Dorland notes that no one in APS has questioned the facts of the cases publicized in Los Angeles. Liu Gang, the dissident who as a physics student helped organize protests on Tiananmen Square and who escaped to the United States in 1996 after he was released from prison, says "I can tell you that I experienced torture by policemen and common prisoners sent by policemen [in my] solitary cell, when I was in prison." *Science* has what is said to be a firsthand account from a source close to Zhu, which reports that while in prison, Zhu was beaten with a bench by an orderly and severely injured, then went on a hunger strike to protest the subsequent lack of medical treatment. Zhu survived, but the dissident network has not been able to confirm his release at the end of his prison sentence 2 years ago.

"We take great efforts to be accurate," Sessler, the APS president, says about the reports on Zhu and Lu. "Very rarely if ever has somebody found that we misspoke, and certainly that hasn't been so in this case." As to the enforced revision, says Sessler, "we're down to a level of detail of what's appropriate to get people's attention."

Sessler says the APS isn't wavering from its commitment to human rights. "There's a long tradition, which I fully support, of the Physical Society being involved in public affairs which concern physicists," he says. "We are concerned about any physicist, anywhere in the world, who is suffering a human-rights attack."

Although that concern is harder than ever to translate into an effective campaign, a handful of organizations say they have found ways to adapt to the changed political landscape. "We're making a greater effort to match cases of imprisoned scientists with individual scientists in their field ... who are interested in that country," says Carol Corillon, director of the Committee on Human Rights of the National Academy of Sciences, the National Academy of Engineers, and the Institute of Medicine. This tailored approach, she says, produces committed activism by scientists who have useful connections. The committee recently reported, for example, that after a visit by committee members, Guatemala indicted three top military officers for the murder of an anthropologist.

There may no longer be a single political route to success in the campaign for human rights. But if the heirs to Sessler's Cold War activism can master the new landscape, scientists may once again find human rights as fascinating as lasers and quantum dots.

–JAMES GLANZ

INFECTIOUS DISEASE

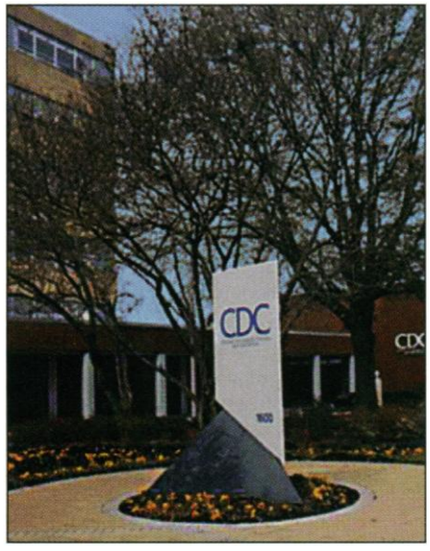
Molecular Methods Fire Up the Hunt for Emerging Pathogens

Combining an early warning system with genetic techniques, microbiologists have stepped up the hunt for emerging pathogens in the United States

When a 3-year-old Connecticut girl was hospitalized with an often-fatal type of kidney failure last year, doctors at first suspected that she was infected with *Escherichia coli* O157:H7, a dangerous strain of bacteria that can cause kidney failure in children. But all attempts to culture this and other pathogens failed. Fortunately, the girl recovered, and the case became one of the thousands of unexplained illnesses put on the books every year in the United States.

This time, however, the story didn't end there. To track down the mystery pathogen, doctors turned over samples of the girl's blood taken during the height of her illness to a specialized pathogen lab in California, via the Unexplained Illness Working Group, a network of infectious-disease experts coordinated by the Centers for Disease Control and Prevention (CDC) in Atlanta. The California lab used sensitive molecular and immunological probes to identify the pathogen: an unknown strain of enterovirus, a large group of microbes that includes the poliovirus. This information came too late to help the Connecticut girl, but researchers are still probing the virus's genome to see if it matches one of the more than 70 known enterovirus strains, or if it is a new pathogen.

This is just one example of how new molecular technologies are speeding the hunt for microbes that have recently begun to attack human hosts, or so-called emerging pathogens. To fight these bugs, researchers are now going beyond the traditional means of identifying pathogens—culturing them in petri dishes and test tubes—and isolating the DNA or RNA that makes up their genomes. The enterovirus that infected the Connecticut girl, for example, was spotted by matching a segment of its RNA to that of other known enteroviruses. The Unexplained Illness Working Group, created by the CDC in 1994, is one leader in this effort, focusing not on the tropics, home to infamous viruses such as Ebola, but on the familiar settings of U.S. hospitals and clinics, where new and deadly strains may also emerge.



CREDIT: CDC

Pathogen central. The CDC in Atlanta is at the hub of a microbe-spotting network.

The network serves as an early warning system for dangerous microbes as well as a focal point for research on new tests. And over the past year the team has revved up to full speed: Some 200 cases of unexplained illness are under active investigation, and results are starting to emerge. The network has tracked down possible new strains of enterovirus—implicated in a number of recent outbreaks of childhood disease in the United States and Asia—and has uncovered evidence that microbes once thought innocuous can cause disease. For example, the team has found that human herpesvirus 6, previously thought to be benign when it infects children, is behind some cases of childhood encephalitis. Once new pathogens have been identified, says CDC epidemiologist Bradley Perkins, the working group's Atlanta-based coordinator, the ultimate goal is to develop a "diagnostic test that a clinician could order in the hospital."

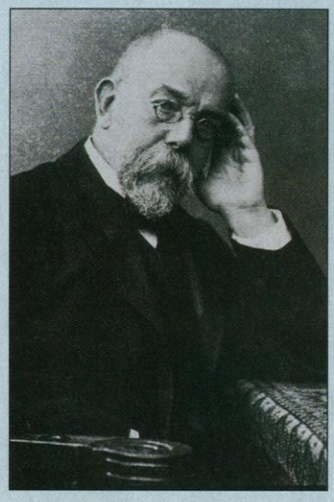
The evidence so far suggests that some unidentified killers may already be out there. In up to 14% of deaths caused by infection in people between the ages of 1 and 49, no known microbe could be identified as the culprit, according to surveys carried out over the past few years by the working group and other collaborators.

But finding these silent killers isn't easy. The time-honored means of identifying an invading microbe is by taking blood and tissue samples and trying to culture the organism in various artificial growth media, then identifying it either under the microscope or with

19th Century Rules of Causation Outdated?

For more than a century, three postulates set down by the German microbiologist Robert Koch have guided the hunt for disease-causing microbes. Koch argued in 1890 that to prove an organism causes a disease, microbiologists must show that the organism occurs in every case of the disease; that it is never found as a harmless parasite associated with another disease; and that once the organism is isolated from the body and grown in laboratory culture, it can be introduced into a new host and produce the disease again. (An oft-stated fourth postulate, that the microbe must be isolated again from the second host, was not part of Koch's original formulation.)

But Koch's criteria are now being swept aside by new technology. Many of the microbes isolated in recent years by molecular techniques that pull segments of their DNA or RNA directly out of infected tissues (see main text) cannot be grown in culture. That makes it impossible to fulfill all three of Koch's postulates. As a result, more and more biologists are agreeing with Stanford University microbiologists David Relman and David Fredricks, who argued a few years ago in the journal *Clinical Microbiology Reviews* that it's time to modify Koch's strict requirements.



Obsolete? After a century, Koch's rules seem outdated.

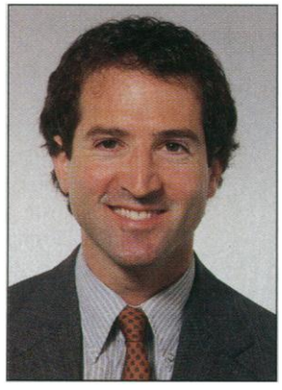
Relman and Fredricks say that researchers can instead build a convincing case against a microbe by examining a wide variety of molecular circumstantial evidence, such as how tightly the suspect microbe is associated with infected tissues and how closely the time course of the disease correlates with the amount of microbial genetic material present. But some microbiologists caution that loosening the rules of evidence too much could lead to mistaken convictions, especially because the human body harbors many seemingly harmless microbes.

Charting the narrow course between accepting molecular evidence and making mistakes is tricky. "If you play the game that you have to fulfill Koch's postulates, you fall into a line of thinking that has been obsolete for decades," says Patrick Moore, a molecular biologist at Columbia University in New York City. He and his wife, Columbia's Yuan Chang, used molecular methods rather than Koch's tenets to finger a herpesvirus as the cause of Kaposi's sarcoma, an AIDS-associated skin cancer.

Still, Moore admits that there is room for error. "The literature is rife with examples of people finding various viruses in tumors and other diseases," he says. For example, last year Makoto Mayumi and colleagues at the Jichi Medical School in Tochigi-Ken, Japan, used molecular techniques to isolate a virus they called transfusion-transmitted virus (TTV). They found this virus in many patients with hepatitis and chronic liver disease and proposed that it might be causing these syndromes. But earlier this year in *The Lancet*, hepatologist Nikolai Naoumov and his colleagues at the University College London Medical School compared patients with liver disease with healthy controls—and found that both groups were infected with TTV at roughly the same rate, implying that it does not cause liver disease. "With the increase in molecular fishing, there is a greater chance of identifying foreign genomes in humans which are not necessarily pathogenic," Naoumov says.

Despite such reservations, most researchers agree that Koch's original postulates no longer work. "We need to define new rules of causality," says Moore. "And I think that [Relman and Fredricks] have made a really wonderful attempt to tackle that." **–M.B.**

physiological and immunological tests. But many organisms can't be cultured, either because no one knows the conditions in which they thrive or because they can't exist outside the body. "Trying to culture organisms has been the downfall of previous attempts to look for unknown pathogens," says Perkins. "It is daunting to think that you are going to be able to culture something when you don't know what it is and you don't know what its growth conditions are."



Oral hygiene. Relman found new microbes in the mouth.

Work reported by Stanford University microbiologist David Relman at a meeting on emerging infectious diseases earlier this year* underscores the limits of the traditional approach. Relman's lab, which collaborates closely with the working group, took a sample of the microbial communities that live in the spaces beneath the teeth and gums and divided it into two parts. One half was cultured in a variety of standard bacterial growth media, and the other half analyzed with the polymerase chain reaction (PCR), which can amplify minute amounts of DNA or RNA. All of the cultured bacteria belonged to known genera, and only 11% appeared to be new species. But of the bacteria identified through PCR analysis, 30% represented new species, and 13% appeared to be from entirely unknown genera—implying that a staggering number of unidentified microbes live in the human mouth alone.

Of course, most unknown organisms probably don't cause disease. To find the ones that do, the working group relies on experts at hospitals and clinics in four states—California, Connecticut, Minnesota, and Oregon—who spot unusual illnesses, then funnel specimens through the network to specialized labs, often run by these states' health departments. The labs hunt for clues about the organism involved, then try to pin down its identity using molecular techniques.

In the case of the Connecticut girl, for example, scientists at the California health department's Viral and Rickettsial Diseases Laboratory in Berkeley suspected that an enterovirus might be responsible, because this type of virus infects many tissues and is implicated in a number of recent outbreaks of childhood diseases, such as encephalitis and liver failure. The researchers used a technique called consensus PCR, so-called because it tests for conserved genetic sequences that are shared by closely related organisms—in this case by all known strains of enterovirus. Such conserved sequences were found in the girl's blood, and an antibody test against enteroviruses then confirmed that these microbes were involved.

Consensus PCR was also used by scientists at CDC and their collaborators to nail the microbe behind the hantavirus outbreak in the southwestern United States in 1993. And Relman led a team that used it to identify the bacterium that causes Whipple's disease, a debilitating syndrome that causes symptoms such as diarrhea and weight loss. The rod-shaped bacteria were spotted in affected tis-

*International Conference on Emerging Infectious Diseases, Atlanta, Georgia, 8–11 March.

CREDIT: (TOP) MARK MARTEN/NATIONAL LIBRARY OF MEDICINE

sue in the 1960s but hadn't been cultured.

When researchers have no clues about what kind of organism is responsible, they sometimes turn to another powerful PCR technique called representational difference analysis (RDA). In this method, both healthy and diseased tissues are subjected to a variant of PCR that "subtracts" sequences common to both specimens, leaving only the genome of the infectious agent. Using RDA, in 1994 molecular biologists Patrick Moore and Yuan Chang at Columbia University in New York City isolated small bits of DNA from a skin lesion in an AIDS patient afflicted with Kaposi's sarcoma, a cancer that often affects HIV-infected people. From these genetic segments the pair was able to sequence the complete genome of a new virus called KSHV, now thought responsible for the cancer.

Powerful as they are, these techniques are laborious and time-consuming—and not always successful. So researchers are working to improve their methods. For example, Relman, working with Stanford biochemist Patrick Brown, has begun exploring the use of "pathogen detection chips," using the DNA chip technology developed by Brown and others (*Science*, 24 October 1997, p. 680). The idea is to put DNA strands from known pathogens on the chip and then see whether labeled DNA from an unknown microbe binds to any of the fixed pathogen DNA.

Relman and Brown have also begun using this DNA microarray technique as "cellular scouts" to detect changes in gene expression in the host, for example in immune system cells. Their goal is to create profiles of the gene expression changes triggered by specific kinds of invaders. Thus they would use the body's own response to identify pathogens, an approach Perkins calls "totally revolutionary." Preliminary results are promising: Brown's lab has shown that white blood cells express different genes when exposed to different combinations of immune signaling proteins called cytokines, which are produced in response to infection. If related microbes provoke similar cytokine responses, Moore says, the scout approach might quickly narrow the hunt to certain groups of organisms.

Meanwhile, the search for new methodologies continues. And researchers say that the molecular identifications thus far suggest that combining heightened surveillance with state-of-the-art techniques is bound to pay off sooner or later. Says Moore of the working group: "I think they have a really good chance of making some great discoveries."

—MICHAEL BALTER

PHYSICS

How Matter Can Melt at Absolute Zero

New tools are revealing the crowd behavior of electrons at close to absolute zero, where freezing and melting are governed by quantum mechanics

If you cool a piece of ice to the very lowest temperatures possible, about the last thing you would expect it to do is melt. But physicists are learning that some exotic crystals made of electrical charges or electron spins do indeed engage in something like that odd behavior: They "melt" at absolute zero, changing from one phase to another. These phase transitions are strictly in the weird realm of quantum mechanics, a world dominated by large fluctuations in energy and momentum even at the lowest temperatures, where classical physics would insist that the opportunity for change is frozen.

Theorists have been exploring these transitions since the 1950s, but now experimenters are actually seeing these strange metamorphoses in the laboratory. With sophisticated tools for building semiconductors and improvements in low-temperature analysis, physicists have been able to watch the melting of an electron crystal and the unusual flip-flops of two-dimensional "gases" of electrons. This new kind of crowd behavior is fascinating in its own right, they say. "These are things that just can't be discussed in terms of single particles at all," says Subir Sachdev, a Yale University physicist. But it may also have some practical implications: By searching for hints of quantum phase transitions in high-temperature superconductors, researchers are hoping to spring the lock on the stubborn mystery of how these materials work.

Classical phase transitions, like the melting of an ice cube, are driven by thermal energy. Heating the ice above the freezing point causes molecules in the solid water to vibrate. Eventually, the jiggling becomes so wild that the molecules are no longer content with their orderly seating arrangement in the ice crystal, and they break loose to become liquid water. Heat them even more, and they don't even want to slosh around in a liquid—they vaporize into steam. Reverse the process, the jiggling slows down, and the molecules fall back into place. The variable that controls all of these transformations is temperature.

Quantum phase transitions are a completely different beast. What opens the way to a quantum phase transition is a change not in temperature, but in some other parameter like the density of a material or the strength of an external magnetic field. Because they don't need thermal energy, quantum transitions can theoretically take place at zero temperature. In fact, they can only be studied at low temperatures, where the thermal fluctuations that cause particles to jiggle subside, revealing the quantum fluctuations in position and momentum that actually trigger the phase transitions.

Steven Girvin, a theorist at Indiana University, Bloomington, likes to explain the notion of a quantum phase shift by citing a textbook concept known as the Wigner crystal. This orderly arrangement of electrons, named after Eugene Wigner, who proposed it in 1938, can form when the electron density is low and the particles sort themselves into a stable spatial array, like soldiers standing in formation. Arrayed charges like these have since been observed in the layers of electrons that collect on the surface of liquid helium and in confined electron layers in sandwichlike semiconductor structures called quantum wells.

To illustrate how quantum mechanics can trigger a phase transition in this arrange-

Letting go. As a lattice of electrons called a Wigner crystal (left) is compressed, the quantum fluctuations in the electrons' positions grow until the lattice melts (right).