For Want of an Inhibitor: Alzheimer's Disease

A biochemical abnormality that impedes production of new protein has now been associated with Alzheimer's disease, a debilitating deterioration of the brain that affects about 2 million elderly people in the United States. Whether this abnormality is the cause of the disease or only a symptom remains to be determined. But, in either case, its discovery may lead to much-needed improvements in diagnosis and treatment.

"It's one of those key pieces of the puzzle of Alzheimer's disease," says Zaven Khachaturian of the National Institute on Aging in Bethesda, Md. "It's extremely important."

A wide variety of abnormalities have been described in the brains of Alzheimer's disease patients. Specific nerve cells die and the tissue becomes studded with unusual structures called neuritic plaques and neurofibrillary tangles. Biochemical deficiencies include a decline in the enzyme that makes the signal chemical acetylcholine. And there is growing evidence of deficiencies of other neurotransmitters as well.

The most recent finding takes a step away from these varied observations to ask what in the molecular machinery of the cell can be causing the many abnormalities. Elizabeth M. Sajdel-Sulkowska and Charles A. Marotta of McLean Hospital in Belmont, Mass., and Harvard Medical School in Boston report in the Aug. 31 SCIENCE that in Alzheimer's victims a change occurs in one step of the basic process by which genetic information is translated into protein.

The researchers worked backwards from observations that brain protein synthesis is decreased to about half the normal level in patients with severe Alzheimer's disease. Marotta and his colleagues found evidence for decreased protein synthesis in laboratory experiments; French scientists have demonstrated such a decrease, detected with positron emission tomography (PET), in living patients.

Sajdel-Sulkowska and Marotta compared samples of brain frozen at autopsy from six patients with Alzheimer's disease, according to strict diagnostic criteria, and from four persons who died with no history of the disease or related ailments. The patient samples were taken from brain areas that were severely affected by Alzheimer's disease and that showed many neuritic plaques and neurofibrillary tangles.

In the diseased brains, the scientists found about half the normal levels of RNA, a key chemical in the production of protein. Moreover, their study revealed increased levels of the active form of an enzyme, alkaline ribonuclease, that breaks down RNA. In the healthy brain the activity of this ribonuclease is moderated by an inhibitory protein. But in the brains from patients with Alzheimer's disease, the inhibitory protein was found to be either absent or ineffective.

"We can say for certain that there is a change in the inhibitor-nuclease interaction," Marotta says. Thus the ribonuclease is unchecked and freely destroys RNA required for protein synthesis. He says another group of scientists several years ago looked at specially stained brain samples prepared for microscopy and also reported decreased RNA levels in Alzheimer's patients.

Marotta's group has further experiments under way to determine whether the inhibitor is present in any form in the affected brain areas of Alzheimer's disease patients and whether there are differences in the inhibitor-nuclease interaction between the severely affected and more normal areas of the brains. "We are very curious to see if this is different in different brain areas, especially tissues with no pathological regions," Marotta says. They also plan to do studies to determine whether the biochemical changes occur within cells or reflect the dramatic loss of nerve cells in the diseased brains.

"Our view is that our findings are compatible with all the changes reported by others — the loss of cells and the loss of enzymes," Marotta says.

Katherine Bick of the National Institute on Neurological and Communicative Disorders and Stroke says, "I think this is a very exciting possibility. It's moving the question back a level. They are not looking at the end process — a tangle or a plaque —but are looking at the process involved."

Khachaturian adds, "In and of itself, the fact that you can work with [frozen] autopsied material and get biochemical results is exciting." —*J. A. Miller*

Heated research of pepper pain

The fire of a red pepper may bring gustatory joy to Mexican food fans, but a too-hot pepper in the wrong dish can cost a spice company hundreds of thousands of dollars in lost business. Researchers at McCormick & Co. Inc., in Hunt Valley, Md., have developed a method of taking a pepper's temperature that they say offers food processors the first reliable quantifiable indicator of a pepper's potency.

The method won't put professional taste panels out of business, says McCormick's Marianne Gillette, but it should ease the load on their taste buds and make their fiery estimates more reliable. Gillette described the work this week in Philadelphia at the American Chemical Society meeting.

Begun in 1912, the traditional method of rating peppers relies on a laborious technique of steeping a sample pepper overnight in ethanol to make a sort of tea, then diluting the extract with a sucrose solution to produce a cordial. Ultimately the mixture is diluted to a range of potencies and tested on the tongues of trained volunteers, who note the weakest dilution at which a burn is detectable; the product is then stamped with a subjective rating.

"Frankly, it doesn't work well, and everybody in industry knows it doesn't work," says Gillette. The test requires the taster to sample several dilutions, and by the third, Gillette says, the heat perception has built up to such an extent that the tongue is no longer sensitive to the fine gradations required to make sure the sharpness of taco sauce can be kept out of pizza.

McCormick instead used sensitive analytical techniques common to chemists, including high-pressure liquid chromatography (HPLC), to measure various forms of capsaicin, the pungent molecule responsible for red pepper's fire. Different variations of the capsaicin molecule have different heat levels. By adding up the amounts of each of the components present in a given pepper, the researchers found they could accurately predict tasters' reactions "almost every time."

For food processors without an HPLC, Gillette has come up with a new sensory test, using water extraction, that significantly reduces the time and complexity of the old tasting method. In multi-center tests, the new method was reliably more precise, he says.

In related work, Harry Lawless, formerly of Monell Chemical Senses Center in Philadelphia and now with S.C. Johnson and Sons, Inc., in Racine, Wis., found that all oral irritants are not alike in the ways they assault the mouth. While red and black peppers burn the tops and sides of the tongue only, ginger scathes the back of the throat as well. Why some eaters enjoy burning their mouths remains to be understood, scientists say. Lawless has found that red pepper inhibits the perception of sour and bitter, while black pepper inhibits all tastes.

—*D. Franklin*