

the presence of alcohol, the climbing fiber activity overwhelms the cerebellum's normal output.

The climbing fibers arise from cells in the area of the brain stem called the inferior olive complex. This area gathers information from other areas of the brain to send on to the cerebellum. Bloom speculates that ethanol may activate the cells of the inferior olive by reacting chemically with a normal neurotransmitter to create an unnatural, stimulatory compound.

A laboratory study of long-term exposure to ethanol has revealed another specific site of alcohol's action, Bloom reports. He and his colleagues acclimated rats to alcohol vapors that produce a blood alcohol level associated with intoxication. They used this procedure to avoid a frustrating problem of animal research on alcoholism: Animals generally refuse to drink a solution containing alcohol unless it is the only liquid available and they are quite dehydrated; thus the animals are generally in poor health. In contrast, animals exposed to alcohol vapor remain

AAAS

Beyond the limits of protein building

Some children may use their Tinker Toys to model the structures printed on the box, perhaps embellishing them with an extra hub or two. But other children may go beyond the toymakers' imaginations, creating structures all their own and adding pencils, forks, twigs and mousetraps to their edifices.

Protein engineering, an activity still in its early stages, attempts to improve upon nature by remodeling existing enzymes to make them more stable or more active or to change the type of reaction they catalyze. But Bruce Erickson of Rockefeller University in New York and his colleagues are taking a more radical approach. They are constructing from scratch a molecule that does not look like any protein in nature, and they plan to add binding and catalytic sites to its basic framework. Erickson reported at the AAAS meeting the successful chemical synthesis of the framework for a new class of molecules, which he calls betabellins.

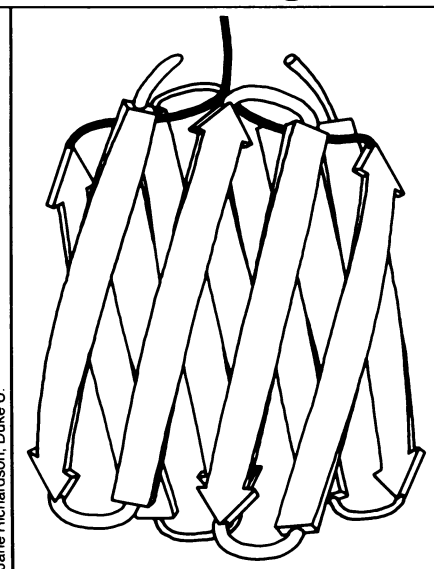
"We are opening up a new vista," Erickson says. "With this approach we are not limited to the 20 L-amino acids in natural proteins. We can put in D-amino acids [the mirror images of the L-amino acids found in nature], and we can use any of the 2,000 non-genetically-coded amino acids."

The basic plan for betabellin's structure comes from a natural structure, idealized for chemistry. Several different proteins, such as immunoglobulins and the enzyme superoxide dismutase, have bell-shaped, slatted regions made up of an arrangement of amino acids called beta sheets. Erickson, in collaboration with Jane and David Richardson of Duke University in Durham, N.C., devised a sequence of amino acids that comprises a structure far

healthy and continue to gain weight, Bloom says. And they become tolerant to the alcohol, so that after three weeks of exposure, cells of the inferior olive no longer show increased activity. But all is not normal. If the flow of alcohol vapor is interrupted, there is a "profound shift" in activity. Bloom has traced this postwithdrawal change to another set of brain cells, the locus ceruleus.

The locus ceruleus offers a tempting explanation of the clumsiness of an intoxicated person. This brain stem area, which sends processes to the cerebellum as well as to other brain regions, normally shows a response with a fixed latency to novel events in an animal's environment. But in the presence of alcohol, the latency becomes variable. Thus, the nerve cell signal loses its time relationship with the triggering event. This discrepancy may make the difference between catching or missing a dropped plate, for example, Bloom speculates. "This may be the start of a biochemical description of the alcohol effect."

—J.A. Miller



The basic shape of betabellin.

more regular than any "beta barrels" seen in nature. Betabellin has two identical flat regions. Each of these sheets is made up of three rows of eight amino acids, with a sharp turn between them, and one row of seven amino acids attached to a special synthetic cross-linker.

The structure of this small, globular protein includes a variety of special features that appeal to organic chemists. Because its two halves are symmetrical, they can be synthesized simultaneously. Betabellin contains internal sites where it can be snipped into pieces appropriate for analyzing the amino acid sequence. And it contains end sites to which binding sites and active sites can later be added. Betabellin also can be crystallized easily.

Erickson found many constraints on the

choice of amino acids in the framework. To form the beta sheets, he had to alternate small hydrophobic (water-shunning) and hydrophilic (water-loving) amino acids. At the tight turns, he used proline and asparagine—originally the L forms, but later he replaced them with the D forms, which fit better in the available space. He included one cysteine in each half of the molecule, and in his most advanced structure he has those amino acids attach to each other in a disulfide bond, thus holding together the two sheetlike sections.

Even the most carefully planned chemical scheme can generate surprises. When Erickson purified the betabellin structure containing the disulfide bond, he obtained two distinct materials with identical amino acid sequences. Erickson and his colleagues are now trying to determine the specific structural difference.

The next step will be to further modify the framework and to add binding and catalytic sites modeled after those found in nature. "We think the present technology is adequate to start evolving proteins with new functional groups at active sites," Erickson concludes. This research, like much of the protein engineering work, is sponsored by the Office of Naval Research.

—J.A. Miller

AAAS

Tracing disease to trace minerals

Trace mineral deficiencies in the diet may play a bigger role in human health than most physicians now realize, according to a series of papers presented last week at the AAAS meeting. Many of these reported links between trace minerals and health problems—such as heart disease and diabetes—are still only suggestive. However, the deficiency levels discussed at the meeting are common in the typical American diet, the researchers warn, and if such subtle deficiencies are definitively found to jeopardize health, they may be affecting millions of people in the United States alone.

For example, while the safe and adequate amount of copper is generally thought to be 2 to 3 milligrams per day, "probably 75 percent of daily diets in the United States contain less than 2 mg of copper," reports Leslie Klevay, acting director of the Agriculture Department's Human Nutrition Research Center in Grand Forks, N.D. Several papers reported data suggesting that copper-deficient diets may increase one's risk of developing a host of health-threatening conditions, including coronary heart disease.

When fed a diet deficient in copper, animals have developed bone fragility, anemia, defects of the connective tissue, arteries and bone, infertility, heart arrhythmias, high cholesterol levels, heart attacks and an inability to control blood sugar levels. Klevay notes that any condi-