in liver and plasma to be of this magnitude, although only 0.2% of a dose of [carbonyl- ^{14}C]warfarin had appeared in the expired carbon dioxide of both normal and resistant rats after 24h.

The conversion of warfarin into 6-, 7- and 8-hydroxywarfarin by rat liver microsomal preparations (Ikeda, Ullrich & Staudinger, 1968) has been confirmed; comparison with a similar preparation from a resistant rat revealed no difference in the rate of formation of these metabolites. Comparisons by other workers of enzyme activities between the two strains of rat have also been reported (Taylor & Townsend, 1970).

Menadione is converted by rats into menaquinone-4 (Martius & Esser, 1958; Taggart & Matschiner, 1969). An analogous reaction could convert warfarin into a lipophilic metabolite that is the true antagonist of vitamin K at the receptor site, and such a conversion may be inefficient in resistant rats. In a large number of experiments the liver lipid from normal rats fed on both large and small, single and multiple, doses of labelled warfarin was chromatographed and the fractions were assayed for radioactivity. Less than 0.005% of the administered dose appeared in the fractions that would contain vitamins K_1 and K_2 ; some radioactivity, however, was associated with compounds less polar than warfarin, and a detailed examination of liver lipid from both normal and resistant rats is being carried out. A recent report (Matschiner, Amelotti, Bell & Knauer, 1969) suggests that the administration of warfarin does in fact affect vitamin K metabolism in normal rats.

Warfarin-resistant rats, rendered vitamin K-deficient, required some 20 times as much vitamin K_1 as normal rats to correct the deficiency (Hermodson *et al.* 1969). The most popular hypothesis on the mode of action of warfarin proposes that the anticoagulant competes directly with vitamin K for a receptor site. Hermodson *et al.* (1969) suggest that warfarin resistance might be explained in terms of a receptor site that, in resistant rats, has only a low affinity for warfarin and vitamin K.

Whatever the true mechanism of warfarin resistance, a study of these animals should be of considerable value in resolving the prevailing confusion about the mode of action of vitamin K and its antagonists.

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Kinetics and Metabolism of Chlorinated Insecticide Residues

By F. KORTE. (*Institut für ökologische Chemie, Schloss Birlinghoven, Organisch Chemisches Institut der Universität Bonn, Bonn, Germany*)

The environmental contamination by chemicals is generally identified by 'residue levels'. While this term has been defined by the FAO/WHO Joint Meeting for pesticide residues, it may have various meanings when applied to other environmental chemicals. Sometimes only parent compounds are involved, but sometimes biotic or abiotic conversion products also. When the term 'general residue levels' is used for the description of environmental quality, this includes different parameters, e.g. concentration of parent compounds, persistence, potential toxicity, biochemical and chemical transformation etc.

The complexity of environmental problems is also a reason for not correlating the term 'persistence' in a generalized way with special classes of chemical compounds. Although many cyclodiene insecticides are persistent in soil, water, plants and animals as the parent compounds, some breakdown products of easily hydrolysed or oxidized insecticides (so-called non-persistent ones) are more persistent than the cyclodiene insecticide β -dihydroheptachlor.

In this context it should be mentioned that as many as 77 out of a total of 220 commercial and experimental organic insecticides contain chlorine and fluorine.

One has to be as careful in the case of toxicological considerations. From the toxicological point of view, β -dihydroheptachlor, although having insecticidal activity similar to that of DDT, has merely an LD₅₀ value for animals in the same range as has sodium chloride. Therefore we should avoid all kinds of generalization and investigate the influence of every individual compound of a substance class on the environmental quality separately.

In view of the considerable amounts of environmental compounds, it is obviously most important to determine the priorities of the substances to be examined. The choice of our programme was determined by the following properties of a compound: (1) production; (2) chemical and metabolic persistence; (3) tendency of worldwide distribution; (4) expectation or proof that the residues have toxicological effects on man and also unfavourable effects on the animal environment.

I would like to discuss briefly some results (with references). For the above reasons, we concentrated our efforts during the last years on investigations of chlorinated hydrocarbons like aldrin, dieldrin, telodrin, heptachlor, chlordane, endrin, dihydroheptachlor, lindane and DDT, and the most important results are the following:

(1) It was shown for the first time experimentally that all chlorinated hydrocarbons are metabolized in micro-organisms and insects (Korte, Ludwig & Vogel, 1962, first publication), mammals (Mörsdorf, Ludwig, Nogel & Korte, 1963, first publication) and higher plants (Klein *et al.*, 1967, first publication). Hitherto, chlorinated hydrocarbons had been considered to be metabolically inert.

(2) We succeeded in proving by feeding experiments, e.g. with aldrin and endrin, that mammals do not accumulate those compounds *ad infinitum* when a constant dose is administered daily. However, a steady state of storage was reached depending on the daily doses, the sex of the animal and the chemical structure of the compound.

(3) Several metabolites could be identified and their toxicological properties characterized.

(4) In the case of heptachlor we succeeded in identifying the first terminal residue in mammals, namely 1-hydroxychlordene 2,3-exoepoxide.

(5) Although it was assumed until 1967 that compounds of this class did not penetrate into higher plants and therefore were not metabolized, we have been able to prove since then that all of the compounds examined did penetrate into the plants after foliar and soil application and were in fact metabolized by them. We also found that, for instance, after foliar application of endrin on white

cabbage, more than 95% of the applied quantity escaped into the atmosphere by evaporation and transpiration within 4 weeks.

(6) Although the presence of many such substances in the air has been increasingly substantiated, so far hardly any reactions have been examined under atmospheric conditions. We found merely that under controlled conditions photoreactions resulting in rearrangement products are possible. Recently we were able to determine the reaction mechanism of these rearrangements. Only for vinyl phosphates did we obtain first results under atmospheric conditions.

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Membrane-Active Antibacterial Compounds

By W. A. HAMILTON. (*Department of Biochemistry, University of Aberdeen, Aberdeen AB9 1AS, U.K.*)

By virtue of the structural organization of the procaryotic cell, the bacterial plasma membrane is the site of many of the biochemical activities within the cell. In addition to the permeability properties demonstrated by all plasma membranes, the procaryotic plasma membrane is also the site of activities otherwise associated with the mitochondrial, endoplasmic reticular and nuclear membranes. Further, the syntheses of cell wall, capsule and extracellular enzymes are membrane-associated phenomena in bacteria. Clearly therefore any compound affecting this structure is a potential antibacterial agent and its biochemical mechanism of action may be expressed in the inhibition or destruction of any one of several of the cell's vital functions.

It is unfortunate therefore that the earliest studies on synthetic detergents and antibiotics, such as the quaternary ammonium salts and tyrocidine, which have their effect at the cell membrane, should have been carried out with compounds whose action is to destroy the permeability barrier of the membrane in an apparently non-specific manner. Since then the demonstration of leakage of intracellular contents has often been taken as full and sufficient proof of the mechanism of cell death being the destruction of the membrane permeability barrier. More often than not this conclusion is incorrect, and even when it is justified it is now pertinent to enquire further into the nature and mechanism of this alteration in the semipermeable character of the membrane.