

# Ag and Food Interprets . . .

- ▶ **Cranberry crisis—what are its implications?**
- ▶ **Wild oats—target for two new carbamate herbicides**
- ▶ **Preneutralization, or prereaction—living up to promise**
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## Cranberry Crisis

What are its lessons?  
What are its implications for the future?

Now that the dust has settled, what lessons can be learned from the battle of the cranberries, and what are its implications for the future?

To recap, briefly, the facts:

April 16, 1958: American Chemical Paint submitted a petition for 1 p.p.m. tolerance for aminotriazole on cranberries.

April 28, 1958: FDA replied that the petition was not suitable for filing because it was incomplete.

Feb. 19, 1959: A new petition was submitted by Amchem Products, Inc. (new name of American Chemical Paint), and American Cyanamid Co.

Feb. 25, 1959: Petition filed.

March 26, 1959: USDA certified that aminotriazole is useful in agriculture.

May 29, 1959: FDA notified petitioners that a tolerance could not be established because toxicity data indicated the compound caused thyroid adenomas in rats, at levels as low as 10 p.p.m. in the diet. Petitioners were advised they had right to withdraw application for a tolerance or to request appointment of a scientific advisory committee to review petitioners' data.

July 1, 1959: Petition withdrawn.

Nov. 6, 1959: Conclusive information received by FDA that residues of aminotriazole had been



HEW Secretary Flemming

found in two shipments of cranberries from the 1959 crop grown in the Pacific Northwest.

Nov. 9, 1959: Secretary of Health, Education, and Welfare Flemming urged at his biweekly press conference that there be no further sales of cranberries or cranberry products produced in Washington and Oregon because of possible contamination by a chemical weed killer—aminotriazole—which, he said, causes cancer in the thyroid of rats when it is contained in their diets. Cranberries from Wisconsin, New Jersey, and Massachusetts were not implicated at this stage. However, consumers had no way of knowing the point of origin of the products offered for sale in the markets, so all cranberries, in effect, were suspect.

Nov. 10, 1959: Investigations were started in Wisconsin, Massa-

chusetts, Michigan, and New Jersey to determine the extent and manner of use of aminotriazole. About 100 FDA inspectors and 60 chemists were assigned to a crash program of analyzing the cranberry crop in a massive attempt to clear sufficient cranberries for the Thanksgiving trade.

Nov. 23, 1959: A plan was announced for certifying sufficient cranberries to meet the Thanksgiving demand.

Once FDA had refused to set a tolerance for aminotriazole, any food containing any residue of the chemical was contaminated, within the meaning of the Food, Drug, and Cosmetic Act. However, aminotriazole could still be used after harvest, and the labels on containers of aminotriazole plainly stated that only post-harvest use was safe.

Why then did cranberry growers use aminotriazole before harvest? Some probably did not read the label, or, if they did, did not follow its warning because of persistent rumors in the growing areas that a tolerance would be set for aminotriazole before harvest time rolled around. For the growers, this was the primary lesson to be learned from the cranberry crisis: Read the label and follow instructions faithfully. This is the message that the National Agricultural Chemicals Association, FDA, and USDA have been preaching since the time the Miller Pesticides Amendment became law.

For the public in general, the cranberry episode had several messages. One of these was brought about by the widely quoted statement, attributed to an American Cyanamid spokesman, that tons of cranberries would have to be eaten daily over a long period of time to cause cancer. FDA disputed this with the statement that:



Aminotriazole will probably continue to find its greatest use in nonagricultural uses such as the spraying (above) for poison ivy control at Valley Forge Park

"No one knows how much or how little of any chemical which produces cancer in the test animal may be required to produce cancer in a human being." Nevertheless, the idea did get across to the public that only small amounts of the chemical were involved, and that much more was needed, over a long period of time, to cause cancer. Thus the public was introduced to the scientific fact that the concept of poison involves more than just the substance itself; also included in the concept of poison are the amount of the substance, the length of time it is administered, the route of administration, and the body chemistry of the animal involved.

Another side effect of the cranberry crisis was the public "discovery" of the Food Additives Amendment of 1958. Already over a year old, it had had almost no notice in the public press. But cranberries brought it to public attention, along with its anticancer provision which prohibits use, in any amount, of any substance which causes cancer in man or animal. Thus, the general public learned that there are laws which effectively protect the food supply from dangerous amounts of chemicals.

For the chemical profession, there was an incidental advantage. It was chemists who ran the analyses that either cleared or banned lots of cranberries. And the public gained some knowledge of the important role of the analytical chemist—what he does, and how he goes about his work. One newspaper even published a résumé of the official method for testing cran-

berries for the presence of the weed killer.

Perhaps the biggest implication for the future is the clear indication that the Food and Drug Administration will fight any attempt to delete the anticancer amendment from the Food Additives law. In recent years, there has been a difference of opinion among scientists as to whether a safe level of intake could be established for a substance that causes cancer. Some argue, and FDA has now stated its agreement with this position, that there is no known method, at present, for establishing a safe level of intake for a carcinogen. Some others believe that safe levels of carcinogens can be established in the same way that safe levels of other substances are set.

What happens to aminotriazole now? Has it been slandered to the extent that its usefulness is permanently impaired? Only time will tell, of course. But the best guess is that it will continue to be used for weed control along roadsides and railroad rights-of-way, and for other nonagricultural uses. These applications of the herbicide are already far more important, in terms of total sales, than are the agricultural uses.

One question still remains unanswered in the minds of those who are familiar with food and drug law and its administration: Why did Secretary Flemming choose this method of enforcing the law? Why was it announced so dramatically at a Cabinet Officer's press conference? (Not surprisingly, the press picked up that announcement and was off and running

with all the sensationalism it could muster. Alternating between seriousness and frivolity, virtually every newspaper front-paged cranberries every day until the eve of Thanksgiving.) The answer may lie somewhere in the future—perhaps in next year's budget hearings, possibly even in next year's political conventions.

## Wild Oat the Target

New herbicide shows promise of bringing relief to northern growers

ONE OF THE BIGGEST WEED PROBLEMS still awaiting effective control is the wild oat. On the North American continent it hits growers of wheat, barley, flax, peas, and sugar beets in the north central states and the prairie provinces of Canada. It causes crop losses estimated at several hundred million dollars per year.

Now control may not be far away. Spencer Chemical and Monsanto Chemical have both come up with new herbicides—both carbamates—for use on wild oats. Spencer's find is trademarked Carbyne and Monsanto's is Avadex. If these chemicals live up to their promise, the wild oat is in for a beating.

Wild oat is a devilish weed, and so far standard control methods have been unable to hold it down. Among the chief reasons is the shattering characteristic of the seed. Jumping from the stem on a spring-like tail, the ripe seed sows itself. And, activated by moisture, it plants itself.

Furthermore, it is no respecter of seasons; it has a variable dormancy. This means that not all seeds germinate at the same time. Thus, growers cannot time cultural practices so as to destroy an emerging population.

For these reasons, Spencer feels a post-emergence herbicide is best, since it can be used when and where it is needed. Such a herbicide is Carbyne. Avadex, on the other hand, is a pre-emergence herbicide. Monsanto feels that through use of its pre-emergence chemical farmers will be able to plant higher yielding crop varieties. This they have not been able to do because of the need to delay seeding until the season's first wild oats had sprouted and could be turned under by cultivation.

Carbyne is the first commercial result of a five-year program by Spencer to find and develop new agricultural

chemicals for the company. A producer of nitrogen fertilizer materials, Spencer wanted to get into pesticides, so in 1954, it started a screening program.

During this screening, Spencer made derivatives of 4-chloro-2-butyn-1-ol, hoping to make use of the compound's chloro group and acetylenic linkage—two groups not normally found in nature. From this work came the family of carbamates, which included barbane: 4-chloro-2-butynyl *N*-(3-chlorophenyl) carbamate. It was the 847th compound made since the start of the program.

Greenhouse tests showed that this compound—later christened Carbyne—had promise as a herbicide for wild oats. The tests also showed that it was a compound with an extremely sensitive structure. Placing the nuclear chlorine in another position, reducing the triple bond to form a double or single bond, replacing the alkyl chlorine with various groups, or supplying the ring with a second substituent—all these experiments destroyed the compound's selective action toward wild oats.

Thus, Spencer speculates, the chemical deals its blow by unlocking the correct enzyme system in the plant, eventually leading to its death. But the exact mechanism is not known. It appears, says Spencer, that 75 to 80% of the chemical is absorbed. The major portion probably moves upward, but some moves downward through the internode to the growing point. Spencer speculates that it is a mitotic poison which inhibits cell growth.

### Selectivity

Spencer classifies Carbyne as an economic control, not a wild oat eradicator. In fact, says the company, it attacks several species other than oats. But, it adds, by taking advantage of differences in morphology and different responses at low application rates, it is possible to have a highly selective chemical.

Proper timing and proper application rate are extremely important. Taking results from some 8000 test plots in five locations, Spencer recommends these amounts: 0.5 lb. per acre for wheat, barley, and flax; 0.5 to 1 lb. per acre for sugar beets and peas. The chemical should be applied, says the company, when the wild oat is in the 1.5 to 2.25 leaf stage.

Carbyne will be marketed as an emulsifiable liquid formulated at 1 lb./gal. There are no serious handling or residue problems, says Spencer. Toxicological studies show an acute

oral LD<sub>50</sub> of 1.3 g. per kg. on rats; no ill effects showed up in low-level animal tests.

Spencer has developed an analytical method for Carbyne which will detect as low as 50 parts per billion. Used to detect the compound on wheat, barley, flax, peas, and sugar beets, the method showed no residues in the final crop when Carbyne was used in recommended amounts, according to the company.

### Holds Patents

Spencer is now waiting for registration of Carbyne by USDA and the Canadian Department of Agriculture. It has formed an agreement with Fisons Pest Control, Ltd., of Essex, England, whereby Fisons will have an exclusive license to distribute and develop Carbyne in Western Europe, Scandinavia, and Commonwealths in the United Kingdom except in the western hemisphere. Spencer holds patents on composition and use of barbane as a wild oat herbicide in the U. S., and has applied for patents in 28 foreign countries.

Actually, next year's marketing will still be part of Spencer's development program. Prices will most likely be set quite high. In this way, the company hopes to control distribution so that it can work with growers using the chemical to make sure it is used properly. Then, in 1961, Spencer will go into full scale marketing with prices that will "interest" the grower troubled by infestations of wild oat.

Spencer has no plans at present to produce the herbicide. Rather it will be made under contract. But the company says facilities to make Car-

byne would fit into any of several of its plants.

Monsanto's product, Avadex, is 2,3-dichloroallyl diisopropylthiocarbamate. Identified only as CP15336, it has given 90 to 98% control of wild oats in wheat, barley, flax, and sugar beets under actual farm conditions when applied at rates of 1.5 to 2 lb. per acre as a pre-plant treatment. It has been tested on more than 190 acres of demonstration farms in Alberta, Saskatchewan, and Manitoba, and in experimental plots at 10 Canadian universities and experimental farms.

Application has been made for Canadian registration and sale of Avadex in 1960 as a product of Monsanto Canada, Ltd.

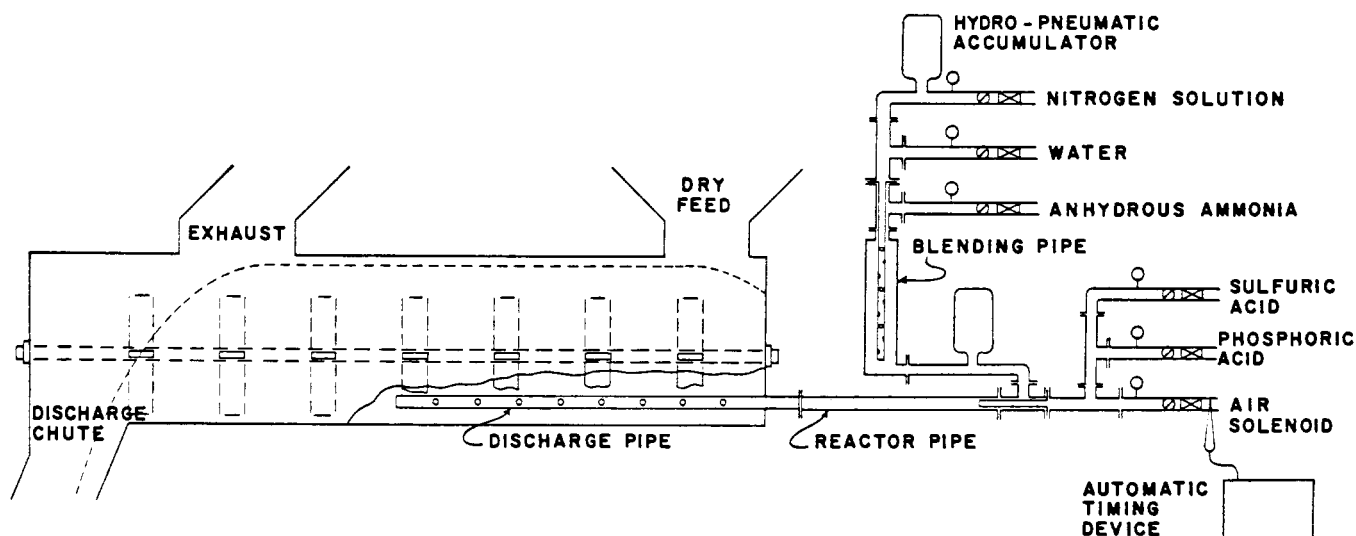
In the U. S. northern prairie, Monsanto has planned an extensive program of field tests to obtain the data required by USDA before the product can be sold in the U. S.

Monsanto says yields from farmers' plots treated with Avadex were 5 to 15 bushels greater than those from adjacent, untreated strips. It is applied to the soil as a liquid spray and is disked down to a depth of 2 to 3 in., as early as three weeks before planting. It remains active in the soil for a period of six to eight weeks or more, during which time it selectively kills wild oats as they germinate.

Radiotracer studies and chemical analyses of crops grown on Avadex-treated soils show no residue of the chemical in crops, even when it is applied at more than double the rate recommended. Relatively rapid breakdown of Avadex in the soil under field conditions prevents a build-up of the chemical from successive applications, says Monsanto.

Wild oats growing in this kale field show how troublesome the weed is to farmers





Arrangement of pre-reaction in granulation pug mixer as devised by Bridger and associates

## Pre-reaction Revisited

Process of neutralizing nitrogen solutions before introduction into granulator seems to be living up to its promise

PRENEUTRALIZATION, widely heralded a year ago as a method for making higher analysis mixed fertilizers, seems to be living up to its promise. It is being actively studied by several companies, and it is being used by a growing number of plants throughout the country.

At the Fertilizer Industry Round-table meeting in Washington, D. C. last month, it drew more attention and audience participation than any other topic on the program. Some new developments were reported, and fine points of the method were thoroughly discussed.

The idea behind preneutralization, or as some call it—pre-reaction—is simple: Free ammonia in the nitrogen solution is neutralized by sulfuric acid (or phosphoric acid in some cases) before the solution goes to the granulator-mixer. This has several advantages:

- Exotic grades such as 20-15-0, 15-15-0, and even X-O-X can be produced.
- Costs may be reduced.
- Less nitrogen is lost.
- Recycle is cut, thus upping production.
- Fuming is reduced.

One of the newest developments in preneutralization is a continuous-flow,

concentric-pipe reactor designed by G. L. Bridger and his associates at W. R. Grace. In their scheme (see illustration), water and nitrogen solution are supplied through 1.5-inch pipes, blend together in a 1.5-in. pipe tee, and then are discharged from a perforated 1.5-inch pipe into a 6-in. pipe section that is 42 in. long. Anhydrous ammonia is supplied through another 1.5-in. pipe, flows through a 3-in. pipe tee and enters the 6-in. pipe section to blend with the nitrogen solution and water. These preblended liquids then flow through a 3-in. pipe section into a 3-in. pipe tee called the reactor tee. Sulfuric and phosphoric acids, supplied through 1-in. lines, preblend in a 1-in. pipe tee and then pass through a 1-in. acid discharge pipe that passes concentrically through the reactor tee and ends in a simple showerhead arrangement three inches inside the reactor pipe section. The showerhead breaks up the acid flow into many small streams, thus assuring that neutralization is largely completed within the reactor pipe section (3 in. in diameter and 4 ft. long). The resulting preblended and preacted liquid is discharged laterally into the lower region of the pug mixer, approximately 2 ft. below the surface of the bed of dry materials.

Bridger says this design has several advantages: simplicity and compactness of construction, elimination of ammonium chloride fume, improvement of ammonia absorption by superphosphates, elimination of undesirable decomposition reaction by carrying out the preneutralization in the presence of a substantial excess of ammonia, and wide flexibility in grades that can be produced, including both low- and high-nitrogen grades.

The pre-reaction developed by Bridger is now being used in Trenton

process granulation operations.

Another company that has been active in preneutralization studies is Spencer Chemical. According to Grant Marburger, Spencer has been studying costs of preneutralization and loading of ammonia and water into the preneutralizer tank. Not every fertilizer plant will be able to take advantage of cost savings made possible by preneutralization, says Marburger, because of plant location—in some areas there is not a sufficient cost spread between solid and liquid forms of nitrogen, or between various forms of phosphates, to justify installation of preneutralization equipment. And raw materials costs seem to be the key to the cost situation. He cited one favorably located plant, which was able to reduce costs by \$3.40 per ton by changing to preneutralization.

At Allied Chemical, studies during the past year have been concentrated on the storage and handling properties of various grades of fertilizers produced with the aid of pre-reaction. G. R. Gilliam reported that with X-O-X grades, coating of the product with dolomite appears necessary, because of a high moisture content. With 16-8-8, little moisture was involved and there was little difference between the coated and uncoated product.

Can nitrogen solutions containing urea be used in preneutralization? According to Frank G. Keenan of Du Pont, urea-containing solutions can be used if there is no ammonium nitrate in the solution. At the temperatures encountered in preneutralizers there is little hydrolysis of urea into carbon dioxide and ammonia, even in strongly acid conditions. He reminded his audience that urea hydrolysis is not an instantaneous reaction—that it proceeds slowly and that for the few min-

utes involved in preneutralization, little hydrolysis takes place. What little carbon dioxide is released, he said, can actually aid steam removal.

At Virginia-Carolina, which was the first firm to announce a preneutralization process, production continues in much the same manner. V-C makes only X-O-X grades with the process. The company did make one change in its setup, said Philip E. Stone. The hot liquor from the preneutralizer now enters the mixer by means of orifices at the bottom of an overflow trough. In the earlier arrangement, the hot liquor overflowed from the trough in sheets into the mixer, but this was abandoned because of solids build-up on the lip of the trough.

## Insect Resistance to Insecticides

Emphasis in insect resistance research is shifting from public health pests to agricultural pests

**I**F, as it often appears, insects are out to take over the world from mankind, they could have struck a telling blow by somehow destroying all the participants in a symposium staged a few weeks ago in Washington, D. C. For that symposium, sponsored by a committee of the National Agricultural Chemicals Association and the Entomological Society of America, attracted what might well have been the greatest concentration of experts on insect resistance ever assembled. And resistance to insecticides is in itself one of the most fearsome weapons the bugs possess. Destroying the men whose minds and talents are being focused on ways of whipping the resistance problem would certainly constitute a major victory for the insects.

By no means a recent development, insect resistance to some insecticides has been known for about a half-century. But the problem has grown more serious as world population has increased, agricultural production has been greatly intensified, and one promising new insecticide or family of insecticides after another has fallen victim to insects' phenomenal ability to survive and multiply in tough, new strains.

While the actual mechanisms of insect resistance are not fully understood, it is generally accepted today that resistance develops entirely

through a process of selection, rather than through genetic mutation produced by the action of pesticide chemicals. The insecticide kills off the susceptible individuals, leaving the stronger, already resistant ones to prosper.

There is strong evidence that the insecticide acts as a selective agent, favoring survival of resistant genes already present, according to James F. Crow of the University of Wisconsin. In laboratory tests, Crow told symposium participants, if nonresistant insects are treated with nonkilling doses of insecticides, resistance does not develop (with *Drosophila*) even in as many as 50 generations.

One or more of several biochemical mechanisms may be involved in the development of insect resistance, says Albert S. Perry of the U. S. Public Health Service. A primary protective mechanism, in some cases, at least, is detoxication—through metabolism of the insecticide, through storage in some safe place within the insect body, through excretion, or through some system of bypassing the sensitive nerves or tissues. Another primary protective mechanism is the development of decreased sensitivity of the nerve fibers and ganglia. Supplementary mechanisms may include reduced absorption of the toxicant, or the development of "vigor tolerance," or a higher lipid content within the insect body.

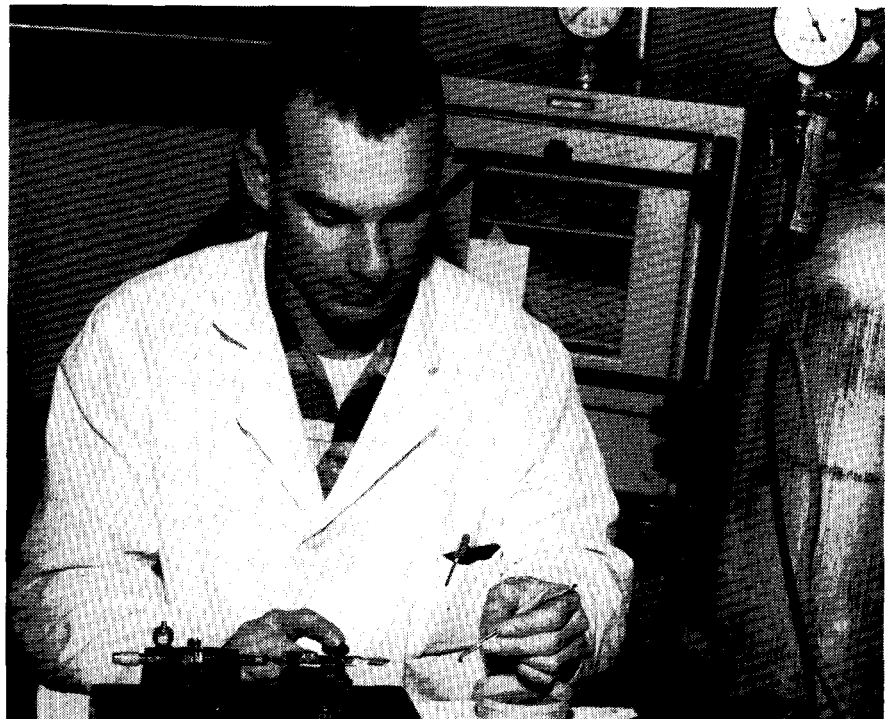
Among examples cited by Perry, all

DDT-resistant strains of houseflies known to date have been found to convert DDT to DDE. In the case of BHC, various investigators agree that breakdown of the toxicant is accomplished by both resistant and susceptible strains, but the metabolism proceeds much faster in the resistant strains. Perry urges more extensive use of radiotracers to study the quantitative metabolism of insecticides. And he strongly opposes the rather widespread practice of analysis "by difference"—that is, measuring the amount of toxicant applied and the amount excreted, and assuming that the rest was metabolized.

While much of the research done to date on insect resistance has been conducted with houseflies and cockroaches, emphasis in recent years has been shifting strongly in the direction of agricultural pests. The introduction of the chlorinated hydrocarbon insecticides during World War II brought a new era in control of agricultural pests. Much of the early optimism was destroyed, however, when resistant strains began to appear. Hopes rose anew with the introduction of the potent organic phosphorus compounds, and for a time it appeared that resistance would not be a problem with these materials. These hopes, too, soon proved false.

More recently, the carbamates have entered the picture, and so far they have escaped the full impact of resistance. To date it appears that in-

Entomologist uses a micro-applicator to apply a measured drop of insecticide to each housefly in a study of the problem of insect resistance to insecticides



sects highly susceptible to a chosen carbamate remain susceptible; the same insects, though, when exposed to less effective carbamates, develop resistance rapidly. And the full impact of developed resistance is certain to strike the carbamates eventually, says H. M. Moorefield of Boyce Thompson Institute. For there is no evidence yet that carbamates can induce a physiological change of susceptibility in insects.

Even the "natural" insecticides, long believed to be beyond the pale of resistance development, can no longer

show an unblemished record. Just this past summer, in Sweden, researchers turned up an instance of resistance to pyrethrins 30 times normal.

What are the practical implications of present knowledge of resistance for future control of agricultural pests? And what is being done to conquer, or in some way to sidestep, the resistance problem?

Expert opinion seems to be divided on the question of practical implications. It has been found, for instance, that resistance to one chlorinated hydrocarbon usually means cross resist-

ance to other compounds of similar chemical structure. It usually does not mean resistance to organophosphorus insecticides, however. On the other hand, according to Ralph B. March of the University of California, the situation is different when resistance develops to organophosphorus materials. In this case, the resistant strains generally show cross resistance to chlorinated hydrocarbons as well.

Because of these differences, according to E. H. Glass of New York State Agricultural Experiment Station, some investigators are now suggesting planned rotation of orchard pesticides. The idea here is that it may be possible to delay and perhaps prevent the development of resistance by switching frequently from one pesticide to another—especially as new and better materials become available.

A different approach is recommended by R. K. Chapman of the University of Wisconsin. Chapman feels that instead of alternating among compounds known to be effective against a given pest, or using combinations of effective materials, it is best to use one chemical until its effectiveness runs out. While using that one to its end point, which can be detected fairly closely if proper tests are run on a continuing basis, research should be under way on the next replacement.

Chapman would also like to see more intensive development of systemic insecticides. In his opinion, 70% control with a systemic is better, in the long run, than 100%—but temporary—control with a contact material.

As for the future, two principal avenues are open, and both will doubtless be pursued. The first of these, used heavily in the past, is the empirical approach of synthesizing and screening chemicals on a more or less random basis. It would be a great mistake to abandon random screening programs, says J. E. Johnson of Dow Chemical; industry, for example, has thousands of chemicals on its shelves available for testing, and any one of those might give at least a partial answer to some segment of the resistance problem.

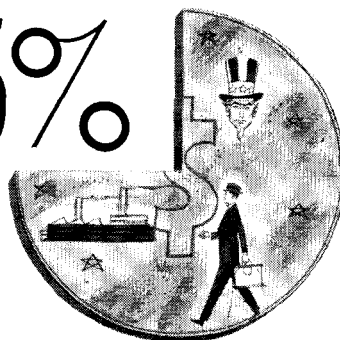
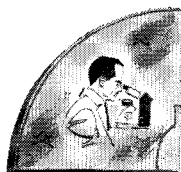
The other avenue is basic research, and this one is receiving increasing attention. While its answers may prove to be more definitive and—hopefully—more nearly final, it may well be that they will also be much longer in coming. Thus while it seems wise to maintain long-range research programs on the physiological and biological processes occurring within insects, it is essential that applied research be continued to prevent the insects from taking over before man finds a definitive answer through basic research.

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