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Historical Review

LOUIS DIAMOND AND HIS CONTRIBUTION TO HAEMATOLOGY

> Some of the old practices like thoughtful, individualized, considerate care of children are still the basis of good paediatrics' Louis K. Diamond (1973)

An earlier review in this series presented the contributions of Sir Leonard Parsons to the scientific basis of paediatric haematology, referring to him as the Grand Old Man of British Paediatric Haematology (Stevens, 2001). Across the Atlantic Ocean, several paediatric haematologists achieved a similar level of distinction, but only one became known as the Father of Pediatric Hematology. That man was Louis K. Diamond, Professor of Pediatrics at Harvard Medical School and later at the University of California San Francisco, who played a leading role in developing a scientific understanding of erythroblastosis fetalis and an effective way to treat it. Diamond also described several well-known syndromes that bear his name and, perhaps most importantly, trained an entire generation of paediatric haematologists who have made a major contribution to the development of the field in the past 50 years.

THE LIFE OF LOUIS K. DIAMOND

Louis Diamond was born in 1902 in Czarist Russia and emigrated to the United States at the age of 2. He grew up in Manhattan where he attended the Townsend Harris Hall school. His application to Harvard College was initially rejected but, after a year at New York University, he applied again. In the autumn, as classes were about to begin, he received an unexpected telegram from Harvard informing him that, if he could present himself the next morning he would be allowed to enrol. After a night train ride from New York, he arrived in Boston and, carrying his own suitcase, walked a considerable distance from the railway station to the neighbouring town of Cambridge, where he began an almost 50-year association with Harvard University (Jared Diamond, personal communication). After graduating from Harvard College and Harvard Medical School, he worked briefly with Florence Sabin at the Rockefeller Institute, and then returned to Boston to train in paediatrics and pathology at Boston Children's Hospital. That hospital had moved in 1914 to a location adjacent to the Harvard Medical School in Brookline (Smith, 1983). A photograph in 1921 suggests a rather more rural location than was in fact the case (Fig 1). In 1929, Diamond married Flora Kaplan, challenging the hospital regulations of the time, which forbade house officers to be married. Flo, an expert pianist and teacher as well as a woman of great social grace, and Lou (Fig 2) had a long, happy marriage and raised two bright accomplished children, Jared Diamond, author and professor of physiology and anthropology at UCLA, and Susan Diamond, a writer for *The New Yorker* and other publications. Flo was an unflagging supporter of Diamond's career. As Diamond observed 'in the lean years of my start in paediatrics, whenever I wondered whether I was on the right course and should continue, I was encouraged by just three words from my wife: ''But of course!''' (Diamond, 1973). Generations of fellows and residents were entertained in their home and received encouragement and advice about their careers. As full-time academic appointments were uncommon in the 1930s, Diamond entered private practice while at the same time continuing his research into blood diseases of children. His rise through the ranks of the paediatric staff at Boston Children's Hospital and at the Harvard Medical School was steady, culminating in his appointment as chief of the haematology division, associate physician in chief and professor of paediatrics (Janeway, 1973). In 1942, he founded the Blood Grouping Laboratory to study erythroblastosis fetalis and apply knowledge about the newly discovered Rh blood group to its management. This was the first facility to identify routinely the blood groups of pregnant women and thereby anticipate possible erythroblastosis in their newborns. At the same time, thanks to a 5-year grant (of the then princely sum of $10 000/year) from the Charles H. Hood Foundation for research in haematology, Diamond was able for the first time to devote his energies full time to academic paediatrics (Janeway, 1973). From 1948 to 1951, because of his expertise in blood banking and transfusion medicine, he was recruited by Professor Edwin Cohn to serve as the first technical director of the National Blood Program that was created after World War II by the American Red Cross (Diamond, 1971; Starr, 1999). In 1968, Diamond retired from Harvard and relocated to San Francisco, where he served as adjunct professor of paediatrics at the University of California San Francisco. He was active in teaching and of great help in recruiting new faculty members to the expanding department of paediatrics there. Along with other colleagues throughout the United States, he established a visiting professor programme that made available the knowledge and skills of eminent, recently retired, paediatric professors like himself to interested institutions. In 1974, Diamond was one of eight leading paediatric haematologists who wrote the

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Fig. 1. Boston Children's Hospital *c.* 1921. Picture taken from the construction site for the future Gardner House. From the author's collection.

Fig. 2. Louis K. and Flora K. Diamond. Obtained with permission from the private collection of Susan Diamond, authorized by the Center for Blood Research, Boston.

inaugural examination for certification by the American Board of Pediatrics in the newly designated subspecialty of paediatric haematology/oncology. To validate their expertise in the field, all eight took a special qualifying examination, made up of previously used American Board of Internal Medicine test questions that related to paediatric haematology/oncology. All eight passed and were certified. Diamond received certificate number one and thus his name stands first in a lineage that, by 2000, included 1602 diplomates (Pearson, 2002). A professorial chair, named in his honour, was endowed by colleagues, friends and former patients in the 1980s at the University of California San Francisco.

In 1987, he retired again and moved to Los Angeles, remaining in touch with the discipline of paediatric haematology until his death at the age of 97 years.

DIAMOND'S ROLE IN THE TRAINING OF A GENERATION OF PAEDIATRIC HAEMATOLOGISTS

As mentioned, Louis Diamond has often been referred to as the father of the discipline of paediatric haematology. Beginning in the 1940s and ending with his retirement from Harvard in 1968, he inspired a cadre of talented young paediatricians to receive training under him at Boston Children's Hospital in the (new) subspecialty of children's blood diseases (Fig 3). He continued this important work for an additional decade after his relocation to the University of California San Francisco. His 'men' as he put it (actually 71 men and seven women) became the nuclei of academic haematology programmes that sprang up in paediatric haematology departments throughout the United States, Canada and overseas. Many served as division chiefs, and at least 14 became chairmen of paediatric departments. Particularly illustrious members of this group included David Nathan and Frank Oski, who served for many years as department heads at Boston Children's Hospital and at the Harriet Lane Hospital at Johns Hopkins, respectively, and who together, until Oski's death, edited *Hematology of Infancy and Childhood*, the leading American textbook in the field of paediatric haematology. Dennis Miller, with the assistance of Robert Baehner, Campbell McMillan and Howard Pearson, all former Diamond trainees, has, for many years, edited *Blood Diseases of Infancy and Childhood*, another major American textbook in the field. In addition, Oski and Laurence Naiman, yet another Diamond trainee, collaborated to produce three editions of a widely

Fig. 3. Louis Diamond, relaxing on Lake Como during an international symposium on Diamond–Blackfan anaemia in 1974, sponsored by the Rockefeller Foundation and held at the Villa Serbelloni in Bellagio. Also shown are James Wolff (middle) and the author (left), one of the first (J.W.) and one of the last (W.M.) of Diamond's fellows at Boston Children's Hospital. From the author's collection.

used textbook of neonatal haematology, *Hematologic Problems in the Newborn*.

The modest stipends awarded to these trainees pale in comparison to the more handsome remuneration available today; National Institutes of Health (NIH) support through the mechanism of training grants is now widely available. In contrast, money for Diamond trainees came not only from the NIH but also through donations and grants made by private individuals, often the grateful parents of children cared for by Diamond. The earmarking of these funds for the training of fellows reflected the high priority he placed on training his successors. He was also generous in providing small stipends to support new research projects initiated by junior members of the faculty.

His style of teaching emphasized the bedside approach and care of the patient. More than one former trainee described Diamond as the best general paediatrician they had ever encountered, a quality clearly evident in his presidential address to the American Pediatric Society in 1969 (Diamond, 1969). Careful observation of the condition of the patient and meticulous recording of these observations was emphasized. It was not uncommon for trainees to have their ward notes extensively and critically edited by Diamond, often to their discomfiture. However, perhaps that is why so many trainees eventually excelled as editors themselves. Rounds with Diamond at Boston Children's Hospital, while perhaps not so 'grand' as those of his first chief, Dr Blackfan (depicted in Fig 4), usually involved a retinue of junior faculty, fellows, residents and medical students and could at times be intimidating, particularly for those who had not been diligent in their study of the diseases under discussion. Zuelzer, who was a 'lowly' intern at the time of his first meeting with Diamond, described him as 'rather fierce-looking in a dark, Assyrian sort of way', an impression that soon gave way to an appreciation of his 'kindness and unfailing courtesy' (Zuelzer, 1998).

DIAMOND'S SCIENTIFIC ACCOMPLISHMENTS

Erythrocytosis fetalis

The important scientific contributions of Louis Diamond to the understanding and treatment of erythroblastosis fetalis have been reviewed recently by Naiman & de Alarcon (2001). Shortly after completing his paediatric training and setting up a haematology research programme at Boston Children's Hospital, Diamond, together with Kenneth

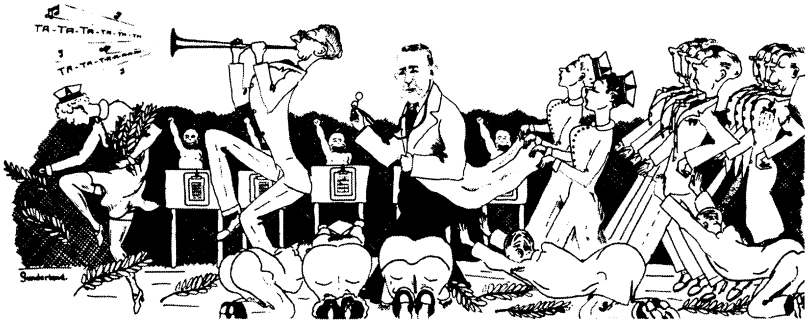

Fig. 4. Dr Blackfan on Grand Rounds at Boston Children's Hospital – a student's view. From Smith (1983). Copyright, Lippincott Williams & Wilkins, Baltimore, MD, USA.

Blackfan and James Baty, published the first clear description of what is today known as haemolytic disease of the fetus and newborn resulting from Rh incompatibility (Diamond *et al*, 1932). They showed that four apparently distinct entities, universal oedema of the fetus, erythroblastosis fetalis, icterus gravis neonatorum and anaemia of the newborn, were, in fact, all manifestations of the same underlying disease entity. Diamond felt the condition was due to 'a disturbance of the metabolism of the haematopoietic system resulting first in either a failure of maturation of erythrocytes or in an overgrowth of immature forms of erythrocytes; second, in the delivery of immature nucleated erythrocytes in large numbers to the peripheral circulation; and third, in the increased destruction of erythrocytes, including the nucleated forms'. The primary role of blood group incompatibility was unrecognized because the responsible blood groups had not yet been discovered. Landsteiner & Wiener (1940) found that rabbits challenged by rhesus monkey red cells produced antibodies that cross-reacted with some but not all human red cells. They called the newly identified human antigen 'Rh' or rhesus. Soon after, Levine *et al* (1941) demonstrated that most cases of erythroblastosis fetalis resulted from an antibody produced by a Rh-negative mother that reacted with the red cells of her Rh-positive fetus. Diamond contributed to these important studies by Levine, making available blood from mothers whose infants had erythroblastosis fetalis (Stockman & de Alarcon, 2001). Later, when it turned out that the human Rh antigen was slightly different from that detected by rabbit antirhesus antibodies, an alternative nomenclature was proposed. Rh or rhesus factor has remained popular, however, in part perhaps because, as Diamond (1974) observed, the name rhesus factor should be retained to 'remind us that we are not too far removed from (our) animal ancestry'.

Stimulated by identification of the Rh blood factor, in 1942, Diamond established the Blood Grouping Laboratory at a site adjacent to Boston Children's Hospital in order to define antibodies responsible for haemolytic disease of the newborn and for transfusion reactions as well as to identify new red cell antigens. Within 3 years, scientists at the Blood Grouping Laboratory had devised more accurate ways to identify and titrate Rh antibodies in the blood of mothers and infants with haemolytic disease of the newborn. Diamond & Abelson (1945) used thick blood on a warmed slide, whereas Diamond & Denton (1945) suspended target red cells in bovine serum albumin instead of saline. Use of these improved techniques as well as the Coombs antiglobulin test (Coombs *et al*, 1945), which had just been developed in the UK, made it possible to define better the presence of Rh isoimmunization in a mother and, in some cases, to predict the severity of its effect upon the fetus and newborn.

Once the pathophysiology of haemolytic disease of the newborn due to Rh incompatibility was worked out, the concept of treatment by removal of damaged red cells and their replacement by normal Rh-negative cells arose. This required the development of a safe method to carry out exchange transfusion in small infants. Although exchange transfusion had been performed in newborns as early as 1925, difficulties with vascular access greatly limited its use until, in 1946, Diamond and his colleague, Fred Allen, showed that the umbilical vein could be cannulated with flexible plastic tubing to provide an easily accessible, reusable portal of entry to the circulation (Diamond *et al*, 1951). Their technique was rapidly adopted, and exchange transfusion quickly became the standard of care worldwide for the treatment of severe Rh disease. Diamond (1983) estimated that, in its heyday, the use of exchange transfusion saved at least 8000 newborn lives annually in the United States alone. In addition, reduction of hyperbilirubinaemia by exchange transfusion proved an effective way of eliminating kernicterus and its devastating neurological sequelae (Allen *et al*, 1950; Allen & Diamond, 1957). For these achievements, Diamond received an award for scientific research in mental retardation from the Joseph P. Kennedy, Jr International Foundation, the Mead Johnson Award from the American Academy of Pediatrics and the Philip Levine Award from the American Society of Clinical Pathologists.

Atlas of the Blood in Children

By 1944, Diamond had nearly two decades of experience in the evaluation and management of children with blood diseases. In *Atlas of the Blood in Children* (Blackfan *et al*, 1944), he described many of the diseases he had encountered, using case reports from his own practice as well as abundant citations from the literature of the time. The book is notable in several ways. First and most striking is the use of lovely watercolour paintings, prepared by his co-author C. M. Leister, to illustrate the morphology of the blood as seen under the microscope (Fig 5). Second is the absence of equivalent illustrations of bone marrow morphology in the diseases under discussion. This omission was the result of the practice at Boston Children's Hospital of requiring

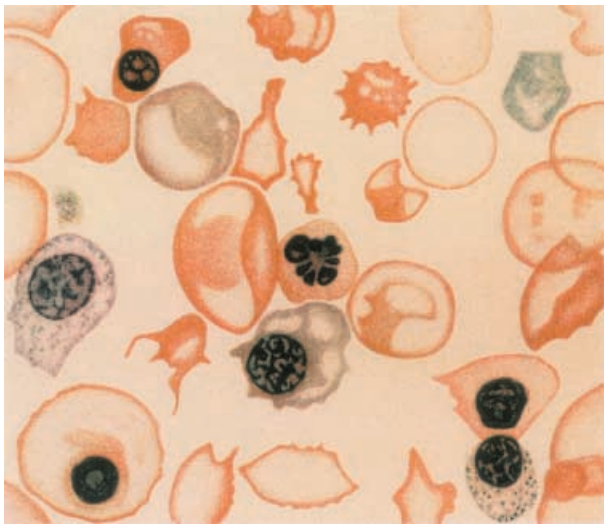

Fig. 5. Plate 27. Mediterranean anaemia severe form, after splenectomy. From Blackfan *et al.* (1944) with permission from the publisher.

surgical biopsy rather than the simpler procedure of marrow aspiration for examination of the marrow, which greatly limited the use of this procedure (Diamond, 1978; Zuelzer, 1998). Third is the selective nature of the diseases included, because of the authors' desire to limit their discussion to 'conditions with which we have had close personal experience'. Thus, the section on haemolytic anaemias takes up the topics of Mediterranean anaemia, sickle cell anaemia, acute (autoimmune) haemolytic anaemia, congenital haemolytic anaemia (hereditary spherocytosis) and haemolytic anaemia of the newborn, but leaves out malaria, a condition rarely encountered in Boston. Last is the absence of so much of the technology that we take for granted today. For example, although anaemias are classified by red cell size and haemoglobin content, these variables are estimated by microscopy. The accurate automated cell counting techniques required to derive the red cell indices easily would not arrive for more than a decade. Overall, the atlas, with its emphasis on careful clinical description and morphological examination of the blood, reflected the state of advancement of the field of paediatric haematology oncology as World War II neared its conclusion.

New clinical syndromes

Three syndromes, first described by Louis Diamond and colleagues, carry his name, reflecting his acute powers of clinical observation and his realization, in his own words, that 'what is atypical of a typical disease entity is more likely typical of a different condition' (Diamond, 1973).

Diamond–Blackfan syndrome. Diamond & Blackfan (1938) described four children with congenital hypoplastic anaemia that began in infancy and required red cell transfusions at regular intervals. Similar cases had been recognized earlier by Josephs (1936), but the condition became known as Diamond–Blackfan anaemia (DBA). The aetiology of DBA was obscure but thought to be either a deficiency of marrow tissue or 'an inborn error in the metabolism of some important blood building substance' (Diamond & Blackfan, 1938). Later articles by Diamond *et al* (1961), Allen & Diamond (1961) and Diamond *et al* (1976) provided long-term follow-up information about the presenting clinical and laboratory features, clinical course and response to corticosteroid therapy of additional patients. However, despite vigorous and persistent efforts by Diamond to stimulate research on the underlying basis for DBA, it remained undefined. Diamond (1978b) explained the frustrating lack of progress: 'We are not a group of blind men each trying to describe an elephant but several semiblind observers trying to characterize a herd of elephants from a distance. Since I do not have a telescope nor binoculars, I cannot see closely enough to describe the elephants, and there may be not only elephants but a mixture of elephants and rhinoceroses, all grey and indistinct from a distance, or there may be large and small elephants. I do not know, but I hope that other more acute observers with their new telescopes and microscopes will eventually be able to tell what these elephants really look like'. The 'new telescope' turned out to be advances in molecular biology, which, by the time of Diamond's death in 1999, revealed that approximately 25% of DBA cases result from mutations in RPS 19, a ribosomal protein, located on chromosome 19. Another DBA locus, as yet undefined, is present on chromosome 8, while nearly 20% of DBA families are not linked to either chromosome 8 or 19 (Vlachos *et al*, 2001). Thus, it appears that, peering through the telescope today, Diamond would perceive elephants, rhinos and other creatures as well, confirming his impression (Diamond *et al*, 1961) that 'it is likely that not all of the anaemias with this clinical picture are of the same aetiology'.

Gardner–Diamond Syndrome. Frank Gardner and Louis Diamond provided a detailed clinical description of recurrent purpura occurring in four women and showed, by intradermal injection of red cells or red cell stroma into those affected, that the cause was autoerythrocyte sensitization (Gardner & Diamond, 1955). The disorder is also known as psychogenic purpura and, although approximately 200 additional cases have been described, not much more has been learned about it since the pioneering work of Gardner and Diamond (Rees & Rodgers, 1999).

Shwachman–Diamond Syndrome. A new syndrome of exocrine pancreatic insufficiency, failure to thrive and bone marrow failure was recognized in six children studied at the Boston Children's Hospital by the gastroenterology (Shwachman) and haematology (Diamond) services and reported by Shwachman *et al* (1964). The aetiology was obscure, but it was thought to be inherited. It was clearly distinct from cystic fibrosis. Other features of the syndrome, described later and summarized by Dror & Freedman (2002), include metaphyseal dysostosis and evolution of the haematological abnormalities to myelodysplasia/acute myeloid leukaemia. The responsible gene has recently been mapped to chromosome 7, and its identity should soon be defined (Dror & Freedman, 2002).

Other accomplishments. Space does not allow a full recital of all Diamond's scientific accomplishments, but a few other highlights should be mentioned. He was co-author on the landmark paper in 1948 that reported the first successful use of a chemotherapeutic agent in the treatment of leukaemia (Farber *et al*, 1948), was the first paediatrician to use a purified human plasma fraction to treat haemophilia (Janeway, 1973) and, with his co-workers, wrote an extensive description of the clinical features of β-thalassaemia major (Baty *et al*, 1932) that added important details to the earlier report by Cooley & Lee (1925). A report on the indications for splenectomy in childhood (Diamond, 1938) was followed 29 years later by a warning about the risks of overwhelming infection following splenectomy (Eraklis *et al*, 1967). Overall, his bibliography lists over 150 articles.

CONCLUSION

In presenting Louis Diamond with the John Howland Award in 1973, the highest recognition conferred by the American Pediatric Society, Charles Janeway acknowledged Diamond as 'a great paediatrician, an extraordinarily effective teacher, a remarkably productive clinical investigator, and

for part of his career, an important public servant'. To this one can only add that he was a wonderful role model of a compassionate academic physician who stimulated scores of his successors to attempt to emulate his devotion to the care of children and to the pursuit of new knowledge about the diseases that afflict them.

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