

Historical Review

ORIGINS OF THE DISCIPLINE 'NEONATAL HAEMATOLOGY', 1925–75

In every modern neonatal intensive care unit (NICU), haematological problems are encountered daily. Many of these problems involve varieties of anaemia, neutropenia or thrombocytopenia that are unique to NICU patients. A characteristic aspect of these unique problems is that, if the neonate survives, the haematological problem will remit and will not recur later in life, nor will it evolve into a chronic illness (although the problem might occur in a future newborn sibling). This characteristic comes about because the common haematological problems of NICU patients are not genetic defects but are environmental stresses (such as infection, alloimmunization or a variety of maternal illnesses) that are imposed on a developmentally immature haematopoietic system.

In the USA, and in some parts of Europe, the unique haematological problems that occur among NICU patients are diagnosed and treated by neonatologists, not by paediatric haematologists. Although these haematological conditions were generally first described by haematologists, the conditions occur, obviously, in neonates. Thus, the neonatologist, who is familiar with intensive care management of neonates, has also become familiar with the diagnosis and management of the neonate's common haematological disorders. A growing number of neonatologists have sought specific additional training in haematology, with the goals of discovering the mechanisms underlying the unique haematological problems of NICU patients and improving the management and outcome of the patients who have these conditions. These physicians have remained as neonatologists and they do not practice paediatric haematology, although their research contributions certainly come under the purview of haematology, or more precisely under the discipline of 'neonatal haematology'. In many places in Europe, it is the haematologists rather than the neonatologists who have an academic and clinical interest in neonatal haematology.

The roots of the discipline of neonatal haematology can be traced to the early application of haematological methods to animal and human embryos and fetuses, such as found in the reports of Maximow (1924) and Wintrobe & Schumacker (1936). The clinical underpinnings of this discipline include reports of anaemia (Fikelstein, 1911) and jaundice (Blomfeld, 1901; Ylppö, 1913) among neonates.

Most of the clinical observations upon which neonatal haematology was founded were published during the 50-year period 1925–75. That is the period that will be examined in this review. Owing to page limitations, this

report cannot review all reports from that 50-year period that are relevant to neonatal haematology and, therefore, an attempt was made to review representative key publications that laid the framework for understanding pathogenesis and treatment. The review is not intended as a state-of-the-art review of neonatal haematology, but rather as a historical review, covering the period 1925–75, and centring on a few pivotal developments. The review is organized into six topics: (1) The beginnings of academic neonatology, (2) New textbooks and new journals, (3) Normal haematological values of preterm and term infants, (4) The neutropenia of neonatal sepsis, (5) The anaemia of prematurity, and (6) Other significant advances in neonatal haematology during this 50-year period.

THE BEGINNINGS OF ACADEMIC NEONATOLOGY

Before the 1930s, very few studies and very few published clinical case reports originated from premature nurseries. Such nurseries had dubious beginnings, which were criticized by some physicians as more resembling circus exhibitions than medical care wards (Bonar, 1932). These units generally had mortality rates greatly exceeding 50% on the day of admission, with the majority of the first-day survivors having late deaths or serious long-term morbidity. A prevalent attitude of paediatricians towards premature nurseries was reflected in a 1928 review of the experiences of nurseries in Philadelphia, in which Capper stated, 'the immature infant will become a backward school child'. He stated further that premature nurseries contained the future inmates of homes for imbeciles and idiots (Capper, 1928). This sentiment was echoed 4 years later in a review of premature nurseries by Bonar from Salt Lake City, Utah (Bonar, 1932).

It was not until publication of the review of premature nursery care at the Children's Hospital of Michigan, in 1932, that it was clear that some units had instituted systematic attempts to monitor and improve outcomes. A special care nursery had been established at the Children's Hospital in 1926 and, in 1932, Drs Marsh Poole and Thomas Cooley reported their experience in that unit (Poole & Cooley, 1932). The report included incubator design with temperature and humidity control, growth curves of patients on various feeding practices, mortality statistics and attempts to determine causes of death. This publication undoubtedly began to change the minds of some critics of premature nurseries, at least with regard to the lack of scholarly practice aspects of this particular nursery. In some

ways, this publication marked the beginning of the academic aspects of neonatology.

NEW TEXTBOOKS AND NEW JOURNALS

At the time premature nursery care was beginning to merit academic credentials, reports were published of haematological problems that were unique to the neonate. These papers included the seminal publication on erythroblastosis fetalis by Drs Diamond (Fig 1), Blackfan and Baty (Diamond *et al.*, 1932), and the report of sepsis neonatorum at the Yale New Haven Hospital by Ethyl C. Dunham (Fig 2) (Dunham, 1933).

The first major textbook devoted to clinical haematology, as well as the first textbook of neonatology, contained very little information about what are today's common NICU haematological problems. For instance, in the first edition of *Clinical Hematology* by Dr Maxwell M. Wintrobe (Fig 3), of the Johns Hopkins University Hospital (Wintrobe, 1942), several topics related to paediatric haematology were reviewed, but discussions of the haematological problems of *neonates* were limited to three – erythroblastosis fetalis, haemorrhagic disease of the newborn and the 'anaemia of prematurity'. Similarly, *Premature Infants: A Manual for Physicians*, the original neonatology textbook, published in 1948 by Dr Ethyl C. Dunham (Fig 2; Dunham, 1948), had only a few pages devoted to haematological problems – the same three discussed by Dr Wintrobe. Also, the classic neonatology text book, 'The Physiology of the Newborn Infant', published in 1945 by Dr Clement A. Smith, contained almost no discussion of haematological problems (Smith, 1945). Thrombocytopenia, which is now diagnosed among 25–30% of NICU patients, and neutropenia, now diagnosed in 8–10% of NICU patients, were not mentioned



Fig 1. Louis K. Diamond, MD, at Children's Hospital, Boston, Massachusetts, date unknown (obtained with the kind assistance of Charles F. Simmons, MD, Harvard University).



Fig 2. Ethyl C. Dunham, MD, at Yale New Haven Hospital, Connecticut; date unknown (obtained with the kind assistance of Patrick G. Gallagher, MD, Yale University).

in any of these first editions, as neither had yet been recognized as relevant clinical issues.

Similar to the textbooks, the first volumes of two new American medical journals devoted exclusively to paediatrics contained relatively little of what we today would classify as neonatology, and contained almost no mention of neonatal haematological problems (with the notable exception of erythroblastosis fetalis). For instance, the *Journal of*



Fig 3. Maxwell M. Wintrobe, PhD, MD, at Johns Hopkins Hospital, Baltimore, MD 1940 (by the kind permission of Susan Wintrobe Walker, Salt Lake City, Utah).

Paediatrics began publication in January of 1932 and the 11 monthly issues of volume one that followed contained 64 articles of original observation, research or reviews. Seven of the 64 papers dealt with neonatology, but only two involved haematological problems of neonates – both were that of anaemia. One was Dr Diamond's classic description of erythroblastosis fetalis, and the second was a report of three cases in one family of congenital hyporegenerative anaemia that presented in the neonatal nursery and remitted after multiple transfusions from the mother, father and paternal uncle.

A new paediatric journal, simply called '*Paediatrics*' was begun in 1948. Volume one contained 85 articles of original observation, research or reviews, but only five involved neonatology and none dealt with neonatal haematological problems. The first article published in *Paediatrics* dealing with a neonatal haematological problem was in volume two, in which Dr Diamond detailed his technique for performing a replacement transfusion (which later became known as an 'exchange' transfusion) as a treatment for erythroblastosis fetalis (Diamond, 1948). The second paper published by *Paediatrics* containing aspects of neonatal haematology was 1 year later, when Sliverman & Homan (1949) described leucopenia among neonates with sepsis. Most of the 25 infants they described, who were treated at Babies Hospital in New York over an 11-year period, had 'late-onset' sepsis, beginning after 3 days of life. They reported 14 neonates with *Escherichia coli* sepsis and four with streptococcal or staphylococcal sepsis, and observed that leucopenia occurred occasionally among these patients but was uncommon. (Indeed, today neutropenia remains uncommon in 'late-onset' sepsis, but common in congenital or 'early onset' sepsis.)

NORMAL HAEMATOLOGICAL VALUES OF PRETERM AND TERM NEONATES

Diagnosing neutropenia, anaemia or thrombocytopenia in a neonate obviously requires knowledge of the expected normal range for neutrophil concentration, haematocrit and platelet concentration in the appropriate reference population. Early contributions to neonatal haematology included the publications of these reference ranges. The landmark studies included the range of blood leucocyte and neutrophil concentrations in neonates published in 1935 by Dr Katsuji Kato from the Department of Paediatrics at the University of Chicago (Kato, 1935). He tabulated the leucocyte concentrations and differential counts of 1081 children, ranging from birth to 15 years of age. A striking finding of his report (Fig 4) was the very high neutrophil counts during the first hours and days of life. Blood neutrophil concentrations among neonates with infections were published during the early and mid-1970s by Dr Marietta Xanthou (Fig 5) at the Hammersmith Hospital in London (Xanthou, 1970, 1972), and by Drs Barbara Manroe and Charles Rosenfeld (Fig 6) at the University of Texas South-western Medical Center in Dallas, Texas (Manroe *et al.*, 1977).

An important observation was published by Drs Leon

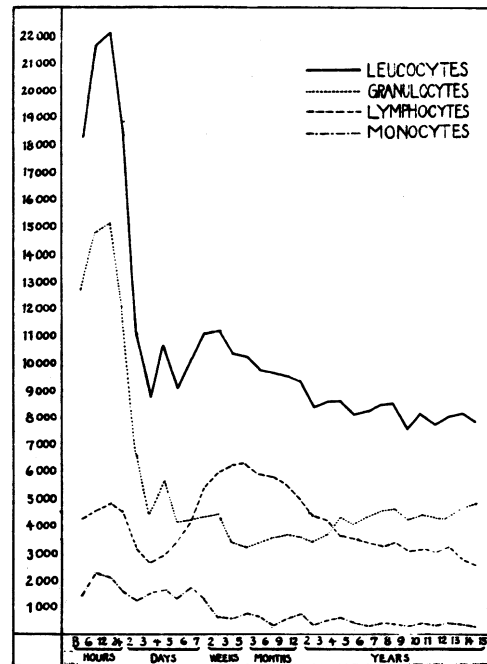


Fig 4. Blood leucocyte concentrations on patients ranging from birth to 15 years of age at the University of Chicago [by permission; *The Journal of Paediatrics* (Kato, 1935)].

Oettinger and Willard B. Mills from Vanderbilt University at the Nashville General Hospital (Oettinger & Mills, 1949). They were struck by the wide range in published haemoglobin concentrations of apparently healthy term



Fig 5. Marietta Xanthou, MD, at Hammersmith Hospital, London 1969 (by the kind permission of Dr Xanthou, Athens, Greece).



Fig 6. Charles R. Rosenfeld, MD, at Parkland Memorial Hospital, Dallas, Texas 1975 (by the kind permission of Dr Rosenfeld, Dallas, TX).

neonates, ranging from 15.5 to 23.4 g/dl, with no apparent explanation for these differences. Much of the disparity was reconciled by their observation that haemoglobin values obtained by capillary stick (they performed lancet punctures of the great toe) produced values significantly higher than those obtained simultaneously using venepuncture. This observation was subsequently confirmed by the work of Dr Peter Johan Moe of the Department of Paediatrics at the University of Bergen, Norway, who was the first to report umbilical cord blood to quantify the blood haemoglobin concentration of neonates (Moe, 1967, 1970).

Normal values for haemoglobin, haematocrit, erythrocyte indices and leucocyte concentrations were refined by DeMarsh *et al* (1942, 1948), and in a series of publications in the early 1950s in *Archives of Diseases of Children* by Gairdner *et al* (1952a, b). These were followed by observations on human fetal haematopoiesis by Thomas and Yoffey in the *British Journal of Haematology* (Thomas & Yoffey, 1962, 1964), and by the work on blood volume during the 1960s (Usher *et al*, 1963, Usher & Lind, 1965; Yao *et al*, 1967, 1968). Normal ranges for blood platelet counts in ill and well preterm and term infants were published in the early 1970s (Sell *et al*, 1973; Corrigan, 1974).

THE NEUTROPENIA OF NEONATAL SEPSIS

The first report of leucopenia in a neonate with sepsis was published in 1933, when Dr Ethyl Dunham (Fig 2) detailed 39 patients with sepsis neonatorum from the Yale-New Haven Hospital (Dunham, 1933). She reported that, when leucopenia was found, no survivors occurred, but differential leucocyte counts were not given, and this association between leucopenia and poor survival was not specifically

discussed. The first publication addressing the problem of neutropenia accompanying fatal early onset bacterial sepsis was that of Tygstrup *et al* (1968). This was a report of a near-term male with congenital *Listeria* sepsis who lived for only 4 h. The platelet count was $80 \times 10^9/l$ and the leucocyte count was $13.7 \times 10^9/l$, but no granulocytes were observed on the differential count, which consisted of 84% lymphocytes, 8% monocytes and 8% leucocyte precursors. A sternal marrow aspirate was taken of the infant shortly before death that revealed myeloblasts, promyelocytes and myelocytes, but no band or segmented neutrophils. Eosinophils and erythrocytes were reported as normal. At autopsy, Gram-positive rods and neutrophils were abundant in the placenta, and bacteria but relatively few neutrophils were noted in the lungs and other organs. The authors speculated that the neutropenia might have been: (1) infantile genetic agranulocytosis [a syndrome reported by Kostmann (1956)], (2) an immunological reaction or drug reaction, or (3) as a result of a toxic influence of the bacteria.

An important advance in understanding the blood neutrophil count during neonatal sepsis occurred with the back-to-back papers in *Archives of Diseases of Childhood* in 1972 by Dr Marietta Xanthou of Hammersmith Hospital, London (Xanthou, 1972), and Drs Gregory and Hey of Babies' Hospital, Newcastle upon Tyne (Gregory & Hey, 1972). Both papers reported that neonates who had life-threatening (or indeed fatal) infections became neutropenic prior to death. Dr Xanthou reported 35 ill preterm and term babies within their first 28 d of life. Twenty-four were ill but not infected, and these had normal blood neutrophil concentrations and morphology. However, among the 11 who were ill with a bacterial infection, neutrophilia was observed in the survivors, but neutropenia, a 'left shift', and toxic granulation were observed in the non-survivors. Consistent with this observation, Gregory and Hey reported three neonates who died with overwhelming bacterial sepsis and noted that all had profound neutropenia. Two years later, these reports were further confirmed in a publication from Henderson General Hospital, Hamilton, Ontario, Canada, by Akenzua *et al* (1974). The authors reported nine neonates with sepsis during the first 5 d of life (seven *E. coli*, one group A streptococcus, one *Staphylococcus epidermidis*). Neutrophilia was common among the survivors and neutropenia, a 'left shift', and specific neutrophil morphological changes were seen among those who subsequently died.

With the awareness brought about by the publications of Xanthou (1972), Gregory and Hey (1972), and Akenzua *et al* (1974), new researchers were drawn into this field. A pivotal publication that launched the search for mechanistic information and successful treatments was that of Dr Barbara Manroe, a fellow in Neonatal Medicine, and her mentor Dr Charles Rosenfeld (Fig 6) from the University of Texas, South-western, Parkland Hospital in Dallas, Texas (Manroe *et al*, 1977). Dr Rosenfeld was primarily interested in finding rapid methods of differentiating hyaline membrane disease from 'early onset' group B streptococcal (GBS) disease. To accomplish this, he evaluated 45 neonates who

had culture-proven GBS infection and found that 39 had abnormal leucocyte counts: 25 neutrophilia and 14 neutropenia, and that 41 had a 'left shift'. This paper was the first to quantify the 'left shift' using a method that has since become popular in neonatology – the ratio of immature neutrophils to total neutrophils on the differential cell count.

From these beginning, hundreds of studies using experimental models and clinical observations and trials were published, detailing the kinetic and molecular mechanisms accounting for this common variety of neutropenia. Marked improvements in the survival of neonates with this condition have come about through combined efforts, including early maternal screening for GBS carriage, early anti-microbial administration to ill neonates, non-specific antibody administration and a variety of measures to improve supportive care of neonates with early onset sepsis.

THE ANAEMIA OF PREMATURITY

In the early 1930s, Dr Helen Mackay worked as a paediatrician in Mother's Hospital, a maternity hospital located in the north-east section of London. Acting on the observation of Lichtenstein (1921) that infants of subnormal birth weight regularly became anaemic in the first months of life, she measured and reported serial heel-stick haemoglobin levels on 150 infants during their first 6 months. Thirty-nine of these infants weighed under five pounds at birth (six were under four pounds), 52 weighed five to six pounds, and 59 weighed six pounds and upwards. She showed that babies of the lightest birth weights had the most rapid fall in haemoglobin and that these fell to lower levels than those of babies of heavier birth weight (MacKay *et al*, 1935). Figure 7 contrasts this fall in babies weighing '3–4 lbs odd at birth' with those weighing '5 lbs odd at birth'.

Dr MacKay asserted (but with no confirming data) that anaemia rendered these preterm infants more susceptible to infection. Acting on the basis that this anaemia was detrimental, she attempted, unsuccessfully, to prevent the anaemia by administering intramuscular or intravenous injections of citrated blood (15 cc) obtained from either the mother or father. Twenty-one neonates received this injection once during their first 3 d of life, while 17 infants did not receive injections and acted as controls. The treatment failed to prevent the anaemia and had no measurable effect on the lowest haemoglobin level reached. Therefore, she next attempted to prevent the anaemia by the oral administration of iron and ammonium citrate ($4\frac{1}{2}$ to $6\frac{3}{4}$ grains daily). This also failed to prevent the anaemia. She found no difference in the minimum haemoglobin level of 20 preterm infants given this medication for 45 d than 20 infants of similar weight who were not treated in this way. Although her attempts to prevent the anaemia of prematurity failed, her work constituted the first clear definition of the 'anaemia of prematurity' and showed that iron administration did not prevent this condition.

In the early 1950s, Douglas Gairdner, John Marks and Janet D. Roscoe, of the Department of Pathology of Cambridge Maternity Hospital, published pioneering studies in blood

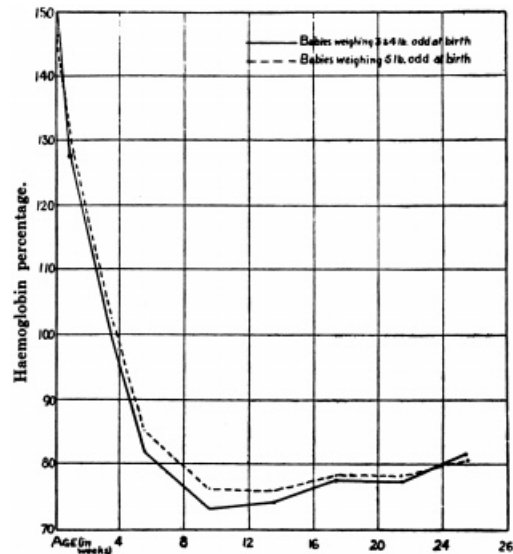


Fig 7. Haemoglobin levels during the first 25 weeks of life among neonates in London [by permission; *Archives Diseases of Children*, (MacKay, 1935)].

formation in infancy (Gairdner *et al*, 1952a, b). Studying 105 blood samples and 102 bone marrow samples, they concluded that 'erythropoiesis ceases when the oxygen saturation just after birth increases from about 65% in the umbilical vein to >95% just after birth'. Publications by Dr Irving Schulman, in the mid- to late 1950s, defined three phases of the anaemia of prematurity and provided a mechanistic explanation for the anaemia (Schulman & Smith, 1954; Schulman, 1959). At the time of this work, Dr Schulman (Fig 8), a paediatric haematologist, worked at Children's Memorial Hospital in Chicago, Illinois (he later served as Chairman of the Department of Paediatrics at Stanford University School of Medicine 1972–90). His work illustrated that the early and intermediate phases of this anaemia occur in the face of relative iron excess and are unaffected by prophylactic iron administration.

In 1963, Dr Sverre Halvorsen of the Department of

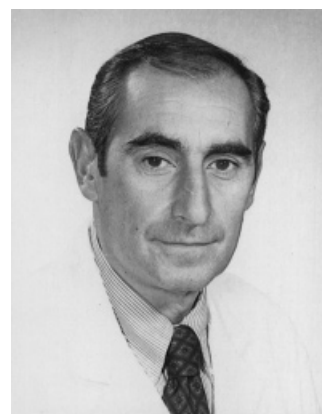


Fig 8. Irving Schulman, MD, at Children's Memorial Hospital, Chicago, Illinois 1970 (by the kind permission of Dr Schulman, Stanford, CA).

Paediatrics at Rikshospitalet in Oslo, Norway (Fig 9), provided an underlying explanation for the observations made by MacKay, Gairdner and Schulman (Halvorsen, 1963). Specifically, Dr Halvorsen quantified plasma erythropoietin concentrations of neonates over the first 8 weeks of life. He reported on three infants with cyanotic heart disease, four infants with erythroblastosis fetalis and 16 healthy neonates. Plasma erythropoietin concentrations were assayed using transfusion-induced polycythaemic mice as recipients of the test plasma, followed by Fe⁵⁹ incorporation into the mice red cells as a measure of the erythropoietin in the test plasma. He observed that, compared with the blood of healthy adults, umbilical cord blood of healthy neonates had a high erythropoietin concentration, but the concentration was considerably higher in the plasma of severely erythroblastotic, anaemic infants. Among the healthy infants, erythropoietin levels fell to unmeasurably low concentrations after delivery, but levels remained elevated in hypoxic and cyanotic infants. Dr Per Haavardsholm Finne, also of the Children's Department, Paediatric Research Institute and Department of Obstetrics and Gynaecology at Rikshospitalet in Oslo, observed high concentrations of erythropoietin in the amniotic fluid and the umbilical cord blood after fetal hypoxia (Finne, 1964, 1967).

In subsequent studies, Dr Halvorsen observed lower plasma erythropoietin concentrations in the cord blood of preterm infants at delivery than in term neonates at delivery (Halvorsen & Finne, 1968). These observations supported the concept of Gairdner *et al* (1952a, b) that the postnatal fall in erythropoiesis (the 'physiologic anaemia' of neonates) is as a result of an increase in oxygen delivery to tissues following birth and is mediated by a fall in circulating erythropoietin concentration. The observations gave rise to the postulate that the 'anaemia of prematurity' was an exaggeration of this physiological anaemia and involved a

limitation of preterm infants to appropriately increase erythropoietin production.

OTHER SIGNIFICANT ADVANCES

Many landmark reports of haematological findings of neonates that were published between 1925 and 1975 were not detailed in this review because they were outside the restricted topics selected. These significant other advances included differentiating adult from fetal haemoglobin in bloody stools by Apt and Downey (1955), diagnosing fetal to maternal haemorrhage (Kleihauer *et al*, 1957), Pearson's measurement of the life span of fetal erythrocytes (Pearson & Vertrees, 1961; Pearson, 1967), Zipursky's description of the morphology of erythrocytes of neonates (Zipursky, 1965), Miller's description of the poor chemotaxis of neutrophils of neonates (Miller, 1971), Boxer's description of congenital neutropenia of immune origin (Boxer & Stossel, 1974), Hathaway's work on the unique coagulation system and bleeding disorders of neonates (Hathaway, 1970, 1975), descriptions of neonatal immune-mediated thrombocytopenia by Irving Schulman in 1960 and by Nathan Schulman in late 1950s and 1960s (Schulman, 1958; Schulman *et al*, 1964), Bracci's studies of glutathione peroxidase and hydrogen peroxide (Bracci *et al*, 1970a, b), and the work of Dr David Nathan's group on *in utero* diagnosis of haemoglobinopathies (Fig 10) (Chang *et al*, 1974). Indeed, Dr Nathan figures very prominently in the history of neonatal haematology (Nathan, 1958; Nathan *et al*, 1975) because he was responsible for training so many of the paediatric haematologists who made basic and clinical discoveries central to this field.



Fig 9. Sverre Halvorsen, MD, at the Paediatric Research Institute, Rikshospitalet, University of Oslo, Norway 1966 (by the kind permission of Dr Halvorsen, Oslo, Norway).



Fig 10. David G. Nathan, MD, at Children's Hospital, Boston, Massachusetts, about 1975 (by the kind permission of Dr Nathan, Boston, MA).

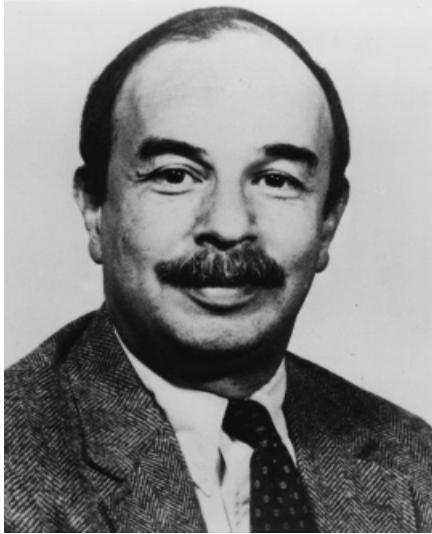


Fig 11. Frank A. Oski, MD, at the Department of Paediatrics, State University of New York, Upstate Medical Center, Syracuse, New York 1977 (kindly obtained by Dr Douglas J. Barrett, Gainesville, Florida).

From one point of view, the field of neonatal haematology was inaugurated in 1966 by the publication of a textbook, *Hematologic Problems in the Newborn*, by Frank A. Oski, MD (Fig 11), Assistant Professor of Paediatrics at the University of Pennsylvania School of Medicine, and J. Lawrence Naiman, MD, Assistant Professor of Paediatrics at Temple University School of Medicine (Oski & Naiman, 1966). This text, written by two paediatric haematologists, had a profound effect on the developing field of neonatology. In fact, that book and its two subsequent editions, published in 1972 and 1983, served as the principal haematological reference for neonatologists for the next 20 years.

During the 1970s, neonatology became an officially recognized subspecialty of paediatrics, with the first American subboard examinations offered in 1975. Neonatology quickly became the most popular subspecialty selection for paediatric residents in the USA. From that time to the present, all neonatologists have surely recognized the accuracy of a statement made by Drs Oski and Naiman in the preface of their textbook; namely, 'During the first few weeks of life, there are more diagnostic problems with haematological aspects than at any time thereafter'. Indeed, the abundance of these unique haematological problems of neonates constitutes a sizeable fraction of neonatology practice. It is these diagnostic problems, and the hope for more complete mechanistic understanding and better treatments, that continue to attract neonatology fellows to careers dedicated to the unique haematological problems of neonates.

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