Down's Syndrome and Thiamine Deficiency

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Etiological factors in Down's Syndrome (trisomy 21) were considered and a common factor, namely maternal thiamine (B1) deficiency, is discussed. Vitamin profiles were carried out in three male patients with Down's Syndrome to see if a vitamin B-1 metabolic disturbance existed. All three showed vitamin B-1 disturbance on the transketolase test, despite a normal diet.

Vitamin B1 supplements (50 mg thrice daily) were given, and the beneficial changes in behavior and affect are discussed.

A hypothesis suggesting maternal thiamine deficiency as a possible cause of Down's Syndrome (and trisomy 21 of bone marrow preleukemia) is outlined.

Primary, secondary, and tertiary prevention of Down's Syndrome is discussed in the light of the findings and this hypothesis.

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Introduction

Milunsky et al., (1970) discussed the practical importance of Down's Syndrome pointing out that with mothers aged 45 years and over, the incidence of Down's Syndrome is one in 46, and from their experience with patients with Down's Syndrome in the State of Massachusetts, the average sum expended on institutional care for each patient during his or her life would total $60,000 and that, even if no other children with Down's Syndrome were born in that state, the present affected population would cost a total of $180,000,000 during their lifetime in institutions. These estimates are several years old.

More recently, Hagard and Carter (1976) have carried out a cost-benefit analysis concerned with preventing the birth of infants with Down's Syndrome. They pointed out that an increasing proportion of infants with Down's Syndrome survive, and that 20 percent of children with Down's Syndrome have an IQ in the range 50-69, 75 percent in the range of 20-49, and the rest are below 20, and so a high percentage are institutionalized. The cost of institutional care for each mentally handicapped person in Australia is around $6,500 per annum ($100,000,000 is the total annual cost of
Australia and $26,000,000 for N.S.W.) (Cox, 1975).

Thus if the etiology of Down's Syndrome were better understood it could mean: (a) a great reduction in its incidence, (b) if the Down's Syndrome child is detected and treated early enough it could be born with fewer stigmata (e.g., less heart defects) and could be less mentally retarded, possibly with a near normal IQ (not needing institutionalization), (c) more of those already in institutions would be able to leave or work in sheltered workshops if there were a factor that could easily improve their behavior, affect, and help their concentration and ability to learn new skills, (d) cost benefits would be enormous, and finally, (e) women over 35 could become less afraid to have children in case they had one with Down's Syndrome.

The etiology of Down's Syndrome (trisomy 21) is unknown. It is thought to be due to hyperploidy for all or part of the small acrocentric chromosomes. Trisomy is by far the most common cause and is presumably the result of meiotic nondisjunction.

It is known that the prevalence of Down's Syndrome birth increases with age and mothers who give birth to mongols are usually over 35 (Penrose, 1951), may have hyperthyroidism prior to conception or during early pregnancy (Fialkow et al., 1971), may have had viral infections such as hepatitis (Stoller and Collman, 1969), are often anemic (Harlap, 1973), have depression, vomiting, and fatigue in early pregnancy and a history of miscarriage prior to birth of the mongol child, and often have vaginal bleeding in the first trimester (Ingalls et al., 1957). Also oestriol production is usually less than in normal pregnancy and may be associated with maternal anemia (Symonds, 1974; Beischer et al., 1968).

One factor is common to all the above findings—namely, thiamine (B-1) deficiency (other B group vitamins and hormones which are synergistic are also likely to be important).

Thiamine deficiency which is present in about 20 percent of the adult population (Wood and Pennington, 1974), tends to increase with age, and there is a high requirement in pregnancy, hyperthyroidism, and in infections (Marks, 1968). Oestriol production by the placenta depends on a normal functioning adrenal cortex which is thiamine dependent. The fetal adrenal gland produces dehydroepiandrosterone which is the major precursor of urinary oestriol, and thiamine deficiency can interfere with its synthesis, possibly causing the low oestriol levels in mongol pregnancies.

Thus a maternal thiamine deficient/dependent state seems associated with all these etiological factors in Down's Syndrome.

Vitamin profiles were carried out in three male patients with Down's Syndrome to see if: (1) a B-1 or other metabolic disturbance existed, (2) if so would treatment with B-1 improve their behavior, affect, mental functioning, and workshop skills.

### Methodology and Results

The subjects of the study, which was conducted in 1973, were three male Down's Syndrome patients aged between 22 and 23 years, hospitalized since early childhood.

The following investigations were performed.

1. **Dietary data**

   The diet of the three patients was closely supervised by the hospital dietitian and found satisfactory according to Australian Standard (National Health and Medical Research Council, 1971). Although the three patients were depressed they were not anorexic and ate well. They did not consume sugar or foodstuffs with high sugar content excessively, resulting in higher than normal B-1 requirements.

2. **Physical examination**

   The body weight of the three patients was normal (Australian Institute of Anatomy, 1957). Clinical signs of vitamin deficiency such as peripheral neuropathy, angular stomatitis, glossitis, etc., as listed by Jelliffe (1966) were not noted. There was no evidence of thyroid disorder.

3. **Blood analysis**

   The three patients were fasted overnight
and blood was taken for a vitamin profile, and for routine pathology and hematology tests.

(a) **Vitamin profile:** 20-40 ml venous blood were collected into heparinized test tubes. Plasma levels were determined for vitamin A (retinol), its precursor B-Carotene, vitamin E (Alpha-Tocopherol), vitamin C (ascorbic acid and dehydro-ascorbic acid), and vitamin B12 (cyanocobalamin). Vitamins B-1, B2, and B6 were assessed by means of functional tests in the erythrocytes which measure enzyme activity and the reactivation effect on addition to the system of the specific coenzyme, i.e., vitamin B-1: transketolase activity and thiamine pyrophosphate—TPP% effects-vitamin B2: glutathione reductase activity and flavin adenine dinucleotide—FAD% effect; vitamin & (: glutamate oxaloacetate transaminase activity and pyridoxal-5-phosphate-PALP% effect (Nobile, 1974).

**Acceptable Vitamin Levels:** The results in relation to acceptable blood levels of vitamins (Sauberlich et al., 1974; Nobile and Woodhill, 1976; Nobile et al., private communication) are shown in Table 1. All three patients had low transketolase activity. Patients 1 and 2 had marginal levels of vitamin C and patient 2 was deficient in vitamin B6-

(b) **Routine pathology tests:** Included measurements of serum electrolytes, serum levels of magnesium, calcium, urea nitrogen, creatinine, uric acid, inorganic phosphorus, sugar, alkaline phosphatase, S.G.O.T., S.G.P.T., bilirubin, copper oxidase, cholesterol, triglycerides, total protein, albumin, and Alpha 1, Alpha 2, Beta, and Alpha globulins. The results are shown in Tables 2 a. and b.

Patient 1 had marginally raised chloride and 3 had raised chloride. All three had raised creatinine, and raised inorganic phosphorus; 1 and 3 had raised uric acid; 2 and 3 raised serum alkaline phosphatase. Patient 1 had raised S.G.O.T. and S.G.P.T. Triglycerides were marginally raised in patient 1; total protein marginally low in patient 2. Albumin was raised in patient 1 and marginally so in patient 3. Patient 1 had low Alpha 1, Alpha 2 and Beta globulins. Patient 2 had low Beta globulin and patient 3 low Alpha globulin.

### TABLE 1
Results of Vitamin Analysis in Blood

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age(Yrs.) Date of Sampling</th>
<th>Plasma Levels</th>
<th>Functional Tests in Erythrocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vit. A IU/100ml</td>
<td>B-Carotene ug/100ml</td>
</tr>
<tr>
<td>1.</td>
<td>22 8.11.73</td>
<td>201.6</td>
<td>0</td>
</tr>
<tr>
<td>2.</td>
<td>23 8.11.73</td>
<td>236.2</td>
<td>57.1</td>
</tr>
<tr>
<td>3</td>
<td>22 8.11.73</td>
<td>226.1</td>
<td>11.4</td>
</tr>
</tbody>
</table>

**Acceptable Levels**

<table>
<thead>
<tr>
<th></th>
<th>120-230</th>
<th>20-100</th>
<th>&gt;0.70</th>
<th>&gt;0.70</th>
<th>184-800</th>
<th>0-15</th>
<th>&gt;140</th>
<th>0-100</th>
<th>&gt;330</th>
<th>0-5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TPP = Thiamine pyrophosphate.**

**PALP = Pyridoxal-5’-phosphate.**

**FAD = Flavin adenine dinucleotide.**

**ETKA = Erythrocyte Transketolase activity.**

**EGOT = Erythrocyte glutamate oxaloacetate transaminase (activity).**

Heavy print - abnormal results
TABLE 2 (a)

**Pathology Results**

<table>
<thead>
<tr>
<th>Date of Sampling</th>
<th>Sodium meq</th>
<th>Potassium meq</th>
<th>Chloride meq</th>
<th>Calcium mg</th>
<th>Magnesium mg</th>
<th>Urea</th>
<th>Nitrogen</th>
<th>Serum Creatinine</th>
<th>Inorganic Phosphorous</th>
<th>Serum Uric Acid</th>
<th>Fast ing Blood Sugar S.G.</th>
<th>S.G. O.T.</th>
<th>SF</th>
<th>SF</th>
<th>Bilirubin</th>
<th>Copper Oxi dase</th>
<th>O.T. S.G.</th>
<th>P.T. SF</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.11.73 1</td>
<td>140</td>
<td>5.0</td>
<td>107</td>
<td>10.3</td>
<td>1.97</td>
<td>14.5</td>
<td>1.3</td>
<td>4.6</td>
<td>10.0</td>
<td>67</td>
<td>12.8</td>
<td>40.0</td>
<td>58.0</td>
<td>2 2</td>
<td>327</td>
<td>not increased</td>
<td>327</td>
<td></td>
</tr>
<tr>
<td>8.11.73 2.</td>
<td>138</td>
<td>4.8</td>
<td>103</td>
<td>9.5</td>
<td>2.30</td>
<td>13.0</td>
<td>1.5</td>
<td>5.8</td>
<td>6.0</td>
<td>84</td>
<td>14.7</td>
<td>22</td>
<td>27</td>
<td></td>
<td>309</td>
<td>not increased</td>
<td>327</td>
<td></td>
</tr>
<tr>
<td>8.11.73 3.</td>
<td>139</td>
<td>4.2</td>
<td>109</td>
<td>10.0</td>
<td>2.28</td>
<td>11.0</td>
<td>1.3</td>
<td>4.9</td>
<td>8.3</td>
<td>67</td>
<td>14.1</td>
<td>25</td>
<td>20</td>
<td></td>
<td>335</td>
<td>not increased</td>
<td>327</td>
<td></td>
</tr>
<tr>
<td>Normal Results</td>
<td>135-150</td>
<td>3.7-5.3</td>
<td>96-107</td>
<td>9.4-11</td>
<td>1.86-2.34</td>
<td>6.5-18.5</td>
<td>0.4-1.2</td>
<td>2.7-4.5</td>
<td>2.0-6.5</td>
<td>65-110</td>
<td>4.13</td>
<td>5-30</td>
<td>5-35</td>
<td></td>
<td>280-570</td>
<td>not increased</td>
<td>327</td>
<td></td>
</tr>
</tbody>
</table>

Heavy print - abnormal results

TABLE 2(b)

**Pathology Results**

<table>
<thead>
<tr>
<th>Date of Sampling No.</th>
<th>Cholesterol mg/100</th>
<th>Triglycerides mg%</th>
<th>Total Protein g%</th>
<th>Albumin g%</th>
<th>Alpha 1 Globulin g%</th>
<th>Alpha 2 Globulin g%</th>
<th>Beta Globulin g%</th>
<th>Gamma Globulin g%</th>
<th>Blood Film, Hemoglobin, Hematocrit, ESR, M.C.H.C, M.C.U</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.11.73 1</td>
<td>225</td>
<td>140</td>
<td>7.3</td>
<td>5.3</td>
<td>0.19</td>
<td>0.40</td>
<td>0.49</td>
<td>0.92</td>
<td>Blood film normal, other tests within normal limits</td>
</tr>
<tr>
<td>8.11.73 2.</td>
<td>205</td>
<td>45</td>
<td>6.6</td>
<td>4.3</td>
<td>0.27</td>
<td>0.48</td>
<td>0.45</td>
<td>1.10</td>
<td>Blood film normal, other tests within normal limits</td>
</tr>
<tr>
<td>8.11.73 3.</td>
<td>245</td>
<td>90</td>
<td>7.4</td>
<td>5.0</td>
<td>0.16</td>
<td>0.37</td>
<td>0.51</td>
<td>1.36</td>
<td>Blood film normal, other tests within normal limits</td>
</tr>
<tr>
<td></td>
<td>150-250</td>
<td>20-140</td>
<td>6.7-7.77</td>
<td>3.6-5.0</td>
<td>0.22-0.38</td>
<td>0.40-0.74</td>
<td>0.49-1.0</td>
<td>0.76-1.4</td>
<td></td>
</tr>
</tbody>
</table>

Heavy print - abnormal results.
(c) Routine hematology tests: hemoglobin, hematocrit, ESR, MCHC, MCV, and blood film were tested. All tests were within the normal limits.

(4) Behavior and affect

According to the result of the trans-ketolase tests all three patients presented a biochemical vitamin B-1 deficiency. They were treated with 50 mg vitamin B-1 t.d.s. for 18 months, and then the therapy was withdrawn for the following six months. Behavior and affect before and after treatment and during withdrawal of the vitamin were noted.

The results shown in Table 3 indicate a marked improvement in behavior and affect of all three patients during B-1 therapy and a marked deterioration when they were taken off it.

Discussion

The results reported in this paper confirm the later findings of Schmid et al. (1975). These authors investigated the status of vitamins B-1, B2, and B6 in Down's Syndrome looking at 110 children (90 mongoloid and 20 control) aged between 0 and 16 years. They, too, "established the existence in Down's Syndrome of a disturbance in vitamin B-1 metabolism demonstrated by the transketolase test" and concluded the "disturbance was not due to nutritional differences since the mongoloid children received the same basic diet as the controls; they were also given supplementary vitamins, so they were well supplied with B-1. The cause of this metabolic disturbance has not yet been established with any

| TABLE 3 |
| Response to Thiamine (B-1) treatment observed by staff and relatives, and by interviewing the patients |

<table>
<thead>
<tr>
<th></th>
<th>Before commencing Thiamine (B1)</th>
<th>On Thiamine 50/mg t.d.s. for over 18 months</th>
<th>Off Thiamine for over 6 months (before recommencing Thiamine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mood (affect)</td>
<td>Depressed, prone to weeping spells often.</td>
<td>Far more cheerful, spoke spontaneously, weeping spells ceased.</td>
<td>Again became very depressed, quiet, shy and withdrawn.</td>
</tr>
<tr>
<td>Workshop skills</td>
<td>Sluggish, uncooperative.</td>
<td>Work output increased, more motivated.</td>
<td>Slow, uncooperative.</td>
</tr>
<tr>
<td>2 Mood (affect)</td>
<td>Depressed, tearful.</td>
<td>Far less depressed. Spoke more spontaneously, not weepy.</td>
<td>Very weepy, depressed.</td>
</tr>
<tr>
<td>Workshop skills</td>
<td>Very hard to get him to work. Slow and uncooperative.</td>
<td>Far more motivated.</td>
<td>Refused to work, most uncooperative.</td>
</tr>
<tr>
<td>Behavior</td>
<td>Very attention seeking behavior. Negativistic Hypochondriacal 1 headaches and abdominal pain).</td>
<td>Far less attention seeking behavior and much less negativistic.</td>
<td>Tended to isolate. Attention seeking behavior predominant.</td>
</tr>
<tr>
<td>Workshop skills</td>
<td>Would refuse to work in the afternoon. Very reluctant to work in the morning.</td>
<td>Motivated to work and output increased.</td>
<td>Refused to work in the afternoons. Lacked motivation.</td>
</tr>
</tbody>
</table>

Low in B6 as well. For the trial period had there been minimal or no improvement on B1, then B6 would have been added.
certainty, "and disturbances in phosphorylation or a cell membrane disorder, are equally conceivable." They rightly say "these metabolic changes in mongolism should receive greater attention, since a more profound knowledge of these disturbances should offer a new approach for effective therapy."

It is well known B-1 deficiency can cause depression (Marks, 1968) and the favorable affective response to B-1 could be the result of its antidepressant action or just the correction of the low B-1 state. Similarly B-1 deficiency can result in apathy, irritability, impairment of memory, concentration, and motor skills, and, these can respond to B-1 therapy as was seen in the three patients (Table 3). Harrell (1946) measured the progress in mental and physical skills of 120 children living in an orphans' home. Half received B-1 and half did not. Those treated with B-1 (2 mg daily) showed improvement where measurements of performance were carried out, such as acuity of vision, skills at games, reaction time, reading, arithmetical processes, memory tests, and intelligence tests; and they regressed in some tests when B-1 was ceased as occurred in all three patients under study (Table 3).

The question arises, "If Down's Syndrome is a B-1-dependent condition, how early could they benefit from additional B-1? At birth? Or in utero? If so at what stage(s) of intrauterine development?" B-1 deficiency is not uncommon in pregnancy. In one survey of 599 pregnant women (Heller et al., 1974) 25-30 percent were found to be B-1 depleted in respect to the erythrocyte transketolase saturation. This proportion remained constant throughout gestation, and they recommended B-1 supplementation to prevent subclinical metabolic disturbance of B-1—dependent enzyme systems. In another survey (Migasena et al., 1974) 42 percent of pregnant women at full term had B-1 deficiency. Thus the depression, vomiting, fatigue, anemia, and low oestriol production in the mongol pregnancy may well be due to low B-1, and the mongol fetus could well benefit from correction of the deficiency as many of the stigmata of mongolism suggest B-1 deficiency during fetal development. For instance chronic alcoholics are often B-1 deficient (Wood and Pennington, 1974; Wood, 1972). Chronic alcoholic mothers are known to have offspring with craniofacial abnormalities, congenital heart defects, and dermatoglyphic abnormalities such as simian palmar crease (Jones et al., 1973; Jones et al., 1974) and difficulty moving their little fingers, and may be mentally retarded (fetal alcohol syndrome).

Down's Syndrome patients also have craniofacial abnormalities, heart defects, simian palmar creases, short little fingers, and mental retardation. In the adult, B-1 deficiency affects the brain, heart, eyes, and peripheral nerves and so in the developing mongol fetus (?) B-1 dependent/deficient), B-1 deficiency may affect the developing eyes, brain, and neural crest, resulting in mental retardation and congenital abnormalities respectively, such as heart defects and damage to the peripheral nerve network (anything that traumatizes the developing neural crest may cause certain congenital abnormalities). (McCredie, 1974).

Abnormal dermatoglyphics can develop due to damage to the underlying peripheral nerve network. If the ulnar nerve and its deep terminal branch in the hand was affected (underdeveloped) more by B-1 deficiency than the other nerves, then one could expect a short little finger (supplied by the ulnar nerve) and an abnormal palmar crease (due to the underlying damaged deep terminal branch). B-1 deficiency also affects connective tissue and mucopolysaccharide development. Certainly microdactyly is associated with thickening of the nerves (mainly median). Tsuge and Ikuta (1973) and Havard Skre (1962) compared thalidomide deformities with those resulting from avitaminosis B, and thalidomide has an antivitamin action. Also many of the factors in the mother associated with the birth of a congenially deformed child (such as diabetes, over 45, on the contraceptive pill not realizing they were pregnant, alcoholism, depressive illness, anemia, etc.) suggest thiamine deficiency could be an important common factor.

In Down's Syndrome clumping of chromatin in the iris (of neural crest origin)
during early fetal development results in Brushfield's spots (Ingalls et al., 1957). Thiamine deficiency can cause clumping or condensation of chromatin in certain B-1 sensitive cells (Manocha, 1972). The addition of cAMP to certain cells can cause diffuse dispersal of chromatin (the opposite of chromatin clumping and condensation) (Kano et al., 1972) and B-1 deficiency can upset cAMP release (as occurs at the adrenal cortex in response to ACTH upsetting the steroidogenic action of ACTH) (Meikle et al., 1972). Also normal oocytic meiosis is dependent on cAMP (Koch et al., 1974). It is not known whether B-1 deficiency is the cause of the meiotic nondisjunction in mongolism; however, if B-1 deficiency interferes with the release of cAMP by ovarian cells in response to LH (luteinizing hormones), as it can upset release of cAMP at the adrenal cortex in response to ACTH, then abnormal oocytic meiosis may result and meiotic nondisjunction. Certainly B-1 deficiency may result in anovulation and ovarian atrophy. Thus maternal/fetal B-1 deficiency may blight the developing fetal ovary and oocytes such that the daughter is at risk to have mongol children especially when she is over 35 and becomes B-1 deficient herself, as then the B-1 deficient damaged oocytes may be selected for ovulation rather than normal ones. (Women over 35 tend to shed more damaged ova.) Of interest, leukemia occurs more commonly in mongolism (Schuler et al., 1972) and trisomy 21 can occur in bone marrow cells alone and this condition is preleukemic. (It is not known at this stage whether these cells are B-1 dependent as in mongolism.) It is possible B-1 deficiency is also the factor blighting the fetal bone marrow development and can cause vacuolization of bone marrow and iris cells in such conditions as B-1-dependent Leigh's Syndrome (Simopoulos et al., 1972; Howard and Albert, 1972). If B1 deficiency can induce a malignant change in the first place (preleukemia) then, if it persists, it may induce frank leukemia as is sometimes seen in mongol children at birth or with aneuploidy of bone marrow cells. Finally the above findings and correlative evidence suggest that a B-1 -deficient or dependent state in the mother prior to conception or at conception induces chromosomal changes such as mongolism and then continues to act on vulnerable tissues at critical periods in fetal development. Thus children with an abnormal karyotype and very few stigmata may have had adequate nutrition (their B-group vitamin needs were met) especially during early pregnancy, as mongols can be born with no heart defects and minimal brain damage. Similarly a B-1-deficient state may result in heart defects and minimal retardation, and mongoloid faces with a normal karyotype.

**In Conclusion, correction of B1 deficiency**

(a) **Prior to conception and ovulation:** may result in:
(1) Ovulation of normal oocytes (not preferential selection of previously B1-damaged oocytes for ovulation), or (2) Normal ovulation (B1 deficiency not upsetting the final stages of oocyte maturation and ovulation). (3) Far fewer mongol births.

(b) **During the first trimester (especially) and throughout pregnancy:** may result in:
(1) Normal development of fetal ovaries (such that the daughter hasn't blighted ovaries (oocytes) and at risk to have children with Down's Syndrome many years later). (2) Normal bone marrow development (not trisomy 21 and other preleukemic changes).
(3) The birth of a mongol child with minimal stigmata, especially heart defects and mental retardation.
(4) Fewer mongol children will be born with leukemia (B-1 supplements may prevent the leukemic change in the preleukemic trisomy 21 cells).

(c) **After birth and throughout life in the person with Down's Syndrome**
(1) Will help more normal maturation of the central nervous system.
(2) Improve motor skills, affect, and behavior.
(3) Help prevent early senescence as B1 requirements increase with age and mongols are more prone to dementia such as Alzheimer's disease. It is hoped this article will stimulate further research into B-1 deficiency in Down's Syndrome and Leukemia and in the development of congenital abnormalities, especially heart defects.

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REFERENCES


