The effects of oral iodized oil on intelligence, thyroid status, and somatic growth in school-age children from an area of endemic goiter[1-3]

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ABSTRACT One hundred goitrous school children received 475 mg iodized oil by mouth, while 100 controls received mineral oil, on a double-blind basis. On follow-up 22 months later the urinary iodine had increased and goiter size had decreased in both groups, more strikingly in the iodine-treated children. There were no consistent differences between the two treatment groups in rate of somatic growth or performance on the Stanford-Binet and Bender tests. Because of the complexities introduced by increases in urinary iodine in the controls, we compared goiter reduction with improvement in IQ score in all children, regardless of group, and found a significant relationship ($p = 0.014$), particularly in girls ($p = 0.029$). We conclude that oral iodized oil is an attractive alternative to its injection but we recommend an approximate doubling of the dose used here for more effective control. Also, while our data are not conclusive, they support the possibility that correction of iodine deficiency may improve mental performance in school age children, particularly girls. *Am J Clin Nutr* 1982;35:127-134.

KEY WORDS Endemic goiter, cretinism, iodine deficiency, intelligence testing, iodized oil, thyroid

Introduction

Numerous clinical observations have established an association between severe iodine deficiency and endemic cretinism (reviewed in References 1-5). The latter condition has gross irreversible mental retardation as its cardinal feature (6). The presumed mechanism is perinatal hypothyroidism at a critical stage in the maturation of the central nervous system, but this has been difficult to prove (7). The incidence of cretinism in a population can be roughly correlated with the degree of iodine lack, and the condition will disappear with the introduction of adequate iodine (6).

In recent years, it has been proposed that areas of iodine deficiency are not limited to two discrete populations—cretins and "normals"—but instead contain a continuum, from frank cretinism through varying degrees of mental retardation and other stigmata of cretinism to apparent normality (4, 8). This concept has the practical implication that all members of an iodine-deficient area may be at risk for intellectual impairment. Part of this risk would come from irreversible damage during early development of the CNS, but it is possible that there is an additional component which is chronic and reversible.

The present study examines the hypotheses that iodine deficiency has continuing adverse effects on intelligence long after infancy, and that these can be reversed with correction of iodine deficiency. We have approached these questions by studying the effects of oral iodized oil on school children in an area of iodine deficiency.

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Methods

Subjects

These consisted of school children in Tiquipaya, a small village 2645 m above sea level in highland Bolivia, near Cochabamba. The inhabitants are Quechuan and most have obvious goiters without clinical evidence of protein-caloric malnutrition. Agriculture and small crafts are the chief occupations. A brief study in 1970 showed a mean serum protein bound iodine of 1.7 μg/dl (9). Initially, we examined 408 children, representing the entire available school population, and reported data on height, weight, head circumference, thyroid size, and academic performance (10). From these we chose at random for further study 100 boys and 100 girls, all between ages 5½ and 12 yr and all with some degree of thyroid enlargement.

Assessment

Thyroid size was estimated by a modification of the method of MacLennan and Gaitan (11) as previously described (10). Briefly, this involved measuring the height and width of the gland and assigning it to one of six arbitrary groups on the basis of the calculated areas. Groups 0, 1, 2, 3, and 4 correspond very roughly to stages O-A, O-B, I, II, III, respectively, of the Pan American Health Organization classification scheme (6) which is based on estimates by palpation and inspection. Group 5 corresponds to a stage IV used by some (12) to denote a huge goiter visible at some distance.

IQ was measured by the Stanford-Binet test, 3rd revision (13). Initially, we gave all items at each age level of the test in Spanish translation to 20 representative students (not included in the study) and on the basis of their performance selected four items at each age level for use in the study. These were generally the same items as the four recommended for the "short form" test (13). The items omitted from the list usually were based on elements or experiences foreign to the culture of this village, and were poorly answered by most of the 20 children regardless of age. Two of us (PB and AB), fluent in Spanish and experienced in intelligence testing, administered the test to all the children. Some of the youngest children were given the same test in Quechua by one of us (AB) fluent in that language. For each child the same examiner using the same language conducted the initial and final testing. The IQ was calculated from the 1972 norms of Terman and Merrill (13) for the United States to obtain a number for comparisons within this group of subjects. We do not suggest that this calculated score be used for comparisons between this and other groups.

The Bender Gestalt was administered and scored by number of errors (14). School grades for the academic year were obtained from the teachers and were reported on a scale from 0 (worst) to 7.0 (best) with 3.5 a passing grade.

Most laboratory tests were performed in the Laboratory of Nuclear Medicine at the University of San Simon Medical School. Urinary iodine was measured on a random sample from each subject by chloric acid digestion and ceric sulfate reduction (15); from this, a value for 24-h urinary iodine excretion was calculated using creatinine determinations from the same sample and the formula of Jolin and Escobar del Rey (16) for iodine/creatinine ratios. Pretell et al. (12) and others have confirmed the validity of this extrapolation. In a random sample of 25 students, we performed serum PBI, serum total protein, and thyroidal ^{131}I uptake (33 students) by routine laboratory methods. Serum thyroid-stimulating hormone (TSH) was measured in the same group by radioimmunoassay (17) at the University of Virginia School of Medicine.

Administration of iodine

After initial assessment, children in equal numbers were placed into one of two groups. Assignment was random for each age and sex. Each child in the first group received under observation an oral dose of 1.0 ml iodized poppyseed oil (Ethiodol) containing 475 mg iodine. Children in the second group received 1.0 ml noniodine-containing mineral oil of a similar brown color. Subsequent assessment was double-blind, with the group designation of a particular child unknown to his examiners.

Follow-up

At 6-month intervals, we repeated the urinary iodine and physical examinations for thyroid size, height, and weight. Twenty-two months after beginning the study, a full scale repeat of the initial assessment was made. This included height, weight, thyroid size, urinary iodine, IQ, Bender Gestalt, and school grades on all children. The children initially selected for further studies had repeat PBI, total serum protein, ^{131}I uptake, and TSH determinations.

Data analysis

Differences in parameters between experimental and control groups were examined by analysis of variance, employing a general linear model procedure (GLM procedure, Statistical Analysis System, SAS Institute Inc., Cary, NC). Preexperimental values were examined using one-way analysis of variance. Postexperimental values were analyzed using preexperimental values as a covariate to remove subject-to-subject variation in initial values.

Bivariate regression analysis was used to explore the relationship between changes in parameters and changes in goiter size. The analysis was conducted again using general linear models, in which the preexperiment parameter value was placed in the model as the first independent variable in order to remove subject-to-subject variation in initial measurements. The remaining variation was then related to changes in goiter size as the second independent variable in the model.

Pearson product-moment correlation coefficients were calculated among testing indices for data before and after the experiment.

Results

Table 1 shows the changes in each of the measured items from the beginning to the end of the study by age, sex, and treatment group. **Table 2** compares the two treatment

TABLE 1
Data at beginning (B) and end (E) of study; iodine group received 475 mg iodized oil orally, control group received mineral oil; follow-up was 22 months after treatment

Age group	Treatment group	n	Mean age	Urinary iodine B‖	Urinary iodine E‖	Height B	Height E	Weight B	Weight E	Goiter* B	Goiter* E	IQ† B	IQ† E	Bender‡ B	Bender‡ E	School grades§ B	School grades§ E
yr			yr	μg/24 h		cm		kg									
Girls																	
5½–7	Iodine	8	6.7	15	47	111	122	19	24	3.9	1.6	68.2	76.4	8.1	5.7	3.9	4.2
	Control	6	6.7	10	34	107	117	16	21	4.0	3.5	74.2	75.0	7.7	4.7	4.7	4.1
7–8	Iodine	9	7.6	11	59	112	125	19	25	3.9	1.9	68.9	69.0	6.6	4.8	4.4	4.2
	Control	10	7.5	11	29	113	123	19	24	3.8	3.4	71.6	72.6	6.7	4.3	4.8	4.6
8–9	Iodine	7	8.5	13	64	114	125	18	25	3.5	1.8	68.8	69.3	2.8	3.3	5.0	4.2
	Control	9	8.5	20	43	116	127	21	28	4.0	3.4	73.4	76.3	3.1	3.0	4.8	4.6
9–10	Iodine	12	9.6	15	45	124	135	24	31	3.5	1.7	65.7	70.7	3.9	2.6	4.7	4.0
	Control	11	9.5	17	24	123	135	22	31	3.7	3.7	64.4	68.3	3.2	1.4	4.5	4.7
10–12	Iodine	14	11.0	16	60	130	138	27	34	3.7	1.5	64.0	65.0	3.7	4.0	4.6	3.8
	Control	14	11.0	14	30	129	138	24	33	3.7	3.4	68.5	69.7	3.0	1.9	4.4	4.7
Boys																	
5½–7	Iodine	8	6.5	12	55	108	116	16	21	4.6	1.6	76.4	75.5	7.0	1.9	4.3	4.5
	Control	6	6.5	12	34	105	115	16	20	4.3	3.3	72.5	72.3	7.8	5.0	4.4	4.4
7–8	Iodine	6	7.3	9	39	116	124	19	25	4.2	1.7	67.8	71.7	6.8	4.3	5.1	4.6
	Control	8	7.4	13	35	111	120	17	22	4.1	3.1	70.5	74.2	5.4	4.4	4.5	4.0
8–9	Iodine	8	8.5	11	41	116	124	20	26	4.1	1.6	63.1	68.9	5.2	4.0	4.5	4.0
	Control	7	8.4	15	37	114	123	18	23	4.0	3.0	65.6	71.6	5.1	3.0	4.3	4.1
9–10	Iodine	15	9.5	13	56	123	133	23	31	3.9	1.8	65.8	58.2	3.4	2.6	4.4	4.6
	Control	13	9.5	17	33	124	132	23	28	3.9	2.9	65.1	65.5	3.1	2.9	4.9	4.2
10–12	Iodine	8	10.3	15	58	124	133	24	30	3.6	1.6	58.0	64.1	4.7	2.4	4.2	4.7
	Control	10	10.4	15	36	123	131	22	28	4.0	3.1	58.2	65.9	3.6	2.0	4.6	4.5

* Scale is from 0 (no goiter) to 5 (huge goiter); see "Methods" for details.
† IQ calculated from Stanford-Binet 1972 norms for United States, see "Methods."
‡ Bender Gestalt scores recorded as number of errors; see "Methods."
§ School grades represent teachers' assessment for current year, from scale of 1.0 (worst) to 7.0 (best).
‖ Mean of values, 6, 12, 18, and 22 months after administration of iodine or mineral oil.

groups at the beginning and at the end of the study, and also shows the probability of a significant difference between the two groups in regard to the change from "before" to "after." **Table 3** shows the mean levels of urinary iodine at several times during the study. The following results are shown by Tables 1 to 3.

1) Urinary iodine excretion increased approximately 4-fold in the iodine-treated group and doubled in the controls. As shown in Table 3, the mean urinary iodine levels remained fairly constant, around 50 μg/day, during the first 18 months after iodine administration, with a slight subsequent decrease at 22 months. The group to be treated with iodine had a slightly lower initial mean level of urinary iodine than the controls, and the difference was significant at $p = 0.04$. This was much less than the highly significant difference ($p = 0.0001$) after treatment. The increases in the control group and the large SD's in both groups suggest the introduction of iodine into the community from other sources, or perhaps a recycling of the administered iodine within the population.

2) Goiter size decreased markedly in the iodine-treated children and decreased slightly in the controls (Tables 1 and 2). The control girls showed the least change.

3) The IQ scores increased in both groups, and the increments did not differ significantly between the two groups.

4) There was a net decrease in errors in the Bender test in both groups, as expected, since this is an age-dependent test. There was no significant difference in rate of change between the two groups.

5) There were no significant changes in school grades.

6) Height and weight increased in all children, as expected. The mean height and weight for each age were substantially less than those published for American normals

TABLE 2
Comparison of iodine-treated group with controls before and after treatment

	Before			After			Probability of difference in change between treatment groups†
	Iodine	Control	p*	Iodine	Control	p*	
Height (cm)	119.2	118.6	0.64	128.6	127.6	0.49	0.55
Weight (kg)	21.8	21.0	0.20	27.8	26.6	0.17	0.74
Goiter‡	3.83	3.96	0.25	1.68	3.26	0.001	0.0001
IQ‡	66.05	66.32	0.86	69.43	70.31	0.57	0.86
Bender‡	5.02	4.81	0.66	3.43	3.11	0.43	0.49
Grades‡	4.47	4.58	0.34	4.34	4.40	0.53	0.64
Urinary I (μg/24 h)	13.5	15.2	0.04	53.4	32.3	0.0001	0.0001
PBI (μg/100 ml)	4.76	4.68	0.82	6.38	5.73	0.06	0.52
Serum protein (g/100 ml)	6.53	6.60	0.77	7.06	6.46	0.02	0.31
TSH (uU/ml)	5.33	3.46	0.01	4.37	3.53	0.16	0.22
^{131}I uptake 2 h (%)	46.5	35.8	0.05	19.9	30.9	0.04	0.15
^{131}I uptake 24 h (%)	86.3	79.7	0.06	74.4	82.4	0.11	0.09

* Probability of significant difference between iodine and control groups.
† Probability that iodine and control groups differ from each other in the degree of change from "before" to "after".
‡ Units of measure described in text and Table 1.

TABLE 3
Urinary iodine levels at various times after treatment of children with either iodine or noniodinated mineral oil

Treatment	Time after treatment				
	0	6 mo	12 mo	18 mo	22 mo
Boys					
Iodine	12.0 ± 1.1*	51.2 ± 6.5	44.3 ± 9.1	58.7 ± 8.8	39.9 ± 3.2
Control	14.7 ± 0.9	32.1 ± 3.9	35.3 ± 7.1	35.1 ± 4.4	30.9 ± 2.9
Girls					
Iodine	14.1 ± 0.7	57.9 ± 8.2	46.3 ± 7.9	57.4 ± 7.9	42.7 ± 4.3
Control	15.0 ± 0.9	27.1 ± 4.8	23.4 ± 3.8	35.6 ± 6.6	29.4 ± 2.3

* μg I/24 h ± SD.

(18) but were similar to those found in another Quechuan population from an area of Peru reportedly free of goiter (19).

7) Changes in the protein bound iodine, serum protein, TSH, and radioiodine uptake were all greater in the iodine-treated group than in the controls, but none of these differences between the two groups achieved statistical significance in the small subgroup tested. The distribution of patients who received special testing was examined against the quartile values for the total subject population, in terms of age, height, weight, IQ, and grades. No differences were found, using χ^2 goodness of fit test to the expected quartiles ($p > 0.05$).

The group comparisons were complicated by an apparent increase in iodine ingestion by the controls. Therefore, we examined change in goiter size in all children, regardless of group designations, as an alternative measure of iodine effect. **Table 4** relates changes in goiter size to changes in other parameters. For most of these, the associations were closer in girls than in boys. Of the intelligence tests, the IQ showed significant dependency on change in goiter size at a probability level of 0.014 for the two sexes combined. The probability of dependence of an improved Bender score on change in goiter size was 0.077 for girls, but only 0.55 for boys. Conversely, school grades significantly worsened for girls, while they improved for boys, in relation to change in goiter size. The decrease in TSH and in ^{131}I uptake correlated with a decrease in goiter size for girls, but not for boys; these associations were limited by the small numbers involved. Change in goiter size was highly dependent on change in urinary iodine in all subjects, although at a lower significance level in boys.

Table 5 presents correlations among the

TABLE 4
Relation of decrease in goiter size to changes in other parameters: bivariate regression analysis

Parameter	p	
	Girls	Boys
Ht (increase)	0.081	0.43
Wt (increase)	0.15	0.25
IQ (increase)	0.029	0.088
Bender (decrease)	0.077	0.55
Grades*	0.0075	0.073
Urinary I (increase)	0.0001	0.019
PBI (increase)	0.64	0.22
Serum proteins (increase)	0.92	0.18
TSH (decrease)	0.073	0.26
^{131}I uptake 2 h (decrease)	0.027	0.26
^{131}I uptake 24 h (decrease)	0.43	0.13

* Increase for boys, decrease for girls.

TABLE 5
Correlations among intelligence measures

Measures	Before		After	
	r*	p†	r	p
IQ and Bender	−0.141	0.05	−0.105	0.18
IQ and grades	0.193	0.01	0.261	0.001
Bender and grades	−0.334	0.0001	−0.343	0.0001

* Correlation coefficient.
† Significance level of r.

measures of intelligence at each time of testing. A negative correlation coefficient for the Bender with the other two parameters is appropriate, since a lower score in this test indicates improved performance. In general, the correlations among the tests were significant, despite the limitations of each test and the subjectivity of grades.

We did not do specific testing for hyperthyroidism in the iodine-treated children. The laboratory tests and growth pattern showed no evidence for this complication at the 22 month follow-up. At the 6-month intervals, when we collected urine samples, there were no obvious clinical features or volunteered symptoms of hyperthyroidism.

Discussion

A major objective of this study was to assess the effects of iodine deficiency and its correction on intelligence in late childhood. There are few published investigations on this subject. Fierro-Benitez et al. (20) reported in Ecuador that children with iodine sufficiency from the moment of conception had higher IQ's than controls who were iodine deficient for three or more months after conception. In the same area, Dodge et al. (21) using the Goodenough Draw-a-Man test compared children age 6 to 10 who had received intramuscular iodized oil 2 yr earlier with a control group from a nearby village. In girls, but not in boys, they found a higher intelligence level ($p < 0.001$) in the group treated with iodine.

A recent paper by Bleichrodt et al. (22) compares children in an iodine deficient village of Indonesia with those from an area of adequate iodine. Using a variety of tests they found a significantly superior performance in the 9- to 20-yr olds in the iodine sufficient subjects, and a tendency in that direction in 6- to 8-yr olds. The iodine-deficient village had a poorer educational background, so they also tested in a third village which was "iodine deficient" but had an educational level similar to that of the iodine sufficient. They found few significant differences between this additional village and the iodine-sufficient village. They concluded that it was the educational level rather than the iodine which was responsible for differences in the first two villages. They note that the third village had received iodized oil 2 yr before testing, and further state "it is unlikely, however, that this iodine administration had any corrective influence on mental abnormalities, since it is known that this can only be expected when intervention occurs during the first years of life." (22; p. 61). We believe an equally tenable interpretation for their results is that iodine deficiency may lower mental performance in school-age children, and its correction leads to improved test scores. Other important limitations of their study include a small population sample and dependence on the assumption that all factors save iodine deficiency were similar in the two villages. Thus, while the work of Bleichrodt et al. (22) is an important contribution to a difficult field, it does not provide a definitive answer to the question it addresses.

Our study differs in several ways from these previous reports. It was prospective and the testing of each child receiving iodine could be compared with his previous performance as well as with that of the control group. Administration of iodine and subsequent assessment were double-blind. Several independent markers of intelligence were used and could be related to urinary iodine, change in thyroid size, and other factors, as well as to the administration of iodine.

The apparent introduction of some exogenous iodine into the community during our study complicated interpretation of the results. Fortunately, this could be monitored by the urinary iodine levels. Change in thyroid size gave another independent marker of the effective amount of iodine each child was receiving.

We did not identify the source of the increased iodine in the controls. Iodized salt was available in nearby Cochabamba, but not widely used there because of its cost, and was not sold in Tiquipaya. No educational programs promoting iodination were being conducted during the study. Recycling of excreted iodine within a community has been a significant source of iodine conservation in other endemias (23). We cannot say whether it was a likely factor in this study.

The definition and measurement of intelligence are fundamental problems in a study such as this. These are complex enough in any society, but are particularly difficult in cultures foreign to those for which tests were devised and where complicating factors such as malnutrition, disease, and poor schooling exist. A number of books and conferences (e.g., References 24 and 25) have emphasized these difficulties. However, while IQ scores are nearly always lower in remote cultures than in the American children for whom they were standardized, the tests are useful for comparing individuals of similar background within such cultures (26) as was done by us. We added the Bender Gestalt because it is nonverbal and correlates significantly with IQ (27, 28). In a study of disadvantaged city children in the United States (27), the mean numbers of errors in 7- and 8-year-olds were 8.41 ± 3.42 and 6.43 ± 3.23, respectively. These are similar to the scores in our study and considerably poorer than the 4.80 ± 3.61 and 3.70 ± 3.60 described by Koppitz (14) for more affluent American children at those ages. In our study as well as in that of Welcher et al. (27) the correlation between Bender Gestalt and IQ was significant. School grades were the most subjective and least valuable indices in our study, but still showed a good correlation with the Stanford-Binet and Bender Gestalt.

With these problems of assessment in mind, we can consider the results of the present study. Our most positive finding was the highly significant relationship between decrease in goiter size and improvement in IQ, and this was particularly prominent in girls. This conclusion agrees with the preliminary studies of Dodge et al. (21), cited above. The Bender score also improved in girls in relation to decrease in goiter size. However, the school grades worsened. We could not show a positive correlation between increase in mean urinary iodine excretion and increase in IQ. The urinary iodine values are limited by the wide fluctuations in the means at the 6-month intervals shown in Table 3.

The present study does not answer the question of whether correction of iodine deficiency improves intelligence. Decrease in goiter size was significantly associated with both improvement in IQ score and increased urinary iodine. These findings offer indirect support for the hypothesis that correction of iodine deficiency improves mental performance. Future work should provide a clearer view of this possible relationship. Meanwhile, the results of the present study can be used as supporting reasons for prompt measures to eliminate iodine deficiency, in addition to the many already established.

Another object of our study was the effectiveness of oral iodized oil in combatting endemic goiter. The experience of several groups (12, 29–33) has shown that a single intramuscular injection of iodized oil, in amounts ranging from 475 to 1600 mg, produces dramatic reduction in goiter size and achieves levels of urinary iodine above 50 μg/day for 2 to 4 yr. This form of therapy has been recommended for severe endemias in areas unlikely to be reached by effective salt iodization within several years (34, 35). Jodbasedow has been rare, mild, and usually limited to older patients with nodules (36).

In a study of subjects age 6 or greater without nodules from the goitrous area of Neuquen, Argentina, Watanabe et al. (33) gave 23 persons 475 mg iodized oil intramuscularly and gave 25 subjects 1.4 times that dose orally. The two treatments appeared equally effective in goiter reduction. Three patients developed hyperthyroidism in the injected group, none in the oral group. The oral route provided lower but still normal levels of urinary iodine 2 yr after administration. Somewhat similar results were found in other age categories at other dose levels. Our study differed in several ways: the iodine deficiency was more severe, as judged by the lower initial urinary iodine levels (14 versus 24 μg/day in Neuquen); we studied more subjects restricted to a narrower age range; and the dose of oral iodine was lower (475 versus 666 mg). In addition, there were undoubtedly differences in nutrition, genetic background, and environmental factors. We found that 475 mg iodized oil orally gave marked reduction in goiter size and provided levels of urinary iodine in the 50 μg/day range. This level is considered barely adequate for iodine sufficiency (6). It is considerably below the levels reported after injected iodized oil (37). From our data and those of Watanabe et al. (33), a more reasonable initial oral dose for this age group would be 700 to 1000 mg. The oral route is simpler and cheaper than the intramuscular one, and offers an attractive alternative when planning prophylaxis with iodized oil.

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