A Retrospective View of Iodine Deficiency, Brain Development, and Behavior From Studies in Ecuador

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Beginning in the early 1960s Rodrigo Fierro–Benitez and his colleagues (1) carried out an extensive series of studies of endemic goiter and cretinism in Ecuador. This chapter will review the most salient aspects of these findings. The investigations by Fierro–Benitez and his group were carried out mainly in eight rural villages in the north and central highlands of Ecuador where surveys indicated that the prevalence of goiter ranged from 3 to close to 55% of the total population. Because iodized salt was not widely available in Ecuador at that time, it was decided to evaluate the efficacy and safety of depot iodination as a means of ameliorating the problem of iodine malnutrition and its subsequent developmental sequelae. To that end a program of depot iodination was begun in one village (Tocachi) and the population of a second nearby village served as a noniodinated control (2,3). The populations of these villages and the children born into them have subsequently been studied longitudinally and constitute a unique corpus of data on the epidemiology of endemic goiter and cretinism and associated developmental defects in highland Ecuador and the effect of this public health intervention on the children born into these isolated rural communities.

Tocachi (the iodinated community) and La Esperanza (the noniodinated community) are located in the Province of Pichincha approximately 70 k north of Quito. The communities are located 6 miles apart, with Tocachi at an altitude of 2952 m and La Esperanza at an altitude of 2993 m. The communities are generally comparable, although significant differences do exist which will be discussed below. In March 1966 the population of Tocachi was 1100 and that of La Esperanza was 2500. Just prior to the beginning of the iodination program the prevalence of goiter was 69.7% in Tocachi and 52.8% in La Esperanza and the prevalence of cretinism was 8.2% in Tocachi and 6.0% in La Esperanza. Urinary iodine excretion was 10.4 μg/0.9 g creatinine in Tocachi and 17.7 in La Esperanza (2). In March 1966 a public health program of depot iodination was begun in Tocachi with La Esperanza serving as the noniodinated control population.

The following discussion of these studies is divided into four parts that review different aspects of the neural consequences of iodine malnutrition. The first section presents an overview of endemic cretinism in these communities that serves to provide a baseline description of the severe neurological deficits observed in these populations. The second section discusses the program of depot iodination and its effect in eliminating endemic cretinism. It also reviews, in some detail, the studies that have evaluated the impact of the iodination program in ameliorating the mild to moderate degrees of cognitive and psychomotor deficit in children, which are so common in these populations. The third section reviews studies that have attempted to describe the continuum of neurological and behavioral deficits among adults in these populations. These investigations further document the profound degree of neurobehavioral deficits that existed in these populations. The data generated from them serves as a baseline for the comparison of the development of the children born into both the iodinated and noniodinated populations. A fourth section touches on the issue of dietary goitrogens and a final section makes suggestions for future investigations.

ENDEMIC CRETINISM IN HIGHLAND ECUADOR

A number of studies by Fierro–Benitez and his colleagues have provided a rich source of data on endemic cretinism in highland Ecuador and have played an important role in developing an appreciation of the various manifestations of this phenomenon worldwide (1,4–11). In their various publications they note that the prevalence of severely mentally retarded and deaf-mute individuals is clearly associated with the prevalence of goiter, but clearly state that the severity of the endemia of cretinism is related more to the socioeconomic circumstances of the various communities than to the magnitude of the iodine deficiency, which did not vary greatly among them (1,9). This is an extremely important observation relative not only to the etiology of endemic cretinism but to the moderate and mild neurobehavioral deficits observed among members of these communities. This is discussed more fully below.

In their early publications Fierro–Benitez and his group noted that for evaluating cretinism, "the fundamental factor taken into account was the mental deficiency of the subject. The mental deficiency should be obvious in the opinion of the surveyor, and confirmed by the manner in which the subject lived in relation to the rest of the community" (12). These individuals were referred to as *sordo-mudos* (deaf-mutes) by the members of the community and were readily identified by local assistants. Goiter prevalence among the cretins ranged from 60 to 80% in different samples and only about 10% manifested clinical signs of hypothyroidism. There was no relationship between thyroid size and mental development among these defectives. There was a clear familial tendency toward cretinism in that there were 144 such individuals in 116 families. This suggests the possibility that genetic, dietary, or socioeconomic factors may be contributory (1,2,4–7,12). The stature for the adult cretins ranged from 111 to 158 cm in different samples, with the means for males and females around 144 and 136 cm, respectively (4,10,13).

DeLong (10) carried out extensive neurological evaluations on a sample of 67 cretins from Tocachi and La Esperanza. The pattern of neurological deficits found in these subjects included varying degrees of the following: deaf-mutism or lesser degrees of bilateral hearing loss and dysarthria; proximal limb spasticity and rigidity involving the lower extremities to a greater degree than the upper; mental deficiency; and extrapyramidal disorders as reflected in rigidity and bradykinesia characterized by plastic resistance to passive abduction and extension of the shoulder and upper arms. About half the subjects studied by DeLong were completely deaf and this was confirmed by studies of auditory brain stem evoked potentials that showed no cochlear or brain stem response even to loud sounds, which is consistent with a cochlear lesion. Subjects with decreased hearing showed a preferential high tone deficit. DeLong reported that all of the totally deaf cretins were mute as well and that only 18 of the 67 had intelligible speech and that this was always dysarthric.

On the basis of the above clinical assessment and a review of the experimental literature, DeLong (10) suggested that the neurological cretinism (14) observed in Ecuador is the probable consequence of the joint effects of maternal and fetal hypothyroidism occurring early in the second trimester when the cochlea (10–18 weeks) takes form and when the neurons of the cerebral cortex and basal ganglia (14–18 weeks) are undergoing rapid hyperplasia. He suggests that this is followed by compensation in fetal thyroid function in the third trimester due to hypertrophy, resulting in a euthyroid infant at birth that has irreversible brain and inner ear deficits due to midtrimester hypothyroidism.

Although the mental retardation of these cretins is unquestionable, several studies by Fierro–Benitez et al. attempted to quantify these deficits for descriptive purposes by using formal psychometric tests. These assessments also provided baseline data on a population with clear nutritionally caused neurological and behavioral deficits to which the "normal" members of these communities could be compared in order to formally evaluate the hypothesis that there is a

Table 1. Bender Gestalt Scores of 45 Deaf-Mute Cretins in La Esperanza

Males	
Bender score	9.8 ± 5.7
Age	43.3 ± 11.2
Number	25
Females	
Bender score	15.9 ± 4.6
Age	33.0 ± 12.2
Number	20

Adapted from Greene (16).

continuum of mental and psychomotor deficit in these populations.

Greene (13,15–17) administered the Bender Gestalt test, utilizing Koppitz' Developmental Bender Scoring System (18), to 45 deaf-mute cretin individuals in La Esperanza. This is a simple, untimed, paper and pencil task that had been successfully administered to children above 6 years of age in this population as part of another study. Sixteen of the subjects (36%) who had the most profound mental or neuromotor deficits were unable to reproduce the drawings and were given an arbitrary error score of 20. The other 29 deaf-mute cretins understood the directions as given by a local assistant and cheerfully attempted to copy the drawings. The mean error scores of the deaf-mute males was 9.8 and those of the females was 15.9 (Table 1). These scores compared to mean Bender scores of 11.2 among male and 12.1 among female children, 6–7 years of age in Tocachi and La Esperanza and mean error scores of 6.4 among 6–7 year-old North American children in the North American standardization sample (Table 2). The distribution of Bender Gestalt error scores for the sample of children between 6 and 15 years of age in Tocachi and La Esperanza is also shown in Table 2, and the distribution for the deaf-mute cretin group is shown in Table 3. These data indicate that excluding those cretins with the most profound mental and neuromotor deficits (>15 errors), the modal number of errors for the remaining 29 individuals (7–9 errors) is comparable to the mean number of errors of 6–7 year-old children in these same populations.

Table 2. Mean Bender Gestalt Scores of Ecuadorean Andean Children and the North American Standardization Sample

	Mean Scores		
	Ecuador		North America
Age (years)	Males	Females	Both Sexes
6–7	11.2	12.1	6.4
7–8	8.3	8.0	4.7
8–9	5.2	7.6	2.5
9–10	6.2	6.9	1.6
10–11	3.9	3.8	1.5
11–12	3.4	5.4	
12–13	2.1	4.0	
13–14	2.5	3.3	
14–15	2.6	2.9	

Adapted from Greene (13).

Table 3. Distribution of Bender Gestalt Scores of the Deaf-Mute Cretins in La Esperanza

Number of Errors	*n*	Percent of Deaf-Mute Sample
>15	16	35.6
13–15	4	8.9
10–12	4	8.9
7–9	15	33.3
4–6	4	8.9
1–3	1	2.2
0	1	2.2
Total	45	100

Adapted from Greene (16).

On the basis of observations of the 45 deaf-mute cretins in La Esperanza and information provided by their families or informants, Greene (16) divided the deaf-mute cretins into four groups that reflected their different behavioral capabilities. Routine tasks were easily mastered by group I individuals, many by those of group II, and some by group III. These individuals demonstrated a range of capabilities that permitted them to do much of the routine work in this agricultural–pastoral economy. Although quantitative data are lacking, it was apparent that the cost to a household of maintaining the deaf-mute individuals was much below that of the economic benefits derived from their daily labor. This was especially true of the individuals in group I who were capable of most of the work that was performed by normal individuals and were available on a 24-h basis and at a much lower cost. The deaf-mutes were also extremely docile and accepted unpleasant work without complaint. In sum, these qualitative behavioral studies indicated that the deaf-mute cretins were valued and that many of them were economically productive members of this society.

IMPACT OF DEPOT IODINATION ON NEUROLOGICAL DEVELOPMENT OF CHILDREN IN HIGHLAND ECUADOR

Background

The program of intramuscular depot iodination began in Tocachi in March 1966. The iodized oil was Ethiodol (37% iodized poppy seed oil, each milliliter containing 475 mg of iodine, from E. Fougera, Inc., Hicksville, New York). The following dosages were used:

Age (years)	Iodized Oil (ml)
<2	0.5
2–6	0.5
6–12	1.0
>12	2.0

Ninety percent of the inhabitants of Tocachi received these injections. Women of childbearing age and children born in Tocachi were reinjected or injected in 1970, 1974, 1978, 1982 and 1986 (19). The urinary excretion of iodide remained below 50 μg/g creatinine in the untreated population until 1978 and half of this population manifested symptoms of iodine deficiency until 1981. It was only in the mid-1980s that the use of iodized salt with adequate levels became widespread in these communities (19). All children born into the two study populations were examined at the time of birth and at regular intervals thereafter. These data provide the basis for evaluating the effect of the program of depot iodination on the psychomotor and mental development of the children born into these populations.

First Phase Studies up to 1973

1969 Publications.

Upon reexamination in April 1968 the prevalence of total goiter in the iodinated population had declined from 69.7 to 45.3% (2). Three children with characteristics of neurological cretinism had been born into the noniodinated population but no children with such severe deficits were born into the iodinated population. Therefore, it appears that the program of depot iodination was successful in preventing second trimester maternal and fetal hypothyroidism and the risk of severe brain damage in these populations. The Gesell scales were used to evaluate neuromotor development of the children during these early years. The mean developmental quotient of children 9–18 months of age was 92.77 in Tocachi and 89.0 in La Esperanza (3). Although the children in the iodinated population showed some developmental advantage at this time, it was not statistically significant. During this series of investigations Dodge administered the Goodenough-Draw-A-Man Test to 96 first and second grade children in these two populations (20). The mean intelligence quotients derived from these tests were 102.92 and 97.38 for boys and girls, respectively, in the iodinated population compared to 94.24 and 84.50 for boys and girls in the noniodinated population. The iodinated/noniodinated differences were significant for females ($p < 0.001$), but not for males, However, it was not possible to categorically impute these differences to the effect of the iodination program because there had not been a baseline psychometric evaluation of the two populations prior to the implementation of the iodination program.

1972 Publications.

A second series of reports in 1972 evaluated the effect of the iodination program on neuromotor development in children born up to August 1971, some of whom were then 5 years of age. Data on neuromotor maturation using the Gesell Scales indicated that neuromotor development was somewhat more advanced in the children from the iodinated compared to the noniodinated population and that the social and language functions were the ones most depressed in both populations (21). At this time six children with severe mental and neuromotor deficits had been born into the noniodinated population and no such severe deficits had been observed in the iodinated population.

In another study carried out at this time Trowbridge (22) used a modified version of the Stanford–Binet test to assess intelligence on a sample of 51 children from the iodinated population and 60 children from the noniodinated population who were between 3 years 10 months and 5 years 4 months of age. There were no differences in the mean IQ scores between the two populations. The data were then divided into three groups:

1. *Group I*: children born in the 9-month period before the iodination program began. In the iodinated population these children received the iodine injection some time between birth and 9 months of age.
2. *Group II*: children born in the 9-month period immediately after iodination. In the iodinated population, these were children born to moth-

Table 4. Mean IQ Scores of Children 3–15 Years Old in Tocachi (Iodinated) and La Esperanza (Noniodinated)

	Tocachi			La Esperanza		
Group	Male	Female	Total	Male	Female	Total
I	66	61	65.2	69	70	69.9
II	75	68	72.3	66	70	69.0
III	73	78	76.8	72	72	72.4
Total			72.2			70.4

Adapted from Trowbridge (22).

ers who had received the iodine injection at some point during gestation.

3. *Group III*: children born from 9 to 18 months after iodination. In the test (iodinated) population, these were children born to mothers who had received depot iodine supplementation prior to conception.

When the sample was so divided there was a progressive increase in the mean IQ in the iodinated population from Group I–Group III, with both Group III and Group II children having IQ scores significantly higher than the children in Group I in the iodinated population (Table 4) (22). Among the iodinated females, there were statistically significant differences between Groups II and I and between Groups III and II. Among the males, significant differences were found between groups II and I. Although the sample sizes are small, these data suggested that the iodine prophylaxes of mothers before conception or during gestation had a beneficial effect in improving intelligence test performance of their children when compared to children who were not exposed to the iodine supplementation until after birth. The within-population comparisons eliminate the possible confounding effect of socioeconomic and other differences between the iodinated and noniodinated populations, although there is a chance that the presence of the research team in these two communities precipitated economic and other changes that had a secular effect on child development independent of the effect produced by the iodination program.

In another evaluation of mental development in these children, Fierro–Benitez and coworkers (23) assessed IQ using a locally modified version of the Stanford–Binet test on a sample of 150 children (67 iodinated, 83 noniodinated) over 3 years 4 months of age. The children born into the iodinated population (Tocachi) were divided

Table 5. Mean Bender Gestalt Scores of Children in Tocachi (Iodinated) and La Esperanza (Noniodinated)

	Tocachi		La Esperanza	
Age (years)	Males	Females	Males	Females
6–7	11.8	12.2	10.6	12.0
7–8	9.3	7.7	7.2	8.3
8–9	4.9	7.3	5.5	7.8
9–10	8.3	6.7	4.6	7.0
10–11	4.0	5.2	3.8	6.5
11–12	4.4	5.4	2.7	5.3
12–13	2.7	2.8	1.6	5.3
13–14	2.6	2.2	2.4	4.2
14–15	2.3	3.3	2.9	2.5

Adapted from Greene (13).

into two groups:

1. *Group I*: children who received iodine during the last period of fetal life, during lactation, and directly by intramuscular administration;
2. *Group II*: children who received iodine early in intrauterine life, during lactation, and directly by intramuscular injection.

The mean IQ score in Tocachi Group I was 67.0, in Tocachi Group II was 80.1, and in La Esperanza it was 70.1. The children in the Tocachi group II sample had a mean IQ score significantly higher than that of the children in Tocachi Group I and of the La Esperanza sample. There were no significant differences in the mean scores of the Tocachi Group I and La Esperanza samples. Based on these data Fierro–Benitez and his colleagues concluded that iodine supplementation of the mother after the fifth month of intrauterine life had little or no prophylactic effect in preventing mental retardation (23).

In 1971 Greene studied the physical growth and psychomotor development of 348 children from 6 to 15 years of age, 170 from Tocachi and 178 from La Esperanza (13,24). This was a random sample that comprised approximately 85% of the children in these age ranges in Tocachi and 55% of those from La Esperanza. These were children who were between 1 and 10 years of age when the iodination program began in Tocachi.

The mean Bender Gestalt test scores for the children from both populations are shown in Table 5. There were no significant differences between the iodinated and noniodinated samples when the sexes were combined; however, the iodinated females had consistently better scores than the noniodinated females. Paradoxically, the scores of the iodinated males were consistently poorer than the scores of the noniodinated males. This is reflected in a significant population by sex interaction in the analysis of variance ($F = 4.92$, $df = 1/311$, $p < 0\text{-}.03$).

Because there were no baseline data on neurological development in these populations, it is difficult to interpret these findings. If it is *assumed* that the preiodination level of neurological maturation was *likely* to have been lower in Tocachi (Tocachi had a higher prevalence of goiter and cretinism prior to the iodination program and its adults were shorter and weighed significantly less than the La Esperanza adults), then it can be concluded that the program of depot iodination had a significant beneficial effect on neurological maturation among the females, but not the males. The lack of a sex difference in the Bender scores in Tocachi would seem to indicate that the females benefitted from the iodination program and had achieved a level of visuo-motor development on a par with the male children, as is the case in the North American standardization sample. The enigma is why the La Esperanza noniodinated males scored so much better than both sexes in Tocachi as well as the La Esperanza females.

1974 Publications.

This study utilized the Stanford–Binet Intelligence Scale combined with the Catell Infant Intelligence Scale to evaluate mental development in 216 children (103 from the Tocachi iodinated population, and 113 from the La Esperanza noniodinated population) who had been born into the study communities during the 7 years subsequent to the program of depot iodination and who were at least 3 years of age at the time of testing (25). The subjects were divided into the following groups:

1. *Tocachi Group I*: children in whom correction of iodine deficiency occurred between the fourth to seventh month of fetal life directly by intramuscular injection of the mother;
2. *Tocachi Group II*: children of mothers who had been given iodized oil prior to conception;
3. *La Esperanza Group I*: children pair-matched by age and sex, one for each child in Tocachi Group I;
4. *La Esperanza Group II*: children pair-matched by age and sex, one for each child in Tocachi Group II.

The mean IQ score of Tocachi Group I was 71.72 and in La Esperanza Group I it was 69.16, which were not significantly different. The differences between the mean IQ score of 83.66 in Tocachi Group II and 72.74 in La Esperanza Group II were significant ($p < 0.002$) (Table 6). Furthermore, only 9.5% of the children in Tocachi Group II had IQ scores below 70 compared to 40% in Tocachi Group I, 50% in La Esperanza Group I, and 34.8% in La Esperanza Group II. These data strengthened the findings of the 1972 publications that depot iodination prior to conception greatly ameliorates the spectrum of severe mental deficits that occur in regions where goiter and cretinism are endemic. Fierro–Benitez and his colleagues noted that correction of iodine deficiency after the third month of intrauterine life does not appear to have a salutary effect on future intellectual capacity as measured by these studies. This is consistent with the observation that neuronal proliferation in the cerebral cortex is largely completed by week 18 of gestation (10). Thus depot iodination administered to the mother after that period of time would have little or no effect on neuron development.

Table 6. Mean IQ of Children 3–5 Years of Age in Tocachi (Iodinated) and La Esperanza (Noniodinated)

Group	Male	Female	Mean IQ (Range)	±	SD	p
Tocachi Group I	24	16	71.72 (41–101)	±	14.6	NS
La EsperanzaI Group I	26	24	69.16 (42–105)	±	13.3	
Tocachi Group II	36	27	83.66 (55–105)	±	13.4	<0.002
La Esperanza Group II	32	31	72.74 (40–105)	±	14.0	

NS, not significant. Adapted from Fierro–Benitez et al. (39).

Second Phase Studies Beginning in 1981

1986 Publications.

The next phase of studies by Fierro–Benitez and his colleagues began in 1981 and was carried out on 128 children from the Tocachi iodinated population and 293 children from the La Esperanza noniodinated population who were then between 8 and 15 years of age. All of the Tocachi children had been born to mothers who had received depot iodination before conception or during the first 3 months of pregnancy. The studies evaluated school performance of children who had stayed in school at least an entire year and had started a new year, irrespective of whether they had completed the second year (26).

The investigation found that the percentage of untreated (noniodinated) children who were taken out of school for mental incapacity was more than twice that of treated (iodinated) children (13.3 vs. 5.4%). Also, 58% of the treated children had not failed a grade compared to only 36% of the untreated children. Although the school performance of the two groups was similar, a higher percentage of the treated children received good grades (16 vs. 9%). Twenty-six percent of treated children and 46% of untreated children were 1 year behind their expected grade. Taken together, these data indicate notably poorer school performance in the children from the noniodinated population compared to those from the iodinated population. However, these findings may be a consequence of a number of factors besides iodine malnutrition. Interpopulation differences in the prevalence of protein-energy malnutrition may be one confounding factor. Another possible confounding factor could be differences in the difficulty of the two school systems, and it is entirely possible that the educational program was more rigorous in the school in the noniodinated community than the school in the poorer iodinated community. A stronger study design would have been the addition of a comparison of children born within the iodinated population at various periods before the initiation of depot iodination and those born after its implementation. Such a study would have controlled for intercommunity differences in school systems and may also have controlled for nutritional and microenvironmental differences to a certain degree. A sibling comparison design would add further strength to such studies by controlling somewhat for variability in genetic and familial factors.

In this same series of studies Fierro–Benitez and his colleagues administered a variety of intelligence and psychomotor tests (Terman–Merrill version of the Stanford–Binet, Wechsler, Goodenough Draw-A-Man Test, Goddard, Bender Gestalt, and Raven Progressive Matrices) to treated and untreated subjects 8–15 years of age, with different tests and sample sizes at different ages (26). There were no significant differences in the mean scores of the two samples on the Terman–Merrill, Wechsler, and Goodenough tests, and the treated subjects did significantly better on the Goddard and Bender Gestalt protocols.

The authors noted that the intelligence tests confirmed the data on school performance that indicated a significant percentage of mentally subnormal individuals in both communities. They concluded that because these tests did not show significant differences between treated and untreated children it can be assumed that the observed deficits are caused by factors other than iodine malnutrition. Protein–energy malnutrition was widespread, as was clear from the obvious poverty of these populations, the results of several nutritional surveys, and the relatively short stature of individuals in these communities. Fierro–Benitez et al. (26) and Greene (24,27) noted that human adaptation to caloric deficit involves a shift in the deiodination of T_4 to reverse T_3 (rT_3), which is metabolically inactive, as a means of conserving the limited calories that are available to the individual in order to preserve life (28–31). Although the rT_3 pathway facilitates adaptation to caloric deficit, it compromises adaptation to low iodine intake by depriving the body of the limited amounts of available T_4 that could be converted to metabolically active T_3. Thus, protein–energy malnutrition hampers thyroidal adaptation to low iodine intake. The simultaneous occurrence and interaction of these two phenomena in the pregnant woman, the developing fetus, and the infant and early toddler may be a significant factor contributing to the pattern of mental deficits seen in these populations.

Selection bias may be another factor that accounts for the lack of advantage in IQ scores found in the members of the iodinated population compared to the noniodinated population, and for the overall depression of IQ scores in these samples. This would occur if the more capable individuals and their families emigrated from these isolated rural communities and if this phenomenon was more marked in Tocachi due to the beneficial effects of the iodination program. Subsequent studies have not provided unequivocal support for this hypothesis (see below).

Third Phase Beginning in 1987

1989 Publications.

In October 1981 Fierro–Benitez and his group (19) reviewed a number of findings on the children born into the treated and untreated populations between October 1966 and October 1973 and noted that 30.9% of these "early treated" children in Tocachi had emigrated from that community compared to 8.0% of the untreated children in La Esperanza. This observation prompted the question as to whether the higher rate of emigration of treated individuals (who were be-

Table 7. Educational Histories of 51 Individuals From Tocachi (Iodinated) and 49 Individuals From La Esperanza (Noniodinated) Who Completed Elementary School and Continued Their Studies

Studies	Iodinated (%)	Noniodinated (%)
Seamstress school	7.8	24.5
Vocational high school	5.9	2.0
High school	76.4	67.3
University	9.8	6.1

Adapted from Fierro–Benitez et al. (19).

tween 14 and 21 years of age in 1981) was a consequence of a higher level of mental ability in this group and consequently greater employment options in Quito (the destination of most migrants) than individuals who had grown up in the untreated population. If this is the case, such differential migration of mentally capable individuals could account for the lack of difference in intelligence test scores of the treated and untreated children in the 1986 publications discussed above.

In order to evaluate these possibilities, in 1987 Fierro–Benitez and workers located and collected data on 134 of the 138 treated individuals who had entered school up to 1981. For comparison purposes they located and collected data on 120 untreated subjects born between October 1966 and October 1973 who had not migrated by 1981 and who had entered school. The average age of the individuals in both groups was approximately 17.6 years with a range from 14 to 21 years. There were no significant differences in educational attainment between the treated and untreated individuals. Roughly equivalent percentages of the two samples completed elementary school but did not continue their education, compared to those who completed elementary school and did continue their studies. In a sample of 51 treated and 40 untreated subjects who completed elementary school and continued their studies, a greater percentage of the subjects from the treated population went to vocational school, high school, and a university than did subjects from the untreated population (Table 7) (19).

Compared to 49.2% of the untreated individuals 79.1% of the treated individuals had emigrated, and only subjects from the treated population had emigrated beyond the Andean region. Data from psychometric tests that had been collected in the course of the longitudinal study were then compared among the following subject categories: treated nonmigrating; treated migrating; untreated nonmigrating; untreated migrating. There were higher mean Terman–Merrill/Weschler IQ scores for treated migrating (93.50) compared to untreated migrating (88.16) subjects ($p < 0.01$), and on the Goddard test of psychomotor development the treated migrating subjects also had higher IQ scores (93.38) than the untreated migrating subjects (84.56) ($p < 0.01$). These results suggest that there may be differential migration of more capable individuals from the treated compared to the untreated population; however, there is no indication in this report that the IQ scores of the migrants from either population are significantly higher than those of the nonmigrant groups (19). This undermines the explanation that the lack of difference in IQ measures between the treated and untreated populations is a function of differential out-migration of the more capable members of that population.

An assessment of the monthly salaries of subjects in these four groups indicated that the *untreated* subjects in both the migrating and nonmigrating groups had higher mean monthly salaries than the subjects from the iodinated population. Fierro–Benitez and his colleagues account for these findings (19) by suggesting that the lower salaries of the treated nonmigrating subjects are a function of the greater poverty of the iodinated community and that the lower salaries of the treated migrants are a function of the fact that four times as many treated, as compared to untreated, subjects emigrated before the age of 12.

CONTINUUM OF NEUROBEHAVIORAL DEFICIT IN HIGHLAND ECUADOR

A third goal of the investigations of Fierro–Benitez et al. was to describe the continuum of neurobehavioral deficit that exists in these populations in which goiter and cretinism are endemic. It was obvious that the deaf-mute cretins were only the most severely affected segment of the population and that many individuals in these communities appeared to display more moderate and mild neurobehavioral limitations. Several studies were carried out to assess quantitatively the spectrum of neurobehavioral deficit among the adult members of these populations through the use of formal psychometric tests.

In one of these investigations Greene administered the Bender Gestalt test to a sample of 275 individuals between 15 and 54 years of age in La Esperanza (13,15–17). These were individuals who had never received depot iodination. The intent of this study was to provide a baseline description of the continuum of neurobehavioral deficit in an adult sample (brain development completed) from a population that is experiencing severe iodine malnutrition, probably compounded by intercurrent protein energy malnutrition. The Bender Gestalt test requires that the subject copy a series of nine simple geometric forms, each of which is on a separate card and is administered individually. There was no time limitation and the test was administered in a standardized fashion with the aid of a local assistant. Adult members of the community were entirely familiar with the use of paper and pencil and many had attended the local school or had children who attended the school. The test protocols were evaluated using the Developmental Bender Scoring System (18). Evaluations of the protocols were done at the same time as were evaluations of the protocols of the deaf-mute cretins and the sample of children 6–15 years of age. These protocols were mixed together and the evaluator was blind as to the age, sex, or status of the individual who had produced each protocol.

The mean number of errors on this test made by normal North American children decreases with their increasing chronological age, reaching an asymptote at about 9.5 years. There are no significant sex differences in the North American data. Normal children studied beyond the age of 9.5 years made an average of 1.5 ± 2.0 errors. The test can thus distinguish those adult individuals whose visuo-motor perceptive function has failed to mature beyond the level of a normal 9.5 year-old North American child due to neurological injury or "familial retardation." The Koppitz scoring system does not penalize for errors in fine motor control and artistic quality of the reproduction that are characteristic of individuals who are inexperienced in the use of the pencil, but does penalize heavily for errors in the disintegration, expansion, and rotation of the gestalten. These latter types of errors are normal in the immature child and are characteristic of older children and adults with neurologic deficits that affect visuo-motor perception. Those adults in La Esperanza whose scores fell more than two standard deviations below the mean of 9.5 year-old North American children were operationally defined as having moderate deficits in visuo-motor perception. Comparison of these adult scores to those of the deaf-mute cretin individuals and children 6–15 years of age in La Esperanza validated the operational definition.

The mean error scores for these adult subjects was 1.8 ± 2.9 for males and 3.8 ± 2.9 for females. Of these adult individuals 17.5% (48/275) made six errors or more and were considered to have moderate deficits in visuo-motor perception. Table 8 shows the distribution of the Bender scores of the 275 normal adults and the 45 deaf-mutes discussed previously. It is readily seen that there is a broad overlap of scores between the normal and deaf-mute sample in the 7–15 error range where 11.3% (31/275) of the population have Bender scores that overlap with those of 52% (23/45) of the deaf-mute cretin individuals. It thus is entirely reasonable to suggest that somewhere between 11.3 and 17.5% of the normal adult individuals in this sample have moderate deficits in visuo-motor perception. Such deficits place them at a level of visuo-motor development comparable to that of children between 6 and 10 years of age in their own population (see Table 5).

Table 8.
Bender Gestalt Scores of 45 Deaf-Mute Cretins and 275 Normal Individuals in La Esperanza

	Deaf-Mute Cretins		Normal Individuals	
Number of Errors	*n*	%	*n*	%
>15	16	35.6	0	0
13–15	4	8.9	1	.4
10–12	4	8.9	8	2.9
7–9	15	33.3	22	8.0
4–6	4	8.9	67	24.4
1–3	1	2.2	114	41.5
0	1	2.2	63	22.9
Total	45	100	275	100

Adapted from Greene (16).

NATURALLY OCCURRING GOITROGENS OF PLANT ORIGIN

Ermans et al. documented the role played by naturally occurring goitrogens of plant origin in the goiter and cretinism endemia in the Ubangi and Idjwi regions of Zaire (32). Their main interest has been in cassava as the source of the antithyroid compounds and thiocyanate as the ultimate goitrogen. Their overall findings suggested that despite uniformly low iodine intake across a wide region the prevalence of goiter increased and biochemical measures of thyroid function decreased in populations and subjects with high dietary intake of cassava (33). Fierro-Benitez and colleagues have also noted wide variability in the prevalence of goiter and cretin-

Table 9. Kendall Partial Rank Order Correlation Coefficients (Tau) of PTC Taste Sensitivity With Bender Gestalt Score Controlling for Age in Children 6–15 Years of Age

	Tau	*n*	*p*
Tocachi (iodinated)			
Male + Female	0.10	131	n.s.
Male	0.11	66	n.s.
Female	0.11	65	n.s.
La Esperanza (noniodinated)			
Male + Female	0.25	133	0.002
Male	0.22	70	0.03
Female	0.28	63	0.01

Adapted from Greene (33).

ism among different populations despite a narrow range of urinary iodide excretion (1). Population differences in the consumption of food crops containing goitrogens may account for an aspect of the variability as may population differences in intercurrent protein-energy malnutrition.

Greene postulated that naturally occurring goitrogens of plant origin were affecting thyroid function and growth and development in these populations but did not have the resources to test this hypothesis directly. However, he was able to carry out an indirect test of the hypotheses (13,17,24,34). He suggested that the commonly studied genetic trait called PTC (phenylthiocarbamide) taste sensitivity reflects taste sensitivity to bitter-tasting naturally occurring antithyroid compounds of plant origin, like the glucosinolate goitrin [5-vinyloxasolidine-2-thiones] that is found in most *Brassica* (35). Further, he suggested that this genetic system functions to regulate the intake of these substances, with sensitive tasters avoiding foods that contain them or they wash and boil the foods excessively, and nontasters being more likely to consume unmodified the foods that contain these substances.

A study was carried out in a subsample of the children 6–15 years of age from Tocachi (131) and La Esperanza (133) to evaluate the relationship between PTC taste sensitivity and Bender Gestalt scores in these subjects. A nonparametric correlation analysis controlling for age indicated that there was a significant relationship between these variables in the noniodinated, but not the iodinated, population (Table 9) (34). The fact that there was a significant relationship between these variables provides some indirect support for the hypothesis that dietary intake of bitter-tasting goitrogens of plant origin may have an influence on growth and development in these populations and that this influence is greater when iodine intake is low (in the noniodinated population), and that individuals with genetically determined low taste sensitivity to such substances may be at increased developmental risk when iodine intake is low.

A multiple regression analysis on the full sample of 348 children 6–15 years of age from both populations indicated that, after age, a measure of socioeconomic status and PTC taste sensitivity were the two strongest statistical predictors of visuo-motor development in these children (24). These two variables were taken to indicate the cumulative effects of protein–energy malnutrition (SES status) and glucosinolate goitrogen intake (PTC taste sensitivity) on the neurological development of these children throughout their lives. Although Greene was not able to measure the dietary intake of various goitrogen-containing foods, he suggested that the chocho bean (*Lupinus mutabilis*) may contain such compounds. In 1971, households surveyed in Tocachi harvested an average of 50.4 lb. of chocho and those in La Esperanza harvested an average of 67.1 lb. (13).

INBREEDING AND NEUROBEHAVIORAL DEFICITS

In order to assess the possible influence of inbreeding depression (36,37) in producing the observed developmental deficits in these populations Greene (24) compared stature and Bender Gestalt scores among adult subjects in La Esperanza's noniodinated population who were living in three different social segments (*anejos* or *barrios*) of the community that were also located in three different altitudinal–ecological zones. Inbreeding was estimated on the basis of isonomy, the frequency of marriages between persons of the same surname (38,39). Although the coefficient of inbreeding (*f*) was highest in the upper zone and lowest in the lower zone, mean stature and Bender Gestalt scores were generally taller/better in the more inbred portions of the community and shorter/poorer in the least inbred portion of the community (24). Therefore, there is no evidence that inbreeding depression is a significant cause of the developmental defects in these communities.

SUMMARY

1. The investigations in highland Ecuador carried out by Fierro–Benitez and his group over the past 30 years have provided a wealth of information on the effect of iodine malnutri-

tion on the developing brain. It is clear from these studies that: there is a broad spectrum of neurobehavioral deficit in human populations living in regions where iodine deficiency is severe; that intercurrent protein–energy malnutrition is probably a contributory factor by itself and may further exacerbate the iodine deficiency by hampering thyroidal adaptation to low iodine intake; depot iodination provides prophylaxis against the severe developmental defects of endemic cretinism, but there is still a spectrum of moderate to mild neurobehavioral deficit in iodinated populations in these regions; dietary intake of glucosinolates and other goitrogens of plant origin may have a significant impact on neurological growth and development in these populations, with some modulation of that effect as a function of individual taste sensitivity to PTC. Although the program of depot iodination provided prophylaxis against the development of endemic cretinism, it did not eliminate the mild to moderate neurobehavioral and intellectual deficits observed in these populations. The latest and most comprehensive psychometric assessments of children born into these populations indicated that there generally were not significant neurobehavioral and intellectual differences between children 8–15 years of age in the iodinated and noniodinated populations (25). Intercurrent protein–energy malnutrition and the consumption of dietary goitrogens may be factors that affected brain development adversely in the iodinated population. Also, as noted above, if there has been differential outmigration of more capable individuals from the iodinated population, then selection bias in the sampling for these studies may have obscured the beneficial influence of the iodination program.

2. Because it was not possible to monitor continuously thyroid function in this, or any other, human study, it was not possible to evaluate quantitatively the impact of mild iodine deficiency, or mild hypothyroidism, on neurological development in individuals living in these populations. As a consequence of the program of depot iodination, it is likely that hypothyroidism was less common in the Tocachi iodinated population over this period of time. The fact that no cretins were born into the population subsequent to the commencement of that program, lends strong support to that supposition. However, although iodide excretion was lower in the noniodinated population, the frequency and degree of hypothyroidism in that population has not been well-established. Were most individuals compensated, except for those who experienced intercurrent protein–energy malnutrition or who had high intakes of dietary goitrogens? Did a higher prevalence of protein–energy malnutrition and a greater intake of dietary goitrogens in Tocachi increase the prevalence of functional hypothyroidism despite a lower prevalence of goiter? Unfortunately, these questions cannot be answered. The lack of baseline psychometric data prior to the beginning of the iodination program also makes it quite difficult to interpret the effects of the program on brain development and behavior.
3. Given the wealth of already existing data on these populations and the fact that the two communities may not be entirely comparable, it would be useful to focus future studies on within-population comparisons. It can probably be assumed that iodine nutriture has been adequate in Tocachi and that the pattern of developmental defects in that population may be related to protein–energy malnutrition or the intake of dietary goitrogens or both. A possible study is one in which children born into the iodinated population are grouped by birthweight into high and low deciles, or quartiles, in order to distinguish retrospectively children who may have experienced protein–energy malnutrition during gestation from those who had not (on a background of adequate iodine nutriture). Comparison of later IQ in such study groups may indicate the degree to which early protein–energy malnutrition has contributed to the developmental defects observed in these communities. To control for familial factors, low birthweight could be compared to high birthweight sibling controls as a further refinement on the above design. In a similar fashion, older children within the iodinated population could be grouped by highest and lowest deciles for height, age and sex as a way of estimating the influence of postnatal protein–energy malnutrition on mental development. The above two designs could also be combined.
4. Additional studies could evaluate PTC taste sensitivity (and taste sensitivity to a control substance like sodium chloride) among low IQ subjects and high IQ subjects in both the iodinated and noniodinated populations to evaluate whether there are significant differences in PTC taste sensitivity among these

two groups and whether these differences are causally related to the observed developmental outcomes. More direct tests of the relationship between PTC taste sensitivity and urinary excretion of glucosinolate goitrogens or their metabolites would provide a crucial test of the hypothesis that the dietary intake of these substances is regulated by what we call PTC taste sensitivity.

5. Over the past 30 years, Fierro–Benitez and his group have carried out pioneering studies on the relationship of iodine malnutrition and brain development. Additional analyses of the accumulated data from these studies, plus new and highly focused investigations, will further contribute to our growing appreciation of the relationship between iodine and protein–energy malnutrition and brain development.

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