The Effects of Some Terpenoids and other Dietary Anutrients on Hepatic Drug-Metabolizing Enzymes

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At birth, many of the hepatic enzymes that metabolize foreign compounds are relatively inactive, but they increase rapidly to reach normal adult values a few weeks after birth. Further, these enzyme activities may be induced by treatment of the foetus or neonatal animal with phenobarbitone and other foreign chemicals (Fouts & Hart, 1965). This may suggest that these enzymes, which give protection against the toxic action of foreign chemicals, are normally induced by naturally-occurring foreign compounds present in the diet of the neonatal animal. A further induction of these enzymes may be obtained in the weanling or adult animal by pretreatment with various drugs, insecticides, polycyclic hydrocarbons and food additives (Conney, 1967), and it has been suggested that for a foreign compound to be an inducer of the drug-metabolizing enzymes it has to be lipid-soluble and not rapidly excreted (Gillette, 1963).

To elucidate these points, studies have been made of the effects of terpenoids, and other dietary anutrients, on the activities of hepatic drug-metabolizing enzymes. Rats were pretreated for 3 days with terpenoids administered by intraperitoneal injection or by admixture with their food, and biphenyl 4-hydroxylase (Creaven, Parke & Williams, 1965), glucuronyl transferase (Bollet, Goodwin & Bron, 1959), and 4-nitrobenzoate reductase (R. Gingell, personal communication) activities and cytochrome *P*-450 were determined in 10000*g* supernatants of the liver homogenates.

Pretreatment with β-ionone resulted in increases in the activities of all three enzymes and cytochrome *P*-450 of about 50–75%, and hexobarbitone sleeping times were decreased to half the normal. Limonine, borneol, citral and terpineol produced smaller increases of the order of 25%. Linalool, nerolidol and squalene produced no increase in the activities of biphenyl 4-hydroxylase, glucuronyl transferase or cytochrome *P*-450, but increased the activity of 4-nitrobenzoate reductase by 25–50%. The induction produced by β-ionone was maximal after a single treatment and showed no further increase when treatment was continued daily for 28 days. Liver weights and liver protein did not increase significantly.

All of these terpenoids are very lipid-soluble, and it may be significant that β-ionone, which shows the maximum inductive effect, is the only one of those compounds studied that is known to be metabolized by hydroxylation. The other terpenoids are metabolized by reduction and conjugation with glucuronic acid, and it would appear that, with this class of substances at least, a compound induces those enzymes that are involved in its own metabolism.

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The Effect of Pregnancy on the Hydroxylation and Reduction of Drugs and cytochrome *P*-450 content of Rat Liver Microsomes

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The hydroxylation of foreign compounds by microsomal preparations of rat liver is inhibited during pregnancy (Creaven & Parke, 1965), and by progesterone and progestogens (Neale & Parke, 1968), and it has been suggested that the inhibition during pregnancy might be due to the high blood concentrations of progestogens (Creaven & Parke, 1965).

We investigated the following parameters in liver microsomal preparations from full-term pregnant rats: hydroxylation of biphenyl, reduction of *p*-nitrobenzoic acid, microsomal protein and cytochrome *P*-450. When these are expressed as a function of liver weight, the reductase activity and the protein content of the pregnant livers are unchanged, but the 4-hydroxylation of biphenyl and cytochrome *P*-450 content are both significantly decreased by 22%. When the results are expressed as a function of total liver weight, all four parameters are significantly increased in the pregnant animals, as there is an increase in liver weight accompanying pregnancy. Thus the total capacity of the pregnant animal to metabolize foreign compounds is increased, but since the pregnant animal also increases in weight, comparable to the gain in liver weight, the hydroxylating activity and cytochrome *P*-450 content per unit body weight decrease. This is confirmed by the fact that the sleeping time in rats dosed with 100mg. of hexobarbital/kg. is increased by 32% in full-term pregnant rats.

Thus it is probable that the decreased biphenyl hydroxylase activity of liver microsomal prepara-