Starving in the Midst of Plenty

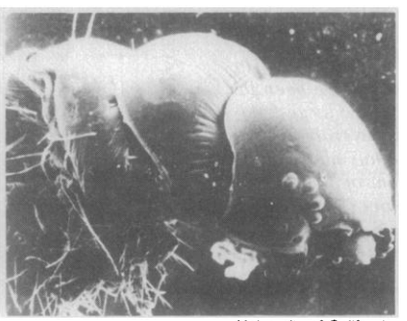
Two chemicals that kill certain agricultural pests by inhibiting molting (ecdysis) have been isolated from the East African medicinal plant *Ajuga remota* (Labiatae) by investigators from the University of California at Berkeley. Isao Kubo, James Klocke, and Shoji Asano told the American Chemical Society* that the chemicals, called phytoecdysones, cause insect caterpillars to grow as many as three new head coverings or cuticles without shedding any old ones. Their mouths become buried so deeply inside the coverings, says Kubo, that they are physically unable to eat and starve to death. Some of the caterpillars live as long as 3 days after ingesting the compounds, growing new head capsules even while starving.

Kubo first noticed *Ajuga* when he was studying locust migrations in East Africa; it was the only plant the locusts did not touch. A local Bwana Mganga, or medicine man, told him that the bitter tasting leaves and roots of the plant were used to treat such diseases as malaria and high blood pressure. Subsequent studies in his own laboratory showed that an ether extract contained four antifeedants, chemical agents that prevent certain insects from eating by destroying their sense of taste.

Extraction of the plants with methanol yielded two new compounds, cyasterone and ecdysterone, whose basic structures are similar to that of cholesterol. When tested in the laboratory these agents interfered with the molting cycle of two cotton pests common in the United States, the pink bollworm (*Pectinophora gossypiella*) and the fall armyworm (*Spodoptera frugiperda*). They also have the same effect on the silkworm, *Bombyx mori*. They have no effect, however, on two other troublesome pests, the corn earworm and the tobacco budworm.

The phytoecdysones apparently act by upsetting the time sequence of molting—presumably, says Kubo, by stimulating secretion of the enzyme phenol oxidase, which is responsible for cuticle hardening. Newly synthesized cuticle hardens before it expands, so that the previous cuticle remains stuck to it. This process repeats itself until individual larvae have as many as three head capsules. In some cases, the larvae also have impaired locomotor and excretory functions because the whole body is compressed as a result of retention of the cuticular skin.

*181st National Meeting of the American Chemical Society, 29 March to 3 April, Atlanta, Georgia.



University of California

"Three-headed monster"

A fall armyworm with three head capsules—resulting from ingesting a phytoecdysone—is physically unable to eat because its mouth is too deeply recessed.

Kubo and his colleagues hope to test the new chemicals in the field soon, since they should be both nonpolluting and highly specific in activity. The investigators do not yet have sufficient quantities of the chemicals, however, and are synthesizing simpler analogs that they hope will retain phytoecdysone activity.

New Ways to Use Metals for Arthritis

Gold compounds have been used successfully for more than 50 years for the treatment of rheumatoid arthritis, a painful inflammation of the joints that is generally marked by progressive deterioration of the cartilage that surrounds, cushions, and protects joints. Gold sodium thiomalate and gold thioglucose are, in fact, among the few agents that can halt that progression. But both these drugs must be given by painful intramuscular injections that produce high initial serum gold levels that can damage the kidney and produce other undesirable side effects. Thus, only about 100,000 of the nation's 6.5 million arthritics receive the drugs.

Most of these problems can be overcome with new gold derivatives that can be taken orally, according to David T. Hill, Blaine Sutton, and their colleagues at Smith Kline & French Laboratories in Philadelphia. The best of these, triethylphosphine gold peracetylthioglucose, known as auranofin or Ridaura, is as effective as injected gold in halting disease progression, but is accompanied by none of the side effects, primarily because the effective dose is much lower. Weekly injections release a dose of about 50 milligrams of gold, whereas a daily oral dose of auranofin releases only about 6 milligrams.

In the injectable drugs, gold is linked only to a sulfur atom, whereas in auranofin it is linked to both sulfur and phosphorus. This change converts the drug from an oligomer to a monomer and makes it fat soluble, so that it can be absorbed when ingested. The nature of the sugar in the new compounds is crucial, Hill told the ACS meeting. Several auranofin analogs tested by the group either were not absorbed or were not effective even though they released a significant concentration of gold into the blood serum. Smith Kline has tested auranofin in more than 1000 arthritics since the early 1970's, and next month will apply to the Food and Drug Administration for permission to market the drug.

A potential new class of therapeutic agents, called osmarins, was described by Conrad C. Hinckley of Southern Illinois University. These are osmium-carbohydrate polymers that, when injected into the joints of dogs and pigs, have been found to be potent anti-inflammatory agents.

Osmium tetroxide has been used on a limited basis in Europe for some 30 years for the treatment of arthritis, but that use is controversial since it is very toxic. The chemical supposedly performs a "chemical synovectomy"—destroying the synovial membrane around the joint. Recently, says Hinckley, a group of Swiss scientists reported that osmium-containing deposits remain for a long time in the joints of people who have been helped by osmium tetroxide. Hinckley suggests that these deposits catalytically remove superoxide ion, O_2^-, which is thought to break down synovial fluid and contribute to inflammation.

The osmarins, he continues, com-

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bine with proteins and adhere to tissues in the joint, but are relatively nontoxic. In his preliminary experiments, he adds, he has found long-term retention of the osmarins in joints and firm evidence of protection. He is now investigating the chemical interaction of superoxide and osmium compounds in vitro, and hopes soon to extend his studies to other species.

On the Trail of a Fire Ant Remedy

A potential new way to attack the imported fire ant, a pest of the southern United States that has tremendous reproductive capacity, extremely aggressive behavior, and a potent sting, has been found by Robert K. Vander Meer and his colleagues at the U.S. Department of Agriculture (USDA) in Gainesville, Florida. They have isolated and characterized four trail-marking pheromones secreted by fire ants to lead other members of their colony to food sources. Vander Meer told the ACS meeting that the pheromones could be used to lure fire ants to baited traps where they could be poisoned. This approach could be especially valuable because the Environmental Protection Agency banned mirex in 1978, and there has since been no effective control agent for fire ants that can be used on agricultural land (a new pesticide, Amdro, recently introduced by American Cyanamid Company can be used only on pastureland).

The chemicals, which are produced in the Dufour's gland attached to the sting apparatus in the ants' abdomens, are present in only very small quantities, so that the investigators had to use about 1 million ants to isolate sufficient material. Two of the pheromones are sesquiterpenes known as farnesenes, and two are related homosesquiterpenes that have never been reported. The most active of the compounds is effective when streaked onto paper at a concentration of only 10^{-13} gram per centimeter.

Preliminary studies in the laboratory, Vander Meer says, show not only that the pheromones attract fire ants to baited traps but also that they induce the ants to eat more vigorously once they are there. The USDA team plans to conduct more such feeding studies and to define the species specificity of the pheromones before attempting field tests with these chemicals.

Another Potential Problem in Drinking Water

A new class of potentially hazardous compounds, dihaloacetonitriles (DHAN's), appears to be present in drinking water throughout the United States. The DHAN's were first observed in 1975 in tap water from Raleigh, North Carolina, by J. D. McKinney and his colleagues at the National Institute of Environmental Health Sciences. At last fall's ACS meeting, Theodore I. Bieber and M. L. Trehy of Florida Atlantic University reported finding them in tap water from various locations in southeastern Florida. At the most recent meeting, Lawrence H. Keith and his colleagues at the Radian Corporation in Austin, Texas, reported finding DHAN's in drinking water from several Texas locations. These findings suggest that the chemicals may be ubiquitous.

The DHAN's are apparently produced by the action of chlorine on amino acids and other naturally occurring organic materials in water during disinfection. Dichloroacetonitrile, the most prevalent member of this class of compounds, has been found to be a mutagen by the Ames test. Other members of the class are under study in the National Toxicology Program. Dichloroacetonitrile and trichloroacetonitrile can also break down into chloroform, which is known to be carcinogenic.

The DHAN's have not been recognized as fairly common pollutants previously, Keith says, because they are destroyed by the usual methods for analyzing organic pollutants before they can be detected and measured. Radian has been able to detect them routinely, however, using a computerized gas chromatograph, a newly developed, highly sensitive detector, and a technique called two-dimensional gas chromatography; the new detector was developed under a contract from the Environmental Protection Agency (EPA). Two-dimensional gas chromatography recycles an isolated sample through a second gas chromatograph column to provide additional sensitivity and selectivity.

EPA has been cautious in assessing the potential risks associated with DHAN's, primarily because so little is known about them yet. It now seems likely that the agency will fund further studies to see how widespread the chemicals are and what biological effects they produce. According to one EPA scientist, however, it will probably be at least a year before the agency will know whether there is really a problem.

Analgesic from Mushrooms Begins Clinical Trials

A potent analgesic that is as strong a pain-killer as morphine, but that works by a completely different mechanism and that has shown no signs of being addictive, is now undergoing clinical trials in Europe, its inventor, Poul Krogsgaard-Larsen of the Royal Danish School of Pharmacy reported at the ACS meeting. The compound is a structural analog of muscimol, one of the two active constituents of the toxic mushroom, *Amanita muscaria*. Muscimol itself is structurally related to the brain neurotransmitter GABA (γ-aminobutyric acid), but is too toxic for use in humans. The new agent, tetrahydroisooxazolo-[5,4-*c*]-pyridine-3-ol or THIP, is a variant of muscimol in which part of the molecule is held in a more rigid conformation; it shows very little toxicity in clinical studies.

The mechanism of action of THIP is not known, but its analgesic effect is not inhibited by the narcotic antagonist naloxone, which indicates that the mechanism is different from that of morphine. The agent is very unusual, Krogsgaard-Larsen says, in that it can cross the blood-brain barrier even though it carries a charge; it can also be taken orally, and a dose of about 10 to 15 milligrams appears to be as effective as an injection of morphine. The clinical trials are being conducted by Lundbech and Company of Copenhagen and Sandoz Ltd. of Switzerland.

Thomas H. Maugh II