Growth and Development of Central American Children

II. The Effect of Oral Administration of Vitamin B_{12} to Rural Children of Preschool and School Age

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THE DISCOVERY of vitamin B_{12} and its stimulatory effect on the growth of experimental animals under certain conditions soon led to studies of its influence on the growth of children, particularly on those whose development appeared to be retarded. Unfortunately, these studies have frequently yielded quite conflicting or inconclusive results, as recently reviewed by Howe.[1]

The first report[2] on the administration of vitamin B_{12} introduced an experimental design and statistical procedures which are still controversial. In this study the authors concluded that 5 of 11 children responded in a dramatic and highly significant manner. This has been followed by the inconclusive results of Chow[3,4] and reports of suggestive positive effects on at least some children by O'Neil and Lombardo,[5] Bidault,[6] Wetzel *et al.*,[7] Wilde,[8] Jolliffe and his associates,[9] Larcomb and collaborators,[10] Crump and Tully,[11] and Grüninger and co-workers.[12] Negative reports also appeared beginning with Benjamin and Pirrie[13] and Spies and his associates.[14] The papers of Scrimshaw and Guzmán,[15] Someswara Rao *et al.*,[16] and Mackay *et al.*,[17] deal with poorly nourished children showing a considerable degree of retardation in growth and development, and all failed to find a significant stimulatory effect of orally administered vitamin B_{12} despite the relatively large numbers and careful balancing of control and placebo groups. Moreover, Downing,[18] Mitchell *et al.*,[19] and Rascoff *et al.*,[20] administering vitamin B_{12} to premature infants, were unable to demonstrate any significant effect on growth. The second paper by Wetzel[7] gave additional data to support his original hypothesis but as before did not make use of placebo controls. More recently, Montoye *et al.*[21] found no positive effect of vitamin B_{12} administration to school children, and Howe[1] cites a dissertation by Wittich[22] in which this vitamin stimulated the growth of school children.

The present study is an attempt to determine with reasonable certainty whether or not 20 μg of vitamin B_{12} administered daily by mouth has any tendency to improve the growth of rural Guatemalan children of either preschool or school age. The growth and development of these children were, on the average, markedly retarded, and their intake of protein of animal origin extremely low. The trials were run concurrently with those of Mackay *et al.*[17] in Jamaica and have yielded similar results.

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TABLE I

Average Monthly Height and Weight Gains of Preschool Children Given Orally 20 μg Vitamin B_{12} Daily

Period	Height (cm)		Weight (kg)	
	Control	B_{12}	Control	B_{12}
	N = 26	N = 24	N = 26	N = 24
I	0.70	0.65	0.16	0.17
	N = 15	N = 20	N = 15	N = 20
II	0.48	0.43	0.18	0.17
	Approx. L.S.D.$_{0.05}$ = 0.08 cm		Approx. L.S.D.$_{0.05}$ = 0.05 kg	

MATERIAL AND METHODS

Fifty preschool children in the small rural highland village of San Lorenzo el Cubo (SLC) and 228 school children in four other villages—Magdalena Milpas Altas (MMA), Santa María Cauqué (SMC), San Antonio las Flores (SAF), and Chinautla (CHI)—in the same area were ranked by age and sex and randomly assigned to placebo or experimental groups. Tablets containing 20 μg of vitamin B_{12} or placebo identical in appearance were administered daily by mouth six days a week. In physical appearance and development, social and economic status, as well as dietary habits, the children included in this study were similar to those described for previous field experiments.[15,23] Their diets provided protein of animal origin in the range of only 8 to 14 g daily and their height, weight, and bone maturation were approximately two to four years behind those of well-nourished children of comparable age in the United States and Guatemala. All children were eating ad libitum in their own homes throughout the study.

Height and weight measurements were obtained monthly and a careful record of attendance kept. Personnel administering the tablets had no knowledge as to which children were receiving placebos. It was possible to administer the treatment without substantial interruption to preschool children, but treatment of the school children was discontinued during the school vacation, from October through December. The study of preschool children was begun in October, 1954, and terminated in October, 1955; that of school children was started in March, 1954, and finished in October, 1955, during 12 weeks of which time they were on vacation and did not receive treatment.

Both height and weight gains were adjusted by multiple regression methods for initial differences in age, height, and weight. No effect of frequency of treatment was encountered, so that no correction for this variable was made in the data presented. The approximate least significant differences (α = 0.05) were calculated using pooled estimates of error.

RESULTS

The results of the administration of vitamin B_{12} to the preschool children are shown in Table I. There is no suggestion in these data of a positive effect of vitamin B_{12} at this dose on rate of gain in either height or weight.

Similarly, the data for the school children (Table II) make possible twelve sets of com-

TABLE II

Average Monthly Gains of School Children Given Orally 20 μg Vitamin B_{12} Daily

Village	First 6 mo		Second 6 mo		Third 6 mo	
	Control	B_{12}	Control	B_{12}	Control	B_{12}
Height (*cm*)						
MMA	0.36	0.37	0.41	0.36	0.42	0.36°
SMC	0.41	0.37	0.42	0.53°	0.43	0.42
SAF	0.42	0.45	0.44	0.45	0.47	0.44
CHI	0.37	0.34	0.51	0.46	0.27	0.26
Weight (*kg*)						
MMA	0.18	0.20	0.11	0.08	0.22	0.20
SMC	0.14	0.12	0.18	0.26°	0.20	0.16
SAF	0.19	0.22	0.18	0.14	0.20	0.19
CHI	0.18	0.21	0.08	0.08	0.19	0.21

Approx. L.S.D.$_{0.05}$ = 0.06 cm in height; 0.06 kg in weight. ° Indicates significant differences.
Approx. Number: MMA-83, SMC-53, SAF-58, CHI-34.

parisons, one for each of three 6-month periods in four villages. Of the twelve comparisons for the effect of vitamin B_{12} on height, one is significantly positive, one significantly negative, and ten show no effect. Of those for weight, eleven show no significant difference. The single period in which a positive effect on height and weight was observed in one village had the lowest frequency of treatment due to the 3-month school vacation.

DISCUSSION

The data presented provide no basis for assuming that vitamin B_{12} has any effect, positive or negative, on growth as estimated by the rate of gain in either height or weight. Although subjective benefits from vitamin B_{12} administration have often been mentioned in the literature, such alterations as were noted by teachers and field workers in our experiment seemed to occur with equal frequency in the experimental and control groups. The data available did not permit any further attempt to appraise subjective changes.

It was felt that such a study in a population known to be greatly retarded in growth and development and subsisting on a diet containing sufficient calories and total protein but only a small amount of animal protein would give the maximum opportunity for demonstrating a vitamin B_{12} effect. Even if the effect of vitamin B_{12} were only to stimulate appetite, the children should have been able to show a response, since they were on an ad libitum diet which was limited more by quality than quantity, and in most cases a child could have had greater quantities of food if he had desired it. It is noteworthy that our results are identical with those of a parallel field trial by Mackay *et al.*[17] and also those of Someswara Rao *et al.*,[16] whose studies failed to show a positive effect on undernourished Jamaican and Indian children, respectively.

In view of the earlier concept that vitamin B_{12} might improve the growth of children on diets low in animal protein by supplying a missing "animal protein factor" or by improving the utilization of protein of vegetable origin, the studies by Someswara Rao *et al.*[16] in undernourished Indian children, Kaye *et al.*,[24] and Chow *et al.*[3] in infants 3–6 and 3–12 months of age are significant. All these studies failed to demonstrate a significant effect of vitamin B_{12} on nitrogen retention, although the Indian workers tested it as an addition to both restricted and adequate vegetarian diets and the other investigators studied it with intakes of high and low protein content. Closely related to the problem is the failure of Aguirre and Scrimshaw[25] to find any effect of vitamin B_{12} on hematologic values in the same or similar children.

It is possible in theory, as Howe[1] suggests, that these children would have responded to vitamin B_{12} administration if some other factor had not been more limiting. Although the design of the present study does not specifically exclude such a possibility, previous trials in both Guatemala and El Salvador[15] failed to demonstrate a statistically significant difference between vitamin B_{12} and placebo when included in dietary supplements designed to make up existing deficiencies. Although the intake of vitamin A in these trials was below the recommended dietary allowance, subsequent experiences indicate that this vitamin was not a limiting factor.

Many of the reported studies suffer from deficiencies in experimental design and interpretation of the data which make them inconclusive. One is the danger of using children of one village as a control and those of another as an experimental group. The difference in growth rates among villages shown in Table II is such that any conclusion could have been obtained by chance, had this practice been followed in the present study. Equally unreliable is the use of a group as "its own control." The variations from one 6-month period to the next are so great that had the previous or subsequent growth experience of any of these groups been used for comparison with a period of vitamin B_{12} administration, again any conclusion could have been obtained fortuitously. Another procedure has been to pick out those children in an experimental group showing growth spurts during the experimental period and call attention to them as examples of significant and unexpected response. Analysis of our own data has shown that individual spurts

of growth during an experimental period are equaled by individual spurts in the control groups, and our groups are of sufficient size to validate this observation.

We also feel that undue significance has been attached in some studies to the month-to-month fluctuations in the height and weight measurements recorded for individual children. Although the curves for child growth which have been developed from the analysis of the data from large numbers of individuals give the impression of a smooth progression, many individuals do not follow such a pattern in a regular manner. The fine studies of the growth of individual children (Stuart *et al.*[26,27] and Reynolds and Sontag[28]) show that many children grow with types of variation similar to those characterized by some authors as "growth failure" and "growth response."

It is noteworthy that vitamin B_{12} has been without effect in studies conducted in technically underdeveloped areas with children showing some degree of malnutrition and growth retardation. On the basis of these reports and our own experience there would appear to be no indication for the use of vitamin B_{12} in public health or school programs designed to improve the nutritional status of children whose growth and development are retarded.

The present data do not preclude the possibility that occasional apparently well-nourished children whose growth and maturation are chronologically retarded will respond to vitamin B_{12} administration. This question will have to be resolved by additional critical studies among well-nourished groups of children.

SUMMARY

The daily oral administration of 20 μg of vitamin B_{12} in controlled trials involving 50 preschool children in one rural village and 228 school children in four rural schools in Guatemala did not produce any effect on their rates of gain in either height or weight. These data illustrate some of the errors in interpretation which can result from the considerable variation and apparently fortuitous changes commonly observed in the rates of growth and maturation in children. The present findings are in agreement with the results of trials conducted in other areas involving children showing some degree of malnutrition and growth retardation and subsisting on relatively inadequate diets.

On the basis of the foregoing it appears that the growth retardation commonly observed in technically underdeveloped areas will not be affected by the administration of vitamin B_{12}.

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