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Can nutritional supplements help mentally retarded children? An exploratory study

(genetotrophic disease/nutrition/Down syndrome/megavitamins)

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ABSTRACT **To explore the hypothesis that mental retardations are in part genetotrophic diseases (diseases in which the genetic pattern of the afflicted individual requires an augmented supply of one or more nutrients such that when these nutrients are adequately supplied the disease is ameliorated), we carried out a partially double-blind experiment with 16 retarded children (initial IQs, ≈17–70) of school age who were given nutritional supplements or placebos during a period of 8 months. The supplement contained 8 minerals in moderate amounts and 11 vitamins, mostly in relatively large amounts. During the first 4-month period (double-blind) the 5 children who received supplements increased their average IQ by 5.0–9.6, depending on the investigator, whereas the 11 subjects given placebos showed negligible change. The difference between these two groups is statistically significant ($P < 0.05$). During the second period, the subjects who had been given placebos in the first study received supplements; they showed an average IQ increase of at least 10.2, a highly significant gain ($P < 0.001$). Three of the five subjects who were given supplements for both periods showed additional IQ gains during the second 4 months. Three of four children with Down syndrome gained between 10 and 25 units in IQ and also showed physical changes toward normal. Other evidence suggests that the supplement improved visual acuity in two children and increased growth rates. These results support the hypothesis that mental retardations are in part genetotrophic in origin.**

About 30 years ago Williams and coworkers (1, 2) formulated the concept of genetotrophic disease. A genetotrophic disease is one in which, because of his genetic nature, the afflicted person requires an augmented supply of one or more specific nutrients and in which fulfilling these needs prevents or at least ameliorates the disease.

The genetotrophic hypothesis was in mind when G.S., a severely retarded child, was treated by the senior author. When first seen, the patient was 7 years old and in diapers, could not speak, and had an estimated IQ of 25–30. At her instigation, his blood and tissues were analyzed in the laboratories of Mary B. Allen, a biochemist in Richmond, VA. With the cooperation of a physician, Allen devised a nutritional supplement and G.S.'s parents agreed to administer it. There were no noticeable results for several weeks, but after some constituents of the supplement were increased G.S. suddenly began to improve. In a few days he was talking a little; in a few weeks he was learning to read and write, and he began to act like a normal child. When G.S. was 9 years old he read and wrote on the elementary school level, was moderately advanced in arithmetic, and, according to his teacher, was mischievous and active. He rode a bicycle and a skate board, played ball, played a flute, and had an IQ of about 90.

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It appeared that, even after 7 years of deprivation, G.S. responded to some nutrients in the supplement in a remarkable fashion. His case seemed to support the genetotrophic hypothesis as applied to mental retardation.

On the basis of G.S.'s remarkable response and the somewhat less striking responses of several others, we decided to carry out a controlled study of children classified as retarded (IQ less than 75).

EXPERIMENTAL

Plan. Allen died in 1977. From her records and the laboratory records in our own file it became evident that her subjects showing mental response were those given a supplement similar to that given G.S. We decided to give our subjects this supplement, consisting of 11 vitamins and 8 minerals as shown in Table 1.

We also decided to include in the program of supplements, as Allen frequently did, extra thyroid hormone for those children found to be in need of it. All subjects except one were found to

Table 1. Daily doses of supplementary vitamins and minerals (six tablets)

Vitamin A palmitate	15,000 IU*
Vitamin D (cholecalciferol)	300 IU
Thiamin mononitrate	300 mg
Riboflavin	200 mg
Niacinamide	750 mg
Calcium pantothenate	490 mg
Pyridoxine hydrochloride	350 mg
Cobalamin	1,000 μg
Folic acid	400 μg
Vitamin C (ascorbic acid)	1,500 mg
Vitamin E (*d*-α-tocopheryl succinate)	600 IU
Magnesium (oxide)	300 mg
Calcium (carbonate)	400 mg
Zinc (oxide)	30 mg
Manganese (gluconate)	3 mg
Copper (gluconate)	1.75 mg
Iron (ferrous fumarate)	7.5 mg
Calcium phosphate ($CaHPO_4$)	37.5 mg
Iodide (KI)	0.15 mg

The daily dose was 6 tablets. The tablets also contained microcrystalline cellulose, povidone, stearic acid, sodium silicoaluminate, hydroxypropylmethylcellulose, propylene glycol, silica gel, polyethylene glycol, titanium dioxide, oleic acid, and tribasic sodium phosphate as excipients. The placebo tablets contained lactose, microcrystalline cellulose, stearic acid, povidone, propylene glycol, hydroxypropylmethylcellulose, titanium dioxide, and oleic acid.
* IU, international units.

need thyroid according to the Barnes method (3) (morning axillary temperature below 36.6°C), and thyroid was administered from the beginning for both experimental and control subjects, with the exception of two whose parents refused this part of the program (see Table 2). All parents were asked to restrict the patients' intake of less nutritious, sugary foods and soft drinks and to supply fruits and milk freely.

The study consisted of two 4-month experimental periods. During the first period, one group of subjects (group I) received supplements and the other group (group II) received placebos. During the second period both groups received supplements. (We recruited the subjects with the understanding that all would eventually receive supplements.)

Mental tests and other measurements were carried out before the supplement or placebo regimen was started and were repeated at the end of each 4-month period. The other measurements included height, weight, and urine tests for pH, specific gravity, protein, and blood cells. Electroencephalograms were also made.

Parents' reports of compliance and observations were obtained when they returned to obtain monthly supplies of tablets.

Subjects. Twenty-two retarded children living in or near Norfolk, VA, were enrolled by their parents. We accepted all volunteers as they were available. About one-third had Down syndrome (see Table 2) and the rest were unclassified (none was microencephalic). About one-third were Black and the rest were Caucasian. Their initial intelligence test scores and other information were sent to William Shive (The University of Texas at Austin) who divided the subjects into two groups matched primarily on the basis of IQ. Originally, there were 10 subjects in group I and 12 subjects in group II. These group assignments were not made known to any of the experimenters until all of the test data were collected and recorded in Shive's office.

The group assignments were made known to Bronson Pharmaceuticals (La Canada, CA), the company that furnished the supplements and placebos. Sealed bottles of tablets were given to the parents each month, each bottle labeled only with the child's name and the dosage: six tablets to be swallowed each day, preferably two at each meal.

During the first 4 months, six subjects dropped out, mostly because of transfers of military families to new locations. Five of these were in group I.

The 16 subjects who completed the first 4-month experimental period are described in Table 2, which also shows their initial IQ scores. The groups of 5 and 11 members were reasonably well matched with respect to IQ (mean ± SEM IQ 46.3 ± 3.6 and 48.5 ± 5.2, respectively).

Mental Tests. Parents were asked to obtain two mental tests of their child during each of the three testing periods; one test was administered by the principal investigator (R.F.H.) and the other by the parents' choice among six local psychologists. All seven psychologists were either licensed or certified; some were school psychologists and others were in private practice. When two concurrent IQ scores differed by 10 points or more a third test by a third examiner was sought.

Most testing (84%) was done with the Stanford–Binet Intelligence Scale, Form L-M, because it is standardized for the low mental age of most of our subjects. R.F.H. used the Stanford–Binet test throughout, except that for two mute children (D.D. and D.H.) the Cattell Infant Scale was used. The

Table 2. Descriptions of subjects and measured IQs

Subject	Sex	Initial age, yr/mo	Thyroid, grains/day	Measured IQ		
				Initial	After 4 months	After 8 months
Group I:						
L.A.	M	5/8	1	39:45	54:50	64:
D.M.	F	11/8	1.5	49:49	50[a]:45[a]	58[a]:52[a]
B.P.	F	11/5	1.5	38:	43:42	54:[b]
S.R.	F	8/5	1.5	61:57	74:63[c], 70[d]	:70[e]
B.S.	F	5/0	—	43:44[f]	57:35[f], 44[f]	56:[g]
Group II:						
J.B.	M	5/3	1	52:	54:58	68:61
T.C.	M	9/2	2	64:65	68:	:78,80
D.D.	M	9/9	1.5	20:	20:23	35:36
C.D.	F	7/2	—	63:67	61:56	76:58[h]
D.H.	M	11/9	2	18:16	18:22	18,30[i]:15
E.H.	F	9/2	0.5	47:49	47:40	Withdrew[j]
B.M.	F	14/9	1.5	47:40	44[a]:42[a]	50[a]:44[a]
S.O.	F	6/8	1.5	60:64	60:50	71:68
R.S.	M	5/7	0	67:72	73:71	88:88
M.W.	F	15/3	2.5	42:43	44:40	49:40
G.W.	F	13/1	2	52:47	55:54	71:[g]

IQs measured by R.F.H. are shown to the left of colons. Group I received supplements during both 4-month periods. Group II received placebos the first 4 months and supplements during the second. Subjects L.A., S.R., D.D., C.D., and E.H. were diagnosed as having Down syndrome.

[a] Poor compliance with taking tablets.

[b] Judged unresponsive and impossible to test by two school psychologists; both estimated IQ < 50.

[c] Score reduced by not deleting tests requiring visual acuity (child has incipient cataracts).

[d] Verbal portion of Wechsler WISC-R test.

[e] Incomplete test finished by principal investigator.

[f] Scores possibly reduced by failure of these examiners to detect subject's deafness.

[g] Subject refused to take further tests.

[h] This score was obtained 10 days after the 76 and 1 day after mother's delivery of new baby which caused vehement sibling rivalry and depression in subject.

[i] Test repeated at school, without mother present, because teacher reported "100% improvement since Christmas" (when use of active supplements began).

[j] Parents were disturbed by subject's new nondocile and defiant behavior and her oddly colored urine.

Wechsler Intelligence Scale was used by the other testers to obtain the following results: D.M., 49; S.R., 70, 70; J.B., 61; T.C., 65, 80; D.D., 36; E.H., 40; B.M., 40; S.O., 50; M.W., 43; G.W., 47. R.F.H. knew that all subjects at the third (8-month) testing had received supplements (hence this portion of the experiment was not double-blind); the other testers did not know this.

Testing these severely retarded children was difficult because some of them had multiple handicaps. Some were subject to seizures and were taking anticonvulsive drugs, some were unresponsive or hostile, two were mute, and some had impaired vision or hearing. In two children, vision or hearing impairments were sometimes not detected or allowed for in the testing (see Table 2).

RESULTS

Intelligence Quotients. Table 2 lists all the IQ measurements obtained for the 16 subjects who completed the first 4-month period. Table 3 shows an analysis of the data. Initial IQs ranged from about 70 to 17. IQ changes after 4 and 8 months are shown in Table 3 in two ways: (*i*) based upon the means of measurements by two or more of the seven psychologists, and (*ii*) based upon the measurements by the principal investigator (R.F.H.) only.

The results after the first 4-month period appear promising. The mean value for the five subjects given the supplement increased by a mean of 5.0 (for R.F.H. values, 9.6), whereas that for the 11 placebo subjects did not increase significantly (0.0; R.F.H. values, 1.1). This difference between supplemented and placebo subjects is statistically significant by the one-tailed *t* test: $P < 0.05$ (R.F.H. values, $P < 0.005$). If we exclude the subject who took supplements only sporadically and exclude the other dubious measurements noted in Table 2, the mean increase in four subjects is 10.8 (R.F.H. value, 10.3), compared to minor changes in the placebo subjects (0.1; R.F.H. value, 1.5). This exclusion increases the statistical significance to $P < 0.001$ (R.F.H. value, $P << 0.001$).

By the end of the second 4-month period the 10 remaining subjects of group II showed a mean IQ increase of 10.2 (R.F.H. value, 11.2). These increases are statistically significant compared to the minor changes for the same subjects on placebos: $P < 0.001$ (R.F.H. value, $P << 0.001$). If we exclude the dubious IQ measurements marked by footnotes in Table 2, the mean IQ improvement increases slightly to 11.2 (R.F.H. value, 11.3). According to the IQs measured by R.F.H., 13 of 14 children given supplements showed IQ score improvement of 6 or more, up to 25. The one exception (B.M.) was known to have often refused the tablets. Score differences of 6 or more are probably real, because only 1 of 11 of R.F.H.'s measurements in the placebo subjects indicated changes of more than 4. Six of the 14 children given supplements displayed gains of 15 or more as measured by R.F.H. At least three of the five children who received supplements during both 4-month periods showed further improvements in IQ during the second period, for an overall average gain of nearly 16.

After completion of the planned 8-month experiment the children in group II were given supplements for an additional 4 months, for a total of 8 months of supplementation. Their IQs then were measured by one of us (R.F.H.) and compared to the initial IQs measured by her. With the exception of subject B.M., who was known to take supplements only sporadically and whose improvement in IQ score was only 2, the increases after 8 months of supplementation ranged from 12 to 24 for the nine subjects measured. The mean (±SEM) increase was 16.0 ± 2.2, which is similar to the gain (15.8 ± 3.4) found for group I after 8 months of supplementation (Table 3).

Judging from modest but statistically significant non-zero linear correlation coefficients, the data indicate that the greatest improvements tended to occur in the younger children. However, G.W. was a notable exception (age 13; IQ increase, 19

Table 3. Analysis of IQ changes

	Mean IQ			IQ change		IQ change by R.F.H.	
Subject	Initial	4 mo	8 mo	4 mo	8 mo	4 mo	8 mo
Group I:							
L.A.	42	52	64	10	22	15	25
D.M.	49	47.5	55	−1.5	6	1	9
B.P.	38	42.5	54	4.5	16	5	16
S.R.	59	69	70	10	11	13	—
B.S.	43.5	45.3	56	1.8	12.5	14	13
Mean	46.3			5.0	13.5	9.6	15.8
± SEM	3.6			2.3	2.7	2.8	3.4
Group II:							
J.B.	52	56	64.5	4	12.5	2	16
T.C.	64.5	68	79	3.5	14.5	4	—
D.D.	20	21.5	35.5	1.5	15.5	0	15
C.D.	65	58.5	67	−6.5	2	−2	13
D.H.	17	20	21	3	4	0	6
E.H.	48	43.5	*	−4.5	*	0	*
B.M.	43.5	43	47	−0.5	3.5	−3	3
S.O.	62	55	69.5	−7	7.5	0	11
R.S.	69.5	72	88	2.5	18.5	6	21
M.W.	42.5	42	44.5	−0.5	2	2	7
G.W.	49.5	54.5	71	5	21.5	3	19
Mean	48.5			0.0	10.2	1.1	12.3
± SEM	5.2			1.3	2.3	0.8	2.0

Group I received supplements during both 4-month periods. Group II received placebos for 4 months, followed by supplements for 4 months.
* Withdrew.

points), and we hesitate to emphasize this analysis on the basis of our limited study.

Heights and Weights. In both groups, during their first 4 months of supplementation the children gained in height on the average more than twice as much as did the group II subjects on placebo: 2.13 ± 0.64 cm in 4 months for 14 measured subjects vs. 0.89 ± 0.43 cm in 4 months for 11 subjects (means ± SEM). Weight changes were too irregular to be meaningful.

Urinalyses. Routine urinalyses made by the Department of Pathology of Norfolk General Hospital at 4-month intervals were monitored by two of us (J.P. and L.R.R.). All values of pH, specific gravity, protein, and blood cell counts were normal.

Electroencephalograms. Two encephalographers at the same hospital, James E. Ethridge, Jr., and one of us (L.R.R.), found no changes that could be correlated with the regimen of supplements.

Visual Acuity. During the second or third mental testing periods, one of us (R.F.H.) noted that three of the four subjects who wore glasses (J.B., S.R., and C.D.) removed their glasses when they wished to see the task at hand clearly. After the code was broken she found that in each case this observation was made after the child had received supplements for 4 months. Subsequently, two of the children (S.R. and C.D.), long accustomed to wearing glasses, were advised by their ophthalmologists to discontinue wearing them.

One child (S.R.), a 9-year-old girl with Down syndrome, developed cataracts which were discovered by her ophthalmologist at about the time the experiment began. S.R. received supplements throughout the experiment. At 6-week intervals the ophthalmologist examined S.R.'s eyes for growth of the cataracts. After 8 months, near the study's end, he reported the condition as "stabilized, not worsening, not progressing as most cataracts do." This finding is consistent with earlier findings in humans (4) and in animals (5) that cataracts may be prevented or delayed by nutritional improvements.

Improvements in Down Syndrome. The children with Down syndrome were the only ones whose physical appearance changed notably during the study. These changes were noted by the principal investigator and by the parents and were visible in photographs taken of the subjects at 4-month intervals. Three of these children (C.D., S.R., and L.A.) tended to lose the accumulated fluid in their faces and extremities. The largest IQ gain observed (25 units) occurred in L.A. after 8 months of supplementation. The lone drop-out during the second period (E.H.) occurred because the parents were unprepared for the changes in the formerly docile subject's personality.

Other Effects. Several children improved greatly in school achievement. For example, J.B. (age 5–6), who said only single words such as "Mama" or "bye-bye" initially, could recite without prompting the Pledge of Allegiance after 8 months of supplementation and could read the first-grade primer. Two (T.C. and R.S.) have been transferred from programs for the mentally retarded to regular schools and grades, on their teachers' recommendations. There were no unfavorable side effects noted or brought to our attention in any of the children. There were some favorable reports on improved texture of finger nails, healthier hair or skin, and (in six cases) cessation of hyperactivity.

DISCUSSION

The concept of genetotrophic disease prompted the clinical trials that led to this exploratory study. According to this concept, maladies of many sorts may be caused by genetically determined insufficiencies that may be prevented or at least ameliorated by an augmented supply of one or more specific nutrients.

There are a number of well-recognized genetic diseases that clearly are genetotrophic in origin, in particular several diseases that respond to increased intakes of vitamin B6 (6) or of vitamin D or its metabolites (7). In some cases the augmented supply of nutrients appears to enhance the impaired activity of defective enzymes that use vitamin B6 as a cofactor or to increase the availability of biochemically active derivatives of vitamin D. In view of the ubiquitous occurrence of biochemical individuality (2), including the vast amount of genetic variability that is detectable in humans and in other species by protein electrophoresis (8), it seems likely that the currently recognized examples of genetotrophic disease represent only the most simple and obvious members of a large class.

Although none of our 15 subjects given supplements responded as spectacularly as did G.S., and further studies are required, our exploratory double-blind study supports the hypothesis that mental retardations in part have genetotrophic origins and that suitable nutritional intervention can improve the IQ and functioning of severely retarded children. All of our subjects who cooperated in taking the supplements showed improvement, sometimes dramatic and surprising to the teachers and other professionals who dealt with them. If our findings are confirmed by more extensive experiments, they bring new hope for improving the quality of life for the mentally retarded 3.2% of our population.

We hope that our results will attract other competent investigators to this field and that nutritional studies to explore the prevention and treatment of mental retardation will become commonplace. There are many questions such as the effects of age, initial IQ, type of retardation, and characteristics of the supplementation that can be answered only by more extensive studies.

It is likely, on theoretical grounds and on the basis of our evidence of a correlation with age, that the earliest possible use of supplementation for potentially retarded children will bring the greatest improvements. Prenatal supplementation should be considered in this connection.

It seems certain that better supplements can be found than the particular combination we tested. Our supplement includes no provision for anyone who needs augmented intakes of the individual essential amino acids, choline (9), fatty acids, biotin, vitamin K, or trace minerals such as chromium, selenium, or molybdenum. And it fails to provide normal metabolites or food factors that ordinarily are not dietary essentials, such as vitamin metabolites, glutamine (10, 11) and other "nonessential" amino acids, inositol, pangamic acid, and coenzyme Q. All of these items must be considered in any thorough attempt to discover and prevent genetotrophic diseases.

Ultimately it should be possible to tailor supplements to meet individual needs, at which time perhaps several of the nutrients we included could be reduced or eliminated in individual cases (different nutrients for different individuals), and even greater amounts of specific nutrients might be called for on an individual basis. This will require long and careful research aimed at answering specific detailed questions.

The administration of a number of drugs at the same time, sometimes referred to as the "shotgun" approach, is a dubious procedure. The administration of several nutrients at the same time should not be confused with this approach because of the scientific fact that a number of nutrients often do work together as a team to promote normal metabolism (5). At least until adequate methods become available for assessing the needs of individual mentally deficient children, we suggest that the most rapid and greatest potential benefits for them will come from research using generous, limited-risk supplements at least as broad as the one we tested.

The lack of IQ changes in the placebo subjects indicates that, in this experiment, thyroid administration alone had no appreciable effect on IQ.

Related Research. One of us (R.F.H.) has published several related studies in which children's IQs have been raised slightly by the administration of thiamin (12, 13) and in which the children of pregnant and nursing mothers, given limited supplements had statistically higher IQs measured at age 3 (14). Hall has reviewed a large number of suggestive reports on the effect of various nutrients on subjects with mental retardation or other mental problems (15).

Kubala and Katz (16) found the average IQ score to be 4.5 higher in 72 students with plasma ascorbic acid levels >1.1 mg/dl than in 72 students matched by socio-economic criteria but with plasma levels <1.1 mg/dl. Most of this difference in IQ was abolished after both groups were given supplemental orange juice for 6 months. From these statistically significant results they concluded that some of the variance in intelligence-test performance is determined by the "temporary nutritional state of the individual, at least with regard to . . . ascorbic acid."

Kershner and Hawke (17) recently studied the effects of an improved diet and four vitamins on the IQ, school achievements, and other measurements in 20 learning-disabled children. For 6 months, large amounts of ascorbic acid, niacinamide, calcium pantothenate, and pyridoxine were given to 10 of the children on a double-blind basis. The improved diet seemed to produce benefits, but the supplement added to the diet produced little additional effect. However, there were suggestive improvements in IQ and in reading tests that occurred only in the group given the supplement.

Several physicians have reported that nutritional supplements help ameliorate Down syndrome, but the reports of benefits, including IQ improvements, are difficult to evaluate. Many drugs were used concurrently, and the reports generally lack data or statistical analysis (18, 19).

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