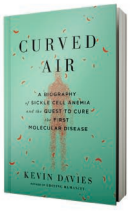
MEDICINE

The history and future of sickle cell disease

Promising new gene therapies have arrived, but it is too soon to claim a medical victory

Adrian Woolfson



Kevin Davies
Belknap Press, 2026. 352 pp.

CURVED AIR | In 1874, the West African physician James Africanus Beale Horton described patients with fever, recurrent pain crises that worsened during the rainy season, and blood abnormalities that today would be recognized as consistent with sickle cell disease (SCD). His observations initiated a journey that moved this disease from clinical description to molecular explanation and, ultimately, genomic intervention.

The distorted red blood cells present in those with SCD clog small blood vessels, reducing oxygen delivery to tissues and precipitating excruciatingly painful vaso-occlusive crises. Oxygen starvation generates a cascade of pathologies, ranging from pneumonia, anemia, and jaundice to avascular necrosis, blindness, strokes, cognitive impairment, end-stage organ damage, and premature death. SCD is more common in certain ethnic groups, including people of African descent. Life expectancy is between 5 years and 50, depending on the availability of medical care.

In his powerful and compelling book *Curved Air*, geneticist Kevin Davies takes readers on a whirlwind, and at times heart-wrenching, tour of the history and nature of SCD, which the American chemist Linus Pauling referred to as "the first molecular disease." Davies uses SCD to illustrate the remarkable successes and limitations of molecular genetic medicine, while providing a rigorous critique of the deeply ingrained prejudices, denial, indifference, stereotyping, ignorance, injustice, and inequality of the American health care system.

In 1949, Pauling and his colleagues transformed SCD from a blood disorder into the first disease understood at the molecular level, tracing its origin to an abnormal β-globin subunit in the oxygen-carrying molecule hemoglobin. The British biochemist Vernon Ingram showed in 1956 that this resulted from a mutation that changes a negatively charged glutamic acid residue into an uncharged valine. This makes sickle hemoglobin polymerize under deoxygenated conditions, distorting red blood cells into their characteristic shape and coaxing them to self-assemble into rodlike fibers.

The book interweaves patient narratives with epidemiology, pathology, genetics, and physiology. Among these are accounts of two young African American women with SCD: Victoria Gray, the first patient to be treated with the CRISPR-Cas9 gene-edited cell therapy Casgevy, and Brittany Hightower, who died from complications of the disease that may, at least partially, have resulted from medical neglect. Their stories are told alongside tales of the US's shameful history of slavery, eugenics, and unethical medical experimentation on African Americans. The ideologies underlying this mistreatment remain endemic, readers learn, and continue to inform and perpetuate institutionalized medical racism throughout the country.

Davies also touches on the social history of SCD, including the interventions made by Black Panther cofounder Bobby Seale and US President Richard Nixon, whose actions increased disease awareness, helped to establish dedicated community clinics, and facilitated home testing. His analyses are contextualized with the psychological traumas, social pathology, and personal tragedies that accompany this complex, relentless, and devastating disease.

Despite their remarkable efficacy, the approved SCD therapies Casgevy, which uses CRISPR-Cas9 to reactivate fetal hemoglobin production, and Lyfgenia, a gene addition therapy that introduces an anti-sickling β-globin variant, are unlikely to be received by more than a small fraction of eligible patients because of their eye-watering price tags ($2.2 million and $3.1 million, respectively). Many SCD patients in the US face poverty, unstable employment, inadequate medical insurance, and barriers to accessing care. In Africa, even the mainstay drug hydroxyurea is barely affordable to many patients.

Curved Air succeeds because it refuses to equate molecular mastery with medical victory. The story of SCD reminds us that scientific breakthroughs alone cannot transform global health care without affordability and social systems to deliver them. □

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