Custom tailored chemicals: New drugs

Using detailed knowledge of biochemistry, chemists are synthesizing potential drugs that meet very specific criteria. If a disease is caused by a slight alteration in body chemistry, changing a single enzyme may be the best cure. The less specific medications that have been available often influence many body processes and result in a host of side effects.

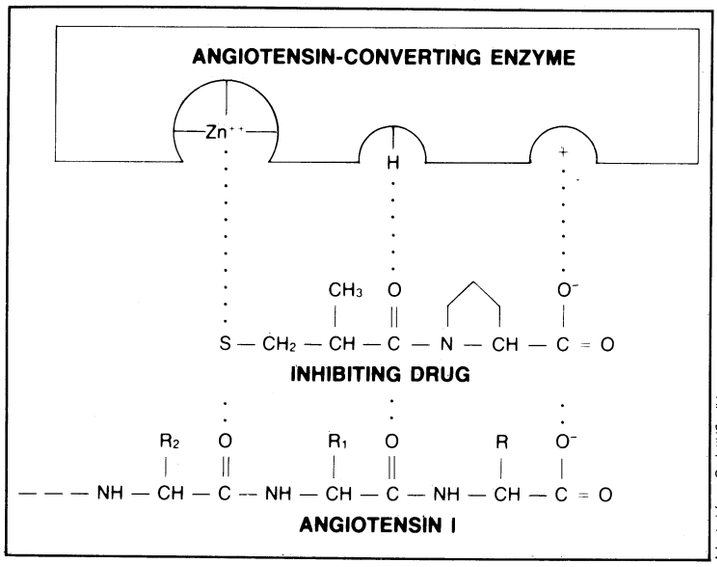
Last week at the national meeting of the American Chemical Society in New Orleans scientists reported progress on making medicines truly specific for a disease. David W. Cushman and Miguel A. Ondetti of the Squibb Institute for Medical Research in Princeton described a drug, which is beginning clinical trials, for treating high blood pressure.

Hypertension, estimated to occur in 20 million people in this country, is thought to be caused by overproduction of a blood component called angiotensin II. An angiotensin-converting enzyme cleaves angiotensin I, an inactive protein, to make the active molecule. The researchers interfered with the formation of angiotensin II by inactivating angiotensin-coverting enzyme. The new drug, in low oral doses, reduced blood pressure of hypertensive animals, the researchers report, and doses at least 1,000 times greater did not show unwanted side effects. Preliminary clinical trials in Switzerland show that the drug reduced the level of angiotensin II.

"This is one of the few drugs actually designed by chemists," Cushman told a news conference. The researchers wanted a chemical that would attach tightly to the portion of the angiotensin-converting enzyme where angiotensin I normally binds. Then there would be little chance of the enzyme producing angiotensin II.

The researchers did not know the exact chemical structure of the enzyme, but because it contains zinc and cleaves a protein, they guessed that the active area would resemble that of a better-analyzed enzyme, carboxypeptidase A. From their knowledge of the two enzymes, Cushman, Ondetti and Bernard Rubin made a hypothetical model of the active site and then synthesized compounds that should bind with strong interactions, for example, by attraction of positive and negative charges. After determining, in a test tube, the interactions of each compound with the enzyme, the researchers altered their model and synthesized more compounds. "We modified the molecule until it fit like a hand in a glove," Ondetti says.

The most potent inhibitor was a sulfur-containing derivative of the naturally occurring amino acid proline. The enzyme binds that chemical with 10,000 to 100,000 times the affinity it shows for angiotensin I.



"Like a hand in a glove": Inhibiting drug designed to fit hypothetical active site of angiotensin-converting enzyme.

"This amino acid derivative is not similar to angiotensin I," Ondetti says. "It is only one-sixth as big." The researchers do not expect the drug to affect the activity of other enzymes in the body. For example, it does not inhibit carboxypeptidase A, the enzyme they used in making their models.

An even newer approach to drug design, also described at the meeting, is the synthesis of chemicals called "suicide enzyme activators." These molecules destroy the enzyme that acts on them. Robert H. Abeles and Richard B. Silverman of Brandeis University designed chemicals that so closely resemble an enzyme's normal substrate that the enzyme not only binds the chemical, as in the angiotensin drug research, but also acts on it. The enzyme-altered chemical, in turn, binds to the active portion of the enzyme, making it useless. This drug should be especially free of side effects because the active form is never free in the blood or tissues; it is generated right at the site where it acts.

Suicide enzyme inactivators, Abeles suggests, could block specific reactions in either people or in invading microorganisms. They could also be used to produce animal models for human diseases where a specific enzyme is missing, such as cystathioniuria, an inheritable disorder associated with mental retardation. Using laboratory animals, more effective dietary restrictions for people could be determined.

So far, the researchers report, they have designed a number of suicide inactivators for several enzymes and have deduced two or three general principles which should aid synthesis of more compounds potentially valuable as very specific drugs. □

Beauty products cause cancer?

Shampoos and cosmetics have joined that ever-expanding pool of common products that are suspected of causing cancer. A team of scientists reported at the American Chemical Society meeting in New Orleans last week that research just completed on cosmetics, skin lotions and shampoos indicates the presence in many of a compound known to produce liver tumors in rats.

David H. Fine and co-workers at Thermo Electron Research Center in Waltham, Mass., and G. P. Arsenault and Klaus Biemann at the Massachusetts Institute of Technology identified N-nitrosodiethanolamine (NDELA) by analytical chemical techniques. They think that the substance is formed in the toiletries by a reaction of nitrite and an additive, triethanolamine or diethanolamine.

Other research has demonstrated that NDEIA causes liver cancer when fed to rats. Because no studies have examined the effect of this nitrosamine applied to the skin, there is no good way to assess the potential hazard, Fine says. The researchers are concerned that a significant amount of the chemical may be absorbed through skin because triethanolamine is used industrially to increase penetration of chemicals into wood and paper. "There is a fair possibility that it [NDELA] may be absorbed," Fine says.

The researchers reported their findings to the Food and Drug Administration, which is now beginning to examine the data. Fine would not reveal brand names, but the FDA identified the products to reporters.

Max Factor Ultralucent Whipped Creme Makeup had the highest concentration of NDELA, followed by Revlon Moondrops and Helena Rubenstein Silk Fashion. Lotions and shampoos had less. Of the lotions, Johnson's Baby Lotion and Scholl Rough Skin Remover had the most NDELA, and Clairol's Herbal Essence topped the list of shampoos. No NDELA