

Rebuttal to Dr. Leshin's & Quackwatch's Article, "Nutritional Supplements for Down Syndrome: A Highly Questionable Approach"

Last updated January 2008

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There is an ongoing debate between doctors, professionals, researchers and parents regarding the use of Targeted Nutritional Intervention (TNI) for Down Syndrome (DS). Nutritional supplementation is used by thousands of parents and is accepted and promoted by some doctors, professionals and researchers.

TNI is used to improve symptoms and alter the course of the syndrome. There have been studies done to show the beneficial effects of TNI, such as, enhancing the immune system, improving muscle tone, decreasing rate of infections, reducing oxidative stress, increasing antioxidant levels, and helping normalize homocysteine levels.

A handful of studies have been done which show little or no effect, but increasingly more studies have been done which show a beneficial effect. Len Leshin, M.D. wrote an article in the mid-1990's to try to refute the use of TNI and this article is still being used (as of this writing) as evidence that nutritional supplementation is very dubious in helping to change any outcomes in DS. The purpose of this paper is, by review of the literature, to rebut Dr. Leshin's article, through showing the usefulness and large asset that TNI does have. Although this author uses TNI in her own family, no personal or financial relationship exists with any company providing supplementation or alternative therapy.

Down Syndrome (DS) is a genetic disorder caused by a triplication of the 21st chromosome. Down syndrome was first discovered by Dr. John Langdon Down in 1866 [431]. In 1958 Professor Jerome Lejeune discovered Down syndrome was caused by a third copy of the 21st chromosome - Trisomy 21 [430]. It is the most common genetic cause of mental retardation in society [36], occurring 1 in every 750 live births [412]. Down syndrome has a higher rate of developing congenital heart defects, leukemia, Alzheimer's Disease, immune dysfunction, cognitive defects, thyroid disorders, gastrointestinal anomalies [432], and nutrient deficiencies than the general population. It is believed to be due to this aneuploidy [433] of the syndrome causing gene over-expressions [255, 257-259, 400, 412-421]. It has been confirmed by a few studies that the "gene dosage effect" hypothesis is true [420-427]. That is, the phenotype of DS is caused by the over-expression of certain genes on the human chromosome 21 [420-427]. There are 225 more genes in an individual with DS [413], due to the trisomy of chromosome 21, than in an individual without DS, some of which are over-expressed. Surprisingly, chromosome 21 is a gene-poor chromosome, having only 225 genes [413], as in comparison to chromosome 22 which has 545 genes [413]. Due to the low amount of genes on chromosome 21, it makes it one of the only living autosomal trisomies (see endnote 413).

It can be seen from the study, *The "gene dosage effect" hypothesis versus the "amplified developmental instability" hypothesis in Down syndrome* [420], that evidence for the "gene dosage effect" does exist.

Herein, we review recent data and present evidence to support the theory that the phenotypic traits of aneuploid syndromes, and DS in particular, result from the increased dosage of genes encoded on the triplicated chromosome.

In other words, the above abstract is giving evidence which supports that the phenotype of DS is a result from an over-expression (increased dosage) of genes on the extra 21st chromosome.

Due to the over-expression of genes in Trisomy 21, it creates deficiencies in certain nutrients, excess and imbalances of other nutrients and processes, and altered metabolic and biochemical courses (see evidence for this below). Because of this, those involved with research regarding DS, doctors who have patients with DS, and parents of children with DS, have looked into nutritional supplements being able to ameliorate [434] some of the problems present in DS. There is much evidence of oxidative stress [256-257, 259, 317-341, 401], low antioxidant levels [70-75, 79-82, 84-85, 89-103], nutrient deficiencies [69-103, 253-254, 450] and excesses [104-113], and other processes which do not function properly [123-136]. Targeted Nutritional Intervention (TNI) has been shown to be beneficial and help amend the problems present in DS. Please see endnotes 1-38, 100-101, 254, 256, 259, 449, 451.

Now, Targeted Nutritional Intervention is various vitamin, mineral, amino acid and antioxidant supplements specifically formulated for individuals with Down syndrome. The idea of TNI has been around since the 1940's, with the work of Dr. Henry Turkel. Since that time, there have been several different formulas made. There is much difference though from the first formulas made and the present TNI formulas. The present formulas do not use mega-doses of ingredients, as the first formulas, such as Dr. Turkel's, did. At the time of Dr. Turkel's work, he did not have the knowledge that is present now that DS is caused by a triplication of the 21st chromosome. Due to the large amount of scientific evidence and research that is now present, the TNI formulas have been improved greatly. The most common ones are Hap Caps by Dr. Jack Warner (www.warnerhouse.com), Nutrichem's MSB Plus V7 (www.Nutrichem.com) and International Nutrition's Nutrivene-D and Nutrivene-AD (www.nutrivene.com). TNI targets Down syndrome's specific and different metabolic needs.

The subject of nutritional supplements for Down Syndrome (DS) tends to come up often in the world of Down syndrome. Due to the controversy regarding this subject, some who oppose Targeted Nutritional Intervention (TNI) often cite the article, "Nutritional Supplements for Down Syndrome: A Highly Questionable Approach" by Len Leshin, M.D., F.A.A.P. and published on Quackwatch's website. Through this rebuttal, a different perspective regarding TNI will be given. It will be shown, through research, that TNI is beneficial for the majority of those with Down syndrome. Majority, that is, because there are few who are not able to handle TNI, because not every person, including people with DS, are the same. TNI can be customized for some of the children who cannot handle the regular formula.

Dr. Len Leshin is a pediatrician in Corpus Christi, Texas and is the father of a boy with Down syndrome. He has a website with some information regarding Down syndrome health issues and is very opposed to Targeted Nutritional Intervention, as can be seen from his website (www.ds-health.com). Quackwatch is a website (www.quackwatch.org) that is against many things related to alternative, holistic or natural medicine.

Although Dr. Leshin's article is referenced often and viewed as a good article by those not in favor of TNI, one thing that should be noted in the very beginning of this rebuttal is that Quackwatch's article was last revised in October 1998. There has been much advance in the research regarding Down syndrome since that time [see endnote 444].

From what will be shown, it should be evident that most individuals with Down syndrome can benefit from taking a multi-vitamin that is targeted to their needs, because, their DNA (Deoxyribonucleic Acid) is *completely* different than someone without DS and therefore they have specific needs.

Now onto Dr. Leshin's article.

Dr. Leshin writes,

Down syndrome is a genetic disorder caused by the presence of a third 21st chromosome. It occurs once in every 600 to 700 births, making it the most common genetic disorder. Its common features include poor muscle tone, short stature, a small nose with flat nasal bridge, small skin folds on the inner corner of the eyes (epicanthal folds), dry skin, immune-system suppression, developmental delays, speech difficulties, and mental retardation.

The above statement regarding the typical common features of an individual with Down syndrome is true. With TNI some of these symptoms can be ameliorated [404], such as immune system suppression, mental retardation, poor muscle tone and the like. The reason these symptoms can be amended is by overcoming the deficiencies which are present in Down syndrome and slowing the degenerative disease process by supplementing with various vitamins, minerals, amino acids and antioxidants. This will be discussed below, as to how these common features can be improved, in the majority of DS.

Dr. Leshin writes,

Vitamins. *Supplementation with both single vitamins and vitamin mixtures have been studied in children with Down syndrome. Although sporadic reports of vitamin deficiencies have been published, most studies reveal none,*

Actually many studies have shown that supplementation may indeed *help* the individual with Down syndrome. Please see endnotes 1-38, 100-101, 254, 256, 259, 449, 451. There have been a few studies to try to disprove the “vitamin theory.” Yet, it can be seen that there is substance to the reason for a Targeted Nutritional Intervention program regarding DS by looking at all the numerous studies showing gene over-expressions [39-68], protein over-expressions [55-68], articles that show and suggest nutritional supplementation [1-38, 100-101, 254, 256, 259, 449, 451], the many deficiencies that have been shown [69-103, 253-254, 450], and nutrients that are in excess [104-113]. The whole entire purpose for TNI is to target the abnormal deficiencies, gene and protein over-expressions and the nutrients that are in excess and supplement accordingly. The makers of the TNI formulas have looked at the research showing the above problems that occur in DS and made a supplement that best counter-acts the abnormalities that are present in the DS population. Therefore, it is not consistent with present research to say TNI is “unhelpful” for the individual with Down syndrome, as Dr. Leshin says at the end of his article [see endnote 114 for the quote].

In the above quote, Dr. Leshin cites two articles stating deficiencies in DS have been noted. Actually there were *twenty-five* studies done showing deficiencies in DS prior to the writing of Dr. Leshin’s and Quackwatch’s article [70, 72, 75-76, 80-82, 84, 86-88, 90-103]. And *many* more studies have been done showing consistent deficiencies. Please see endnotes 69-103, 253-254, 450. While there have been few studies stating there are no deficiencies in certain nutrients [115-121], several of these same studies have also shown a deficiency in other nutrients [116, 118, 199].

Dr. Leshin writes,
many studies have found that vitamin supplementation with either RDA doses or megadoses have no effect on mental ability or behavior. The present supplements tend to use RDA values, although levels of vitamin A high enough to be toxic are still occasionally promoted.

Down syndrome should not be compared with the general population, because in Down syndrome there are numerous other metabolic and biochemical processes that do not function properly, as the studies above reveal. The RDA (Recommended Daily Allowance [445]) is based on the general population, not someone who has 47 chromosomes instead of the normal 46. Research indicates those with an extra chromosome cannot exactly follow the RDA, because their nutrient needs are different than the general population. The RDA is meant to meet the “*known nutrient needs of practically all healthy people.*” This does not cover people who have genetic abnormalities, such as those with Down syndrome. While the RDA is a good guide to ensure that people do not get very high amounts of certain nutrients, it cannot be applied to individuals with DS all the time.

In looking at the different levels of the vitamins, minerals and amino acids that are in the TNI formulas, it will be seen that those levels that are above the RDA are levels that have been shown to be altered or deficient in an individual with Down syndrome. It can also be noted that most of the time there are a lot more nutrients in the TNI formulas compared to a general multi-vitamin. This is for the same reason as certain levels being above RDA values; that is due to an altered or deficient system. Again, for the same reason, there are certain nutrients that are not in TNI formulas. Please see endnote 448.

Take Vitamin B12 as an example. Studies indicate that the gene, Cystathione-Beta-Synthase (CBS) is over-expressed in DS [123-134]. This creates the SAM (S-adenosyl-Methionine or SAMe) cycle to function improperly [134-136]. Therefore, it creates a B12/folate deficiency [135-139], which can be seen in an elevated MCV (Mean Corpuscular Volume) that is common to DS [140-146]. Supplementation with B12 or folate (and it may need to be above RDA levels), can bring the MCV down. If there is no supplementation with B12 or folate, and the MCV level is not brought down, it can lead to Leukemia [146-150]. It is also against research to suggest that TNI has “*no effect*” on mental ability. Quackwatch did indeed cite a few references to try to show that TNI has no effect on mental ability. Many of the articles Dr. Leshin cited were done specifically for refuting the “vitamin therapy theory” in DS. Yet, it can be seen that a couple of the articles cited show that TNI *did* have a beneficial effect on mental ability. See endnotes 315, 405. Plus, many more studies have been done that show a benefit from TNI [1-38, 100-101]. Oxidative stress [401], as an example, affects mental ability in a bad way. It is part of the pathogenesis of mental retardation in Down syndrome [151-160, 256], Alzheimer’s Disease (AD) [158-168] and neurodegenerative diseases [169-182]. As some examples of that, here are quotes from a couple studies,

The study, *Oxidative Damage Is the Earliest Event in Alzheimer Disease* [409], states the following,

Our findings show that oxidative damage is quantitatively greatest early in the disease . . . Our observations indicate that increased oxidative damage is an early event in AD. . .

The above study was done in 2001, and it shows that oxidative stress is the earliest event in AD. In other words, it is involved in the pathogenesis of Alzheimer's Disease.

Another study, *Oxidative stress: A bridge between Down's syndrome and Alzheimer's disease* [159] shows the following,

Besides the genetic, biochemical and neuropathological analogies between Down's syndrome (DS) and Alzheimer's disease (AD), there is ample evidence of the involvement of oxidative stress (OS) in the pathogenesis of both disorders.

This study confirms that there is ample evidence of oxidative stress.

Supplementing with a high amount of anti-oxidants has been shown to definitely affect mental ability in a good way. See endnotes 183-196. This is accomplished by reducing free radicals [402], which normally cause oxidative stress when they are not reduced and by increasing antioxidant levels [183-196].

To see more on this subject matter, a good reference book is *Oxidative Stress in Cancer, AIDS and Neurodegenerative Diseases* edited by Luc Montagnier, Rene Olivier and Catherine Pasquier [410].

Dr. Leshin writes,

Minerals. *Several studies have shown zinc and selenium serum levels are decreased among children with Down syndrome. Some studies on zinc report increased growth, improved thyroid and lymphocyte functions, and increased survival of white blood cells with supplementation; however, these are mostly unconfirmed [20,32]. Selenium is a cofactor in glutathione peroxidase, an enzyme that helps scavenge oxygen radicals. Selenium supplementation may improve certain indicators of immune functioning, but the supporting research has only been preliminary.*

There have been quite a few studies done on zinc in Down syndrome. About four studies claim there is no deficiency [115-116, 118-119], but twenty-five of them show that there is commonly a zinc deficiency in Down syndrome [197-219, 252, 254, 450]. It is believed that deficiency is due, at least in part, to the over-expression [400] of the gene Cu/Zn Superoxide Dismutase [220-221].

Zinc is an important part of the immune system [222-228] and plays a vital role in the thyroid functioning properly [229-238]. Thyroid problems are extremely common in Down syndrome [229-250]. So common, in fact, that it has been proposed to start all children with Down syndrome on thyroid medications at birth [251]. There are several studies to show zinc actually does help the thyroid to function properly [229-238].

Zinc is also an anti-oxidant [260-262]. Those with Down syndrome have high oxidative stress [401] and a pro-oxidant state [263-272, 403], which is in part due to the over-expression of SOD (Superoxide Dismutase). The study, *Markers of oxidative stress in children with Down syndrome* [334], shows that oxidative stress is caused by over-expression of SOD:

Persons with Down syndrome have increased vulnerability to oxidative stress caused by overexpression of superoxide dismutase, an antioxidant enzyme coded on chromosome 21.

Oxidative stress [401] is associated with neurodegenerative diseases such as Alzheimer's Disease [158-168]. Those with Down syndrome are at a pre-disposed risk of developing AD at an earlier age than the general population [272-277].

Down syndrome has also been shown to have Selenium deficiency [278-283]. Selenium is an important anti-oxidant [291] for the immune system to operate properly [284-288] and the thyroid to function [289-291]. Antioxidants are especially important in Down syndrome, due to the pro-oxidant state [263-272, 403] and elevated levels of oxidative stress [401] (as noted above in endnotes cited).

Low selenium levels have also been reported in children with cancer [292-299]. Oxidative stress is part of the pathogenesis of leukemia [300-302]. Therefore, because those with Down syndrome already have a high oxidative stress state and low selenium levels, it is not unreasonable to conclude that this is one of the reasons they have a higher risk of developing leukemia.

Dr. Leshin writes,

Amino acids. All three popular formulas (MSB Plus, NuTriVene-D, and Haps Caps) include amino acids. This supplementation is based on a study of adults with Down syndrome published in 1992 by Jerome Lejeune, M.D. This study reported a consistent deficiency of serine and excess of cysteine and lysine, which Lejeune felt were caused by overexpression of certain genes on the 21st chromosome. He postulated that the supplemental amino acids balanced the blood levels, making the biochemical workings of the body normal. However, a subsequent study of 22 children found no such abnormalities in serum or urinary amino acid levels.

There have been several studies done on Down syndrome that show an imbalance in amino acids [303-307, 407]. Also, it must be noted that the two studies Dr. Leshin cites are not comparable. The one study was on children and the other on adults. The metabolism of adults and children are likely to be different. By looking at the references that are cited in this rebuttal regarding amino acids in DS, it can be seen that both children and adults with DS have abnormalities in amino acids [303-307, 407]. Not all of the abnormalities of amino acids are the same in both children and adults.

As an example of how this actually does occur, the study, *Variation of amino acids in relation to age in Down Syndrome subjects* [122], shows evidence that there are differences in amino acid abnormalities in children and adults. This study is comparing individuals with Down syndrome aged 0-60 years old and individuals without Down syndrome aged 0-94 years old. Notice what the results of the study say,

Two major changes were found in Down's syndrome: a decrease in plasma concentration of serine at any age, which could be due to a dosage effect of cystathionine-beta-synthase, and an increase in plasma lysine concentration in patients above 10 year's old, probably due to premature aging. Other minor changes were also present in plasma and urine, also possibly explained by premature aging.

Therefore, this study indicates exactly what was mentioned above, that amino acids vary depending on age. Everything is not the same with adults and children. There are certain amino acids, as the above quote shows, that are increased or decreased in *all* individuals with DS regardless of the age. Other amino acids are also higher or changed at *certain* ages, as it says above, “an increase in plasma lysine concentration in patients above 10 year's old.” The above study therefore speaks contrary to the argument given above by Quackwatch against amino acid use in Down syndrome.

Plus, it must be addressed that the article Dr. Leshin cites goes directly against his own argument where he says, “However, a subsequent study of 22 children found no such abnormalities in serum or urinary amino acid levels.” The very abstract he cites [407] says nothing about no abnormalities were found, but it does say the following,

The only significant difference between the groups was a higher mean plasma lysine concentration in Down's syndrome patients compared to controls.

The higher mean plasma of lysine is an abnormality. That can be seen through the study, in that the controls (without DS) did not have higher mean plasma of lysine. The article Dr. Leshin cites proves the point even further regarding abnormalities in amino acids in Down syndrome. And, it shows that in DS there are abnormalities compared to the general population. Thus, we can see that the studies done by Jerome Lejeune on amino acids in DS are significant to the relevance of TNI [305].

There are certain amino acids that they are high in [303-307, 407] and that they are low in [303-307, 407]. Amino acid supplementation, in children with DS, has been shown to be beneficial [305].

Dr. Leshin writes,

Some proponents claim that overexpression of the cystathione beta-synthase gene causes a "functional" folic acid deficiency in which serum levels are normal but the body can't use all of it and is unable to repair damaged DNA. Supplementation supposedly alleviates this alleged problem. This theory has yet to be demonstrated in a scientific study. The FDA has just funded such a study, which should be completed in 1999. However, it is not clear that cystathione beta-synthase levels are elevated in Down syndrome. One study showed increased amounts, but two others did not.

It is quite well known and has been shown over and over again that the gene Cystathionine Beta-Synthase is over-expressed in individuals with Down syndrome [123-134]. There were four studies done before the time of Dr. Leshin's article to show the over-expression of the CBS gene [125-126, 131-133].

Moreover, the functional folate deficiency is true as well [134].

There are quite a few studies and evidence to support the over-expression of the CBS gene creating a folate deficiency. Here are some examples. Those with Down syndrome have high MCV blood values [see endnotes 140-146], which is caused by a folate (B12) deficiency [see endnotes 135-146]. They also have low homocysteine levels [see endnotes 308-310], which is due to the CBS gene as well [see endnotes 309-310]. Their low levels of folate and B12 are also due to the CBS gene and SAM cycle that doesn't function properly [see endnote 310].

Dr. Leshin writes,

Another amino acid being promoted is tryptophan, which the body uses to synthesize serotonin. Decreased serum levels of serotonin have been found among people with Down syndrome [38]. However, it is not yet been possible to study serotonin levels in the brain, so it is not known whether the brain serotonin levels are also low. Oral administration of 5-hydroxytryptophan, a compound the body uses to make serotonin, has produced no apparent benefits [15, 38-40].

Tryptophan has been shown in a few studies to be deficient in those with DS [311-316]. There have also been a few studies showing that Tryptophan supplementation increases serotonin levels [314-316] and improves muscle tone [314-316] in children with Down Syndrome. To say that it produces no benefits, is quite contrary to research. There were two studies done prior to the writing of Quackwatch's article that showed benefits from supplementing with Tryptophan [315-316]. Also, Dr. Leshin cites the study, *5-hydroxytryptophan and pyridoxine. Their effects in young children with Down's syndrome* [315], to try to support that Tryptophan supplementation produces no apparent benefit. But the study shows just the opposite. The study says the following,

Detailed studies of cognitive-adaptive function of children in the various groups found a significant difference. . . In other words, one of the studies Quackwatch cites proves that Tryptophan supplementation actually is beneficial. It has been shown by several studies that it is helpful [311-316].

Dr. Leshin writes,

Antioxidants. ... However, no evidence of this oxidative damage has been found in living humans with Down syndrome...

This is a completely false statement. There are many studies that have been done, both prior to [318, 320, 324, 331-332, 338] the writing of Dr. Leshin's article and after [317, 319, 321-323, 325-330, 333-337, 339-341, 256-257, 259], that show evidence of

oxidative damage [401] in Down syndrome [317-341]. Dr. Leshin's says there is no evidence of oxidative damage in living humans with DS, when there were three studies done before the writing of Quackwatch's article that show evidence of oxidative damage in living humans with DS [332, 338-339]. There have also been several studies since the writing of Quackwatch's article to show that [332-341].

Here is a quote from one of the articles that was done at the time of Dr. Leshin's article. The study, *Localization of superoxide dismutases in Alzheimer's disease and Down's syndrome neocortex and hippocampus*, which was done in 1995 [338] states the following,

The observed changes . . . in cases of Alzheimer's disease and Down's syndrome support a role for oxidative injury . . .

The above study was done in individuals with Down syndrome and Alzheimer's Disease. Thus, it can be seen, that there is evidence of oxidative damage in living humans with DS.

There are other studies that show a pro-oxidant state [317-333] and increased oxidative stress [317-333, 256] in DS as well. The fact that they are prone to Alzheimer's Disease [272-277], congenital heart defects [342-345], leukemia [300-302, 344-347], respiratory problems [348-350], cataracts [351-352], thyroid problems [229-250], mental retardation [151-160], pre-mature aging and cell death [317-333] all show that they do have increased oxidative stress (which is causing oxidative damage). All of the health issues above are related to or associated with oxidative stress (see cited articles above). Part of the reason they have a high amount of oxidative stress is because they have low antioxidant levels [70-75, 79-82, 84-85, 89-103, 253]. Low antioxidants also play a role in many of the above health problems. As a few examples: the flu and lung infections are partly due to low antioxidant levels [349-350]; cataracts are partly due to low antioxidants [351-352]; infants with congenital heart defects have low antioxidants [343].

Low antioxidants are associated in the phenotype of an individual with DS [70-75, 79-82, 84-85, 89-103]. This is also partly why they have increased oxidative stress (damage). It is also due to the over expression of the gene Superoxide Dismutase 1 [353-365]. Antioxidant supplementation has a beneficial effect on mental capacity and cognition [183-196], by reducing oxidative stress [183-196], therefore it makes it extremely important for DS.

Dr. Leshin writes,

Docosahexaenoic acid (DHA). . . Promoters of DHA for older children with Down syndrome claim that its use will improve eye and neurologic development. No research indicates that children with Down syndrome lack DHA, cannot make enough, or can benefit from DHA supplements. Further, studies have shown that the critical period for supplementing DHA in preterm infants is the first two months of life [43] and little benefit beyond that should be expected. Likewise, the promotion of the use of other fatty acids has no proven benefit for children with Down syndrome.

It is true that DHA supplementation improves eye and neurological development and function [366-376]. Studies indicate it is not true that DHA supplementation is only beneficial the first two months of life in preterm infants. In fact, it has been shown through studies that DHA supplementation in infants, children, and even adults is beneficial [376-380]. It has been shown that DHA supplementation may actually improve and treat Alzheimer's Disease [381-383]. The above shows that it is even more beneficial to supplement DHA, especially for those with DS, since they are at a pre-disposed risk of developing AD and eye problems. They need all the help they can get in the area of improving neurological development and function.

Dr. Leshin writes,

Stating speculations as fact. Supplement promoters commonly claim that "infants with Down syndrome become retarded largely because of the overexpression of" superoxide dismutase, and that supplements can compensate for this. Some promoters append a long list of scientific articles to their promotional pieces, implying that they all support what the promoter has written. Generally, however, many of the studies have little to do with nutritional supplementation, and of those that do, the vast majority actually conclude that

supplementation is not beneficial. Such lists can be very misleading to the parent with no medical background or a physician who lacks the time to investigate the actual articles or even read the abstracts..

It is very true that individuals with Down syndrome are mentally retarded partly because of the over-expression of superoxide dismutase, but it is also due to the other genes that are on the 21st chromosome. This can be known by looking at the evidence that superoxide dismutase is over expressed [353-365]. This then in turn creates the hydroxyl radical (which is a deadly free radical) that causes cell death [384]. This is partly a problem as well because in DS their antioxidants are not high enough to counter the bad effects of SOD1 (Superoxide Dismutase 1), as was shown above. The over expression of the cystathionine beta-synthase gene also leads to mental retardation, by creating a folate along with a B12 deficiency [135-146]. It should be obvious that there is something (a lot of things actually) that cause mental retardation in DS. Those with DS are not mentally retarded for no reason, it is due to something. Through present research that “something” appears to be over-expressed genes, deficiencies in antioxidants and other nutrients, elevations in other areas and numerous other problems. All of the metabolic and biochemical problems are not yet known. There is much more to be done in this area of research in the Down syndrome population. But, there has been a tremendous amount of research done in this subject thus far, such as the recent finding of the APP (Amyloid-beta precursor protein) gene by Professor Mobley at Stanford University and how that gene plays a role in the pathogenesis of Down syndrome [385].

Dr. Leshin writes,

Dubious claims of benefits. *The claims range from the mild, such as an increase in growth rate and decrease in rate of infections, to the extreme of normalizing such items as cognition, muscle tone, sleep habits, speech, visual acuity and even facial features.*

In light of the research, they are not “dubious claims.” They are well researched out and can be scientifically backed up. The points are:

1) *“an increase in growth rate and decrease in rate of infections.”* If it is understood that those with DS are deficient in the essential trace mineral Zinc [197-219, 252, 254, 450], it would be seen that this “claim” is well substantiated in medical research. It can be shown through research that Zinc supplementation decreases the rate of infections and enhances growth in those with Down Syndrome [200, 202, 210, 213, 215, 408]. There were six studies done several years prior to the writing of Quackwatch’s article that displayed a decrease of infections and increase of growth rate in DS [200, 202, 210, 213, 215, 408]. This is not a “dubious claim.” It is very well supported by scientific evidence.

It can also be seen through further studies that zinc plays a crucial role in growth [252]. Zinc also plays a large role in the immune system and good health [222-228].

Glutathione and Selenium are low in DS [253, 278-283, 387-389]. Glutathione is very important in the health of the respiratory system and reduces flu symptoms [349-350, 386]. Selenium is a key component in the health of the immune system and it functioning properly as well [284-288]. Selenium has also been shown to reduce the rate of infections in children with DS and it has an immunoregulatory effect on them [285].

2) *“normalizing such items as cognition.”* Perhaps not normalize, but research supports that it may very well improve their cognition greatly, to help “normalize” it at least to some degree [1-38, 100-101, 151-160, 183-196]. There are numerous ways of doing this. One of the ways is by decreasing oxidative stress and increasing antioxidants, as was discussed above. Due to the deficiencies present in DS, this may also have an effect on cognitive abilities. The study, *Immune-endocrine status and coeliac disease in children with Down’s syndrome: relationships with zinc and cognitive efficiency* [206], suggests the following,

Altered intestinal absorption of nutrients may in turn affect endocrine functions, brain development, and cognitive performances.

In the above study they showed that zinc levels were deficient in the DS population and that it may have an effect on

endocrine functions, brain development and cognitive performances.

3) “normalizing such items as . . . muscle tone.” In the muscle tone area, for some, it may be able to normalize it. There are some children who do not have as bad of muscle tone as others, so they may improve even more. Research indicates you can certainly help by supplementing Tryptophan [316]. One study states the following after supplementation with Tryptophan in individuals with Down Syndrome,

An increase in muscle tone and an improvement of motor behaviour were the only long-lasting results. [316]

4) “normalizing such items as . . . sleep habits.” Their sleeping habits may be able to be helped, but not necessarily normalized, by supplementing L-Tryptophan [316] and Melatonin [390].

5) “normalizing such items as . . . speech.” If their cognitive abilities are improved (see above) and their oral muscles are functioning properly, speech should be affected and improve.

6) “normalizing such items as . . . even facial features.” It could not be supported through research that the facial features, such as the flat nasal bridge, flat forehead, upward slanted eyes, etc., would most definitely improve to normal. But, it would be safe to say that because there are nutritional deficiencies in DS, if those levels were normalized, the facial features may improve [391]. What may improve may be the appearance. They may look healthier, have more color to them, brighter and have a fuller face, by overcoming the nutritional deficiencies that are typically present in DS [69-103].

Dr. Leshin writes,

Targeted nutrition. *The NuTriVene-D program is said to be specifically designed for individuals with Down syndrome -- to enable better absorption of nutrients and provide "essential nutrients that are typically deficient." [47] International Nutrition and the [Trisomy 21 Research Institute](#) refer to NuTriVene-D as "Targeted Nutrition Intervention" ("TNI"). However, they do not recommend testing vitamin and mineral levels before use of the product is begun (and do not recommend amino acid testing at all).*

While Trisomy 21 Research says nothing of having blood tests done prior to starting the use of Nutrivene-D, they do recommend blood testing be done [392] to ensure no fat soluble vitamins are being stored and to also determine any nutritional deficiencies. Nutrichem (MSB Plus V7) does recommend amino acid testing [411], although this was not published at the time of Dr. Leshin’s article.

Dr. Leshin writes,

No definitive research has been published showing consistent nutrient deficiencies among children with Down syndrome.

Actually, there have been numerous studies showing consistent deficiencies in Down Syndrome [69-103, 253-254, 450], both prior to the writing of Quackwatch’s article and after, as was already discussed. As some examples, here are some quotes from a few studies. 5 of the 6 studies below were already published at the time of Quackwatch’s article.

1) *Diminished zinc plasma concentrations and alterations in the number of lymphocyte subpopulations in Down's syndrome patients [74],*

Alterations of plasma levels of zinc and in the immune system in Down's syndrome (DS) have been reported. . . .Significantly diminished zinc plasma levels, . . . were found in DS patients by matching with control group.

2) *Changed serum trace element profile in Down's syndrome. [95],*

Serum zinc and selenium levels were significantly lowered in DS subjects.

3) *Glutathione peroxidase activity, lipid peroxides and selenium status in blood in patients with Down's syndrome.* [90],

The selenium concentration in whole blood, erythrocytes and plasma was significantly lower in trisomy 21 patients than in normal subjects (p less than 0.001) in both age groups.

4) *Lipid peroxides in blood plasma and enzymatic antioxidative defence of erythrocytes in Down's syndrome.* [91],

The concentration of selenium in erythrocytes of Down's syndrome patients was reduced.

5) *Trace element profiles in individual blood cells from patients with Down's syndrome.* [96],

The median levels of zinc in erythrocytes. . . were significantly lower in DS than in control children.

6) *Evaluation of plasma zinc levels in patients with Down syndrome* [97],

the plasma concentrations of zinc were measured in 32 patients with Down's syndrome (DS) and in 44 healthy controls (C). An obvious and significant decrease in the levels of this element was observed in the trisomic subjects.

Dr. Leshin writes,

Use of anecdotal evidence. *Many parents report that their child improved after starting supplements. Stories of increased health, normal growth, children acting "brighter" or "more with it" are abundant and can be very alluring to the interested parent or doctor. However, such testimonials have been shown to be affected strongly by the parent's bias.*

“Increased health, normal growth, children acting ‘brighter’ or ‘more with it’” was shown above (after the quote “dubious claims of benefits”) to be improved or attainable by TNI. There is some anecdotal evidence, but that is not what is being shown in this article. This article gives scientific evidence behind the use of TNI for someone with DS. The research shown here is plenty to strongly support the use of TNI.

Dr. Leshin writes,

Misrepresenting the nature of Down syndrome. *Some promotional literature refers to Down syndrome as a "progressive, metabolic, degenerative disease that if left untreated, would lead to poor health, mental retardation and ultimately premature death." [49]*

Research indicates this is true, that Down syndrome is a “progressive, degenerative disease” [393]. It is not “misrepresenting the nature of Down Syndrome.” The fact that they are classified as a neurodegenerative disease [257, 394-398] shows that it is a “progressive, degenerative disease.” While those with Down syndrome do live longer and healthier lives than they did 30 or more years ago, there are still problems that are present in the DS population. They still account for the vast majority of Mental Retardation in the population. Plus, they still have a high risk of developing Alzheimer’s Disease, Leukemia, Cataracts, Dementia, Respiratory Infections, Immune Suppression and other health problems. This is what TNI is for - to prevent and help “slow down” the “progressive, degenerative disease” process and improve the health of those with Down Syndrome.

Dr. Leshin writes,

The Bottom Line *An estimated 5,000 children with Down syndrome have been placed on one of these supplements. The number still taking them is unknown, but interest in these treatments remains high. 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. No matter how alluring the theories are, or how convincing the anecdotal evidence may seem, it's important to remember that these theories have not been proven, past experience with similar claims have been proven unhelpful, and the currently promoted formulas have not been scientifically proven safe or effective."

Once again, this quote is quite contrary to present research. A recent figure, as of fall 2006, by Dr. Lawrence Leichtman, who is a pediatrician and clinical geneticist and who is also on the scientific advisory board of the Trisomy 21 Research Foundation, was that approximately 35,000 people with Down syndrome are taking TNI [399]. There have been several studies to show the benefit of TNI [1-38, 100-101, 449]. There is so much other research to show all that was mentioned above (e.g. deficiencies of certain nutrients, over expressions of certain genes, proteins and so on), that is, in part, what makes TNI so worth it. Why sit around and wait until 10, 20 years down the road when it may be finally accepted and realized by all that TNI really does improve cognitive abilities, mental capacity, health, immune function and so forth? When, if you wait 10, 20 years down the road there may be already a lot of damage done by the numerous metabolic problems. This rebuttal will be ended with a recent study that shows, on a small scale, that Targeted Nutritional Intervention for Down syndrome is beneficial,

Amino acid profile and oxidative status in children affected by Down syndrome before and after supplementary nutritional treatment.

[Ciaccio M](#), [Piccione M](#), [Giuffre M](#), [Macaione V](#), [Vocca L](#), [Bono A](#), [Corsello G](#). Universita degli Studi di Palermo, Palermo, Italy. June 2003

Down syndrome is the most common autosomal aberration among liveborns, characterised by several clinical features and metabolic disturbances. Aminoacid pathways abnormalities and defective oxidative balance are the most common metabolic problems in Down Syndrome. To evaluate the biochemical responses of children with Down Syndrome to a nutritional regimen supplemented with aminoacids, vitamins and polyunsaturated fatty acids, we submitted 86 subjects divided in two groups (0-6 and 6-12 years) to the dosage of plasma levels of aminoacids, antioxidant enzymes activities and reactive oxygen species, before and after 12 months of such nutritional supplementation and in relation to normal controls. **The results obtained showed a tendency towards the values of normal subjects with statistically significant differences. Although other studies must be performed to confirm and define such report, our experience supports the usefulness of a nutritional supplementation with aminoacids, vitamins and polyunsaturated fatty acids, also considering the absence of side effects.**

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402. Free radicals play a role in a number of processes, some of which are essential for life. But, they can also do damage that results in cell death. The damage occurs when antioxidants cannot minimize and reduce the free radicals.
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