not be metabolized by the host before it could act

Another approach to viral chemotherapy is development of drugs that induce production of interferon, a special protein that stimulates production of antibodies, is effective against practically all viruses, and is thus the body's natural antiviral weapon. A drug that would induce interferon production in a controlled manner might be a panacea for viral disease. Some drugs with interferon-induction activity have been developed, though none is yet in clinical use. And those developed so far can only be used as preventives since they apparently must be administered before virus infection occurs in order to have any significant effect.

Virazole, Dr. Sidwell says, does not act by inducing interferon production. It apparently interferes with the virus's ability to reproduce itself. Tracer studies in rabbit kidney cell cultures using radioactive thymidine indicate that Virazole inhibited the rate of DNA synthesis by as much as 90%, according to Dr. D. G. Streeter.

More than 500 potential antiviral compounds have been designed and synthesized at ICN's nucleic acid research institute in the past two years. More than 100 of these have shown significant antiviral activity. Virazole shows the greatest potential as a broad spectrum agent. According to Dr. Roland K. Robins, ICN's vice president for research and development and director of the institute, preclinical studies of Virazole are in progress with a view to clinical evaluation.

Research heightens concern over PCB's

PESTICIDE—The controversy over the effects of polychlorinated biphenyls in the environment and in biological systems is relatively recent, but already PCB's are vying for a share of the dubious limelight accorded DDT. Recent research on PCB's was highlighted at the opening session of the Division of Pesticide Chemistry.

- A trace contaminant has been identified in one lot of Aroclor 1254, a commercial PCB made by Monsanto Co., the sole U.S. producer of PCB's. Although it has not yet been conclusively identified, the contaminant may be a tetrachlorodibenzofuran, a toxic material already found in some European-made PCB's.
- PCB's mimic the action of DDT in their effects on some biological systems. Unlike DDT, however, PCB's do not appear to cause the production of thin eggshells in Japanese quail.
- The residue behavior of Aroclor 1254 in cow's milk is similar to that of DDE, a persistent metabolite of DDT.

Distribution. It is only in the past few years that PCB's have been found extensively distributed in the environment, particularly in wildfowl, although PCB's have been used since at least 1930 as plasticizers in paints, resins, and plastics, as well as in insulators, heat exchangers, and other applications.

In 1970 Monsanto discontinued all sales of PCB's for such open systems as plasticizers and sealants. Late in 1971 the firm began to phase out sales of PCB's for heat transfer systems. When the phase out is completed this year, the only sales of PCB's by Monsanto in the U.S. will be for closed-system electrical uses.

Nevertheless, even as the uses of PCB's are being limited in the U.S. by Monsanto, scientific data on the action of PCB's are beginning to accumulate at a rapid rate. One discovery about PCB's, likely to create considerable concern at Monsanto, comes from the Environmental Protection Agency's Chamblee, Ga., Toxicology Laboratory. August Curley and coworkers V. W. Burse and Ralph Jennings have found a nonpolychlorinated biphenyl in the urine of rats fed 100 and 500 p.p.m. Aroclor 1254 for 58 and 252 days, respectively. They find the same nonpolychlorinated biphenyl in the Aroclor 1254 that was administered to the rats, thus eliminating the possibility that the substance in the rat urine was derived solely by metabolism.

The substance identified by the Georgia chemists has a mass spectra number (m/e) of 304. A contaminant with m/e 304 has already been identified as tetrachloroparadibenzofuran in two European PCB's—Phenoclor DPG, a French product, and Clophen A 60, a West German product—by Dr. J. G. Vos and coworkers at the Institute of Veterinary Pathology, Utrecht, the Netherlands. Tetrachlorodibenzofurans are highly toxic substances and are suspected teratogens. At the time he tested European products, Dr. Vos did not find the substance in the Monsanto product (Aroclor 1260) he tested. In fact, even to date tetrachlorodibenzofurans have not been identified conclusively in Monsanto's PCB's.

Mr. Curley and his colleagues identified a trace concentration of the contaminant m/e 304 of less than 1 microgram per gram in the Aroclor 1254 he tested using the combined gas chromatography-mass spectrometry method of Dr. Vos [*Food Cosmet. Toxicol.*, **8**, 625 (1970)]. Mr. Curley emphasizes that mass spectral data alone have not proved conclusively the identity of the component having m/e 304. But, he says, "It is certain that the component is not the result of fragmentation of a higher molecular weight component of the Aroclor preparation." The component m/e 304 could be tetrachloromethyl biphenyl, which would give the same mass spectra peak as tetrachlorodibenzofuran. Methyl biphenyls are present in trace concentrations in the feedstocks used to make PCB's.

However, Mr. Curley points out that toxicological and chemical evidence by his group and other workers suggests that his substance could be tetrachlorodibenzofuran. His own toxicological studies on rats fed various doses of Aroclor ranging from 0 to 500 p.p.m. for eight months reveal that at the higher dietary levels rats have enlarged livers and other abnormalities in the liver cells. Whether trace quantities of the 304 component in the diet might have contributed to the toxic effects is not yet known, he points out.

Eggshell. Mr. Curley's study is part of a larger one to determine the effects of PCB on heme synthesis and intermediate metabolism. Another area in which PCB's are being extensively investigated is their role in the formation of thin eggshells produced by some birds of prey. Incorporation of calcium in eggshells is the end result of a complex pathway of calcium metabolism. Inhibition of a crucial step in the pathway by PCB's or DDT, or any other material for that matter, could result in the production of thin eggshells, many scientists suggest.

In eggshell formation, dietary calcium is absorbed from the intestine into the blood. This transfer is mediated by vitamin D, which must first be metabolized to an active form. From the blood the calcium is deposited in medullary bone for storage until it is mobilized for eggshell formation. Mobilization occurs by a synergistic action between androgens and estrogens. Calcium is reabsorbed into the blood from the medullary bone transported across the eggshell gland and deposited in the shell as calcium carbonate.

Biochemists at the University of California, Riverside, have studied the effects of PCB's and DDT at several points of this pathway. For instance, the effects of PCB and DDT on the metabolism and functioning of vitamin D have been studied by Dr. Henry G. Nowicki, (now at the 5th Army Medical Laboratory, St. Louis, Mo.) and Dr. Anthony W. Norman. They find that rachitic (vitamin D deficient)

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chickens pretreated with PCB's show significant decreases in intestinal calcium transport when given vitamin D. In addition, pretreating the rachitic chicks with PCB blocked the ability of vitamin D, when it was administered, to mobilize bone calcium. These are essentially the same findings that the two biochemists had found last year for DDT. Their results, Dr. Nowicki explains, provide a partial explanation for the involvement of PCB in thin eggshell formation and subsequent reproductive failure of some avian species.

Since both PCB and DDT treatment blocked the response to vitamin D, the biochemists examined the chlorinated chemicals to determine if they act by altering the metabolism of vitamin D. Vitamin D must go through at least two conversions to an active form prior to stimulating intestinal calcium transport. The biochemists find that neither DDT nor PCB appears to interfere with the metabolic conversion of vitamin D. Thus, this result does not explain how PCB and DDT inhibit the biological response to vitamin D.

PCB's and DDT did appear, however, to exhibit similar responses in the biological systems studied. Dr. Nowicki, Dr. Norman, Richard Wong, and Betty Murray decided to see if both PCB's and DDT would cause the thin eggshell syndrome in Japanese quail, a game bird that adapts well to laboratory conditions. Chronic exposure of Japanese quail to DDT for 14 weeks resulted in eggs that had a thickness index 18% lower than the eggs of quail that were not fed DDT. PCB treatment, however, showed no deleterious effects on the eggshells of the quail compared to the controls, either in thickness or in cross-sectional morphology.

Milk. Biochemical similarities between PCB's and DDT—which do not hold in all cases—are further substantiated by Dr. George F. Fries at USDA's research center at Beltsville, Md. PCB-contaminated silage has caused PCB residues in milk above the levels recommended by the Food and Drug Administration, Dr. Fries explains, and a few farmers have had to remove their milk from the market.

Dr. Fries and coworkers studied nine cows fed 200 mg per day of Aroclor 1254 for 60 days. They find an average concentration of PCB in milk after 40 days of 60.9 ±4.3 micrograms per gram of fat. When feeding stopped, PCB concentration in milk fat declined 50%, but after 15 days the rate of decline was quite small. In these respects the residue behavior of Aroclor 1254 is similar to that of DDE, the most persistent degradation product of DDT, Dr. Fries says.

H-bonding studied by neutron diffraction

PHYSICAL—X ray diffraction is the key tool for determination of the three-dimensional structure of biological molecules, but it is a virtually useless tool for locating the hydrogen atoms that, through hydrogen bonds, control the ultimate stereochemistry of such macromolecules. X ray diffraction can rarely determine the position of hydrogen atoms to an accuracy better than 0.2 A, says Dr. Walter C. Hamilton of Brookhaven National Laboratory, whereas a change in bond length caused by hydrogen bonding may be on the order of 0.01 to 0.05 A. But neutron diffraction, he points out, can determine the position of hydrogen atoms to an accuracy much better than 0.01 A, and is thus becoming a valuable technique for examining the links that control, among other things, the α-helix in protein structures and base pairing in nucleic acids.

Neutron diffraction is a young technique, however, and much of the work with it has been on simple compounds such as amino acids. Dr. Hamilton and his Brookhaven associates—Dr. Thomas F. Koetzle, Dr. Mogens S. Lehmann, Dr. M. Frey, Dr. J. Goñe, Dr. P.-G. Jonsson, Dr. A. Kvick, and Dr. Jacques J. Verbist—have so far completed single crystal neutron diffraction studies on some 14 amino acids and the dipeptide glycylglycine · HCl.

Nature. These measurements, Dr. Hamilton and Dr. Koetzle told the Boston meeting, have yielded much information about the nature of hydrogen bonds:

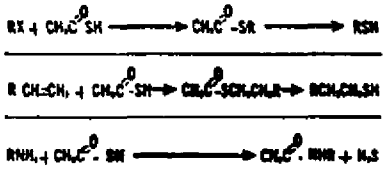
- There is an excellent inverse correlation between N — H and H · · · O distances in N — H · · · O hydrogen bonds. N · · · O distances are less important. Many hydrogen bonds are considerably bent.
- Barriers hindering rotation of ammonium groups, as well as other thermal parameters, are sensitive functions of hydrogen bond strengths. One hydrogen of the $^{+}NH_3$ of lysine · HCl, for example, forms a very strong bond with a neighboring carboxyl group. The barrier to rotation of this ammonium group is 7.0 kcal/mole; the barrier for the amino group, which does not form such a strong bond, is 2.9 kcal/mole.
- A Van der Waals radius of 1.0 A seems more appropriate for hydrogen bonded crystals than is the commonly adopted 1.2 A.
- True bifurcated hydrogen bonds rarely exist in these compounds.



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