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Sorsby's Pseudoinflammatory Macula Dystrophy—Sorsby's Fundus Dystrophies

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Summary
The findings are presented on the updated Kempster pedigree with Sorsby's fundus dystrophy. The study confirms the features described in other families: autosomal dominant inheritance with complete penetrance, loss of central vision due to subfoveal ingrowth of new vessels, and progressive peripheral chorioretinal atrophy. By contrast to other reports the family in the current study have peripheral retinal dysfunction, a deposit of a subretinal yellow material throughout the fundus and a tritan colour defect, all prior to the loss of central vision; in some patients there was loss of central vision from atrophic disease, rather than from ingrowth of subretinal new vessels; and, there was a different temporal progression of the central subretinal neovascular complex. These features suggest the possibility of genetic heterogeneity.

In 1949 Sorsby described a progressive fundus disorder which had three key features.[1] The inheritance was autosomal dominant, there was bilateral loss of central vision in the fifth decade of life from subretinal neovascularisation, and progressive atrophy of the peripheral choroid and retina leading to loss of ambulatory vision by the seventh decade in most cases. The disorder was reported in five families who had a widespread distribution: the Carvers came from Cumbria, the Kempsters and Randalls from London, and the Ewbanks from the southeast England. The histopathology on the Cranston sisters has been described,[2] but dominant inheritance was never proven so that some doubt must remain about the diagnosis. The peripheral chorioretinal atrophy which occurred in all families has been overlooked more recently and the condition was called a macular dystrophy by Duke Elder and Perkins.[3]

In 1971 Fraser and Wallace described a pedigree with similar features;[4] subsequent information has shown these patients to be a branch of the Randall family.[5] Some of the asymptomatic progeny had a deuteranomalous defect, raising the possibility of a functional deficit prior to the onset of an observed fundus change.

Hoskin and others published their findings on an updated pedigree of the Ewbank family in 1981.[6] Prior to any reduction of central acuity in this family, the authors found fine drusen in some patients, and in others a confluent deposit of yellow subretinal material at the macula. There was no colour vision abnormality at this stage. They concluded that these anatomical changes were reliable markers of the abnormal genotype.

In this paper the fundus findings of an updated pedigree of the Kempster family are presented. Certain features described here

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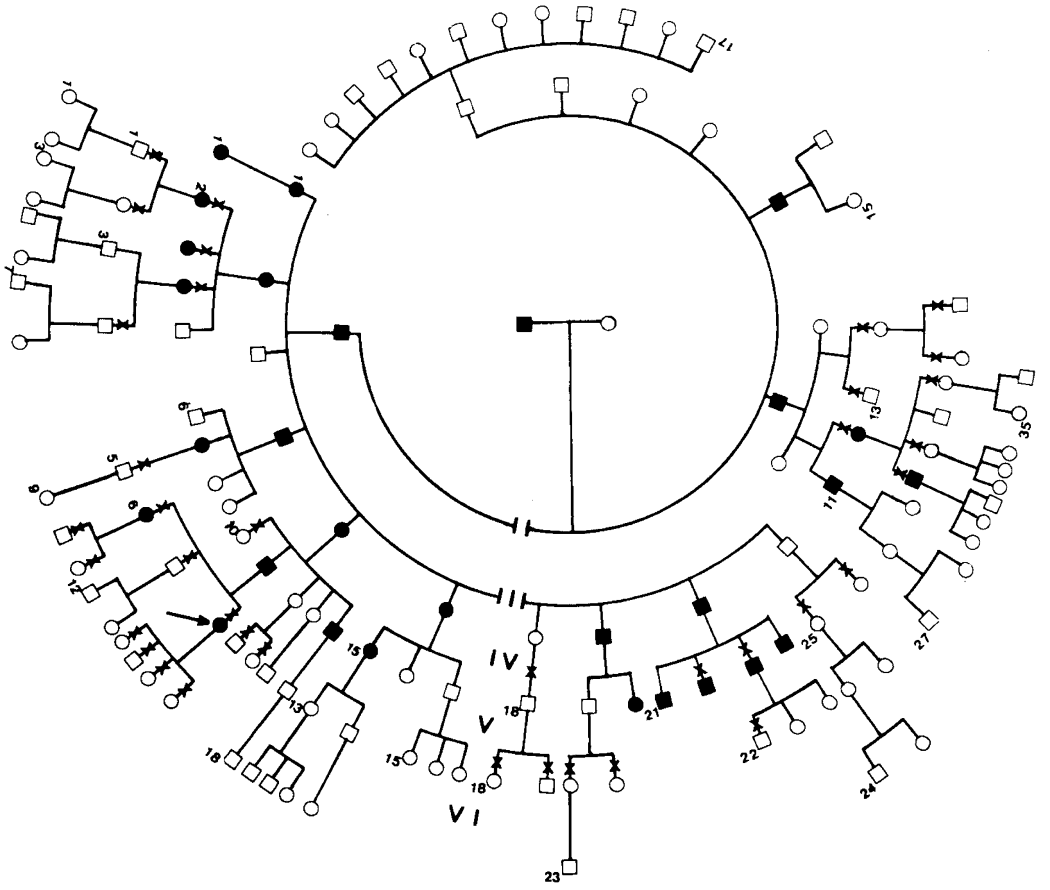

Fig. 1. *Kempster family pedigree.* ○, □ *unaffected female, male;* ●, ■ *affected female, male;* × *patient examined in this study.*

differ from other descriptions and imply possible genetic heterogeneity.

Materials and Methods

This study describes 37 previously unreported descendants of the Kempster family[1] (Fig. 1). These patients were reviewed over a period of 2 to 12 years and agreed to participate in further study: those at risk of having the abnormal genotype or who had lost vision in one eye were investigated by fluorescein angiography and Panel D-15 colour vision assessment.

Of these patients 10 were affected: seven had lost central vision in both eyes and two patients in only one eye. The remaining member had good vision with deposits of drusen and confluent yellow subretinal material in both fundi. Psychophysical testing (dark adaptation, static perimetry and fine matrix perimetry) was undertaken on two of the three affected patients with good central vision in one or both eyes. Dark adaptation and static perimetry were performed using an automated modified Lister perimeter as described by Ernst *et al.*[7] This apparatus uses red and green stimuli which enables separation of the relative contributions of rods and cones. Dark adaptation was evaluated at 25° in the nasal field after a standardised two minute bleach of that area. Photoreceptor sensitivity was investigated further under scotopic conditions using static perimetry at multiple extramacular sites and at varying degrees of eccentricity and meridional arcs. The technique of fine matrix perimetry allows

a sensitive analysis of photoreceptor function within a defined area and under a predetermined background luminance.[8] The apparatus consists of a high resolution television screen which presents a matrix of pulses of blue light covering 7×7 degrees of arc. In the one member of this family studied with fine matrix perimetry scotopic conditions were used and a paramacular test area was chosen. Results of all three tests are expressed in log unit elevation of threshold above normal.

Electroretinography (ERG) and electrooculography (EOG) were performed on the three patients with good central vision.[9,10]

Results

Inheritance

In generations III and IV all affected patients had an affected parent and 50 per cent of the children of all those with the abnormal genotype manifested the disease (Fig. 1). In subsequent generations some members had not reached the age at which the disease could become manifest.

Night Blindness

The first symptom suggesting the abnormal genotype was difficulty with night vision. It occurred up to 25 years prior to the loss of

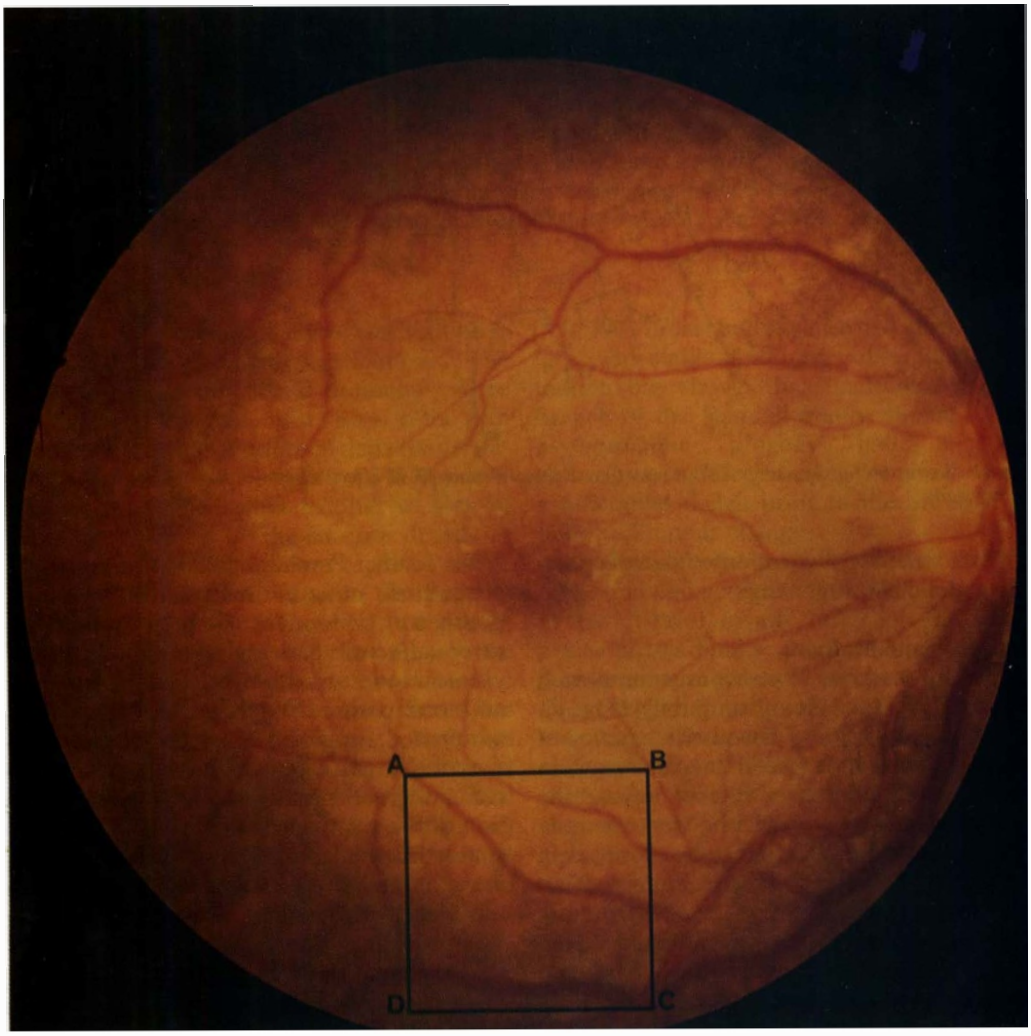

Fig. 2a.

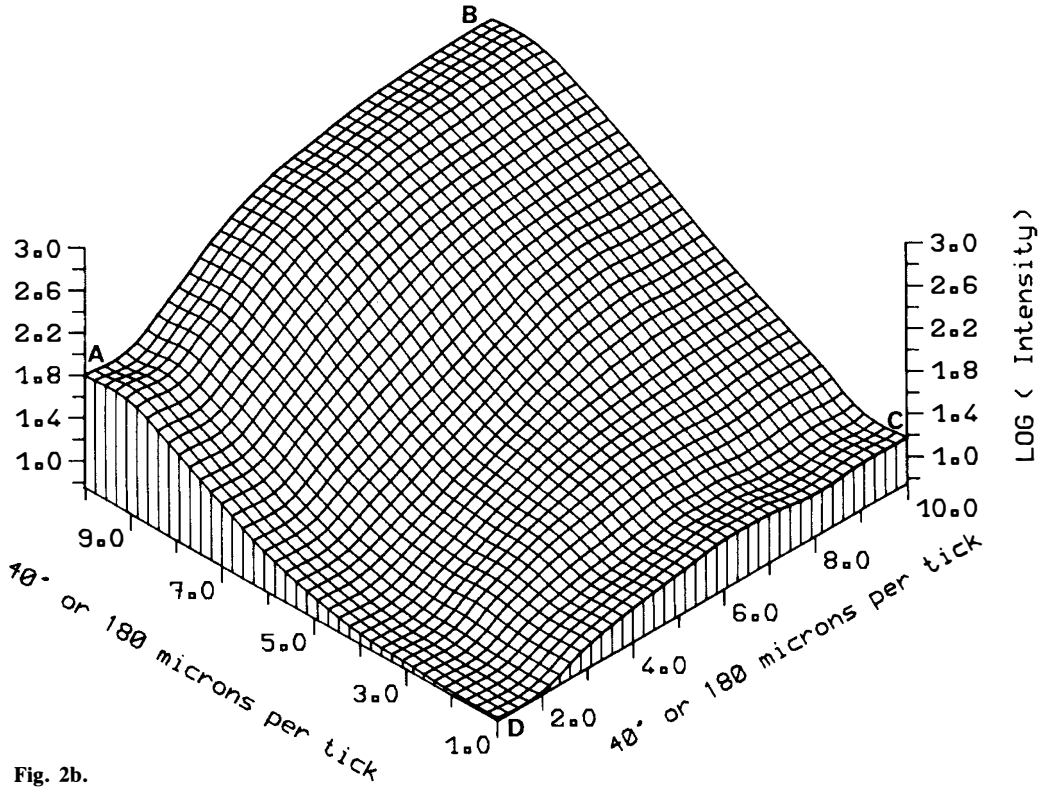

Fig. 2b.

Fig. 2. *Posterior pole of patient V/8 (2a). The square, labelled A BCD, shows the area tested by fine matrix perimetry which is plotted in Fig 2b. This area includes some of the more prominent subretinal yellow material.*

Computerised plot of the fine matrix perimetry on patient V/8 (2b—see text for details). Log intensity of threshold is plotted on the ordinate and the retinal coordinates on the abscissa. The greater the height in the plot the greater the sensitivity loss. Points A, B, C and D correspond to those similarly labelled in figure 2a. All areas show an elevated threshold and there are abrupt changes in threshold within the test area (7° × 7°) from 0.8 to 3.0 log units.

central vision and was clearly recalled by 8 of the 10 affected patients. The dark adaptation, performed in the midperiphery of the nasal field was abnormal in the 2 patients who were tested. In one patient, in whom pre-bleach dark adapted thresholds were elevated above the normal mean, dark adaptation following the bleach took over one hour which is about twice the normal time. Static perimetry showed widespread increases in rod thresholds with the baseline sensitivity 0.5 log units above normal. There were regional variations, with some areas having a reduction in sensitivity by at least 3.5 log units, the maximum measurable value of this apparatus. In the paramacular area tested with fine matrix perimetry, the thresholds ranged from 0.8 to 3 log units above normal i.e. a 6 to 1000 fold reduction in sensitivity (Fig. 2).

Colour Defect

An asymptomatic tritan colour defect was found at presentation in the three patients (four eyes) and this persisted until loss of central vision occurred.

Early Ophthalmoscopic Signs

Fundus changes were always bilateral but asymmetric. The three patients (four eyes) who were seen with good vision in at least one eye were examined in the fourth decade of life. At that stage these eyes had both drusen and confluent yellow subretinal material. The drusen were fine and densely packed and could extend from the macula to the equator. The yellow deposit initially appeared as a subtle discoloration, occurred throughout the fundus and was evident earlier in the periphery than the macula.

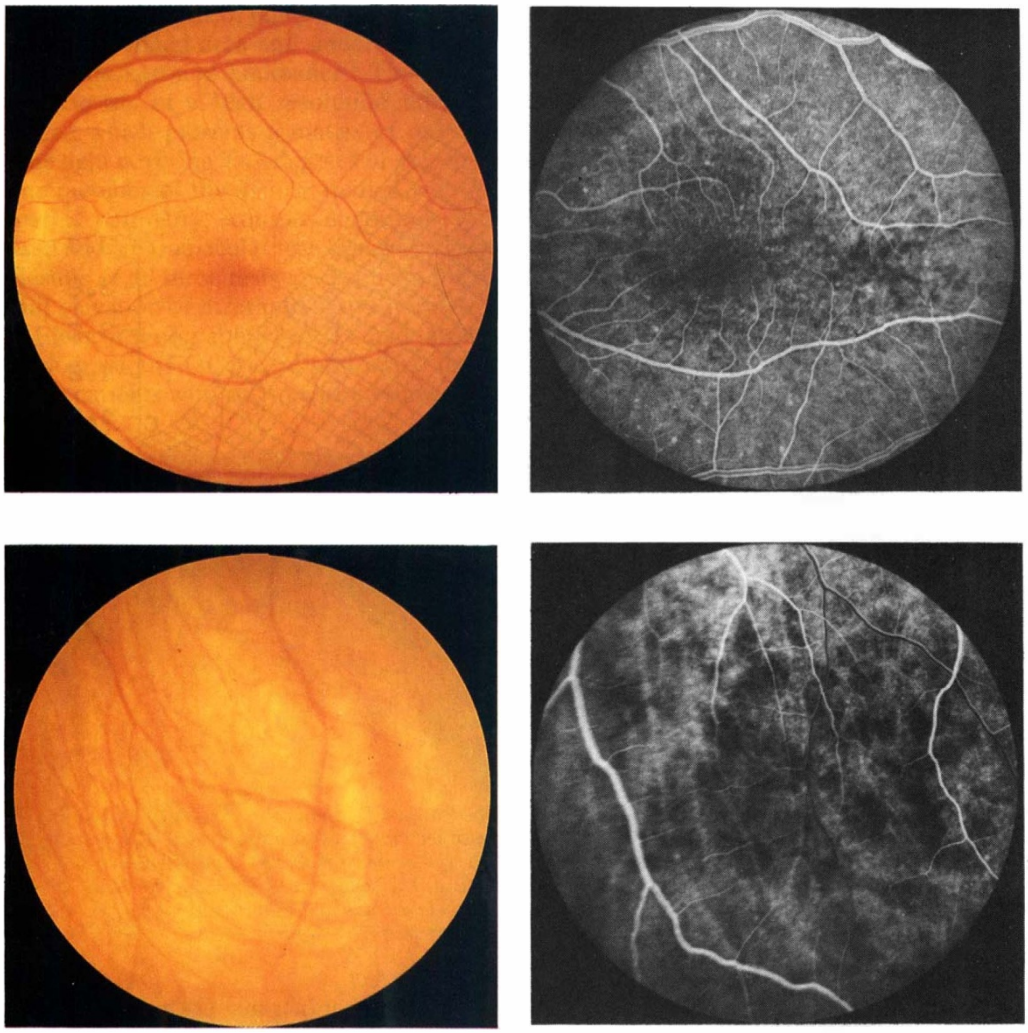

Fig. 3. *Macula of patient IV/29 who retained normal central vision in both eyes (3a). Drusen are clearly visible. Within the area of yellow material there is mottled choroidal hypofluoresence temporal to the fovea in the early part of the transit (3b). In the midperipheral fundus yellow subretinal material (3c) corresponds to the area of choroidal hypofluoresence and choroidal vessels are visible deep within this area (3d).*

Similar characteristics were seen on fluorescein angiography in both the macula and peripheral fundus (Fig. 3) but were more marked in the latter site. Mottled choroidal hypofluorescence occurred in the early part of the eye transit (Fig. 3b and d) which corresponded with the area of subtle yellow material.

In the eyes with normal vision the ERGs had normal a and b wave amplitudes, latencies and wave forms, using scotopic and photopic stimuli. The EOG results showed a reduced light rise in all cases with a range from 120 per cent to 165 per cent.

Macular Changes

Nine patients had lost central vision in one or both eyes prior to this review. In 7 patients it was clear by ophthalmoscopy that the visual deficit was due to a subfoveal disciform lesion. The remaining 2 patients had choroidal atrophy at the macula but no evidence of a disciform reaction (Fig. 4).

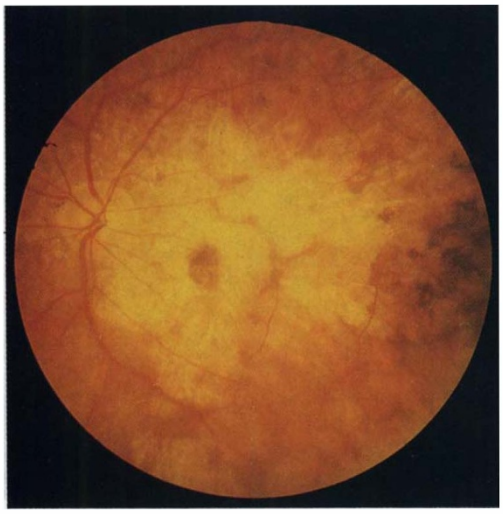

Fig. 4. *Macula of 60 year old patient IV/22 with count fingers vision. There is a large area of atrophy of the outer retina and choroid but no evidence of subretinal neovascularisation. Similar areas of atrophy extended out to the equatorial fundus.*

In the 7 patients with subretinal neovascularisation, central visual loss occurred at ages ranging from 38 to 53 years. Two of the 7 could recall a gradual loss of central vision over several months. The disciform scars were always large and became pigmented in the late stages. As the scar flattened atrophy became the predominant feature and after several decades had an appearance similar to choroidal sclerosis. Involvement of the fellow eye occurred in most patients up to 18 months after the first but one patient retained good central vision in the second eye at the time of last review, 3 years after losing central vision in the first eye. The evolution of macular disease was closely recorded in the second eye of one patient (Fig. 5). The hypofluorescence on angiography became much more marked with time as the yellow deposit increased and the large choroidal vessels were visible deep to this material. Occult new vessels were seen at presentation in this woman but remained inactive for 9 months with preservation of good acuity until a subfoveal disciform developed.

The two remaining patients who lost central vision prior to the review, had outer retinal and choroidal atrophy involving the macula. These patients were brothers, and good vision was preserved until the middle of the sixth decade of life. One of the brothers (Fig. 4) had a long history of nyctalopia and had multiple patches of chorioretinal atrophy throughout the postequatorial fundus in addition to that at the macula.

Peripheral Chorioretinal Atrophy

Progressive chorioretinal atrophy of the peripheral fundus leading to social blindness occurred in five of the six patients who had reached the age of 60 years. In addition, three younger patients, still in the fifth decade of life, had identifiable peripheral fundus change. These eight patients included all who gave a history of difficulty with night vision.

Discussion

In this study we have presented the fundus findings of the updated pedigree of the Kempster family.[1] This confirms the autosomal dominant inheritance pattern described originally by Sorsby and later by Hoskin,[6] and in this study we have demonstrated complete penetrance. Of the nine patients who lost central vision in one or both eyes, there was ingrowth of subretinal new vessels beneath the fovea in seven patients. We have also found late peripheral chorioretinal atrophy as reported by Sorsby. In the Ewbank family this change was seen in sixty per cent of patients by the age of seventy years[6] and this was not different to the Kempster family.

However this family study shows four features which are different from those reported in other pedigrees and specifically in the Ewbank family:[6] prior to the loss of central vision there was peripheral retinal dysfunction in most patients and a tritan colour defect in those seen with early macular disease; the subretinal yellow material was not limited to the macular area but occurred throughout the fundus; some patients lost central vision from atrophic disease rather than the ingrowth of subretinal new vessels; and there was a different temporal progression of the subretinal neovascularisation leading to loss of central vision.

Signs Before Central Visual Loss

The peripheral retinal dysfunction which was manifest as difficulty with night vision was

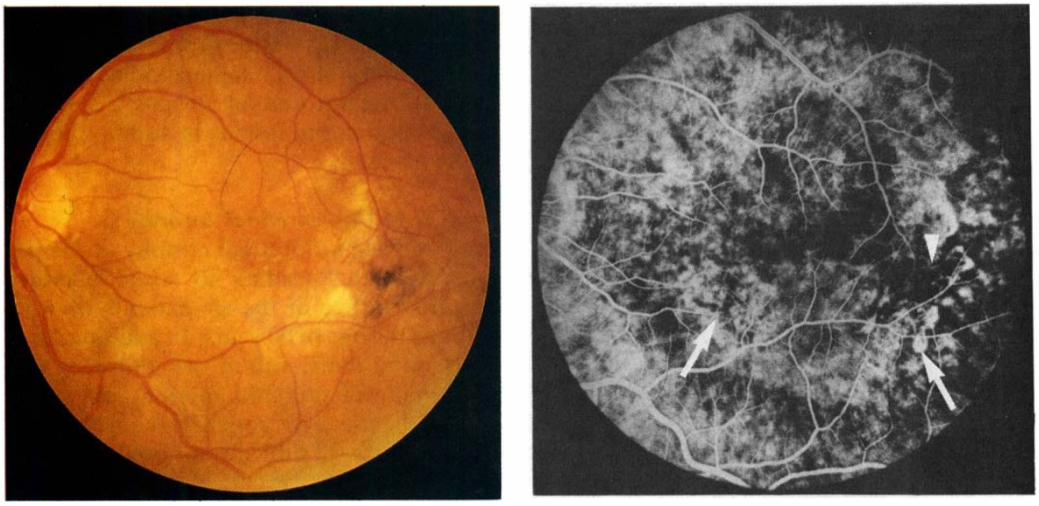

Fig. 5. *Posterior pole of 44 year old patient V/6 who was observed during evolution of subretinal new vessels. The area of yellow subretinal material (4a) corresponds with the area of choroidal hypofluoresence in this early part of the dye transit (4b). Large choroidal vessels are visible deep within the lesion temporal to the fovea (arrow head). Multiple areas of subretinal new vessels are seen (arrows).*

progressive and was symptomatic for up to 25 years before loss of central acuity. The prolonged dark adaptation times imply abnormal rod mediated function in the test area. Static perimetry also demonstrated abnormal rod function throughout the fundus with further increases in threshold by as much as 3.0 log units in local regions. Fine matrix perimetry showed this abnormality to be present in the macular area and that abrupt changes in threshold occurred over a very small area. These psychophysical findings imply a diffuse disease process throughout the fundus but with multiple localised areas of increased abnormality. Further, our data suggest the possibility that psychophysical tests may detect earlier changes in patients at a younger age which may help to typify the metabolic abnormality of this disease.

The presence of a tritan colour defect is not surprising in view of the known propensity for blue cone damage in early macular disease. In our study the colour defect was present when first tested at the time when a subtle yellow deposit was visible at the macula. If the functional defect was present before any ophthalmoscopic change as suggested by Fraser and Wallace[4] this could be used to detect the abnormal genotype.

The electrophysiological results imply that a functional defect of the retinal pigment epithelium occurs early in the disease.

Subretinal Yellow Material

The yellow subretinal material was visible throughout the fundus in all the patients in the current study who were seen in the fourth and fifth decades of life. By contrast in the Ewbank family the yellow material was reported to be localised to the macula.[6] In the older members of the Kempster family this material was sometimes less evident. This could be because the material had decreased in amount or that it was obscured by the peripheral chorioretinal pigmentary change. Fluorescein angiography in the Kempster family demonstrated similar changes in the areas of this deposit in the peripheral fundus to that at the macula (Fig. 3). These angiographic features were also seen in the Ewbank family: the yellow material corresponded to the area of choroidal hypofluorescence during the early part of the dye transit but the large choroidal vessels remained visible.[6] This supports Hoskin's conclusion that the hypofluorescence could not be explained by obscuration alone but implied delayed and uneven perfusion of the choriocapillaris in that region. This

may be homologous with the histological observation of a widening of the intercapillary pillars of the choriocapillaris in the eyes of the elderly.[11]

Central Acuity Loss

Neovascular ingrowth was the cause of loss of central vision in 8 of 10 patients. This was preceded in one eye by occult neovascularisation (Fig. 5) which exhibits different growth characteristics to manifest, well-defined subretinal complexes.[12,13] Gradual loss of central vision in three other eyes suggests that occult subretinal new vessels may be common in this family. This contrasts with the rapid loss of central vision due to manifest new vessels seen in the Ewbank family.

The age of onset and the temporal progression of the neovascularisation at the macula is strikingly different between the Ewbank and Kempster families.[6] In the former there was precipitous loss of central vision up to twenty years earlier than in the Kempsters and occult neovascularisation was never seen. Thus the disease in the Ewbank family is characterised by the rapid onset of loss of central vision at a much earlier age compared with the Kempster family.

Atrophic macular disease without evidence of choroidal neovascularisation was responsible for the loss of central vision in two patients. Both retained good vision until the sixth decade of life and manifested changes resembling that seen in geographic atrophy in the elderly. This does not exclude the possibility of neovascularisation having occurred at some stage. However it is possible that the subretinal disease alone may have induced receptor cell and retinal pigment epithelial cell death. These findings may reflect variable expression of the abnormal gene in the Kempster family and further distinguishes the disorder in this family from that reported in the Ewbank family.

Conclusions

The differences between the manifestations of the disorder in the family in this study and the Ewbank family suggest the possibility of genetic heterogeneity. Subsequent clinical and psychophysical assessment of these and other families with this disorder plus histological examination of affected eyes may support this. In addition, linkage studies offer the possibility to determine if more than one gene locus is involved in the transmission of the disease.

In all families described so far the disorder has involved not only the macula but also the peripheral fundus. This feature has been ignored in some of the recent descriptions where the disorder has been labelled a macular dystrophy. Because of widespread fundus involvement we believe that it is better termed a fundus dystrophy.

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