box is treated as a uniform area source; emitted material and transported material are assumed to be distributed uniformly in time.

In this model the uniform concentration within a particular box at any time is a function of the box volume, the rate at which material is being imported, the emission rate, the concentration within the box in the preceding time increment, and residual fractions of the three mass terms that describe the amount of material remaining in the box. For box n, that functional relationship is

$$C_{n,t} = \frac{1}{V_{n,t}}(r_{n,t}q_{n,t} + R_{n,t}Q_{n,t}) + \rho_{n,t}C_{n,t-1}$$

where $C_{n,t}$ and $C_{n,t-1}$ are concentrations at time t and $t-1$; $V_{n,t}$ is the box volume, $q_{n,t}$ is the mass of material advected into box n, and $Q_{n,t}$ is the mass of material emitted within box n during time increment t; and $r_{n,t}$, $R_{n,t}$, and $\rho_{n,t}$ are the residuals of $q_{n,t}$, $Q_{n,t}$, and $C_{n,t-1}$, respectively, which remain in box n at the end of time increment t.

The dimensionless residual fractions are simple geometrical relationships between the wind vector and the box dimensions (*5*). The computational time increment used here is 5 days in order to enhance the validity of the uniform distribution assumption within these large boxes. If better data were available, it would probably be preferable to use smaller boxes and shorter time intervals to allow for differences and changes that can easily occur on smaller scales.

Seasonal wind data are available in the form of mean vector components and standard deviations along meridional cross sections (*7*). From these, I constructed wind fields for the 850-mb surface over the area between 10°W and 30°E longitude and 44°N and 70°N latitude. On the basis of these mean wind fields, the seasonal concentration patterns very much resemble large plumes extending from Western Europe through Poland.

However, the vector components of the wind are essentially normally distributed about the means (*7*); thus numerical simulation is easy and should provide a realistic approximation of individual or sequential wind data. I simulated values of each component at an arbitrary point and constructed new vector fields in such a way that the patterns for each component were the same as in the original mean vector fields of the components. Because the simulated components vary randomly and independently, the total field of vector sums also varies from one time interval to the next. The concentration pattern shown in Fig. 1 illustrates one simulated 10-day episode of light southwesterly wind, based on the winter season means. The pattern is similar, both quantitatively and qualitatively, to those found by de Bary and Junge (*8*) and by Odén (*9*). Two additional patterns, calculated with the wind field of the same simulated episode, show the effects of closing down all fuel sources of sulfur in the United Kingdom (Fig. 2) and all those in Germany, Belgium, Luxembourg, and the Netherlands (Fig. 3). Separate elimination of various major source areas in this way gives some indication of the relative contributions these source areas might be making to the overall pattern in Northern Europe.

In all cases, the concentration indicated is of total sulfur, uniformly distributed in a layer of air 3 km deep. No natural sources have been included, nor is any removal mechanism considered. The sulfur might therefore be in the form of sulfur dioxide, sulfate, or sulfuric acid. Robinson and Robbins (*10*) estimate that nearly twice as much sulfur enters the atmosphere in the form of hydrogen sulfide as is absorbed in the form of sulfur dioxide by the oceans and vegetation. They also estimate that 80 percent of the remainder ultimately is removed in precipitation.

Concern over long-range transport of various pollutants appears to be growing, and the results shown here suggest that during periods of dry weather, when the major removal mechanism is not operating, sulfur in some form may be carried substantial distances. A cooperative international program to provide all the necessary data is the only way to confirm the extent of that transport.

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Chemically Induced Porphyria: Prevention by Prior Treatment with Phenobarbital

Abstract. *The excessive induction of hepatic δ-aminolevulinic acid synthetase in rats after the administration of porphyria-inducing compounds is prevented by prior treatment with phenobarbital. Studies in vivo and in vitro indicate that phenobarbital prevents the induction of chemical porphyria by increasing the rate of detoxification of inducers by way of drug-metabolizing enzymes of the hepatic endoplasmic reticulum.*

The basic defect in chemically induced and genetically transmitted porphyria is reflected by an increased activity of hepatic δ-aminolevulinic acid synthetase, the first and rate-controlling enzyme in porphyrin and heme biosynthesis (*1*). Although there are several hypotheses regarding the mechanism of induction of this enzyme (*2*), virtually nothing is known about the metabolic fate of porphyria-inducing compounds. This latter facet is of importance since the duration and intensity of action of many drugs are largely determined by the speed at which they are metabolized in the liver. Moreover, the activities of drug-metabolizing enzymes in liver microsomes are increased when animals are treated with various hormones, drugs, insecticides, and carcinogens (*3*). Phenobarbital (PB) has been used as a prototype of the compounds known to stimulate drug metabolism. For example, PB stimulates bishydroxycoumarin [which is 3, 3′-methylene-bis-(4-hydroxycoumarin)] metabolism in vivo in the dog and man, resulting in a decrease of its anticoagulant activity (*4*). We now show that inducers of porphyria are metabolized by microsomal en-

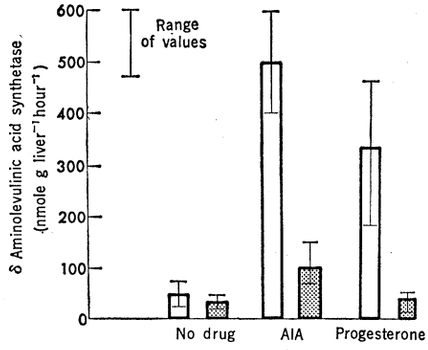

Fig. 1. Effect of PB treatment (shaded bars) and saline treatment (open bars) on the subsequent induction of hepatic δ-aminolevulinic acid synthetase by porphyria-inducing compounds in the rat. The PB (80 mg/kg) and saline were administered subcutaneously for 5 days. The AIA was dissolved in saline (300 mg/kg) and the progesterone was dissolved in sesame oil (300 mg/kg); both were injected intraperitoneally. Controls received the vehicle only. Each bar represents an average (12 animals).

zymes in the liver and that augmentation of this detoxification by prior treatment with PB prevents the induction of experimental porphyria.

Sprague-Dawley female rats (100 to 150 g) were fed laboratory chow freely and one group was treated with isotonic saline and another was treated with PB for 5 days. After fasting for 40 hours, animals from each group were further treated with porphyria-inducing drugs: either 2-allyl-2-isopropylacetamide (AIA) or progesterone. Control rats did not receive any further treatment. Sixteen hours later, the animals were killed and liver homogenates were assayed for δ-aminolevulinic acid synthetase (*5*). Prior treatment with PB or saline alone does not significantly affect the hepatic level of this enzyme. As expected, in the saline-treated rats, administration of AIA or progesterone results in striking increases of hepatic δ-aminolevulinic acid synthetase (10 to 30 times normal). However, prior treatment with PB diminishes their capacity to induce porphyria (Fig. 1).

It is unlikely that this protective effect of PB is due to competition with the porphyrogenic compounds for the same receptor sites in the liver, because 40 hours elapsed between the last dose of PB and the injection of the porphyrogenic compound. That this period is sufficiently long so that no PB remains in the liver is suggested by the observation that 36 hours after an injection of [^{14}C]PB into rats there is no detectable radioactivity within the liver. Phenobarbital does not inhibit δ-aminolevulinic acid synthetase activity because addition of liver homogenate from PB-treated animals to porphyric liver does not reduce δ-aminolevulinic acid production. Finally, since succinyl coenzyme A (CoA) is a substrate of this enzyme and is not added in excess to the assay system, it is conceivable that PB acts by decreasing the amount of succinate stored in the liver. However, this is unlikely because addition of a succinyl CoA–generating system (*6*) to the assay in vitro does not influence the PB-mediated effect on the activity of this enzyme. Therefore, it seems likely that prior treatment with PB, known to stimulate hepatic microsomal drug-metabolizing enzymes, increases the rate of detoxification of the porphyrogenic compounds and thereby prevents the induction of porphyria. To test this hypothesis, the following aspects of drug metabolism in rats receiving prior treatment with PB or saline were investigated: (i) the disposition of the parent porphyria-inducing drug in the blood and liver in vivo; (ii) the appearance of drug metabolites in the liver in vivo; and (iii) the metabolism of the drug by liver microsomes in vitro.

In order to detect small quantities of a porphyria-inducing drug in vivo, crystalline [2-^{14}C]AIA was synthesized (*7*). The compound was radiochemically pure as evidenced by a single peak of radioactivity on thin-layer chromatography (TLC) on silica gel G with an isooctane, acetic acid (100 : 7) ascending solvent system (R_F, 0.70). Rats given prior treatment with saline or PB were injected intraperitoneally with a porphyria-inducing dose of [^{14}C]AIA (75 mg/kg; specific activity 0.36 mc/mmole), and tail-vein blood was obtained at hourly intervals. The parent compound, AIA, was separated from its metabolites by solvent partition (*8*). Serum was diluted with 1.0*M* glycine buffer, *p*H 9.0, and extracted twice with three volumes of ethylene dichloride. In this way 85 to 90 percent of the AIA was extracted by the organic solvent, and the polar metabolites remained in the aqueous phase. The compound was identified by TLC, and quantitated by standard liquid-scintillation techniques.

In the PB-treated rats (eight in each group), the rate of disappearance of the drug from the serum increased approximately tenfold as compared to controls (mean $t_{1/2}$ was 30 minutes compared to 5 hours, respectively). In addition, the PB treatment enhanced the disappearance of the parent compound, AIA, from the liver (Fig. 2). Because of the

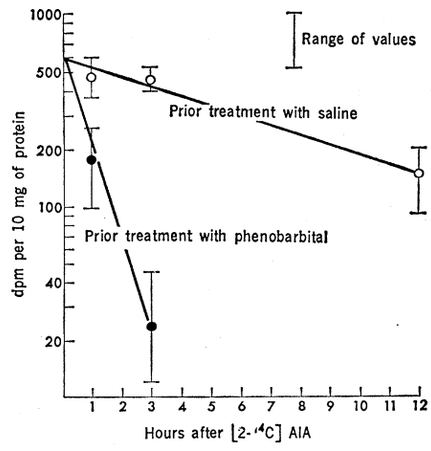

Fig. 2. Effect of prior treatment with PB or saline on the subsequent disappearance of labeled AIA from the liver of the rat after an intraperitoneal injection of [^{14}C]AIA. The radioactivity is expressed per 10 mg of homogenate protein after perfusion of the livers in situ. Each point represents an average (eight animals).

simultaneous accelerated disappearance of the drug from both the liver and blood of these animals, it is unlikely that PB decreases the hepatic uptake of AIA.

To determine whether this PB-augmented hepatic disposition of AIA could be due to an increased metabolism of AIA in the liver, the hepatic intracellular distribution of AIA metabolites was studied. The rats treated with PB or saline were killed 1 hour after the injection of [^{14}C]AIA. The livers were perfused in situ with ice-cold 0.9 percent NaCl, and homogenized in 0.25*M* sucrose, and the subcellular fractions were isolated by differential centrifugation (*9*). The polar metabolites of AIA in each subfraction were determined after the nonpolar, un-

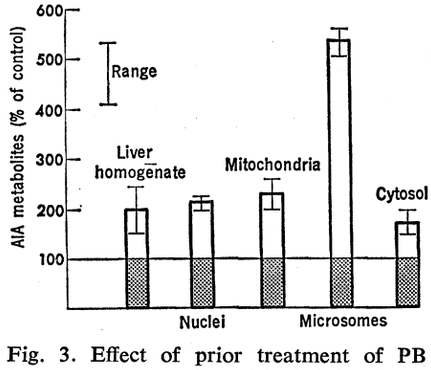

Fig. 3. Effect of prior treatment of PB (open bars) or saline (shaded bars) on the accumulation of AIA metabolites in rat liver and their intracellular localization after an injection of [^{14}C]AIA. Each value represents an average (eight animals).

changed AIA was extracted with ethylene dichloride. These metabolites migrated in the isooctane, acetic acid system with an R_F of 0.15. The PB treatment caused a twofold increase in the amount of AIA metabolites in the whole liver as compared to the saline treatment. Moreover, these metabolites were preferentially located in the microsomal fraction (Fig. 3).

Confirmation in vitro of this hypothesis was obtained by the following experiment. Microsomes (equivalent to 1.0 to 1.5 mg of protein) from PB-treated and control rat liver (eight rats per group) were incubated at 37°C with reduced nicotinamide adenine dinucleotide phosphate (NADPH) (0.67 μmole), tris buffer, *p*H 7.5 (35 mmole) in a final volume of 0.81 ml. After the addition of AIA (5 μmole) to the reaction vessel, oxygen consumption was measured polarographically with a Clark oxygen electrode (*10*). Hepatic microsomes of the PB-treated rats oxidize AIA at an increased rate as compared to control microsomes (mean of 4.6 compared to 2.5 μmole of O_2 consumed per minute per milligram of protein, respectively).

These data indicate that inducers of chemical porphyria are detoxified by drug-metabolizing enzymes of hepatic endoplasmic reticulum and that augmentation of this detoxification so reduces the amount of inducers that they are no longer effective. This has the following implications.

The first is that enzyme induction is influenced by the rate of biotransformation of the inducer in a target organ, as has been suggested (*11*). The second is the relevance of these findings to the human disorder. It is possible that the biochemical abberation in human genetic porphyria may be modified by reduced metabolism of circulating inducers of porphyrin biosynthesis. Indeed, observations in our laboratory and by others (*12*) have indicated that in human hepatic porphyria, endogenous inducers may be present in the blood in increased quantities, particularly during acute attacks. Thus, the rate of metabolism of these naturally occuring substances may be an important factor in the regulation of hepatic δ-aminolevulinic acid synthetase in the human disease.

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Pigeon Control by Chemosterilization: Population Model from Laboratory Results

Abstract. *Reproductivity of pigeons is inhibited with mestranol incorporated in a synthetic grit; continual erosion releases daily doses. Young squabs may be permanently sterilized when fed crop milk by treated birds. A theoretical model of pigeon population dynamics using laboratory-obtained data shows the advantages of chemosterilization over killing as a means of pigeon control.*

The feral pigeon, *Columba livia*, has become a problem in several areas, mainly by virtue of its numbers and unsanitary habits of dwelling in cities and parks, and harassing the feed lots and graneries of rural areas. Reproductive inhibitors have been tried for population control of pigeons (*1*), but the same problems always arise—how to get the inhibitor into the animals, and how to obtain more than a temporary effect.

Laboratory experiments to test dosage effects of the synthetic steroid mestranol [17α-ethynyl-3-methoxyestra-1,3,5(10)-trien-17β-ol] for avian inhibition of reproduction were run by Wentworth (*2*) and by Wentworth, Hendricks, and Sturtevant (*3*), with the Japanese quail (*Coturnix coturnix*) used as the experimental animal. The natural estrogen, ethynyl estradiol, is methylated to give the orally active estrogen mestranol. Once this synthetic estrogen, mestranol, enters any biological system, from microflora or -fauna to the human being, demethylation occurs to give, again, the natural steroid ethynyl estradiol. The half-life of available mestranol in a biological system is less than 6 hours (*4, 5*). Thus there is no retention or accumulation of mestranol in the ecosystem, hence no danger of contamination of the environment from mestranol.

Previous experiments on Japanese quail with mestranol (*2, 3*) indicated a potential use for control of pigeon populations. In 1968 I began laboratory testing of mestranol incorporated in synthetic grit on pigeons (*6*). Pigeons were fed pelleted pigeon food containing the synthetic grit, which then eroded in the gizzard. The rate of mestranol release through grit erosion was approximately 183 μg daily per treated bird, a dosage high enough to reduce the fertility of the first clutch of eggs after treatment to 26.4 percent and that of the following two clutches to 67.0 percent, as compared with 90.3 percent fertility of the controls.

When parental pigeons were treated with mestranol in grit approximately 4 days after laying a fertile clutch of eggs, the young hatched from these eggs were fed crop milk by the parents (a natural phenomenon) and some grit was passed to the young during feeding. Macroscopic changes in the reproductive tracts of adult F_1 birds receiving crop milk or grit or both from their parents the first several days posthatch were evident in 26.0 percent of all first-clutch birds; depressed fertility was statistically significant in males. Thus mestranol or its metabolites were passed to the young in crop milk or the grit or both (*6, 7*). The potential of F_1 sterilization is evident; I believe the results would be even more positive, however, if the level of mestranol in grit were increased.

A concurrent experiment was run in