True, True . . . But Are They Related?

HEPATOLOGY is assuredly the last refuge of the general internist in a world of specialists. After all advanced liver disease is an extrahepatic disorder, manifestations of which are seen throughout the body from the integument to the vital organs, from the brain to the bones, and from the gonads to the glands. In the blood circulation, the diseased liver prejudices the humors of the coagulation and anti-coagulation cascades, subverts the red and white corpuscles, and depletes the minute disci that the dynamic, graceful, sociable and occasionally pugnacious Italian pathologist Guilio Bizzozero[1] called *piastrine,*[2] or *Blutplättchen* in German,[3] *petites plaques* or *plaquettes* in Fench,[4] and platelets in English. Not without controversy was Bizzozero's claim to their discovery,[5,6] which some attributed instead to the distinguished French microscopist, Alexandre Donne, 40 years earlier.[7] Irrespective of who discovered them, platelets are everywhere. Mammals have anucleate platelets, lower species like fish have nucleated platelets,[8] and horseshoe crabs have phagocytic cells that double as platelets.[9] Why even dinosaurs may have had platelets.[10] Is there not hematopoietic irony, therefore, in the paradox that the liver and spleen, which are the founts from which the formed elements of the blood issue forth in embryonic life,[11-13] are so very deleterious to the hematological system when the liver is diseased?

The characteristic paucity of circulating white cells and platelets that is seen in patients with cirrhosis is usually ascribed to the increased voracity of the plethoric portal hypertensive spleen. However, the myriad changes of form that affect the red cells are more intriguing and not as simply explained. Also, anemia is not as common in cirrhosis as are leukopenia and thrombocytopenia. Admittedly, reduced thrombopoietin synthesis by the diseased liver[14-16] and increased destruction of thrombopoietin on splenic-sequestered platelets[17] may contribute to the reduction in platelet numbers. In contrast, it was seemingly familiar in the 19th Century to observe anemia in patients with splenomegaly, as in the so-called "splenic anemia"[18] that misled poor Guido Banti, in Florence, Italy, into reasoning that the *splenopathy* of a toxic spleen[19] (Banti's disease) injures the liver and causes cirrhosis in a syndrome that he termed *hepatosplenopathy*,[20] which was later named after him (Banti's syndrome). Instead, in liver disease we frequently see red cells of unusual sizes, shapes and forms, which classically-inclined hematopathologists named so exotically that we must immediately reach for our Greek lexicons to understand them. This would surely have surprised Jan Swammerdam, the 17th Century Dutch naturalist and pioneer in the use of the microscope, who first saw what he called "ruddy globules" when he peered through his new instrument at the fluid of life.[21] Although cells flowing through capillaries had been seen earlier by Marcello Malpighi,[22] the significance of these red biconcave discs was lost on Swammerdam, however, and even on his more illustrious visionary countryman Antonj van Leeuwenhoek,[23] but not on 18th Century Englishman William Hewson, who also recognized the white blood cells. Hewson concluded that these red particles of the blood must be important to life because they are present in great abundance.[24] He even presented cogent experimental evidence for the concept of a cell membrane that bounds the red blood corpuscles.[25]

Although we contrive to reduce the names of the different red cell forms to the vernacular, it is satisfying *one-upmanship* (a practice known in the United States by the unfortunate term of "pimping") to question our trainees on ward rounds about the original Greek terms and expect them to know the derivations. After all, is not *erythrocyte* itself the Greek term for a red hollow or receptacle? In this endeavor, hepatologists are blessed for we can boast almost as many different erythrocyte configurations as seen by other specialists. Given the effect of liver disease on anti- and pro-coagulants, and on leukocytes, erythrocytes and thrombocytes, hepatologists are but one letter away from being hematologists. Liver disease brings forth macrocytes, spherocytes, stomatocytes, acanthocytes, echinocytes and codocytes, i.e. red cells that are large or spherical, have mouths or thorns, resemble hedgehogs or look like bells that become targets when squashed on a slide, respectively (Fig. 1), at least according to their Greek etymology. How many hepatologists, though, would recognize a knizocyte, a triconcave or "pinched" cell that appears in dried blood films to have not one mouth like a stomatocyte with its single concavity, but two. If only liver disease was responsible for drepanocytes, keratocytes, dacryocytes, elliptocytes, poikilocytes, meniscocytes and schizocytes, our joy would be complete. The hepatological changes in red cell shape that likely reflect alterations in the lipid composition of the red cell membrane caused by liver disease, are fully reproduced in the blood of healthy astronauts during space flight,[26]

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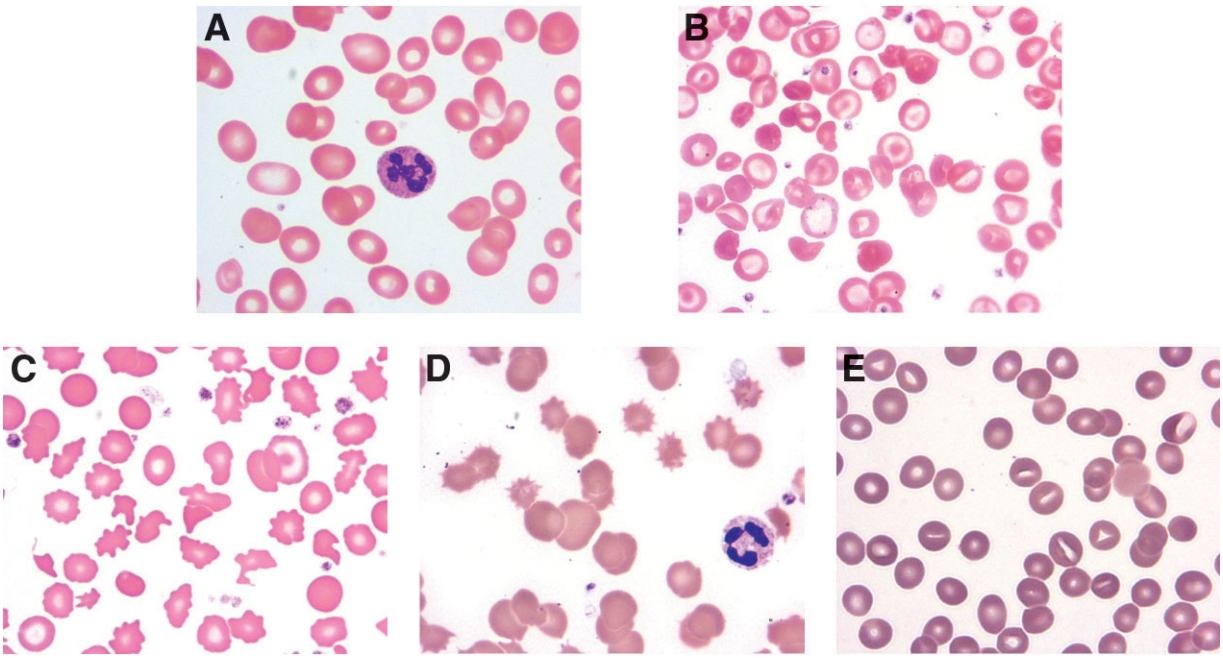

Fig. 1. The spectrum of red cell contortions seen in patients with liver disease. (A) macrocytes, (B) target cells (codocytes) and spherocytes, (C) acanthocytes (burr cells), (D) echinocytes (spur cells) and (E) stomatocytes.

whose red cell lecithin shows temporary but dramatic quantitative and qualitative changes too. The attraction of these red baubles is not simply aesthetic, however, but it is their clinical importance, for many of them are fragile and some, like spherocytes, burr cells and particularly spur cells, are prone to hemolysis that can cause or contribute to anemia in the patient with liver disease. In these individuals, the diagnosis can sometimes be clinched only by identifying the abnormal erythrocytes on a blood cell smear. With this frame of reference, it is worth recalling that almost 50 years ago, the first description of a syndrome of hemolytic anemia, jaundice and hyperlipemia associated with alcoholic fatty liver and cirrhosis[27] was reported, which later started a controversy that has not yet been completely resolved.

In 1958, Leslie Zieve (Fig. 2) published an account of 20 alcoholic men whom he had seen over an 8-year period at the Minneapolis Veterans' Hospital, with symptoms, findings and a predictable course that led him to the inescapable conclusion that they exhibited a previously unrecognized but distinct syndrome.[27] Constitutional symptoms were common and fever was the rule. Upper abdominal pain, sometimes severe but not due to pancreatitis, was almost universal. Jaundice was invariable but fluid retention was not, and though marked hepatomegaly was present initially, it soon receded. Liver tests were only mildly deranged but the liver showed steatosis, often severe, and mild to moderate cirrhosis in 90% of those biopsied. Anemia without overt bleeding was marked with either macrocytosis or spherocytosis, and the red cells, when tested, showed osmotic fragility. Reticulocytosis and often striking hypercholesterolemia completed the picture. Such was the clinical puzzle that many explanations were entertained for this illness, *e.g.*, obstructive

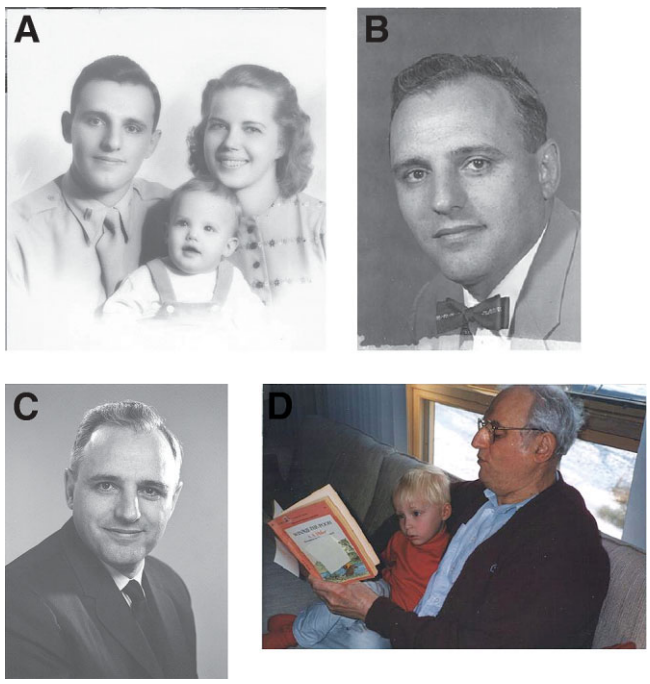

Fig. 2. Dr. Leslie Zieve (8/6/1915 – 5/13/2000) soldier (A), scholar-physician and scientist (B-C) and grandfather (D).

jaundice and viral hepatitis. The rapid resolution of the syndrome with abstinence from alcohol, contradicted all tentative diagnoses. The report of this new syndrome was initially received with apathy, and certainly Zieve did not consider this publication a high point in his otherwise celebrated career. Other cases were soon recognized elsewhere but it was the publication from the State Veterans' Hospital in Rocky Hill, Connecticut 4 years later, of a cohort of 6 similar cases[28] that introduced the term Zieve's syndrome for the first time and marked Leslie Zieve with an eponymous notoriety that he never sought. As Zieve commented 25 years later,[29] the understanding that the coexistence of jaundice, hyperlipidemia and hemolysis in an alcoholic patient was an entity with a predictable rapid recovery rate, was important because the possibility of more serious and prolonged liver diseases could be eliminated and meddlesome interference, such as surgical exploration, could be avoided — especially in those days when endoscopic retrograde cholangiopancreatography was not available as a substitute for clinical acumen.

Outside of Minnesota, Leslie Zieve's many accomplishments are not widely appreciated, whereas in Minneapolis and in the Veterans' medical community, he was legendary. He was honored with the Middleton Award, the VA's highest honor for scientific achievement in biomedical research, and he was recognized for outstanding achievement as a Laureate Awardee of the Minnesota Chapter of the American College of Physicians. Following internship in Philadelphia, he served as a battalion surgeon in the Second World War, with sole responsibility for casualties. He returned to his home state (where he had been raised by his sisters as the only boy in the family), to join the Veterans' hospital in Minneapolis. With an interest in mathematics and statistics, and what his friends still vividly recall as "a passion for research", he became Chief of the Radioisotope Service. He was given the uninspiring title of Assistant to the Director of Professional Services but when the title of the position (but not its substance) was changed to the Associate Chief of Staff for Research, somehow this more imposing appellation enabled him to build up a research empire there of unprecedented success. A compassionate family-oriented man, intellectually rigorous and therapeutically vigorous, he was an excellent teacher and popular general medicine attending, who encouraged young investigators who did exciting research in all fields of internal medicine. His interest in liver disease was broad, with extensive evaluations of liver function tests and forays into porphyria inspired by Cecil Watson, the laboratory investigation of lipids and an abiding preoccupation with many facets of hepatic coma. Stimulated by the syndrome that he noticed, not surprisingly Zieve also maintained an interest in the hemolytic anemia of liver disease,[30] of which he contrasted a severe hypersplenic type and a mild hyperlipidemic type.[31]

After a latent period of indifference to the initial publication[27] that ended with interest kindled 4 years later,[28] two opposing camps formed of those who accepted that there is a distinct constellation of jaundice, hyperlipidemia and transient hemolytic anemia in some patients with alcoholic fatty liver cirrhosis, and of skeptics, who dismissed the "so-called Zieve's syndrome" as representing an association of common independent occurrences in alcoholic patients.[32] Yet case reports of Zieve's syndrome continued to be published from around the world.[33-39] Some authors point out that the hepatic steatosis may actually mask underlying alcoholic hepatitis,[34,38] whereas others emphasized related complications such as porphyrinuria,[40] fatality following hepatic angiography,[41] intracranial hemorrhage,[42] severe myalgias[43] and retinal injury.[44] Zieve's original concern that the patient with this syndrome might be mistakenly thought to require surgical intervention, was rediscovered 40 years after the original warning.[45] Protagonists for the existence of a distinct Zieve syndrome have postulated several mechanisms for the transient hemolysis that is a key feature of the illness. Such explanations include the presence of an undetermined extracorpuscular factor,[46] abnormal red cell membrane lipids,[47] especially phospholipids[48] and vitamin E deficiency-induced increases in red cell membrane cholesterol and polyunsaturated fatty acids[49] that may lead to instability of red cell membrane enzymatic function, *e.g.*, pyruvate kinase.[50] Others say that the changes that are measured in plasma lipids, red cell membrane lipids, etc. are true, true but unrelated to the hemolytic process.[51,52] Reams have been published about the interrelationships between alcohol abuse, liver disease, lipid metabolism and hematological disorders. And yet it is still difficult to tell whether Zieve's original syndrome truly represents a unique clustering of pathological findings. For what it is worth, most hematologists that the author questioned were inclined to think that it is. Equally important, however, is the common observation that the disorder that Zieve described is rarely seen nowadays. Zieve's memory may therefore be linked inextricably with the question not so much whether there is an association between hemolysis, hyperlipidemia and jaundice in alcoholic patients, but are these factors causally related or unrelated. A far more fitting testimony to Zieve's memory, however, can be found in the Veterans' Affairs medical community and especially in Minneapolis. As Michael Levitt said in the eulogy he delivered after Zieve's passing, quoting from the epitaph for Sir Christo-

pher Wren in St. Paul's Cathedral, "*Si monumentum requires, circumspice.*" "If you seek his monument, look around you." Zieve's real legacy is the love of science and discovery that he instilled in his colleagues, students and successors, which they perpetuate to this day.

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