Microglial *MADNESS*

When the brain's immune system turns from friend to foe

By ELIZABETH PENNISI

Sixty years ago, a Spanish neuroanatomist noticed a peculiar kind of cell scattered throughout brain tissue. Called microglia, these cells make up the brain's private immune system. They share the same ancestry as other immune system cells but are sequestered in the brain early in life.

For decades afterwards, researchers didn't think these cells did much, so they didn't pay much attention to them.

Now, however, microglia have come back into focus, so to speak. New imaging and analytical techniques have enabled neurobiologists to gather evidence that these immune system cells play critical roles in the destruction of injured or aging nerve cells, in brain development, and in AIDS-related problems in the central nervous system. "Microglia are in fact extremely important in neuropathology," says Carol A. Colton, a neurobiologist at Georgetown University School of Medicine in Washington, D.C.

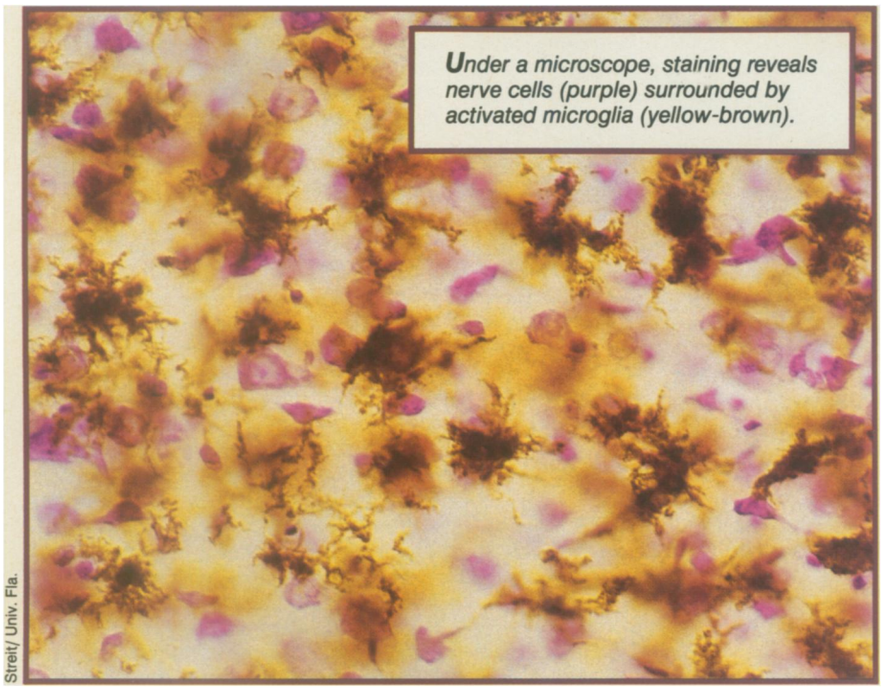
"You can get a good indication that something is wrong [in the brain] by looking at the microglia," adds Wolfgang J. Streit of the University of Florida College of Medicine in Gainesville.

Normally, these wispy cells arrange themselves in a lacy network throughout the brain's gray and white matter. Their many appendages radiate outward but do not touch the appendages of other microglial cells. When the brain gets into trouble, microglia become activated: In just 20 minutes, they can thicken, withdraw their appendages, and move toward an injury or problem site, Streit says.

There they may gobble up unwanted substances around them, says Lynn S. Perlmutter of the University of Southern California School of Medicine in Los Angeles. In addition, microglia may secrete substances that speed or cause cell death.

Yet microglial cells can also release substances that promote the recovery of nerve cells, or neurons, says Pat R. Levitt of the Robert Wood Johnson Medical School in Piscataway, N.J. "The question is, Which one is the overriding feature [of microglia]?" In November, at the Society for Neuroscience annual meeting in Washington, D.C., researchers discussed the cells' Jekyll-and-Hyde activity.

Colton studies microglia by growing brain tissue in laboratory dishes and examining the effects of various substances on these cells. She finds that some immune system messengers cause microglia to make highly reactive, charged molecules, such as free radicals (SN: 8/14/93, p.109), that can wreak havoc on nearby tissue. Other chemicals, such as acetylcholine, stem this production. "The take-home message is that microglia are capable of producing a variety of molecules that can be damaging under some circumstances but which are tightly controlled," Colton says.



Under a microscope, staining reveals nerve cells (purple) surrounded by activated microglia (yellow-brown).

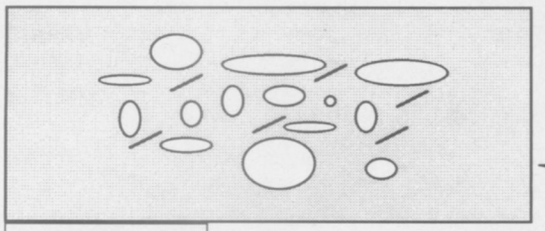
Streit/ Univ. Fla.

During a stroke, blood flow to some parts of the brain stops, depriving those areas of oxygen. Some nerve cells die right away; others succumb slowly; still others may survive. From his studies of stroke damage in animals, Streit has concluded that microglia seem to know which neurons are doomed. Their movement toward such cells "can be a very sensitive indicator of imminent neuronal death," he says. However, Streit cannot tell yet whether microglia contribute to the cells' demise or simply stand by as it happens.

Dying neurons secrete substances that attract immune system cells, reports Levitt. The developing fetal nervous system creates and later dismantles extra nerve cells. As these cells die, they appear to secrete an opioid-like protein fragment that attracts immature immune system cells into the brain, Levitt reports. "This is really the first evidence that the brain makes an opioid peptide [of use] to the immune system," he says.

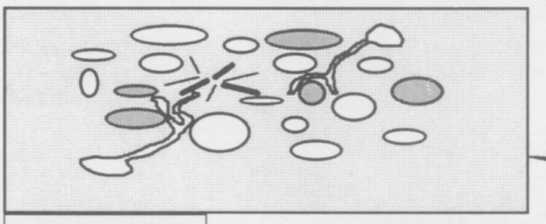
The attracted cells transform into macrophages, scavenging lipids and other debris released by the disintegrating cells. Some of these immune system cells then leave, "but at least some of them probably transform into microglial cells," Levitt adds.

Because microglial cells surround and become interlaced with the edges of the amyloid plaques that form in the brains of people with Alzheimer's disease, Perlmutter has examined microglia from autopsied tissue of people of different ages. Even though microglia are distributed throughout the brain, they have become activated in the brains of healthy elderly people, Perlmutter and her colleagues

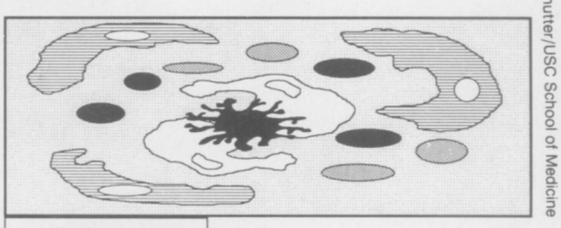


DIFFUSE PLAQUE

Alzheimer's beginnings? Benign, diffuse plaques (thin rods) form when beta proteins precipitate. However, increased deposition can lead to primitive beta-amyloid plaques (thicker rods) that may attract microglia (branching white globs). This sets off a chemical cascade leading to a classic plaque of amyloid interlaced with microglia.



PRIMITIVE PLAQUE



CLASSIC PLAQUE

Perlmutter/USC School of Medicine

report. This age-related change "may be priming these cells to exacerbate pathological processes in Alzheimer's," Perlmutter says.

She and others suspect that these plaques indicate a chronic inflammatory response in which nerves get caught in the crossfire between microglia and the plaque. Medications that stop this reaction may help prevent nerve cell destruction and loss of brain function, they suggest.

Work by Jean Merrill and her colleagues at the University of California, Los Angeles, School of Medicine, also implicates microglia in AIDS-related brain damage. By studying cells grown in a laboratory dish, she has examined how HIV, the virus that causes AIDS, affects brain tissue. HIV – even pieces of the virus' protein coat – can activate microglia without necessarily infecting these cells, Merrill says.

Activated microglia then begin producing destructive substances. Also, the presence of HIV may set off a chemical cascade that can cause microglia to merge into giant killer cells that contain many nuclei and can churn out large amounts of the toxic substances, she notes.

These researchers' results, like those of others, make a strong case against microglia, one that has motivated several drug companies to develop drugs to shut these cells down or counter their toxic effects, Colton notes.

Yet microglia can't be all bad, the researchers add.

"If that were the case, I don't think there would be much left of the brain," Streit says. □