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THE ROLE OF NUTRITION IN TOXICOLOGY

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INTRODUCTION

Toxicology is a rapidly developing new science, with facets affecting medicines, food, agricultural chemicals, manufacturing industry, and the environment. It is the basis of safety assessment of chemicals by regulatory

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bodies that can have the most profound effects upon society for good community health, abundant food supplies, a thriving and prosperous industry, and an unpolluted environment. Recent experience suggests that in many instances the data obtained from toxicology conducted in laboratory animals does not always accord with human epidemiology and experience; and it has long been recognized that various factors, primarily species differences and different exposure levels, are responsible for this. However, during the past few years it has been increasingly realized that nutrition also is a major factor affecting the toxicity of chemicals. The quality of nutrition of the laboratory animals may profoundly affect the toxicity of chemicals under test, thereby leading to false assessments of risk. And the nutritional status of human populations, and of individuals, may result in increased or decreased susceptibility to chemicals found in food, administered as drugs, or present in the natural or work environment. These effects are multiple, complex, and of paramount importance to both toxicologists and nutritionists. It is in the hope of encouraging more nutritionists to focus on these new problems that this brief, but wide-ranging, review is written.

In both animal experiments and in human epidemiological investigations, it is obviously essential to have knowledge of the diets whose qualitative and quantitative composition may induce imbalances likely to result in responses to toxic chemicals greater or less than those that would normally be produced (191). A study of the effects of diet on the toxicity of 5-fluorouracil to rats has shown that animals maintained on laboratory chow exhibit greater weight gains, higher leucocyte counts, and longer survival times than those maintained on purified hydrolyzed-casein diets (20), possibly the consequence of certain protective factors (not fiber or arachidonic acid) present in the natural food. A further aspect of the problem is seen in the differences between the diets of human and laboratory animals. For example, the relatively high content of nitrate in human diets compared with those of laboratory animals may be the reason gastric carcinoma associated with the endogenous formation of nitrosamines from certain drugs and chemicals has been observed in man but not in carcinogenicity studies in laboratory animals (72). Furthermore, human food is usually cooked, and protein pyrolysis products produced in grilling and roasting contain potent mutagens unlikely to be found in the uncooked diets of laboratory animals (141). Data concerning the effects of diet and nutrition on the toxicity of drugs and chemicals in human subjects are less numerous, but malnutrition, prevalent in developing countries, results in changes to the drug-metabolizing enzymes (11, 31), and to significant increases in the activities of certain drugs (113).

Relationships between nutrition and toxicology fall into three major categories; (*a*) The effect of nutritional status on the toxicity of drugs and

environmental chemicals (xenobiotics); (*b*) the additional nutritional demands that result from exposure to drugs and environmental chemicals; and (*c*) the presence of toxic substances in foods. This review is addressed primarily to the first two categories; for the last category, the reader is directed to recent reviews (7, 47, 154, 156, 180). Further examples of interactions of toxicants and nutrients, especially in relationship to other environmental factors, such as sunlight, are reviewed by Newberne et al (144) and by Hathcock & Coon (85a).

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DETOXICATION AND ACTIVATION OF DRUGS AND TOXIC CHEMICALS

The innovations of the chemist and the pharmacologist have led to the synthesis of a vast number of compounds used as drugs, pesticides, food additives, and industrial chemicals, adding to the even greater number and diversity of chemicals provided by nature. Not all of these environmental chemicals (xenobiotics) are beneficial, and many have marked deleterious effects. Nevertheless, the living organism is equipped with an efficient chemical defence system, which deals with these non-nutritive xenobiotics by metabolically converting them into polar, inactive compounds that are then more readily eliminated. The duration of action of all biologically active compounds is dependent on their absorption, on their tissue distribution and reaction with specific cellular receptors, and on the rates of their metabolic deactivation and elimination from the body. This last factor is generally considered to be the most important and is the aspect most studied in respect to the effects of nutrition on chemical toxicity.

The enzyme systems primarily responsible for the detoxication processes are the ubiquitous mixed-function oxidases (MFO) and the conjugases, both localized in the intracellular endoplasmic reticulum (microsomes). The liver is the most efficient tissue in this respect, but many other tissues, such as the small intestine, kidney, and lung, also contribute to the overall metabolism of chemicals. Xenobiotic metabolism may be considered to occur in two phases. Phase 1 metabolism, or biotransformation, involves reactions like oxygenation, oxidation, reduction, dehalogenation, and desulfuration, which introduce new functional groups into the lipophilic drug molecules, thereby making them more hydrophilic and more readily excretable. The microsomal MFO, the enzyme system(s) responsible for many aspects of phase 1 metabolism of xenobiotics, are also involved in the biosynthesis and catabolism of many endogenous substrates, such as fatty acids, cholesterol, bile acids, steroid hormones, prostaglandins, and thromboxanes. Phase 2 metabolism, or conjugation, comprises synthetic reactions in which small

endogenous molecules, such as glucuronic acid, sulfate, glutathione, glycine, and other amino acids, are added to the functional groups of the drug, or its phase 1 metabolites, making them even more polar and readily excretable. A compound may be detoxicated by either one or both phases of metabolism. For example, aniline undergoes phase 1 oxygenation to *p*-aminophenol, which is then conjugated with glucuronic acid to form *p*-acetamidophenyl glucuronate (see Figure 1). In contrast, the food preservative benzoic acid is metabolized only by conjugation with glucuronic acid and glycine.

It is now realized that, paradoxically, the same enzyme system whose primary function is detoxication can also bring about the reverse effect, namely activation, and transform a biologically inert compound into a potentially toxic entity. For example, carbon tetrachloride is converted to the highly reactive free radical $\dot{C}Cl_3$(177), and paracetamol is metabolized to a toxic quinoneimine (136). Similarly, most chemical carcinogens require metabolic activation to form proximate and ultimate carcinogens that alkylate DNA to give rise to mutations and carcinogenesis. Benzo(a)pyrene and 2-acetamidofluorene are C- and N-oxygenated, respectively, to generate reactive species that are further converted to ultimate carcinogens. Phase 2 metabolism may also form metabolites that are more active than the parent compounds. The β-blocker acebutolol forms an N-acetyl conjugate that acts as a β-antagonist (78), and the sulfate ester of N-hydroxy-2-acetamidofluorene is an ultimate carcinogen. Detoxication and activation of an environmental chemical may proceed simultaneously as competing reactions (see Figure 2), with the predominating reaction depending on level of dosage, species and genetics, and nutritional status.

The microsomal MFO require NADPH and molecular oxygen for activity and catalyze the insertion of one atom of oxygen into the xenobiotic molecule, with the second giving rise to water (Figure 3). This enzyme system is bound to the membranes of the endoplasmic reticulum, but it has been solubilized and shown to comprise essentially an NADPH-dependent flavoprotein (cytochrome P-450 reductase), the terminal oxygenase (cytochrome P-450), and a phospholipid factor (phosphatidylcholine). Its activity is affected by age, genetics, other chemicals, and nutritional status.

Although the metabolism of xenobiotics by mammalian enzymes is the most important, the microorganisms of the mammalian intestines, which catalyze mostly reductive and hydrolytic changes to environmental chemicals, make a substantial overall contribution to the mammalian metabolism of xenobiotics (179). The nature of the microorganisms of the gastrointestinal tract, and hence the nature and extent of their metabolism of ingested toxic chemicals (171), is known to be affected by the diet. However, this is as yet a largely uncharted area.

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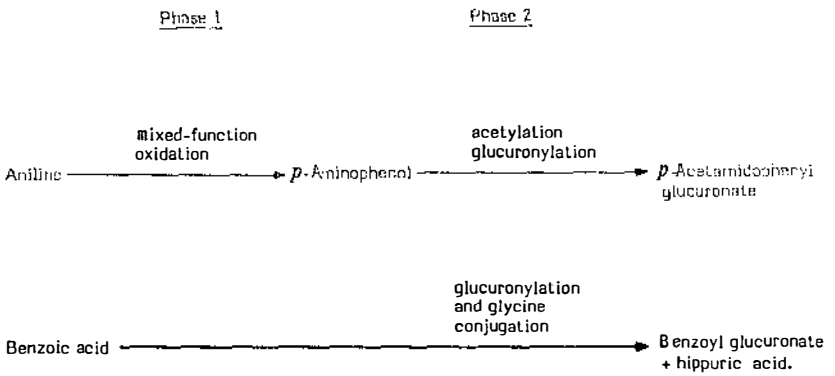

Figure 1 Phase 1 and phase 2 metabolism of environmental chemicals.

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MICROSOMAL ENZYME INDUCTION AND DIET

Many compounds of widely diverse chemical structures induce the MFO in the liver and other tissues, with accompanying proliferation of the endoplasmic reticulum and cellular hypertrophy (45, 153). *Enzyme induction* implies synthesis of new enzymic protein, but it is often used more broadly to denote stimulation of enzyme activity. As many of the drugs used today are inducing agents, enzyme induction may have important clinical implications (92). Induction of the MFO is associated with increased biosynthesis of the hemoprotein cytochrome P-450, which requires synthesis of new protein, but not of heme, since the heme pool can usually meet the increased requirement (94). The most potent inducers are substrates whose rates of metabolism are slow, so that they remain associated with the enzyme for long periods of time (93).

Some types of food have high contents of natural xenobiotics, which are strong inducers of the MFO, e.g. safrole, flavones, xanthines, and indoles. Rats maintained on a diet containing cruciferous vegetables, such as sprouts and cabbage, probably because of their high content of indoles, exhibit high levels of intestinal MFO activity (151) and exhibit an altered response to chemical carcinogens (199, 200). Humans on similar diets showed enhanced intestinal metabolism of orally administered phenacetin and enhanced hepatic metabolism of antipyrine (152). Inducing agents may find their way into food during cooking, and charcoal-broiled beef, because of the high levels of aromatic polycyclic hydrocarbons, stimulates rat placental and intestinal drug metabolism (85) and similarly increases the hepatic metabolism of antipyrine and theophylline, and the intestinal metabolism of phenacetin in humans (46, 100).

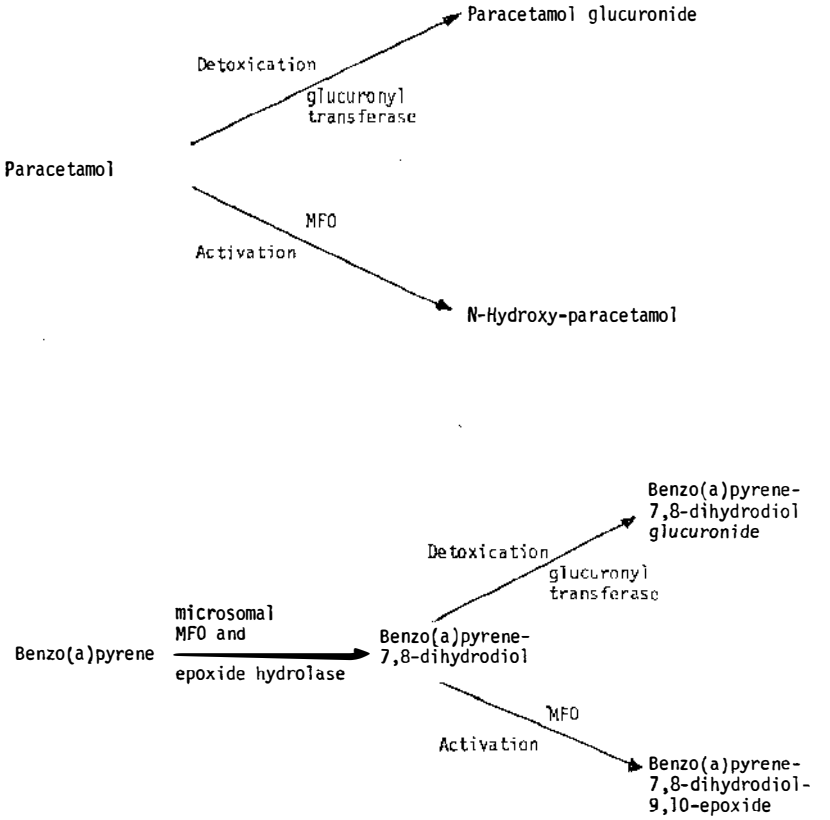

Figure 2 Detoxication and activation of xenobiotic chemicals.

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THE ROLE OF LIPIDS IN MICROSOMAL MFO

The endoplasmic reticulum, like other cellular membranes, contains considerable amounts of lipids, especially phospholipids, with high proportions of unsaturated fatty acids (166). Phosphatidylcholine is an essential component of the hepatic microsomal MFO system (187), and the reconstituted solubilized component enzymes require phosphatidylcholine for full enzymic activity (95, 123, 192). Nonionic detergents, such as Triton X-100, can replace phosphatidylcholine in the reconstituted MFO system (123), which suggests that phosphatidylcholine has a physicochemical role and allows coupling of the cytochrome P-450 with its reductase (57, 184). Induction of the liver microsomal MFO by pretreatment with phenobarbitone also increases the microsomal phospholipids, and it has been suggested that a distinctive species of phospholipid-containing linoleic acid in the

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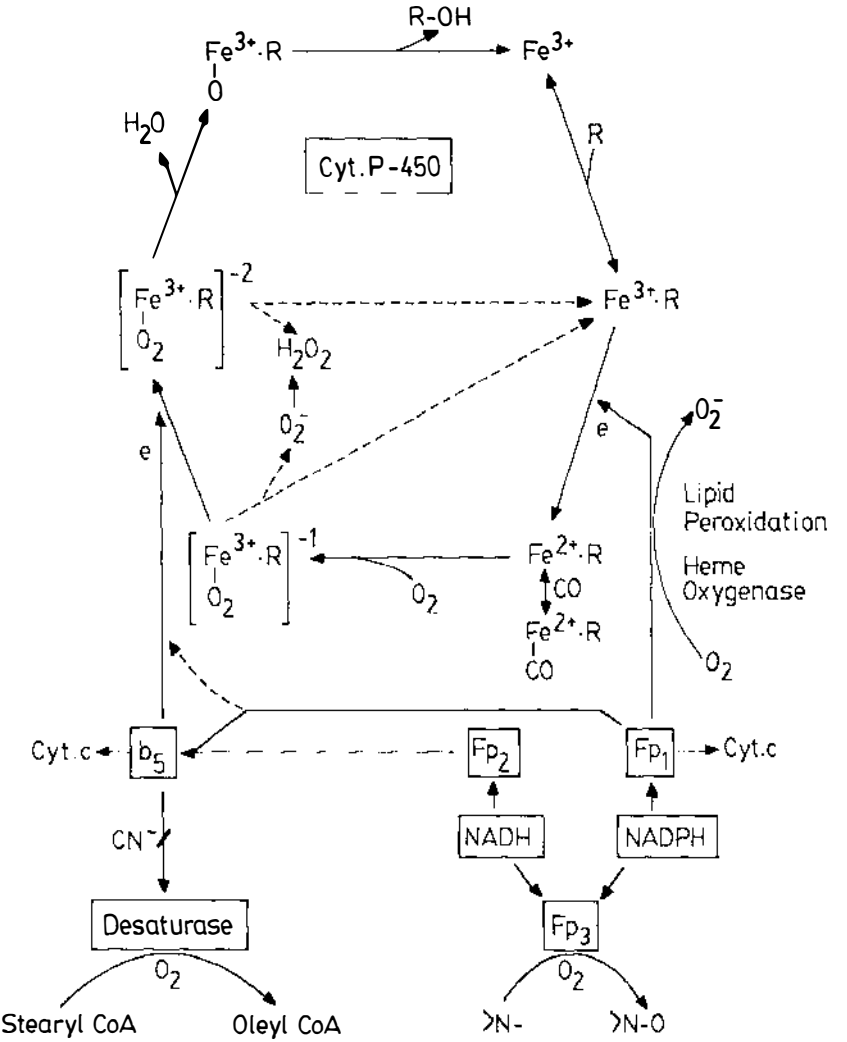

Figure 3 MFO and related redox reactions occurring in liver microsomes. Cytochrome P-450 is depicted by the oxidation state of the iron of the hemoprotein (Fe^{3+}, etc). R, the substrate for cytochrome P-450; Fp_1 is NADPH-cytochrome P-450 reductase; Fp_2, NADH-cytochrome b_5 reductase; Fp_3, amine N-oxygenase; b_5, cytochrome b_5. From (64).

β-position is necessary for liver MFO activity (52). The ratio of phosphatidylcholine/phosphatidylethanolamine (ca 2.5) is of importance in the hydroxylation of xenobiotics and is disturbed by dietary deficiencies in choline, vitamin B_{12}, or methyl group donors (lipotropes) (2, 69).

After feeding diets containing corn oil or methyl linoleate, linoleic and

arachidonic acids are readily incorporated into liver microsomal phospholipids (36, 146), with corresponding increases in MFO activity (147, 195). Dietary lipid also affects cytochrome P-450 concentration and the rate of oxidative demethylation in rat liver; these were lowest on a fat-free diet (see Table 1), higher on a diet containing 10% lard (saturated and monounsaturated fatty acids, with 6% linoleic acid), but highest on a diet containing 10% corn oil (50% linoleic acid) (166). Thus, dietary linoleic acid is important in determining the normal levels of hepatic microsomal enzyme activities; it also results in correspondingly greater increases in cytochrome P-450, MFO (166), and UDP-glucuronosyltransferase activities (120) following phenobarbital-induced hepatic microsomal enzyme induction (see Table 1). However, higher doses of linoleic acid decrease hepatic cytochrome P-450 and MFO activity (87), and unsaturated fatty acids added to rat and rabbit liver microsomes in vitro inhibit MFO activity with type I substrates (*p*-nitroanisole, benzphetamine), probably because the fatty acids function as competitive substrates (58). ω3-Polyunsaturated fatty acids may have a similar effect, for diets containing 10% herring oil (mostly $C_{20:5}$ and $C_{22:6}$ fatty acids) result in incorporation of large amounts of these polyunsaturated fatty acids into the endoplasmic reticulum and to increased MFO activity (aminopyrine demethylation) and result in increased enzyme induction following phenobarbital treatment (83).

Microsomal lipid peroxidation, which may be greatly augmented by toxic chemicals such as carbon tetrachloride and paracetamol, involves breakdown of polyunsaturated fatty acids of the microsomal phospholipids, destruction of cytochrome P-450, and loss of activity of the MFO and glucose 6-phosphatase (90, 206). Antioxidants, such as vitamin E, maintain the integrity of the microsomal unsaturated fatty acids, and of the MFO, by decreasing microsomal lipid peroxidation (34). However, the principal function of vitamin E is probably protection of microsomal selenide proteins (60). The lipid peroxide content of the rat hepatic endoplasmic reticulum, and the rate of NADPH-linked lipid peroxidation, were much greater on a 10% corn oil diet than on a 10% lard or fat-free diet (166). Moreover, the extent of lipid peroxidation, as measured by alkane production (62), following administration of carbon tetrachloride to rats, was much less on vitamin E-supplemented diets (168), and vitamin E supplementation protected rats against paracetamol-induced hepatic necrosis (196).

Cholesterol also affects the microsomal MFO system and a 2–4% cholesterol-supplemented diet increased rat liver cytochrome P-450, cytochrome P-450 reductase, *p*-nitroanisole-O-demethylase, and UDP-glucuronosyltransferase (119) and also increased benzo(a)pyrene hydroxylase and UDP-glucuronosyltransferase of rat intestine (88).

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PROTEIN-CALORIE MALNUTRITION, MICROSOMAL MFO, AND CHEMICAL TOXICITY

When the dietary intake of energy is low, tissue protein is catabolized as a source of energy, and consequently decreases occur in the tissue concentrations of (*a*) the drug-metabolizing enzymes and (*b*) amino acids and peptides (glutathione) used as cosubstrates in conjugation reactions (59). The consequence is decreased drug metabolism, especially detoxication, enhanced pharmacological activity, and increased toxicity. Dixon, Shultice & Fouts (61) were the first to show that starvation of male mice for 36 h decreases the metabolism of drugs in vivo and the hepatic microsomal MFO in vitro. This effect of starvation is more complex than was originally supposed, and in male rats it leads to impairment of those enzymes that show sex dependence (hexobarbital hydroxylase, aminopyrine N-demethylase), but does not decrease those enzymes not sex dependent (*p*-nitroanisole O-demethylase, zoxazolamine hydroxylase, aniline hydroxylase); in female rats, starvation stimulates certain MFO activities (103). Subsequent work showed that starvation impairs the action of androgen to enhance the affinity of cytochrome P-450 for substrates (104). The various effects of starvation on chemical toxicity and hepatic microsomal MFO activity in different animal species have been reviewed by Kato (102). Starvation also decreases the activities of the intestinal MFO (198) and hepatic (102) and intestinal glucuronide conjugation (128).

Quantitative and qualitative changes in dietary protein affect the toxicity of many chemicals (42). Animals on low protein diets were more susceptible to the toxic effects of drugs (21, 105) and pesticides (22, 112) (see Table 2). In contrast, if the chemical exerts its toxicity through a metabolic intermediate, protein deficiency exerts a protective role, e.g. the toxicity of heptachlor, which is metabolized to a toxic epoxide, was decreased (202, 203); and the generation of the toxic $\dot{C}Cl_3$ radical from carbon tetrachloride was similarly decreased (132). Dimethylnitrosamine, a carcinogen that requires activation, was less mutagenic to bacteria when the liver microsomes (S9 mix) were isolated from protein-deficient mice, but conversely, the mutagenicity of the direct acting carcinogen N-methyl-N'-nitro-nitrosoguanidine (MNNG) was increased by protein deficiency (49). Animals fed protein-deficient diets during the administration of aflatoxin B_1 had fewer precancerous lesions and liver tumors (124), and the binding to DNA was decreased by 70% (30). In contrast, increasing dietary protein fed prior to (but not following) administration of the breast carcinogen 7,12-dimethylbenz(a)anthracene (DMBA) to rats stimulated hepatic metabolism of DMBA, decreased the DMBA metabolites reaching the mam-

Table 1 The effect of dietary lipid on rat liver microsomal MFO[a]

Determinants	Treatment	Diet		
		Fat free	10% Lard	10% Corn oil
Cytochrome P-450	basic	0.36	0.47	0.62
(nmol/mg of protein)	induced	0.62	1.15	1.48
Aminopyrine N-demethylase	basic	0.44	0.49	0.55
K_m (mM)	induced	0.34	0.41	0.46
V_{max} (nmol/min per mg	basic	2.9	4.5	6.1
of protein)	induced	6.4	11.0	13.2

[a] Diets were fed for 21 days before determination of basic or induced (phenobarbitone) microsomal MFO parameters. Results are mean values. From (166).

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mary gland, increased the tumor latent period, and decreased the numbers of tumors formed (43) (see Table 3). This indicates that dietary protein is important in diminishing the initiation phase of DMBA mammary carcinogenesis, but it has no effect on the promotional phase.

These studies indicate that the effects of protein malnutrition on chemical toxicity are related to changes in the activities of the microsomal MFO enzymes (32, 105, 135, 157). In studies of reconstituted liver microsomal MFO systems from rats fed a cereal-based natural stock diet, or synthetic high and low protein diets, the marked loss of MFO activity seen in preparations from animals on the synthetic diets are due to changes in the interactions between cytochrome P-450 and its reductase, rather than to changes in specific activities of the individual components (142). Dietary protein also affects the hepatic cytochrome P-450 in rainbow trout (186). In contrast to the effects on phase I metabolism, protein deficiency does not impair conjugation and may even result in an increase of hepatic glucuronylation (63, 207).

The limited number of observations in humans show a similar picture. When volunteers maintained on a high protein, low carbohydrate diet were changed to a low protein, high carbohydrate diet, the biological half-lives of antipyrine and theophylline increased by 63 and 46%, respectively (101). Children with kwashiorkor excreted a higher ratio of the antimalarial drug chloroquine to its metabolites (205) and showed diminished hepatic biotransformation of chloramphenicol (134). Nutritional rehabilitation from kwashiorkor decreased the plasma half-life and increased the clearance of isoniazid (26). Impaired renal function may also contribute to the effects of kwashiorkor on drugs; protein-calorie deficiencies have been correlated with decreases in glomerular filtration and renal plasma flow, resulting in prolongation of the half-life of gentamicin (25). Although marked hypoal-

buminemia is characteristic of kwashiorkor, the plasma protein binding of a number of drugs showed little or no change likely to be of therapeutic consequence (27, 28).

EFFECT OF VITAMINS AND MINERALS ON MICROSOMAL METABOLISM AND CHEMICAL TOXICITY

Vitamin C

Vitamin C-deficient guinea pigs are more susceptible to the pharmacological action of drugs (pentobarbital, procaine, antipyrine) and chemicals (aniline, acetanilide) (8, 162), and this has been attributed to decreases in their rates of oxidative metabolism (8). Although oxidative metabolism of coumarin (54), hexobarbital (106), and zoxazolamine (106) were similarly decreased in scorbutic guinea pigs, other aspects of drug metabolism (aminopyrine N-demethylation, *p*-nitroanisole O-demethylation, *p*-nitrobenzoate, and *p*-dimethylaminoazobenzene reduction) were unaffected (106). A later, more comprehensive study (209) showed that vitamin C-deficient guinea pigs have an overall deficiency in drug oxidation, with decreases in aniline hydroxylation, aminopyrine N-demethylation, and *p*-nitroanisole O-demethylation of the order of 50–65%; and decreases in the contents of cytochrome P-450 and cytochrome P-450 reductase of 40 and 85%, respectively. The binding of the chemical substrates to the cytochrome, as measured by the K_m values, did not show any correlation with ascorbate deficiency, for although that for aniline was decreased by 70%, those for aminopyrine and *p*-nitroanisole were increased by 140 and 240%, respectively (209). Administration of ascorbate to the deficient animals for 6 days reversed these losses of MFO activity. Treatment of the vitamin C-deficient guinea pigs with the microsomal enzyme-inducing agent phenobarbitone resulted in increases in cytochrome P-450 (100%), cytochrome P-450 reductase (200%), and MFO activity (100 to 500%) similar to those seen in nondeficient animals (209). However, this may be due to the increases in microsomal NADPH-cytochrome *c* reductase and endogenous ascorbate biosynthesis known to occur on phenobarbitone treatment. The MFO (7-ethoxycoumarin dealkylation) of the lung of ascorbate-deficient guinea pigs was similarly decreased, but the intestinal activity of these enzymes was unchanged, indicating that the effect of vitamin C is tissue dependent (114).

Although little or no evidence exists of a similar effect in man, it has been suggested that the present recommended human dietary allowances for ascorbic acid may be inadequate for optimal metabolism of drugs and other xenobiotics (208). However, recent studies with cynomolgous monkeys showed that ascorbate depletion did not change the plasma clearance of

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Table 2 Acute oral LD_{50} for several pesticides administered to rats on low and high protein diets[a]

Pesticide	Low protein diet[b]	Normal protein diet[b]	Ratio of normal/low protein diets
Chlordane	135 ± 30	265 ± 45	2.0
Lindane	95 ± 35	185 ± 16	2.0
Malathion	600 ± 140	1,400 ± 100	2.3
DDT	165 ± 35	480 ± 15	2.9
Endosulfan	24 ± 10	100 ± 16	4.2
Carbaryl	89 ± 11	575 ± 51	6.5
Parathion	4.9 ± 1.3	37 ± 5	7.6
Captan	480 ± 110	12,600 ± 2,100	26

[a] Albino rats were fed 28 days from weaning on the low protein diet (3.5% casein) and normal protein diet (26%). From (23).
[b] Milligrams per kilogram of body weight.

antipyrine, although administration of the vitamin C antagonist erythorbic acid did decrease the plasma half-life of antipyrine by 50 to 60% (148).

Although vitamin C deficiency was stated to decrease the levels of certain hepatic cytochromes (53, 55), deficiency in the guinea pig affected neither the enzymes of heme biosynthesis nor the catabolism of cytochrome P-450 (149, 150, 163, 197). However, ascorbate deficiency does decrease microsomal phospholipid (172) and also produces selective changes in the electrophoretic pattern of partially purified cytochrome P-450 polypeptides (163, 170). Decreases of cytochrome P-450 were not accompanied by any increase in cytochrome P-420, which might have been expected if the effect of ascorbate depletion had been to increase tissue lipid peroxidation (175).

A dietary excess of vitamin C, as from megadose ingestion, might also prove hazardous, since ascorbate is metabolized by conjugation with sulfate (9), and ingestion of large amounts of the vitamin may lead to impairment of sulfate conjugation. Drugs such as salicylamide, which depend on sulfate conjugation for deactivation, may accumulate in the body with increasing risk of drug toxicity (91).

Vitamin A

Vitamin A and its synthetic analogues have been shown to prevent the development of carcinomas in animals exposed to chemical carcinogens (140, 143), by a mechanism not yet fully elucidated. Rats deficient in retinol showed decreased levels of liver cytochrome P-450 and ethylmorphine N-demethylase and aniline hydroxylase activities (44). Golden Syrian hamsters on a vitamin A-deficient diet had a slightly higher lung aryl hydrocarbon hydroxylase activity, but the pulmonary metabolic profile of

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Table 3 The effects of dietary protein on 7,12-dimethylbenz(a)anthracene mammary carcinogenicity in rat[a]

Determinants	Dietary protein (%)		
	7.5	15	45
Final body wt (g)	125 ± 4	160 ± 5	143 ± 5
Liver lipid/DNA (mg/mg)	40 ± 4	18 ± 1	18 ± 1
Liver protein/DNA (mg/mg)	57 ± 2	68 ± 1	82 ± 3
Liver aromatic hydroxylase (nmol of 3-hydroxybenzo(a)pyrene/ 30 min per mg of protein)	0.25 ± 0.1	0.8 ± 0.1	1.4 ± 0.2
Latent period (days from DMBA) exposure to first palpable tumor)	84 ± 7	119 ± 7	126 ± 7
Tumor incidence (% rats with tumors)	85	52	30
Tumorigenicity (% rats with tumor × average no. tumors per rat)	187	73	33

[a] From (43).

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3,4-benzo(a)pyrene was unchanged (19). Vitamin A deficiency in guinea pig decreased liver cytochrome P-450 and MFO enzymes in vitro, but increased the activities of these enzymes in the intestine, whereas the lung enzymes were unaffected (137). Similar observations were made in rabbit (137) and rat (86). Thus, the effect of vitamin A deficiency on the MFO enzymes depends on the substrate, tissue, and animal species. Microsomal epoxide hydrolase and cytosolic glutathione S-transferase, enzymes associated with deactivation of carcinogens, were unaffected. Therefore, it is unlikely that vitamin A deficiency acts primarily on the metabolic activation of carcinogens, but it may facilitate the interaction of the ultimate carcinogen with DNA, since the binding of 3,4-benzo(a)pyrene to hamster tracheal epithelial DNA was shown to be higher in vitamin A-deficient animals (70). Since vitamin A is required in the differentiation of epithelial cells (56), it is possible that deficiency may affect the transformation of epithelia and thus predispose the tissue to neoplastic changes (84).

Vitamin D

The occurrence of rickets and osteomalacia, and decreased plasma calcium levels, after the chronic ingestion of anticonvulsant drugs has raised the question as to whether or not drugs might affect vitamin D turnover (39). Since anticonvulsant drugs, such as phenobarbitone and phenytoin, are potent inducers of the hepatic microsomal MFO, it was reasonable to expect that the activation and catabolism of vitamin D by this system might be involved. Cholecalciferol (vitamin D_3) is hydroxylated in the liver to 25-hydroxycholecalciferol and in the kidney to 1,25-dihydroxycholecalciferol,

the active form of the vitamin (108). The 25-hydroxylation of cholecalciferol requires NADPH, O_2, and an enzyme that has the properties of the microsomal MFO (15, 125, 127). Furthermore, 25-hydroxy-vitamin D_3 competitively inhibits the in vitro demethylation of aminopyrine, a typical cytochrome P-450 reaction (41, 125), and reconstituted preparations of rat liver cytochrome P-450, with its reductase and phospholipid, exhibited higher cholecalciferol 25-hydroxylase activity than crude liver microsomes (15). Patients suffering from drug-induced osteomalacia show increased rates of metabolism of vitamin D_3 to 25-hydroxy-vitamin D_3 (82, 130). The enzyme catalyzing the hydroxylation of 25-hydroxy-vitamin D_3 to 1,25-dihydroxy-vitamin D_3 occurs in kidney (67), is a typical mitochondrial cytochrome P-450 steroid hydroxylase (71), and reconstituted with ferredoxin and ferredoxin reductase exhibits characteristic hydroxylase activity (158). Inducing agents, such as anticonvulsant drugs, also stimulate the activity of this enzyme (121). The metabolism of vitamin D_3 and its regulation are discussed in more detail in a recent review (66).

The increased synthesis of 1,25-dihydroxycholecalciferol, observed after administration of anticonvulsant drugs, cannot account for the drug-induced osteomalacia. However, it is possible that the inducing agents may enhance further metabolism of hydroxy- and dihydroxy-vitamin D_3 to inactive compounds, and indirect evidence of this has been obtained from in vitro enzyme kinetics (16, 82). Furthermore, cholecalciferol may be metabolically inactivated in the liver, and animals given phenobarbitone excreted increased amounts of inactive vitamin D_3 metabolites in the bile (176). The nature of the inactive metabolites is not yet known but may involve further hydroxylation of 25-hydroxy-vitamin D_3 to 24,25-dihydroxycholecalciferol (66, 115, 126). At present, drug-induced osteomalacia in epileptics on long-term anticonvulsant therapy is corrected by administration of vitamin D and 25-hydroxy-vitamin D_3 (39, 40, 182), but our understanding of this iatrogenic disease will be enhanced only when the activation and deactivation pathways of vitamin D are fully elucidated.

Vitamins B

Rats fed a high thiamine diet (2.0 mg/animal per day) exhibited decreased liver cytochrome P-450 and cytochrome P-450 reductase activities, with similar decreases in the rates of microsomal hydroxylation of aniline, zoxazolamine, and aminopyrine (75). Deprivation of thiamine resulted in the expected decrease in glucose 6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase activities but had little effect on the microsomal MFO activity. A more detailed study (194) showed that thiamine deficiency in a synthetic diet increased rat liver cytochrome P-450 reductase and MFO activity, whereas high dietary thiamine decreased these activities. The

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effects of riboflavin and pyridoxine were also examined (194), but the results did not show as clear an effect as those of thiamine, probably because supplementation of the synthetic diets with riboflavin and pyridoxine was inadequate.

Iron

Cytochrome P-450, the essential component of the microsomal electron transport chain, requires iron for its biosynthesis and deficiency of this metal might be expected to lead to loss of MFO activity. However, chronic deficiency of iron in adult mice led to stimulation of some MFO enzymes whereas others were unaffected (35); studies in rats showed similar effects (13). In both cases the concentration of cytochrome P-450 was unchanged, and it is possible that the liver pool of iron was not depleted, even though the hemoglobin was only 35% of normal, for it is difficult to produce intracellular iron deficiency in the liver (51). In contrast, the villous cells of rat duodenal mucosa, where most of the drug-metabolizing enzymes of the intestine are located, rapidly lose their cytochrome P-450 content and MFO activity when dietary iron is restricted (89). The NADPH-stimulated, spontaneous lipid peroxidation of liver microsomes is dependent on liver Fe^{2+} concentration (109) and is stimulated by ascorbate. In contrast, chemical-induced (e.g. CCl_4) microsomal lipid peroxidation is dependent on cytochrome P-450 and NADPH and proceeds even in the absence of Fe^{2+} (110). This may imply that high hepatic levels of nonheme iron could lead to excessive lipid peroxidation and hepatocellular damage.

Microsomal Enzyme Induction and Folate Deficiency

Chronic administration of drugs, such as anticonvulsants (37, 118, 161), methotrexate (10), and oral contraceptives (122, 159, 178), has been associated with deficient folate status and megaloblastic anemia. Folate functions in one-carbon metabolism in the form of tetrahydrofolic acid. It is important in the biosynthesis of purines so that its deficiency will affect DNA synthesis. It is involved in the biosynthesis of cytochromes (155), and it has also been suggested to act as a cofactor for the hepatic MFO (81, 190). The precise mechanism by which drugs cause folate deficiency is not fully understood, but it may involve one or more of the following: (*a*) impairment of folate absorption; (*b*) inhibition of conversion of folate to active tetrahydrofolate; and (*c*) increased folate requirements for syntheses. The antitumor drug methotrexate gives rise to symptoms of acute folate deficiency through its inhibition of the dihydrofolate reductase (201). Other drugs may elicit different mechanisms.

Decreased levels of folate in the serum, erythrocytes, and cerebrospinal fluid of epileptics on long-term anticonvulsant therapy is well documented

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(107, 118). Anticonvulsants are potent inducers of the cytochrome P-450 MFO enzymes, and since folate acts as a cofactor in cytochrome biosynthesis, folate deficiency occurs as a result of the increased enzyme synthesis (117, 155). When folate deficiency ensues, further administration of inducing agents (phenobarbitone, phenytoin, imipramine) to animals is not accompanied by induction of the drug-metabolizing enzymes (117, 155). Similar observations were made in patients chronically receiving anticonvulsants and phenothiazines (118). The MFO activity in these patients was increased during the first year of treatment, then declined rapidly; folate deficiency was evident after 2–5 years of drug treatment. It is obvious that folate deficiency limits enzyme induction, and when this condition is reached, the rate of drug metabolism is decreased, and the anticonvulsant drugs accumulate in the body, giving rise to toxicity (Figure 4). Administration of folate to these patients accelerates the metabolism of the anticonvulsant (116), decreasing the serum and cerebrospinal fluid drug concentrations (12, 97, 131) with subsequent disappearance of symptoms.

Congenital abnormalities in neonates born to epileptic mothers on anticonvulsant therapy have been reported (68, 133). Rats dosed with therapeutic levels of phenobarbitone and phenytoin, and maintained throughout gestation on a low folate diet, gave birth to offspring with marked deformities of the bones and soft tissues. Only when the diet was supplemented with folate were no adverse effects seen from the administration of the drugs (117, 155).

Although the evidence that folate deficiency following long-term therapy with inducing agents is the result of increased demand due to enzyme induction, impaired absorption cannot be excluded and has been demonstrated for phenytoin (50). Folate deficiency also developed in women taking oral contraceptives (159, 160, 174, 178) and was reversed within 3 months of withdrawal of the pill. The decreased folate status observed may also be related to increased folate requirements, since these steroids are enzyme inducers (24) at relatively high dosage.

NUTRITIONAL DEFICIENCIES, CHEMICAL TOXICITY, DISEASE STATES, AND THERAPEUTICS

As the drug-metabolizing enzymes have normal physiological functions, e.g. the biogenesis of steroid hormones, and the conjugation of bilirubin, in addition to their role in the metabolism of drugs and environmental chemicals, the effects of nutritional deficiencies on these enzymes may also affect physiological processes, resulting in the exacerbation, or even initiation, of pathological changes and disease states. Furthermore, the increased load on these enzymes occasioned by the prolonged administration of drugs will make increased demands on nutrition.

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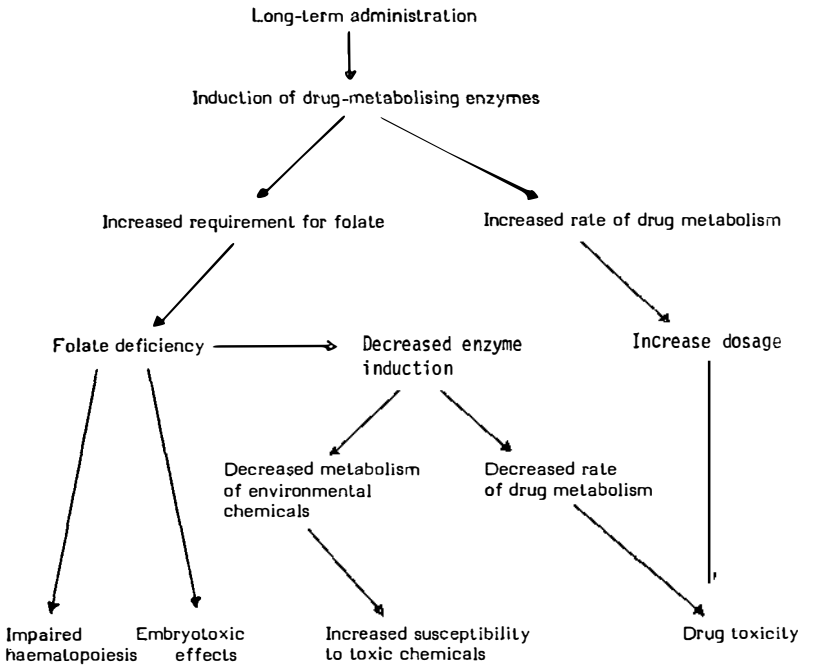

Figure 4 Long-term effects of drug administration on folate metabolism and toxic side effects of drugs.

Nutrition and Cancer

Much human cancer is now believed to result from exposure to environmental chemicals, and although the mechanisms of carcinogenesis are still not fully understood, numerous examples of chemical-induced carcinogenesis in experimental animals have been documented. Although species and genetic differences in response to chemical carcinogens are undoubtedly of great significance, diet and nutrition also play a major role.

LIPIDS Recent epidemiological studies have associated high incidence of human cancer, particularly carcinoma of the colon, with high levels of dietary fat (204). Many substances that are not themselves carcinogens are now recognized as cocarcinogens (e.g. saccharin) or co-mutagens (e.g. harman) (6), potentiating the action of chemical mutagens/carcinogens and increasing malignancy. Cholesterol is a dietary co-carcinogen in that it promotes induction of colon cancer by dimethylhydrazine in the rat (48). Similarly, a high fat diet (30% beef fat) increased the intestinal tumorigenicity of azoxymethane in rats (29), and a high fat diet, slightly deficient in lipotropes (choline), increased chemical-induced tumorigenesis some two- to eight-fold, according to the carcinogen used (165) (see Table

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4). However, although a similar high fat diet, marginally deficient in lipotropes (30% beef fat and 2% corn oil), increased the hepatocarcinogenicity of aflatoxin B_1 (see Table 5), it also markedly decreased the microsomal MFO and the acute hepatotoxicity of the mycotoxin (164). The mechanism of the co-carcinogenic effects of high fat and low lipotrope diets are unknown, but a dietary excess of fat might accumulate in the hepatic endoplasmic reticulum, resulting in increased lipid peroxidation. Mice fed a fat-free, high carbohydrate diet produce a liver cytosolic factor that inhibits NADPH-Fe^{2+} lipid peroxidation (188). Also, deficiencies of lipotropes or of biological anti-oxidants result in increased autoxidation (38) and may consequently promote the autoxidation-mediated mutations of certain carcinogens (185). Antioxidants (vitamin C, vitamin E, selenium, and butylated hydroxytoluene) can markedly decrease the bacterial mutagenicity of the lipid peroxidation products malondialdehyde and β-propiolactone (173), and at dietary levels of 1-5 ppm, selenium decreased the rate of tumorigenesis by 1,2-dimethylhydrazine, methylazoxymethanol (96), 3'-methyl-4-dimethylaminoazobenzene (74), and 2-acetamidofluorene (129).

PROTEIN Present knowledge of the role of dietary protein in chemical carcinogenesis precludes generalizations (193) and depends on the nature of the carcinogen and many other factors. Protein deficiency decreases the tumorigenicity of aflatoxin B_1 (124) and increases the tumorigenicity of 7,12-dimethylbenz(a)-anthracene (43).

VITAMIN C Ascorbic acid has some interesting effects on the pathogenesis of cancer. It inhibits the in vitro metabolic conversion of the proximate carcinogen N-hydroxy-2-acetamidofluorene to ultimate carcinogens (65) and also inhibits the covalent binding of N-hydroxy-2-acetamidofluorene to protein and DNA (189). Ascorbate also protects against the carcinogenic and toxic effects of nitrosamines formed in vivo from the action of dietary

Table 4 Effect of high fat diet on tumorigenesis in rats[a]

	Tumor incidence (%)	
Carcinogen	Normal diet	High fat diet
Aflatoxin B_1 (375 μg)	11	87
N-Nitrosodiethylamine (40 ppm, 12 weeks)	24	60
2-Acetamidofluorene (0.02%; 18 weeks)	19	41
1,2-Dimethylhydrazine (150 mg/kg)	56	85

[a] The high fat diet is slightly deficient in lipotropes (choline). From (165).

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Table 5 Effect of lipotropes on aflatoxin carcinogenesis and hepatic MFO[a]

Determinants	Diet	
	Minimal lipotrope	Control
Aflatoxin acute toxicity (intragastric; 2-week mortality)		
Fischer strain	0/10	10/10
Sprague-Dawley strain	0/5	3/5
Aflatoxin hepatocarcinomas (%)		
After 6 months	25	0
After 12 months	60	30
Aminopyrine demethylase (μg/h)	305 ± 25	480 ± 60
Benzopyrene hydroxylase (U)	100 ± 10	180 ± 20

[a] From (164).

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nitrite and nitrate on secondary and tertiary amines, such as dimethylamine (33) and aminopyrine (73, 99). The effect of the vitamin is primarily on the nitrosation reaction (5, 138), but it also inhibits the bacterial mutagenesis of the direct-acting carcinogen N-methyl-N'-nitronitrosoguanidine (MNNG) (79, 80) and decreases its damage to mouse gastric cell DNA (111).

VITAMIN A Animals with retinoid deficiency exhibit enhanced susceptibility to carcinogens and human epidemiological studies (14) lend support to these observations. Lung cancer induced in rats by 3-methylcholanthrene was increased by inadequate vitamin A (140, 143), although vitamin A deficiency suppressed the induction of colon tumors in rats given the direct-acting carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (139). Similarly, humans with a relatively low dietary intake of vitamin A had a higher incidence of lung cancer when matched for smoking habits. Administration of vitamin A and its synthetic analogues decreased the incidence of chemically induced tumors in respiratory tract (167), skin (17), mammary tissue (76), bladder (77), and colon (145). The mechanism of action is not understood, but it is unlikely to involve metabolic generation of ultimate carcinogens since the vitamin was active even when administered after completion of treatment with the carcinogen (17, 76, 77, 181). Possibly, the retinoids prevent the progression of premalignant states to cancer and this is related to the role of the vitamin in the control of normal differentiation of epithelial tissue.

Many other examples of the effects of diet on spontaneous and experi-

mental carcinogenesis are to be found in the recent review by Newberne et al (144).

Nutrition and Atherosclerosis

It has been suggested (18) that environmental mutagens in the circulating blood may be activated by the microsomal MFO enzymes present in the wall of the aorta and other vessels (98) to initiate somatic cell mutations and produce subsequent atherosclerotic lesions. Treatment of chickens with benzo(a)pyrene or 7,12-dimethylbenz(a)anthracene increases the number and rate of development of aortic plaques (3). The hyperlipidemia/hypercholesteremia and high fat/cholesterol diets associated with cardiovascular disease could lead to changes in microsomal lipids, decoupling of the MFO (184), and enhanced autoxidation resulting in increased somatic cell mutations.

Nutrition and Therapeutics

The recommended allowances for various nutrients made by government agencies are generally those amounts that will maintain normal healthy individuals free from deficiency. They seldom take into account the effects of disease or the iatrogenic effects of medical treatment. There is now an extensive literature indicating that drugs may impair the absorption of nutrients or increase requirements by affecting pathways of intermediary metabolism (59). Oral contraceptive steroids induce riboflavin deficiency (169); isoniazid (183), penicillamine (4), and oral contraceptive progestogens (1) lead to pyridoxine deficiency; long-term therapy with anti-convulsants result in folate deficiency (118); and *p*-aminosalicylate, oral contraceptives, and smoking decrease the plasma levels of vitamin B_{12} by impairing its absorption or increasing its utilization in enzyme induction or the detoxication of cyanide (59).

It is to be regretted that the interrelationships of drugs and nutrition in the treatment of patients is not always accorded the attention its importance deserves (59).

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