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Acanthocytosis—Biochemical and Physiological Considerations

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ABSTRACT

Acanthocytosis represents an unusually pathological variant of red cell morphology which is encountered in a diverse group of inherited and acquired disease states. While the morphological features are similar in all instances, the biochemical lesions frequently differ. Most demonstrable abnormalities involve lipids although those acanthocytes associated with the McLeod phenotype are probably due to an alteration in a membrane protein. Acanthocytes, regardless of their etiology, usually have a decreased survival in the circulation owing to splenic sequestration and destruction.

Introduction

A great deal of interest has been generated by observation of the wide array of pathological and physiological forms that can be assumed by the normally biconcave human red blood cell, the discocyte. To survive its normal 100 to 120 days' life span, the red cell must undertake a continuous circulatory journey, approximating 175 miles, frequently requiring negotiation of capillaries and slit-like spaces as small as 1/20 its diameter. Its biconcave configuration with optimal surface-to-volume ratio enhances its ready deformability to negotiate those tight spaces without damage, and also best serves its gas exchange function with its freely movable molecular hemoglobin content (figure 1).

Young red cells, known as reticulocytes, with a frequently folded excess membrane, persist approximately two days in the peripheral blood while their cytoplasmic organelles are discharged, and each undergoes remodeling with symmetrical membrane loss to assume its normal discocyte configuration. As the cell ages, a series of changes occur including additional membrane loss, increased corpuscular hemoglobin concentration because of water and cation loss, decreased enzyme activity, increased methemoglobin content and decreased deformability. It is probably largely because of the latter that these senescent primarily now spherical cells are detected and destroyed by the spleen as they attempt to pass its narrow passages. The vast majority of normal circulating cells are,

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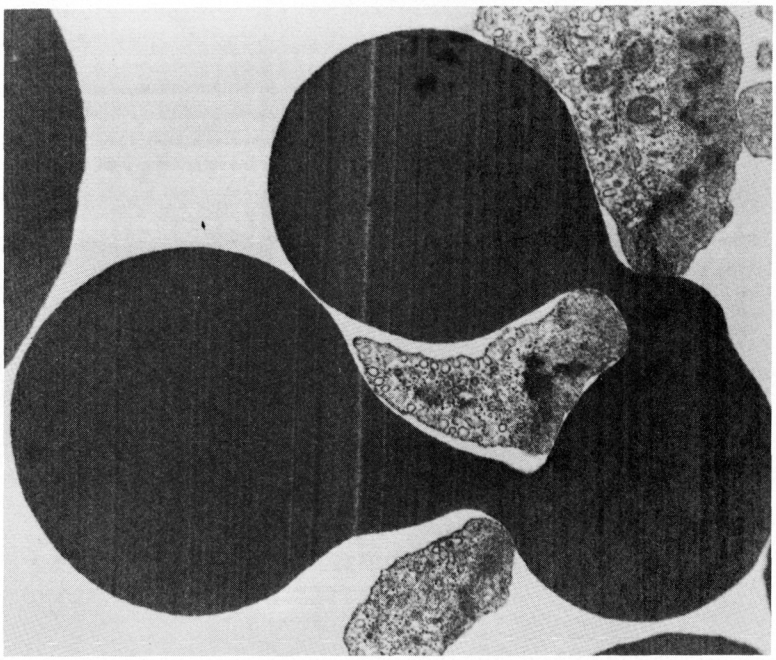

FIGURE 1. The marked alteration of shape is portrayed as a normally deformable erythrocyte negotiates a tight interendothelial cell space of the spleen (10,000 ×).

however, discocytes which, when observed while flowing *in vivo*, assume a vast variety of dynamic transitions in form largely related to flow rates and vessel size.[31]

The following discussion pertains to deformed red cells which are spiculated and specifically known as acanthocytes. These must be differentiated from a variety of red cells known to have one or more spiny projections. Many of these cells are of well defined pathogenesis, e.g., sickle cells associated with sickle cell hemoglobin; schizocytes (helmet, fragmented or triangular cells), associated with microangiopathic hemolytic anemia where the cells are injured by intravascular fibrin strands, diseased vessel walls, or by cardiac valve prostheses; and tear drop cells (dacrocytes), typically associated with myelofibrosis or abnormal hematopoiesis. Lastly, there is the echinocyte, (burr, crenated or berry cell), which is an ovoid or spherical cell with 10 to 30 spicules evenly distributed over its surface.

The report of Brecher and Bessis[9] has well illustrated the stages of discocyte-echinocyte transformation and ellucidated many of the factors associated with echinocyte formation. Extrinsic factors causing crenation include plasma incubated at 37°C for 24 hours, lysolecithin, high levels of fatty acid and many others. Intrinsic factors include aging of red cells which is probably related to depressed adenosine triphosphate, (ATP) and washing cells in saline and the "glass effect" of observing cells between slide and cover slip. Brecher and Bessis feel that echinocytes probably occur in various diseases but that previous reports of such must be carefully reevaluated by examination of fresh cells between plastic cover slips to exclude artifactual crenation.

Acanthocytes (spur or acanthoid cells), on the other hand, are distinctly different cells having 5 to 10 spicules of varying length irregularly distributed over the red cell surface (figure 2). The individual spicules have knobby ends. Under the

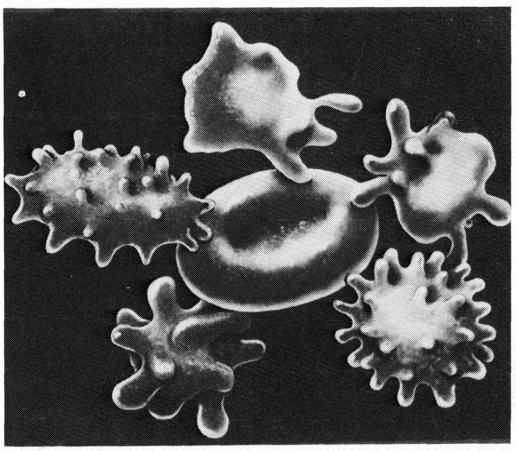

FIGURE 2. Artistic composite illustrating a centrally placed discocyte with acanthocytes at the 12, 2, and 7 o'clock positions and echinocytes at 4 and 9 o'clock.

light microscope on an air dried smear, acanthocytes and echinocytes may occasionally be difficult to differentiate. However, typical echinocytes have a serrated outline with small projections more or less evenly spaced over the circumference of the red cells while acanthocytes have a few spicules of varying length and thickness projecting irregularly from the cell surface.

Wet preparations have the advantage of allowing more of a three dimensional appearance, which is often helpful. Brecher and Bessis[9] also suggest adding an echinocytogenic substance, such as plasma with lysolecithin, in doubtful cases. This will convert the discocytes to echinocytes which will then stand out in sharp contrast to acanthocytes which will be converted to acantho-echinocytes, recognizable by bifurcation of the spicules. Lastly, scanning electron microscopy following immediate fixation of fresh blood has provided the reference standard by which the subtle diferences in spiculated cells have been defined.[4]

While originally described as one of the diagnostic hallmarks of abetalipoproteinemia (ABL),[3] acanthocytes have been described in a number of seemingly related and unrelated conditions, which will be discussed (see table I). Regardless of their etiology, they almost invariably have a decreased life span although this may range from a severe hemolytic anemia requiring transfusions to a mild, barely detectable compensated hemolytic state. For a thorough discussion of the implications of altered red cell shape, their membranes, deformability, and hemolytic anemia, the reader is referred to the following comprehensive reviews; Weed,[54] Shohet and Ness,[46] Lessin et al[31] and Mohandas et al.[39]

TABLE I

Diseases Associated with Acanthocytosis

Majority of red cells are acanthocytes
1. Spur cell anemia with severe liver disease
2. Abetalipoproteinemia
3. Homozygous hypobetalipoproteinemia
4. McLeod phenotype
Minority of red cells are acanthocytes
1. Certain neurological disorders without lipid abnormalities
2. Infantile pyknocytosis - vitamin E deficiency
3. Miscellaneous conditions

Red Cell Membranes—General Background

The basic lesion in the acanthocyte appears to be limited to its membrane since, to date, there has been no abnormality demonstrated in hemoglobin, cation transport, red cell antibodies or glutathione and ATP levels.[26] The more commonly encountered forms of acanthocytosis exhibit rather marked alterations of the red cell membrane lipids although there is increasing evidence that proteins play a major role in membrane properties.

To date, methods for isolation and characterization of membrane proteins are less well developed than those for lipids, so our information regarding proteins is less complete.[45] Hence, while most of the following discussion will

dwell upon lipid alterations, it should be borne in mind that proteins may also be changed either primarily or secondarily. To illustrate this point, one instance of acanthocytosis is cited, namely the McLeod phenotype, where a protein alteration is the probable principle or primary lesion.

The red cell membrane is composed of lipid and protein in approximately equal amounts by weight. Phospholipids and free cholesterol constitute nearly 95 percent of the total lipid and, on a molar basis, phospholipids and cholesterol are present in nearly equal amounts.[45] The molecular arrangement of the membranes is unknown although the various studies have generally evolved into two basic concepts, namely; the membrane is visualized as a sea of lipid containing islands of protein[47] or as a protein membranous skeleton containing lakes of lipid.[35] Both concepts suggest that the zones of fluid lipid within the membrane form the environment for membrane proteins. Much of this lipid is in the form of a bilamelar leaflet with the hydrophilic portions of the phospholipids facing the aqueous environment on either side, and the hydrophobic portions situated within the central core of the bilayer.[11]

The membrane phospholipids consist predominatly of four classes which are asymmetrically distributed. Phosphatidylethanolamine and phosphatidylserine are preferentially on the inner lamella, and phosphatidylcholine (lecithin) and sphingomyelin on the outer lamella. Free cholesterol is envisioned as being packed within the lipid phase of the membrane in an intermediate position between parts of both the head groups and the hydrocarbon tails of the phospholipids, serving to "tighten-up" the lipid core. Cholesterol and phospholipids are not synthesized by the red cells, and the membranes and serum lipoproteins are in general equilibrium so that the membrane lipids reflect their plasma counterparts. For details of the various theories of membrane structure and lipid exchange, the reader is referred to several excellent recent reviews of the subject.[11,35,45,54]

Spur Cell Anemia

Abnormalities in serum lipoproteins are known to induce secondary changes in red cells by modifying the equilibrium of the passive exchange of lipids between plasma and erythrocytes.[45] In liver disease of both the obstructive or hepatocellular type, the red cells may become laden with cholesterol and, to a lesser extent, phospholipid. Thus, the membranes exhibit a marked increase in the cholesterol-phospholipid (C/P), ratio. When examined on air-dried blood smears, they are frequently "targeted," reflecting the acquisition of membrane surface area caused by the added cholesterol.

Using osmotic fragility as an indirect measure of membrane surface, it has been found that these cells exhibit increased osmotic resistance as expected. To this extent these changes are usually of little clinical significance. However, in fulminating hepatocellular disease, particularly that of advanced alcoholic cirrhosis, this process may be exaggerated leading to massive accumulation of cholesterol in excess of phospholipid leading to acanthocyte formation (spur cells). Under these circumstances, red cell survival is markedly decreased and is associated clinically with hemolytic anemia. The studies of Cooper et al[16] have indicated that this abnormality is acquired by mature erythrocytes during equilibration with serum lipoproteins which, because of hepatic dysfunction, are laden with free cholesterol.

Cooper et al[16] suggest that the production of spur cells (acanthocytes) occurs in two phases. First is the selective acquisition of cholesterol which increases the membrane surface area and causes development of a scalloped or regularly

spiculated contour. This occurs in 12 to 24 hours and can be demonstrated *in vivo* or *in vitro* by incubation of normal cells in serum from patients with spur cell anemia. The second phase has been referred to as "splenic conditioning" and consists of nonspecific loss of membrane surface accompanied by transformation of the spicules into a bizarre and irregular contour in six to eight days. This occurs *in vivo* only in conjunction with a functioning spleen.

While the cholesterol laden regularly spiculated or targeted red cells are osmotically resistant reflective of their increased membrane area, acanthocytes when formed are osmotically normal. This is probably a result of "splenic conditioning" with nonspecific membrane loss and/or perhaps much of the membrane excess is contained in the peripheral spikes of the acanthocytes, and is unavailable for cell expansion under osmotic threat.[45] Following splenectomy, the cholesterol laden cells of such cases maintain their orderly spiculation, are osmotically resistant, and do not develop the bizarre morphology of acanthocytes.[16]

Several mechanisms have been suggested for the massive accumulation of membrane cholesterol associated with severe liver disease. These include decreased lecithin-cholesterol acyltransferase (LCAT) activity owing to increased surface active bile acids[15] and the presence of an abnormal lipoprotein in obstructive liver disease.[49] Interestingly, in the rare familial disorder, LCAT deficiency, there is an equally great free cholesterol accumulation by the red cell membranes, but these red cells remain targeted and do not develop spicules. Obviously, cholesterol accumulation alone cannot fully explain acanthocyte formation in severe liver disease.

Deformability is a specific functional characteristic of red cell membranes that allows the red cell to undergo extreme changes in shape during circulation through the vascular tree, including capillaries having lumens considerably smaller than the cell itself. This feature is particularly important during passage through the spleen when red cells are forced to traverse narrow interendothelial clefts or slits (approximately 0.5 to 1.0 μm wide). Normally, deformable human red cells are able to move through the slits, but any reduction in deformability owing to membrane changes, alteration in the cytoplasmic state, or reduction in the surface area-to-volume ratio of the cells, makes this passage difficult and leads to splenic sequestration and destruction.[39] Reduced deformability of spur cells from severe alcoholic cirrhosis cases has been demonstrated using viscometric and micropore filtration techniques.[36]

Splenic sequestration, particularly associated with the congestive splenomegaly of cirrhosis, has been shown to be the dominant factor in their reduced survival. Similarly, Cooper's patients[16] who showed a 55 percent increase in red cell membrane free cholesterol with essentially no change in phospholipid have shown decreased deformability of the red cells before and after splenectomy, as indicated by increased filtration time. It is suggested that the increased microviscosity of the spur cell membrane may explain why the passage of these cells is retarded both through filters of small pore size *in vitro* and through the spleen *in vivo* and it, therefore, appears to represent the minimal cell defect responsible for hemolysis in this disorder. Since the membrane microviscosity is directly related to the disproportionate excess of membrane cholesterol, the magnitude of the cholesterol balance would be anticipated to correlate, in turn, with the degree of anemia. This correlation was demonstrated in Cooper's patients with spur cells.[16]

With increasing evidence that the membrane proteins play a dominant role in the regulation of membrane properties while lipids contribute only minimally,

Mohandas et al[39] have found it difficult to rationalize the correlation between decreased lipid fluidity and reduced cellular deformability. On the other hand, Lux[35] cited evidence that the protein membrane skeleton might not be involved in the acanthocytes of ABL and spur cell anemia. He has noted that membrane skeletons always retain the shape of the ghosts from which they were prepared.

For example, the ghosts and skeletons of sickled cells, hereditary elliptocytes and hereditary pyropoikilocytes retain the abnormal cellular shape of the parent cell. Thus, the membrane skeleton seems to be the major determinant of shape in normal and some pathologic red cells. However, when ghosts and skeletons of acanthocytes of ABL and spur cell anemia were prepared by the Triton extraction procedure, they reverted to the usual round shape. Thus it would appear that the abnormality in the lipid bilayer is the more important or only change.

Abetalipoproteinemia

Acanthocytes were first demonstrated in 1950, in association with ABL, and remain one of the characteristic hallmarks of that rare inherited disease.[3] As of 1978, over 40 cases of ABL had been reported and summarized,[26] with the emergence of the classical clinical presentation of malabsorption of fat, retinitis pigmentosa, severe neuropathy and acanthocytic red blood cells. The terms "abetalipoproteinemia" and "ApoB-deficiency"[30] reflect the unique feature of the disease, namely, the absence of and apparent inability to synthesize Apolipoprotein B (Apo B). Consequently, these patients with no trace of betalipoprotein in their plasma are unable to elaborate chylomicrons and very low density lipoproteins (VLDL) and exhibit marked hypocholesterolemia and hypotriglyceridemia.

Acanthocytes constitute the majority of the red cells in patients with ABL, ranging from 50 to 90 percent. The exact mechanism of formation of acanthocytes is unknown although the demonstrated biochemical abnormalities have been limited to the cell membranes. The studies of Ways et al in 1963 demonstrated red cell and plasma lipid abnormalities in three cases of ABL.[52] These showed essentially normal values for total lipid, cholesterol and phospholipid in the red cell membranes, but an increase in sphingomyelin and a decrease in lecithin, (reversed sphingomyelin/lecithin [S/L] ratio). Total plasma phospholipids were less than 20 percent of normal values with a comparable reversed S/L ratio owing to a proportional increase in sphingomyelin and a corresponding decrease in lecithin.

Ways et al[52] also noted a profound deficiency in linoleic acid in the acanthocytic membrane and plasma lipids. Linoleic acid normally accounts for 10 to 14 percent of the esterified fatty acids in the red cell membrane, whereas only 2 to 3 percent were found in acanthocytes. This reduction is most notable in that linoleic acid is esterified in lecithin.

Attempting to find a uniform mechanism, McBride and Jacob[36] studied acanthocytes from human ABL, experimental ABL of rats fed orotic acid, rabbits on high cholesterol diets and human spur cell anemia. Elevated cholesterol and C/P ratios were found in all types of acanthocytes. While cholesterol normally flows bidirectionally between red cell membranes and plasma lipoproteins, plasma from these instances of acanthocytosis were uniformly inefficient in accepting cholesterol flux from the affected erythrocytes. This inefficiency could be corrected by addition of concentrated human betalipoprotein to the ABL plasma.

McBride and Jacob[36] also demonstrated increased rigidity and resistance to flow of the acanthocytes as manifested by increased viscosity in cone-plate viscosimeters and diminished filterability through micropore filters. While acknow-

ledging differences such as the reversed S/L ratio in ABL acanthocytes, it was concluded that a uniform mechanism could be applied to the formation of acanthocytes, namely, accumulation of, and even more importantly, stagnation of cholesterol on the red cell membranes.

When studying ABL acanthocytes, Cooper et al[12,13] reported that membrane cholesterol was within the high limits of normal and phospolipids were within the low limits of normal resulting in a slight increase in C/P ratio. These values were more comparable to those of most previous investigators.[52] A marked increase in sphingomyelin with a decrease in lecithin was also demonstrated, as well as poor deformability of the acanthocytes to the increased S/L ratio. Similar results were noted in the microviscosity of liposomes of varying S/L mole ratios prepared from brain sphingomyelin and egg lecithin with equimolar cholesterol. Cooper et al[12,13] concluded that the increased S/L ratio was responsible for the decreased membrane fluidity of the ABL acanthocytes, whereas it was the increased cholesterol and C/P ratio that was responsible for decreased membrane fluidity in spur cells associated with liver disease.

ABL acanthocytes have an increased rate of autohemolysis which can be corrected by addition of normal serum. Ways and Simon[53] have shown that the protective factor(s) in serum are contained in low density lipoprotein (LDL) and high density lipoprotein (HDL). Vitamin E, in its role as a biological antioxidant, appears to be related to the tendency toward autohemolysis of acanthocytes. Kayden and Silber[18] have shown that the major lipoprotein for plasma transport of vitamin E is the LDL 1.006 to 1.063 fraction, (betalipoprotein). Lacking betalipoprotein, vitamin E levels in ABL patients are the lowest recorded in all human diseases. Those small amounts of detectable vitamin E in these patients are predominantly carried by HDL. It has also been shown that the autohemolysis test can be corrected *in vitro* by adding vitamin E to acanthocytes or *in vivo* by parenteral injections to ABL patients.[29]

One of the earliest manifestations of Vitamin E deficiency is the production of hemolysis by exposure of red cells to small amounts of hydrogen peroxide (i.e., hydrogen peroxide hemolysis test). This test is strikingly positive in ABL patients, but it can be corrected by addition of vitamin E.[20] Acanthocyte microviscosity is not related to vitamin E levels,[12] nor is acanthocyte morphology altered by its oral administration to ABL patients.[5] However, it has been impossible to determine which features of ABL are due to genetic alterations and how many may be due to deficiency of absorption of essential substances in the diet such as vitamin E. Muscular weakness and dystrophy, central nervous system lesions and ophthalmic changes, including retinal destruction and increased hemolysis of red cells, are all features of experimental vitamin E deficiency in animals. If, as suggested, the major role of vitamin E is as an antioxidant, it may be that the central nervous system and opthalmic lesions of ABL are also related to vitamin E deficiency.[29] Reports of the benefit of long term vitamin E therapy in ABL hold promise that it may delay the development or progression of the neurological and retinal lesions.[40]

Red cell survival in ABL is usually shortened and patients have frequently shown mild anemia, decreased haptoglobin, reticulocytosis and bone marrow erythroid hyperplasia. Acanthocytes have decreased membrane fluidity and increased microviscosity owing to an increase in the S/L ratio. It seems likely that these changes account for the premature destruction of the ABL acanthocytes, particularly older ones, by the spleen. While the hemolytic state is never so marked as that associated with spur cell anemia, this may be accounted for by the absence of

congestive splenomegaly which is so characteristic of severe liver disease with portal hypertension. Otherwise, it seems likely that the spleen behaves as has been previously demonstrated in spur cell anemia, that is, conditioning the acanthocytes to transform them from a scalloped contour to a thorny shape and then finally destroying them.[12]

Hypobetalipoproteinemia

Familial hypobetalipoproteinemia (HBL) is an inherited disorder of lipid metabolism which has been reported in approximately 12 families.[26] The heterozygous state seems to be characterized by reduction in the rate of synethesis of structurally normal LDL[33] and clinically is usually asymptomatic although some patients have had neurological problems.[37] Acanthocytes are either absent or infrequently seen.[7] Mars et al[37] demonstrated "acanthocytes" in apparent heterozygotes who had serum cholesterol of less than 100 mg per dl after incubation in tissue culture media and autologous serum, but they were not noted spontaneously on peripheral blood smears. In addition, they reverted to normal shape upon addition of hyperlipemic or hypercholesterolemic serum, suggesting to some that they may not have been true acanthocytes. Lipid analysis of red cell ghosts has shown normal total cholesterol, phospholipid and S/L ratio.[37]

The homozygous state of HBL is clinically and biochemically indistinguishable from classical ABL.[6,7,17,26,42] Acanthocytes are fully as numerous in homozygous HBL as in classical ABL. The red cell lipids from Salt's[42] patients were studied by Shacklady et al[44] who reported results that were indistinguishable from those of classical ABL, i.e., increased cholesterol and sphingomyelin content and reduced linoleic acid and increased oleic acid esterified to phosphatidylcholine.

Secondary or acquired HBL has been reported in a wide variety of malabsorption states and has occurred both with and without acanthocytosis. Gracey et al[24,25] cite nine instances of malnutrition and intestinal malabsorption in Australian aboriginal infants with prominent acanthocytosis and HBL. The acanthocytosis proved to be transient, disappearing when general nutrition and serum betalipoproteins returned to normal. The possible role of vitamin E deficiency in the infants was not investigated but warrants consideration.

Acanthocytosis with Neurological Disease in the Absence of Plasma Lipid Abnormalities

Acanthocytosis has been reported in a number of families in association with neurological disease but without discernible serum lipid abnormalities.[2,8,18,19,21,32,34] The neurological abnormalities have been rather varied, suggesting similarities to Huntington's chorea, Charcot Marie-Tooth Disease and the Gilles de la Tourette syndrome rather than the long tract signs with ataxia usually associated with ABL. Critchley et al[19] described the distinctive clinical features as an extrapyramidal movement disorder with dystonic, choreiform and athetoid movements, and a wide variety of oro-facial tics. The mode of inheritance has appeared to be both autosomal dominant and recessive. The acanthocytes have had typical morphology, but are quantitatively less than those seen in ABL, having been reported as up to 50 percent of the red cell population, but more often less than 20 percent. All of the cases have had normal serum lipids. Studies of the red cell lipids have revealed normal cholesterol and phospholipid with no change in the S/L ratio.[2,8,21]

Linoleic acid content was described as normal by Estes et al[21] and decreased by 25 percent by Bird et al.[8] A number of instances were reported where normal red cells were converted to acanthocytes

when incubated in patient's compatible serum, suggesting that some serum factor may be responsible for the acanthocytosis.[2,21]

Infantile Pyknocytosis—Vitamin E Deficiency

In 1959, Tuffy et al[50] first described a brisk hemolytic anemia in infants in association with up to 50 percent distorted and contracted erythrocytes which were referrred to as pyknocytes. Comparison was drawn to the acanthocytes in ABL from which their "pyknocytes" could not be differentiated on a morphologic basis. The etiology of the anemia was undetermined, but it was transient and responded to transfusion therapy. Similarly in 1967, Oski and Barness[41] reported a hemolytic anemia in 11 low birth weight infants at six to 11 weeks of age, which they attributed to vitamin E deficiency. These infants had "pyknocytes" that were similar to those of Tuffy et al,[50] abnormal hydrogen peroxide hemolysis tests and low vitamin E serum levels. The hemolytic state and acanthocytosis were corrected by administration of vitamin E. It was suggested that inadequate serum vitamin E, a known potent antioxidant, was associated with peroxidation of red cell lipids which bound free sulfhydryl groups leading to decreased red cell life span.

This mechanism has been supported by the comprehensive studies of vitamin E deficient rats by Jacob and Lux.[28] The cases of acanthocytosis secondary to malabsorption and hypobetalipoproteinemia reported by Gracey et al[24,25] bear great similarity to those of infantile pyknocytosis, suggesting that these infants may also have had vitamin E deficiency.

McLeod Phenotype of the Kell Blood Group System

In 1961, Allen et al[1] reported a new Kell blood group system phenotype which was designated McLeod. The report of Wimer et al[55] in 1977 drew attention to the fact that the red cells in the McLeod phenotype showed prominent acanthocytosis and were associated with a compensated hemolytic process. In studying the propositus's peripheral blood over a period of several months, the proportion of acanthocytes varied from eight to 85 percent with approximately 25 percent found with immediate fixation as used for scanning electron microscopy. Serum triglycerides, lipoproteins and cholesterol were performed ruling out the possibility of ABL. There was evidence of a compensated hemolytic state with moderate reticulocytosis, decreased serum haptoglobin and slight splenomegaly with normal osmotic fragility and autohemolysis. The propositus' mother and two daughters were mosiacs when tested in the Kell blood group, and they also had up to 10 percent acanthocytes. Their reticulocytes were also slightly elevated. The work of Marsh[38] has demonstrated that the McLeod phenotype is inherited as an X-linked characteristic and their red cells lack Kx, a precursor-like substance, that appears to be necessary for the proper biosynthesis of Kell antigens. Marsh also reported that normal phagocytic leukocytes have Kx antigen whereas the leukocytes of male patients with chronic granulomatous disease (CGD) do not.

Because of the Lyon phenomenon of X chromosome inactivation, female carriers of the McLeod phenotype and CGD have mosiac populations of Kx positive and negative red cells, or Kx positive and negative leukocytes, respectively. It is proposed that, the common allele called X^1k orders synthesis of Kx by phagocytic leukocytes and red cells in healthy people, whereas inheritance of a variant Xk allele leads to absence of Kx on leukocytes and CGD, absence of Kx on red cells and the McLeod syndrome or absence of Kx on both leukocytes and red cells in patients with both diseases.[38]

The mosiacism of females proves that the Kx is a property of the red cells themselves and is not acquired by passive absorption from plasma. This is further supported by the inability to convert McLeod acanthocytes to normal morphology by incubation in normal plasma or convert normal cells to acanthocytes by incubation in McLeod plasma.[22] Galey et al[22] in studying McLeod acanthocytes found them to have normal membrane lipids, microviscosity and electrolyte transport, but osmotic water permeability was 30 percent below normal.

Little is known of the biochemical nature of the antigenic determinant of the Kell system. Indirect evidence, however, suggests that the Kell antigen system may be attributable to a polysaccharide, and it has been suggested that the Kx antigen may be a marker on a structural protein to which the Kell specific sugars are attached.[38] Galey et al also cite indirect evidence related to the demonstrated decreased osmotic water permeability and its known association with altered sulfhydryl bonds to suggest that the McLeod cell abnormality is due to a protein alteration. Obviously, confirmation must await a detailed study of its membrane proteins.

In any event, McLeod acanthocytes, which are morphologically indistinguishable from all other acanthocytes, are somewhat unique in that while most others have some demonstrable lipid abnormality, these, instead, have normal lipids and a high probability of a primary membrane protein alteration. Such an association of an altered membrane structural protein with acanthocytosis would be comparable to that stomato-spherocytosis and hemolytic anemia shown to be characteristic of the Rh null blood type.[48] As recently suggested by Schmidt,[43] the possibility of finding additional null blood types in a wide variety of hemolytic states with altered red cell morphology, may be a fertile field for investigation in the future.

Miscellaneous Conditions

Acanthocytes have also been reported in a number of diverse clinical situations. Brecher et al[10] have noted two to 10 percent acanthocytes in post-splenectomy patients. It is suggested that these cells are probably continually made and promptly removed by the spleen. Noting that their numbers gradually increase for several weeks following splenectomy, it appears that they then enjoy a longer survival until a stable plateau is reached. Two to five percent acanthocytes were found in hypothyroidism, reticulum cell sarcoma, psoriatic skin lesions and in one infant with unexplained possibly congenital hemolytic anemia. Horton et al[27] reported rare acanthocytes in 19 percent of their patients with hypothyroidism. Their incidence could not be correlated with the level of serum cholesterol or thyroxine, but they felt that they tended to be associated with the more advanced cases of hypothyroidism.

For the most part, the acanthocytes disappeared following response to therapy. Wardrop and Hutchinson,[51] while not specifically referring to them as acanthocytes, reported the association of similar cells in hypothyroidism. Other cited conditions in which acanthocytes have been found include anorexia nervosa, panhypopituitarism, carcinoid tumor metastatic to the liver with hemolysis and hypoplastic anemia.[14] They have also been found in dogs in association with splenic neoplasms consisting of hemangiomas or hemangiosarcomas.[23]

The common feature shared by all of the these conditions is that those acanthocytes which were noted have formed a minor proportion of the total red cell population. In those instances where membrane lipids have been measured, they have been normal. Furthermore, it is not entirely clear from the published reports whether all of the cells have been true acanthocytes. Clearly, the possibility

of echinocytes, schizocytes and non-specific poikilocytes may not have been completely excluded.

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