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Modern Review of Congenital Hypoplastic Anemia

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In 1938, Louis K. Diamond was a sufficiently junior pediatrician that the article he presented to the American Pediatric Society required co-authorship by the chairman of his pediatrics department, Kenneth D. Blackfan. They reported four children with "an intermediate type of anemia—hypoplastic rather than completely aplastic." Their names have been linked ever since to the syndrome described in that article, congenital red cell aplasia (1). A few years later, they co-authored the *Atlas of the Blood in Children*, in which the sequence of authors was reversed (2), leading to the syndrome being known as either Diamond–Blackfan anemia (DBA), used in North America, or Blackfan–Diamond anemia, used in Europe. To Dr. Diamond, however, it was always known as congenital hypoplastic anemia. He was waiting for the pathophysiology and molecular cause to be identified, at which time he would then apply the appropriate name to the disorder. Other names for this condition have included chronic congenital aregenerative anemia, hereditary red cell aplasia, pure red cell aplasia, congenital erythroid hypoplasia, erythrogenesis imperfecta, chronic idiopathic erythroblastopenia with aplastic anemia (type Josephs-Diamond–Blackfan), and DBA (3,4).

The treatment proposed by Dr. Diamond in his first article was red cell transfusion support, and he noted that "the gradual wearing out of the cells necessitated readmissions and transfusions." He mentioned a variety of unsuccessful treatment modalities, including intramuscular pentnucleotides, oral iron with either cobalt, copper, oral bone marrow and spleen extract, high-protein and vitamin diets, and vitamin C (1). Although the now common use of corticosteroids was initially suggested by Conrad Gasser (5), Dr. Diamond was certainly instrumental in rapidly demonstrating its efficacy (6). However, even now we rely heavily on transfusions, as he noted more than 60 years ago.

Although the names of Diamond and Blackfan are now inextricably linked to inherited pure red cell aplasia, Josephs had in fact described similar cases earlier (7). In fairness, keeping up with the literature in 1938 was even more onerous than it is now with computerized searches, and thus the earlier report may have been overlooked. In addition, whether Diamond was the first to recognize this disorder is probably less important than the fact that he focused much of his career on DBA and trained many hematologists who have continued this research.

Would this classic article from 1938 be accepted by journal editorial boards in the year 2000? These days, case reports have a low priority, as do articles lacking hypothesis-driven research or molecular models. However, unfashionable though it may seem, novel case reports are still important today, and the reviewers in 1938 were probably as unaware of the report by Josephs as were Diamond and Blackfan. Alert clinical observations have frequently led to seminal etiologic research. Recent examples include Wilms tumor/aniridia, clear cell carcinoma of the vagina and diethylstilbestrol, angiosarcoma of the liver and polyvinyl chloride, and the Li–Fraumeni syndrome. It is quite possible that today, Dr. Diamond and Dr. Blackfan might have received a rejection letter or have been instructed to return when they had identified the mutant gene responsible for DBA.

Dr. Diamond was determined that the cause of congenital hypoplastic anemia be identified in his lifetime. During the 1970s, after he had retired from Harvard Medical School and moved on to his second 20-year career as an Emeritus Professor at the University of California San Francisco Medical School, he organized a series of symposia focusing on congenital hypoplastic anemia (8), and he maintained his clinical interest in DBA until his death in 1999 at the age of 97. The first DBA gene was localized to 19q13 in 1997 and cloned in 1999, and the first major molecular piece of this puzzle was identified before he died (9,10).

It is now apparent that there is genetic heterogeneity within DBA, with a second gene recently mapped to 8p23 and the recognition of other involved genes (11). Despite this genetic diversity, Dr. Diamond was correct in his inclusiveness, considering congenital hypoplastic anemia as a single entity with phenotypic diversity. When Aase and Smith described an apparently new disorder characterized by triphalangeal thumbs and congenital red cell aplasia, Dr. Diamond commented to me that he had clearly included similar patients in his comprehensive case series in 1961 (12,13). This led to an editorial in *Pediatrics* entitled "Thumbs and Anemia," in which it was noted that the outcome in the patients with so-called Aase syndrome was indistinguishable from those with DBA, and that "lumping" the patients together might be more informative than "splitting" them into subsets (14).

Dr. Diamond directly trained approximately 75 hematologists at Boston Children's Hospital (4), the first generation of pediatric hematologists. The number in the second

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generation is difficult to ascertain because this family tree is extremely large. If we restrict the "tree" to those trained at Boston Children's Hospital, there were more than 80 in the generation trained by Dr. Diamond's successor, David G. Nathan, and there have been more than 70 trained by Samuel E. Lux, who succeeded Dr. Nathan. We are now well into the third generation, and thus Louis K. Diamond is indeed the "father" of pediatric hematology. For those "offspring" who continue to work on DBA (or congenital hypoplastic anemia), there seems to have been a "founder" effect, and the founder was Louis K. Diamond.

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