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 acclimatized 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 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

AAAS

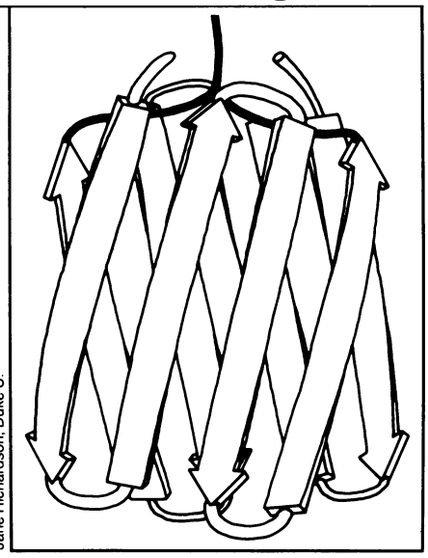
Beyond the limits of protein building

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 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.



Jane Richardson, Duke U.

The basic shape of betabellin.

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-

tion associated with coronary heart disease in humans can be triggered in laboratory animals merely by putting them on a copper-deficient diet.

And he recently did. Using mice, he attempted to repeat a study performed 20 years ago, which had reported finding a link between dietary fat and coronary heart disease-type effects. But there was a "hidden variable" in that earlier diet, Klevay says, because it had been low in copper. When he compared the disease effects reported with factors linked elsewhere to copper deficiency, he says, it became apparent that nearly all the factors attributed to fat could be accounted for by the copper deficiency alone. To test that, he repeated the study with copper being the only variable. And his results, published in the February ATHEROSCLEROSIS, matched those of the earlier study — serious heart disease.

In another previous study, 13 of 15 animals on copper-deficient diets had dropped dead in the fifth week of a six-week study. "Limited autopsies showed ruptured hearts and aneurysms," Klevay says. In later, similar tests, he identified major electrocardiogram (EKG) changes as well. While puzzling over the EKG changes, Klevay ran across a reference to EKG changes in human participants in the famous Framingham study (SN: 1/24/81, p. 55) that were deemed predictive of an individual's potential for developing heart disease. Klevay's animals had exhibited two of those predictive EKG changes.

Harold Sandstead, former director of the Agriculture Department's Human Nutrition Research Center on Aging at Tufts University in Boston, described his research showing elevations in one man's blood cholesterol — from 206 mg/deciliter of blood to 235 mg/dl — after the man was put on a diet having only 0.8 mg of copper for 105 days. The man's cholesterol levels dropped back to 200 once he resumed a copper-adequate diet.

Copper is found in such foods as beef liver, nuts and seeds, dark chocolate, breakfast cereals and goose breast. But eating 2 mg worth of copper daily won't ensure a sufficiency of the mineral. Sandstead cites animal studies by Sheldon Reiser at the Agriculture Department's Carbohydrate Nutrition Lab in Beltsville, Md., that suggest that diets high in fructose — a simple sugar contained in ordinary sucrose, or table sugar — reduce the body's ability to absorb copper. In fact, Reiser says, copper-deficient animals fed fructose will start dying in five weeks of catastrophic heart disease — such as ruptured hearts — while similarly copper-deficient animals whose sugar source was cornstarch survive comfortably. Reiser says that in the fructose group, "every index of unfavorable metabolic effect was magnified."

Fructose appears to be only one of a group of chemicals that raise cholesterol and inhibit copper metabolism, Klevay says. Moreover, there is also a group that lowers cholesterol and enhances the body's uptake of copper; it includes aspirin, calcium and carbonates.

Walter Mertz, director of the Agriculture Department's Beltsville Human Nutrition Research Center, focused on chromium. In humans, he says, this is one of the few trace elements "that consistently declines with age." In the United States and other industrialized countries, he notes, glucose tolerance — the rate at which the body metabolizes excess sugar — also declines with age. Since chromium is known to help bring the hormone insulin together with insulin receptors on a cell's surface, there's growing suspicion that some element of mature-onset diabetes may be fostered by a chromium deficiency. Animals with chromium deficiency will metabolize sugar at almost half the normal rate, Mertz says, "which means, at least in animals, that chromium is necessary for maximum effectiveness of insulin." Currently, he is trying to find out "in what cases and under what conditions we can improve the glucose metabolism of middle-aged people." He's also trying to identify what conditions, such as exercise, influence human chromium requirements.

New data from Japan suggest a second major role for chromium, Mertz says — the stimulation of DNA transcription within cells. While it's still too early to be sure, he says, chromium seems to be a part of a very specific protein that influences a cell's nucleic acid metabolism.

Work by Herta Spencer is showing that through their dietary choices, many people risk developing serious zinc deficiencies. New data by Spencer, chief of the metabolic section at the Veterans Administration Hospital in Hines, Ill., on obese men hospitalized to lose weight, show that weight loss generally correlates with losing zinc. Zinc deficiency can cause skin rashes, appetite loss, poor wound healing, mental lethargy, hair loss and taste disturbances.

The recommended daily allowance (RDA) for zinc is 15 mg. However, many diets — even those where weight reduction is not a goal — are deficient in this essential metal. One analysis Spencer performed on hospital diets showed that zinc levels in supposedly well-balanced, calorie-adequate diets could range from 4.6 mg to 19 mg per day. Zinc levels tended to vary with dietary levels of animal protein, especially fish and red meat (though legumes, wheat germ and cheese are also good sources). Because weight-reducing diets are frequently low in animal protein, they risk being low in zinc, Spencer says. However, it's not just the inherent zinc level that makes such diets a threat to zinc sufficiency. Preliminary data suggest that protein is needed to carry zinc across the intestinal lining so that it can be absorbed, she says. What's more, certain chemicals like EDTA — used for removing lead from the body — will pull huge quantities of zinc, her research shows. In persons who had been excreting 0.4 mg of zinc daily in urine, three days of EDTA treatment was enough to pull 64 mg of zinc from their body stores.

Ironically, the use of concentrated zinc supplements to counteract this problem may only create another — a calcium deficiency. In a just-completed study, Spencer found that high levels (140 mg) of zinc reduced the body's ability to absorb calcium — from a normal 69 percent to only 39 percent — when the diet contained only a quarter of the RDA for calcium. Spencer notes that for women whose diets are already seriously low in calcium — as most U.S. women's diets are — such zinc supplementation might increase their risk of postmenopausal bone loss. *— J. Raloff*

A new look at arthritis origins

People with rheumatoid arthritis generally have hot, swollen, inflamed joints, and this process of inflammation is generally considered to be the root of the disease.

But according to evidence presented this week at the meeting in Anaheim, Calif., of the American Rheumatism Association, and in the May ARTHRITIS AND RHEUMATISM, the inflammation may be secondary to proliferation of the synovial cells lining the joint.

Researchers from World Health Organization arthritis centers at the University of Alabama at Birmingham (UAB) and Mainz, West Germany, have found that, at least in the mouse model they are studying, the earliest change in tissues destined to become arthritic is not inflammation but an uncontrolled reproduction of synovial cells. Using a strain of mice that spontaneously develop arthritis, they observed a "clear-cut dissociation" between tissue destruction and overt inflammation.

"It suggests an alternative mechanism of joint destruction other than classical inflammation," says UAB's William Koopman. "Whether it will hold true [in humans] is speculation."

One factor supporting the theory, Koopman told SCIENCE NEWS, is that anti-inflammatory drugs, while relieving some of the symptoms of rheumatoid arthritis, don't prevent joint destruction.

"There are patients who don't seem to have a lot of inflammation — their joints are not warm, swollen or tender — yet there is evidence of joint destruction," notes Koopman.

Hans-Georg Fassbender of the arthritis center in Mainz looked at more than 20,000 tissue biopsies from people diagnosed with rheumatoid arthritis, and found that some of these people had little inflammation. Fassbender's pathological evidence, combined with the clinical evidence of "symptomless" patients, suggests that inflammation is not the whole story in hu-