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COMMUNICATIONS

ON SOME ANOMALOUS FORMS OF AMAUROTIC IDIOCY AND THEIR BEARING ON THE RELATIONSHIP OF THE VARIOUS TYPES

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(Conclusion)

Anomalous Types

The occurrence of certain anomalous types has been doubted by some authors, *e.g.*, Sorsby, but the departures from the typical features are not uncommon. Mention will be made of some of these and examples given from personal cases.

A. INFANTILE TYPE.

1. *The presence of a cherry-red spot in other than infantile cases.*—Torrance in 1921, collected nine examples in which he considered a cherry-red spot had been present at the macula in juvenile cases. The description in most of these does not carry conviction, the appearances were not typical and were merely slight variations of the pigmentation usually occurring in the juvenile type, *e.g.*, cases of F. E. Batten, R. D. Batten, Kuffler, Ichikawa, and Rogalski. Gordon's cases were misdiagnoses for the Laurence-Moon-Biedl syndrome. Of the others, Wolfsohn's case, beginning

at three and a half years, showed at each macula a brownish-red spot surrounded by a greyish area with no other retinal changes. One of Condes and Horner's Japanese cases described as infantile, set in at one and a half years of age. In Higier's (1906) Jewish family, the fourth child had a typical cherry-red spot at the macula, when seen at the age of thirteen months. One of Liener and Goodhart's Jewish cases had its onset at the age of nine months. Greenfield and Nevin's non-Jewish case died shortly after being seen for the first time at the age of two years and ten months, and a red spot was present at the macula with a greyish area around it. In Case 7, the brother of their case, the first symptoms occurred at the age of ten months but the child did not die until three years later. The eldest patient in our L. family did not develop symptoms until the age of eighteen months although in two of the other siblings the onset of visual failure occurred before the age of one year. Case 10 in the Ha. family had no symptoms until the age of eight years and a typical cherry-red spot was present when seen two years later. She is by far the oldest patient in which such a sign has been recorded. The family are non-Jewish, there was no consanguinity and an elder sister died from the infantile type of the disease under the age of one year. The mother also showed mental symptoms, epilepsy and optic atrophy.

2. *Absence of the cherry-red spot.*—This occasionally occurs as in the cases of Hassin and Parmelee, Schlesinger *et al.*, Weber, Higier (1906) and the third case of the L. family. In all these cases the findings were those of a simple optic atrophy, but this may precede the development of a cherry-red spot as in Koller's case and it seems probable that had some of the cases been followed further, the typical cherry-red spot would have appeared. Further the appearance of the cherry-red spot may change as in Buchanan's case, where the red spot was surrounded by a greyish rather than a white zone. In Case 7, the brother of Greenfield and Nevin's case, the cherry-red spot was also surrounded by only a faint greyish zone.

Bertrand and V. Bogaert mention a family in which two infantile cases occurred and a third member showed dementia, the first symptoms occurring at the age of three. The patient was alive at the age of eighteen years, but the retinae were normal and this was thought to be a case of amaurotic idiocy without eye signs. It is probable that, just as in the brain, the severity of the changes varies from region to region, so in the retina, which may or may not be heavily involved.

3. *Occurrence among non-Jews.*—Slome, in 1933, found eighteen authentic non-Jewish cases among the two hundred or so reported. Examples are those of Cockayne and Attlee, Turner,

Levy, Magnus, Pooley, Muggia et al., Gil et al., Schlesinger et al., and Greenfield and Nevin (references will be found in the papers of Cohen and Condes and Horner). Seven further cases occurring in four further families are recorded here. (Cases 3-7 and 9-10).

4. *The onset of symptoms after the first year of life, and association of cases occurring in the infantile and late infantile periods in the same family.*—Typical examples of the former were found in the cases of Liener and Goodhart, Greenfield and Nevin, Higier (1906, fourth child), Condes and Horner, the first two patients of the L. family and in Case 10. Only the first and third of these cases was Jewish. A remarkable fact in some of these families is that some of the patients may be under the age of a year at the onset, *i.e.*, infantile, while in others the onset of symptoms is somewhat later and falls in the late infantile period. In addition some members of a family may show a typical cherry-red spot and others only optic atrophy, *e.g.*, Higier's (1906) Jewish family. In this family in which four children were affected the first and second cases began to lose their sight in the first year and only optic atrophy was present. In the third child no symptoms occurred until the fourth year and again only optic atrophy was present with mild imbecility. The fourth child was seen at the age of thirteen months and a cherry-red spot was found at the macula. This family cannot therefore be considered as an example of the association of juvenile and infantile cases as has been stated by previous authors, *e.g.*, Sorsby, but rather of cases with their onset at ages falling within the infantile and late infantile period. A similar association occurred in our J. family in which the elder patient (reported by Greenfield and Nevin) did not show symptoms until the third year of life while a younger brother (Case 7) began to deteriorate at the age of ten months. In our L. family, the first child had no symptoms until the age of eighteen months, the second until twelve months, both showing the typical cherry-red spot, while in the third visual failure began at five months of age and he died without the appearance of a cherry-red spot in the fundus.

In the H. family, the second child died of the infantile type of the disease under one year of age and the third child is still alive at the age of ten years, having had visual symptoms since the age of eight but is normal mentally and has a cherry-red spot at the macula. Sjögren, in his study of fifty-nine cases of the juvenile type could find no example of the infantile type in his families. *It has been impossible after an exhaustive search of the literature to find any example of a family in which infantile and juvenile types of the disease have occurred.*

5. *The disease may run a chronic course.*—Several examples

of cases which have survived considerably longer than the age of two years are on record. In Peterson's family one child lived to the age of five and a half years, and Koller mentions a patient alive, but an idiot, at the age of four years. In the Ha. family, the third child (Case 10) was well, apart from visual symptoms at the age of ten years, and in the L. family two children are alive but idiots at the age of seventeen and seven years respectively. Case 7 had its first symptoms at the age of ten months but did not die until almost four years of age.

6. *The presence of a cherry-red spot in some members of a family with only optic atrophy in others.*—Such an association was present in Higier's (1906) family, and in our L. family.

7. *Congenital cases may occur.*—Norman and Wood have recorded a case of amaurotic idiocy dying at the age of eighteen days with typical histological findings but did not record any retinal changes.

B. JUVENILE TYPE.

1. *Occurrence in Jews.*—Occasional examples of this have been recorded as in the family cited by Higier (1896) and that of Kuffler.

2. *The presence of a cherry-red spot in the retina.*—No example of this has been recorded. In Wilson's book there is a drawing of a fundus with a cherry-red spot, stated to be present in a man of twenty-five with no other symptoms. This unfortunately was an error and the fundus drawing was that of Case 7 (aged $3\frac{1}{2}$ years). Our Case 10, while occurring in this age group was obviously of the infantile type suggesting strongly therefore that *two types of the disease occur which are not identical.*

3. Families have been recorded in which the typical macular changes are present in some members while optic atrophy only is present in others, e.g., Kuffler, and Torrance. It would seem probable that optic atrophy may precede macular changes in some cases, as in the infantile type.

4. *Juvenile cases occurring in the late infantile period.*—Families are recorded in which the onset of symptoms may be in the typical juvenile period in some members but in the third to fifth years or late infantile period in others. For example, F. E. Batten's typical juvenile cases occurred in the third year, Ichikawa's in the fifth year and Torrance's in the second year. In Mühlberger's family one child aged three and a half years had macular changes resembling the juvenile type, while the other child of fifteen months had a normal fundus. Bielschowsky's four cases, all showing optic atrophy only, occurred in the fourth year. In Vogt's second family one child showed the first signs of the disease at four years and died three years later, the second began to have

failure of vision at four years, dying two years later, while the third began to fail in the second year and died within the third year. Case 11 began to have symptoms at the age of three years and had typical eye changes at the age of four and a half years.

5. Although the patients usually die by the age of eighteen years they occasionally survive much longer as in our Cases 21, 23 and 24.

6. One of our cases (9) was born with a tumour on the ear.

C. LATE INFANTILE TYPE.

Under the title "Late Infantile Familial Amaurotic Idiocy with Cerebellar Symptoms" Bielschowsky described an intermediate group between the infantile and juvenile types of the disease. His cases began in the fourth year and the eye signs appeared late and usually consisted of optic atrophy only. Histologically the cerebral lesions are the same as those in the two other types. It is usually considered that cases with their onset between the ages of one and four years fall into this group. Although attempts have been made to differentiate this type of the disease from the two preceding, it is doubtful if such is possible. We have seen above that the cherry-red spot may occur in this period and that a patient exhibiting this sign may be one of a sibship in which the onset of the condition is usually in the infantile period. Further, in some families in which some members have a typical cherry-red spot, others have merely optic atrophy and either of these findings may be present, whether the case occurs in the infantile or late infantile periods. We have also noted that families exist in which some members of a sibship have the typical macular changes of the juvenile type and others only optic atrophy. *No family has been described in which a cherry-red spot has occurred in some members and the peppered pigmentary changes in others.* Optic atrophy is a common sign of degeneration of the retina and it may occur in association with a cherry-red spot or the pigmentary-retinal changes of juvenile cases, or alone. The last finding has been suggested by some authors, *e.g.*, Greenfield and Nevin, as the basis of considering such cases occurring in the late infantile period as transitional between the two main groups, but, as we have seen, it may occur in association with either of the two main types. There are no grounds to justify the separation of a late infantile type from the infantile and juvenile types. In the period from one to four years may occur cases of the infantile type having an onset later than usual and also, cases of the juvenile type coming on earlier. All that can be said is that, when cases occur in this period the retinal changes tend to be those of optic atrophy only, but both types of the disease may occur.

D. LATE JUVENILE TYPE.

Apart from the two main types previously considered occasional cases with typical retinal changes and histological findings may occur with the first symptoms showing themselves at puberty or shortly afterwards. Such cases have been mentioned by Kufs, and by Paton, but little attention has been paid to them previously. Two further families of this type are now described, the Da. and

FIG. 9.

Fundus of a late juvenile case. (Case 26.)

Ho. families, Cases 25-27. They resemble the juvenile cases in the retinal changes except that these tend to be less marked than usual (see Fig. 9). Only in one of our cases did any convulsions occur and then only a small number at the beginning of the illness. It is obvious that these cases are the same as the juvenile type, but with a later onset, as in Case 27 there was a younger brother who died from the disease at the age of six years. The course tends to be slower and the symptoms of the disease chiefly due to cerebellar and pyramidal tract involvement causing considerable progressive ataxia, spasticity and dementia.

The Ho. Family

Parents alive and well, English, from Halifax, Yorks. Two children, a boy (Case 25) and a girl (Case 26): No nervous disease on either side of the family. The mother had two brothers and a sister but all had died. Grandparents healthy. The father had two sisters alive and well.

CASE 25. Joseph Ho.

History.—Full-time child, instrumental delivery, breast-fed for $4\frac{1}{2}$ months, "milestones" normal. At the age of twelve he had a few convulsions but these only lasted for a week and there had been none since then. At the age of fourteen he began to drag one leg. He was able to walk, however, until the age of eighteen when both legs had become very stiff and his arms began to shake so much that he spilt things and was unable to write. His speech became affected. Later he became childish, but not facile. Towards the end his sight began to fail and he became completely bedridden for the last two months of his life and quite helpless. There was no sphincter disturbance. He died at the age of twenty-six years of cerebro-macular degeneration.

CASE 26. Kathleen Ho., aged 24 years. Admitted to the National Hospital on November 21, 1928, under the care of Dr. Collier.

History.—Normal delivery. Breast-fed to the age of 13 months. "Milestones" normal. Went to school at the age of six and considered to be quite normal. She left school at the age of fourteen and was considered to be normal or perhaps a little backward mentally. She went to work until the age of eighteen. At the age of sixteen she was noticed to be stooping a little and this had tended to get worse. At the age of seventeen both legs began to get stiff and this interfered with her working and caused her to give up a year later. Since that time the stiffness had gradually become more marked, causing an aching in the legs, which frequently let her down and caused her to fall. In the last three years she had used her hands very little for knitting or writing but there had been no tremor. Two years before admission she began

to laugh excessively and increasingly so, and about the same time complained of failure of vision but was still able to read on admission. Throughout her illness there had been some hesitancy in commencing micturition. Her speech had also grown somewhat slower but there had never been any convulsions or loss of weight.

Examination.—Gross degree of dementia. Visual acuity 6/24 right and left. Fundi: (Mr. Paton), vessels rather numerous, scattered patches of pigment in perimacular region with a little redness round each. Small area of atrophy close to macula with a little irregular pigment, discs being normal. Both eyes similar (Fig. 9). Fields: relative central scotoma in both eyes. Very slight tremor of outstretched hands with intention tremor on movement. Spastic paraplegia. No ataxia in lower limbs. Sensation normal. All tendon jerks brisk. Abdominal reflexes only just elicited. Bilateral extensor plantar responses. Gait, spastic right more than left. Hands and legs red and cold with some oedema below the knee. Nil palpable in abdomen. C.S.F. normal. Pr. 0.04 per cent.

The patient remained unchanged while in hospital.

The Da. Family

Father alive and well from the London area. Mother alive suffering from left hemiparesis of nine months duration. The children were:—

1. Case 27, a boy.
2. A younger brother suffering from convulsions and blindness and he died at the age of six years from cerebro-macular degeneration.
3. Stanley, aged thirteen, had a fit aged three weeks but none since. He wore glasses at the age of five. At the age of nine he had an operation on his left eye for squint. Examination showed visual acuity on right to be 6/9 and left had movements only. Fundi normal.

CASE 27. Dennis Da., aged 20 years. Admitted to the National Hospital, December 17, 1934, under the care of Dr. Martin.

History.—From birth to the age of fifteen years he was abnormally fat, at the latter age weighing twelve stone eight pounds. Seven months before admission, while playing tennis, he found difficulty in following a fast moving ball and in judging its distance from him. Three months later he had difficulty in seeing in the dark. He could see car lights but not people, especially if they were standing still, and, a month later still, he noticed tiny moving spots dancing in front of his eyes. One month before admission, at night the sky seemed to be pink, but the moon and stars appeared yellowish-white. During the past two years he had

noticed a shaking of his hands when he was nervous and, if he placed his toes on the ground when sitting, they went into clonic movements.

Examination.—A well-built man, six feet in height. Quiet, intelligent and co-operative. Not emotional. Memory and speech normal. Visual acuity 6/36 right and 6/60 left. Fundi: (Mr. Paton) at the maculae of both eyes was an area about half a disc in diameter consisting of a pigmented network around a hyperaemic area suggesting early cerebro-macular degeneration. Discs normal. Pupils, large, react normally. No other physical signs in the central nervous system. Spleen and liver not palpable. C.S.F. normal. Pr. 0.05 gms. per cent.

E. ADULT TYPE.

Apart from the cases considered, a few have been described with typical histological findings occurring in adults. When this happens it is common to find that the whole syndrome is not present, either the retinal or cerebral symptoms being absent.

1. *Adult amaurotic idiocy without eye signs.*—Walter reported on a family of which three members were affected with idiocy and nervous lesions but showed no eye changes. The youngest died at twenty-three but the others were alive at twenty-four and twenty-nine years of age. Post-mortem examination showed changes similar to those in amaurotic idiocy. Kufs reported two cases, one beginning at twenty-six and dying at thirty-eight and the other beginning at forty-two and dying at fifty-nine years. No eye changes were present. Schob and also Meyer have reported similar cases. Schaffer also thinks that such cases occur. Case 8, the mother of two cases of the infantile type developed epilepsy and mental deterioration at the age of thirty-one and is still alive at the age of forty with some degree of optic atrophy in both eyes. Whether this is an example of an adult type of amaurotic idiocy it is impossible to say, but in view of the presence of the disease in two children it would seem probable that such was the case. It must be a matter for conjecture as to whether two types of the disease exist comparable to the two types of amaurotic idiocy.

2. *Eye signs occurring alone.*—Oatman suggested such cases occurred and he has recently been supported by Kufs, who thinks that some late juvenile cases do not develop eye changes, but it is common to find that one or more ascendants of such a case have typical retinal lesions but never develop any mental or motor symptoms. The father of Ford's case had *pigmentary degeneration* of the retina from early life with only slow deterioration of vision. In Case 24 it was only by careful observation that any mental or physical changes could be noticed and apart from the

retinal changes there were no abnormal physical signs. No cases in which macular changes of the infantile type (cherry-red spot) occurred alone have been reported previously but such was present in Case 10.

The condition of macular heredo-degeneration is brought to mind by the above cases. This may occur at different ages ranging from an infantile to a senile type; most cases have their onset between six and twenty years. The evidence that these cases are related to amaurotic idiocy is doubtful. Clinically the macular changes are similar but the fact that no families have been reported in which the two diseases have occurred together and the presence of pigmentary degeneration of the retina in the father of Ford's juvenile case would seem evidence that the diseases are not associated. This contention receives support when the mode of inheritance of macular heredo-degeneration is studied. It appears to be inherited in a dominant manner. Examples of two such family trees are given below.

(a) The Re. family, living in London, a member of which was seen at the Royal Westminster Ophthalmic Hospital on January 17, 1940, by Mr. J. G. Milner. The onset of symptoms in this family occurred about the age of puberty and the pigmentation was present as fine flecks at both maculae.

(b) The Pa. family, with onset of symptoms about the age of seven or eight years. This family also lived in London and one member was seen at the Royal Westminster Ophthalmic Hospital recently.

It seems improbable therefore that heredo-degeneration is related to amaurotic idiocy.

The Relationship of Amaurotic Idiocy to the Lipoidoses

In 1916, Knox, Wahl and Schmeisser observed the occurrence of Tay-Sachs' disease (infantile) in cases of Niemann-Pick's disease and this had since then been noted on a number of occasions. Lindau, in 1930, found the typical changes in the nervous system in a case of Gaucher's disease and Ashby et al. case of Gargoylism. Earlier histologists had stressed the fact that although the cells in Tay-Sachs' disease may be filled with pre-lipoid, the fibres of the cells may be normal and argued that its presence does not represent the products of nerve cell degeneration but a faulty general metabolism with fat deposition in the nervous tissues. In Niemann-Pick's disease there is a widespread lipoid histiocytosis with deposition of phosphatides (lecithin) most prominently in the spleen and liver, but also in other organs such as bone-marrow, adrenals, lymph nodes and blood. The blood cholesterol may be raised to 650 mgms. per cent. but may be normal. The serum may be cloudy and there may be large vacuoles of lipoid material in the lymphocytes, polymorphs and monocytes, and this may be diagnostic. The similarity in the reaction of the abnormal cell contents in the liver in Niemann-Pick's disease and in the brain in Tay-Sachs' disease is very striking. Tay-Sachs' disease has been regarded by Bielschowsky, Kufs, Spielmeyer, etc., as a localised histological expression of a metabolic disorder. On the contrary, Schaffer and others have thought that only the Niemann-Pick's disease was the result of metabolic disorder and that Tay-Sachs' disease was due to a lipoid degeneration of the nervous tissue, the fat originating locally, and Rintelen supported this view on the ground that in a case of Niemann-Pick's disease, with a cherry-red spot at the macula, the optic nerve was histologically normal. Van Bogaerts observation, in which Tay-Sachs' and Niemann-Pick's diseases occurred in the same family, is, however, strong evidence of unity in the pathology of these affections, and our observation in Case 2 of a raised blood cholesterol seems to furnish evidence that a generalised metabolic disturbance is present. Evidence of unsuspected lipoid changes in the liver, spleen, etc., in amaurotic idiocy has been present in some infantile cases but not in the juvenile type, thus Brouwer found "foam" cells in the spleen of an infantile case. Similar evidence was found by Pick, Schob and Walter. Norman and Wood in their congenital case found involvement of the reticulo-endothelial system in a minor degree in the spleen, liver, suprarenals and lymph nodes, in which lipoid deposits were present in the cells. The histological finding in the brain varied from the normal in the histochemical

reactions of the intracellular lipid and the deposition of extracellular cholesterol crystals. In this regard the findings of an enlarged liver and spleen in Case 6 and of raised blood lipoids in Case 10 are significant, whereas in Case 2 the faecal fat content and splitting were normal.

Klenk has recently shown that in juvenile amaurotic idiocy there is present in the brain an unknown lipid substance with a melting point of 195°C . and containing nitrogen and sugar. In this respect it resembled the other lipoidoses such as Gaucher's disease in which abnormally high amounts of cerebroside are present in the liver and spleen, and Niemann-Pick's disease in which sphingomyelin infiltrates the parenchyma of the various organs. From a histochemical point of view, the lipid in the cells in amaurotic idiocy is to be regarded as composed of chemical substances allied to those entering into the formation of normal myelin. From its solubility it is probably related to the normal cerebroside. There is reason to believe that in the lipoidoses some step in the metabolic processes of lipoids is faulty resulting in the storage of unmetabolised products and that this is due to lack of specific enzymes differing in the different types of diseases and in the different types of amaurotic idiocy.

Case 10 deserves further consideration. On the unitary conception of all forms of amaurotic idiocy a case occurring at the age of eight years would be expected to show the retinal changes usually present in the juvenile type of case, but in Case 10, on the contrary, a cherry-red spot was found, no mental or neurological symptoms being present. On the supposition that Tay-Sachs' disease is part of a general lipid dystrophy, of which Niemann-Pick's disease is the full syndrome, this case can be regarded as a monosymptomatic form of such a lipoidosis. By extensive investigation evidence of general lipid disturbance could be obtained in the high blood fats. Behr has described late forms of the Christian-Schuller syndrome of a monosymptomatic type, no change in the blood lipoids being found. This disease was previously regarded as infantile and Case 10 may be looked on as a congruent form in Niemann-Pick's disease.

With the above facts in mind, attention must be drawn to the histochemical findings. In the infantile type of the disease the substance deposited in the cells of the nervous system and retina is of a "pre-lipoid" nature, whereas in the juvenile type it is of a lipid nature, the two types differing in this respect. Again, as already mentioned, no record of the association of Niemann-Pick's disease with the juvenile type of amaurotic idiocy has occurred either directly or in a family. Niemann-Pick's disease, like the infantile type of the disease, is especially liable to affect Jewish

children. It is probable therefore that two distinct types of amaurotic idiocy exist:—

1. An infantile, mainly confined to Jews, usually, but not always, rapidly fatal and almost always with the onset before the third year. Occasionally only optic atrophy occurs instead of the usual macular cherry-red spot. It is probably related to Niemann-Pick's disease.

2. A juvenile, with onset chiefly about six to eight years of age, but sometimes as early as the second year or as late as the twenties. It occurs chiefly in non-Jews, has a slower course and also occasionally shows optic atrophy instead of the pigmentary macular changes, the final retinal picture resembling retinitis

X = Cases of infantile type reported in England and Scotland.

O = Cases of juvenile type reported in England and Scotland.

Geographical distribution of cases of infantile and juvenile amaurotic idiocy in this country.

pigmentosa. It is unrelated to the infantile type genetically or histochemically and its relationship to macular heredo-degeneration is doubtful. Often only cerebral or retinal changes are present in older cases.

Geographical Distribution of Cases

The map shows the geographical distribution in England and Scotland of my own and other reported cases.

Summary

A number of typical and atypical cases of amaurotic idiocy are reported and evidence is brought forward that two types of the disease, infantile and juvenile, exist which are not related to one another, except in their similar histological appearances. It is probable that atypical types of the juvenile disease occur in which either the retinal or cerebral manifestations are absent especially in older patients. It seems likely that the disease is unrelated to macular heredo-degeneration.

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REFERENCES

1. ASHBY, W. R., STEWART, R. M. and WALKER, J. N. (1937).—*Brain*, Vol. LX, p. 149.
2. BEHR, C. (1937).—v. *Graefe's Arch. Ophthalm.*, Vol. X, p. 303.
3. BATTEN, F. E. (1903).—*Trans. Ophthalm. Soc. U.K.*, Vol. XXIII, p. 386.
4. BERTRAND, I. and v. BOGAERT, L. (1934).—*Encéphale*, Vol. XXIX, p. 505.
5. BIELSCHOWSKY, M. (1914).—*Deutsch. Z. Nervenheilk.*, Vol. L, p. 7.
6. ——— (1928).—*Jl. Psychol. Neurol.*, p. 1, Vol. III, pp. 36, 103.
7. BRODMAN (1914).—*Z. ges. Neurol. Psychiat.*, Vol. C, p. 91.
8. BROUWER, B. (1936).—*Proc. Roy. Soc. Med.*, Vol. XXIX, p. 579.
9. BUCHANAN, M. (1905).—*Amer. Jl. Med. Sci.*, Vol. CXX, p. 31.
10. COCKAYNE, E. A. and ATTLEE, J. (1914).—*Proc. Roy. Soc. Med.*, Vol. V, pt. 3 (Ophthalmological Section), p. 65.
11. COHEN, M. (1923).—*Arch. Ophthalm. N.Y.*, Vol. LII, p. 140.
12. CONDES, F. C. and HORNER, W. D. (1929).—*Amer. Jl. Ophthalm.*, Vol. LII, p. 558.
13. FALKENHEIM (1901).—*Jb. Kinderheilk.*, Vol. XXXIV, p. 123.
14. FORD, F. K. (1937).—*Diseases of the Nervous System in Infancy, Childhood and Adolescence*. Baillière, Tindall and Cox, London.
15. FRETS, G. P. and OVERBUSCH, J. F. A. (1923).—*Jl. Amer. Med. Ass.*, Vol. LXXXI, p. 2158.
16. GIL, R. and BERANGER, R. P. (1930).—*Arch. Oftal. B. Aires.*, Vol. V, p. 36.
17. GORDON A. (1907).—*N.Y. Med. Jl.*, Vol. LXXXV, p. 295.
18. GREENFIELD, J. G. and HOLMES G. (1925).—*Brain*, Vol. XLVII, p. 183.
19. GREENFIELD, J. G. and NEVIN, S. (1933).—*Trans. Ophthalm. Soc. U.K.*, Vol. LIII, p. 170.

20. HASSIN, G. B. (1926).—*Arch. Neurol. Psychiat. Chicago*, Vol. XI, p. 708.
21. HASSIN, G. B. and PARMELEE, A. H. (1928).—*Amer. Jt. Dis. Child.*, Vol. XXXV, p. 87.
22. HIGIER, H. (1897).—*Deutsch. Z. Nervenheilk.*, Vol. IX, p. 1.
23. ——— (1901).—*Neurol. Zbl.*, Vol. XVIII, p. 843.
24. ——— (1906).—*Deutsch. Z. Nervenheilk.*, Vol. XXXI, p. 231.
25. ICHIKAWA K. (1909).—*Klin. Mbl. Augenheilk.*, Vol. XLVII, p. 73.
26. KLENK, E. (1939).—*Hoppe-Seyl. Z.*, Vol. CCLXII, p. 128.
27. KNOX, J., WAHL, R. and SCHMEISSER, H. C. (1916).—*Johns Hopk. Hosp. Bull.*, Vol. XXVII, p. 1.
28. KOLLER, C. (1896).—*Trans. Amer. Ophthal. Soc.*, Vol. VII, p. 661.
29. KUFFLER, O. (1910).—*Beitr. Augenheilk.*, Vol. VIII, p. 18.
30. KUFES, H. (1928).—*Z. ges. Neurol. Psychiat.*, Vol. CXVII, p. 753.
31. ——— (1929).—*Z. ges. Neurol. Psychiat.*, Vol. CXXII, p. 395.
32. LIENER, J. H. and GOODHART, S. P. (1927).—*Arch. Neurol. Psychiat. Chicago*, Vol. XVII, p. 616.
33. LEVY, A. (1923).—*Amer. Jt. Ophthal.*, Vol. VI, p. 408.
34. LINDAU, A. (1930).—*Acta Psychiat.*, Vol. V, p. 167.
35. MAGNUS, H. (1885).—*Klin. Mbl. Augenheilk.*, Vol. XXIII, p. 42.
36. MARINESCO, G. (1930).—*Jl. Psychol. Neurol.*, Vol. VIII, pt. 1, pp. 41, 1.
37. MAYOU, M. S. (1904).—*Trans. Ophthal. Soc. U.K.*, Vol. XXIV, p. 142.
38. MUGGIA, A. and VITA, A. (1930).—*Minerva Med. Roma.*, Vol. II, p. 5.
39. MUHLBERGER, A. (1903).—*Munch. Med. Wschr.*, Vol. L, p. 1,968.
40. NORMAN, R. N. and WOOD, M.—*Jl. Neurol. Psychiat.*, Vol. IV (N.S.), p. 175.
41. OATMAN, E. L. (1911).—*Amer. Jl. Med. Sci.*, Vol. CXLII, p. 221.
42. PATON, L. (1932).—*Trans. Ophthal. Soc. U.K.*, Vol. LIII, p. 226.
43. PETERSON, F. (1898).—*Jl. Nerv. Ment. Dis.*, Vol. XXV, p. 529.
44. PICK, L. (1932).—*Amer. Jl. Med. Sci.*, Vol. CLXXXV, p. 453.
45. POOLÉY. Quoted by Falkenheim.
46. RINTELEN. Quoted by Sorsby.
47. ROGALSKI, T. (1910).—*Arch. Psychiat. Nervenkr.*, Vol. XLVII, p. 1,195.
48. SACHS, B. (1887).—*Jl. Nerv. Men. Dis.*, Vol. XIV, p. 541.
49. SCHAFFER, K. (1931).—*Arch. Psychiat. Nervenkr.*, Vol. XCIII, p. 767.
50. SCHLESINGER, B., GREENFIELD, J. G. and STERN, R. O. (1934).—*Arch. Dis. Child.*, Vol. IX, p. 1.
51. SCHOB, F. (1912).—*Z. ges. Neurol. Psychiat.*, Vol. X, p. 303.
52. ——— (1912).—*Pathologische Anatomie der Idiotic Bumkes*, Handbuch der Geisteskrankheiten Berlin, Vol. VII, p. 779.
53. SjöGREN, T. (1931).—*Hereditas (Lund) (Die juvenile Amaurotische Idiocy)*, p. 14.
54. SLOME, D. (1933).—*Jl. Genet.*, Vol. XXVII, p. 363.
55. SORSBY, A. (1937).—*Brit. Encyclop. of Med. Pract.*, Vol. III, p. 30.
56. SPIELMEYER, M. (1906).—*Neurol. Zbl.*, Vol. XXV, p. 57.
57. ——— (1918).—*Jl. Psychol. Neurol.*, Vol. XXXVIII, p. 120.
58. TAY, W. (1881).—*Trans. Ophthal. Soc. U.K.*, Vol. I, p. 55.
59. TORRENCE, H. W. (1922).—*Glasg. Med. Jl.*, Vol. XCVII, pp. 193, 1.
60. TURNER, J. A. (1912).—*Proc. Roy. Soc. Med.*, Vol. V, pt. 1, p. 3.
61. VOGT, H. (1905).—*Mschr. Psychiat. Neurol.*, Vol. XVIII, p. 161.
62. WALTER, F. K. (1918).—*Z. ges. Neurol. Psychiat.*, Vol. XL, p. 349.
63. WILSON, S. A. K. (1940).—*"Neurology," E. Arnold, London*, ii, p. 882.
64. WEBER, F. P. (1910).—*Proc. Roy. Soc. Med.*, Vol. III, p. 58.
65. WOLFSOHN, J. M. (1915).—*Arch. Intern. Med.*, Vol. XVI, p. 257.