Sickle cell disease: a lethal advantage

Slave ships and sickle cells

SUSAN RAE
Studies in the 1940's throughout the America's, confirmed that sickle cell disease was indeed a problem wherever African slaves had been taken. But in Africa, while carriers of the S gene with sickle cell trait were found to be very common, as many as 40% in some populations, few adults could be found with the disease itself, which suggested that most sicklers were dying in childhood.

This high mortality rate presented a puzzle. How had the Sickle Cell gene become so common? Genetic disorders that are fatal in infancy are usually extremely rare. The frequency of the gene in the population should be reduced at each generation because people with the disorder die before they can reproduce and pass on their genes.

TONY ALLISON
I was a medical student in 1951 and we went on an Oxford University expedition to Mount Kenya. And I was a so called anthropologist which meant that I was taking blood samples from east Africans and looking at different blood characters, one of which was this sickle cell condition.

And it was obvious that it was not uniformly distributed in Kenya where I was working, that there were high frequencies among the people near the coast, and there were high frequencies in the people near lake Victoria, and there were low frequencies in people in the high country and in the dry country. So this suggested that there might actually be some environmental factor that was involved, because the populations involved had different blood groups, they had different languages, so it looked as though there might be some type of natural selection operating.

At the same time I did some work in hospitals, in Kisumu as it's called which is close to lake Victoria, and Mombassa which is close to the coast. And in the paediatric wards of those hospitals a lot of cases of sickle cell disease were becoming apparent. So we had a paradox. On the one hand you had the expected numbers of sickle cell disease patients, and these were not surviving. And yet you had this common gene, common in certain parts of the country not in other parts, and so this suggested the idea that there might be some selective factor that was operating to provide an advantage for carriers of this sickle cell gene in areas where selection was operating and the distribution suggested that malaria might be the relevant factor.

SUSAN RAE
Malaria is a disease that is carried by female mosquitoes which feed on blood. As mosquitoes need water in which to reproduce, they are more common in wet regions than in dry, and so therefore is malaria. Allison had observed that sickle cell trait appeared to be more common in the wetter areas of Kenya, where there were more mosquitoes and so more malaria, than in the drier, less malarial regions.

TONY ALLISON
Later many studies elsewhere in Africa confirmed the observation that you have the high frequencies of the sickle cell character only in regions which are malarious in Africa.

SUSAN RAE
When the distribution of sickle cell disease around the world, which included parts of the Mediterranean, Arabia and south Asia, was compared with the historical distribution of severe malaria it was found that they corresponded very well.

It appeared then, that children with sickle cell trait might have some resistance to severe malaria, which is often fatal to young children, and even today is responsible for a quarter of all infant deaths in Africa. If this was proved to be the case it would explain the prevalence of the sickle cell gene in malarial regions. Children with sickle cell trait would be less likely to die of malaria than those with normal haemoglobin. So they would be more likely to reach adulthood, to reproduce and to pass on the S gene to their children.

TONY ALLISON
Observations were made on children who were admitted to hospital in Kampala, Uganda and in other countries in Africa, with potentially lethal malaria. And in those individuals hardly ever is the sickle cell trait seen, much less than you would expect by chance, in all of these populations. So this I think is really compelling evidence that if an African child has the sickle cell trait, he or she is less likely to die of malaria than an individual with normal haemoglobin.

SUSAN RAE
The precise mechanism by which children with sickle cell trait derive their resistance to malaria is still not clear. It is known however, that the malaria parasite spends part of its life cycle inside red blood cells, and that sickle cells are in some way inhospitable to the parasite.

Unfortunately children with sickle cell disease do not have the same resistance to malaria as those with trait. In West Africa where malaria is still a major killer of children, about a quarter of the adult population have sickle cell trait. What would happen though, if lethal malaria was removed from the picture, as when slaves were taken from Africa to North America?

TONY ALLISON
If malaria were to disappear, and the selective advantage of the sickle cell trait were to be lost, one would then expect the frequency of the gene to fall in the population. This may have happened when Africans were transported from West Africa to the New World,particularly in the United States where its malarial selection disappeared.

And if you compare the frequencies of approximately twenty percent over a large region of west Africa, with the frequency of eight percent or less, which is found in the US today, then it is likely that there has actually been a fall of the sickle cell trait fairly close to the expectation, and to the degree of that mixture with none African blood which one can calculate quite accurately from other genetic markers.