

HISTORY OF MEDICINE

## Sickle Cell Disease — A History of Progress and Peril

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Given the prevalence of sickle cell disease among black Americans, vexing questions of race and stigma have shadowed the history of its medical treatment. Recent developments

in treating pain crises and gene therapy are part of a complex history of slow progress tinged with constant peril.

A century ago, people with sickle cell disease were clinically invisible. Even after James Herrick identified the “peculiar elongated and sickle-shaped red blood cells” associated with the disorder in 1910, it was often and easily misdiagnosed. Vulnerable to infectious diseases in a time when infant mortality ran high, most children would have been diagnosed not with sickle cell disease but with whatever infectious disease was currently prevalent. When Johns Hopkins–trained pathologist Lemuel Diggs began focusing on the disease in the 1920s, the malady was still rarely diagnosed. It was easy to misinterpret the recurrent fever, frequent infections,

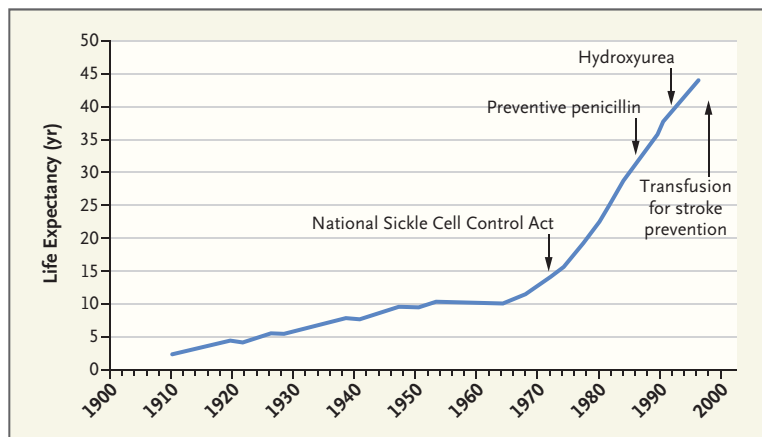
enlarged spleen, and excruciatingly painful episodes as indications of a bout of malaria, which was endemic in the Memphis region where Diggs worked. Through the 1930s, diagnosis remained challenging, and therapy generally consisted of treating the symptoms. As one observer commented in the 1950s, sickle cell disease was “a great masquerader.”<sup>1</sup>

Midway through the 20th century, diagnosis and therapy changed dramatically — first with Linus Pauling’s discovery of hemoglobin’s role in causing red blood cells to sickle, and then, quite separately, with the advent of antibiotics. Pauling’s discovery that a missubstituted amino acid on the complex hemoglobin molecule caused sickling turned the disease from an obscure curiosity into the first “molecular disease.”

The rise of molecular biology as a field owed much to this exemplary disease, and as the new science developed, so did clinical awareness of the painful malady that rendered patients particularly prone to infections. Since hemoglobin caused the disease, dreams of hemoglobin cures followed. As one scientist predicted in 1951, biochemists “may be able to devise a small innocuous molecule which might lock on to the defective hemoglobin and prevent the abnormal molecule from misbehaving.”<sup>2</sup>

In reality, it was not antisickling agents, but antibiotics — an outgrowth of wartime and post-World War II biomedical innovation — that transformed infection management and related mortality in the postwar decades. And when the infections afflicting patients were treated, the underlying disorder came more fully into clinical and social view.

By the 1960s, a new political context gave the disease wider cultural meaning — and height-



Increases in Life Expectancy in Persons with Sickle Cell Disease, 1910–2000.

ened patients' therapeutic expectations. As a disease of pain and suffering that affected black Americans, sickle cell disease became a political symbol — for patients, doctors, politicians, and others seeking recognition, compassion, and equal rights. A 1959 *Time* magazine profile, for example, pictured a young black woman with sickle cell disease pursuing her dream at an integrated college. She was aided by “living on borrowed blood . . . living from crisis to crisis, and being pulled through each time by blood transfusion.”<sup>3</sup> A decade later, campaigns led by black athletes, television programs and movies like *A Warm December* (featuring Sidney Poitier as a physician who loves a woman with the disease), and related Black Panther activism made the disease a widely known civic cause.

Responding to growing social awareness, in 1971 President Richard Nixon called for enhanced funding for diagnosis of sickle cell disease, prevention through genetic counseling, and treatment. Along with the “war on cancer,” Nixon insisted in a “Health Message” that “a second targeted disease for concentrated research should be sickle cell anemia. . . . It is a sad and shameful fact that

the causes of this disease have been largely neglected throughout our history. We cannot rewrite this record of neglect, but we can reverse it.” In 1972, the President signed into law the Sickle Cell Anemia Control Act.

Since that time, many sickle cell interventions have been hailed as breakthroughs; some have delivered on the promise, some have failed to live up to the hope and hype, and others have produced new controversy. The hope that urea would be the desickling agent that molecular biology had long promised collapsed with the recognition of its toxic effects; aggressive counseling of couples with sickle cell trait to avoid having children ran into accusations of racial genocide. Pauling contributed to the controversy by suggesting that “there should be tattooed on the forehead of every young person a symbol showing possession of the sickle-cell gene or whatever other similar gene . . . [because] if this were done, two young people . . . would recognize this situation at first sight, and would refrain from falling in love with one another.”<sup>4</sup> Even Nixon's promise of funding proved divisive when it became clear that without congressional appropriations, the money for the


initiative would have to come from elsewhere in the budget of the National Institutes of Health. One scientist, Alfred Kraus, reflected that cardiovascular disease, which lost funding in the bargain, “never got over it.” An astute editorialist, William Hines, saw the shift as a cynical example of “robbing Peter to pay Paul for Dick's benefit.”

Even as these controversies over therapy, prevention, and funding flared, antibiotics were slowly and dramatically improving the life expectancy of patients with sickle cell disease (see graph). In addition, the advent of Medicaid in the mid-1960s meant that payment for health care services was now in reach for millions of Americans who had previously been unable to afford it; but the program became a flashpoint for battles over containment of costs for the frustratingly chronic childhood malady.

In the past 30 years, no area of sickle cell therapeutics has been more contentious and maddening than pain care, owing to pervasive battles over control of potentially addictive drugs. Amid a national “war on drugs,” relief from the recurring painful crises of sickle cell disease has long depended on supportive, trusting physicians. But medical attitudes toward pain care vary widely. As Kraus, who was based in Memphis, remarked, “Chicago [physicians] may have done it differently from here. I know the Oakland people disagree violently with what we do. They are very strong on management of the crises with pain killers, opiates and what-not. They feel that we under treat. We don't give it; we are too scared.” Diggs had warned in 1968: “Narcotics should be used sparingly in order to avoid addiction.” Therapeutic judgments about sickle

cell pain continue to be shaped by these social considerations.

By the 1980s, it was widely known that people with sickle cell disease seeking pain relief (particularly those seeking care in urban emergency departments) were stigmatized as drug seekers. For patients and their advocates, the reality of therapy was that, as one author commented in *Discover* in 1993, “before you can get past the agony, you have to get a doctor to believe it’s real.”<sup>5</sup> Even more challenging to physicians and nurses is that patients with sickle cell disease often know better than their caregivers what cocktail of agents (meperidine [Demerol], codeine, and other opioids)

 An audio interview with Dr. Wailoo is available at NEJM.org

best relieves their pain during acute episodes. So it was particularly cheering in the 1990s that the drug hydroxyurea sidestepped some of

these battles by significantly reducing the annual number of crises.

Recent findings on the benefits of crizanlizumab and gene therapy (of the type reported by Ribeil et al. in this issue, pages 848–855) are new chapters in this history of therapeutic progress and peril. Patients with sickle cell disease have come a long way from their clinical obscurity 100 years ago. The search for a magic bullet continues, though most clinicians acknowledge that therapies won’t cure the disease but merely enhance long-term management. Even the best therapy is a double-edged sword, presenting new conundrums. While bone marrow transplantation offers a possible cure, it brings the risk of graft-versus-host disease; the peril of gene therapy includes, for example, insertional oncogenesis — curing one disease but producing another. Meanwhile, a pri-

mary challenge for many patients with sickle cell disease remains a social one: being seen and treated as individuals who deserve relief, and being supported rather than stigmatized in a highly charged atmosphere.

Disclosure forms provided by the author are available at NEJM.org.

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## Focusing on High-Cost Patients — The Key to Addressing High Costs?

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Given the rampant waste in the U.S. health care system,<sup>1</sup> evidence that a large proportion of health care spending is concentrated among a small proportion of patients has galvanized a focus on high-cost patients. On the surface, this response may seem sensible: in terms of clinical outcomes, the system fails the highest-need patients the most, and insofar as its failures can be addressed through better care coordination and management, devoting resources to high-risk patients could enhance these efforts’ cost-effectiveness.

If the objective is to reduce wasteful spending, however, that

logic may not hold. For providers participating in payment models rewarding lower spending, such as accountable care organizations (ACOs), interventions focused on specific patients might facilitate spending reductions for patients covered by the models without eroding fee-for-service revenue for other patients. Beyond this appeal, however, viewing the cost problem through a patient-centered lens may not offer clear resolution, for three related reasons. Targeting patients with high spending may not effectively target the spending that should be reduced. Longitudinal patient-specific investments that are im-

portant for coordinating care and improving quality may be less important for curbing wasteful spending. And potentially more effective system changes that reduce wasteful care for all patients have different cost structures that may not require patient targeting to maximize savings.

Thus, a focus on high-cost patients may not only fail to contain health care spending, it may help to entrench the status quo, since targeting specific patients suits existing provider structures developed under fee-for-service incentives.

Setting aside prices, lowering health care spending requires re-