and R. W. Lam. Use of 8-anilino-1-sulfonic acid (ANS) in radioimof triiodothyronine (T<sub>3</sub>) in unex-1m. Am Fed Clin Res XX: 216,

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y our criteria they would still be in reason we think deaf-mutism cretinism syndrome is that we id it in the normal population, subjects with other features of would say that endemic deafnot be an entity to be conely from endemic cretinism. We that if you want to do quick population, there will be good retinism if you find impaired tones of more than 40 decibels. n with cretinism is 92 per cent. The whole field of this associaby the fact that in any populagoing to find an occasional d an occasional patient with mpairment. Such patients might ion to endemic cretinism. It is fficult to recognize such patients re there is known endemic cre-

I would like to challenge Dr. ement that deaf-mutism is a good er for cretinism. Last summer I he Uele region in Africa, where I 00 people and found a prevalence atous cretinism of 1.5 per cent. se of deaf-mutism was only 0.1 per s the same as might be expected in ulation in any region of the world. this example deaf-mutism should arded as a universal tracer for inism.

# THE ROLE OF IODINE IN INTELLECTUAL DEVELOPMENT IN AN AREA OF ENDEMIC GOITER

RODRIGO FIERRO-BENITEZ, M.D.,\* IGNACIO RAMIREZ, M.D.,\* EDUARDO ESTRELLA, M.D.,† AND JOHN B. STANBURY, M.D.,‡

Well-documented studies on endemic cretinism have demonstrated that this disorder is found in geographic association with endemic goiter (1-6). Traditionally, the term "endemic cretin" has been applied to subjects with obvious mental retardation and defects in hearing, speech, and walking. As has been demonstrated in the Ecuadorean Andes (6, 7), the incidence of endemic cretinism is related more to the socioeconomic situation of a community than to the magnitude of its iodine deficiency. The following questions, among others, remain to be answered: What is the extent of intellectual deficiency in areas where endemic cretinism is highly prevalent? Can iodine deficiency, which may lead to cretinism, also cause less obvious intellectual deficiencies? What time factors are involved in the effects of iodine deficiency on intellectual development? These questions are particularly important when we consider that areas of endemic cretinism usually harbor, in addition to iodine deficiency, protein-calorie malnutrition, cultural deprivation, and adverse socioeconomic and sanitary conditions.

The study presented here is part of a program to prevent goiter by the administration of iodized oil in an endemic area of rural highland Ecuador (8, 9). It was designed to evaluate the role of iodine in intellectual development in areas of endemic goiter, i.e., the role of iodine in endemic mental retardation, including both obvious and more subtle degrees of mental retardation.

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Several general observations indicated to us the need for such a study. We carried out an epidemiologic inventory of the total population of eight rural villages in those provinces of the Ecuadorean Andes which are most affected by goiter (3, 7, 10, 11), and demonstrated a close relationship between the serverity of the endemia and the incidence of cretinism. In that survey we regarded mental deficiency as the most distinguishing feature of the cretin. To support this diagnosis, we required that mental deficiency be obvious to the examiners and be confirmed by the manner in which the subject lived in relation to the rest of the community. By this we mean that his family would consider him incapable of performing the normal activities of the average inhabitants of his village. such as agricultural tasks and minor crafts. This criterion was employed because many residents of these communities exhibit a degree of simplicity and naivité in comparison with urban dwellers. The surveyors had the strong impression that rather than two absolute and discrete conditions, there was a continuum in levels of intelligence from "normal" subjects to those diagnosed as cretins.

The present study is presented as additional support for such a continuum. It is based on studies of two groups of subjects in two of the previously studied communities, Tocachi and La Esperanza. These were done on a "defective group" of 77 persons ranging from 9 to 60 years of age, including almost everyone who had obvious abnormalities in walking, speech, hearing, and mental capacity, separately or combined, and a "normal group" of 50 adults chosen at random or by intention, including local leaders, artisans, farmers, and servants. In these two groups intelligence was scored by

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using adaptations of the Gesell, Leiter, and Binet-Simon tests, the first two for the subject who was deaf or mute (12). By the Stanford-Binet classification (13), the "defective group" scored in the idiocy, imbecility, mental weakness, and borderline defective categories. The "normal group" scored in the mental weakness, borderline defective, low average, normal, and high average categories. Thus, overlapping was found between the "defective group" and the "normal group" when they were compared in terms of mental age and IQ's (Table 1). The results indicated also that in these communities a significant percentage of the "normal" population could, in fact, be classified as mentally weak or borderline defective. Nevertheless, there are inherent difficulties, which we recognize, in any direct comparison of these IQ values with those obtained in another culture.

Two periods during embryogenesis are important in considering the effects of iodine deficiency on intellectual development. One is the first 8 weeks of gestation, when the central nervous system begins to form and develop (14). The other is the initiation of fetal synthesis of thyroid hormones, which occurs at about the 12th week of intrauterine life (15).

In the present study we were aware that intelligence is an elusive entity and that under any conditions intelligence tests are only estimates of mental capabilities. Furthermore, assessment of intellectual capacity presents

additional problems when one is working across cultural barriers among persons largely deprived of educational opportunities and for whom social contacts are limited or vitually non-existent.

#### SUBJECTS AND METHODS

This study was conducted in Tocachi and La Esperanza, two remote and entirely comparable neighboring rural Andean communities (8). Severe chronic iodine deficiency, proteincalorie malnutrition, and a high prevalence of goiter and cretinism are the most important characteristics of these Spanish-speaking villages.

In March 1966, every person in Tocachi was injected with iodized oil. In December 1968, all women of childbearing age were reinjected and all children born after 1966 were injected. La Esperanza remained the control village. Details of this iodine supplementation program and of ongoing studies have been reported elsewhere (8, 9, 16-18).

The children born in Tocachi during the seven-year period of the study were divided into two groups:

Tocachi Group 1: Children in whom correction of iodine deficiency occurred between the fourth to seventh month of fetal life directly by intramuscular injection of the mother.

TABLE 1. Distribution of "defective" and "normal" persons from Tocachi and La Esperanza, Ecuador, by IQ's in the Stanford-Binet classification.\*

Intelligence quotient (IQ)	Defectives (No.)	Normals (No.)	Classification (Stanford-Binet)	
0-19	35		Idiocy	
20-49	40		Imbecility	
50-69	1	9	Mental weakness	
70-79	1	22	Borderline defective	
80-89		5	Low average	
90-10 <b>9</b>		13	Normal or average	
110-119		1	High average	

<sup>\*</sup>Terman, L. M., and M. A. Merrill, Stanford-Binet Intelligence Scale, Houghton Mifflin Company, Boston, 1962.

Tocachi Group 2: Children iodized oil prior to conce

The children from La Esp whom received iodine, were gro

La Esperanza Group 1: matched by age and se child in Tocachi Group than one child was avail particular child in Tocac tion was used.

La Esperanza Group 2: matched by age and se child in Tocachi Group random selection when n

The principal test used was the Stanford-Binet Intelligence adaptation involved picture vocabulary with local characte for ages 2 through 9 years w translated into Spanish by a dorean physicians who had we and La Esperanza for more tl had a good knowledge of the habits, and speech patterns. tested were at least 36 months failed to successfully comple ford-Binet items for the 2-ver latter children, three were from 1, one from Tocachi Group Esperanza Group 1, and thre

TABLE 2. Numi

Group
Tocachi Group 1
La Esperanza Group 1
Tocachi Group 2
La Esperanza Group 2

<sup>\*</sup>Spiegel, M. R. Star

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Classification (Stanford-Binet)
Idiocy
<b>Imbecilit</b> y
Mental weakness
Borderline defective
Low average
Normal or average
High average
ntelligence Scale, Houghton

Tocachi Group 2: Children of mothers given iodized oil prior to conception.

The children from La Esperanza, none of whom received iodine, were grouped as follows:

La Esperanza Group 1: Children pairmatched by age and sex, one for each child in Tocachi Group 1. When more than one child was available to match a particular child in Tocachi, random selection was used.

La Esperanza Group 2: Children pairmatched by age and sex, one for each child in Tocachi Group 2, again with random selection when necessary.

The principal test used was an adaptation of the Stanford-Binet Intelligence Scale (13). The adaptation involved picture recognition and vocabulary with local characteristics. The tests for ages 2 through 9 years were adapted and translated into Spanish by a team of Ecuadorean physicians who had worked in Tocachi and La Esperanza for more than 10 years and had a good knowledge of the villages' customs, habits, and speech patterns. All the children tested were at least 36 months of age, but some failed to successfully complete all the Stanford-Binet items for the 2-year level. Of these latter children, three were from Tocachi Group 1, one from Tocachi Group 2, four from La Esperanza Group 1, and three from La Esperanza Group 2. For them, items from the Catell Infant Intelligence Scale were used to establish the baseline at which all test items could be completed successfully. Once established, this baseline was used for scoring in the same manner as the baseline established with the Stanford-Binet items. Other details of the methods used in this study have appeared in three preliminary reports (19-21).

A total of 216 children were tested: 103 (60 males and 43 females) in the treated village, Tocachi, and 113 (57 males and 56 females) in the control village, La Esperanza. Only children who manifested appropriate behavior during examination were included. We rejected those who refused to cooperate at any time during the test. These consisted of five from Tocachi Group 1, two from Tocachi Group 2, and eleven from the two La Esperanza groups. Most of these rejected children were reexamined one year later (five in Tocachi Group 1, two in Tocachi Group 2, and eight in the La Esperanza groups). Also rejected were one boy and one girl (twins), on the grounds of extremely poor physical condition and severe malnutrition; they would have belonged to Tocachi Group 2.

#### **RESULTS**

As shown in Table 2, the mean IQ score in Tocachi Group 1 was 71 and in La Esperanza

TABLE 2. Number, sex, mean IQ scores and range, SD and "Z" Test\* value of p of the children tested from Tocachi and La Esperanza.

Group	Number M F		IQ Mean value (range)	SD	"Z" Test Value of p
Tocachi Group 1	24 16		71.72 (41-101)	14.6	
La Esperanza Group 1	26	24	69.16 (42-105)	13.3	- No sig.
Tocachi Group 2	36	27	83.66 (55-105)	13.4	. 0 000
La Esperanza Group 2	32	31	72.74 (40-105)	14.0	- p < 0.002

<sup>\*</sup>Spiegel, M. R. Statistics. McGraw-Hill, Mexico City, 1970, 169 pp.

Group 1 it was 69. This difference was not significant. In Tocachi Group 2 the mean 1Q value was 83, and in La Esperanza Group 2 it was 72, a highly significant difference (p <0.002).

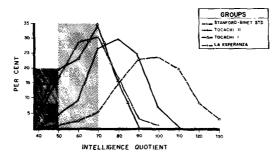
Since children with IQ scores below 70 are considered mentally retarded, many children in both villages must be regarded as mentally defective (Table 3). However, only 9.5 per cent of the children in Tocachi Group 2 scored in the mentally defective range. Furthermore, in this group there were no children scoring below 50, the range corresponding to idiocy-imbecility. The lowest IQ's in Tocachi Group 1, La Esperanza Group 1, and La Esperanza Group 2 were 41, 42, and 40, respectively. Not a single subject had an IQ below 20, the range corresponding to idiocy. The highest IQ was 105, found in children belonging to Tocachi Group 2 and in both La Esperanza groups.

When the distribution of IQ scores of each group is charted (Figure 1), the curves of Tocachi Group 1 and of both La Esperanza groups tend to be skewed in the direction of mental deficiency, while the curve of Tocachi Group 2 has a clear tendency toward normal.

# DISCUSSION

Three facts emerge from our findings: 1) The general performance of the children was poor. 2) The spectrum of intellectual capacity was wide, covering practically all mental categories. 3) The children in whom chronic iodine deficiency was corrected prior to conception showed less intellectual impairment.

FIGURE 1. Distribution of IQ scores within each of the study groups from Tocachi and within the combined groups from La Esperanza.



Note: The Stanford-Binet standard is given for comparison. The darkly shaded area corresponds to the "idiocy-imbecility" category, the lightly shaded to "mental weakness."

We have presented elsewhere the limitations of the methods of intellectual assessment used in this study (19, 20). Nevertheless, there are good reasons for believing that the poor general performance of the children did not reflect difficulty in comprehension of the test beyond that expected from their low intelligence. More than 70 per cent of the children comprehended the tests and completed them satisfactorily. A greater number of children in Tocachi Group 2 performed the tests successfully. Furthermore, the results obtained in the children were quite similar to those found in adults of the same communities, except that defective adults had lower IQ's than the lowest IQ's found in children. This might be partly explained by the severely deprived conditions under which the mentally retarded live in these communities (21, 22).

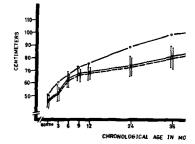
TABLE 3. Distribution of IQ scores for each group of children tested from Tocachi and La Esperanza.

Tocachi Group 1		La Esperanza Group 1		Tocachi Group 2		La Esperanza Group 2		Classification Stanford-Binet	
	No.	%	No.	%	No.	%	No.	%	Stamord-Binet
90-109	4	10.0	3	6.0	21	32.8	10	15.8	Normal or average
80 -89	9	22.5	7	14.0	20	31.7	9	14.2	Low average
70 -79	11	27.5	15	30.0	16	25.3	22	34.9	Borderline defective
50 -69	13	32.5	21	42.0	6	9.5	19	30.1	Mental weakness
0 -49	3	7.5	4	8.0	_	_	3	4.7	Idiocy and imbecility

The poor general intellectua these children, including even Group 2, may be considered in nutritional and environmenta They live in communities in w daily diet does not reach 1,90 sumption of animal proteins These conditions have bee worsening for generations (25 development of children from retarded in relation to that o children from developed count illustrated in Figures 2 and 3.

Additional understanding occurring during the growing gained from a consideration ( This measure is not constant in increments in growth vary w Height increases rapidly during followed by a period of decele 9, at which time it accelera adolescence. As illustrated in F difference can be noted on coi curves of Tocachi and La Espe curve established by Wilkins American children. Not only is Ecuadorean children generally deceleration stage is more pro critical period from the first to t life. In this period, growth is go by genetic factors but by environmental ones as well (2) life and particularly during the

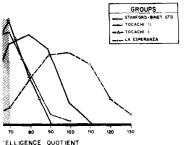
FIGURE 2. Height (mean ± st from birth to 5 years, of children bo La Esperanza during 7-year period of



Note: Comparative values for United States are taken from Nelson (

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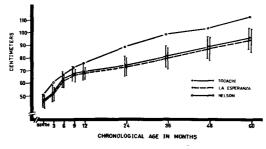
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Esperanza Group 2	Classification Stanford-Binet				
15.8	Normal or average				
14.2	Low average				
34.9	Borderline defective				
30.1	Mental weakness				
4.7	Idiocy and imbecility				

The poor general intellectual performance of these children, including even those of Tocachi Group 2, may be considered in relation to their nutritional and environmental circumstances. They live in communities in which the average daily diet does not reach 1,900 calories. Consumption of animal proteins is minimal (8). These conditions have been progressively worsening for generations (23). The physical development of children from both villages is retarded in relation to that of well-nourished children from developed countries (24, 25), as illustrated in Figures 2 and 3.

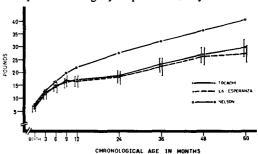
Additional understanding of the changes occurring during the growing period can be gained from a consideration of growth rates. This measure is not constant in the child, since increments in growth vary widely with age. Height increases rapidly during the first year, followed by a period of deceleration until age 9, at which time it accelerates again with adolescence. As illustrated in Figure 4, a great difference can be noted on comparison of the curves of Tocachi and La Esperanza with the curve established by Wilkins (25) for North American children. Not only is the rate of the Ecuadorean children generally slower, but the deceleration stage is more pronounced in the critical period from the first to the third year of life. In this period, growth is governed not only by genetic factors but by nutritional and environmental ones as well (26). During fetal life and particularly during the first two years

FIGURE 2. Height (mean ± standard deviation) from birth to 5 years, of children born in Tocachi and La Esperanza during 7-year period of study.



Note: Comparative values for normals in the United States are taken from Nelson (24).

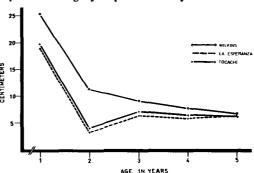
FIGURE 3. Weight (mean ± standard deviation) from birth to 5 years, of children born in Tocachi and La Esperanza during 7-year period of study.



Note: Comparative values for normals in the United States are taken from Nelson (24).

of postnatal life, nutritional factors have important physical, chemical, and functional effects on the human brain (27-30). Severe limitations during this period lead to exaggerated responses to certain stimuli, poor ability to extinguish responses, and decreases in cognitive and perceptual development. Perhaps a great deal more could be said if one could determine the effects of alienating forces, such as cultural deprivation and the precarious physical and emotional condition of the family, on the total development of the child. Some of these factors are explored in the studies of Cravioto et al. on rural Mexican children (31).

FIGURE 4. Annual increment of height from birth to 5 years of males born in Tocachi and La Esperanza during 7-year period of study.



Note: Comparative values for normals in the United States are taken from Wilkins, L. A., Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, C. C. Thomas, Springfield, Ill., 3rd ed., 1961.

In this study we noted levels of intelligence that ranged from normal to the obviously retarded with IQ's below 50. If, by convention, we define endemic cretins as those with a mental capacity at the idoicy-imbecility level, we can state that correction of iodine deficiency before conception prevents endemic cretinism. On the other hand, correction of iodine deficiency after the third month of intrauterine life appears to have no effect on future intellectual ability, at least under the conditions of our field trials. This suggests that the mental development of a child may be dependent on maternal thyroid function during embryogenesis or perhaps, as a working hypothesis, that it may be related to an extrathyroidal action of iodine on the development of the central nervous system during early embryogenesis. Possibly maternal thyroid function may be important to adequate placentation.

Endemic cretinism has not been reported in areas where, despite severe chronic iodine deficiency, the diet is adequate or in places where, despite severe protein-calorie malnutrition, the iodine supply is adequate. The present work indicates that iodine deficiency is a necessary condition for the appearance of endemic cretinism in a community. Whether it alone is a sufficient condition for endemic cretinism cannot be answered at present.

Even in Tocachi Group 2, a significant number of children showed mental retardation. This suggests that factors other than iodine deficiency play a role in their intellectual development. When intellectual deficiency persists in areas of endemic goiter after correction of iodine deficiency, other causes should be searched for, particularly protein-calorie malnutrition.

#### **SUMMARY**

This study assesses the effects of prenatal iodine administration on intelligence in children from an iodine-deficient area of rural Ecuador.

In one village, Tocachi, all inhabitants were injected with iodized oil in 1966. Two years later, all children born since 1966 were injected and all women of childbearing age were reinjected. A neighboring village, La Esperanza, provided untreated controls. The children of Tocachi were divided into two groups: Group 1 had been exposed to adequate iodine supply beginning at the fourth to seventh fetal month, while in Group 2 adequate iodine had been available from the moment of conception. The children of La Esperanza were divided into two groups to correspond chronologically with those of Tocachi. An approach to intellectual assessment was conducted, using the Stanford-Binet Intelligence Scale as modified by the authors.

The mean IQ values for Tocachi Group 1 and for the two groups from La Esperanza ranged from 69 to 73, with no significant differences. Group 2 from Tocachi had a mean value of 84, which was significantly greater than its control group in La Esperanza (p < 0.002). In Tocachi Group 2, no child had an IQ below 50, in contrast to the other three groups.

If cretins are defined as subjects with mental capacities at the idiocy-imbecility level (i.e., obvious mental retardation), provision of adequate iodine supplies from the time of conception onward appears to prevent endemic cretinism.

# **ACKNOWLEDGMENTS**

The help of José Suárez, M.D., and of Edgar Viteri, Víctor Espinoza, and José Reinhart, medical students, is gratefully acknowledged.

The studies related to endemic cretinism in Ecuador were sponsored by the Pan American Health Organization, the United States National Institutes of Health, the United States National Association for Retarded Children, and the Public Health Ministry of Ecuador.

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# **DISCUSSION**

Dunn: I think this study is very important, because it shows that with iodine deficiency the population is not sharply divided between obvious cretins and completely normal subjects, but there seem to be many gradations between these two. Thus the whole population is at risk for some impairment of intellectual function. The economic consequences of this to a community must be enormous. Dr. Bautista has been doing a somewhat similar study in a village in Bolivia with severe iodine deficiency, and he has found mean scores on the Stanford-Binet test of approximately 70-75, as you have. Finding a culture-free test of intelligence is an old problem, and there are certainly many difficulties in comparing test scores of isolated rural populations with those of North American urban children. This does not affect the use of this test for comparative purposes within a community, but I think it is less certain that a score of 70 implies the same degree of mental deficiency in rural Ecuador that it does in urban United States. The Bolivian study will attempt to correlate the Stanford-Binet with the Bender-Gestalt, class rankings by the teachers, and probably an analysis of the subsets in the Stanford-Binet testing; and perhaps from all this Dr. Bautista will be able to tell us which measures are the most valuable for grading intelligence in these cultures.

Finally, I wonder if you can tell us whether iodine given between conception and the fourth

month of gestation affects later IQ scores. This would help to pinpoint the time at which iodine is most critical.

Fierro: We did try dividing our data into several other groups and found no differences. The only improvement was in the children exposed to adequate iodine from the moment of conception.

Perinetti: The original studies in schoolchildren in Mendoza before iodization did not show a decrease in intellectual capacity, height, or weight in comparison with nonendemic regions. Perhaps the difference is that some of the other factors described by Dr. Fierro, such as malnutrition, were not present.

Pretell: In our experience in Peru, iodine deficiency may be associated with impaired intellectual capacity but does not seem to affect height or weight. This is our conclusion from data on children followed for five years after injection of iodized oil, when compared with uninjected controls from the same community. We do note growth retardation when compared with the American standards, but the growth rate is the same as that of noniodinedeficient Peruvian population from the coast. We thus would attribute this to a population standard and not to iodine deficiency or its correction. Also, from very careful anthropometric measurements, we do not find malnutrition to be a contributing factor.

# **IODINE DEFICIENCY**

EDUARDO A. PRET: MARTHA WAN, Q.F.,<sup>2</sup>

Dietary deficiency of iodia sequence, endemic goiter, con of the most extensive prob malnutrition in the world. In American countries, endemic been recognized as a severproblem, with the most affecte Andean region of Ecuador (1). Bolivia (4). Nevertheless, littl been paid to the implemental programs for prophylaxis a indeed, the prevalence of ende have worsened during the past de World Health Organization h demic goiter a relatively low pr attention, chiefly because the disease on development in the born periods have not been w

The association of endemic endemic goiter is well recogr increases the importance of because it has adverse effects ament of the community. The instead among cretins may be quit who survive into adulthood adegrees of physical or mental in severely limits their value to the to the community.

Querido has strongly advarthesis that the prevalence of creto the severity of iodine deficie

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