

Sickle-cell disease: a call to action

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The inherited disorders of haemoglobin are the commonest monogenic diseases. It has been estimated that over 300 000 babies are born each year with one of these conditions, either sickle-cell disease or severe forms of thalassaemia.¹ Normal adult haemoglobin (HbA) consists of two α - and two β -globin chains ($\alpha_2\beta_2$), each with an associated heme group, which are regulated by duplicated *HBA1* genes and a single *HBB* gene, respectively. Sickle-cell haemoglobin (HbS) results from a single point mutation at position 6 in the *HBB* gene that causes the substitution of glutamic acid for valine in the β -globin chain. In conditions of reduced oxygen tension, this leads to polymerisation, a change of shape of the red blood cells, and hence to chronic anaemia, acute painful crises due to blockage of small vessels, and often to progressive damage to multiple organs, including the brain, kidneys, lungs, bones and the cardiovascular system.² These complications are almost entirely restricted to those with sickle-cell anaemia, i.e., individuals who have inherited the sickle-cell mutation from both parents (SS); heterozygous carriers, who have inherited a single copy of the gene (AS), are asymptomatic, except in conditions of exceptional hypoxia.

While the clinical severity of sickle-cell disease has been clearly described, its clinical course can be extremely variable and difficult to anticipate.³ This is true for sickle-cell anaemia, as well as for other sickle-cell disorders such as HbSC disease or HbS β -thalassaemia, and has important implications for the development of procedures for the prevention and treatment of these disorders. Although a few genes have been identified as modifiers of the clinical course of sickle-cell disease, much work remains to be done in this important field. In contrast, the sickle-cell trait (AS) offers a very high degree of protection against infection with *Plasmodium falciparum* malaria.⁴ Recently, however, although this observation has been widely confirmed, it has been found that parasite-infected blood from sickle-cell heterozygotes is

several times more infectious to the *Anopheles* vector than that of normal subjects.⁵ This suggests, of course, that the advantage of HbS heterozygotes is not only balanced by the cost of potential homozygous offspring but also by that of increased malaria transmission to the general population.

There is still some doubt about the origins of the sickle-cell mutation and where it arose for the first time. Although the hypothesis of five independent origins, four in sub-Saharan Africa (named Bantu, Benin, Cameroon and Senegal) and one in the Middle East and India (Arab-India) is almost universally accepted, both early and recent work supported the alternative hypothesis of a single origin.^{6,7} Significant differences in the level of foetal haemoglobin (HbF) between the sub-Saharan African haplotypes and the Asian might suggest that the sickle-cell mutation has arisen at least twice. While the Arab-India haplotype is usually described as associated with a milder clinical course of the disease, growing evidence indicates that its severity might have been underestimated.^{8,9}

Sickle-cell disease is highly prevalent in sub-Saharan Africa, and parts of the Mediterranean region, the Middle East and the Indian subcontinent. Estimates suggest that 75% of annual conceptions with sickle-cell anaemia occur in sub-Saharan Africa and demographic projections support the fact that this share is likely to grow further in coming decades.¹⁰ The sickle-cell mutation was later spread to the Americas and western Europe through the trade of African slaves, and over recent decades to most countries worldwide due to increasing international movements. Universal newborn screening programmes were implemented more than a decade ago in the UK and across all states in the USA.¹¹ Meanwhile, the implementation of such national programmes has not been possible in any African country, nor in India (despite recent progress, especially in the States of Gujarat, Maharashtra and Chhattisgarh), where they would have had the most impact.

Clearly, much work requires to be done towards the prevention and management of sickle-cell disease. As regards to early management, neonatal screening followed by prophylactic vaccination and antibiotics has led to a dramatic decrease in the mortality in early life in many high-income countries.¹² There is now increasing evidence that a similar approach would be of great value in low- and middle-income countries.¹³ Regarding prenatal diagnosis and termination of pregnancy, this has been much less widely applied than in the case of thalassaemia. At least in part, this is undoubtedly due to the ethical difficulties of counselling due to uncertainties about the future clinical course of any particular patient. Clinical trials of hydroxyurea have now shown that the drug is of definite value both in adult and paediatric populations.¹⁴ Bone marrow transplantation has also been fairly limited for this disease, partly because of the paucity of donors and again because of the risks involved and the uncertainties in the prognosis for the disease. Nevertheless, there have been genuine improvements in the management of sickle-cell disease and it is critical that these approaches become available to the low- and middle-income countries.

Although WHO recognised sickle-cell disease as a worldwide public health issue in 2006 and a resolution on the prevention and management of birth defects, including those resulting from sickle-cell disease, was adopted a couple of years later at the 63rd World Health Assembly, a public health agenda to prevent and control this disease is still lacking in most countries of high prevalence. As recently highlighted for infectious diseases such as Ebola and HIV, there is an urgent need for better health-care systems in low- and middle-income countries, particularly in sub-Saharan Africa. While events and celebrations organised for the World Sickle Cell Day on 19 June will hopefully contribute to raise awareness about this disease, such overall improvements in public health access and care are a prerequisite to improve the survival and quality of life of patients with sickle-cell disease in tropical regions.

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