EPIDEMIOLOGY

A moving target

Migration has led to an increase in the occurrence of sickle-cell disease in countries with previously low incidence of the disorder.

BY SIMON PLEASANTS

Sickle-cell disease is a heritable blood disorder that can have devastating effects. It is the result of a minor genetic change — a single error in a single gene — yet it is one of the most common genetic causes of sickness and death[1]. It is also on the rise. According to a study published last year, approximately 305,800 children were born with sickle-cell disease in 2010, about two thirds of them in Africa[2]. By 2050, the study authors predict, those numbers will increase by more than 25%, to more than 400,000 babies born annually with the disorder.

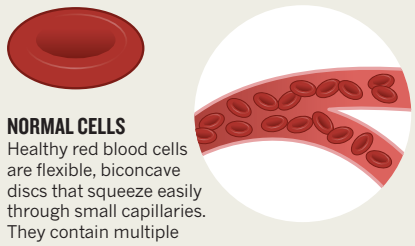
The disease-causing mutation occurs in a gene responsible for the production of haemoglobin, the protein in red blood cells that carries oxygen to tissues throughout the body. Individuals who inherit only one mutant gene typically experience no ill effects, but those who have two faulty copies develop the full-blown disease. The mutation itself is tiny: it replaces one amino acid (called glutamic acid) with another (valine) at one location in the haemoglobin protein. This small change has a major consequence — it turns the flexible, disc-shaped red blood cells rigid, giving them a distorted, sickle-like appearance.

Sickled cells are not only less pliable than healthy red blood cells, they're also stickier. This causes them to adhere to each other and plug up narrow blood vessels, reducing blood flow and preventing adequate oxygen from being delivered to the tissues that need it. This in turn leads to many complications, some of which are life threatening. People with sickle-cell disease commonly experience episodes of acute pain, known as crises, that can last from a few hours to a few days. Other complications include anaemia, leg ulcers, jaundice, kidney damage, high blood pressure, gallstones, increased susceptibility to infections and stroke. These problems arise from a variety of complex mechanisms, such as altered pain receptors (see page S8) and the decreased lifespan of red blood cells[1].

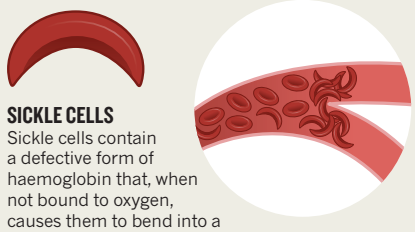
In high-income countries, improved management of the disease and medication, including strong painkillers, has meant that patients with sickle-cell disease can expect a better quality of life. In low-income nations, however, those with sickle cell are not as fortunate: in Africa, at least 50% of children born with the condition die before their fifth birthday[3].

Sickle-cell disease is most prevalent in areas with hot climates — Africa, the Indian subcontinent and the Caribbean are all affected. There is evidence to suggest that the geographic concentration of people with sickle-cell disease arose because people with sickle-cell trait — those who carry the sickle-cell gene but are generally healthy — have enhanced resistance to malaria[4], resulting in preferential selection of the gene.

The malaria-causing parasite typically invades red blood cells and multiplies inside them. But although sickle-cell carriers can be infected, the presence of sickle haemoglobin confers resistance to malaria. There are a number of different theories, one of which is that subtle biological changes in the blood — possibly higher carbon monoxide levels[5] or the interaction between oxygen and sickle haemoglobin[6]— makes people with the sickle-cell trait less of a hospitable host to the parasite and usually prevents the disease from taking hold.



NORMAL CELLS
Healthy red blood cells are flexible, biconcave discs that squeeze easily through small capillaries. They contain multiple haemoglobin molecules that carry oxygen from the lungs to tissues throughout the body. Red blood cells are made in bone marrow and have a lifespan of 120 days.



SICKLE CELLS
Sickle cells contain a defective form of haemoglobin that, when not bound to oxygen, causes them to bend into a crescent shape. The sticky, rigid cells block small capillaries, which results in pain and other serious complications. Sickle cells have a lifespan of 10–20 days.

About 70% of global cases of sickle-cell disease are in Africa. The World Health Organization estimates that in some African countries, including the Democratic Republic of Congo, Ghana and Nigeria, prevalence of sickle-cell trait is between 10% and 30%, resulting in an estimated disease prevalence of at least 2% in most of Africa — a crippling health burden in a region that is ill-equipped to bear it, and one that lacks the financial and health-care resources present in wealthy countries.

ON THE MOVE

Increased population movement associated with globalization is bringing sickle cell to regions that previously had negligibly low incidences of the disease. Migration of people with the sickle-cell trait or sickle-cell disease caused the faulty gene to flow from high-frequency sickle-cell gene areas, such as Africa and India, to western Europe, the eastern coast of South America, and North America[7]. These migrations have increased disease prevalence in areas not previously associated with the disorder. The Sickle Cell Disease Association of America estimates that there are about 100,000 people living with the disorder in the country. The US Department of Health and Human Service's National Heart, Lung and Blood Institute suggests that sickle-cell disease affects about 1 in 500 African American babies, a number about ten times greater the general population.

"In Africa, at least 50% of children born with sickle-cell disease die before their fifth birthday."

Ironically, improved medical treatment leading to longer life expectancy is contributing to the increased prevalence of sickle-cell disease. Penicillin, taken daily, helps to prevent and treat infection in young children, folic acid stimulates the production of red blood cells, the drug hydroxycarbamide (known as hydroxyurea in the United States) reduces the number and severity of painful crises, and blood transfusions help to temper acute cases of the disease. With so many interventions, more people will survive to pass on sickle-cell genes to their children. ■

Simon Pleasants *is a copy editor at* Nature.

1. Makani, J. *et al. Sci. World J.* http://dx.doi.org/10.1155/2013/193252 (2013).
2. Piel, F. B. *et al. PLoS Med.* http://dx.doi.org/10.1371/journal.pmed.1001484 (2013).
3. Grosse, S. D. *et al. Am. J. Prev. Med.* **41,** S398–S405 (2011).
4. Allison, A. C. *Br. Med. J.* **1,** 290–294 (1954).
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6. Cyrklaff, M. *et al. Science* **334,** 1283–1286 (2011).
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CARRIED IN THE BLOOD

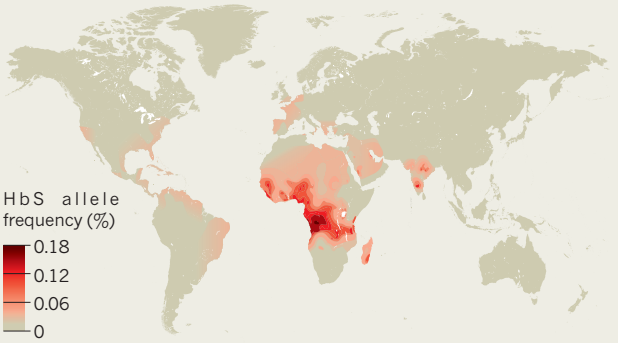
Sickle-cell disease is often fatal in low-income nations. But researchers are beginning to understand more about the disease and how to treat it. By **Simon Pleasants**.

FATED LINK

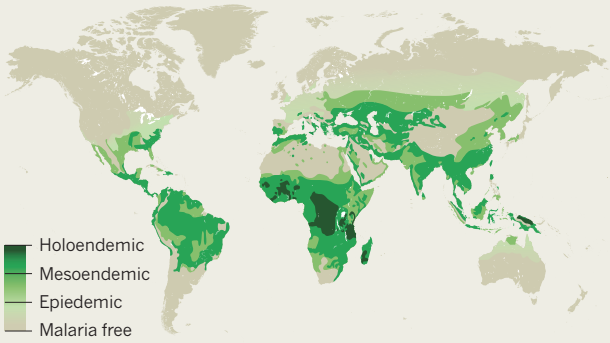
It is no coincidence that sickle-cell disease and malaria share similar global distributions. The gene responsible for sickle haemoglobin confers increased resistance to the malaria parasite when inherited from only one parent. Such a trait allowed carriers of the gene (HbS distribution, on the map below in red)[1] to survive and reproduce in areas where malaria is present (green)[2].

Although malaria is indigenous in many areas, the sickle haemoglobin gene has a more narrow distribution than malaria because the mutation arose in Africa. Limited migration from Africa to certain regions (for example, China) has restricted its spread.

HbS allele frequency

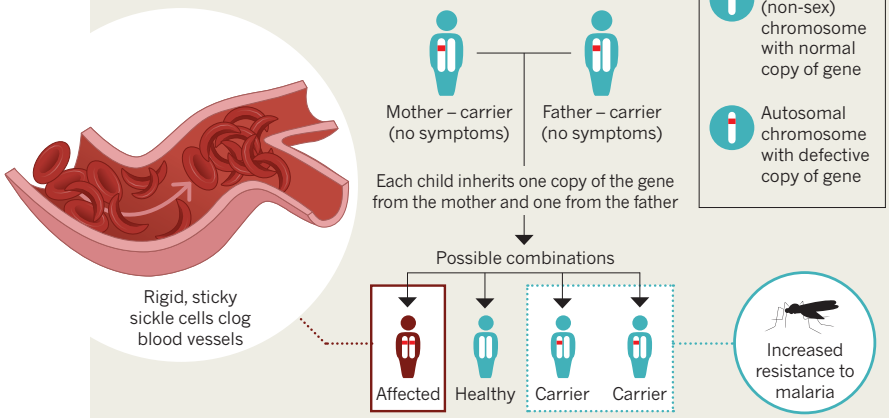


Malaria endemicity



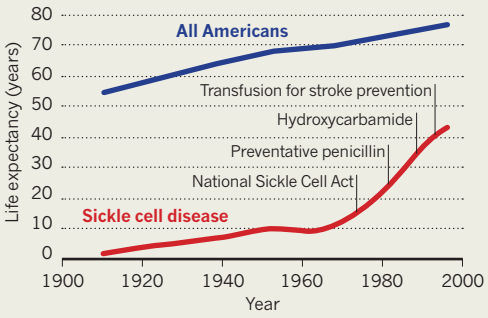
GENETIC ROULETTE

If both parents are carriers of the sickle haemoglobin gene, each child has a one-in-four chance of inheriting the full-blown disease.



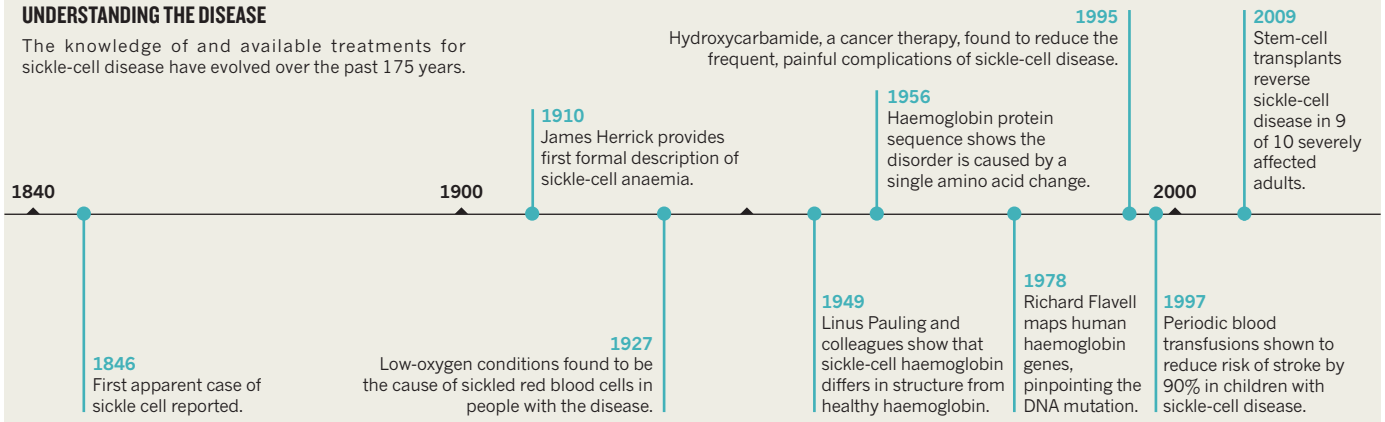
HEALTH IMPROVEMENT

As a result of more effective treatments, the life expectancy of people with sickle-cell disease in the United States has increased dramatically. Most developing nations, however, have yet to see such a change[3].



UNDERSTANDING THE DISEASE

The knowledge of and available treatments for sickle-cell disease have evolved over the past 175 years.



References: 1. Piel, F. B. *et al. Lancet* **381,** 142–151 (2013); 2. Piel, F. B. *et al. Nature Comms.* 1, 104 (2010); 3. US National Institutes of Health: National Heart, Lung and Blood Institute, available at: go.nature.com/4cuwgj.

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