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MULTI-NUTRIENT FORMULAS AND OTHER SUBSTANCES AS THERAPIES FOR DOWN SYNDROME: AN OVERVIEW

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Theories advocating the supplementation of various vitamins, minerals, amino acids, enzymes, hormones and the drug Piracetam, in various quantities, are sources of considerable controversy within the Down syndrome community. Although vitamin and mineral supplements have been proposed sporadically since the 1940s, little scientific evidence has been accumulated that suggests that their use, or the use of any single ingredient, has any benefit as a general therapy for individuals with Down syndrome. Moreover, research into the general effects of vitamins and minerals in humans, and particularly the long-term effects of supplementation over and above average dietary requirements, is still progressing. An overview of supplementation theories in Down syndrome, and some of the issues that are raised by the advocates of such theories as well as some associated issues is presented.

Keywords: Down syndrome, health, nutrition, vitamins, minerals, amino acids, Piracetam, unorthodox treatments

1. Introduction

Claims for the usefulness of multi-nutrient formulations in improving or alleviating certain features of Down syndrome are not new. Neither are such claims for such formulations restricted to Down syndrome. Claims of benefits for individuals with other disabling conditions have been made as frequently [1]. It would be quite remarkable if similar multi-nutrient formulations, that conveniently 'side-step' the rigorous tests required of medications, should be shown to be beneficial in a range of conditions as diverse as Down syndrome, autism, fragile X syndrome, attention deficit disorder, Parkinson's disease and cancer.

Nor is the controversy that is ignited by such claims new. Despite lacking rigorous scientific examination, such 'treatments' attract committed adherents who become convinced that they observe clear 'benefits' and that these are attributable to the 'treatments'. Proponents of such therapies claim that observations of 'improvements' in individual cases provide evidence of the therapies' usefulness. Meanwhile, others question the scientific validity of such claims and insist that anecdotal observations are insufficient to demonstrate general usefulness.

Some proponents of unproven therapies do seek to support their claims with 'scientific' rationales. In the case of multi-nutrient formulations and Down syndrome, these rationales rely on assertions about the mechanisms and effects of the various biochemical processes in which nutrients are, or may be, involved. As might be expected, many of these start with the effects that the presence of the additional chromosome 21 has, or may have, and then suggest that the multi-nutrient formulations (or constituent ingredients) 'correct' or 'compensate' for these effects.

These rationales usually appear to be 'scientific', and, indeed, some seem quite plausible. However, simply because assertions appear to have a scientific basis, does not mean that they are necessarily firmly grounded in scientific fact, nor that the treatments are of any use. Theories are only confirmed as fact through scientific observations under controlled circumstances. The only approach to the difficult problem of ascertaining the usefulness of treatments is to rely upon the evidence provided by properly conducted clinical trials. Unfortunately, some proponents of these formulations are quite prepared to

make extensive therapeutic claims without any supporting clinical evidence.

Moreover, some proponents seem inclined to try and support their position with speculation about the motives, abilities or even 'hidden agendas' of those who disagree with them. We were recently forwarded a copy of correspondence from one proponent regarding an article (by a respected medical professional) that was critical of multi-nutrient formulations. Despite the proponent also being an 'academic' scientist (who therefore should have known better), the response was based more on vitriolic personal attack than rational debate. When the arguments 'degenerate' to such tactics, they do not assist anyone.

In this article, we hope to outline some of the background and some of the issues involved in this debate. We have referenced many of our statements fairly thoroughly for those wishing to investigate further. As far as possible, we have tried to keep the article as accessible as possible to an audience with a variety of backgrounds, and where we think a reference is similarly accessible, we have marked it with an asterisk (*). Also, where possible, we have provided references to material that is freely accessible on the Internet.

2. Background to 'nutrition therapies'

2.1 Early speculations

Speculation as to the chromosomal difference in Down syndrome was made in the 1930s and suggestions of the possible amelioration of the effects of Down syndrome with nutritional substances can be traced back nearly as far. Various therapies involving vitamins and minerals have been advocated as useful in Down syndrome, and other conditions resulting in mental disabilities, since the 1940s and 1950s. Henry Turkel advocated one such therapy from 1940 [2]. Described as an 'orthomolecular therapy' [3], his "U series" contained around 50 substances and claims for its effects included "straightening of the first finger, regression of premature ageing, improvement in IQ, and improvement of aesthetic appearances" [2]. In the UK, Rex Brinkworth suggested a similar formulation some 20 years ago [4].

2.2 Developments in the 1980s & 1990s

Further interest in such therapies was rekindled during the 1980s when Ruth Harrell and colleagues reported that vitamin, mineral and thyroid hormone supplementation improved IQ scores and caused "physical changes toward normal" in a group of mentally deficient children [5]. However, this was a poor study, and subsequent attempts to replicate its findings failed. Yet, following these claims, a number of parents and doctors adopted the Harrell protocol.

2.2.1 HAP CAPS

A derivative of Turkel's "U series" (called "HAP CAPS"), developed during the 1980s, is currently promoted by Dr. Jack Warner and colleagues through "The Warner Clinic". It contains a variety of vitamins and minerals [6]. There have been no structured studies of the effects of "HAP CAPS". Warner claims that records on the 4,200 'patients' who have received "HAP CAPS" are kept, yet admits that no attempt has been made to analyse them in any systematic way. Neither have these records been made available for others to analyse. Yet, he and his 'clinic' continue to promote this formulation with unsupported claims, such as the formulation being responsible for speech improvements, the tightening of ligaments, attaining 'normal' height, and even curing cardiac defects in developing babies when administered to pregnant women. It is also claimed that patients 'regress' to their previous state if the tablets are discontinued. At a recent presentation by Warner and colleagues in London, the few medical professionals in the audience voiced considerable criticism of Warner's claims, pointing out that evidence was required. Moreover, they pointed out that some 'results' were exceedingly unlikely to have been influenced by the formulation. (A report from this conference from two parents who attended appears in this issue on pages 84-85).

2.2.2 "Nutrivene-D" and "MSB"

In the late 1980s, Dixie Lawrence Tafoya, the mother of a child with Down syndrome, began investigating and subsequently modifying Turkel's formula. A supplement similar to her formula was marketed by "Nutri-Chem Labs" in Canada as "MSB" in the early 1990s. In 1996, Lawrence started promoting a formula called "Nutrivene-D", manufactured by International Nutrition Inc. in the USA. A non-profit company was established, called the Trisomy 21 Research Foundation and it set up a "Scientific Advisory Committee" which reportedly controls modifications to the "Nutrivene-D" formula (though not the MSB formula).

Television programmes, broadcast in the US during the past few years, have drawn considerable attention to these formulas [e.g. 7,8]. Both of these programmes included claims from parents who were using these formulations that they were having improvement on their children's cognitive and physical development. Similar claims are propounded through various Internet sites, including 'before and after' pictures and glowing testimonials, and through seminars.

2.3 Cautionary reactions to recent developments

Warnings about these various formulations' efficacy and safety being unproven have been issued by national Down syndrome organisations and respected professional bodies in the USA: The National Down Syndrome Congress (USA) has issued position statements on "HAP CAPS", "Megavitamins", and the drug Piracetam (see below). The statement on Piracetam concluded that "without the benefit of studies and research information on the usefulness, effect and risks of Piracetam we cannot recommend its use at this time." Both statements on vitamin, mineral and amino acid formulations concluded that:

"I. To-date, no vitamin or mineral nutritional supplement is known that will alter significantly the intelligence, physical characteristics or behavioural features of Down syndrome and, thus, none are supported by the National Down Syndrome Congress.

"II. Any substance that is claimed to significantly affect intelligence must be carefully evaluated with control individuals utilised and multiple variables measured such as thyroid function, other nutritional substances being taken, stimulation and general state of health.

"III. Certain vitamin supplements are potentially toxic and can alter liver function. Vitamin A in excess can cause neurologic and dermatologic abnormalities. Vitamin C in excess can cause urinary tract irritation and frequency. Long-term effects of megavitamin therapy are not known.

"IV. Metabolism of cells in persons with Down syndrome may indeed be altered but, to-date, no specific vitamin or mineral regimen has been found in any way to ameliorate the features of Down syndrome as noted before.

"V. Claims made by certain programs that particular vitamins 'relieve', 'improve', 'promote', 'delay' or 'aid' aspects of Down syndrome are not scientifically proven in persons with Down syndrome." [9,10*]*

In 1996, the American College of Medical Genetics stated that it was not aware of any scientific proof that treatment with amino acids supplements and Piracetam could improve cognitive function in children with Down syndrome [11*]. During 1997, the National Down Syndrome Society (USA) issued a position statement that stated:

"The administration of the vitamin related therapies -- e.g. the vitamin/mineral/amino acid/hormone/enzyme combination, has not been shown to be of benefit in a controlled trial, that the rationale advanced for these therapies is unproven, and that the previous use of these therapies has not produced any scientifically validated significant results. Moreover, the long term effects of chronic administration of many of the ingredients in these preparations are unknown. Despite the large sums of money which concerned parents have spent for such treatments in the hope that the conditions of their child with Down syndrome would be bettered, there is no evidence that any such benefit has been produced." [12]*

Other Down syndrome organisations around the world have also issued similar position statements. Similarly, respected professionals involved in the care of people with Down syndrome, and respected professionals involved in research, have cautioned parents and professionals against the use of these various formulations, old and new [e.g. 13,14,15*,16,17,18].

Nonetheless, the publicity, various promotions, and anecdotal testimonies to these formulations, are inviting to parents anxious to help their children, and many have chosen to use them. Advocates of these formulations estimated 12,000 people with Down syndrome were receiving "some form of specialised supplement" world-wide in 1996 [19]. It is understandable that parents are tempted to try a therapy that appears to hold promise, particularly when assured that they are not harmful, and when associated with the various 'positive' connotations surrounding vitamins and minerals [20*]:

"Told that the nutritional therapies can't hurt and might help, many parents decide that the therapies are 'worth a try'. Also, with so much research in Down syndrome focusing on prenatal testing or presenile dementia, many parents feel abandoned by the medical

establishment. For these parents, the supplement promoters seem to be the only ones interested in 'ending the implications of Down syndrome', as one newsletter puts it."

3. The speculation

The manufacturers do not, themselves, explicitly promote these multi-nutrient formulations as 'treatments'. This avoids legislative definitions of medicines (and therefore the controls that accompany substances being defined as 'drugs'). However, the manufacturers do make some statements about Down syndrome, which we presume they intend readers to relate to their formulations. Moreover, the advocates of 'targeted nutritional intervention', do make various statements about the theories behind these formulations.

3.1 General claims of nutritional deficiencies

It is suggested that individuals with Down syndrome are deficient in certain nutrients. There is no clear evidence to support this statement. It should also be noted, that, in general, nutritional deficiencies have severe, and therefore clear, consequences. These are not apparent in the vast majority of individuals with Down syndrome consuming a reasonable diet.

3.1.1 Ascertaining general nutritional deficiencies

Unfortunately, many of the reports of deficiencies have a number of methodological problems that raise questions about their validity as reliable indications of the general nutritional status of individuals with Down syndrome. Many involve small samples, some only examine individuals living in institutions, and some utilise measures that are questionable.

Many variables need to be considered when investigating the nutritional status of any given population. Ideally, in addition to blood or serum levels, these should include detailed measures of dietary intake, and the levels 'stored' elsewhere in the body.

3.1.2 Vitamins

Deficiencies of vitamin A [21,22], vitamin B12 [23] and vitamin C [24] in individuals with Down syndrome have been reported. Other studies have failed to provide evidence of deficiencies in vitamin A [25,26,27], vitamin B12 [28], or vitamin D [29].

3.1.3 Minerals

A considerable number of studies have looked at the role of zinc in Down syndrome. Serum levels of zinc have been reported as below normal [30,31,32,33], as well as plasma levels [34,35,36] and whole blood levels [24]. One study, however, did not find a general deficiency [37].

Whole blood levels and plasma levels of selenium have also been reported to be below normal in children and adults with Down syndrome [38,39]. However, a larger study failed to observe lower plasma levels of selenium in children or adults with Down syndrome [40]. It did note higher levels of selenium in the erythrocytes of children with Down syndrome and that these children reached adult levels of selenium in the erythrocytes earlier than the control group. There was no difference in levels of selenium in the erythrocytes of adults with Down syndrome and the control group.

3.1.4 Amino acids

Imbalances in amino acid levels have been claimed in adults with Down syndrome [41]. Lejeune and others [42] suggested that supplemental amino acids would balance the blood levels, making the biochemical workings of the body normal. A recent study of 22 children with Down syndrome did find slightly raised plasma concentrations of one amino acid. However, it found no other imbalances [43]. It concluded, "that when studied under carefully controlled conditions there are no differences in amino acid concentrations between control children and Down syndrome patients that would justify dietary supplementation, as recommended by Professor Lejeune."

3.2 Theories of 'imbalances'

3.2.1 Superoxide dismutase and reactive oxygen species

The roles of reactive oxygen species in numerous processes in living organisms has been, and continues to be, an area of considerable research. Much of it is complicated and not yet fully understood. Molecules called reactive oxygen species are present in all human beings. They arise from natural biochemical processes in all aerobic organisms. A very common reactive oxygen species in human metabolism is the 'radical', superoxide - a by-product of ordinary respiratory processes. Superoxide molecules are reduced to hydrogen peroxide by one of a few enzymes, called the superoxide dismutases, depending on location. Hydrogen peroxide is a 'non-radical' reactive oxygen

species and it reduced to water by either catalase or glutathione peroxidase, again depending on location. One of the gene sequences on chromosome 21 is involved in the production of one of the SOD enzymes - copper-zinc superoxide dismutase (SOD1). Proponents of nutritional formulations suggest that the 'overexpression' of SOD1 requires treatment with antioxidant vitamins based on an argument that runs much as follows:

(a) the additional copy of chromosome 21 in individuals with Down syndrome leads to elevated levels of the SOD1 enzyme, and
(b) elevated levels of the SOD1 enzyme increase the reduction of reactive oxygen species to hydrogen peroxide, and
(c) without corresponding increases in levels of glutathione peroxidase and/or catalase to break down hydrogen peroxide, levels of hydrogen peroxide remain elevated, and
(d) the elevated levels of hydrogen peroxide lead (indirectly) to elevated levels of damage (or, 'oxidative stress') to cells and DNA, and
(e) this additional damage leads to premature ageing and dementia (and, according to some more excited advocates, mental retardation), and
(f) that antioxidant vitamins can intervene in this process by 'mopping up' the 'loose' reactive oxygen species.

As a *theory*, this is plausible but unproven. There are a number of studies indicating increased levels of SOD1 in individuals with Down syndrome in blood cells [44,45,46,47,48,49,50,51,52,53]. Levels in other tissues have not been determined.

However, a number of these studies have indicated that there may be mechanisms that compensate for the effects of increased SOD1 levels (in blood cells) by elevating levels of glutathione peroxidase and/or catalase to meet the demand for reducing hydrogen peroxide [44,45,46,47,49,50,53,54] or through interaction with other superoxide dismuates enzymes [47]. There is no direct evidence that elevated levels of SOD1 are causing increases in levels of hydrogen peroxide.

Furthermore, it is not clear whether supplementation with high doses of antioxidant vitamins would be an effective intervention. Antioxidants have been a particular source of hope for beneficial effects, both for general proponents of vitamins' curative or preventative effects, and for proponents of nutritional supplementation in Down syndrome. Although epidemiological studies suggest protective effects from diets that are rich in antioxidants, clinical trials have so far not been successful [55,56,57,58,59,60]. We therefore find it difficult to agree that this argument provides "the logic behind using additional antioxidants in Down syndrome" [61].

3.2.2 Cystathionine beta-synthase
Another gene on chromosome 21 is involved in the production of the multifunctional enzyme, cystathionine beta-synthase. It is suggested that the cystathionine beta-synthase is overexpressed in individuals with Down syndrome, and that this 'over-stimulates' the reaction of homocysteine with serine to form cystathionine. It is further suggested that this leads to the 'disruption' of a number of other biochemical pathways and (among other things) causes a depletion of the levels of folate. One study has indicated elevated cystathionine beta-synthase levels [62] and two have not [63,64]. The US Food and Drug Administration has funded a study to examine some of these issues which should be completed in 1999.

4. Concerns

4.1 The lack of scientific evidence of efficacy or safety
One of the problems with evaluating treatments that include anything up to 50 different ingredients is identifying which component is doing what. It is quite conceivable that some of the ingredients are doing something useful, while others are not. Well-constructed clinical trials of the effects of particular substances are required if we are to significantly advance our understanding of these theories. Such trials would need to be based on reasonable hypotheses, double-blind in structure, with adequate controls and be amenable to appropriate statistical analysis.

4.1.1 Studies of individual nutrient supplementation
Studies of the effects on individuals with Down syndrome of supplementation with vitamin B6 have shown no improvement and side effects were reported [65,66,67]. There is some evidence that zinc plays a role in thyroid function and the wider immune system [36,68,69,70,71]. Studies on the effects of zinc supplementation have reported reduced infections [36,72] though another failed to find a correlation between zinc deficiency and

the recurrence or intensity of infections [35]. Lockitch et al. [33] observed only fewer instances of cough and fever and no changes in other clinical variables in a double-blinded crossover trial of zinc supplementation. They concluded, "Long-term, low-dose oral zinc supplementation to improve depressed immune response or to decrease infections in children with Down syndrome cannot be recommended."

Selenium supplementation has been reported to lower infection rates [73] and to influence immune system function in people with Down syndrome [74]. It has also been postulated that selenium supplementation may enhance the activity of glutathione peroxidase in erythrocytes and perhaps lead to improved protection against reactive oxygen species (see discussion of SOD1, above). However, selenium supplementation has been observed to decrease glutathione peroxidase in erythrocytes [73], leading the researchers to conclude that "Until we gain more knowledge about the biological functions of selenium in man and the role of oxygen metabolism in the development of presenile dementia in Down syndrome, universal selenium supplementation in Down syndrome patients cannot be recommended."

Tryptophan (an amino acid) is included in relatively large doses in both the 'day time' and the 'night' formulas in Nutrivene-D. Tryptophan is used in a large number of metabolic processes including the synthesis of serotonin. However, studies to see if supplementation with 5-hydroxytryptophan (which the body uses to make serotonin) produced any apparent benefits were negative [75,76,77].

4.1.2 Studies of multi-nutrient supplementation
Considerable scientific effort has been spent investigating the effects of individual supplements and high-dose multivitamin supplements. As commented elsewhere [14]:

"…glowing reports of the use of supplementary multivitamins and nutrients to overcome malabsorption in a group of Down syndrome children are published every so often, and such reports require many hours of investigators' time to sort out the evidence and determine whether there is any underlying validity to these claims. What has happened is that after an enormous amount of research effort on the part of many physicians and families, the indiscriminate use of a standard cocktail of vitamins and minerals for all children with Down syndrome is discredited by double-blind studies, and the Down syndrome community sits back waiting for the next dramatic claim of miraculous vitamin therapy to pop up."

Various studies investigated the claims that earlier multivitamin preparations were beneficial to individuals with Down syndrome during the 1960s, 1970s and 1980s. As Mary Coleman, a respected paediatrician and researcher, has summarised [78*]:

"Because of the claims of Haubold et al. [79], Turkel [2,3] and Harrell et al. [5] and because physicians understood so little about metabolism in Down syndrome and hoped that children with Down syndrome perhaps could be helped, an enormous amount of time and energy was spent at university research centers checking these claims. Studies were undertaken, using placebo, double-blind and other scientific techniques comparing children receiving these therapies to untreated controls, by White and Kaplitz (1964) [80], Bumbalo et al (1964) [81], Bremer (1975) [82], Hitzig (1975), Coburn et al. (1983) [83], Ellman et al. (1984) [84], Smith et al. (1984) [85], Menolascino et al. (1989) [86] and Bidder et al. (1989) [87]. The controlled studies were uniformly negative finding no difference between the treated and untreated children, except for the complex Bidder study which documented an actual decrease in developmental progress and various side-effects of the multivitamins and minerals. No study that adhered to even minimal scientific methods documented any definite improvement or even suggestive trends in intelligence, speech or language, neuromotor function, height or health. Preuss et al. [88] reviewed the literature in 1989 and flatly stated that indiscriminate multivitamin therapy was not useful in Down syndrome."*

4.2 Use of the drug 'Piracetam'
Although not a nutrient, Piracetam is often recommended as 'part' of 'targeted nutritional intervention'. Advocates claim that "Piracetam enhances communication between the right and left hemispheres of the brain, a critical aspect of information processing, which is the foundation of learning and remembering, and is an integral step in both understanding spoken communication and formulating speech." [19] This statement is not supported by direct evidence of any kind.

Piracetam is a member of a family of structurally-similar compounds often referred to as 'nootropics'. The nootropic racetams' biochemical actions and their effects on

seizures, cognition and memory (to name a few) have been studied since 1965. However, no commonly accepted mechanism of action has yet been established, and clinical uses of the racetams are limited [89].

The only reported study that we are aware of that involves individuals with Down syndrome was not blinded and not controlled [90]. The manufacturer of Piracetam does not encourage its use in individuals with Down syndrome and does not intend to pursue research into the drug's use in Down syndrome. However, introductory studies of the use of Piracetam in Down syndrome are taking place in North America. A study in Canada was completed in April of this year, and should be reported on some time in the next year.

Though not considered particularly serious in short-term clinical use, common side effects of Piracetam are diarrhoea, weight gain, depression and insomnia. The consequences of the long-term use of Piracetam are unknown but problems can occur in individuals who have been taking Piracetam if it is withdrawn abruptly.

4.3 Misleading promotions
Proponents of unorthodox therapies seem prone to inaccurate statements and unsupported claims of efficacy.

4.3.1 Incorrect or misleading statements
It should be noted that the manufacturers do not claim that their concoctions are 'treatments' per se and that this avoids the legal definition of a 'medicine' in some countries. However, the manufacturers seem content to postulate theories on their web sites in the hope readers will perceive there to be positive benefits from their products. For example, statements on one manufacturer's web site, such as "many children with Down syndrome suffer from malabsorption, celiac disease and lactose intolerance", "all nutrient needs may not be met in the diet alone" and "the excess activity of superoxide dismutase may be very damaging" [91] are exaggerations or speculations or both. In our opinion, they are unjustifiably alarming, given current scientific knowledge.

Even more misleading is the claim (on another manufacturer's web site) that "This extra or 'overexpressed' chromosome causes the depletion of body stores of antioxidants, amino acids, digestive enzymes, and other essential nutrients. Consequently, metabolism, growth, and development patterns are negatively impacted in individuals with Down Syndrome." [92] This manufacturer goes on to state that "Targeted Nutrition Intervention (TNI), is the replenishment of the depleted stores of essential nutrients in very specific and targeted amounts that *may possibly reduce* the effects of the metabolic imbalance" (our emphasis). This sounds 'scientific' and precise (indeed the manufacturer claims that their supplement is "the most technologically advanced formula for Down Syndrome"), yet, again, these statements do not stand up to serious scientific scrutiny.

Other advocates are less restrained than the manufacturers with incredible unsubstantiated claims for the effectiveness of these formulas [19]:

> *"The use of Targeted Nutritional Intervention in patients with Down syndrome may help relieve and/or prevent many of the disabling effects of Trisomy 21, including mental retardation and chronic illness"*

They also seem quite content to offer confident unsubstantiated reassurances about the safety of these formulations:

> *"Targeted Nutritional Intervention, in the form of Nutrivene-D, when properly administered, IS definitely safe. The ingredients found in this supplement are available through dietary sources - the foods your child eats. Sadly, it is impossible for anyone to adequately enforce a diet to insure that all nutritional needs are being met. It is not harmful to give your child with DS Nutrivene-D." [19]*

4.3.2 Misrepresentations of Down syndrome
Perhaps the most disconcerting statements made in support of nutritional supplementation are those that misrepresent Down syndrome. Some advocates of nutritional supplementation seem to believe the outlook for children with Down syndrome is extremely bleak. We have witnessed numerous claims such as Down syndrome is a "progressive, metabolic, degenerative disease that if left untreated, would lead to poor health, mental retardation and ultimately premature death" [cited in 20]. These are at best mistaken or, at worst, deliberate attempts to mislead.

It is well known that individuals with Down syndrome are faced with a number of medical and cognitive challenges. However, despite these difficulties, it is wrong to assume that

the outlook for people with Down syndrome is bleak. Indeed, in many of the world's societies, the outlook has never been more positive. Advances in medical care, effective developmental and educational interventions, and opportunities to learn, work and live in 'normal' social environments are helping them to overcome many of these challenges and to lead more independent and fulfilling lives than ever before. Many of the most significant advances have resulted from general scientific advancements that are not specific to Down syndrome such as modern cardiac surgery and the development of antibiotics. Other advances continue to be made at an increasing rate.

One wonders why some advocates of these therapies make such misrepresentations. If some people using these formulations have misconceptions about the potential of children with Down syndrome, then it would be of little surprise to hear startling anecdotal claims that these 'treatments' have surprising effects. Meanwhile, the fact that children not on these supplements are making similar progress is frequently overlooked.

> *Unfortunately, as noted elsewhere, "This tactic tends to prey mostly on the parents of infants and young children with Down syndrome, who are most vulnerable to the suggestion that they might be bad or neglectful parents if they don't give their children these products." [20]*

4.4 Perspectives on nutrients

> *"The mystique, the magic, the allure of vitamins have fascinated people from the time the word was coined in 1912. Undeniably, the micronutrients produced miraculous cures in cases of gross deficiency diseases. These wonders inspired speculation about vitamins' other health-giving and health-preserving actions, speculation built on public announcements about the role of vitamins in human nutrition. In our consumer culture, vitamins became a symbol of the benefits of science available to all. Yet the scientific evidence remained inconsistent and in dispute. Increasingly sophisticated studies produced more questions than they answered, and we continue to debate the crucial role of vitamins in good health and the significance of vitamins for optimal well-being." [93]*

A vitamin is simply a substance, present in foodstuffs, required in small quantities for the normal functioning of the body. Yet, the cultural views and perception, business interests, and science surrounding vitamins have had a remarkable history. Over the past 50 years, a variety of claims for the curative or preventative effects of vitamins have been made, yet few have withstood serious scientific scrutiny. Claims for "mega-vitamin" or "orthomolecular" therapies have not been restricted to Down syndrome. Other diseases, disorders and disabilities have been similarly targeted with dubious claims of cures and prevention, including Parkinson's disease, Alzheimer's disease, autism, epilepsy, and even the common cold and cancer.

Whilst scientific study has generally discounted these wilder claims for the effects of vitamins, considerable debate continues about their precise effects and the levels required to promote good health, and, in particular, the ranges within which they are safe, whether individually or in combination. Many nations have guidelines as to the recommended quantities of various nutrients that people require, on average, to maintain good health. Although these are occasionally contested and are modified from time to time in the light of advances in scientific understanding, they represent the best approximation of what are safe and adequate intakes at the present time.

4.5 Potential safety issues and uncertainties

These formulations are promoted as *supplements*. Individuals with Down syndrome who consume a well-balanced diet, and who have no additional medical problems, are already most likely receiving their recommended dietary allowance (RDA) from ordinary food sources. It is therefore important to remember that the doses provided by these supplements need to be evaluated as *additional* to average intake. Despite their advocates' expressed confidence in their safety (see above), and claims that they are "referenced" to recommended dietary intakes, there is, again, insufficient evidence to support such certainty.

Primarily of concern is the lack of studies of the effects of long-term nutritional supplementation (whether of individual nutrients or multi-nutrient mixtures) over

and above an ordinary diet. We cannot therefore be confident of any predictions of the outcomes of such actions. Furthermore, it is known that many nutrients' actions can depend on interactions with other nutrients, and that some form of 'balance' may be necessary to promote individual nutrient's effects. Dosing with supplements may interfere with such 'balances'.

There are also specific concerns about individual nutrients. Nutrivene-D and MSBPlus supplement vitamin A (retinol) at around RDA levels (US and EC), and beta carotene at around 2½ to 3 times RDA levels (US and EC). High doses of vitamin A can accumulate in the liver and can be toxic. Although beta-carotene (often proclaimed as the 'safe form' of vitamin, as opposed to retinol) appears to be free from immediate side effects in high doses, longer term effects of supplementation are unknown. Elevated risks of disease have been observed in clinical trials involving vitamin A supplements. These observations recently led the European Commission's Scientific Committee on Food to recommend further research, "thereby allowing the establishment of an upper safe limit for beta-carotene intake both alone and in combination with other antioxidants to be used for the general public and for special population groups at risk." [94]

The antioxidative effects of vitamin C (ascorbic acid) in doses above RDA levels have been questioned [95,96,97]. *Pro-oxidative* effects from vitamin C have been observed in human adults ingesting 500mg/day [98] - half of that provided by Nutrivene-D or MSB for older children.

Concerns about the neurotoxicity of supplementary doses of vitamin B6 in the UK led the government to propose tighter controls over supplements containing vitamin B6 [99] (and to a predictable outcry, led by the supplement industry eager to protect its £35m. p.a. trade in B6 supplements [100]). The three nutritional supplements promoted for use in Down syndrome supplement vitamin B6 at between 12 and 17 times RDA levels.

We are fully aware that none of these studies and concerns conclusively demonstrate that these supplements are harmful. However, we believe that they are more than adequate to demonstrate that categorical assurances about the safety of these substances cannot honestly be given, that a degree of caution would be prudent, and that they emphasise the importance of properly-designed controlled studies.

5. Conclusions

It is quite natural for people who care for, or treat, individuals with conditions that cannot be completely rectified, to wish for 'cures'. Psychological factors, such as denial, anxiety, fear, and anger, often occur, and these can sometimes cloud our judgement. Moreover, these can fuel our desire to feel that we are 'doing our best' for those close to us. Sometimes these desires, needs and emotions can distract us from the basic issues. The absence of clear answers can be frustrating and, in such circumstances, it is understandable that we may wish to seek out apparently plausible explanations.

There are undoubtedly many exciting possibilities for further advancements in the care of individuals Down syndrome, as well as further challenges. Advancements in our understanding of the roles of the gene sequences on the additional chromosome are likely to be the sources of future advancements. The idea that we could intervene in biochemical processes that are 'disrupted' by the extra genetic material present in Down syndrome (whatever they may be) is admittedly alluring. The view that any such intervention is likely to yield a 'cure' is, unfortunately, deceptively simple. It is important not to overlook the fact that, as well as biological determinants, there are numerous environmental influences that contribute to the progress and well being of all people. The additional chromosome in individuals with Down syndrome is critical, but we should keep it in perspective.

It is important to emphasise that, like the population at large, the range of abilities, problems and differences at the molecular biology level in people with Down syndrome is enormous, and that a great deal of work remains to be done.

"There is a great deal we do not know about Down syndrome in spite of many advances in recent decades. Everyone who cares about the special needs of these children welcomes advances in the field if they are based on solid evidence. Indeed, there may be malabsorption of vitamins or

minerals in some children; there may be co-enzyme methods of curbing the elevations of so many biochemical products measured in these children. There may be a way to protect these children by altering their immune systems in a positive way. We look forward to future scientific research.

"Until then, we must be careful not to interfere with the metabolism of children with Down syndrome until we understand what we are doing. Properly handled from birth with knowledgeable educational and medical care, the overwhelming majority of children with Down syndrome now have great potential for a good life and it is important not to experiment on them for the sake of an elusive miracle cure." [78]

Generally, the best care for people with Down syndrome should be broadly based in that appropriate emphasis should be given to educational, language, medical, leisure, emotional and social development. Any signs and/or symptoms should be dealt with according to current medical practice and the screening protocols for cardiac, thyroid, hearing and other functions should be carried out according to prevailing recommendations [17,101]

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