

A Triple Hematologic Nightmare: Underdiagnosing and Not Treating the Most Common US Genetic Disorder (Iron Overload): Discarding Each Year Tons of Their Good Donor Blood, Creating Artificial Donor Blood Shortages in Each of the Past 30 Years

To the Editor: In the September 1, 1997 *US News and World Report (USNWR)*, senior writer Dana Ilawkins brought to the nation the full extent

of this problem in her story "Throwing Out Good Blood." [1]. She was able to do this because of massive help lining up the facts, the doctors, and the patients who could confirm them, through three officers of the Iron Overload Diseases Association (IODA): Director of Public Relations Sandra Thomas, IODA Treasurer David Snyder (both acting for IODA President Roberta Crawford), and myself as an IODA Advisory Board member.

Mount Sinai's Blood Bank Director Morton Spivack, M.D., wrote in his September 29, 1997 letter to the editor of *USNWR* [2]: "I have been Director of various blood banks and a member of the American Association of Blood Banks (AABB) for 34 years. In this capacity, I have lived through many blood shortages, including one just this past summer. The use of blood drawn from the many otherwise healthy patients with hemochromatosis would go a long way toward alleviating these recurrent shortages. The inability of the various regulatory agencies to see this has always amazed me. There have been arguments made that this issue is either a safety or a financial issue. Safety should not be an issue since these donors are under medical care, and in their frequent donations they are tested by a battery of tests designed to ensure the safety of their blood. As to the financial issue, this argument pales into insignificance when we consider the great addition to the US blood supply that these donors could make."

All Americans should be blood tested (by both serum-ferritin and serum transferrin percent saturation with iron) for iron overload [3]. After these two tests confirm the diagnosis, liver biopsy is desirable to quantitate the size of liver stores and degree of liver fibrosis. High stores and fibrosis predict liver cancer if the stores are not removed. Approximately 12% of Americans (approximately 30% of African Americans) have genetic heterozygous hemochromatosis (H) (moderate iron overload) and approximately one in 100 to 200 (approximately one in 100 African Americans) have homozygous hemochromatosis (HH) (excessive iron overload) [3]. Those with H absorb approximately 50% more iron from their daily food than the rest of us, and thus need approximately four to six therapeutic phlebotomies/year to get rid of their excess body iron and maintain normal levels [3-5]. Most patients with HH are not diagnosed until organ damage (pancreas, liver, gonads, heart, joints, etc.) appears; many die undiagnosed, with autopsy revealing that their diabetes, cirrhosis, liver cancer, sterility, cardiomyopathy, arrhythmias, and/or arthritis were due to untreated iron overload. HH patients absorb daily three times the normal food iron.

When the diagnosis of H or HH is made, the patient and next-of-kin must be forcefully and directly informed that they need regular therapeutic phlebotomies and must henceforth abstain from alcohol and supplements containing iron and/or vitamin C, because any of the three will increase iron absorption and speed early organ destruction, liver cancer, and death [3-5].

FDA regulations copy those of the AABB and require that H and HH phlebotomies be stigmatized by labeling them "therapeutic phlebotomy—patient has iron overload," creating an unwarranted fear resulting in healthy donor blood being thrown out rather than offered without stigma to recipients who need it, creating artificial [1,2] donor blood shortages through the US and our military overseas (including during the Gulf War, in which I served as an active-duty Green Beret Medical Officer).

On September 5, 1996, I filed a petition with the FDA to destigmatize H and HH blood [6]. On June 19, 1997, the petition was rejected on the grounds that there was not enough evidence to support it. In fact, the weekly *ABC* (American Blood Centers) *Newsletter* (November 8, 1996, p. 10) states that the FDA had recently met with the AABB, and they agreed to reject my petition on the grounds that it is not a blood bank safety issue, but a money issue (approximately \$200 million/year profit from phlebotomies [1,2], therefore in the province of HCFA and not of FDA! Despite this fact, almost a year later, a Red Cross spokesman alleged (with no evidence from H or HH patients) that it was a safety issue, because H and HH individuals are "not volunteer donors" [7]. Blood bank director Spivack made clear [2] that this was a specious argument (see his quote in the second paragraph above).

I replied to FDA on August 14, 1997 that "donor blood from persons with H or HH is the best donor blood for two reasons: 1. Unlike other donors, H and HH donors almost never receive transfusions, and thus almost never receive blood contaminated with AIDS or hepatitis virus; 2.

Most who need blood are iron-deficient. H and HH blood is high in iron." I did not mention, but should have, that multiple phlebotomized hemochromatosis donors have normal to low circulating iron, and so are ideal donors for patients with anemia due to genetic hemolytic disorders (thalassemia, sickle cell disease, G6PD deficiency, etc.). Implementation of the above actions is overdue, as we noted in a recent paper [4] which focuses mainly on our new assay for ferritin iron, i.e., mean number of iron atoms per molecule of ferritin protein (the number is low in deficiency, normal in inflammation, and grossly elevated in iron overload) [5]. An FDA spokesperson telephoned me about August 28 to inform me that the FDA had received and was seriously considering my August 14 letter, but it would take some time to reach a conclusion.

Commercially available serum assay for the hemochromatosis gene [8, 9] is of less value than measuring the duo of serum ferritin protein and percent saturation of transferrin [3,5], or measuring the even better duo of serum ferritin protein and serum ferritin iron [5]. In approximately 15% of those with phenotypic iron overload disease, the currently isolated relevant genes are not found [8,9]. Also, 15% with the genotype do not express the phenotype [8,9]. Therefore, we should not, for ethical and legal reasons (i.e., losing a lawsuit to an erroneously stigmatized plaintiff), stigmatize genotypes (or adequately phlebotomized phenotypes) as having iron overload disease because about 30% do not. In early phenotypes, iron overload and its accompanying early liver fibrosis may disappear with adequate phlebotomy [10] (also see Powell [11]).

Massive further documentation of all of the facts delineated above can be found in the papers presented by many of the world's leading iron researchers, including those at blood banks all over the US and Canada, and Laurie Powell of Australia, at the CDC's second workshop on iron overload held in Atlanta, GA, March 3-5, 1997 [11]. The first such CDC workshop was on February 26 and 27, 1996, also in Atlanta. It was coordinated by Ray Yip and Sharon McDonnell. The IODA has sponsored for 15 years excellent annual Hemochromatosis Symposia. An unofficial summary of the proceedings of the 1997 workshop is available from Roberta Crawford, President, Iron Overload Diseases Association, 433 Westwind Drive, North Palm Beach, FL 33408 (Tel: 407-840-8512, 3). An excellent longitudinal review of diagnosing and treating 410 Canadians and French people with hemochromatosis appeared in *Hepatology* in January, 1997 [12]. Even more recently, HH was found in about 1% of German Caucasians [13]. The title of that 1998 paper echoes the title of our 1992 paper [3] in which we cited (our ref. 26 [3]) an open letter of January 20, 1992, from Dr. R. Gambino, in which he reported that a large US commercial laboratory, using measurements of serum TIBC with ferritin redux, detected iron overload in about 1% of several million patients visiting physicians' offices.

I urge *American Journal of Hematology* readers to protect their patients and themselves [14] by doing universal screening for iron overload [3,13] and to write letters in support of our petition to FDA (FDA Docket Number 96-0328/CP 1, filed September 5, 1996) [6] to destigmatize hemochromatosis blood. Write to: Dockets Management Branch, Food & Drug Administration, Department of Health and Human Services, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857. Also, Fax your letter to the FDA Dockets Management Branch at 301-594-3215.

Note: Canada ended the official stigmatization of hemochromatosis donor blood in 1991.

NOTE ADDED IN PROOF

After reviewing all the evidence, an expert panel of the CDC (Centers for Disease Control and Prevention) and the NHGRI (National Human Genome Research Institute) published in great detail [15] agreement with the position stated in the current communication, i.e., "Genetic testing is not recommended at this time in population-based screening for hereditary hemochromatosis. . . ."

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