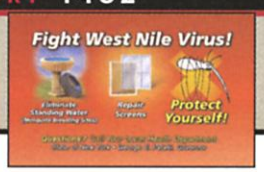
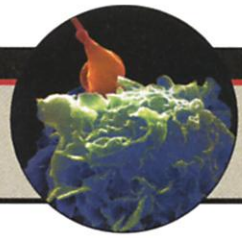






increasingly visible in the next few years. It may also become even more contentious. With research in the postgenome world demanding a skyrocketing number of rats and mice, says Rich, "anyone who believes that we're going to eliminate pain and distress over the next 20 years just does not understand biological science."

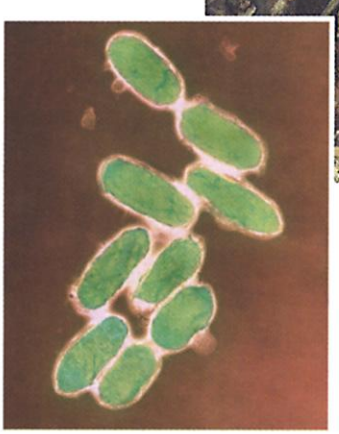
–CONSTANCE HOLDEN

MICROBIOLOGY

## Unlocking the Secrets Of the Grim Reaper

During the 14th century, the Black Death swept Asia and Europe, littering streets with corpses. Why, the people wondered? Was the Plague the work of an angry God? A medieval curse? As it happens, the real culprit was a tiny bacterium: *Yersinia pestis*. Centuries later, scientists are still learning how *Y. pestis* does its dirty work. Now, on page 1594, a new study adds another piece to the puzzle. The work may also shed light on the modus operandi of other noxious bacteria.

In the study, researchers led by biochemist Jack Dixon of the University of Michigan, Ann Arbor, unveil the workings of YopJ, one of a group of nefarious proteins that *Yersinia* bacteria, including *Y. pestis*, deploy. Early in the disease, *Yersinia* bacteria inject YopJ into macrophage cells of the immune system, beginning the cycle of destruction. There, the researchers have now found, YopJ acts like scissors—or more precisely, a cysteine protease—cleaving the macrophage proteins that would normally send an SOS to other immune cells for help. "YopJ cuts the macrophage's communication lines," says Dixon. Leaving the macrophage stranded, he adds, YopJ clears the way for other *Yersinia* proteins to destroy the cell.



"Very nice," says microbiologist Brett Finlay, of the University of British Columbia in Vancouver, about the new study. Bit by bit, Finlay says, researchers are unraveling the half-dozen virulent proteins that pack *Yersinia*'s punch. "This work takes us a step farther, defining the molecular machinery that allows YopJ to quiet the immune system," Finlay says.

*Yersinia* is infamous for causing the bubonic plague, which still affects at least 1000 people a year—and its brilliant biochemistry. Rather than climb inside macrophage cells, the bacteria hover outside and, like a molecular syringe, shoot six Yops (*Yersinia* outer proteins) into the cells. In itself a team of assassins, each Yop protein plays a distinct role in killing the cell. Last year, Dixon and his colleagues reported (*Science*, 17 September 1999, p. 1920) that YopJ blocks two signaling pathways—mitogen-activated protein kinase (MAPK) and nuclear factor κB—that the macrophage activates to send an SOS, in the form of tumor necrosis factor (TNF), to the immune system's B and T cells.

But how, exactly, does YopJ accomplish this? That question inspired the new study. To find out how YopJ works, the researchers ran computer programs that predicted YopJ's structure, based on its amino acid sequence. That analysis showed that YopJ closely resembles adenovirus protease (AVP), a well-known viral protein, as well as the AvrBsT protein in plant bacteria. These proteins all share a stretch of four amino acids—and it's this conserved catalytic region, Dixon knew, that makes AVP a cysteine protease and determines which substrates it can cleave. By extension, he reasoned, YopJ and AvrBsT must also be cysteine proteases, acting on similar substrates.

To test that idea, the researchers created three YopJ mutants, each altered in the key catalytic region shared with AVP. Without this region intact, the team found, each YopJ mutant failed to block the MAPK pathway—and stop production of TNF—in macrophage cells. By contrast, wild-type YopJ proteins stopped MAPK activity cold, silencing the macrophage's call for help. "Without this working catalytic site," Dixon concludes, "YopJ can't do its job."

To hammer the point home, Dixon decided to test the same mutations in AvrBsT, the plant homolog. He called Brian Staskawicz, a plant biologist at the University of California, Berkeley. And sure enough, when Staskawicz's lab mutated the same catalytic region in AvrBsT, that protein also failed to provoke its usual host response—in this case, localized cell death in tobacco leaves. Like YopJ, AvrBsT appears to be a cysteine protease, Staskawicz says. The first lurks behind the Black Death; the second, black spot disease. What's striking, adds Staskawicz, is that bacteria have evolved to unleash the same biochemistry in such different settings. Dixon adds: "Basically, the same thing that killed millions in Europe is sitting in your front yard." Not to mention elsewhere—YopJ homologs can also be found in bacteria such as salmonella and *Rhizobium*.

**Black Death.** *Yersinia* bacteria (left) caused the bubonic plague that ravaged Europe in the 14th century. Italian artist Francesco Traini depicted the plague in this 14th century painting, "Triumph of Death."

The *Yersinia* saga continues. Dixon's team is still searching for the unlucky host proteins cleaved by YopJ and AvrBsT. The current study suggests that both clip an assortment of so-called ubiquitin-like proteins used for signaling inside cells. The researchers hope to catch this action in vitro. Until they do, some hesitate to label YopJ a cysteine protease. "This is a very interesting idea, but more work needs to be done," cautions microbiologist Olaf Schneewind of the University of California, Los Angeles. Even now, *Y. pestis* perplexes the crowd.

–KATHRYN BROWN

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