

## Historical Review

### INHERITED BONE MARROW FAILURE: THE MEN BEHIND THE EMPTY SPACE

The inherited bone marrow failure syndromes account for approximately one third of all cases of childhood aplastic anaemia. Although these syndromes almost always present in childhood with symptoms related to the predominant cytopenia, some patients may present as late as the fifth decade of life. Physical abnormalities may or may not be obvious at presentation, and in the majority of cases a single cytopenia is usually the commonest haematological feature which in time may evolve into hypoplastic anaemia or bone marrow aplasia. The syndromes that continue as single cytopenias include Kostmann's syndrome (neutropenia), Diamond-Blackfan anaemia (anaemia), and thrombocytopenia absent radii (thrombocytopenia), whilst patients with Fanconi anaemia, dyskeratosis congenita, Shwachmann-Diamond syndrome and amegakaryocytic thrombocytopenia usually go on to develop bone marrow aplasia. Common to all of these syndromes is a predisposition to malignant change, particularly leukaemia; however, epithelial tumours are not uncommon in Fanconi anaemia and dyskeratosis congenita, especially in the older patient. In the recent past the inheritance patterns of these syndromes have begun to be delineated and we now know that all types of inheritance have been documented in these syndromes. Indeed, X-linked and autosomal inheritance may be seen in dyskeratosis congenita with two-thirds of patients having X-linked recessive inheritance, whilst 10% of patients with Diamond-Blackfan anaemia demonstrate autosomal dominance inheritance.

Although Paul Ehrlich is associated with the first description of acquired bone marrow failure (aplastic anaemia) in a young woman who died after developing severe anaemia, bleeding into her skin and retinae and high fever (Ehrlich, 1888), syndromes of inherited bone marrow failure only began to be characterized in the late 1920s. Not surprisingly the majority of the people involved in defining these syndromes since this time have predominantly been paediatricians with an interest in childhood blood diseases (Fig 1). By the 1960s a crude classification was proposed by O'Gorman Hughes, entitled the constitutional aplastic anaemias (O'Gorman Hughes, 1966). These were simplistically divided up into three groups: type I was Fanconi anaemia which is aplastic anaemia with physical abnormalities, type II, Estren-Dameshek, familial aplastic anaemia without physical abnormalities, and type III amegakaryocytic thrombocytopenia. The first two were subsequently shown to be cases of Fanconi anaemia. Although this was the first real attempt to group and differentiate these so-called constitutional aplastic anaemias, in fact this classification added very little in terms of understanding disease aetiology and treatment. Today the inherited bone marrow failure

syndromes are named, in the main, after the people who described the syndrome (Table I). It should be remembered that the original descriptions of these syndromes were made decades before the modern era of molecular and cellular haematology. Below are brief descriptions of the lives of some of the main persons whose names we tend to associate with the inherited bone marrow failure syndromes.

#### *Kenneth D. Blackfan*

Kenneth D. Blackfan became Professor of Paediatrics at Harvard University and director of the Boston Children's Hospital during the second quarter of the present century. He was born into a medical family in Cambridge, New York, in 1883 and qualified in medicine from Albany College in 1905. Following graduation he joined his father in general practice but after 4 years he realized that he needed more of an academic challenge and so returned to Albany. He subsequently moved to Philadelphia, St Louis and the Johns Hopkins Hospital, Baltimore, where, under the tutelage of John Howland, one of the great figures of paediatrics in the United States, he undertook advanced training in paediatrics. In 1926 Blackfan moved on to the University of Cincinnati, taking the chair of paediatrics, and in 1931 was called to Harvard University where he became Director of Clinical Services at the Children's Hospital and Professor of Paediatrics. The early years at Harvard were spent in developing and establishing a programme of clinical paediatric teaching for medical students and nurses, emphasizing and stimulating research into the cause, prevention and cure of disease processes in infancy and childhood. He occupied these posts until his death in 1941. Despite considerable contact with the medical students, Blackfan maintained a reserved, formal attitude, insisting on quiet and discipline during his ward rounds. He was slightly built and modest but firm, forceful and determined, and he was known to his students as 'the little giant'. He was critical of his residents, demanding high standards and emphasizing that his patients' interests were always pre-eminent.

In 1920 at the age of 37 years he married, became devoted to his family, and was a great companion to his son, especially during summer holidays, which were spent on a lake near his native town of Cambridge, New York. Throughout most of his adult years he was greatly handicapped by trigeminal neuralgia, and although surgery relieved his pain he had residual unilateral anaesthesia of the face and tongue which was complicated by recurrent eye and sinus infections. He later developed a malignant brain tumour, and although he managed to continue his clinical activities he died on 29 November 1941 at the age of 58.

Blackfan's main research interests were in nutrition and childhood blood diseases, and his publications were largely in these fields. During the last years of his life, in conjunction with his colleague, Louis Diamond, he wrote *Atlas of the*

Correspondence: Dr Owen P. Smith, Consultant Paediatric Haematologist, St James's Hospital, James's Street, Dublin 8, Ireland. e-mail: [osmith@stjames.ie](mailto:osmith@stjames.ie).

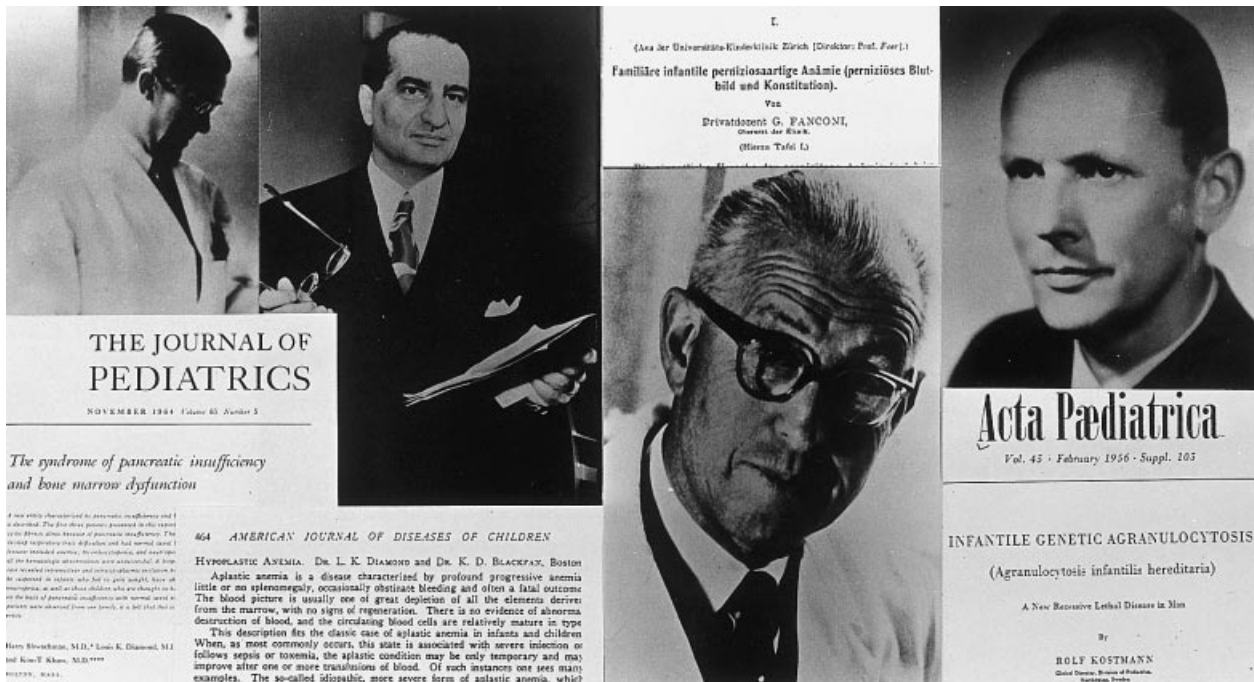


Fig 1. From left to right: Kenneth Blackfan, Louis Diamond, Guido Fanconi and Rolf Kostmann. Also shown are the frontispieces from each of the original descriptions of the syndromes.

*Blood in Childhood* (Blackfan & Diamond, 1944), an outstanding achievement in its day. This work was published posthumously. Apart from clinical paediatric teaching, his other great contribution to the field of paediatrics was establishing paediatrics as a medical speciality in its own right. In 1934 he was offered deanship of Harvard Medical School but declined in order to remain active in clinical paediatrics.

Towards the end of his career, Blackfan turned his attention to hypoplastic anaemia of childhood. In 1938, in conjunction with Louis Diamond who was then a junior member of his staff, Blackfan presented case details of four children with this form of anaemia at a paediatric society meeting. These findings were subsequently published in their joint names (Diamond & Blackfan, 1938). Blackfan had great difficulty in writing medical articles and it is probable that Diamond wrote the actual text, while Blackfan contributed to concepts and investigations. The conjoint eponym

soon came into use, and although Diamond was initially accorded priority, alphabetical order is now generally accepted. The names of Josephs and Kaznelson were sometimes added, as these authors had described earlier cases, but this convention has now been abandoned (Josephs, 1936; Kaznelson, 1922). Apart from the eponymous title, the condition has numerous descriptive names including hereditary red cell aplasia, erythrogenesis imperfecta, pure red cell aplasia, and congenital erythroid hypoplasia.

Perhaps the biggest single contribution Kenneth Blackfan made to haematology was providing guidance and encouragement to two of his protégés: Louis Diamond who would go on to establish paediatric haematology as a separate discipline (see below), and Sidney Farber, a paediatric pathologist, who carried out both the preclinical and clinical evaluation of aminopterin, a folate antagonist in childhood acute lymphoblastic leukaemia, showing for the first time

Table I. Inherited bone marrow failure syndromes.

Syndrome	Inheritance	Malignancy	Reference
Fanconi's anaemia	AR	Leukaemia and cancer	Fanconi (1927)
Diamond-Blackfan anaemia	AR, AD, sporadic	Leukaemia	Diamond & Blackfan (1938)
Shwachmann-Diamond syndrome	AR	Leukaemia	Shwachmann <i>et al</i> (1964)
Kostmann's syndrome	AR	Leukaemia	Kostmann (1956)
Dyskeratosis congenita	XLR, AR, AD	Cancer	Zinsser (1910); Engman (1935)
Thrombocytopenia absent radii	AR	Leukaemia	Gross <i>et al</i> (1956)
Amegakaryocytic thrombocytopenia	AR, XLR	Leukaemia	Bernheim <i>et al</i> (1963)

AR, autosomal recessive; AD, autosomal dominant; XLR, X-linked recessive.

that induction of clinical and haematological remission in this disease was achievable (Farber *et al*, 1948). These findings promoted Farber as the 'father' of the modern era of chemotherapy for neoplastic disease, having already been recognized for a decade as the 'father' of modern paediatric pathology.

#### *Louis Diamond*

Louis Diamond's contribution to the field of paediatrics and haematology is enormous, not only in terms of publication but also the fact that he became mentor to a whole new generation of paediatric haematologists, and therefore he is considered by many the 'father' of paediatric haematology.

Louis K. Diamond was born in New York City in 1902, studied medicine at Harvard, and trained in paediatrics at the Boston Children's Hospital, becoming a faculty member in 1933. In 1926, as a third-year medical undergraduate, he was attracted to haematology by the rapid response that he observed following the administration of iron supplementation in children with iron deficiency anaemia. During that summer he met Nathan Rosenthal, one of the first haematologists to develop haematology at postgraduate level at Mount Sinai Hospital, New York. This exposed him to a variety of haematological disorders at the hospital and also in Rosenthal's busy private practice. At this time haematology was only beginning to develop as a separate speciality, with few haematologists in practice and no paediatric haematologists. During an elective month on the wards at the Boston Children's Hospital, Diamond had an opportunity to help care for a 3-year-old child who was transferred from a hospital in Connecticut for what was thought to be an 'acute form' of Hodgkin's disease. As a junior house officer he examined the blood film and found a moderately elevated white cell count with approximately 35% large abnormal-looking lymphocytes. A lymph node section which arrived with the child appeared atypical to the professor of pathology, and there were other features that today would readily have lead to the correct diagnosis, but at the time the features were puzzling. On discussing the case with Kenneth Blackfan, he recalled that several years previously while at Johns Hopkins his colleagues Sprunt and Evans described similar cases with favourable outcomes. Diamond had the gratification of seeing his patient recover and the opportunity to present at a grand meeting all the then known information about glandular fever/infectious mononucleosis.

Following graduation in 1927, Diamond spent a year as a fellow in pathology because house officers at the Children's Hospital were not accepted until after at least one post-graduate year. The fellowship proved extremely useful as he had the opportunity to work part-time at the Thorndike Memorial Laboratory, Boston City Hospital (the first clinical research facility in a municipal hospital in the U.S.A.) with at George Minot, Nobel Prize winner in physiology and medicine for his work on pernicious anaemia. During this same period he also spent 4 months with Florence Savin at the Rockefeller Institute in New York, where he was exposed to exciting experiments relating to the cellular phases of the immune response in disease. In addition, under Blackfan's supervision and at his suggestion, Diamond set up a small

haematology research laboratory at Boston Children's Hospital. So, by the time he started his paediatric internship in 1928 all the haematological problems encountered in the outpatient department and on the wards of the Children's Hospital were being referred to him. Although he was only beginning to learn about haematology himself, he knew more than anyone else there. Moreover, he now had contacts in Dr Minot and his colleagues at the Thorndike Memorial Laboratory from whom he could seek help.

Diamond's first research project was a collaborative effort with Dr Slavin on reaction of monocytes in active tuberculosis. He also studied a case of what later came to be called Cooley's anaemia (thalassaemia) which was at first labelled von Jaksch's anaemia; many more cases followed. In addition, by 1932 he had collected another group of 20 infants with anaemia present at birth or shortly thereafter. He reported three of these cases under the title of erythroblastosis foetalis. Seven years later Philip Levine showed that this condition was the result of blood group incompatibility between mother and child (Levine *et al*, 1941).

By 1942 the demand for rhesus blood typing and for the detection of rhesus antibodies with particular reference to transfusion reactions and problems in pregnancy resulting from erythroblastosis foetalis was such that Diamond established the blood-grouping laboratory at the Children's Hospital in Boston. This enabled him and his associates to uncover several variants of rhesus, and with E. H. Allen to recognize the Kidd antigen system. Important contributions to blood-grouping techniques were also made, for example a rapid slide test and a method for the detection of rhesus and other antibodies, through the use of albumin instead of saline as the suspension medium, were introduced. The blood-grouping laboratory came to serve the whole state and even the entire country as a consultative centre for blood-grouping problems, and ultimately expanded its research activities in immuno-haematology.

One of Louis Diamond's most practical contributions was the introduction of his relatively simple method for exchange transfusion in the treatment of haemolytic disease of the newborn, a procedure first carried out in Canada by A. P. Harte in 1925. During World War II he worked with Professor E. J. Cohns' team in separating and testing fractions of blood plasma such as serum, albumin, gammaglobulin and fibrinogen. An important by-product of the last was an anti-haemophilic fraction. Blood-grouping antibodies also were concentrated and extracted from the blood. When the war ended he added the technical directorship of the American National Red Cross programme to his other responsibilities.

Diamond's interest in other aspects of haematology was not diminished by all these responsibilities. In 1938 in collaboration with Kenneth Blackfan they published their seminal paper 'Hypoplastic anemia' (now known as the Diamond-Blackfan syndrome) in the *American Journal of Diseases of Children/Society Transactions* (Diamond & Blackfan, 1938). They described four cases of congenital hypoplastic anaemia, calling it an 'intermediate type of anemia – hypoplastic rather than completely aplastic. This condition has been characterized by slowly progressive anemia beginning early in infancy, without any hemorrhagic tendency,

with only moderate leukopenia and with the production of a small and inadequate number of reticulocytes from bone marrow which shows moderate hypoplasia. . . . . By means of blood transfusions given as often as necessary, the interval between them being 6–12 weeks, the patients have been kept in relatively good health, and, contrary to the usual experience with severe anemia in this age group, they have grown and developed normally. . . . it is indeed surprising that these highly anemic children are not more susceptible to infection, as are patients with other forms of severe anemia. In fact, these four patients have had much less infection than would ordinarily be expected in normal healthy children of the same age group.' At the time of the original presentation Diamond was probably aware that the condition was a unique entity; many years later at a birth-defect conference Diamond stated 'I have found from experience that atypical cases usually turn out to be typical cases of something else. The job is to identify the something else'.

With Sydney Farber he was among the first to use antifolates in the treatment of leukaemia and with Park Gerald in 1958 he showed that HbA<sub>2</sub> was increased in one of the parents of a child with Cooley's anaemia. He then went on to discover haemoglobin Lepore. Simultaneously with all this he trained about 75 haematologists; these included many outstanding haematologists in the U.S.A. and some in other countries. Diamond spent more than 40 years in Boston, many of them as chief of haematology at the Children's Hospital. On reaching emeritus status in 1968, Diamond moved to San Francisco as Professor of Pediatrics at the University of California and Hematologist at Moffitt Hospital. His contribution to the field of transfusion and the management of blood disorders were acknowledged with several honours and awards.

#### *Harry Shwachman*

Harry Shwachman studied in the Massachusetts Institution of Technology and subsequently obtained a medical qualification in 1936 at the Johns Hopkins Medical School, Baltimore. He trained in paediatrics at the Children's Hospital, Boston, and became associate professor at Harvard Medical School in 1947. In 1962 Shwachman was appointed clinical Professor of Pediatrics and chief of the Laboratory of Clinical Pathology at the Boston Children's Hospital. He became Professor of Pediatrics at Harvard University and was granted emeritus status when he retired in 1976. Shwachman's career had been centred around the investigation and management of cystic fibrosis, and for many years he was head of the world's largest clinic devoted to this disorder. Shwachmann was the founder of the U.S. National Cystic Fibrosis Research Foundation and served as chairman of its Medical Scientific Advisory Council. In 1964 Shwachman, together with Louis Diamond, Frank Oski and Kon-T. Khaw, published a paper in the *Journal of Pediatrics* entitled 'The syndrome of pancreatic insufficiency and bone marrow dysfunction', now commonly known as the Shwachman-Diamond syndrome (Shwachmann *et al.*, 1964). They described five children with neutropenia and pancreatic insufficiency which was not part of a generalized cystic fibrosis as none of the children had chronic respiratory

disease and the concentrations of sweat electrolytes were normal in all cases. Harry Shwachmann will also be remembered for the numerous contributions he made to the field of paediatric gastroenterology.

#### *Guido Fanconi*

Guido Fanconi is perhaps the best known of the group, not simply because of his association with marrow failure but because of his huge contribution to paediatrics in the middle of this century at a time when Europe was in great turmoil following World War II. He was born 1 January 1892 at Poschiavo, a small village in the canton of Grisons in the Italian-speaking region of Switzerland. After studying at Lucerne, Munich, Zurich and Berne he qualified in medicine in 1918 and for the following 10 years he gained post-graduate experience throughout Europe, specializing in paediatrics. By 1929, at the age of 37, he succeeded Professor Fear as Professor of Paediatrics at the University of Zurich and also director of the Children's Hospital where he had worked for 6 years. For the following 32 years he remained a Professor of Paediatrics, but non-paediatricians are aware of the many disease states and syndromes associated with his name. He immersed himself in all aspects of paediatric research and is considered by many to have been the 'father' of paediatric clinical research as we know it today, namely bringing together the scientific methodology of biochemistry and physiology to the investigation of clinical disease, and for this reason alone he is considered to be the founder of modern paediatrics.

His major contribution to haematology came in 1927 when he described a family in which three male children between the ages of 5 and 7 years had pancytopenia and birth defects (Fanconi, 1927). The observations he made in this family and in future families led him to assign chief criteria for making the diagnosis of Fanconi which included pancytopenia, hyperpigmentation, skeletal malformations, small stature, urogenital abnormalities and familial occurrence; all of these phenotypic correlations we still use today. Four years later Nagelly, according to Fanconi, suggested that the term 'Fanconi anaemia' be used for patients where there was a familial aplastic anaemia and congenital physical abnormalities. Interestingly, Fanconi called the anaemia 'perniziosiforme' because it was macrocytic. Fanconi anaemia is probably the biggest misnomer in haematology, given the fact that the vast majority of cases initially present with evidence of thrombocytopenia. Fanconi was awarded honorary doctoral degrees by nine universities of different countries. He died aged 88 following a protracted illness.

#### *Rolf Kostmann*

Rolf Kostmann was born in Abo, Finland, on 18 September 1909. He was educated in medicine at the Karolinska Institutet, Stockholm, where he received his M.D. in 1937. Following graduation he chose paediatrics as a career, studying mostly in Stockholm. By 1942 he had become Chief of Paediatrics and indeed was the sole paediatrician in Boden's Hospital. It was during his time there that he became interested in childhood neutropenia. He stayed

at Boden's Hospital for approximately 10 years and in 1952 he moved to Norrköping's Hospital where he remained until his retirement. In 1956 Kostmann published his main contribution to paediatric haematology on a syndrome that now bears his name which he originally called infantile genetic agranulocytosis (Kostmann, 1956). The syndrome is also known as severe chronic neutropenia or severe congenital neutropenia. In his original description Kostmann described 14 cases and a subsequent 10 cases where members of a large intermarried kinship from Overkalix, a village in Northern Sweden, bore children with extreme neutropenia, severe pyogenic infections and early deaths. Cases have also been reported in all ethnic groups including Blacks, native Americans and Asians; at least 10 were in families with paternal consanguinity and more than 20 affected siblings. Rolf Kostmann died on 8 June 1982.

#### CONCLUSION

The central problem with any review of an aspect of the history of medicine is perhaps the question of balance, as each author will view and interpret the past differently, but also will be guided by a different background and different values in assigning importance to past events and ultimately will emphasize some aspects more and others less. For our part, we have chosen five individuals whom we believe made a major contribution to our understanding of the clinical correlates of the inherited bone marrow failure syndromes. These five individuals are not only household names in the world of paediatrics, but also we believe that they have also contributed significantly to establishing paediatric haematology as a subspeciality. We had wanted to mention Zinsser and Engman who were the first to describe dyskeratosis congenita, albeit 25 years apart (Zinsser, 1910; Engman, 1935), and indeed others who in the first part of this century made a contribution to defining this group of rare disorders, but we could not find any significant biographical detail in any of the reference sources searched.

Finally, this article is directed primarily to those young haematologists, both paediatric and adult trained, who may feel that each current line of clinical and basic research in inherited bone marrow failure has arisen *de novo* and without antecedents.

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*The National Centre for  
Inherited Coagulation Disorders,  
Dublin, Ireland*

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Ireland*

JOHN COX

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