Blood, Genes, and Malaria (condensed version)

Long before chemical antimalarials, we had evolved genetic ones to give us some protection – but at a price

by Jared Diamond

The headaches that I had been having for several days grew rapidly worse during my physiology lecture to UCLA medical students. By the end of the hour, it was painful to look at a light, and I felt as if knives were being pressed against my eyes from inside my skull. I barely got through the lecture, went out into the hall, vomited, and checked into a UCLA hospital bed. There I broke out in a sweat, pushed all the bedcovers off, then felt so cold that I pulled up the covers and two blankets, only to become hot and drenched in sweat again. My physician, who had drawn a sample of my blood, soon confirmed what I already suspected: I had malaria.

I cursed my bad luck. If only I had been quicker at swatting those damned mosquitoes in New Guinea a few months ago, perhaps I wouldn't be lying in a hospital in such absolute misery.

A year later, I instead was feeling lucky. After seven more attacks of diminishing severity at intervals of 48 days, my malaria disappeared. I wasn't stuck with it for life, as some people are, nor did I have to resort to dangerous and sometimes lethal drugs to eradicate it, as other people do.

In another sense, though, I could still be called unlucky. Hundred of millions of people born where malaria is endemic belong to populations that have evolved a resistance to malaria. Because my ancestors came from malaria-free regions of Europe, I was genetically unprotected.

Malaria is the world's most important infectious disease, affecting more than a hundred million people each year. In some areas, it kills nearly 10% of the population in childhood. Today, those malaria victims who are lucky enough to share my access to modern medicine get treated, with varying success, with antimalarial drugs. Most victims, however, have to rely on their body's own genetic antimalarials. Just as plant species native to regions with browsing mammals evolved many natural antibrowser defenses (such as sharp spines and toxic chemicals), so humans in malarial regions have evolved dozens of chemical defenses against malaria.

Sickle-cell hemoglobin is probably the best-known genetic antimalarial. Like other such defenses, it provides some protection against one disease, while causing another – in this case, sickle-cell anemia. Taken collectively, genetic antimalarials constitute the commonest single-gene disorders in the world and are carried by more than 300 million people. In their paradoxical combination of protecting against one disease while causing another, they give us our best-understood paradigm for the origin of other, widespread genetic diseases.

Genetic antimalarials also provide a paradigm of human evolution. We often consider the evolution of the human body to have ended by Cro-Magnon times 35,000 years ago, but genetic antimalarials have been continuing to evolve in the last few centuries, practically under our noses. Finally, they have proved unexpectedly interesting to historians, through leaving genetic mileposts by which to reconstruct the trans-Saharan caravan trade, as well as the countries of origin of American blacks. Thus, the infectious diseases that most concerns me personally also draws the interest of physicians, evolutionary biologists, and historians….

The first evidence of a genetic antimalarial came from study of the disease that it causes, rather than of the disease against which it protects. In 1910, a Chicago physician treating an anemic black student noticed that some of the patient's red blood cells, instead of having their usual shape of a filled doughnut, were sickle shaped. It turned out that many black Africans suffer from such an anemia, characterized by sickle-shaped red cells and leading to bacterial infections, painful episodes of blocked circulation, and degeneration of some organs. Until the advent of modern medicine, many victims died in childhood….

Genetic studies proved that sickle-cell disease is due to a single gene for which patients are homozygous, that is, the patients inherit one copy of the gene from their fathers and a second copy from their mothers. So-called heterozygotes, or people who inherit only one copy of the gene, experience either a much milder anemia or no symptoms at all.

Thus, a mutation in one out of the 287 amino acids in one of the body's thousands of different proteins is ultimately responsible for all the symptoms of a serious disease. Even more than for its elucidation of sickle-cell anemia, this remarkably simple discovery is remembered for having launched the molecular study of disease that has revolutionized modern medicine.

Since patients in rural Africa who were homozygous for the sickle-cell gene usually died in childhood, it was initially amystery why natural selection hadn't quickly eliminated the sickle-celel gene by killing off its

bearers. The first clue to this mystery emerged aout 1946, when a physician in Rhodesia noticed that children heterozygous for the sickle-cell gene had an advantage over normal children: Their blood contained fewer malaria parasites. This suggested that the sickle-cell gene might have persisted by doing both good and harm: harm, because homozygotes tended to die of anemia; but good, because heterozygotes might be less likely than normal people to die of malaria.

In animals, it would have been easy to put this malaria-protection hypothesis to a decisive experimental test. One need only have injected both normal and sickle-cell heterozygous animals with malaria parasites to see if more of the normal animals became infected. Of course, ethical considerations today should bar this experiment in humans. Incredibly, however, the human experiment was nevertheless performed in the 1950s on 30 African volunteers. Fourteen of the 15 who lacked the sickle-cell gene became infected, but only 2 of the 15 sickle-cell heterozygotes fell ill.

While these results supported the malaria-protection hypothesis, the number of experimental subjects was too few (thank God!) to be decisive. Instead, five indirect types of evidence have been gathered in support of the hypothesis:

The natural distribution of sickle-cell genes is confined to certain areas of the world where malaria has long been endemic. These are tropical sub-Saharan Africa, plus parts of North Africa, Mediterranean Europe, Arabia, and India. In some areas of Africa, 40% of all people carry the gene as heterozygotes. the slave trade brought the gene to the New World, where it now occurs in about 1 out of every 10 American blacks.

In malarial regions of Africa, children under 5 are twice as likely to have heavy natural infections of malaria parasites, and far more likely to die if they lack the sickle-cell gene than if they carry it.

In those same regions, the fraction of the population carrying the gene increases from birth until age 5 … because that fraction suffers fewer deaths from malaria by age 5 than does the fraction not carrying the gene. African couples in which one partner is a sickle-cell heterozygote and the other is normal have more offspring who survive, and fewer who die, than do couples in which both partners lack the sickle-cell trait and thus are more likely to die of malaria.

Taken together, these five types of indirect evidence provide strong support for the malaria-protection hypothesis. In malarial areas, people heterozygous for the sickle-cell gene are more likely to survive malaria, produce children, and pass on their genes. It's true that when two heterozygotes marry, one-quarter of their children are apt to be homozygotes and die of sickle-cell anemia. But advantage enjoyed by the more numerous heterozygotes balances the deaths of the rarer homozygotes, hence the gene persists.

In some malarial areas, no one carried the gene. There, other red cell genetic abnormalities may be functioning as antimalarials, although the evidence is the case of the sickle-cell gene. Often, the same human population, and even the same individual, carries more than one of these genetic antimalarials. Most of these other antimalarials offer weaker protection against malaria and produce milder disease of their own than does the sickle-cell gene.

Let's now move from these medical questions to evolutionary ones. How long have genetic antimalarials been present in human populations at high frequencies? Here we have to speculate, since thalassemias[1] and abnormal hemoglobins haven't yet been diagnosed in ancient bones or mummies.

Many physicians favor the interpretation that malaria became a common human disease only after the rise of agriculture had created the ponds in which malaria's mosquito vectors breed abundantly in sub-Saharan Africa. Theoretical calculations show that, starting out with a sickle-cell mutation, natural selection by malaria could boost the sickle-cell gene to Africa's present high frequency within only 1,000 to 2,500 years. That would allow plenty of time, since the rise of agriculture began about 4,000 years ago in sub-Saharan African and earlier in the Mediterranean, Asia, and New Guinea.

It is also possible that malaria and genetic antimalarials have been with us for much longer. In Southeast Asia and India, the mosquito vectors of malaria breed in hill forests or fast-flowing streams and don't depend on agricultural ponds. In Asia, but not in Africa, human malaria occurs in wild monkeys, providing a natural reservoir of infection even before agriculture brought on a human population explosion. Africa's Eastern Pygmies, though not the Western Pygmies, have been reported to have a high frequency of the sickle-cell gene dspite being nonagricultural hungeter-gatherers. Thus, I regard it as still uncertain whether genetic antimalarials were already widespread among human hunter-

[1] genetic disorder that involves the decreased and defective production of hemoglobin, a molecule that's found inside all red blood cells and is necessary to transport oxygen throughout the body

gatherers or whether they rose to high frequency only since the rise of agriculture.

In contrast, natural selection has certainly been causing genetic antimalarials to disappear rapidly in some populations. Recall that the sickle-cell gene tends to kill off its homozygous bearers. Heterozygous bearers may also face an increased risk of death during heavy exertion, as suggested by an analysis of otherwise unexplained deaths of U.S. Army black recruits during basic training. In malarial regions, these drawbacks of the sickle-cell gene are offset by the protection it affords against malaria. In the absence of malaria, however, this benefit would disappear, and natural selection should gradually tend to eliminate the gene by preferentially killing its bearers – especially in the era before modern medicine.

This is exactly what seems to have happened in two New World black populations whose ancestors brought the sickle-cell gene from Africa. The gene is less common in blacks who live on the malaria-free Caribbean island of Curacao than in blacks from nearby, malria-ridden Surinam, although the ancestors of both populations had similar African origins. In Georgia blacks, the sickle-cell gene is much less common than in others. Since Curacao and Georgia blacks both began migratin gfrom Africa to their new homes only a few centuries ago, the gradual elimination of their sickle-cell genes by natural selection in malaria's absence has been proceeding virtually before our eyes….

These seem to me beautiful examples of how evolution works in our own species. Malaria, one of the world's leading killers of humans, has been a prime target for natural selection. Mutations produced thousands of red cell abnormalities, most of which are useless for protecting against malaria. Dozens did prove useful and have repeatedly arisen identically or with slight variation. All these useful antimalarials rose independently to high frequencies through n atural selection. Most differ in detail, but they resemble each other in the result: antimalaria efficacy. Their similarities are an example of convergent evolution at the molecular level, just as the similarly streamlined bodies of whales, sharks, and extinct marine reptiles constitute convergent evolution[2] at the level of gross anatomy.

Finally, what about the interest of genetic antimalarials for historians? I'll give two examples. First, the transatlantic slave trade that brought millions of Africans to the New World tore them brutally from roots all over black Africa. Many white Americans, but few black American, can precisely trace their Old World origins through written records such as birth certificates. But sickle-cell hemoglobin arose independently in at least three parts of Africa, each time with a different fine genetic structure. By analyzing frequencies of hemoglobin genes in black-Americans living in Baltimore, Ronald Nagel obtained molecular estimates of their family trees: About 18% of their ancestors came from Bantu Africa, 15% from West Africa's Atlantic.

The second example of interest to historians involves the sickle-cell gene in North Africa and Mediterranean Europe. It turns out not to represent a distinct origin but instead to be in most cases identical with the gene of central West Africa. Those African genes are a legacy of the trans-Saharan caravan trade that flourished before written records. To central west Africa, the caravans brought horses, cattle, salt, copper, and manufactured goods. To Europe, they brought ivory, gold, slaves, and among the slaves' genes, a genetic antimalarial new to Europe.

Now that much is understood about genetic antimalarials, they provide a model for trying to understand the persistence of other genetic diseases. In the Old World tropics, malaria has been the most important infectious disease, and we now know that it elicited red cell disorders as a genetic response. In northern Europe, the leading infectious diseases instead included small pox, measles, bubonic plague, tuberculosis, and bacterial diarrhea. At the same time, northern Europe evolved a different set of genetic diseases, including cystic fibrosis, Tay-Sachs, diabetes, and genetically based ulcers. We are just starting to ask which of these northern genetic diseases provided protection against which of those northern infectious diseases. But the story of that search will have to wait for a future column.

[2]the development of similar characteristics by taxonomically different organisms, usually because of adaptation to similar environments