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Editorial

A new era dawns on sickle cell disease in India

The severity of sickle cell disease (SCD) is frightening as 50-90 per cent of children do not live to celebrate their 5th birthday in Africa and India, while millions continue to suffer life-threatening comorbidities[1-3]. The first inception of molecular medicine is marked by the description of sickle haemoglobin in SCD by Linus Pauling in 1949[4]. In three quarters of a century since Pauling's discovery, this scientific milestone is yet to be translated into clinical success; the estimated life expectancy of SCD patients remains only about 54 yr, almost two decades lower than non-SCD cohorts in the United States[5]. Although the characteristic sickling of red blood cells (RBCs) is well described, the mechanisms underlying disease-related morbidity and mortality are complex and remain poorly understood - thus precluding advances in disease-modifying and disease-mitigating therapies[6].

Victory over genetic conditions such as SCD, however daunting, requires a distinctly optimistic approach, leaving no scope for pessimism, particularly for a race who mapped the human genome ahead of the deadline. However, victory can only be achieved through a vision encompassing the interdisciplinary nature of the challenge. Herein, we outline the foundational tenets of this approach - from microscopic cellular perturbations to macroeconomic impacts, local and culturally specific solutions to international collaborations and tangible lived experiences to intangible bioethical principles. These include: (*i*) organizational: Sickle India Consortium: to unify all states and union territories; Sickle India Registry: for screening and evaluation of outcomes and Sickle India Database: to record birth, survival, hospitalization, clinical diagnosis, comorbidities, treatment and outcomes, (*ii*) management: skill building for healthcare, training physicians and healthcare professionals, hydroxyurea (HU) availability and bone marrow transplant, family counselling, advocacy and awareness, nutrition and psychosocial support, maternal and child health, transition from paediatric to adult care, integrative/complementary strategies and interventions and bioethical issues, and (*iii*) India specific research: bioinformatics, Omics-GWAS - transcriptomic, epigenomics, proteomics and metabolomic, correlations with geographical distribution, nutrition, pollution, income, *etc*., mechanism-based analysis, novel drug development, translational studies and clinical trials. Many of these are in the pipeline and/or envisioned by the government and academics in India.

Sickle cell disease is caused by the sickle mutation on the beta (β)globin gene (Glu6Val, βS) of haemoglobin that confers a sickle shape to RBCs under conditions of low oxygen. Besides the most common and severe form, sickle cell anaemia, other forms of SCD include compound heterozygous conditions such as haemoglobin C with HbS (HbSC), HbS with β-thalassaemia (HbS/β0-thalassaemia or HbS/β+-thalassaemia) and HbS with other beta-globin variants such as HbSD or HbSOArab - all of which express sufficient HbS to cause intracellular sickling[7]. The diagnosis of SCD too is relatively simple since HbS and variant haemoglobins can be identified by electrophoresis, as well as newer rapid diagnostics, but the majority of individuals in India living with the condition remain undiagnosed. A robust diagnostic paradigm is thus essential to characterize the disease burden of SCD and facilitate resource allocation. This includes integration of SCD diagnostics into comprehensive newborn screening programmes, development and implementation of rapid, cost-effective molecular assays and prospective epidemiologic cohort studies.

Globalization has advanced hygiene, nutrition and public health measures in low- and middle-income countries (LMICs), with dramatic reductions in overall infant and childhood mortality. However, the increasing

proportion of individuals with SCD surviving beyond early childhood concomitantly increases the population of adolescents and adults living with the condition. In this context, the socioeconomic burden of the disease in countries such as the United States provides a timely warning - whereas death from SCD in childhood is rare (<4%), and annual expenditures on medical care for the condition exceeding US $1 billion[6]. However, this convergence also highlights that LMICs no longer face entirely distinct challenges, but rather that all nations share a common destiny, and with it a common set of obligations to improve the human condition even beyond their borders.

India is well positioned to lead global SCD efforts because of being a powerhouse of technology, drug manufacturing (colloquially known as the 'pharmacy of the world') and even medical tourism - replete with destination medical practices performing complex procedures such as bone marrow transplantation, organ transplantation and neurological surgery at comparatively low cost. This unique combination of infrastructure and human capital, made India the leading choice for hosting the 3rd Global Congress of SCD in 2017, which was held in Odisha. The conference was a unique confluence of leaders in science, clinical care, non-profit work and governance related to SCD. The meeting was critical for setting in motion an action plan enacted through the central- and state-level governments. India established a global presence by aiming to eliminate SCD by 2047 through the 'test-track-educate-treat-council' programme. Collectively, this effort impacts 70 million people in tribal areas; fund allocations through the Ministry of Health are at a 60:40 ratio between central and state governments, respectively. Key provisions include making HU, a lifesaving SCD therapy, freely available to all patients. The low manufacturing cost of HU in India compared to most other nations should be further leveraged to enable access to a broader array of South Asian, African and other nations. Additional priorities include enhanced nutrition for mothers and children, and diagnosis of silent strokes in children. Indeed, stroke-related deaths and disability are several times higher in LMICs, and impact survival at all ages[8]. Research and health related leadership training programmes are also essential; it is critical that the phylogeny, ontogeny and the evolving status of SCD are updated globally through high-impact peer-reviewed publications from India.

Bioethical considerations are also of paramount importance, and have historically been neglected in SCD-related efforts. Health related data collection, sharing and utilization necessitate rigorous and standardized privacy protections, particularly in studies involving children. Measures to increase awareness and health literacy such as issuing color-coded cards may have advantages in certain settings but may also cause segregation and societal stigma. Similarly, disease prevention efforts such as counselling homozygous couples against bearing children may compromise dignity and threaten a fundamental human right. Bioethicists should thus be involved at all levels of policymaking in order to protect fundamental tenets of beneficence, human dignity and inclusivity.

Whereas epidemiologic projections from one decade ago portended a reduction in SCD morbidity and mortality based on the milder disease phenotypes observed in India[9], recent screening programmes have called these estimates into question[10]. Indeed, the situation in India appears to be closer to that in Africa in terms of both the number of individuals affected and the severity of disease, particularly in early childhood[2,10,11]. Screening conducted by the Indian Council of Medical Research (ICMR), Department of Health Research, Ministry of Health and Family Welfare and the Ministry of Tribal Affairs, Government of India, in 2016-2018 found 47,311 individuals living with the disease and 949,057 with sickle cell trait out of 11,383,664 people screened[12]. However, these numbers possibly represent only the tip of the iceberg in a country of more than 1.4 billion people where prevalence varies widely between different regions. Therefore, a critical need is to have a unified national approach with robust organizational, disease management and research programmes to address the true numbers, and map the nature of SCD and region/community-specific needs. International partnerships such as with pan-African programmes supported by the United States NIH and other global organizations can provide key infrastructure and best practices[13-16].

In spite of ongoing challenges, India has surpassed expectations in the performance of myriad measures including SCD screening programmes, delivery of HU therapy and bone marrow transplantation. These successes could not have been realized without increased investments over the past several years. Catalyzed by the 3rd Global Congress and countless other advocacy efforts in the private, non-profit, academic and public sectors, the ICMR and the Indian College of Hematology published landmark national guidelines for SCD management[17]. Collectively, these

lessons underscore the need for ongoing partnerships and interdisciplinary forums to advance India's leadership in the new global era of SCD.

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