Bassen-Kornzweig Syndrome

Present Status

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A reprint of the original paper 'Malformation of Erythrocytes in a Case of Atypical Retinitis Pigmentosa' (Bassen and Kornzweig, 1950) was sent to Professor Arnold Sorsby in 1951. It came too late to be included in his latest book, *Genetics in Ophthalmology*. There was just room for a single reference to the title in his selective bibliography (Sorsby, 1951). Since that time, 19 years later, 19 cases have been reported and the literature on the subject has expanded voluminously. It has become a well-documented clinical entity with implications for general medicine that vastly overshadow its relative infrequency of occurrence.

The clinical picture that emerges from the reported cases has the following characteristics. A child is born at full term, usually of consanguineous parents or grandparents. Several months after birth it begins to develop steatorrhoea and does not gain weight. Coeliac disease is suspected and the child is put on a low fat diet. If a blood work-up is done it will be noted that a large number of red blood cells are peculiar in that they show a crenated appearance; many are small and deeply stained, others resemble beetles, crabs, or turtles, or are star shaped. These are the acanthocytes first described by Bassen and Kornzweig (1950). It is the earliest diagnostic sign and the most constant (Fig. 1). The term acanthocytes was first used by Singer, Fisher, and Perlstein (1952). It was later modified by Druez (1959), who dropped the letter 'r' and made the term acanthocytes (Greek-Akantha-Thorn or Spine). A low sedimentation rate and absence of rouleaux formation are also noted.

The blood cholesterol is very low. This significant finding was first reported by Jampel and Falls (1958), as 37 mg./100 ml., the lowest ever reported at their institution. They were the first to suggest that the syndrome might be an inborn error of fat metabolism producing a harmful effect on erythrocytes and nerve cells. This very important finding

was further elaborated by Salt *et al.* (1960), who found a blood cholesterol of 22 mg./100 ml. in their 17-month-old child. In addition, there was almost a complete absence of β -lipoprotein, lowering of phospholipids, and no particulate fat in the plasma (chylomicrons) after a fatty meal. Plasma vitamin A was grossly deficient and the carotenoids were absent. In the parents and one grandparent of their patient the β -lipoprotein was reduced to about half the normal level.

The child continues to develop poorly, and at about the age of 6 begins to show signs of ataxia (Fig. 2). One case reported by Druez (1959) showed signs of ataxia at the age of 2 years. There is difficulty in walking, the child falls frequently, and there is unsteady gait. These signs are progressive, so that by age 10 to 15 the child has to be supported and cannot walk by himself. There is a generalized muscle weakness, deep reflexes are absent, and a Babinski sign appears. Position sense and vibratory sense are diminished or absent. This type of ataxia, resembling Friedreich's ataxia, shows diffuse disease of the central nervous system involving the posterior columns, the pyramidal tracts, and cerebellar pathways.

Signs of ocular involvement now begin to appear. These may affect the vision or the extraocular muscles or both. There may be partial ptosis, unilateral exotropia, and nystagmus. The vision becomes poorer, and by age 17 or 18 may be down to 20/400. Examination of the fundi will show some form of pigmentary degeneration of the retina with or without involvement of the macula, usually the former (Fig. 3). There is night-blindness, ring scotomata (Fig. 4), and inability to read large print. The electroretinogram will show a complete absence of electrical response as shown by Jacobson (Kornzweig and Bassen, 1957). There are also signs of mental retardation, mild in most cases and more extreme in an occasional patient. In addition, several cases have shown evidence of cardiac involvement (Schwartz *et al.*, 1961; Druez 1959; Sobrevilla, Goodman, and Kane, 1964). In the last

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FIG. 1. Note the generally crenated appearance of the cells and the variations in size. The smaller, deeply stained cells resembling spherocytes undergoing crenation stand out sharply.

FIG. 2. Posterior photograph illustrates kyphoscoliosis, thin habitus, and inability to stand alone. (A) illustrates exaggerated lordosis and inability to stand alone. (B) shows facial appearance. There is bilateral ptosis, but ocular movements are normal. (From Schwartz *et al.*, 1963).

case, the cardiac decompensation eventually led to death.

The clinical picture is now complete. Consanguineous parents, steatorrhoea, acanthocytosis, cerebrospinal disease, essentially cerebellar ataxia,

pigmentary degeneration of the retina, very low blood cholesterol, and α - β -lipoproteinaemia.

Acanthocytosis

Since the red cell malformation was the first

FIG. 3. Drawing of fundus. Fundus photography was precluded by nystagmus. The artist has attempted to illustrate the following characteristics. A waxy-appearing disc, attenuation of the venules and arterioles, disorganization of the pigment in the midperiphery overlaid by glistening highlights, and a distinct gliosis of the macula (from Jampel and Falls, 1958).

FIG. 4. Peripheral fields at the age of 15 years, showing a complete ring scotoma in the right eye and a partial ring scotoma in the left eye (from Kornzweig and Bassen, 1957).

unusual discovery in the Bassen-Kornzweig syndrome, much investigation was undertaken to determine the cause, and several interesting observations were made.

Acanthocytes are not converted to normal cells by incubation in normal plasma for 24 hours, and normal cells are not converted to acanthocytes by incubation in abnormal plasma for a similar length of time (Lamy *et al.*, 1961). However, the abnormal acanthocytes may assume a normal shape partially or completely by immersion in a 5% albumin solution, by lowering the pH of a suspension of cells to

FIG. 5. Photomicrographs of small intestinal epithelial villi obtained by peroral biopsy. The upper figures are stained with fast-magenta and eosin. The lower figures are stained with oil red O. *Top left.* Upper villous tip from a normal subject. The cytoplasm of all the villous lining cells (N.C.) are of a homogeneous grey intensity. ($\times 300$) *Top right.* Upper villous tip from a subject with a β -lipoproteinaemia. Note that the cytoplasm of every intestinal epithelial cell appears foamy and vacuolated (F.C.). This abnormal appearance is caused by the presence of abundant amounts of unstained lipid. *Bottom left.* Middle and lower portion of villi from a normal subject. Lipid is generously distributed throughout the villous core (V.C.), and may be seen not only within the epithelial cells but indistinctly in some of the intercellular spaces (I.S.). Evidence for the precise location of lipid in these intracellular spaces comes from electron micrographs. *Bottom right.* Middle and lower portion of villi from a subject with a β -lipoproteinaemia. Note increasing amounts of lipid as the tip of the villus is approached (the tip is not shown but contained cells more heavily stained than those marked X). In the region towards the villus base, where the epithelial cells are only partly filled with lipid, no lipid is seen in the intercellular spaces (I.S.). Also, lipid in cells closest to the villus base appears abnormally concentrated towards the villus core (C.L.). Finally, also in contrast to the normal (*bottom left*) no lipid is present in the villous core (V.C.) (from Farquhar and Ways, 1966).

5.8 in isotonic buffer, and by adding large amounts of non-ionic detergents/or small amounts of cationic detergents. These observations seem to indicate that the shape of the cell is inherent in the erythrocyte and not in the serum but that it is influenced

by the surface tension or surface charge of the cell membrane (Farquhar and Ways, 1966).

Much interest has centred on the lipids in the cell membrane of the acanthocytes. The total lipid content is normal, but the phospholipids are low and the fatty acid distribution is abnormal. This is similar to the significant changes found in the plasma. It is suggested that abnormalities of phospholipids in acanthocytes are secondary to similar abnormalities in the plasma (Ways, Reed, and Hanahan, 1963).

Other findings are an absence of rouleaux formation, a decrease in sedimentation rate, and a slight increase in resistance to fragility in hypotonic salt solution and on exposure to cold agglutinins and shaking, as described by Stats. The sternal marrow is normal, but the number of acanthocytes seems to increase with ageing of the erythrocyte.

'The sum of evidence at this time is that the erythrocyte defect in the Bassen-Kornzweig syndrome is an intrinsic structural disorganization of the membrane due to an abnormal lipid composition. How it occurs in this disease must still be discovered. Since cells presumed to be younger are quite normal in lipid composition, it is probable that the erythrocyte abnormality is acquired during their circulation in lipid-poor plasma' (Farquhar and Ways, 1966).

A- β -lipoproteinaemia

A constant finding in the Bassen-Kornzweig syndrome is an absence or marked diminution of low density lipoproteins, less than 1.063. The plasma cholesterol and phospholipids are below 60 mg./100 ml. As reported by Salt *et al.* (1960), no β -lipoprotein could be detected by paper electrophoresis. All low density lipoproteins are absent in the plasma in the fasting state. All these abnormalities are apparently the result of the patient's inability to absorb the fatty contents of his food from the intestinal tract, and this defect is also indicated by the absence of chylomicrons from the circulating blood after ingesting a fatty meal. There have been several reports of diminished lipoproteinaemia in families that do not show the characteristics of the complete syndrome. The first such report was that of Salt *et al.* (1960), in which the parents and one grandparent of the affected child had much reduced blood lipoprotein to about 60% of the mean concentration in a general population. Kuo and Bassett (1962) reported finding the deficiency in one male and two female members of the affected family. The most extensive report was that of Van Buchem *et al.* (1966) from Holland. Reports are given of three

brothers, 38, 39, and 46 years of age: the oldest had a blood cholesterol of 70–78 mg./100 ml., and an obvious reduction of β -lipoprotein by paper electrophoresis; other blood lipids were also low, especially phospholipids and triglycerides; the other brothers had similar reductions but not to the same degree. These reports called attention to several degrees of a- β -lipoproteinaemia. The clinical evidence of the Bassen-Kornzweig syndrome was not present in these cases, indicating that only those patients with extreme degrees of deficiency of β -lipoprotein show all the stigmata of the disease. It is possible that deficient β -lipoproteinaemia is more widespread than originally believed. If there is still about 10 to 20% of β -lipoprotein present, steatorrhoea, fat accumulation in the epithelium of the intestinal mucosa, neurological disturbances, and acanthocytosis are absent. The changes in the lipids and fatty acid patterns in plasma and red blood cells, however, are the same as those present in the absence of β -lipoprotein (Sturman, 1968).

Malabsorption Syndrome

The steatorrhoea noted early in the disease indicates an inability to absorb the fat in the diet. This has proved to be a constant finding in the fully established cases of the Bassen-Kornzweig syndrome. It also causes poor absorption of carotene and vitamin A. The absence of the β -lipoprotein, low concentration of cholesterol, phospholipids, carotene, and vitamin A are probably responsible for the symptomatology of this disease, since these substances are necessary for the proper function of the involved tissues, the central nervous system, the erythrocytes, and the retina.

This failure of absorption has been shown pathologically by biopsy of the small intestinal villi taken perorally (Fig. 5). The epithelial cells of the villi contain large amounts of lipid substance as shown by fat droplets, especially triglycerides. But none of this substance gets into the stroma or core of the villi. No chylomicrons are present in the circulating blood. Normally such concentration of fatty droplets is absent or diminished in the epithelial cells, but is present in the intercellular spaces in the epithelium and in the villous core or stroma. It is possible that a primary defect in absorption would initiate all the other features of the symptom complex. This appears to be the crux of the problem.

Genetics

Affected children probably are homozygous for a single recessive gene. Males and females are

equally afflicted, and consanguinity has been present in 7 of the reported 14 families. No partial defect has been observed in heterozygous parents, with the exception of the report by Salt *et al.* (1960) of the parents and one grandparent of the proband. These persons showed a β -lipoprotein of about 60% of the mean concentration in a control population. Also important in this respect are the findings of Kuo and Bassett (1962), and that of Van Buchem and his associates (1966) of a moderate deficiency of β -lipoprotein and other lipids, mentioned above under α - β -lipoproteinaemia.

A total of 19 cases has been reported, 17 of which are certain and 2 are probable. These last 2 were sibs of patients who died in infancy with a history of steatorrhoea. More than one sib was affected in four families. The proportion of affected children in the sibs of the proband is 5 in 29 (0.17), and is in fair agreement with the expected 1 in 4 (0.25).

The small number of reported cases and the high frequency of parental consanguinity are consistent with a comparatively low gene frequency in the population, even when compared to other rare genetic disorders. A gene frequency of 0.005%, or 1 in 20,000, was calculated from the frequency (31%) of first cousin parents of the affected children. This calculation involved an estimate of the normal or 'background' frequency of cousin marriages in the general population, assumed to be 0.25% (or 1 in 400) for the United States, a factor subject to considerable variation. All but 1 of the 15 subjects described in the United States were born in the north-eastern section; 9 were Jewish and 3 were Italian. Since the background cousin-marriage rate for these groups is probably higher than that of the general population, the validity of the calculation is questionable (Farquhar and Ways, 1966) and see p. 289 this issue (Alström, 1970).

Findings at Necropsy

The case reported by Sobrevilla *et al.* (1964) died, aged 36 years, of cardiac failure. A necropsy showed extensive demyelination of the posterior columns and spino-cerebellar tracts of the spinal cord; a loss of anterior horn nuclei, loss of nuclei of the cerebellar molecular layer, and a loss of Betz cells of the cerebral cortex. In addition, focal areas of demyelination were present in the peripheral nerves. These findings suggest that demyelination is extensive in this disease. The cause of this neurological disturbance is obscure. The eyes showed obvious optic nerve and macular atrophy. The coronary ostia and coronary arteries were free of atheromatous involvement which may

correlate with deficiency of β -lipoprotein and low blood cholesterol.

The second patient reported by Kornzweig and Bassen (1957), a brother of the first published case, died of a cardiac disorder at the age of 27, in the Medical Center of the National Institute of Health at Bethesda, Maryland, early in 1969 (L. Von Sallman, 1969, personal communication). An extensive necropsy was performed, but the report has not been published yet. We await this report with great interest, since this patient was studied so intensively clinically. In addition, it would be of special interest to see the effect of the abnormally low blood cholesterol and other lipid substances on the condition of the blood vessels, to see if it agreed with the findings on the first necropsied case.

However, the histopathological changes in the eyes were reported by Von Sallmann, Gelderman, and Laster (1969). At the time of death the vision was still 20/30 in each eye, but the fields of vision were constricted to a very small central island. The findings, described for the first time, are fully compatible with those of advanced retinitis pigmentosa. There was complete absence of rods and cone processes except for the macular area. Pigmented cells had invaded the retina and were especially obvious around blood vessels. Unusual deposits, shown only in frozen sections, were present in the optic nerve and optic tract. These bodies were not stained with oil red O or sudan black, but were PAS and Alcian blue positive. Many of the bodies displayed birefringence. The nature and significance of these changes is not known.

Summary

A composite clinical picture of patients with the Bassen-Kornzweig syndrome has been presented. It is a rare disease, inherited as an autosomal recessive from consanguineous parents or grandparents who are presumably heterozygous. The diagnostic features of the disease are steatorrhoea in childhood due to gross engorgement of intestinal epithelial cells with triglycerides; unusual crenation of erythrocytes which is unique in this disease (acanthocytosis); progressive degeneration of the cerebellum and postero-lateral columns causing weakness and ataxia in childhood, getting gradually worse as the patient grows older so that he is unable to stand by himself by the time he is 20; pigmentary degeneration of the retina usually involving the macula; and a conspicuous decrease in blood cholesterol, phospholipids, and triglycerides (α - β -lipoproteinaemia).

The primary defect is not clear. The underlying

pathology appears to be an inability to remove the fat in the diet from the intestinal tract. It remains in the epithelial cells of the intestinal villa but does not get into the core. Another possibility is a failure or inability to form a protein necessary for low density lipoprotein molecules. The absence or diminution of these low density lipoproteins in the blood may account for all the observed phenomena in the red blood cells, the central nervous system, and the eyes.

Considerable reference has been made to 'Abetalipoproteinemia' by John W. Farquhar, and Peter Ways (1966), especially for laboratory data. I am grateful for this excellent reference and recommend it to the reader who desires more complete information.

The second reference that was extremely helpful was written by Robert M. Sturman (1968).

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