COMMUNICATIONS

DOYNE'S HONEYCOMB RETINAL DEGENERATION*† CLINICAL AND GENETIC FEATURES

BY

W. G. PEARCE

M.R.C. Population Genetics Research Unit, Oxford

IN 1899 Doyme described a fundus condition which he had observed in four sisters. The ophthalmoscopic appearance was of closely-grouped white spots involving the disc-macular area in a pattern he termed "Honeycomb". He believed the lesions were probably due to an exudate in the choroid, and therefore called the condition honeycomb choroiditis (Doyme, 1910), although it was shown shortly afterwards by Treacher Collins (1913) that the white spots were nodular thickenings of Bruch's membrane and that the choroid was essentially normal. The number of white spots increased with ageing until late in life when they became confluent to produce a homogeneous atrophic area enclosing the optic disc and macular areas.

Doyme recognized that the lesion was inherited and even drew up a pedigree (unpublished) of three families in which the condition had been found. He was unable to comment on the type of heredity as at that time mendelian principles were only just being rediscovered.

Later, some of Doyme's families were followed up and reported on, notably by Tree (1937) and Franceschetti, François, and Babel (1963). The condition has been found to exist elsewhere in Britain (Foster, 1932) and in other parts of the world (Alper and Alfano, 1953; Pajtaš, 1950; Fuchs, 1956).

A genetical survey of this condition was recently undertaken in the areas from which Doyme drew his cases and various aspects of this survey are described in a separate paper (Pearce, 1967). The present communication outlines the main genetic findings and describes, among those found affected, the considerable variation noticed both in the ophthalmoscopic appearance and in the degree of visual disturbance. The value of these features in assessing prognosis is also discussed.

Methods of Investigation

Altogether 296 members of six different families were examined in their homes with a direct ophthalmoscope. The corrected near visual acuity, using the charts approved by the Faculty of Ophthalmologists, was recorded for each eye. If the fundus pattern appeared to be in any way unusual, the retina was photographed with a KOWA fundus camera with Kodachrome II film. 10 ml. of blood were taken by venepuncture for blood group determination.

Genetic Findings

The pedigrees of the six families in which 76 members were found to be affected are shown on the insert. Three of the families (A¹, A², B) had been described originally by Doyme

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† Address for reprints: M.R.C. Population Genetics Research Unit, Old Road, Headington, Oxford.

and it was possible to trace their descendants by using Doyne's unpublished pedigree of 1910. Two of the other three families (C and E) were referred by general practitioners in the south-eastern area of the Oxford Regional Board in response to our request for information about patients with Doyne's honeycomb degeneration. The final family (D) was ascertained through a search of the medical records at the War Memorial Hospital, High Wycombe.

Families C and D originated from the same area as Doyne's families A₁ and A₂. Although it was not possible to integrate these two new families into the older kindreds, it appeared quite possible that they shared a common ancestor. Family E originated from another area of the country, and was ascertained only because one of its members had moved into the area surveyed. Although it was possible to link the families studied with those examined by Doyne 60 years ago, genetic analysis has been restricted to those examined during the present survey.

Cases were assumed to be familial if one of their parents was found to be affected or, if these were dead, affected cases were found among their parents' siblings or their offspring. In only one case (D II 4) was there a possibility that the condition was not familial, and was due to a mutation. This was unlikely but as neither parents nor siblings of this patient were available for examination she has been excluded from the genetic analysis. The affected individuals fell into two classes, depending on whether the affection of the parent could be confirmed (E) or only assumed (NE).

Class E consisted of those families in which the affected parent was examined during the present survey (Pedigree-Category E) or had previously been examined by an ophthalmologist (Pedigree-Category EE). Amongst these the combined ratio of affected to unaffected was 49 : 73, and the sex ratio of those affected was 20 males to 29 females.

Class NE consisted of those families in which the parent could not be examined but was known to have affected sibs as well as affected children and could therefore be assumed to be probably affected (Pedigree-Category PA). For some of these parents there was a history of visual defect consistent with Doyne's degeneration (Pedigree-Category PA₁) but others had either died before the age when visual symptoms usually begin or had no history of visual impairment (Pedigree-Category PA₂). Amongst these the ratio of affected to unaffected was 26 : 27, and the sex ratio of those affected was 10 males to 16 females.

Factors supporting an autosomal dominant gene as the cause of the degeneration were:

(i) Affected individuals were always found to have an affected parent whenever the parent was available for examination.

(ii) Transmission through three generations was found during the present survey in four of the six sibships.

(iii) The number of affected males (30) compared with that of affected females (45) was not significantly different ($\chi^2 = 3.00$).

(iv) The number of affected individuals (75) compared with the number of unaffected (100) was not significantly different ($\chi^2 = 3.57$).

The autosomal dominant gene was transmitted in a "regular" manner—*i.e.* all affected cases had an affected parent. No cases were seen in which transmission occurred in an "irregular" dominant manner, as suggested by the pedigrees of Tree (1937) and Franceschetti (1961), which is characterized by skipping a generation—*i.e.* an unaffected child of an affected parent in turn produces affected children.

PEDIGREE A1

PEDIGREE A2

PA Probably affected - not examined by ophthalmologist
PA1 With history of eye defect
PA2 No history of eye defect
CA Confirmed affected - seen by ophthalmologist
NA Not affected - seen by ophthalmologist
U Unknown diagnosis
NT Not traceable
E Examined 1965-66
R Refused examination
EE Examined elsewhere by ophthalmologist
NE Not examined
? Too young for diagnosis
* Eyes examined by Collins (1933)
? Number not known
◇ Sex not known
Propositus

PEDIGREE B

Clinical Findings

76 members of six families were found to have Doyme's honeycomb degeneration. In all cases the lesions were bilateral and usually symmetrical. Any asymmetry was slight and only detectable by minor differences in the visual acuity.

Doyme's honeycomb degeneration was not detectable in children or adolescents and was first observed in those between the ages of 20 and 30 years. Initially, a few small round white "colloid" bodies appeared in the peripapillary area and frequently in the macular area as well (Fig. 1c). They usually increased in number but not in size until late middle age, by which time the posterior pole was often covered with small white spots (Fig. 1d). At this stage the spots coalesced and the overlying retina became thin and atrophic (Fig. 1a). However, there were numerous exceptions to these stages of development, even within the same family and age group (Figs 1a and b).

The variations in ophthalmoscopic appearance are illustrated in the fundus photographs (Fig. 1, facing p. 76).

The 76 affected individuals were divided into two groups, depending on their reading visual acuity. These are summarized in Table I, which shows the age of each person in the appropriate group.

TABLE I
76 AFFECTED PERSONS GROUPED BY DEGREE OF VISUAL ACUITY AND AGE

Group		I (32)	II (44)			
Visual Acuity		Unable to read N5 with one or both eyes	Able to read N5 with both eyes			
Retinal Involvement		Macula affected	(1) Macula affected	(2) Macula not affected		
Age of each Individual (yrs)		90				
		89 88 85 84 82				
		79 76 72 72 71	70		75	
		68 67 66 66 65	65 64		68 67 65 65 64	
		65 64 64 64			62 60	
		64 62 61 61				
		58 57 54	56 55 50		56 55	
		45 43 42	47 46 43 43 41		48 43	
			40 40 40			
		35	39 39 37 35		39 38 35	
			32 30		33 33 32	
		27	27		29 29 28 27 23	
Total Cases	35 yrs and over	31	18	15		
	Under 35 yrs	1	3	8		
	All ages	32	21	23		

Group I.—32 individuals who were unable to read N5 with one eye or both: 26 were unable to read N5 with either eye and they all had symptoms, while of the six who could read N5 with one eye, only one had symptoms (Table II, overleaf).

Group II.—44 individuals who were able to read N5 with both eyes: in 21 of them (II₍₁₎) both the peripapillary and the macular areas were involved and in the other 23 patients (II₍₂₎) the optic disc area only was affected—no lesions being detectable at the macula.

TABLE II
GROUP I—VISUAL ACUITY LESS THAN N5

Eyes Affected	One	Both	Total
Symptoms	1	26	27
No Symptoms	5	0	5
Total	6	26	32

In younger patients one could not be confident that the number and distribution of lesions would remain constant. However, by the age of 35 years, the distribution of lesions was relatively fixed, although some increase in number would be expected as the individual aged. For the 64 individuals in both groups who were aged 35 or over, the mean age, standard deviation, etc., are given in Table III.

TABLE III
AFFECTED PERSONS AGED 35 YEARS AND OVER GROUPED
BY VISUAL ACUITY

Group	I	II ₍₁₎	II ₍₂₎
No. aged 35 years or over	31	18	15
ΣX	2,059	845	840
ΣX^2	142,533	41,487	49,232
$(\Sigma X)^2/n$	136,757.45	39,668.06	47,040
SS	5,775.55	1,818.94	2,192
$\bar{X}$	66.42	46.94	56.00
S.D.	13.87	10.34	12.51

Group II₍₂₎ contained fifteen (23.4 per cent. of those aged 35 or over) with normal visual acuity in each eye in whom the lesions were found only in the peripapillary area. Their mean age was 56 years. Group II₍₁₎ contained eighteen individuals (28.1 per cent. of those aged 35 or over) who also had normal visual acuity in each eye but who showed involvement of the macular area as well as of the optic disc. Their mean age was 46.94 years. The age distribution of the Group II individuals aged 35 years or over is shown in Fig. 2. Comparing Groups II₍₁₎ and II₍₂₎ ($t_{31} = 2.28^*$), the probability (P) that they would occur by chance within the examined population was between 1 and 5 per cent.

FIG. 2.—Age distribution of persons in Group II aged 35 years and over.

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FIG. 1.—(a) Family C, IV. 13, aged 64, right eye. Near visual acuity = Counting fingers
 (b) Family C, IV. 12, aged 65, right eye, brother of (a). Near visual acuity = N6
 (c) Family D, IV. 2, aged 40, left eye. Near visual acuity = N5
 (d) Family A₁, IV. 25, aged 61, right eye. Near visual acuity = Counting fingers
 (e) Family A₁, IV. 31, aged 65, right eye. Near visual acuity = N5
 (f) Family E, IV. 1, aged 42, left eye. Near visual acuity = N8

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Group I contained 31 individuals (49.5 per cent. of those 35 or over) and the mean age was high (66.42 years). Comparing I with II₍₂₎ ($t_{44} = 2.46^*$), the probability (P) that they would arise by chance from the examined population was also 1 to 5 per cent.

The significant difference between these two latter groups is probably due to the large number of very elderly persons in Group I; with six aged 82 to 90 years the distribution skewed toward the older ages.

The significant difference in age between II₍₁₎ and II₍₂₎ appeared most likely to be due to the different distribution of the lesions. With increasing age, the visual acuity of those in II₍₁₎ who had macular involvement eventually deteriorated because of foveal disturbance so that the subjects slipped over into Group I. Those in II₍₂₎ who had no involvement of the macular area did not develop severe visual alteration as they aged and therefore remained in Group II₍₂₎.

Discussion

The pedigrees given by Franceschetti, François, and Babel (1963) and Tree (1937) both suggested that Doyme's honeycomb degeneration was due to a dominant gene. This has been confirmed in the present study. Furthermore, the dominant gene mutation has been shown to be most probably inherited in a regular manner. This conclusion is based on the absence of unaffected parents of affected individuals. No cases were found of an unaffected parent transmitting the condition to his children.

Although the area of gene effect was limited to the inner layer of Bruch's membrane at the posterior pole of the eye, considerable variation was found in the ophthalmoscopic appearance. This variation occurred within as well as between the different families (Fig. 1). Variability of expression has been detected in other conditions which are due to a dominant gene where the gene is manifested in the heterozygous state, as in Marfan's syndrome (François, 1961) and in Rieger's malformation (Pearce and Kerr, 1965). Variable gene effect was also the most probable explanation for the differences in ophthalmoscopic appearance in Doyme's honeycomb degeneration.

The accuracy of Doyme (1899, 1910) and of Tree (1937) in describing the disease has been confirmed by this study. In the absence of a long-term follow-up, nothing appeared during the present study to invalidate the progressive stages of the disease as described by the above authors in the majority of cases. Here, in the early stage, usually between 20 and 30 years of age, white spots appeared in the peripapillary areas and usually in the macular area as well. During the second phase, approximately 35 to 60 years, the lesions multiplied, although little change occurred in their distribution. In the late stages the white bodies became confluent to produce a white atrophic area. However, a number of cases did not follow this usual course, and in them lesions were not detectable in the macular region.

The absence of lesions in the macular area in a 35-year-old subject can be regarded as a favourable prognostic sign (Fig. 1e). With lesions involving the macula, good visual acuity remained until the fovea itself was implicated. The time taken for this to occur appeared to vary considerably from case to case, but once visual deterioration began, it proceeded rapidly to leave the patient with a dense central scotoma and a mean visual acuity of less than N48. This final visual deterioration paralleled the confluence of the separate white spots into an amorphous atrophic area enclosing the disc-macula region.

Although lesions in the macular area were absent in fifteen cases, lesions in the peripapillary area were always present. The appearance of white colloid bodies on the nasal side of the optic disc may be regarded as virtually pathognomonic of Doyme's honeycomb degeneration, as was suggested by Purvis (1966), although they may rarely be detected on the temporal side of the disc only (Fig. 1f). This feature, with the usual accompanying family history, will help to differentiate Doyme's degeneration from those other pre-senile and senile degenerations in which "colloid" bodies are frequently found involving the macular area.

Summary

A study of 76 patients with Doyme's honeycomb retinal degeneration has shown the condition to be due to a dominant gene mutation most probably inherited in a regular manner.

The condition first appeared in individuals aged between 20 and 30 years. By age 35 the areas of the retina which were to be affected showed evidence thereof. It was found that, of 64 patients aged 35 or over, 49 (76.5 per cent.) followed the pattern of evolution previously described by Doyme and Tree. Within this group there were considerable variations in the distribution of the lesions but the macular area was always involved. The remaining fifteen patients (23.5 per cent.) were less severely affected, the lesions being restricted to the peripapillary area. A better prognosis could therefore be given to persons in this latter category.

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