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Sickle Cell Disease: A Review Article on Social Pathology, Social Determinants, and Poverty

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Abstract

Sickle cell disease (SCD) is a complex genetic condition intertwined with social justice issues. Despite continuous medical advancements, addressing the deep-seated disparities and historical inequalities that disproportionately affect marginalized communities is crucial for effective treatment and support. This report explores the historical understanding of SCD pathophysiology, the origins of the sickle cell gene mutation, and its global epidemiology. It delves into the significant socio-economic disparities perpetuated by the disease, particularly through the lens of social pathology and social determinants of health, including the pervasive impact of poverty and systemic racism within healthcare, with a specific focus on the challenges faced by Scheduled Castes and Scheduled Tribes in India due to the caste system. The report also details strategic initiatives, such as India's ambitious National Sickle Cell Elimination Mission, highlighting the global shift towards comprehensive, equitable approaches. It is argued that SCD is not merely a genetic disorder but a "social disease," where societal structures and historical injustices amplify its burden. Effective management and eventual elimination of SCD necessitate a social justice framework that tackles structural inequalities, promotes equitable healthcare access, and empowers affected communities.

Keywords

Sickle Cell Disease, Social Justice, Health Disparities, Systemic Racism, Social Determinants of Health, Caste, Equitable Healthcare, SCD Elimination Mission, Poverty

Introduction

Overview of Sickle Cell Disease (SCD) as a Genetic Condition

Sickle cell disease (SCD) is an inherited red blood cell disorder characterized by abnormal haemoglobin (HbS), which causes red blood cells to adopt a rigid, sickle

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shape. This abnormal morphology leads to premature cell death and the blockage of blood vessels, resulting in severe complications such as intractable pain, heightened susceptibility to infections, acute chest syndrome, and stroke. The condition encompasses a group of genetic disorders arising from the inheritance of the sickle cell gene, either in a homozygous state (HbSS) or as a double heterozygote with another interacting gene, such as HbSC or HbS/beta-thalassemia.

The genetic basis of SCD is remarkably simple, stemming from a single point mutation in the haemoglobin beta (HBB) gene on chromosome 11a, where valine is substituted for glutamic acid in the beta-globin protein. This genetic simplicity allowed SCD to serve as a foundational model for advances in molecular genetics, including the detection of DNA mutations by restriction fragment enzyme analysis and the proof of principle for polymerase chain reaction (PCR). However, this genetic simplicity stands in stark contrast to the disease's complex, multi-organ pathophysiology, which involves chronic inflammation, hypercoagulability, oxidative stress, and nutritional deficiencies. This fundamental disconnect between the straightforward genetic defect and the convoluted biological and social implications highlights why a purely biomedical approach, focused solely on the molecular anomaly, proves insufficient for comprehensive care and effective management of SCD. The disease's impact extends far beyond the cellular level, manifesting as a systemic challenge influenced by a myriad of external factors.

SCD as a Social Justice Issue: Disparities and Historical Inequalities

SCD is profoundly intertwined with social justice issues, with its pervasive impact increasingly recognized as a direct outcome of social disparities, historical inequalities, and systemic discrimination. Despite its discovery in Western medicine over a century ago—with the first known case described in the United States in 1910 by Herrick, and the disease name coined in 1922 by Vernon Mason—SCD has historically received significantly fewer health resources compared to other diseases of similar severity.

This historical underinvestment, particularly when juxtaposed with the substantial research funding allocated to diseases predominantly affecting white populations (e.g. cystic fibrosis, which affects three times fewer Americans but receives approximately ten times more research funding per person), underscores a critical manifestation of systemic racism within the healthcare and research funding ecosystems. The disproportionate impact of SCD on marginalized communities, particularly those experiencing poverty and predominantly individuals of African and Mediterranean descent, is deeply rooted in these historical and systemic inequalities, including discriminatory policies and implicit biases within the medical system. This pattern of neglect has effectively devalued the health and lives of predominantly Black populations affected by SCD, transforming a genetic predisposition into a profound societal disadvantage.

Global and Historical Context of SCD

SCD has existed for generations in families of African and Mediterranean descent. In local African medical literature, around the 1870s, the disease was described with the phrase "ogbanjes," translating to "children who come and go," reflecting the tragically high mortality rate of infants with this condition. One Ghanian family was able to trace the inherited disease back to 1670.

The prevalence of the sickle cell trait is notably high in regions with a history of malaria, reaching as high as 40 per cent in sub-Saharan Africa, eastern Saudi Arabia, and central India. This distribution is explained by the survival advantage conferred by the sickle cell trait against *Plasmodium falciparum* malaria, particularly in early childhood. Scientists realized this protective effect in the 1950s, observing that individuals with the sickle cell trait show decreased parasite counts if they contract malaria. In India, the sickle cell gene is widespread among tribal populations, with carrier frequencies reaching up to 35 per cent in certain tribes, likely due to historical selection pressure from malaria, as the sickle cell trait confers some resistance to the disease.

Regarding the origin of the SCD mutation, two models have been proposed: a multicentric model suggesting four independent genetic mutations (three in Africa, one in Saudi Arabia or central India) occurring 70,000 to 150,000 years ago, and a unicentric model. The most recent and universally adopted evidence supports the unicentric model, positing that the sickle cell mutation originated in a single individual in Western Africa, likely in the rainforest of present-day Cameroon, approximately 7,300 years ago, prior to the eastward and southward African Bantu migration. All five haplotype variations of the SCD gene are present in Cameroon and Egypt, indicating a longer presence in these regions.

The evolutionary advantage of the sickle cell trait in malaria-endemic regions, while a biological adaptation, has created a demographic reality where SCD disproportionately affects populations historically subjected to colonialism, forced migration, and ongoing systemic inequities. The very mechanism that offered a survival advantage in one environment has, through historical injustices and population movements, led to a concentrated burden of a severe genetic disease in marginalized communities across different parts of the world. This historical-biological intersection underscores the deep roots of global health disparities in SCD.

Purpose and Scope of the Article

This article aims to provide a comprehensive exploration of sickle cell disease, moving beyond its biomedical definition to analyze its profound social dimensions. It will examine the historical understanding of SCD pathophysiology, the origins and global spread of the sickle cell gene mutation, and the current epidemiology and prevalence of the disease. A central focus will be on dissecting the significant socio-economic disparities that SCD perpetuates and is, in turn, exacerbated by, with a particular

emphasis on the impact of the caste system in India. The report will detail strategic initiatives designed to address these complex issues, emphasizing that effective SCD management and ultimate elimination necessitate a social justice lens, tackling systemic inequalities and promoting equitable healthcare access for all affected populations.

Methodology

Approach to Literature Review and Data Synthesis

This report employs a systematic approach to synthesize information derived from the provided research material, encompassing medical research, public health reports, and social science literature. The methodology section outlines the process of how the information was gathered and analyzed, providing transparency and ensuring the rigor of the presented findings. Given that this report is a synthesis of pre-selected material rather than an independent literature search, the "search" and "selection criteria" aspects of a typical systematic review are adapted to reflect the scope of the provided data.

The integration of medical and social science data within this report necessitates an interdisciplinary methodological approach. This acknowledges that a purely biomedical lens is insufficient to address the complexities of SCD, which are deeply rooted in societal structures and historical contexts. The approach aims to bridge the gap between clinical understanding and the lived experiences of individuals with SCD, thereby providing a more holistic and actionable perspective on the disease. This deliberate choice of methodology underscores the importance of examining not only the biological aspects of SCD but also the profound influence of social, economic, and political factors on its prevalence, progression, and management.

Criteria for Information Inclusion and Synthesis

Information for this report was drawn directly from the provided research snippets. The primary focus was on identifying data points and narratives related to the core themes of the user query: SCD pathophysiology, its historical context, global epidemiology, the multifaceted impact of social determinants of health (including economic stability, education, healthcare access and quality, neighborhood and built environment, and social and community context), the pervasive nature of systemic racism, current diagnostic and management strategies, and emerging therapeutic advancements.

Priority was consistently given to information that highlighted the intricate intersection of SCD with social justice, poverty, and health disparities. In instances where multiple snippets contained repetitive information, the most comprehensive, authoritative, or detailed source was prioritized to ensure accuracy and depth (e.g. for methodology details for structural racism for management strategies). This selective approach ensured that the narrative was built upon the most robust evidence available within the provided material, allowing for a focused and impactful discussion of the disease's social dimensions.

Framework for Analyzing Social Determinants and Poverty in SCD

The analysis of social determinants of health (SDoH) within this report is guided by the established understanding that these are the "conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks". This framework recognizes that SDoH are "upstream" factors, meaning they are fundamental societal conditions that precede and profoundly influence individual health outcomes.

The five domains of SDoH, as defined by Healthy People 2030, serve as a structured framework for organizing the discussion on how poverty and broader social factors impact SCD. By explicitly adopting this recognized SDoH framework, the report moves beyond anecdotal observations to provide a structured, evidence-based analysis of how societal factors systematically influence SCD outcomes. This legitimizes the social justice argument within a public health context, demonstrating that simply promoting healthy individual choices is insufficient to eliminate health disparities in SCD. Instead, it underscores the necessity of addressing the underlying systemic conditions that create and perpetuate health inequities. This approach fundamentally reframes SCD as a public health and social policy challenge, not solely a medical one.

Socio-Pathology of Sickle Cell Disease

Systemic Racism and Discrimination in SCD Healthcare

Systemic racism, also referred to as societal or structural racism, represents a pervasive set of institutional, cultural, and historical systems that inherently grant white individuals greater access to healthcare, education, and wealth. Given that the majority of people with SCD in the United States are Black, their healthcare experiences and overall quality of life are directly and profoundly affected by these ingrained racial inequalities. Black Americans, along with other racial and ethnic minorities such as Hispanic Americans, consistently receive poorer quality care and face greater barriers to accessing routine medical services compared to White Americans. This disparity directly contributes to worse medical outcomes and higher mortality rates within these marginalized groups. For instance, Black infants experience mortality rates two to three times higher than other racial groups.

In India, the caste system functions as a deeply entrenched form of systemic discrimination, officially recognizing the Dalit community as 'Scheduled Castes' and Adivasis as 'Scheduled Tribes', while simultaneously perpetuating widespread bias despite constitutional bans on caste-based discrimination. These communities, constituting about 25 per cent of India's population, have historically faced systemic exclusion from basic services, including healthcare, education, and land access. This persistent structural poverty and deprivation manifests in all aspects of their lives,

leading to significantly poorer health outcomes and lower healthcare utilization compared to higher caste groups.

Implicit racial bias among healthcare professionals significantly influences treatment decisions. Studies have shown that healthcare professionals are less likely to diagnose coronary heart disease with certainty among Black patients and are less inclined to prescribe narcotic medications to Black patients as their pro-White bias increases. Similarly, in India, Dalits and Adivasis face overt discrimination in healthcare settings. Studies reveal that healthcare workers, once aware of a patient's caste status, may provide less information about health services, refuse entry into private health centers, exhibit indifference, or even refuse to touch patients to understand their condition. This persistent disparity in healthcare quality for SCD patients, despite ongoing medical advancements, reveals that the healthcare system itself is a perpetuator of health inequities. Implicit bias and systemic racism/casteism act as insidious "social pathogens" that compound the biological burden of SCD. The system is not merely flawed; it is inherently structured in ways that lead to a lower standard of care for an entire patient population based on race or caste. This means that prejudice and stigma associated with SCD are, in effect, shortening the lives of those with the disease faster than the disease's biological mechanisms alone.

Patient Experiences: Bias, Mistrust, and Inadequate Pain Management

Patients living with SCD frequently report experiencing profound stigmatization within healthcare settings, often being labeled as drug-seeking or drug addicts, and consistently having their severe pain discredited. Anecdotal accounts from the SCD community vividly describe the struggle to convince medical staff of their pain's reality, encountering negligent doctors, enduring slow emergency department services, and facing a pervasive lack of knowledgeable healthcare professionals. Research substantiates these experiences, indicating that Black patients with SCD experience 25 per cent longer wait times to see a physician in emergency departments compared to the general patient population.

In India, Dalits and Adivasis face similar, if not more severe, forms of discrimination. They experience longer waiting times in private facilities, and doctors may refuse treatment based on the mistaken assumption that they cannot afford care. Reports indicate that 94 per cent of Dalit children surveyed faced discrimination in the form of touch, dispensing of medicines (91 per cent), and conduct of pathological tests (87 per cent), with 81 per cent not being given as much time as other children. These repeated experiences of discrimination foster deep medical mistrust among SCD patients, which, in turn, is directly linked to reduced engagement in preventative care, poorer disease management, and lower adherence to prescribed treatments. Consequently, many adults with SCD express a reluctance to seek healthcare services, often delaying care until it becomes a last resort, due to the anticipated racism and discrimination they expect to encounter. This pervasive discrimination and medical mistrust create a vicious cycle: patients avoid necessary proactive care, leading to an exacerbation of their condition and an increased reliance on emergency services

for acute crises. This pattern highlights a systemic failure to provide empathetic and effective care, transforming the healthcare system into a source of additional suffering and poor health outcomes for individuals with SCD.

Impact of Stigma and "Invisibility" on SCD Outcomes

Sickle cell disease is frequently described as an "enduring—and often invisible—condition". This inherent invisibility, coupled with widespread societal stigma and misconceptions about the disease, extends its detrimental impact far beyond clinical symptoms and healthcare interactions, profoundly affecting patients' social integration, educational attainment, and overall quality of life. Misconceptions within the general public can lead to social isolation for individuals with SCD, making it difficult for them to form and maintain friendships and romantic relationships.

Furthermore, the disease significantly hinders academic progress for adolescents. Studies show that 60 per cent of adolescents with SCD report that the disease interferes with their school performance, and 40 per cent report being retained at least one grade level, compared to a national average of 24 per cent. In India, historical caste divisions persist in the education sector, influencing unequal access, biased treatment, and limited representation for marginalized groups. Dalits and Adivasis have historically been denied access to education, leading to significant educational gaps. Students from these backgrounds often endure social stigma and discrimination within educational settings, negatively impacting their learning experiences and psychological well-being. This "invisibility" of SCD contributes to a lack of public awareness and empathy, which can translate into lower policy prioritization and resource allocation for the disease. Simultaneously, the direct stigma impacts patients' social well-being and limits their life opportunities, collectively demonstrating a broader societal pathology that compounds the challenges of living with SCD.

Historical Neglect in Research Funding and Resource Allocation

Despite being documented over a century ago and recognized as the most common genetic disorder globally, SCD has historically suffered from a severe lack of research funding, significantly impeding the development of new and effective treatments. Until 2017, only one disease-modifying treatment was available for SCD. This stands in stark contrast to cystic fibrosis, an inherited disease that affects three times fewer Americans but has historically received approximately ten times as much research funding per person, resulting in 15 approved drugs.

This profound disparity in research funding is directly attributable to structural racism. Funding agencies and pharmaceutical companies have historically not prioritized SCD research, potentially due to perceptions of lower profitability given the disease's prevalence primarily within marginalized communities, and also due to challenges such as low enrollment in SCD clinical trials. This historical underfunding, when juxtaposed with the disproportionate investment in diseases affecting predominantly white populations, exposes a deep-seated economic and racial bias within the scientific and pharmaceutical industries. This bias transforms a genetic

predisposition into a systemic disadvantage, as reduced investment translates directly into slower drug development, fewer therapeutic options, and ultimately, poorer health outcomes and reduced life expectancy for individuals with SCD.

Poverty and Social Determinants of Health in SCD

Defining Social Determinants of Health (SDoH) and their Relevance to SCD

Social Determinants of Health (SDoH) are fundamental conditions within the environments where individuals are born, live, learn, work, play, worship, and age, which collectively influence a broad spectrum of health, functioning, and quality-of-life outcomes and risks. These "upstream" factors are critical drivers of wide health disparities and inequities, indicating that simply promoting healthy individual choices is insufficient to eliminate these disparities. Instead, addressing SDoH necessitates systemic action to improve the fundamental conditions in people's environments.

SCD disproportionately affects marginalized communities, particularly those experiencing poverty, making SDoH a critical lens through which to understand and address the disease. In India, SCD is particularly prevalent among socioeconomically disadvantaged Scheduled Caste (SC) and Scheduled Tribe (ST) populations, who constitute about 25 per cent of the country's population. The acknowledgment that SDoH are foundational societal factors and that individual-level interventions alone cannot resolve health disparities represents a crucial shift from individual blame to systemic responsibility. This fundamentally reframes SCD as a public health and social policy challenge, rather than solely a medical one. It implies that even with optimal medical care, if the underlying social and economic barriers are not addressed, individuals with SCD will continue to face significant obstacles to achieving optimal health.

Economic Instability and its Impact on SCD Morbidity and Mortality

Economic instability significantly exacerbates the burden of SCD. Youth diagnosed with SCD who live below the poverty line face an increased risk for morbidity, mortality, and substantial financial burden. The average total healthcare costs for individuals with SCD can reach $1 million by age 45, with annual costs averaging around $10,000 for children and $30,000 for adults. This immense financial strain, coupled with pre-existing economic instability, creates a detrimental cycle of poverty and poor health outcomes.

In India, caste discrimination contributes to deep poverty, with approximately one in three Dalits living in multidimensional poverty (monetary, education, and basic infrastructure). This limits their access to even public hospitals due to widespread under-the-table corruption and out-of-pocket costs, which are unaffordable for those living on less than three dollars a day. Dalits and Adivasis have the lowest healthcare utilization and outcome percentages, and their life expectancy is significantly lower at 63.0 and 64.0 years, respectively, compared to the general population. Financial

constraints in economically disadvantaged neighborhoods often compel families with SCD to reside in substandard housing and rely on low-quality childcare settings, which further increases their social, clinical, and nutritional vulnerabilities. The protective effect of economic support is evident in studies showing that Medicaid receipt among youth with chronic illnesses, including SCD, is associated with an increased frequency of well-child visits and a decrease in emergency room (ER) and inpatient visits. This indicates that economic support can directly mitigate negative health outcomes, highlighting policy-level interventions as crucial for improving the lives of SCD patients. The disease not only causes financial hardship but also limits opportunities for economic advancement, thereby trapping families in a disadvantaged state.

Education Access and Quality: Influence on Health Literacy and Management

Education, particularly parental education, serves as a significant protective social determinant against adverse health outcomes in SCD. Research indicates that children with SCD residing in households where an adult holds at least one bachelor's degree are 33 per cent less likely to experience acute care utilization (ACU) and hospitalizations. This suggests that higher parental education levels are associated with improved health literacy, enhanced advocacy skills, and greater access to resources, all of which can profoundly mitigate the negative health impacts of SCD, even when other social determinants present challenges.

Conversely, the disease itself can impede educational attainment. Academic progress for adolescents with SCD is often hindered by frequent disease-related school absences. For example, 60 per cent of adolescents surveyed reported that SCD interfered with their school performance, and 40 per cent stated they had been retained at least one grade level. In India, the education sector is deeply affected by caste discrimination, leading to unequal access, biased treatment, and limited representation for marginalized groups. Historically, Dalits and Adivasis were denied access to education, resulting in significant educational gaps. Despite legal protections and affirmative action policies, lower caste applicants often face discrimination in admission processes and experience lower acceptance rates in colleges, even with similar academic qualifications. This illustrates that education is not merely about knowledge acquisition; it is a critical proxy for broader socioeconomic stability and the ability to navigate complex healthcare systems. Therefore, interventions that focus on educational support for families and patients could yield significant downstream health benefits, extending beyond purely medical treatment.

Neighbourhood and Built Environment: Food Deserts and Transportation Barriers

The characteristics of an individual's neighborhood and built environment directly influence health outcomes for SCD patients. Preschool-aged children with SCD who live in food deserts—areas with limited access to affordable and nutritious food—and have limited access to transportation face a significantly greater risk for acute

complications and hospitalizations. Specifically, living more than one mile from a supermarket was associated with a 44 per cent increase in hospitalizations and a 37 per cent increase in acute care utilization among young children with SCD. The risk is further compounded when living more than a mile from a grocery store *and* without a vehicle, which is linked to a significantly higher likelihood of hospitalization.

In India, Dalits historically lived on the outskirts of villages, working as bonded laborers and lacking access to basic amenities like water and land. This historical marginalization contributes to the current mismatch between where health facilities are located (predominantly urban) and where Dalits and Adivasis live (nearly 90 per cent in rural settings), creating fundamental barriers to healthcare access. Their geographic isolation further exacerbates these challenges, along with internal communication barriers. Food insecurity and housing instability are highly prevalent in the under-resourced communities where children with SCD often reside, and these conditions are directly associated with poorer diet quality, characterized by higher intake of dairy and pizza and lower intake of whole grains. Adequate nutrition is known to influence the pathophysiology of SCD, and undernourished individuals are more likely to experience impaired immune function and disease exacerbation. These geographic and environmental disadvantages are not mere inconveniences; they create a direct pathway to worsened SCD outcomes, demonstrating how systemic urban planning failures and resource allocation inequities become clinical barriers, irrespective of medical advancements or individual efforts. Addressing SCD effectively thus requires interventions in urban planning, infrastructure development, and food policy, extending far beyond the traditional medical domain.

Healthcare Access and Quality Disparities for Marginalized Communities

Healthcare access and quality are critical social determinants that disproportionately affect marginalized communities with SCD. The healthcare system itself is influenced by structural racism, which contributes to a notable shortage of doctors with expertise in treating SCD; only 20 per cent of family doctors report feeling comfortable managing the disease. This lack of specialized knowledge often prevents patients from receiving routine, preventative care, consequently pushing them towards emergency rooms for crisis management.

In India, Dalits and Adivasis face direct discrimination in the private healthcare system, including disparity in care, denial of entry into private clinics, and longer waiting times. They are less likely to receive maternal healthcare and to give birth at hospitals or be assisted by a health professional during delivery, even when controlling for other factors like age and education. Only 4 per cent of Adivasi and 15 per cent of Dalits utilize private facilities, largely due to the unaffordable out-of-pocket expenditure, which is 524 per cent higher than in public facilities. Health insurance schemes like PMJAY have also failed to adequately cover these communities, with only a small fraction of private hospital admissions under the scheme coming from Dalits and Adivasis compared to their eligible population share. During the COVID-19 pandemic, these groups faced greater difficulty in securing healthcare,

with reports of villages not allowing SC families access to public health centers and a lack of connections to arrange transportation, oxygen, or beds in private hospitals. This confluence of provider discomfort, insurance-based access barriers, and a lack of specialized support creates a fragmented and inequitable healthcare landscape for SCD patients. The burden of navigating this dysfunctional system falls disproportionately on already vulnerable individuals, leading to higher utilization of acute care services (emergency department visits and hospitalizations) due to insufficient preventative and specialized outpatient care. This results in a less efficient and more costly healthcare system overall.

Addressing Social Determinants and Systemic Inequalities in SCD Care

Adopting a Social Justice Lens for SCD Interventions

Effectively addressing SCD necessitates a fundamental shift towards a social justice lens, one that explicitly recognizes the profound impact of social determinants of health and actively confronts structural inequalities. This approach moves beyond a purely biomedical focus, which, while vital, is insufficient to resolve the deep-seated issues surrounding SCD. It implies a fundamental reorientation of public health efforts, shifting the emphasis from individual patient management to systemic societal reform as a core component of disease control and eventual elimination.

This social justice framework includes advocating for equitable access to healthcare for all, actively challenging the pervasive stigma and discrimination faced by SCD patients, and promoting comprehensive policies that address the root causes of health disparities. Furthermore, effective interventions for SCD demand a community-based approach that empowers communities to actively participate in developing and implementing solutions. An intersectional approach is also crucial, acknowledging how multiple forms of social inequality—such as race, class, and gender—intersect to shape the unique experiences and outcomes of individuals living with SCD. This paradigm shift is not merely a recommendation; it is a necessary evolution in how SCD is understood and managed, recognizing that medical advancements alone cannot overcome the barriers imposed by societal inequities.

Community-Based Solutions and Empowerment Strategies

Community-based solutions and empowerment strategies are critical for building trust and ensuring culturally competent care, especially given the historical medical mistrust and systemic discrimination experienced by SCD patients. Effective interventions for SCD require a community-based approach that actively involves addressing social determinants of health and empowering affected communities to participate in the design and implementation of solutions.

Examples of this approach are evident in initiatives like India's National Sickle Cell Elimination Mission (NSCEM), where community-level work includes screening

activities conducted by Community Health Officers (CHOs) and the establishment of patient support group meetings. These efforts are vital for fostering self-advocacy and ensuring that interventions are tailored to the lived realities of the affected populations, thereby counteracting the historical disempowerment they have faced. The advocacy efforts of pioneers like Dr. Charles F. Whitten in the early 1970s, which contributed to the foundation of the Sickle Cell Disease Association of America (SCDAA), further underscore the transformative power of community organization and patient advocacy in shaping healthcare priorities and improving access to care. Such initiatives are not just about service delivery; they are about rebuilding relationships, fostering resilience, and ensuring that the voices of those most affected are central to the solutions.

Policy Recommendations and Strategic Initiatives

The global landscape for SCD care is witnessing a significant shift towards comprehensive, system-level elimination efforts, marked by the emergence of ambitious national and international strategic plans.

India's National Sickle Cell Elimination Mission (NSCEM) 2047: This mission embodies a proactive approach to addressing SCD as a public health problem. Its overarching vision is to eliminate SCD in India before 2047. The strategy is built upon three core pillars:

1. *Health Promotion:* This includes widespread awareness generation and pre-marital genetic counseling to inform potential carriers.
2. *Prevention:* Universal screening and early detection are key components, targeting a broad population from birth up to 40 years of age, with an initial focus on tribal and high-prevalence areas. The mission specifically prioritizes 17 high-prevalence states, including those with significant Scheduled Caste and Scheduled Tribe populations, recognizing their disproportionate burden of the disease.
3. *Holistic Management & Continuum of Care:* This pillar focuses on providing comprehensive treatment at primary, secondary, and tertiary healthcare levels, establishing robust patient support systems, and promoting community adoption of prevention and management practices.

The NSCEM aims to screen approximately 7 crore (70 million) people, provide counseling for prevention, and ensure care for individuals with SCD within a three-and-a-half-year period (2023-2026) across 17 high-focus states. Key operational components include capacity-building initiatives for healthcare providers, establishing diagnostic facilities at the district level, developing mobile applications for data collection and patient follow-up, ensuring the availability of essential drugs, and creating standardized treatment protocols, alongside nutritional services. Policy elements central to NSCEM's success involve establishing national registries for surveillance, fostering research, engaging in political advocacy, implementing government insurance schemes for patients, and ensuring multi-stakeholder involvement. Anticipated outcomes include improved functionality of screening,

diagnosis, and treatment facilities, better access to medicines, increased community awareness, provision of nutritional services, improved quality of life for patients, reduced school dropouts, increased blood availability, and a decrease in SCD-related deaths. The mission aims to combine national policy with community-driven efforts to eliminate SCA as a public health issue by 2047, improving the lives of millions in its most marginalized communities.

Sickle in Africa Consortium: This collaborative initiative, comprising eight African countries, leverages a robust infrastructure to advance SCD research and care across the continent. It has established the largest global SCD database and patient registry, currently enrolling over 34,000 patients, which includes detailed demographic, clinical, and management information. SickleInAfrica has also contextually adapted clinical guidelines for managing SCD across all levels of care, used by providers at their facilities. The consortium actively engages in high-level advocacy through platforms like the 77th UN General Assembly and the US-Africa Leaders' Summit, promoting awareness, fostering partnerships, and influencing policy. Their focus spans biomedical science to enhance an understanding of SCD in African patients, implementation research to improve delivery of life-saving interventions (e.g. newborn screening, community mobilization), and partnerships for therapeutic development, including gene therapy. The consortium emphasizes the critical need for bilateral and multilateral partners across the entire chain of SCD comprehensive care, from newborn screening to curative therapies.

The emergence of these national and international strategic plans signals a growing global recognition of SCD as a public health priority, marking a significant shift from reactive clinical management to proactive, comprehensive, and system-level elimination efforts. However, the ultimate success of these plans hinges on their ability to overcome the very social determinants and systemic biases they aim to address. The challenge lies not just in the blueprint but in the effective implementation, particularly in resource-constrained settings and against deeply entrenched systemic racism/casteism. These plans serve as crucial frameworks for *how* to address SDoH and disparities, and their effectiveness will be the true measure of whether policy can successfully overcome ingrained social pathology.

Role of Advocacy and Intersectoral Collaboration

Advocacy plays a pivotal role in driving change for SCD patients. The advocacy efforts of individuals like Dr. Charles F. Whitten were instrumental in the early 1970s, contributing to the foundation of the Sickle Cell Disease Association of America (SCDAA). Today, individuals are encouraged to support or join groups that actively advocate and fight for equity in healthcare for SCD patients.

The complexity of SCD necessitates broad intersectoral collaboration. Partnerships across governmental, public health, academic, non-profit, and private organizations are essential to secure political will, pool resources, gather expertise with an understanding of local contexts, and allow for the integration of comprehensive care into all levels of existing local healthcare structures and the wider society. The

SickleInAfrica consortium, for instance, exemplifies this by fostering cross-border dialogues and emphasizing the need for robust partnerships from grassroots to global alliances to increase awareness, promote policy advocacy, and establish SCD Centers of Excellence and genomics capacity-building initiatives. In India, advancing tribal health requires a foundational shift towards evidence-based governance, prioritizing the collection and analysis of health data disaggregated by ethnicity, and strengthening institutional capacities to address specific health issues of tribal populations. Furthermore, the involvement of indigenous communities in the planning, delivery, and monitoring of health services is crucial to build trust and ensure culturally appropriate interventions. Such collaborative efforts are vital for developing and implementing sustainable solutions that address the multifaceted challenges of SCD.

Management and Diagnostic of SCD

Historical Context of Pathophysiology Discoveries

The understanding of SCD pathophysiology has evolved significantly over the past century. In 1927, Hahn and Gillespie made the groundbreaking discovery that red blood cells sickled upon the removal of oxygen in a carbon dioxide-saturated cell suspension. They further observed that this sickling characteristic could occur in the absence of the full disease, noting that patients with SCD had relatives who exhibited the sickling characteristic without having the disease themselves; this phenomenon was later identified as "sickle trait".

Further advancements in the late 1940s and early 1950s clarified the inheritance pattern of SCD. In 1949, two independent publications described its autosomal recessive mode of inheritance: one by Col. E. A. Beet in an African medical journal, and another by Dr. James V. Neel in the American journal *Science*. These physicians detailed how individuals with "sickle trait" were heterozygous carriers of the gene variant, possessing one normal gene and one variant gene without manifesting the disease, while the disease itself appeared in individuals with two copies of the variant gene. A pivotal moment occurred in 1951 when Dr. Linus Pauling and Dr. Harvey Itano discovered the differing chemical structure of oxygen-carrying haemoglobin in the red blood cells of individuals with SCD. This landmark discovery established SCD as the first identified disease caused by dysfunctional proteins dueining to their abnormal molecular structure. In 1956, Dr. Vernon Ingram further detailed the exact structural alteration in the haemoglobin protein, identifying the substitution of valine for glutamic acid at the sixth amino acid position in beta globin.

Current Understanding of Pathophysiology

Beyond simple vascular blockage, SCD is now understood as a complex condition involving a cascade of physiological abnormalities. These include chronic inflammation, a hypercoagulable state, pervasive oxidative stress, and nutritional deficiencies. Oxidative stress plays a particularly significant role, characterized by an excessive production of reactive oxygen species (ROS) due to mechanisms such as

HbS autooxidation, NADPH activation, and elevated mitochondrial retention, coupled with impaired antioxidant activity. This imbalance leads to structural defects in red blood cell membranes.

Furthermore, hemolytic processes, which result in the release of cell-free haemoglobin into the plasma, contribute to ROS generation and initiate lipid peroxidation. Ischemia-reperfusion events, triggered by vaso-occlusive crises, also contribute to oxidative stress. Excessive ROS generation and ROS-dependent signaling significantly contribute to functional alterations in other crucial cell types. For instance, cell-free heme induces neutrophil activation and upregulates cell adhesion, while excessive mitochondrial ROS generation in platelets is associated with increased thrombus formation. Oxidative stress also contributes to endothelial cell dysfunction and activation, leading to the production of inflammatory molecules and adhesion molecules that recruit leukocytes and red blood cells to vessel walls, thereby driving vaso-occlusive processes. Reduced activity of antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT) is observed in SCD patients, correlating with increased oxidative markers and contributing to complications such as pulmonary hypertension and chronic lung disease.

Diagnostic Techniques

Early and accurate diagnosis of SCD is crucial for timely intervention and improved outcomes. Several diagnostic techniques are employed across different stages of life:

Prenatal Diagnosis: SCD can be diagnosed before birth, as early as 8 to 10 weeks into pregnancy, through prenatal screening. Two primary methods are utilized:

- *Amniocentesis:* Typically performed between 16 and 18 weeks of pregnancy, this outpatient procedure involves inserting a needle into the womb to obtain a small sample of amniotic fluid, which contains fetal cells. These cells are then grown in a laboratory for genetic testing to detect the sickle cell gene or other chromosomal abnormalities.

- *Chorionic Villus Sampling (CVS):* Performed earlier, around week 9 or 10 of pregnancy, CVS involves taking a small amount of material from the developing placenta. The placental cells are genetically identical to the baby's and can reveal the same types of genetic disorders as amniocentesis. While CVS carries a slightly higher risk of miscarriage than amniocentesis, it offers the advantage of earlier results. Both techniques can be used to test for the specific type of haemoglobin the baby has, with CVS often preferred for its ability to collect more cells.

Newborn Screening: All 50 states in the United States, along with many other countries, have universal newborn screening programs for SCD. This involves a heel prick to collect drops of blood on a special card, which are then tested for various treatable conditions, including SCD. Common laboratory methods used include high-performance liquid chromatography, capillary electrophoresis, and isoelectric

focusing. If initial results indicate the possibility of SCD or sickle cell trait, a special follow-up team contacts the parents for retesting to confirm the diagnosis, and genetic counseling is offered. This early identification is vital for initiating preventative care and significantly reducing early childhood mortality from infections.

Blood and Genetic Tests: For individuals who do not know their sickle cell status or for confirmation of newborn screening results, blood tests can determine the presence and quantity of haemoglobin S protein. Genetic testing can ascertain whether an individual carries one or two copies of the sickle cell gene and can also identify other abnormal haemoglobin types, such as those causing thalassemia, which may coexist with the sickle cell gene. Genetic tests are particularly useful for confirming a diagnosis when blood test results are inconclusive.

Current Management Strategies

The management of SCD focuses on preventing and treating pain episodes and other complications, aiming to improve quality of life and extend lifespan.

General Prevention Strategies: Lifestyle behaviors play a significant role in preventing complications. Patients are advised to drink plenty of water, avoid extreme temperatures, and limit exposure to high altitudes or low oxygen levels (e.g. during unpressurized flights or strenuous exercise). Infection prevention is paramount, emphasizing frequent handwashing, safe food preparation, and ensuring up-to-date vaccinations, including annual flu and pneumococcal vaccines. Young children with HbSS (the most common form of SCD) are prescribed daily penicillin until at least 5 years of age to greatly reduce infection risk.

Pain Crisis Management: Acute pain crises, often the hallmark of SCD, require prompt and effective management. Clinical management typically involves intravenous fluids and pain-reducing medications, with hospitalization necessary for severe crises. Optimal management necessitates a multidisciplinary team, including haematologists, nurses, pain specialists, and social workers, to provide empathetic, consistent, and continuous care. Pain assessment tools, such as visual analog scales, are used to quantify intensity. Mild pain can often be managed at home with oral fluids and non-narcotic analgesics like acetaminophen or NSAIDs. Moderate to severe pain requires opioid analgesics, with parenteral morphine being the treatment of choice due to its effectiveness and the neurotoxic risks associated with meperidine. Patient-controlled analgesia (PCA) is often utilized to prevent fluctuations in drug levels and empower patients in their pain management. Adjuvant agents like antihistamines and antiemetics, along with non-pharmacologic techniques such as physical therapy, heat application, and cognitive-behavioral therapies, also contribute to pain relief. Oxygen therapy is administered only if hypoxemia is present.

Complication Prevention: Regular medical screenings and interventions are crucial. Yearly eye doctor visits are recommended starting at age 10 to check for retinal damage and prevent vision loss. Transcranial Doppler (TCD) ultrasound identifies children at risk for stroke, with frequent blood transfusions recommended to prevent stroke if TCD is abnormal. Blood transfusions are also used to treat severe anemia,

particularly sudden worsening due to infection or spleen enlargement. However, frequent transfusions can lead to iron overload, necessitating iron chelation therapy to prevent life-threatening organ damage.

Disease-Modifying Medications: Several medications are approved to prevent or reduce pain crises and other SCD complications. Hydroxyurea increases fetal haemoglobin production, reducing sickling and disease severity. L-glutamine (ENDARI®) reduces oxidative injury to red blood cells and lowers pain crisis incidence. Crizanlizumab (ADAKVEO®), a monoclonal antibody, reduces cellular adhesion within vasculature, leading to significant reductions in pain episodes and hospitalizations. It is important to note that voxelotor (Oxbryta) was voluntarily withdrawn from the market in September 2024 as its benefits did not outweigh the risks for the approved SCD population.

Emerging and Curative Therapies

The landscape of SCD treatment is rapidly evolving, with significant advancements in curative and disease-modifying therapies.

Bone Marrow Transplant (BMT): Historically, bone marrow transplant has been the only potential cure for SCD. This procedure involves replacing the patient's diseased bone marrow with healthy blood-forming stem cells from a donor who does not have SCD. The new bone marrow then produces healthy red blood cells without abnormal haemoglobin S. A close match, usually a sibling, is required for this procedure, and it is most commonly performed in severe SCD cases for children with minimal organ damage. While effective, BMT is limited by the availability of suitable donors and the risks associated with the procedure.

Gene Therapies: Gene therapy has emerged as a transformative and potentially curative approach for SCD, particularly for patients who lack a matched sibling donor. In a historic move in December 2023, the U.S. Food and Drug Administration (FDA) approved two cell-based gene therapies for the treatment of SCD in patients aged 12 years and older:

- *Casgevy™ (exagamglogene autotemcel):* Developed by CRISPR Therapeutics and Vertex Pharmaceuticals, Casgevy is the first FDA-approved therapy in the U.S. that utilizes CRISPR-Cas9 gene-editing technology. This *ex vivo* autologous therapy involves collecting a patient's own hematopoietic stem cells, which are then genetically modified outside the body using CRISPR to produce high levels of fetal hemoglobin (HbF). The modified cells are subsequently re-infused into the patient after high-dose chemotherapy to remove existing bone marrow cells. The increase in HbF replaces the mutated adult hemoglobin, alleviating disease symptoms. Clinical trials have shown promising results, with 93.5% of evaluated patients achieving freedom from severe vaso-occlusive crisis episodes for at least 12 consecutive months.

- *Lyfgenia™ (lovotibeglogene autotemcel):* Developed by Bluebird Bio, Lyfgenia utilizes a lentiviral vector for genetic modification. In this therapy,

> the patient's blood stem cells are genetically modified to produce HbAT87Q, a gene-therapy-derived hemoglobin that functions similarly to normal adult hemoglobin (hemoglobin A). Red blood cells containing HbAT87Q have a lower risk of sickling and occluding blood flow. Like Casgevy, this is a one-time, single-dose infusion of the patient's own modified stem cells after chemotherapy. In clinical studies, 88 per cent of patients achieved complete resolution of vaso-occlusive events.

These gene therapies represent a significant leap forward, offering the potential for a functional cure and sustained therapeutic benefit, including transfusion independence, for many patients. However, challenges remain, including the need for refined delivery methods and addressing potential oncogenic risks. Research continues to explore in vivo gene therapy approaches, which would involve direct delivery of gene-editing components to the patient, and to identify multiple gene targets that could address issues beyond sickling, such as chronic inflammation and cellular adhesion.

Discussion

Sickle cell disease, at its core, is a genetic disorder, yet the evidence overwhelmingly demonstrates that its burden is profoundly amplified by social pathology, particularly poverty and systemic inequalities. The historical trajectory of SCD research and care reveals a consistent pattern of neglect, directly linked to the racial demographics of the affected population. The underfunding of SCD research, starkly contrasted with investments in diseases affecting predominantly white populations, exposes a deep-seated economic and racial bias within the scientific and pharmaceutical industries. This bias has transformed a genetic predisposition into a systemic disadvantage, limiting treatment options and exacerbating suffering.

The healthcare system itself acts as a significant perpetuator of health inequities. Systemic racism and implicit biases among healthcare professionals lead to poorer care, delayed treatment, and inadequate pain management for SCD patients, particularly Black Americans. In India, the pervasive caste system further compounds these issues, with Dalits and Adivasis facing overt discrimination, refusal of care, longer waiting times, and a general indifference from healthcare providers. These experiences foster deep medical mistrust, creating a vicious cycle where patients avoid necessary preventative care, leading to worsened outcomes and an increased reliance on emergency services. This fragmentation of care, coupled with a lack of specialized expertise and support roles, underscores a dysfunctional system that disproportionately burdens vulnerable individuals.

Furthermore, the influence of social determinants of health extends beyond direct healthcare interactions. Economic instability, limited access to quality education, and adverse neighborhood conditions—such as food deserts and inadequate transportation—directly contribute to increased morbidity, mortality, and acute care utilization among SCD patients. In India, caste-based poverty limits access to even public hospitals, and historical marginalization has resulted in a mismatch between

healthcare infrastructure and the rural populations of Dalits and Adivasis. These factors highlight how systemic failures in urban planning, resource allocation, and social support become critical clinical barriers, regardless of medical advancements. The "invisibility" of SCD and societal misconceptions further compound these challenges, leading to social isolation and hindering educational attainment, thereby impacting overall quality of life.

However, the landscape is shifting. The emergence of national and international strategic plans, such as India's National Sickle Cell Elimination Mission and the SickleInAfrica Consortium, signals a growing global recognition of SCD as a public health priority. These initiatives represent a crucial move from reactive clinical management to proactive, comprehensive, and system-level elimination efforts. They emphasize health promotion, universal screening, holistic management, and the critical role of intersectoral collaboration and patient advocacy. The recent FDA approvals of groundbreaking gene therapies like Casgevy and Lyfgenia offer unprecedented hope for curative options, representing a significant scientific triumph.

Despite these medical breakthroughs, the success of these strategic plans and the equitable deployment of new therapies hinge on overcoming the very social determinants and systemic biases they aim to address. The challenge lies not just in the scientific innovation but in ensuring equitable access, dismantling structural barriers, and fostering an environment where social justice is integral to healthcare delivery

Conclusion

Sickle cell disease stands as a stark example of a condition where biological complexity is profoundly magnified by deeply entrenched social pathology. While significant strides have been made in understanding its pathophysiology and developing advanced treatments, including transformative gene therapies, the pervasive impact of poverty, systemic racism, and adverse social determinants of health continues to disproportionately burden affected communities. The historical neglect of SCD research and the ongoing disparities in healthcare access and quality underscore that the disease's trajectory is not solely determined by genetics but by societal structures and historical injustices.

Effective SCD management and the ambitious goal of its elimination necessitate a holistic approach that transcends traditional biomedical interventions. It requires a fundamental reorientation of public health efforts towards a social justice framework, prioritizing equitable access to care, challenging discrimination (including caste-based discrimination in India), and addressing the root causes of health disparities. The strategic initiatives emerging globally, such as India's National Sickle Cell Elimination Mission and the SickleInAfrica Consortium, represent a vital shift towards comprehensive, system-level solutions. However, their ultimate success will depend on a sustained, multi-sectoral commitment to dismantle the systemic barriers that perpetuate health inequities. Only by integrating medical advancements with robust

social policy and community empowerment can the full potential for health and well-being be realized for all individuals living with sickle cell disease.

References

1956: cause of disease traced to alteration. National Human Genome Research Institute. Updated April 23, 2013. Accessed November 4, 2021.

About Sickle Cell Association St Louis. Sickle Cell Association. Accessed November 4, 2021.

Berghs, M., Ola, B., De Chavez, A.C. et al. (2020). *Time to apply a social determinant of health lens to addressing sickle cell disorders in sub-Saharan Africa.* BMJ Global Health, 5 (7). e002601. ISSN 2059-7908

Esoh K, Wonkam A. (2021). Evolutionary history of sickle-cell mutation: implications for global genetic medicine. *Hum Mol Genet*. 30(R1):R119-R128. doi:10.1093/hmg/ddab004

Frenette P.S., Atweh, G.F. (2007). Sickle cell disease: old discoveries, new concepts, and future promise. *J Clin Invest*. Vol. 117, No. 4, pp. 850–858. doi:10.1172/JCI30920

Gabriel Salinas Cisneros Swee L Thein. (2020). Recent Advances in the Treatment of Sickle Cell Disease Gabriel Salinas Cisneros 1,2 and Swee L. Thein1*. May 20; Vol. 11, p. 435. doi: 10.3389/fphys.2020.00435.

Guideline for National for Prevention &management of Sickle Cell Diseases. National Sickle Cell Anaemia Elimination Mission 2023.Govt of India 2022.

Herrick, J.B. (1910). Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. *Arch Intern Med (Chic)*. Vol. VI, No. 5, pp, 517–521. doi:10.1001/archinte.1910.00050330050003

History of sickle cell. Sickle Cell Association Of New Jersey. Accessed November 4, 2021.

Ingram, V.M. (2004). Sickle-cell anemia hemoglobin: the molecular biology of the first "molecular disease"–the crucial importance of serendipity. *Genetics*. Vol. 167, No. 1, pp. 1–7. doi:10.1534/genetics.167.1.1

Savitt, T.L., Goldberg, M.F. (1989). Herrick's 1910 case report of sickle cell anemia. The rest of the story. *JAMA*. Vol. 261, No. 2, pp. 266–271.

Serjeant, G.R. (2013). The natural history of sickle cell disease. *Cold Spring Harb Perspect Med*. Vol. 3, No. 10, a011783. doi:10.1101/cshperspect.a011783

Shriner, D., Rotimi, C.N. (2018). Whole-genome-sequence-based haplotypes reveal single origin of the sickle allele during the Holocene wet phase. *Am J Hum Genet*. Vol. 102, No. 4, pp. 547–556. doi:10.1016/j.ajhg.2018.02.003

Winter, W.P. A brief history of sickle cell disease. Howard University Hospital. Accessed November 4, 2021.