**Mark L. Wahlqvist and Delia M. Flint**
**Deakin University, Geelong, Victoria**

# Megavitamin Therapy: What Is the Evidence?

## There is a need for better understanding of the advent of megavitamin usage as a popular phenomenon

Much controversy surrounds the use of vitamins in amounts beyond the physiological range. The problem is not simply a question of altered requirements under different physiological and pathological circumstances, but whether there is special merit in short term or long term use of amounts several-fold the upper limit of what might be required as a vitamin in even a disease state. Some claims for megavitamin therapy have a reasonable basis in terms of relative deficiency resistant to physiological amounts or to pharmacological rather than physiological properties of these compounds; other claims have been advanced on the basis of interesting postulates, without substantiating evidence; yet other claims are in the realm of quackery or pseudoscience.

### What Is a Vitamin?

There is no chemical similarity amongst vitamins. All that they have in common is that they are essential nutrients required in small amounts for normal metabolic functions and are not synthesised in the body so that there must be exogenous sources.

There are 13 such substances recognised by various national and international expert committees. Four of these are the fat soluble vitamins, A, D, E, and K. Nine are water soluble: $B_1$ (thiamine), $B_2$ (riboflavin), niacin (or nicotinic acid – sometimes referred to as $B_3$), $B_6$ (which includes 3 naturally occurring related compounds, pyridoxine, pyridoxal and pyridoxamine), folacin (also referred to as folic acid, although folic acid as such is not found in food, but rather in medication), $B_{12}$, biotin, pantothenic acid and C (ascorbic acid).

Although exogenous sources may be necessary, vitamin D can be formed in the body from 7-dehydrocholesterol, vitamin A from carotenoids and niacin from tryptophan. The exogenous sources of vitamin K and biotin include gut microflora as well as food.

National committees have made recommendations about daily allowances or intakes (RDAs or RDIs) in the case of some vitamins and about safe and adequate ranges of intakes in the case of others where less information is available. These are shown in table I with reference to adult men and women. Adjustments are required, in general, for children and for women during pregnancy and lactation. They may also be required with advancing years. Requirements are less than allowances. An RDA or RDI will be a satisfactory intake for almost all healthy individuals in a community.

### What Is a Megadose?

An intake of a vitamin several-fold the amount required for normal bodily metabolism can be regarded as a megadose. At these levels, it is the pharmacological or toxicological properties rather than the physiological properties of a vitamin which are under consideration. Indeed, although one is still talking about the

**TABLE I.** Recommended daily allowances for adults in various countries for safe and adequate intakes of vitamins

| Sex | A (RE µg) | D (µg) | E (mg) | K (µg) | $B_1$ (mg) | $B_2$ (mg) | Niacin (mg) | $B_6$ (mg) | Folacin free (µg) | Folacin total (µg) | $B_{12}$ (µg) | Biotin (µg) | Pantothenic acid (mg) | C (mg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Australia** | | | | | | | | | | | | | | |
| M | 750 | - | - | - | 1.1 | 1.4 | 18 | - | 200 | - | 2.0 | - | - | 30 |
| F | 750 | - | - | - | 0.8 | 1.0 | 13 | - | 200 | - | 2.0 | - | - | 30 |
| **UK** | | | | | | | | | | | | | | |
| M | 750 | - | - | - | 1.2 | 1.6 | 18 | - | - | 300 | 3-4 | - | - | 30 |
| F | 750 | - | - | - | 0.9 | 1.3 | 15 | - | - | 300 | 3-4 | - | - | 30 |
| **USA** | | | | | | | | | | | | | | |
| M | 1000 | 5 | 10 | 70-140 | 1.4 | 1.6 | 18 | 2.2 | - | 400 | 3 | 100-200 | 4-7 | 60 |
| F | 800 | 5 | 8 | 70-140 | 1.0 | 1.2 | 13 | 2.0 | - | 400 | 3 | 100-200 | 4-7 | 60 |

same chemical, one is no longer, conceptually, referring to a vitamin. There is an exception to this view in so far as inherited metabolic disorders are concerned, since here a pharmacological dose may be required for the vitamin to have its physiological effect.

It is particularly important to appreciate that because a small amount of a chemical is essential, *more is not necessarily better* – to take such a view is to deny the scientific disciplines of pharmacology and toxicology.

## Acceptable Uses of Megadose Therapy with Vitamins (table II)

### Inherited Metabolic Disorders

*Thiamine-responsive Inborn Errors of Metabolism:* Several metabolic disorders have been described which are responsive to large doses of thiamine including:

1. Leigh's necrotising encephalopathy – abnormal inhibition of synthesis of thiamine triphosphate in neural tissue.
2. Maple syrup urine disease variant (branched chain ketoaminoaciduria) – mutant multienzyme complex.
3. Lactic acidosis – low hepatic pyruvate carboxylase activity.
4. Thiamine-responsive megaloblastic anaemia – unknown basis.
5. Intermittent cerebellar ataxia – abnormal pyruvate dehydrogenase.

*Hartnup Disease:* Where the clinical features of pellagra are found in the presence of an apparently adequate intake of niacin, a metabolic problem in niacin formation from tryptophan, or in its utilisation, should be suspected. In Hartnup disease, the most important abnormality is reduced absorption of tryptophan, but there is also an increased renal clearance of tryptophan and other amino acids. It is not usually necessary to give large doses of niacinamide (rather than niacin) to overcome the metabolic problem.

In the carcinoid syndrome, an increased need for niacinamide can also exist, because of the diversion of tryptophan away from niacin synthesis to that of serotonin.

*Inherited Vitamin $B_6$ Dependency Syndromes:* Amongst the disorders responsive to large doses of vitamin $B_6$ are:

1. Infantile convulsions – decreased affinity for $B_6$ of apoenzyme for glutamic acid decarboxylase with inadequate formation of the neurotransmitter $\gamma$-aminobutyric acid.
2. Sideroblastic anaemia (hypochromic) – abnormal apoenzyme for $\delta$-amino levulinic acid synthetase.
3. Xanthurenic aciduria (urticaria) – mutant apoenzyme for kynureninase.
4. Cystathioninuria (usually no clinical manifestations) – mutant apoenzyme for cystathionase.
5. Homocystinuria (clinical features may include mental retardation, premature atherosclerotic vascular disease, thromboembolism, osteoporosis and dislocated optic lens) – inadequate cystathionine synthase.

*Methylmalonicaciduria:* In this condition, which appears early in life and which is associated with homo-

cystinuria and hypomethioninaemia, there is a defective synthesis of the cobalamin (vitamin $B_{12}$) coenzymes, methylcobalamin and adenosylcobalamin. Doses of 1 to 2mg $B_{12}$ daily are helpful.

*Multiple Carboxylase Deficiency:* There are 4 carboxylase enzymes which have biotin as a prosthetic group. They are involved in the degradation of branched chain amino acids, leucine, isoleucine and valine, and in the propionate-methylmalonate pathway. Their disorder is reflected in organic acidaemia and aciduria. Maple syrup urine disease is one such disorder.

*Leiner's Disease:* This disorder of infancy is an erythroderma with exfoliation. It has been found responsive to 5 to 10mg biotin daily. Seborrhoeic dermatitis has also been found responsive to biotin.

## Medication-induced Increased Requirements

*Methotrexate and Pyrimethamine:* These drugs bind dihydrofolate reductase, although to a greater extent for methotrexate than for pyrimethamine. Less folacin polyglutamates are formed and DNA, RNA and protein synthesis reduced. However, folinic acid can still be used in the presence of inhibited reductase enzyme. With pyrimethamine, large doses of folic acid may overcome the inhibition.

*Isoniazid, Cycloserine, Penicillamine, Hydralazine, and Levodopa* [1]*:* These drugs form complexes with vitamin $B_6$ complexes and inhibit pyridoxal kinase enzymes. Increased intakes of vitamin $B_6$ may be required to deal with the problem, though care must be taken lest supplemental $B_6$ interferes with the therapeutic efficacy of these agents.

*Anticoagulant Overdosage:* The carboxylation of glutamic acid in coagulation factor proteins is dependent on vitamin K. Coumarin anticoagulants, like warfarin, probably act by inhibiting the regeneration of vitamin K from the storage form vitamin K 2,3-epoxide. Amounts of vitamin K in the milligram range reactivate prothrombin synthesis within minutes, leading to adequate levels within hours.

## Hyperlipidaemia

Niacin or nicotinic acid but not niacinamide, in gram dosage (usually about 3g daily in divided dosage) is one of the most effective agents available for the management of hyperlipidaemia of most kinds. It lowers cholesterol and triglyceride concentration and increases high density lipoprotein cholesterol concentrations. These are directional changes of potential value in decreasing risk of atherosclerotic vascular disease. It is also valuable in combination with clofibrate and especially the resins cholestyramine and colestipol for additional lipid-lowering effectiveness. In the past, its main problem has been vasodilator effects during introduction of therapy. These are prostaglandin-mediated and are largely prevented by 1 aspirin tablet daily. Slow increases in the dosage of nicotinic acid over a month minimises any risk of increased plasma levels of hepatic enzymes. Gout and hyperuricaemia are relative contraindications. Diabetes is also a relative contraindication to its use.

**TABLE II.** Acceptable uses of megavitamin therapy

| Disorder | Vitamin |
|---|---|
| **Inherited Metabolic Disorders** | |
| Leigh's necrotising encephalopathy, lactic acidosis, 'maple syrup' urine disease | Thiamine |
| Hartnup disease | Niacinamide |
| Inherited vitamin $B_6$ dependency | Vitamin $B_6$ |
| Methylmalonicarduria | Vitamin $B_{12}$ |
| Multiple carboxylase deficiency | Biotin |
| Leiner's disease | Biotin |
| **Drug-induced increased requirement** | |
| Methotrexate and pyrimethamine | Folinic acid |
| Isoniazid, cycloserine, penicillamine, hydralazine and levodopa | Vitamin $B_6$ |
| Anticoagulant (warfarin) overdosage | Vitamin K |
| **Hyperlipidaemia** | Nicotinic acid |
| **Wernicke's encephalopathy and beriberi heart disease** | Thiamine |
| **Disfiguring acne** | Vitamin A analogues |
| **Malabsorption syndromes** | Vitamins A, D, E and K, folacin, $B_{12}$ |
| **Urinary tract infection** | Vitamin C |

## Wernicke's Encephalopathy (cerebral beriberi and beriberi heart disease)

With Wernicke's encephalopathy, it is important to correct the thiamine deficiency as quickly as possible.

**TABLE III. Possible uses of megavitamin therapy**

| Disorder | Vitamin |
|---|---|
| Prevention of congenital abnormalities | |
| Neural tube defects | B group vitamins<br>Folacin |
| Cleft lip | B group vitamins<br>Folacin |
| Treatment of cervical dysplasia | Folacin |
| Reduction in risk of certain tumours (lung, prostrate) | Vitamin A analogues<br>Carotenoids |
| Diminution of symptoms of common cold | Vitamin E |
| Reduction in symptoms of premenstrual tension, menopause, 1st trimester of pregnancy and oral contraceptive pill | Vitamin $B_6$ |
| Symptoms for osteoarthritis and rheumatoid arthritis | Pantothenic acid |
| Treatment of toxic amblyopia | Vitamin $B_{12}$ |
| Prevention of retrolental fibroplasia | Vitamin E |
| Prevention of postoperative thromboembolism | Vitamin E |

Thus, although 2 to 3mg thiamine will ameliorate the ophthalmological signs, it is recommended that a parenteral dose of 50mg daily be given until food intake is normal. A similar approach is used with beriberi heart disease.

### Disfiguring Acne

It has long been recognised that topical vitamin A acid (retinoic acid) affects keratinisation and can be useful in the management of acne. It can also be used orally for the same purpose. In a normal diet, very little vitamin A activity is obtained as the acid, most being preformed retinol or its ester, retinyl ester, on the one hand, or pro-vitamin A carotenoids, such as $\beta$-carotene on the other. Plasma levels of retinoic acid are very much lower than those of retinol or $\beta$-carotene. Side effects of oral retinoic acid are few for intakes of 20 to 40mg daily with toxicity emerging at 100mg daily. More recently, an analogue of retinoic acid, 13-cis-retinoic acid (isotretinoin) has been shown to be of particular value in the treatment of severe acne; it is also being evaluated for prophylaxis and management of certain epithelial tumours.

### Malabsorption Syndromes

Where the underlying cause of a malabsorption syndrome cannot be corrected, as in cystic fibrosis or chronic pancreatitis, it may be necessary to administer higher than normal recommended amounts of the fat soluble vitamins A, D, E and K as well as certain water soluble vitamins such as folacin and vitamin $B_{12}$.

### Urinary Tract Infection

When urinary pH is below 5.5 it tends to be antibacterial, thus substances which can acidify the urine can be helpful in dealing with urinary bacterial infections. There are several such agents in use such as ammonium chloride, mandelic acid and ascorbic acid. With chronic use of ascorbic acid in large doses, however, it must be remembered that it is also uricosuric and may predispose to uricosuria.

**There is controversy as to the protection against infection by the common cold virus conferred by vitamin C**

## Possible Uses of Megavitamin Therapy (table III)

### Prevention of Congenital Abnormalities

The possible prevention of neural tube defects by periconceptual vitamin supplementation has been the subject of several British studies [2,3]. The matter is of particular importance to prospective parents where 1 child has already been affected, since the risk for a further child is about 4% as opposed to 0.2% for Australasia in general. Diet has been suspected for some time as a factor, especially in groups where the incidence of neural tube defects is high. Most attention has been focused on folic acid as the supplement most likely to be effective, but dosage has ranged from 360 to 4,000$\mu$g daily. There were problems in design, analysis and interpretation of each study unfortunately, so the findings are not conclusive. The ethical debate about further trials may prevent a definitive answer being obtained.

Yet another study in Czechoslovakia by Tolarova [4] has suggested that a periconceptional multivitamin preparation and 10mg folic acid per day supplement may reduce the risk of cleft lip.

### Treatment of Cervical Dysplasia

Another possible use for folic acid supplementation is in women with cervical dysplasia. An American study has indicated that 10mg of folic acid daily for 3 months led to a reduction in cervical dysplasia [5].

### Reduction in Risk of Certain Tumours

Several studies have indicated that a diet characterised by a high intake of green, leafy and yellow vegetables is associated with a lower risk of lung cancer [6]. The same may also be true for prostatic and other tumours. Taken together with experimental evidence, it has been suggested that the carotenoids contained in these vegetables are the most likely candidates for this protective effect. However, other properties of these foods may also be important. A controlled trial is now under way amongst American medical practitioners to evaluate the place of carotenoid supplementation in prevention of tumour development.

### Diminution of Symptoms of Common Cold

Although it is known that scorbutic individuals are prone to infection, there is controversy as to the protection against infection that large doses of vitamin C might confer on apparently healthy individuals [7]. It does not necessarily follow that, because tissue levels of ascorbic acid fall during an infection, more is required or that, if more had been provided before the infection, the infection might not have supervened. The most common model for a protective effect of vitamin C against infection is that of the common cold virus. There have been many trials of this kind, with varying effects and interpretations of those effects. A recent Australian study of 95 pairs of identical twins reflects the results obtained from a majority of these trials [8]. The study was conducted by Carr and colleagues of the Department of Pharmacology at the University of Sydney, comparing the effects of vitamin C tablets with placebo. The dose was 1g daily and the study was double blind. Subjects were followed for 100 days. Vitamin C did not reduce the number of episodes of the common cold and therefore was not effective in its prevention. The average duration of the cold was, however, reduced from 6.4 to 5.2 days, a reduction of 19%. This effect was statistically significant although the severity of the cold was not significantly different.

Thus, a decision must be made whether the benefits of the use of large doses of vitamin C outweigh the inconvenience of the need for continuous medication and the risks of the high dosage. In a study in southern Wales by Baird and colleagues in 1979 [9], supplementation with a much smaller dose of 80mg ascorbic acid daily led to a barely significant reduction in symptoms of the common cold. This dosage, however, is much closer to the recommended daily allowances for ascorbic acid. The body has a number of different mechanisms for dealing with infectious agents, be they bacteria or viruses, which include the production of antibodies and cellular mechanisms. There is some evidence that some of the cellular actions may involve ascorbic acid. In itself, this is not necessarily an argument for 'the more the better' [10].

## Uncertainty surrounds the use of vitamin $B_6$ for correction of sex hormone change-related malaise in women

### Reduction in Symptoms of Premenstrual Tension, Menopause, 1st Trimester of Pregnancy and Oral Contraceptive Pill

The requirement for vitamin $B_6$ is increased in a number of situations [11,12]. Although some of the metabolic changes that occur in pregnancy suggest vitamin $B_6$ deficiency, supplementation has, in general, not affected the outcome of pregnancy. Sometimes vitamin $B_6$ is used to prevent morning sickness, but the evidence for its effectiveness is equivocal. Similarly, the use of the oral contraceptive pill can produce changes in tryptophan metabolism that suggest vitamin $B_6$ deficiency. Up to 30mg of vitamin $B_6$ may be required to correct these abnormalities, more than can be obtained from food. In 1970 a study by Baumblatt and Winston [13] suggested that some women on the oral contraceptive pill who were given vitamin $B_6$ supplements had less malaise. The problem of malaise should now be

less as the oestrogen content of the pill is lower than previously. Moreover, work by Bender and Wernicke in 1981 indicated that the effects of oral contraceptives on tryptophan metabolism might not be due to a direct effect of oestrogen metabolites on vitamin $B_6$-dependent enzymes [14].

The same uncertainty surrounds the use of vitamin $B_6$ supplements in menopausal women as in other situations where changes in sex hormones are taking place.

## Symptoms of Osteoarthritis and Rheumatoid Arthritis

Although induced pantothenic acid deficiency in man is not associated with joint symptoms, work in the early 1960s in rheumatoid arthritis by Barton-Wright and Elliott and, in osteoarthritis, by Annand, suggested that pantothenic acid supplementation might ameliorate symptoms. The matter was taken up again by the UK General Practitioners Research Group in 1980 [15]. The study involved 94 patients and was double blind with the dosage built up over several days to a total daily dose of 2g calcium pantothenate orally. Patients with both osteoarthritis and rheumatoid arthritis were included. For the total patient group, treatment with calcium pantothenate revealed no benefits over treatment with placebo. However, the subgroup of patients with rheumatoid arthritis who completed the study recorded significant reductions in morning stiffness, degree of disability and severity of pain with calcium pantothenate, but not with placebo. It would appear that further trials with calcium pantothenate in rheumatoid arthritis are justified.

## Treatment of Toxic Amblyopia

That optic neuropathy or amblyopia can be of nutritional origin seems clear. It has been seen particularly during war time and also in association with alcohol and tobacco use. The particular deficiency of nutrient(s) responsible, however, has not been elucidated. Deficiencies of thiamine and of vitamin $B_{12}$ can produce degenerative changes in the optic nerve. It was suggested that degeneration of cyanide by tobacco smoke might cause the problem, especially in association with vita-

min $B_{12}$ deficiency since hydroxocobalamin can serve to reduce cyanide load through its conversion to cyanocobalamin. However, there are sufficient data to be sure that tobacco does indeed have these effects. Where vitamin $B_{12}$ has been used in the management of amblyopia, it has been administered as hydroxocobalamin in doses of about 1mg daily.

### Reduction of Retrolental Fibroplasia

The problem of retrolental fibroplasia still occurs despite the recognition of the effects of high oxygen tension in premature infants. Vitamin E supplementation may have a place in its prevention [16], and may aid the prevention of postoperative thromboembolism.

## Unacceptable Uses of Megavitamin Therapy (table IV)

### Prevention of Ischaemic Heart Disease

Probably the most widespread claim for vitamin E is that it protects against and is useful in the treatment of coronary heart disease. That vitamin E might be helpful is plausible, but not proven, on the following counts. Firstly, dietary polyunsaturated fatty acids help to lower blood cholesterol level and reduce the risk of atherosclerotic disease. Vitamin E helps to prevent the breakdown of polyunsaturated fatty acids and therefore may make those ingested more useful. Secondly, the fats of the cell membranes of cardiac muscles may be stabilised by vitamin E, but it is another matter whether this could play a role in terms of heart disease. Impetus to the idea that vitamin E may be useful in prevention and treatment of heart disease was provided by R.J. Shute and his 2 sons, Evan and Wilfrid [18]. They used this vitamin first in a gynaecological practice and thought it alleviated chest pain in patients with heart disease. In 1946, they reported their results which were then publicised by Time Magazine. Since then, the idea has been popularised. Despite several attempts, these results have not been confirmed by other investigators. The concern that increased intake of polyunsaturated fatty acids in developed countries has not been accompanied by a concomitant intake of vitamin E is also not well-founded since most of the polyunsaturated fatty

acids come from vegetable oils which are also good sources of vitamin E.

### Management of Schizophrenia and Other Psychoses

The advocacy of large doses of vitamins, especially niacin, but also thiamine, vitamin $B_6$, vitamin C and folic acid began in 1973 and 1974 with Abram Hoffer and Linus Pauling. It was in this context that the concept of orthomolecular psychiatry and medicine arose. Pauling defined it as 'the achievement and preservation of mental health by varying the concentration in the human body of substances that are normally present such as vitamins'. This view appeared in the American Journal of Psychiatry in 1974. Although a great deal of basic research has proceeded on vitamin transport into and metabolism in the central nervous system, no convincing supportive evidence has been forthcoming since their views were first published. Although it is conceivable that, in rare genetic diseases, brain apoenzymes may require larger amounts of vitamins, the general application of large doses of vitamins to psychiatric disorders would appear unwarranted.

**Large doses of vitamin C and the B group vitamins in the management of hangover are not recommended**

### 'Minimal Brain Dysfunction' and Learning Difficulties

It is not unusual for children with chronic neuro-psychiatric disorders to be subjected to various therapies and the use of megadoses of vitamins has been one such approach. The basis for this approach is somewhat akin to that advanced for the management of psychotic disorders. It has also been tied in with the views of Feingold that food sensitivity can lead to hyperactivity; it has been suggested that large doses of vitamins might offset this problem. In fact, the connection between diet and behaviour seems somewhat tenuous on the basis of the literature currently available, except for a few children who might be sensitive to compounds like the colouring agent, tartrazine. Problems of nutrient intake are more likely to emerge as a consequence of the diet applied to these children since they are often unduly restricted even in so far as fruits and vegetables are concerned.

**TABLE IV.** Unacceptable uses of megavitamin therapy

| Disorder | Vitamin |
|---|---|
| Prevention of ischaemic heart disease | Vitamin E |
| Management of schizophrenia and other psychoses | Niacin |
| Minimal brain dysfunction and learning difficulties | Multivitamin preparations |
| Management of 'hangover' following alcohol abuse | Multivitamin preparations |

### Management of 'Hangover' Following Alcohol Abuse

The use of vitamins in the management of hangover has been of 2 kinds, one the use of large doses of vitamin C, advocated by Pauling, and the other use of large doses of B group vitamins, especially thiamine. Again, Pauling's rationale is along the lines advanced for neuropsychiatric disease. There are little data to support this view. The suggested use of various vitamins also derives, in part, from the well-recognised tendency of alcohol abuse to lead to nutrient deficiency, especially where food intake has suffered as a result of alcohol abuse. It may well be that many of the symptoms of hangover are related to a combination of the metabolic acidosis that arises from alcohol ingestion along with the associated dehydration following inhibition of antidiuretic hormone secretion. It is a fundamental error in health logic to think that because alcohol produces one kind of problem, another consequence can be rectified in the same way. The pathways to these consequences appear to be quite different and the only common recommendation that can be made is to avoid alcohol abuse.

## Risks of Megavitamin Therapy

### The Problem of Poor Health Logic

Errors in thinking about the cause, development and management of disease can be important factors add-

ing to ill-health. The notion that if a substance is an essential nutrient more of it will be better is a fundamental error in thinking, at least as it applies to the majority.

Another error that could lead to inappropriate nutrient supplementation would be that symptoms which can arise because of a nutritional problem but which are arising for non-nutritional reasons, are attributed to the possible nutritional aetiology. Errors in thinking about health from a nutritional point of view are also likely to occur in a wider range of health problems.

### A Sense of False Security About One's Health

Such a host of disorders, not all of which are covered in this paper, have been advanced as responsive to megadose vitamin therapy, that it would be very easy for a delay in diagnosis and management of a non-nutritional health problem to occur. There is particular difficulty where the approach to megavitamin therapy has reached the point where it is a belief or creed. Dogma of this kind has always been rejected as an acceptable part of the western tradition of scientific medicine.

### Low Cost-Benefit

For the application of megadose vitamin therapy to areas where there is little evidence to justify it, only a placebo effect may be obtained. This, of course, may be of value provided no harm is done. Cost also remains an important consideration under these circumstances. It is not uncommon for patients to commit 10 to 15% of an average weekly income in the purchase of an array of vitamin pills. The effects of such a financial outlay on the remainder of the essential household budget need careful reflection.

### Toxicity

Much is known about the toxicity of the fat soluble vitamins A and D, but much less about the effects of E and of the water soluble vitamins. A particularly important consideration here is that it is one thing to observe acute toxicity and another to allow for the emergence of long term toxicity with chronic usage. Since most vitamins have only become available in quantity since the 1950s, sufficient time may not have elapsed for chronic toxicity to have been evidenced. This applies particularly to the institution of long term vitamin supplementation in children.

An important general risk of prolonged megadose therapy is that dependency may arise. This does seem to be the case with at least vitamin $B_6$ and vitamin C where rapid reduction in dose can lead to the appearance of deficiency-like features.

Since megadose vitamin C has been one of the most popularised of all megadose therapies, it may be worthwhile indicating the sorts of risks which are becoming apparent. Rebound scurvy on reduction of dosage has already been mentioned, oxaluria does occur, but the risks of oxalic acid stones have probably been overstated. There is a possible risk of uric acid stones arising on account of the induced uricosuria. However, this problem is theoretical and there has been no reported increased incidence of uric acid stones with megadose use of ascorbic acid. There may be some adverse nutrient interaction with high dose vitamin C ingestion. For example, Herbert has produced some evidence that the availability of vitamin $B_{12}$ might be reduced [19].

**A general risk of prolonged megavitamin therapy, particularly with vitamin $B_6$ and C, is that a rapid reduction in dose may lead to deficiency-like features**

Vitamin C can make iron from plant sources more available and this might, in general, be an advantage, but may become a risk in subjects prone to iron storage diseases. Vitamin C can also increase absorption of toxic metals, such as mercury and this might be a hazard in those having a large intake of fish with a high mercury content. There are several possible interactions of vitamin C with drugs including warfarin aspirin and antidepressants. There have been mixed reports about the impairment of fertility by high dosage vitamin C. In the experimental animal, there is limited evidence that a diabetes-like state might be induced by high doses of vitamin C, possibly because of increased levels of dehydroascorbic acid. Some work suggests that those

on vitamin C supplements might be more prone to deep vein thrombosis. There is presently controversy about the combined use of vitamin C and desferrioxamine in the management of iron storage disease because of possible effects on cardiac function.

### Undue Emphasis on Medication

Perhaps one of the major concerns about megadose use of vitamins, in its popularised form, is that people have been encouraged to attend to their nutritional problems through the use of medication rather than through the use of food. For a child, this may be of even more consequence, since this approach is being learned for life.

*In summary,* the use of vitamins in large doses has been greatly popularised in recent years. It seems likely that much of the impetus for this has been either commercial, or erroneous thinking about strategies which might allow improvement of health as opposed to the correction of definable nutrient deficiency. However, there is a group of disorders, affecting small numbers of people, in which the use of doses of vitamins several-fold the recommended intakes for healthy persons, is justified. These include inherited metabolic disorders, medication-increased requirement, hyperlipidaemia, disfiguring acne, malabsorption syndromes and urinary tract infections. There are other possible uses, but much work needs to be done to clarify the role of megadose vitamin therapy in these situations. Of even more importance is the need for better understanding of the advent of megavitamin usage as a popular phenomenon. It is estimated that in excess of 10% of Australasians regularly consume nutrient supplements. □

Authors: **Mark L. Wahlqvist** is Foundation Professor of Human Nutrition at Deakin University, Geelong and Consultant Physician, Prince Henry's Hospital, Melbourne. His research interests include energy metabolism, carbohydrate and lipid disorders, nutritionally vulnerable groups in the Australian community, and the nutrient composition of food.

**Delia M. Flint** is Lecturer in Dietetics, Department of Human Nutrition, Deakin University, Geelong and Consultant Dietitian, National Research Institute for Gerontology and Geriatric Medicine, Mt Royal Hospital, Melbourne. Her research interests include the nutritional problems of elderly Australians and practical methods used to assess the nutritional status of individuals and groups.

## References

1. Anonymous: Vitamins to prevent neural tube defects. Lancet 2: 1225-1256 (1982).
2. Roe, D.: Drug nutrient interaction incompatibilities; in Clinical Nutrition for the Health Scientist, pp.85-97 (CRC Press, Florida 1979).
3. Sheffield, L.J. and Pollard, A.C.: Neural tube defects: Can they be prevented? Current Therapeutics 23: 7-12 (1982).
4. Tolarova, M.: Periconceptional supplementation with vitamins and folic acid to prevent recurrence of cleft lip. Lancet 2: 217 (1982).
5. Check,W.A.: Folate for oral contraceptive users may reduce cervical cancer risk. Journal of the American Medical Association 244 (7): 633-634 (1980).
6. Bonjour, J-P.: Biotin-dependent enzymes in inborn errors of metabolism in humans. World Review of Nutrition and Dietetics 38: 1-88 (1981).
7. Phillips, M. and Betz, A. (Eds): Diet and resistance to disease; in Advances in Experimental Medicine and Biology, Vol. 135 (Plenum Press, New York 1981).
8. Carr, A.B.; Einstein, R.; Lai, L.Y.C.; Martin, N.G. and Starmer, G.A.: Vitamin C and the common cold, using identical twins as controls. Medical Journal of Australia 2 (8): 411-412 (1982).
9. Briggs, D.R.; Jones, G.P. and Wahlqvist, M.L.: Vitamins E, C and the B-complex: Their uses and misuses. Australian Family Physician 11 (4): 270-278 (1982).
10. Wahlqvist, M.L. and Huang, S.S.: Use and Abuse of Vitamins (Sun Books, Melbourne 1983).
11. Mattes, J.A. and Martin, D.: Pyridoxine in premenstrual depression. Human Nutrition: Applied Nutrition 36A: 131-133 (1982).
12. Rutishauser, I.H.E.: Vitamin B-6. Journal of Food and Nutrition 39: 158-167 (1982).
13. Committee on Dietary Allowances, Food and Nutrition Board: Recommended Dietary Allowances, 9th revised edition (National Academy of Science, Washington DC 1980).
14. Counsell, J.N. and Hornig, D.H. (Eds): Vitamin C: Ascorbic acid (Applied Science Publishers, London and New Jersey 1981).
15. General Practitioner Research Group: Calcium pantothenate in arthritic conditions. The Practitioner 244: 208-211 (1980).
16. Hittner, H.M.; Godio, L.B.; Rudolph, A.J.; Adams, J.M.; Garcia-Prats, J.A.; Friedman, Z. et al.: Retrolental fibroplasia: Efficacy of vitamin E in a double-blind clinical study of preterm infants. New England Journal of Medicine 305: 1365-1371 (1981).
17. Kanofsky J.D. and Kanofsky, P.B.: Prevention of thromboembolic disease by Vitamin E. New England Journal of Medicine 305: 173-174 (1981).
18. Cunliffe, W.J.: Vitamin A in dermatology: in Briggs (Ed.) Vitamins in Human Biology in Medicine, pp.157-185 (CRC Press, Florida 1981).
19. Department of Health and Social Security: Recommended daily amounts of food energy and nutrients for groups of people in the United Kingdom (Her Majesty's Stationery Office, London 1979).

## Further Reading

Flint, D.M.; Wahlqvist, M.L. and McLennan, E.A.: Determination of vitamin requirements in human nutrition. Proceedings of the Nutrition Society of Australia 5: 52-62 (1980.)

Goodhart, R.S. and Shils, M.E.: Modern Nutrition in Health and Dis-

ease, 6th Edition (Lea and Febiger, Philadelphia 1980).
Haydey, R.P.; Reed, M.L.; Dzubow, L.M. and Shupack, J.L.: Treatment of keratoacanthomas with oral 13-*cis*-retinoic acid. New England Journal of Medicine 303 (10): 560-562 (1980).
Herbert, V.: Nutrition Cultism: Facts and Fictions (George F. Stickley, Philadelphia 1981).
Jukes, T.H.: Megavitamins and food fads; in Hodges (Ed.) Human Nutrition: A Comprehensive Treatise, volume 4, Nutrition: Metabolic and Clinical Applications pp.257-292 (Plenum Press, New York 1979).
Mullen, D.P.R.; Lloyd, J.K. and Wolff, O.H.: Vitamin E and neurological function. Lancet 1: 225-227 (1983).
McMichael, A.J.: Orthomolecular medicine and megavitamin therapy. Medical Journal of Australia 1: 6-8 (1981).
National Health and Medical Research Council: Dietary allowances for use in Australia (Australian Government Publishing Service, Canberra 1979).
Paul, A.A. and Southgate, D.A.T. : In McCance and Widdowson (Eds) The Composition of Foods, 4th revised edition (Her Majesty's Stationery Office, London 1978).
Strauss, B.J.G.; Huang, S.S. and Wahlqvist, M.L.: Long term mineral and vitamin supplements: Which patients will need them? Current Therapeutics 23: 59-66 (1982).
Thomas, S. and Corden, M.: Metric Tables Composition of Australian Foods (Australian Government Publishing Service, Canberra 1977).
Wahlqvist, M.L.: Effects on plasma cholesterol of nicotinic acid and its analogues; in Briggs (Ed.) Vitamins in Human Biology and Medicine (CRC Press, Florida 1981).
Wahlqvist, M.L. (Ed.): Food and Nutrition in Australia (Methuen, Sydney 1982).