Structure-activity relationships of insecticides have been a subject of investigations for many years since the development of synthetic insecticides such as DDT and organophosphates. In most cases, these studies were based on the comparison of insect killing potencies of a variety of analogs and derivatives of a parent compound. However, since the action of an insecticide in killing insects is exerted as a result of a chain of reactions, it is difficult to relate such killing potencies to the chemical structures of the insecticide. The process of toxic action of an insecticide is summarized as follows.

After entering the insect body through the cuticle or other routes, an insecticide may be detoxified to non-toxic chemicals. For example, DDT is metabolized to DDE and DDA depending on the animal species used. Certain insecticides are converted into more toxic chemicals. A number of examples are known among organophosphate and carbamate insecticides. For instance, parathion is activated to paraoxon to inhibit cholinesterases. The activated compounds may also undergo detoxication. In any case the toxic component can eventually reach the target site which for many insecticides is the nervous system. Stimulation of the nerve as a result of the primary action of the active form of insecticide may lead to release of a toxic component from the nerve which in turn stimulates and paralyzes the nerve. These symptoms of poisoning of the nervous system cause the secondary and tertiary effects on the insect such as fatigue and metabolic exhaustion which in turn lead the insect to death. Therefore, the killing action involves a variety of reactions and the death is caused as a final product of this chain of reactions. Thus it is illogical to try to relate the killing potency to the chemical structure of the insecticide.
The structure-activity relationships are expected to be elucidated more clearly if the direct action of insecticides on the target site is compared. Thus the experiments would be straightforward and relatively easy if the target site is clearly identified and isolated in vitro. This is indeed the case for cholinesterases which are major targets for organophosphate and carbamate insecticides. A large amount of data has been accumulated along this line (Fukuto, 1971; Metcalf, 1971). Another example of such studies, though not as extensive as the anticholinesterases, is seen with rotenone. The potencies to inhibit glutamic dehydrogenase to block nerve conduction and to kill insects were compared among a variety of rotenone derivatives (Fukami et al., 1959). These three potencies ran parallel with each other.

However, for most other insecticides the target site is not so well defined. Many insecticides such as DDT, lindane, cyclodiene and pyrethroids modify the nervous function, but the real target site in the nervous system still remains to be seen. It is likely that the target sites for these insecticides are not enzyme systems, since most of them are known to directly interact with nerve membrane ionic channels or synaptic junctions. Therefore, the only practical way of comparing the direct action on the target site would be to use the appropriate nerve preparations.

**DDT AND ITS ANALOGS**

DDT analogs have been studied extensively for their structure-activity relationships (e.g. Holan, 1969, 1971a,b; Metcalf and Fukuto, 1968; Fahmy et al., 1973). However, the major approach to this problem has been to compare the potencies of various analogs and derivatives in killing insects. As has been discussed in the preceding section, several factors such as penetration of insecticides through the cuticle and metabolism of insecticides in the animals have to be taken into consideration to interpret the killing potency in the light of the molecular structure of the insecticides. Then a question arises regarding the real target site of DDT. There is no doubt that DDT acts primarily on the nervous system thereby causing a variety of disorders such as hyperexcitability, ataxia, convulsions and paralysis.

It has been well established that DDT causes repetitive discharges in various nerve tissues including certain sensory receptors and nerve fibers (see Narahashi, 1971, 1976 for comprehensive literature). In the nerve fibers, repetitive activity is initiated at least in part, as a result of an increase in negative (depolarizing) after-potential (Narahashi and Yamasaki, 1960). The increased and sustained depolarization that follows the action potential serves as a stimulus thereby triggering a train of action potentials.