MICROBIOLOGY

Versatile Gene Uptake System Found in Cholera Bacterium

Bacteria are promiscuous gene swappers. Their ability to pass genes for antibiotic resistance from one strain to another is legendary (*Science*, 15 April 1994, p. 375). Now, with more and more microbial genome sequences pouring out, researchers are stumbling across unexpected resemblances between the DNAs of evolutionarily distant species—some of which can best be explained by the transfer of other kinds of genes as well. Just how bacteria sustain this traffic in genes has been a puzzle. But in this issue of *Science*, a research team led by molecular microbiologists Didier Mazel of the Pasteur Institute in Paris and Julian Davies of the University of British Columbia in Vancouver may provide an answer.

On page 605, the researchers describe new evidence showing that the cholera bacterium *Vibrio cholerae* has a versatile acquisition system—called an integron—that may capture many different types of genes. Until now, integrons, strips of DNA containing repetitive sequences that allow genes from one organism to be used by another, had been associated only with genes conferring antibiotic resistance.

The Davies team's proof that *Vibrio* has a functioning integron system includes the cloning of a *Vibrio* gene for an enzyme that splices genes into the microbe's integron. In other bacteria, this enzyme, called an integrase, is needed to move antibiotic resistance genes into and out of their genomes, and the cloning of the *Vibrio* enzyme is the best evidence yet that this pathogen can acquire genes from its fellow microbes.

But it's also a sign that the integrase/integron system could have a much broader role than people had thought, because *Vibrio* has an integron-like stretch of DNA that is studded with genes for everything from adhesion proteins to toxins—all possibly acquired from other bacteria. "[The work] is the first clear demonstration that the integron system is [used] for the dissemination of other types of genes [besides those for antibiotic resistance]," says integron discoverer Hatch Stokes of Macquarie University in Sydney, Australia.

Other examples may soon follow, for researchers are also finding evidence that pathogens such as *Escherichia coli*, which has been linked to several deadly episodes of food contamination, have picked up genes from other organisms that make them more virulent. By boosting researchers' understanding of how bacteria use each other's genes to both enhance their virulence and counteract antibiotics, these findings should ultimately "lead to more effective therapeutics and new vaccines," says James Musser, a microbiologist and pathologist at Baylor College of Medicine in Houston.

Until now, most researchers would not have suspected that integrons play a part in the pathogenicity of microorganisms like the deadly *E. coli*, because all the known integrons were associated with antibiotic resistance. But Mazel, Davies, and a few other people thought they saw evidence in *V. cholerae* that the integron system might be capable of ferrying more genes than had been thought. *Vibrio* has repeated sequences that look like those in known integrons, and the sequences flank not only antibiotic resistance genes but also genes coding for toxic proteins and enzymes that put methyl groups on DNA as well as several genes of unknown function, says molecular microbiologist Paul Manning of the University of Adelaide in Australia. Manning discovered *Vibrio*'s repeating sequences, which occur roughly 80 times in one region of the microbe's chromosome, in the 1980s, and in the December 1997 issue of *Molecular Microbiology* he suggested that the repeats are part of a giant integron.

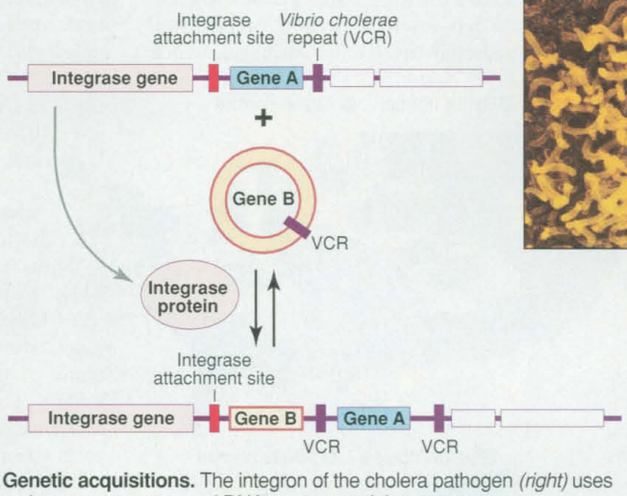
In the current work, Mazel and Davies tested whether the *V. cholerae* repeat is in fact part of an integron. In integrons, a repetitive sequence serves to signal the presence of a gene that can be incorporated into the genome. The researchers made a gene "cassette" that contained a *Vibrio* gene and a marker gene—which would enable them to tell whether these genes were being expressed—between two copies of the repeat. They then inserted the cassette into a circular piece of DNA called a plasmid and allowed the plasmid to be taken up by another bacterium, *E. coli*. The *E. coli* started using the foreign genes. "We showed we could move [the genes] using the *Vibrio cholerae* repeats," says Davies. The *E. coli* cells used the integrase in their own integron, which carries antibiotic resistance genes, to splice the cassette into that integron where the genes can be expressed.

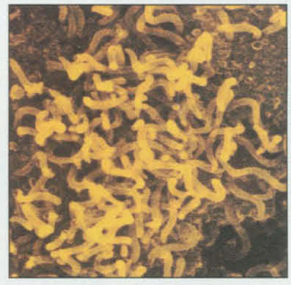
But complete proof that *Vibrio* can both take up foreign genes and donate its own required the identification of the pathogen's integrase, and in their initial search, Mazel and Davies were unable to track down the enzyme. Then Mazel spotted a DNA segment in the incomplete *Vibrio* genome that seemed to have the right sequence to encode a portion of the integrase. He, Davies, and their colleagues went on to clone that gene and have now shown in *E. coli* that it can splice out gene cassettes. "The assumption is that if it can take [the gene] out, it can put it back in," he says. "They've done the experimental work" to show that the *Vibrio* sequence is an integron, comments Milton Saier, a microbiologist at the University of California, San Diego.

Davies and his colleagues also found integrons in *Vibrio* samples stored since 1888, which shows that the gene uptake system predates antibiotics. This finding, combined with the integron's large size—it takes up 5% of the chromosome and has 10 times as many genes as any known integron—has led Davies to suggest that it may even be the predecessor to integrons in other pathogens, which may have adapted them to acquire antibiotic resistance genes.

Whether or not that's the case, this integron could bode ill for new vaccines being developed against cholera, Manning warns. He worries that a live vaccine that uses *Vibrio* strains whose virulence genes have been removed may still be capable of getting new virulence genes through its integron. "One would need to knock out the integrase," he says.

Researchers don't yet know whether integrons have also enabled other microbes to acquire virulence genes. Some genes with an





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Genetic acquisitions. The integron of the cholera pathogen *(right)* uses an integrase enzyme and DNA repeats to pick up genes.

inherent ability to be expressed may have gotten into bacteria and thus wouldn't require integration through an integron. But there is plenty of evidence that, somehow, such gene transfers do take place. For example, at the Conference on Microbial Genomes, which was held in February in Hilton Head, South Carolina, geneticist Fred Blattner reported that his team at the University of Wisconsin, Madison, has found that the pathogenic *E. coli* strain O:157 has a million extra base pairs of DNA compared to a laboratory strain. This extra DNA includes a few genes that are quite similar to genes that code for toxins produced by *Yersinia*, the flea-borne pathogen that causes bubonic plague.

And Dieter Söll, Michael Ibba, and their colleagues at Yale University have discovered the gene for an enzyme that seems to have escaped from a microbe that lives in hot environments and taken up residence in the spirochetes that cause Lyme disease and syphilis. Although the gene is not directly related to virulence, its enzyme product might still be a good target for therapy because it is not found in most bacteria. This could lead to a spirochete-specific antibiotic, Söll says.

As researchers decipher more and more microbial genomes, the transfer of virulence genes by integrons may become a common theme, says Stokes. His prediction: "What we're seeing is the tip of the iceberg."

–Elizabeth Pennisi

CLIMATE PREDICTION

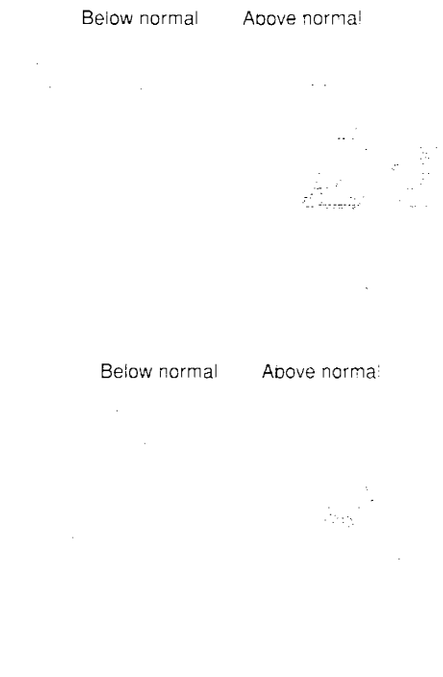
Models Win Big in Forecasting El Niño

Predictions of the most recent El Niño were widely regarded as a stunning success: Forecasters warned of torrential rain in California this winter and drought in Indonesia, and they were right. But if meteorologists had dared to rely more heavily on their computer models, those predictions could have been even better—and next time, they may be. That's because this year's El Niño, one of the strongest in a century, was a proving ground for the models, showing which types do the best job at predicting this warming of the tropical Pacific and its effects on global weather patterns. When it comes to models, forecasters learned this year, bigger is better.

In a recent ranking of predictive efforts, the most ambitious models—which chew up hours of supercomputer time simulating how winds, water, and heat shuttle among land, ocean, and atmosphere—all came in near the top, while less sophisticated models often faltered. "For the first time, the big models got it right," says tropical meteorologist Peter Webster of the University of Colorado, Boulder. As meteorologist Eugene Rasmusson of the University of Maryland, College Park, puts it, "the more bells and whistles, the better." Knowing which models to trust, says Jagadish Shukla of the Institute of Global Environment and Society in Calverton, Maryland, "is a big breakthrough. We now have confidence in 6-month forecasts based solely on a model."

Even veteran El Niño forecasters who have seen the models fail in the past now say that this year's success has won the models a larger role in forecasting. "My guess is that next time we will rely much more heavily on the [big computer] models than we did this time," says Ants Leetmaa, director of the Climate Prediction Center (CPC) at the U.S. Weather Service's National Centers for Environmental Prediction (NCEP) in Camp Springs, Maryland, and co-developer of one of the most sophisticated models. That next test—predicting whether El Niño will linger through the fall or switch to its mirror image, La Niña—is already looming. By Christmas, this more difficult test will provide even more convincing proof of the models' mettle—or expose their weaknesses.

The value of the more complex El Niño models emerged when climate forecaster and statistician Anthony Barnston of the CPC rated a dozen different methods on how well they predicted the Pacific warming, which peaked at the end of last year. As he describes in a paper in the proceedings of the October 1997 Climate Diagnostics and Prediction Workshop, Barnston looked at the predictions each model was offering in February and March of 1997 for the coming fall. Six of the models were so-called empirical models, which make no attempt to simulate the real-world interplay of winds and currents that actually leads to an El Niño. Instead, these models are in essence automated rules of thumb, doing what human forecasters do but in a more objective way. They compare current observations of the tropical Pacific Ocean and atmosphere with comparable data for the periods leading up to El Niños of the past 40 years and issue predictions based on the resemblance. But as a group, these models did poorly this time, as they often have in the past. Three of the six called for only a moderate El Niño by the fall, while three predicted weak warmth or normal conditions.



It's a match. Complex computer models helped forecasters last November to predict a wet winter for the southern United States and dryness in spots in the north *(top)*. Actual precipitation *(bottom)* fell much as predicted.

Even a more complex model, which won fame in 1986 by being the first to successfully predict an El Niño (*Science*, 13 February 1987, p. 744), "fell flat on its face" this time, observes Barnston. This so-called dynamical model, run by Mark Cane and Stephen Zebiak of Columbia University's Lamont-Doherty Earth Observatory in Palisades, New York, does simulate ocean-atmosphere interactions, although only in the tropical Pacific. This time the model predicted only a gradual warming to near-normal conditions rather than intense warming. Cane can't say exactly why the model failed so spectacularly, but it seems to have something to do with the wind observations used to get the model started, which are sparse in the southeast Pacific.

In contrast, the most sophisticated modeling efforts rated by Barnston scored an impressive success. These more complex models also couple ocean and atmosphere but do so worldwide, like the large-scale models that scientists have developed over several decades to forecast global warming. Researchers have been struggling to construct these "coupled" models for much of this decade by cobbling together parts of weather and climate models; their creations perform millions of calculations and have insatiable appetites for computing time.

In early 1997, all four of the bigger