The various entities generally called sickle cell disease (SCD) share two characteristics: sickle erythrocytes in the blood and clinical illness as a result of having these abnormal red cells. They include the homozygous HbSS condition sickle cell anemia, and the compound heterozygous states HbSC disease and HbS/thalassaemia, but not sickle cell trait (HbAS). Oral history passed down through generations in Africa relays accounts of an inherited illness that manifests as recurrent episodes of sudden onset bone pain, and death during childhood [1]. In the medical literature, the earliest publication of the features of the disorder now called sickle cell disease was in 1874 by Africanus Horton [2]. Born of Igbo parents from Nigeria who lived in Sierra Leone, Horton graduated from the medical school of King’s College London, and served as a colonel in the British army (Fig. 1). In his book *The Diseases of Tropical Climates and Their Treatment*, Horton [2] described the recurrent pain that is the hallmark of clinical manifestation of sickle cell disease, as well as the association of fever and cold weather. The characteristic hematological feature of sickle cell disease, “peculiar elongated and sickled red cells” was published in the 1910 issue of *Archives of Internal Medicine* by James Herrick, a Chicago cardiologist [3]. It was the first account of the pathology of SCD, and gave the condition the name it bears today.

Since 1910, there have been remarkable advances in understanding the pathological basis of SCD. Three disease mechanisms stand out: haemolysis, vaso-occlusion, and impaired defense against infections. Premature destruction of red blood cells is mostly the end effect of erythrocyte sickling and membrane damage induced by crystallization and polymerization of deoxy-HbS [4]. However, in the uncommon condition of hyperhaemolysis syndrome, immunological mechanisms appear to play a dominant role in destruction of both the patient’s own and transfused red blood cells [5]. Blood vessel occlusion in SCD is a process fairly simple in conception. However, the cellular and molecular details are complex. Various gaps in knowledge notwithstanding, the current model of vaso-occlusion in SCD views the process as the result of interactions between sickled and unsickled erythrocytes, leukocytes, platelets,
plasma proteins, and the blood vessel wall [6,7]. The causes of impaired defense against infections in SCD include splenic hypofunction [8], a defect in the alternative pathway of complement [9,10], and possible reduction in the microbicidal capacity of white blood cells [11,12]. Despite substantial developments in understanding the pathophysiology of SCD, application of this immense body of knowledge to medical treatment remains a major challenge. Interference with various disease mechanisms is the basis of many treatment modalities in SCD. This review will discuss new and developing therapies for SCD as a whole, and for specific manifestations of the hemoglobinopathy.

**HYDROXYUREA THERAPY**

Although it is licensed in the United States for administration to sickle cell patients who have ≥3 crises a year in steady state, hydroxyurea (HU) remains unlicensed in most countries where it is regarded as an experimental drug [13,14]. In the author’s hospital in the United Kingdom, where HU is unlicensed for SCD, it is offered to patients who have ≥5 crises a year; or 3–4 crises a year with either neutrophil count ≥10 × 10⁹/L or platelet count ≥500 × 10⁹/L in...
steady state [7]; bearing in mind that the reference range for neutrophil count in black people is $1–3 \times 10^9/L$ [15,16], and is $100–300 \times 10^9/L$ for platelets [17]. Since high neutrophil count in steady state is a marker of severe SCD [12,18–22], these criteria usually identify individuals who have a clinical course sufficiently severe to ensure that the benefits of hydroxyurea therapy justify the potential risks. HU therapy is offered if the patient does not want to have (more) children, and is weighed against any severe impairment of liver or kidney function, or blood cytopenia. HU is unlicensed in most countries because the long-term adverse effects are unknown, not because the clinical efficacy is in doubt. In fact, after over 9 years of follow-up, HbSS subjects who received HU in the US placebo-controlled trial, had significantly less painful crises, acute chest syndrome, and mortality [23]. Potential long-term toxic effects that reduce enthusiasm for HU include teratogenicity, carcinogenesis and, for young children, impaired cognitive development.

How much of an issue have these potential adverse effects been in clinical practice? With respect to possible effects on unborn babies, about 15 women have taken HU all through pregnancy, and none of the children had a congenital anomaly [24,25]. Although these reports may reduce anxiety about the outcome of pregnancy in humans taking HU, it is a cytotoxic drug, teratogenic in mice [26]. Therefore, the manufacturers and most clinicians currently hold the view that HU is contra-indicated in pregnancy, and advise contraception in patients of child-bearing age who take the medication [27]. Sperm banking before starting HU therapy may be considered in males who plan to have children later. Neurocognitive deficits have not been observed in children who have sickle cell disease who are taking HU [28], who may indeed have better school performance than those not on the therapy. Twenty-nine children who have sickle cell disease (median age 14 months) treated for 2 years with HU at the initial dose of 20 mg/kg, then had the dose increased to 30 mg/kg. At a time when 19 of the 29 had completed a median treatment period of 2.8 years, growth and development remained normal [29]. A much longer median follow-up period of 5 years in 60 children taking HU for secondary erythrocytosis has resulted in no malignant disease in any of the cohort [30]. Acute leukemia has developed in 3 sickle cell patients on HU, in 2 of the 3 patients, after 6 and 8 years respectively of treatment [31–33]. However, the leukemogenic risk of HU therapy is difficult to quantify from these case reports because the total number of patients treated and the duration of therapy are not certain. The Medical College of Georgia (Augusta, GA) recently published their 15 years of experience with HU therapy in SCD. Leukemia was not reported among the 226 patients treated [34]. After 9 years of follow-up, the US multi-center trial observed 2 cases of cancer among 204 sickle cell subjects who actually took HU (irrespective of the original randomization to the drug or placebo), and 1 case among 96 subjects who never did [23]. The data do not suggest a significant increase in the risk of malignant disease caused by HU therapy. As a ribonucleotide reductase inhibitor that is mutagenic [35] and impairs DNA and protein synthesis with adverse effects on cell division, HU has a theoretical potential to be carcinogenic.
Whether this will translate into a practical problem in hematology clinics, remains to be seen.

The clinical benefits of HU are mediated by increased total HbF, mean cell HbF, number of erythrocytes with detectable amounts of HbF and possibly nitric oxide [36,37], as well as with reduction in reticulocyte, leukocyte, and platelet counts, and in the expression of adhesion molecules in blood and vascular endothelial cells [38,39]. The dose of HU used in SCD is 5–35 mg/kg/d. In the author’s hospital, treatment of adults is started with 0.5 g/d, and increased by 5 mg/kg every 6 weeks, until clinical benefit is observed. Clinical experience shows that the maximum tolerable dose (as used during the initial trials) is not necessary to achieve the benefits of HU therapy in SCD. The short-term adverse effects of HU, such as blood cytopenias, are more likely to occur with higher doses and, though not yet proven, it is possible this may also apply to the long-term toxicities. Therefore, in the author’s hospital, the minimum effective dose is used, where about 25 adult sickle cell patients are on HU 1–2 g/d, with good effect. The dose at which side effects or clinical benefits occur may vary between individuals. Therefore, it is important to monitor each patient for adverse effects, especially during the initial period of treatment. Blood cell counts and chemistry to assess liver and renal functions are done every 2 weeks in the first month, monthly for the next 3 months, and every 2–3 months thereafter. Treatment is suspended in black patients if the neutrophil count drops below 1 × 10⁹/L, and the platelet or reticulocyte count below 80 × 10⁹/L. HU therapy is restarted at a lower dose when neutrophil count rises to 2 × 10⁹/L, platelet count to 100 × 10⁹/L, and reticulocyte count to 100 × 10⁹/L. For white patients who have higher reference ranges of blood cell counts, the criteria for suspending therapy are neutrophils <2 × 10⁹/L, platelets <100 × 10⁹/L, and retics <80 × 10⁹/L. Other therapeutic agents that increase HbF levels are used less extensively than HU in SCD. This is probably because, despite their effectiveness, these agents lack the convenience of oral administration. Arginine butyrate infused once or twice a month led to a remarkable rise in HbF sustained for 1–2 years [40]. Subcutaneous infusion of decitabine, an analog of azacytidine that is less cytotoxic than HU, significantly increased total Hb level and percentage HbF in HbSS patients who did not have such improvements in hematological parameters during previous treatment with hydroxyurea [41].

OMEGA-3 FATTY ACIDS

These food substances that occur naturally in fish oil are essential to humans because we do not have the biosynthetic machinery. They are important structural and functional components of the membranes of cells and various organelles. In a placebo-controlled pilot trial, oral supplements of two omega-3 polyunsaturated fatty acids (PUFA)—docosahexanoic acid (DHA) and eicosapentanoic acid (EPA)—reduced the mean number of sickle cell crises requiring hospital attendance from 7.8 per year to 3.8 per year in 5 HbSS individuals [42]. By contrast, 5 HbSS patients who received placebo (olive oil) had pre- and post-treatment crisis rates of 7.6 per year and 7.1 per year, respectively. In
addition, the thrombogenicity of blood (as measured by various coagulation parameters) and expression of the adhesion molecule platelet selectin (CD62P) were significantly reduced. Omega-3 PUFA was given as 0.25 g/kg/d of menhaden fish oil containing 18% DHA and 12% EPA. The placebo was given at the same dose. If confirmed in a controlled trial involving a large number of sickle cell patients, the dramatic reduction in the number of crises would hold promise for the future. This is because, unlike hydroxyurea, DHA and EPA are not cytotoxic, they are naturally occurring nutrients, they are more widely available and affordable in developing countries where the majority of SCD patients live, and they will be more acceptable to both patients and physicians. Concerns about carcinogenicity, teratogenicity and impaired cognitive development are far less likely to arise. Fish oil is generally consumed as a food substance in many countries. Supplements of DHA and EPA have been safely given in previous studies to pregnant women, as well as term and pre-term babies [43,44]. In fact, there is evidence that DHA enhances development of the brain and nervous system [45,46].

Hongmei Ren and coworkers [47–49] have studied omega-3 fatty acids in steady state sickle cell disease, and observed a striking correlation between the proportions of DHA and EPA in the blood, and indices of disease severity. There was global reduction of DHA and EPA in erythrocytes, leukocytes, platelets, and plasma of sickle cell patients relative to healthy HbAA controls. In addition, steady state hemoglobin levels increased with the proportion of omega-3 PUFA in red cell membranes, and patients with complications of SCD had significantly less platelet DHA than those who have uncomplicated disease. Several factors may contribute to the biological basis of these findings. As stated previously, omega-3 fatty acids are vital to the structural integrity of erythrocyte membranes. So, increased proportions confer resistance against hemolysis, as demonstrated following dietary supplementation in animal models [50]. This improves hemoglobin levels in SCD because haemolysis is the dominant cause of anemia in this hemoglobinopathy. Also, increased proportions of DHA and EPA inhibit production of pro-inflammatory cytokines, activation of vascular endothelium, and adhesion of blood cells to the vessel wall [51–53]. In SCD, the end-effect is reduction in vaso-occlusive episodes, ischemic organ damage, and disease complications. Together with reduced blood coagulability and adhesion molecule expression reported in the pilot trial [42], the findings of Ren and colleagues [47–49] have shed some light on how omega-3 fatty acid therapy confers clinical benefit in SCD. Administration of these PUFA ameliorates various diseases of the cardiovascular, skeletal, and other organ systems [54–56]. Available data provide sufficient grounds for a large clinical trial of omega-3 fatty acids in the multi-system disorder that is SCD.

**GARDOS CHANNEL BLOCKERS**

A calcium-dependent mechanism for potassium transport across cell membranes, the Gardos channel, regulates K⁺ ion and water loss from erythrocytes. In humans and animal models who have SCD, inhibition of this potassium flux...
system by the antifungal clotrimazole, prevented intra-cellular dehydration of erythrocytes and reduced the polymerization of HbS and sickling of red blood cells [57]. An analog of clotrimazole that is less toxic to the liver and urinary tract because it has no imidazole moiety, ICA-17043 is a more potent Gardos channel inhibitor and specifically blocks potassium efflux from red blood cells mediated by this transport mechanism [58]. In a phase II placebo-controlled clinical trial reported by Ataga and colleagues [59], oral ICA-17043 10 mg/d for 12 weeks raised the mean steady state Hb by 0.68 ± 0.11 g/dL; with significant reduction in reticulocyte count, bilirubin level, and lactate dehydrogenase (\(P < .001\)). The main side-effects of ICA-17043 were nausea and diarrhea. The beneficial effects of this Gardos channel inhibitor on hematological indices has prompted a phase III multi-center clinical trial designed to find out if it reduces the frequency of vaso-occlusive events in SCD.

**PROSPECTS FOR ANTI-ADHESION THERAPY**

Adhesion of blood cells to each other and the vascular endothelium contributes to vaso-occlusion in SCD [6,7]. Therefore, the molecules that mediate these cellular interactions are potential targets in the treatment of sickle hemoglobinopathies. There are prospects for the use of chemical or biological agents to interfere with the intercellular adhesions that facilitate blood vessel obstruction. Such anti-adhesion therapy could reduce tissue ischaemia or infarction, and ameliorate the clinical manifestations of vaso-occlusion in SCD. Early investigators recognized that sickled erythrocytes are rigid, a property that facilitates mechanical obstruction of the micro-vasculature [60]. More recent studies demonstrate that both sickled and unsickled erythrocytes bind to blood vessel walls via adhesion molecules [61]. So, red blood cells also contribute to vaso-occlusion in SCD through an active process distinct from passive mechanical obstruction. \(\alpha_5\beta_3\)-integrin on vascular endothelium is the ligand for several adhesion molecules on erythrocytes (eg, phosphatidyl serine, sulfated glycosans, CD47, and CD36) [6]. Administration of a monoclonal antibody to \(\alpha_5\beta_3\)-integrin led to remarkable inhibition of vaso-occlusion in a mouse model that had SCD [62]. Therefore, \(\alpha_5\beta_3\)-integrin is a candidate adhesion molecule for targeted blockade or reduction, with the hope of achieving clinical benefit in SCD. Since vascular obstruction in SCD also involves adhesion of leukocytes and platelets to other blood cells and the endothelium, these cellular interactions present opportunities for therapeutic intervention. Two molecules that mediate leukocyte adhesion to vascular endothelium—L-selectin (CD62L) and \(\alpha_M\beta_2\)-integrin (CD11b and CD18)—are highly expressed by individuals who have severe manifestations of SCD; such as vaso-occlusive crisis, stroke, nephropathy, and other organ complications [38]. Reducing the surface expression of these adhesion molecules or blocking their interactions with vascular endothelial ligands could reduce vaso-occlusion and yield clinical benefits in SCD. There is evidence to suggest that two new therapies already tried in SCD work partly by reducing intercellular adhesion. An early clinical benefit of hydroxyurea therapy, amelioration of mild ‘niggling’ pains experienced even during
steady state, is reported by patients within a month of commencing treatment, at a time when leukocyte adhesion molecule expression has fallen significantly, without a significant rise in HbF level [38]. HU therapy also reduces the expression of adhesion molecules on erythrocytes, evidenced by decreased in vitro adherence of sickle erythrocytes to thrombospondin and laminin [39]. An emerging therapy for SCD that has shown clinical benefit in a pilot trial, oral supplementation with omega-3 fatty acids, reduces platelet expression of the adhesion molecule CD62P (platelet selectin) [42], the counterpart of leukocyte selectin (CD62L) that is down-regulated by HU therapy [38].

How do hydroxyurea and omega-3 fatty acids reduce adhesion molecule expression on blood cells? A plausible explanation is that by inhibiting DNA synthesis, HU ultimately interferes with protein synthesis. This effect of HU appears to be non-specific because different adhesive proteins on leukocytes, erythrocytes, and possibly vascular endothelial cells, are reduced during therapy. With regard to omega-3 fatty acids, it is recognized that the lipid composition of the cell membrane affects not only its structure and function, but also membrane expression of adhesion molecules [51]. It has been demonstrated that administration of omega-3 fatty acids increases the proportion of these lipids in the membranes of blood cells [42]. This alteration of membrane lipid constitution is thought to modulate the expression of adhesion molecules. Anti-adhesion therapy has some prospects in SCD. Targeted inhibition, blockade, or down-regulation of specific adhesion molecules most relevant to intercellular bonding is preferable to global reduction. This strategy will minimize interference with normal body function dependent on physiological processes that require different adhesive proteins and their ligands.

TREATMENT OF SPECIFIC MANIFESTATIONS
Pulmonary Hypertension
Acute lung injury, manifesting as the chest syndrome, is the leading cause of death in adults who have sickle hemoglobinopathy [21,63]. The overall increase in survival of sickle cell patients means that chronic sickle lung disease, including pulmonary hypertension, is becoming increasingly important as a cause of poor health. That lung disease is a dominant cause of morbidity and mortality in SCD is hardly surprising considering the crucial role of the organ in oxygenation of the blood, and that it is hypoxaemia that causes sickling of erythrocytes. The normal blood pressure in the pulmonary artery is 25/15 mm Hg, with a mean pulmonary artery systolic pressure (PASP) of 18 mm Hg. Pulmonary hypertension (PHT) is defined as pulmonary artery systolic pressure >30 mm Hg, or mean PASP >25 mm Hg, or tricuspid valve regurgitant jet velocity (of blood flow) >2.5 m/s. The pathogenesis of PHT in SCD is probably multi-factorial. However, intravascular haemolysis with binding of free plasma hemoglobin to endogenous nitric oxide (NO, a natural vasodilator) is thought to play an important causative role. This concept is supported by the occurrence of PHT in other hemolytic conditions such as thalassaemia [64]. The development of PHT in SCD carries a poor prognosis [65], and there is no generally used
effective therapy for this complication. The effects include reduced blood oxygen saturation in steady state (SaO₂ < 90%), fatigue, chronic chest pain, dyspnoea on exertion, a loud pulmonary component of the second heart sound, pansystolic murmur if there is tricuspid regurgitation, ECG changes of right ventricular hypertrophy, syncope, and sudden death [64]. Several new therapies for PHT in SCD are coming into clinical practice. The rationale for these treatment modalities is to interfere with the pathogenesis of PHT. Regular exchange blood transfusion reduces the rate of haemolysis by replacing erythrocytes containing HbS with normal red blood cells. Inhalation of NO to replenish the endogenous gas consumed by free plasma Hb corrects the relative NO deficiency that occurs in sickle cell patients including the pulmonary vasculature, stimulates vasodilation, and reduces the pulmonary blood pressure [66]. Oral administration of arginine (the natural substrate for synthesis of NO) at a dose of 0.1 g/kg three times daily, reduced high pulmonary blood pressure in 9 out of 9 sickle cell patients [67]. L-carnitine, an analog of the naturally occurring fatty acid carnitine, is thought to stabilize the red cell membrane, and so inhibits haemolysis. Oral L-carnitine, 1 g three times daily, reduced the mean PASP from 40.2 ± 7.2 mm Hg to 32 ± 6.5 in 14 of 18 sickle cell patients age 4–16 years [68]. Oxygen inhalation lowers pulmonary BP in SCD patients with secondary PHT who have steady-state hypoxaemia, or a drop in pulmonary BP following oxygen administration during cardiac catheterisation. Home oxygen therapy may be combined with other treatment modalities for greater benefit.

Primary Stroke Prevention

Stroke prevention has come to be regarded as standard clinical practice since the United States Stroke Prevention Trial in Sickle Cell Anemia (STOP) was terminated ahead of schedule [69]. Interim analysis of the study data showed clearly that regular blood transfusion significantly reduced the incidence of clinically overt stroke in sickle cell patients who have blood velocity ≥ 200 cm/s in the middle cerebral or terminal part of the carotid artery. Such a high blood velocity indicates an increased risk of cerebrovascular accident (CVA) in sickle cell patients [70]. Stroke is a devastating complication of SCD. It adversely affects the life of not only the patient, but also the family, caregivers, and society as a whole. Therefore, every effort ought to be made to prevent stroke. Before the STOP trial, blood transfusion therapy had been effectively used to reduce the risk of recurrent CVA in sickle cell patients [71]. Proactive measures should be taken to prevent CVA in those patients at higher risk. There is a 200-fold increased risk of stroke in the general sickle cell population relative to healthy HbAA controls, and a higher risk in individuals who have carotid or middle cerebral artery blood velocity ≥ 200 cm/s compared with other sickle cell patients. Indeed, current efforts to prevent CVA in SCD have advanced beyond prophylactic transfusions in patients who have blood velocity ≥ 200 cm/s. Michael DeBaun and co-workers [72] involved in the Silent Cerebral Infarct Transfusion Trial are addressing the question whether prophylactic blood transfusions can reduce the proportion of sickle cell patients who have silent
cerebral infarction (another index of increased risk of CVA in SCD) and blood velocity < 200 cm/s who develop clinically overt stroke.

**Oral Therapy for Iron Overload**

Oral therapy for iron overload has been desired for many years by hemoglobinopathy patients and physicians alike because of the daunting challenges of poor compliance and sheer inconvenience associated with long-term infusions of the main iron-chelating drug, desferrioxamine. Whereas compliance with parenteral iron chelation therapy is generally good in young children supported by the highly motivated parents, adherence to the treatment regimen tends to decline (understandably) in adolescents and young adults who are beginning to live independently. Unfortunately, this tends to coincide with the time that sickle cell patients increasingly need chelation therapy, because they have had cumulated iron loading from blood transfusions since childhood. Deferiprone (L1) was the first oral iron chelator that came into clinical use. It was licensed in 1995 in India, and in Europe 4 years later. A bi-dentate ironophore, smaller and more able to diffuse into cells than desferrioxamine, deferiprone has been shown to reduce or prevent increases in liver iron concentration and mean serum ferritin levels in most patients who need regular blood transfusion [73]. Its greater ability to penetrate myocardial cells may account for significantly improved MRI scans, consistent with reduced cardiac iron load and function in patients taking deferiprone, compared with those on desferrioxamine [74]. The side-effects of deferiprone include mild gastrointestinal symptoms of nausea, vomiting, and abdominal discomfort, chelation and loss of zinc from the body leading to deficiency of this trace element, and joint pains. Granulocytopenia is the most important problem from deferiprone encountered in hematology clinics. The incidence is 0.6/100 patient-years [75].

Deferasirox (ICL670 or Exjade) is a new oral iron chelator which, to date, has not been reported to affect granulocyte count [76]. This tridentate bis-hydroxyphenyl-triazole with high specificity for iron showed clinical efficacy comparable to that of desferrioxamine in phase II trials in patients who have transfusion hemosiderosis [77]. The results of a phase III clinical trial in sickle cell patients are awaited. The side effects of deferasirox include mild to moderate nausea and vomiting, mildly increased urinary $\beta_2$-microglobulin and, occasionally, skin rash. The absence of agranulocytosis or the deficiencies of zinc, copper, magnesium, and calcium in those on treatment indicate that the safety profile of deferasirox might be promising.

Although a definitive cure is yet to be found for sickle cell disease, its treatment remains the subject of intense research in the public and private sectors. It is hoped that these efforts and the large body of information generated will translate into effective new therapies available to people who have this hemoglobinopathy across the world.

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