GENERAL CONSIDERATIONS

The problem of "poor appetite" in normal children has been a frequent concern to lay individuals. It is inevitable that an emotional reaction may be engendered in parents and that physicians often are requested to recommend a "tonic" or supplement for their patients. The alert physician should be justifiably concerned about the usefulness of appetite stimulators and growth-promoting substances. It seems necessary to re-evaluate the presently available literature which deals with vitamins B1 and B12 and to objectively assess those data upon which a variety of claims have been made that these substances increase growth and stimulate appetite.

It is important to again emphasize that phases of irregular growth are normal and that a period of "growth spurt" is an expected occurrence in normal adolescence. It is, therefore, necessary to place the term appetite in correct focus when dealing with growth in different age groups.

A multiplicity of factors control this subjective interest in food, and some of these have a greater or lesser part to play in the particular problem of the individual child. Food habits, particular likes and dislikes and cultural influence are all important in assessing the subjective interest in eating. The emotional make-up of a particular child, personality factors, intrafamilial tensions and other psychogenic factors certainly contribute to the problems of appetite and food intake. The unattractive preparation of food, intercurrent infection and chronic disease may all contribute to decreased food intake. The interaction of these factors may confound the situation and make difficult any assessment of the need for a single or several nutrients by any group of children.

Any attempt to determine the value of a particular vitamin for increasing caloric intake necessitates careful consideration because of the difficulty in assessing which factors influence appetite. This memorandum is concerned only with vitamins B1 and B12, not only because of their current clinical interest, but also because of the greater amount of information available.

THIAMINE (VITAMIN B1)

Early work with thiamine had shown the effectiveness of this vitamin in overcoming depression of growth in a variety of animals made deficient in vitamin B1. Thiamine-deficient monkeys showed symptoms of ataxia, seizures and decreased food intake. These manifestations were much more severe than the borderline, multiple-deficiency syndrome first described in humans as beriberi by earlier nutritionists. When the metabolic defect accompanying the severe experimental avitaminosis was corrected, weight gain occurred as food intake increased. These observations erroneously led some to suspect that the vitamin per se increased appetite.

While it is commonly believed that loss of appetite is an early effect of thiamine deficiency, in actual fact, observations with humans do not indicate this to be the case. Up to the present no evidence has been put forth that the vitamin acts directly to increase appetite. An abundance of data offers no definite proof that thiamine stimulates the appetite, but it is quite clear that, once the metabolic defect is corrected by thiamine administration, food intake improves.
The marked improvement in food intake of experimental animals made deficient in thiamine, when thiamine is replaced, should not be used as a basis for claims that thiamine is an appetite stimulator when given to children consuming diets containing thiamine, e.g., cereal, milk, etc. It is clear that when a definite thiamine deficiency exists sufficiently severe to affect metabolism of foodstuffs, only administration of thiamine can correct the deficiency and restore normal metabolism and, in turn, restore the appetite and feeling of well-being. This degree of thiamine deficiency fortunately does not exist among children in the United States except in rare instances.

The intake of thiamine by infants is directly dependent on the intake of milk and supplemental foods in the first few months after birth. Some work by Clements described manifestations as due to thiamine deficiency in breast-fed infants, which were attributed to suboptimal quantities in the mothers' milk, probably from inadequate maternal diet; the nurslings failed to gain weight, were constipated and vomited frequently. The great wealth of experience indicates that breast-fed infants thrive when the maternal diet is adequate. The experience of physicians during the past 30 years indicates that commercially processed milks and milk formulas serve as adequate substitutes for human milk in the feeding of infants.

Thiamine deficiency in infants is less likely than in preschool or school-age children. A large number of studies have been conducted to determine the nutritional status of children in regard to thiamine, using dietary surveys, concentration of thiamine in the blood and urinary excretion of thiamine. Because this vitamin is labile and likely to be a limiting factor, many workers believed that studies on thiamine would be indicative of the child's nutritional state. Despite claims of the efficacy of supplemental thiamine, Robertson et al. who utilized 44 sets of twins, 7 to 15 years of age, demonstrated that the thiamine-supplemented twin was not superior to the unsupplemented control twin in height, weight, manual dexterity or retentive memory.

**CYANOCOBALAMIN (VITAMIN B₁₂)**

With the isolation of the crystalline form of vitamin B₁₂, it was possible to test the role of this vitamin in a variety of biologic systems. It was only natural to test the growth-promoting activity of vitamin B₁₂ in children after it became firmly established that the vitamin was necessary for normal growth in bacteria, mice, rats, chicks and hogs. Observations on the effect of vitamin B₁₂ on growth of premature, undernourished children, normal children and chronically-ill children are provided in Table I.

The initial work by Wetzel et al. was an exploratory study with 11 children and served as the forerunner for the more intensive study 3 years later. While the latter report is a good example of the application of the Wetzel Grid technique for evaluating growth, the data have been justly criticized in several reviews.

**Prematures**

The study by Downing, using 48 premature infants, and that of Rascoff, with 40 premature infants, furnished data which failed to demonstrate a beneficial effect of this vitamin in stimulating weight gain above that of unsupplemented premature infants. Mitchell observed 76 premature infants, 52 of whom received 10 µg of vitamin B₁₂ daily, and concluded that this vitamin did not improve growth whether given with or without a supplement of folic acid.

In a study of 54 premature infants who received 30 µg of vitamin B₁₂ daily and 63 unsupplemented premature infants as controls, Finberg and Chow found no beneficial effect on growth.

**Infants**

Four infants studied by Chow did not respond, although they received 10 µg of vitamin B₁₂ intramuscularly in a short-term experiment. With chronically-ill children given 25 µg of vitamin B₁₂ orally, this same author observed improvement; unfortu-
nately, there was no control period of preliminary observations. The special attention paid to the patients and the concern for them during the experiment certainly may have played an indefinable role. In the same study the results with 18 normal patients supplemented with 25 μg of vitamin B₁₂ were equivocal. In short-term experiments with 23 newborn infants receiving 5 μg of vitamin B₁₂ daily, Chinnock¹⁶ found no response in growth. The nine patients studied by Wilde¹⁷ received only 2 μg of vitamin B₁₂ daily but provided no satisfactory or convincing evidence for usefulness in stimulating growth.

Children

Spies et al.,¹⁸ were similarly unable to find any beneficial effect in nine children with “growth failure” ranging in age from 7 to 14 years. In a large-scale study in London by Benjamin and Pirnie,¹⁹ 247 children who received 10 μg of vitamin B₁₂ daily failed to achieve an increase in growth over that which occurred in 486 untreated patients. Larcomb et al.²⁰ obtained equivocal results in several groups of children. In one group of “underweight children” the weight increased when vitamin B₁₂ was given. The vitamin B₁₂ had no influence in normal children. In overweight children, the group receiving vitamin B₁₂ showed a very slight weight gain. In underweight children and in normal children “no appreciable improvement in the rate of height gain was obtained.” The overweight group showed some height increase. Crump and Tully²¹ studied 32 patients who received vitamin

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TABLE I

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Subjects Treated</th>
<th>Number of Control Subjects</th>
<th>Daily Dose of Vitamin B₁₂</th>
<th>Evaluation of Response as to Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wetzel⁷</td>
<td>11</td>
<td>0</td>
<td>10 μg orally</td>
<td>Doubtful</td>
</tr>
<tr>
<td>Downing¹¹</td>
<td>25</td>
<td>23</td>
<td>10 μg intramus.</td>
<td>No</td>
</tr>
<tr>
<td>Chinmack¹⁶</td>
<td>23</td>
<td>3</td>
<td>12—5 μg/day for 60 days</td>
<td>No</td>
</tr>
<tr>
<td>Wilde¹⁷</td>
<td>9</td>
<td>0</td>
<td>2 μg</td>
<td>Yes</td>
</tr>
<tr>
<td>Chow²²</td>
<td>4</td>
<td>0</td>
<td>10 μg intramus.</td>
<td>No</td>
</tr>
<tr>
<td>Chow¹⁸</td>
<td>21 ill</td>
<td>24 ill</td>
<td>25 μg orally</td>
<td>Doubtful</td>
</tr>
<tr>
<td>Rascoff²²</td>
<td>40 prematures</td>
<td>857</td>
<td>5 μg/day orally</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>7 twins</td>
<td>7</td>
<td>10 μg/day orally</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>8 prematures</td>
<td>0</td>
<td>10 μg/day orally</td>
<td>No</td>
</tr>
<tr>
<td>Spies¹⁸</td>
<td>9</td>
<td>0</td>
<td>10—25 μg three times weekly</td>
<td>No</td>
</tr>
<tr>
<td>Mitchell¹³</td>
<td>52</td>
<td>39</td>
<td>10 μg/day orally</td>
<td>No</td>
</tr>
<tr>
<td>Wetzel⁹</td>
<td>36</td>
<td>20</td>
<td>20—10 μg/day for 16 weeks orally</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>16—10 μg/day for 6 weeks orally</td>
<td>Doubtful</td>
</tr>
<tr>
<td>Finberg and Chow¹⁴</td>
<td>54</td>
<td>63</td>
<td>30 μg/day orally</td>
<td>No</td>
</tr>
<tr>
<td>Benjamin and Pirnie¹⁹</td>
<td>247</td>
<td>239</td>
<td>30 μg/day orally</td>
<td>No</td>
</tr>
<tr>
<td>Larcomb²⁰</td>
<td>60</td>
<td>72</td>
<td>30 μg/day orally</td>
<td>Yes</td>
</tr>
</tbody>
</table>
B₁₂, but no control patients were listed; of the 32, 16 responded with growth increases; of 18 patients who had growth failure, 16 responded. It is of interest that Patrick could not influence the concentration of vitamin B₁₂ in the plasma in Jamaican children by oral administration of the vitamin.

Chow studied further a group of chronically ill and clinically healthy children. The chronically ill were a diffuse group with a variety of disorders from rheumatic heart disease to mental retardation. The apparently healthy children varied in age from 18 to 47 months and were observed in a foundling home. This study was not conclusive of the beneficial effects of vitamin B₁₂.

Scrimshaw and Guzmán studied school children in Guatemala and were unable to demonstrate a significant response in height or weight of either a school-lunch program or the addition of vitamin B₁₂ and/or aureomycin, except in one village where the results with either of the latter two supplements reached a level of significance. The significant observation was that no better results were obtained with vitamin B₁₂ despite the low level of animal protein in the diets.

Working in Italy, Jolliffe and coworkers compared 172 children who received vitamin B₁₂ with 179 controls. A significant increase in weight was observed without a significant difference in height. However, when the groups were divided into boys and girls on the basis of age, etc., the results were less valid. This study shows that the natural variation in growth in children was so large that the relatively small effect of vitamin B₁₂ was difficult to demonstrate under ordinary conditions even when the diet was low in animal proteins.

CONCLUSIONS

The great mass of information on the beneficial influence of thiamine in markedly deficient animals is probably not applicable to any but the most severely deprived humans. No secure data are at hand that thiamine administration to humans "stimulates" appetite; this does not conflict with the well-recognized fact that the vitamin is essential for body processes.

The evidence for appetite-stimulating or growth-promoting effects of vitamin B₁₂ is not convincing. Whatever the specific medical or nutritional indications for vitamin B₁₂ may prove to be, in children, it is clear that this vitamin does not encourage appetite so as to cause increased growth in children. Admitting that the design of experimental work with humans is fraught with difficulties, the lack of scientifically acceptable control subjects makes much of the evidence advanced in support of specific effects of vitamin B₁₂ unacceptable.

The impression should not be conveyed to the physician that "growth failure" is commonplace and that all flagging appetites are due to inadequate intake of either or both of these vitamins. On the basis of current knowledge, claims for any effect of these vitamins in either stimulating appetite or promoting growth are not justified. Present evidence is insufficient to show any effect of vitamin B₁ and vitamin B₁₂ on stimulation of appetite or growth except in deficiency states.

This discussion in no way detracts from the metabolic significance or usefulness of these two important vitamins. It is clear that, at present, we do not yet fully understand appetite or all the factors which affect growth. Humility should govern the attitudes of manufacturers and physicians alike when it is urged that growth-promoting substances be given to large groups of children.

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October 7, 1957
REFERENCES

COMMITTEE ON NUTRITION: Appraisal of the Use of Vitamins B1 and B12 as Supplements Promoted for the Stimulation of Growth and Appetite in Children

*Pediatrics* 1958;21:860

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COMMITTEE ON NUTRITION: Appraisal of the Use of Vitamins B1 and B12 as Supplements Promoted for the Stimulation of Growth and Appetite in Children

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