Sickle cell disease (SCD) is the most frequent monogenic disorder and hereditary hematologic disease worldwide. Currently afflicting well over 300,000 live births each year, such rates are expected to markedly increase in the years ahead. In its discovery, pathobiology, and therapeutic challenges, SCD stands entirely apart from any other known clinical disorder. Features of SCD have been recognized in Africa for centuries, and in the English literature, sickle red blood cells (RBCs) were first described in a West Indian student studying dentistry in Chicago who presented with fevers, pain, leg ulcers, jaundice, and pulmonary symptoms. Other case reports then documented the presence of such cells in similarly symptomatic patients, and the seminal observation was made that deprivation of oxygen ex vivo rapidly triggered the sickling of RBCs obtained from patients with this disease. Sickle cell disease ushered in the age of the molecular disease paradigm: in the case of SCD, a DNA point mutation in the β gene led to the substitution of a single amino acid (valine for glutamic acid) in β-globin; this created a mutant hemoglobin protein (hemoglobin S [HbS]) prone to polymerize under hypoxia and other stress conditions. The resulting RBC sickling, vaso-occlusion, and attendant tissue ischemia, it was recognized, contributed to the harrowing crisis episodes experienced recurrently by patients with SCD.

Progress in the field of SCD also included the following salient insights. First, RBC sickling occurs not only in individuals homozygous for the β* gene (generally the most severe form of SCD and termed sickle cell anemia) but also in patients with compound heterozygous conditions (for example, the combined presence of HbS and another mutant β-globin protein); the term SCD is used to encompass all such conditions. Second, heterozygous inheritance of the β* allele leads to sickle cell trait, a largely asymptomatic condition. However, sickle cell trait confers resistance to malaria, and this biological benefit along with natural selection likely explains why SCD and its mutant genes endured. Third, the clinical course of SCD is characterized by repeated episodes of acute vaso-occlusive processes (for example, acute painful episodes, acute chest syndrome, stroke, and priapism) superimposed on chronic progressive multiorgan involvement (for example, chronic kidney disease, pulmonary hypertension, hepatopathy). Fourth, there is marked heterogeneity in disease severity even for patients with sickle cell anemia, and this is explained, in part, by the prevailing accompanying levels of fetal hemoglobin, the latter inhibiting polymerization of HbS.

For much of its history, the treatment of SCD has been supportive and directed to the relief of pain. The introduction of long-term treatment with RBC transfusions and hydroxyurea in the 1990s heralded an expanding therapeutic promise for this disease. In this issue of Mayo Clinic Proceedings, Kapoor et al comprehensively and superbly review the spectrum of advances in the therapeutic approach in SCD. In their timely synthesis of this field, these authors discuss the roles of hydroxyurea, novel antisickling agents, long-term transfusion therapy, hematopoietic stem cell transplant, and gene therapy; they then discuss therapeutic strategies that are under translational exploration including assorted antioxidants, agents that inhibit cellular adhesion, and agents that inhibit platelet activation.

That such a spectrum of specific therapeutic strategies, as summarized by Kapoor et al, is currently under examination speaks to the complexity of organ and tissue injury in SCD: namely, SCD involves diverse interdigitating pathogenetic processes that go far beyond RBC sickling itself; indeed, it may be fairly said that SCD involves virtually all major pathogenetic processes implicated in the causation of disease.
salient pathogenetic pathways and offers a perspective on how they may interact and summate in provoking tissue injury in SCD.\textsuperscript{8} Polymerization of HbS, the prelude to RBC sickling, occurs when levels of deoxyHbS attain a certain threshold.\textsuperscript{8} RBC sickling and attendant microvascular stasis lead to two major outcomes. The first is vaso-occlusion. Unremitting vaso-occlusion causes frank tissue infarction, whereas, as is more likely to occur, vaso-occlusion abates and tissue perfusion resumes. In this way, at numerous foci in the microvasculature, SCD continually drives repetitive cycles of ischemia-reperfusion (IR); these cycles of IR are catalytic because IR-triggered processes such as oxidant stress, inflammation, and endothelial dysfunction, among others, all magnify ongoing tissue injury.\textsuperscript{8} Inflammatory responses, occurring locally, can lead to systemic inflammation, which in turn incites more generalized endothelial dysfunction (Figure).\textsuperscript{8,9}

The second major outcome of RBC sickling is hemolysis.\textsuperscript{8,10} Free HbS in plasma binds nitric oxide (NO) with high affinity, thereby depriving the vasculature of its major vasorelaxant anti-inflammatory species. Free HbS is also auto-oxidized and degraded, ultimately giving rise to heme, which is pro-oxidant and proinflammatory and causes endothelial activation and dysfunction, in part through the TLR4 receptor.\textsuperscript{8,10} Hemolysis also releases other damage-associated molecular patterns from RBCs that amplify tissue injury.\textsuperscript{8,10}

Endothelial dysfunction is a vital participant in tissue injury in SCD through diverse adverse consequences (summarized in the Figure), but primarily because endothelial dysfunction in SCD facilitates endothelial adhesion of RBCs and WBCs.\textsuperscript{7,8} Sickle RBCs and reticulocytes are also intrinsically adherent to the endothelium. Such adherence markedly delays the passage of RBCs through the microvasculature such that their duration of transit is considerably longer than the time needed for the sickling process; the inevitable consequence is that RBC sickling (and vaso-occlusion) occur in the microvasculature.\textsuperscript{8}

These considerations underscore the challenges in devising new therapies for SCD, as pointed out by Kapoor et al.\textsuperscript{6} Any recruited pathophysiologic process can instigate others that may not only provide a positive feedback to the proximate trigger, but can also elicit...
more distal and different ones. Additionally, the relative contribution of any given step to the overall pathogenesis of tissue injury may not be fully resolved, as would the potential benefit of inhibiting such steps as a therapeutic strategy. Moreover, any given pathway may be mediated by multiple mechanisms. For example, oxidative stress in SCD may be caused by glutamine deficiency, heme, uncoupling of endothelial NO synthase, nicotinamide adenine dinucleotide phosphate oxidase, up-regulation of other oxidant-generating pathways, and down-regulation of oxidant-scavenging pathways. Similarly, enhanced cellular adhesion of RBCs and WBCs to the endothelium in SCD may be driven by assorted mechanisms resident on each cell as well as systemic processes. Thus, for antioxidant and anti-cell adhesive therapies to be effective in SCD, they should be capable, ideally, of interrupting the critical drivers in either pathway. Critical requirements for effective therapies also include adequate delivery of a putative therapeutic compound to tissues where it is most needed and the assurance that its downstream target is capable of responding. In this regard, as noted by Kapoor et al., strategies employed thus far to deliver NO have been ineffective in SCD, despite the fact that SCD is recognized as a NO-deficiency state. The inefficacy of such therapies may reflect the fact that the requisite elevation in NO concentrations may not be achieved at the needed sites in the vasculature because of rapid binding of delivered NO by HbS or avid consumption by reactive oxygen species, or because the major downstream target for NO, guanylate cyclase, is relatively dysfunctional in SCD.

As discussed by Kapoor et al., mortality has decreased in SCD as acute complications of SCD and infections are more effectively managed. Such success has uncovered chronic organ and tissue injury as a major challenge in the current therapeutic management of patients in SCD. For example, chronic kidney disease (CKD) and pulmonary hypertension are significant contributors to mortality in SCD and both tend to be progressive diseases. As new therapies are introduced to reduce organ-specific complications, such therapies would also contribute to therapeutic advances in SCD. For example, there are persuasive experimental data demonstrating that increased production of endothelin-1 contributes to the complications of SCD and that endothelin-A receptor antagonists retard the progression of CKD in a murine model of CKD. Therapeutic advances in SCD will thus also come from novel therapies designed and utilized for chronic organ-specific complications of SCD.

Of all the therapeutic advances summarized in this review, there is a certain inherent appeal for the definitive therapies for SCD such as stem cell transplant and gene therapies. However, as pointed out by Kapoor et al., these therapies are still very much in their nascency with their own unique challenges and major hurdles. As these challenges are being addressed, the concomitant exploration of diverse strategies that interrupt RBC sickling and other key pathogenetic steps thus provide an important complementary therapeutic approach, especially so should progress in stem cell transplant and gene therapy be delayed or thwarted. Reviewed in their totality, as so comprehensively and thoughtfully done by Kapoor et al., these current, emerging, and anticipated therapies in SCD hold out hope for less morbidity and mortality and an overall improved welfare and quality of life for patients with this once recalcitrant disease.

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