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VITAMIN TOXICITY

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It is the best of times and the worst of times for vitamins. Through the use of modern instrumentation and techniques, research on vitamin functions has provided a mass of accurate data upon which the rational use and avoidance of toxicity should be based (1). Many physicians, however, are lacking in sound knowledge of nutrition and the sensible use of vitamin supplementation. Also, there is a growing therapeutic cult for pharmacological and "megavitamin" doses of vitamins for various diseases (2). A battle rages between legislators and the FDA concerning control of advertising of OTC vitamin preparations (3). The consumption of vitamins increases yearly in the USA and this may be one important factor contributing to the increased incidence of toxicity.

FAT-SOLUBLE VITAMINS

Vitamin A

Extensive articles testify to the toxicity of hypervitaminosis A (4–19). Ever since the curious syndrome of headache, vertigo, and diarrhea following ingestion of bear liver was noted by Arctic explorers in 1857, reports have continued to appear (4). Modern, sophisticated techniques have provided a wealth of detailed data but the exact pathogenesis of toxicity remains obscure.

There is a tendency to associate toxicity with membrane phenomena. Small amounts of vitamin A are essential to maintain stability by providing cross-linking between the lipid and protein of the membrane. Large amounts of vitamin A combine with membrane lipoprotein and then with an exogenous protein to lyse red blood cells (20, 21).

A retinol-binding protein that has an important role in transport has been characterized. It has been suggested that clinical toxicity results in hypervitaminosis A when the amount of retinol binding protein is insufficient to bind and the cell membrane is exposed to unprotected vitamins (22).

This is also true for fibroblastic membranes and for intracellular particles and the degradation of cartilage matrix in vitro (23, 24). The mechanism of increased

cerebrospinal fluid pressure so characteristic of vitamin A toxicity remains unresolved but one wonders whether this may not be related to an altered membrane function in the choroid plexus (25, 26). Recent studies in animals have elaborated on this issue (27, 28).

Normally vitamin A is not found in the urine. Yet, in lipoid nephrosis and glomerulonephritis, increased blood levels are found and such patients are intolerant to ordinary doses (29). The mechanism may be related to a carrier and storage disturbance caused by endogenous renal dysfunction. The anorexia, skin dryness, nausea, headache, and other symptoms seen in advanced renal disease may be related to this high serum vitamin A level (30).

Chronic hypervitaminosis A results in a cirrhotic-like liver syndrome including portal hypertension. Liver biopsy shows typical lesions (31). Alcoholic liver cirrhosis may also be associated with vitamin A (32). A detailed study of the microanatomy of the liver in hypervitaminosis A in man and the rat is available (33). Special studies indicate storage of vitamin A in fat storage cells in the perisinusoidal spaces (34).

Cases of hypercalcemia, bony changes, and premature epiphysial closure as a result of hypervitaminosis A continue to be reported (35–39). Older studies linked vitamin A with calcium and phosphorus metabolism although there is some question of contamination of the preparations with vitamin D (39). No clear explanation of the pathogenesis exists.

The tendency to treat acne vulgaris with large doses of vitamin A is attended by much clinical toxicity (18–39). Topical application is safer but still results in erythema and peeling (40, 41). Another therapeutic indication, childhood blindness, seldom produces benefit and contributes to toxicity (42).

There is considerable evidence of the teratogenic effects of vitamin A in the mouse, rat, hamster, and guinea pig. Malformations include cleft palate, fused ribs, spina bifida, meningocele, hydronephrosis, and heart and genitourinary abnormalities (43–46). A human case with congenital renal anomalies resulting in a salt-losing nephritis has been reported (47).

Interaction of vitamin A with vitamin E has been described by several authors (48, 49). A study in normal children showed no greater retention of vitamin A when vitamin E was simultaneously administered (50). On the other hand vitamin E enhances vitamin A utilization in rats. This suggests a degree of protection afforded by vitamin E (48).

Women taking oral contraceptives show an increased serum blood level of vitamin A (51, 52). The suggestion has been made that this could result in fetal abnormalities in women who become pregnant immediately after prolonged oral contraceptive therapy. However, a retrospective study of such women did not reveal increased incidence of birth defects (53).

Vitamin D

Among the fat-soluble vitamins, vitamin D, like A, is a cause of overt toxicity. In the past, therapy of arthritis with large and prolonged doses gave rise to the greatest incidence of overt toxicity, but there are now many such examples in routine

nutritional therapy, in infancy, in pregnancy, and in renal disease. All relate to calcium metabolism in all of its intricacies (54–58).

Recent advances in the metabolism of vitamin D and the chemistry and physiology of its metabolites contribute heavily to the understanding of its toxicity (59). There is a growing tendency to regard vitamin D as a hormone rather than as a vitamin. First of all under normal circumstances it is not a dietary requirement. Ultraviolet light converts the "prohormone" 7-dehydrocholesterol in the skin to cholecalciferol (vitamin, D_3). This enters the bloodstream and in the liver vitamin D_3 is metabolized to 25-OH D_3 which then is transported to the kidney where conversion to 1,25$(OH)_2$ D_3, 24,25$(OH)_2$ D_3, and 1,24,25$(OH)_3$ D_3 occurs. Little is known of the function of the latter two metabolites but 1,25$(OH)_2$ D_3 proceeds to bone where it influences both deposition and mobilization of calcium and to the intestine where it controls absorption of calcium.

Of interest to toxicologists is the fact that 25-hydroxylation of vitamin D is accomplished by the microsomal fraction of liver homogenates requiring an unidentified cytoplasmic factor (60, 61). Since the reaction is not inhibitied by carbon monoxide, this system is apparently different from the all-inclusive P450 microsomal metabolizing enzyme system of the liver. Suggestive experiments indicate that the rate of this metabolism is inversely related to the blood level of vitamin D_3. This offers some but not complete protection from overdoses. The system responsible for hydroxylation of 25-OH D_3 to 1,25$(OH)_2$ D_3 in the kidney is associated with the heavy mitochondrial homogenate fraction. It is dependent on oxygen, Mg^{2+}, and malate and is sensitive to carbon monoxide (62). The most important factor regulating the rate of this conversion is the level of blood calcium. High levels result in greater production of the less active metabolite 24,25$(OH)_2$ D_3; conversely, hypocalcemia results in high yields of 1,25$(OH)_2$ D_3 (63). A scheme whereby low blood calcium stimulates secretion of parathyroid hormones (PTHs), which in turn is responsible for the increased production of 1,25$(OH)_2$ D_3, has been proposed (59). Obviously in turn the higher level of 1,25$(OH)_2$ D_3 causes increased absorption of intestinal calcium which provides the inhibiting feedback loop for PTH secretion. Not all investigators accept this explanation (64). Nevertheless, calcium has the pivotal role in the production of the active metabolite.

The above metabolic scheme provides a veritable mecca for drug interaction, for antagonism and stimulation. An earlier observation showed that dactinomycin prevented the in vivo actions of vitamin D. This was presumed to be due to RNA synthesis. (65). It is now believed that the mechanism results from a depressed RNA protein synthesis upon which the rapid turnover rate of the 1-hydroxylase system of the kidney is dependent (66). In rats dactinomycin and cycloheximide inhibit the conversion of 25-OH D_3 to 1,25$(OH)_2$ D_3 (67). It might be supposed that vitamin D is necessary for the decalcification of bone by calcitonin. However, no such relationship has been found.

A consistent observation is that adrenal cortical steroids reduce the elevated serum calcium concentration found in hypervitaminosis D, sarcoidosis, and idiopathic hypercalcemia of infancy (69). The mechanism is associated with decreased intestinal calcium absorption. An enigma in this case is that hydrocortisone stimu-

lates vitamin D–dependent intestinal calcium-binding protein (70). In this regard puromycin has been reported to block calcium-binding protein and hence to decrease calcium absorption (71).

Another drug interaction involving intestinal absorption of calcium pertains to the ability of vitamin D_3 to cause increases in brush border alkaline phosphatase (72). The increase is blocked by cycloheximide, suggesting that vitamin D causes de novo synthesis of this enzyme.

Oddly, few drug interactions have been reported for vitamin D despite its tremendous potential in this regard. Hypoparathyroid patients require large doses of vitamin D to maintain plasma calcium concentrations; also, vitamin D–resistant hypoparathyroidism has been reported (73–74). These patients ideally should be treated either with a combination of PTH and vitamin D or with $1,25(OH)_2$ D_3.

An older observation is the amelioration of hypervitaminosis D with large doses of vitamin A (75). There does not seem to be a rational explanation for this phenomenon. It has been reported that epileptics on long-term phenytoin therapy have an increased incidence of rickets which is cured by vitamin D (76). Anticonvulsant osteomalacia also shows resistance to low doses of vitamin D_3 (76). More recently in a controlled study the frequency of epileptic seizures was reduced by the addition of vitamin D but not placebo to the usual anticonvulsant drugs (77, 78). The results were not related to serum calcium or magnesium. Another study reports that phenobarbital induces the conversion of vitamin D to more polar metabolites which are more rapidly excreted (79). This appears unlikely, because hydroxylation of vitamin D_3 is accomplished by a different microsomal liver enzyme system than that induced by phenobarbital. This lead needs in vivo work plus identification of the metabolites.

An interesting study relates coronary heart disease and a high blood cholesterol to the high vitamin D diet of a group of farmers (80). A follow-up investigation demonstrated that Vitamin D increases uptake of ^{32}Pi and its incorporation into phospholipids. There was also increase in hepatic cholesterol, total fat, and fatty acid content (81).

Previous studies indicated the propensity of hypervitaminosis D to induce nephrocalcinosis. Recent studies define the histological changes caused by vitamin D in rabbits(82). The exact mechanism remains obscure (83). In jirds, both hypothroidism and hyperthyroidism increased the sensitivity to renal damage to hypervitaminosis D. The pathology differed in the two sets of jirds, suggesting that mitochondria serve as temporary ion buffering systems which are stimulated in the hyperthyroid state (84). A peripheral study related the calcium-mobilizing effect of large doses of vitamin D_3 in anephric rats (85). High doses in rats receiving low calcium, normal vitamin D diets showed no change in serum calcium. On the other hand vitamin D–deficient rats showed variances in serum calcium when challenged with large doses of vitamin D_3. Removal of parathyroids and thyroid did not suppress this effect.

Mobilization of calcium from bone and various degrees of osteoporosis are characteristic features of hypervitaminosis D. Recent studies in mature thyroparathyroidectomized rats show that pharmacological doses of vitamin D produce

osteoclastic resorption, pronounced osteoblastic hyperplasia, and proliferation of chondrocytes in the epiphysial plates (68, 86). An ultrastructural evaluation of the effects of pharmacological doses of vitamin D and uremia on bone in the rat characteristically showed increased serum calcium levels, decreased metabolic activity of osteocytes, decreased activity of osteoblasts, and an increased number of osteoclasts (87). In tissue culture, the bone resorptive activity of 25-hydroxydihydrotachysterol (3) is easily demonstrated (88).

Infants are peculiarly susceptible to vitamin D. When the diet of infants is oversupplemented, as occurred in England in World War II, the incidence of infantile hypercalcemia rises. The syndrome consists of cerebral, cardiovascular, and renal damage (89). In particular, supravalvular aortic stenosis is associated with this syndrome (90). An experimental study in pregnant rabbits demonstrated that placental crossing of vitamin D does occur. The offspring showed a high incidence of supravalvular aortic stenosis similar to that seen in man (91).

Vitamin K

Relatively few toxic reactions have been reported for vitamin K in recent years. This is no doubt because it is not available in multivitamin preparations and because no fads have developed for therapeutic use other than specific indications. In addition, vitamin K is seldom administered for prolonged periods; therefore, chronic toxicity is seldom a factor.

The basis of toxicity of vitamin K has been well established as residing mainly in the water-soluble synthetic analogues of which menadione is a prime example. In contrast to phytonadione (vitamin K_1) the water-soluble derivatives act as oxidants in the body, causing red blood cell instability and hemolysis (92). The mechanism is presumed to be similar to that of the oxidant metabolites of primaquine which cause hemolysis in glucose-6-phosphate dehydrogenase–deficient individuals. The effect is more pronounced in the newborn and particularly premature infants (93). Not all agree with the exact mechanism (94). Vitamin K_3 (similar to menadione) oxidizes hemoglobin to methemoglobin in vitro (95).

Toxicity of menadione-like compounds is dose-dependent, especially in infants, and there are now adequate data to provide safe ranges of administration with therapeutic effect and absence of drug-induced hyperbilirubinemia and kernicterus (96). In general, vitamin K_1 is to be preferred in hemorrhagic disease of the newborn (97). However, it is to be noted that intramuscular injection of K_1 into the buttock may cause sciatic nerve paralysis (98).

Vitamin K, especially water-soluble forms, induces radiosensitization. This has been used to amplify the therapeutic effectiveness of X rays (99). Another observation supports the view that vitamin K increases the analgesic effect of opiates and salicylates. This interaction has not resulted in clinical toxicity but has been used therapeutically (100).

Few other drug interactions have been reported. Obviously, vitamin K will antagonize the anticoagulant effects of the coumarins. In this regard vitamin K_1 is used exclusively (101). Too large a dose may wipe out the anticoagulant effect for days. Some have even suggested a thrombotic effect (102).

Experimentally in chicks, actinomycin D antagonized the prothrombin formation induced by vitamin K. The antinomycin D doses used inhibited the synthesis of RNA in the liver. This suggests a genetic action of vitamin K in inducing RNA formation for the synthesis of clotting proteins (103).

An interesting observation demonstrated that vitamin K is a potent inhibitor of choline acetylase (104). If true, chronic administration should result in profound symptoms relative to the functions of acetylcholine. None have been reported. Perhaps this is because reserve stores of acetylcholine are so great that only very large doses for prolonged periods could cause deficiency. It would seem worthwhile to explore this observation further.

Vitamin E

No other vitamin has been as much the target of serious investigators on the one hand and cultists and fadists on the other as α-tocopherol. It continues to be the subject of studies in humans to determine its efficacy for such diverse conditions as heart disease, arteriosclerosis, progressive muscular dystrophy, habitual and threatened abortion, sterility in the male, retrolental fibroplasia, hemolytic disease of the newborn, and many other conditions (105–115). A recent study subjected 28 adults to 100 to 800 international units (IUs) of vitamin E daily for a period of three years. On the average, plasma α-tocopherol was elevated from the control of 650 μg/100 ml to 1340 μg/100 ml under treatment. No apparent toxicity was found but neither were there any objective health improvements. Half of the subjects said they "felt better." Perhaps the only significant finding was a corollary increase in plasma vitamin A level (116).

The difficulty in dealing with vitamin E is that its exact role in metabolism remains conjectural. Most investigators agree that it has antioxidant function but do not understand its role. Many attempts have been made to assign vitamin E as a general protector of structural lipoproteins or of oxidizable lipid components of enzymes. More recently the discovery that selenium is an essential component of glutathione peroxidase, which destroys H_2O_2 and organic hydroperoxides and thus protects against oxidative damage to cell membranes, has implicated vitamin E. In this system the latter is assigned the role of preventing the formation of liquid hydroperoxides (117). In chicks it can be shown that both selenium and vitamin E are essential nutrients for protection against exudative diathesis resulting from increased capillary permeability (118). If this is an important role of vitamin E, how can toxicity be predicted on this basis? Can it be reasonably assumed that an excess presence of an antioxidant ought not to be toxic since it is only protective and is not an actual component of the reaction? It would appear to be so from the lack of toxicity of high doses of vitamin E in many studies (105, 110). On the other hand, in the rat diets high in selenium, vitamin E, and ethyl alcohol showed increased fat deposition in the liver as compared with controls (119).

In man the only significant toxicity seems to be allergy to vitamin E aerosol deodorant (120). In lower animals many toxicities have been reported, but the doses achieved have been much higher. Growth rate, thyroid function, mitochondrial respiration rate, bone calcification, and hematocrit are depressed, and reticulocytosis is increased in the chick (121, 122). Testicular atrophy leading to decreased spermato-

genesis but not endocrine functions in the hamster has been reported (123). Secondary sex characteristics are slow to develop in roosters subjected to high doses of vitamin E (124). A teratogenic tendency has been reported in mice (125). Vitamin E or other antioxidants (vitamin C) injected into fertile chicken eggs causes lethality (126).

Among the few drug interactions reported for vitamin E are the increased requirements for vitamins A and D (127). Whether or not this is of clinical significance remains to be confirmed. According to one clinical study the maintenance dose of digitalis should be reduced by 50% in the presence of high doses of vitamin E (128). Oral contraceptives lower the serum level of α-tocopherol and may promote a deficiency (129).

An interesting approach to the reduction of toxicity of the alkyl mercurials is to take advantage of the stabilizing effect of vitamin E on membranes. In tissue culture of rat cerebella DL-α-tocopherol acetate showed considerable protection against the inhibition of development by methylmercuric chloride of nerve fibers, glial cells, and fibroblasts (130). Protection against ozone pulmonary epithelial damage, maintenance of embroynic growth, and enhancement of in vitro immune response are miscellaneous actions of vitamin E recently reported (131–133). It has been known for some time that vitamin E can protect experimentally against carbon tetrachloride hepatotoxicity, but recent studies show that the mechanism is not one of prevention of the perioxidation of this chemical (134).

WATER-SOLUBLE VITAMINS

Thiamin

Aside from hypersensitivity reactions, few instances of toxicity of thiamin have been reported in the recent literature. Numerous reports of thiamin toxicity have appeared in the literature of the forties and fifties primarily showing effects on the cardiovascular system and nervous system. Effects of excess thiamin on the nervous system include nervousness, convulsions, headache, weakness, trembling, and neuromuscular paralysis. Reports of thiamin toxicity on the cardiovascular system include rapid pulse, anaphylactic shock, peripheral vasodilatation, cardiac arrhythmias, and edema (135–141). The decreased use of thiamin, especially parenterally, for various functional disorders appears to have resulted in a reduction of toxic reactions.

Niacin

Reports of niacin toxicity began appearing in the literature coincident with its use in the treatment of schizophrenia, as part of what has become known as the orthomolecular psychiatry therapeutic regimen. Toxic effects of niacin observed in this treatment can be summarized as follows: flushing, pruritus, skin rash, heartburn, nausea, vomiting, diarrhea, ulcer activation, abnormal liver function, hypotension, tachycardia, fainting, and hyperglycemia (142).

The most common serious toxicities reported for niacin are abnormal liver function and jaundice (143–150). Niacin is used physiologically in the formation of the

pyridine nucleotides DPN (diphosphopyridine nucleotide or NAD) and TPN (triphosphopyridine nucleotide or NADH). These nucleotides act as coenzymes for a number of dehydrogenase enzymes in oxidation-reduction reactions, which serve to initiate the transfer of reducing equivalents from metabolites to DPN or TPN. Many of the dehydogenases are found in the liver, and alteration of their activity by large amounts of niacin may explain the reports of abnormal liver function.

Niacin has also demonstrated activity on the cardiovascular system. A transient vasodilatory effect, thought to be a direct action on small blood vessels, is a well-known action of nicotinic acid. In examination of its possible use in coronary heart disease, the Coronary Drug Project Research Group conducted a study on the effectiveness of niacin to reduce the incidence of a second myocardial infarction. This study demonstrated very little benefit, but considerable toxicity, showing a greater incidence of atrial fibrillation and other cardiac arrhythmias in the niacin group than in the placebo control (151).

Miscellaneous toxicities of niacin include skin changes with alterations of color and pigmented hyperkeratosis (152, 153).

Riboflavin

Riboflavin has demonstrated very little toxicity. However, in view of the current surge in cancer research, several interactions of riboflavin with other compounds may be of interest. Riboflavin deficiency has been shown to stimulate azo dye carcinogenesis and inhibit tumor growth in man and animals (154, 155). Riboflavin has also been shown to inhibit the uptake of methotrexate into neoplastic cells (154), and to have a slight inhibitory effect in 3,4-benzopyrene-induced skin tumors (156).

Considering the role of riboflavin as a coenzyme in the forms flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) and the dependence of folic acid metabolism on a flavin cofactor, there may be an interaction with the flavins and neoplasias yet unknown that may aid in cancer research.

Pyridoxine

Pyridoxine causes convulsive disorders due both to an excess of the vitamin or to a deficiency state (156–158). The problem as to how the convulsant effect of the vitamin is manifested is also demonstrated with the interaction of pyridoxine and the antituberculosis agent isonicotinic acid hydrazide (INH) or isoniazid. One of the side effects of isoniazid therapy is a convulsive disorder, which may or may not be due to pyridoxine deficiency or to the drug itself. It has been generally believed that these convulsive disorders were not due to pyridoxine deficiency; however, some reports have indicated that patients on isoniazid therapy who developed seizures were quickly stabilized by the administration of pyridoxine (159–161). Chemically, it is known that the two agents, pyridoxine and isoniazid, will react together to form a hydrozone which is excreted, eliminating the pyridoxine from the system (162). It is also known that the pyridoxal hydrozones are 10 to 100 times more potent as convulsants than are the parent hydrazides (163, 164). A recent report describes the use of pyridoxine in a case of hydrazine-induced coma (165).

Interactions of pyridoxine with other agents have also been reported. Among these is the ability of pyridoxine to reverse the therapeutic effect of levodopa used

in parkinsonism (166). The mechanism of this interaction is apparently due to the increased pyridoxine acting as a stimulator in its coenzyme role in the decarboxylation of dopa to dopamine in the periphery, resulting in less dopa to exert a central nervous system (CNS) effect.

Other toxic effects of pyridoxine have been reported and are adequately described elsewhere (158). Examples of other effects of pyridoxine not covered in this review include the interactions of pyridoxine with oral contraceptives (167), the antagonism of quinidine-induced atrial contractions (168), and the antagonism of penicillamine used in the treatment of Wilson's disease (169).

Folic Acid

Folic acid toxicity has been reported in the CNS and the renal system. Concerning the CNS, folate toxicity deals primarily with epileptic patients and interactions with phenytoin (diphenylhydantoin, DPH). Considerable controversy exists as to whether or not the fit-frequency of epileptics is increased or decreased with the administration of folic acid. Several reports indicate that folic acid therapy causes no change in the fit-frequency of the majority of patients on anticonvulsant drugs (170–175). Others report an increase in the fit-frequency (176–178). A direct convulsant effect of folic acid has also been demonstrated experimentally (179, 180). It seems most likely that the reports showing a decrease in DPH levels and a decrease of DPH effect due to the coadministration of folic acid would favor the reports of increase in fit-frequency with folate (181, 182). Possible explanations of this effect have been proposed. One theory suggests that folic acid alters the metabolism of DPH to an unknown route resulting in rapid inactivation of the anticonvulsant agent (181). Other theories also concern metabolism but suggest an alteration of existing pathways of brain amines causing the convulsant effect (178, 183). Either of these theories could explain the convulsant effect of folic acid.

The other major area of folic acid–induced toxicity is in the area of renal cell hypertrophy. In these studies the effect of large doses of folic acid given to experimental animals caused an immediate increase in DNA synthesis and total protein content along with hypertrophy and hyperplasia of the kidney epithelial cells (184–186). It is suggested that the mechanism for this phenomenon is a regenerative process of the epithelial cells due to folate deposition in the tubule (187–189).

Other miscellaneous toxicities of folic acid have also been controversial. Mental changes, sleep disturbances, gastrointestinal upset, malaise, irritability, and excitability in normal volunteers have been reported (190). In contrast, numerous others have shown no effects of folic acid in normal subjects (191–193).

Ascorbic Acid

Ascorbic acid recently has received considerable exposure in the literature concerning its use as a prophylactic measure against the common cold. The effectiveness of this regimen has yet to be definitively confirmed or disproven (194). There has been very little known concerning the toxicity of ascorbic acid. Recently, it has been demonstrated that large doses of ascorbic acid may cause diarrhea and acidification of the urine causing the precipitation of cystine or oxalate stones in the urinary tract (195). Also, it has been shown that if large doses of ascorbic acid are taken during

pregnancy, the infant may develop scurvy when removed from this high ascorbic acid environment by birth (195).

There have been interactions of ascorbic acid with other agents reported. Ascorbic acid has been shown to shorten prothrombin time when the patient is maintained on heparin or warfarin (196). Ascorbic acid has also recently been shown to destroy substantial amounts of vitamin B-12 when it is ingested with food (197, 198). This could develop into a very serious problem since many people use high dose ascorbic acid therapy to prevent the common cold. Should the person continue to destroy vitamin B-12 with this type of self-medication over a period of years the development of megaloblastic anemia may be a potential hazard. Ascorbic acid in a dose of 8.0 g for 3 to 7 days caused sustained uricosuria associated with a fall in uric acid of 1.2–3.1 mg/dl. Possibly, this could cause precipitation of gouty arthritis or renal calculi in susceptible persons (199).

CONCLUSIONS

Excessive and indiscriminate use of vitamins is associated with severe and incapacitating toxicities. This is especially true of vitamins A and D, particularly when used in larger doses, but even in special circumstances when administered in supplemental doses. The water-soluble vitamins have been virtually nontoxic when used in ordinary doses. The advent of medical fadism in the form of "megavitamin" doses has led to serious toxicities in the case of niacin and possibly ascorbic acid. Even folic acid may be toxic in exceptional circumstances. Vitamin E, even though it has been most used in so-called megavitamin doses for a large variety of disorders, has had very little reported toxicity.

There is now advanced and well-documented information of the metabolic role of vitamins in nutrition and in disease. It seems inappropriate that self-medication by the public on the one hand and pharmacological and megavitamin doses of vitamins by the medical profession on the other are allowed to continue indiscriminately without some measure of control.

Literature Cited

1. Sebrell, W. H. Jr., Harris, R. S., eds. 1971. *The Vitamins.* Vols. I–VII. New York & New London: Academic
2. Am. Psychiatr. Assoc. July 1973. *Megavitamin and Orthomolecular Therapy in Psychiatry, Task Force Rep. 7,* Washington DC
3. Drug Res. Rep. February 25, 1976. *"The Blue Sheet."* 19: No. 8
4. Knudson, A. G. Jr., Rothman, P. E. 1953. Hypervitaminosis A. *Am. J. Dis. Child.* 85:316–34
5. Wolf, G. 1969. Symposium on the metabolic function of vitamin A. *Am. J. Clin. Nutr.* 22:897–1138
6. Roels, O. A. 1966. Present knowledge of vitamin A. *Nutr. Rev.* 24:129–32
7. Persson, B., Tunell, R., Ekengren, K. 1965. Chronic vitamin A intoxication during the first half year of life. *Acta Paediatr. Scand.* 54:49–60
8. Bieri, J. G. 1974. Fat soluble vitamins in the eighth revision of the RDA. *J. Am. Diet. Assoc.* 64:171–74
9. Bauernfield, J. C., Newmark, H., Brin, M. 1974. Vitamins A and E nutrition via intramuscular or oral route. *Am. J. Clin. Nutr.* 27:234–53
10. Soler-Bechara, J., Soscia, J. L. 1963. Chronic hypervitaminosis A. *Arch. Int. Med.* 112:462–66
11. Muenter, M. D., Perry, H. O., Ludwig, J. 1971. Chronic vitamin A intoxication in adults. *Am. J. Med.* 50:129–36

12. Mickelsen, O., Yary, M. G. 1968. In *Modern Nutrition in Health and Disease*, ed. M. G. Wohl, R. S. Goodhart, 473–74. Philadelphia: Lea & Febiger
13. Marks, J. 1974. The fat-soluble vitamins in modern medicine. *Vitam. Horm. NY* 32:131–54
14. Jennekens, F. G. I., VanVeelen, C. W. M. 1966. Hypervitaminose A. *Presse Med.* 74:2925–28
15. Goodhart, R. S. 1968. See Ref. 12, pp. 213–27
16. DeLuca, H. F., Suttie, J. W., eds. 1970. *The Fat Soluble Vitamins.* Madison: Univ. Wis. Press
17. Am. Acad. Pediatr. 1974. The use and abuse of vitamin A. *Nutr. Rev.* 32: Suppl., 41–43
18. Berger, S. S., Roels, O. A. 1965. Hypervitaminosis A. *Am. J. Clin. Nutr.* 16:265–69
19. Am. Acad. Pediatr. 1971. The use and abuse of vitamin A. *Pediatrics* 48: 655–56
20. Dingle, J. T., Glauert, A. M., Daniel, M., Lucy, J. A. 1962. Vitamin A and membrane systems. 1. The action of the vitamin on the membranes of cells and intracellular particles. *Biochem. J.* 84:76 pp. (Abstr.)
21. Lucy, J. A., Dingle, J. T. 1962. Vitamin A and membrane systems. 2. Membrane stability and protein–vitamin A–lipid interactions. *Biochem. J.* 84:76 pp. (Abstr.)
22. Smith, F. R., Goodman, D. S. 1976. Vitamin A transport in human vitamin A toxicity. *N. Engl. J. Med.* 294:805–8
23. Fell, H. B., Dingle, J. T. 1963. Studies on the mode of action of excess of vitamin A. *Biochem. J.* 87:403–8
24. Dingle, J. T., Lucy, J. A. 1965. Vitamin A, carotenoids, and cell function. *Biol. Rev.* 40:422–61
25. Maddux, G. W., Foltz, F. M., Nelson, S. R. 1974. Effect of vitamin A on intracranial pressures and brain water in rats. *J. Nutr.* 104:478–82
26. Morrice, G., Havener, W. H., Kapetansky, F. 1960. Vitamin A intoxication as a cause of pseudotumor cerebric. *J. Am. Med. Assoc.* 173:1802–5
27. Eaton, H. D. 1969. Chronic bovine hypo- and hypervitaminosis A and cerebrospinal fluid pressure. *Am. J. Clin. Nutr.* 22:1070–80
28. Frier, H. I., Gorgacz, E. J., Hall, R. C., Gallina, A. M., Rousseau, J. E., Eaton, H. D., Nielsen, S. W. 1974. Formation and absorption of cerebrospinal fluid in adult goats with hypo- and hypervitaminosis A. *Am. J. Vet. Res.* 35:45–55
29. Kagan, B. M., Thomas, E. M., Jordan, D. A., Abt, A. F. 1950. Serum vitamin A and total plasma lipid concentrations as influenced by oral administration of vitamin A to children with nephrotic syndrome. *J. Clin. Invest.* 29:141–45
30. Yatzidis, H., Digenis, P., Fountas, P. 1975. Hypervitaminosis A accompanying advanced chronic renal failure. *Br. Med. J.* 3:352–53
31. Russell, R. M., Boyer, J. L., Bagheri, S. A., Hruban, Z. 1974. Hepatic injury from chronic hypervitaminosis A resulting in portal hypertension and ascites. *N. Engl. J. Med.* 291:435–40
32. Muenter, M. D. 1974. Hypervitaminosis A. *Ann. Intern. Med.* 80:105–6
33. Lane, B. P. 1968. Hepatic microanatomy in hypervitaminosis A in man and rat. *Am. J. Pathol.* 53:591–98
34. Kobayashi, K., Takahasi, Y., Shibusaki, S. 1973. Cytological studies of fat-storing cells in the liver of rats given large doses of vitamin A. *Nature New Biol.* 243:186–88
35. Frame, B., Jackson, C. E., Reynolds, W. A., Umphrey, J. E. 1974. Hypercalcemia and skeletal effects in chronic hypervitaminosis A. *Ann. Intern. Med.* 80:44–48
36. Jowsey, J., Riggs, B. L. 1968. Bone changes in a patient with hypervitaminosis A. *J. Clin. Endocrinol. Metab.* 28:1833–35
37. Fisher, G., Skillern, P. G. 1974. Hypercalcemia due to hypervitaminosis A. *J. Am. Med. Assoc.* 227:1413–14
38. Pease, C. N. 1962. Focal retardation and arrestment of growth of bones due to vitamin A intoxication. *J. Am. Med. Assoc.* 182:980–85
39. Nieman, C., Klein Obbink, H. J. 1954. The biochemistry and pathology of hypervitaminosis A. *Vitam. Horm. NY* 12:69–100
40. Bradford, L. G., Montes, L. F. 1974. Topical application of vitamin A in Acne vulgaris. *South. Med. J.* 67: 683–87
41. Kligman, A. M., Mills, O. H., Leyden, J. J. 1974. Acne vulgaris—a treatable disease. *Postgrad. Med.* 55:99–105
42. Olson, J. A. 1972. The prevention of childhood blindness by the administration of massive doses of vitamin A. *Isr. J. Med. Sci.* 8:1199–1206
43. Murakami, U., Kameyama, Y. 1965. Malformations of the mouse fetus cause by hypervitaminosis A of the mother

during pregnancy. *Arch. Environ. Health* 10:732–41
44. Robens, J. F. 1970. Teratogenic effects of hypervitaminosis A in the hamster and the guinea pig. *Toxicol. Appl. Pharmacol.* 16:88–99
45. Lopes, R. A., Valeri, V., Iucif, S., Azoubel, R., Campos, G. M. 1974. Effect of hypervitaminosis A on the testes of the rat during lactations. *Int. J. Vitam. Nutr. Res.* 44:159–66
46. Nolen, G. A. 1969. Variations in teratogenic response to hypervitaminosis A in three strains of the albino rat. *Food Cosmet. Toxicol.* 7:209–14
47. Bernhardt, I. B., Dorsey, D. J. 1974. Hypervitaminosis A and congential renal anomalies in human infant. *Obstet. Gynecol.* 43:750–55
48. Bieri, J. G. 1973. Effect of excessive vitamins C and E on vitamin A status. *Am. J. Clin. Nutr.* 26:382
49. Bauernfield, J. C., Newmark, H., Brin, M. 1974. Vitamin A and E nutrition via intramuscular and oral route. *Am. J. Clin. Nutr.* 27:234–53
50. Kusin, J. A., Reddy, V., Sivakumar, B. 1974. Vitamin E supplements and the absorption of a massive dose of vitamin A. *Am. J. Clin. Nutr.* 27:774–76
51. Briggs, M., Bennun, M. 1972. Steroid contraceptives and plasma carotenoids. *Contraception* 6:275–80
52. Gal, I., Parkinson, C., Craft, I. 1972. Effects of oral contraceptives on human plasma vitamin A levels. *Br. Med. J.* 2:436–38
53. Wild, J., Schorah, C. J., Smithells, R. W. 1974. Vitamin A, pregnancy, and oral contraceptives. *Br. Med. J.* 1:57–59
54. Comm. Nutrit. Misinf. 1975. Hazards of overuse of vitamin D. *Nutr. Rev.* 33:61–62
55. Mickelsen, O., Yang, M. G. 1968. See Ref. 12, pp. 474–75
56. Yendt, E. R., DeLuca, H. F., Garcia, D. A., Cohanim, M. 1970. See Ref. 16, pp. 125–58
57. Medical Letter. 1974. New developments in pharmacology of vitamin D. *Med. Lett.* 16:15–16
58. Food Nutr. Board, Div. Biol. Sci., Assem. Life Sci., Natl. Res. Counc. 1975. Hazards of overuse of vitamin D. *Am. J. Clin. Nutr.* 28:512–13
59. Omdahl, J. L., DeLuca, H. F. 1973. Regulation of vitamin D metabolism and function. *Physiol. Rev.* 53:327–92
60. Pondron, G., DeLuca, H. F. 1969. Metabolites of vitamin D_3 and their biological activity. *J. Nutr.* 99:157–67
61. Bhattacharyya, M. H., DeLuca, H. F. 1973. The regulation of rat liver calciferol-25-hydroxylase. *J. Biol. Chem.* 248:2969–73
62. Fraser, D. R., Kodicek, E. 1970. Unique biosynthesis by kidney of a biologically active vitamin D metabolite. *Nature* 228:764–66
63. Boyle, I. T., Gray, R. W., DeLuca, H. F. 1971. Regulation of calcium of in vivo synthesis of $1,25.(OH)_2D_3$ and $21,25,(OH)_2 O_3$. *Proc. Natl. Acad. Sci. USA* 68:2131–34
64. Larkins, R. G., Colston, K. W., Galante, L. S., MacAuley, S. J., Evan, I. M. A., MacIntyre, I. 1973. Regulation of vitamin D metabolism without parathyroid hormone. *Lancet* 2:289–91
65. Zull, J. E., Cz rnowska-Misztal, E., DeLuca, H. F. 1966. On the relationship between vitamin D action and actinomycin-sensitive processes. *Proc. Natl. Acad. Sci. USA* 55:177–84
66. Tanaka, Y., DeLuca, H. F., Omdahl, J., Holick, M. F. 1971. Mechanism of action of 1,25-dihydroxycholecalciferol on intestinal calcium transport. *Proc. Natl. Acad. Sci. USA* 68:1286–88
67. Gray, R. W., DeLuca, H. F. 1971. Metabolism of 25-hydroxycholecalciferol and its inhibition by actinomycin D and cycloheximide. *Arch. Biochem. Biophys.* 145:276–82
68. Morii, H., DeLuca, H. F. 1967. Relationship between vitamin D deficiency, thyrocalcitonin and parathyroid hormone. *Am. J. Physiol.* 213:358–62
69. Kimberg, D. V., Baerg, R. D., Gershon, E., Graudusius, R. T. 1971. Effect of cortisone treatment on the active transfer of calcium by the small intestine. *J. Clin. Invest.* 50:1309–21
70. Eilon, G., Mor, E., Karaman, H., Menczel, J. 1971. In *Cellular Mechanisms for Calcium Transfer and Homeostasis,* ed. G. Nichols Jr., R. H. Wassemian, 501–2. New York: Academic
71. Bronner, F., Maddaiah, V. T. 1969. In *Symposium on Membrane Proteins,* 134–36. New York: Little, Brown
72. Norman, A. W., Mircheff, A. K., Adams, T. H., Spielvogel, A. 1970. Studies on the mechanism of action of calciferol. *Biochem. Biophys. Acta* 215:348–59
73. Ramussen, H., DeLuca, H., Arnaud, C., Hawker, C., von Stedingk, M. 1963. The relationship between vitamin D and parathyroid hormone. *J. Clin. Invest.* 42:1940–46

74. Pak, C. Y. C., DeLuca, H. F., Chavez de los Rios, J. M., Suda, T., Ruskin, B., Delea, C. S. 1970. Treatment of vitamin D–resistant hypoparathyroidism with 25-hydroxycholecalciferol. *Arch. Intern. Med.* 126:239–47
75. Clark, I., Bassett, C. A. L. 1962. The amelioration of hypervitaminosis D in rats with vitamin A. *J. Exp. Med.* 115:147–55
76. Kruse, R. 1968. Osteopathien bein antiepilepthisches langzeittherapie. *Monatsschr. Kinderheilkd.* 116:378–81
77. Rowe, D. J. F., Stamp, T. C. B. 1974. Anticonvulsant osteomalacia and vitamin D. *Br. Med. J.* 1:392
78. Christiansen, C., Rodbro, P., Sjo, O. 1974. Anticonvulsant action of vitamin D in epileptic patient? A controlled pilot study. *Br. Med. J.* 2:258–59
79. Hahn, T. J., Birge, S. J., Scharp, C. R., Avioli, L. V. 1972. Phenobarbital-induced alterations in vitamin D metabolism. *J. Clin. Invest.* 51:741–48
80. Dalderup, L. M., Stockmann, V. A., Rechsteiner de Vos, H., Slikke, G. T., van der 1965. Survey on coronary heart disease in relation to diet in physically active farmers. *Voeding* 26:245–75
81. Dalderup, L. M. 1968. Vitamin D, cholesterol, and calcium. *Lancet* 1:645
82. Arya, S. N., Das, G. C. 1973. Nephropathy after acute hypervitaminosis D. *J. Indian Med. Assoc.* 61:503–6
83. Avioli, L. V. 1972. Vitamin D, the kidney and calcium homeostasis. *Kidney Int.* 2:241–46
84. Newman, R. J. 1973. The effects of thyroid hormone on vitamin D induced nephrocalcinosis. *J. Pathol.* 111:13–21
85. Pavlovitch, H., Garabedian, M., Balsan, S. 1973. Calcium-mobilizing effect of large doses of 25-hydroxycholecalciferol in anephric rats. *J. Clin. Invest.* 52:2656–59
86. Weisbrode, S. E., Capen, C. C., Nagode, L. A. 1973. Fine structural and enzymatic evaluation of bone in thyroparathyroid-ectomized rats receiving various levels of vitamin D. *Lab. Invest.* 28:29–37
87. Weisbrode, S. E., Capen, C. C., Nagode, L. A. 1974. Ultrastructural evaluation of the effects of vitamin D and uremia on bone in the rat. *Am. J. Pathol.* 76:359–76
88. Trummel, C. L., Raisz, L. G., Hallick, R. B., DeLuca, H. F. 1971. 25-hydroxydihydrotachysterol$_3$-stimulation of bone resorption in tissue culture. *Biochem. Biophys. Res. Commun.* 44:1096–1101
89. Seelig, M. S. 1969. Vitamin D and cardiovascular, renal and brain damage in infancy and childhood. *Ann. NY Acad. Sci.* 147:537–82
90. Taussig, H. B. 1966. Possible injury to the cardiovascular system from vitamin D. *Ann. Intern. Med.* 65:1195–1200
91. Friedman, W. F., Roberts, W. C. 1966. Vitamin D and the supravalvular aortic stenosis syndrome. *Circulation* 34: 77–86
92. Finkel, M. J. 1961. Vitamin K, and the vitamin K analogues. *Clin. Pharmacol. Ther.* 2:794–814
93. Vest, M. 1966. Vitamin K in medical practice: Pediatrics. *Vitam. Horm. NY* 24:649–63
94. Harley, J. D., Robin, H. 1962. Haemolytic activity of vitamin K_3 evidence for a direct effect on cellular enzymes. *Nature* 193:478–80
95. Broberger, O., Ernster, L., Zetterstrom, R. 1960. Oxidation of human hemoglobin by vitamin K_3. *Nature* 188: 316–17
96. Owens, C. A. Jr. 1971. In *The Vitamins: Chemistry, Physiology, Pathology, Methods*, ed. W. H. Sebrell, R. S. Harris, 505–10. New York: Academic
97. Shirger, A., Spittell, J. A. Jr., Ragan, P. A. 1959. Small doses of vitamin K_1 for correction of reduced prothrombin activity. *Proc. Staff Meet. Mayo Clin.* 34:453–58
98. Willi, H., Vest, M., Kaser, O. 1959. Das hamatologische verhalten der fruhgeborenen unter der einwirkung hoher und niederer dosen von vitamin K_1 (Konakion). *Gynaecologia* 147:481–92
99. Deutsch, E. 1966. Vitamin K in medical practice: adults. *Vitam. Horm. NY* 24:665–80
100. Jurgens, R. 1958. Zur analgetischen wirkung von 1,4,naphthochinonen. *Arzneim. Forsch.* 8:25–28
101. Shoshkes, M., Willner, M., Chiong, R., Palmeri, R. 1962. Oral vitamin K_1 (Phytonadione) as prophylaxis for hypoprothrombinemia in full-term and premature infants. *J. Newark Beth Isr. Hosp.* 13:95–102
102. Geill, T., Ling, E., Darn, H., Sondergaard, E. 1954. Studies on the efficiency of vitamin K_1 in small doses as antidote against anticoagulants of the dicumerol type. *Scand. J. Clin. Lab. Invest.* 6:203–9
103. Olson, R. E. 1964. Vitamin K induced

prothrombin formation: Antagonism by actinomycin D. *Science* 145:926–28
104. Wang, D. H., Koblick, D. C. 1959. Effects of menadione on active sodium transport in isolated frog skin. *Am. J. Physiol.* 196:1112–14
105. Murphy, B. F. 1974. Hypervitaminois E. *J. Am. Med. Assoc.* 227:1381
106. Marks, J. 1962. Critical appraisal of the therapeutic value of αtocopherol. *Vitam. Horm. NY* 20:573–98
107. Briggs, M. H. 1974. Vitamin E in clinical medicine. *Lancet* 1:220
108. Lancet. 1974. Vitamin E in clinical medicine. *Lancet* 1:18–19
109. Berneske, G. M., Butson, A. R. C., Gauld, E. N., Levy, D. 1960. Clinical trial of high dosage vitamin E in human muscular dystrophy. *Can. Med. Assoc. J.* 82:418–21
110. Roels, O. A. 1967. Present knowledge of vitamin E. *Nutr. Rev.* 25:33–37
111. Symp. Vitam. E Metab. 1962. *Vitam. Horm. NY* 20:373–660
112. Anderson, T. W. 1974. Vitamin E in angina pectoris. *Can. Med. Assoc. J.* 110:401–6
113. Weber, H. U. 1973. Hazards of vitamin excess. *Am. J. Clin. Nutr.* 26:1043–44
114. "Therapy" with vitamin E. 1960. *Nutr. Rev.* 18:227–28
115. Olson, R. E. 1973. Vitamin E and its relation to heart disease. *Circulation* 48:179–84
116. Farrell, P. M., Bieri, J. G. 1975. Megavitamin E supplementation in man. *Am. J. Clin. Nutr.* 28:1381–86
117. Holkstra, W. G. 1975. Biochemical function of selenium and its relations to vitamin E. *Fed. Proc.* 34:2083–88
118. Combs, G. F. Jr., Noguchi, T., Scott, M. L. 1975. Mechanisms of action of seleniums and vitamin E in infection of biological membranes. *Fed. Proc.* 34:2090–2100
119. Levander, O. A., Morris, V. C., Higgs, D. J., Varma, R. N. 1973. Nutritional interrelationships among vitamin E, selenium, antioxidants, and ethyl alcohol in the rat. *J. Nutr.* 103:536–42
120. Aeling, J. L., Panagotacos, P. J., Andreozzi, R. J. 1973. Allergic contact dermititis to vitamin E aerosol deodorant. *Arch. Dermatol.* 108:579–80
121. March, B. E., Coates, V., Biely, J. 1968. Reticulocytosis in response to dietary antioxidants. *Science* 164:1398–99
122. March, B. E., Wong, E., Seier, L., Sim, J., Biely, J. 1973. Hypervitaminosis E in the chick. *J. Nutr.* 103:371–77
123. Czyba, J. C. 1960. Effets de l'hypervitaminose E sur le testicule du hamster dore. *C.R. Soc. Biol.* 160:765–68
124. Hill, H., Hamed, M. Y. 1960. Vitamin E metabolism. *Arch. Tierernaehr.* 10: 129–41
125. Hook, E. B., Healy, K. M., Niles, A. M., Skalko, R. G. 1974. Vitamin E: Teratogen or anti-teratogen. *Lancet* 1:809
126. Bencze, B., Ugrai, E., Gerloczy, F., Juvancz, I. 1974. The effect of tocopherol on the embryonal development. *Int. J. Vitam. Nutr. Res.* 44:180–83
127. Bieri, J. G. 1975. Vitamin E. *Nutr. Rev.* 33:161–67
128. Vogelsang, A. 1970. Twenty-four years using α tocopherol in degenerative cardiovascular disease. *Angiology* 21: 275–79
129. Aftergood, L., Alfin-Slater, R. B. 1974. Oral contraceptive—α tocopherol interrelationships. *Lipids* 9:91–96
130. Kasuya, M. 1975. The effect E on the toxicity of alkyl mercurials on nerves tissue in culture. *Toxicol. Appl. Pharmacol.* 32:347–54
131. Warshauer, D., Goldstein, E., Hoeprich, P. D., Lippert, W. 1974. Effect of vitamin E and ozone on the pulmonary antibacterial defense mechanisms. *J. Lab. Clin. Med.* 83:228–39
132. Steele, C. E., Jeffery, E. H., Diplock, A. T. 1974. The effect of vitamin E and synthetic antioxidants on the growth *in vitro* of explanted rat embryos. *J. Reprod. Fertil.* 38:115–23
133. Campbell, P. A., Cooper, H. R., Heinzerling, R. H., Tengerdy, R. P. 1974. Vitamin E enhances in vitro immune response by normal and non-adherent spleen cells. *Proc. Soc. Exp. Biol. Med.* 146:465–69
134. DeFerreya, E. C., Castro, J. A., Diaz Gomez, M. I., D'Acosta, N., Castro, C. R., deFenos, O. M. 1975. Diverse effects of antioxidants on carbon tetrachloride hepatotoxicity. *Toxicol. Appl. Pharmacol.* 32:504–12
135. Stiles, M. H. 1940. Hypersensitivity to thiamin chloride with a note on sensitivity to pyridoxine hydrochloride. *J. Allergy* 12:507–9
136. Effects of excesses of thiamine and pyridoxine. 1960. *Nutr. Rev.* 18:95–96
137. Mills, C. A. 1941. Thiamin overdosage and toxicity. *J. Am. Med. Assoc.* 116:2101
138. DiPalma, J. R., Hitchcock, P. 1958. Neuromuscular and ganglionic block-

ing action of thiamine and its derivatives. *Anesthesiology* 19:762–69
139. Leitner, Z. A. 1943. Untoward effects of vitamin B. *Lancet* 2:474–75
140. Haley, T. J., Flesher, A. M. 1946. A toxicity study of thiamin hydrochloride. *Science* 104:567–68
141. Eisenstadt, W. A. 1942. Hypersensitivity to thiamine hydrochloride. *Minn. Med.* 25:861–63
142. Ban, T. A. 1974. Negative findings with nicotinic acid in the treatment of schizophrenias. *Int. Pharmacopsychiatry* 9:172–87
143. Ananth, J. V., Ban, T. A., Lehmann, H. E. 1973. Potentiation of therapeutic effects of nicotinic acid by pyridoxine in chronic schizophrenics. *Can. Psychiatr. Assoc. J.*
144. Berge, K. G. 1961. Side effect of nicotinic acid in treatment of hypercholesteremia. *Geriatrics* 16:416–22
145. Berge, K. G., Achor, R. W. P., Christensen, N. A., Mason, H. L., Barker, N. W. 1961. Hypercholesteremia and nicotinic acid. *Am. J. Med.* 31:25–36
146. Christensen, N. A., Achor, R. W. P., Berge, K. G., Mason, H. L. 1961. Nicotinic acid treatment of hypercholesteremia. *J. Am. Med. Assoc.* 177:547–50
147. Pardue, W. O. 1961. Severe liver dysfunction during nicotinic acid therapy. *J. Am. Med. Assoc.* 175:137–38
148. Parsons, W. B. 1961. Studies of nicotinic acid use in hypercholesteremia. *Arch. Int. Med.* 107:653–67
149. Sugerman, A. A., Clark, C. G. 1974. Jaundice following the administration of niacin. *J. Am. Med. Assoc.* 228:202
150. Winter, S. L., Boyer, J. L. 1973. Hepatic toxicity from large doses of vitamin B_3 (nicotinamide). *N. Engl. J. Med.* 289:1180–82
151. Coronary Drug Proj. Res. Group 1975. Clofibrate and niacin in coronary heart disease. *J. Am. Med. Assoc.* 231:360–81
152. Wittenborn, J. R., Nenno, R., Rothberg, H., Shelley, W. B. 1974. Pigmented hyperkeratosis among schizophrenic patients treated with nicotinic acid. *Adv. Biochem. Psychopharmacol.* 9:295–300
153. Ruiter, M., Meyler, L. 1960. Skin changes after therapeutic administration of nicotinic acid in large doses. *Dermatologica* 120:139–44
154. Rivlin, R. S. 1973. Riboflavin and cancer: A review. *Cancer Res.* 33:1977–86
155. Roe, F. J. C. 1962. Effect of massive doses of riboflavin and other vitamins of the B group, on skin carcinogenesis in mice. *Br. J. Cancer* 16:252–57
156. Hunt, A. D., Stokes, J., McCrory, W. W., Stroud, H. H. 1954. Pyridoxine dependency: Report of a case of intractable convulsions in an infant controlled by pyridoxine. *Pediatrics* 13:140–45
157. Effects of excesses of thiamine and pyridoxine. 1960. *Nutr. Rev.* 18:95–96
158. Holz, P., Palm, D. 1964. Pharmacological aspects of vitamin B_6. *Pharmacol. Rev.* 16:113–78
159. Parks, R. E., Kidder, G. W., Dewey, V. C. 1952. Thiosemicarbazide toxicity in mice. *Proc. Soc. Exp. Biol. Med.* 79:287–89
160. Jenney, E. H., Smith, R. P., Pfeiffer, C. C. 1953. Pyridoxine as an antidote to semicarbazide seizures. *Fed. Proc.* 12:333
161. T.B. therapy. 1969. *Med. Lett.* 11:10
162. Horton, R. W., Meldrum, B. S. 1973. Seizures induced by allyl-glycine, 3-mercaptopropionic acid, and 4-deoxypyridoxine in mice and photosensitive baboons, and different modes of inhibition of cerebral glutamic acid decarboxylose. *Br. J. Pharmacol.* 49:52–63
163. Dubnick, B., Leeson, G. A., Scott, C. C. 1960. Effect of forms of vitamin B_6 on acute toxicity of hydrazines. *Toxicol. Appl. Pharmacol.* 2:403–9
164. Dixon, R. H., Williams, H. L. 1962. The toxicity of pyradoxal and pyridoxal phosphate hydrazones in mice. *Fed. Proc.* 21:338
165. Kirklin, J. K., Watson, M., Bondoc, C. C., Burke, J. F. 1976. Treatment of thydrazine induced coma with pyridoxine. *N. Engl. J. Med.* 294:938–39
166. Winkelman, A. C., DiPalma, J. R. 1971. Drug treatment of Parkinsonism. *Semin. Drug Treat.* 1:10–62
167. Winston, F. 1973. Oral contraceptives, pyridoxine, and depression. *Am. J. Psychiatry* 130:1217–21
168. Levine, R. R., Smith, E. R., Clark, B. B. 1960. The effect of pyridoxal and other compounds on the mechanical activity and the sodium and potassium content of isolated rabbit atria. *J. Pharmacol. Exp. Ther.* 128:159–67
169. Heddle, J. G., McHenry, E. W., Beaton, G. H. 1963. Penicilliamine and vitamin B_6 interrelationships in the rat. *Can. J. Biochem. Physiol.* 41:1215–22
170. Houben, P. F. M., Hommes, O. R., Knaven, P. J. H. 1971. Anticonvulsant drugs and folic acid in young mentally retarded epileptic patients. *Epilepsia* 12:235–47

171. Gibberd, F. B., Nicholl, A., Dunne, J. F., Chaput de Saintonge, D. M. 1970. Toxicity of folic acid. *Lancet* 1:360–61
172. Mattson, R. H., Gallagher, B. B., Reynolds, E. H., Glass, D. 1973. Folate therapy in epilepsy. *Arch. Neurol.* 29:78–81
173. Norris, J. W. 1970. Folate and vitamin B_{12} in epilepsy. *Br. Med. J.* 4:119
174. Norris, J. W., Pratt, R. F. 1975. A controlled study of folic acid in epilepsy. *Neurology* 21:659–64
175. Ralston, A. J., Snaith, R. P., Hinley, J. B. 1970. Effect of folic acid on fit-frequency and behavior in epileptics on anticonvulsants. *Lancet* 1:867–68
176. Reynolds, E. H. 1967. Effects of folic acid on the mental state and fit-frequency of drug-treated epileptic patients. *Lancet* 1:1086–88
177. Strauss, R. G., Bernstein, R. 1974. Folic acid and dilantin antagonism in pregnancy. *Obstet. Gynecol.* 44:345–48
178. Ch'ien, L. T., Krumdieck, C. L., Scott, C. W. Jr. 1975. Harmful effect of megadoses of vitamins: electroencephalogram abnormalities and seizures induced by intravenous folate in drug-treated epileptics. *Am. J. Clin. Nutr.* 28:51–58
179. Baxter, M. G., Miller, A. A., Webster, R. A. 1973. Some studies on the convulsant action of folic acid. *Br. J. Pharmacol.* 48:350–51
180. Spector, R. G. 1970. Folic acid and convulsions in the rat. *Biochem. Pharmacol.* 20:1730–32
181. Olesen, O. V., Jensen, O. N. 1970. The influence of folic acid on phenytoin (DPH) metabolism and the 24 hours fluctuation in urinary output of 5-(-p-hydroxyphenyl)-5 phenyl hydantoin (HPPH). *Acta Pharmacol. Toxicol.* 28:265–69
182. deWolff, F. A., Hillen, F. C., Sprangers, W. J. J. M., Suijkerbuijk-VanBeek, M. M. A., Noach, E. L. 1971. The influence of folic acid on the action of diphenylhydantoin. *Arch. Int. Pharmacodyn. Ther.* 194:316–17
183. Hunter, R., Barnes, J. 1971. Toxicity of folic acid. *Lancet* 1:755
184. Threlfall, G. 1968. Cell proliferation in the rat kidney induced by folic acid. *Cell Tissue Kinet.* 1:383–92
185. Threlfall, G., Taylor, D. M., Buck, A. T. 1967. Studies of the changes in growth and DNA synthesis in the rat kidney during experimentally induced renal hypertrophy. *Am. J. Pathol.* 50:1–14
186. Searle, C. E., Blair, J. A. 1973. The renal toxicity of folic acid in mice. *Food Cosmet. Toxicol.* 11:277–81
187. Preuss, H. G., Weiss, F. R., Janicki, R. H., Goldin, H. 1972. Studies on the mechanism of folate induced growth in rat kidneys. *J. Pharmacol. Exp. Ther.* 180:754–58
188. Hsueh, W., Rostorfer, H. H. 1973. Chemically induced renal hypertrophy in the rat. *Lab. Invest.* 29:547–55
189. Taylor, D. M., Threlfall, G., Buck, A. T. 1968. Chemically-induced renal hypertrophy in the rat. *Biochem. Pharmacol.* 17:1567–74
190. Hunter, R., Barnes, J., Oakeley, H. F., Matthews, D. M. 1970. Toxicity of folic acid given in pharmacological doses to healthy volunteers. *Lancet* 1:61–63
191. Hellstrom, L. 1971. Lack of toxicity of folic acid given in pharmacological doses to healthy volunteers. *Lancet* 1:59–61
192. Richens, A. 1971. Toxicity of folic acid. *Lancet* 1:912
193. Sheeby, T. W. 1973. Folic acid: lack of toxicity. *Lancet* 1:37
194. Am. Acad. Pediatr. Comm. Drugs. 1974. Vitamin C and the common cold. *Nutr. Rev.* 32:Suppl., 39–40
195. Cochrane, W. A. 1965. Overnutrition in prenatal and neonatal life: A problem? *Can. Med. Assoc. J.* 93:893–99
196. Rosenthal, G. 1971. Interaction of ascorbic acid and warfarin. *J. Am. Med. Assoc.* 215:1671
197. Herbert, V., Jacob, E. 1974. Destruction of vitamin B_{12} by ascorbic acid. *J. Am. Med. Assoc.* 230:241–42
198. Hines, J. D. 1975. Ascorbic acid and vitamin B_{12} deficiency. *J. Am. Med. Assoc.* 234:24
199. Stein, H. B., Hasan, A., Fox, I. R. 1976. Ascorbic acid-induced uricosuria. *Ann. Int. Med.* 84:385–88