the same places as the cut marks on the human bones.

The researchers consulted Pat Shipman of Johns Hopkins University School of Medicine, asking whether the marks were indeed cut marks and not just marks from scraping of the bones across the cave by carnivores or marks from weathering. "What came across very clearly for my part was that if anything is a cut mark, these are cut marks," Shipman says. "The marks are *extraordinarily* well preserved. They are in very pristine condition."

With Russell, Shipman did experiments to determine when after death the cut marks on the bones were made. If the cut marks were made during a secondary burial, the bones would have been older than the marks. If they were made during cannibalism, the bones and the marks would have been contemporaneous. Their conclusion, says Shipman, is that, "you can distinguish between immediate and delayed processing. It has to do with the weathering of the bone and the weathering of the mark. Within the limits that we can detect—and there is some slop in there—the bones were not weathered when the marks were made."

"From the evidence we have, it looks like there wasn't any distinction between people and animals," Shipman remarks. "If that was true—and it's a big if—that says something very interesting. These *were* people. They were *Homo sapiens*, they had domestic animals and pots." Perhaps the Fontbrégoua residents did not eat each other but instead ate members of other tribes. They may not have distinguished between members of other tribes and animals, Shipman speculates. "Many tribal people have as words for themselves 'humans' and for all others 'non-humans.' It is the ultimate sort of us and them."

But, of course, the Fontbrégoua site is far from ironclad evidence of cannibalism, and even if it were cannibalism, there is no way of knowing whether it was survival cannibalism or whether is was a systematic, cultural practice of eating other human beings. Since saying that others are cannibals is perhaps the ultimate derogatory comment, Arens notes, and since "there is no evidence of cannibalism, we have a moral responsibility not to portray people in such a way." ■

GINA KOLATA

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Lost Neurons Identified in Alzheimer's Disease

The mental deterioration of Alzheimer's disease is caused by an extensive and irreversible degeneration of brain neurons, especially in regions, such as the cerebral cortex and hippocampus, that are concerned with memory. For the most part, however, little is known about the specific identities of the neurons lost from the cortex and hippocampus, and the biochemical changes underlying the neuronal degeneration also remain mysterious. As Carol Miller of the University of Southern California in Los Angeles points out, "You can't do molecular biology on what has already been lost," unless you have some way of identifying the affected neurons before they degenerate.

Speaking at a recent meeting* in Galveston on "Molecular Neuroscience: Expression of Neural Genes," Miller described research from her laboratory that may contribute to a better understanding of Alzheimer's disease by doing just that. "We have identified a cortical subset of cells that may be selectively vulnerable in Alzheimer's disease," she concludes.

For the past few years, Miller and her colleagues have been using monoclonal antibodies to define populations of human brain neurons that are chemically and, presumably, functionally distinct. Many of the antibodies were originally produced by Seymour Benzer and his colleagues at the California Institute of Technology to antigens from the brains of the fruit fly *Drosophila melanogaster*. Somewhat to the surprise of Benzer and Miller, nearly half of the *Drosophila* antibodies also proved to stain specific cells in the human brain.

In the current work, the USC workers compared the antibody-staining patterns of brains removed at autopsy from Alzheimer's patients with the staining patterns of brains from individuals who died of other causes. One antibody, which was made against a human brain antigen, stained a broad group of nerve cells in the hippocampus and cerebral cortex.

Staining with two of the *Drosophila* antibodies identified two distinct subsets within this group. One antibody reacted with the stellate neurons in layers 4 and 6 of the cortex and the second stained a subset of pyramidal cells located in layers 2, 3, and 5 of the cortex and also in some areas of the hippocampus. The pyramidal subset was associated with cellular pathology and the corresponding antigen was reduced in the Alzheimer's brains.

This fits, Miller notes, with what is already known about the patterns of neuronal loss in the disease. Cortical and hippocampal pyramidal cells are decreased in the patients' brains. There may be more than one type of pyramidal cell, however, and use of the antibodies may help to pinpoint the losses more accurately.

The cholinergic neurons of the basal forebrain, which use acetylcholine as their neurotransmitter and innervate the hippocampus and parts of the cortex, also decline in Alzheimer's disease. Miller is currently determining the relation between the pyramidal subset identified in her laboratory and the cholinergic neurons. ■

*The meeting was held at the University of Texas Medical Branch in Galveston on 8 to 10 May.

Nerve Activity Alters Neurotransmitter Synthesis

As researchers begin to apply the techniques of molecular biology to the study of nerve cells, they are finding that neurotransmitters may have a broader role than was previously thought. Neurotransmitters, the chemical signals released by nerve cells onto their target cells, are known to act within milliseconds to bring about target responses. The new work is showing that the agents may also have much longer-term effects that can alter the activities of responding nerve cells for days and weeks. Such alterations may contribute to memory formation.

Ira Black of Cornell University Medical College in New York City provided a recent case in point at the Molecular Neuroscience symposium. He and his colleagues have been studying how stimulation, or the lack thereof, alters neurotransmitter synthesis by peripheral and brain neurons. For example, peripheral neurons from the sympathetic ganglion make the classic neurotransmitter norepinephrine and also the neuroactive peptide substance P. When the nerve cells are grown in culture, where they are deprived of the incoming nerve signals that they would receive in the living animal, their concentrations of substance P increase. According to Black, this effect is preceded by an increase in the amount of the messenger RNA (mRNA) for the peptide and may

therefore result from augmented expression of the gene encoding substance P.

The neurotransmitter that would normally activate the sympathetic ganglion neurons is acetylcholine. The Cornell workers find that agents that mimic acetylcholine's effects on the neuronal membranes block the increase in substance P by decreasing the amount of mRNA for the peptide. At the same time, the agents stimulate the synthesis of tyrosine hydroxylase, an enzyme needed for making norepinephrine. The researchers have made similar findings with adrenal medulla cells, in which stimulation increases epinephrine production while decreasing the synthesis of the opioid peptide leu-enkephalin. "The same stimulus can have opposite effects on different neurotransmitters," Black concludes.

In addition, alterations of neurotransmitter synthesis are not limited to peripheral neurons. Treatment with a stimulatory agent increases tyrosine hydroxylase production in cells of the locus coeruleus, a brain center involved in maintaining attention and arousal, and contributes to increased dopamine production in neurons of the substantia nigra, the brain center that deteriorates in Parkinson's disease.

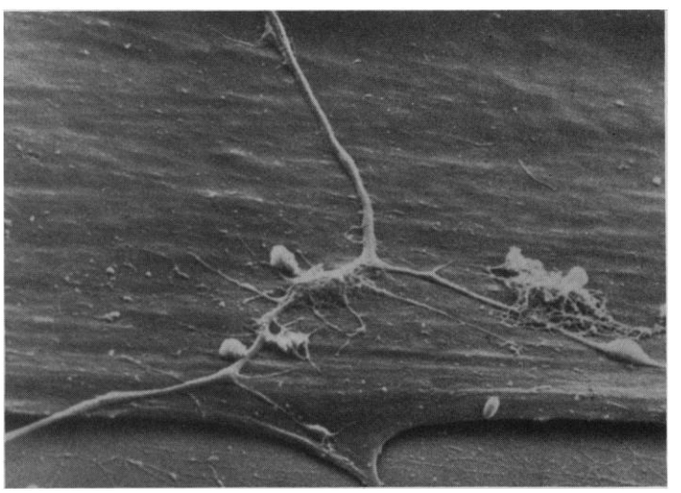
The effects on neurotransmitter synthesis can be maintained for days or weeks after the exciting stimulus has been withdrawn. "This is in the range of intermediate-term memory," Black says. "The very mechanism that allows the nervous system to work may be capable of carrying out that function as well."

Moreover, many types of neurons contain two or more neuroactive agents. If the concentrations of these agents can change differentially within a single neuron in response to stimulation, the effect might be to increase the already enormous capacity of the nervous system to acquire and transmit information. "In addition to dealing with approximately 100 billion neurons, each of which has on average 10,000 connections, we now have to realize that individual neurons may use different signals at different times, depending on the stimuli they receive. The combinatorial power is staggering," Black says. ■

Trophic Factor Aids Synapse Formation

Developing nerve cells send out long projections called axons that must find and make connections with the correct target cells if the axons and the nerves themselves are to survive. At the Molecular Neuroscience meeting, Gerald Fischbach of Washington University School of Medicine in St. Louis described his group's progress toward understanding how neurons form synaptic connections with muscle cells. The results show, Fischbach says, "that formation of synapses is not a passive affair. One cell modifies another." In particular, the neurons may release one or more proteins that elicit the assembly of synapse structures in the muscle cell membrane.

For their experiments, the St. Louis workers grow embryonic chick muscle cells in tissue culture and then add either embryonic motor neurons from the chick spinal cord or ciliary ganglion neurons, which in the living animal innervate the muscles controlling the pupil and lens of the eye. Both types of neurons use the neurotransmitter acetylcholine. In the adult animal, the receptors to which the acetylcholine must bind to exert its stimulatory effects on muscle are concentrated in the muscle cell membranes at the synaptic sites.



Nerve muscle junction. *The scanning electron micrograph shows a growing neuronal projection as it courses over a cultured muscle cell.* [*Source: E. Frank and G. D. Fischbach,* J. Cell Biol. *83, 143 (1979)*]

One of the first detectable signs of synapse formation between a growing axon and a muscle cell is the clustering of acetylcholine receptors. "Soon after the nerve contacts a muscle cell, the receptors begin to accumulate," Fischbach says. "It only takes 3 to 5 hours." Although a single axon may have several synapses distributed along its length, Fischbach speculates that the growing tip of the fiber triggers the formation of all of them as it moves across the muscle cell surface.

Other investigators have found that innervating neurons induce the clustering of acetylcholine receptors in amphibian muscle by causing receptors that are already present in the membrane to come together. But the interaction between chick muscle cells and neurons is different in this regard. Eighty percent of the receptors were inserted into the membrane after the neurons arrived," Fischbach reported.

The acetylcholine receptor is a fairly complicated molecule consisting of four different protein subunits, one of which is present twice. The growing neurons may increase receptor insertion into the muscle cell membrane either by stimulating the synthesis of the receptor subunits by the muscle cells or by fostering the assembly of those proteins into the complete receptor.

The supposition is that growing neurons release one or more substances that influence receptor insertion into target cell membranes and other aspects of synapse formation. Fischbach and his colleagues turned to whole chick brains as a possible source of such substances because the peripheral neurons they had been using could not be obtained in sufficient quantities to isolate a material likely to be present in low concentrations. They have now purified from the brains a glycoprotein with a molecular weight of about 42,000 that can both increase the insertion of acetylcholine receptors into the membranes of chick muscle cells and also enhance the formation of receptor clusters.

The next step is to make antibodies to the glycoprotein and see whether they prevent the receptor insertion brought about by the neurons themselves. If that proves to be the case, it would indicate that the glycoprotein is the cause of the effect.

Ultimately, the research might lead to a better understanding of diseases such as muscular dystrophy or myasthenia gravis in which nerve and muscle cell interactions are faulty. "If we can characterize a protein that promotes one or more trophic interactions between nerve and muscle we might gain some insight into what happens when things go wrong," Fischbach suggests. ■