The mold that infested Ireland's potato fields in the 1840s has spread around the globe—and grown more aggressive than ever; researchers are working to contain it

Taking the Bite Out Of Potato Blight

Even in Russia's relatively well-off St. Petersburg region, it's a rare household that can keep itself fed without a reliable supply of potatoes from the family plot. So the alarm level was high when people recognized symptoms of late blight on their staple crop last summer.

The first signs of impending disaster usually appear on the leaves, initially as brownish or purple-black lesions at the margins, then spread over the rest of the blade. The stalk and stem turn to black slime. Sometimes, the infecting spores attack the tubers directly; when that occurs, damage appears first as dark blotches on the skin of the potato. As the incursion progresses, secondary invasions turn the weakened flesh to mush. Within a week, an entire field can be wiped out.

This aggressive, funguslike affliction, *Phytophthora infestans*, has been ravaging more of the Russian crop than at any time in memory. When it turned up in the late 1990s, yields on some Russian plots were slashed as much as 70%. This summer, in some gardens, not a plant remained alive.

Late blight ranks as world agriculture's most destructive disease. It's the same scourge that laid waste to Ireland in the 1840s, when more than a million people starved to death and at least as many were forced to leave their homeland. A century and a half of research has failed to subdue the highly adaptable organism. Moreover, in the past decade or so, *P. infestans* has acquired new traits that make it more threatening than ever; virulent, fungicide-resistant strains have turned up all over the world.

In the few countries that can afford fungicides—mainly in North America and Western Europe—losses typically reach 15%, despite the application of chemicals in quantities unmatched for any other crop. In developing countries, where high cost and difficulties in distribution put fungicides out of reach, the annual toll already comes to billions of dollars. Says Wilbert Flier, a specialist at Plant Research International (PRI) in Wageningen, the Netherlands: "The impact of shifting *Phytophthora* populations, especially in the developing world, will cause dramatic constraints on potato production on a scale not experienced before."

In countries such as Russia, where for many people there's little to eat *except* potatoes, an epidemic could prove catastrophic, warns K. V. Raman, a professor of plant breeding at Cornell University and executive director of the Cornell–Eastern Europe–Mexico project (CEEM), an effort formed several years ago to keep the disease at bay.

Heavy toll. Late blight has returned with a vengeance to potato plots in the St. Petersburg region in Russia, where some farms lost 70% or more of their crop.

"The conditions prevalent in today's Russia," he says, "are all too reminiscent of those of Ireland in the mid-19th century."

Even Western farm operations, for all their sophistication, could be overwhelmed by this persistent foe. One problem, says Harold Platt, a plant pathologist at the University of Prince Edward Island and the Agriculture and Agri-Food Canada Research Centre, is near-total dependence on fungicides, which are losing their effectiveness as resistant strains spread. "A hundred and fifty years of relying on a single management tool has been to our detriment," he says. Another problem is that the United States and Canada, in particular, have come to rely on just a few vulnerable potato cultivars—most prominently, the versatile Russet Burbank, great for baking and the mother of most fast-food French fries, and good "chippers," such as Ranger. "As potato diversity shrinks and *Phytophthora* strains multiply," says Platt, "entire crops are at risk of being wiped out."

In response to the burgeoning risk, scientists in 1996 established the Global Initiative on Late Blight (GILB), an undertaking of some 700 researchers in 76 countries to conduct and coordinate research into the potato and the pathogen. The same year, in recognition of the special vulnerability of Russia and Eastern Europe, a group of plant pathologists at Cornell undertook to organize CEEM. Such efforts are beginning to pay off as researchers uncover potential vulnerabilities in the pathogen and outline better defensive strategies.

Home in Toluca

Much remains to be learned about late blight, but there is general agreement on its place of origin: the Toluca Valley, an hour and a half drive southwest of Mexico City. The valley is the center of *P. infestans* diversity. (Once classed as fungi, phytophthorae are in fact oomycetes, or water molds.)

Although travelers carried the potato (*Solanum tuberosum*) from the Americas back to Europe as early as the 1500s, the disease seems not to have made the trip until the 1840s. Initially, when *P. infestans* did appear in Europe, it was unstoppable. It was only thanks to the discovery of the organism in the 1860s—and fungicides to fight it—that the Irish disaster wasn't more common. In countries that have been able to afford fungicides, frequent applications during the growing season—although imperfect, expensive, and hardly environment friendly—have held the disease at bay. But even that is changing.

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No fungicide has ever been found to which *P. infestans* could not ultimately adjust. Metalaxyl, for years the most commonly used, appeared increasingly impotent starting in the 1990s. And it was never effective against established infection. Cultivated potato varieties that in the past showed a measure of resistance to late blight, moreover, succumb readily to newer strains. Indeed, no potato has ever been developed with defenses that *Phytophthora* could not ultimately breach. And the attacker's arsenal is growing more elaborate.

SEARCHING FOR POTATOES IN A STUBBLE FIELD.

Famine. The 1840s European debut of late blight is etched into Ireland's history.

Until recently, most infections outside Mexico were caused by a single type of *P. infestans* (A-1), which reproduces asexually and can survive only in the potato's tissues. Infected tubers used for seed, left in cull piles, or unharvested in the ground have been the sources of spores from one growing season to the next. But starting in the late 1980s, a second mating type, or "sex" (A-2), previously limited to the Toluca Valley, escaped from Mexico, allowing sexual reproduction with A-1 in new areas.

Individually, A-1 and A-2 produce sporangia, reproductive bodies that are short lived and require a moist environment. But when A-1 and A-2 are introduced to each other, they mate to form multitudes of thick-walled oospores that can persist independent of the host plant—in soil and during drought, for example. Sexual recombination also allows the organism to adapt more readily to adverse conditions.

The consequences are already apparent. In the past, most *Phytophthora* races in North America had one, two, or at most three virulence genes; in Western Europe they had no more than four or five. In recent tests around St. Petersburg, 80% of the *Phytophthora* races had six or more such genes. Some had as many as 10. In addition, in the 1990s, especially aggressive and fungicide-resistant strains of the simple A-1 type started to appear.

For most countries, fungicides have never been an option. And the new fungicide-resistant races of *P. infestans* have upset the balance of power even in rich countries. Everywhere, in short, it's assumed that the most promising and sustainable solutions will involve not new fungicides but genomics: genetic manipulation aimed at deactivating the organism or engineering potatoes that have "durable resistance," lasting 10 years or more. Although the genomics projects are young, they are making progress.

Gene warfare

The organization coordinating the counterattack on *P. infestans* is the 6-year-old GILB, which held its triennial meeting in Hamburg, Germany, last summer. The session yielded some encouraging news. Phytopathologist Christiane Gebhardt of the Max Planck Institute for Plant Breeding Research in Cologne, for example, reported the first-ever cloning of a potato gene that confers resistance. The gene (*R-1*) engineers a sort of pyrrhic victory called hypersensitive response, in which cellular suicide at the site of invasion isolates the pathogen by destroying the plant tissue around it. Although *Phytophthora* long ago evolved ways around this gene and similar ones, the cloning of *R-1* is an important step. It is located on a DNA "hot spot" containing genes that code for other known defenses against viruses, bacteria, mildew, and even nematodes. In addition, its genetic structure appears to resemble those other genes, an observation that might contribute to a clearer understanding of how these defenses work.

A Dutch group led by E. Van der Vossen of PRI in turn reported the first-ever cloning of a gene that plays a role in another kind of defense, called rate-reducing resistance, which allows for fewer infections or diminished sporulation. The gene, *Rpi-blb*, is found in a highly *P. infestans*–resistant but inedible Mexican wild potato called *Solanum bulbocastanum*.

And more genes are coming. Just weeks before the conference, a worldwide research consortium funded prominently by the multinational agribusiness Syngenta announced that it had accomplished a first-run "shotgun" sequence of *Phytophthora*'s huge 237-megabase genome. According to Marc Law, Syngenta's Fungal Program leader, the consortium sequenced 75,000 expressed sequence tags (ESTs), telltale sequences that code for biologically significant proteins. Among those ESTs, says Law, were identifiers of both "pathogenicity factors" and "avirulence genes," which elicit defense responses in the plant. As a bonus, the researchers also found genes that encode *Phytophthora* enzymes for "housekeeping," signaling, and cell-cycle regulation.

The goal of the genetic studies, says Ralph Dean, director of North Carolina State University's Fungal Genomics Laboratory in Raleigh, is to "identify all genes in the pathogen and the host that are functionally responsible for controlling … whether you have disease or whether you don't." Researchers then hope to use that knowledge to breed, find, or engineer resistant varieties.

Adapting. Versatile new mating forms of *P. infestans* have appeared in Europe and North America.

Updating the potato

The traditional strategy against late blight has been to seek potatoes, whether in the wild or in germ-plasm archives, that might prove resistant. But resistance is not enough. A potato that's worth its salt must be edible too, of course, and possess the literally scores of characteristics that make for commercial success. For example, says Kenneth Deahl, head of the late-blight project at the U.S. Department of Agriculture's (USDA's) Beltsville Agricultural Research Center, near Washington, D.C., "I have a potato right now that's resistant." In size and shape, however, he says it's more like a peanut than a potato. Or take the cultivar Lenape: It's "resistant to late blight *and* a great 'chipper,' " he says. "But it's also poisonous."

A more cutting-edge technique than combing through germ-plasm archives is

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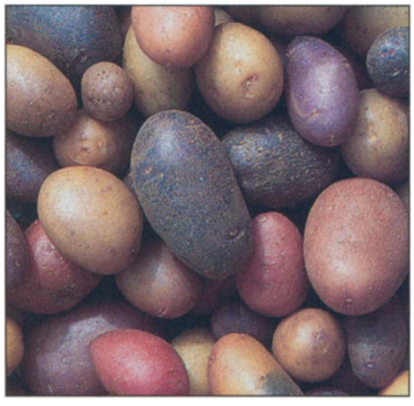
learning how some potatoes recognize the pathogen and elicit a defensive response. Of the two main types of resistance, hypersensitive response is the more straightforward—a process thought to involve "gene-for-gene recognition," in which a single resistance gene in the host recognizes a protein produced by a particular gene in the pathogen. The problem with single-gene resistance, says Deahl, is that *Phytophthora* is "an artful creature," and it can get around that kind of resistance with a simple mutation.



In reserve. Researchers are scanning all varieties for blight-resistance genes.

Considered more promising, therefore, is rate-reducing resistance, which is based on sets of genes that might collaboratively inhibit infection. And there's no dearth of resistant potatoes on which to draw.

The largest group addressing the challenge through molecular genetics is the Potato Functional Genomics program, funded by the National Science Foundation. It includes Barbara Baker, a molecular biologist at the University of California, Berkeley; plant pathologist William Fry of Cornell; John Helgeson, a U.S. Agricultural Research Service plant pathologist at the University of Wisconsin, Madison; and The Institute for Genome Research in Rockville, Maryland. The project has so far generated 60,000 ESTs from core potato tissues: shoots, leaves, stolons, tubers, and roots.

It might also be possible to learn something from "not-potatoes," says Sophien Kamoun of Ohio State University, Wooster. He is looking at *Arabidopsis*, for example, because he says it "exhibits active defense responses [including hypersensitive cell death] to *P. infestans*." And he wonders whether resistance genes from such nonhost plants can be transferred to the potato.

At the University of Victoria in British Columbia, molecular biologists William Kay and Santosh Misra say they have already achieved something of the sort. They've engineered potatoes with genes encoding segments of antimicrobial proteins from silkworm moths and honey bee venom—and the plants have shown late-blight resistance.

Some wild Mexican and South American potato species produce toxic glycoalkaloids that appear to help them resist insects. John Bamberg of the USDA Agricultural Marketing Service's Potato Project in Sturgeon Bay, Wisconsin, is studying how they work and whether these substances might confer resistance to late blight as well. A caveat, he acknowledges, is that the very toxins that make some potato varieties resistant to late blight might also make them poisonous to people and livestock. Some researchers are thinking about finding ways of designing plants to confine glycoalkaloids to the aboveground plant. One possibility might be to make them sunlight-activated, sparing the plant from disease without poisoning the tubers. And Dilip Shah, at the Donald Danforth Plant Science Center in St. Louis, is studying a vaccinelike procedure to see whether exposing the potato plant to the pathogen's proteins can stimulate generalized defenses.

Understanding the products of resistance genes and their biochemical interactions with the pathogen could put scientists a step closer to conferring resistance to plants that lack it. As Helgeson puts it, "What we need to know is, what's the product of these genes? What do they do? Look at the dialogue."

Whatever the dialogue, it's not likely to be produced by old-fashioned crossbreeding of potatoes. This has never been an easy affair, because many of the wild potatoes in which resistance genes have been found are genetically diploid (having two sets of chromosomes), whereas *tuberosum*, the world's beloved, is an unwieldy tetraploid (with four sets).

Helgeson sees hope in the news from Hamburg, however. Now that resistance genes have begun to be cloned, he says, it might be possible to put them "straight into a tetraploid." He thinks that in the next 5 years, researchers will clone and sequence three, four, or even more such genes. From there, it would not be long before those genes could be "pyramided" into a single supercultivar.

"Of course," says Helgeson, "getting McDonald's to accept a 'transgenic' potato is another matter." **–GLENN GARELIK**

Glenn Garelik is a writer in Falls Church, Virginia.

REGULATORY RESEARCH

A Centennial Letdown for FDA's Biologics Group

A planned overhaul of CBER that would take away its special status as both a regulator and a researcher has staff members threatening to quit

Do regulation and research mix? New leaders at the Food and Drug Administration (FDA) are pushing a big shakeup of the division that oversees biologics in a way that seems to de-emphasize research, although they cite other reasons for making changes.

With little advance warning and no input at all from his scientific advisory panel, FDA Deputy Commissioner Lester Crawford declared on 6 September that much of the Center for Biologics Evaluation and Research (CBER)—which regulates therapies ranging from monoclonal antibodies to gene transfer—would be transferred to the Center for Drug Evaluation and Research (CDER), which regulates more conventional, chemically derived small-molecule drugs. Crawford said the consolidation—the precise details of which have not been worked out—will make the review of new drugs more efficient and consistent.

Over the past few weeks, however, many CBER researchers and outside scientists have begun arguing that the real purpose of the move is to strip away CBER's special status as a regulator that also supports substantial intramural research. This self-directed program, which is based on the campus of the National Institutes of Health (NIH), is supposed to keep regulators at the cutting edge of fast-moving areas of biotechnology. The research effort is the envy of other FDA divisions that don't enjoy such free rein, and some FDA observers—including drug companies that help pay FDA's costs—have long argued that intramural research should be trimmed.

The overhaul came as a complete surprise to most CBER staffers. They were planning to celebrate the division's 100th anniversary this fall and had already prepared a history, passed out commemorative coffee mugs, and scheduled a symposium for late September. Then the FDA bosses rained on their parade.

CBER's friends on the outside were shocked. "There is no good rationale for what is being proposed," says Leslie Benet, a professor of biopharmaceutical sciences at the University of California, San Francisco, who chaired an FDA advisory committee

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