that high levels of NO might kill *Plasmodium falciparum* parasites in the liver, where the parasite first gets a foothold and begins to multiply. But somewhat surprisingly, the new mutation mitigates the severity of the disease without reducing the number of parasites in the bloodstream: Children with the mutation had parasite levels comparable to those of children without it.

NO might play a variety of other protective roles. Animal experiments have shown that NO reduces expression of adhesion molecules on cell surfaces, which prevents infected red blood cells from sticking to blood vessel walls and causing the restricted blood flow associated with deadly cerebral malaria. NO also limits production of cytokines—proteins that stimulate immune responses and might contribute to tissue damage in malaria.

Still, although researchers welcome the new finding as a basic insight into human immune defenses, they say it probably won't lead to immediate improvements in malaria treatment. "NO won't be the panacea for malaria; it's just one piece of the puzzle," says study co-author Nicholas Anstey, an infectious disease specialist at the Menzies School of Health Research in Darwin, Australia.

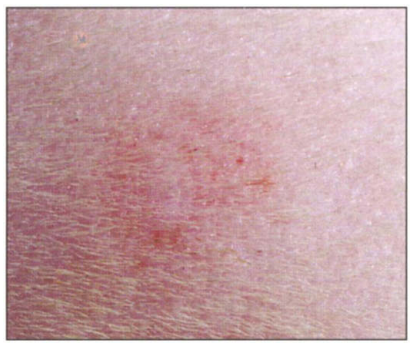
–DEBORAH HILL

Deborah Hill is a science writer in Idaho Falls, Idaho.

IMMUNOLOGY

Antibodies Kill by Producing Ozone

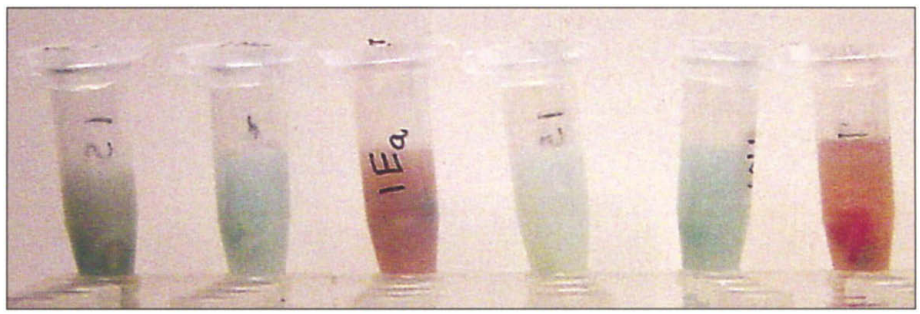
Antibodies have long been known as the immune system's reconnaissance forces: scouts that seek out foreign antigens and summon up the big guns to wipe them out. But evidence now indicates that antibodies may also be killers in their own right.



In work published online today by *Science* (www.sciencemag.org/cgi/content/abstract/1077642), Paul Wentworth, Richard Lerner, and their colleagues at the Scripps Research Institute in La Jolla, California, report evidence that antibodies, when provided with appropriate starting materials, catalyze the production of highly active forms of oxygen, likely including ozone. This can not only kill bacterial pathogens directly but might also promote inflammatory and other immune responses. The work puts antibodies in a whole new light, says immunologist Carl Nathan of the Weill Cornell Medical Center in New York City. Because they weren't supposed to have such direct effects, "it will be hard to think of antibodies in the same way [as before]."

Hints of antibodies' lethal nature began surfacing about 2 years ago. Thanks partly to early work from Lerner's lab, antibodies are known to have catalytic activities. And Wentworth, Lerner, and their colleagues showed that when they are supplied with a reactive form of oxygen known as singlet oxygen, antibodies can generate hydrogen peroxide from water (*Science*, 7 September 2001, pp. 1749 and 1806). Hydrogen peroxide is a well-known bacteria killer; it's often used as an antiseptic. But because the Scripps team generated singlet oxygen in a highly nonphysiological way and didn't show directly that bacteria die from the hydrogen peroxide produced, "people said, 'What does this have to do with biology?' " recalls Lerner.

The new work addresses that issue and suggests a surprising new twist to antibodies' modus operandi. First, the Scripps researchers demonstrated that antibodies can kill bacteria without help from any other immune system forces. In one set of test tube experiments, they showed that antibodies, in conjunction with a singlet oxygen-generating system that could not kill bacteria on its own, wiped out more than 95% of *Escherichia coli* bacteria.



Ozone indicator. In the Arthus reaction, skin becomes inflamed at the site of antibody injection (*lower left*). Biopsies of such inflamed sites (tubes 3 and 6 from left), but not of normal skin (tubes 1, 2, 4, and 5), contain ozone as indicated by their reaction with the dye indigo carmine.

But the experiments turned up a puzzle: The antibodies weren't generating enough hydrogen peroxide to account for all the cell killing. That suggested that some other, more powerful bactericidal agent was also being formed.

Evidence from a series of experiments pointed to ozone as the most likely suspect. For example, the researchers found that antibodies provided with singlet oxygen produce an oxidizing agent that splits the dye indigo carmine, just as ozone does. Ozone hadn't previously been implicated in immune responses. "We're now in brand-new territory," Nathan says.

The work still left one big question hanging: Is there a plausible physiological source of singlet oxygen? (The Scripps team had again used a nonphysiological source.) Wentworth, Lerner, and their colleagues believe they have an answer. They report evidence that immune cells called neutrophils, which help destroy invading bacteria, can generate singlet oxygen.

In addition to showing that antibodies can produce hydrogen peroxide and ozone, the team has linked this activity to an inflammatory response called the Arthus reaction in living rats. In this system, inflammation is induced by injecting an antigen—the researchers used bovine serum albumin—into the animals' bloodstream and simultaneously injecting antibodies to it into their skin; the skin becomes inflamed at the injection sites. Analysis of the inflamed skin tissue showed that it, too, contained an oxidizing agent that behaves just like ozone.

Chemist Chris Foote of the University of California, Los Angeles, describes the work as "amazing." It shows, he says, that "there's a powerful oxidant there that no one suspected." He cautions, however, that the current experiments don't totally prove that the oxidant is ozone. Lerner concedes the point but says that other work now under way, including studies of atherosclerosis, will provide definitive proof.

Meanwhile, Nathan suggests that antibody-mediated ozone production could contribute to a variety of inflammatory conditions, including rheumatoid arthritis and inflammatory bowel disease. He notes, for example, that the inflamed joints of arthritis patients contain something called rheumatoid factor, which is actually an antibody directed against other antibodies, as well as neutrophils. If this leads to antibody-catalyzed production of hydrogen peroxide and ozone, the result could be a double whammy, causing damage to the joint directly and also indirectly by enhancing the activity of neutrophil products. More work will be needed to test these ideas, but antibodies now appear to have more tricks up their sleeves than anyone expected.

–JEAN MARX

CREDITS: P. WENTWORTH ET AL.