GROWTH FAILURE in School Children

Further Studies of

VITAMIN B₁₂ DIETARY SUPPLEMENTS

By Norman C. Wetzel, M.D., Howard H. Hopwood, M.D., Manuel E. Kuechle, M.A.,
and Robert M. Grueninger, Ph.D.

The first clinical investigation of vitamin B₁₂ dietary supplements for children with simple growth failure was carried out at the Fresh Air Camp of Cleveland in 1949, and that report, for brevity, may be referred to as the FAC Pilot Study. Significantly positive effects on growth along with better appetite and general clinical improvement were found, not in a series of normal children who had been growing satisfactorily, but rather in 5 of a small group of 11 children who had been under regular institutional care for growth failure, and who had, in addition, received daily oral supplements of crystalline vitamin B₁₂.

Not only were the responses to B₁₂ supplementation—measured as differences between before and after rates of gain—in each of those 5 subjects quite substantial, but they were highly significant in the statistical sense, as well. Actually, the probability, p, that the results might have occurred by chance proved to be less than 0.001 in 4 of the 5 subjects (and a value of \( t = 8.96 \) was even obtained for one child [Case 5] for whom a particularly long and stable set of prior data had been available). Assurances of such degree are rarely expected in ordinary clinical work, and, when attained, they convey unmistakable meaning. In the FAC study they had, in fact, a double significance, for they indicated not only that vitamin B₁₂ has a definite growth effect in children with growth failure, but also that child growth itself, when properly followed, is much less erratic in its trends and behavior than many are inclined to believe.

The FAC observations were made at a time when B₁₂ was dispensed in ampoule form only,
and when hypodermic injection was the regular mode of administration, largely because pernicious anemia was the only known clinical indication for its use. They happened also to have been made at the time when a re-survey of the prevalence and distribution of simple growth failure in the public schools of Shaker Heights, Ohio, had been completed under supervision of the Medical and Health Departments. Just as others which preceded it, the survey dealt with precisely the same clinical entity that had been under observation in the FAC vitamin B₁₂ study. The survey findings revealed what had long been known to the Medical Department and what has more recently been confirmed by Deisher and Bryan¹ and by Clemons and Williams,⁵ namely, that simple growth failure in the school population continued to be as great a challenge as ever, individually as well as from the standpoint of preventive group health work. Thus, the desirability of arranging for a critical study of vitamin B₁₂ dietary supplements in conjunction with a School Nutrition Program, similar to extra-milk or hot-lunch projects, was naturally suggested by the FAC results, and the suggestion itself was clearly supported by a number of other important and practical considerations that deserve brief mention.

In the first place, simple growth failure even among children of high-income areas had been, and continues to be, on the increase. Poor or faulty nutrition may, or may not, happen to be involved as a primary cause of growth failure in such areas, but good nutrition, on the other hand, is always a necessary part of recovery from growth failure and hence of any efforts to promote recovery. Moreover, growth failure left to itself tends to get worse, and institutionalization is certainly not the only nor, in most instances, a practical solution. Therefore, if growth failure is to be handled successfully it must be taken care of “on location”—which is to say, in the very environment and under the very conditions that have allowed it to develop, namely, in the ebb and flow of a child’s home and school life.

There was, however, no evidence available at the time to show whether B₁₂ supplements are as effective outside of an institution as they had proved to be for the children under Fresh Air Camp care. Indeed, since no “out-of-FAC-comparisons or controls” had been provided, the original findings, strictly speaking, were valid only for children living in an institution and not for children living at home. Yet, knowledge on how effective B₁₂ supplements are for “growth failures” in the natural environment of their own home life is just the kind of information which physicians and pediatricians require when considering recommendations for children with simple growth failure whom they encounter in practice. Thus, group studies, properly organized and carried out under suitable auspices, could add materially to individual case reports; and, by proper design, they could especially lead to more precise information on the extent to which other factors influence outcome to B₁₂ supplementation. In any event, much wider study of vitamin B₁₂ as a dietary supplement for children with growth failure was clearly called for.

Meanwhile, a number of other studies have been reported. Chow⁴ noted favorable effects on weight gains, as did O’Neil and Lombardo;⁶ although English workers, in an exceedingly brief statement,⁶ deny such effects. Wilde,⁷ utilizing the Grid technique to study growth failure in Aleutian children, found that 7 out of 9 subjects responded with an average increase of 0.45 level/month over prior rates of growth and this effect was attributed to B₁₂ supplementation. On the other hand, comparisons between supplemented and unsupplemented premature infants have not yielded any differences in favor of the former.⁸–¹⁰ Such null effects, however, should hardly have been unexpected, in view of the naturally high speeds (30–60 lev./mo.) which premature regularly generate and maintain, as well as from the further fact that those who do so are certainly not in growth failure. Thus, while disparities in results are partly explained by differences in methods of dealing with child growth, they are due principally to unfamiliarity with the role which growth failure itself plays or can be made to play in studies of child nutrition.

* See Addendum.
THE NATURE AND GENERAL IMPORTANCE OF GROWTH FAILURE IN SCHOOL CHILDREN

By its very nature, simple growth failure in children of school age is, without any reasonable doubt, a generalized deficiency state in which physical growth is measurably below par.\textsuperscript{11-13} This disorder, arising as it does during the natural course of child life and under the very momentum of growth itself, is associated with slight but sufficient transgressions of nutritional law that help to produce it. As a result, it represents in human beings a condition that is virtually, if not entirely, comparable with various states of impaired growth that may be experimentally induced in animals, and like them, or better like an indefinite mixture of them, it may be expected to respond to a number of different specific or even non-specific changes in nutritional or other habits. More directly, however, it is the existence of growth failure in certain children—not the fact that they are small, or slender, or young—that is decisive. Yet this distinction and what it implies have not received the attention they deserve, either from the standpoint of what growth failure signifies for the individual child, for the family, and the school, or, on the other hand, from the standpoint of the very important role it plays as a crucial test situation against which the worth of almost any school or child health project—not simply the value of B\textsubscript{12} or of other supplements—may be gauged.

On the nutritional side, simple growth failure involves both substance as well as fuel debts\textsuperscript{11} which must be paid up before recovery is fully achieved; but, in spite of those debts, it remains an entity that is remarkably free from specific organic lesions or symptoms. Its outward signs are few: loss of physique, fatigue, and dry skin are but rarely so pronounced as to be recognized on their own.\textsuperscript{12} Indeed, even to the experienced eye, the existence of growth failure is less readily apparent in the subjects themselves than it is in their Grid record of physical growth and development,\textsuperscript{2,8,11} a fact that is clearly illustrated by comparing the tell-tale evidence of Figure 1 with the photograph of Figure 2.

The example shown in Figure 1 is typical and it demonstrates two essential signs of simple growth failure quite unmistakably: (1) loss of physique along the entire segment (1–2) in the channel system, more especially as this girl drifted from the upper half of physique channel B\textsubscript{2} over into the lower part of B\textsubscript{3}, and (2) slow-down in her rate of development from the time she entered school but particularly during the 2 years preceding B and thus during the period of greatest channel drift and greatest physique loss. Her average rate of progress for the 53 levels she actually advanced along AB during 63 months was 0.84 lev./mo., whereas she would have originally been expected to average about 1.065 lev./mo. for the 67 levels along AD, her expected auxodrome. Slow-down along AB thus resulted not only in an accumulation of 14 levels of lag corresponding to the vertical difference between points B and D on her actual and expected auxodromes, respectively, but also in the accumulated fuel debt which is proportional to the cross-hatched area ABD and which amounted at B to 153,000 calories.\textsuperscript{11}

Her response to 16 weeks of supplementation with vitamin B\textsubscript{12} is likewise to be followed in both panels of Figure 1. The change in channel direction, with forward progress in B\textsubscript{3} in place of continued deviation into B\textsubscript{4}, did not result in any appreciable restoration of physique, but it does indicate that further physique losses had been halted simultaneously with the upturn of her auxodrome along BC. The net effect of these changes, however slight they may appear in Figure 1, owing to scale, is to suggest the onset of a definite tendency toward recovery even though she continued to remain about 15 levels short of closing her lag-gap while proceeding along BC. This suggestion that she had entered upon a newly established recovery phase as a result of B\textsubscript{12} supplementation is fully confirmed by an analysis of her rates of gain for the 21/2 years prior to B (i.e., during her years of lowest gain) and for the 9 months thereafter (the first 4 with, the last 5 without, B\textsubscript{12}). These rates, accordingly, represent "before" and "after" values, respectively, and they correspond to the slopes of the two regressions that intersect at B in Figure 1.
Fig. 1. A typical example of simple growth failure as revealed by plotting periodic heights and weights on a Grid. The essential signs of growth failure which this girl (shown in Fig. 2) revealed during her 5-year course of unsatisfactory growth between points 1 and 2 in the channel system, and along her actual auxadrome AB, are: (1) loss of physique from channel M to B, and (2) slow-down in the rate of development which would normally have carried her along the expected auxadrome AD. The vertical distance BD of 14 levels represents growth lag at B and is equivalent to about 11/4 years’ development. The character of growth throughout her Elementary School years up to points 2, and B is typical of the growth failure group of children in the Nutrition Study prior to supplementation. See text for discussion of her response to vitamin B12.
Numerically, they work out as follows:

\[
\begin{align*}
\text{Before:} & \quad 0.666 \pm 0.054 \text{ lev./mo.} \\
& \quad (4 \text{ d.f.}) \\
\text{After:} & \quad 1.087 \pm 0.056 \quad " \quad (15 \text{ d.f.}) \\
\text{Response} = \text{Difference:} & \quad + 0.421 \pm 0.092 \text{ lev./mo.} \\
& \quad (19 \text{ d.f.})
\end{align*}
\]

* d.f.—degrees of freedom.

so that \( t = 4.55 \) (before rounding) and \( p \) is very considerably less than 0.001 even for the 2-tail test. In applications of this type, however, the single-tail \( t \) test is employed since it is difficult to conceive of \( B_12 \) inducing a child to gain less rapidly than it did during the prior control period. But if the “after” slope turns out to be less than the “before” rate, as sometimes happens, the “negative” response, though actually representing outcome so far as change in growth rates is concerned, would hardly be attributable to the supplement so much as it would be to many other factors that do cause a child’s growth to slow down.

The curves of Figure 1 thus define the more important features of simple growth failure as this is traced out year after year in a child’s Grid record, and they illustrate, in particular, the result so frequently encountered that growth failure, left to itself, tends to get worse. It is very striking, indeed, that the only time during this girl’s entire school career of 6 years in which she even came close to “holding her own” or to showing any tendency to reverse the unsatisfactory trends that had persisted ever since she entered school, coincided exactly with the 4-month period of vitamin \( B_12 \) supplements following the observations at points \( 2 \) and \( B \). The evidence that this is hardly a chance coincidence is given, of course, by the 4.55 value of \( t \) reported above. Thus one may infer that, without supplementation, the girl would have lost still more physique by deviating over into channel \( B_1 \), and that she would have accumulated still more lag as well as an even greater fuel debt than she did —provided only that no other agencies had intervened and produced a set of effects similar to the \( B_12 \) response. Finally, since the results in Figure 1 represent, at best, only partial recovery from moderately severe growth failure, they also illustrate the rather common finding that complete recovery is more successfully and more readily achieved under institutional care than it is in the environment which originally permitted growth failure to develop in the first place.

**Significance of Growth Failure in the School Health Program**

For the better part of the past decade a greater and greater share of the work carried on by the Medical and Health Departments of the Shaker Heights Schools has been devoted to those pupils who have developed the pathognomonic evidence of growth failure in their own Grid records which has just been described for the example in Figure 1.

A main reason for the ever-increasing interest and effort devoted to numerous aspects of this problem is that the prevalence of growth failure in the Shaker Heights Schools is essentially what it is elsewhere, despite the socio-economic fact that these schools are located in a high-income suburban community. This area is not one that is characterized by
marginal living. Its children and its general population are not obliged to subsist on marginal diets. It is not in the torrid zone; it is not depleted of protein, and there is certainly no Kwashiorkor reported in the neighborhood; yet simple growth failure exists in the usual ratio of about 1 in 3 despite some opinion, but no facts, to the contrary.

Viewed from the school playground, the need for dealing with simple growth failure is rarely apparent. Because of its subtle, insidious, and elusive nature (Fig. 1), this disorder passes unsuspected for the most part through classroom and clinic in the guise of children who are ostensibly well as long as they are able (Fig. 2) to attend school and participate in regular activities. Its mark, however, and its traces through preceding months and years are to be found instead, as Figure 1 shows, in a child's own record of growth and development once this has been plotted out from sequential data on weight and height.

When Elementary or Junior High records are periodically reviewed, examiners are invariably impressed with two contrasting facts: (a) the steady regularity with which 2 out of 3 boys and girls follow out their own Grid patterns of development, and (b) how stubbornly simple growth failure, once established, tends to persist and, indeed, as Figure 1 clearly shows, to get worse in the same children year after year.

What is thus being observed is an entity at work that lowers physique, lessens physical vigor, and slows down the progress of all growth and development. Efforts to handle this problem through periodic health reports or consultations have, in the main, achieved much less than had been intended, for later investigations with exasperating frequency have shown "little or no improvement." Over the years we have consistently employed close follow-up with repeated medical examinations, reports, parent-teacher and private physician consultations, all involving exchange of information intended to form the basis for recommendations suited to individual needs: home life and school progress, both academic and extra-curricular, have received attention; change in curriculum, restriction of athletic or

gymnasium privileges, extra rest hours, relief from homework, television restraint, and similar measures have all been tried from time to time without producing the results that had originally been expected of them.

Meanwhile, we have had the unwanted opportunity of seeing the incidence of growth failure increase, and we have been obliged more often to watch it increase in individual boys and girls—as it did in Figure 1—than to see it vanish as a result of suggestions from any source.

Perhaps the most compelling reason for devoting more and more intensive study to the problem of growth failure resides in the plain fact—and we have had abundant evidence over the years to support it—that physical growth failure invariably hampers academic progress and achievement. That it also detracts from physical and athletic performance goes without saying. Since none of these conclusions is any longer in serious contention among us, as they once were, we have come to suspect that the consequences of growth failure flow over into every aspect of child life and that they can be discovered, if looked for, well beyond the schoolyard limits themselves. Whether as cause or as effect, we have learned that this distinctive entity exists at the core of every child problem no less than it exists in every problem child. On the other hand, the records of honor students and champion athletes offer a conspicuous and a challenging contrast: what imperfections of growth or growth trends they show are slight and, at the most, of evanescent duration. These things being so, there exists somewhere the responsibility not only for identifying growth failure as early as possible, but also for attempting to prevent its taking the "course of least resistance"—namely, what Figure 1 shows—that of getting worse. What many must learn, including pediatricians, is that growth failure is not openly apparent (Figs. 1 and 2) and that the needs of a child so handicapped are easily overlooked; they must learn, too, that efforts to deal successfully with growth failure will call for more cooperation and understanding on the part of parents, school personnel, and private physicians than is ever demanded for
occasions short of epidemics. The clear objective of all such efforts must be to restore physique and to repay fuel debts, but these ends cannot be achieved without direct action that provides a good diet and its effective utilization—with all that the latter implies—regardless of original cause, nutrition is always involved in the processes that lead to the resumption of growth and ultimately to recovery from growth failure.

As for contributing causes, the list reported almost 10 years ago is still valid:

"... unsupervised diets, poor preparation and selection of foods, inadequate milk, poor home management, with domestic stress and strife even where socio-economic conditions were otherwise satisfactory, repeated infections, allergy, general hygienic neglect, dental caries, not doing well at school but quite regular attendance at 'movies.'"

The impact of television is regarded by some as a possible new addition to this list. On the other hand, "adherence to family-type" cannot be accepted as a main cause of simple growth failure such as that illustrated by the example in Figure 1 without at the same time accepting Williams' concept of genetotrophic disease and his rationale of unusually high requirements for various nutrients.\(^{15}\)

**The Nutrition Study Groups**

Simple growth failure has been studied by the Medical and Health Departments of the Shaker Heights Schools since 1941, but it became a subject of special interest when the Grid was adopted and established as the official school health record throughout the system a few years later. As a result, about 4500 long-term records have been continuously available for analysis and follow-up, among which are those of senior high students whose earliest data for 1940–41 considerably antedate the discovery of the very supplement (vitamin B12) which some of these children were later to receive. The entire set of Grid records is subject to continuing review and classification into 3 groups: satisfactory, unsatisfactory, and questionable growth—from each of which the Nutrition Study draws its members by invitation.

Children with satisfactory growth compose about \(1/4\) to \(1/3\) of all those in the Study. These serve as "Normal Controls" and, as such, receive no supplements. The remainder are "Growth Failures" of the type illustrated in Figure 1, some with moderate, others with more severe, forms of this disorder. The average value of lag, for example, was 14 levels, with a range of 5–30 levels and the duration of failure extended from \(1\frac{1}{2}\) years. These values are quite representative of the degree of failure commonly found among elementary school populations in the 4th, 5th and 6th grades.

**Methods and Procedures**

Weights and heights along with other measurements to evaluate physical performance (grip and back strength) were originally taken each week by a team of 4 persons assisted by the regular school nurses and occasionally by principals who acted as recording clerks. This experience showed that over-all efficiency could be increased by enlarging the number of children in the Nutrition Groups with a reduction from weekly to monthly measurements. Regular platform beam balances were employed with usual precautions as to calibration and check. For convenience and consistency, stature was measured either with a portable anthropometric rule and angle, or by means of a fixed wall scale, observing Krogman's directions\(^{14}\) as closely as possible. Measurements were taken to the nearest \(1/4\) pound and millimeter or \(1/8\) in. respectively, the corresponding Grid level values being computed to 4 significant figures (i.e., second decimal; see data tabulated in chart of Fig. 1) with an error of less than 5 units in the last figure.\(^{13}\)

A brief physical examination by a physician was given each child each week during the first year, with special reference to the condition of the hair, skin, conjunctivae, nose, throat, tongue, mucus membranes, and cervical lymph nodes—in order to detect the earliest signs of upper respiratory tract infection, but also to note changes that might occur during supplementation. Later, annual, semi-annual, or more frequent medical examinations were
given as required. All subjects, however, were under daily observation by the school nurses who referred children for medical check as necessary. In these examinations and inspections no specific lesions were encountered that could be associated with possible B\textsubscript{12} deficiency.

To assure minimum loss of scholastic time, a strict schedule for examinations and measurements was maintained. During successive weeks, for instance, a given child would be put through the weighing, measuring, testing, and examining routines within 10–15 minutes of the same hour on the same week day, thus, providing almost exact 7-day intervals between successive observations. Similar arrangements applied when observations were made at monthly intervals. All children were measured between 10 A.M. and Noon in order to reduce fluctuations and particularly those associated with breakfast, recess, and lunch. All readings were taken by observers working in pairs without knowledge of previous values, though frank discrepancies as noted by assistants were called upon for immediate check.

Supplements of vitamin B\textsubscript{12} (2 × 5 µg. crystalline* or concentrate equivalent) in tablet form were administered orally, once a day, by the school nurses, complete ingestion being verified and recorded. Saturday and Sunday supplements were “doubled-in” on Fridays and Mondays. As a rule, the regular period for supplementation was confined to the second semester of the school year particularly to assure that growth had been acceptably stable during the 5 months immediately preceding supplementation. Home visits were made by the nurses to administer B\textsubscript{12} in case of a child’s absence. Except in a few instances, supplements were not provided during the 7 days of the Easter vacation. No supplements, of course, were given without explicit written permission from the parents who, as a matter of policy, are continually advised to consult their own physicians on all health problems discovered through routine check-ups.

Control supplements consisting of Lactose, U.S.P., 0.32 Gm./day, in tablets of various sizes, shapes, and colors have been employed from time to time either preliminary to eventual supplementation with B\textsubscript{12} or in parallel growth failure groups in order to check possible indirect (e.g. psychological) effects, but no significant increases over prior rates of growth have been encountered with supplements of this kind. The more usual outcome, in fact, has again been that of continued slowdown, as represented, for example, in a typical “response” to Lactose, made by a group of 14 growth failures, namely, —0.036 ± 0.060 lev./mo., the latter value being considerably removed from −0.3 which must ordinarily be exceeded in groups of that size to attain significance at the 5% level of confidence (cf. Table I). Lactose supplements, in other words, have not led to changes in growth rates comparable with those for Groups B and C of Tables I and II.

**RESULTS AND DISCUSSION**

I. Groups A, B, C, and D—60 Subjects—Crystalline vitamin B\textsubscript{12} only—Simple Block Design—Tables I–IV

Over-all response to supplementation in this series is summarized in Table I, separate values for boys and girls being given in Table II. Before and after values, as well as differences, are shown along with their standard errors for the two groups of growth failure children who received B\textsubscript{12}, namely, groups B and C, for the 20 normal controls comprising group A, and finally for the unsupplemented growth failure controls in group D.

A total of 23 out of 36 children in groups B and C who received B\textsubscript{12} supplements for 16 and 6 weeks, respectively, responded definitely to them. This figure is slightly larger than the 5 of 11 originally reported for institutionalized children in the FAC Study, but it does not exceed the latter ratio significantly.

Mean responses as represented by before and after differences for the supplemented groups B and C show statistically significant growth effects. In the B group, \( p < .001 \), but \( p < .05 \) in group C, the latter having received B\textsubscript{12} for only 6 weeks. The number of posi-
TABLE I
Summary of Responses in Groups A, B, C, and D: Incidence, Mean Effects and Standard Errors

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>No. Positive Responses</th>
<th>Rate of Gain—Level Lines per Month Before</th>
<th>After</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Normal Controls</td>
<td>20</td>
<td>—</td>
<td>1.102 ± 0.042</td>
<td>1.72 ± 0.068</td>
<td>0.70 ± 0.048</td>
</tr>
<tr>
<td>B. Growth failure—16 weeks' supplementation</td>
<td>20</td>
<td>16</td>
<td>0.693 ± 0.053</td>
<td>1.293 ± 0.093</td>
<td>0.600 ± 0.091*</td>
</tr>
<tr>
<td>C. Growth failure—6 weeks' supplementation</td>
<td>16</td>
<td>7</td>
<td>0.860 ± 0.10</td>
<td>1.26 ± 0.17</td>
<td>0.40 ± 0.17†</td>
</tr>
<tr>
<td>D. Growth failure—unsupplemented</td>
<td>4</td>
<td>0</td>
<td>0.62 ± 0.13</td>
<td>0.50 ± 0.54</td>
<td>-0.13 ± 0.60</td>
</tr>
</tbody>
</table>

*p < 0.001; †p < .05. Subjects in B and C selected by randomization; withdrawals from C carried along as D.

tive responses is also greater in group B but their prior rate of gain was slightly lower than the corresponding group C mean, although both groups gained alike while under supplementation. Mean values for boys and girls were practically the same (Table II) except in group C where the difference between the two sexes, though significant at the 5% level, is just barely so.

As explained in connection with the example of Figure 1, growth responses to supplementation always involve two before and after comparisons, namely, changes in channel as well as in auxodrome slopes, the former representing changes in physique, the latter changes in level rate of gain, each with respect to its own prior (control) value. Each thus leads to differences that will be = 0. For practical purposes, however, responses to supplementation, or to other conditions are sufficiently represented, especially during their earlier phases, in terms of rate changes alone. Hence, when the “after” > (exceeds) the “before” rate of gain, the “response” is said to be “positive” (cf. Fig. 3); the question as to whether or not an individual difference or response is statistically significant depends, of course, on the precision with which such differences can be estimated from the number and reliability of the data that are available for both before and after periods. Thus, while 16 subjects in group B of Table I showed an increase over prior rates, i.e. positive responses, as just defined, 4 showed either 0 or negative differences, which, nonetheless, were included in the group estimates, so that the latter represent actual net effects. Despite this, however, the group B and C responses are clearly significant.

TABLE II
Comparison of Boys' and Girls' Responses in Groups A, B, and C of Table I

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>No. Positive Responses</th>
<th>Rate of Gain—Level Lines per Month Before</th>
<th>After</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Normal Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>9</td>
<td>—</td>
<td>1.056 ± 0.068</td>
<td>1.138 ± 0.084</td>
<td>0.082 ± 0.049</td>
</tr>
<tr>
<td>Girls</td>
<td>11</td>
<td>—</td>
<td>1.140 ± 0.082</td>
<td>1.20 ± 0.11</td>
<td>0.059 ± 0.079</td>
</tr>
<tr>
<td>B. Growth failure—16 weeks' supplementation</td>
<td>8</td>
<td>6 75</td>
<td>0.78 ± 0.12</td>
<td>1.32 ± 0.13</td>
<td>0.54 ± 0.11</td>
</tr>
<tr>
<td>Boys</td>
<td>12</td>
<td>10 83</td>
<td>0.634 ± 0.037</td>
<td>1.28 ± 0.13</td>
<td>0.64 ± 0.13</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Growth failure—6 weeks' supplementation</td>
<td>6</td>
<td>1 15</td>
<td>0.756 ± 0.087</td>
<td>0.739 ± 0.078</td>
<td>-0.017 ± 0.14</td>
</tr>
<tr>
<td>Boys</td>
<td>10</td>
<td>6 60</td>
<td>0.93 ± 0.16</td>
<td>1.57 ± 0.22</td>
<td>0.64 ± 0.23</td>
</tr>
</tbody>
</table>
All values in Tables I and II are net, that is, they include the response of every child in a given group regardless of whether or not that was significant, or again, whether the after rate turned out to be greater or less than the control rate. On the average, the children who were supplemented for 16 weeks (Group B) showed a 0.60 lev./mo. increase over and above their 0.693 rate prior to supplementation, the standard error being 0.091 so that there can be no question as to statistical significance. Groups A and D in Table I showed "no-difference" for the corresponding "before and after" period of observation. This, of course, is as it should be. Moreover, real consistency in growth trends is reflected by the small standard errors for the normal children in group A. The group D "after" rate actually turned out to be less than their prior rate by −0.13 lev./mo. and thus illustrates the fact, repeatedly emphasized, that growth failure, left to itself, tends to get worse, though the drop is not, in this case, significantly different from 0. All values in the "after" column, with the exception of D are essentially alike, a result that warns of what is apt to happen when attempts are made to evaluate vitamin effects by the method of parallel group comparison so commonly employed in animal nutrition rather than by the before and after technique.

When the data of Table I are reduced to the analysis of variance form, as given in Table III, the conclusions already reached are again very strongly supported. In particular, F for groups A—D, with 3 and 56 d.f. is significant at the 1% level which is to say that the mean values of A, B,..., are actually different from each other. Examination of the 3 separate mean squares corresponding to the orthogonal comparisons in Table III shows that only the last is significant, with p almost exactly equal to 0.001. Therefore, groups A and D may be considered to have behaved alike in that neither showed an increase over control rates; groups B and C behaved alike in that both did show such an increase, and, finally, all supplemented children (B and C) responded quite differently than all the unsupplemented subjects (A and D) did.

Since the B vs. C mean square is insignificant (boys and girls taken together) average response tended to be the same for those who received the supplements for 6 weeks (C) as for those who had B throughout the entire second semester (B). Continued supplementation, accordingly, did not further augment a

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**Table III**

Analysis of Variance of Individual Responses to Vitamin B₆ Supplementation for Groups A, B, C and D

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>Degree of Freedom</th>
<th>Sum of Squares</th>
<th>Mean Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups: A, B, C, D...</td>
<td>3</td>
<td>−3.6960</td>
<td>1.2320*</td>
</tr>
<tr>
<td>Normal vs. unsupplemented growth failures, i.e., A vs. D</td>
<td>1</td>
<td>0.1262</td>
<td>0.1262</td>
</tr>
<tr>
<td>16 vs. 6 weeks' supplementation, i.e., B vs. C</td>
<td>1</td>
<td>0.3702</td>
<td>0.3702</td>
</tr>
<tr>
<td>All supplemented vs. unsupplemented, i.e., (B + C) vs. (A + D)</td>
<td>1</td>
<td>3.1936</td>
<td>3.1936†</td>
</tr>
<tr>
<td>Residual (Error)....</td>
<td>56</td>
<td>15.9800</td>
<td>0.2714</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>18.8940</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.01; †p = 0.001

For group differences, F = 4.54; Fₚₐ = 4.16

For all supplemented vs. all unsupplemented, F = 11.77, Fₚₐ = 7.12. This same comparison with 58 d.f. for error yields: F = 11.80; hence t = 3.435, so that p = 0.001 almost exactly.

response rate that had been generated during the first 6 weeks.

This result, as it happens, is actually exemplified in Figure 3 (discussed below) wherein the first response CD, during 6 weeks of supplementation consisted of a greater elevation (1.2) above the control trend AF than the second response during 4½ months' supplementation showed along (3A) with respect to the same control regression, AF, which traverses the p = 0.001 confidence band. Thus, although response I exceeded II, since its change in rate was greater, the total level gain, associated with the upturn in I, was considerably less than in II because the rate along (1.2) endured for a much shorter period than the more prolonged elevation (3A) did during the second period of supplementation. Consequently, whereas the "response to" or the "effect of" B₆ supplementation is preferably measured and expressed in terms of change in rate itself, the ultimate benefit from such increased rates depends also on the duration through which they are maintained. Hence, a decision on how long such supplements might be continued depends, among other things, upon the amount of lag still remaining to be made up at any given time (cf. Fig. 1).

The highly significant result represented in Table III by the single degree of freedom for the comparison between all supplemented (B and C) and all unsupplemented children (A and D) with its m.s. of 3.1936 and F = 11.80, i.e., t = 3.44 and p = 0.001, taken in conjunction with insignificant values for the two other d.f. indicates that crystalline vitamin B₆ supplements were undeniably associated with the re-
responses which groups B and C, and these alone, made; and, unless a chance event, with probability \( p = 0.001 \) had intervened, that the supplements were responsible for increasing the prior rates of groups B and C to the extent presented by the "before" and "after" differences in . 

TABLE IV

<table>
<thead>
<tr>
<th>Groups</th>
<th>Prior or Control Period Range—Levels per Month</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of positive responses . . .</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>No. of 0 (zero) and negative responses . . .</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Totals . . .</td>
<td>22</td>
<td>10</td>
</tr>
</tbody>
</table>

In Table IV, the proportion of positive responses to B12 supplements falls off considerably as prior control rates approach and exceed the normal value for school children of 1 lev./mo.* This result has been confirmed in the factorial design of Series II (below) and it would appear to indicate that renewal of growth takes place preferentially in those with greatest need, that is, in those children who have been gaining most slowly during the period preceding supplementation. That it does not, however, exclude the possibility of a B12 effect when prior rates in growth failure are as high as 1 lev./mo. is shown by the two distinct responses made by the girl whose long record is illustrated in Figure 3.

* Attention should again be drawn to the important fact that 1 lev./mo. is a universally valid standard for the rate of gain in normal healthy children of school age and, as such, that it is independent not only of race, sex, socio-economic status, and relative growth advancement, but also of body measurements, e.g., of weight and height, as well as of physique and body size, and, finally—up to maturation—of age as well. This means that growth rates expressed in Grid levels/month are independent of level itself, and that levels as well as level rates are additive—a most important property not shared by weight or height, and a prerequisite that must be satisfied if analysis of variance is to be employed. For practical purposes, level rate of gain is thus subject to environmental factors alone, more particularly those concerned with food supply and its utilization for growth. Lastly, a warning on interpretation may be mentioned: the fact that a given child is, or has recently been, gain-

II. Groups E and F—236 Subjects—Crystalline and Concentrate Vitamin B12, 3 \( \times \) 2\(^4\) Factorial Design

In a similar but much more highly expanded 5-factor investigation involving 236 children, no differences were found for equivalent dosages of crystalline and concentrate forms of vitamin B12, the mean being 0.244 ± 0.067 lev./mo. increase over prior rates. This value is again net, that is, it includes all responses, positive, zero as well as negative. While these results cannot be discussed in full here, it may be remarked that when corrections for differences in prior rate, sex, and other factors are made, mean effects are considerably higher (0.9 lev./mo. in certain groups) thus equaling and even exceeding values in Table I.

III. Two Different Periods of Supplementation in the Same Child—Case S.P.-14

This girl was originally one of the members of group C in Table I. Her first response to 6 weeks' B12 supplementation is shown by the segment CD in Figure 3, with prior control period AC. From D to F she received no B12. Since the trend from E to F turned out to be no different statistically from the first control trend AC, a common regression AF, with slope 1.112 ± 0.023 lev./mo., may be used for both comparisons. The "after" slope (1.2) during supplementation I was: 2.610 ± 0.41. Her second period of supplementation (II) resulted in the response FG with slope 2.159 ± 0.098 lev./mo. along the regression (3,4). It is obvious from these numerical values as well as from Figure 3 that both responses were highly significant.

IV. Caloric Intake

Unfortunately it was impossible to make a complete diet survey of all children participating in the Nutrition Study. Records on 45 boys and girls receiving either crystalline or concentrate vitamin B12 supplements have been very carefully analyzed from the stand-
Fig. 3. Two independent and significant responses to oral vitamin B₁₂ dietary supplements in the same child, S.P.-44. The first is shown by CD during a 6 weeks' period of supplementation (I), the second by the response FG during 4 months (II) of oral B₁₂. Note importance of scale magnification as compared with Fig. 1. The common regression AF with its corresponding 0.001 confidence bands represents both prior control periods AC and EF. This long-term auxodromic record shows maintenance of excellent statistical control, i.e., high stability during periods without B₁₂, so that deviations from the basic trend AF are associated with, and only with, each of the two periods of supplementation.

Other observations encountered between the growth responses and other measurements such as physical performance measured by change in grip, back or leg strength; nor with seasonal climatological changes in temperature, humidity, and barometric pressure, nor again with economic trends as reflected in various indexes.

Comment

Unless some extraordinary chance event, with a probability of less than 1 in 1000 trials had befallen this Shaker School Nutrition Study, it is impossible to avoid the conclusion that the vitamin B₁₂ supplements and the
growth responses we have observed are related as cause and effect. From the clinical side, it is quite impossible, of course, to accept the idea that there exists but one cause of simple growth failure in school children. But, just as there would appear to be no such single cause, it is equally plain that no single remedy exists which could assure recovery from this disorder, or, even if one substance should seem to do so, that it would be acting alone. Hence, the role of vitamin B₁₂ dietary supplements in inducing renewal of growth in children with simple growth failure would appear to be more that of a marshaling agent which effects reorganization of a variety of metabolic derangements involved in that disorder than that of meeting a single specific deficiency as it is considered to do in pernicious anemia. Consistent with this view are the recent studies of James and Abbott who were able to show stimulation of protein synthesis associated with increased nitrogen and phosphorus utilization, with changes in uric acid excretion and with changes in plasma potassium values.

We were prepared, accordingly, for the possibility that still fewer of these children would respond to B₁₂ supplements, living as they did under the "open" conditions of customary school attendance, variable home and outside influences, or pressures, as compared with the "closed" circumstances of an institutional program such as that carried out at the Children's Fresh Air Camp.

From one point of view the response rates appear to be comparatively high, yet, from another, they might be considered to be relatively low. It must not be forgotten that all values are net, so that an average increase of 0.4–0.6 leu./mo. over prior rates, in even a single instance, would have its own proper worth. It would mean, concretely, an advantage of 6 months' extra growth and development within a single year, and thus a six months' step toward recovery and toward a physical state more nearly "up to par." This average must also be understood to imply that some children had accelerated considerably more than that; in fact, a few increased their prior rates by as much as 1.50–1.70 leu./mo. Certain individual subjects in this study, therefore, even without benefit of institutional management, were able, under regular home and school conditions, to generate after rates that amounted to 60–70% of those measured under the more highly stable conditions of the FAC group. This, of course, is consistent with other knowledge on the nature of growth failure and how it tends to respond to proper management, for it has long been realized that recovery is much more difficult to achieve at home than it is at an institution such as the Fresh Air Camp.

**Conclusion**

All of the foregoing evidence, therefore, supports the conclusion that vitamin B₁₂ does exert a "growth-promoting-effect" when given as a dietary supplement to children in growth failure—and this evidence is exceptionally strong. There is less need of reaffirming such results than there is of extending observations in order that many agencies which help to determine, or are capable of influencing, these growth responses can be more clearly understood.

Finally, from the standpoint of the Nutrition Program as a whole, it should be remarked that the general benefits derived from the present study of vitamin B₁₂ dietary supplements were felt well beyond the point at which individual children developed recovery responses. The most immediate reactions were noted, as might be expected, by the personnel of the medical and nursing departments, but almost simultaneously by teachers in the classrooms who became aware that at least some of the pupils were improving in behavior, attitude, and scholastic work—or that they were showing less strain and fatigue, or, on the other hand, greater interest and attention, and hence better all-around progress than before. Voluntary expressions of similar import were offered by parents. The fact that the children themselves were well disposed toward the program is attested to, of course, by the fine attendance record they made, and by their willingness to participate faithfully in the extra routine of all tests, measurements, and supplements.
ACKNOWLEDGMENTS

We wish to express sincere appreciation for professional assistance, well beyond the call of duty, which has been contributed to the work of the Nutrition Study by the School Nurses and Secretaries, in particular by Miss Besse Phare, Miss Dorothy Swancott, Miss Barbara Hlavin, Mrs. Margaret Hurley, Mrs. Manuel E. Kuechle, Mrs. Elizabeth Beemer, and Mrs. Katherine Sia, as well as to the teachers and principals of the various schools in the Shaker Heights District. We are likewise deeply grateful to Dr. Francis Bayless and Miss Edna Chapman for blood laboratory work, and to Miss Esther Uhiman for diet surveys; to Barney Tautkins, Ralph F. Deucker, H. H. Young, Gene Myslenki, William Goellner, and David Hill for expert technical assistance in measurements and computing. It has been a pleasure to discuss statistical design, methods, and results with Prof. Fred Leone of Case Institute of Technology and with Dr. David Frazier. Yet, without the long discussions, foresight, and tactful guidance of William Slade, Jr., Superintendent of Schools, neither the prior surveys on which the Nutrition Program so much depended, nor the Study itself, could have been carried out at this time. To his splendid leadership, we owe a particular note of appreciation.

REFERENCES


ADDITIONAL IN PRESS

The investigation which English workers announced as not confirming the FAC results turns out, from later details (Med. Offic.: Apr. 5, 1952, 137) to have had little in common (methods, case selection, etc.) with the FAC study aside from $B_{12}$ given little to 418 children attending open-air schools but living at home—a sample more comparable with our Series II than with the FAC group. Differences in wt. and/or ht. gains were declared insignificant though no estimates of precision were given. From their data, however, overall response to $B_{12}$, expressed in Grid units, works out as: $+0.05 \pm 0.12 \text{ lev.}/\text{mo.}$ (21 d.f.), the 5% confidence limit, $+0.30$, considerably overlapping our Series II mean: $0.244 \pm 0.067 \text{ lev.}/\text{mo.}$ which, in contrast, carries more than a 1,000:1 chance of differing from 0. Consequently, their “null-effect”—though not different from 0, is, at the same time, not significantly different from, and hence, actually compatible with, our findings. Their standard error (0.12), notably large despite 3 to 4-fold greater replication, reflects inefficient design and method. Such inflation of error, inevitable in wt.-ht.-age averages, cannot be overcome by mere replication, especially with subjects gaining more than 1 lev./mo. (see Table IV),
as the majority of their groups did. Even the unquestionable responses revealed by the Grid technic in Figures 1 and 3 could not withstand "dilution" by the data of 1 or 2 randomly selected children, not to mention their complete obliteration by being averaged with data from 400 or more!

**Resumen**

*Crecimiento defectuoso en niños de escuela—Estudios ulteriores sobre los suplementos dietéticos vitamínicos B₁₂*

A no ser que algún acontecimiento fortuito extraordinario sobreviniese en este estudio nutritivo en las escuelas Shaker—y la probabilidad de tal acontecimiento es menor de 1 en 1,000 pruebas—es imposible evitar la conclusión de que los suplementos vitamínicos B₁₂ y las respuestas de crecimiento por nosotros observadas guardan una relación de causa a efecto. Desde el ángulo clínico, claro está, es imposible admitir la idea de que no existe sino una causa única del crecimiento defectuoso en niños de escuela. Pero lo mismo que parece no haber tal causa única, es igualmente claro que no existe un remedio único que pudiera asegurar la recuperación en este desequilibrio, e incluso si tal substancia pareciera actuar de esa manera, que actúase por sí sola.

Estábamos, pues, preparados para la posibilidad de que todavía un menor número de estos niños respondiera a los suplementos de B₁₂, viviendo como vivían bajo las condiciones escolares corrientes y las influencias domésticas y exteriores variables, en comparación con las limitaciones de un programa institucional tal como el realizado en el Children's Fresh Air Camp.

Desde cierto punto de vista, los grados de respuestas parecen relativamente altos, pero desde otro ángulo, pueden ser considerados relativamente bajos. No debe olvidarse que todos los valores son netos, así que un aumento medio de 0.4—0.6 niveles por mes sobre los valores anteriores, incluso en un caso único, tendría su propio valor. Significaría, concretamente, una ventaja de 6 meses de crecimiento y desarrollo adicionales durante un solo año, y así de un paso de 6 meses hacia la recuperación y hacia un estado físico más cerca de lo normal. Este es un promedio, y hay que no olvidar que algunos niños habían acelerado mucho más; en efecto, algunos adelantaron su velocidad anterior hasta 1.5 —1.70 niveles por mes. Ciertos casos aislados, aun sin beneficio de la dirección institucional, fueron capaces, bajo las condiciones normales del hogar y de la escuela, de iniciar velocidades posteriores que igualaban a un 60—70 por 100 de las medidas bajo las condiciones más estables del grupo FAC. Lo que, claro está, es conforme a otros conocimientos de la naturaleza del crecimiento defectuoso y de como tiende este a responder a un control adecuado, pues se conoce hace tiempo que es mucho más difícil lograr la recuperación en casa que en un instituto tal como el FAC.

Todo lo expuesto sostiene la conclusión de que la vitamina B₁₂ ejerce un efecto "estimulador de crecimiento" cuando se da como suplemento dietético a niños con crecimiento defectuoso—y esta evidencia es extremadamente sólida. Hay menos necesidad de reafirmar tales resultados que no de extender las observaciones, para que los muchos factores que ayudan a determinar, o que son capaces de influir sobre estas respuestas de crecimiento puedan llegar a ser más claramente conocidas.

Finalmente, hay que notar que los beneficios generales derivados del estudio corriente de los suplementos vitamínicos B₁₂ se han hecho sentir más allá del punto en que casos aislados alcanzaron respuestas recuperativas. Las reacciones más inmediatas eran apreciadas, como era de esperar, por el personal de los servicios de medicina y enfermería, pero casi simultáneamente por los maestros en las clases, quienes notaban que algunos de los estudiantes mostraban menos tensión y fatiga, o, expresándolo de otro modo, mayor interés y atención. Y por eso un mejor progreso general. Expresiones voluntarias de sentido semejante eran ofrecidas por los padres. El hecho de que los mismos niños estaban bien dispuestos para con el programa seguido se atestigua por su excelente asistencia, y por su participación fial y de tan buena gana en la rutina suplementaria constituida por todas las pruebas, mediciones, y suplementos.