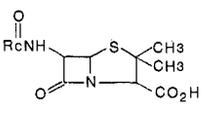
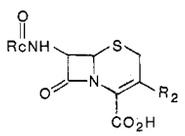
A New Generation of Antibiotics

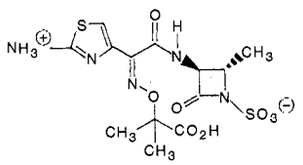
A new generation of antibacterial agents, the first ever to be derived from bacteria themselves, will shortly undergo clinical trials in humans. The "monocyclic, bacterially produced, β-lactam" antibiotics, or monobactams, are structurally related to the penicillins and cephalosporins, but have a much simpler structure, said Christopher M. Cimarusti of the Squibb Institute for Medical Research, Princeton, at the recent American Chemical Society (ACS) meeting.* The monobactams, furthermore, are most effective against Gram-negative bacteria, which are difficult to kill with either



Penicillins



Cephalosporins



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penicillins or cephalosporins. The Gram-negative bacteria, such as *Pseudomonas*, *Klebsiella*, and the Enterobacteriaceae, are responsible for a large percentage of the current rash of nosocomial (hospital-derived) infections.

The β-lactam antibiotics are characterized by a four-membered ring containing an amide group. In the penicillins, which were originally obtained from a fungus, this ring is fused to a five-membered ring through the amide nitrogen and an adjoining carbon. In the cephalosporins, also derived from fungi, it is fused to a six-membered ring in the same manner. The fused ring system distorts the β-lactam ring, increasing its reactivity; the lactam then, apparently, reacts with enzymes involved in the synthesis of bacterial cell walls, inhibiting that synthesis. It has generally been believed that a simpler β-lactam ring would not possess this activity.

The monobactams were originally discovered by Richard B. Sykes and his colleagues at Squibb after they had screened more than 1 million bacterial isolates from around the world. Ironically, the first monobactam was found in a soil sample from the Pine Barrens, a wetlands located only a few miles from the Squibb Institute. The new antibiotics do not have a ring fused to the β-lactam. Instead, they have a sulfate moiety attached to the amide nitrogen. The sulfate does not distort the ring structurally, but apparently its strong electronegativity is sufficient to activate the β-lactam ring.

The Squibb team reported the isolation and characterization of seven naturally occurring monobactams earlier this year, about the same time as two others were reported by A. Imada and his colleagues at the Takeda Laboratories in Japan. All had only modest antibiotic activity. Cimarusti and his colleagues thus synthesized a series of analogs with different side chains. The best of these synthetics, called SQ 26,776 or az-threonam, he told the ACS, is the compound that is now being studied for safety in humans and that will soon undergo clinical trials for efficacy. Az-threonam has few side effects, he says, and is expected to be a very safe drug. It should also be inexpensive, since it is synthesized relatively easily from the amino acid threonine.

*182nd National Meeting of the American Chemical Society, 24 to 28 August, New York.

Pesticides May Not Persist in the Tropics

Developing countries frequently have insect problems that represent hazards both to food crops and to human health. Many of those countries, however, restrict the use of DDT and other pesticides because of evidence developed in the United States that these chemicals persist in the environment for long periods. But evidence obtained in temperate climates may not be germane in the hot and humid tropics, says N. S. Talekar of the Asian Vegetable Research and Development Center in Taiwan. He told the ACS meeting that DDT and four other pesticides are broken down much more rapidly in tropical and subtropical climates.

Talekar applied each pesticide in the field twice per year at rates approximately double those normally used by farmers—4.5 pounds per acre (5 kilograms per hectare) for DDT and dieldrin, and twice as much for fonofos, phorate, and carbofuran. He then measured the concentration of each chemical in the top 15 centimeters of soil. He found that the pesticides accumulated during the cooler months after the fall application, but broke down rapidly during the hot, humid summer months. With the exception of dieldrin, the amount of pesticide residues in the soil at the end of summer was lower than the levels before the spring application, indicating that part of the winter accumulation was also destroyed during the summer. Dieldrin, which is known to be more persistent than the others, showed a slight accumulation.

"Many authors claim for chemicals like DDT a half-life in terms of years," Talekar says. "But in the tropics, we find the half-life to be less than 6 months. The environmental health hazard standards established for pesticides in the United States and Europe do not seem to be relevant to the tropics."

What Gives Limburger Its Unique Odor?

Lovers of cheese might demur, but surely one of the least appetizing foods consumed by Western civilization is Limburger cheese. This redolent product of whole cow's milk is a semisoft cheese with a water content slightly less than that of cottage cheese. Its characteristic flavor is produced by a progressive growth on its surface of yeast, micrococci, and *Brevibacterium linens*, with the most important contribution coming from the last of these. Despite several earlier investigations that have shown part of the odor to arise from hydrogen sulfide, methyl mercaptan, and several α-keto acids, the exact source of Limburger's unique fragrance was still a mystery.

Some cheeses obtain their flavor and aroma from a small group of chemicals, says Thomas H. Parliment of the General Foods Technical Center in White Plains, New York. Blue cheese, for example, gets its aroma

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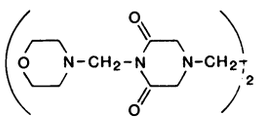
from a series of 5-, 7-, and 9-carbon methyl ketones. Others are somewhat more complex, although individual flavor notes can be detected: dimethyl disulfide, which on dilution gives an onion- or tomato-like odor, is a major component of cheddar cheeses, whereas the nutty taste of Swiss cheeses arises from pyrazines. But the flavor and aroma of Limburger, he reported at the ACS meeting, appears to be derived from a whole series of chemicals.

Parliment and his associates analyzed the volatile components of imported Limburger cheese by gas chromatography and mass spectrometry as part of a continuing study of the sources of cheese flavor. They found, surprisingly, that more than 50 percent of the volatiles were phenols, including indole and acetophenone. Phenol itself has very little odor, but acetophenone has a pungent-sweet floral aroma and indole is tarry-repulsive when concentrated. They also found methyl ketones similar to those in blue cheese, and several sulfur compounds in addition to hydrogen sulfide, methyl mercaptan, and dimethyl disulfide. Methional has a cheesy or potato-like flavor and methyl thioacetate has an aroma similar to cooking cauliflower. They also found significant quantities of butyric, octanoic, and decanoic acids, whose odors are sour, rancid, and sweaty, respectively. Parliment is confident he could now reproduce the characteristics of Limburger in an artificial cheese.

A New Multipurpose Drug from China

Bimolane, a new synthetic drug that is a diketopiperazine derivative, possesses strong activity toward psoriasis, uveitis, and several types of tumors, according to Ren Yun-feng and Shu Han-li of the Shanghai Institute of Materia Medica and Zhang Tan-mu and Lin Chen of the Institute of Honan Medical Sciences in Zhengzhou. The drug also potentiates the effects of radiation in cancer therapy.

Orally administered bimolane produced more than a 50 percent regression of tumors in 24 of 155 patients studied since 1978, Ren told an ACS symposium. The effects were more pronounced in particular subgroups of patients: a greater than 50 percent regression was observed in 4 of 9 patients with Hodgkin's disease, 12 of 22 with non-Hodgkin's lymphoma, and in 3 of 3 patients with cancer of the vulva. Significant effects were also



Bimolane

observed in another 64 of the 155 patients. The drug was also given as an adjuvant to radiotherapy in 96 patients with squamous carcinoma, lung tumors, and sarcomas of soft tissues. Complete or partial response was observed in 61 cases. In patients with lung tumors, a response was observed in 26 of 38 patients given bimolane, but in only 12 of 31 patients treated with radiation alone.

In 290 patients with psoriasis (most of whom had already received extensive treatment), there was a complete or nearly complete response in 113, a significant response in another 73, and an improvement in 56. And finally, there was a complete response in 51 of 123 eyes treated for various types of uveitis, and improvement in another 54. The only significant side effects in all of the patients were a mild gastrointestinal toxicity and a slight decrease in leukocyte count.

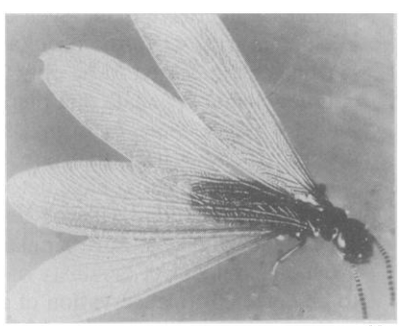
New Fluorinated Pesticides Have Delayed Activities

Two new types of fluorinated pesticides that are highly insect-specific and environmentally safe have been developed by Glenn D. Prestwich and his colleagues at the State University of New York at Stony Brook. Both types work by delayed action.

The first family of chemicals, developed by Prestwich and Joan F. Carvalho, are glycerol esters containing fluoroalkyl or fluoroacyl moieties in the ω-position of the acid constituents. The actual poison, Carvalho reported, is fluoroacetate, which is released from the glycerol esters by enzymes in termites. The compounds, along with termite attractants, can be impregnated in small blocks of wood and buried near termite colonies. The termites find the wood and carry it back to the colony before they die. Individual termites are killed by only 20 to 200 nanograms of the compounds, and death is delayed for 24 to 72 hours after ingestion. A mature colony of eastern termites could be destroyed by as little as 10 milligrams of the fluorinated fat.

The second family of chemicals, synthesized by Prestwich, Toni B. Kline, and Hong-Ming Shieh, are fluorinated versions of naturally occurring sterols. These sterols are obtained from plants and animals by certain types of insects and converted to molting hormones, such as ecdysone, that regulate the transformation of insects from larvae to pupae to adult. Kline reported that the fluorinated sterols block the metabolism of sterols by these insects, but are apparently harmless to plants and animals. They have found, for example, that feeding the compounds to tobacco hornworms (*Menduca sexta*) results in stunted growth, difficulty in larval molting and pupation, and death. Prestwich thinks that the compounds will also be useful against mosquitoes and other insects that molt.

Another approach to inhibition of molting has been adopted by Albert B. Demilo of the U.S. Department of Agriculture in Beltsville, Maryland. He has synthesized a series of analogs of



USDA

Winged termite

thiosemicarbazones of 2-acetylpyridine. In tests by Thomas J. Kelly and Robert E. Redfern of USDA, Demilo reported, several of the analogs kept larvae of the milkweed bug (*Oncopeltus fasciatus*) locked in their old outer cuticles, even though each had grown to normal size and produced a new cuticle under the old one. The larvae literally rolled over and died several days after they were due to molt. In preliminary tests, the materials also showed activity against fall armyworms and common houseflies.

Thomas H. Maugh II