

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.

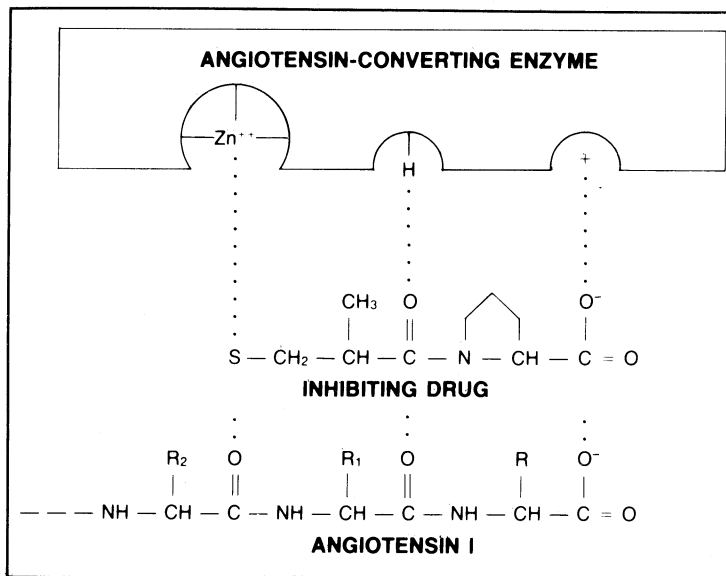
Last week at the national meeting of the American Chemical Society in New Orleans scientists reported progress on making medicines truly specific for a disease. David W. Cushman and Miguel A. Ondetti of the Squibb Institute for Medical Research in Princeton described a drug, which is beginning clinical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

Adapted from Ondetti/Squibb

"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 cystathioninuria, 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 NDELA 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 Ultrucent 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 Clairrol's Herbal Essence topped the list of shampoos. No NDELA

was found in Neutraderm Dry Skin Lotion or Diaparene Cradol Shampoo.

The range of concentrations of NDELA among the 27 products tested ranged from 48,000 parts per billion to less than 1 part

per billion. "It is likely, therefore, that if the mechanism of contamination were identified, technology might exist for eliminating the carcinogenic impurity," the researchers conclude. □

U.S. children give families high marks

Although American children worry about their home and family environment, the vast majority of them view their family as a cohesive, "happy" force, according to preliminary results of a nationwide study of 7 to 11-year-olds. The youngsters' reflections do "not support the position that the American family is in decline," reports Nicholas Zill, project director for the National Survey of Children and senior staff scientist for the Foundation for Child Development, which sponsored the research.

More than 2,200 children and 1,700 of their parents were interviewed in late 1976 by researchers from Temple University's Institute for Survey Research, which conducted the survey for the foundation. The sample is designed to represent the country's 17.7 million children.

"We wanted to give kids a chance to speak for themselves," Zill explains. "In the past, most studies have focused on parents, teachers, doctors . . . with no input from the children. We see this survey as a benchmark—we're trying to see what effects social changes are having on kids, and would like to see [similar] surveys done in the future."

In the youngsters' views, the researchers see an overall positive picture of the family unit, although some children say they are "worried" and "afraid" of aspects of their life both in and out of the home. More than 9 of 10 children pointed to a happy face to convey how they feel about their families. Ninety percent of the youngsters agreed with the statement, "I like being the way I am," and over 75 percent said they were "lucky."

But 8 of 10 also said they worried about their families—that figure rose to nearly 100 per cent in families where the mother described the marriage as "not too happy." "People talk about the increase in separations and divorce in this country—and we do see a detrimental effect on kids in some of these households," Zill says. However, the survey also suggests that having both parents together does not guarantee a child's happiness. In families with both husband and wife present, nearly half of the children wished their fathers would spend more time with them, and more than one-third expressed the same desire about their mothers.

"Apparently it's not the absence of a parent *per se*" that has negative effects on a child, Zill says. The data suggest that a single parent may be better than two in some cases if he or she has adjusted well

to that role. But if the single parent felt depressed or nervous about the separation, the child tended to feel bored and lonely. In double-parent families, one of five youngsters in marriages described as "not too happy" by the mother got into fights at school, as opposed to one of ten youngsters from well-adjusted marriages. The most influential factors in a child's well-being hinge on the relationship between husband and wife in two-parent families, or the single parent's own well-being and ability to cope, Zill says.

Parents' education levels have risen steadily during the last decade, Zill says, and this has had a positive influence. Among the children surveyed, the proportion of those reporting they had "interesting things to do most after-

noons" (about one-third of the total children questioned) rose steadily with the parents' educational level. "But I am also concerned with the growing percentage of kids whose mothers never married and dropped out of high school," the psychologist says. "These mothers tend to describe their kids in very negative terms."

The researchers will pull together all the data and begin analyzing the results later this spring, according to Zill. Among the other results of the survey are:

- More than two-thirds of the children expressed fear "that somebody bad might get into my house."

- One-fourth said they are afraid that someone might "hurt" them when they leave their house.

- One-fourth reported being afraid of "TV programs where people fight and shoot guns." Frequent young viewers were twice as likely to express that fear as occasional (less than four hours daily) TV watchers.

- In all types of American communities, a majority of the children surveyed described their neighborhood as less than a "very good" place to grow up in. □

Child abusers: Signaling for help

Ever since the battered child syndrome was first described in 1962, more and more cases have been reported. In one of the more recent ones, a couple actually killed their child. Researchers have been gaining more insight into the causes of child abuse. Child abuse, it appears, is usually inflicted by parents who were themselves beaten as youngsters. They identify with an aggressive, authoritarian parent, yet are also angry at the parent for this treatment and take their wrath out on their own children.

How can this destructive family behavioral pattern be broken? Two 1976 studies described factors in infancy, at birth or even in the womb, that may identify children at risk of being beaten. As a result, doctors and nurses engaged in prenatal and postnatal care can keep a lookout for such factors and intervene before parents start striking their children. Now evidence reported in the March 14 *JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION*, by R. Peter Mogielnicki and his colleagues at the University of Colorado Medical Center and Colorado General Hospital in Denver, shows that child abusers or potential abusers may suffer weakness, paralysis or other physical symptoms as a result of their psychological trauma over beating, or thinking about beating, their youngsters. Thus doctors and nurses in hospital emergency rooms and in private practices can be on the alert for such parents and try to help them stop battering their children or even keep them from doing so in the first place.

The evidence reported in *JAMA* consists

of three case histories from the Colorado General Hospital. In one, a 24-year-old woman came to the hospital's emergency department with chest pain, headaches, weakness, dizziness, appetite loss, numbness on her right side and transient blindness of her right eye. No physical cause for these symptoms could be found. Psychiatric examination was arranged and showed that she had recently thrown her two young daughters against a wall. She agreed to psychiatric hospitalization; her children were sent to live with her sister-in-law.

In a second case, a 31-year-old man came to the hospital's emergency department with complaints of chest pain and weakness in the legs. No physical cause for these symptoms was discovered. Nor did the patient show much concern about them. Mogielnicki and his co-workers suspected that the patient was suffering from psychologically induced symptoms, and psychiatric probing revealed that he had gained custody of his six-year-old son two weeks before the start of his symptoms. He described his son as "hateful" and "obstinate" and admitted that he was afraid of inflicting injury on the boy. Once he became aware of the link between his fear and his symptoms, and arrangements were made for someone else to care for his son, his symptoms went away.

In the third case, a 23-year-old man came to the hospital emergency department with right-sided weakness, visual blurring, numbness and weakness of his right arm and both legs. No physical cause could be discovered. When the patient