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Historical Review

THE EMERGING UNDERSTANDING OF SICKLE CELL DISEASE

The first indisputable case of sickle cell disease in the literature was described in a dental student studying in Chicago between 1904 and 1907 (Herrick, 1910). Coming from the north of the island of Grenada in the eastern Caribbean, he was first admitted to the Presbyterian Hospital, Chicago, in late December 1904 and a blood test showed the features characteristic of homozygous sickle cell (SS) disease. It was a happy coincidence that he was under the care of Dr James Herrick (Fig 1) and his intern Dr Ernest Irons because both had an interest in laboratory investigation and Herrick had previously presented a paper on the value of blood examination in reaching a diagnosis (Herrick, 1904–05). The resulting blood test report by Dr Irons described and contained drawings of the abnormal red cells (Fig 2) and the photomicrographs, showing irreversibly sickled cells, leave little doubt that the diagnosis was SS disease. The subsequent history of Dr Walter Clement Noel, that first patient, is described in a fascinating account by Dr Todd Savitt (Savitt & Goldberg, 1989) who found that, on Dr Noel's return to Grenada in 1907, he set-up a dental practice in the capital St. Georges, died from the acute chest syndrome aged 32 years and is buried in the Catholic cemetery at Sauteurs in the north of Grenada (Fig 3).

The second case, Ellen Anthony, aged 25 years, had already been under observation in the wards of the University of Virginia Hospital from 1907 and the strange blood film sent to pathologists at Johns Hopkins University Hospital was considered an unusual case of pernicious anaemia (Savitt, 1997). The diagnosis became clear with the publication of Herrick's paper in November, 1910 (Herrick, 1910) and, within 3 months, this second case was reported in February 1911 (Washburn, 1911) (Fig 4). The third case, a woman aged 21 years, reported from Washington University Medical School in 1915 (Cook & Meyer, 1915), raised suspicions of a genetic basis, as three siblings had died from severe anaemia, and blood from both the patient and her asymptomatic father showed a sickling deformity of the red cells on incubation (Emmel, 1917). The fourth case was a 21-year-old black man in the wards of Johns Hopkins Hospital (Mason, 1922). It was Mason who noted the similar features of the first four case reports, he was the first to use the term 'sickle cell anaemia' and, finding that the cases were all black, he began the popular misconception that the disease was confined to people of African origin.

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Genetics of sickle cell disease

The discovery by Emmel (1917) of the sickle cell phenomenon in the father of the third case not only suggested a genetic basis for sickle cell disease, but led to a period of confusion in the genetics of the disease. Both Huck (1923) and Sydenstricker *et al* (1923) noted 'latent sicklers' among relatives of patients with the disease, and further analysis of the pedigree of Huck's patients led to the conclusion that the sickle cell phenomenon was inherited as a Mendelian autosomal characteristic (Taliaferro & Huck, 1923). People with positive sickle tests were divided into asymptomatic cases, 'latent sicklers', and those with features of the disease, 'active sicklers', and it was Dr Lemuel Diggs of Memphis who first clearly distinguished symptomatic cases called sickle cell anaemia from the latent asymptomatic cases which were termed the sickle cell trait (Diggs *et al*, 1933).

Several years were to elapse before the relationship of the trait and the disease was clarified. A review of 32 apparent cases of the disease with data in both parents showed sickling in both parents in 10 cases, in one parent in 15 cases and in neither parent in seven cases (Neel, 1947). Prospective data collection in 29 cases of the disease showed sickling in all 42 parents tested (Neel, 1949), providing strong support for the theory of homozygous inheritance. A Colonial Medical Officer working in Northern Rhodesia (Beet, 1949) reached similar conclusions at the same time with a study of one large family (the Kapokoso-Chuni pedigree). The implication that sickle cell anaemia should occur in all communities in which the sickle cell trait was common and that its frequency would be determined by the prevalence of the trait did not appear to fit the observations from Africa. Despite a sickle cell trait prevalence of 27% in Angola, Texeira (1944) noted the active form of the disease to be 'extremely rare' and similar observations were made from East Africa (Lehmann & Milne, 1949; Mackey, 1949; Raper, 1949; Lehmann, 1951), West Africa (Edington, 1954) and Northern Rhodesia (Beet, 1947). In Uganda, Lehmann and Raper (1949, 1956) found a positive sickling test in 45% of one community, from which homozygous inheritance would have predicted that nearly 10% of children had SS disease, yet not a single case was found. The discrepancy led to a hypothesis that some factor inherited from non-black ancestors in America might be necessary for expression of the disease (Raper, 1950).

The explanation for this apparent discrepancy gradually emerged. Working with the Jaluo tribe in Kenya, Foy *et al* (1951) found five cases of sickle cell anaemia among very young children and suggested that cases might be dying at an age before those sampled in surveys. A similar hypothesis

Fig 1. Dr. James Herrick (1861–1954) taken in 1925. Photo courtesy of the late Dr. L. W. Diggs.

The Presbyterian Hospital, Chicago, Ill.

EXAMINATION OF BLOOD.

Case Number

Name of Patient Noel

Date 12/31 1904

Room or Ward 7

MACROSCOPICAL AND QUANTITATIVE.

Appearance pale

Coagulability

Erythrocytes per cu. mm. (Thoma Zeiss). 2,880,000

Leucocytes per cu. mm. (Thoma Zeiss). 15,250.

Hemoglobin (Von Fleischl) 50% Dare Corrected

Specific gravity

Color index

Volume index

per cu. mm. 3700, cells & very small reg. & stellate nucleated (nucleated reds?) (red count preparation)

MICROSCOPICAL.

Fresh Specimen.

Erythrocytes—Color

Size irregular

Shape very irregular many elongated forms

Rouleaux formation

Leucocytes—Apparent increase in number average size almost normal

Ratio of granular to non-granular

Fibrin

Blood-platelets

Pigment

Plasmodium malariæ

Miscellaneous

Fig 2. Report of blood test on Walter Clement Noel dated 31 December 1904.

Fig 3. The tombstone of Walter Clement Noel in the Catholic cemetery of Sauters in the north of Grenada. The tombstone of his father John Cornelius Noel is on the right.

was advanced by Jelliffe (1952) and was supported by data from the then Belgian Congo (Lambotte-Legrand Lambotte-Legrand, 1951, Lambotte-Legrand, 1952, Vandepitte, 1952).

Although most cases were consistent with the concept of homozygous inheritance, exceptions continued to occur. Patients with a non-sickling parent of Mediterranean ancestry were later recognized to have sickle cell-β thalassaemia (Powell *et al*, 1950; Silvestroni & Bianco, 1952; Sturgeon *et al*, 1952; Neel *et al*, 1953a), a condition also widespread in African and Indian subjects that presents a variable syndrome depending on the molecular basis of the β thalassaemia mutation and the amount of HbA produced. Phenotypically, there are two major groups in subjects of African origin, sickle cell-β^+ thalassaemia manifesting 20–30% HbA and mutations at −29(A→G) or −88(C→T), and sickle cell-β^0 thalassaemia with no HbA and mutations at IVS2–849(A→G) or IVS2–1(G→A). In Indian subjects, a more severe β thalassaemia mutation IVS1–5(G→C) results in a sickle cell-β^+ thalassaemia condition with 3–5% HbA and a relatively severe clinical course.

Other double heterozygote conditions causing sickle cell disease include sickle cell-haemoglobin *C* (SC) disease (Kaplan *et al*, 1951; Neel *et al*, 1953b), sickle cell-haemoglobin O Arab (Ramot *et al*, 1960), sickle cell-haemoglobin Lepore Boston (Stammatoyannopoulos & Fessas, 1963) and sickle cell-haemoglobin D Punjab (Cooke & Mack, 1934). The latter condition was first described in siblings in 1934, who were reinvestigated for confirmation of HbD (Itano, 1951), the clinical features reported (Sturgeon *et al*, 1955) and who were finally identified as HbD Punjab (Babin *et al*, 1964), representing a remarkable example of longitudinal observation and investigation in the same family over 30 years.

Concept of balanced polymorphism

The maintenance of high frequencies of the sickle cell trait in the presence of almost obligatory losses of homozygotes in Equatorial Africa implied that there was either a very high frequency of HbS arizing by fresh mutations or that the sickle cell trait conveyed a survival advantage in the African environment. There followed a remarkable period in the 1950s when three prominent scientists were each addressing this problem in East Africa, Dr Alan Raper and Dr Hermann Lehmann in Uganda and Dr Anthony Allison in Kenya. It was quickly calculated that mutation rates were

Fig 4. Benjamin Earle Washburn. From the University of North Carolina 1906 Yearbook. Note that his paper was incorrectly attributed to R. E. Washburn. Photo courtesy of Dr. Todd Savitt and reproduced with the permission of the Virginia Medical Quarterly.

far too low to balance the loss of HbS genes from deaths of homozygotes (Allison, 1954a). An increased fertility of heterozygotes was proposed (Foy *et al*, 1954; Allison, 1956a) but never convincingly demonstrated. Raper (1949) was the first to suggest that the sickle cell trait might have a survival advantage against some adverse condition in the tropics and Mackey & Vivarelli (1952) suggested that this factor might be malaria. The close geographical association between the distribution of malaria and the sickle cell gene supported this concept (Allison, 1954b) and led to an exciting period in the history of research in sickle cell disease.

The first observations on malaria and the sickle cell trait were from Northern Rhodesia where Beet (1946, 1947) noted that malarial parasites were less frequent in blood films from subjects with the sickle cell trait. Allison (1954c) drew attention to this association, concluding that persons with the sickle cell trait developed malaria less frequently and less severely than those without the trait. This communication marked the beginning of a considerable controversy.

Two studies failed to document differences in parasite densities between 'sicklers' and 'non-sicklers' (Moore *et al*, 1954; Archibald & Bruce-Chwatt, 1955) and Beutler *et al* (1955) were unable to reproduce the inoculation experiments of Allison (1954c). Raper (1955) speculated that some feature of Allison's observations had accentuated a difference of lesser magnitude and postulated that the sickle cell trait might inhibit the establishment of malaria in non-immune subjects. The conflicting results in these and other studies appear to have occurred because the protective effect of the sickle cell trait was overshadowed by the role of acquired immunity. Examination of young children before the development of acquired immunity confirmed both lower parasite rates and densities in children with the sickle cell trait (Colbourne & Edington, 1956; Edington & Laing, 1957; Gilles *et al*, 1967) and it is now generally accepted that the sickle cell trait confers some protection against falciparum malaria during a critical period of early childhood between the loss of passively acquired immunity and the development of active immunity (Allison, 1957; Rucknagel & Neel, 1961; Motulsky, 1964). The mechanism of such an effect is still debated, although possible factors include selective sickling of parasitized red cells (Miller *et al*, 1956; Luzzatto *et al*, 1970) resulting in their more effective removal by the reticulo-endothelial system, inhibition of parasite growth by the greater potassium loss and low pH of sickled red cells (Friedman *et al*, 1979), and greater endothelial adherence of parasitized red cells (Kaul *et al*, 1994).

Distribution of sickle cell disease

The occurrence of the sickle cell mutation and the survival advantage conferred by malaria together determine the primary distribution of the sickle cell gene. Equatorial Africa is highly malarial and the sickle cell mutation appears to have arisen independently on at least three and probably four separate occasions in the African continent, and the mutations were subsequently named after the areas where they were first described and designated the Senegal, Benin, Bantu and Cameroon haplotypes of the disease (Kulozik *et al*, 1986; Chebloune *et al*, 1988; Lapoumeroulie *et al*, 1992). The disease seen in North and South America, the Caribbean and the UK is predominantly of African origin and mostly of the Benin haplotype, although the Bantu is proportionately more frequent in Brazil (Zago *et al*, 1992). It is therefore easy to understand the common misconception held in these areas that the disease is of African origin.

However, the sickle cell gene is widespread around the Mediterranean, occurring in Sicily, southern Italy, northern Greece and the south coast of Turkey, although these are all of the Benin haplotype and so, ultimately, of African origin. In the Eastern province of Saudi Arabia and in central India, there is a separate independent occurrence of the HbS gene, the Asian haplotype. The Shiite population of the Eastern Province traditionally marry first cousins, tending to increase the prevalence of SS disease above that expected from the gene frequency (Al-Awamy *et al*, 1984). Furthermore, extensive surveys performed by the Anthropological Survey of India estimate an average sickle cell trait frequency of 15% across the states of Orissa, Madhya Pradesh and Masharastra which, with the estimated population of 300 million people, implies that there may be more cases of sickle cell disease born in India than in Africa. The Asian haplotype of sickle cell disease is generally associated with very high frequencies of alpha thalassaemia and high levels of fetal haemoglobin, both factors believed to ameliorate the severity of the disease.

Pathophysiology of sickling

The promotion of sickling by low oxygen tension and acid conditions was first recognized by Hahn & Gillespie (1927) and further investigated by others (Lange *et al*, 1951; Allison, 1956b; Harris *et al*, 1956). The morphological and some functional characteristics of irreversibly sickled cells were described (Diggs & Bibb, 1939; Shen *et al*, 1949), but the essential features of the polymerization of reduced HbS molecules had to await the developments of electron microscopy (Murayama, 1966; Dobler & Bertles, 1968; Bertles & Dobler, 1969; White & Heagan, 1970) and Xray diffraction (Perutz & Mitchison, 1950; Perutz *et al*, 1951).

The early observations on the inducement of sickling by hypoxia led to the first diagnostic tests utilizing sealed chambers in which oxygen was removed by white cells (Emmel, 1917), reducing agents such as sodium metabisulphite (Daland & Castle, 1948) or bacteria such as *Escherichia coli* (Raper, 1969). These slide sickling tests are very reliable with careful sealing and the use of positive controls, but require a microscope and some expertise in its use. An alternative method of detecting HbS utilizes its relative insolubility in hypermolar phosphate buffers (Huntsman *et al*, 1970), known as the solubility test. Both the slide sickle test and the solubility test detect the presence of HbS, but fail to make the vital distinction between the sickle cell trait and forms of sickle cell disease. This requires the process of haemoglobin electrophoresis, which detects the abnormal mobility of HbS, HbC and many other abnormal haemoglobins within an electric field.

The first molecular disease

The contributions of several workers on the determinants of sickling (Daland & Castle, 1948), birefringence of deoxygenated sickled cells (Sherman, 1940) and the lesser degree of sickling in very young children which implied that it was a feature of adult haemoglobin (Watson, 1948) led Pauling to perform Tiselius moving boundary electrophoresis on haemoglobin solutions from subjects with sickle cell anaemia and the sickle cell trait. The demonstration of electrophoretic and, hence, implied chemical differences between normal, sickle cell trait and sickle cell disease led to the proposal that it was a molecular disease (Pauling *et al*, 1949). The chance encounter between Castle and Pauling who shared a train compartment returning from a meeting in Denver in 1945, its background and implications, has passed into the folklore of medical research (Conley, 1980; Feldman & Tauber, 1997).

The nature of this difference was soon elucidated. The haem groups appeared identical, suggesting that the difference resided in the globin, but early chemical analyses revealed no distinctive differences (Schroeder *et al*, 1950; Huisman *et al*, 1955). Analyses of terminal amino acids also failed to reveal differences, although an excess of valine in HbS was noted but considered an experimental error (Havinga, 1953). The development of more sensitive methods of fingerprinting combining high voltage electrophoresis and chromatography allowed the identification of the essential difference between HbA and HbS. This method enabled the separation of constituent peptides and demonstrated that a peptide in HbS was more positively charged than in HbA (Ingram, 1956). This peptide was found to contain less glutamic acid and more valine, suggesting that valine had replaced glutamic acid (Ingram, 1957). The sequence of this peptide was shown to be Val-His-Leu-Thr-Pro-**Val**-Glu-Lys in HbS instead of the Val-His-Leu-Thr-Pro-**Glu**-Glu-Lys in HbA (Hunt & Ingram, 1958), a sequence which was subsequently identified as the amino-terminus of the β chain (Hunt & Ingram, 1959). This amino acid substitution was consistent with the genetic code and was subsequently found to be attributable to the nucleotide change from GAG to GTG (Marotta *et al*, 1977).

Recognition of clinical features

Haemolysis and anaemia. The presence of anaemia and jaundice in the first four cases suggested accelerated haemolysis, which was supported by elevated reticulocyte counts (Sydenstricker *et al*, 1923) and expansion of the bone marrow (Sydenstricker *et al*, 1923; Graham, 1924). The bone changes of medullary expansion and cortical thinning were noted in early radiological reports (Vogt & Diamond,

1930; LeWald, 1932; Grinnan, 1935). Drawing on a comparison of sickle cell disease and hereditary spherocytosis, Sydenstricker (1924) introduced the term 'haemolytic crisis' that has persisted in the literature to this day, despite the lack of evidence for such an entity in sickle cell disease. The increased requirements of folic acid and the consequence of a deficiency leading to megaloblastic change was not noted until much later (Zuelzer & Rutzky, 1953; Jonsson *et al*, 1959; MacIver & Went, 1960).

The haemoglobin level in SS disease of African origin is typically between 6 and 9 g/dl and is well tolerated, partly because of a marked shift in the oxygen dissociation curve (Scriver & Waugh, 1930; Seakins *et al*, 1973) so that HbS within the red cell behaves with a low oxygen affinity. This explains why patients at their steady state haemoglobin levels rarely show classic symptoms of anaemia and fail to benefit clinically from blood transfusions intended to improve oxygen delivery.

Aplastic crisis. Sudden cessation of bone marrow activity, manifested by absence of reticulocytes from the peripheral blood and a rapidly falling haemoglobin level, termed the 'aplastic crisis', was first recognized by Singer *et al* (1950), whose original case report contained many features characteristic of this complication. Following a vague respiratory illness, a 9-year-old boy became weak and pale, the haemoglobin fell from 8·6 to 3·5 g/dl within 3 d and reticulocytes were virtually absent. Marrow examination revealed an extreme depression of red cell precursors which was replaced 9 d later by intense erythropoietic hyperplasia with an outpouring of normoblasts and reticulocytes into the peripheral blood. His 11-year-old sister was admitted to another hospital with similar symptoms on the same day. The tendency for aplastic crises to affect predominantly children, to occur in epidemics and to affect siblings was consistent with an infection, but it was not until a chance observation in London (Pattison *et al*, 1981) that the cause of the aplastic crisis was shown to be human parvovirus infection (Serjeant *et al*, 1981). Bone marrow recovery always occurs after 7–10 d aplasia and, provided oxygen carriage is maintained by transfusion, the outcome is uniformly benign. Recurrent parvovirus aplasia has never been described.

Gallstones. The rapid haemolysis increases bilirubin excretion and pigment gallstones featured in several early reports (Washburn, 1911; Graham, 1924; Hamilton, 1926; Hein *et al*, 1927). The lack of data on the natural history of pigment gallstones led to assumptions derived from cholesterol stones and a tendency to prophylactic cholecystectomy. However, recent data from the Jamaican Cohort Study report a prevalence of 50% by the age of 25 years, and no significant differences between patients with and without gallstones or within patients with gallstones before and after their development (Walker *et al*, 2000). Jamaican experience supports conservative management of asymptomatic gallstones and cholecystectomy has been indicated by specific symptoms in only 7 out of 96 SS patients with known gallstones.

Vaso-occlusion. The contribution of vaso-occlusion was recognized more slowly. Wedge-shaped areas of pulmonary consolidation were described by Graham (1924) and Wollstein & Kreidel (1928), and Steinberg (1930) noted that 'small and medium sized pulmonary vessels contained fresh and organized blood thrombi and a consequence of fresh and old infarcts'. Infarction of the kidneys and lungs was recognized (Yater & Mollari, 1931; Baird, 1934) and Diggs (1935) noted the contribution of repeated splenic infarction to progressive splenic fibrosis. Increasing knowledge of the pathogenesis of polymerization and sickling led Ham & Castle (1940) to advance an early model of the pathophysiology of vaso-occlusion as a vicious cycle in which increased viscosity compromised blood flow, further reducing oxygen tension, leading to more sickling and further viscosity. These models have become much more complex with the extensive work on endothelial adherence of HbS-containing cells pioneered by the groups of Hebbel & Mohandas (1994) and Kaul *et al* (2000). To these studies focusing on the abnormal red blood cells must be added the increasing data on the possible relevance of high white cell counts (Balkaran *et al*, 1992; Platt *et al*, 1994) and increased platelets to the pathophysiology of vaso-occlusion.

Spleen. The spleen featured prominently in early observations of sickle cell disease. A striking splenic atrophy occurred in the first autopsy (Sydenstricker *et al*, 1923), leading to the belief that splenic pathology might account for the repeated attacks of abdominal pain and the proposal that the disease was a familial and hereditary defect of the spleen. Rich (1928) interpreted splenic pathology as a malformation of the splenic sinuses allowing free escape of blood into the pulp, but this concept was contested by Tomlinson (1945a) who considered the splenic pooling to be the result of circulating sickled cells.

There was controversy on splenic size. Atrophy was characteristic of early autopsy reports (Graham, 1924; Jaffe, 1927; Bennett, 1929; Steinberg, 1930; Yater & Mollari, 1931; Corrigan & Schiller, 1934), but splenomegaly was common in young patients (Jamison, 1924; Archibald, 1926; Alden, 1927), intermittent in others (Dreyfoos, 1926) and, in some, the spleen appeared to enlarge during painful crises (Stewart, 1927; Josephs, 1928; Wollstein & Kreidel, 1928). Occasionally, marked enlargement extended to the iliac crest (Hahn & Gillespie, 1927) and spleens weighing 180–210 g were removed in children under 3 years of age (Bell *et al*, 1927; Wollstein & Kreidel, 1928).

Order emerged from this confusion with the realization that the spleen was frequently enlarged in young children and became smaller with age (Wollstein & Kreidel, 1928). The concept of progressive splenic atrophy was anticipated by Hahn & Gillespie (1927) when they wrote that the spleen 'is nevertheless greatly injured by its long continued overuse, and completes its life history as an atrophic remnant of a once enlarged organ', and the pathological sequence of this process was illustrated by Diggs (1935).

The role of splenectomy remained confusing. Dramatic haematological improvement followed removal of some large spleens (Hahn & Gillespie, 1927; Hahn, 1928; Landon & Lyman, 1929) but effects were less obvious in others (Bell *et al*, 1927), and the removal of an impalpable spleen weighing 46 g achieved nothing (Stewart, 1927). The

concept of hypersplenism with significant chronic sequestration of red cells evolved much later (Jandl *et al*, 1956) and is still poorly defined and characterized in sickle cell disease. Recurrent acute splenic sequestration was first recognized by Tomlinson (1945b), features reviewed by Seeler & Shwiaki (1972), and the role of splenectomy in management and of parental education in early diagnosis at home was highlighted by Emond *et al* (1985).

Overwhelming infections. In addition to the effects of acute and chronic enlargement, the early loss of splenic function (Pearson *et al*, 1969) renders patients prone to overwhelming septicaemia, especially with the pneumococci. Pneumococcal meningitis was first described by Wollstein & Kreidel (1928), but the importance and epidemiology of this relationship was addressed much later (Robinson & Watson, 1966; Kabins & Lerner, 1970; Barrett-Connor, 1971). Pneumococcal infection may be prevented by prophylactic penicillin in early childhood (John *et al*, 1984; Gaston *et al*, 1986) and by pneumococcal vaccine at later ages, and effective prophylaxis contributes to significantly improved survival (Lee *et al*, 1995). These policies may need reassessment in the future with the rapid emergence of penicillin-resistant pneumococci and the development of a conjugated pneumococcal vaccine that may be effective when given at 2, 4 and 6 months.

Stroke. A left hemiparesis occurred in a 3-year-old boy reported by Sydenstricker *et al* (1923) and the first major review (Hughes *et al*, 1940) described six patients and reviewed 25 cases from the literature. This review established the early age of involvement and the high frequency of recurrence, features stressed in subsequent reviews (Greer & Schotland, 1962; Powars *et al*, 1978). A thrombotic mechanism was proposed (Arena, 1935; Kampmeier, 1936) and confirmed by Hughes *et al* (1940), and partial or complete occlusion of major cerebral arteries occurred in six out of seven children (Stockman *et al*, 1972). Major clinical features of stroke in SS disease included the young age of involvement (median age 6 years), the predominance of cerebral infarction in children and of haemorrhage in adults, and a 50–70% tendency to recurrence within 3 years of the initial episode (Powars *et al*, 1978; Balkaran *et al*, 1992). Lack of understanding of the primary event does not allow prevention and treatment is confined to prophylaxis of recurrent events by chronic transfusion programmes. Recently, early detection of stenoses of cerebral vessels by transcranial Doppler and institution of chronic transfusion therapy has significantly reduced initial stroke (Adams *et al*, 1998), but the many problems with chronic transfusion remain.

Bone changes. The first review of bone changes (Diggs *et al*, 1937) was followed by reports of the bone changes associated with dactylitis (Danford *et al*, 1941), cortical infarction (Kraft & Bertel, 1947; Legant & Ball, 1948) and avascular necrosis of the femoral head (Bauer & Fisher, 1943; Kraft & Bertel, 1947). Necrosis of metabolically active bone marrow accounts for pain and swelling of the small bones of the hands and feet in children under 5 years (hand–foot syndrome or dactylitis), and a similar pathology affecting the juxta-articular areas of long bones, spine, pelvis, ribs and sternum in older children and young adults causes the painful crisis. The features of dactylitis were first reviewed by Watson *et al* (1963) and the pathology of avascular necrosis in the painful crisis by Charache & Page (1967). Necrotic bone marrow is prone to infection especially by salmonella but, despite several reports (Carrington & Davison, 1925; Diggs *et al*, 1937; Seidenstein, 1945), the association was not acknowledged until Hodges & Holt (1951).

Painful crises. The painful crisis is currently the most frequent cause of recurrent morbidity in SS disease and accounts for 70–90% of sickle cell-related hospital admissions in the UK and the USA. Considering its high frequency, it is remarkable that systematic studies have only recently detailed risk and precipitating factors (Baum *et al*, 1987; Platt *et al*, 1991), clinical features (Serjeant *et al*, 1994), mechanism (Serjeant & Chalmers, 1990), associated morbidity (Platt *et al*, 1994) and prophylaxis (Charache *et al*, 1995). Although commonly assumed to be vaso-occlusive in origin (hence the term vaso-occlusive crisis), the frequency of cold as a precipitating factor (Redwood *et al*, 1976), greater prevalence in genotypes with less intravascular sickling (SS disease and homozygous α thalassaemia and sickle cell-β^0 thalassaemia), and significantly bilateral and symmetrical distribution are difficult to explain on this basis, leading to the hypothesis that this may represent a steal syndrome (Serjeant & Chalmers, 1990). Many painful crises may be prevented by identifying and avoiding precipitating factors, of which skin cooling is the most frequent in Jamaica. The importance of a high haemoglobin as a risk factor (Baum *et al*, 1987; Platt *et al*, 1991) argues for venesection, but currently only anecdotal data are available. Treatment includes rest, reassurance, warmth, rehydration and pain relief. Although most attention has been directed to the pharmacology of pain relief, it is clear that a patient's ability to cope with pain is determined by many factors, of which social and psychological assume particular importance.

Leg ulcers. Ulceration around the ankles occurred in all of the first four case reports but, despite a series of cases presented at the Dermatological Societies of Cleveland (Netherton, 1936; Cummer & LaRocco, 1939), Bronx (Schwartz, 1938) and the Central States (Krugh, 1939), it was not until 1940 that ulceration became recognized as a specific complication of the disease (Cummer & LaRocco, 1940). Leg ulcers occur in other haemolytic syndromes (β thalassaemia, hereditary spherocytosis), suggesting common aetiological factors, although they are almost certainly multifactorial with contributions from venous stasis, local trauma and cutaneous vaso-occlusion producing spontaneous painful deep ulcers suggestive of skin infarction (Serjeant, 1974). The tendency to heal on complete bed rest and deteriorate on prolonged standing are common to venous ulceration. Little progress has been made in the management of this complication which, although rarely causing mortality, is a major contributor to morbidity of the disease especially in areas such as Jamaica, where up to 70% of adult SS patients have been affected (Serjeant, 1974).

Pulmonary involvement. The major cause of mortality after

the age of 2 years, it is surprising that few early papers focused on this area. Pulmonary thrombo-embolism was first reported by Steinberg (1930) and others recorded the increased frequency of thrombi, recanalized thrombi and pulmonary infarcts (Diggs & Ching, 1934; Yater & Hansmann, 1936). The pathological processes causing pulmonary pathology include infection, pulmonary infarction, fat embolism (Vichinsky *et al*, 1994) and acute pulmonary sequestration (Lanzkowsky *et al*, 1978). Surprisingly, documented infection plays a minor role, bacteria being isolated from 14% of infants and less than 2% of cases aged over 10 years (Vichinsky *et al*, 1997). Acute pulmonary sequestration may be associated with rapidly deteriorating pulmonary function and a high mortality, which may be reduced by close monitoring using pulse oximetry and emergency exchange transfusion (Lanzkowsky *et al*, 1978; Davies *et al*, 1984). Rib or sternal infarction may cause pleuritic pain limiting chest movement and predisposing to secondary pulmonary changes (Rucknagel *et al*, 1991), the frequency of which may be reduced using incentive spirometry (Bellet *et al*, 1995). This variety of pathological processes and the poor response to therapy that suggested a complex pathology with several components led Charache *et al* (1979) to introduce the term 'acute chest syndrome' for all acute pulmonary pathology in sickle cell disease. Recurrent acute chest syndrome may be associated with a progressive deterioration of pulmonary function that contributes significantly to mortality among adults. The frequency and severity of chronic sickle cell lung disease is not widely documented, although the high frequency in Southern California (Powars *et al*, 1988) suggests symptomatic selection or important local factors.

Pregnancy. Early reports stressed the infrequency of pregnancy, the adverse effects of pregnancy on the clinical course of sickle cell disease, and the occurrence of fetal and maternal deaths (Yater & Mollari, 1931; Lash, 1934; Lewis, 1937; Sodeman & Burch, 1937; Page & Silton, 1939). In the first major review, Kobak *et al* (1941) summarized the outcome in 37 pregnancies among 17 women noting the frequent pre-eclamptic toxaemia, fever, pneumonia, sepsis, high fetal loss and a 33% maternal mortality. Two reports, both in 1949, illustrate the conflicting experience with pregnancy in sickle cell disease. Fouche & Switzer (1949) described pregnancies in six patients from South Carolina, three with toxaemia and four maternal deaths, and argued that the serious outcome justified therapeutic sterilization, whereas Anderson & Busby (1949), reviewing a 20-year experience at Johns Hopkins Hospital, reported 11 deliveries without maternal mortality, concluding that therapeutic abortion and sterilization were rarely indicated.

This controversy continues to daunt the clinical practice of obstetrics in mothers with sickle cell disease. As recently as the 1970s, arguments were made in the USA that 'the expected rate of reproductive success, when considered in conjunction with the negative attributes concerning motherhood, does not justify a young woman with sickle cell disease being exposed to the risks of pregnancy', advocating primary sterilization, abortion if conception occurs and sterilization for those that have completed pregnancies' (Fort *et al*, 1971). Such recommendations conflict with the improving experience that saw a decline in maternal mortality from 33% between 1924 and 1940 (Kobak *et al*, 1941) and 11% between 1945 and 1955 (Eisenstein *et al*, 1956) to 0% between 1953 and 1972 (Pritchard *et al*, 1973). As has often happened with sickle cell disease, published experience is heavily biased by hospital-dependent severely affected cases, whereas patients with milder clinical courses and repeated uneventful pregnancies may pass unreported.

Controversy has also affected the recommendations for contraception in sickle cell disease, which, although there are almost no published data, leads to patients being refused the most effective contraception, such as the pill, injections of medroxyprogesterone acetate or intrauterine devices, because of theoretical objections on the use of hormonal therapy or risks of intrauterine infection. In addition to being an effective contraceptive, a controlled study of medroxyprogesterone acetate demonstrated beneficial effects on the haematology as well as bone pain (De Ceulaer *et al*, 1982).

Priapism. The first reported case of priapism appears to have been presented at the New York Society for Clinical Psychiatry in 1932 as a 'castration fear complex' (Obendorf, 1934), but the association with sickle cell disease was recognized by Diggs & Ching (1934) and has been the subject of several reviews (Hasen & Raines, 1962; Sousa *et al*, 1962). However, the high prevalence affecting 40% of post-pubertal males was not appreciated until epidemiological studies in Jamaica (Emond *et al*, 1980) that defined two patterns; short lived, nocturnal or stuttering events with normal intervening sexual function, and major attacks lasting more than 24 h and commonly followed by impotence. The use of stilboestrol to prevent stuttering attacks (Serjeant *et al*, 1985) and of penile prostheses in the management of impotence (Douglas *et al*, 1990) followed recognition of the frequency of the problem in Jamaica.

Growth. Menarche was delayed to 18 years in Washburn's (1911) case and Mason (1922) reported a slender build, absence of axillary and scant pubic hair in a 21-year-old man. Further papers commented on the tendency of sickle cell patients to be tall and slim (Diggs & Ching, 1934; Sharp & Vonder Heide, 1944) and early anthropometric studies recorded the long thin limbs, narrow pectoral and pelvic girdles, hoop shaped chest and low body weight (Winsor & Burch, 1944, 1945). The abnormal growth and some of its determinants have been documented from both the Cooperative Study in the USA (Platt *et al*, 1984) and the Jamaican Cohort Study (Stevens *et al*, 1986). Contributing to this abnormal growth is the high metabolic demand in patients with sickle cell disease (Singhal *et al*, 1993). Furthermore, the patients manifesting abnormal growth represent only one end of the broad spectrum of SS disease, many patients showing normal physical development and a normal body build.

Chronic end organ damage. The improving survival in SS disease has highlighted the problem of cumulative end organ damage, especially affecting the lungs and kidneys. Recurrent acute chest syndrome may lead to pulmonary

fibrosis, pulmonary hypertension and respiratory failure, and chronic renal impairment is an important contributor to death in older patients with SS disease. Glomerular filtration rates, which are supranormal in young children, decline steeply with age resulting in renal impairment that may be underdiagnosed when defined by the range of serum creatinine levels in normal populations. In SS disease, creatinine levels are low and significant renal impairment may be present with creatinine levels above 60 mmol/l. Renal failure is typically clinically silent and may only be manifested by falling haemoglobin levels as a result of low erythropoietin production.

Natural history

The symptomatic bias present in so much of the published work on sickle cell disease creates the impression of a uniformly severe condition with many complications and death in childhood or early adult life. This picture, which characterized the sections on sickle cell disease in medical textbooks until the 1960s and early 1970s, clearly conflicted with that seen in Jamaica, where survival of SS patients to 40 and 50 years of age was not unusual. However, publication of the features in 60 Jamaican SS patients over the age of 30 years (Serjeant *et al*, 1968) was initially treated with incredulity, then with doubts on the diagnosis and, finally, with the assumption that the Jamaican disease was different. Mildly affected cases and long-term survivors are now widely recognized in many areas and this illustrates the enormous change that has occurred in the concept of SS disease over the last 30 years. To some extent, there has been a real improvement in survival (Lee *et al*, 1995) owing to better prophylaxis and management of the disease, but much of the changing emphasis results from better epidemiology and less biased patient experience. Median survival of SS patients in the USA was recently estimated as 42 years for men and 48 years for women (Platt *et al*, 1994).

However, this benign picture does not characterize the disease in Equatorial Africa, where a high early mortality persists in many areas and survival beyond 5 years remains uncommon (Fleming, 1989). Factors contributing to this poor outcome include malaria, other infections, infestations and malnutrition. Although the solution to these problems lies largely in public health measures, the limited resources and scale of the problem in many developing countries (estimates in Nigeria suggest 100 000 babies with SS disease are born each year) are daunting. It is also inappropriate to assume that the clinical patterns observed and management recommended in SS patients in the developed world also apply to the developing countries. There are suggestions of important differences and local studies are needed to define the pattern of clinical problems and their most appropriate prevention or therapy.

In SS disease, some die in the first year of life, yet others are alive and well at the age of 80 years, so what contributes to this remarkable heterogeneity of expression? Genetic factors modifying severity include genes for the heterocellular hereditary persistence of fetal haemoglobin, still poorly defined but recognizable from a modest elevation of HbF in an AS parent (Mason *et al*, 1982). These genes appear to determine much greater elevations of HbF in their SS offspring, inhibiting intravascular sickling and reducing end organ damage. Alpha thalassaemia commonly coincides with SS disease, occurring in 35–40% of Jamaicans, reducing the mean corpuscular haemoglobin concentration of red cells and so inhibiting sickling (Higgs *et al*, 1982). Other genetic factors, less well defined, may determine endothelial adhesion and steady state white cell counts that may modify expression of the disease. Of the environmental factors, socio-economic status is one of the most important and probably represents the multifactorial effects of better nutrition, public health measures, easier access to medical care and parents more capable of responding to emergencies.

Major contributions to the understanding of the natural history of sickle cell disease have come from two research initiatives, the Jamaican Cohort Study (Serjeant *et al*, 1974) based at the University of the West Indies, initiated in 1973 and funded by the British Medical Research Council, and the Cooperative Study of Sickle Cell Disease (Gaston & Rosse, 1982) involving 23 institutions in the USA, initiated in 1988 and funded by the Sickle Cell Disease Branch of the National Heart, Lung and Blood Institute. The first has focused on newborn recruitment with long-term follow-up compared with control subjects with a normal haemoglobin genotype, whereas the Cooperative Study has focused on detailed appraisals of individual complications in patients recruited at various ages.

Treatment

Inhibition of sickling. The treatment of individual complications has been addressed in the previous system-specific sections, but approaches to a more general inhibition of sickling have included anti-sickling agents, cyanate, hydroxyurea, chronic transfusion programmes, bone marrow transplantation and, possibly, gene therapy in the future. The usual target end-point is painful crisis frequency, which has the disadvantage of being multifactorial in origin and subjective in severity. Furthermore, in the established painful crisis, even effective anti-sickling agents such as oxygen have little effect because the pathology may be irreversible and agents cannot reach the site of pathology.

Controlled studies of cyanate showed effective carbamylation of HbS molecules and reduced sickling, but had no effect on pain crisis frequency (Harkness & Roth, 1975) and had potentially serious side-effects.

Hydroxyurea. Hydroxyurea is a potentially less toxic agent that increases the HbF level; an uncontrolled open-label study in 32 SS patients confirmed that oral therapy increased HbF and total haemoglobin levels at a dose tolerated without serious toxicity (Charache *et al*, 1992). A subsequent placebo controlled trial of 299 adults with SS disease and at least three painful crises in the year preceding the trial showed significantly less painful crises, acute chest syndrome and transfusion requirements in the hydroxyurea group, and the trial was stopped prematurely after 21 months of the projected 24 months (Charache *et al*, 1995).

The apparent clinical success and lack of serious toxicity in adults has led to studies in children, in whom uncontrolled trials confirmed increases in HbF, total haemoglobin and mean cell volume, and a reduced frequency of painful crisis (Jayabose *et al*, 1996; Scott *et al*, 1996; de Montalembert *et al*, 1997; Rogers, 1997) and of the acute chest syndrome (Rogers, 1997), results essentially confirmed in a controlled, single-blind, crossover study of 25 patients (Ferster *et al*, 1996).

Concerns about the use of hydroxyurea include the variable and poor response in some patients, the occurrence of serious complications in the presence of high and presumed protective levels of HbF (Vichinsky & Lubin, 1994), and the theoretical dangers of mutagenesis, teratogenesis and leukaemogenesis, which can only be answered by long-term follow-up. As effective doses may be only marginally below those causing neutropenia, patients require close and careful monitoring. Despite these concerns, some patients on hydroxyurea have demonstrated dramatic improvements in clinical course.

Transfusion. Simple transfusion may be life saving in relieving the acutely lowered haemoglobin of the aplastic crisis or acute splenic sequestration, or in maintaining the chronically lowered haemoglobin in chronic renal failure. Exchange transfusion is used to rapidly replace HbS-containing cells and may have a dramatically beneficial effect in acute pulmonary sequestration of the acute chest syndrome (Davies *et al*, 1984). Chronic transfusion programmes (Wayne *et al*, 1993) are widely used for a variety of indications of which prevention of recurrent stroke (Pegelow *et al*, 1995) and acute chest syndrome (Styles & Vichinsky, 1994) are the most established. Although there is little doubt regarding their short-term effectiveness, they may be seriously limited in the long term by problems of increasing red cell alloimmunization (Rosse *et al*, 1990; Vichinsky *et al*, 1990), non-haemolytic transfusion reactions (Friedman *et al*, 1996), delayed haemolytic transfusion reactions (Petz *et al*, 1997), iron accumulation requiring chelation (Cohen & Schwartz, 1979), transfusion-acquired infections (Castro *et al*, 1990) and venous access (Abdul-Rauf *et al*, 1995; McCready *et al*, 1996).

Bone marrow transplantation. Bone marrow transplantation (BMT) in SS disease was first reported in an 8-year-old girl with acute leukaemia who was successfully transplanted with the bone marrow of her AS brother (Johnson *et al*, 1984). Although the indication for this first BMT was the acute leukaemia, the increasing success and lowered morbidity with the procedure has allowed its use in severely affected patients with SS disease (Sullivan *et al*, 1997). The major concern in defining its use is the current inability to predict a severe clinical course, especially in children, which limits the counselling options and may contribute to parental refusal (Walters *et al*, 1996a). Other problems include the low availability of suitable HLA-matched donors, a relatively high short-term mortality, and complications that may include acute and chronic graft-vs.-host disease, graft rejection in approximately 10% of cases (Bernaudin *et al*, 1997; Vermylen *et al*, 1997), sometimes marrow aplasia (Walters *et al*, 1996b), neurological complications (Kalinyak *et al*, 1995; Walters *et al*, 1995, 1996b), and concerns regarding the effect of the conditioning regimes on subsequent growth and sexual development (Walters *et al*, 2000).

On the positive side, results from an international study of 32 patients indicate survival of over 90% and event-free survival of 74% (Sullivan *et al*, 1997), updated to 94% and 84% in 50 patients (Walters *et al*, 2000), with corresponding figures of 93% and 82% in 50 patients over 11 years from Belgium (Vermylen *et al*, 1998) and of 91% and 85% among 34 patients treated in France (Bernaudin, 1999). Painful crises are abolished, and there is some evidence of restored splenic function (Ferster *et al*, 1993; Vermylen *et al*, 1998) and resolution of cerebrovascular disease (Vermylen *et al*, 1997; Bernaudin, 1999). However, despite these encouraging results, the high expense and expertise required make it improbable that it will be applicable to many of the countries where sickle cell disease is a major public health problem.

Other approaches. The problems related to gene therapy are only recently becoming apparent and it will probably be many years before this technology can contribute to the management of sickle cell disease. There is no doubt that education of patients and their families can have a marked impact on disease outcome and this must be practiced as widely as possible.

If I may end on a personal note, some 10 years ago I met a lady in Grenada who had originally been identified by Dr Todd Savitt. At the time she was aged 97 years and 81 years earlier had developed toothache while attending the Convent School in St. Georges, the capital. She was taken to see a dentist named Walter Clement Noel, the first case of sickle cell disease to be reported. She could recall and describe him, illustrating the point that the entire published history of sickle cell disease, until recently, fell within the life of a single individual. With over 12 000 papers currently on Medline, much knowledge has been accumulated, but much remains to be achieved to improve the understanding and management of this disease. It is hoped that a knowledge of the history, including the origin of the many misconceptions, will contribute to this end.

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