TOR teams have reported that many ill or dead seals were underweight and some were emaciated, which may point to a food shortage. Wilson carried out a limited survey of seal feces collected on Apsheron last year and found that kilka appeared to make up only a tiny proportion of their diet, suggesting that the seals had to make do with less-nutritious prey. "We need to extend these diet studies," Wilson says. But it does seem to bear the tentacle-marks of *Mnemiopsis*.

Dumont and other experts argue that steps must be taken quickly to rein in *Mnemiopsis*. After *Mnemiopsis* levels in the Caspian last fall exceeded those ever reached in the Black Sea, a scientific advisory committee called on littoral nations to approve plans to unleash a predator this spring to control the invader. Their choice was *Beroe ovata*, a heftier comb jelly that dines almost exclusively on *Mnemiopsis*. *Beroe* slipped into the Black Sea in 1997 and quickly brought the villain to heel. There, *Mnemiopsis* populations had plunged so low by last year that it was hard to find specimens for analysis. *Beroe*, says Dumont, "is almost too good to be true."

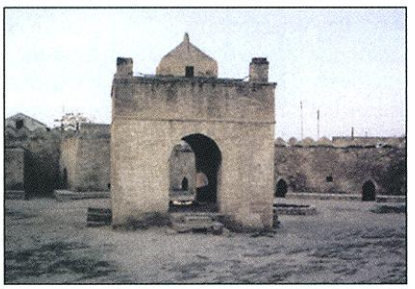
Azerbaijan and Iran are pressing hard for *Beroe* to be introduced, but it's unclear whether the other Caspian governments will climb aboard. Signs look unfavorable for agreement on something as contentious as biological pest control—no matter how benign *Beroe* would appear—when tensions are already running high over oil rights.

**Political hardball**

Like 49ers staking claims in California, the five littoral nations have asserted overlapping territorial claims in the Caspian itself. Last summer, Iranian gunships chased an Azeri research vessel out of waters claimed by both countries. A meeting planned for last October at which the countries had agreed to demarcate borders was abandoned after the 11 September terror attacks, although the leaders of Azerbaijan and Turkmenistan are scheduled to visit Moscow later this month in part to revive the negotiations.

The Caspian nations are playing hardball because their oil is considered a major prize by Western powers. The newly independent states could act as a counterweight to OPEC, because the Caspian oilfields would greatly augment the few reserves—including Siberia and the North Sea—not controlled by the Middle East–dominated cartel. Caspian oil "can offset [OPEC's] efforts to keep prices high and their use of high prices for political dictates," says Brenda Shaffer, research director of Harvard University's Caspian Studies Program.

Apart from Russia, the three countries with the largest Caspian reserves—Azerbaijan, Kazakhstan, and Turkmenistan—have welcomed alliances with the West, which they think will help them convert their black gold into cash and limit Russian influence in their affairs. Beyond oil and gas, the region is important to the United States, which "needs to develop friends like Azerbaijan and Kazakhstan in the Muslim world, due to their clear separation of religion and state," says Shaffer. Russia, meanwhile, has bolstered its sphere of influence by strengthening ties with Iran and forming alliances with other ex-Soviet littoral states.



**Eternal flames.** At the Surakhany Fire Temple, ancient Persians meditated on Baku's perpetually burning hills, including the Kirmaky gas seep (*left*).

Sound like a powder keg waiting to be lit? Quite so, says Terry Adams, a senior associate at Cambridge Energy Research Associates and founding president of the Azerbaijan International Operating Company oil consortium: "The seeds of future Caspian conflict were planted early." And with an international effort to safeguard the Caspian's ecology nowhere in sight, the lake itself can only suffer in the process. –RICHARD STONE

CREDIT: MIKE SIMMONS/CASP

MEETING INFECTIOUS DISEASES

# New Weapons in the Battle of the Bugs

**CHICAGO—Postponed from its original late-September schedule following 11 September, a meeting* on infectious diseases sponsored by the American Society for Microbiology finally convened here last month. Two families of potential antibiotics had attendees talking, and one team presented a possible treatment for the deadly tropical Chagas disease.**

## Giving Chagas the Kiss-Off

You may call it just a kiss, but a quick peck from a kissing bug can mean big trouble. The cockroach-sized insects spread the parasite that causes Chagas disease, also known as American trypanosomiasis. Left untreated, the infection lingers for decades, causing devastating heart and intestinal problems that kill 50,000 people a year. No effective drugs exist for the more than 16 million people, most of them poor people in Central and South America, who have chronic infections. But a new strategy, so far successful in lab dishes, aims to stop the parasite in its tracks.

The approach, presented by Julio Urbina of the Venezuelan Institute for Scientific Research in Caracas and his colleagues, blocks the parasite from making ergosterol, a fatty, cholesterol-like molecule that the parasite needs to keep its cell membranes working properly, among other key functions. "It's a very promising target," says parasitologist Juan B. Rodriguez of the University of Buenos Aires, Argentina.

The kissing bug emerges at night from thatched roofs and cracks in the walls of adobe houses. It bites sleeping people and defecates on their skin, depositing the parasite. When people scratch the bite or touch their eyes or mouth, the parasite, a protozoan called *Trypanosoma cruzi,* enters its victim. Others are infected from their mothers at birth or when nursing, and still others receive transfusions of contaminated blood.

In the past decade, South American governments and the World Health Organization have funded a campaign to cut Chagas transmission by plastering walls, spraying insecticide, and pushing blood banks to screen for the parasite. The campaign has been remarkably effective, but new drugs for Chagas disease are still desperately needed for the millions who are already, or will become, infected. The two drugs used today to treat acute cases have severe side effects, and they can't touch parasites that have burrowed into the heart and intestine of chronically infected patients.

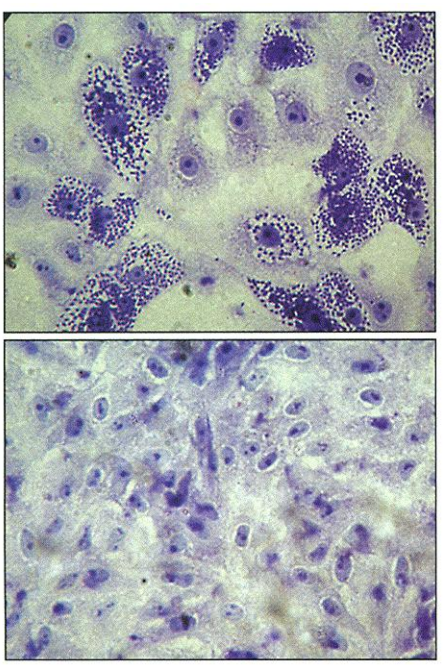
To find a new Chagas drug, Urbina's

* Interscience Conference on Antimicrobial Agents and Chemotherapy, 16–19 December 2001.

team focused on compounds likely to cripple key parasite enzymes. Like other researchers in developing countries working on diseases that afflict the world's poor, Urbina and colleagues tested hand-me-down drugs developed by pharmaceutical companies for other conditions. In earlier work, the Venezuelan team had tested several antifungal drugs that blocked ergosterol biosynthesis. One such drug appeared to rid mice of both the acute and chronic infection (*Science*, 16 August 1996, p. 969). That research continues, but the antifungal drugs have yet to prove themselves in clinical trials on Chagas patients.

This time the researchers turned to a fledgling anticholesterol drug developed by AstraZeneca in London. In both people and parasites, the compound, abbreviated BPQ, blocks an enzyme called squalene synthase. This in turn blocks cholesterol synthesis in humans and ergosterol synthesis in trypanosomes.

In laboratory cultures, Urbina reported, low doses of the compound killed a free-living form of the parasite, called the epimastigote. And it mowed down the most dangerous form of the parasite—the amastigote, which infects human heart and intestinal tissue—as it grew



**Out, damned spots.** Cells infected with the Chagas disease parasite (*top*) are jammed with protozoans (small purple spots). An experimental anticholesterol drug largely rids cells of this burden (*bottom*).

inside cultured monkey kidney cells. The drug spares host cells, probably because they replace missing cholesterol from their surroundings, but it kills the parasites, which can't replace their ergosterol, Urbina says.

"It's very interesting and good work, but it's very early on," says Louis Kirchhoff of the University of Iowa, in Iowa City, who notes that the drug has yet to be tested in animals or humans. But for chronic Chagas disease, he adds, there are not a lot of alternatives.

## Antibiotic Contenders

As antibiotic-resistant superbugs spread worldwide, researchers have stepped up the hunt for new drugs to fight them. It's been difficult: In the last 3 decades, just one new class of antibiotic has made it to the clinic. At the meeting, researchers described two new contenders that kill drug-resistant superbugs, one in animal tests and one in lab cultures. If they hold up under further testing, the compounds could one day offer an edge in the ongoing arms race against the most dangerous of bacteria.

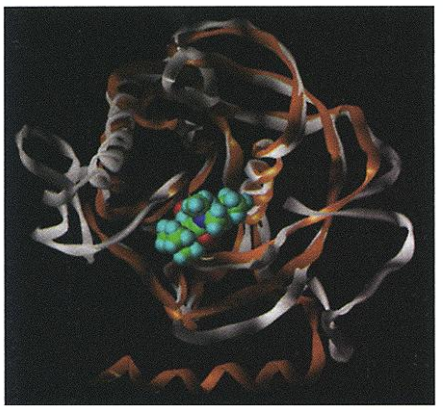
Almost all of today's antibiotics use one of three strategies. They block microbes from assembling a cell wall, manufacturing new proteins, or copying their DNA. As bacteria evolve ways to outwit these strategies, new targets are urgently needed.

One possible target is the bugs' DNA. Roland Bürli and his colleagues at GeneSoft Inc. in South San Francisco, California, have been trying to improve upon a well-studied class of synthetic compounds, some of which can kill bacteria by binding to their DNA. GeneSoft's team engineered compounds called heteroaromatic polycycles (HARP); these compounds nestle into DNA at specific sequences called promoters that flank genes and control their expression. Once there, the compounds stop the microbes from activating genes. They also bind sequences used by DNA replication enzymes, which interferes with bugs' ability to copy their genome.

To test the compounds' power, the team screened 200 versions against three nasty bugs: methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis*, and penicillin-resistant *Streptococcus pneumoniae*. Four of the 200 compounds killed the bugs at relatively low doses. By binding to promoters, the four compounds prevented the bacteria from transcribing key genes, according to results from another GeneSoft team headed by James Ge.

One looming hurdle remains in the drugs' way: Human DNA could be disrupted by such compounds as well. To demonstrate that the compounds can be made specific to bacteria, Bürli's team tweaked them so they killed bacteria but not yeast, whose chromosomes resemble those of human cells.

The HARP compounds "have the potential to be a real drug," says Jianshi Tao, director of molecular biology at Cubist Pharmaceuticals in Lexington, Massachusetts. But pharmacologist Steven Projan, who directs antibacterial research at Wyeth-Ayerst Research in Pearl River, New York, cautions that long-term animal studies are needed: "It's usually the case that things that interact with DNA are toxic."



**Tenacious.** A possible antibiotic (blue beads) latches onto the active site of an enzyme essential to pathogens. The *Escherichia coli* version of the enzyme is in red, the *Streptococcus pneumoniae* version in light gray.

Another new class of antibiotic blocks an enzyme called peptide deformylase (PDF) that is essential to bacteria but not to mammals. The killing tactic is simple: Most newly made bacterial proteins are tagged with a one-carbon unit called a formyl group, which is clipped off later by PDF to activate the protein. Higher organisms don't use this sort of protective wrapping on their proteins, so a compound that blocks PDF should in theory stop bacterial growth but leave human and animal cells alone.

Early results in animal models suggest that it does. John Clements and colleagues at British Biotech Pharmaceuticals Ltd. in Oxford have designed and chemically synthesized PDF inhibitors based on knowledge of the enzyme's three-dimensional structure. The inhibitors block the enzyme by clinging to a metal atom in the active site of the enzyme. One of the lead compounds, called BB-83698, effectively treated pneumonia in mice, overpowering even the penicillin-resistant microbes most dangerous to humans.

Another type of PDF blocker clears *Staphylococcus aureus* infections from the bloodstream of mice, Zhengyu Yuan and colleagues at Versicor Inc. in Fremont, California, reported at the meeting. The compounds, called urea hydroxamates, also fit into the active site of the enzyme, Yuan says.

Although PDF is a "good target," compounds that block it could run into problems, cautions Malcolm Page, head of discovery biology at Basilea Pharmaceutica Ltd. in Basel, Switzerland. Bacteria might evolve resistance easily, and at least some strains can get by even with minimal PDF, he says.

Hurdles aside, the two classes of antibiotics are "exciting new possible therapeutic agents," says microbiologist Abigail Salyers of the University of Illinois, Urbana-Champaign. With drug resistance on the rise, she adds, "we really need to have as many backups as possible."

—DAN FERBER

CREDITS: (LEFT TO RIGHT) JULIO URBINA; JOHN CLEMENTS/BRITISH BIOTECH PHARMACEUTICALS LTD.