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COMMUNICATIONS

DEAFNESS AND THE LAURENCE-MOON-BIEDL SYNDROME*

BY

R. A. BURN

*Assistant to the Ophthalmic Research Unit, Royal College of
Surgeons and Royal Eye Hospital, London*

IN this report two families are described, one showing the syndrome with deafness, the other the syndrome alone. The literature of the subject as a whole is reviewed to complement the last extensive survey of Sorsby, Avery, and Cockayne, which closed in 1937. In addition, all case reports published since 1864 in which deafness is recorded in connection with the syndrome are analysed to determine whether any relation exists between the two.

CASE REPORTS

The H—family.

Attention was drawn to this family when the two sisters with ocular defects attended the Royal Eye Hospital. The parents are first cousins and they have had nine children.

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FIG. 1. Pedigree of the H- family (condensed).

(IV, 1) The first son was not seen. He is an intelligent man who has won scholarships and is a well-qualified musician. The parents say he has no defects. He is 33 years old.

(IV, 2) The second son was examined. He is 32 years old, and a deaf mute. His intelligence is normal and he plays chess. He is married. There is no visual defect and the fundi are normal. There is no polydactyly and x ray of the hands and feet shows no abnormality of the bones. He is thin. The ear drums are normal. The deafness is complete and of the nerve type. He has never been able to hear. X ray of the skull shows a small sella turcica.

(IV, 3 and 4) The third and fourth children were not seen, but the parents say they have no defects and lead normal lives. The fourth is married and has one child, a few weeks old, which is said to be normal (V, 1).

(IV, 5) The fifth child, a daughter, died of diphtheria at the age of ten months. She is said to have had one extra toe.

(IV, 6) The sixth child, Hilda H—, was examined and shows all the components of the Laurence-Biedl syndrome except hypogenitalism.

History. She was backward and suffered from night blindness in childhood. As a result, she was sent to a blind school, and now works filling flour bags on a machine. Menstruation started at 13 years and was normal. She has lately married.

Examination. Her behaviour is that of a cheerful child. She is plump, not grossly obese, but the fat is unevenly distributed over the proximal parts of the limbs and lower abdomen. There are striae over the hips and abdomen. She was menstruating at the time of examination. Development of breasts and distribution of axillary and pubic hair are normal.

The fingers and toes are short, and there are old scars on the outer borders of the feet where extra toes have been removed. The second and third toes of both feet are webbed. X ray showed angulation of the outer border of the right fifth metatarsal, suggesting that a bifid portion had been removed. There was a rough place on the lateral aspect of the left fifth metatarsal, probably for the same reason. The middle phalanges of the index and little fingers of both hands were abnormally short.

Her eyes showed fine rotatory nystagmus. The pupils reacted sluggishly to light. She was only able to count fingers at 3 ft. with or without glasses. The optic discs were atrophic, the arteries grossly attenuated, and there was much pigmentation of the fundus. The pigment was collected in coarse clumps and masses, mostly equatorial in distribution, though there was some finer stippling at the maculae. There was approximately -4D. of myopia in each eye.

There was no abnormality of the other systems on clinical examination. Her speech and hearing were normal. X ray of the skull showed no significant abnormality.

(IV, 7) The seventh child, a man, aged 23 years, was examined. He is a deaf mute, and at present a patient in a mental hospital.

History. His hospital record shows that he is emotionally unstable, became violent towards his mother, and has delusions that he is suffering from infantile paralysis.

Examination. He is not as intelligent as his deaf brother, but much of his dullness may be attributed to his psychosis.

There is no obesity and the sexual organs and secondary characteristics are fully developed.

There is no polydactyly or other anomaly of the hands or feet, either clinically or visible on x ray.

The pupils react normally to light and accommodation. He is able to read type equivalent approximately to Jaeger 1. There is no abnormality in the fundi.

Wassermann reaction and Kahn test are both negative. X ray of the skull shows no abnormality.

He is completely deaf and almost entirely dumb. The deafness is of the nerve type, and the ear drums are normal.

Like his deaf brother, he shows none of the components of the Laurence-Biedl syndrome.

(IV, 8) Elizabeth H—, the eighth child, was examined.

History. She showed night blindness and backwardness in childhood, and was sent to a blind school. She does not work. Menstruation started at the age of 12 and has remained normal.

Examination. There was a marked facial "tic" and her mentality was behind that of her affected sister. The degree and type of obesity was similar to that of Hilda, and the secondary sexual characteristics were similarly developed. The condition of the eyes, including the fundus, was practically the same. X ray of the skull showed no significant abnormality, apart from a deep sella turcica. Other systems were normal on clinical examination.

There was no polydactyly or syndactyly but x ray showed that the terminal phalanges of the toes were small and fused to the middle phalanges, while the fingers are similar to Hilda's.

She shows, therefore, the same components of the syndrome as her sister, except that her digital anomalies do not include polydactyly or syndactyly.

(IV, 9) The ninth child, a daughter, aged 21 years, was not examined, but was reported to be normal in all respects.

Both parents were examined and showed no abnormality of importance. There was a mosaic of small yellowish spots at both maculae in the mother. This is probably an unrelated senile change and does not impair vision.

Details of the pedigree and antecedents were provided by the parents, who are both intelligent and well-informed on family matters. No significant family abnormality was reported in the antecedents or collaterals, except for a mentally deficient child, a cousin on the father's side. As he was the first-born of his mother at the age of 44, the fact is probably not relevant.

The salient features in this family are therefore:—

(1) The parents are first cousins and they had nine children, of whom five were abnormal.

(2) Two female sibs show the complete syndrome except for hypogenitalism. One female sib died young and was reputed to have had polydactyly.

(3) Two male sibs are deaf mutes but show none of the components of the Laurence-Biedl syndrome.

(4) There is no history of any related abnormality in the parents, ascendants or collaterals.

The B—family.

Details of this family, which have not previously been published, were kindly supplied by Dr. Raymond Greene.

The parents were not related. There were no other sibs.

Diana B—, first seen October 28, 1947, aged 12 years.

History. Her mother complained that she had been overweight since the age of four and that her weight had rapidly increased during the last four years. She was said by a schoolmistress to be three years behind her age intellectually. She

had never menstruated. Apart from measles she had had no illness. A sixth digit had been removed from each foot.

Examination. She was a grossly fat girl with no sign of sexual development. The breasts were prominent, but the prominence was due to fat and no mammary tissue could be palpated. The forearms were hairy. The hair distribution otherwise was normal except for a complete absence of pubic and axillary hair. Height 4 ft. 8½ ins., weight 12 st. 7 lbs. Pulse 80.

The fundi showed the characteristic picture of retinitis pigmentosa with considerable optic atrophy and greatly reduced vision. X ray of the skull was normal.

Antony B—, admitted to the Royal Northern Hospital January 3, 1948, aged 16 years.

History. He had been obese since the age of two, was mentally backward, was partially blind and had never developed sexually. He had a mild attack of chorea at the age of 8, severe hemichorea on the right side at the age of 11 and on the left at 12. At 15 he had a further severe bilateral attack.

Examination. He was grossly overweight. The genitalia were extremely small; sparse pubic hair of female distribution was present, but body hair was otherwise absent. There was severe genu valgum. Vision was considerably reduced and there was convergent strabismus. The fundi showed attenuation of the arteries and there were scattered spots of black pigment in the lower periphery of both eyes.

There was no record of any significant abnormality in parents, ascendants or collaterals.

The salient features in this family then are :—

- (1) The parents are unrelated and had only two children, both affected.
- (2) The girl shows the complete syndrome; in the boy, polydactyly is lacking on clinical examination.
- (3) There is no record of abnormality in the ascendants or collaterals.

LITERATURE

The first cases reported as a separate clinical entity were those of Laurence and Moon from the Royal Eye Hospital in 1866. Höring (1864) and Stör (1865) had reported cases of retinitis pigmentosa combined with other anomalies which were probably unrecognized cases of the syndrome. Cockayne, Krestin, and Sorsby (1935) and Sorsby, Avery, and Cockayne (1939) have reviewed the literature up to 1937. The present review deals with the cases recorded since then; and surveys, from the literature as a whole, all the recorded cases in which deaf-mutism has occurred.

THE LITERATURE SINCE 1937

The total number of cases reviewed by Cockayne and others (1935) and Sorsby and others (1939) up to 1937 was 178, distributed in 121 families. The corresponding figures for 1938-48 are 82 and 57, excluding a small number of reports which were unobtainable.

Because of the inconstancy of expression in members of the same sibship cases have been accepted as belonging to the Laurence-Biedl group if they showed three of the five classical

components of the syndrome. Doubtful cases have been included if there were records of other components occurring in relatives; for example, the case of Warkany and Weaver (1940) which had obesity, hypogenitalism, mental deficiency, and unilateral microphthalmos, has been accepted because an uncle was reported to have had polydactyly. A number of doubtful cases, which have been rejected from the analysis, are nevertheless described at the end of this section because they are probably allied to the syndrome.

Ascendants and Collaterals.

Obesity in ascendants is reported by Likins and others (1947), Taylor (1947), Demirag (1944), Ruggeri (1938), Laborne (1944), and Bergouignan and Viaud (1946); polydactyly by Scott and Johnson (1942), Ellis and Law (1941), Lurie and Levy (1942), Wolff (1938), Warkany and Weaver (1940), Muthayya and Iyer, quoted by Kutumbiah and Abbu (1942), and Marmor and Lambert (1938). There are reports of mental defect by Likins and others (1947), Demirag (1944), Kutumbiah and Abbu (1942), and Scott and Johnson (1942); visual defect by Baldi (1945), and Taylor (1947); miscarriages by Taylor (1947); and epilepsy by Schwartz and Boudreau (1940).

The only defects reported in collaterals were retinitis pigmentosa, and retinitis pigmentosa with obesity in second cousins (Laborne, 1944); undiagnosed visual defect in two cousins (Baldi, 1945); and dementia praecox in a cousin (Novick, 1939).

Transmission.

Apparently direct transmission is recorded by Laborne (1944), and by Lurie and Levy (1942).

(i) Laborne (1944).

In this case the affected father married a second cousin. Two out of three children were affected. The pedigree shows the occurrence of the partial syndrome in ascendants and collaterals and direct transmission from father to children.

FIG. 2. Pedigree condensed from Laborne (1944).

(ii) Lurie and Levy (1942).

In two families one component only, syndactyly, was directly inherited, in the one case from the mother and in the other from the father. In the former case transmission was known to two generations only. In addition a cousin on the mother's side was affected. In the latter there was evidence of transmission through three generations, the patient, father, and a paternal grandfather being affected. These cases are more fully described in the section on deafness. Baldi (1945) reports the birth of an apparently normal child to an affected woman.

Sibs.

The syndrome may vary in its manifestations within the sibship. Polydactyly alone in deceased members is often reported (Borsotti, 1939; Radner, 1940; Ruggeri, 1938; Montanaro and others, 1942; D'Abreu and Ferriman, 1941). But variation is often seen in living affected members. In the family of D'Abreu and Ferriman there were seventeen members. One had adiposo genital dystrophy and a retinal lesion with cataract, another was said to have had polydactyly with normal vision, four more were said to have been blind from birth but there is no record of obesity or polydactyly. The children of the patient reported by Laborne were differently affected. One had polydactyly only, another had polydactyly, obesity and a retinal lesion, the third was normal. Taylor's case (1947) with the complete syndrome was said to have had a sister still-born with polydactyly and "part of the head missing." In Snell's (1942) sibship of eight, one had the complete syndrome, one died young and was reported to have obesity and polydactyly, one other was examined and found to have only the retinal lesion and shortening of the fourth metacarpals with thickening of the skull bones.

Isolated abnormalities as distinct from partial expressions of the syndrome are rare. Mental deficiency is reported in one sib by Ellis and Law (1941). There are other reports suggesting mental defect in otherwise normal sibs (Muthayya and Iyer, quoted by Kutumbiah and Abbu, 1942; Marmor and Lambert, 1938; Novick, 1939). The present report shows two affected children and two deaf mutes in the same sibship.

Components of the Syndrome.

(a) *Obesity*. This component was definitely absent in 6 cases only (Roth, 1947; Snell, 1942; Borsotti, 1939; Laborne, 1944). In Roth's cases of four affected sibs two were obese and two not. In Snell's case the other living affected sib was fat and one dead sib was reported to have had polydactyly and obesity. In Borsotti's cases not only obesity but also hypogenitalism and mental defect appear to have been missing in both cases. In Laborne's case one child had polydactyly only, while the other had obesity and retinitis pigmentosa as well. Obesity without hypogenitalism was recorded in four instances (Snell, 1942; Baldi, 1945; Laborne, 1944; Graham Anderson, 1948). Hypogenitalism without obesity was recorded by Roth in two of four affected members of the same sibship.

(b) *Hypogenitalism*. This component was much less constant than obesity. It is difficult to assess, especially in young girls, and in 20 cases the diagnosis was doubtful. It was definitely absent in 14 cases (see Appendix A). In Baldi's (1945) case a woman with otherwise the complete syndrome gave birth to an apparently normal child.

(c) *Polydactyly*. Anomalies of the extremities varied from complete supernumerary digits to syndactyly and irregularities in the length of the metacarpals. Short "podgy" hands are frequently described, as well as incurving of the little finger.

Polydactyly was absent, and there was no mention of any other definite abnormality of the extremities in 18 cases (see Appendix A), digital anomalies being reported in the relatives of five.

(d) *Ocular defects*. In the great majority of cases the defect was retinal and was first noticed in early childhood. The most usual type was some variant of the classical picture of retinitis pigmentosa, the pigment being the least and the optic atrophy and vascular narrowing the most constant features. Macular lesions were reported by Taylor (1947) and by Borsotti (1939). Low myopia is noted in the present study in combination with the retinal lesion. Unilateral microphthalmos was reported in the case of Warkany (1940).

(e) *Mental deficiency*. This component was definitely absent in 11 cases (see Appendix A). Either the record or the diagnosis was doubtful in 13 cases.

Pathology.

Reports of two post-mortem examinations have been added to the literature since 1938 (N. L. Anderson, 1941; Radner, 1940).

(i) *N. L. Anderson (1941).*

The reproductive organs were rudimentary, the anterior lobe of the pituitary consisted chiefly of basophil and eosinophil with very few chromophobe cells, there was a colloid goitre, and the brain and its blood vessels were normal.

(ii) *Radner (1940).*

The only point of importance was the finding of uterus duplex.

Race.

Cases have been reported in Indians (Kutumbiah and Abbu, 1942; and Muthayya and Iyer, quoted by Kutumbiah and Abbu, 1942) and in Negroes (Roth, 1947; Snell, 1942; Scott and Johnson, 1942).

Associated conditions.

(a) *Ocular.* Nystagmus was recorded by many authors (Taylor, 1947; Roth, 1947; Garcin, Mann, and Piguët, 1945; Beato Forn, 1940; Marques, 1941; Kloess, 1941; Baldi, 1945; Family H—, present report). Strabismus was noted by Bergouignan and Demirag (1944), Montanaro and Turro (1942), Lurie and Levy (1942), and in Family B— of the present report; ptosis by Lurie and Levy (1942), and Krarup (1939).

(b) *Skeletal.* Genu valgum and pes planus occurred together in several instances (Garcin, Mann, and Piguët, 1945; Parella, 1938; Marmor and Lambert, 1938; Montanaro and Turro, 1942; Beato Forn, 1940; Kutumbiah and Abbu, 1942). The former, with no mention of the latter was recorded by Taylor (1947), Warkany (1940), Marques (1941), Scott and Johnson (1942), and N. L. Anderson (1941), and in Family B— above. Kyphosis, with or without lordosis, was mentioned by Garcin, Mann, and Piguët (1945), Attiah and El Gamal (1940), and Kutumbiah and Abbu (1942). Dorsal scoliosis is recorded by Taylor (1947). Bowing of one leg with a slipped epiphysis was described by Scott and Johnson (1942). Genu valgum, pes planus, and dislocation of the hip were reported by Jaso and Arbelo (1945) in a case of doubtful diagnosis (see below), the outstanding feature of which was enormous obesity in a boy of 9½ years.

An abnormally high palate was observed by Attiah and El Gamal (1940), and by Scott and Johnson (1942)—in the latter case combined with hypoplasia of the mandible. Warkany and Weaver (1940) reported enlarged parietal openings and overflexible joints. Dwarfism was recorded in one case (Ellis and Law, 1941).

(c) *Abnormalities of the central nervous system.* Ataxia and scanning speech were reported by Roth (1947); ataxia, adiadokokinesis, and excessive spontaneous blinking by Garcin, Mann, and Piguët (1945); excessive blinking by Beato Forn (1940); and difficult speech by McCullagh and Ryan (1941). Tremor, deviation of the tongue, and Rombergism were described by Lurie and Levy (1942), and epilepsy is mentioned by Schwartz and Boudreau (1940).

(d) *Metabolic disturbances.* Diabetes insipidus was recorded by Lyle (1946), Morgensen (1941), Bernard and Chassagne (1938), Lurie and Levy (1942). No polydipsia or polyuria was recorded by Lyle (1946), Garcin and others (1945), Montanaro and Turro (1942), or Lurie and Levy (1942). Polyphagia was reported by Likins and others (1947), and Lurie and Levy (1942); its absence was noted by Lurie and Levy (1942). The basal metabolic rate was low in most of the cases where it was recorded (see Appendix B). Glucose tolerance was reported normal by Likins and others (1947), Montanaro and Turro (1942), Garcin and others (1945), Krarup (1939), Morgensen (1941), Ruggeri (1938), and Wolff (1938); and as increased by Attiah and El Gamal (1940), Lurie and Levy (1942), and Wendt (1941).

Tetany of unknown cause, with normal blood calcium and phosphorus, was reported by D'Abreu and Ferriman (1941).

(e) *Developmental abnormalities.* Atresia ani, in a deceased sib with polydactyly, and uterus duplex are reported by Radner (1940). Hypospadias is mentioned by N. L. Anderson (1941).

Doubtful cases not included.

Two cases, reported by Ciotola (1938), of polydactyly or syndactyly with microphthalmos, occurring in separate non-consanguineous sibships, have not been

included. They were quite free from any other component of the syndrome, except for unilateral undescended testicles in one child aged two, nor is there any record of affected sibs or ascendants.

The family reported by Jaso and Arbelo showed obesity and a retinal condition in which vascular stasis appears to have been the leading feature. There is no mention of any component, other than obesity, in the relatives and the pedigree shows direct transmission of this defect from parents to children in three generations.

Marañón (1941) describes a family of 11 in which two sisters and one brother were affected. The elder sister had hypogenitalism and obesity due to a proved pituitary tumour. Another sister had obesity, hypogenitalism and abnormalities of the hands and feet—gross inequality in length of toes and dwarfing of thumbs. The younger brother was reported, on medical evidence, to be mentally defective and to have a slight degree of oxycephaly and malformation of the ears. Nothing is said about consanguinity. No abnormalities were known in the parents or antecedents.

DEAFNESS IN THE LITERATURE AS A WHOLE

In families affected by the Laurence-Biedl syndrome, deafness occurs both in combination with and independent of the syndrome. In the literature reviewed by Sorsby and his colleagues up to 1937, there are reports of deafness occurring in 7 families and affecting 13 individuals. From 1938-48 there are 6 families and 9 individuals affected, including this record, making a total in the literature of 13 families and 22 individuals.

Deafness in cases of the syndrome.

Nine family groups and thirteen individuals come under this heading.

(i) *Boenheim (1929)*. A sibship in which three brothers were affected. The number of normal sibs is not stated. One showed mild obesity and hypogenitalism, retinitis pigmentosa, and partial nerve deafness which appears to have been first noticed between 16 and 17 years old. There was no polydactyly or mental deficiency. Another brother was said to complain of night blindness and to be mentally normal. The third brother had retinitis pigmentosa, hypogenitalism, mental deficiency and impaired hearing. He was thin and had no polydactyly. The parents were not related.

(ii) *Weiss (1932)*. Two sisters showing obesity, hypogenitalism, mental deficiency and nerve deafness. There were no ocular defects or polydactyly, but one of the father's relatives was said to have had six fingers. Two other sisters were normal. There is no statement as to consanguinity of the parents.

The deafness in one was only noticed at the age of 6, and she talked normally; in the other it was not discovered till about 10 years old, though she talked with difficulty. It seems probable, despite the late onset, that this was a true nerve deafness of genetic origin, since both sisters were similarly affected.

(iii) *Steinberg (1937)*. Family 1. Five siblings of whom the third and fourth were normal, the first and fifth had retinitis pigmentosa and mental defect, and the second had polydactyly in addition. The three affected female sibs were congenital deaf mutes. The parents were first cousins and healthy apart from some nerve deafness in the mother, probably of senile type.

(iv) *Steinberg (1937)*. Family 2. A boy suffering from obesity, hypogenitalism, mental deficiency, and retinitis pigmentosa. He had no polydactyly but was a congenital deaf mute. The father and three sisters were healthy. The mother had a degree of acquired deafness but no other abnormality of importance. There is no mention of whether the parents were related or not.

(v) *Becker (1937)*. Four siblings, of whom one died young, two sisters were well and one brother had the complete syndrome except for polydactyly. He was also a congenital deaf mute. Nothing is said of consanguinity in the parents or components of the syndrome in ascendants.

(vi) *Attiah and El Gama! (1940)*. A boy with the complete syndrome and impaired hearing. The parents were first cousins and there was a history of developmental anomalies and defective vision amongst the grandparents. The siblings were a younger brother who had the syndrome but not deafness, and a male child who died aged 2 years. It is not possible to be certain whether the deafness was of genetic origin or not.

(vii) *Lurie and Levy (1942)*. Family 1. A boy with mild obesity and hypogenitalism, mental deficiency, syndactyly, and impaired hearing of nerve type present since early infancy. The eyes were normal. The parents were not related. The father was normal, but the mother had syndactyly of both feet. One maternal uncle and one maternal aunt were blind from early life. One female cousin on the mother's side had syndactyly. There were five other siblings all older and all normal.

(viii) *Lurie and Levy (1942)*. Family 2. This was a girl with obesity, hypogenitalism, polydactyly and syndactyly, mental impairment and defective hearing of nerve type present since early infancy. The visual acuity was normal but there was a suspicion of some retinal degeneration seen with the ophthalmoscope. The parents were not related. The mother was normal, but the father had syndactyly of both feet. One paternal grandfather and one paternal uncle were feeble-minded and the grandfather had syndactyly of both feet.

(ix) *Scott and Johnson (1942)*. Four sibs, of whom two were affected. One boy showed the complete syndrome plus deafness—apparently congenital. The other was reputed to have obesity, visual defect, mental backwardness and polydactyly, but is not recorded as deaf.

The parents are not related, but there is a history of polydactyly in the father's family.

Deafness in unaffected relatives.

This is recorded in three family groups and six individuals.

(i) *Lhermitte and Bollack (1936)*. Deaf mutism in the maternal aunt of a patient showing the complete syndrome. No mention is made of consanguinity in the parents. One paternal great uncle had polydactyly.

(ii) *Novick (1939)*. A family in which deafness appeared in the descendants of the affected sibship. The parents were normal and not related. There were 12 children—three normal, one with the complete syndrome, and the remainder showing one or other component in some degree, e.g., obesity, mental dullness or visual defect. Of the latter, two had each a child with defective hearing, although neither of them shows the syndrome, and neither of the marriages was consanguineous. One member of the affected sibship is reported as having defective hearing, but it is not clear which.

(iii) *The present record. Family H—*.

FIG. 3. The Pedigree of Herrlinger.

The Pedigree of Herrlinger (quoted by Nettleship, 1908).

This family tree extends over four generations and is of special interest as it includes cases of deafness both in the syndrome and in apparently normal antecedents.

In generation I, 2 was deaf mute and 3 an idiot. IV, 1 was an idiot, partly deaf, and had retinitis pigmentosa and polydactyly; IV, 2 was an idiot with retinitis pigmentosa; IV, 3 was also an idiot with retinitis pigmentosa and polydactyly; IV, 6, a cousin, was deaf mute and blind.

DISCUSSION

THE SYNDROME

Pathology.

The association of obesity of the pituitary type with hypogenitalism suggests an underlying pituitary or hypothalamic defect. The occurrence of other apparently related abnormalities such as diabetes insipidus and increased sugar tolerance points in the same direction. Marañon (1941) regards them all as one component—adiposo-genital dystrophy.

In reporting his finding of an excess of basophil and eosinophil cells in the anterior lobe of the pituitary, N. L. Anderson (1941) quotes two other cases with a similar post mortem finding—one of Griffith in a girl with the syndrome, and one of Stewart in a boy showing pseudo-hermaphroditism, adiposity, polyuria and hypoglycaemia. In only four cases of the syndrome has a post mortem description of the pituitary been given, and in only two is it given in detail. In both of them this finding has been made.

Genetic Data.

(a) *Ratio of affected to normal sibs.* Table Ia shows records of 54 complete sibships. They contain 99 affected, and 148 normal sibs. This gives a proportion of 1:1.49, very much higher than the theoretical 1:3 of a recessive defect. If the material of Cockayne and others (1935) and Sorsby and others (1939) be added, the proportion falls to 1:1.75. In recessive defects sibships where the children are all normal cannot be recognized, since the parents are almost always phenotypically normal heterozygotes. This tends to make the proportion of affected children too high. Various corrections have been devised to overcome this difficulty. Streiff and Zeltner (1938) have applied four of them with results varying from 30.4 per cent. affected (Weinberg) to 22.1 per cent. affected (Weinberg proband method), the mean being 26.9 per cent. Macklin (1938), using Hogben's method, corrected 28.5 per cent. The proportion is compatible with a recessive defect. It is however high, and this suggests a high rate of expression.

(b) *Consanguinity.* Of 57 sibships in Table I, the parents were first cousins in 11, second cousins in two, and related in other

degrees in 4. They were unrelated in 24 and not recorded as either in 16. If those not recorded are counted as unrelated, the proportion of first cousin marriages is 19.2 per cent., as compared with 0.8 per cent. in the general population (Fraser Roberts, 1940). The incidence of consanguinity of all degrees is 29.8 per cent. Cockayne (1935) found 23 per cent. in the complete sibship and 18 per cent. in all. Sorsby (1939) taking the complete sibships in which a definite statement was made, found 38.7 per cent.

(c) *Sex ratio.* In Table I, including the incomplete sibships, there are 102 sibs known or reputed to be affected and 148 known or reputed to be normal. Of the affected sibs, 60 were males, 35 females, and in 7 cases the sex is not recorded. Of the normal sibs, 47 were males, 42 females and in 59 cases the sex was not recorded. This excess of males agrees with the figures of Cockayne *et al.* (1935), who found 44 affected males and 28 affected females in the completed sibships, and Sorsby and others (1939) who found 33 affected males and 16 affected females. Both authors found no excess of males amongst normal sibs.

Sorsby and others (1939) tried to explain this excess of males by applying a method used by Haldane (1938) to account for the excess of males amongst albinos. Haldane held that males were more likely to come under observation than females. If this is the reason for the excess, the probands in sibships with two or more affected should be in the same sex ratio as in those with only one. On this assumption, the probands can be extracted from the former sibships and the excess of males should disappear in the secondary sibs. Sorsby and others (1939) using 80 sibships, found that it did not. In Table III, the method is applied to 175 complete fraternities—all the complete sibships of Cockayne and others (1935), Sorsby and others (1939) and all except family B—in the present review. It will be seen that although the percentage of males amongst secondary sibs is reduced, yet it is still significantly high. The excess of affected males therefore cannot be regarded as artificial.

(d) *Direct transmission and digital anomalies.* The only case of direct transmission of the whole syndrome is that of Laborne (1944). In this case an affected man married his second cousin, who may well have been a carrier, so that there is no evidence of simple dominance.

Single components of the syndrome however occur fairly frequently in the antecedents. Of these, the most often recorded is polydactyly (or other digital anomalies). In the literature from 1938-48, out of 57 sibships polydactyly in ascendants is mentioned in 8, obesity in 6, mental defect in 4, and visual defect of unknown cause in 2. In addition the two families of Lurie and Levy (1942)

show direct transmission of syndactyly to two and three generations respectively.

On the other hand, polydactyly is more often absent in cases of the syndrome than any other component. Of 82 cases analysed in the appendix, digital anomalies were definitely absent in 18 cases, hypogenitalism in 14, mental deficiency in 11, obesity in 6, and the retinal lesion in 3. Since the diagnosis of hypogenitalism and mental deficiency is often doubtful, as shown by the high percentage of queries in the appendix, it is probable that these figures are too high.

Polydactyly therefore would appear to be the component most frequently found in antecedents and most frequently absent in cases of the syndrome.

Polydactyly alone in the sibs of affected individuals (apart from those dying young) is only recorded in two instances, both somewhat doubtful (Laborne, 1944; D'Abreu and Ferriman, 1941).

Mode of Inheritance.

(a) *Chance association.* Warkany and Weaver (1940) hold that these cases do not constitute a true clinical entity but only a chance association of rare defects. If this were so, the condition would certainly be much rarer than it is. Radner (1940) has calculated that the chance of a single case occurring would be so slight that the syndrome could hardly have emerged at all. In fact, 102 cases have been reported in the last ten years—and many more must exist unreported.

(b) *Single gene recessive.* It has been suggested that the syndrome may be due to a single recessive autosomal mutant gene with multiple effects. This theory is strongly supported by Streiff and Zeltner (1938) and Fraser Roberts (1940).

We have seen that the proportion of affected to normal children is compatible with this idea. The high incidence of consanguinity in the parents is strongly in favour of a recessive condition. The appearance of polydactyly in the ascendants can be explained if it is assumed that the gene is incompletely recessive, and certain of its effects, notably polydactyly, appear in a proportion of heterozygotes. To explain the frequent absence of polydactyly in affected individuals, it is further necessary to assume that although expressed in a proportion of heterozygotes, it is not expressed in a number of homozygotes, whereas the other effects rarely, if ever, present in heterozygotes are expressed in a higher proportion of homozygotes. Supposing that this can be accepted, it follows that, parents of affected individuals being heterozygous, a certain proportion of them should be polydactylous. The only recorded cases are those of Lurie and Levy described above. It is clear that the single gene theory does not easily fit all the facts, although it does

account for the most important ones. It does not in itself provide any explanation of the excess of affected males.

(c) *Two gene theories.* Rieger and Trauner (1929) postulated two linked autosomal recessive genes, one responsible for the abnormalities of ectodermal origin (obesity, hypogenitalism, retinal lesion, mental defect) and the other for those of mesodermal origin (polydactyly and other skeletal abnormalities). Their view is supported by Sorsby and others (1939). Bauer (1927) regarded polydactyly as dominant and independent of the other components.

If it is assumed that one of the genes is dominant, or at any rate incompletely recessive, these theories have the advantage that the behaviour of polydactyly can be explained by dissociation of genes. They demand, however, equally with the single gene hypothesis, that a proportion of the heterozygous parents should be polydactylous. In addition, a number of the sibs of affected individuals would carry the polydactyly gene alone and in a proportion of these cases, the gene would be expressed. There are no definite records of polydactyly occurring by itself in the sibs of individuals with the whole syndrome.

Like the single gene hypothesis, these theories fit the observed facts as to the proportion of affected to normal offspring and consanguinity of parents sufficiently well. They do not in themselves provide any explanation of the excess of males any more than it does. There is little to choose then, between them; but *a priori*, a two gene hypothesis is less likely as an explanation of a rare abnormality than a single gene one.

(d) *Sex-linked theories.* Macklin (1938) has tried to explain the sex distribution by postulating a sex-linked gene. According to her theory, the syndrome is caused by one dominant autosomal mutant gene and one sex-linked recessive. It is assumed that the presence of both genes is necessary for full expression. The hypothesis faces two serious objections. In the first place, it requires five times as many families with males only affected as with females or both sexes affected. Table II shows 30 out of 57, that is approximately equality. Sorsby and others (1939) found 9 families with two and more affected males and 17 with affected children of both sexes. In the second place, the hypothesis of recessive sex-linkage in general demands that the sex incidence of the condition must be equal in sibships containing affected females. Csik and Mather (1938) applying this principle, tested the hypothesis in respect of several hereditary abnormalities. In the case of the Laurence-Moon-Biedl syndrome, they found that the excess of males could not be attributed to sex-linkage. The idea then must be rejected. It may be noted that partial sex-linkage can also be rejected, as it cannot lead to a regular excess of males.

(e) *Sex limitation.* We have seen that there is a true excess of males which cannot be regarded as artificial, and that none of the genetic theories account for it. Csik and Mather (1938) have suggested a relatively low penetrance in the female. On these lines, a possible explanation might be a sex limiting autosomal modifying gene preventing expression in the female, such as Harris (1948) has suggested for multiple exostoses. Unfortunately the method he employs for testing the hypothesis cannot be readily applied to a recessive condition such as Laurence-Biedl syndrome. There is, however, an objection to this explanation. It involves a reduced penetrance and therefore the proportion of affected to normal sibs after correction should be low. It has been shown to be high. There is thus at present no satisfactory explanation for the excess of affected males.

In conclusion, it may be said that the sex-linked hypothesis is untenable. The single gene recessive and two gene theories are very imperfect but the former is a priori the least objectionable.

DEAFNESS

Incidence of congenital deaf mutism in the general population.

Grant Keddie (1945) in a survey of congenital deaf mutism in Scotland from 1918-37 found an incidence of 3.88 deaf mutes per 10,000 live births. This is an incidence of 0.038 per cent. at birth. He states that this rate of incidence is certainly low since ineducable cases have been excluded.

Eichholz (1932) in a survey for England and Wales comparing the number of deaf mutes in special schools of the 15-16 age group with the general school population in the 14-15 age group gives an incidence of 1:1,160 or 0.086 per cent.

Best (1943) gives the number congenitally deaf per 1,000,000 of the population of the United States in 1920 as 157, that is, .0157 per cent.

As an approximation, we may take it that the incidence is in the region of 0.05 per cent.

Incidence of congenital deaf mutism in the Laurence-Biedl syndrome.

Out of a total of 178 family groups reported (including incomplete records), congenital nerve deafness has been recorded in 13, with a total of 22 individuals affected. In order to obtain a figure comparable with those given for the general population, the incidence in affected individuals or their sibs only has been taken. This excludes relatives who were only reported because they were deaf. Sibs who died in infancy so that their deafness could not

have been known, have been excluded. Where there is doubt as to the age of death, they have been included.

On this basis, out of a total of 611 members of affected sibships, 18 were deaf—an incidence of 2.94 per cent. or nearly 60 times as great as in the general population. If the cases of Boenheim, Weiss, and Lurie and Levy be excluded, as not true cases of the syndrome, and those of Attiah and El Gamal and Novick, on account of uncertainty as to the cause of deafness, 10 cases of congenital deaf mutism are left—an incidence of 1.63 per cent. or 30 times that in the general population.

THE SYNDROME WITH ITS ASSOCIATED AND ALLIED CONDITIONS

These figures suggest strongly that deaf mutism does not occur merely by chance in the Laurence-Biedl syndrome and that it is in some way related to it. It seems likely that many of the associated conditions described above are also related, and that the conditions classed as doubtful cases or allied conditions may be variants of the syndrome. Sorsby (1939) described as allied conditions a number of syndromes such as somatic and psychic infantilism with coloboma of the iris and skeletal anomalies (Biernard's syndrome); mental deficiency, hypogenitalism, Friedrich's ataxia and choroidal sclerosis; cerebellar ataxia, nystagmus, exophthalmos and brachydactyly; anomaly of stature and retinal degeneration; obesity with microphthalmos and other ocular anomalies; etc., etc. The original case reports by Laurence and Moon had no polydactyly but were dwarfed and ataxic. It is not clear what is the relation of these conditions to the syndrome and each other, but it is probably diverse. Amongst the associated conditions, for example, genu valgum and pes planus are, almost certainly secondary mechanical effects caused by excessive obesity in young persons. Nystagmus is the result of the retinal lesion. The metabolic disturbances, such as diabetes insipidus and obesity, may well be endocrine effects at second or even third hand. Other variations and complications may conceivably arise from the action of modifying genes.

In its broad outlines, the Laurence-Moon-Biedl syndrome is perfectly straightforward. It is a hereditary condition with recessive transmission. In its details it shows endless variability, seems closely related to a number of other conditions, and will not fit properly into any precise genetic scheme. The reason probably is that the underlying genetic cause is simple—a single recessive autosomal mutation—while its manifestations are rendered complex and variable by the action of secondary mechanical effects, endocrine disturbances and genetic modifying factors.

SUMMARY AND CONCLUSIONS

Two new families of the Laurence-Biedl syndrome are reported.

(1) The H— family, offspring of a first cousin marriage, consisting of two females with the complete syndrome, one female who died young, and was reputed to have had polydactyly, two male deaf mutes, two normal females and two normal males.

(2) The B— family, offspring of unrelated parents, consisting of two affected sibs only, one female showing the complete syndrome, one male lacking polydactyly.

The literature of the syndrome as a whole is reviewed over the last ten years. In addition, all case reports mentioning deafness published since 1864 are reviewed in detail.

From this survey, the following points emerge :—

(1) The incidence of congenital deaf mutism in Laurence-Moon-Biedl cases and their sibs is thirty times as high as in the general population.

(2) In the syndrome as a whole, there is an excess of affected males which cannot be explained as artificial.

(3) Polydactyly is the component most frequently present in ascendants and most frequently absent in affected individuals.

(4) What post-mortem evidence there is points to a pituitary abnormality with an excess of basophil and eosinophil cells in the anterior lobe. It is, however, very scanty.

The possible theories of inheritance are discussed. It is shown that there are serious objections to all of them and that some can be definitely rejected. The least objectionable theory is that of a single recessive autosomal mutation.

It is concluded that deaf mutism is related in some way at present unknown to the syndrome. The suggestion is made that the syndrome, with its associated conditions, and possibly allied syndromes, are due to a single recessive autosomal mutation with multiple effects, and that the complexity and variability of its manifestations are caused by secondary mechanical and endocrine factors and possibly the influence of modifying genes.

I wish to express my gratitude to Dr. Raymond Greene for his kindness in supplying the details of the B— family, and to Mr. H. E. Hobbs, F.R.C.S., for his help. I am indebted to Mr. J. E. Cole of St. Thomas's Hospital for his help in interpreting the x-ray films and to Dr. G. A. Lilly, Physician Superintendent of Crane Hill Hospital, Coulsdon, for allowing me to examine a member of the H— family and for supplying x rays.

I wish to thank Professor Sorsby for his unstinted help and encouragement and valuable suggestions.

(a) *Complete Sibships, 1938-48*

Author	Total Sibs.	♂	♀	●	♂	♀	○	Consanguinity of parents	Remarks	Race or Nationality
Anderson, Graham (1948)	2	1	—	—	—	—	—	—	Two half-brothers, one half-sister reputed normal.	—
Anderson, N. L. (1941)	1	1	—	—	—	—	—	None	♂ died aet. 2. Two abortions. One affected deaf.	Greek
Attiah and El Gamal (1940)	3	2	—	—	—	—	—	First cousin	● four reputed blind from birth—three died young.	—
D'Abreu and Ferriman (1941)	17	—	1	—	—	—	11	None	♀ one polydactyly, reputed normal vision, died young.	—
Demirag (1944)	5	1	—	—	—	—	—	—	Two stillbirths.	—
Baldi (1945)	5	—	3	—	—	—	—	None	—	—
Bergouignan and Viaud (1946)	2	1	1	—	—	—	—	None	♀ twin died aet. 3, reputed normal.	—
Bernard and Chassagne (1938)	2	1	—	—	—	—	—	—	Mother is the daughter of her husband's first cousin.	—
Beato Forn (1940)	10	—	1	—	—	—	9	Yes	● died young. Reputed to have polydactyly.	—
Borsotti (1939)	6	2	—	—	—	—	2	First cousin	○ died young. Reputed normal.	—
Bregat (1947)	1	1	—	—	—	—	—	—	One of the normal sisters is dead but reputed normal.	—
Cavallaci (1939)	3	1	—	—	—	—	—	None	—	—
Corcelle and Berthon (1939)	2	—	1	—	—	—	—	—	Mother married her half-sister's son.	—
Delmas-Marsalet et al (1938)	1	1	—	—	—	—	—	Yes	One ♂ died at birth—reputed normal.	—
Ellis and Law (1941)	4	—	1	—	—	—	—	None	One of the reputed normal sisters was known to have tuberculosis and to be M.D.	—
Grant and Smith (1942)	5	—	1	—	—	—	4	—	Two of the normal sibs. were fat.	—
Garcin et al (1945)	2	1	—	—	—	—	—	First cousin	—	—
Kielholz (1946)	2	—	1	—	—	—	—	None	—	—
Kloess (1941-2)	4	1	—	—	—	—	—	None	—	—
Krupar (1939)	2	1	1	—	—	—	—	None	—	—
Kutumbiah and Abbu (1942)	5	1	—	—	—	—	—	First cousin	The affected brother is only recorded as having polydactyly and cryptorchidism.	Indian
Laborne (1944) (i)	5	1	—	—	—	—	—	None	♂ died aet. 1, reputed normal.	—
" (ii)	3	1	1	—	—	—	—	Second cousin	Two ♂ died young reputed normal. Children of affected male in (i), by his second cousin. The affected boy had polydactyly only.	—
Likins et al. (1947)	8	1	1	—	—	—	5	—	● died young—reputed to have had polydactyly.	—
Lurie and Levy (1942) (i)	6	1	—	—	—	—	—	None	Affected male deaf.	—

TABLE I—(continued)

Author	Total Sibs.	♂	♀	●	♂	♀	○	Consanguinity of parents	Remarks	Race or Nationality
Lyle (1946) (i) ...	3	—	1	—	1	1	—	—	—	—
" " (ii) ...	2	—	1	—	—	—	1	—	—	—
Marmor and Lambert (1938) (i) ...	1	1	—	—	—	—	—	None	—	—
" " (ii) ...	2	1	—	—	1	—	—	First cousin	Unaffected brother was dull.	—
Marques (1941) ...	10	1	—	—	—	—	9	None	Seven of the sibs. reputed normal had died of unknown causes.	—
McCullagh and Ryan (1941) ...	5	4	—	—	1	—	—	First cousin	—	—
Montanaro and Turro (1942) ...	3	—	2	—	—	—	—	Yes	Maternal great grandmother and paternal grandmother were sisters.	—
Morgensen (1941) ...	4	1	—	—	2	1	—	First cousin	♂ dead—reputed to have polydactyly.	—
Muthayya and Iyer (1939) (i) ...	6	2	—	—	2	1	—	—	The unaffected sister has hydrocephalus.	Indian
(Quoted by Kutumbiah and Abbu, 1942)									One ♂ had polydactyly (?) died young.	
Novick (1939) ...	12	—	1	—	5	6	—	None	One of the unaffected boys was dull.	—
									Of the unaffected sibs. four were normal, four were dull and/or had visual defect, three were obese. One was deaf and two had deaf children.	—
Parella (1938) ...	6	2	—	—	1	—	—	None	One ♀ one ♂ died young, reputed affected.	—
Radner (1940) ...	6	—	2	—	2	—	—	None	One ♂ died young, reputed to have had polydactyly.	—
									One ♀ died young, reputed to have had polydactyly and atresia ani.	
Rathmell and Burns (1938) ...	11	1	1	—	2	3	—	First cousin	One (?) affected, not seen.	Russian Jews
									One ♂ died young (?) affected.	
									One ♂ died young (three weeks).	
									One ♂ died young (first year).	
Rojas Loa (1939) ...	2	1	—	—	—	1	—	—	The unaffected sister was obese.	Americans of Czechoslovak origin
Roth (1947) ...	6	4	—	—	1	1	—	None	—	—
Ruggeri (1938) ...	5	2	1	—	—	—	—	Second cousin	Two ♂ died young, reputed to have had polydactyly. One abortion.	—
Schwartz and Boudreau (1940) ...	9	1	—	—	2	1	—	—	Four ♂ died young, cause unknown.	—
									One died at. 2, scarlet fever. One still-born.	
Scott and Johnson (1942) ...	4	1	—	—	—	—	2	None	One affected brother was not seen but was reputed to have obesity, visual defect, mental defect, and polydactyly.	Negro one affected deaf.

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Author	Total Sibs.	♂	♀	●	♂	♀	○	Consanguinity of parents	Remarks	Race or Nationality
Snell (1942)	8	—	2	—	1	4	—	None	♂ died aet. 8, reputed to have had obesity and polydactyly.	Negro
Taylor, (1947)	1	1	—	—	—	—	—	None	One sister still-born, reputed to have had polydactyly and part of head missing.	—
Urechia et al (1939)	8	1	—	—	—	—	—	None	Six ♂ died in infancy.	—
Vraa-Jensen (1945)	2	2	—	—	—	—	—	First cousin	● died in infancy, reputed to have had polydactyly.	—
Wang (1945)	3	1	1	—	2	—	—	—	—	—
Warkany and Weaver (1940)	1	1	—	—	—	—	—	—	—	—
Wendt (1941)	4	1	—	—	—	—	3	None	—	—
Wolff (1938) (i)	2	1	—	—	1	—	—	First cousin	—	—
" " (ii)	4	1	—	—	1	—	—	—	Two ♀ died young.	—
Present record. H-family	9	1	2	—	4	2	—	First cousin	♂ died young, reputed to have had polydactyly. Two unaffected deaf.	English
" " B-family	2	1	1	—	—	—	—	None	—	—
	247	51	28	—	41	38	46			
Died young, probably affected		7	79	6	—	125	—			
Not seen, " " normal		2	4	1	—	—	—			
Died young, " " normal		—	—	—	6	4	13			
		60	32	7	47	42	59			
	247		99			148				

(b) Incomplete Sibships

Author	♂	♀	Consanguinity of parents	Remarks	Nationality
Lurie and Levy (1942) (ii)	—	1	None	Nerve deafness.	—
Lyle (1946) (iii)	—	1	—	—	—
Muthayya and Iyer (1939) (ii)	—	1	Yes	Mother married maternal uncle.	Indian
(Quoted by Kutumbian and Abbu, 1942)					
Total ...	—	3	—	—	—

♂—affected; ♀—normal; ●—sex not stated.

TABLE II.—*Nerve Deafness in relation to the Laurence-Biedl Syndrome*
1. Deafness in cases of the syndrome.

Author	Partial Syndrome	Complete Syndrome	Total
Boenheim, 1929	2	—	2
Weiss, 1932	2	—	2
Steinberg, 1937 (1)	3	—	3
" " (2)	1	—	1
Becker, 1937... ..	1	—	1
Attiah and El Gamal, 1940	—	1	1
Lurie and Levy, 1942 (1)	1	—	1
" " (2)	1	—	1
Scott and Johnson, 1942	—	1	1
Herrlinger (Nettleship, 1908)	—	2	2
Total	11	4	15

Total number of Laurence-Moon-Biedl cases reported 1864-1948, including cases probably affected	275
--	-----

2. Deafness in unaffected relatives.

Author	Number
Lhermitte and Bollack. 1936	1
Novick, 1939	3
Herrlinger (Nettleship, 1908)	1
Present record	2
Total	7

TABLE III.—*Complete Sibships for correction of Sex Ratio.*

Number with Laurence-Moon-Biedl Syndrome	1	1 male: 73. 1 female: 37.					
	2	2 males: 16. 1 male + 1 female: 19. 2 females: 6.					
	3	3 males: 3. 2 males + 1 female: 7. 1 male + 2 females: 4. 3 females: 2.					
	4	4 males: 2. 3 males + 1 female: 2. 2 males + 2 females: 4. 1 male + 3 females: 0. 4 females: 0.					
		Male	Female	Percentage Males	Secondary Males	Secondary Females	Percentage Males in second sibs.
1	73	37	66.3	—	—	—	
2	51	31	62.1	23.9	17.1	58.2	
3	27	21	56.2	16.4	15.6	51.2	
4	22	10	58.7	16.7	7.3	69.5	
Total	173	99	63.6	57.0	40.0	58.7	

Including all the complete sibships reviewed by Sorsby, Avery, and Cockayne (1939), Cockayne, Krestin, and Sorsby (1935) and the present review (excluding family B—).

APPENDIX A

Incidence of Individual Components (cases reported 1938-48)

Author	Digital Anomalies	Retinal Lesion	Obesity	Hypo-genitalism	Mental Defect	Remarks
D'Abreu and Ferriman (1941)	—	+	?	+	—	Lens opacities
Anderson, Graham (1948) ...	+	+	+	—	—	
Anderson, N. L. (1941) ...	+	?	+	+	+	
Attiah and El Gamal (1940) (i)	+	+	+	+	+	
" " " " (ii)	+	+	+	+	?	
Baldi (1945) (i) ...	+	+	+	—	+	
" " " " (ii) ...	—	+	?	—	+	
" " " " (iii) ...	+	+	+	?	?	
Beato Forn (1940) ...	+	?	+	?	+	
Bergouignan and Viaud (1946) (i)	+	+	+	?	—	
" " " " (ii)	—	+	+	+	?	Macular defect
Bernard and Chassagne (1938)	+	—	+	+	—	
Borsotti (1939) (i) ...	+	+	—	—	—	
" " " " (ii) ...	—	+	—	—	—	
Bregeat (1947) ...	+	+	+	+	+	Polydactyly not mentioned
Cavallaci (1939) ...	+	+	+	+	?	
Corcelle and Berthon (1939) ...	?	+	+	?	+	
Delmas-Marsalet et al (1938) ...	+	+	+	+	+	
Demirag (1944) ...	+	+	+	+	—	Children of (i) by his second cousin
Ellis and Law (1941) ...	—	+	+	+	—	
Garcin, Mann, and Piguët (1945)	+	+	+	+	+	
Grant and Smith (1942) ...	+	+	+	?	+	
Kielholz (1946) ...	+	+	+	+	+	
Kloess (1941) ...	—	+	+	+	+	
Krarup (1939) ...	+	+	+	+	+	
Kutumbiah and Abbu (1942) ...	+	+	+	+	—	
Laborne (1944) (i) ...	—	+	+	?	—	
" " " " (ii) ...	+	—	—	—	?	
" " " " (iii) ...	+	+	+	?	?	Deaf. Not related to (ii) Deaf. Not related to (i)
Likins, Scott, and Handelman (1947) (i) ...	+	+	+	?	+	
Likins, Scott, and Handelman (1947) (ii) ...	+	+	+	?	+	
Lurie and Levy (1942) (i) ...	+	—	+	?	+	
" " " " (ii) ...	+	?	+	+	+	Deaf descendants. Unilateral optic atrophy
Lyle (1946) (i) ...	+	+	+	—	—	
" " " " (ii) ...	+	+	+	?	+	
" " " " (iii) ...	+	+	+	+	+	
Marmor and Lambert (1938) (i)	+	+	+	+	+	
" " " " (ii)	+	+	+	+	+	
Marques (1941) ...	+	+	+	+	+	
McCullagh and Ryan (1941) (i)	—	+	+	?	+	
" " " " (ii)	—	+	+	?	+	
" " " " (iii)	—	?	+	?	?	
" " " " (iv)	—	+	+	—	+	Deaf descendants. Unilateral optic atrophy
Montanaro et al (1942) (i) ...	+	+	+	?	+	
" " " " (ii) ...	+	+	+	?	+	
Morgensen (1941) ...	+	+	+	?	+	
Novick (1939) ...	+	?	+	+	+	
Parrella (1938) (i) ...	+	+	+	+	+	
" " " " (ii) ...	+	+	+	+	+	
Radner (1940) (i) ...	+	+	+	+	+	
" " " " (ii) ...	+	+	+	+	+	
Rathmell and Burns (1938) (i)	+	+	+	+	+	
" " " " (ii)	+	+	+	+	+	

APPENDIX A—(continued)

Author	Digital Anomalies	Retinal Lesion	Obesity	Hypo-genitalism	Mental Defect	Remarks
Rojas Loa (1939)	+	+	+	+	+	{
Roth (1947) (i)	—	+	—	+	+	
" " (ii)	—	+	—	+	?	
" " (iii)	—	+	+	+	?	
" " (iv)	—	+	+	+	—	
" " (v)	+	+	?	—	+	{
Ruggeri (1938) (i)	+	+	+	+	+	
" " (ii)	+	+	+	+	+	
" " (iii)	+	+	+	?	?	{
Schwartz and Boudreau (1940)	+	—	+	+	+	
Scott and Johnson (1942) (i)	+	—	+	+	+	
" " " " (ii)	+	+	+	?	+	{
Snell (1942) (i)	+	+	+	—	+	
" " (ii)	+	+	—	—	—	
Taylor (1947)	+	+	+	+	+	{
Urechia et al (1939)	+	+	+	+	+	
Vraa-Jensen (1945) (i) ...	+	+	+	—	—	
" " (ii)	+	+	+	—	—	{
Wang (1945) "	+	+	+	+	+	
Wendt (1941)	—	+	+	+	?	
Warkany and Weaver (1940)	—	?	+	+	+	{
Wolf (1938) (i)	+	+	?	+	?	
" " (ii)	+	+	+	+	+	
Present record. H—Family (i)	+	+	+	—	+	{
" " " " (ii)	+	+	+	—	+	
" " " " B—Family (iii)	+	+	+	+	+	
" " " " (iv)	—	+	+	+	+	
Muthayya (Quoted by Kutumbiah and Abbu, 1942) (i) ...	+	+	+	+	+	{
Muthayya (Quoted by Kutumbiah and Abbu, 1942) (ii) ...	+	+	+	+	?	
Total —	18	3	6	14	11	{
" ?	1	6	4	20	13	
" +	63	73	72	48	58	
	82	82	82	82	82	

Cases in which the record leaves any doubt as to the presence or absence of a component have been marked ?

Members of the same sibship are bracketed

APPENDIX B

Cases in which Basal Metabolic Rate is recorded

Author	Percentage	
Likins et al (1947)	—6	
Lyle (1946)	—8	—28
Attiah and El Gamal (1940)	—20	—22
D'Abreu and Ferriman (1940)	+14	
Kielholz (1946)	—21.2	
Montanaro et al (1942)	—16	—18
Wendt (1941)	—4	
Ruggeri (1938)	—2	
Wolff (1938)	—21	+16

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* May refer to same cases as in section (a).

† Inaccessible. Quoted by Nettleship, 1908.