

interest than no such broad AEC fellowship program at all."

The part of the statement entitled "Annex" is to be regarded as an appendix which might be made the subject of discussion with you.

STATEMENT CONCERNING THE AEC FELLOWSHIP PROGRAM
PREPARED BY THE COUNCIL OF THE NATIONAL ACADEMY
OF SCIENCES AND SUBMITTED BY ITS PRESIDENT

The Council of the National Academy of Sciences has considered the request of the Atomic Energy Commission for advice as to the scope and future of the fellowship program, in the light of the restriction placed upon it by the amendment to the Independent Offices Appropriation Act of 1950.

In our opinion the requirement of FBI investigation and Atomic Energy Commission clearance is ill-advised for those fellows who neither work on secret material, nor are directly preparing for work on Atomic Energy Commission projects. We are convinced that by this restriction the value of the broad program has been greatly reduced; we have grave doubts whether the continuance of the Atomic Energy Commission Fellowship Program thus restricted is in the national interests. In these views we concur with the opinion expressed by the Executive Board of the National Research Council.

Since we hold these views, we believe that the National Research Council should not accept the responsibility for administering the altered fellowship program.

We hope that, to the extent to which the Atomic Energy Commission continues the program, it will find it possible to administer it without our help. Nevertheless, in the measure in which our advice in one form or another may prove necessary to the Commission, we recognize an obligation to provide such advice.

We would further urge the Atomic Energy Commission to take all proper steps to see that these restrictive provisions be omitted from future legislation. We in turn shall make known to the Government of the United States the reasons for the views here expressed.

ANNEX

1. We hope the Atomic Energy Commission will itself operate this program.
2. We regard it as a proper function to advise on setting up Atomic Energy Commission panels to select fellows.
3. If it is not possible for the Atomic Energy Commission to set up panels, the National Research Council will upon request make an assessment of the qualifications of the fellows and a report on the progress of their work.

4. Announcements should be made by the Atomic Energy Commission and the extent of the participation if any of the National Research Council should be made clear.
5. In announcing the fellowships we believe it the duty of the Atomic Energy Commission to see that the prospective fellows are told the nature of FBI investigation and the criteria by which decisions are to be made by the Atomic Energy Commission.
6. Our special misgivings about FBI investigation and Atomic Energy Commission clearance do not apply to candidates for secret work.

October 26, 1949

Letter dated November 17 from Carroll L. Wilson, general manager of the U. S. Atomic Energy Commission, to Alfred N. Richards, president of the National Academy of Sciences:

We have considered your letter of November 2, 1949, and its attached statement prepared by the Council of the National Academy of Sciences. We understand that the Academy does not believe that the National Research Council should accept the responsibility for administering the Atomic Energy Commission fellowship program as altered by the amendment to the Independent Offices Appropriation Act of 1950. We regret that the restrictions imposed by the fellowship rider have made it necessary for the National Academy of Sciences to come to that conclusion. We feel, and we know you must also feel, that fairness to prospective fellowship applicants demands a statement in the near future of the status of the fellowship program. We are therefore writing to inquire if it would be acceptable to the National Academy of Sciences to have the National Research Council administer a fellowship program limited, during the period the restrictions of the amendment apply, by the conditions listed below.

1. No new appointments are to be made to predoctoral fellowships, except possibly for a small number of fellowships in secret fields.
2. The present broad program of postdoctoral fellowships is to be limited to those candidates whose proposed research is such that, in the opinion of the Commission, a high probability exists of subsequent employment requiring access to secret data. Fellows would not be obligated, however, to accept subsequent employment by the Commission or one of its contractors. We would expect this limitation to confine postdoctoral fellowships in the physical sciences to fewer fields than are now open. The present program of postdoctoral fellowships in the bio-

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Growth Failure in School Children as Associated with Vitamin B₁₂ Deficiency—Response to Oral Therapy

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DESPITE ITS ORIGINAL PROPERTY as a growth-promoting agent for certain bacteria (4) and subsequent evidence that it stimulates animal growth (1, 2), studies of vitamin B₁₂ in man have been confined to its hemo-

poietic, clinical, and neurological effects in disease—viz., pernicious anemia and sprue. Information on its more general nutritional value has thus far had to come from animal work, in which growth could be experimentally held in check as desired, through purified diets, and thus through deprivation of B₁₂ or of other food constituents, with or without caloric restric-

¹ With the technical assistance of Dr. Francis Bayless, Edna Chapman, and Barney Tautkins.

tion. Since deliberate depletion in children is excluded, the growth effects of B_{12} must be studied under constraints which parallel those in anemia, in the sense that results must be appraised, not under normal blood or growth conditions, but in states of hematopathology and of growth failure, respectively. In the case of growth disturbance, however, the constraints are even more rigid, for, although it is permissible to follow B_{12} hematopoiesis in "untreated" or in "recently untreated" patients—that is, essentially under initial conditions of depletion—it happens that any one of a number of nonspecific agents, even mere environmental change, can set recovery from growth failure in motion. What this means is that a growth stimulus attributable to vitamin B_{12} must be demonstrated in the face of whatever recovery had already set in, and hence by potentiation of such prior effects, which had themselves, moreover, been sufficiently stable to be taking place under a condition of statistical control. Technically, the problem is one of "improving an improvement" and of measuring both.

Certain other aspects should be considered in order to clarify interpretations. Onset of simple growth failure in school age children, as evaluated by the Grid technique (5), is characterized by quite specific deviations beyond known tolerance values for two chief parameters, the *direction* (Fig. 1-A) and the *speed* of physical development (B), with associated deviations in body *size* (level) and *shape* (physique channel) and with the consequent accumulation of corresponding caloric "fuel debts" (6). Recovery, on the other hand, is measured by reversal of such trends and, in particular, by the extent to which physique is restored, lag made up, and fuel debt repaid.

For practical purposes, the chief tolerance values in healthy growth may be taken as follows: no child should lose more than $\frac{1}{2}$ channel of physique in 10 levels of advancement and it should not fail by more than 2 or 3 levels to attain its expected year-end level position if it is to develop at the normal rate of 1 level per month or 12 levels per year. These parameters and tolerances, it may be emphasized, are independent of race, sex, weight, height, size, shape, and—up to maturation—of age.

As a rule, recovery from and treatment of simple growth failure in school children, whether mild, moderate, or severe as regards physique loss, level lag, or caloric debt, is readily achieved through systematic programming designed to meet individual needs (6). Some of the prominent elements of such programs are good hygiene, balance between exercise and rest, planned caloric conservation, and emotional calm, all aimed at restoring physique to par, and eliminating lag and fuel debts. The affliction is peculiarly ame-

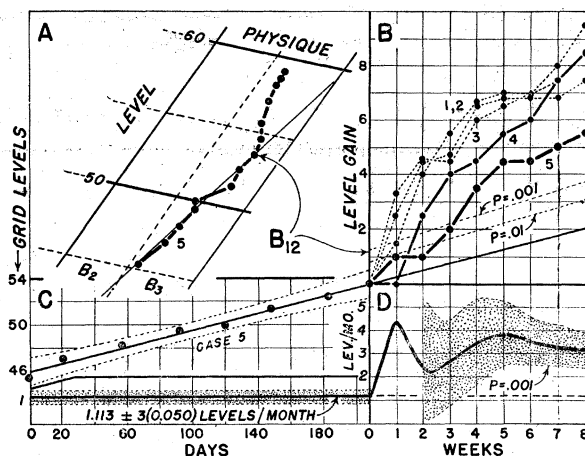


FIG. 1. Growth responses to oral vitamin B_{12} . A—Directional shift with increasing physique in Case 5. B—Level gains in five reactors with confidence bands for No. 5. C—The previous 208-day regression of Grid level on time with its 0.001 confidence band; data show existence of Shewhart (3) state of control. Lower C—Rate of development for No. 5, with standard error and error band. D—Velocity surge in No. 5 following administration of B_{12} and the 0.001 confidence band.

nable to group or institutional management when individual personality problems can be worked out. Obviously, diets must supply all daily needs including overages to cover fuel debts (6); composition approximates carbohydrates 50 percent, fats 35 percent, and proteins 15 percent. On occasion, vitamin supplements are required. Nutrition is clearly to be emphasized because it is always involved in recovery, regardless of the main or inciting cause or causes that led to growth failure.

We have repeatedly observed beneficial effects from vitamin supplements or from oral administration of whole liver extract² which are specially prescribed when progress has been delayed out of proportion to physical or other findings. On the other hand, we have been impressed with unaccountably slow progress in spite of intensive effort to seek out causes and to establish more satisfactory recovery rates. At such times, the possibility of unknown and otherwise unheralded deficiencies has naturally suggested itself.

In August 1949 we began to administer 10 μ g of crystalline vitamin B_{12} orally³ to 11 children (6 boys, 5 girls; ages 5–12 years) 3 of whom (Nos. 2, 4, 5 of Fig. 1) were selected on account of slow progress, the remaining 8 at random from a group of 76 under regular care for varying degrees of malnutrition and in varying states of recovery from simple growth

² First suggested to us by Paul György in 1941.

³ Crystalline vitamin B_{12} (Cobione[®]) was kindly supplied by the Medical Division of Merck & Company, Inc. of Rahway, New Jersey.

failure. Oral administration of the same dose was continued daily at the time of the usual midmorning milk offering. Heights and weights (clothes off) were

TABLE 1
RATES OF DEVELOPMENT, STANDARD ERRORS, ETC.

Case No.	Levels per month			Degrees of freedom	<i>t</i>	<i>p</i>
	Before	After	Difference*			
1	2.50 ± 0.40	5.30 ± 0.42	2.80 ± 0.56	9	5.00	0.001
2	0.65 ± 0.12	3.40 ± 0.66	2.74 ± 0.63	15	4.35	0.001
3	0.65 ± 0.38	4.52 ± 0.60	3.87 ± 0.68	7	5.66	0.001
4	1.89 ± 0.62	4.71 ± 0.31	2.81 ± 0.69	10	4.09	0.01
5	1.113 ± 0.050	3.18 ± 0.25	2.06 ± 0.23	13	8.96	0.001
65						
Controls	2.27 ± 0.13			317	...	...
6 Non-reactors	1.86 ± 0.12	2.00 ± 0.70	0.00	...	...	...

* Errors of differences computed from pooled variances.

remeasured weekly at the same hour. All other program elements were strictly maintained as before on an individual basis. A child, for example, who had been getting extra rest, or another who had been receiving whole liver extract, continued to do so.

Five of the original 11 subjects responded dramatically to this single change in routine represented by the administration of B₁₂, the effects being objectively measured by physique and level gains as charted on each child's Grid record and, for utmost accuracy, as calculated from the corresponding equations for physique, *P*, and level of development, *D* (5). Before and after values of regression coefficients, standard errors thereof, and confidence bands for values of *p* = 0.01 and 0.001 were likewise computed, with due allowance for degrees of freedom available from the number of previous observations. Untreated resident children were a time-place-season control group.

Results summarized in Table 1 and in Fig. 1-B show that 4 of the 5 reactors achieved an average gain of more than 8 levels in 8 weeks, and thus somewhat more than the response of Case 5 who, though gaining only 5½ levels in the same interval, nevertheless exceeded her own 8th week expectancy (as estimated from the extension [B] of the regression [C]) by 3.6 levels, so that *t* = 12.3 and *p* is considerably less than 0.001 for the 6 degrees of freedom contributed by the previous 208-day control period in C. The response of Case 5 is further defined in Fig. 1-A, -C, and -D. In particular, her course of development in 1-A, which had

been deviating by more than ½ channel per 10 levels advance, shifted promptly in the direction of increasing physique; in upper 1-C are the linear regression of level on age (time) and the confidence bands for *p* = 0.001; in lower 1-C, the corresponding constant rate of development, 1.113 ± 0.050 levels per month, with its associated error band of 3σ_b. The statistical evidence of 1-C illustrates the attainment of Shewhart (3) conditions of control prior to administration of vitamin B₁₂. Finally, in section Fig. 1-D is shown the pulselike surge in the speed of development corresponding to the level gains of Case 5 in 1-B, along with the 0.001 confidence band based on the degrees of freedom available at successive weekly observations. From Fig. 1-B and -D the effect of B₁₂ had become statistically significant at the *p* = 0.01 level by the end of the third week, and at the *p* = 0.001 value by the fourth week.

Clinical examinations prior to B₁₂ ingestion revealed no characteristic or even suggestive regional signs in hair, skin, eyes, mouth, or nervous system. The only noticeable clinical changes after B₁₂ administration were those of increased physical vigor, alertness, better general behavior, but above all, a definite increase in appetite, manifested by demands for "second helpings," as contrasted with comparatively indolent food habits before. Moderate eosinophilia (6-8 percent) and reticulocytosis (0.6-0.9 percent) were found in 9 of the 11 subjects.

The most dramatic general effects were shown by Case 2, a boy with severe allergic bronchitis, whose sleep for 12 months before had been regularly interrupted by asthmatic attacks and whose daytime wheezing permitted little desire for food, not to mention time for eating it. His growth response was accompanied by a remarkable attenuation of symptoms; in fact, these simply vanished during the first week, to the surprise of every attendant, lay or professional. What possible connections there may be between B₁₂, its influence on protein metabolism, and allergic disturbance, are questions for further investigation.

Taken together, the foregoing results speak, and they speak with measurable statistical certainty, of what may be termed B₁₂ functional deficiency, that was definitely benefited by oral therapy. As a final measure of effects it may be remarked that the growth responses were equivalent to another 100-240 days of regular institutional care without the help of B₁₂.

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