HEREDITARY DEGENERATION OF THE MACULA

BY Derrick Vail, M.D., AND (BY INVITATION) David Shoch, M.D.*

Degenerations of the retina have been known for many years and a variety of names has been applied to the various forms based in large part either on the ophthalmoscopic appearance of these lesions or on the age and mode of onset. Such terms as tapeto-retinal degeneration, primary degeneration, abiotrophy, progressive atrophy, and retinal dystrophy have been used interchangeably. However, as the anatomy and pathology of the diseased structures were studied, a more rational classification became possible. Thus macular degenerations were at one time divided into those with and without central nervous system involvement. It is now felt that degenerations of the retina associated with cerebral disease are generally due to lipid infiltration of the central nervous system and are localized in the retina in the ganglion cell layer. The entity discussed here is perhaps best described as a heredodegeneration of the central neuroepithelium or, more simply, macular dystrophy. Sorsby (20) lists the essential characteristics of this group as “1. familial occurrence, 2. a bilateral fundus lesion confined essentially to the macular area, 3. onset at about 8–14 years of age and 4. progressive course leading to loss of central vision and no peripheral involvement.” To this might be added a fifth criterion: complete absence of associated systemic or local disease. These criteria would seem to eliminate congenital macular affections such as Best’s disease (4), although using the time of birth as a biologically significant moment in the development of the macula is open to criticism (16). Furthermore, Falls (8) in a presentation of a pedigree illustrating this disease, advances the possibility that the underlying pathology may be in the choriocapillaris rather than in the neuro-epithelium. The entity most resembling the affection described here is Stargardt’s disease. The first such report is apparently that of Batten (1) in 1897. Stargardt’s original paper appeared in 1909 (22) and further papers by him followed in the next ten years (23, 24). In 1920

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Behr (2) further classified these cases according to age of onset. Many reports on this condition have appeared since, and almost all have been sporadic cases of obvious recessive pedigree (5, 6, 12, 15, 18, 26). However the more uncommon dominant form of this disease has recently been described by Berkley and Bussey (3), Davis and Hollenhorst (7), Sorsby and Davey (21) and Steinmetz, Ogle, and Rucker (25). The family to be reported here falls into this group.

**CASE REPORTS**

The family (Figure 1) consists of 42 persons (including available mates) of whom 8 are known to have visual defects. Of these 8, 6 were available for examination. One person from each generation will be described to illustrate the progression of the lesion.

![Hereditary Degeneration Pedigree](image)

**Figure 1. Pedigree of family with hereditary degeneration of the macula transmitted as an autosomal dominant trait**

**Case 1.** The propositus (IV-6) was first seen at age nine with a complaint of poor vision of one year’s duration. His vision was recorded as 20/70 in each eye. A preliminary complete physical examination was reported as negative. This included neurologic examination and psychometric tests. His I.Q. was 90. Further ocular examinations revealed almost complete
absence of color sense as measured by Ishihara pseudoisochromatic plates and a bilateral central scotoma (Figure 2). Peripheral fields were normal. Night vision was normal. Examination of the fundi showed a loss of the normal foveal reflex and a very slight stippling of the macula in each eye (Figures 3A and B).

**CASE 2.** The previous findings led to the examination of the patient's mother who is represented as III–14 on the pedigree chart (Figure 1). At

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**FIGURE 2. CENTRAL FIELDS**
Case 1, age 9.

**FIGURE 3. FUNDUS PHOTOGRAPHS OF MACULAR REGION**
Case 1, age 9: A, right eye; B, left eye.
Hereditary Degeneration of the Macula

the time of examination she was 30 years old and gave a history of poor vision beginning at about age 12. She too had a complete physical examination which was entirely negative. Visual acuity was 20/200 in each eye and again color vision was almost completely absent as measured by Ishihara plates. Visual fields were normal peripherally, but central fields showed a bilateral central scotoma (Figure 4). Night vision was normal. Examination of the fundi showed a mottling and depigmentation of the macula in each eye and a beginning clumping of pigment (Figures 5A and B). This patient’s father and aunt had had bilateral extracapsular cataract extractions and gave a history of poor vision of many years’ duration. The father (II-14)

![Figure 4. Central Fields](image)

**Case 2, age 30.**

![Figure 5. Fundus Photographs of Macular Region](image)

**Case 2, age 30: A, right eye; B, left eye.**
Derrick Vail and David Shoch

had a phthisis bulbi of the right eye and no light perception. The left pupil was drawn up and occluded, but the fundus could be seen. It showed advanced pigmentary degeneration of the macula. The fundi of the aunt were easier to visualize and photograph. She is therefore reported here rather than the grandfather of the propositus.

Case 3. The great-aunt of the propositus (II-10) was 65 years old, had had bilateral extracapsular cataract extractions at age 45, but gave a history of poor vision from the age of 12. Physical examination was completely negative. Visual acuity was 10/200 in the right eye and 2/200 in the left eye. There was a complete lack of color vision as measured with Ishihara plates. Visual fields showed a bilateral central scotoma (Figure 6). Peripheral vision was normal as was night vision. Both pupils were partially occluded by a postoperative pupillary membrane, but the macular region could be visualized in each eye. However, only the right fundus could be photographed. The fundi showed a far-advanced pigmentation and de-

generation of the maculas, but here the pigmentation had progressed to involve the whole area between the disc and the macula with some progression to the nasal side of the disc (Figure 7). This patient reported that she had a daughter with defective vision (III-8), who was unavailable for medical examination because of conflicting religious beliefs.
DISCUSSION

The findings given above indicate that this family shows a bilateral hereditary degeneration of the macula transmitted in a dominant fashion. It appears to start in late childhood with minimal ophthalmoscopic changes. These changes become more marked with age until an almost generalized dystrophy of the posterior pole develops. Similar changes are reported by Rosehr (19) who examined some of Stargardt's cases 50 years after their initial description. There is an associated loss of color vision and central scotomas but no reported difficulty in seeing at night. These findings most closely resemble those of Stargardt's disease. However, Stargardt's disease is usually transmitted as a recessive characteristic while the family reported here appears to show an autosomal dominant type of transmission. Penetration is high in the generations traced and expression is uniform for each age group.

The etiology of this abiotrophy is as yet unknown, but the pathology appears to be a primary degeneration of the macular neuroepithelium with secondary changes in the pigment epithelium. The histopathology
of a case of senile heredodegeneration of the macula is described by Dr. Bertha Klien (14). She states that hers is the fourth such pathologic report. More recently in a paper by McFarland (17) a fifth report is made by Dr. Klien and again she notes an extensive defect of the first neuron with secondary pigment changes. Recent physiologic studies (9, 10, 11, 13) seem to bear out the premise that this is primarily a cone degeneration. Such studies are planned on this family with particular reference to flicker fusion and electroretinography.

SUMMARY AND CONCLUSIONS

A family has been presented who show a hereditary degeneration of the macula. This dystrophy appears to be progressive with age and the gene for this disorder is inherited as an autosomal dominant trait. Penetration is high and expression uniform. The characteristics of this expression are: (i) a symmetrical bilateral lesion of the macula showing a pepper and salt stippling early and progressing to rather extensive scarring of both maculas; (ii) onset at about puberty; (iii) associated poor visual acuity, poor color vision and central scotomas; (iv) complete absence of other local or systemic disease.

REFERENCES

Hereditary Degeneration of the Macula 65


DISCUSSION

Dr. Arthur J. Bedell. The authors have presented an interesting family history, subscribed to Sorsby's "four essential characteristics, familial occurrence, a bilateral fundus lesion confined essentially in the macular area, onset about 8 to 14 years of age and progressive course leading to the loss of central vision and no peripheral involvement," and added a fifth, in my mind an important one, complete absence of associated systemic or local disease.

The ophthalmoscopic picture is not always the same so that a few Kodachromes will be demonstrated to illustrate some of the variations.

A boy 11 years of age had binocular involvement, vision 20/200, with a central scotoma. The disc was clearly outlined with a few general vitreous reflexes, one partly demarcating the inner margin of the macula. There were several, separate pigment specks and two oval areas close to and over the fovea: one was pigmented, the other to the outer side was pink like blood. Small, poorly defined, pale deposits were in contact with these and
also over the retinal vessels. In the region between disc and macula there were many, clearly defined drusen. The pattern was the same in both eyes.

His 15-year-old brother with similar reduction in vision had been conscious of poor sight for at least five years. The changes in the right macular region were somewhat similar to those found in his brother, the main differences being in the foveal and perifoveal regions, which were less pigmented. The drusen were smaller and more numerous. In his other eye the vitreous reflexes were prominent, particularly about the upper border of the macula. There were many fine drusen in the macula and a small, reddish oval, seemingly retinochoroidal.

A complete, detailed genealogic search back to the great grandparents on both sides failed to disclose any suggestive ocular condition.

The fundus of a 12-year-old girl with vision in the right eye of 20/200 and in the left 18/200, and central scotomas had had difficulty in seeing for six years. The disc was clearly outlined with many vitreous reflexes including a small one in front of the fovea. In the center of the macular region there was a deep, darkly pigmented area with several spots of partially absorbed choroid.

In the left eye the vitreous reflexes were more numerous; one outlined the upper margin of the macula. Pigmented granules and fine deposits occupied the foveal region. This was the only case in the family.

These three cases illustrate the commonest form of juvenile macular degeneration, characterized by collections of granular pigment and small, discrete, light-colored areas usually similar in appearance to but smaller than the drusen of middle age.

Loss of the so-called foveal reflex is of no significance for it is frequently absent even when other vitreous reflexes are discernible.

Heavily pigmented macular juvenile pigmentation is represented by a woman of 20 who had had poor sight for six years with a central scotoma. Vision was 20/200. An almost 4/5 disc diameter sized, darkly mottled, circumscribed area with a pale band inside the outer ring and a denser, granular pigmented center occupied the macular region.

The macular lesion in the other eye was more quadrate and the pigmentation both in the pale zone and over the fovea was greater. Vision was 20/100.

Her mother and a sister had the same fundus changes.

A man was first seen 20 years ago when he was 18 and after four years of poor sight. The vision was 12/200 with a central scotoma and a brownish, granular macular region, a local retinochoroidal scar. The left eye was more involved. Examination of his body failed to disclose any other abnormalities. Two years later the circumscribed destruction was greater and now there is a classical patch of choroidal vessel sclerosis.

In 1928 the justly famous, beloved Dr. Arnold Knapp presented a paper before this society on the subject and published a drawing.
Hereditary Degeneration of the Macula

A ten-year-old boy had widespread, irregular-shaped drusen-like specks, irregular macular depigmentation, reduced central vision with a scotoma in each eye. This case is similar to Dr. Knapp's.

We thank the authors for bringing the subject to our attention, but wonder how they determined that the first ancestor had juvenile macular degeneration and also how the last case could be so diagnosed.

DR. HAROLD F. FALLS. I wish to congratulate Drs. Vail and Shoch for having presented to us this important subject of heredodegenerative ocular disease. As the audience is well aware such disease is becoming much more prevalent in our daily office practice and it thus becomes increasingly important that we have some understanding of its etiology and management.

There are two major causes of disease—heredity and environment; neither can exist without the other. Each human disease entity represents the end product of a complicated interplay between these two causative agents. To be sure, in certain diseases, environment may constitute the major role and in others heredity will be more important. In general, however, one's constitution (hereditary potentialities) determines the extent of reaction to environmental agents unless they are overwhelmingly deleterious.

In respect to the hereditary mode of inheritance of this type of macular degeneration Dr. Shoch mentioned that his family exhibited a dominant mode of transmission, whereas in the literature it appears that there are also pedigrees which exhibit a recessive mode of inheritance. This peculiarity of apparently similar clinical entities exhibiting different modes of inheritance is not infrequently encountered in ocular disease; retinitis pigmentosa and albinism are examples. Since this occurs it behooves the ophthalmologist to individualize the patient and the patient's family. This necessitates looking at other members of the family since earlier or later stages of the disease may well permit easier ophthalmoscopic diagnosis. The value of this simple expediency has been admirably demonstrated in the authors' family. In addition, before giving eugenic advice, the ophthalmologist must take the specific pedigree of the family being studied. You must know how the gene behaves in the family which you are studying. The literature dealing with Stargardt's disease emphasizes that the mode of inheritance is recessive. If Drs. Vail and Shoch had not bothered to investigate their family and take a pedigree, but had rather relied on previously reported information, this paper would not have come into being—thus, the importance of taking a pedigree is shown!

What are some of the causations of the apparently same clinical entity exhibiting different modes of inheritance in different families? There are several theories.

(1) We are actually dealing with a different gene but giving the same end product. This explanation has been offered for the extreme high frequency of consanguinity noted in albinism; furthermore, avian albinism
may result from independent genes and through different chemical pathways.

(2) We are dealing with the same gene, but the latter gene reacts differently in a given genetic make-up (milieu). The gene probably experiences the effect of modifying genes. No one gene acts alone and the end product, in the vast majority of cases, represents the interplay of the individual's specific gene make-up. There results a considerable intrafamilial similarity and yet occasionally a detectable dissimilarity between each affected individual. This depends upon the specific genetic make-up of the individual, the stress of daily living, and his age. The age of onset, method of expression, and course may also vary from family to family and yet the mode of inheritance be the same.

I should like to digress and speak of the color vision aberration exhibited in this family. A more critical appraisal, such as luminosity curves and Nagel anomaloscope studies, might exhibit very interesting and possibly different results. I should like to suggest such a study to the authors.

Dr. Vail. I must apologize for the projectionist who is trying to make a square out of Dr. Bedell. Dr. Bedell asked about the great-grandfather and how did we know that he had this macular condition when he was not seen. Actually we do not know except that the family history was very good and very consistent. All the people examined said that great-grandfather had poor eyesight; it was sort of a family tradition. Great-grandfather, incidentally, had nine children. We do have to assume that the great-grandfather had a true macular disease. The other patient who had a cataract removed had a history of bad vision prior to the cataract extraction and the children said that her vision had been very bad for many years, ever since she was a young lady. We are very grateful to Dr. Bedell for showing such beautiful photographs as always and always to the point. We are also very grateful to Dr. Falls for discussing so fluently and making so easy a most difficult subject. I would like to say that we in America have been a little remiss in the study of genetics insofar as ophthalmology is concerned and yet ophthalmology is, you might say, the mother science of genetics. I think one of the reasons for the difficulty is that our families are scattered so that it is impossible often to get the pedigree together satisfactorily, whereas in a small country such as Denmark the pedigrees are well known and well documented. In spite of that there is an upsurge of interest in the study of genetics in ophthalmology and I hope that we will continue to think along these lines, especially along the lines that Dr. Falls has mentioned.