Gene Creates Malaria Drug Resistance

Ending a decade-long quest, scientists have now identified a gene that enables the malaria-causing parasite *Plasmodium falciparum* to mount resistance to chloroquine, a major antimalarial drug that has become increasingly ineffective around the world.

Armed with the new information, investigators will try to develop versions of chloroquine that sidestep the parasite's resistance but still safely kill the bloodthirsty organism, says Thomas E. Wellems of the National Institute of Allergy and Infectious Diseases in Bethesda, Md.

A number of complex variations in the newly discovered gene *cg2* appear to bestow chloroquine resistance upon *P. falciparum*, Wellems and his colleagues report in the Nov. 28 CELL.

Resistance to the drug emerged 40 years ago, notes Wellems, and appeared almost simultaneously in Southeast Asia and South America. Today, the problem has spread worldwide, fueling a resurgence of malaria that kills millions of people annually.

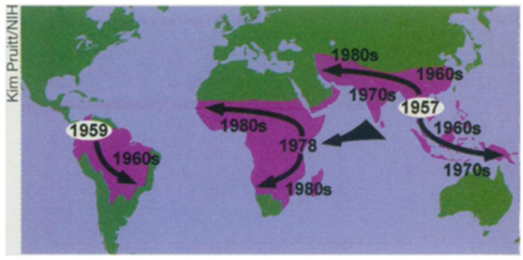
Several years ago, Wellems and his colleagues took a crucial step toward unraveling chloroquine resistance when they bred a drug-resistant strain of *P. falciparum* from Indochina with a chloroquine-sensitive strain from Central America.

By examining the resulting progeny, some of which were resistant and others of which were not, the researchers narrowed the search for a resistance-conferring gene to a small portion of one of the parasite's chromosomes.

The region harbors many genes, but Wellems' team eventually found that *cg2*'s DNA sequence consistently shows more than a dozen differences between chloroquine-resistant and chloroquine-sensitive *P. falciparum* strains .

The elaborate changes observed in *cg2* contrast with the simple gene mutations through which many microorganisms have thwarted other drugs and may therefore explain why chloroquine worked so well for so long. "It took over a decade for resistance to arise," says Wellems.

Investigators believe that chloroquine functions by accumulating within the malaria parasite and that the drug prevents the parasite from sequestering toxic components created as it digests the hemoglobin it steals from blood cells.



The spread of chloroquine-resistant Plasmodium falciparum *strains.*

Some investigators have suggested that chloroquine-resistant strains have an increased ability to pump the drug from their bodies; others contend that resistance stems from changes that prevent chloroquine from entering the parasites in the first place. Also, there's evidence that resistant parasites specifically reduce the concentration of chloroquine in the internal compartments where they digest hemoglobin.

Using antibodies that bind to the protein encoded by *cg2*, Wellems and his coworkers observed the protein in the complex of membranes that separates the parasite from its host blood cell and in the vicinity of the organism's hemoglobin-digesting compartments.

Both locations bolster the hypothesis that the protein plays a role in transporting chloroquine. "It's exactly where it should be, and it fits all the theories," says Wellems.

His group plans to add the resistant version of *cg2* to chloroquine-sensitive *P. falciparum* to confirm the gene's role in protecting the parasites from the drug.

The investigators have found that in South American strains of chloroquine-resistant *P. falciparum, cg2* has a significantly different DNA sequence than it does in either drug-sensitive or drug-resistant Asian strains.

That result "lends support to the hypothesis that there was a separate origin of resistance in the New World," says Daniel E. Goldberg of Washington University in St. Louis.

While the identification of *cg2* may help scientists search for new chloroquinelike drugs, Goldberg suggests it will also enable investigators to develop compounds that specifically block the resistance mechanism.

When used with chloroquine, such agents could restore the drug's effectiveness, he says. First, however, Wellems and his colleagues must determine the function of *cg2*'s protein. —*J. Travis*

Sulfur: Cool, compact, and conductive

Squeezed under enormous pressures and cooled to a chilly 17 kelvins, sulfur turns into a superconductor, according to a new study. Although many of the new ceramic superconductors work at 100 kelvins or more, sulfur sets a record high temperature for a pure element conducting electricity without resistance.

Using a device called a diamond anvil cell, Russell J. Hemley of the Carnegie Institution of Washington (D.C.) and his colleagues compressed sulfur under about 1.6 million times atmospheric pressure (SN: 10/26/96, p. 261). The Carnegie group and a coworker from the Russian Academy of Sciences in Troitsk report their findings in the Nov. 27 NATURE.

"I'm very excited about these results," says Marvin L. Cohen of the University of California, Berkeley. Two years ago, he and his colleagues developed computer models showing that sulfur should turn into a metal at high pressures and superconduct at low temperatures.

Originally, not many people believed the predictions. "You think of sulfur as that yellow powder that you mix into gunpowder," he says. "You don't think of it as a material that would be a metal, particularly a superconductor."

An experiment in the 1970s indicated that sulfur could turn metallic and superconductive, but no one had been able to duplicate those results. X-ray diffraction studies at Cornell University in 1993 showed that sulfur assumes different crystal structures at high pressures. Soon afterward, Cohen's group modeled the behavior of the structural transitions that the element should undergo. The Carnegie experiments now seem to bear out those predictions.

Measuring the electrical conductivity of a material in a diamond anvil cell is tricky. Because of the high pressures and tiny quantities involved, attaching two wires to the sample isn't feasible. Instead, the Carnegie group applied a magnetic field to the cell and monitored the changes in sulfur's magnetic properties that signal its transformation into a superconductor.

Selenium and tellurium, elements chemically similar to sulfur, also superconduct but at much lower temperatures and pressures. Sulfur, a simpler element, may serve as a good test material to study superconductivity theories, says Hemley. Researchers are interested both in superconductivity of the more complex ceramics and in the effects of high pressure on another pure element, hydrogen, which was condensed into a metal for the first time last year (SN: 4/20/96, p. 250). —*C. Wu*