ACQUIRED ACANTHOCYTOSIS AND MYELOPHTHISIS IN A CASE OF EALES'S DISEASE*

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ACANTHOCYTOSIS, a *congenital* anomaly of the erythrocyte surface membranes with thorny protuberances due to a defect of beta-lipoproteins (Singer, Fisher, and Perlstein, 1952; Jampel and Falls, 1958; Mier, Schwartz, and Boshes, 1960; Druez, Lamy, Frézal, Polonovski, and Rey, 1961) has been described in association with atypical retinitis pigmentosa (Bassen and Kornzweig, 1950) and has also been found in association with hereditary vitreo-retinal degeneration (*degeneratio hyaloideoretinalis*: Wagner, 1938; Kahán, Kahán, Benkő, and Mindszenti, 1963). One of the most striking features of the latter is hereditary retinoschisis (Mann and Macrae, 1938; Juler, 1947; Sorsby, Klein, Gann, and Siggins, 1951; Gieser and Falls, 1961) originating, as suggested by Scorciarini-Coppola, Orlando, and d'Antuono (1958), from vaso-obstruction.

A case of Eales's disease with *acquired* acanthocytosis, a very low level of non-esterified cholesterol, and almost complete absence of haematopoiesis in the sternal bone marrow, is described below. Donner (1953) stated that the basic phenomenon of retinal periphlebitis is also an obstruction of vessels by erythrocytes. Reduction or complete disappearance of digitonin-precipitable (non-esterified) cholesterol may also be obtained by the injection of endotoxins (Meier and Schuler, 1957). This change in lipids was found to *induce* transient acanthocytosis.

The biochemical, morphological, and haematological aspects of congenital, acquired, and induced acanthocytosis have much in common, and may have a role in the vascular obstructions of hereditary retinoschisis and retinal periphlebitis, clinical entities of different aetiology but similar pathogenesis.

Case Report

A 57-year-old man with Eales's disease.

History.—The patient lost the sight of the right eye 10 years ago, some amelioration being experienced every summer. He came to the clinic complaining of blurred vision in the left eye.

Family History.—His mother was, and his only daughter is, suffering from severe pulmonary tuberculosis. The latter bears multiple scars from scrophuloderma on the neck and from phlyctenular keratoconjunctivitis in the corneae; she underwent a lobectomy at the age of 27 years, and shows no signs of fundus changes or acanthocytosis. Two siblings died in infancy (cause unknown), and two died later from pulmonary tuberculosis.

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Examination.—The visual acuity in the right eye was finger counting from 0.5 m. and in the left eye 5/10 (emmetropic).

There was a defect in the upper nasal quadrant of the field of vision in the left eye.

The right fundus was obscured by heavy haemorrhages, located below an arched line between the lens and the anterior hyaloid membrane, and by finely dispersed blood in the vitreous.

The laminated structure of the left vitreous was more prominent. The hyaloid membrane, adjacent to the retina on the nasal side, was detached from the posterior pole, and was interrupted in the lower temporal quadrant by multiple holes, one in front of the poorly-vascularized disc, and there was a spider's web opacity surrounded by ill-defined masses in front of the superior temporal vein (Fig. 1).

FIG. 1.—Left fundus, showing periphlebitis of superior temporal vein in a case of Eales's disease.

Pigmentary mottling of the macula developed at the end of angular venous branches. In the nasal periphery was a strikingly corkscrewed venous branch suggesting neoformation with three round haemorrhages nearby. Round chorio-retinal pigmented scars and cystoid degenerations connected by obliterated black vessels were seen in the lower temporal quadrant.

The electroretinogram b-wave, 250 μ V, was normal.

Medical Examination.—The liver was enlarged by one fingers-breadth below the costal margin, with a normal spleen, physical and radiological signs of pulmonary emphysema, and enlargement of the axillary lymph nodes.

The Mantoux reaction was negative (1:100,000).

The heart was enlarged to the left by one fingers-breadth, with a systolic murmur.

Blood Pressure: 190/100 mm. Hg.

Laboratory Findings: Total serum protein: 7.6 g. per cent.; albumin 4.5; α_1 globulin 0.17, α_2 globulin 0.48, β globulin 0.70, γ globulin 1.82 g. per cent.

Total serum lipids: 720 mg. per cent., total cholesterol 315 mg. per cent. Rate of non-esterified cholesterol only 8 per cent. Phospholipids 140 mg. per cent.

Serum iron: 88 μ g. per cent.; serum bilirubin 1.3 mg. per cent., indirect.

Erythrocyte sedimentation rate: 20 mm./hr.

Red blood count 4.3 millions/mm.³, haemoglobin 15 g. per cent., reticulocyte count 1.1 per cent.

White blood count 6,000/mm.³, band form 4 per cent., neutrophils 78 per cent., hypersegmented 1 per cent., eosinophils 5 per cent., lymphocytes 12 per cent., platelets 301,000/mm.³; osmotic fragility 0.44–0.22 per cent. NaCl decreased.

Striking acanthocytosis was seen in Giemsa-stained (Fig. 2a) and natural smears, and even in fresh wet preparations.

FIG. 2 (a–c).—Acquired and induced acanthocytosis. Giemsa-stained blood smears. $\times 420$.

- (a) From a case of Eales's disease.
 (b) From Case D (intra-ocular foreign body) before Pyrexal.
 (c) From Case D 2 hrs after 0.3 gr. Pyrexal intravenously.

Haemoglobin F 0.87 per cent. (Kristoffersen method), but some erythrocytes containing Hb F were found (Fig. 3). Hb A₂: 1.65 per cent.

As no bone marrow was obtained on sternal puncture, even when once repeated, trepanation of the sternal bone marrow was performed. The marrow was extremely hypocellular, the cells being mostly granulocytes and plasma cells, and not elements of haematopoiesis. At a few sites a reduced myelopoiesis was seen. Here and there myelofibrosis was visible, but the dominant feature was myelophthisis (Fig. 4).

FIG. 3.—Erythrocytes containing Hb F from a case of Eales's disease (stained as described by Kleihauer and Betke, 1960). $\times 420$.

FIG. 4.—Histological study of bone marrow obtained by trepanation from a case of Eales's disease. Note myelofibrosis to left and myelophthisis to right. $\times 192$.

A liver puncture showed nothing abnormal.

Diagnosis.—On the above data, a diagnosis of myelophthisis of possibly tuberculous origin was made; the suspicion of a mycobacterial origin of the liver swelling was not confirmed, though it was not excluded by the negative results of the liver biopsy.

Treatment.—Prednisolone and Isoniazid (INH) were administered, and 14 days later, the intra-vitreous haemorrhages of the right eye began to clear, permitting a visual acuity of 5/25 and 30 days later of 5/12. Inspection of the fundus showed superiorly some occluded venous branches, and inferiorly some round haemorrhages.

Result.—44 days after starting the INH and prednisolone therapy, the acanthocytosis and enlargement of the liver *ex juvantibus* (possibly of tuberculous origin) had disappeared.

Induction and Properties of Acanthocytes

Reduction or complete disappearance of digitonin-precipitable (behaving as non-esterified) cholesterol was obtained by an intravenous injection of 0.3 μ g. purified endotoxin prepared from *Salmonella abortus equi* (Pyrexal, Wander) into five healthy subjects (Cases A–E) with perforating eye wounds and consecutive iridocyclitis (Table).

TABLE
CHANGES IN SERUM CHOLESTEROL AND ERYTHROCYTIC MORPHOLOGY
INDUCED BY PYREXAL (0.3 μ g. INTRAVENOUSLY)

Case No.	Age (yrs)	Diagnosis	Time of Determination	Serum Cholesterol			Acanthocytosis
				Total (mg. per cent.)	Esterified (mg. per cent.)	Non-esterified as Percentage of Total	
A	49	Perforating corneal wound	Before Pyrexal	152	125	17	Absent
		Iritis	2 hrs after Pyrexal	122	122	0	Present
B	24	Perforating corneal wound	Before Pyrexal	248	221	11	Absent
		Iritis	2 hrs after Pyrexal	220	220	0	Present
C	19	Perforating corneal wound	Before Pyrexal	148	134	10	Absent
		Iritis	2 hrs after Pyrexal	148	148	0	Present
D	17	Intra-ocular foreign body	Before Pyrexal	265	231	13	Absent
			2 hrs after Pyrexal	162	162	0	Present
E	17	Traumatic cataract	Before Pyrexal	250	219	13	Absent
		Iritis	2 hrs after Pyrexal	220	209	5	Absent

Two hours after the injection, no non-esterified cholesterol was found in four cases, and in three the reduction of the total cholesterol equalled the quantity of free cholesterol originally present. This change in lipids was accompanied by the transient appearance of acanthocytosis for 2 hours in four cases (Fig. 2, *b* and *c*).

This phenomenon, like congenital acanthocytosis or that observed in the case recorded above, was bound to the erythrocytes and was also present in wet preparations of washed erythrocytes suspended in hypotonic Ringer's solution and sealed by a coverslip and Vaseline. However, when they were suspended in isotonic solutions not containing Ca^{++} , the phenomenon did not occur. We were unable to induce acanthocytosis by incubating red cells with Pyrexal *in vitro*, nor was it observed after Pyrexal injection in the case in which non-esterified cholesterol did not disappear; this suggests that it may be a manifestation bound to the presence of Ca^{++} of the induced lipid changes of the cell membranes.

Two *in vitro* properties of acanthocytes of possible significance in the pathogenesis of vaso-obstructive processes should be stressed:

- (a) Their increased mechanical fragility (Singer and others, 1952);
- (b) When pressure is exerted upon the cover slip of wet preparations, the normal erythrocytes make long straight-line excursions, while the motility of acanthocytes is limited to rotating around each other like cog-wheels.

Discussion

The complex ophthalmoscopic pattern of our case may be due to manifestations or late sequelae of retinal periphlebitis: perivenous soft masses, retinal haemorrhages, occluded and new-formed venous branches. The clinical course, beginning in adulthood in a male member of a tuberculous family with ocular and extra-ocular symptoms (liver-swelling, acanthocytosis) which were reversible by the administration of INH, leaving some pigmented chorio-retinal scars and an intact electroretinogram, favours a mycobacterial aetiology as opposed to a heredo-degenerative process.

However, the recorded case of Eales's disease exhibited at least three clinical features in common with those of hereditary vitreo-retinal degeneration (Wagner, 1938):

- (a) Multiple holes in the detached and opaque hyaloid membrane and cystoid degeneration of the retina. These may be explained on the basis of general lipoprotein defects of the cell membranes.
- (b) Occlusion and subsequent new-formation of terminal venous branches. In this connexion one may refer to the description of hereditary retinoschisis by Gieser and Falls (1961) as characterized by "vessel sheathing, arborizing figures and the recognition . . . of a vascular abnormality". The phenomenon may be due to the mechanical fragility and hindered motility of

acanthocytes, again based upon the lipoprotein defects of erythrocytic membranes.

(c) Signs of hindrance of medullary haematopoietic activity leading in the case recorded above to a degree of myelophthisis, and to the presence of erythrocytes containing Hb F, a characteristic finding in cases of hyporegenerative anaemia. In another case of Eales's disease, 2.65 per cent. Hb F was separated and identified by agar-gel electrophoresis. In this connexion it should be remembered that Eales himself stressed the importance of anaemia in this condition.

The tuberculotoxic origin of myelophthisis and osteomyelofibrosis, the finding of poikilocytosis in cases of the latter, bearing a striking resemblance to acanthocytosis (see Stobbe, 1959, Fig. 26b), and the susceptibility of bone marrow degeneration to prednisolone therapy are well known. The appearance of acanthocytosis with lipid changes induced by endotoxins suggested a toxic cause for the changes in the vessels and hyaloid membrane in Eales's disease also (Rempt, 1956), and accordingly these symptoms were also found to respond to prednisolone therapy.

The tentative differentiation between the *hereditary* acanthocytosis found in cases of hereditary vitreo-retinal degeneration (Wagner, 1938) and the *acquired* erythrocytic anomaly of toxic origin found in Eales's disease is a tempting one, but awaits confirmation by haematological findings of further proven cases of each type.

Summary

A case is recorded of Eales's disease with haematological anomalies: myelophthisis, acanthocytosis (thorny erythrocytes), and a decreased level of non-esterified cholesterol. As acanthocytosis may be induced by endotoxins, a tuberculotoxic pathogenesis of the ocular and haematological symptoms described is suggested.

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