

Each series suggests a simple dominant mode of transmission.

2) Sex Incidence

Each series shows approximately 50% affected.

3) Age of Onset

Each series shows onset before 5 years of age.

4) Signs and Symptoms

In no case is there a definite history of onset being noticed, and the general history is that sight has always been bad. The pupil reflexes are present. The affection appears to be stationary.

5) Fields of Vision

In the published cases fields vary. 18 out of 49 cases present considerable contraction in the periphery, and only 4 cases out of 49 present central scotoma or paracentral scotoma. One family presents hemianopic colour fields in some cases.

In the Author's cases, fields were full in every case. There was no central scotoma for white or colour.

6) Ophthalmoscopic Appearance

In each series the disc is pale, more marked on the temporal side, with few, if any, changes in the fundus.

In the Published cases, many show contraction of the vessels.

In the Author's cases, the vessels are normal.

It is concluded that the two series of cases are examples of the same disease, namely that of dominant hereditary optic atrophy of early onset affecting males and females equally, and presenting a full field of vision in the majority of cases, and only exceptionally central scotoma. The fundus shows an atrophic disc with deep cupping extending to temporal side, with no other change, except narrowing of the vessels in some cases.

COMPARISON OF PUBLISHED AND AUTHOR'S CASES

When the figures for the two series are put together, the following figures are obtained:-

	Affected		Unaffected	
	Males	Females	Males	Females
Published cases	31	27	25	18
Author's cases	32	27	36	37
	63	54	61	55
TOTAL	117		116	

This shows 63 males and 54 females affected, and a total of 117 affected and 116 unaffected.

The transmission was from an affected male in 43 cases, and from an affected female in 39 cases.

This substantiates the conclusion that both series are examples of a simple dominant hereditary optic atrophy (of early onset.)

It has been noted that Rifat's case (and possibly Snell's case) is one of recessive hereditary optic atrophy of early onset.

It is therefore concluded that hereditary optic atrophy of early onset can follow a dominant or a recessive mode of transmission.

There is also an example in Knapp's case of a recessive type changing over to a dominant type.

A further example is given by Alsberg (Ped. 903 Bell).

It is possible that Griscom's case exemplifies dominant pedigree changing to a recessive type.

LEBER'S DISEASE

Leber (12.) summarises his cases thus:-

> "A blurring of vision occurs fairly suddenly in the form of a mist. The mist thickens over a period of days or weeks until a serious impairment of central vision results. The maximum damage is usually done within several months, and progress to blindness is unusual.
>
> The common finding is retention of peripheral vision and loss of central vision with absolute central scotoma. The patient can see better at night.
>
> The ophthalmoscopic appearance is similar to that in a case of retro-bulbar neuritis with blurring of disc margin and slight hyperaemia.
>
> Vessels are normal at first and show white streaks or exudates. The later stage shows pallor of the temporal half of the disc, with moderate narrowing of vessels."

He concludes that the disease is of the same group as retro-bulbar neuritis.

Regarding transmission, he shows that it is inherited chiefly by males about 20 from an unaffected mother, but recognises from the writings of others that a dominant transmission may occur.

From a study of Leber's disease, as described by Habershon (13) Nettleship (14) Duke Elder (15) and Julia Bell (16) it appears that little has been added to Leber's original description.

Bell has analysed 1182 cases and it is proposed to draw from her researches, and to consider Leber's disease under the following headings:-

1) Hereditary character and mode of transmission

2) Sex incidence

3) Age of onset

4) Signs and Symptons

5) Fields of Vision

6) Ophthalmoscopic Appearance

7) Association with other disabilities

1) Hereditary character and mode of transmission

Leber's disease is stated to be a sex linked and a recessive hereditary disease, affecting males of 20 without associated constitutional disturbances.

LEBER'S DISEASE

The affection is passed on from a female to 95% cases of males, and to 84% cases of females in European pedigrees (Bell). (In Japanese cases the figures are 87% of males and 92% of females). Of 545 affected males, the mother was unaffected in 85.2% cases (Bell).

Thus the general rule that affection is passed on from an unaffected mother to a son holds, but one cannot study the pedigrees published by Bell without being struck by the occurrence of pedigrees of dominant transmission, where the affection is directly passed on from affected males and females to sons and daughters.

Seven such pedigrees are listed below, but apart from the dominant hereditary, they present the usual features of Leber's disease, viz. onset about 20 with rapid failure of central vision resulting in central scotoma.

The following examples are taken from Julia Bell:-

No. of Pedigree	Author	No. of generations of direct transmission	Onset About	Affected		Unaffected Both Sexes	Inherited from	
				Male	Female		Male	Female
776	Rampoldi	4	37	4	3	3	2	4
828	Sentre	3	35	5	5	6	-	9
832	Strzeminski	3	25	5	2	2	-	6
916	Yo Kansyo	4	28	10	2	20	8	3
922	Inouyi	3	14	2	5	1	-	6
926	Fuzii	3	22	3	5	2	-	7
929	Fusuhira	3	Not given	2	3	3	-	4
				31	25	37	10	39

Total affected 56. 31 male, 25 female.

Total unaffected 37.

The inheritance was from affected males in 10 cases and from affected females in 39.

There are other examples where the transmission is dominant for three generations, and then becomes recessive, e.g. pedigree 750 and 881 Bell; In pedigree 911 many examples of dominant and recessive hereditary are met with in the same family. It would thus appear necessary to divide optic atrophy into dominant and recessive types, and to recognise that one type may change over to the other.

Another example of change in transmission has already been noted in Knapp's case (2).

2) Sex Incidence

Reviewing 1182 cases, Bell gives the following figures:-

	Affected Males	Affected Females	Male sex Incidence %
European cases	863	155	84.8
Japanese "	97	67	59.1

3) Age of Onset

The average age of onset agrees with Leber's original description of 20, and Bell finds the Japanese cases coming on earlier; but many cases have been reported of a much later onset.

		Number	Mean Age	Standard Deviation
European -	Males	669	23.23	9.98
	Females	113	25.15	13.27
Japanese -	Males	74	21.30	8.53
	Females	48	20.50	7.82

It was wondered if the earlier mean age of the Japanese cases was due to the inclusion of a number of cases of early onset, but this is not so; only one case shows onset before 8 years of age in the 122 Japanese cases.

Usher (17) quotes two cases of very early onset in two pedigrees of Leber's disease, where the age of onset in the other cases is about 20.

4) Signs and Symptons

The patient may notice a sudden or gradual blurring of vision coming on in one eye, which progresses in a few days or weeks to a serious loss of central vision. It is generally followed within a few days or weeks by a similar onset in the other eye. There is seldom any further progress after 6 months. Nettleship mentions 25 cases of recovery out of 16 genealogies and has reported such a case fully .

Bell quotes 29% of cases among males as showing improvement. She considers the majority of cases reach maximum disability within two months from the time of awareness of failing vision, and that it is relatively rare for symptoms to advance after six months.

Nettleship advises an optimistic outlook in cases seen within 2 years of the onset.

5) Fields of Vision

A central scotoma is present, according to Bell in 88% of 270 males, and in 82% of 50 females. There is a slight contraction of the peripheral field in 42% cases in 212 males and 62% in 50 females. There is no case of hemianopia or of quadrantic defect.

6) Ophthalmoscopic Appearance

In the initial stages there may be no abnormal appearance, but there is usually some slight haziness of the disc, and in many cases, a definite papillitis, but rarely haemorrhages. The vessels may be normal or slightly congested. This stage is followed in some months by a gradual pallor of the temporal half of the disc with some narrowing of the vessels.

LEBER'S DISEASE

Signs of inflammation are so common that a toxic cause has been supposed. Bell can find no history to support this, and suggests that the signs are due to an increased circulation in an attempt to aid a failing function.

The pathological report of Rehsteiner (19.) supports this view. He finds no evidence of inflammation, but a definite overgrowth of neuroglia.

The pallor of the disc has been observed to increase in later years, to affect the whole disc, and to narrow the arteries. Although the sight improves, the pallor of the disc does not alter.

7) Leber's found his cases to be of the neuropathic type, suffering from headache, vertigo, and epilepsy.

Nettleship has found an occasional association with epilepsy, but there is no later evidence to suggest that cases of Leber's disease are more prone to such afflictions than other people.

POINTS OF DIFFERENCE BETWEEN AUTHOR'S AND LEBER'S CASES

	Author's Cases	Leber's Cases
Inheritance	Simple dominant	Recessive and sex linked
Sex Incidence	Male and Female equal	Male 6 to Female 1
Age of Onset	3	20
Signs and Symptoms	Gradual un-noticed onset No progress	Sudden onset forcibly noticed Some improvement
Fields of Vision	Full Scotoma uncommon	Full Scotoma common
Ophthalmoscopic Appearance	Disc pale Edges clear cut Vessels normal	Disc congested Edges blurred Vessels narrowed
Association with other disabilities	Nil	Nervous type

COMPARISON OF AUTHOR'S CASES WITH LEBER'S DISEASE

1) Mode of transmission is dominant in the Author's cases, but Rifat has published pedigree of recessive transmission in which the affected individuals correspond with the Author's cases.

Leber's cases are recessive, but many examples of dominant transmission are known. Thus the method of inheritance cannot be used to distinguish the two.

2) Sex Incidence varies with the mode of inheritance; It is nearly equal in dominant inheritance, whether of late or early onset.

In the recessive type, the atrophy affects males predominantly in Leber's disease.

In Rifat's case, the numbers are too small from which to draw any conclusions regarding the sex incidence in recessive atrophy of early onset.

3) Age of Onset

The age of onset is a striking difference between the two. Yet age is not a distinguishing factor in either the Author's cases or in Leber's disease. For example, many of the published cases of early onset can be presumed congenital, and in the Author's series the age of onset is 3, but one case developed at 10. In some pedigrees of Leber's disease the onset is in early childhood, for example, Usher's cases (11) and pedigree (913) quoted by Bell, gives the ages of onset in 6 cases out of 9 affected, as between 7 and 14.

Nettleship (14) quotes a family of 6 cases with onset between 8 and 12 (Case 116). (reported by Batten)

Further, Bell quotes 152 cases with age of onset between 28 and 39, and 39 cases between 40 and 51.

The oldest recorded case had onset at 67.

It is also noticeable that the age of onset among European women is roughly equal in all age groups (Bell). It is among the males that the great increase in number about 20 is found.

Therefore, age groups alone cannot be used as a means of classifying such atrophies.

4) Signs and Symptoms

In cases of early onset, the patients are born with poor sight, or are too young to be aware of the change.

In Leber's cases, the onset is sometimes dramatic, but it may be that sight in one eye has been failing slowly for some weeks or months, and that attention is only drawn to it when the other eye fails.

COMPARISON OF AUTHOR'S CASES WITH LEBER'S DISEASE

5) Fields of Vision

Vary in both series.

In the Author's cases, no scotoma was found, but this is not uncommon in Leber's disease (12% had no central scotoma).

In the published cases of early onset, peripheral contraction, paracentral scotoma and hemianopia for colour have been mentioned, but are not constant features.

It is not unreasonable to suppose that fields do vary with the extent of the atrophy and with any special bundles affected.

6) Ophthalmoscopic Appearances are different in the two series, and this may be because the early cases are due to an abiotic atrophy, and Leber's cases to a retro-bulbar neuritis; or it may be, as Bell has suggested, that the signs of neuritis are simulated by a hyperaemia to aid a failing function. In a number of cases of Leber's disease, no hyperaemia is present. From my own experience, the disc changes are not in proportion to the visual disturbance involved.

7) Association with other disabilities

There is not sufficient evidence to prove that cases of Leber's disease are more prone to headache etc. than other people.

CONCLUSION

At first sight, cases of early onset seem to differ markedly from Leber's disease, but if it is agreed that Leber's disease can have a dominant transmission, and if it is considered that the example given by Rifat is a case of recessive hereditary optic atrophy of early onset, and if the ophthalmoscopic appearances are due to a different reaction to a similar process of atrophy, then the only distinction is that of age of onset, and as has been pointed out, this is not sufficient in itself to separate two groups into a different classification.

CONSIDERATION OF CAUSES

The following have been suggested as causes of hereditary optic atrophy:-

1) Toxic

2) Pituitary

3) Abiotic Atrophy

1) Toxic Causes

One would expect a history of the effects of such a toxin in a number of the cases. Bell has been unable to find it, but has found that some patients have been particularly well at the time of onset.

Such investigations as have been done, do not reveal any toxic influence.

In the Author's series, colour vision was the last visual sense to be affected.

In cases of retro-bulbar neuritis, colour is the first to go, and the last to recover.

2) A Pituitary Cause has been suggested by Fisher (20) who postulates that "A tempory disturbance of the pituitary of moderate degree" might explain the onset of hereditary optic atrophy.

In a series of X Rays of the sella in 60 cases of Leber's disease, enlargement has been found in ~~the~~ 14 cases. One can imagine that this theory would have much to commend it if all cases began about puberty, but when it is realised that hereditary optic atrophy commences at any age from birth to 74, the theory loses its chief point.

The fact that hemianopia has only been reported in one series of 9 cases (7) is also against a pituitary cause.

3) Abiotic Atrophy, as suggested by Collins (21) who quotes Gowers theory of a failure from imperfect vitality, seems a more probable cause than the other two.

Collins considers that there is a tendency to atrophy in families of Leber's disease, but that a predisposing factor is necessary to produce the disease.

One argument against the validity of this theory is that an abiotic atrophy would show no signs of recovery. This argument can be met with the supposition that, while one part of the damage is caused by impaired conductivity due to the reactive hyperaemia and congestion, and by the reactive overgrowth of neuroglial tissue, the other part of the damage is due to the atrophy.

When the two former effects have diminished, the release of pressure will remove part of the disability. Cases of complete recovery could be explained by assuming that there is a reserve of tissue in the optic nerve, and that part of the nerve can be destroyed without impairing the ultimate function of the whole.

CONSIDERATION OF CAUSES

Case 18L (in the Author's series,) who had an unmistakable pallor of the temporal half of the right disc, gave no history of any defect of vision, and could read 6/6 and J1.

It is considered that he had an atrophy of some nerve fibres which has not impaired the ultimate function of the whole.

The only pathological report is contributed by Rehsteiner and quoted by Bell.

The examination was done seven years after the disease was manifest. The findings are as follows:-

1) Ganglion tissue and nerve tissue of retina atrophied.

2) The atrophy in the optic nerve affects only certain bundles and leaves other bundles healthy.
In the affected bundles, there is an overgrowth of glial fibres.

3) The main atrophy follows the course of the papillo macula bundle, but involves other bundles as well.

4) No signs of inflammation present, but it is pointed out they might have disappeared.

5) A comparison was made with a non-inflammatory degeneration of the optic nerve, and the two cases showed a strong similarity.

Rehsteiner concludes that the atrophy in Leber's disease is not secondary to an inflammation

It is concluded that the most probable cause of hereditary optic atrophy is abiotic atrophy. It is postulated that there is less reaction to atrophy commencing in childhood, than to atrophy commencing in adolescence, and that this degree of reaction is the chief difference between atrophies of early onset and of late onset, both of which present examples of dominant and of recessive mode of transmission.

S U M M A R Y

It is concluded that the Author's series of cases of dominant hereditary optic atrophy of early onset is part of a group of hereditary optic atrophies, differing in mode of transmission and in age of onset, but otherwise comparable and arising from the same inherited tendency to abiotrophy.

It must be emphasised that hereditary optic atrophy can follow a dominant or a recessive transmission, and that one type can change to the other in an affected family.

It is also emphasised that the age of onset varies from birth to 74, and that while a group of early onset, and of adolescent onset, are recognisable now, it is probable that cases will be published which will obviate the distinction of age of onset.

Fields of vision vary in different cases, and it is probable that the presence or absence of a central scotoma depends on the degree of atrophy in the papillo macular bundle.

The cases are all characterised by a non-progressive course after the initial stages.

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