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The use of micronutrients in megadosage

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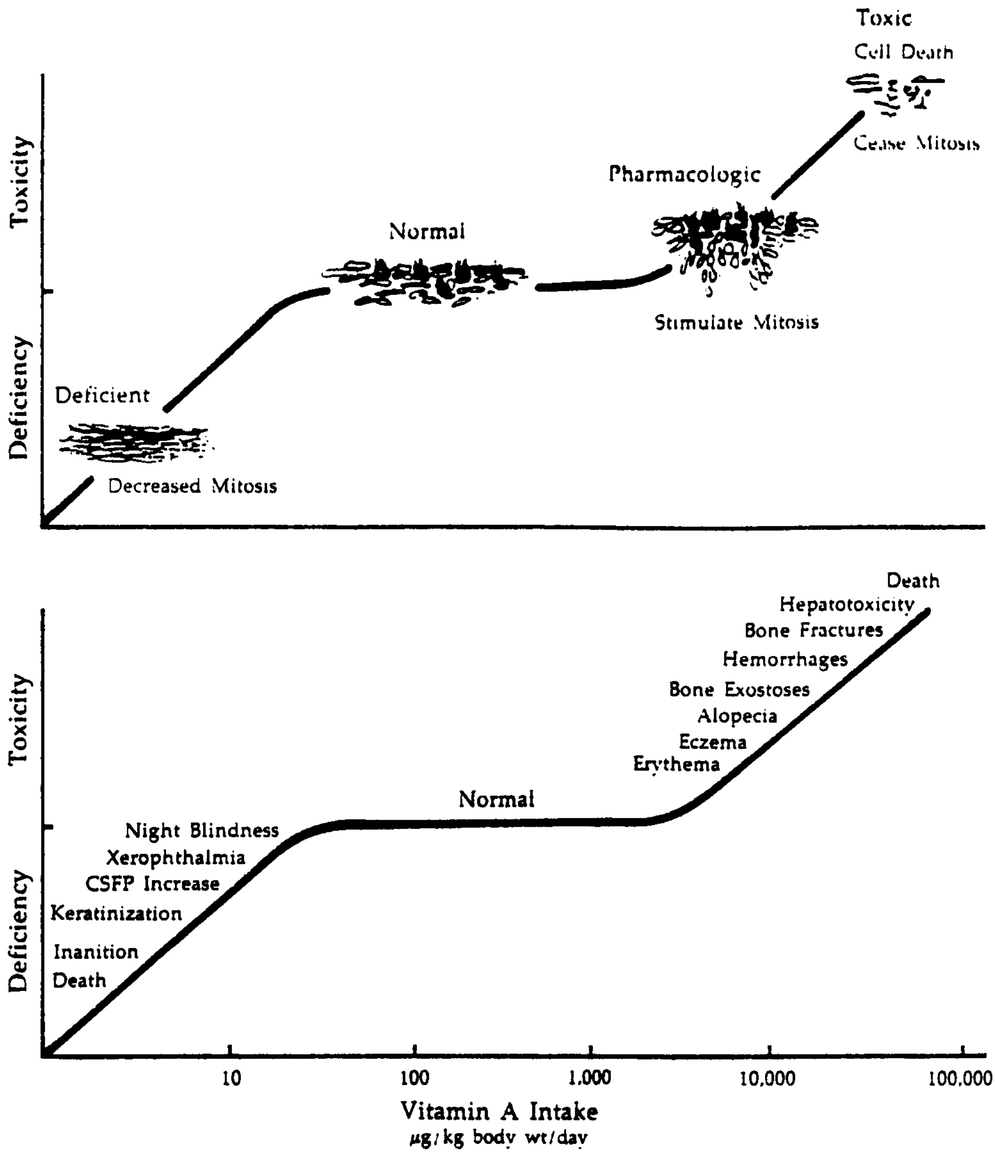
Nutrient intakes

Micronutrients are generally regarded as the vitamins and biological elements in food. Arguably they might include essential fatty acids as well, although these are usually included together with the macronutrient fat. There are 13 vitamins recognized by international agencies and at least 18 essential elements. The vitamins are grouped together more for historical than functional reasons. However, a reasonable definition of a vitamin might be that it is an organic substance found in food, not made in the body, and required in small quantities, usually as a co-factor with enzymes. Even so, there are vitamins, namely vitamin K and biotin, which can be made in the gut, and, of course, vitamin D can be synthesized in the body from precursor 7-dehydro cholesterol under favourable conditions[1,2].

The use of micronutrients in amounts several-fold the recommended dietary intakes (RDIs) is regarded as meganutrient usage. Sometimes this has a rational basis, but mostly it does not.

Nutrient intake may be physiological, pharmacological, or toxicological. The Figure shows an example of the hierarchy of clinical features associated with vitamin A intakes, from the deficiency range through the physiological range to the pharmacological and then toxic ranges.[3]

One of the misconceptions about micronutrient supplementation is that it is a 'natural' thing to do since the chemicals in question are in the food supply. Although micronutrients may be identical in pharmaceutical preparations and food, what makes them natural is that they are found in food and ingested in that physico-chemical and chemical context. 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.



The logarithmic plot of vitamin A intake is depicted as a function of the biological response of man and animals in terms of deficiency, normalcy and toxicity. The scheme at the top illustrates the response of a typical mucous epithelium, but is probably applicable to other undifferentiated blast-cell populations as well. The bottom curve indicates the clinical manifestations resulting from the altered cell function in deficiency and toxicity of vitamin A[8].

Normal physiology at meganutrient intakes

There are situations in which normal physiology cannot be obtained unless micronutrients are ingested in supra-physiological amounts. Principally these circumstances are those of inherited metabolic disease. Requirements can also be increased on account of drug-nutrient interactions and with malabsorption syndromes. Additionally, large doses of micronutrients are often required when body stores are depleted in deficiency states until catch-up is achieved (Table 1).

Table 1. Acceptable uses of megavitamin therapy to obtain normal physiology

Disorder		*Vitamin*
Inherited metabolic disorders	Leigh's necrotizing encephalopathy, lactic acidosis, 'maple-syrup' urine disease,	Thiamin
	Hartnup disease, inherited vitamin B_6	Niacinamide
	dependency,	Vitamin B_6
	methylmalonic aciduria,	Vitamin B_{12}
	multiple carboxylase deficiency,	Biotin
	Leiner's disease	Biotin
Drug-induced increased requirement	Methotrexate, pyrimethamine,	Folinic acid
	barbiturates, phenytoin, isoniazid, cycloserine,	Folacin
	penicillamine, hydralazine and levodopa.	Vitamin B_6
	Anticoagulant (warfarin)	Vitamin K
Profound deficiency	Wernick's encephalopathy and beriberi heart disease	Thiamin
Malabsorption syndromes		Vitamins A, D, E and K, folacin, B_{12}

Pharmacological properties of nutrients

There are very few situations in which the pharmacological properties of micronutrients have been exploited with a valid scientific basis. Nicotinic acid is an interesting example. The proposal that it was an agent worthy of use in psychotic states has now been disproven[4]. However, it has been used successfully for the management of hyperlipidaemia since the initial observations of Altschul as early

Table 2. Clinical features of pyridoxine neuropathy[14]. (Pyridoxine dose was 0.2–5 g/day and duration of consumption before symptoms was inversely proportional to the daily intake)

Age range	25–53		
Female/male	16/0		
Symptoms (16 patients)		Signs (8 patients)	
Numbness	16/16	Sensory deficit	8/8
Paraesthesias	16/16	Sensory ataxia	7/8
Ataxia	13/16	Romberg's sign	7/8
L'Hermitte's sign	8/16	Loss of Achilles reflexes	8/8
Pain	5/16	Loss of other deep tendon reflexes	8/8
Weakness	1/16	Weakness	1/8

as 1955[5,6]; and there is now substantial evidence that when used for this purpose it can contribute to delayed progression and even regression of atherosclerotic lesions[7] and can improve mortality rates[8].

Interesting and possible uses for meganutrient therapy currently being researched are the prevention of congenital abnormalities with folacin (neural tube defects,[9] and cleft lip[10]) and the possible reduction in the risk of certain tumours with carotenoids[11,12].

Meganutrient toxicity

It is often said that fat-soluble *vitamins* are prone to produce toxicity, whereas the water-soluble ones are not. However, among the fat-soluble vitamins, vitamin E has a low level of toxicity, whereas with the water-soluble vitamins, problems are being experienced with vitamin B_6[13–16] (Table 2), and vitamin C, including diarrhoea[17], oxaluria[18], uricosuria, withdrawal scurvy[19–22], iron storage disease[19,23–26], increased toxicity of other metals[27], hypoglycaemic effects[28], gastrointestinal reflux[29], possible increase in requirement for vitamin B-6[30,31], associated excessive sodium intake, dental erosions[32], haemolysis in G-6-PD deficiency[33,34], mutagenic breakdown products[27], interaction with warfarin[25], and gastrointestinal obstruction[35].

In respect of *elements*, problems are being seen with zinc and selenium, whose use is encouraged by alternative medicine and health food shops.

Selenium toxicity in seleniferous parts of the world is associated with alopecia, nail deformity and thickening and loss of nails[36].

Case report

A case of zinc toxicity in a 20-year-old single woman is reported from Prince Henry's Hospital in Melbourne by courtesy of the attending physician, Graeme Brodie. This young woman was advised by a friend to take zinc capsules equivalent to about 450 mg zinc daily for several months to deal with her acne. She was admitted to Prince Henry's Hospital with anorexia, weight loss (height 170 cm, weight 56 kg, BMI 19), amenorrhoea for 5 months, extreme lethargy, extreme pallor and postural dizziness. She was found to have haemorrhages in her optic fundi and hepatomegaly. Her haemoglobin was 3 g/100 ml, her white cell count 2300/mm^3, with 2 percent neutrophils, and falling to 1500/mm^3. Her platelet count was 184 000/mm^3. Her blood film was megaloblastic. Her bone marrow was aplastic with increased megakaryocytes. There was vacuolization of her white cells. Three days after admission her plasma zinc was found to be 68 µmol/l (ref. range 12–23), her plasma copper <5 µmol/l (ref. range 15–29) and her caeruloplasmin 0.03 µmol/l (ref. range 0.15–0.60). Plasma zinc and copper concentrations did not return to the normal reference ranges until 10 weeks after withdrawal of zinc supplements; at ten weeks the plasma zinc was 22 µmol/l and the plasma copper 17 µmol/l. Fourteen weeks after admission, menstruation returned, weight was 61 kg and BMI 21; plasma zinc was maintained at 22 and plasma copper 17 µmol/l. Although excess zinc intake can lead to nausea, it is apparently possible for this to be accepted or overcome, so that zinc toxicity and secondary copper deficiency supervene.

Community practices

Where a self-definition of 'nutrient' is used, adults include vitamins and elements as well as items such as bran and wheatgerm. In a representative sample of the Adelaide population in Australia, Worsley & Crawford[1,37,38] found that 37 per cent of men and 53 per cent of women regularly consumed nutrient supplements. From the National Heart Foundation of Australia Risk Factor Prevalence surveys of 1980 and 1983[39,40] and a health care professional definition of Nutrient, restricted to vitamins and minerals, about 20 per cent of the adult population regularly consume these supplements. Thus nutrient supplementation is a major health phenomenon in Australia, as it appears to be in other developed countries. The practice is not uniform for age, sex, or family membership (Table 3).

Table 3. The percentages of dietary supplement users in families

		Supplement users (%)	*Non-users* (%)
Infants	(0–5 years, n=90)	45.7	18.2
Children	(6–12 years, n=136)	43.3	10.5
Adolescents	(13–18 years, n126)	32.8	7.4
Spouses	(n=500)	40.8	12.0

Judged from the Adelaide surveys, there appeared to be at least two casual pathways which led to dietary supplementation. The first is 'the subjectives well-being pathway'. Supplementers appear to experience more stressful events than non-supplementers. They also report twice as many physical and emotional symptoms, and despite their supplementation, they actually feel less well[1]. The second pathway is that of 'food centredness'. Regular supplementers have a greater interest in and suspicion of the food supply than non-supplementers. They also seem to know more about food in general. Nutrition is much more important to these people. Casual supplementers may expect there to be a nutrient-medicinal solution to an acute medical problem, such as use of B-group vitamins for a hangover, which has no scientific basis as a therapy.

There remains the problem of latent meganutrient toxicity. This is because, firstly, nutrient supplementation is a relatively recent phenomenon; and second, it is being used in children, and amongst the elderly with less good tolerance. With frequent use of medication in the elderly, drug-nutrient interactions are more likely. Because of a lack of monitoring by conventional medicine, adverse outcomes are likely to go unrecognized.

Conclusions

The use of nutrient supplements may result in physiological, pharmacological or toxic effects. In a few situations, meganutrient dosage may be required to achieve physiological effects or realization of pharmacological properties. However, the much wider use of nutrient supplements in the community, sometimes at meganutrient levels, results, in many instances, from a quest for subjective well-being or from a food-centred orientation which lacks an adequate scientific basis.

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CURRENT PROBLEMS IN
NUTRITION PHARMACOLOGY & TOXICOLOGY

Editors
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John Libbey
LONDON · PARIS
· NUTRITION ·

First published 1988 by
John Libbey & Company Ltd
80–84 Bondway, London SW8 1SF, England

British Library Cataloguing in Publication Data

Current problems in nutrition, pharmacology and toxicology.
1. Man. Nutrition. Medical aspects
I. McLean, A.J. (Allan J.)
II. Wahlqvist, Mark
612′.3

ISBN 0–86196–168–4

Photoset by Deltatype, Ellesmere Port
Printed and bound in Great Britain by
Whitstable Litho Ltd., Whitstable, Kent