Biochemistry

Richard Lipkin reports from Washington, D.C., at a meeting of the American Chemical Society

Protecting nerve cells after injury

In some cases, an injury to the head or spine causes damage to nerve cells in phases. First comes the initial injury. Then secondary effects set in: inflammation, tissue breakdown, and a host of other physical reactions to injury.

While medical treatment often can do little to mitigate the effects of initial trauma to nerve cells, many researchers believe that speedy intervention can prevent further degradation of nerves and tissues near the injured site.

John M. McCall, a chemist at the Upjohn Co. in Kalamazoo, Mich., described the ongoing study of a class of compounds that do appear to reduce the secondary phases of nerve damage after injury to the brain or spinal cord, including stroke or hemorrhage, has occurred.

The class of compounds bears the name Lazaroids, also known as 21-aminosteroids. One of those compounds, tirilazad mesylate, is now in the final phase of trials with 1,700 patients. So far, the drug has proved safe and effective for treating certain types of acute head and spinal cord injuries, McCall reports.

In one study of 1,015 patients, researchers saw mortality drop by 43 percent overall among persons with subarachnoid hemorrhages — a specific brain injury due to a ruptured blood vessel. Patients also showed less nerve damage once their bleeding had stopped and improved recoveries, McCall says.

The drug functions as an antioxidant, binding to the lipid bilayer of a cell membrane and serving as a protective agent. Once neurons have experienced trauma, they can suffer an onslaught of oxygen radicals that cause a degenerative condition called cell membrane lipid peroxidation.

"If unchecked, lipid peroxidation spreads over a cell membrane's surface, severely disrupting its function," says McCall.

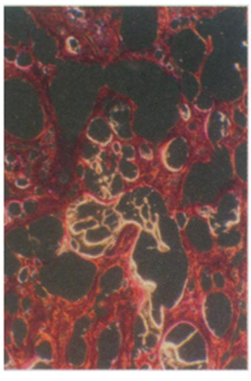
"This is where tirilazad comes in. It blocks lipid peroxidation. On a larger level, it also blocks some inflammatory reactions that lead to further injury. This is part of its neuroprotective effect."

Seeing silicone invade breast tissue

More than 2 million women have breast implants containing a soft polymer called polydimethylsiloxane (PDMS).

Some of those women report illnesses from reactions to the implants, including autoimmune disorders such as lupus, rheumatoid arthritis, and chronic fatigue. In some cases, silicone has invaded the implant's surrounding tissues, or implant capsules, made of connective tissue and macrophages.

To show how foreign materials have disrupted breast tissue and provoked adverse reactions, Jose A. Centeno and his colleagues at the Armed Forces Institute of Pathology in Washington, D.C., describe using Raman microspectroscopy to study tissue samples of 47 implant patients.



Centeno *et al.*

Seeing silicone invade breast tissue.

The researchers focused a laser onto a one-micrometer wide region of tissue, then analyzed the "unique fingerprint" of the scattered light. The method allows them to obtain specific data about the types of molecules that have entered and irritated breast tissue.

Centeno's team looked at three types of implants: ones filled with PDMS gel, ones containing saline, and ones with PDMS gel covered with polyurethane.

Only the saline-filled implants leached no silicone into breast tissues, they report.

Biomedicine

Elizabeth Pennisi reports from Cold Spring Harbor (N.Y.) Laboratory at the Translational Control meeting

Three plus one signals protein's finish

In genetic material, the sequence of nucleotides — the building blocks of DNA and RNA — specifies the order of amino acids in a protein: Three nucleotides define a particular amino acid. During the 1960's, geneticists also recognized that three sets of three nucleotides — the stop codons — told the cell's machinery that it had come to the end of the coding for a particular protein. The triplets UAA, UAG, or UGA (U for uracil; G, guanine; and A, adenine) were as definitive to geneticists as periods at the end of sentences are to grammarians.

Those days of clear-cut meanings have ended. A few molecular biologists now contend that actually four nucleotides — the stop codon plus the next one down the line — control the termination of translation, says Chris M. Brown, now at Iowa State University in Ames.

That fourth nucleotide affects the efficiency of protein synthesis. A purine — adenine or guanine — in that position speeds this process much more than a pyrimidine — cytosine, thymine, or uracil — does.

While at the University of Otago in Dunedin, New Zealand, Brown and his colleagues evaluated almost 24,000 genes from more than 90 species, determining the frequency of each of the twelve possible stop-codon-plus-one combinations. Some foursomes appear much more often at the ends of genes than others, they concluded.

Brown and his coworkers also made 12 RNAs, each coding for the same protein fragment but ending with a different foursome, and timed protein production. "There was a 70-fold difference between the best and the worse," he says.

The research team also evaluated the effect of adding a different fourth nucleotide to a triplet that codes either for a recently discovered amino acid, selenocysteine, or a stop signal, depending on the shape of the nucleotide strand farther down the line. As the researchers expected, "this fourth element changes the meaning," Brown says.

Fragile X repeats clog protein synthesis

In fragile X syndrome, as well as several other disorders with genetic components, problems arise because of mutations in the affected cells' genetic codes (SN: 7/10/93, p.20). For some reason, sections of particular genes contain multiple sets of three nucleotides. Typically, 50 sets of these threesomes exist, one right after another. But in aberrant cells, the number of these so-called trinucleotide repeats can exceed 250.

Most of the time, this excessive stretch of DNA repeats never gets transcribed into messenger RNA, and subsequently translated into a protein. But in at least one man with a mild case of fragile X syndrome, the transcription machinery of some cells waded through the gene's threesomes and sometimes even made protein, says Yue Feng of Emory University School of Medicine in Atlanta.

Feng and her colleagues removed samples of cells from this man and grew them in the laboratory. In these, the affected fmr-1 gene had 57, 168, 182, 207, 266, or 285 repeats. The degree to which these genes were abnormal and unable to transfer their information varied depending on the number of repeats. Cells with genes with 182 or more repeats still made messenger RNA, but in reduced amounts. But the protein-building machinery couldn't handle what little RNA existed in ceils with 266 or more repeats, she discovered.

These data show for the first time that the lack of fmr protein leads to fragile X syndrome. "He makes some protein but not enough," says Feng. Some researchers have sought ways to trick cells with these altered genes to make messenger RNA. But her results indicate that even then the cell may still fail to make functional protein.