COMMUNICATIONS

UNUSUAL RETINAL DETACHMENT, POSSIBLY SEX-LINKED*

BY

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THE occurrence of retinal detachment with some rather unusual features in three brothers, and in the only son of their normal sister, led to the present study. Members of three generations of this family have been examined, and eight affected individuals were discovered, all males (Fig. 1). The ages of the affected individuals ranged from 13 to 60 years. As the appearances in Generation III

FIG. 1.—Pedigree of P. family, showing eight observed cases of cystic detachment of the retina in different stages.

are markedly different from those seen in Generation IV and in the single case in Generation V, and are presumably the later stages of the same progressive affection, an inverse chronological order is observed in recording these cases.

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CASE RECORDS

GENERATION V.

Case 1. Brian S. (V, 5), aged 13. Right eye normal and has full vision. Left eye has always been defective. Both eyes show 1.50 D. hypermetropia. The fundus appearances of the left eye are shown in Fig. 2. The lower half of the retina is detached. A high-water mark extends on either side of the disk, and there is also a similar mark up and in. The detached retina is very much retracted from the ora, and shows two sharp crescentic edges.

GENERATION IV.

Case 2. Peter T. (IV, 9), aged 19. Here, too, the right eye is normal except for a linear scar down and out (Fig. 3). Vision of right eye: 6/12 with +1.25 D. sph. $\ominus$ +0.75 D. cyl. 130°. The left eye is hypermetropic (+3.0 D. sph.) and shows a detachment not unlike that seen in the patient's nephew (V, 5). The detachment extends up to and surrounds the disk, producing an appearance reminiscent of papillitis. There are also some unusual white streaks below the crescentic edge of the detachment temporally.

Case 3. Reginald T. (IV, 8), aged 25. Vision right eye, 6/36; left eye, 6/60. Refraction right: +5.50 D. sph. $\ominus$ +0.5 D. cyl. $\downarrow$ 90°. Refraction left: +5.0 D. sph. Vision has been defective ever since he remembers. In the right eye the lower two-thirds of the retina are detached with sharp crescentic disinsertions below, and a mottled appearance centrally (Fig. 5). In the left eye the detachment is confined to the middle third of the retina; and in the central area there is a depression simulating macular coloboma. Pigment disturbances and hard white dots are seen below this depression (Fig. 6).

Case 4. Fred T. (IV, 6), aged 30. Vision right eye, 6/18; left eye, 6/60. Refraction right: +5.0 D. sph. $\ominus$ +1.50 D. cyl. $\rightarrow$ 180°. Refraction left: +5.0 D. sph. In the right eye there is a shallow detachment in the central part of the fundus with two peripheral disinsertions upwards (Fig. 7). In the left eye the detachment is more extensive, and shows a large central defect—possibly a hole—and five sharply delineated peripheral disinsertions (Fig. 8).

These four patients in the second and third decades of life all show fundamentally similar pictures—a variable degree of detachment with multiple peripheral disinsertions—except that in IV, 8, the picture in the left eye (Fig. 6) departs from the appearances seen in the others in that there is considerable atrophy with pigmentation rather than detachment. The three brothers (IV, 6, 8, and 9) have one normal brother (IV, 7), and a sister (IV, 5) who is also normal. This sister is the mother of V, 5 (see Fig. 2), and of a girl (V, 6) who is normal. The one normal brother in the sibship (IV, 7) has a son aged 2½ (V, 7), who is normal.

GENERATION III.—The parents of the sibship containing three affected brothers are normal; the mother (III, 6) was the only girl in a family of nine, originally consisting of thirteen members, four of whom died in infancy. Of her eight brothers, four (III, 1, 3, 4, 5) died in adult life and were reputed normal. Of these four only the eldest (III, 1) had a child, a son (IV, 1), who is reputed to be normal. The surviving four brothers (III, 9, 8, 7, and 2) were examined and were all found to be affected.

FIG. 2.—Brian S., aged 13 (V. 5), left fundus. Right eye normal.

FIG. 9.—Appearances in left eye of Sidney John P., aged 51 (III, 9), the youngest maternal great-uncle of V, 5.

FIG. 10.—Appearances suggestive of an abortive falciform fold in right eye of Albert P., aged 54 (III, 8), another maternal great-uncle of V, 5. Left eye normal.

FIG. 11.—Appearances in left eye of Percy P., aged 60 (III, 7), a third maternal great-uncle of V, 5. Right eye (not illustrated) shows some central choroidal sclerosis.

FIGS 3 and 4.—Right and left fundi of Peter T., aged 19 (IV, 9), a maternal uncle of V, 5.

FIGS 5 and 6.—Right and left fundi of Reginald T., aged 25 (IV, 8), an older maternal uncle of V, 5.

FIGS 7 and 8.—Right and left fundi of Fred T., aged 30 (IV, 6), the eldest maternal uncle of V, 5.

Case 5. Sidney John P. (III, 9), aged 51. Has had bad sight ever since he remembers. He sustained an injury to the right eye in childhood, and the eye was removed when he was 34 years of age. Unfortunately it is not available for histological examination. The left eye is emmetropic and vision is hand movements. The fundus appearances are shown in Fig. 9. There is nothing now to suggest a detachment.

Case 6. Albert P. (III, 8), aged 54. He first noticed that his right eye was defective after serving in the first world war. The fundus appearances are shown in Fig. 10, where a localized flat detachment with a somewhat atrophic surface is seen over a narrow band above. The left eye is normal.

Case 7. Percy P. (III, 7), aged 60. Vision in both eyes is defective, but has been good in the right eye till recently. This eye shows no detachment, but there is evidence of choroidal sclerosis, most marked centrally (no drawing was made). In the left eye appearances are very much the same as those seen in his younger brother, except that there is rather more pigment disturbance, and the retinal vessels are distinctly thinner (Fig. 11). He is suffering from heart failure.

Case 8. William P. (III, 2), aged 66. He was seen on one occasion and was not co-operative. The right fundus could not be seen owing to cataract. Lens changes prevented a good view of the left fundus, but the impression was gained that it showed a picture similar to that seen in his brother Percy.

DISCUSSION

The Wide Range of Appearances.—It should be noted that the four affected members in generations IV and V are all in the second and third decade of life; two are under twenty, and two are under thirty. The affected individuals in generation III are all thirty to forty years older, and as it is known that their trouble dates back to childhood, it may be assumed that the marked degenerative appearances they show represent a later stage of the unusual detachment seen in the younger generation. In support of this reading are the degenerative changes seen in the left eye of one of the younger generation (IV, 8; Fig. 6). It may perhaps also be assumed that the condition is congenital. The range of ophthalmoscopic appearance, largely, but not exclusively, determined by duration, is considerable, as shown by the mildest changes in Fig. 3, and the most severe in Fig. 11. Fig. 10 suggests an abortive falciform detachment in a man aged 54 years.

Mode of Inheritance.—As can be seen from the protocols in Appendix 1, nothing is known of the first generation, and it would appear that Fred P. (II, 2) had normal eyesight. There is a history of a defective left eye, possibly due to cataract, in the case of his wife (II, 1). Of the observed generations, three and possibly four, of their four surviving sons are affected, and the one daughter (III, 6) is unaffected. Of the three definitely affected sons (III, 7, 8, 9), the eldest has no issue and the two others have not passed on the affection to their descendants. Even if it be assumed that III, 2 is affected, he has not passed on the trouble. Transmission has, however, occurred through the unaffected sister (III, 6). Three of

her four sons (IV, 6, 8, 9) are affected, and her one daughter, unaffected, also has an affected son (V, 5). This suggests a sex-linked recessive condition, and one must assume that III, 6 obtained the pathogenic gene from her mother, who would be a carrier. The evidence for sex-linkage (supported also by the distribution of affected to unaffected in generation III) cannot be regarded as definite, for IV, 10, the only daughter of a known affected man, has no issue and even if it be assumed that III, 2 is affected, his daughter has girls only. Until other families, or further developments in this family, bring other evidence, the assumption of recessive sex-linkage would none the less appear to be likeliest. As the pedigree stands at present a noteworthy feature is that no affected man has transmitted the affection. All that is definite is that over two generations the maternal uncles of affected males have also been affected, and that the ratio of affected to unaffected is consistent with the theoretical expectation of 1 : 1 for recessive sex-linkage.

Relationship to Cystic Detachment of the Retina and to Congenital Vascular Veils.—Juler (1947) has drawn attention to cystic detachment of the retina as seen in children. His records refer to three isolated and unrelated cases in boys aged 5½ to 8 years. He held that these cases had some similarity to congenital falciform folds in the retina and possibly congenital veils in the vitreous as described by Mann and Macrae (1938), and may perhaps be linked up with them.

Mann and Macrae described two brothers, aged 17 and 20 years respectively, and a third unrelated man aged 21 years. In all three, both eyes were affected by congenital vascular veils in the vitreous, and in one there was a detachment. Figs 12 and 13* show the appearances recorded for the two brothers. In the discussion on Juler's paper, Mann agreed that cases with vitreous veil and detachment were probably one entity at different stages—the veils representing ruptured retinal cysts. She also mentioned the case of a boy aged 10 with retinal cysts, whose uncle [? maternal] showed "a vascular veil and a certain amount of choroidal pigmentation" but no cysts.

The four illustrations given by Juler leave little doubt that his cases and those recorded here are of the same nature. That they link up with vascular vitreous veils (not seen in any of our cases) is also fairly certain. All these cases occurred in males, and it is noteworthy that a pair of brothers is recorded by Mann and Macrae, whilst a boy and his [? maternal] uncle are noted by Mann. It is justifiable to conclude that the cases recorded here, as also those of vascular veils in the vitreous and those of cystic detachment of the retina, are all instances of one and the same entity—an affection which is sex-linked or at any rate sex-limited in character and possibly congenital.

* Figs 12 and 13 are reproduced from this Journal, 22, 2, Figs 1 and 3.

FIG. 12.—Congenital vascular veil in the vitreous. Appearances in right eye of John G., aged 17, younger brother of case illustrated in Fig. 13 (after Mann and Macrae, 1938).

FIG. 13.—Congenital vascular veil in the vitreous. Appearances in right eye of Joseph G., aged 20, elder brother of case illustrated in Fig. 12 (after Mann and Macrae, 1938).

*Relationship to Congenital Total Detachment of the Retina (Pseudoglioma).—*The literature contains six records of the familial occurrence of pseudoglioma and these suggest recessive sex-linkage. Figs 14 to 18 show the pedigrees of five of these cases.

FIG. 14.—Pedigree showing bilateral pseudoglioma in two girls, and right pseudoglioma in their brother. Their father may have been affected and the parents were first cousins (after Clark, 1898; and Collins, 1893).

FIG. 16.—Pedigree showing pseudoglioma in two brothers, whose maternal uncle was "blind, deaf, and mentally abnormal" (after Heine, 1925).

FIG. 15.—Pedigree showing pseudoglioma inherited in a presumably recessive sex-linked manner (after Pagenstecher, 1913).

(i) *Clarke* (1898, *Fig. 14*).—This would appear to be the oldest pedigree on pseudoglioma and would suggest recessive autosomal inheritance. It is, however, not inconsistent with the reading of recessive sex-linkage, as it is possible that the father was affected, and that the mother, a first cousin, was a carrier. (A pathological study on an affected member was recorded by Collins in 1893.)

(ii) *Pagenstecher* (1913, *Fig. 15*).—Here the evidence of sex-linkage is fairly definite.

(iii) *Heine* (1925, *Fig. 16*).—This small pedigree is consistent with recessive sex-linkage.

(iv) *Wilson* (1936, Fig. 17).—This pedigree, too, suggests recessive sex-linkage.

(v) *Wilson* (1949, Fig. 18).—This extensive pedigree leaves little doubt that inheritance is in a sex-linked recessive manner. There is, in addition, the possibility of manifestation in a woman.

(vi) *Pajtáš* (1950).—An affected man had an affected grandson, through his daughter, herself unaffected. She in turn has two affected grandsons, through a daughter, also unaffected.

FIG. 17.—Pedigree showing pseudoglioma in boys in three collateral branches and in a maternal uncle (after Wilson, 1936).

FIG. 18.—Pedigree showing recessive sex-linked inheritance of pseudoglioma (after Wilson, 1949).

Relationship to Falciform Detachment.—The hereditary nature of falciform detachment has been stressed by Weve, who found a high incidence of consanguinity. Fig. 19 is a reconstruction from Weve's most fully recorded family. It brings out two points of significance:

- (1) The occurrence of pseudoglioma in a brother of a boy with falciform detachment.
- (2) The occurrence of pseudoglioma in a boy of a collateral branch of the family whose parents were first cousins. Weve has stressed that falciform detachment and pseudoglioma must be regarded as fundamentally the same lesion in different degrees of severity. This pedigree is as consistent with recessive sex-linkage as with an autosomal recessive condition, but neither reading can be regarded as conclusive.

The earlier records appear to show that this affection is confined

almost entirely to boys (Mann, 1935 ; Weve, 1935, 1938), but subsequent records not infrequently refer to girls (Theodore and Ziporkes, 1940). This in itself does not invalidate the reading of recessive sex-linkage, as seen in the Clarke pedigree (Fig. 14) in which the father was affected and the mother was presumably a carrier, but such occurrences are exceptional. Alternatively, there is the possibility that manifestation in women may be fairly high. Fuller pedigrees than are at present available are necessary to clarify this issue.

On the presumably uniform mode of inheritance of these various affections, and on the clinical evidence that falciform detachment is

FIG. 19.—Pedigree showing occurrence of pseudoglioma and congenital falciform fold in two collateral branches of a family (after Weve, 1935).

a variant of pseudoglioma, it is tempting to suggest that congenital total detachment (pseudoglioma), congenital falciform detachment, juvenile (? congenital) cystic detachment, and vitreous vascular veils, are all one and the same entity, constituting a group that is inherited in a recessive sex-linked manner. The most severe manifestation is congenital total detachment, whilst cystic detachment is probably a less severe lesion than falciform detachment. As yet little is known of the end stages of falciform detachment, and the present study suggests

that cystic detachment in boys is a far from stationary lesion.

Genetic Basis of Cystic Detachment.—Regarding the frequency of a genetic factor in cystic detachment of the retina, only two negative findings can be recorded at present. By the courtesy of Mr. Juler, one of us (A.S.) was able to follow up the families of two of his cases, but with negative results. Both families were, however, small. The findings were likewise negative in sixteen cases of cystic detachment of the retina in young men seen at the Royal Eye Hospital during the past five years. As this was a retrospective enquiry and no families, except one, were actually examined, the findings have to be accepted with some reserve.

SUMMARY

(1) An account is given of a family with eight affected men over three generations, the four youngest of which showed cystic detachment of the retina, and two (or possibly three) of the older members

extensive degenerative changes in the fundus, presumably the end stage of the affection.

(2) The range of appearances suggests that cystic detachment is a slowly progressive affection, possibly congenital in origin. The affection may be confined to one eye only, and may occasionally take the form of an abortive falciform detachment or a mere linear scar. Generally the end stage is extensive retinal atrophy.

(3) It is suggested that the affection is sex-linked; and that congenital total detachment of the retina, congenital falciform detachment of the retina, cystic detachment as seen in boys and young men, and vascular vitreous veils, are all different aspects of one and the same entity showing considerable interfamilial variation.

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APPENDIX

Pedigree of the P. Family

(see Fig. 1)

Generation I.—Nothing is known of this generation; their name was L.

Generation II.

(1) *Elizabeth L.* (II, 2), married Fred P. (II, 1) of Cambridge, who is reputed to have had good sight in both eyes, and who died aged 63. He had no brothers or sisters and nothing is known of his parents, except that his mother is reputed to have had good sight. Elizabeth herself had one bad eye, reputedly from cataract, all her life; she died aged 54, having had thirteen children.

(2) — *L.* (II, 3), lived at, or near, Belvedere, Kent. Nothing is known of him. It is possible that he died young.

Generation III.

(1) *Fred P.* (III, 1), died in Manitoba, Canada, aged 40; married, one son.

(2) *William P.* (III, 2), aged 66, of Cambridge; married, three children. Left eye shows a fundus similar to that seen in the left eye of his brother, Percy (III, 7).

(3) *Charles P.* (III, 3), died about 1920; unmarried; reputed to have had good sight.

(4) *Harry P.* (III, 3), died aged 59; married, no children; reputed to have had good sight.

(5) *John P.* (III, 5), died aged 59; married, no children; reputed to have had good sight.

(6) *Ada P.* (III, 6), aged 56; married into T. family, five children; lives at Peterborough; examined and found normal.

(7) *Percy P.* (III, 7), aged 60; unmarried. Left eye (Fig. 11) shows a healed detachment. Right eye shows a lesion suggestive of central choroidal sclerosis. Suffering from severe heart failure.

(8) *Albert P.* (III, 8), aged 54, of Cambridge; married, three children. Right eye (Fig. 10) shows a retinal fold. Left eye is normal.

(9) *Sidney John P.* (III, 9), aged 51, of Cambridge; married, two sons. Right eye, removed in 1932 on account of an accident at about the age of 13 years, is stated to have been defective before the accident. Left eye (Fig. 9) shows a healed detachment.

(10-13). Four other children; their sex and position in the family are unknown; they died young.

Generation IV.

(1) *Son of III, 1*, lives in Canada; reputed to have normal sight.

(2) *Daisy P.* (IV, 2), aged 42, of Cambridge; married into G. family, three daughters; examined and found normal.

(3) *Fred P.*, (IV, 3), aged 40, lives in Australia; married, no children; reputed to have normal sight.

(4) *Charles P.* (IV, 4), aged 37, lives in Bermuda; married, one daughter.

(5) *Irene T.* (IV, 5), aged 32; married into S. family, two children; examined and found normal.

(6) *Fred T.* (IV, 6), aged 30, of Peterborough; married, no children; both eyes affected (Figs 7 and 8).

(7) *Gilbert T.* (IV, 7), aged 28; married, one son; examined and found normal.

(8) *Reginald T.* (IV, 8), aged 25; both eyes affected (Figs 5 and 6).

(9) *Peter T.* (IV, 9), aged 19. Left eye; vision less than 6/60 (Fig. 4). Right eye: vision 6-12, scar in fundus at 7 o'clock (Fig. 3).

(10) — *P.* (IV, 10), aged 26, of Cambridge; married into the H. family, no children; examined and found normal.

(11) *Edward P.* (IV, 11), aged 25; married, no children; examined and found normal.

(12) *Roy P.* (IV, 12), aged 23; married, no children; examined and found normal.

(13) *Geoffrey J. P.* (IV, 13), aged 31, of Cambridge; married, two children; examined and found normal.

(14) *Barry P.* (IV, 14), aged 8; examined and found normal.

Generation V.

(1-3) *Daughters of Daisy G.* (IV, 2): *Betty G.*, aged 21, married into Sk. family; *Mary G.*, aged 17; *Jennie G.*, aged 3; all examined and found normal.

(4) *Daughter of Charles P.* (IV, 4); reputed normal.

(5) *Brian S.* (V, 5), son of *Irene S.* (IV, 5), aged 14 (Fig. 2). Right eye normal. Left eye: vision 6/60.

(6) *June S.* (V, 6), daughter of *Irene S.* (IV, 5), aged 13; examined and found normal.

(7) *Clifford T.* (V, 7), aged 2½, son of *Gilbert T.* (IV, 7); examined and found normal.

(8 and 9) *Sidney and Eleanor P.* (V, 8 and 9), children of *Geoffrey J. P.* (IV, 13) aged 3½ and 2 respectively; both examined and found normal.