neutrino results," says Yoji Totsuka, spokesperson for Japan's Super-Kamiokande group, the other team reporting atmospheric neutrino results.

The Soudan and Super-Kamiokande claims rest on a single calculation: the relative numbers of electron and muon neutrinos created when cosmic rays collide with particles in the upper atmosphere. "This ratio is simple to calculate and is quite robust," says theorist Tom Gaisser of the University of Delaware.

"We have evidence, in fact, I believe strong evidence," that neutrinos have mass.
—Bill Louis

Both Soudan 2 and Super-Kamiokande aim to measure this ratio to see if any of the neutrinos have oscillated to a different type en route between the upper atmosphere and the detectors deep underground. Based in the Kamioka laboratory west of Tokyo, the Super-Kamiokande detector snares neutrinos in a 50,000-ton water tank watched by 13,400 photodetectors. An electron neutrino crashing into nuclei in the water produces an electron, a muon neutrino, and a muon. The electron and muon, being charged, create distinctive flashes of light that are picked up by the detectors. Soudan 2 works on a similar principle, but relies on 1000 tons of corrugated iron sheets interspersed with sensitive charged-particle detectors.

"We have observed a smaller muon-neutrino-to-electron-neutrino ratio as compared to the expectation of the atmospheric neutrino flux calculations," says Kenzo Nakamura, reporting Super-Kamiokande's results at Capri. The Soudan result is "in line" with Super-Kamiokande's, according to Gallagher. "What we've measured is a result which is only about 60% or 65% of what we expect based on the Standard Model," he says, adding, "The fact that they measure essentially the same result in very, very different detector technologies serves as a strong indication that what we're measuring is not some artifact of our experimental apparatus."

Instead of relying on nature to supply their neutrinos, the LSND team at Los Alamos drives a proton beam from an accelerator into a water target to create particles called pions. These then spawn other particles, including muon neutrinos. Thirty meters away is the neutrino detector itself, consisting of 167 tons of mineral oil under the watchful gaze of 1220 photodetectors. The new LSND experiment, reported at Capri by team member Geoff Mills, detected a couple of dozen excess electron neutrinos in the beam, which originally contained only muon neutrinos. If what the group sees really is due to oscillations, then these results, together with their earlier ones, show that "roughly about a third of a percent of the muon neutrinos ... will turn into electron ... neutrinos," says Louis.

Weaving together the threads of evidence is not straightforward, however. "The solar neutrino deficit, atmospheric [neutrinos], and Los Alamos—they are not all consistent," says Adam Para of the Fermi National Accelerator Laboratory near Chicago. "At least one of them must be due to something else, or something that we didn't think of," he says. Louis, however, believes these are simply wrinkles that theorists will be able to iron out. "They could be seeing different aspects of oscillations," he says.

Others, such as physicist Douglas Morrison at the CERN particle physics lab near Geneva, are less sanguine. Morrison suspects that dubious assumptions behind the calculations, rather than oscillating neutrinos, might explain both the solar and atmospheric shortfalls. Although Gallagher, Nakamura, and others say the uncertainty in estimates of the ratio of electron to muon neutrinos generated by cosmic rays is about 5%, "my feeling is that the error is bigger than 5%," Morrison says. As for the LSND result, he says, "I think the majority of the community is skeptical."

But Oxford's Wade Allison, another member of the Soudan 2 team, thinks the evidence for oscillations cannot be discounted: "I am completely convinced there is a real [neutrino] problem, and I also believe that neutrino oscillations are the only show in town to explain that problem." New experiments will win the day, he says, by revealing more of the properties of neutrino oscillations than simple ratios, such as actual mass differences and identity-switching probabilities. Adds Allison: "We've really got to try and tie the thing down, and then it will be convincing."

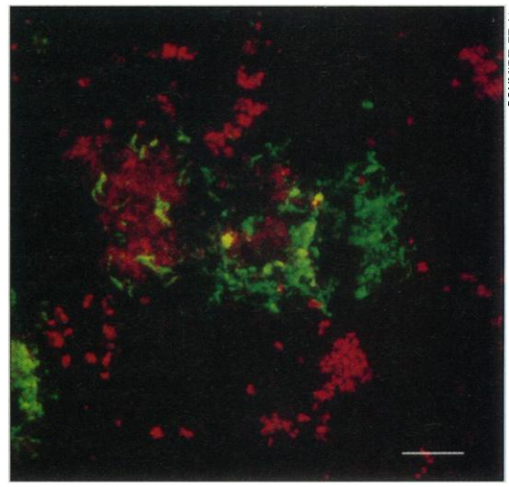
–Andrew Watson

Andrew Watson is a science writer in Norwich, U.K.

ALZHEIMER'S RESEARCH

New Lesion Found in Diseased Brains

For years, researchers praying for clues that might lead to a new treatment for Alzheimer's disease have had two congregations to choose from: the "BAPtists," who attribute the disease mainly to the β-amyloid protein (sometimes known as BAP) found in plaques that riddle the brains of Alzheimer's patients, and the "Tauists," who suspect that the misbehavior of a neuronal protein called tau is more central. Now, with the detection of a third type of lesion that has apparently lain hidden ever since Alois Alzheimer began studying the disease 90 years ago, a new sect may be in the making.



SCHMIDT *ET AL.*

Invisible enemy. Antibody staining reveals AMY plaques (green), which are similar to the more familiar amyloid plaques (red) but have no amyloid core.

The new lesions are known for now as "AMY plaques," because they were initially mistaken for amyloid plaques. They appear to be nearly as widespread in the brains of Alzheimer's patients as the more familiar plaques and tangles of tau proteins, according to a team led by neuropathologist John Trojanowski and neuroscientist Virginia Lee at the University of Pennsylvania School of Medicine in Philadelphia, who report their work in the July issue of the *American Journal of Pathology*. That means the AMY plaques could represent an unrecognized cause of the dreaded memory-depleting disease, which strikes 5% of people over age 65.

"I feel very excited about it," says neuroscientist Zaven Khachaturian, director of the Alzheimer's Association's Ronald and Nancy Reagan Research Institute in Chicago. "This opens new vistas for us in terms of conceptualizing what's happening in the disease, and it may even give us new diagnostic tools and new targets for treatment." But he and others note that this promise won't be realized soon, because researchers still aren't certain how or even whether the familiar amyloid plaques and neurofibrillary tangles cause neuronal deterioration.

The Penn researchers discovered the new lesions by accident while trying to learn more about the tau protein, which is normally found inside neurons but congeals in extracellular masses in the brains of Alzheimer's patients. Two years ago, Trojanowski and Lee reported from studies of biopsied and autopsied tissue

that tau collects this way when phosphatases, enzymes that remove excess phosphate groups from tau, somehow fail to do their job (*Science*, 10 February 1995, p. 793).

To learn whether trouble at tau's phosphate-binding sites contributes to this problem, Marie Luise Schmidt, a researcher in Trojanowski and Lee's laboratory and the study's lead author, reviewed a set of 59 new antibodies designed by Lee to recognize and bind to these sites. While testing the antibodies on tissue slices from Alzheimer's brains, however, Schmidt found that four of them—especially one called AMY 117—didn't bind to tau at all, but sought out plaques instead.

The team suspected that the purified proteins used to create the antibodies weren't pure—that they contained molecules from amyloid plaques, a glitch they had encountered before. But when Schmidt stained brain slices using both AMY 117 and an antibody to β amyloid, she was astonished to find that the two antibody types gravitated to two different sets of plaques—one of which had never before been glimpsed. The new lesions resemble the amyloid plaques from the outside, but inside they lack the core of β-amyloid protein that traditional staining techniques recognize. So the proteins used to make the antibodies must have been contaminated after all—but with proteins from the AMY plaques, not the amyloid plaques. The existence of the new lesions "couldn't have been suspected without these new antibodies," says Trojanowski.

All 32 of the Alzheimer's brains the team examined exhibited the new lesions, usually close to, but not overlapping, the amyloid plaques. That means Alzheimer's researchers now have an entirely new set of pathological mechanisms to explore. Explains Trojanowski: "It could be that if you sweep away amyloid plaques and tangles and still have these AMY plaques, you would only be getting rid of two-thirds of the symptoms."

The Penn team is currently purifying the AMY 117–binding protein with the goal of cloning the gene encoding it. That could eventually lead to an improved means of diagnosing Alzheimer's based on detecting the protein in the blood or cerebrospinal fluid, and perhaps even to a way of blocking the formation of new plaques.

But will Alzheimer's researchers welcome this new denomination to their increasingly ecumenical field? "Heavens, yes," says neuromolecular biologist Marcelle Morrison-Bogorad, associate director of the Neuroscience and Neuropsychology of Aging program at the National Institute on Aging. "The more angles we have, the closer we'll be to understanding what Alzheimer's actually is."

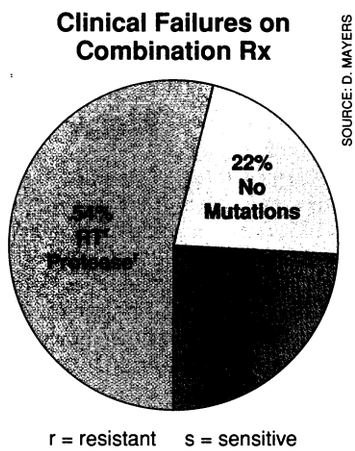
–Wade Roush

AIDS THERAPIES

The Daunting Challenge of Keeping HIV Suppressed

ST. PETERSBURG, FLORIDA—When the media last year trumpeted the great advances being made against HIV, speculating about cures and even the end of AIDS, the researchers' own caveats tended to get drowned out. But at a meeting held here last week, emerging data about treatment failures sounded a discordant note that was hard to miss: While powerful new drug combinations are delaying disease and death, they have serious limitations—and clinicians and patients who ignore these shortcomings do so at their peril.

More than 200 leading AIDS researchers from around the world gathered here from 25 to 28 June for the workshop, which focused on HIV drug resistance, treatment strategies, and the possibility of eradicating the virus from an infected person. One presentation after another reinforced the message that keeping HIV at bay, even with the most potent three-drug cocktails now available, remains a daunting challenge. "Triple combination therapy can fail for a variety of reasons," said John Mellors of the University of Pittsburgh Medical Center, one of the meeting's organizers. As this reality sets in, infected people may end up feeling that their hopes were raised too high last year, he warned. "The pendulum will swing back."



Humble pie. Treatment failures often occur without resistance to reverse transcriptase (RT) or protease inhibitors.

The meeting went into fine detail about why these failures occur. New, more sensitive assays that measure levels of HIV indicate that even the best treatments have a difficult time completely suppressing viral replication, which gives drug-resistant mutants a chance to appear. Less surprisingly, many treatments also fail because patients don't "comply" with therapies that require taking dozens of pills—many of which have serious side effects and dietary restrictions—each day. Although there were encouraging findings about new treatments allowing the immune system to recover if the virus can be suppressed, researchers spelled out just how distant the goal is of completely rebuilding a full range of immune responses in an HIV-damaged body (see sidebar).

Last year's surge in hope was driven by dramatic findings about the wallop delivered by combinations of two drugs that attack HIV's reverse transcriptase (RT) enzyme with one drug from a newer class of compounds directed at the virus's protease enzyme. Several studies showed that such triple combinations—and even some cocktails of RT inhibitors alone—can drive the amount of HIV in a person's blood, the "viral load," down so low that the most sensitive tests could not detect any virus for more than a year in many patients. Researchers warned, however, that just because HIV couldn't be found didn't mean it wasn't there—nor did it mean the virus wasn't replicating.

One of the more disconcerting findings reported here is that, just as researchers feared, the "undetectable" HIV reported last year can routinely be detected with a more sensitive test. A year ago, the most sensitive tests could measure viral levels down to 500 copies of HIV per milliliter of blood. New tests now measure as few as 20 copies per milliliter. Brian Conway, of Vancouver, Canada's BC Centre of Excellence in HIV/AIDS, used such a test in a 151-person study comparing two RT inhibitors to three RT inhibitors. One year after treatment began, 27% of the patients receiving one of the two-drug combos had fewer than 400 copies of HIV. But when the samples were reanalyzed with an assay that went down to 20 copies, only 12% had "unquantifiable" levels. And when Conway ran the test on one sample below 20, he detected the virus three out of 11 times. "A lot of people hear 'unquantifiable,' and they think 'zero,' " said Conway.

John Coffin of Tufts University in Medford, Massachusetts, suggested that researchers consider changing the focus to the number of virally infected cells, which estimates suggest is about 1000 times higher than the HIV copy number detected. So 20 copies, noted Coffin, would equal 20,000 infected cells. "If you say a person has less than 20,000