OPEN DISCUSSION

Moderator: DR. WEIDHAAS

Mr. Cole: I would disagree with Dr. Makara slightly in that most insecticides do not produce an ovicidal effect. Malathion and lindane do produce considerable ovicidal effect which, if it is not 100 per cent, helps in control.

Also, I would like to note that we ran some preliminary tests to see if malathion-resistant lice from Burundi had any tolerance for dichlorvos vapors. Although we did not find any great differences, the differences between the toxicity of dichlorvos vapors for Burundi malathion-resistant lice and standard susceptible colony lice were significant. That was a very preliminary test, but we intend to follow it up.

Dr. Busvine: I would like to ask Dr. Steinberg two questions about his tests. First, what was the dilutant used in the patch tests? Second, I believe that some of these chemicals can induce a kind of permanent allergy, so that in subsequent exposures there is a strong reaction. Do these tests give an indication of the chemicals' ability to induce an allergic sensitivity, apart from their immediate irritant effect?

Dr. Steinberg: We usually used 95 per cent ethanol, but sometimes 70 per cent ethanol, in the patch test on humans. I recognize that most of these compounds are not water-soluble.

Second, allergic sensitivity is one of the hazards in running any test on humans for 21 days, but all these compounds had previously been screened by a guinea pig sensitization test. The latter, of course, does not insure that human sensitization will not result, but it gives a little safeguard. I should add that the 21-day continuous patch test can be very dangerous if not supervised by a well-trained dermatologist. We took a young dermatologist just out of his residency program, trained him to do the animal tests, and then had him conduct the human tests under the supervision of a rather well-known dermatologist who was well acquainted with this type of testing. Dibrom is a sensitizer in man and, as a matter of fact, a couple of subjects did end up sensitized to it.

Dr. Traub: Many effective or promising insecticides and repellents cannot be used because of the dangers of toxicity or environmental contamination. It is therefore important to consider how long it takes to find or make available an effective substitute. How long would it take, if a promising compound were on the shelf, for it to reach the consumer, whether he be in the army or in civilian life?

Second, if there isn't an effective substitute already available and it is necessary to choose or find a new class of compounds, could you hazard a guess how long it would take to come up with an effective compound?

Dr. Weidhaas: Addressing myself to the first part of the question, we did go back and look at some of the data from the cooperative programs already mentioned here, and the data were quite variable. Lindane was in use less than a year after we first received and screened it in our cooperative program with the Department of Defense. Other compounds we have worked on more recently such as malathion, Abate, and Mobam required as much as five or 10 years from screening to field evaluation, but then we must recognize that there was no need to speed the evaluation of these compounds.

On the basis of our laboratory test procedures, I would say that most of the labora-

tory-phase biologic testing could be done in about six months. The question then would be how much time toxicologic and field tests would require.

Dr. Steinberg: I suppose that if the priority were high enough, all testing could be done in about three years. That would be because of present requirements in most countries, and certainly in the United States, for two-year studies of carcinogenicity and life-term feeding. When someone says a "two-year study," there is just no way to get around that requirement. The World Health Organization has been promoting the use of some of the tissue-culture techniques, but one hesitates to call a compound safe solely on the basis of tissue-culture study.

Dr. Traub: We now have three years for toxicity clearance and perhaps five to 10 years for the procedures necessary before a compound is ready for field testing. How long will it be between the field testing and getting it into the consumer's hands? This time lag is a very important matter because we are no longer permitted to use many of the compounds that we know today and may have to find alternate ones. When we need a completely new class of compounds, we may be talking about 20 years.

Dr. Smith: As Dr. Weidhaas said, the answer to that depends partly on the pressure. If you really don't have anything you can use, especially for a specific purpose such as a louse powder, you would move much more quickly than if you had a good louse powder but just wanted to get two or three more to hold in reserve.

Another point is that many times in the past we tried to make one material or formulation do for all personal use. We might be looking for a repellent that would be effective against fleas, mosquitoes, ticks, chiggers, biting flies, and bedbugs, but the more different pests you try to attack with one formulation, the longer the field testing. As I tried to point out, entomologic evaluation often got ahead of toxicologic evaluation in the past. For instance, we worked on some compounds to control chiggers and were all ready to recommend them when we found that they caused sensitization. They were not irritating, but by the time they had been tested and retested on the same individuals, a certain number of the subjects became sensitized.

Nowadays there is not so much time lost —the toxicology goes right along with the entomology, and by the time the final entomologic recommendation is ready there are usually enough toxicity data available so that it does not take too long thereafter till the compound reaches the consumer.

Dr. Gratz: The choice of an insecticide has become a very practical problem for us in the wake of reports of the appearance of malathion resistance in the body lice of Burundi and Egypt. Up to about five or six years ago we were doing reasonably well with our available materials against body lice, but with the spread of DDT and BHC resistance, the appearance of malathion resistance, and the shortage and cost of getting pyrethrins, we have found that our arsenal is not as well stocked as we used to think it was.

In the past we in the World Health Organization would follow the excellent toxicologic work of Dr. Steinberg and his colleagues and wait until the candidate compounds were approved for human use in the United States, and then we would accept them. To duplicate the studies that the toxicologic groups in the United States have been doing would be an extremely expensive proposition.

At the last meeting of the WHO expert committee on insecticides we reviewed the available candidate compounds for body louse control. Several eminent medical toxicologists participated and presented all available human and animal toxicologic data about such compounds as Abate, Mobam,

iodofenphos, and carbaryl. In light of the pressing resistance situation in the field, we asked what their stand was in regard to toxicologic approval of the use of these compounds, even though United States approval had not yet been received. I don't have the expert committee's report with me since the Director General has not yet approved it, but as far as I recall, 2 per cent Abate and carbaryl were cleared for field use if necessary. As I mentioned earlier, iodofenphos (OMS-1211) is already available commercially in Switzerland and a number of other countries.

This does change the procedure we followed in the past, but if governments turn to WHO and tell us that they have a confirmed high degree of resistance to malathion, DDT, and BHC and ask us what to use next, we would be in a difficult position if we did not try to short-circuit the now extremely long testing procedure.

Dr. Busvine: Mr. Cole, in your list of candidate louse powders you did not mention the new pyrethroids resmethrin and bioresmethrin, which would seem very suitable for use against lice because of their noninvolvement in resistance and apparent safety. Comments?

Mr. Cole: They have been tested, but because the tests have not progressed very far I have no information about them.

Dr. Smith: You let a little thing drop there, Dr. Busvine, that always makes my hackles rise. You said "noninvolvement in resistance," but there are already insects resistant to pyrethrins that show cross-resistance to resmethrin and bioresmethrin—the housefly, for instance.

Dr. Busvine: Perhaps I should have said "relative noninvolvement." I think it is true that resistance to pyrethroids is much less common than resistance to almost any other class of insecticides.

Dr. Traub: There is another point that should be stressed about the problems we now face with new insecticides, which is emphasized by recalling how frequently the names of certain commercial companies such as Ciba-Geigy and Hercules were mentioned in our discussion today. That is that there is now little incentive for such companies to look for new insecticides because they may have to invest hundreds of thousands or even millions of dollars to come up with a suitable new compound. There is no guarantee that they would be able to market it because the human sensitivity or toxicity findings might be adverse or because it might be discovered to cause environmental pollution. As a matter of fact, a company might not even be allowed to patent the chemical. Some of these repellents and insecticides must undergo years of additional study before they can be accepted as safe for purchase.

Dr. Makara, are there any toxic side effects from using chlorphenamidine? Many acaracides are toxic.

Dr. Makara: We did not conduct any toxicologic tests before using it because Ciba-Geigy's data were available and showed that the compound had no side effects, including irritation. We tried it first on volunteers in our laboratory in much higher doses and for a much longer time than it would normally be used on humans, and there were no side effects. We then used it on a few hundred men whom we observed carefully, and they showed no side effects either.