Review article

Non-nutritional uses of vitamin B_6

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Vitamin B_6 is a water-soluble vitamin, and is readily metabolized and excreted, so it has generally been assumed to have negligible toxicity, although at very high levels of intake it can cause peripheral nerve damage. Nutritional deficiency disease is extremely rare, although a significant proportion of the population shows biochemical evidence of inadequate status, despite apparently adequate levels of intake. The vitamin has been used to treat a wide variety of conditions, which may or may not be related to inadequate intake. In some conditions use of vitamin B_6 supplements has been purely empirical; in other conditions there is a reasonable physiological or metabolic mechanism to explain why supplements of the vitamin many times greater than average requirements may have therapeutic uses. However, even in such conditions there is little evidence of efficacy from properly conducted controlled trials.

Vitamin B_6: Carpal tunnel syndrome: Glucose tolerance: Premenstrual syndrome

In June 1997 the UK Department of Health Committee on Toxicity proposed limits on the amounts of vitamin B_6 that may be supplied in supplements (Department of Health, 1997). The proposals can be interpreted as an attempt to differentiate between levels of intake that may be considered to be nutritionally relevant and higher levels that can be considered to be for pharmaceutical purposes, to treat a disease or condition:

(1) up to 10 mg may be sold freely as a nutritional supplement (this is some 6-fold higher than the reference nutrient intake (RNI), although the value was derived by extrapolation from toxicological data);
(2) 10–50 mg/d may only be sold in a pharmacy, where professional advice is assumed to be available;
(3) over 50 mg/d may only be provided on prescription, since at or above this level of intake there is considered to be a risk of adverse effects, which therefore have to be balanced against the benefits in treating a clinical condition.

The proposals generated very considerable controversy, with arguments both from those who opposed all regulation of nutritional supplements and those who did not oppose regulation, but questioned the scientific evidence on which the limits had been established. In July 1998 the proposed legislation was put in abeyance, pending further examination of the evidence concerning toxicity of the vitamin. Regardless of arguments concerning the safety of high intakes of vitamin B_6, there is a need to consider the evidence for efficacy of the vitamin in treating the variety of conditions for which it is widely recommended, often at intakes of up to 250–500 mg/d (compared with the RNI of 1·2–1·5 mg/d). The aim of the present review is to examine the evidence for the efficacy of vitamin B_6 supplements in treating a variety of conditions.

Metabolism and metabolic functions of vitamin B_6

Six vitamers have vitamin B_6 metabolic activity: pyridoxine, pyridoxal and pyridoxamine, and their 5′-phosphates. The metabolically active coenzyme is pyridoxal 5′-phosphate (PLP). In the liver there is rapid oxidation of the other vitamers to pyridoxal, and rapid phosphorylation to PLP, which is the main circulating vitamer exported from the liver bound to albumin. Uptake into peripheral tissues is by extracellular dephosphorylation, followed by metabolic trapping intracellularly as PLP. PLP that is not bound to enzymes is rapidly dephosphorylated, and surplus pyridoxal in tissues is oxidized to pyridoxic acid, which is the main urinary metabolite of the vitamin.

In amino acid metabolism PLP reacts with the α-amino group of the substrate; reactions of PLP-dependent enzymes include:

(a) decarboxylation of amino acids to yield amines, which are neurotransmitters or hormones, e.g. γ-aminobutyrate,

Abbreviations: PLP, pyridoxal 5′-phosphate; RNI, reference nutrient intake.

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histamine, noradrenaline (and hence adrenaline), serotonin;
(b) transamination of amino acids to yield their keto-acids (oxo-acids), which are then oxidized as metabolic fuels;
(c) a variety of reactions involving the side-chains of amino acids, including kynureninase (*EC* 3.7.1.3), cystathionine synthetase (*EC* 4.2.1.22) and cystathionase (*EC* 4.4.1.1);
(d) decarboxylation of phosphatidylserine to phosphatidylethanolamine in phospholipid synthesis.

In glycogen phosphorylase (*EC* 2.4.1.1) PLP acts as a phosphate buffer at the active site of the enzyme (Palm *et al*. 1990). Before this catalytic role was established, it was assumed that muscle acted as a storage pool of vitamin B_6; however, PLP is not released from muscle in times of deficiency, although it is released in prolonged fasting, when glycogen reserves are depleted, and there is an increased requirement for PLP in the liver for transamination of amino acids for gluconeogenesis (Black *et al*. 1977, 1978).

PLP also acts to terminate the actions of steroid and other nuclear-acting hormones, including vitamins A and D and thyroid hormone. It binds to a lysine residue in the hormone receptor protein, displacing it from binding to the hormone-response element on DNA, and so ending the enhancement of gene expression. Studies in experimental animals have shown that various steroid hormones are accumulated in the nucleus of target tissues to a greater extent, and for longer, in vitamin B_6 deficiency, with some evidence of enhanced end-organ responsiveness to low doses of hormones (Symes *et al*. 1984; Bowden *et al*. 1986; Bender, 1987). Studies with cells in culture have shown that acute vitamin B_6 depletion (addition of the antimetabolite 4-deoxypyridoxine) leads to a twofold increase in hormone-stimulated rate of expression of genes with a variety of hormone-response elements, and conversely, addition of high concentrations of pyridoxal to the culture medium results in a halving of the rate of gene expression in response to the hormones (Allgood *et al*. 1990; Allgood & Cidlowski, 1992; Tully *et al*. 1994).

Maksymowych *et al*. (1993) reported that pyridoxal had a cytotoxic effect towards melanoma cells in culture, preventing glucocorticoid action. Administration of vitamin B_6 has been demonstrated to prevent the development of fetal abnormalities induced in experimental animals by the vitamin A analogue, etretinate (Jacobsson & Granstrom, 1996), and Key *et al*. (1997) reported a potential protective effect of vitamin B_6 against prostate cancer, presumably due to attenuation of steroid hormone responsiveness of target tissues.

Requirements and reference nutrient intakes

Clinical deficiency of vitamin B_6 is more or less unknown; the only reported cases were in the early 1950s, associated with infant milk formula that had been severely overheated in manufacture, leading to the formation of pyridoxyllysine by reaction between the vitamin and the ϵ-amino groups of lysine in protein (Coursin, 1954). Not only is pyridoxyllysine nutritionally unavailable as a source of the vitamin, but it also has antivitamin activity (Gregory, 1980*a*,*b*).

Estimates of requirements and RNI are based on depletion–repletion studies in which either the plasma concentration of the vitamin or the ability to metabolize a test dose of tryptophan or methionine was used as the index of adequacy (Miller & Linkswiler, 1967; Kelsay *et al*. 1968*a*,*b*; Canham *et al*. 1969). Coburn (1996) has shown that although some 70–80 % of total body vitamin B_6 is associated with muscle glycogen phosphorylase, this pool has a slow turnover; the remaining 20–30 % of the body pool, largely associated with amino acid metabolism (and steroid hormone action), has a more rapid turnover. Therefore it is likely that protein intake, or the burden of amino acids to be metabolized, will have a significant effect on vitamin B_6 requirements. Certainly the depletion–repletion studies of Miller & Linkswiler (1967), Kelsay *et al*. (1968*a*,*b*) and Canham *et al*. (1969) demonstrated that biochemical evidence of depletion developed more rapidly during depletion in subjects fed on a high-protein diet, while repletion required a higher intake of the vitamin than in subjects fed on a low-protein diet. Current RNI are calculated on the basis of 15 μg vitamin B_6/g protein intake (Department of Health, 1991).

Average intakes of vitamin B_6 in Britain are significantly above the RNI, and even people in the lowest 2·5 centile meet the RNI (Gregory *et al*. 1990). However, several studies show that a significant proportion of adults have biochemical evidence of inadequate vitamin B_6 nutrition by one or other of the two criteria most commonly used: plasma concentration of PLP or erythrocyte transaminase activation coefficient (see Table 1). This suggests that current estimates of vitamin B_6 requirements may be too low, although there is little evidence that marginal plasma concentrations of PLP or marginally elevated transaminase activation coefficients have any functional significance.

Kretsch *et al*. (1995) and Hansen *et al*. (1996) have investigated a number of markers of status in vitamin B_6 depletion–repletion studies in women; both studies suggest that the requirement to meet the most sensitive criteria of adequacy indicates an RNI of 20 μg/g protein. It is not clear whether this represents a sex difference (most of the earlier studies were performed on men) or whether the more recent studies were more sensitive in detecting marginal inadequacy.

Potential benefits of higher levels of intake: homocysteine metabolism

The identification of hyperhomocysteinaemia as an independent risk factor in atherosclerosis and CHD (Verhoef & Stampfer, 1995; Boers, 1997; D'Angelo & Selhub, 1997) has led to suggestions that intakes of vitamin B_6 higher than are currently considered adequate to meet requirements may be desirable. Homocysteine is an intermediate in methionine metabolism, and may undergo one of two metabolic fates, as shown in Fig. 1: remethylation to methionine (a reaction that is dependent on vitamin B_{12} and folic acid), or onward metabolism leading to the synthesis of cysteine (trans-sulfuration).

The trans-sulfuration pathway has two PLP-dependent enzymes: cystathionine synthetase and cystathionase, and forms the basis of the methionine load test for vitamin B_6

Table 1. Evidence of inadequate vitamin B_6 nutritional status in developed countries

	n	% Deficient	Criterion	Reference
Breast-fed infants	84	10	Pyridoxal phosphate	Wilson & Davies (1984)
Preschool children	35	9	Pyridoxal phosphate	Fries *et al.* (1981)
Young women embarking on contraceptive study	129	0·8	Pyridoxal phosphate	Bender (1993)
Young women embarking on contraceptive study	129	13·2	Aspartate transaminase activation	Bender (1993)
Adolescent girls	127	13	Alanine transaminase activation	Kirksey *et al.* (1978)
Pregnant adolescents	122	17	Alanine transaminase activation	Martner-Hawes *et al.* (1986)
Low-income pregnant women	127	68	Alanine transaminase activation	Schuster *et al.* (1981)
Pregnant women	458	42	Aspartate transaminase activation	Heller *et al.* (1973)
Hospital patients	650	25	Aspartate transaminase activation	Lemoine *et al.* (1980)
Free-living elderly subjects	198	27	Pyridoxal phosphate	Schrijver *et al.* (1987)
Free-living elderly subjects	198	26	Aspartate transaminase activation	Schrijver *et al.* (1987)
Elderly men undergoing prostate surgery	94	4·3	Pyridoxal phosphate	Bender (1993)
Elderly men undergoing prostate surgery	94	8·5	Aspartate transaminase activation	Bender (1993)
Hospitalized elderly subjects	153	19	Aspartate transaminase activation	Hoorn *et al.* (1975)
Hospitalized elderly subjects	102	28	Alanine transaminase activation	Vir & Love (1978)
Men, various ages	617	25	Pyridoxal phosphate	Rose *et al.* (1976)

status: measurement of homocysteine in plasma or urine after a test dose of methionine (Linkswiler, 1981). It has been considered to be less subject to artifacts and false positive results than the tryptophan load test (Bender & Wynick, 1981).

Selhub *et al*. (1993) reported measurements of plasma homocysteine and vitamin B_6 and folate status in 1160 elderly survivors (aged 67–96 years) of the Framingham study cohort. Hyperhomocysteinaemia was most significantly correlated with low folate status, but there was also a significant association with low vitamin B_6 status. Results from the Nurses' Health Study (Rimm *et al*. 1998) showed that cardiovascular disease risk was lowest among those women with the highest intakes of folate and vitamin B_6. Since the sources of both folate and vitamin B_6 in those people with the highest intakes were fortified breakfast cereals and multivitamin supplements, the authors concluded that it was not possible to distinguish between potential protective effects of the two vitamins.

Ubbinck and coworkers (Ubbinck *et al*. 1994; Ubbinck, 1997) showed that while folate supplements lowered fasting homocysteine levels in moderately hyperhomocysteinaemic subjects, 10 mg vitamin B_6/d had no effect. Dierkes *et al*. (1998) similarly showed that while folate supplements

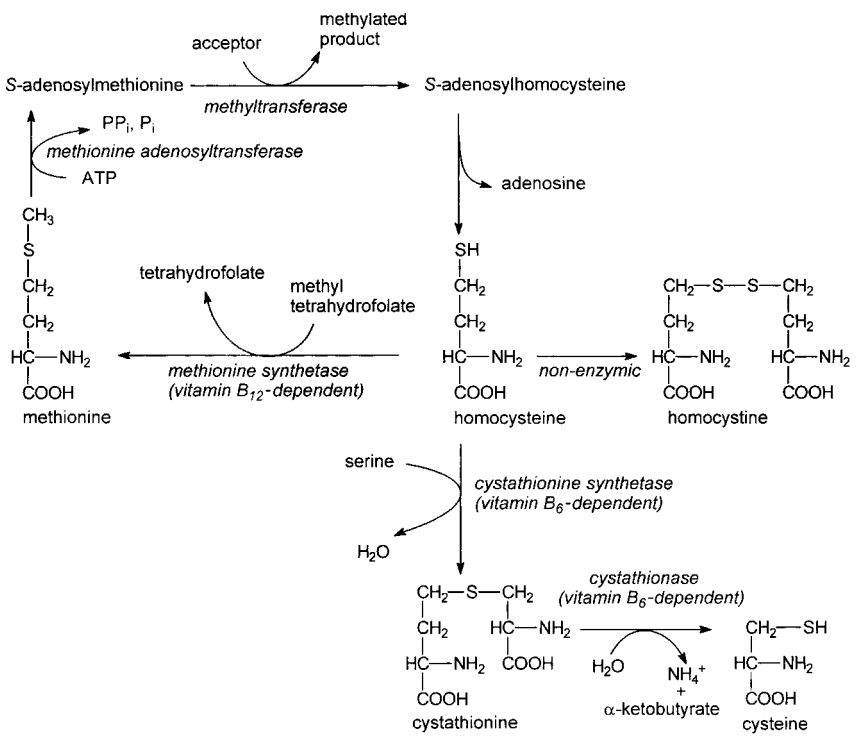

Fig. 1. Methionine metabolism. Methionine synthetase, *EC* 2.1.1.13; methionine adenosyltransferase, *EC* 2.5.1.6; cystathionine synthetase, *EC* 4.2.1.22; cystathionase, *EC* 4.4.1.1.

reduced plasma homocysteine levels in people who were not hyperhomocystinaemic, vitamin B_6 supplements had no effect. In Ubbinck's studies, vitamin B_6 supplements did reduce the peak plasma concentration of homocysteine following a test dose of methionine. This can probably be explained on the basis of the kinetics of the enzymes involved; the K_m of cystathionine synthetase is 10-fold higher than that of methionine synthetase (*EC* 2.1.1.13). Under basal conditions, little homocysteine is metabolized by way of the trans-sulfuration pathway; it is only after a loading dose of methionine, when homocysteine rises to high levels, that the activity of cystathionine synthetase, rather than the concentration of its substrate, is limiting.

Thus it seems unlikely that intakes of vitamin B_6 greater than amounts that are adequate to prevent metabolic signs of deficiency will be beneficial in lowering plasma concentrations of homocysteine. This conclusion is supported by a meta-analysis of intervention studies which demonstrated no effect of vitamin B_6 supplements on plasma homocysteine (Homocysteine Lowering Trialists' Collaboration, 1998).

Pharmacological uses of vitamin B_6

A number of (rare) genetic conditions are known in which a PLP-dependent enzyme has a defect in the coenzyme binding site, and only has significant activity when the tissue concentration of PLP is very much higher than normal. For such conditions (listed in Table 2), supplements of 200–1000 mg/d are required for life (Frimpter *et al*. 1969; Mudd, 1971; Fowler, 1985).

Vitamin B_6 has been reported to be effective in suppression of lactation (Marcus, 1975; Gupta & Sharma, 1990), although other reports have shown no difference from placebo (Macdonald *et al*. 1976). Because the vitamin suppresses the increase in prolactin induced by treatment with the dopamine receptor antagonist pimozide, and because lactation is also suppressed by the dopamine agonist bromocriptine (Boes, 1980), it has been suggested that it acts to stimulate dopaminergic activity in the hypothalamus (Delitala *et al.* 1977). However, it is more likely that its action is by reduction in target tissue responsiveness to steroid hormones that stimulate prolactin secretion.

Supplements of vitamin B_6 ranging from 25 to 500 mg/d have been recommended for treatment of a variety of conditions, discussed later, in which there is an underlying physiological or biochemical mechanism to justify the use of supplements, although in most cases there is little evidence of efficacy. It has also been used empirically, with little or no evidence of efficacy, in the treatment of a variety of conditions, including: acute alcohol intoxication (Mardel *et al*. 1994), atopic dermatitis (Mabin *et al*. 1995), autism (Rimland *et al*. 1978; Rimland, 1988; Lelord *et al*. 1982; Pfeiffer *et al*. 1995; Findling *et al*. 1997), dental caries (Hillman, 1964), diabetic peripheral neuropathy (Levin *et al*. 1981; Cohen *et al*. 1984), Down's syndrome (Pueschel *et al*. 1980; Coleman *et al*. 1985), Huntington's chorea (Barr *et al*. 1978), schizophrenia (Bucci, 1973), and steroid-dependent asthma (Sur *et al*. 1993).

Side-effects of oral contraceptives

The high-dose oral contraceptives of the 1960s had a variety of side-effects, including depression of mood and impaired glucose tolerance. A number of studies showed that supplements of 100 mg vitamin B_6/d relieved the depression and normalized glucose tolerance in women taking contraceptives (Benninck & Schreurs, 1975; Adams *et al*. 1976; Spellacy *et al*. 1977). Villegas-Salas *et al*. (1997) showed that the side-effects of low-dose combined oral contraceptives, such as nausea, vomiting, dizziness, depression and irritability, showed no greater response to 150 mg vitamin B_6/d than to placebo.

Rose (1966*a*,*b*) was the first to report apparent vitamin B_6 deficiency in women taking high-dose oestrogen–progestagen contraceptives. He reported impaired metabolism of tryptophan with increased urinary excretion of xanthurenic and kynurenic acids after a test dose of the amino acid (see Fig. 2). Since then there have been many reports of abnormal tryptophan metabolism in women taking both oral contraceptives and menopausal hormone replacement therapy, which have generally been interpreted as indicating oestrogen-induced vitamin B_6 deficiency or depletion.

In many cases tryptophan metabolism has been normalized by supplements of 20–50 mg vitamin B_6/d, but not by nutritionally relevant amounts. Furthermore, when indices of vitamin B_6 status other than tryptophan metabolism have been assessed (e.g. the metabolism of a test dose of methionine, plasma concentrations of B_6 vitamers or the activation of erythrocyte transaminases by PLP added *in vitro*), these have been normal, suggesting that the impairment of tryptophan metabolism may be due to an effect other than vitamin B_6 depletion.

One explanation of the beneficial effect of vitamin B_6 supplements on tryptophan metabolism in women taking

Table 2. Vitamin B_6-responsive inborn errors of metabolism

	Enzyme affected	*EC* number
Convulsions of the newborn	Glutamate decarboxylase (↓ GABA synthesis)	4.1.1.15
Cystathioninuria	Cystathionase (see Fig. 1)	4.4.1.1
Gyrate atrophy with ornithinuria	Orninthine-δ-aminotransferase	2.6.1.13
Homocystinuria	Cystathionine synthetase (see Fig. 1)	4.2.1.22
Primary hyperoxaluria, type 1	Peroxisomal alanine-glyoxylate transaminase	2.6.1.44
Sideroblastic anaemia	δ-Aminolevulinate synthase (↓ haem synthesis)	2.3.1.37
Xanthurenic aciduria	Kynureninase (see Fig. 2)	3.7.1.3

GABA, γ-aminobutyric acid; ↓, reduced.

oestrogens, and indeed of the extreme sensitivity of tryptophan metabolism as an index of vitamin B_6 status, may lie in the enzymology of kynureninase. In common with a number of other PLP-dependent enzymes, kynureninase catalyses not only its normal reaction (cleavage of the β-C–γ-C bond of the substrate, releasing alanine and hydroxyanthranilic acid), but also, slowly, cleavage of the α-C–amino bond, the half-reaction of transamination (Meister, 1990). This results in formation of pyridoxamine phosphate at the active site of the enzyme, and loss of activity. The enzyme can only be reactivated if there is a sufficiently high concentration of PLP to displace pyridoxamine from the catalytic site and reform the active holo-enzyme. Normally there is a considerable amount of catalytically inactive kynureninase in the liver, which is activated by addition of PLP *in vitro*; this may be either true apo-enzyme or enzyme that has been inactivated by transamination.

Another factor which may account for the reduction in excretion of tryptophan metabolites after a test dose in people receiving relatively high supplements of vitamin B_6 is the effect of PLP on enzyme induction by steroid hormones. The rate of entry of tryptophan into the oxidative pathway is limited by the activity of tryptophan dioxygenase (*EC* 1.13.11.11), which is induced by glucocorticoid hormones; high intakes of vitamin B_6 would be expected to reduce synthesis of the enzyme by terminating hormone action, so reducing metabolic flux through the pathway.

It was noted earlier that there is little evidence that oestrogens cause vitamin B_6 deficiency or depletion, and although the metabolism of a test dose of tryptophan is abnormal, other indices of vitamin B_6 status are not. Bender & Wynick (1981) showed that oestrogen metabolites are competitive inhibitors of kynureninase, and will impair tryptophan metabolism, leading to results of a tryptophan load test similar to those seen in vitamin B_6 deficiency, but by a different mechanism. They concluded that the tryptophan load test was not a useful indicator of vitamin B_6 status for use in field studies, although it is still useful in experimental depletion–repletion studies to determine requirements.

Impaired glucose tolerance and diabetes mellitus

Wynn & Doar (1966) reported impaired glucose tolerance in 18% of women taking (high-dose) oral contraceptives, which returned to normal on withdrawal of the steroids. Impaired glucose tolerance is also common in pregnancy, and may be severe enough to be classified as diabetes mellitus, so-called gestational diabetes, which usually resolves on parturition. In women taking oral contraceptives and in gestational diabetes, several studies have shown that supplements of about 100 mg vitamin B_6/d result in improved glucose tolerance (Benninck & Schreurs, 1975; Adams *et al*. 1976; Spellacy *et al*. 1977). Rose *et al*. (1975) reported that vitamin B_6 deficiency impaired glucose tolerance in women taking oral contraceptive steroids, but not in control women, and the abnormality was corrected by vitamin B_6 supplements.

There are derangements of tryptophan metabolism in pregnancy. As discussed earlier, oestrogen metabolites inhibit kynureninase, and Bender & Totoe (1984*a*) showed that oestrogens lead to reduced activity of kynurenine hydroxylase (*EC* 1.14.13.9) and hydroxyanthranilate oxidase (*EC* 1.13.11.6) although the mechanism is unclear. In animals, Van-de-Kamp & Smolen (1995) showed that pregnancy has effects on tryptophan metabolism that are additive to those seen in vitamin B_6 deficiency, and that are resistant to modest supplements of the vitamin. As a result, in pregnancy or in response to (high-dose) oral contraceptives, tissue concentrations of kynurenine, hydroxykynurenine and xanthurenic and kynurenic acids are higher than normal.

Kotake *et al*. (1975) suggested that the impairment of glucose tolerance was associated with high plasma concentrations of xanthurenic acid, which forms a biologically inactive complex with insulin. The improvement following high doses of vitamin B_6 could then be explained by activation of apo-kynureninase or reactivation of kynureninase that had been inactivated as a result of transamination. However, Cornish & Tesorio (1975) were unable to demonstrate any effect of xanthurenic acid administration on glucose tolerance in rats. Adams *et al*. (1976) suggested that the effect of vitamin B_6 on glucose tolerance in women taking oral contraceptives was due to increased formation of quinolinic acid as a result of relief of the impairment of kynureninase activity; quinolinic acid is an inhibitor of phosphoenolpyruvate carboxykinase (*EC* 4.2.2.31), one of the key enzymes of gluconeogenesis. They demonstrated an improvement in glucose tolerance in response to tryptophan to increase the synthesis of quinolinic acid.

An alternative explanation of impaired glucose tolerance in the presence of tryptophan metabolites that would be reduced by high doses of vitamin B_6 has been proposed by Noto & Okamoto (1978). They reported that xanthurenic and kynurenic acids inhibit the synthesis of pro-insulin in isolated pancreatic islets, and hydroxykynurenine inhibits the secretion of insulin, a finding confirmed by Rogers & Evangelista (1985).

Spellacy *et al*. (1977) reported improved glucose tolerance in thirteen women with gestational diabetes in response to supplements of 100 mg vitamin B_6/d. However, Gillmer & Mazibuko (1979) reported that while a similar supplement normalized urinary excretion of xanthurenic acid in women with gestational diabetes, it resulted in improved glucose tolerance in only two of their thirteen subjects, and led to more impaired glucose tolerance in six subjects.

There are conflicting results on the effects of vitamin B_6 status on glucose tolerance. Rao *et al*. (1980) reported no effect of marginal vitamin B_6 status on glucose tolerance or insulin secretion in response to a glucose load in people with non-insulin-dependent diabetes. Rao (1983) reported that in a group of non-diabetic subjects with marginal vitamin B_6 status glucose tolerance was in fact better than in those with adequate status. The response of plasma insulin to the glucose load was normal, suggesting enhanced sensitivity to the hypoglycaemic action of insulin in marginal vitamin B_6 deficiency. Toyata *et al*. (1981) reported that in insolated pancreatic islets from vitamin B_6 deficient rats there was impaired secretion of insulin, and plasma insulin was significantly lower than normal in the deficient rats in response to a glucose load. Rao & Mohan (1982) reported low plasma concentrations of insulin in vitamin B_6-deficient rats.

There is some evidence that PLP may be beneficial in overcoming some of the effects of poor glycaemic control in diabetes. Hayakawa & Shibata (1991) reported that *in vitro* PLP inhibited the non-enzymic reaction between lysine and glucose (the Maillard reaction). They also showed that administration of PLP to genetically diabetic mice reduced the thickening of the glomerular basement membrane, which has been attributed to non-enzymic glycation of connective tissue proteins. Solomon & Cohen (1989) showed that supplements of 150 mg vitamin B_6/d led to a significant reduction in glycated haemoglobin in men with non-insulin-dependent diabetes, and hence improved O_2 transport capacity, although there was no change in glycaemic control. While these results suggest beneficial effects of vitamin B_6 supplementation in diabetes, the reduced glycation of proteins is due to reaction between PLP and the amino groups that would otherwise be glycated. Ganea & Harding (1996) reported that PLP did indeed decrease the binding of glucose and galactose to lens proteins, but bound itself, causing changes in the absorbance and fluorescence spectra, and inducing aggregation of the proteins.

Overall there is little convincing evidence either that vitamin B_6 supplements will be of any use in the treatment of diabetes (possibly apart from gestational diabetes), or that vitamin B_6 deficiency is a significant factor in the development of diabetes.

Depression

There is a great deal of evidence that deficiency of serotonin (5-hydroxytryptamine) or the catecholamines (dopamine, noradrenaline and adrenaline) is a factor in depressive illness (Ashcroft *et al*. 1972), and many antidepressant drugs act to decrease the catabolism of amines or enhance their interaction with receptors. A key enzyme involved in the synthesis of serotonin and the catecholamines is aromatic amino acid decarboxylase (*EC* 4.1.1.28), which is PLP-dependent. Therefore, it has been suggested that vitamin B_6 deficiency may result in reduced formation of the neurotransmitters, and so be a factor in the aetiology of depression. Conversely, it has been suggested that supplements of vitamin B_6 may increase aromatic amino acid decarboxylase activity, and so increase amine synthesis and have a mood-elevating or antidepress-ant effect.

There is little evidence that vitamin B_6 deficiency affects the activity of aromatic amino acid decarboxylase (Eberle & Eiduson, 1968; Eiduson *et al*. 1972). Perry *et al*. (1985) reported that in patients with kidney failure, undergoing dialysis, the brain concentration of PLP fell to about 50 % of normal, with no effect on serotonin, catecholamines or their metabolites. However, like kynureninase, aromatic amino acid decarboxylase can undergo self-inactivation by catalysing transamination (Meister, 1990), and it is likely that at times of low availability of PLP, reactivation of the enzyme may be impaired.

Dakshinamurti *et al*. (1976) reported a low brain concentration of serotonin, but not catecholamines, in vitamin B_6-deficient rats, and Siow & Dakshinamurti (1985) reported reduced decarboxylase activity towards 5-hydroxytryptophan, but not dopa (3-hydroxytyrosine), in the brains of vitamin B_6-deficient animals. The decarboxylase undergoes mechanism-dependent inactivation in the presence of serotonin, and may thus be more susceptible to inactivation in serotoninergic neurones than in catecholaminergic neurones. It is unlikely that this explains the differential effect of vitamin B_6 deficiency on serotonin and catecholamine formation, since the inactivation is the result of a covalent modification of the catalytic site, not the coenzyme, and is not reversed by incubation with PLP (Bertoldi *et al*. 1996).

Bender & Totoe (1984*b*) showed that in rats high doses of vitamin B_6 (10 mg/kg body weight) led to decreased oxidative metabolism of tryptophan, an increased plasma concentration of tryptophan, and increased uptake of tryptophan into the brain, leading to an increased rate of serotonin turnover. They suggested that vitamin B_6 supplements might be a useful adjunct to tryptophan for the treatment of depression. It is likely that the impairment of tryptophan oxidation was the result of reduced induction of tryptophan dioxygenase by glucocorticoid hormones in the presence of high concentrations of PLP.

Overall, however, there is little or no evidence from clinical trials that vitamin B_6 is effective in the treatment of depressive illness.

The premenstrual syndrome

The studies showing that vitamin B_6 supplements were effective in overcoming some of the side-effects of (high-dose) oral contraceptives have led to the use of vitamin B_6 in treatment of the premenstrual syndrome, the condition of nervousness, irritability, emotional disturbance, headache and/or depression suffered by many women for up to 10 d before menstruation. There is no evidence that women who suffer from premenstrual syndrome have any lower vitamin B_6 status than do others (Ritchie & Singkamani, 1986; van den Berg *et al*. 1986; Mira *et al*. 1988), and the doses used have been in the region of 50–200 mg/d, which is very much higher than would be required to correct any deficiency of the vitamin.

Kleijnen *et al*. (1990) reviewed twelve placebo-controlled double-blind trials of vitamin B_6 in the premenstrual syndrome and concluded that the evidence for beneficial effects was weak. In three of the studies cited there was a significant beneficial effect of vitamin B_6 supplements: Abraham & Hargrove (1980) used a dose of 500 mg/d, Hallman & Oreland (1987) 300 mg/d and Barr (1984) 100 mg/d. A further five studies yielded ambiguous results. Doll *et al.* (1989) reported a significant beneficial effect of 50 mg/d on depression, irritability and tiredness, but none of the other premenstrual symptoms. Kendall & Schnurr (1987) reported that 150 mg/d led to some improvement in dizziness, vomiting and behavioural changes, but considerable physical and affective symptoms remained. Williams *et al*. (1985) showed an improvement for 82 % of subjects receiving 100 mg vitamin B_6/d, and 70 % of those receiving placebo. Smallwood *et al*. (1986) reported a positive trend but no statistical significance using 200 mg/d, and Stokes & Mendels (1972) reported disappointing and 'not clear' results using 50 mg/d. The remaining four studies they reviewed reported no beneficial effects of doses of between 100 and 500 mg/d.

Hagen *et al*. (1985) found no significant difference between vitamin B_6 (100 mg/d) and placebo, but reported that whichever treatment was used second in their double-blind cross-over trial was significantly better than the treatment used first.

Despite the lack of evidence of efficacy, the major use of vitamin B_6 supplements, either prescribed or self-prescribed, is in the treatment of premenstrual syndrome.

Morning sickness

Doses of vitamin B_6 of between 50 and 200 mg have an anti-emetic effect, and the vitamin has been used to overcome the nausea associated with radiotherapy. It was also been used, empirically, since the 1940s to treat morning sickness in pregnancy. It was included together with doxylamine succinate in Bendectin (Debendox), which was prescribed for treatment of morning sickness, and later withdrawn on suspicion of teratogenicity. Brent (1995) concluded that there was no evidence of teratogenic effects of the combined formulation.

There is no evidence that women who suffer from severe nausea and vomiting in pregnancy have any lower vitamin B_6 nutritional status than others (Schuster *et al*. 1985). Leathem (1986) stated that vitamin B_6 is considered safe for use in pregnancy, but noted that its efficacy in treating nausea and vomiting had not been established. Two studies give some evidence of efficacy. Sahakian *et al*. (1991) conducted a double-blind trial of vitamin B_6 (25 mg every 8 h for 3 d); they reported a significant reduction in vomiting, and an improvement in nausea in those who initially reported severe nausea. By contrast, Vutyavanich *et al*. (1995) reported that in their trial (30 mg/d for 5 d) there was a significant decrease in nausea, with a non-significant trend indicating a reduction in vomiting. They noted that as morning sickness is a self-limiting condition, it is difficult to perform well-controlled trials.

Carpal tunnel syndrome

Carpal tunnel syndrome (compression of the median nerve as it passes through the carpal tunnel, the space between the bones of the wrist and the connective tissue over the flexor tendons) is a major source of occupational health problems. A number of studies have suggested that inadequate vitamin B_6 status is an aetiological factor or that supplements may relieve the condition, although there is no physiological reason to expect vitamin B_6 to have any effect on the aetiology or progression of the condition. The early work in this area, and indeed most of the reports of a beneficial effect of vitamin B_6, have come from Ellis and coworkers (e.g. Ellis *et al*. 1976, 1977, 1982; Ellis, 1987; Ellis & Folkers, 1990). These studies suggest that vitamin B_6 deficiency, as assessed by erythrocyte aspartate aminotransferase (*EC* 2.6.1.1.) activity, is associated with carpal tunnel syndrome, and responds only slowly to administration of doses of 100–200 mg vitamin B_6/d. Ellis (1987) reported that 100–200 mg vitamin B_6/d for 12 weeks proved curative for 'a large proportion' of his patients with carpal tunnel syndrome.

Smith *et al*. (1984) found no evidence of inadequate vitamin B_6 status in a small group of patients with carpal tunnel syndrome, and noted that although four out of six patients treated with vitamin B_6 reported some partial symptomatic relief, there was no consistent improvement in clinical findings or neurophysiological measurements.

Amadio (1987) reviewed a number of studies and concluded that vitamin B_6 deficiency was probably not associated with occupational carpal tunnel syndrome. He also noted that all studies published at that time were flawed by the lack of scientific design. Franzblau *et al*. (1996) investigated 125 randomly selected workers, and found that vitamin B_6 status was unrelated to either self-reported symptoms compatible with carpal tunnel syndrome or electrophysiological measurement of nerve function.

Stransky *et al*. (1989) reported that in a double-blind controlled study vitamin B_6 had no advantage over placebo or no treatment at all. Spooner *et al*. (1993) performed a randomized prospective trial of vitamin B_6 or placebo, and showed that there were no differences in electrophysiological signs, clinical signs or symptoms between the two groups. Bernstein & Dinesen (1993) similarly showed no effect of vitamin B_6 on electrophysiological measurements, although they did report a significant improvement in pain scores.

Thus it appears that while there is some suggestion of symptomatic relief in open trials, there is no evidence from double-blind placebo-controlled trials that vitamin B_6 is effective in treating carpal tunnel syndrome.

Hypertension

Dakshinamurti & Lal (1992) have shown that vitamin B_6 depletion leads to the development of hypertension in experimental animals, which is normalized within 24 h by repletion with the vitamin. They have proposed three mechanisms to account for this:

(a) Central effects on blood pressure regulation as a result of decreased synthesis of brain γ-aminobutyric acid and serotonin (5-hydroxytryptamine). Glutamate decarboxylase (*EC* 4.1.1.15) activity in the nervous system is especially sensitive to vitamin B_6 depletion (Bayoumi *et al*. 1972), possibly as a result of mechanism-dependent inactivation by transamination (Meister, 1990). There is no evidence that aromatic amino acid decarboxylase activity is reduced in vitamin B_6 deficiency (Eberle & Eiduson, 1968; Eiduson *et al*. 1972), but there is reduced formation of serotonin in the central nervous system (Dakshinamurti *et al*. 1976).

(b) Increased sympathetic nervous system activity. There is evidence of elevated plasma concentrations of adrenaline and noradrenaline in vitamin B_6-deficient animals (Paulose *et al*. 1988).

(c) Increased uptake of Ca by arterial smooth muscle, leading to increased muscle tone, and hence increased circulatory resistance and blood pressure. This could reflect increased sensitivity of vascular smooth muscle to calcitriol (vitamin D) action in vitamin B_6 deficiency; the membrane Ca-binding protein is regulated by vitamin D and vascular tissue has calcitriol receptors (Viswanathan *et al*. 1991; Lal & Dakshinamurti, 1993, 1995).

In addition to these mechanisms (which are not mutually

exclusive), it is likely that vitamin B_6 deficiency will result in increased end-organ responsiveness to glucocorticoids, mineralocorticoids and aldosterone; over-secretion of (and presumably also enhanced sensitivity to) any of these hormones can result in hypertension. Vitamin B_6 supplementation would be expected to reduce end-organ sensitivity to these hormones, and thus might have a hypotensive action. Fregly & Cade (1995) showed that supplements of 300 mg vitamin B_6/kg body weight per d attenuated the hypertensive response of rats treated with deoxycorticosterone acetate. At a more realistic level of supplementation (five times the usual amount provided in the diet), Lal *et al.* (1996) showed that vitamin B_6 prevented the development of hypertension in the Zucker (*fa*/*fa*) obese rat. Withdrawal of the vitamin supplement led to the development of hypertension. Ayback *et al.* (1995) showed that supplements of 5 mg/kg body weight per d led to reduced blood pressure in patients with essential hypertension.

Drug interactions with vitamin B_6

The antituberculosis drug isoniazid (*iso*-nicotinic acid hydrazide) reacts non-enzymically with PLP to form a metabolically inactive hydrazone, resulting in functional vitamin B_6 deficiency (Vilter, 1964; Standal *et al.* 1974).

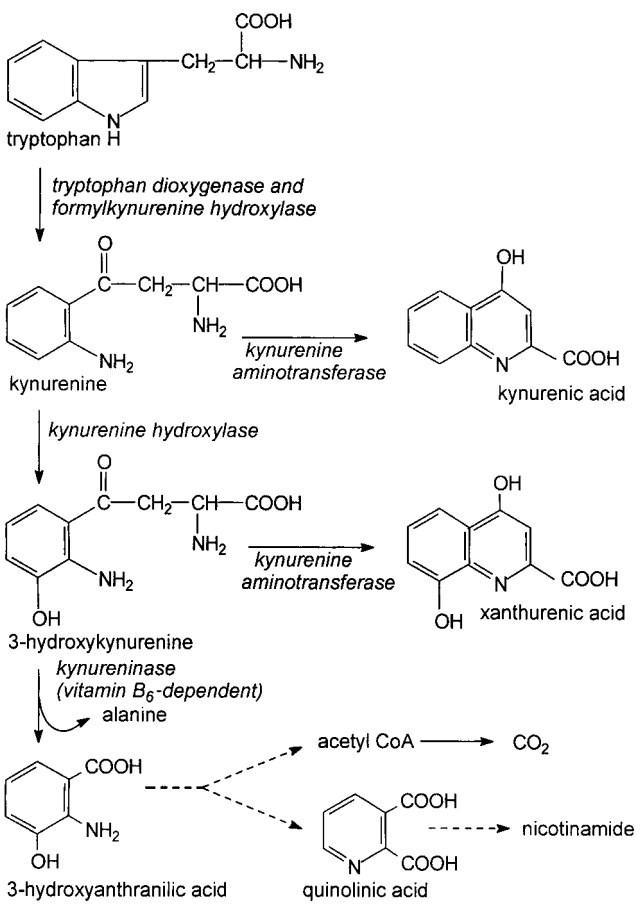

Fig. 2. Tryptophan metabolism. Tryptophan dioxygenase, *EC* 1.13.11.11; formylkynurenine formamidase, *EC* 3.5.1.9; kynurenine hydroxylase, *EC* 1.14.13.9; kynureninase, *EC* 3.7.1.3; kynurenine aminotransferase, *EC* 2.6.1.7 and *EC* 2.6.1.63.

This is most commonly seen as secondary pellagra, due to impaired activity of kynureninase (see Fig. 2), and hence impaired synthesis of nicotinamide nucleotides from tryptophan. The pellagra responds to supplements of vitamin B_6 (Biehl & Vilter, 1954). Isoniazid also leads to the development of peripheral neuropathy, which also responds to vitamin B_6 supplements (Gammon *et al.* 1953). This has led to the belief that vitamin B_6 deficiency causes peripheral neuropathy (Jones & Jones, 1963), although there is no evidence of this. The neuropathy seems to be an effect of isoniazid intoxication; the response to vitamin B_6 is the result of removing isoniazid as the pyridoxal adduct, rather than repleting vitamin B_6-deficient tissues (Snider, 1980). When relatively high doses of isoniazid were used to treat tuberculosis, it was common to give vitamin B_6 supplements; this had no effect on the therapeutic action of the drug, but did prevent the peripheral neuropathy and secondary pellagra (Biehl & Vilter, 1954). When lower doses of isoniazid were introduced, in a therapeutic cocktail with other medication, vitamin B_6 supplementation became less usual. However, cases of isoniazid-induced pellagra have been reported among people taking low doses of isoniazid; it is likely that many of those affected were genetically slow acetylators of isoniazid, so that a low dose was, for them, equivalent to a higher dose for a fast acetylator (Bender & Russell-Jones, 1979). There have been a number of reports of successful treatment of acute isoniazid intoxication with vitamin B_6 supplements (Brent *et al.* 1990; Alvarez & Guntapalli, 1995; Shah *et al.* 1995).

Other hydrazine derivatives can also cause vitamin B_6 depletion by forming hydrazones, leading to the development of secondary pellagra; these include the anti-Parkinsonian drugs Benserazide and Carbidopa (Bender *et al.* 1979; Bender, 1980*a*,*b*).

When dopa was first introduced for the treatment of Parkinsonism, one of the most frequent side-effects was persistent nausea and vomiting. Because of the (slight) evidence that vitamin B_6 has an anti-emetic and anti-nauseant action, supplements were given together with dopa. The result was a considerable reduction in the efficacy of dopa in controlling Parkinsonian signs and symptoms; the magnitude of the effect was related to the dose of pyridoxine given (Hunter *et al.* 1970). The problem was due to the formation of a stable tetrahydroisoquinoline adduct between PLP and dopa (Evered, 1971) which not only reduced the concentration of dopa available for uptake into the brain, but also acted as an inhibitor of aromatic amino acid decarboxylase (Fellman & Roth, 1971).

Theophylline therapy for asthma can cause seizures, apparently as a result of reaction with PLP, leading to low plasma concentrations, and hence reduced synthesis of γ-aminobutyric acid in the central nervous system. Glenn *et al.* (1995) showed that the administration of vitamin B_6 to mice treated with theophylline reduced the number of seizures; in rabbits, vitamin B_6 reversed the changes in electroencephalogram caused by high doses of theophylline.

High doses of vitamin B_6 may lower blood concentrations of anticonvulsant medication such as phenytoin and phenobarbitone, apparently by increasing the rate of metabolism of the drugs (Hansson & Sillanppaa, 1976).

Toxicity of vitamin B_6

Animal studies have shown that vitamin B_6 is potentially neurotoxic, causing peripheral neuropathy, with ataxia, muscle weakness and loss of balance in dogs given 200 mg pyridoxine/kg body weight for 40–75 d (Phillips *et al*. 1978), and the development of a swaying gait and ataxia within 9 d at a dose of 300 mg/kg body weight (Krinke *et al*. 1980). At the lower dose of 50 mg/kg body weight there are no clinical signs of toxicity, but histologically there is loss of myelin in dorsal nerve roots. At higher doses there is widespread neuronal damage, with loss of myelin and degeneration of sensory fibres in peripheral nerves, the dorsal columns of the spinal cord and the descending tract of the trigeminal nerve. The clinical signs of toxicity after 200–300 mg vitamin B_6/kg body weight regress within 3 months after the withdrawal of these massive doses, but sensory nerve conduction velocity, which decreases during the development of the neuropathy, does not recover fully (Schaeppi & Krinke, 1982).

At even higher doses (500 or 1000 mg/kg body weight by intraperitoneal injection) pyridoxine has been shown to cause a decrease in testis weight, histological changes in the testes and reduced spermatogenesis and sperm motility (Mori *et al*. 1992; Tsutsumi *et al*. 1995). The relevance of this, in terms of either the route of administration or the massive doses involved, to high oral intakes of the vitamin in human beings is doubtful.

Schaumburg *et al*. (1983) reported the development of sensory neuropathy in seven patients who had been taking between 2 and 7 g pyridoxine/d for several months (for a variety of reasons). On withdrawal of the vitamin supplements there was considerable recovery of neuronal function, although there was some residual nerve damage in some patients. In a later study, the same authors (Berger *et al*. 1992) gave 1 or 3 g vitamin B_6/d to healthy volunteers, and assessed both clinical signs and symptoms of sensory neuropathy and also quantitative sensory thresholds and other neurophysiology. Electrophysiological and clinical abnormalities developed at the same time, and developed sooner in subjects receiving the higher dose of the vitamin. Symptoms continued to progress for 2–3 weeks after cessation of the supplements before regressing, although plasma concentrations of PLP had returned to normal.

McLachlan & Brown (1995) reported the development of sensory neuropathy within 2 years of starting daily administration of 2000 mg/d to an infant with vitamin B_6-dependent seizures, but noted that over the following 16 years the neuropathy did not progress. However, most reports of patients with vitamin B_6 dependency diseases do not mention sensory neuropathy. Mpofu *et al*. (1991) reported electrophysiological and neurological examination of seventeen homocystinuric patients who had been treated with 200–500 mg vitamin B_6/d for 10–24 years; they found no evidence of neuropathy.

None of the studies in which there has been objective neurological examination has shown any evidence of sensory nerve damage at intakes of vitamin B_6 below 200 mg/d, and most have shown adverse effects only at considerably higher levels of intake.

One study suggests that relatively modest doses of vitamin B_6 may cause sensory nerve damage. Dalton & Dalton (1987) specifically asked patients who were taking 50–100 mg vitamin B_6/d for premenstrual syndrome to report symptoms such as tingling in the fingers, which might be interpreted as evidence of sensory neuropathy; a significant number of women taking 50 mg/d reported such symptoms. However, there was no neurological examination of any of the subjects, and no patients with similar premenstrual symptoms but not taking vitamin B_6 were asked the same questions. By contrast, Brush *et al*. (1988) conducted a retrospective examination of the records of 630 women who had received 40–200 mg vitamin B_6 for treatment of premenstrual syndrome, and noted that no symptoms were reported that suggested peripheral neuropathy.

The mechanism of nerve damage caused by vitamin B_6 supplements is not known. It is likely that PLP itself is responsible. In patients with hypophosphatasia (lack of plasma alkaline phosphatase (*EC* 3.1.3.1)), plasma concentrations of PLP are very considerably higher than normal, even at normal intakes of the vitamin (Whyte *et al*. 1985). However, the On-line Mendelian Inheritance in Man database (http://www3.ncbi.nlm.nih.gov/Omim/) lists seizures as the only neurological sign in the (autosomal recessive) infant and childhood forms of the disease, and no neurological signs at all in the (autosomal recessive) infant form of the disease. Furthermore, plasma concentrations of PLP do not rise above about 1000 nmol/l (10–15-fold higher than normal) even at very high levels of intake of the vitamin. However, plasma concentrations of pyridoxal and 4-pyridoxic acid do continue to increase with increasing intakes of the vitamin (Coburn *et al*. 1983). Schaeffer *et al*. (1995) similarly showed that while plasma concentrations of pyridoxal and 4-pyridoxic acid increased significantly in rats fed up to 250 times the normal of 7 mg pyridoxine/kg diet, for 10 weeks, PLP did not increase. There was no change in the concentration of B_6 vitamers in muscle, liver, kidney or brain, and no evidence of overt toxicity.

Cheng & Mudge (personal communication) have found that Schwann cells in culture grow less well when provided with pyridoxal in the culture medium than when the vitamin B_6 source is pyridoxine. Indeed, in their hands the addition of pyridoxal to the culture medium decreased cell survival even in the presence of an adequate concentration of pyridoxine. This suggests a possible neurotoxic action of pyridoxal. It is not known whether pyridoxal is similarly cytotoxic to other cell types in culture, although they stated that other research groups had observed improved survival of various cells in culture when pyridoxine rather than pyridoxal was added to the culture medium.

While there is no doubt that vitamin B_6 is neurotoxic in gross excess, there is considerable controversy over the way in which toxicological data have been translated into limits on the amounts that may be sold freely as ‘nutritional supplements’. This appears to have been achieved by the application of standard toxicology safety margins, and taking as the upper safe limit of intake 1% of the ‘no adverse effect level’. While this is appropriate for setting limits on additives and contaminants, it can be argued that it is not appropriate as a basis for setting limits on a nutrient; indeed for many nutrients an upper limit of intake

established in this way would be below the average requirement to prevent deficiency. There is little evidence, apart from the report of Dalton & Dalton (1987) of an uncontrolled study, that intakes of up to 200 mg (Bernstein, 1990) or 500 mg (Cohen & Bendich, 1986) vitamin B_6/d for prolonged periods, are associated with any adverse effects; clinical signs of neuropathy are associated with higher levels of intake, typically in excess of 1000 mg/d.

There is little convincing evidence that supplements of vitamin B_6 above levels to prevent deficiency have any beneficial effects, although a considerable number of women report or believe that supplements relieve the symptoms of the premenstrual syndrome. Equally, there is little convincing evidence that the levels of intake that are suggested or believed to be beneficial in treating the premenstrual syndrome are associated with any significant toxic hazard.

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