as the methionine essentially steals tryptophan's light energy and converts it instead to invisible vibrational and electronic energy.

Gruebele and his colleagues used this dimming effect to track protein folding by using genetically engineered *Escherichia coli* bacteria to express the tryptophan and methionine amino acids at different places in the protein sequence. Then they ran their experiment many times on different versions of the protein, gauging how the fluorescence changed when folding began.

Seeing is believing

The results offer tantalizing clues to the sequence of events in protein folding. Apomyoglobin's final shape includes a trio of helixes on different parts of the molecule (see diagram on p. 29), with the so-called H and G helixes spiraling parallel to one another and roughly perpendicular to the A helix. So the researchers engineered their protein to express tryptophan toward one end of the A helix and the methionine on a nearby site on the H helix. They found that the tryptophan stopped fluorescing after a 5-microsecond delay, suggesting that it is at this point that the A and H helixes converge. And using a similar scheme, the researchers concluded that the A helix winds itself into a coil in less than a single microsecond.

Although this sequence of events applies to just one protein, the result is a crucial first step toward understanding the rules of protein folding, says Wolynes. Taken together, the two results suggest that "local" interactions between neighboring amino acids compel the protein to very rapidly adopt some secondary structure—the coil in the A helix—before more "global" interactions push it to acquire the 3D structure that juxtaposes the A and H helixes, says Wolynes. That counters the views of some theorists, who suggested that global structure forms either before or at the same time as local structure, notes Wolynes. "It says that local signals are more important than we thought," he says.

William Eaton, who heads the laboratory of chemical physics at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland, calls the new experiment "just absolutely A^{++} work." He notes, however, that this particular technique won't work for all proteins, because only a relatively small number denature in supercooled water. But researchers have been making recent progress on other fast triggers for protein folding. Eaton and his colleagues, for example, presented preliminary work at a conference earlier this year on a new fluid-mixing technique with a time resolution down to 80 microseconds. Also earlier this year, Winkler, Harry Gray, and their colleagues at Caltech reported that pumping certain proteins with extra electrons triggers folding with a time resolution of about 40 microseconds (*Science*, 15 March, p. 1558).

Theoretical chemists are hopeful that these and related techniques will help resolve the theoretical debate about the meaning of the steps in protein folding. Researchers have known for years that many proteins tend to adopt temporarily stable shapes on their way to their native conformation. Some theorists argue that these "intermediates" are necessary steps along the pathway to proper folding—and so contain clues to the folding process—while others think those steps are merely mistakes, and that proteins can take a variety of twists and turns en route to their final shape.

To distinguish between these theories, it's very important to have experimental verification, theoretical chemists say. By observing whether these intermediates form under a variety of conditions, the new experiments should give researchers clues to just how critical these intermediates are. And that promise itself is likely to trigger a few fast accomplishments of its own.

–Robert F. Service

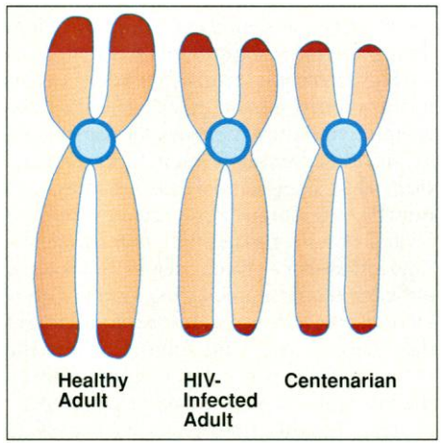
AIDS RESEARCH

Selling the Immune System Short

During the past 18 months, researchers have laid bare two fundamental facts about HIV: It replicates at a blinding rate throughout the course of infection, and viral levels in the body are strong predictors of how quickly a person will progress to full-blown AIDS (*Science*, 28 June, p. 1884). But little noticed amid the excitement surrounding these developments are new findings that may help solve a major outstanding puzzle about the virus: how it causes the immunodeficiency that is the hallmark of the disease.

The key clue comes from a flurry of new studies, the first of which appears in the July issue of *AIDS*, looking at what happens to the telomeres—specialized stretches of genetic material on the chromosome ends—in immune cells from HIV-infected people. In the *AIDS* paper, immunologist Janis Giorgi of the University of California, Los Angeles (UCLA), and her colleagues report that telomeres are significantly shorter in certain immune cells from these people than in controls. Because telomere shortening is considered a sign of cellular senescence, the authors suggest that the battle with the virus is essentially causing premature aging of the immune system, exhausting its ability to fight off pathogens, including HIV itself. "This is a brand-new angle that's never been explored," says co-author Rita Effros of UCLA.

The work, by the UCLA researchers and collaborators at Geron Corp., is attracting widespread attention. "The suggestion that shortened telomeres in [immune cells] of the HIV-infected population might play a role in the functional immunocompetence seen with the infection is intriguing," says Richard Hodes, an immunologist who studies telomeres and also heads the National Institute on Aging.



Premature aging? Telomeres *(red)* in $CD28^-$ $CD8^+$ cells from HIV-infected people resemble those of centenarians.

Giorgi, Effros, and their co-workers got interested in the telomeres of immune cells from HIV-infected people because of an observation Effros and others had previously made while studying the aging immune system. This work had built on the fact that in non–immune cells, telomeres shorten with each cell division, providing a "mitotic clock" that regulates how many divisions can occur. Once the telomeres become too short, cells enter "replicative senescence," at which point they can no longer divide.

Similarly, Effros had found that as people age, for some as yet unknown reason the telomeres of a particular subclass of immune cells—T lymphocytes that bear a CD8 receptor but lack another surface molecule called CD28—shorten. This, she suggested, indicates that the $CD28^-$ $CD8^+$ cells were coming to the end of their replicative life after decades of dividing whenever the immune system revved up to combat invading pathogens. And because CD8 cells play a critical role in clearing viral infections, that could help explain the diminished immune capabilities of the aged.

These immune deficits in some way resemble those of AIDS patients, the researchers realized—for example, both groups may suffer infections such as shingles, caused by

viruses that their immune systems had once had under control. So Giorgi, Effros, and their colleagues decided to look at the telomeres of $CD28^-$ $CD8^+$ T cells from HIV-infected people to see whether they show similar signs of being worn down.

The answered proved to be yes. The researchers found that $CD28^-$ $CD8^+$ cells from seven HIV-infected adults had telomeres that ranged in length from 5.2 to 7.0 kilobases, while in the $CD28^-$ $CD8^+$ cells from five age-matched control subjects they ranged from 7.1 to 8.3 kilobases—a statistically significant difference. Indeed, the telomeres of the HIV-infected patients were as short as those in white blood cells of people who were 100 years of age or older. These data argue, Giorgi says, that in both HIV-infected people and centenarians, "the immune system has become worn out in the process of making the immune response, and it's had to continue to call on the reserves until there's nothing left."

Hodes says that he has preliminary data confirming the telomere finding, as has Frank Miedema, an AIDS immunologist at the University of Amsterdam in the Netherlands, who plans to report his findings this week at the international AIDS conference in Vancouver, Canada. Hodes cautions, however, that much work has to be done before researchers understand the biological relevance of the telomere alterations. "It'll be more challenging to directly demonstrate that telomere shortening has functional consequences in human disease," he remarks.

But Miedema and others are even more interested in the relationship between telomere length and $CD4^+$ T cells, HIV's main target. "The $100 question is what is happening to the CD4s," says Miedema. The popular view is that HIV kills CD4s directly, which should compel the surviving CD4s to divide more frequently as part of the replenishment process. But Miedema's preliminary data do not show shortened telomeres in CD4s from HIV-infected people. He argues that CD4s are not being rapidly destroyed, but rather they may be hiding out somewhere in the body and some unknown mechanism is "blocking" their release.

Virologist David Ho, head of the Aaron Diamond AIDS Research Center in New York and a main proponent of the direct-killing theory, isn't convinced. Ho is also looking at telomere lengths in CD4 cells and says, "We're certainly not ready to draw any conclusions at this point." What's more, he says, evidence from other sources says CD4s are being removed and replaced at a high rate.

Miedema doesn't buy it, but allows that "there are a lot of things to sort out." Whatever the outcome, telomeres are lengthening the reach of AIDS researchers—and promise to extend it even further in the near future.

–Jon Cohen

GEOLOGY

Long Ago, a River Ran Through It

Geologist Nancy Riggs collected rock samples for her most recent work in a shallow canyon tucked among dry, chaparral-covered hills outside Amarillo, Texas, where streams are apt to disappear in the dry season. But by precisely dating 17 microscopic zircon crystals from this area, the geologist from Northern Arizona University in Flagstaff and her colleagues have found that this semiarid region once held the thunderous headwaters of a giant river system. As the researchers report on page 97, these zircon crystals link the source of the river to its mouth, showing that 225 million years ago in the late Triassic, the river rushed 1500 kilometers across the supercontinent of Pangaea with all the muddy glory of the Mississippi.

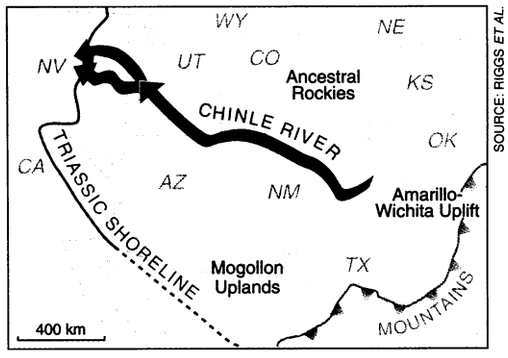
The new work is the first to provide such a detailed map of an ancient river system and is helping to crystallize geologists' view of Pangaea during the first creaks and groans of its breakup. The existence of the river, named the Chinle, is no surprise. But by linking its mouth to its source, the study confirms that much of western Pangaea was drained by this single river system. "This opens up a whole new understanding of that depositional basin and how it evolved," says paleontologist Spencer Lucas of the New Mexico Museum of Natural History and Science in Albuquerque. And the work also demonstrates the utility of a new method, using zircon crystals, to decipher the geography of the past, notes Lucas.

The study was spurred by what Riggs calls a "bizarre finding" made last year by her colleagues George Gehrels and William Dickinson, both of the University of Arizona. They identified Cambrian-aged zircon crystals, 515 million to 525 million years old, that had been incorporated into much younger sandstone in Nevada. The source of those zircons must have been a body of igneous rock of that same age—but there is no such rock anywhere on the western United States. So Riggs, Gehrels, Dickinson, and Tom Lehman from Texas Technical University in Lubbock began to hunt farther east for the zircon's source.

Riggs and other geologists already knew that during the late Triassic the region was drained by some sort of river system, which could have eroded the zircon and carried it westward. The Nevada sandstone bearing the zircon closely matched other outcrops across Utah, Arizona, and New Mexico—all Late Triassic river deposits. But these far-flung beds were difficult to link, and so geologists debated whether one or more river systems connected them, and where the rivers originated.

Riggs realized that zircon crystals offered a new approach to the problem. Unlike most minerals found in stream beds, sturdy zircon resists breakdown, and the uranium trapped within the crystals provides a way to date them, a maker's mark by which the crystals could be traced to a distant source. Using the ratios of radioactive uranium and its daughter product, lead, Riggs and her colleagues matched the Nevada zircon, from near the mouth of the ancient Chinle river, to a distinctive Cambrian rock near Amarillo, Texas, one of the few places in North America with zircon of the right age. That rock had to lie near the river's headwaters. And by including earlier data on sediment deposition and water flow from other outcrops, Riggs and her colleagues approximated the entire course of the Chinle, showing that it drained a vast area of the supercontinent.

Finding the river's source also gives researchers a glimpse of Pangaea's topography.



Triassic topography. The ancient Chinle River once roared from what is now Texas to Nevada.

By the Late Triassic the once mighty mountains of the Amarillo-Wichita Uplift, which had risen 300 million years earlier, were thought to have been eroded down to a plain. But the course of the Chinle implies that the Cambrian rocks in this area were indeed uplifted during the Triassic. "To get zircons flowing out of there, you had to have uplift of the source range," says Lehman. He proposes that the initial opening of the Gulf of Mexico reactivated the faults there, raising the mountains once again and providing a pulse of sediment—including the zircons—that was swept down the Chinle River.

Riggs and others plan more studies of the river and its basin, but one thing is already clear: Geologists may not find much more gold in the hills of the southwest—but they can find zircon. And to a paleogeographer, that may be even better.

–Bernice Wuethrich

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