

## RETINITIS PIGMENTOSA AND GAUCHER'S DISEASE\*

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### Case Report

**A man aged 38, of Jewish descent,** spent his early life in Germany, and came to live in Kenya in 1939.

*Family History.*—There is no history of Gaucher's disease in his family. His mother is alive and well. His father died of cancer of the kidney. He had no brothers or sisters. He was not married.

*Past History.*—He had measles as a child, and had occasionally suffered from malaria, the last attack occurring in 1950; he stated that it took him much longer than the average person to recover from an attack, which usually lasted about a fortnight.

As a baby of about one year he had developed recurrent attacks of pyrexia. His spleen was found to be enlarged, and steadily increased in size. There was no history of jaundice. In 1926, at the age of 12, a diagnosis of Gaucher's disease was made and splenectomy was performed; 2 years later a secondary accessory spleen was said to have been found and also removed. He then believed and felt that he was cured, though his liver steadily increased in size. His only abdominal complaint was one of fullness after meals. He had no other digestive disorder, and did not suffer from nausea or vomiting. His bowels were regular, and he had a very good appetite, though he was thin and did not put on weight. He complained that his liver was painful if knocked. He had no dyspnoea or cough. His stools and urine had always remained of normal colour. After July, 1952, he occasionally woke up with a little blood in his mouth.

The first sign of ocular disease was noticed in 1936, at the age of 22, when he noticed difficulty in seeing at night, but an ophthalmological examination at the Zürich Eye Infirmary revealed no abnormality. After his arrival in Kenya in 1939, his sight steadily deteriorated; his night-blindness became progressively worse and he discovered that he was unable to read a luminous watch at night; he became unable to drive a car at night, and by 1952 was unable to drive even by day. In 1951 he found that the periphery of his field of vision was becoming defective, as exemplified by inability to see a car coming out of a side road when he was driving. During 1951 he found it a strain to read even in a good light. The sight of his left eye had always been worse than that of his right eye.

He rarely drank any alcohol and his smoking averaged 4 to 10 cigarettes a day.

*Examination (July 16, 1952).*—The patient was well built, height 5 ft. 4 in., pulse 78, blood pressure 120/70. He had a rather dark pigmented skin. No enlargement of his lymphatic glands could be detected. There was no pallor of the conjunctivae. The mouth and throat were healthy. No abnormality was found in heart, lungs, or nervous system.

The liver was extremely enlarged, the lower edge being palpable two finger-breadths below the level of the umbilicus on the right side and three finger-breadths below the costal margin on the left side.

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*Ophthalmological Report (Dr. K. Simon).*—In 1945 the vision in the right eye, with a small astigmatic correction, was 6/9, and that in the left eye 6/12. No other abnormality was detected. No change was seen 2 years later. On July 9, 1952, a marked deterioration was observed:

“Both fundi show pigment spots of the bone corpuscle type mainly in the periphery. Left fundus more affected than the right. Left disc pale and of a waxy appearance, blood-vessels thin. The fundi have the characteristic signs of retinitis pigmentosa. Vision in the right eye 6/18 and in the left eye 6/60. The visual fields show a ring scotoma with a small central field defect. In a reduced light this field is even smaller than in normal light.” (Figure.)

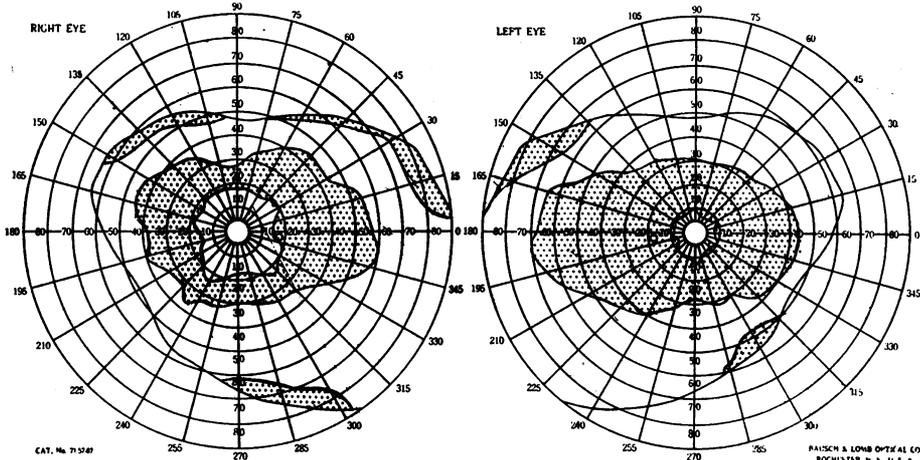


FIGURE.—Visual fields 10 mm. white target in artificial light.  
Right eye July 6, 1952. Left eye July 5, 1952.

*Radiologist's Report.*—An x-ray examination after a barium meal in 1942 is said to have revealed no abnormality except adhesion of the stomach at the site of the old splenectomy operation and straightening out of the duodenum.

An x-ray of the chest by (Dr. W. G. S. Hopkirk) in July, 1952, revealed no abnormality, but the right and left lobes of the liver appeared greatly enlarged, and showed uniform opacity. No splenic shadow could be differentiated. The spine and ribs appeared normal. No recognizable lipoidotic changes were seen in the limbs examined.

*Laboratory Investigations.*—A fractional test meal in 1924 was within normal limits.

Blood Count (July 11, 1952): red cells 4,200,000 per c.mm., haemoglobin 95 per cent., leucocytes 12,800 per c.mm. Differential count: neutrophils 54 per cent., lymphocytes 45 per cent., basophils 1 per cent., one normoblast seen, cells otherwise normal; no poikilocytosis or anisocytosis.

Marrow Biopsy (July 25, 1952): polymorphs, band forms, and metamyelocytes 45 per cent., lymphocytes 35 per cent., eosinophils 1 per cent., myelocytes 9 per cent., normoblasts, various types, 10 per cent. Smudge cells 11 per 100 cells. No Gaucher cells seen. M/E ratio 5.5. Examination of smears from haemolysed deposit showed no Gaucher cells (the late Brig. R. P. Cormack).

Blood Cholesterol (July 11, 1952): 135 mg. per cent.

Serum Protein: total protein 6.8 gm. per cent., albumin 3.6 gm. per cent., globulin 3.2 gm. per cent., A/G ratio 1:1.1.

Thymol Turbidity: 9 units.

Serum Colloidal Gold: quantitative 554100, qualitative positive.

Kahn Test: negative.

Platelet Count: 452,000 per c.mm., prothrombin level 80 per cent. of normal, coagulation time 3.5 min., bleeding time 3.5 min.

Serum Vitamin A Estimation (Mr. A. W. Pearson): Vitamin A determined by the colorimetric method (Dann and Evelyn, 1938): corrected for carotenoids 105.5 international units per 100 ml.

A section of the spleen removed in 1926 had been preserved and was examined in January, 1953, by Dr. G. L. Timms who confirmed the diagnosis of Gaucher's disease.

*Treatment.*—Fifteen intramuscular injections, each of 100,000 units Crooke's vitamin A, were given daily for 9 consecutive days, followed by one injection twice a week. The injections were followed by a course of Crooke's vitamin A capsules of 33,000 units, one capsule three times a day.

*Progress.*—In November, 1952, 3 months after the commencement of vitamin A therapy, the patient thought that there was a slight improvement in his sight. For example, he found that he was able to see a clock in a dark corner of his room, which was previously invisible, and he also noticed an improvement in his reading and in his visual field.

*Ophthalmological Examination (Dr. K. Simon).*—On December 3, 1952, there was a definite improvement in the patient's eyes. The visual acuity of the right eye had improved from 6/18 to 6/12, (that of the left eye, which had always been very poor, was 6/60 and could not be properly recovered owing to considerable amblyopia). The visual field of the right eye had increased by 5° in all directions.

*Result.*—The patient discontinued the vitamin A capsules in March, 1953, owing to nausea. He died in June, 1956, at the age of 42, from a fractured skull caused by walking into a moving lorry, presumably as the result of his defective visual field.

### Discussion

According to Cogan (1950), "the prime pathological changes in retinitis pigmentosa consist in a disappearance of the rods and cones and outer nuclear layer. The inner retinal layers are characteristically preserved, even later in the disease. The pigmentation of the retina is a secondary process, probably conditioned by having the sievelike external lining membrane in contact with the pigment epithelium with subsequent migration of epithelial cells into the retina."

Nicholls (1949) stated that "the cause of retinitis pigmentosa is unknown". Biró (1948) considered that the vascular spasm observed by himself and by Redslob (1947) as an antecedent to retinitis pigmentosa, probably resulted from posterior pituitary hormone (Vasopressin), whereas Verhoeff (1931) believed that the circulatory changes were secondary to the retinal atrophy.

The association of retinitis pigmentosa and Gaucher's disease in the case described above may be a pure coincidence, but the absence of any family history, or of any evidence of subjective or objective eye signs at an early age, favour an acquired cause. It is therefore relevant to consider the features common to the two diseases.

(1) *Abnormalities of Lipoid or Cholesterol Metabolism.*—Gaucher's disease is "thought to be a constitutional disturbance of lipoid metabolism" (Whitby and Britton, 1950). Levy-Wolff (1940) claimed that there was a connexion between retinitis pigmentosa and cholesterol metabolism, finding figures of blood cholesterol at the upper limit of normal (180 to 200 mg. per cent.) in very recent cases, "whereas all of the advanced cases showed increases occasionally up to astonishingly high proportions from 360 to 380 mg. per cent."

(2) *Pigmentation*.—Both diseases are associated with increased pigmentation, which has a predilection for the skin and sclera in Gaucher's disease and for the retina in retinitis pigmentosa. The discovery of a melanophore-stimulating hormone in the urine in cases of retinitis pigmentosa has been cited in favour of the theory of a pituitary origin for this disease (Nicholls, 1949), an argument which receives further support from the occasional association of the disease with the Laurence-Moon-Biedl syndrome.

(3) *Hepatic Disease*.—The case described above showed not only gross hepatic enlargement, but also defective liver function. According to Duke-Elder (1940), hepatic disease has frequently been associated with pigmentary degeneration of the retina, owing to the known association between diseases of the liver and a deficiency in the regeneration of visual purple and night-blindness. A clinical association between cirrhotic and chronic inflammatory conditions of the liver and degeneration of the pigmentary epithelium of the retina was reported by Baas (1894), Hori (1895), Purtscher (1900), and Koyanagi (1920), but although it has been recorded that the subjects of pigmentary degeneration do suffer from hepatic dysfunction (Takahashi, 1925) this association appears to be by no means invariable.

(4) *Vitamin A Metabolism*.—Pillat (1929) reported pigmentation of the conjunctiva resulting from vitamin A deficiency. Levine (1933) considered that retinitis pigmentosa might be caused by lack of vitamin A, but he obtained disappointing results from the administration of large doses of cod-liver oil to his patients, possibly, as he suggests, through the inability of the diseased retina to utilize the vitamin A supplied. Fuchs (1951) described a bilateral disease of the retina, similar to retinitis pigmentosa albescens, which results from vitamin A deficiency and which is cured by vitamin A therapy; retinitis pigmentosa albescens has a relationship to retinitis pigmentosa, the two conditions sometimes coexisting in the same family, hereditary factors being sometimes present, and the characteristic appearance of retinitis pigmentosa albescens having been observed to change to those of retinitis pigmentosa (Carroll, 1950).

According to Cogan (1950), the similarity of the changes observed in chronic experimental avitaminosis "A" and those of retinitis pigmentosa are so striking as to merit consideration:

"These changes, as observed in rats and dogs, consist in degeneration of the rods and cones and of the outer nuclear layer of the retina with preservation of the bipolar cell layers. In other words, chronic avitaminosis "A", which is known to produce the same functional abnormality as is found in retinitis pigmentosa, produces the same histological changes in the retina. . . . It is by no means excluded that the fundamental abnormality is a metabolic one in which the degeneration of the retinal elements is secondary. It is not impossible, for instance, that the prime abnormality is in a local inability to utilize the vitamin A supplied to the pigment epithelium. It would seem reasonable at the present time to suppose that owing to some defect in the enzyme system, the rods and cones or the pigment epithelium were unable to utilize the vitamin A supplied to them. Such a hypothesis seems the most reasonable explanation for the similarity of the pathological changes in retinitis pigmentosa of human beings to those of chronic vitamin A deficiency in animals."

As Leitner (1951) points out, more and more attention is being focused on the disturbance of vitamin A metabolism in diseases of the liver, which has been

shown by Moore (1931) to store about 95 per cent. of the vitamin A reserve. Keratomalacia has been recorded in association with hepatic disease, by early workers (Hori, 1895; Elschning, 1899), and by Bloch (1924), Blegvad (1924), Jeghers (1937), and Haig, Hecht, and Patek (1938). Investigators working for the Medical Research Council (1949) found that the only useful criteria of vitamin A deficiency were the plasma level of vitamin A and the dark-adaptation values. Delayed dark adaptation (Haig and Patek, 1942; Patek and Haig, 1939; Haig and others, 1938), low plasma vitamin A (Harris and Moore, 1947; Popper, Steigmann, and Zevin, 1943; Haig and others, 1942), and slight response to vitamin A in tolerance curves (Popper and others, 1943) are found in cases of hepatic disease. The concentration of vitamin A in the liver was found to be reduced in six cases of cirrhosis (Haig and Patek, 1942), but was discovered to be within normal limits (900 international units/g.) in a case of acute yellow atrophy, in spite of a reduced plasma vitamin A level of only 19 international units per 100 ml. shortly before death (Harris and Moore, 1947).

A study of the literature leaves no doubt that lack of vitamin A may result from hepatic disease, and experimental and clinical evidence supports the view that vitamin A deficiency may be a potential cause of retinitis pigmentosa. It is therefore conceivable that the patient described above may have developed retinitis pigmentosa as the result of vitamin A deficiency secondary to defective hepatic function. The plasma vitamin A value of 105.5 units per 100 ml., which is the lower limit of normal (Bicknell and Prescott, 1946), may be against the theory of vitamin A deficiency, but this figure is lower than the mean normal figure of 121 international units (from estimates on 195 subjects by Medical Research Council, 1949) and the average of 118 international units found in 41 healthy adults by Leitner and Moore (1946). Yudkin (1941) found no standard level of blood vitamin A which can be used as a test for deficiency. The Medical Research Council (1949) showed that no great reliance could be placed on the results of a single estimation of vitamin A in plasma, the values obtained by three different laboratories often varying for the same sample, though the average of a sufficient number yielded consistent results. Harris and Moore (1947) concluded, from investigations on infective hepatitis, that the various mechanisms concerned with the metabolism of vitamin A (its absorption from the intestines, its deposition in the liver, its release from the liver to the plasma, and possibly its stability suffering to varying extents in different individuals) are not always equally affected. Thus, inability of the liver to remove vitamin A from the blood would allow it to pile up to a high level.

The slight response of my patient to vitamin A therapy could be explained by a severe degree of irrecoverable retinal destruction. Patients with cirrhosis of the liver (Patek and Haig, 1939) and even normal subjects receiving a low vitamin A intake (Hecht and Mandelbaum, 1938) may exhibit a sluggish response to vitamin A administration.

### Summary

A case of retinitis pigmentosa associated with Gaucher's disease is described. The symptoms of retinitis pigmentosa did not develop until the age of 22 years. The patient showed evidence of defective liver function.

The suggestion has been made that the retinitis pigmentosa may have been caused by deficiency of vitamin A resulting from failure of liver function.

An interesting point, unconnected with the title of this paper, is the patient's statement that he took much longer than other individuals to recover from attacks of malaria, his lack of resistance being perhaps due to the splenectomy operation performed in childhood.

I wish to express my gratitude to Dr. W. G. S. Hopkirk for his radiological investigations, to Mr. A. W. Pearson and the late Brig. R. P. Cormack for the pathological reports, and to Dr. J. R. Gregory and Dr. L. Hirsch for their kind co-operation.

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