half of which involved either putting on or taking off protecting groups on five different sites around the molecule. At one point in the synthesis, for example, the growing molecule sports an indole group, a five-member ring containing a nitrogen atom that's just begging to react with any electron-hungry compound. The conventional approach caps that nitrogen with a short, chainlike compound called a Boc group to stymie its reactivity.

Baran and his students, however, opted to put the nitrogen's reactivity to use. They reacted the indole with a highly basic compound called LHMDS, which ripped a proton off the nitrogen. They carried out related preparation of another molecular fragment called a terpene. With those groups primed, they then linked two fragments using a specially invented reaction designed to target only the linkage site. By continuing with the strategy, Baran's team cut the synthesis of hapalindole U down to eight steps. Using the same approach, the group turned out another compound in 10 steps that had previously required 25. "This really challenges the rest of us to think that way," Stevenson says.

In addition to making for more efficient syntheses, Baran says he's found that the biggest advantage of using molecular judo is that it forces him to invent new chemistry along the way. Adding protecting groups, Baran says, gives researchers the illusion that they can control the chemistry they are working on. But in reality, protecting groups are added precisely because researchers have not managed to emulate the exquisite knack biological enzymes have for operating on just one bond on a molecule. Removing that safety net forces researchers to find ways to match biology's control. "The point is not to say you should blindly throw away all protecting groups," Baran says. However, he adds, doing so in select cases "is a vehicle for discovery and adventure."

It has a practical upside as well. Fewer synthetic steps mean more of a desired compound at the end, because each added step produces some loss. A 20- to 25-step synthesis typically yields just milligrams of a compound, too little for extensive studies of its biological activity. Baran's approach, by contrast, typically produces final compounds by the gram. Naturally derived compounds, Li points out, remain at least the starting point for about 50% of all new drugs today, excluding small changes to existing compounds. But in many cases, such as with compounds harvested from marine organisms that are difficult to collect, researchers can't get their hands on enough of the naturally occurring compounds for biological tests. Having grams or more of a compound to work with could change things dramatically. "This could potentially revolutionize both [drug] discovery and development," Li says.

Baran, Corey, and others caution that synthetic chemistry's gentle way can't be used in every case. But Baran has already shown that it works with a wide range of complex molecules. That's an achievement in itself and likely a harbinger of many to come.

–ROBERT F. SERVICE

PLANT PATHOLOGY

Deadly Wheat Fungus Threatens World's Breadbaskets

New mutations have put an old killer back on the map. As it spreads, breeders are racing to develop resistant plants

Scientists thought they had beaten *Puccinia graminis* a long time ago, and for good. Before the late 1950s, the fungus was notorious for causing black stem rust, one of the most devastating diseases of wheat. Every few years, outbreaks would lay waste to entire fields somewhere in the world, sometimes sweeping across great swaths of continents in a matter of months.

Salvation came with the development of wheat varieties that resisted the disease, which are widely credited with helping to usher in the green revolution in the 1960s. The new cultivars caught on rapidly, helping ensure bumper crops not just in the United States but in developing countries as well. "Stem rust was something we felt we had solved," says Miriam Kinyua, a plant breeder at the Kenya Agricultural Research Institute (KARI) in Njoro.

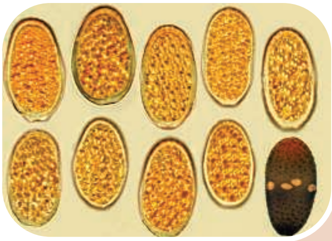
But stem rust is back, and it's more dangerous than ever before. In 1999, a new race of the fungus was discovered in Uganda that can defeat the resistance of most varieties of wheat. The fungus spread in northeast Africa for several years while researchers scrambled for funds to study it. In January, pathologists announced that it had jumped the Red Sea into the Arabian Peninsula—on a path to the major wheat-growing regions of Asia. Compounding matters, a new mutation turned up late last year that enables the fungus to infect even more kinds of wheat. "This is the most virulent strain we've seen in 50 years," says Kay Simmons, the national program leader for plant genetics and grain crops at the U.S. Department of Agriculture (USDA).

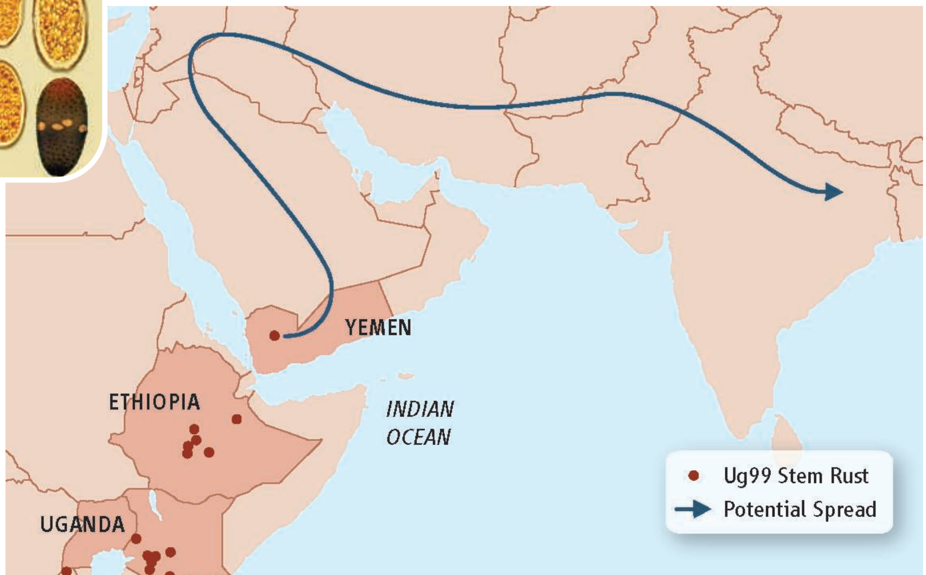
Against the grain. A new race of stem rust, Ug99, could wipe out wheat fields that were once resistant.

CREDIT: DAVID MOWBRAY/CIMMYT

While pathologists nervously track the spread of the disease, breeders have ramped up their search for varieties that can survive it. Already, they've had initial success with two that might help Ethiopian farmers. But it can take years to complete field-testing and generate enough seed to distribute to farmers. With much of the world in need of resistant varieties, the challenge is enormous, says wheat breeder Rick Ward, who coordinates the Global Rust Initiative.

Stem rust is the worst of three rusts that afflict wheat plants. The fungus grows primarily in the stems, plugging the vascular system so carbohydrates can't get from the leaves to the grain, which shrivels. In the 1950s, when the last major outbreak destroyed 40% of the spring wheat crop in North America, governments started a major effort to breed resistant wheat plants. Led by Norman Borlaug of the Rockefeller Foundation and others, researchers succeeded by bundling several genes that conferred powerful resistance in new varieties. One gene, *Sr31*—added later on a large chunk of a rye chromosome—also boosted yield and became widespread in wheat varieties by 1980. *Puccinia*, in contrast, became ever more rare, and fewer new races arose. Researchers turned their attention to the two less devastating wheat rusts, leaf rust and yellow rust, that still cause trouble.





Out of Africa. Blown by winds, stem rust spores (*inset*) are projected to follow the path a related disease took in the 1990s.

Two decades later, pathologists and breeders were caught off-guard when the new race of stem rust turned up in Uganda. It was first detected in 1999 at a research station, where many varieties of wheat were being studied. Ravi Singh, chief wheat breeder and pathologist at the International Maize and Wheat Improvement Center (CIMMYT) in El Batán, Mexico, recalls being alarmed when he heard how many kinds of wheat were susceptible. Most worrying was that this new race—dubbed Ug99—could even kill wheat plants outfitted with the resistance gene *Sr31*. Still, he says, a few new races had turned up in the past decades without causing epidemics. And Ug99 didn't come back the next year. "If it shows up just for 1 year, you can't make any major commitment. It's hard to justify," Singh says.

In 2001, however, Ug99 started infecting wheat cultivars at a research station in Kenya. It was noticed in Ethiopia 2 years later. Still, the response was minimal; CIMMYT was in a budget crunch, and it had little core funding that it could switch to the problem, Singh says. Enter Borlaug, then 90 years old. He and Christopher Doswell of the Consultative Group on International Agricultural Research wrote a memo in 2004 urging CIMMYT leadership to make Ug99 a priority. "We knew the dangers, and we blew the whistle," Borlaug says.

Shortly thereafter, CIMMYT and a sister institute—the International Center for Agriculture Research in the Dry Areas (ICARDA)—started the Global Rust Initiative (GRI) to coordinate efforts to track and study Ug99 and develop resistant varieties of wheat. With funds that Borlaug helped raise from international donors, CIMMYT and ICARDA began to send more seeds from their collections to be evaluated in Kenya, where the pathogen is now endemic—so many seeds that the seven breeders and pathologists at KARI's Njoro research station are increasingly overwhelmed. "Ug99 is so threatening that other problems have almost been overlooked," says Kinyua.

So far, about 90% of the 12,000 lines tested are susceptible to Ug99. That includes all the major wheat cultivars of the Middle East and west Asia. At least 80% of the 200 varieties sent from the United States can't cope with infection. The situation is even more dire for Egypt, Iran, and other countries in immediate peril.

More bad news arrived last December. Tests on sentinel plots by GRI-funded researchers revealed that Ug99 had mutated. Testing at a USDA laboratory in St. Paul, Minnesota, showed that the new race can now also defeat *Sr24*, another key source of genetic resistance. "That was the worst case scenario," says USDA plant pathologist Yue Jin, who did the work. "It's increased the worldwide vulnerability incredibly." Right now, this identification may only be done in midwinter in Minnesota, so that any spores that might escape will be killed by the temperatures. Researchers are hopeful, however, that the recent sequencing of the *Puccinia* genome will speed development of diagnostic tools that can be easily used in Africa.

Meanwhile, Ug99 continues its march. In January, Jin's Minnesota lab confirmed that Ug99 had reached Yemen. The fear is that the spores will quickly spread via winds north through the Middle East and then head to the bread baskets of India and Pakistan, as an epidemic of yellow rust did in the 1990s. That epidemic caused some $1 billion in damage, and stem rust could easily triple those losses, CIMMYT has estimated.

Fungicides can help control the damage from *Puccinia*, and GRI will begin trials in June to figure out the best way to use them. But chemical treatments are too expensive for many farmers in the developing world, Singh says, so plant breeding is the primary strategy.

Two new kinds of wheat have shown promise in Ethiopia. "The yields are very favorable, comparable to the commercial varieties," says Tsedeke Abate, director general of the Ethiopian Institute of Agricultural Research in Addis Ababa, where a half-dozen scientists are working full-time on Ug99. The immediate challenge is to grow enough seed from these resistant strains to distribute to Ethiopian farmers. Last year, researchers harvested 15 kilograms of precious seed. Then, in a painstaking effort, they hand-planted this wheat to maximize seed production. Spread over 4 hectares, the seedlings had extra room to grow and were carefully watered and weeded by hand. The resulting yield was nearly 4 tons of seed of each variety. "They went to extraordinary efforts," Ward says.

Now, that success must be replicated for other regions. Singh says it's important to come up with resistant varieties for countries that aren't yet infected. Planting those before an epidemic strikes could help slow the spread of the disease. Egypt, for example, has vast tracts of wheat. If stem rust infects those crops, they will send enormous quantities of spores throughout the Middle East and toward west Asia. It's a tight race, as several observers suspect that Ug99 could start reaching Egypt later this year.

Despite the world's initial slow response, Borlaug, who turned 93 last week and is battling lymphoma, says he is optimistic that the fungus will be beaten again.

–ERIK STOKSTAD

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