Vitamin use in clinical medicine

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A vitamin is an organic substance that is found in food, is not made in the body, and is required in small quantities, usually as a cofactor for enzymes.[1,2]

The International Union of Nutrition Sciences and other international scientific organizations recognize 13 vitamins. The substances that are recognized as vitamins include four which are fat-soluble, namely, A (retinol, retinyl esters, retinoic acid and carotenoids, of which the most biologically important is beta-carotene), D (cholecalciferol or D_3 and its metabolites, ergocalciferol or D_2, one of the group of sterols that are found in plants), E (tocopherols) and K (phylloquinone or K_1, multiprenyl menaquinones or K_2, menadione or K_3, a synthetic provitamin K); and the nine vitamins which are water-soluble — B_1 (thiamin), B_2 (riboflavin), niacin (nicotinic acid, vitamin P_P or B_3; niacinamide as an alternative form of this vitamin), B_6 (pyridoxine, pyridoxal and pyridoxamine), folacin (folic acid or folates), B_{12} (hydroxocobalamin, cyanocobalamin and other forms), biotin, pantothenic acid and C (ascorbic acid).

Inasmuch as vitamin D can be made in the skin from 7-dehydrocholesterol or ergosterol under the influence of ultraviolet light, it is not necessarily a vitamin; it becomes so when exposure to sunlight is restricted. For vitamin K, probably at least half of its requirements can be obtained from gut bacteria. Biotin can also be made by bacteria in the large bowel, from which it can be absorbed.

Functions of vitamins

The principal functions of vitamins are set out in the box. It does not always follow that the hierarchy with which signs of vitamin deficiency emerge will reflect the perceived hierarchy of principal functions. This may, in part, reflect the conservation of nutrient for one function over another.

Importance of source of vitamins

The only vitamin source that can be regarded as natural is food. Food provides a physicochemical and chemical environment for the presentation of vitamins to the gastrointestinal tract, which cannot easily be simulated pharmaceutically. Examples of relevant physicochemical properties are viscosity, particle size and pH. The chemical environment of food creates significant nutrient–nutrient interactions, such as fat-soluble vitamins with fat, and nutrient–non-nutrient interactions, such as folacin with citric acid. It should, in any case, be remembered that most of the evolutionary experience of our species has been with food and not with other sources of nutrients.[28]

This is not to say that vitamins cannot be synthesized and chemically identical to those in food. However, their bioavailability is likely to be more appropriate when ingested in food and their stability can be more of a problem when they are removed from the food environment. Folic acid as used therapeutically is not found in food in that form; bioflavinoids in food confer stability on ascorbic acid.

A distinction needs to be made between the nutritional physiology of vitamins and their therapeutic use. It is, of course, possible

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Principal functions of vitamins

Vitamin	Function
A[3,4,5]	Vision, pigment epithelial cell function; growth and differentiation; nitrogen metabolism (probable)
D[3,6]	Stimulation of intestinal uptake of calcium; stimulation of dissolution of bone mineral; enhancement of tubular reabsorption of phosphate
E[3,7,8]	Antioxidant or free radical scavenger; inhibition of platelet aggregation (uncertain physiological role); erythropoiesis and red-cell survival; neurological function
K[3,9]	Post-translational formation of gamma-carboxyglutamic acid in proteins in liver (prothrombin, factors VII, IX and X), bone and kidney
B_1[3,10,11]	Energy metabolism (ATP production); synthetic mechanisms (transketolase reaction); membranes and nerve conduction
B_2[3,12,13]	Intermediary metabolism, conversion to the coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD)
Niacin[3,14,15]	As nicotinamide, niacin is part of the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotidephosphate (NADP). NAD is involved in dehydrogenase reactions in fat, carbohydrate and amino acid metabolism and possibly DNA repair. NADP participates in the dehydrogenation reactions and especially the hexose monophosphate shunt of glucose metabolism. Reduced NADP is involved in fat and steroid synthesis
B_6[3,16,17]	Pyridoxal phosphate (PLP) is the principal active form of B_6 and serves as a coenzyme in many areas of amino acid metabolism. Among these are neurotransmitter formation and porphyrin synthesis
Folacin[3,18,19]	Involved in one carbon transfer, from amino acids to other amino acids and in the biosynthesis of the purine and pyrimidine component of nucleic acids; tetrahydrofolate as polyglutamate forms are the natural coenzymes. Cells can not divide without folacin
B_{12}[3,20,21]	In normal haemopoiesis, B_{12} facilitates the cyclic metabolism of folacin, required for nucleic acid synthesis; in the nervous system, myelination, probably related to methyl group transfer; through formation of cyanocobalamin from hydroxocobalamin, cyanide detoxification (a possible minor role)
Biotin[3,22]	Several biotin-dependent carboxylases, where biotin serves as a cofactor for carbon dioxide transfer. Observations of those with deficiency suggest that this is most critical for the integument and nervous system, whether directly or indirectly, because of limited disposal of organic acids
Pantothenic acid[3,23,24]	Part of coenzyme A and of acyl carrier protein (ACP). Involved in the formation of fatty acids, cholesterol, porphyrin and acetyl choline; connective tissue formation (wound healing)[10]
C[3,25-27]	Proline hydroxylation in collagen synthesis; neurotransmitter formation and breakdown; muscle function, carnitine biosynthesis; immune function; detoxification and drug metabolism, prevention of nitrosamine formation and in hepatic microsomal enzyme function; cholesterol metabolism

to use food and/or a nutrient supplement to deal therapeutically with a nutrient deficiency. It is also possible to exploit the pharmacological rather than the physiological actions of vitamins in some cases. The use of nicotinic acid in the management of hyperlipidaemia is one of the few proven examples of this and the amounts of nicotinic acid that are required are not to be obtained from food; the source is a pharmaceutical preparation and the effects are pharmacological.[29] Other suggested pharmacological effects of nicotinic acid in diseases such as psychosis have not stood up to rigorous therapeutic trial.[30] In the rare circumstances of inherited disorders of metabolism, a physiological effect may be achieved by the use of a pharmacological dose of a nutrient to overcome a metabolic block.[31,32]

Good food sources of vitamins are shown in boxes. More detailed information is provided elsewhere.[2,33] It is clear that a wide variety of foods, preferably of high nutrient density, needs to be eaten to reduce the risk of vitamin deficiency. When this is not so, deficiency can be seen.[34]

Good and fair sources of vitamins — fat-soluble*

Vitamin A

In 100 g of:	Retinol (μg)	Carotenes (μg)
Cod liver oil	28 400	1050
Palm oil	0	7000
Lamb's liver (fried)	20 600	10
Carrots	0	2000
Sweet potato	0	670†
Spinach	0	1000
Egg yolk	660	100
Milo	625	0
Butter	890	110
Margarine (table)	580	70
Cheese	250	50
Milk	40	5

In 100 g of:	Vitamin D (μg)
Cod liver oil	210
Fatty fish	5–25
Margarine	8
Milo	8
Egg yolk	5
Butter	1
Cheese	0.2
Milk (for comparison)	0.01

In 100 g of:	Vitamin E (mg)
Wheatgerm	140
Polyunsaturated vegetable oils	20–280
Peanut oil	15–20
Olive oil	5
Egg yolk	1
Nuts	1–20
Green leafy vegetables	0.1–0.5
Carrots	0.5
Milk (for comparison)	0.02

In 100 g of:	Vitamin K (μg)
Cabbage	125
Spinach	89
Pork liver	25
Whole wheat	17
Chicken liver	7

*Adapted from reference 2. †Varies with variety.

Recommended dietary intakes

Recommended nutrient intakes, which are sometimes referred to as recommended allowances, allow for a wide range of circumstances.[2,35] It should be remembered that they have been developed so that they already exceed nutrient requirements and they acknowledge the range of nutrient requirements that are likely to be found in healthy individuals. They do not allow for factors such as illness or interactions with certain drugs. However, for short periods of illness, the storage of vitamins by the body and the early resumption of a normal eating pattern will mean no vitamin deficiency emerges. When a recommended dietary intake (RDI) for a nutrient has not yet been formulated, a "safe and adequate" range can generally be advised. Recommended dietary intakes that are currently in place for Australia are shown in Table 1.

Because the most complete vitamin recommendations are those that are available for the United States,[35] these are also shown (Table 2). The National Health and Medical Research Council of Australia is currently taking steps to formulate recommendations for all vitamins.

Vitamin toxicology

If taken in sufficient quantities over sufficiently long time periods, all chemicals must assume toxicological properties. That the chemical is an essential nutrient does not mean that it is devoid of potential toxicity;

TABLE 1: Recommended daily dietary intakes for different individuals*

Individual/age (years)	Weight (kg)	Energy (kJ)	Energy (kCal)	Protein (g)	Vit. A† (μg)	Vit. D (μg)	Vit. B_1 (mg)	Vit. B_2 (μg)	Niacin (mg)	Vit. B_6 (mg)	Vit. B_{12} (μg)	Folacin (μg)	Vit. C (mg)
Men													
19–64	70	11 600	2800	70	750	—	1.1	1.7	18–20	1.3–1.9	2.0	200	30
65 and older	70	8800	2100	70	750	—	0.9	1.3	14–17	1.0–1.5	2.0	200	30
Women													
19–54	58	8400	2000	58	750	—	0.8	1.2	12–14	0.9–1.4	2.0	200	30
54 and older	58	6400	1500	58	750	—	0.7	1.0	10–12	0.8–1.1	2.0	200	30
Pregnant	68	9000	2150	66	750	—	1.0	1.5	14–16	1.0–1.5	3.0	400	60
Lactating	58	10 800	2600	78	1200	—	1.2	1.5	15–17	1.6–2.2	3.5	300	60
Infants													
0–0.5	—	—	—	—	425	—	0.3	0.4	4	0.25	0.3	50	—
0.5–1	—	460–420 (per kg)	110–100 (per kg)	2–3 (per kg)	300	10	0.4	0.6	7	0.45	0.7	75	30
Children													
1–3	13	5400	1300	20–39	300	10	0.5	0.8	9–10	0.6–0.9	1.0	100	30
Boys													
4–7	19	7200	1700	26–51	350	—	0.7	1.1	11–13	0.8–1.3	1.5	100	30
8–11	28	9200	2200	37–66	500	—	0.9	1.4	14–16	1.1–1.6	1.5	150	30
12–15	41	12 200	2900	51–87	725	—	1.2	1.8	19–21	1.4–2.1	2.0	200	40
16–18	61	12 600	3000	67–90	750	—	1.2	1.9	20–22	1.5–2.2	2.0	200	50
Girls													
4–7	18	7200	1700	25–51	350	—	0.7	1.1	11–13	0.8–1.3	1.5	100	30
8–11	27	8800	2100	36–63	500	—	0.8	1.3	14–16	1.0–1.5	1.5	150	30
12–15	42	10 400	2500	52–75	725	—	1.0	1.6	17–19	1.2–1.8	2.0	200	40
16–18	55	9200	2200	60–66	750	—	0.9	1.4	15–17	1.1–1.6	2.0	200	50

*Adapted from reference 36. †Including provitamin A.

Good and fair sources of vitamins — water-soluble*

In 100 g of:	Thiamin (B_1) (mg)
Brewer's yeast	13.2
Vegemite (yeast extract)	9.7
Marmite (yeast and vegetable extract)	7.0
Wheat germ	2.2
Cornflakes	1.47
Soy beans	1.09
Peanuts, raw, with skin	1.03
Soy flour (full fat)	0.76
Pork (average)	0.60
Wholemeal flour (wheat)	0.51
Lentils, raw	0.46
Lamb's liver, fried	0.31
Peanuts, roasted	0.29
Wholemeal bread	0.27
White flour (wheat)	0.22
Lamb (average)	0.13
White bread	0.13
Spaghetti	0.12
Egg, whole	0.10
Rice, boiled brown	0.08
Beef (average)	0.08
Lentils, boiled	0.08
Chicken, fried	0.07
Fish (average)	0.06
Rice, boiled white	0.03

In 100 g of:	Riboflavin (B_2) (mg)
Vegemite	14.30
Marmite	7.50
Beef extract	2.70
Lamb's liver, fried	2.38
Cornflakes	2.10
Wheat germ	1.30
Almonds	0.75
Cheese	0.50
Egg, whole	0.30
Beef	0.16–0.35
Sesame seeds	0.24
Yoghurt	0.21
Icecream	0.21
Milk	0.17
Peanuts	0.17
Macadamia nuts	0.11
Wholemeal bread	0.09
White bread	0.08
Green leafy vegetables	0.07
Lentils	0.04

	Niacin (mg)	
In 100 g of:	Niacin	Potential niacin from tryptophan
Vegemite	97.0	7
Marmite	60.0	9
Brewer's yeast	30.2	1
Peanuts	16.0	5.3
Lamb's liver, fried	13.4	4.5
Rabbit, stewed	12.0	5.1
Chicken	6.0–10.0	2.0–5.5
Mushrooms	4.0	0.6
Beef	3.0–8.0	2.0–6.5
Fish	3.0–8.0	2.0–4.0
Pork	3.0–5.0	
Pulses	2.5	0.3–3.5
Milk	0.08	0.08
Egg	0.07	3.6

In 100 g of:	Vitamin B_6 (mg)
Marmite	1.3
Brewer's yeast	7
Bananas	0.51
Lamb's liver, fried	0.49
Avocado	0.42
Peanuts	0.40
Chicken	0.20–0.50
Fish	0.20–0.40
Beef	0.20–0.30
Egg yolk	0.30
Potatoes	0.20
Spinach	0.18
Wholemeal bread	0.14
Lentils, boiled	0.11
Apples	0.03

In 100 g of:	Vitamin B_{12} (μg)
Lamb's liver (fried)	81
Sardines	28
Oysters	15
Rabbit (stewed)	12
Egg yolk	4.9
Fish	1–5
Beef	1–2
Cheese	1.2–1.5
Marmite	0.5
Milk	0.3

In 100 g of:	Biotin (μg)
Brewer's yeast	200
Egg yolk	60
Rice bran	60
Soya beans	60
Liver	40
Wholemeal bread	6
Lobster	5
Avocado	3.2
Fish	3–10
Milk	2.0
Cheese	1–6
Cauliflower	1.5
Nuts	0.4–2.0
Apples	0.3
Spinach (boiled)	0.1

In 100 g of:	Pantothenic acid (mg)
Lamb's liver (fried)	7.6
Egg yolk	4.6
Beans, broad (boiled)	3.8
Lobster (boiled)	1.6
Apricots	0.7
Sweet potatoes (boiled)	0.7
Beef	0.5–0.8
Broccoli (boiled)	0.4
Celery	0.4
Milk	0.4
Peas (boiled)	0.3
Nuts	0.2–2.7
Fish	0.2–1.0

In 100 g of:	Ascorbic acid (C) (mg)
Green peppers (raw)	235
Blackcurrants (cooked)	209
Capsicum (baked)	184
Parsley (raw)	178
Brussel sprouts (cooked)	83
Papaya (paw paw)	64
Strawberries	58
Spinach (boiled)	56
Cauliflower (cooked)	52
Oranges	50
Lemon	47
Cabbage (cooked)	42
Grapefruit	40
Spinach (cooked)	33
Cantaloupe (rockmelon)	32
Broad beans (boiled)	15
Avocado	13
Lamb's liver (fried)	12
Endive	12
Potatoes (cooked)	11
Celery (raw)	7
Watermelon	6
Apple	6
Grapes	4
Milk	1.5

In 100 g of:	Folacin (total) (μg)
Brewer's yeast	300–1400
Marmite	1010
Wheat germ	730
Cabbage (boiled)	230–430
Lamb's liver (fried)	260
Spinach (boiled)	140
Peanuts	110
Okra	100
Peas	78
Avocado	66
Egg yolk	52
Wholemeal bread	30
Oranges	37
Lettuce	34
Tomatoes	28
Bananas	22
Grapefruit	12
Lemon	7

*Adapted from reference 2.

TABLE 2: Recommended daily dietary intakes in some developed countries*

	Australia		United Kingdom		United States	
	Men	Women	Men	Women	Men	Women
Age (years)	19–64	19–54	18–35	18–35	23–50	23–50
Weight (kg)	70	58	65	55	70	55
Energy (kJ)	11 600	8400	12 000	9200	11 300	8400
Energy (kCal)	2800	2000	2900	2200	2700	2000
Protein	70	58	72	54	56	44
Vitamin A (μg of retinol equivalents)	750	750	750	750	1000	800
Vitamin D (μg)	—	—	—	—	5	5
Vitamin E (mg)	—	—	—	—	10	8
Vitamin K (μg)†	—	—	—	—	74–140	70–140
Vitamin B_1 (mg)	1.1	0.8	1.2	0.9	1.4	1.0
Vitamin B_2 (mg)	1.7	1.2	1.6	1.3	1.6	1.2
Niacin (mg of niacin equivalents)	18–20	12–14	18	15	18	13
Vitamin B_6 (mg)	1.3–1.9	0.9–1.4	—	—	2.2	2.0
Vitamin B_{12} (μg)	2.0	2.0	—	—	3.0	3.0
Biotin (μg)†	—	—	—	—	100–200	100–200
Pantothenic acid (mg)†	—	—	—	—	4–7	4–7
Folacin (mg)	200	200	300	300	400	400
Vitamin C (mg)	30	30	30	30	60	60

*Adapted from reference 33. †Estimated safe and adequate range of daily dietary intakes.

TABLE 3: Vitamin toxicity

Vitamin	Adverse effects	Daily intake above which adverse effects are seen
A	Neurological[42,44] Alopecia[42,44] Bone[42,44]	200–1000 μg/kg body weight
	Teratogenicity[45,46]	700–800 IU (210–240 μg RE) μg/kg/day
D	Hypercalcaemia and its effects[46]	Possible at 10 000 IU (240 μg) a day over several months but 50 000–500 000 IU a day for several years may be necessary for toxicity to develop. But because of the expression of teratogenicity in countries where the intakes are in the region of 3000–4000 IU (75–100 μg) with fortification, it would seem prudent to keep intakes as near to 400 IU (10 μg)/day as possible. Problems have been seen in infants at 90–100 μg/day[47]
	Possible hypercholesterolaemia[46] Developmental abnormalities[47]	
E	Interference with absorption of A and K Minor gastrointestinal side-effects (nausea, flatulence, diarrhoea)[8,48]	300–600 mg
K	Long-term effects uncertain. In infants, haemolytic anaemia.[46] Increased analgesia in interaction with opiates and salicylates[46]	5–10 mg/day in infants may lead to haemolytic anaemia
B_1	Hypersensitivity reactions, parenterally[2,11]	Very low level of toxicity
B_2	Not described[12]	Very low level of toxicity. Limited water-solubility and therefore urinary excretion limited
Niacin	Niacinamide has little adverse effect compared with niacin.[14] Vascular dilatation (flush) experienced at any dose which leads to a fluctuation in blood levels.[14,29] Slow introduction of pharmacological amounts can avoid changes in hepatic enzymes. Variable hyperuricaemia and levels of uric acid should be checked[14,29]	50–100 mg
B_6	Sensory neuropathy,[49–51] phocomelia (possible),[52] withdrawal depression (a clinical observation requiring a formal study)	Greater than 500 mg
Folacin	Exacerbation of B_{12} deficiency, secondary zinc deficiency[53]	Problem occurs with the folic acid form of folacin. Preferable to keep dosage within 2 or 3 orders of RDI
B_{12}	None recognized	Not established
Biotin	None recognized in humans. In experimental animals, interference with reproductive function	Not established
Pantothenic acid	Diarrhoea[54]	10 000–20 000 mg
C	Diarrhoea,[55] oxaluria,[56] uricosuria, withdrawal scurvy,[57–60] iron storage disease,[61–65] increased toxicity of other metals, hypoglycaemic effects[66]	Adverse effects seen at levels greater than 100–1000 mg
	Gastrointestinal reflux[67]	
	Possible increase in requirement for vitamin B_6,[68,69] associated excessive sodium intake, dental erosions,[70] haemolysis in G6-PD deficiency,[71,72] mutagenic breakdown products,[73] interaction with warfarin,[74] gastrointestinal obstruction[75]	

RE = retinol equivalent. RDI = recommended dietary intake. G6-PD = glucose-6-phosphate dehydrogenase.

TABLE 4: Vitamin deficiency states

Vitamin	Functional abnormality[3]	Clinical features
A	Impaired dark adaptation, possibly taste and olfactory acuity	Xerophthalmia
D	Hypocalcaemia, hypophosphataemia, elevated alkaline phosphatase, decreased serum 25-hydroxy-vitamin D	Rickets, osteomalacia
E	Impaired dark adaptation, increased erythrocyte fragility (hydrogen peroxide haemolysis), altered platelet aggregation	Haemolytic anaemia, neuromuscular dysfunction
K	Coagulopathy	Haemorrhagic state
B_1	Transketolase activity[76]	Wernicke's encephalopathy, Korsakoff's psychosis, peripheral neuropathy (dry beriberi), high output cardiac failure (wet beriberi)
B_2	Erythrocyte glutathione reductase activity[12]	Angular stomatis, glossitis, seborrhoeic dermatitis (nose, scrotal or vulval), corneal vascularization (?)
Niacin	Excretion of metabolites in urine[14]	Pellagra (dermatitis, diarrhoea and dementia)
B_6	Erythrocyte glutamic pyruvate transaminase activity, erythrocyte glutamic oxaloacetate activity, alanine aminotransferase activity. However, pyridoxal-5-phosphate measurements are more sensitive and reproducible as assays for B_6 status[16]	Convulsions, peripheral neuropathy, angular stomatitis, cheilosis, glossitis, anaemia, immunosuppression (decreased antibody formation), pellagra-like symptoms
Folacin	DNA synthesis, D-uridine suppression test	Macrocytic (sometimes megaloblastic) anaemia, thrombocytopenia, neutropenia, malabsorption
B_{12}	(See box showing principal functions of vitamins) D-Uridine suppression test	Anorexia, macrocytic/megaloblastic anaemia, peripheral neuropathy, subacute combined degeneration of the spinal cord
Biotin	(See box showing principal functions of vitamins)	Anorexia, paraesthesiae, myalgia, glossitis, dermatitis, organic aciduria
Pantothenic acid	(See box showing principal functions of vitamins)	
C	Capillary fragility	Poor wound healing, scurvy

what varies is the safety margin for different vitamins.[1,2,37-41]

The level of regular intake at which the side-effects of vitamins are seen is shown in Table 3. Even though toxicity may not have been seen acutely, it still remains possible that it may be seen with long-term usage.

The best safeguards against vitamin toxicity are to ingest vitamins as food and to eat as wide a variety of foods as possible. Variety is important not only in providing a full spectrum of essential nutrients, but also in diluting out toxic amounts. One of the few food sources of vitamins that can lead to toxicity are the livers of marine and arctic animals because of the large amounts of preformed vitamin A.[42] However, their occasional inclusion among a wide variety of foods would not be a problem. It is of interest that provitamin A or carotenoids do not pose the problem of vitamin A toxicity — the foods that are concerned here are green leafy and yellow vegetables and yellow or orange fruits.[43,33]

Vitamin deficiency states

Florid vitamin deficiency states (Table 4) are rarely seen in developed countries. However, it may be possible to recognize a functional problem more frequently.[3]

It should be noted that a high level of specificity for the clinical features or even functional abnormality does not necessarily exist. As in other areas of clinical medicine, diagnostic certainty comes by way of the collation of various pieces of evidence and by not being dependent on any one. For example, glossitis might be due to B_2, niacin, B_6, folic acid or B_{12} deficiency.[2,77,78] Depression is much more likely to have a non-nutritional than a nutritional basis.

It is worth noting that deficiency may occur when a high dosage of some vitamins, for example, vitamin C[57-60] and vitamin B_6 is reduced abruptly, although with the latter vitamin clinical observations need to be investigated more formally.

Vitamin deficiency in enteral and parenteral nutrition

With the currently available nutritionally complete enteral nutrition formulations, vitamin deficiency is unlikely to occur unless there is some other factor to alter nutrient absorption or utilization. However, sometimes specific nutrient supplementation may be required for a minimal energy increment. With the scarcity of nutritionally complete formulations, the low-energy products such as Modifast (one sachet contains only about 630 kJ and yet about one-third of the RDIs for all essential nutrients [vitamins, elements]) can be used, at least by mouth. Vitamin deficiencies that are seen even with current regimens of total parenteral nutrition include those of vitamins A and E, folacin and biotin.[79]

Prevention of vitamin deficiency

Nutritional counselling to prevent vitamin deficiency can, in its own right, be reassuring for concerned patients. This will include: discussion about vitamin retention in foods, with various storage and processing techniques;[2,33] encouragement to be as physically active as possible so that more food can be eaten; emphasis on nutrient-dense rather than energy-dense foods; encouragement to eat a wide variety of foods; caution about alcohol abuse — a safe level for most adults is one to two standard drinks a day, on average; the avoidance of cigarette smoking, which at the very least decreases interest in food, but also lowers vitamin C levels in blood; and attention to nutritional support — in the form of food wherever possible — at times of protracted illness.

Assessment of nutritional status

In a developed country such as Australia, with an abundant food supply, the chances of developing a micronutrient deficiency are not high. One aspect of clinical medicine is to know the prevalence of problems in the community one services. Another is to know where problems are likely to arise. In the case of vitamin deficiency, this means knowing the vulnerable groups, which are socio-economically disadvantaged persons; institutionalized persons; persons who are receiving medication; infants (especially premature infants);[80] the elderly; persons who abuse alcohol; women in childbearing years; food faddists; and those with low levels of physical activity.

Usually the presence of one risk factor is not sufficient to lead to a vitamin deficiency, but a combination makes it more likely. An example would be an elderly person, in an institution, who is also receiving medication; another would be an impoverished pregnant teenager.

Therefore, the first steps to be taken in the assessment of vitamin status are to recognize risk factors or vulnerable groups; to take a food and beverage history and to interpret it with the aid of food composition tables or lists of good sources of vitamins and in accordance with RDIs; to take special note of the variety of foods that are ingested; to take a life-style history and to include physical activity, alcohol and drug abuse and cigarette smoking; to be aware of the

TABLE 5: Effects of drugs on vitamins*

Vitamin	Drug affects absorption	Drug serves as antinutrient	Alteration but significance uncertain
Fat-soluble			
A			Oral contraceptive agents
D	Laxatives	Anticonvulsant agents	
E	Cholestyramine		
K	Antibiotic agents	Warfarin	
Water-soluble			
B_2		Chlorpromazine	
B_6		Isoniazid Hydralazine Cycloserine Levodopa	Oral contraceptive agents
Folacin	Cholestyramine Anticonvulsant agents Sulphasalazine	Pyrimethamine Methotrexate Trimethoprim Triamterene	Oral contraceptive agents
B_{12}	Colchicine		Oral contraceptive agents

*Taken from reference 2.

previous medical and surgical history — nutrient requirements could be increased by a wasting disorder, or an inherited disorder of metabolism — and to ask oneself whether a malabsorption state is present or whether past gastrointestinal surgery (for example, gastroplasty) could have reduced the food intake; and to take a medication history (including supplements, and so on) and to ask oneself whether a symptom or sign is present which could have nutrient deficiency as a basis[2] (Table 5). In patients in whom a vitamin deficiency is suspected, relevant and marker laboratory investigations of nutritional haematological and biochemical status, for example, a full blood examination and the measurement of folacin and vitamin B_{12} levels should be undertaken.

Supplementation for nutrient deficiency

As already been pointed out, nutrient supplements should only be used when a food solution can not be found. Unless a specific nutrient deficiency has arisen because of a nutrient-selective disorder or problem, it is preferable to use the full range of micronutrients in amounts that relate to the RDIs, that is, the 13 vitamins and the several essential elements. This is because one nutrient problem will usually be a reflection of a wider food, and therefore, general essential nutrient disorder. Nutrient-selective situations include inherited disorders of metabolism; drug-nutrient interactions; and specific nutrient malabsorption, for example, of folacin in patients with jejunal dysfunction or of vitamin B_{12} in patients with pernicious anaemia.

In advanced nutrient deficiency, which is seen mainly in developing countries, it can be worth while to replenish body stores with the single nutrient the deficiency of which is the principal problem. Riboflavin deficiency in southern China[77,78] and vitamin A deficiency in southeast Asia constitute examples of this situation.

There has been particular concern about the use of folacin supplements in patients in whom vitamin B_{12} deficiency might exist, for fear of precipitating subacute combined degeneration of the spinal cord. At the levels of folacin that are found in food, this would seem an unreasonable fear. Moreover, since among the vitamin deficiencies, folacin is probably the most common in developed countries, whereas vitamin B_{12} deficiency is uncommon, the over-all risk–benefit ratios for the community of supplement users must be taken into account. If there is any justification for nutritional supplementation in at-risk groups, it is falsely reassuring to use a supplement which does not contain folacin.

The considered clinical approach to nutrient supplementation is in great contrast to the widespread community supplementation phenomenon which affects at least one in five adult Australians.[81] There is no good evidence that nutrient deficiency exists to this extent in the Australian community. Errors in thinking about nutrition and health account for the phenomenon.

Preventive supplementation

There are some areas where supplementation in the range which may be found with food might be preventive. These are under active investigation at the moment and until all the risks and benefits are understood, a cautious approach should be adopted. These supplements include betacarotene to reduce the risk of certain neoplastic diseases such as lung and colorectal cancer;[82] and the administration of folic acid around the time of conception to reduce the risk of neural-tube defects.[30]

Supplements and athletic performance

Sportsmen, sportswomen and athletes often undertake nutrient supplementation. The great difficulty in assessing the benefit of this is the small increments in function that are required by these persons and the small numbers who actually achieve these levels of performance, making experimental design most difficult.[83]

The problem of megavitamin therapy

A megadosage is several-fold the amount of a vitamin that is required for normal body metabolism. Pharmacological or toxicological properties of the vitamin may emerge. Acceptable, unacceptable and possible uses of megavitamin therapy are shown in the boxes; more background information is contained in recent reviews.[81,32]

In a recent report of a randomized double-blind trial of megavitamin C in patients with

Acceptable uses of megavitamin therapy*

Disorder	Vitamin
Inherited metabolic disorders	
Leigh's necrotizing encephalopathy, lactic acidosis, "maple syrup" urine disease	Thiamin
Hartnup disease	Niacinamide
Inherited vitamin B_6 dependency	Vitamin B_6
Methylmalonic aciduria	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	Thiamin
Disfiguring acne	Vitamin A analogues
Malabsorption syndromes	Vitamins A, D, E and K, folacin, B_{12}
Urinary tract infection	Vitamin C

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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" after alcohol abuse	Multivitamin preparations

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Possible uses of megavitamin therapy*

Disorder	Vitamin
Prevention of congenital abnormalities	
Neural-tube defects	B group vitamins, folacin
Cleft lip	B group vitamins, folacin
Treatment of cervical dysplasia	Folacin
Reduction in risk of certain tumours (lung, prostate)	Vitamin A analogues, carotenoids
Diminution of symptoms of common cold	Vitamin C
Reduction in symptoms of premenstrual tension, menopause, first trimester of pregnancy and oral contraceptive pill	Vitamin B_6
Symptoms for osteo-arthritis and rheumatoid arthritis	Pantothenic acid
Treatment of toxic amblyopia	Vitamin B_{12}
Prevention of retrolental fibroplasia	Vitamin E
Prevention of postoperative thromboembolism	Vitamin E

*Taken from reference 32.

advanced cancer, no evidence was found that it was of benefit.[84,85]

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