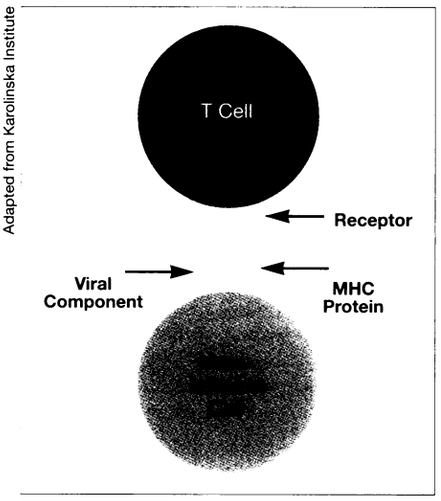
Nobel prize honors insight into immunity

Microscopic hit men roam the blood of humans and other animals. These single-minded killers, white blood cells called cytotoxic T cells, normally destroy only cells infected by viruses.

This year's Nobel Prize in Physiology or Medicine honors two scientists, Peter C. Doherty of St. Jude's Children's Research Hospital in Memphis and Rolf M. Zinkernagel of the University of Zurich, whose fundamental discovery helped explain how these T cells recognize the targets they're assigned to kill.



Adapted from Karolinska Institute

The T cell's receptor protein must bind to a piece of virus and an MHC protein before it kills a cell.

The researchers were working at the John Curtin School of Medical Research in Canberra, Australia, in the early 1970s when they began to study how genetic variability influences the response of cytotoxic T cells.

The duo infected mice with a virus to obtain T cells that would kill the rodents' virus-infected cells. However, the T cells failed to kill infected cells from another strain of mice. This distinction, the two concluded, stemmed from the different cell surface proteins of each strain.

All mouse cells, and all human cells, carry surface proteins encoded by genes from the so-called major histocompatibility complex (MHC). But MHC genes vary so tremendously that the set of MHC proteins on an animal's cells serves as a molecular identification card. At the time of Doherty and Zinkernagel's work, researchers had already discovered that differences in MHC proteins could cause rejection of organs transplanted between unrelated people.

"Everybody knew these were important molecules, but nobody understood how the molecules were working in the immune system," says Ronald H. Schwartz of the National Institute of Allergy and Infectious Diseases in Bethesda, Md.

Doherty and Zinkernagel offered a compelling theory about the role of MHC proteins. They argued that before cytotoxic T cells kill an infected cell, they recognize both a piece of virus and an MHC protein characteristic of the animal. The immune cells of the first mouse strain ignored infected cells of the second strain because the strains' MHC proteins differed.

"The whole field was in a mess. We were very confused about what T cells were up to," recalls Phillipa Marrack of the National Jewish Center for Immunology and Respiratory Medicine in Denver. "It wasn't until they made the observation that the T cell somehow has to recognize the two [signals] at the same time that the whole thing made sense."

More recent research has illuminated how this dual recognition occurs. Infected cells chop up viruses inside them and attach the viral pieces to MHC proteins. The cells then transport the combination to the cell surface so that cytotoxic T cells can have access to them. The T cells have surface proteins, called T cell receptors, that simultaneously recognize a viral component and an MHC protein.

Doherty notes that investigators are now using cytotoxic T cells to rid bone marrow transplants of viral infections and are designing vaccines, including those for AIDS, to generate these virus-killing cells. —*J. Travis*

Alzheimer's disease takes a curious turn

Physicians have described several cases of an extremely rare form of Alzheimer's disease that primarily assaults not memory but visual perception. Although sufferers possess no eye defects, they often find themselves unable to drive a car in a straight line or to determine their distance from other cars while driving. Their ability to perform many other tasks that require hand-eye coordination or sustained visual attention also declines sharply.

Cerebral defects that trigger this type of Alzheimer's disease, which includes only moderate memory difficulties, may differ greatly from those that contribute to the condition's more common incarnation, a new study finds.

"We've found that Alzheimer's disease can begin in a separate neuronal system from the one it's usually thought to be linked to," contends study director Pietro Pietrini, a neuroscientist at the National Institute on Aging in Bethesda, Md. "In this subgroup of patients, Alzheimer's disease may occur well before any memory complaints."

Pietrini's group examined 10 individuals diagnosed with Alzheimer's disease who displayed primarily visual and spatial perception problems but some memory loss as well. Three of the patients have since died, and analyses of their brains revealed tissue changes consistent with Alzheimer's disease, Pietrini says.

The study also included 22 people whose Alzheimer's disease featured severe memory impairment without visual complaints and 25 adults without the disease. Volunteers in all three groups averaged 65 years old.

As each participant rested with his or her eyes covered and ears plugged, researchers took positron emission tomography (PET) scans of cerebral glucose use, an indicator of the vigor with which groups of neurons function.

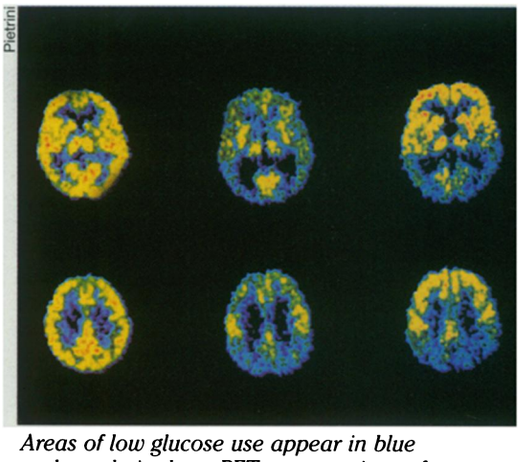
Relative to healthy adults, those with the visual variant of Alzheimer's disease displayed markedly lower glucose use in areas at the back of the brain, including the primary visual cortex, Pietrini and his coworkers report in the October AMERICAN JOURNAL OF PSYCHIATRY. The same individuals showed relatively normal activity in other regions, including some of those associated with memory.

In contrast, Alzheimer's disease patients who had no visual problems exhibited declines in glucose use throughout much of the brain, but the visual cortex was largely spared.

The visual form of Alzheimer's disease may stem from disconnections in a brain pathway that mediates the perception of motion and spatial relations among objects, Pietrini theorizes.

This unusual condition may fall at one end of a continuum of Alzheimer's disease symptoms, or it may represent a distinctive disorder, notes neuroscientist James V. Haxby of the National Institute of Mental Health in Bethesda, Md.

—*B. Bower*



Pietrini

Areas of low glucose use appear in blue and purple in these PET cross sections of the brain of a healthy volunteer (left), a person with typical Alzheimer's disease (center), and a person with the visual variant of Alzheimer's (right).